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ORIGINAL RESEARCH ARTICLE

N-terminal pro brain natriuretic peptide eliminates the prognostic effect of atrial fibrillation in patients with chronic heart failure

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Abstract

Aims Co-morbid atrial fibrillation (AF) increases both mortality and N-terminal pro brain natriuretic peptide (NT-proBNP) concentrations in patients with chronic heart failure (CHF). It is unclear whether AF worsens prognosis independently from NT-proBNP concentrations. If AF was an independent risk factor, NT-proBNP levels for outcome prediction would need to be adjusted in patients with AF. We aimed to analyse the influence of AF on the prognostic value of NT-proBNP in patients with CHF.

Methods and results A total of 2541 consecutive CHF patients with sinus rhythm (SR) or AF were identified in the outpatients' CHF registry of the University of Heidelberg, Germany. Of these, 250 patients with SR were individually matched to 250 patients with AF with respect to NT-proBNP, New York Heart Association functional class, sex, age, and aetiology of CHF. In the general sample, both AF and NT-proBNP were associated with all-cause mortality [hazard ratio (HR) = 1.96, 95% confidence interval (CI) 1.61–2.39, $P < 0.001$; and HR = 1.03 per 1000 ng/L increase, 95% CI 1.02 to 1.04, $P < 0.001$, respectively]. After matching, NT-proBNP retained its prognostic power (HR = 1.13 per 1000 ng/L increase, 95% CI 1.10 to 1.16, $P < 0.001$), but AF did not (HR = 0.91, 95% CI 0.66 to 1.25, $P = 0.56$). Despite similar prognosis, matched patients with SR were in more advanced CHF than were AF patients as indicated by a lower left ventricular ejection fraction (30 ± 13% vs. 34 ± 14%, $P < 0.001$).

Conclusions The prognostic value of NT-proBNP in CHF is not influenced by concomitant AF. AF, in return, might be a surrogate of a worse cardiac condition rather than an independent risk factor.

Keywords Chronic heart failure; Atrial fibrillation; NT-proBNP; Prognosis

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Introduction

Chronic heart failure (CHF) and atrial fibrillation (AF) are both highly prevalent in industrial countries.[1–4] Co-morbidity of CHF and AF is common and conveys a poor prognosis.[5–9] Whether AF is an independent risk factor in CHF or a surrogate of advanced CHF disease, however, is still under debate.[10]

In patients with CHF, AF is associated with higher levels of N-terminal pro brain natriuretic peptide (NT-proBNP).[11–13] Elevated NT-proBNP concentrations, in turn, are related to increased mortality.[14–16] On the other hand, the prognostic power of NT-proBNP may differ by patient characteristics and hence compromise its use as a prognostic marker for CHF in daily clinical practice.[17] The effect of AF on the prognostic value of NT-proBNP regarding all-cause mortality in patients with CHF remains unclear.[18–22]

If AF was an independent risk factor—leading by itself to increased levels of NT-proBNP—patients with similar NT-proBNP but different in rhythm would differ in prognosis. Therefore, cut-off levels for outcome prediction would need to be adjusted in patients with AF.[21] For example, if patients

with AF had better prognosis than had sinus rhythm (SR) patients with similar NT-proBNP concentrations, NT-proBNP cut-off levels for risk prediction would need to be increased. If AF was rather reflecting more advanced disease—potentially indicated by elevated NT-proBNP levels—the prognosis of these patients would be similar. We addressed the influence of AF on the prognostic value of NT-proBNP in a sample of 2541 ambulatory patients with stable CHF.

Methods

Patient selection

Patients' data were extracted from the Heidelberg Heart Failure Registry as described subsequently. All patients with stable CHF who attended the specialized heart failure outpatient clinic of the University Hospital Heidelberg, Germany, for evaluation of heart failure were offered inclusion into the local heart failure registry. Less than 1% refused to participate. Inclusion into the heart failure registry is continuous and ongoing. To be eligible for this study, patients were selected from the registry according to the following inclusion criteria:

(i) diagnosis of CHF,
(ii) presentation at the specialized heart failure outpatient clinic of the University Hospital Heidelberg, Germany, for evaluation of heart failure between 1995 and 2014,
(iii) signature of written informed consent for inclusion into the Heidelberg Heart Failure Registry,
(iv) diagnosis of either SR or AF, and
(v) measurement of NT-proBNP at the time of presentation.

The diagnosis of CHF was established according to the European Society of Cardiology guideline criteria[5] on the basis of typical symptoms in the presence of objective abnormalities of cardiac function on echocardiography or left heart catheterization. Inclusion into the present study was independent from underlying left ventricular ejection fraction (LVEF). Thus, the study cohort comprised patients with reduced, mid-range, or preserved ejection fraction. The diagnosis of SR or AF was based on a 12-lead electrocardiogram (ECG) recorded at the same day as the blood sample was taken. Interpretation of the ECG was performed with respect to guideline recommendations.[6] Every patient with AF on 12-lead ECG at baseline was classified as AF. Blood samples for NT-proBNP analyses were taken from a peripheral venous catheter using EDTA vacutainers. NT-proBNP was measured according to the standard protocol of the fully automated Elecsys® Roche Diagnostics 2010 analyser. Assay precision, analytical sensitivity, interferences, and stability for this method have been described previously.[23]

Baseline characteristics included medical history, physical examination, 12-lead ECG, LVEF, blood count and standard chemistry, and medication. Medication was at the discretion of the referring physician.

If multiple visits were available, only the first visit was chosen. The study conformed to the principles of the Declaration of Helsinki and was approved by the local ethics committee.

Follow-up and endpoint

Surviving patients were followed up for a minimum of 365 days. Information on survival status was collected by scheduled visits to the outpatient clinic, telephone calls either to the patients' homes or to their physicians, or hospital electronic records.

Primary endpoint of this study was all-cause mortality. Patients who received cardiac transplantation were followed up until transplantation and censored thereafter.

Matching

In order to analyse the impact of AF on the prognostic value of NT-proBNP, CHF patients with AF were individually matched with patients with SR with respect to NT-proBNP levels. For NT-proBNP concentrations, a deviation of ±15% was permitted. This range was chosen as it represents half of the intra-individual biological variation of NT-proBNP described in prior studies.[14,24] To account for possible confounders, additional matching criteria were: sex, age, New York Heart Association (NYHA) functional class, and aetiology of CHF. We chose these variables because they have an influence on both mortality[5,25,26] and NT-proBNP concentrations[14] in patients with CHF. With regard to age, a variation of ±5 years was tolerated.

Automated matching was performed using a 'visual basic for applications' code, as follows: first, pseudonymous data of CHF patients with AF and of those with SR were listed separately into two Excel® files. Both lists were put in random order, using Excel® random number generator. Then, beginning with the first patient with AF, the first patient on the SR list who fulfilled every single matching criterion was chosen. The pair was then removed from both lists, and the matching routine continued with the next patient on the AF list. In case no matching patient with SR could be identified, the AF patient was removed from the AF sample, and the matching cycle continued with the next AF patient. In addition, we performed a reverse matching starting with the first patient with SR. As results of the reverse matching were similar to those of the original matching, only results from the original matching are presented.

Subgroups

All analyses were repeated in subgroups with respect to age (≤65 vs. >65), sex (male vs. female), aetiology (ischaemic, cardiomyopathy, and others), NYHA (I/II vs. III/IV), LVEF (≤30% vs. >30%), estimated glomerular filtration rate (eGFR) (≤60 vs. >60 mL/min/1.73 m^2) calculated using the Modification of Diet in Renal Disease equation,[27] chronic obstructive pulmonary disease (COPD) (yes vs. no), diabetes (yes vs. no), heart rate (≤75 vs. >75 b.p.m.), and systolic blood pressure (SBP) (≤120 vs. >120 mmHg). Cut-offs for age, LVEF, eGFR, heart rate, and SBP represent the median of the respective variables in the matched sample.

Statistics

Calculations were performed using Excel® 2013 (Microsoft, Redmond, USA), IBM SPSS® Statistics version 21 (IBM, Ehningen, Germany), and MedCalc® (MedCalc® Software bvba, Ostend, Belgium). Figures were created with GraphPad® PRISM 6 (GraphPad® Software Inc., La Jolla, USA). Results are presented as numbers (%), mean ± standard deviation, or median [inter-quartile range], as appropriate. To test for significant differences between groups, Student's *t*-test, χ^2 test, odds ratio (OR), or Mann–Whitney *U*-test were used, where appropriate. To estimate cut-off levels of NT-proBNP as a predictor of 1 year mortality, receiver operating characteristic (ROC) curves were used. The Youden index of ROC was used to identify the best cut-off levels of NT-proBNP as a predictor of 1 year mortality.[28] Survival was analysed in the general as well as matched sample using Cox proportional hazard models and displayed by Kaplan–Meier product limit method. As matched patients with SR and AF differed in a number of baseline variables, we performed a sensitivity analysis using stepwise multivariable Cox regression analysis in the matched sample. Covariates included all variables that significantly differed between matched patients with AF and SR. In addition, we performed additional matching procedures with respect to NT-proBNP (±15%), eGFR (±10%), and LVEF (±5%), and NT-proBNP (±15%), age, sex, and eGFR (±10%). Univariable and multivariable survival analyses were repeated in the additional matched samples.

All tests are two tailed. A *P*-value of <5% was regarded as statistically significant.

Results

Baseline characteristics and follow-up

A total of 2541 patients fulfilled the inclusion criteria outlined previously. Of these, 2110 patients were with SR, while 431 patients had AF. After matching with respect to NT-proBNP, age, sex, NYHA functional class, and aetiology of CHF, 250 pairs of CHF patients with AF or SR were identified. In 181 AF patients, no matching SR patient could be identified. These patients were therefore excluded from the matched analyses.

Baseline characteristics of the general and matched samples are shown in *Table 1*. In the general sample, patients with SR and AF differed in most characteristics, whereas patients in the matched sample were similar with regard to the matching criteria age, sex, NYHA functional class, NT-proBNP, and aetiology of CHF. However, matched patients with AF were more likely to have diabetes ($P = 0.025$) or hypertension ($P = 0.025$) than were patients with SR. In addition, body mass index, diastolic blood pressure, and resting heart rate were higher in CHF patients with AF than in those with SR ($P < 0.001$, $P = 0.007$, and $P < 0.001$, respectively). On the other hand, patients with SR had a lower LVEF ($P < 0.001$) and a lower eGFR ($P = 0.012$). A total of 1506 (59%) and 362 (72%) patients in the general and matched sample had an LVEF ≤ 40%.

In the general sample, the diagnosis of AF was associated with higher levels of NT-proBNP as compared with SR (2051 ng/L [985–4246 ng/L] vs. 466 ng/L [142–1508 ng/L], $P < 0.001$). Median NT-proBNP concentrations with respect to LVEF and heart rhythm are shown in *Table* S1. By definition, NT-proBNP levels did not differ between patients with AF and SR in the matched sample (1621 ng/L [858–3017 ng/L] vs. 1555 ng/L [846–3014 ng/L], $P = 0.774$).

Total follow-up in the general sample was 9717 patient-years. During that time, 507 (20.0%) patients died, 132 (30.6%) with AF and 375 (17.8%) with SR. One-year mortality was 9.3% and 4.0% [OR = 2.04, 95% confidence interval (CI) 1.62 to 2.58, $P < 0.001$] for patients with AF and SR, respectively.

Total follow-up in matched CHF patients was 1847 patient-years. During that time, 157 (31.4%) patients died, 72 (28.8%) with AF and 85 (34.0%) with SR. One-year mortality was 7.6% and 9.2% (OR = 0.81, 95% CI 0.43 to 1.53, $P = 0.52$) for patients with AF and SR, respectively.

Prognostic significance of atrial fibrillation and N-terminal pro brain natriuretic peptide

General sample

In the general sample, the diagnosis of AF was associated with a higher all-cause mortality than the diagnosis of SR (HR = 1.96, 95% CI 1.61 to 2.39, $P < 0.001$, for AF vs. SR). The Kaplan–Meier survival curves of patients with AF and SR in the general sample are depicted in *Figure 1*.

Increasing levels of NT-proBNP were associated with increasing mortality (HR = 1.03 per 1000 ng/L increase, 95% CI 1.02 to 1.04, $P < 0.001$). This was true for patients with

Table 1 Baseline characteristics of the general chronic heart failure patient sample and of chronic heart failure patients with atrial fibrillation matched to chronic heart failure patients with sinus rhythm with respect to N-terminal pro brain natriuretic peptide, age, sex, New York Heart Association functional class, and aetiology

	General sample			Matched sample		
Characteristics	AF (n = 431)	SR (n = 2110)	P-value	AF (n = 250)	SR (n = 250)	P-value
NT-proBNP (ng/L)	2051 [985–4246]	466 [142–1508]	<**0.001**	1621 [858–3017]	1555 [846–3014]	0.774
Age (years)	65.9 ± 11.6	55.9 ± 14.8	<**0.001**	64.3 ± 10.7	64.2 ± 10.6	0.860
Men, *n* (%)	341 (79.1)	1518 (71.8)	**0.002**	210 (84.0)	210 (84.0)	1.000
NYHA			<**0.001**			1.000
I, *n* (%)	95 (22.0)	861 (40.8)		56 (22.4)	56 (22.4)	
II, *n* (%)	140 (32.4)	687 (32.5)		92 (36.8)	92 (36.8)	
III, *n* (%)	189 (43.8)	545 (25.8)		101 (40.4)	101 (40.4)	
IV, *n* (%)	7 (1.6)	17 (0.8)		1 (0.4)	1 (0.4)	
Aetiology			**0.001**			1.000
Ischaemic, *n* (%)	207 (47.9)	1041 (49.3)		156 (62.4)	156 (62.4)	
Cardiomyopathy, *n* (%)	133 (30.8)	771 (36.5)		71 (28.4)	71 (28.4)	
Other, *n* (%)	92 (21.3)	301 (14.3)		23 (9.2)	23 (9.2)	
BMI (kg/m^2)	27.8 ± 4.9	27.3 ± 5.1	0.107	28.5 ± 5.0	27.0 ± 4.4	<**0.001**
HR (1 b.p.m.)	80 ± 19	71 ± 14	<**0.001**	81 ± 18	71 ± 13	<**0.001**
Hypertension, *n* (%)	366 (84.7)	1708 (80.8)	0.066	219 (87.6)	195 (78.0)	**0.025**
SBP (mmHg)	120 ± 19	120 ± 19	0.779	120 ± 19	118 ± 20	0.265
DBP (mmHg)	74 ± 12	75 ± 12	0.178	75 ± 11	72 ± 11	**0.007**
LVEF (%)	35 ± 15	37 ± 15	**0.030**	34 ± 14	30 ± 13	<**0.001**
6MWT (m)	420 ± 127	478 ± 117	<**0.001**	430 ± 120	438 ± 120	0.532
Diabetes, *n* (%)	146 (33.8)	438 (20.7)	<**0.001**	96 (38.4)	68 (27.2)	**0.025**
COPD, *n* (%)	32 (7.4)	106 (5.0)	**0.045**	19 (7.6)	18 (7.2)	0.864
eGFR (mL/min/1.73 m^2)	73 ± 27	83 ± 29	<**0.001**	77 ± 26	71 ± 23	**0.012**
Haemoglobin (g/dL)	13.9 ± 0.8	13.8 ± 1.9	0.83	14.1 ± 1.7	13.6 ± 1.9	**0.008**
Serum cholesterol (mg/dL)	171 ± 41	186 ± 46	<**0.001**	175 ± 43	183 ± 48	0.140
ACEI, *n* (%)	310 (71.9)	1462 (69.2)	0.278	182 (72.8)	177 (70.8)	0.619
ARB, *n* (%)	128 (29.7)	535 (25.3)	0.061	80 (32.0)	68(27.2)	0.240
Beta-blocker, *n* (%)	382 (88.6)	1760 (83.3)	**0.006**	222 (88.8)	216 (86.4)	0.416
MRA, *n* (%)	211 (49.0)	795 (37.6)	<**0.001**	131 (52.4)	129 (51.6)	0.858
Digitalis, *n* (%)	237 (55.0)	384 (18.2)	<**0.001**	140 (56.0)	55 (22.0)	<**0.001**
Statin, *n* (%)	246 (57.1)	1187 (56.2)	0.754	150 (60.0)	165 (66.0)	0.165
Oral antidiabetics, *n* (%)	77 (17.9)	250 (11.8)	**0.001**	52 (20.8)	29 (11.6)	**0.005**
Anticoagulation, *n* (%)	392 (91.0)	803 (38.0)	<**0.001**	230 (92.0)	126 (50.4)	<**0.001**

P-values < 0.05 are printed in bold letters.
6MWT, 6 min walk test; ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association functional class; SBP, systolic blood pressure; SR, sinus rhythm.

AF as well as for those with SR (HR = 1.02 per 1000 ng/L increase, 95% CI 1.01 to 1.03, $P < 0.001$; and HR = 1.03 per 1000 ng/L increase, 95% CI 1.02 to 1.04, $P < 0.001$, for patients with AF and SR in the general sample, respectively).

The prognostic information of rhythm and NT-proBNP was independent one from the other in the common Cox proportional hazard model (HR = 1.82, 95% CI 1.49 to 2.22, $P < 0.001$, for AF vs. SR; and HR = 1.03, 95% CI 1.02 to 1.03, $P < 0.001$, per 1000 ng/L increase of NT-proBNP).

Matched sample

After matching for age, sex, NYHA functional class, NT-proBNP, and aetiology of CHF, no difference in mortality was noted between CHF patients with AF and those with SR (HR = 0.91, 95% CI 0.66 to 1.25, $P = 0.56$, for AF vs. SR). The Kaplan–Meier survival curves of patients with AF and SR in the matched sample are shown in *Figure 2*.

In contrast, NT-proBNP retained its prognostic power in the matched sample (HR = 1.13 per 1000 ng/L increase, 95% CI 1.10 to 1.16, $P < 0.001$). Again, this was true for patients with AF as well as for those with SR (HR = 1.12 per 1000 ng/L increase, 95% CI 1.08 to 1.16, $P < 0.001$; and HR = 1.14 per 1000 ng/L increase, 95% CI 1.10 to 1.18, $P < 0.001$, for patients with AF and SR in the matched sample, respectively).

The prognostic information of NT-proBNP remained independent from rhythm in the common Cox proportional hazard model (HR = 0.89, 95% CI 0.65 to 1.23, $P = 0.48$ for AF vs. SR; and HR = 1.13, 95% CI 1.10 to 1.16, $P < 0.001$, per 1000 ng/L increase of NT-proBNP).

Sensitivity analyses

Results were confirmed after adjusting for covariates in multivariable Cox regression analyses of the matched sample. Again, there was no significant difference in survival between

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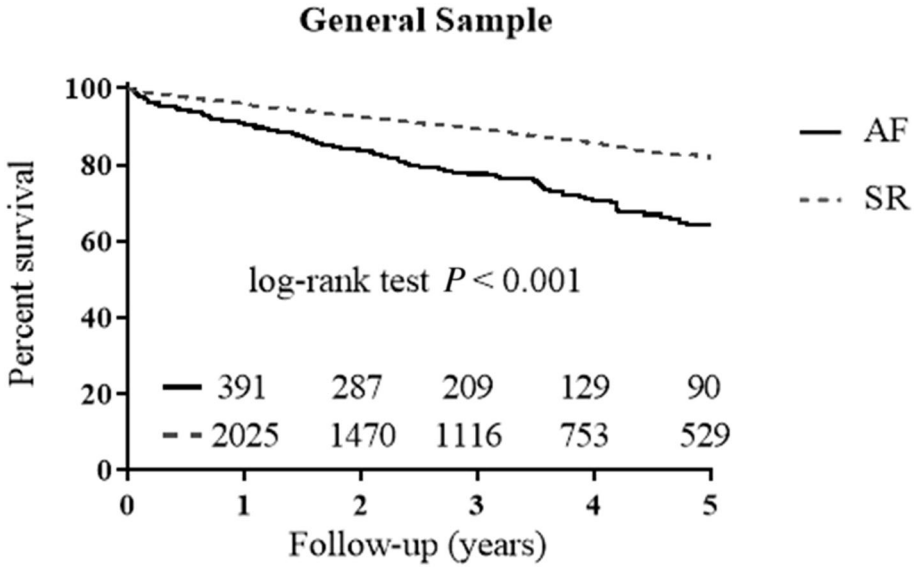
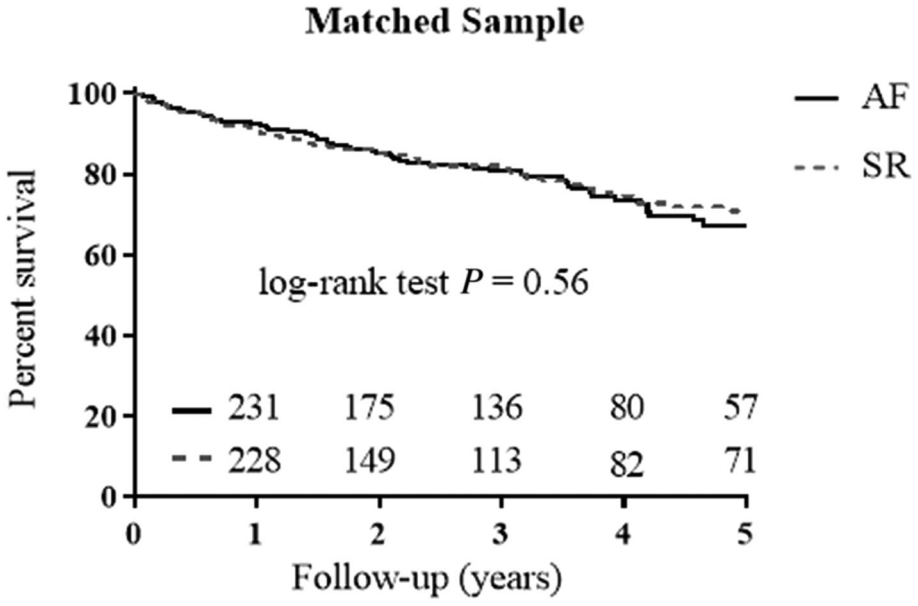
Figure 1 Kaplan–Meier survival curves for 5 year survival for CHF outpatients with respect to heart rhythm (general sample).



patients with AF and SR (P = 0.66), while increasing NT-proBNP levels were associated with increasing mortality ($P < 0.001$). In addition, survival analyses were repeated in another sample of patients who were matched with respect to NT-proBNP, eGFR, and LVEF. Baseline characteristics of the second matched sample are presented in *Table* S2. Similar to the results from our main analyses, no difference in mortality was noted between CHF patients with AF and those with SR (HR = 1.04, 95% CI 0.68 to 1.59, P = 0.86, for AF vs. SR), whereas NT-proBNP retained its prognostic power (HR = 1.13 per 1000 ng/L increase, 95% CI 1.07 to 1.19, $P < 0.001$). Again, results were confirmed after adjusting for covariates in a multivariable Cox regression analyses: there was no significant difference in survival between patients with AF and SR (P = 0.89), while increasing NT-proBNP levels were associated with increasing mortality (P = 0.03). Finally, survival analyses were repeated in a third sample of patients who were matched with respect to NT-proBNP,

Figure 2 Kaplan–Meier survival curves for 5 year survival for CHF outpatients with respect to heart rhythm (matched sample).



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age, sex, and eGFR. Baseline characteristics of the third matched sample are presented in *Table* S3. Again, no difference in mortality was noted between CHF patients with AF and those with SR (HR = 0.735, 95% CI 0.51 to 1.05, $P = 0.09$, for AF vs. SR), whereas NT-proBNP retained its prognostic power (HR = 1.19 per 1000 ng/L increase, 95% CI 1.13 to 1.24, $P < 0.001$).

Area under the curve and cut-off

In the matched sample, the area under the ROC curve for NT-proBNP as a predictor of 1 year mortality was 0.79 in AF patients and 0.80 in SR patients ($P = 0.88$). Both for AF and SR, cut-off values for risk prediction were comparable (*Table 2*). The ROC curves for patients with AF and SR are depicted in *Figure 3*.

Subgroups

Subgroup analyses with respect to age, sex, aetiology, NYHA functional class, LVEF, eGFR, COPD, diabetes, heart rate, and SBP did not detect any statistically significant difference in survival between matched patients with AF and SR in any of the predefined subgroups (*Table 3*).

Discussion

The objective of the present study was to clarify the impact of heart rhythm on the prognostic value of NT-proBNP in patients with CHF. We therefore analysed survival of 2541 CHF patients with respect to underlying heart rhythm. We repeated our analyses in a sample of 500 matched CHF patients.

Our main findings are as follows:

- High levels of NT-proBNP were associated with higher mortality independent of underlying heart rhythm.
- Survival, however, was independent of underlying rhythm after matching for NT-proBNP, sex, age, NYHA functional class, and aetiology of CHF.
- Results were confirmed in multivariable analyses as well as in predefined subgroups with respect to age, sex, aetiology, NYHA functional class, LVEF, eGFR, COPD, diabetes, heart rate, and SBP.
- While patients different in rhythm but similar (matched) in NT-proBNP, sex, age, NYHA functional class, and aetiology of CHF had a similar prognosis, they were still different in severity of heart failure as indicated by a lower LVEF in patients with SR.

We confirmed the known independent prognostic value of NT-proBNP in patients with CHF.[14–16] Individual patient characteristics such as AF, however, may influence NT-proBNP levels and consequently affect the prognostic value of NT-proBNP.[14,17] Although some studies have reported a positive association between AF and increased NT-proBNP levels,[11–13] the effect of AF on the prognostic value of NT-proBNP is still under debate.[13,19–22,29]

This is because AF has been described as an independent determinant of increased NT-proBNP levels in patients with CHF.[13,20,21,29] Although no specific NT-proBNP cut-off levels have been established for risk prediction in CHF, some authors conclude that the threshold level for outcome prediction of NT-proBNP is higher in patients with AF than in patients with SR.[21] Our data do not support this notion.

The present study significantly extends the data from Rienstra *et al*.[19] in terms of cohort size, extent of disease covered, follow-up duration, and scrutiny of methodology. We identified NT-proBNP as an independent determinant of prognosis in advanced CHF irrespective of the underlying rhythm. Then again, Linssen *et al*. observed that AF was an independent determinant of elevated NT-proBNP levels in hospitalized heart failure patients with preserved ejection fraction but not in patients with heart failure with reduced ejection fraction (HFrEF).[22] Accordingly, the risk of hospitalization for heart failure or death was independent of underlying rhythm in the HFrEF group.[22] Interestingly, NT-proBNP concentrations were similar between HFrEF patients with AF and those with SR in their study. This would rather support our observation that NT-proBNP retains its prognostic power in CHF patients irrespective of underlying rhythm.

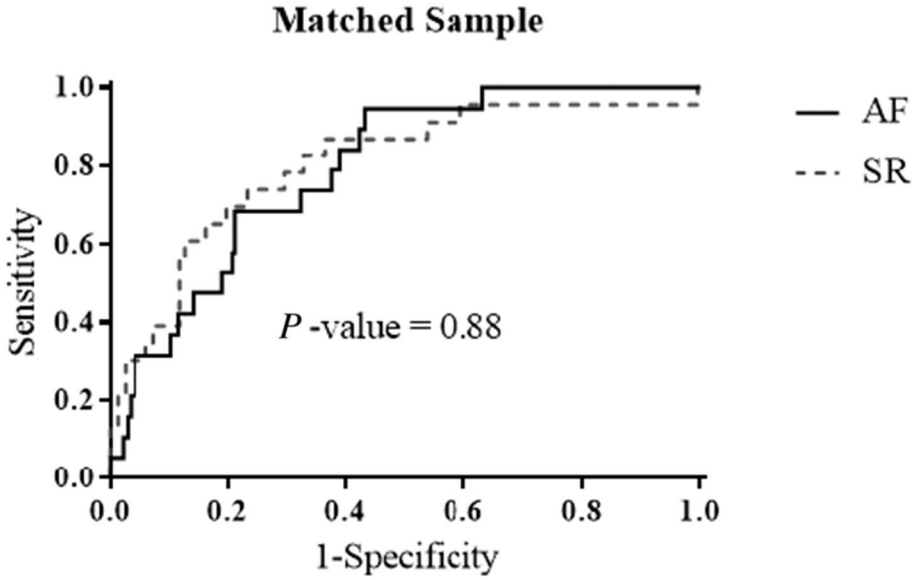
In the present study, the presence of AF was associated with higher mortality in the general sample. However, after matching for NT-proBNP, age, sex, NYHA functional class, and aetiology, survival was similar in patients with AF and SR, while NT-proBNP retained its prognostic power. Results were confirmed after adjusting for additional covariates including LVEF as well as in subgroup analyses.

Table 2 Best cut-off values of N-terminal pro brain natriuretic peptide for the prediction of 1 year mortality for matched chronic heart failure patients with atrial fibrillation and sinus rhythm, respectively

AF				SR			
NT-proBNP (ng/L)	Sensitivity	Specificity	YI	NT-proBNP (ng/L)	Sensitivity	Specificity	YI
1751	0.95	0.57	0.51	2684	0.74	0.77	0.51
1730	0.95	0.56	0.51	1912	0.87	0.63	0.50
1703	0.95	0.56	0.51	2666	0.74	0.76	0.50
1685	0.95	0.55	0.50	1904	0.87	0.63	0.50

AF, atrial fibrillation; NT-proBNP, N-terminal pro brain natriuretic peptide; SR, sinus rhythm; YI, Youden index.

Figure 3 ROC curves for patients with AF and SR, respectively (matched sample).



Interestingly, matched patients with AF had less severe heart failure than had those with SR as indicated by a lower LVEF in patients with SR. At the same time, NT-proBNP retained its prognostic power independent of the underlying heart rhythm. This finding would support the interpretation that both the presence of AF and a low LVEF represent certain complementary aspects of 'advanced state' in CHF. It is this advanced state that is reflected by an increase of NT-proBNP levels. NT-proBNP release has been associated with cardiac stress such as wall stress, neuroendocrine activation, vascular stiffness, high blood pressure, wall motion abnormalities, and AF. It may therefore integrate the 'risk sum' of progress/advance in the course of CHF—with LVEF or AF as (to a certain extent) mutually complementary indicators of its state. Our study therefore also argues against the adjustment of NT-proBNP cut-off levels in patients with AF.

Table 3 Cox regression analyses for all-cause mortality in matched chronic heart failure patients with respect to heart rhythm (atrial fibrillation vs. sinus rhythm) in subgroups

Subgroup		HR	95% CI	*P*-value
Age (years)	>65	0.89	0.57 — 1.40	0.62
	≤65	0.90	0.57 — 1.41	0.64
Sex	Male	0.92	0.66 — 1.29	0.62
	Female	0.82	0.32 — 2.09	0.67
Aetiology	Ischaemic	0.97	0.66 — 1.44	0.89
	Cardiomyopathy	0.86	0.46 — 1.64	0.65
	Other	1.30	0.42 — 3.99	0.65
NYHA	III/IV	1.05	0.66 — 1.66	0.83
	I/II	0.80	0.51 — 1.25	0.32
LVEF (%)	>30	0.81	0.47 — 1.42	0.47
	≤30	1.11	0.75 — 1.65	0.61
eGFR (mL/min/1.73 m^2)	>60	0.95	0.60 — 1.49	0.82
	≤60	0.94	0.55 — 1.62	0.82
COPD	Yes	1.33	0.37 — 4.73	0.66
	No	0.90	0.65 — 1.26	0.55
Diabetes	Yes	0.72	0.43 — 1.22	0.22
	No	0.99	0.65 — 1.51	0.96
Heart rate (b.p.m.)	>75	0.71	0.45 — 1.12	0.14
	≤75	0.96	0.60 — 1.54	0.87
SBP (mmHg)	>120	0.98	0.58 — 1.66	0.95
	≤120	0.86	0.57 — 1.29	0.46

Cut-offs for age, LVEF, heart rate, and SBP represent the median of the respective variables in the matched sample.
CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; HR, hazard ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; SBP, systolic blood pressure.

There is an ongoing discussion about NT-proBNP-guided management of patients with stable CHF.[30–32] One major requirement for a practicable clinical use of NT-proBNP as a leading instrument in the therapy of CHF would be a universal interpretability. As our work shows, the prognostic information of NT-proBNP is independent of the underlying heart rhythm. The present study therefore adds important information to this discussion.

Limitations

Owing to the observational nature of our study, the reported relationships between heart rhythm, NT-proBNP concentrations, and mortality are associative and not causal. As with any non-randomized design, we cannot rule out hidden bias due to unmeasured confounders. However, our study includes a well-characterized patient sample with continuous inclusion and close surveillance. As we analysed data from a university hospital setting, patient selection may be biased, and thus, included patients may differ from the general

population. For example, the matched sample comprised only 80 (16%) women. Therefore, results in this subgroup may only be interpreted with caution. Moreover, our data do not allow differentiation between paroxysmal, permanent, and persistent AF in patients classified as having AF. We therefore cannot comment on differences between these types of AF. Then again, it was reported that the different types of AF do not significantly affect NT-proBNP concentrations.[19,33] Then again, we found that 22 (1.0%) patients with SR in the general sample and 6 (2.4%) patients with SR in the matched sample had a history of paroxysmal AF. As these patients were with SR at the index visit, they were classified in the SR group. As the proportion of patients with paroxysmal AF in the SR groups was thus very low, this may not have a major impact on our results.

In the matching process, 181 AF patients without a matching SR partner were removed from the matched sample. This may have caused a skewed selection, because AF patients with very high NT-proBNP levels may have been excluded from further analyses. As patients with NT-proBNP levels >10 000 ng/L are underrepresented in the matched sample (3.2% of the AF patients in the matched sample vs. 9.5% of the AF patients in the general sample), our findings have to be interpreted carefully in this subgroup. All-cause mortality was the primary endpoint of the present analysis. As we do not have any information about implantation of extracorporeal membrane oxygenation or left ventricular assist devices during follow-up, we cannot comment on results in this subgroup.

Conclusions

In patients with CHF, NT-proBNP predicts all-cause mortality independent from underlying heart rhythm. As the prognostic value of NT-proBNP is not influenced by concomitant AF, there is no need to adjust NT-proBNP-levels in these patients. Presence of AF, on the other hand, balances the negative prognostic effect of advanced CHF as indicated by a lower LVEF. Our findings strengthen the importance of NT-proBNP as a prognostic marker in patients with CHF, while they would favour the interpretation that AF is a surrogate of a worse cardiac condition rather than an independent cardiac risk factor.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Median NT-proBNP levels (ng/l) with respect to LVEF and heart rhythm in the matched and general sample, respectively.
Table S2. Baseline characteristics of the general patient sample and of CHF patients matched with respect to NT-proBNP, eGFR and LVEF (stratified by rhythm).
Table S3. Baseline characteristics of the general CHF patient sample and of CHF patients matched with respect to NT-proBNP, age, sex and eGFR (stratified by rhythm).

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