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ORIGINAL RESEARCH

Interactions Between Atrial Fibrillation and Natriuretic Peptide in Predicting Heart Failure Hospitalization or Cardiovascular Death

Paul F. Brady , Mpharm; Winnie Chua , PhD; Frantisek Nehaj, PhD; Derek L. Connolly , PhD; Alya Khashaba , BMedSc; Yanish J. V. Purmah, MD; Muhammad J. Ul-Qamar , MD; Mark R. Thomas, PhD; Chetan Varma, MD; Renate B. Schnabel , MD; Tanja Zeller, PhD; Larissa Fabritz , MD; Paulus F. Kirchhof , MD

BACKGROUND: Natriuretic peptides are routinely quantified to diagnose heart failure (HF). Their concentrations are also elevated in atrial fibrillation (AF). To clarify their value in predicting future cardiovascular events, we measured natriuretic peptides in unselected patients with cardiovascular conditions and related their concentrations to AF and HF status and outcomes.

METHODS AND RESULTS: Consecutive patients with cardiovascular conditions presenting to a large teaching hospital underwent clinical assessment, 7-day ECG monitoring, and echocardiography to diagnose AF and HF. NT-proBNP (N-terminal pro-B-type natriuretic peptide) was centrally quantified. Based on a literature review, four NT-proBNP groups were defined (<300, 300–999, 1000–1999, and ≥2000 pg/mL). Clinical characteristics and NT-proBNP concentrations were related to HF hospitalization or cardiovascular death. Follow-up data were available in 1616 of 1621 patients (99.7%) and analysis performed at 2.5 years (median age, 70 [interquartile range, 60–78] years; 40% women). HF hospitalization or cardiovascular death increased from 36 of 488 (3.2/100 person-years) in patients with neither AF nor HF, to 55 of 354 (7.1/100 person-years) in patients with AF only, 92 of 369 (12.1/100 person-years) in patients with HF only, and 128 of 405 (17.7/100 person-years) in patients with AF plus HF ($P<0.001$). Higher NT-proBNP concentrations predicted the outcome in patients with AF only (C-statistic, 0.82; 95% CI, 0.77–0.86; $P<0.001$) and in other phenotype groups (C-statistic in AF plus HF, 0.66; [95% CI, 0.61–0.70]; $P<0.001$).

CONCLUSIONS: Elevated NT-proBNP concentrations predict future HF events in patients with AF irrespective of the presence of HF, encouraging routine quantification of NT-proBNP in the assessment of patients with AF.

Key Words: atrial fibrillation ■ cardiovascular death ■ cohort study ■ heart failure ■ hospitalization ■ N-terminal pro-B-type natriuretic peptide

Heat failure (HF) and atrial fibrillation (AF) are found in 1% to 2% (HF) and 2% to 3% (AF) of the adult population in developed countries. Their prevalence is much greater in the elderly.^{1–4} Both conditions are major drivers of cardiovascular morbidity and mortality.^{5–7} Up to 50% of patients with AF suffer symptomatic HF, and comorbid AF plus HF is associated with higher morbidity and mortality than either condition alone.^{5–7}

Natriuretic peptides are released by cardiomyocytes upon stretch. They inhibit the effects of the renin-angiotensin-aldosterone system and the sympathetic system, lead to vasodilation, and induce diuresis.^{8,9} Deletion of the natriuretic peptide receptor in the heart or in the endothelium causes cardiovascular dysfunction.^{10–12} Concentrations of BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal pro-B-type

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CLINICAL PERSPECTIVE

What Is New?

- NT-proBNP (N-terminal pro-B-type natriuretic peptide), a biomarker known to be elevated in patients with atrial fibrillation (AF), predicts future heart failure events in unselected patients with AF.
- A threshold of 1000 pg/mL is useful in identifying high-risk patients with AF, whether or not they are diagnosed with heart failure at the time of assessment.
- Similar to previous findings in heart failure, even after adjusting for important confounding variables, this threshold predicts future risk of heart events in patients with AF.

What Are the Clinical Implications?

- Based on our findings, quantification of NT-proBNP should be part of the initial assessment of unselected patients with AF to improve prediction of future cardiovascular events.

Nonstandard Abbreviations and Acronyms

ESC	European Society of Cardiology
HFpEF	heart failure with preserved ejection fraction
HFREF	heart failure with reduced ejection fraction

natriuretic peptide) are elevated in patients with HF.^{8,9,13} Their quantification is recommended to diagnose HF in patients presenting with dyspnea^{8,9,14} and more generally to establish or rule out HF.^{1,14,15} Natriuretic peptide concentrations also correlate with prognosis in patients with HF, informing therapeutic decisions such as cardiac transplantation.^{14,15}

It has long been known that natriuretic peptides are also elevated in patients with supraventricular arrhythmias,¹³ including in patients with AF.¹⁶ In addition to HF and AF, several additional factors increase the concentrations of natriuretic peptides, including age, sex, kidney function, and obesity.^{8,9} As HF is often present in patients with AF, it is unclear to what extent the association of natriuretic peptides and outcomes is driven by HF.^{8,9,14,17} Current guidelines for the diagnosis of HF do not advocate an adjustment of the diagnostic threshold for diagnosing HF in patients with AF.^{1,14} The European Society of Cardiology (ESC) guidelines, for example, recommend an NT-proBNP cutoff of 125 pg/mL in the nonacute setting and 300 pg/mL in the acute setting, to preserve the sensitivity of the test.¹⁴ There is currently no definitive cutoff value

recognized for prognostication in HF. Using natriuretic peptides as a continuous variable is important to maximize the information provided by a given measured value.^{8,9} However, studies indicate that even after adjustment for variable such as age and renal function, elevated NT-proBNP levels >1000 pg/mL in patients with chronic HF identify patients at high risk of cardiovascular complications.^{18–20}

To clarify the prognostic role of natriuretic peptides in patients with and without AF and HF, we quantified NT-proBNP in an unselected contemporary cohort of multimorbid patients with cardiovascular conditions. We evaluated the risk of HF hospitalization or cardiovascular death in patients with neither AF nor HF, AF only, HF only, or AF plus HF, and determined whether NT-proBNP concentrations predict future composite outcome in each group of patients.

METHODS

Study Population

The Birmingham and Black Country Atrial Fibrillation registry enrolled consecutive patients presenting to a large teaching hospital serving a population of ≈500 000 (Sandwell and West Birmingham NHS Trust) with either diagnosed AF or at least 2 cardiovascular conditions. Details have been published.²¹ Exclusion criteria were age <18 years, inability to consent, and a life expectancy <1 year. Clinical information was collected from a detailed interview, review of written and electronic hospital records, and review of medical charts for each patient. Blood pressure and anthropometric measurements including weight, height, and body mass index were recorded at baseline. A 12-lead ECG and echocardiography were performed in all patients. All patients without diagnosed AF underwent 7-day ambulatory ECG monitoring and were subsequently reclassified if AF was detected. Patients with atrial flutter were included in the AF group.²²

AF and HF phenotypes were determined on the basis of the clinical, ECG, and imaging findings. HF was defined on the basis of established clinical parameters defined as (1) left ventricular ejection fraction of <50%, (2) a clinical diagnosis of stable HF, or (3) New York Heart Association Functional Classification class II to IV. Stable HF was defined as a preexisting diagnosis of HF on the basis of primary and secondary care records encompassing HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFREF). A broad definition of HF was selected for this study to include patients across the full spectrum of HF. Patients with a history of paroxysmal AF, persistent AF, permanent AF, or atrial flutter were included in the AF phenotype groups.²² Three patients with a history of atrial high rate episodes²³ who did not fully fit into

any of the phenotype groups were excluded from analysis (Figure 1).

Data can be made available for noncommercial use after sponsor review. Please email the corresponding author at p.kirchhof@uke.de.

Biomarker Quantification and Natriuretic Peptide Thresholds

At baseline, blood samples taken from all patients were immediately spun, fractionated, frozen, and stored at -80°C until analysis. NT-proBNP concentrations were quantified in a single run using commercially available Roche immunoassays (cobas Elecsys NT-proBNP II; Roche Diagnostics, Penzberg, Germany) by personnel blinded to clinical data and outcomes. Based on a literature review, 4 NT-proBNP concentration ranges were defined to stratify patients: <300 , 300 to 999, 1000 to 1999, and ≥ 2000 pg/mL. An NT-proBNP concentration <125 pg/mL provides a high negative predictive value for HF in the nonacute setting in patients with mild symptoms and underpins ESC guidelines for the diagnosis of HF.⁹ However, an NT-proBNP concentration <300 pg/mL also has high diagnostic utility, with a sensitivity of 99% and a negative predictive value of 98% for the diagnosis of HF.^{14,24} This cutoff is also recommended in the 2016 ESC guidelines for the diagnostic workup of HF in the acute setting.¹⁴ This study was conducted in an acute setting (ie, secondary care

hospital), and an NT-proBNP concentration 300 pg/mL was therefore selected for this study in line with ESC guidelines. The cutoff of 1000 pg/mL was selected on the basis of a number of studies demonstrating prognostic value in HF with NT-proBNP levels above this threshold.^{18–20} Finally, a cutoff of 2000 pg/mL was selected on the basis of evidence showing a high specificity for the diagnosis of HF at this threshold in the nonacute setting.²⁵

Follow-Up and Outcome Data Collection

To obtain systematic information on cardiovascular death, HF hospitalizations, and other cardiovascular events, all patients were invited to attend a nurse-led follow-up appointment at 2 years. Data on the predefined major adverse cardiovascular events including HF hospitalization, hospitalization for acute coronary syndrome or myocardial infarction, and stroke were collected. In addition, hospital letters and discharge summaries were interrogated to extract further information on these outcomes. Hospital Episode Statistics data from the National Health Service database were also obtained for all patients. In addition, community general practitioner records were also reviewed to identify events not captured on hospital records. All events were cross-checked and adjudicated by 3 of the authors (P.B., F.N., and P.K.). Mortality data were obtained from the centralized national database

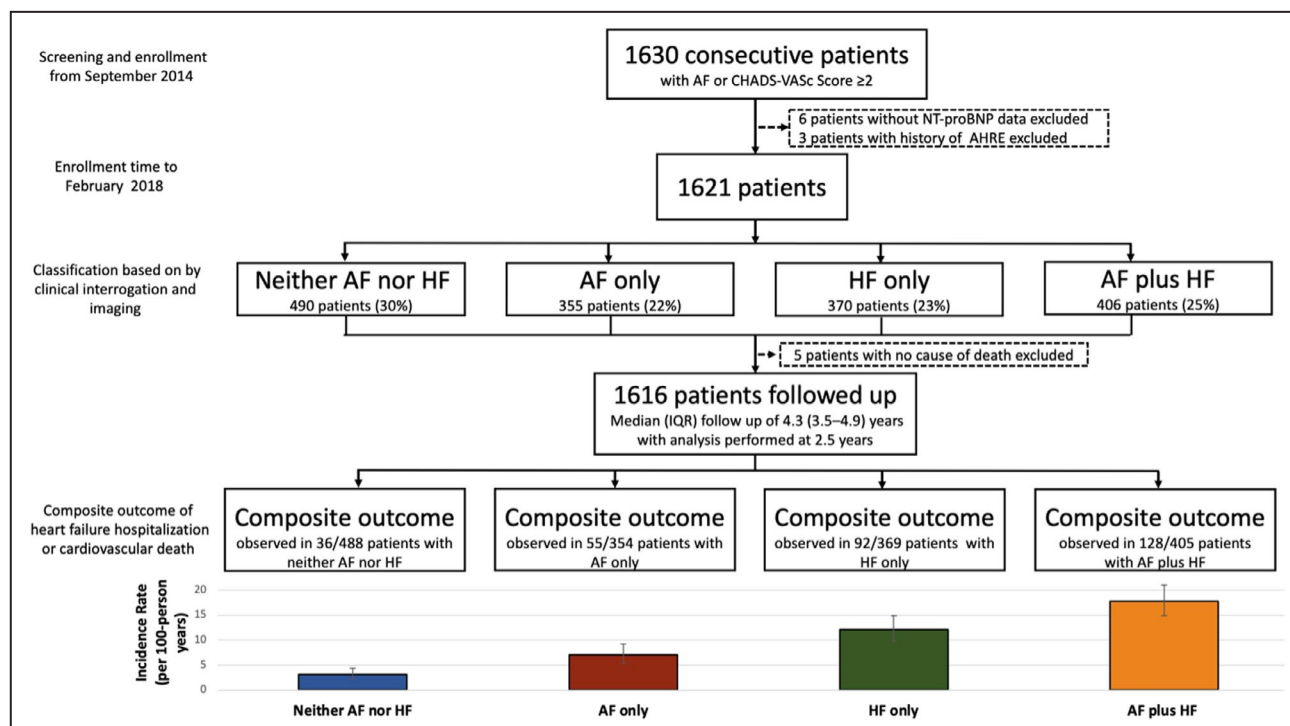


Figure 1. Flowchart outlining patient selection and follow-up.

AF indicates atrial fibrillation; AHRE, atrial high rate episode; HF, heart failure; IQR, interquartile range; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

via National Health Service Digital including certified cause of death. The Medical Research Information Service Flagging Current Status Report, general practitioner records, and local death certificates were reviewed to determine cause of death. Death was classified as cardiovascular death on the basis of disease-specific *International Classification of Diseases* codes (*ICD 10*). This included acute and chronic ischemic heart disease, stroke, systemic embolism, HF, and fatal arrhythmia as the immediate or underlying cause of death (Table S1). Other deaths were classified as noncardiovascular. HF hospitalization was defined as a discharge diagnosis of decompensated HF or a discharge diagnosis of HF that required inpatient treatment with intravenous diuretics. The primary outcome for this analysis was a composite of HF hospitalization and cardiovascular death censored at 2.5 years in all patients.

Ethics

This study was approved by the National Research Ethics Service Committee (Birmingham and Black Country Atrial Fibrillation registry, West Midlands, UK; Integrated Research Application System ID 97753) and sponsored by the University of Birmingham, UK. All patients provided written informed consent. This study complied with the Declaration of Helsinki.

Statistical Analysis

Patients were categorized into 4 phenotype groups for analysis, namely:

1. Patients who had neither AF nor HF,
2. Patients with AF only,
3. Patients with HF only, and
4. Patients who had AF plus HF.

To describe the clinical characteristics of the cohort, continuous variables were expressed as mean (SD) or median (interquartile range [IQR]) for normal and non-normal distributions, respectively. Normality was tested using the Shapiro-Wilk test. The Student *t* test or 1-way ANOVA was used for continuous variables with normal distribution and 2 or >2 groups, respectively. Likewise, the Wilcoxon rank-sum test or Kruskal-Wallis test was used for continuous variables with nonnormal distribution and 2 or >2 groups, respectively. Categorical variables were reported as counts and percentages (*n* [%]), and comparisons between groups were performed using the χ^2 test.

Event rates were reported per 100 person-years of follow-up. Kaplan-Meier curves were created to determine the prognostic significance of each patient group on the composite outcome. The end point distributions were compared using the log-rank test. Multivariate

Cox proportional hazard regression of the composite outcome (HF hospitalization or cardiovascular death) at 2.5 years against AF and HF phenotype and pre-defined NT-proBNP concentration ranges in each of these phenotype groups.

The primary analysis determined the risk of the composite outcome attributable to AF, HF, and comorbid AF and HF, in these patients. Multivariate Cox proportional hazard regression of the composite outcome (HF hospitalization or cardiovascular death) at 2.5 years against AF and HF phenotype groups was performed adjusting for confounding variables. The group with neither AF nor HF was used as a reference group. Adjustment variables were selected a priori on the basis of existing literature for their relation to cardiovascular death or HF hospitalization.^{14,26} These variables were age, sex, race, obesity (body mass index ≥ 30 kg/m²), hypertension, diabetes, coronary artery disease, severe valvular heart disease, left bundle-branch block, hyponatremia (sodium <135 mmol/L), estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation), medical treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, diuretics (thiazide or loop diuretics), and anticoagulants (novel oral anticoagulant or vitamin K antagonist). All adjustment variables were evaluated for collinearity. Variables including urea and hemoglobin were excluded as adjustment variables because of significant collinearity with estimated glomerular filtration rate and age. Left ventricular ejection fraction was also excluded as an adjustment variable given that it was used to define phenotype groups. The proportional hazards assumption was ascertained by visual examination of log (survival) graphs to ensure parallel slopes.

The secondary analysis determined the utility of NT-proBNP for predicting the composite outcome in the 4 phenotype groups. To evaluate the value of NT-proBNP in predicting the composite outcome of HF hospitalization or cardiovascular death, NT-proBNP was separately analyzed in the 4 phenotype groups controlling for known confounding variables. Kaplan-Meier curves were constructed for each patient group stratified according to the predefined NT-proBNP concentration ranges (<300, 300–999, 1000–1999, and ≥ 2000 pg/mL). Multivariate analysis of the composite outcome (HF hospitalization or cardiovascular death) at 2.5 years against NT-proBNP concentration range groups was performed in each patient group adjusting for the clinical parameters listed above. The lowest NT-proBNP group (<300 pg/mL) was used as a reference group. This was adjusted for confounding variables listed above.

To evaluate the impact of noncardiovascular death, competing-risks regression based on Fine and Gray's proportional subhazards model was performed as an

additional analysis. Harrell's C-statistic was calculated to determine the performance of NT-proBNP in each patient group for predicting the composite outcome. This was also performed on secondary outcomes, which were defined as the individual components of the composite outcome, and all-cause mortality for sensitivity analysis. NT-proBNP was used as a continuous variable in this analysis. Supplementary analysis to evaluate each cutoff by measuring discrimination (Harrell's C-statistic), calibration (Brier score, Bayesian information criterion, Akaike information criterion, and likelihood ratio), and reclassification (integrated discrimination improvement and net reclassification improvement) were derived using an NT-proBNP cutoff of 300 pg/mL as a reference where appropriate. The optimum concentration of NT-proBNP to predict the composite outcome in the entire cohort and each patient group using Youden's index was performed and evaluated with each predefined cutoff.

For multivariate analysis only, a multiple imputation technique based on a Markov chain Monte Carlo approach was used to estimate missing values for baseline body mass index, hemoglobin, and urea.²⁷ A 2-sided *P*-value of <0.05 was considered statistically significant. Analyses were performed using Stata version 16.1 (StataCorp, College Station, TX).

RESULTS

A total of 1616 patients were analyzed, with a median age of 70 (IQR, 60–78) years, 40% (*n*=644) were female, and 77% (*n*=1238) were White. A total of 488 patients had neither AF nor HF, 354 patients had AF only, 369 patients had HF only, and 405 patients had AF plus HF (Table 1, Figure 1). Patients with AF plus HF were oldest, followed by patients with AF only, then patients with HF only, and finally patients with neither AF nor HF (*P*<0.001). Median NT-proBNP concentration increased gradually from 215 (IQR, 71–625) pg/mL in patients with neither AF nor HF, to 607 (IQR, 217–1831) pg/mL in patients with AF only, to 889 (IQR 261–2584) pg/mL in patients with HF only, and to 1669 (IQR 607–4238) pg/mL in patients with AF plus HF (Figure 2).

In 1616 of 1621 patients (99.7%), vital status and cause of death could be ascertained. It was not possible to determine the cause of death for 5 patients. These patients were excluded from the main analysis of cardiovascular death, as their cause of death could not be classified (Figure 1). The composite outcome was observed in 311 patients (19.3%) in the entire cohort (9.2/100 person-years) with 202 HF hospitalizations and 109 cardiovascular deaths. The full baseline characteristics of each patient group according to presence or absence of the composite outcome at 2.5 years follow-up are given in Table S2. Baseline data were missing in 3.6% of the study population for body

mass index and 2.8% for sodium, and these data were imputed for multivariate analysis.

Impact of HF and AF on Outcomes

AF and HF were associated with increased risk of the composite outcome, and multivariate regression identified a graded increase in the adjusted risk for the composite outcome across the phenotype groups (Figures 3 and 4). HF hospitalization or cardiovascular death was observed in 36 (7.4%) patients with neither AF nor HF (3.2/100 person-years), 55 (15.5%) patients with AF only (7.1/100 person-years), 92 (24.9%) patients with HF only (12.1/100 person-years), and 128 (31.6%) patients with AF plus HF (17.7/100 person-years) (Figure 1, Table S3). The AF-only phenotype remained a predictor of the composite outcome after adjustment for other variables with an adjusted hazard ratio of 2.35 (95% CI, 1.45–3.81; *P*=0.001). The AF-plus-HF phenotype was associated with the highest risk of the composite outcome, with an adjusted hazard ratio of 3.46 (95% CI, 2.20–5.46; *P*<0.001) (Figure 4).

Added Information From NT-proBNP

The NT-proBNP concentration ranges enabled risk stratification for the composite outcome at 2.5 years' follow-up in the 4 phenotype groups (Figure 5). Using the NT-proBNP <300 pg/mL concentration range as a reference group, both the NT-proBNP 1000 to 1999 pg/mL and the NT-proBNP ≥2000 pg/mL concentration ranges were significantly predictive of the composite outcome in the AF-only and HF-only phenotype groups in univariate and multivariate analyses (Table 2). In multivariate analysis, there was an incremental risk associated with higher NT-proBNP levels in all 4 phenotype groups. In patients with HF, the increase in risk of the composite outcome reached a plateau at NT-proBNP concentration of ≈1000 pg/mL (Figure 6). These NT-proBNP concentration ranges also remained significantly predictive in additional competing-risks analysis using noncardiovascular death as a competing risk (Table 2).

Discrimination

NT-proBNP had a higher C-statistic for the composite outcome in the 2 phenotype groups without HF. This was 0.73 (95% CI, 0.65–0.81; *P*<0.001) in patients with neither AF nor HF and 0.82 (95% CI, 0.77–0.87; *P*<0.001) in the AF only group. Conversely, the HF-only and AF-plus-HF phenotype groups had a C-statistic of 0.66 (95% CI, 0.60–0.72; *P*<0.001) and 0.66 (95% CI, 0.61–0.70; *P*<0.001), respectively (Table S4). The impact of the presence of HFrEF compared with HFpEF on the utility of NT-proBNP to predict the composite outcome in patients with HF only and AF plus HF was

Table 1. Descriptive Baseline Statistics

	Neither AF nor HF (N=488)	AF only (N=354)	HF only (N=369)	AF plus HF (N=405)	P value across all groups
Clinical characteristics					
Age, y, median (IQR)	65 (56–74)	71 (62–79)	68 (59–77)	74 (67–81)	<0.001
Female sex, n (%)	222/488 (45)	150/354 (42)	128/369 (35)	144/405 (36)	0.002
Race, n (%)					<0.001
White	332/488 (68)	302/354 (85)	264/369 (72)	340/405 (84)	...
Asian	100/488 (20)	31/354 (9)	63/369 (17)	30/405 (7)	...
Afro-Caribbean	55/488 (11)	20/354 (6)	42/369 (11)	34/405 (8)	...
Other	1/488 (0.2)	1/354 (0.3)	...	1/405 (0.3)	...
Heart rhythm, n (%)					<0.001
Sinus rhythm	488/488 (100)	...	369/369 (100)
Paroxysmal AF	...	195/354 (55)	...	184/405 (45)	...
Persistent AF	...	76/354 (21)	...	100/405 (25)	...
Permanent AF	...	69/354 (19)	...	102/405 (25)	...
Atrial flutter	...	14/354 (4)	...	19/405 (5)	...
BMI, kg/m ² , median (IQR)*	29 (25–33)	29 (25–33)	28 (25–32)	29 (25–33)	0.640
Systolic BP, mm Hg, median, (IQR)	127 (113–140)	129 (117–143)	122 (110–136)	121 (109–138)	<0.001
Heart rate/min, median (IQR)	68 (61–79)	68 (58–82)	72 (63–82)	76 (64–90)	<0.001
Ejection fraction, %, median (IQR)	61 (57–68)	61 (56–68)	46 (35–58)	46 (35–58)	<0.001
Ejection fraction <50%, n (%)	224/357 (63)	232/388 (60)	<0.001
Previous diagnosis of stable HF	152/369 (41)	203/405 (50)	<0.001
Symptomatic HF	<0.001
NYHA II HF, n (%)	143/369 (39)	159/401 (40)	...
NYHA III HF, n (%)	84/369 (23)	111/401 (28)	...
NYHA IV HF, n (%)	20/369 (5)	31/401 (8)	...
LBBB, n (%)	6/488 (1)	6/354 (2)	24/369 (7)	22/405 (5)	<0.001
Medical history, n (%)					
Diabetes	212/488 (43)	75/354 (21)	166/369 (45)	112/405 (28)	<0.001
Hypertension	322/488 (66)	205/354 (58)	220/369 (60)	199/405 (49)	<0.001
Coronary artery disease	224/488 (46)	58/354 (16)	203/369 (55)	144/405 (36)	<0.001
Hyponatremia (Na <135 mmol/L)*	77/481 (16)	43/327 (13)	71/366 (19)	57/397 (14)	0.115
Severe valvular heart disease	9/488 (2)	17/354 (5)	12/369 (3)	41/405 (10)	<0.001
HF hospitalization at presentation	23/369 (6)	16/405 (4)	<0.001
Laboratory measurements					
eGFR, mL/min per 1.73 m ² , (CKD-EPI), median (IQR)	81 (62–94)	73 (58–87)	71 (52–89)	63 (44–82)	<0.001
NT-proBNP pg/mL, median, (IQR) in entire cohort	215 (71–625)	607 (217–1831)	889 (261–2584)	1669 (607–4238)	<0.001
NT-proBNP pg/mL, median (IQR) in patients with HFpEF	347 (108–1243)	1051 (420–2745)	<0.001
NT-proBNP pg/mL, median, (IQR) in patients with HFrEF	1286 (502–3642)	2385 (961–5712)	<0.001
NT-proBNP ≥125 pg/mL, n (%)	298/488 (61)	295/354 (83)	312/369 (85)	382/405 (94)	<0.001
NT-proBNP concentration range, n (%)					<0.001
<300 pg/mL	286/488 (59)	121/354 (34)	100/369 (27)	56/405 (14)	...
300–999 pg/mL	107/488 (22)	101/354 (29)	99/369 (27)	87/405 (21)	...
1000–1999 pg/mL	44/488 (9)	58/354 (16)	56/369 (15)	79/405 (20)	...
≥2000 pg/mL	51/488 (10)	74/354 (21)	114/369 (31)	183/405 (45)	...

(Continued)

Table 1. Continued

	Neither AF nor HF (N=488)	AF only (N=354)	HF only (N=369)	AF plus HF (N=405)	P value across all groups
Sodium, mmol/L, median (IQR)*	138 (136–140)	139 (137–141)	138 (135–140)	139 (136–141)	0.316
Urea, mmol/L, median (IQR)*	5.5 (4.4–7.2)	5.8 (4.8–7.4)	6.2 (4.7–8.5)	6.9 (5.1–10.3)	<0.001
Hemoglobin, g/L, median (IQR)*	133 (119–145)	135 (121–146)	129 (116–143)	126 (112–140)	<0.001
Pharmacotherapy, n (%)					
Beta blocker	265/488 (54)	182/354 (51)	232/369 (63)	229/405 (57)	0.013
ACE inhibitors or ARB	241/488 (49)	161/354 (45)	215/369 (58)	199/405 (49)	0.005
NOAC	9/488 (2)	158/354 (45)	9/369 (2)	190/405 (47)	<0.001
Warfarin	5/488 (1)	78/354 (22)	13/369 (4)	110/405 (27)	<0.001
Diuretic	97/488 (20)	90/354 (25)	159/369 (43)	229/405 (56)	<0.001
MRA	6/488 (1)	9/354 (3)	45/369 (12)	44/405 (11)	<0.001
Complex device (ICD or CRT)	5/488 (1)	5/354 (1)	26/369 (7)	38/405 (9)	<0.001

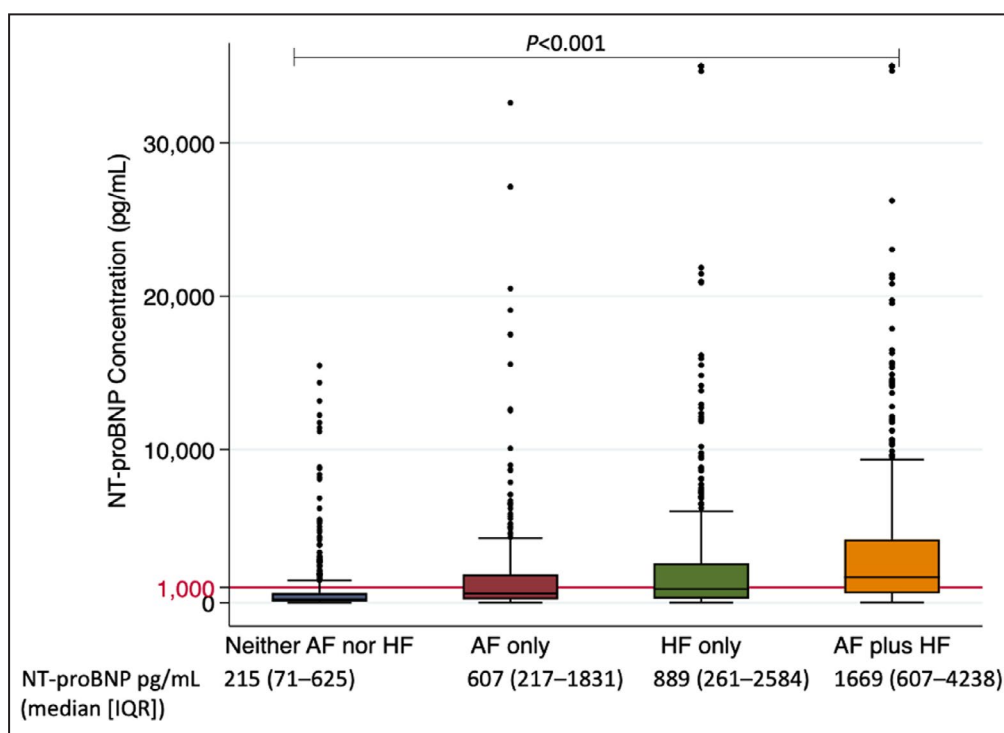
ACE indicates angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LBBB, left bundle-branch block; MRA, mineralocorticoid receptor antagonist; NOAC, novel oral anticoagulant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

*Baseline data were missing in 3.6% of the study population for BMI, 2.4% for hemoglobin, and 2.8% for urea and sodium.

also determined as a sensitivity analysis. The C-statistic of NT-proBNP was similar in patients with HFrEF and HFpEF in patients with HF only and patients with AF plus HF. Ejection fraction was an important prognostic factor, but it had a limited impact on the predictive utility of NT-proBNP. This was also the case for AF status, which had limited impact on the utility of NT-proBNP

in predicting the composite outcome in patients with HFrEF and HFpEF (Figure 7).

In terms of the predefined cutoffs, an NT-proBNP cutoff of 1000 pg/mL performed best at discriminating the composite outcome, with a time-to-event analyses (Harrell's) C-statistic of 0.70 (0.67–0.73) in the entire cohort and 0.74 (0.68–0.80) in patients with AF only (Table S5).

**Figure 2. Boxplot showing NT-proBNP concentrations in each patient group.**

AF indicates atrial fibrillation; HF, heart failure; IQR, interquartile range; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

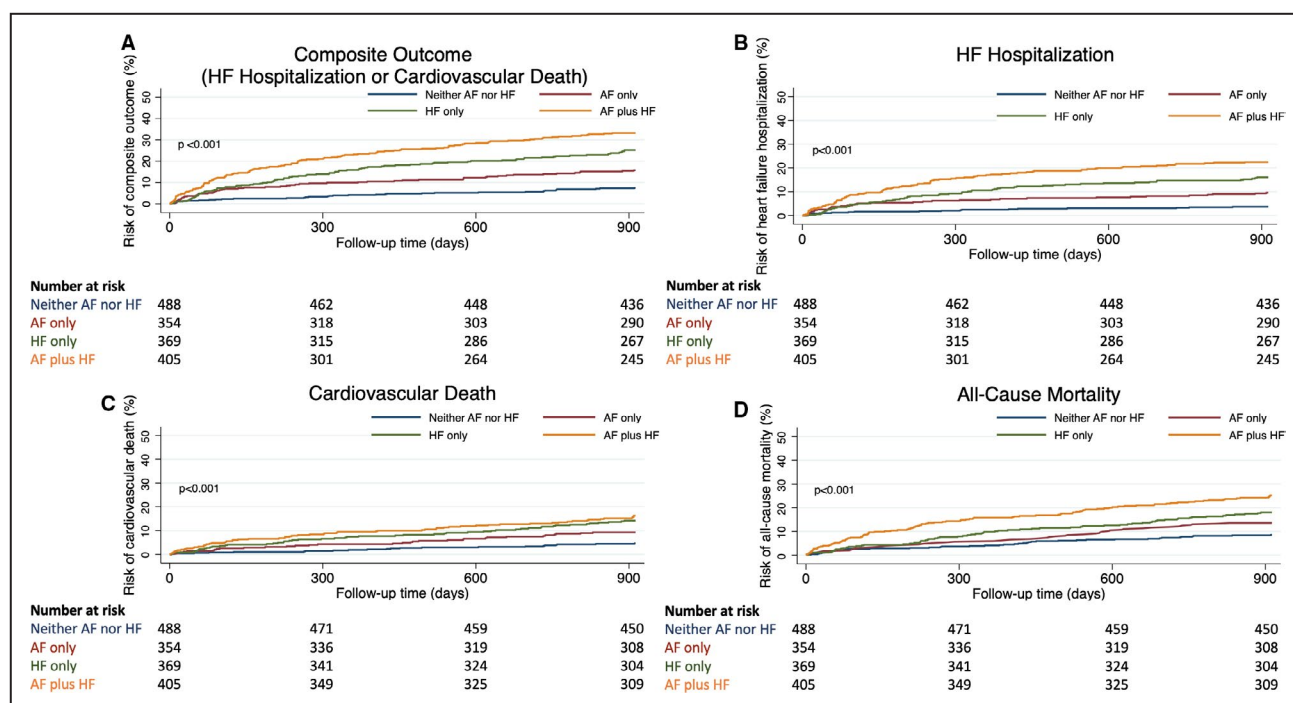


Figure 3. Kaplan-Meier curves stratified according to AF and HF phenotype groups at 2.5 years for (A) the composite outcome, (B) HF hospitalization, (C) cardiovascular death, (D) all-cause mortality.

AF indicates atrial fibrillation; and HF heart failure.

Calibration

The Brier score evaluates the accuracy of probability of the best-performing model, which is defined as the mean squared difference between the observed and

predicted outcome. Brier scores range from 0 to 1.00, with 0 representing the best possible calibration. The 1000 pg/mL cutoff had the lowest Brier score when applied to the entire cohort (Table S6). The Akaike

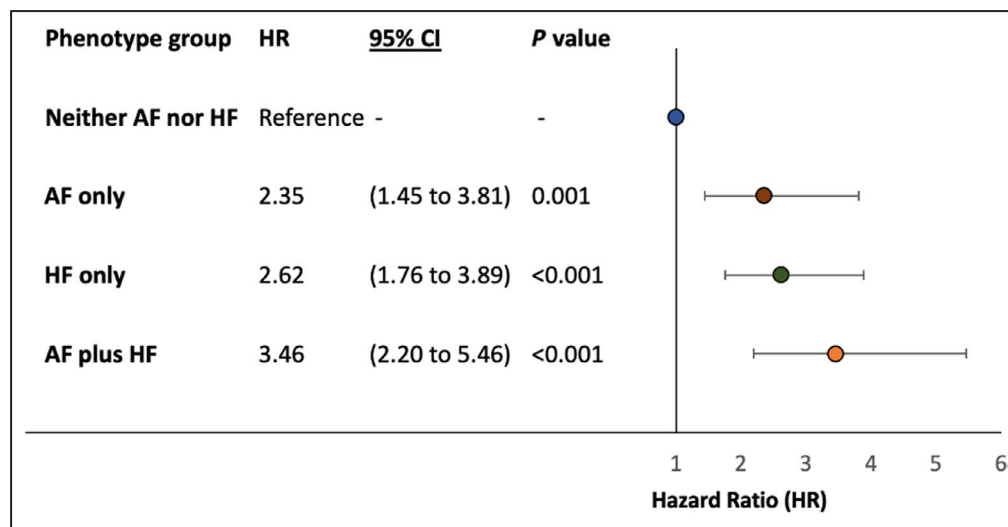


Figure 4. Forest plot showing the results of multivariate Cox proportional hazards analysis for the composite outcome at 2.5 years against AF and HF phenotype groups.

Adjusted for age, sex, race, obesity (body mass index ≥ 30 kg/m²), hypertension, diabetes, coronary artery disease, severe valvular heart disease, left bundle-branch block, hyponatremia (sodium < 135 mmol/L), estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation), medical treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta blockers, diuretics (thiazide or loop diuretics), and anticoagulants (novel oral anticoagulant or vitamin K antagonist). AF indicates atrial fibrillation; and HF heart failure.

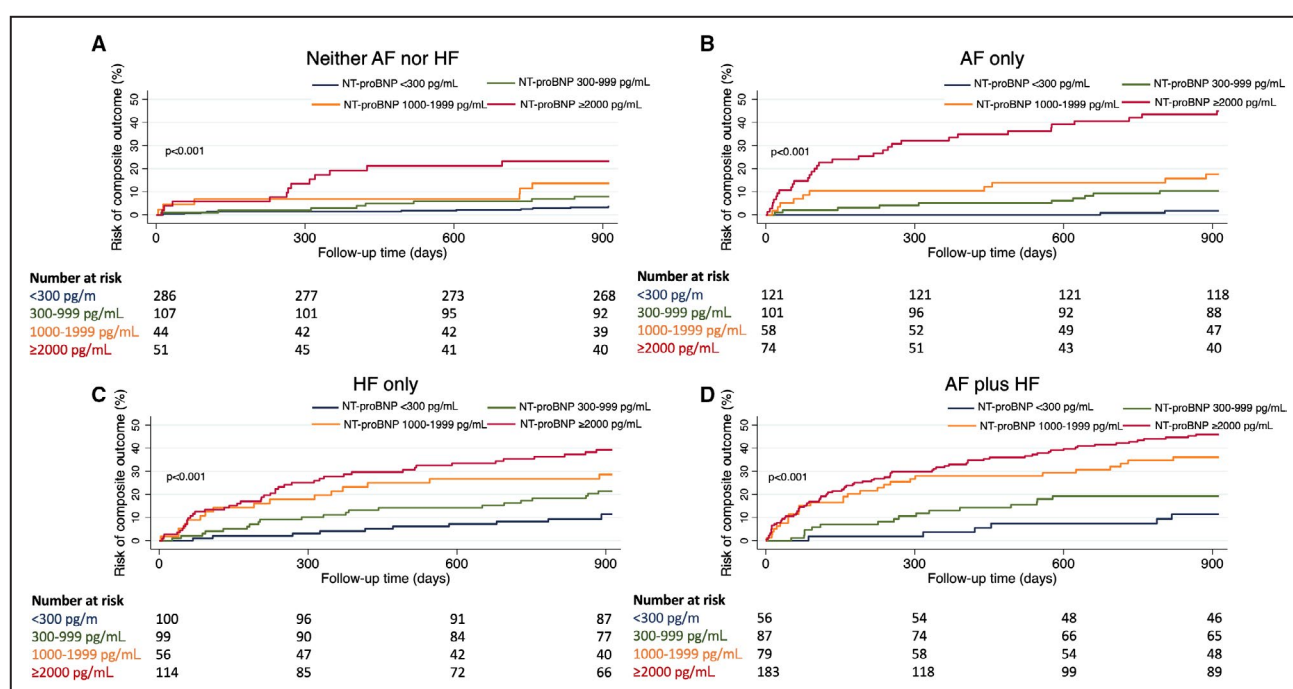


Figure 5. Kaplan-Meier curves of the composite outcome at 2.5 years against baseline NT-proBNP concentration ranges in patients with (A) neither AF nor HF, (B) AF only, (C) HF only, (D) AF plus HF. AF atrial fibrillation; HF heart failure; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

information criterion and the Bayesian information criterion were also calculated to evaluate calibration for each NT-proBNP cutoff. The Akaike information criterion and Bayesian information criterion are both measures of the goodness of fit of a statistical model, with lower values indicating better models. The NT-proBNP 1000 pg/mL cutoff had the lowest value when applied to the entire cohort (Table S7). The global goodness of fit of each model was also evaluated using the likelihood ratio test, with a significant *P* value suggesting that the newly added variable significantly improves the accuracy of the model. Relative to the NT-proBNP 300 pg/mL cutoff, the addition of the NT-proBNP 1000 pg/mL cutoff resulted in a statistically significant change in the likelihood ratio (Table S6).

Reclassification

Integrated discrimination improvement measures the ability of a model to improve the average sensitivity without reducing average specificity. This was performed to evaluate each NT-proBNP cutoff relative to the NT-proBNP 300 pg/mL cutoff as a reference. The NT-proBNP 1000 pg/mL cutoff resulted in a statistically significant integrated discrimination improvement relative to the NT-proBNP 300 pg/mL cutoff as a reference. Net reclassification improvement was used to evaluate the ability of each NT-proBNP cutoff to reclassify risk. This was used to evaluate the proportion of individuals reclassified correctly relative to the NT-proBNP

300 pg/mL cutoff as a reference. Currently, no meaningful risk categories exist for the composite outcome, and categorical net reclassification improvement was performed by nominally defining low and high risk as predicted risks of <20% and ≥20% for the composite outcome, respectively. Relative to the NT-proBNP 300 pg/mL cutoff, the NT-proBNP 1000 pg/mL cutoff resulted in a statistically significant reclassification in the entire cohort but this was not observed for the NT-proBNP 2000 pg/mL cutoff (Table S6).

The optimum NT-proBNP concentration for predicting the composite outcome in the entire cohort using Youden's index was 1079 pg/mL (Table S5). While the optimum NT-proBNP concentration varied across the 4 phenotype groups, an NT-proBNP >1000 pg/mL was a significant predictor of the composite outcome in the AF and HF phenotype groups in multivariate analysis after adjusting for confounding variables. This was also the case across all 4 phenotype groups in competing-risks analysis after adjusting for confounding variables (Table 2).

DISCUSSION

This analysis of carefully phenotyped unselected patients with and without AF and HF diagnosed by clinical interrogation and imaging, using centrally quantified NT-proBNP and with near-complete 2.5-year outcomes identified several important findings:

Table 2. Univariate and Multivariate Cox Proportional Hazards Analysis and Fine and Gray Regression Analysis (Noncardiovascular Death as a Competing Risk) for the Composite Outcome (HF Hospitalization or Cardiovascular Death) at 2.5 Years Against Baseline NT-proBNP Strata in Each Patient Group

Patient group	NT-proBNP concentration ranges	Univariate HR (95% CI)	P value	Multivariate HR (95% CI)	P value	Competing risks Univariate subdistribution HR (95% CI)	P value	Competing risks Multivariate subdistribution HR (95% CI)	P value
Neither AF nor HF	<300 pg/mL	Reference	...	Reference	...	Reference	...	Reference	...
	300–999 pg/mL	2.24 (0.88–5.67)	0.090	2.07 (0.79–5.44)	0.141	2.18 (0.86–5.50)	0.099	1.94 (0.73–5.17)	0.186
	1000–1999 pg/mL	4.05 (1.47–11.15)	0.007	3.71 (1.26–10.91)	0.017	4.14 (1.51–11.38)	0.006	3.77 (1.40–10.13)	0.008
	≥2000 pg/mL	7.56 (3.26–17.50)	<0.001	7.97 (2.87–22.10)	<0.001	7.72 (3.33–17.93)	<0.001	8.15 (3.28–20.25)	<0.001
AF only	<300 pg/mL	Reference	...	Reference	...	Reference	...	Reference	...
	300–999 pg/mL	6.36 (1.40–29.05)	0.017	4.15 (0.89–19.28)	0.069	6.23 (1.38–28.14)	0.017	3.95 (0.87–17.97)	0.076
	1000–1999 pg/mL	11.71 (2.56–53.43)	0.001	7.99 (1.68–37.99)	0.009	11.50 (2.54–52.12)	0.002	7.82 (1.74–35.11)	0.007
	≥2000 pg/mL	37.05 (8.88–154.55)	<0.001	21.42 (4.77–96.18)	<0.001	36.27 (8.85–148.67)	<0.001	20.44 (4.94–84.67)	<0.001
HF only	<300 pg/mL	Reference	...	Reference	...	Reference	...	Reference	...
	300–999 pg/mL	1.87 (0.92–3.81)	0.083	1.44 (0.69–2.99)	0.333	1.88 (0.94–3.77)	0.074	1.46 (0.71–2.99)	0.308
	1000–1999 pg/mL	2.76 (1.31–5.83)	0.008	2.28 (1.04–4.99)	0.040	2.78 (1.32–5.87)	0.007	2.33 (1.06–5.14)	0.035
	≥2000 pg/mL	3.96 (2.09–7.52)	<0.001	2.34 (1.10–4.97)	0.026	3.87 (2.07–7.24)	<0.001	2.36 (1.07–5.21)	0.034
AF plus HF	<300 pg/mL	Reference	...	Reference	...	Reference	...	Reference	...
	300–999 pg/mL	1.84 (0.72–4.69)	0.205	1.56 (0.60–4.04)	0.363	1.82 (0.73–4.57)	0.200	1.61 (0.63–4.07)	0.317
	1000–1999 pg/mL	3.97 (1.64–9.60)	0.002	3.92 (1.59–9.71)	0.003	4.02 (1.69–9.54)	0.002	4.04 (1.67–9.74)	0.002
	≥2000 pg/mL	5.35 (2.33–12.27)	<0.001	4.47 (1.86–10.71)	0.001	5.04 (2.25–11.32)	<0.001	4.30 (1.84–10.05)	0.001

Multivariate analysis adjusted for age, sex, race, obesity (body mass index ≥ 30 kg/m²), hypertension, diabetes, coronary artery disease, hyponatremia, valvular heart disease, left bundle-branch block, estimated glomerular filtration rate, medical treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, beta blockers, diuretics (thiazide or loop diuretics), and anticoagulants (novel oral anticoagulant or vitamin K antagonist). Baseline data were missing in 3.6% of the study population for body mass index, 2.8% for sodium and these data were imputed for multivariate analysis. AF indicates atrial fibrillation; HF, heart failure; HR, hazard ratio; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

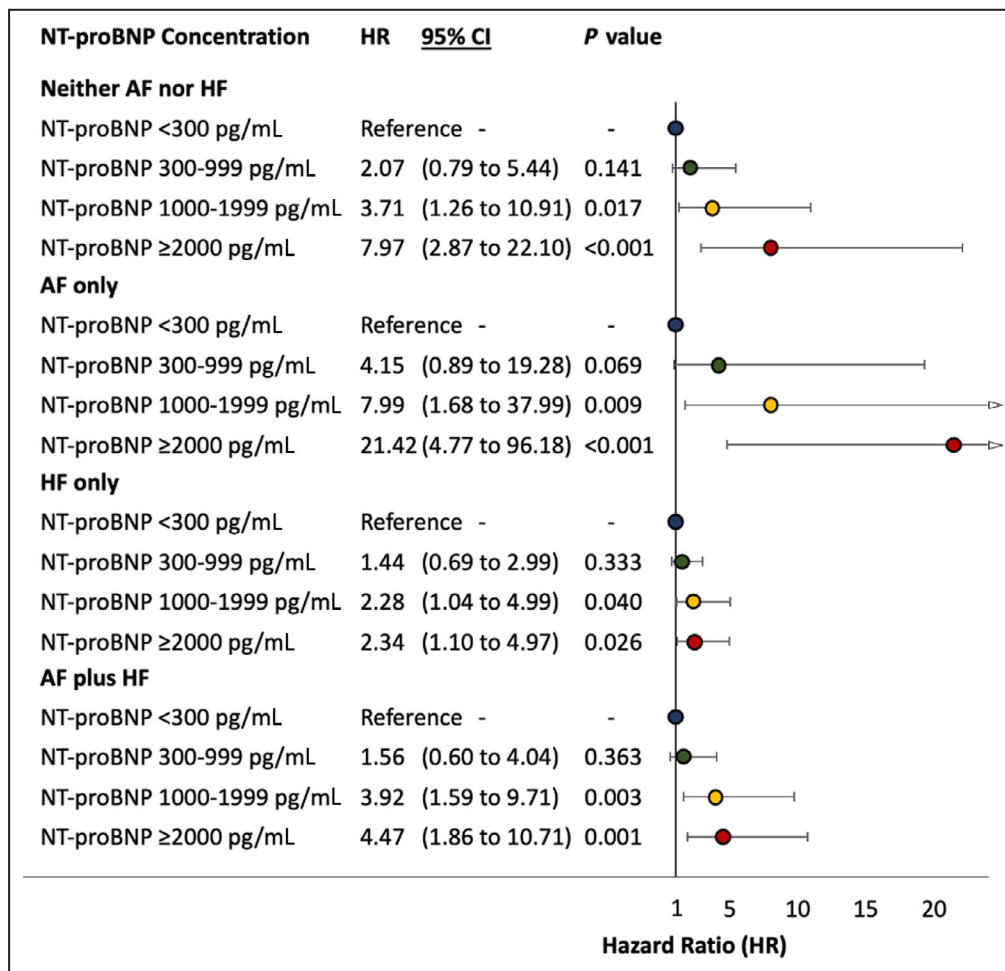


Figure 6. Forest plot showing Cox proportional hazards analysis for the composite outcome at 2.5 years against baseline NT-proBNP concentration ranges in each patient group based on AF and HF status.

Adjusted for age, sex, race, obesity (body mass index ≥ 30 kg/m²), hypertension, diabetes, coronary artery disease, hyponatremia, valvular heart disease, left bundle-branch block, estimated glomerular filtration rate, medical treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, beta blockers, diuretics (thiazide or loop diuretics), and anticoagulants (novel oral anticoagulant or vitamin K antagonist). AF indicates atrial fibrillation; HF heart failure; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

1. In unselected patients presenting to a hospital, AF is predictive of HF hospitalization or cardiovascular death in patients without clinical or echocardiographic signs of HF.
2. NT-proBNP plasma concentrations improve risk stratification in patients with AF with and without HF.
3. Previously developed NT-proBNP concentration thresholds can be applied to estimate risk of future cardiovascular events in patients without HF, including patients with AF (Figure 8).

HF hospitalizations occur in 20% to 30% of all patients with AF,²⁸ reflecting that a high proportion of patients with AF suffer from heart failure, with the majority

having HFpEF.^{29,30} Our data show that patients with AF, but without an established diagnosis of heart failure, had high rates of HF hospitalization and cardiovascular death. This is important, as it highlights the need to consider adverse HF-related outcomes in all patients with AF rather than solely in patients with HF as an established comorbidity, as currently recommended in an integrated care approach to patients with AF.² One important caveat to this is that in our study, we included unselected patients presenting to secondary care. More research is needed to evaluate the risk of adverse HF-related outcomes in patients with AF but without established HF in the community or primary care setting.

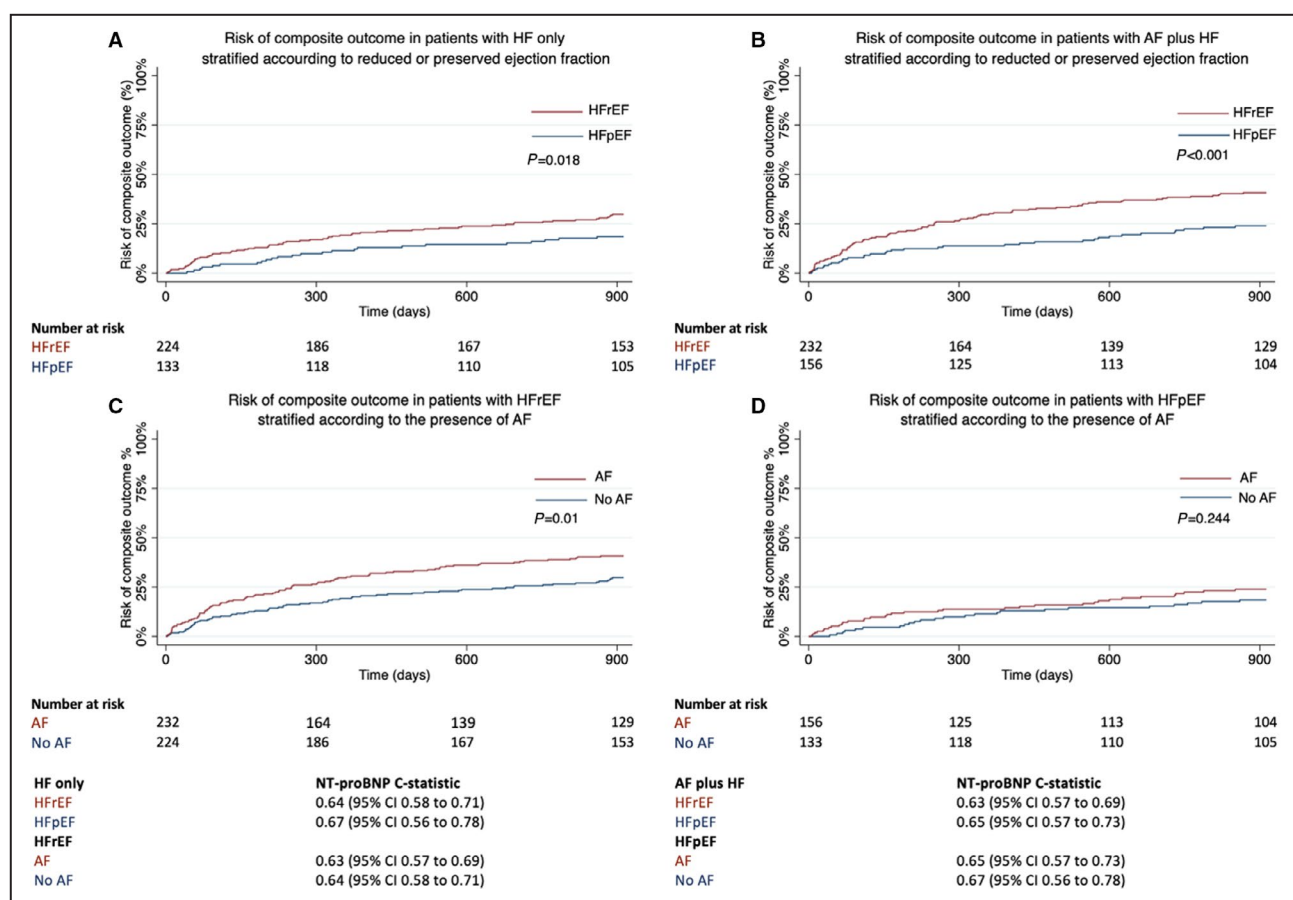


Figure 7. Kaplan-Meier curves of the composite outcome at 2.5 years in (A) patients with HF only stratified according to the presence of reduced or preserved ejection fraction, (B) patients with AF plus HF stratified according to the presence of reduced or preserved ejection fraction, (C) patients with HFrEF stratified according to the presence of AF, and (D) patients with HFpEF stratified according to the presence of AF.

Prognosis is worse in patients with HFrEF than in those with HFpEF, and worse in those with AF than in those without AF. C-statistic of baseline NT-proBNP for the composite outcome in each sub-group also shown. AF indicates atrial fibrillation; HF heart failure; HFpEF, heart failure with preserved ejection fraction; and HFrEF heart failure with reduced ejection fraction; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

The median NT-proBNP in patients recruited to this study with AF only, that is, patients without established HF, was higher than the current ESC cut-off for diagnosing HF in the acute setting. This study therefore highlights potential limitations in the diagnostic utility of NT-proBNP for diagnosing HF in patients with AF. Conversely, this study also highlights that NT-proBNP has high prognostic utility in terms of predicting future HF hospitalization or cardiovascular death in patients with AF only. These results encourage the routine quantification of NT-proBNP concentrations in the assessment of patients with AF, adding to a growing body of evidence supporting the use of this biomarker in AF for risk stratification, and elevated concentrations are associated with stroke and mortality in patients with AF.³¹ Based on these findings, the use of elevated NT-proBNP concentrations to guide screening for AF is currently being evaluated.³²

AF and atrial flutter are associated with higher concentrations of natriuretic peptides and commonly exceed the diagnostic thresholds for HF, even in the absence of further clinical evidence to support a diagnosis of HF.⁹ In terms of prognosis, because of uncertainty about the prognostic significance of elevated natriuretic peptides in AF, randomized controlled trials in patients with HF have traditionally used higher natriuretic peptide thresholds in their inclusion criteria for patients with AF. Likewise, while HF risk prediction models have been developed for patients with AF, none of these models included natriuretic peptides.³³ In this study, the primary outcome of future HF hospitalization or cardiovascular death occurred more frequently in patients with AF compared with patients without AF. Even after adjusting for clinical parameters,³³ NT-proBNP remained an important predictor of HF hospitalization or cardiovascular death in those patients with AF.

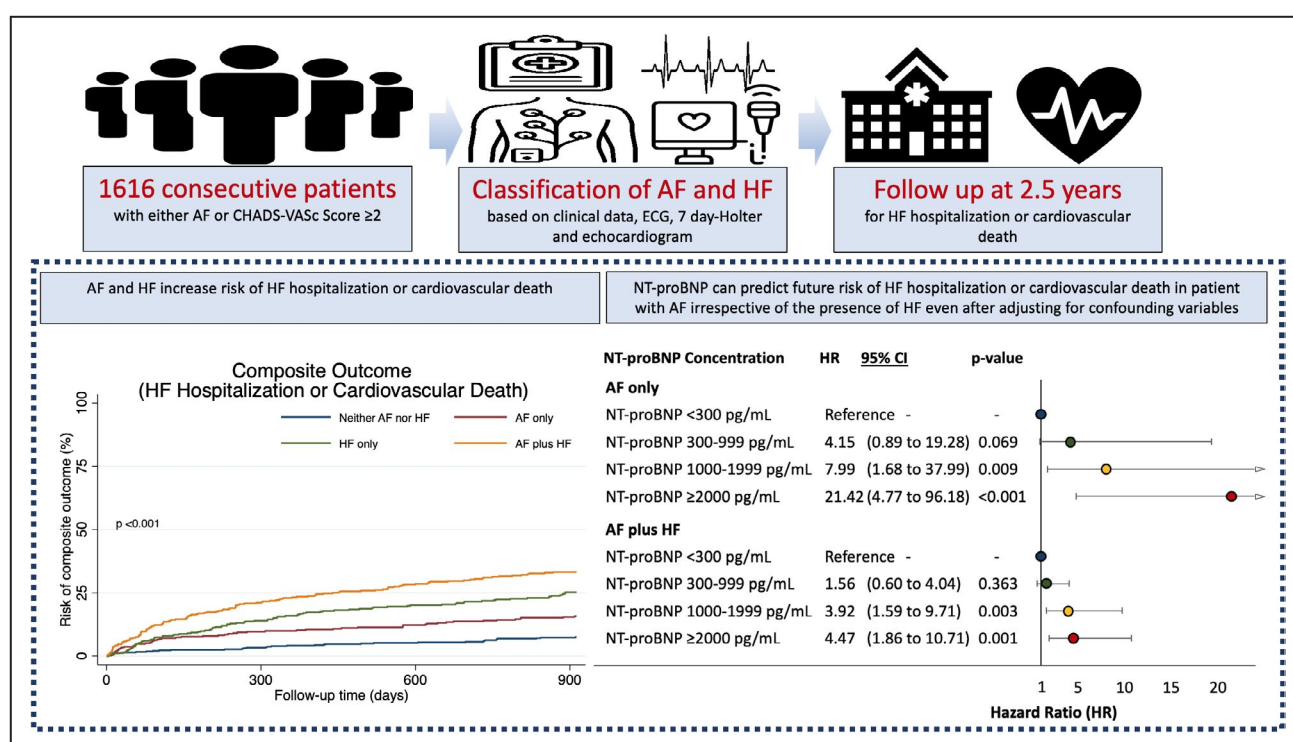


Figure 8. Summary of our findings.

A single quantification of NT-proBNP provides prognostic information in patients with atrial fibrillation irrespective of the presence of heart failure. AF indicates atrial fibrillation; HF heart failure; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

In patients with established HFrEF (left ventricular ejection fraction <35%), higher NT-proBNP concentrations are associated with HF hospitalization or cardiovascular death, in both patients with and without AF.³⁴ In a similar study that included patients with HFpEF, NT-proBNP did not predict outcomes in patients with AF as clearly.³⁵ This outcome may be attributable to different populations being used in different analyses. In the present study, unselected patients presenting to a hospital for cardiovascular conditions were analyzed.³⁵ In this setting, the risk of HF hospitalization or cardiovascular death increased at higher NT-proBNP levels in all 4 phenotype groups. Furthermore, the association between elevated NT-proBNP concentrations and outcomes was comparable, if not stronger, in patients with AF than in patients with HF. Treatments that are used to manage HF could explain this, such as diuretics. While diuretics reduce NT-proBNP concentrations in patients with HF, they do not affect outcomes, suggesting that the reduction in biomarker levels attributable to diuretic therapy may be disproportionate to the associated impact on outcome.^{8,9,14}

Clinical Implications

This study suggests that elevated NT-proBNP concentrations are associated with future HF hospitalization or

cardiovascular death in patients with AF. This association was consistent in patients with and without clinically diagnosed HF. Hence, whenever risk prediction is clinically desired, NT-proBNP concentrations should be measured in patients with AF. Elevated NT-proBNP concentrations should trigger a thorough specialist evaluation, irrespective of the presence of HF.

As more disease-modifying evidence-based treatments become available for the management of cardiovascular disease, a major challenge for clinicians going forward will be determining what treatments to initiate for patients at risk of adverse outcomes related to HF morbidity and mortality while avoiding unnecessary treatment burden to patients and health care systems. Our data suggest that biomarkers such as natriuretic peptides, used routinely, can identify patients at risk of HF for this purpose. In line with data from previous studies in patients with HF, this study suggests that an NT-proBNP threshold of 1000 pg/mL identifies a group of patients at high risk of future HF events.

The results of this study suggest that there is no need to adapt NT-proBNP thresholds in patients with AF for clinical studies using HF hospitalization or cardiovascular death as an outcome, supporting previous proposals.³⁴ NT-proBNP concentrations can accurately risk stratify patients with AF (with and without HF) for HF hospitalization or cardiovascular death.

In this study, the predictive utility of NT-proBNP at discriminating end points including HF hospitalization and cardiovascular death was reduced in phenotype groups with HF compared with those without HF. The weaker association between outcomes and NT-proBNP concentrations may be attributable to complex interactions between NT-proBNP, the HF syndrome, and HF treatment, and may limit the effectiveness of NT-proBNP as a prognostic marker in patients with HF. This finding warrants more research into the use of additional biomarkers to complement NT-proBNP to help refine the prognostic assessment of patients with HF.

Limitations

This was a single-center study that enabled comparable and comprehensive clinical phenotyping with near-complete patient follow-up. However, the results require external validation in different care settings. While the ceiling effect for prognostic interpretation around NT-proBNP concentrations of <1000 pg/mL was reported before,²⁰ its interpretation requires caution and testing in large populations with concentrations above that threshold. A broad definition of HF was selected for this study to encompass patients across the spectrum of HF, based on current guideline recommendations including systematic imaging. While this has the important advantage of preventing patients with AF and HF being misclassified as having AF only, the use of a heterogeneous HF population and inclusion of patients with cardiomyopathy (ie, ejection fraction <50%) but potentially without established HF may increase the possibility of confounding factors in these subgroups.

Further studies are needed to elucidate if disease-modifying evidence-based treatments can be used to reduce the risk of future adverse events in patients with AF but without a diagnosis of HF, identified as high risk using an NT-proBNP threshold of 1000 pg/mL. High NT-proBNP in patients with AF may be reflective of a significant underlying atrial cardiomyopathy, and it is possible that even in the absence of symptoms, this patient group may benefit from disease-modifying treatments to reduce the risk of future adverse events. In particular, strategies to reduce the risk of HF hospitalization in this high-risk patient group remains a major unmet need.

CONCLUSIONS

In unselected patients presenting to a hospital, a single measurement of NT-proBNP adds valuable prognostic information in unselected patients with AF, including patients without established HF. NT-proBNP should be

used to risk-stratify unselected patients with AF with or without established HF. In line with previous studies on HF, an NT-proBNP threshold of 1000 pg/mL is useful to identify high-risk patients with AF whether or not they are diagnosed with HF at the time of assessment (Figure 8).

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S7

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Supplemental Material

Table S1. International Statistical Classification of Diseases-10th Revision (ICD-10) codes used to define cardiovascular death.

Diagnosis	Version	Code
Ischemic Heart Disease	ICD-10	I20* I21* I22* I23* I24* I25*
Heart Failure & cardiomyopathy	ICD-10	I10* I11* I12* I13* I14* I15* I16* I42* I255 J81 I50* I517
Valvular heart disease	ICD-10	I34* I35* I36* I37*
Cardiac arrest (due to cardiac condition)	ICD-10	I462
Ventricular tachycardia and ventricular fibrillation	ICD-10	I470 I472 I4901 I4902
Acute stroke (ischemic, non-ischemic and hemorrhagic)	ICD-10	I60*, I161*, I63* I64* I65*, I166*, I67* I68* I69* G46*
Cardiogenic shock	ICD-10	R570
Thromboembolism	ICD-10	I26* I82*
Peripheral vascular disease	ICD-10	I70* I71* I72* I73* I74* I75* I76* I78* I79* I79*
Infective endocarditis	ICD-10	I33* I38*
*All digits after omitted		

Table S2. Baseline characteristics of AF and HF phenotype groups according to the composite outcome (HF hospitalization or cardiovascular death) at 2.5 years.

Baseline Characteristic	Neither AF nor HF (N=488)		AF only (N=354)		HF only (N=369)		AF plus HF (N=405)	
	Without Event (N=452)	With event (N=36)	Without Event (N=299)	With event (N=55)	Without Event (N=277)	With event (N=92)	Without Event (N=277)	With event (N=128)
<u>Clinical characteristics</u>								
Age, median, (IQR)	65 (56–73)	70 (65–79)	70 (61–78)	79 (69–85)	68 (59–76)	72 (57–79)	74 (67–81)	75 (67–81)
Female sex, n (%)	205/452 (45)	17/36 (47)	120/299 (40)	30/55 (55)	98/277 (35)	30/92 ((33)	107/277 (39)	37/128 (29)
Race, n (%)								
Caucasian	306/452 (68)	26/36 (72)	253/299 (85)	49/55 (89)	209/277 (75)	55/92 (59)	239/277 (86)	101/128 (79)
Asian	92/452 (20)	8/36 (22)	29/299 (10)	2/55 (4)	44/277 (16)	19/92 (21)	18/277 (7)	12/128 (9)

Afro-Caribbean	53/452 (12)	2/36 (6)	17/299 (6)	3/ 55 (5)	24/277 (9)	18/92 (20)	19/277 (7)	15/128 (12)
Other	1/452 (0.2)	-	-	1/55 (2)	-	-	1/277 (0.4)	-
Heart Rhythm, n (%)								
Sinus Rhythm	452/452 (100)	36/36 (100)	-	-	277/277 (100)	92/92 (100)	-	-
Paroxysmal AF	-	-	178/299 (60)	17/55 (31)	-	-	137/277 (49)	47/128 (37)
Persistent AF	-	-	57/299 (19)	19/55 (35)	-	-	66/277 (24)	34/128 (27)
Permanent AF	-	-	52/299 (17)	17/55 (31)	-	-	59/277 (21)	43/128 (34)
Atrial Flutter	-	-	12/299 (4)	2/55 (4)	-	-	15/277 (5)	4/128 (3)
BMI, kg/m ² , median, (IQR) *	29 (25–33)	29 (25–33)	29 (26, 33)	27 (23–32)	28 (25–32)	28 (24–32)	29 (25–33)	29 (26–33)
Systolic BP, mmHg , median, (IQR)	126 (113–140)	131 (111–145)	130 (118–145)	123 (109–135)	122 (110–137)	120 (106–130)	121 (110–140)	119 (106–134)
Heart rate/min, median, (IQR)	68 (61–78)	73 (60–89)	68 (58–80)	71 (59–88)	72 (63–81)	74 (62–83)	76 (63–90)	77 (64–89)

Ejection fraction, %, median, (IQR)	61 (57–68)	60 (54–71)	62 (57–68)	58 (54–68)	47 (38–59)	39 (29–52)	49 (40–58)	40 (27–52)
Ejection fraction <50%, n (%)	-	-	-	-	158/267 (59)	66/90 (73)	141/262 (54)	91/126 (72)
Previous diagnosis of stable HF	-	-	-	-	99/277 (36)	53/92 (58)	123/277 (44)	80/128 (63)
Symptomatic HF								
NYHA II HF, n (%)	-	-	-	-	118/277 (43)	25/92 (25)	120/275 (44)	39/126 (31)
NYHA III HF, n (%)	-	-	-	-	52/277 (19)	32/92 (32)	65/275 (24)	46/126 (37)
NYHA IV HF, n (%)	-	-	-	-	11/277 (4)	9/92 (9)	16/275 (6)	15/126 (12)
LBBB, n (%)	6/452 (1)	0/36 (0)	5/299 (2)	1/55 (2)	15/277 (4)	11/92 (12)	12/277 (4)	10/128 (8)
Medical history, n (%)								
Diabetes	195/452 (43)	17/36 (47)	59/299 (20)	16/55 (29)	113/277 (41)	53/92 (58)	66/277 (24)	46/128 (36)
Hypertension	299/452 (66)	23/36 (64)	167/299 (56)	38/55 (69)	166/277 (60)	54/92 (59)	130/277 (47)	69/128 (54)
Coronary artery disease	206/452 (46)	18/36 (50)	50/299 (17)	8/55 (15)	155/277 (56)	48/92 (52)	88/277 (32)	56/128 (44)

Hyponatremia (Na <135 mmol/L)*	71/445 (16)	6/36 (17)	30/272 (11)	13/55 (24)	46/274 (17)	25/92 (27)	28/270 (11)	29/127 (23)
Severe valvular heart disease	9/452 (2)	0/36 (0)	8/299 (3)	9/55 (16)	7/277 (3)	5/92 (5)	21/277 (8)	20/128 (16)
HF hospitalization at presentation	-	-	-	-	15/277 (5)	8/92 (9)	4/277 (1)	12/128 (9)
Laboratory measurements								
eGFR mL/min/1.73m ² , (CKD-EPI), median, (IQR)	81 (64–95)	66 (43–86)	75 (62–88)	56 (42–75)	75 (57–91)	59 (44–77)	66 (47–82)	56 (40–78)
NT-proBNP pg/mL, median, (IQR)	192 (68–558)	968 (250–2478)	485 (167–1191)	2580 (1204–6465)	659 (218–2067)	1801 (522–4752)	1279 (461–3330)	2793 (1220–6314)
NT-proBNP ≥125pg/ml, n (%)	266/452 (59)	32/36 (89)	240/299 (80)	55/55 (100)	225/277 (81)	87/92 (95)	256/277 (92)	126/128 (98)
NT-proBNP groups, n (%)								
<300pg/mL	276/452 (61)	10/36 (28)	119/299 (40)	2/55 (4)	88/277 (32)	11/91 (12)	50/277 (18)	6/128 (5)

300–999pg/mL	99/452 (22)	8/36 (22)	91/299 (30)	10/55 (18)	78//277 (28)	21/91 (23)	71/277 (26)	16/128 (13)
1000–1999pg/mL	38/452 (8)	6/36 (17)	48/299 (16)	10/55 (18)	40//277 (14)	16/91 (18)	51/277 (18)	28/128 (22)
≥2000pg/mL	39/452 (9)	12/36 (33)	41/299 (14)	33/55 (60)	71//277 (26)	43/91 (47)	105/277 (38)	78/128 (61)
Sodium mmol/L, median, (IQR) *	138 (136–140)	138 (136–140)	139 (137–141)	139 (135–141)	138 (136–140)	137 (134–140)	139 (137–141)	138 (135–140)
Urea mmol/L, median, (IQR) *	5.5 (4.4–7.0)	6.4 (5.0–10.3)	5.6 (4.6–6.9)	6.9 (5.8–9.1)	5.8 (4.5–7.2)	7.8 (5.7–11.8)	6.3 (4.9–8.8)	9.2 (6.1–13.1)
Hemoglobin g/L, median, (IQR) *	134 (121–145)	119 (109–134)	137 (124–148)	124 (105–137)	131 (118–144)	122 (105–139)	130 (116–142)	121 (110–136)
Pharmacotherapy, n (%)								
Beta-blocker	247/452 (55)	18/36 (50)	153/299 (51)	29/55 (53)	173 /277 (63)	59/92 (64)	161/277 (58)	68/128 (53)
ACE-inhibitors or ARB	223/452 (49)	18/36 (50)	137/299 (46)	24/55 (44)	164/277 (59)	51/92 (55)	138/277 (50)	61/128 (48)
NOAC	9/452 (2)	0/36 (0)	133/299 (44)	25/55 (45)	6/277 (2)	3/92 (3)	133/277 (48)	57/128 (45)

Warfarin	4/452 (1)	1/36 (3)	65/299 (22)	13/55 (24)	8/277 (3)	5/92 (5)	72/277 (26)	38/128 (30)
Diuretic	83/452 (18)	14/36 (39)	59/299 (20)	24/55 (44)	97/277 (35)	30/92 (33)	135/277 (49)	41/128 (32)
MRA	6/452 (1)	0/36 (0)	5/299 (2)	4/55 (7)	23/277 (7)	22/92 (24)	20/277 (7)	24/128 (19)
Complex device (ICD or CRT)	4/452 (1)	1/36 (3)	2/299 (1)	3/55 (5)	14/277 (5)	12/92 (13)	20/277 (7)	18/128 (14)

ACE, Angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRT, cardiac resynchronization therapy; eGFR, estimate glomerular filtration rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LBBB, left bundle branch block; MRA, mineralocorticoid receptor antagonist; Na, sodium; NOAC, Novel oral anticoagulant; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VKA, vitamin K antagonist.

* Baseline data were missing in 3.6% of the study population for BMI, 2.4% for hemoglobin, 2.8% for urea and sodium.

Table S3. Outcomes stratified according to AF and HF phenotype groups.

Patient Group	Composite outcome	HF Hospitalization	Cardiovascular Death	All-Cause Mortality
	Events/person-yrs	Events/person-yrs	Events/person-yrs	Events/person-yrs
	(incidence/100 person-yrs)	(incidence/100 person-yrs)	(incidence/100 person-yrs)	(incidence/100 person-yrs)
Entire Cohort	310/3381 (9.2)	202/3686 (5.5)	168/3657 (4.6)	254/3657 (7.0)
Neither AF nor HF	36/1135 (3.2))	18/1190 (1.5)	22/1160 (1.9)	40/1159 (3.4)
AF only	55/775 (7.1)	34/826 (4.1)	32/819 (3.9)	47/819 (5.7)
HF only	91/759 (12.1)	59/824 (7.2)	52/828 (6.3)	66/828 (8.0)
AF plus HF	128/722 (17.7)	91/846 (10.8)	62/850 (7.3)	101/850 (11.9)

Table S4. C-Statistic of NT-proBNP as a continuous variable in each patient group for the composite outcome, its individual components i.e., HF hospitalization and cardiovascular death, and all-cause mortality.

Patient Group	Composite Outcome C-Statistic (95% CI)	P Value	HF Hospitalization C-Statistic (95% CI)	P Value	Cardiovascular Death C-Statistic (95% CI)	P Value	All-Cause Mortality C-Statistic (95% CI)	P Value
Entire Cohort	0.74 (0.72 to 0.77)	<0.001	0.72 (0.69 to 0.75)	<0.001	0.76 (0.73 to 0.80)	<0.001	0.72 (0.69 to 0.75)	<0.001
Neither AF nor HF	0.73 (0.65 to 0.81)	<0.001	0.74 (0.64 to 0.84)	<0.001	0.74 (0.63 to 0.85)	<0.001	0.67 (0.59 to 0.76)	<0.001
AF only	0.82 (0.77 to 0.87)	<0.001	0.79 (0.72 to 0.85)	<0.001	0.86 (0.80 to 0.91)	<0.001	0.79 (0.73 to 0.85)	<0.001
HF only	0.66 (0.60 to 0.72)	<0.001	0.64 (0.57 to 0.71)	<0.001	0.71 (0.64 to 0.78)	<0.001	0.70 (0.63 to 0.77)	<0.001
AF plus HF	0.66 (0.61 to 0.70)	<0.001	0.61 (0.55 to 0.66)	<0.001	0.68 (0.62 to 0.75)	<0.001	0.65 (0.59 to 0.71)	<0.001

Table S5. Optimal cut-point in the entire cohort and each patient group (Youden index) and important cut-offs with associated area under the ROC curve, sensitivity, specificity, positive predictive value and negative predictive value of NT-proBNP for the composite outcome (heart failure hospitalization or cardiovascular death).

NT-proBNP cut-off	Patient Group	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Optimal cut-point						
(Youden index)						
1079pg/ml	Entire Cohort	0.70 (0.68 to 0.73)	71% (66% to 76%)	69% (67% to 72%)	36% (32% to 39%)	91% (89% to 93%)
229pg/ml	Neither AF nor HF	0.68 (0.61 to 0.75)	81% (64% to 92%)	55% (51% to 60%)	13% (9% to 18%)	97% (95% to 99%)
1182pg/ml	AF only	0.77 (0.71 to 0.83)	78% (65% to 88%)	75% (70% to 80%)	36% (28% to 46%)	95% (91% to 97%)
1407pg/ml	HF only	0.64 (0.58 to 0.70)	60% (49% to 70%)	68% (62% to 74%)	39% (31% to 47%)	84% (78% to 88%)
2128pg/ml	AF plus HF	0.62 (0.57 to 0.67)	60% (51% to 69%)	64% (58% to 69%)	43% (36% to 51%)	78% (72% to 83%)
Important cut-offs						

125pg/ml	Entire Cohort	0.60 (0.59 to 0.62)	97% (94% to 98%)	24% (22% to 27%)	23% (21% to 26%)	97% (94% to 98%)
	Neither AF nor HF	0.65 (0.59 to 0.71)	89% (74% to 97%)	41% (37% to 46%)	11% (7% to 15%)	98% (95% to 99%)
	AF only	0.60 (0.58 to 0.62)	100% (94 to 100%)	20% (15% to 25%)	19% (14% to 24%)	100% (94% to 100%)
	HF only	0.57 (0.53 to 0.60)	95% (88 to 98%)	19% (14% to 24%)	28% (23% to 33%)	91% (81% to 97%)
	AF plus HF	0.53 (0.51 to 0.55)	98% (95% to 100%)	8% (5% to 11%)	33% (28% to 38%)	91% (72% to 99%)
300pg/ml	Entire Cohort	0.66 (0.64 to 0.68)	90% (0.87 to 0.93)	41% (38% to 44%)	27% (24% to 30%)	95% (93% to 96%)
	Neither AF nor HF	0.67 (0.59 to 0.74)	72% (55% to 86%)	61% (56% to 66%)	13% (9% to 18%)	97% (94% to 98%)
	AF only	0.68 (0.64 to 0.72)	96% (88% to 100%)	40% (34% to 46%)	23% (18% to 29%)	98% (94% to 100%)
	HF only	0.59 (55 to 0.64)	87% (78% to 93%)	32% (26% to 38%)	30% (24% to 36%)	88% (80% to 94%)
	AF plus HF	0.57 (0.54 to 0.60)	95% (90% to 98%)	18% (14% to 23%)	35% (30% to 40%)	89% (78% to 96%)
1000pg/ml	Entire Cohort	0.70 (0.67 to 0.73)	73% (67% to 78%)	67% (64% to 69%)	34% (31% to 38%)	91% (89% to 93%)
	Neither AF nor HF	0.67 (0.58 to 0.75)	50% (33% to 67%)	83% (79% to 86%)	19% (12% to 28%)	95% (93% to 97%)

2000pg/ml	AF only	0.74 (0.68 to 0.80)	78% (65% to 88%)	70% (65% to 75%)	33% (25% to 41%)	95% (91% to 97%)
	HF only	0.62 (0.56 to 0.68)	64% (54% to 74%)	60% (54% to 66%)	35% (28% to 42%)	83% (78% to 88%)
	AF plus HF	0.63 (0.59 to 0.68)	83% (75% to 89%)	44% (38% to 50%)	41% (35% to 47%)	85% (78% to 90%)
	Entire Cohort	0.67 (0.64 to 0.70))	53% (48% to 59%)	80% (78% to 83%)	39% (35% to 44%)	88% (86% to 90%)
	Neither AF nor HF	0.62 (0.54 to 0.70)	33% (19% to 51%)	91% (88% to 94%)	24% (13% to 38%)	95% (92% to 96%)
	AF only	0.73 (0.66 to 0.80)	60% (46% to 73%)	86% (82% to 90%)	45% (33% to 57%)	92% (88% to 95%)
	HF only	0.61 (0.55 to 0.66)	47% (36% to 57%)	74% (69% to 79%)	38% (29% to 47%)	81% (75% to 85%)
	AF plus HF	0.62 (0.56 to 0.67)	61% (52% to 69%)	62% (56% to 68%)	43% (35% to 50%)	78% (71% to 83%)

Table S6. Performance of important cut-offs at predicting the composite outcome evaluated using discrimination, calibration, and reclassification. An NT-proBNP cut-off of 300pg/ml was used as a reference for NRI with two risk levels were selected: >20% and <20% risk of the composite outcome.

NT-proBNP		Discrimination	Calibration	Reclassification				
Cut-off		C-Statistic	Brier Score	AIC	BIC	Likelihood Ratio	NRI (20%)	IDI
125pg/ml	Entire Cohort	0.60 (0.58 to 0.61)	0.12 (0.10 to 0.13)	4425	4430	$p=0.013$	No change	0.001 ($p=0.040$)
	Neither AF nor HF	0.65 (0.60 to 0.70)	0.06 (0.04 to 0.08)	428	432	$p=0.076$	No change	0.003 ($p=0.120$)
	AF only	0.59 (0.57 to 0.61)	0.11 (0.08 to 0.14)	615	619	$p=0.101$	No change	-0.003 ($p<0.001$)
	HF only	0.56 (0.53 to 0.59)	0.13 (0.11 to 0.16)	1050	1054	$p=0.270$	No change	0.002 ($p=0.298$)
	AF plus HF	0.53 (0.51 to 0.54)	0.14 (0.12 to 0.16)	1472	1476	$p=0.679$	No change	0.0001 ($p=0.734$)
300pg/ml	Entire Cohort	0.65 (0.63 to 0.66)	0.11 (0.09 to 0.12)	4364	4370	Reference	Reference	Reference
	Neither AF nor HF	0.66 (0.59 to 0.74)	0.06 (0.41 to 0.08)	428	432	Reference	Reference	Reference
	AF only	0.67 (0.64 to 0.70)	0.90 (0.72 to 0.12)	601	605	Reference	Reference	Reference

1000pg/ml	HF only	0.59 (0.55 to 0.62)	0.13 (0.11 to 0.16)	1047	1051	Reference	Reference	Reference
	AF plus HF	0.56 (0.54 to 0.58)	0.14 (0.12 to 0.16)	1463	1467	Reference	Reference	Reference
	Entire Cohort	0.69 (0.66 to 0.71)	0.10 (0.09 to 0.12)	4345	4350	$P<0.001$	0.08 ($p=0.003$)	0.04 ($p<0.001$)
	Neither AF nor HF	0.66 (0.58 to 0.74)	0.06 (0.04 to 0.08)	425	429	$P=0.017$	No change	0.02 ($p=0.013$)
	AF only	0.73 (0.68 to 0.78)	0.09 (0.06 to 0.11)	590	594	$P<0.001$	0.12 ($p=0.062$)	0.06 ($p<0.001$)
2000pg/ml	HF only	0.62 (0.57 to 0.67)	0.13 (0.11 to 0.15)	1043	1047	$P=0.008$	No change	0.02 ($p=0.014$)
	AF plus HF	0.62 (0.59 to 0.65)	0.13 (0.11 to 0.15)	1448	1452	$P<0.001$	0.13 ($p=0.002$)	0.04 ($p<0.001$)
	Entire Cohort	0.66 (0.63 to 0.69)	0.11 (0.10 to 0.12)	4372	4377	$P<0.001$	0.03 ($p=0.507$)	0.05 ($p<0.001$)
	Neither AF nor HF	0.62 (0.54 to 0.70)	0.06 (0.04 to 0.08)	428	432	$P=0.014$	No change	0.02 ($p=0.028$)
	AF only	0.72 (0.66 to 0.78)	0.08 (0.06 to 0.10)	586	590	$P<0.001$	0.10 ($p=0.263$)	0.11 ($p<0.001$)
	HF only	0.60 (0.55 to 0.65)	0.13 (0.11 to 0.16)	1046	1050	$P=0.008$	No Change	0.02 ($p=0.016$)
	AF plus HF	0.61 (0.56 to 0.65)	0.14 (0.11 to 0.16)	1458	1462	$P<0.001$	No Change	0.03 ($p=0.001$)

Table S7. Univariate Cox proportional hazards models based on cut-offs with B coefficient and baseline hazard in the entire cohort.

NT-proBNP cut-off	B coefficient	95% Confidence Interval	Standard Error	Z score	<i>p</i> value	Baseline Hazard
125pg/ml	2.08	1.48 to 2.69	0.31	6.79	<0.001	0.03
300pg/ml	1.78	1.39 to 2.15	0.19	9.20	<0.001	0.05
1000pg/ml	1.55	1.30 to 1.80	0.13	12.17	<0.001	0.08
2000pg/ml	1.40	1.18 to 1.63	0.11	12.32	<0.001	0.11

Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Checklist for Prediction Model Development (Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement).

Section/Topic		Checklist Item		Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3-4
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	6-7
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6-7
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	7-8
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	7-8 Figure 1
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers.	7-8
	5b	D;V	Describe eligibility criteria for participants.	7-8
	5c	D;V	Give details of treatments received, if relevant.	n/a
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	9-10
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	n/a
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured.	11-13
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	n/a
Sample size	8	D;V	Explain how the study size was arrived at.	7-8
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	11-13
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	11-13
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	11-13
	10c	V	For validation, describe how the predictions were calculated.	n/a

	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	11-13
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	11
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	n/a
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Figure 1
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	n/a
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	14 Figure 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	Table 2
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Table 2 Supplemental Materials Table 7
	15b	D	Explain how to use the prediction model.	15-18
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	Supplemental Materials Table 5, Supplemental Materials Table 6
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	22
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	n/a
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	18
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	20-21
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	n/a
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	23