No Impact of Atrial Fibrillation on Mortality Risk in Optimally Treated Heart Failure Patients

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ABSTRACT

Background: Several studies have shown that atrial fibrillation (AF) is associated with increased risk of death in heart failure (HF) patients. However, it is not clear whether this increased risk is independent of other risk factors.

Hypothesis: We hypothesized that AF would be an independent risk factor for death in a large cohort of HF patients.

Methods: Patients referred to Norwegian HF outpatient clinics were enrolled between October 2000 and February 2008. Patients with heart rhythm other than AF or sinus rhythm were excluded. Mortality data were obtained from the National Statistics Bureau, Statistics Norway with the last update February 2008.

Results: There were 4048 patients included in the analysis, with a median follow-up of 28 months. Adherence to guidelines regarding medical treatment was high. In univariate analysis, AF patients ($n = 1391$) had a higher risk of death than patients in sinus rhythm ($n = 2657$) (hazard ratio [HR] 1.181; 95% confidence interval (CI), 1.044–1.336; $P = 0.008$). However, after adjusting for confounding factors (age, New York Heart Association class, coronary artery disease as the main cause of HF, use of any loop diuretic, hemoglobin level, and serum creatinine), AF was no longer associated with increased risk of death (HR 1.037; 95% CI, 0.901–1.193; $P = 0.619$).

Conclusions: In this cohort of heart failure patients receiving optimal medical treatment at specialized HF clinics, AF was not associated with increased risk of death after adjusting for confounding factors.

Introduction

The population prevalence of both atrial fibrillation (AF) and heart failure (HF) have been estimated to be >1%, steeply increasing by age.¹ A marked increase in the incidence and prevalence of these conditions has been projected for the next decades, mainly due to an aging population.^{2–4} Both conditions are independently associated with increased risk of morbidity and mortality, and they constitute large burdens on society.⁵ AF may cause HF and vice versa, and their coexistence appears to be associated with increased mortality risk.⁶

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During the last decades, progress has been made regarding medical treatment in HF patients, including in particular angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and β -blockers.⁷ Systematic use of these medications has improved symptoms and reduced the risk of death in HF patients.

Several studies have addressed the impact of AF on mortality risk in HF patients. Most studies were subset analyses of randomized clinical trials investigating the effects of ACE-inhibitors, ARBs, β -blockers, or digoxin in HF patients.^{8–14} In addition, several observational studies have been reported.^{6,15–26} In most studies, the presence of AF in HF patients was associated with an increased risk of death; however, in some studies this increased risk was no longer present after adjusting for other risk factors. Two recent studies have suggested that the predictive value of AF may be dependent on underlying heart disease or patient age.^{27,28}

It is not known whether optimal medical treatment for HF will have an impact on the increased risk of death found

in HF patients with concomitant AF. The aim of this study was to investigate the impact of AF on mortality in a large registry of HF patients treated at specialized outpatient HF clinics in 24 hospitals in Norway, focusing on optimization of treatment and patient education.

Methods

Patients referred to Norwegian HF outpatient clinics were enrolled between October 2000 and February 2008. Initially, there were 10 participating hospitals, but the number of participating sites gradually increased to 24 by 2004. Seven of the 8 university hospitals and 10 of the 21 central hospitals in Norway were represented. Many local hospitals did not have dedicated heart failure clinics and could therefore not join the network. All participating hospitals have cardiologists responsible for their HF clinics, and these sites are well distributed in all regions of the country.

Patients of both genders with a diagnosis of HF, according to the European Society of Cardiology, were enrolled in the registry. The intention was to register consecutive patients. At the first visit (visit 1), all relevant medical history, physical examination data, 12-lead electrocardiogram (ECG), blood chemistry results, and management regimens, including medical treatment, were recorded in the registry database. Heart rhythm was recorded as sinus rhythm, atrial fibrillation, or other as assessed by the local physician based on the ECG recording made at the first visit. Registration from visit 2 was entered when all information and optimal titration of drugs had been performed. Thus, the number of follow-up attendances between visit 1 and 2 was decided at each hospital according to the patient's needs. An optional visit 3 was arranged 6 months after visit 2. Mortality data was obtained at regular intervals from the National Statistics Bureau, Statistics Norway. The last update with regard to mortality for this study was February 2008.

No one was offered incentives to participate except for the interest in being part of the network and the possibility of joining a meeting about the registry once a year. The investigation conforms to the principles outlined in the Declaration of Helsinki. All patients gave their written informed consent. The study was approved by the Regional Committees for Medical and Health Research Ethics and the Norwegian Data Inspectorate.

Statistical Analysis

Continuous variables were tested for normality of distribution and are presented as mean $\pm$ standard deviation (SD), whereas categorical variables are presented as numbers (%). Student *t* test and χ^2 test were used for comparison of baseline characteristics between the AF and sinus rhythm groups. A Kaplan-Meier survival curve was constructed to illustrate the impact of AF on the risk of death. Continuous variables were grouped as quartiles to assess linearity with respect to survival. Univariate Cox regression analysis was used to investigate the impact of AF and other variables on survival. Multivariate analysis was performed using Cox regression models, including variables related to both AF and risk of death with a *P* value of <0.1 . A stepwise backward strategy was used, excluding the variable with the highest *P* value at each step. AF was kept in the model

at all steps, and the final model included AF and all variables with a *P* value of <0.05 . Subgroup analyses were performed for all confounders, analyzing each category separately for categorical variables, and patients with below or above mean values separately for continuous variables. New York Heart Association (NYHA) class I/II and class III/IV were grouped together for this subgroup analysis. Subgroup analyses of patients recruited before and after January 1, 2005, were also performed to investigate whether the relation between AF and survival was consistent over time. A 2-sided *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc for Windows version 11.1.1.0 (MedCalc Software, Mariakerke, Belgium).

Results

Twenty-four hospitals participated in this registry, of which 4 did not register mortality data. Out of 4961 patients in the complete registry, 4048 were eligible for this comparison between AF patients (*n* = 1391) and patients in sinus rhythm (*n* = 2657) (Figure 1). Baseline characteristics are presented in Table 1. Median follow-up was 28 months (range, 0–93 months).

In univariate analysis, the presence of AF at baseline was associated with an increased risk of death (hazard ratio [HR] 1.181; 95% confidence interval [CI], 1.044–1.336; *P* = 0.008) (Figure 2). However, the AF patients differed from patients in sinus rhythm in several respects. Most notably, AF patients were on average 6 years older than patients in sinus rhythm, and the proportion of men was higher. Furthermore, AF patients had slightly higher ejection fraction (EF), less frequently coronary artery disease as the main cause of HF, and more often hypertension or valvular heart disease as the main cause. AF patients had a slightly higher ventricular heart rate than patients in sinus rhythm.

Adherence to guidelines regarding medical treatment was high; 88.4% received ACE-inhibitors and/or angiotensin receptor blockers (ARBs), whereas 82.8%

Figure 1. Flow chart of the study. Abbreviation: N, number of patients.

Table 1. Baseline Characteristics

Variable	Sinus Rhythm, n = 2657	Atrial Fibrillation, n = 1391	P
Age, y	68 ± 13	74 ± 10	<0.001
Male gender	1800 (68%)	1039 (75%)	<0.001
EF (%)	32 ± 11	34 ± 12	<0.001
NYHA functional class			
I	157 (5.9%)	36 (2.6%)	
II	1197 (45.1%)	551 (39.6%)	
III	1222 (46.0%)	747 (53.7%)	<0.001
IV	37 (1.4%)	28 (2.0%)	
Unknown	44 (1.7%)	29 (2.1%)	
Etiology			
Coronary artery disease	1637 (61.6%)	612 (44.0%)	<0.001
Hypertension	204 (7.7%)	150 (10.8%)	0.001
Idiopathic dilated cardiomyopathy	374 (14.1%)	174 (12.5%)	0.182
Valvular heart disease	121 (4.6%)	123 (8.8%)	<0.001
Other/not specified	321 (12.1%)	332 (23.9%)	
Systolic blood pressure, mm Hg	127 ± 23	127 ± 21	0.792
Heart rate, bpm	72 ± 14	76 ± 17	<0.001
Medication			
ACE inhibitor and/or angiotensin receptor blocker	2354 (88.6%)	1224 (88.0%)	0.421
ACE inhibitors	2052 (77.2%)	1053 (75.7%)	0.238
Angiotensin receptor blockers	333 (12.5%)	198 (14.2%)	0.145
ACE inhibitor and angiotensin receptor blocker	28 (1.1%)	27 (1.9%)	0.031
β-blockers	2238 (84.2%)	1116 (80.2%)	0.005
Furosemide	1306 (49.2%)	737 (53.0%)	0.023
Bumetanide	877 (33.0%)	518 (37.2%)	0.008
Any loop diuretic	2178 (82.0)	1249 (89.8%)	<0.001
Thiazide	88 (3.3%)	66 (4.7%)	0.029
Aldosterone antagonist	590 (22.2%)	341 (24.5%)	0.106
Warfarin	683 (25.7%)	1198 (85.9%)	<0.001
Blood analysis			
B-hemoglobin, g/100 mL	13.7 ± 1.6	14.0 ± 1.8	<0.001
S-creatinine, μmol/L	107 ± 47	110 ± 53	0.030
S-sodium, mmol/L	140 ± 3	140 ± 3	0.915

Abbreviations: ACE, angiotensin converting enzyme; EF, ejection fraction of the left ventricle; NYHA, New York Heart Association. Data are presented as number (%) of patients or mean ± standard deviation.

received β-blockers. The use of ACE-inhibitors and/or ARBs was similar in the 2 groups, whereas β-blockers were more frequently used among patients in sinus rhythm. Metoprolol was the most frequently used β-blocker (65.4%), with a mean

daily dose at last follow-up of 117 ± 64 mg in AF patients and 106 ± 63 mg in patients with sinus rhythm ($P < 0.001$). There was no trend toward increasing doses by recruitment year from 2000 to 2008. Loop diuretics were more frequently

Figure 2. Kaplan-Meier survival curves illustrating the impact of atrial fibrillation on risk of death in univariate analysis. Abbreviations: AF, atrial fibrillation; SR, sinus rhythm.

used among AF patients. Most AF patients received anticoagulant treatment with warfarin, compared to approximately 25% of the patients in sinus rhythm. Adherence to warfarin therapy was high, and out of 858 patients on warfarin therapy at baseline who attended the optional 6 months follow-up visit, 772 patients (90.0%) were still on warfarin. Hemoglobin levels and serum creatinine was slightly higher in AF patients, whereas sodium levels were similar.

Several factors differing between patients with AF and patients with sinus rhythm also had an impact on risk of death, and thus constituted potential confounding factors. In univariate analysis, age ($P < 0.001$), NYHA class ($P < 0.001$), ischemic heart disease as the main cause of HF ($P < 0.001$), blood hemoglobin level ($P < 0.001$), serum creatinine ($P < 0.001$), use of β -blockers ($P = 0.001$), and loop diuretics ($P < 0.001$) all had an impact on survival. The relation between EF and risk of death was complex, in the sense that the 3 lowest EF quartiles showed an inverse relationship to risk of death, whereas the highest EF quartile (corresponding to EF $> 40\%$) had similar mortality risk as the 3 lowest quartiles combined. Heart rate was not associated with risk of death ($P = 0.311$).

In the final Cox regression multivariate model, age, NYHA class, coronary artery disease as the main cause of HF, use of any loop diuretic, hemoglobin level, and serum creatinine remained as significant confounders. Adjusting for these confounders, the presence of AF was no longer associated with increased mortality risk (HR 1.037; $P = 0.619$) (Table 2). Age was the most important confounding factor. Adjusting for this covariate alone, AF was no longer a statistically significant predictor of death.

Subgroup analysis suggested that AF was a stronger predictor of death in NYHA class I/II ($P = 0.009$) and in patients with ischemic heart disease as the main cause of HF ($P < 0.001$). However, even in these subgroups, the relation between AF and risk of death disappeared when

Table 2. Multivariate Analysis. Relation Between Atrial Fibrillation and Risk of Death After Adjustment for Confounding Factors

Covariate	Adjusted HR	95% CI of HR	P
Atrial fibrillation	1.037	0.901–1.193	0.619
Age	1.040	1.032–1.047	< 0.001
NYHA Class	1.441	1.282–1.619	< 0.001
Coronary artery disease as the main cause of heart failure	1.225	1.066–1.408	0.045
Use of loop diuretics	1.368	1.071–1.748	0.013
Hemoglobin level	0.912	0.876–0.950	< 0.001
Serum creatinine	1.004	1.003–1.005	< 0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; NYHA, New York Heart Association.

adjusted for confounders. In the subgroup of patients with coronary artery disease as the main cause of HF, previous revascularization was associated with improved survival. However, this variable did not retain its statistical significance in multivariate analysis.

Discussion

In this study on 4048 HF patients treated at specialized HF clinics, AF was associated with increased risk of death. However, after adjustment for age, NYHA class, coronary artery disease as the main cause of HF, hemoglobin level, serum creatinine, and use of loop diuretics, this association was no longer present. Similar findings have been reported by other investigators.^{11,12}

Our findings contrast with a recent meta-analysis concluding that AF was an independent predictor of death in HF patients.²⁹ However, 6 out of 12 studies reporting multivariate analysis in this meta-analysis were statistically nonsignificant with regard to AF as an independent risk factor for death. The proportions of patients on ACE-inhibitors and/or ARBs, and in particular β -blockers, were significantly higher in our study than in the studies included in the meta-analysis. In addition, 86% of AF patients received warfarin in our cohort, demonstrating stronger adherence to guidelines regarding anticoagulant treatment in AF than in all previous studies. This improved medical treatment of HF and optimized thromboprophylaxis in AF may have reduced the impact of AF on prognosis in HF patients.

We investigated HF patients attending specialized HF outpatient clinics only, and hence our findings may not be valid for other clinical settings. For instance, new-onset AF in patients hospitalized for exacerbation of HF may have a different prognostic impact.

The mean age in our study was higher than in most other studies, and perhaps more representative for the general HF population today. AF patients were on average 6 years older than the HF patients in sinus rhythm, and unsurprisingly, this age difference had a major impact on the risk of death. In fact, adjusting for age alone as a covariate, AF lost its significance as an independent predictor of death.

Although an inverse relationship between EF and risk of death was found in the lower 3 EF quartiles, the highest EF quartile (corresponding to EF >40%) showed somewhat unexpected behavior with a similar mortality risk as all other quartiles put together. Any use of loop diuretics was associated with an increased mortality risk, probably reflecting more severe HF. Ischemic heart disease as the main cause of HF also remained statistically significant as an independent risk factor for death in the multivariate analysis. An inverse relationship was found between blood hemoglobin levels and risk of death, and conversely, increasing levels of serum creatinine were associated with increased mortality risk. These findings have also been variably reported in previous studies.^{11,12,15,25}

A previous report concluded that AF was an independent prognostic marker only in patients with ischemic heart disease²⁷; however, even in this subgroup of patients the relation between AF and risk of death was lost after adjustment for confounders. Whether these different findings may be related to higher proportions of patients receiving β -blockers and ACE-inhibitors or ARBs in our study remains speculation.

Limitations

The implantable cardioverter-defibrillator (ICD) implantation rate for HF indication is very low in Norway and was not recorded in our study. However, we find it unlikely that ICD implants would have had an impact on the relation between AF and risk of death in this study. Except for β -blocking agents, use of antiarrhythmic drugs and digoxin (or digitoxin, which is the preferred digitalis glycoside in Norway) was not systematically recorded in this study, and some of these drugs may be associated with adverse outcomes. However, there is reason to believe that these drugs would be used more often in AF patients; therefore, inclusion of this variable would probably weaken the association between AF per se and risk of death further. Information on the temporal pattern of AF (ie, paroxysmal, persistent, or permanent) or duration of AF was not available for this analysis.

Conclusion

In this cohort of HF patients receiving optimal medical treatment at specialized HF clinics, AF was not associated with increased risk of death after adjusting for confounding factors.

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