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ORIGINAL ARTICLE

Relationship of diabetes, heart failure, and N-terminal pro-B-type natriuretic peptide with cardiovascular outcomes in patients with atrial fibrillation

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Abstract

Aims We aim to explore the relationship of heart failure (HF) and diabetes with cardiovascular (CV) death or hospitalization for HF (HHF) and to study the clinical utility of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in an unselected patient population with atrial fibrillation (AF).

Methods and results Patients with AF admitted to a tertiary academic center between January 2005 and July 2019 were identified through a search of electronic health records. We used Cox regression models adjusted for age, sex, estimated glomerular filtration rate, diabetes, HF, body mass index, prior myocardial infarction, coronary artery disease, hypertension, smoking, C-reactive protein, and low-density lipoprotein cholesterol. To select the most informative variables, we performed a least absolute shrinkage and selection operator Cox regression with 10-fold cross-validation. In total, 7412 patients (median age 70 years, 39.7% female) were included in this analysis and followed over a median of 4.5 years. Both diabetes [adjusted (Adj.) HR 1.87, 95% CI 1.55–2.25] and HF (Adj. HR 2.57, 95% CI 2.22–2.98) were significantly associated with CV death/HHF after multivariable adjustment. Compared with patients with diabetes, HF patients had a higher risk of HHF but a similar risk of CV and all-cause death. NT-proBNP showed good discriminatory performance (area under the curve 0.78, 95% CI 0.77–0.80) and the addition of NT-proBNP to the covariates used for adjustment resulted in a significant area under the curve improvement ($\Delta = 0.04$, $P < 0.001$). With least absolute shrinkage and selection operator, the strongest associations for CV death/HHF were obtained for NT-proBNP [HR 1.91 per 1-SD in log-transformed biomarker], HF (HR 1.72), and diabetes (HR 1.56).

Conclusions Diabetes and HF were independently associated with an increased risk of CV death/HHF in an unselected AF patient population, and NT-proBNP improved risk assessment. These findings suggest that AF patients with diabetes and/or HF should be managed not only for their risk of stroke and systemic embolic events but also for CV death/HHF.

Keywords Heart failure; Diabetes mellitus; NT-proBNP; Atrial fibrillation

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Introduction

Heart failure (HF) and diabetes mellitus are both highly prevalent co-morbidities that promote atrial fibrillation (AF) and are associated with aggravated symptom burden and worse outcomes in patients with AF.[1,2] Both conditions are components of the CHA_2DS_2-VASc score, and their presence requires the initiation of oral anticoagulation to prevent a stroke or a systemic embolic event in patients with AF or atrial flutter. However, despite significant advances in managing AF patients, including the development of direct oral anticoagulants and more refined ablation techniques, AF remains associated with low quality of life, cognitive decline, hospitalizations, HF, stroke/systemic embolic events, and

death. Because of the available effective anticoagulation options, patients with AF are now more likely to develop other adverse events (particularly HF) than a stroke or a systemic embolic event.[3–5] As such, appropriate risk stratification of patients with AF should consider the risk not only for stroke but also for HF events.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a widely available biomarker that reflects haemodynamic stress and has been shown to predict HF and death in a broad range of individuals ranging from the general population to patients with diabetes, or HF.[6,7] Although it is well-known that NT-proBNP concentrations increase during episodes of AF, only limited data of its predictive value and optimal threshold exist in patients with known AF.[8,9]

Therefore, the objectives of the present study were to explore the relationship of diabetes and HF with cardiovascular (CV) death or hospitalization for HF (HHF) and to study the clinical utility of NT-proBNP in an unselected patient population with AF.

Methods

Study population

We identified patients with AF, who were admitted between January 2005 and July 2019 to the Vienna General Hospital (Medical University of Vienna) and required inpatient care through a search of electronic health records and collected available data (including patients' demographics, medical history, echocardiograms, and laboratory measurements) for all eligible patients. The presence of AF, diabetes, and HF was determined using the International Classification of Diseases (ICD) codes reported on the patients' discharge letter (Supplementary Methods). The study protocol complied with the declaration of Helsinki and was approved by the local ethics committee of the Medical University of Vienna (EK 2249/2018). In accordance with the ethics committee, no informed consent was necessary due to the retrospective nature of this study.

Laboratory measurements

Serum NT-proBNP concentrations, measured in the clinical core laboratory of the Vienna General Hospital (Medical University of Vienna) using an immunoassay on a Roche Diagnostics Cobas, were available in 4205 patients. This assay's detection limit was 3 pg/mL, and the analytical range was between 5 and 35 000 pg/mL. The intra-assay imprecision profile was 17.2 pg/mL for a mean value of 1014 pg/mL with a coefficient of variation of 1.7%.

Outcomes

The primary outcome of interest was a composite of CV death or hospitalization for HF (HHF). Secondary outcomes were the individual components of the primary composite endpoint and death from any cause. The patients' cause and date of death were assessed through the national death registry, while HHF was determined using the Vienna Healthcare Group hospitalizations database ('Wiener Gesundheitsverbund'). All outcomes were determined using the ICD codes reported on the death certificate or the admission diagnosis in the Vienna Healthcare Group hospitalizations database, respectively (detailed information are available in the Supplementary Methods).

Statistical analysis

Continuous data are shown as medians with interquartile range (IQR) and categorical variables as counts and proportions. We report the median observation time and the median follow-up using the reverse Kaplan–Meier estimator.[10] Five-year Kaplan–Meier (KM) event rates were compared using the logrank test. NT-proBNP was modelled as a continuous standardized log-transformed variable, as well as using quartiles and clinically established thresholds (i.e. 125 and 450 pg/mL). An NT-proBNP threshold was delineated using the maximally selected logrank statistic and the Youden index (=sensitivity + specificity $-$ 1).[11,12] We used Cox regression models adjusted for age (included as a continuous variable), sex, estimated glomerular filtration rate [eGFR, included as a continuous variable (mL/min/1.73 m^2)], body mass index [included as a continuous variable (kg/m^2)], prior myocardial infarction, coronary artery disease, hypertension, smoking, C-reactive protein [included as a continuous variable (mg/dL)], and low-density lipoprotein cholesterol [included as a continuous variable (mg/dL)] to assess the relationship between diabetes, HF, and NT-proBNP and the outcomes of interest. The results are presented as hazard ratio (HR) and the respective 95% confidence interval (CI). Moreover, to select the most informative variables and overcome the limitations of stepwise regression procedures, we performed a least absolute shrinkage and selection operator (LASSO) Cox regression in a model that incorporated diabetes, HF, NT-proBNP, and the covariates for adjustment in combination with 10-fold cross-validation. LASSO Cox regression was performed using the R package 'glmnet'. Continuous data were included as standardized variables in the model. We further used the C-statistic, the net reclassification improvement (NRI) at the event rate, and the integrated discrimination increment (IDI) to assess and compare the discriminatory performance of NT-proBNP with the clinical covariates used for adjustment.[13] Calibration was ensured by visually inspecting the calibration plot and the Hosmer–Lemeshow test. All *P*-

values were based on two-sided tests and were considered statistically significant at $P < 0.05$. We did not adjust for multiple testing. All statistical analyses were performed using R (version 4.0.4; R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

In total, 7412 patients were included and followed over a median of 4.5 years (IQR 1.8 to 5.3 years). The median follow-up time using the reverse KM estimator was 7.0 years. The patients' median age was 70 years (IQR 61 to 78 years), 2945 (39.7%) patients were female, and 2536 (34.2%) had a prior myocardial infarction. The median CHA_2DS_2-VASc score was 3 (IQR 1–4). Among those patients with known type of AF, 1214 (72.4%) patients had paroxysmal AF, and 462 (27.6%) patients had permanent/persistent AF. Information on baseline medication was only recorded from 2012 onwards. Among patients with available information on baseline medication (3835, 51.7%), 718/3835 (18.7%) received a vitamin K antagonist and 1701/3835 (44.4%) a direct oral anticoagulant (Supporting Information, *Table S1*). Of note, direct oral anticoagulants were not approved in Austria before 2012, and as such, all patients receiving anticoagulation were treated with phenprocoumon.

Among the study population, 1355 (18.3%) patients had known diabetes, and 1668 (22.5%) patients had established HF; thereof, 481 (6.5%) patients had both diabetes and HF (*Table 1*, Supporting Information, *Table S2*). An echocardiogram within 3 months of the index date was available for 4543 (61.3%) patients. Among the 1219 patients with HF and available echocardiography, 777 (63.7%) patients had a documented LVEF ≤40%.

The median eGFR was 65 mL/min/1.73m^2 (IQR 50 to 81 mL/min/1.73m^2), and the median NT-proBNP levels were 1167 pg/mL (IQR 338 to 2963 pg/mL). Patients with higher NT-proBNP quartiles were more likely to be older, have diabetes, HF, and prior myocardial infarction but lower eGFR levels (all $P < 0.001$; Supporting Information, *Tables S3* and *S4*). The median NT-proBNP levels were 695 pg/mL (IQR 206 to 1884 pg/mL) in patients who had neither HF nor diabetes, 1234 pg/mL (IQR 465 to 2474 pg/mL) in patients with diabetes but no HF, 2873 pg/mL (IQR 1224 to 6314 pg/mL) in patients with HF but no diabetes, and 3220 pg/mL (IQR 1530 to 7136 pg/mL; *P*-value <0.001) in patients who had both diabetes and HF (Supporting Information, *Table S2*, *Figure S1*).

Relationship of diabetes and heart failure with hospitalization for heart failure and death in patients with atrial fibrillation

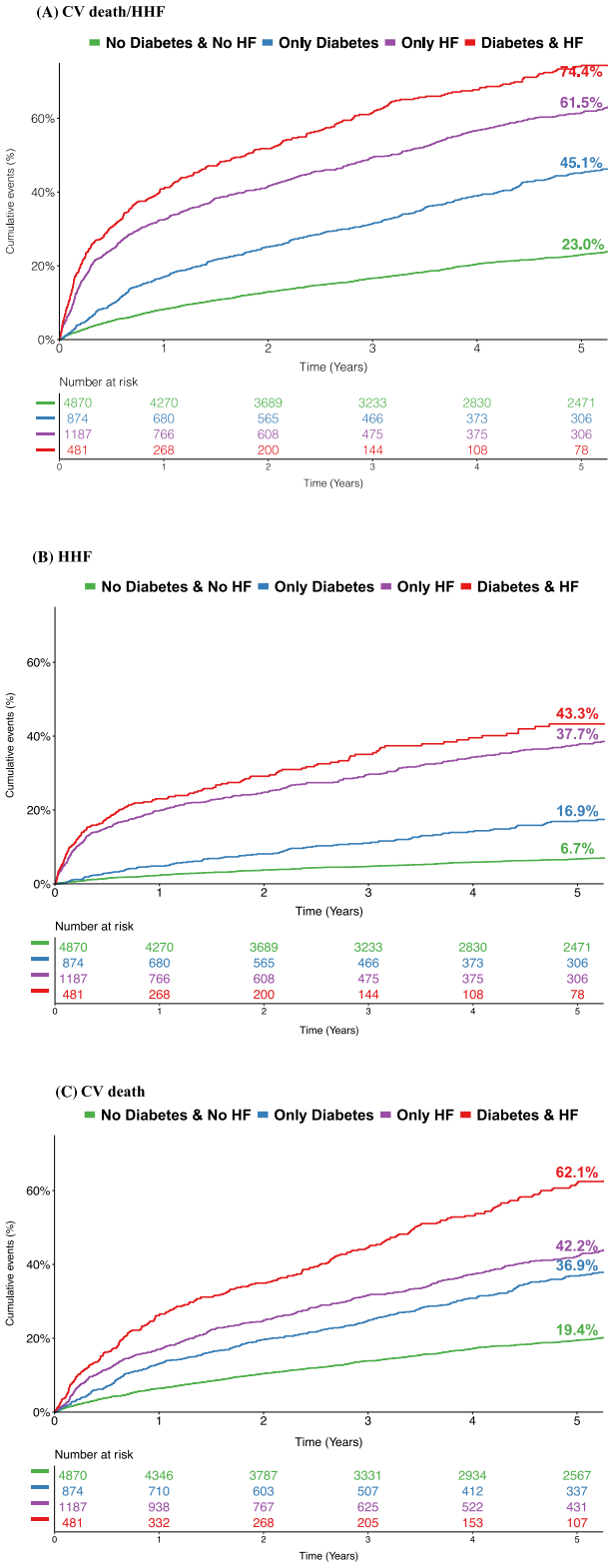
There was a significant stepwise increase in event rates for the composite of CV death/HHF among patients without diabetes or HF (KM event rate at 5 years: 23.0%), patients who had diabetes but no HF (KM event rate at 5 years: 45.1%), patients with HF but no diabetes (KM event rate at 5 years: 61.5%), and those who had both HF and diabetes (KM event rate at 5 years: 74.4%; *P*-logrank <0.001; *Figure 1A*). A similar pattern was observed for HHF, CV death, and all-cause death (*Figure 1*, Supporting Information, *Figure S2*). Patients with HF and LVEF ≤40% had significantly higher rates of CV death/HHF than HF patients without known LVEF ≤40% (KM event rate at 5 years: 68.8% vs. 61.9%; *P*-logrank 0.049; Supporting Information, *Figure S3*).

Table 1 Baseline characteristics

	All (n = 7412)	Diabetes (n = 1355)	HF (n = 1668)
Age, years	70 (61–78)	73 (66–79)	72 (64–79)
Female, sex, *n* (%)	2945 (39.7)	522 (38.5)	486 (29.1)
BMI, kg/m^2	27 (24–30)	29 (26–33)	27 (24–31)
LVEF ≤40%, *n* (%)	777/4543 (17.1)	231/908 (25.4)	777/1219 (63.7)
Hypertension, *n* (%)	3582 (48.3)	983 (72.5)	853 (51.1)
Diabetes, *n* (%)	1355 (18.3)	1355 (100)	481 (28.8)
HF, *n* (%)	1668 (22.5)	481 (35.5)	1668 (100)
Prior MI, *n* (%)	2536 (34.2)	771 (56.9)	884 (53.0)
Valvular heart disease, *n* (%)	671/5211 (9.1)	154/1011 (11.4)	261/1345 (15.6)
CHA2DS2-VASc score	3 (1–4)	4 (3–5)	4 (3–5)
eGFR, mL/min/1.73 m^2	65 (50–81)	56 (42–72)	56 (42–72)
eGFR <60 mL/min/1.73 m^2 (%)	2456 (40.5)	711 (55.9)	898 (58.0)
HbA1c, %	5.8 (5.5–6.3)	6.8 (6.2–7.7)	6.0 (5.6–6.6)
NT-proBNP, pg/mL	1167 (337–2963)	1680 (720–3911)	2988 (720–6742)
CRP, mg/dL	0.5 (0.2–1.3)	0.6 (0.3–1.5)	0.7 (0.3–1.6)
LDL-C, mg/dL	95 (71–125)	79 (58–102)	86 (62–111)

Continuous data are reported as median (interquartile range).
BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HF, heart failure; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

Figure 1 Kaplan–Meier curves and the corresponding 5-year Kaplan–Meier event rates for (A) the composite of cardiovascular death or hospitalization for heart failure, (B) hospitalization for heart failure, and (C) cardiovascular death stratified by presence of diabetes and/or heart failure. CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure.



Both conditions, diabetes and HF, remained independently associated with CV death/HHF and its components after multivariable adjustment (*Figure 2*). Of note, this relationship's magnitude was similar for CV death (diabetes: Adj. HR 1.80 vs. HF: Adj HR 1.85, *P*-value for heterogeneity 0.84) and all-cause death (diabetes: Adj. HR 1.82 vs. HF: Adj HR 1.90; *P*-value for heterogeneity 0.74). In contrast, the association with HHF was significantly larger for HF (Adj HR 4.07) than diabetes (Adj HR 1.97; *P*-value for heterogeneity <0.001; *Figure 2*).

A sensitivity analysis with further adjustment for NT-proBNP (diabetes: Adj HR 1.81, 95% CI 1.46 to 2.25 vs. HF: Adj HR 1.92, 95% CI 1.60 to 2.29) and HbA1c (diabetes: Adj HR 1.63, 95% CI 1.32 to 2.02 vs. HF: Adj HR 2.60, 95% CI 2.23 to 3.03) yielded similar results for CV death/HHF.

Relationship between N-terminal pro-B-type natriuretic peptide and hospitalization for heart failure and death in patients with atrial fibrillation

Patients with higher NT-proBNP quartiles (Q) had higher rates of CV death/HHF (Q1: 8.8%, Q2: 27.7%, Q3: 49.2%, Q4: 70.9%; *P*-trend <0.001; *Figure 3*). Similarly, a significant gradient of risk was observed when NT-proBNP was cut at 125 pg/mL (3.2% vs. 44.0%, *P*-logrank <0.001; *Figure 4*) or 450 pg/mL (11.3% vs. 51.1%; Supporting Information, *Figure S4*), respectively. Moreover, such stepwise increase of risk was also observed among patients who had neither diabetes nor HF (Q1: 6.8%, Q2: 19.0%, Q3: 36.6%, Q4: 62.5%; *P*-trend <0.001; Supporting Information, *Figure S5*).

In the present study, an NT-proBNP cut-point of 1284 pg/mL yielded the maximum selected logrank statistic, thus offering the best separation (Supporting Information, *Figure S6*). This threshold indicated a gradient of risk across patients irrespective of the presence or absence of diabetes and/or HF (Supporting Information, *Figure S7*). When determining the optimum cut-off using the Youden index, we determined a similar threshold for NT-proBNP of 1243 pg/mL.

After multivariable adjustment, NT-proBNP modelled as a continuous variable (Adj. HR for a 1-unit increase in standardized log-transformed biomarker 1.86, 95% CI 1.67 to 2.07; *Figure 2*) as well as using quartiles (Supporting Information, *Table S5*) remained independently associated with the risk of CV death/HHF. This relationship was similar for the individual components of the composite endpoint and all-cause death (*Figure 2*). A sensitivity analysis with further adjustment for HbA1c yielded similar results for CV death/HHF (Adj. HR for a 1-unit increase in standardized log-transformed biomarker 1.86, 95% CI 1.67 to 2.08).

With 10-fold cross-validated LASSO regression, the strongest associations for CV death/HHF were obtained for

Figure 2 Relationship between diabetes, heart failure, and NT-proBNP and cardiovascular outcomes. Cox regression models were adjusted for age, sex, estimated glomerular filtration rate, diabetes, heart failure, body mass index, prior myocardial infarction, coronary artery disease, hypertension, low-density lipoprotein cholesterol, C-reactive protein, and smoking. CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure.

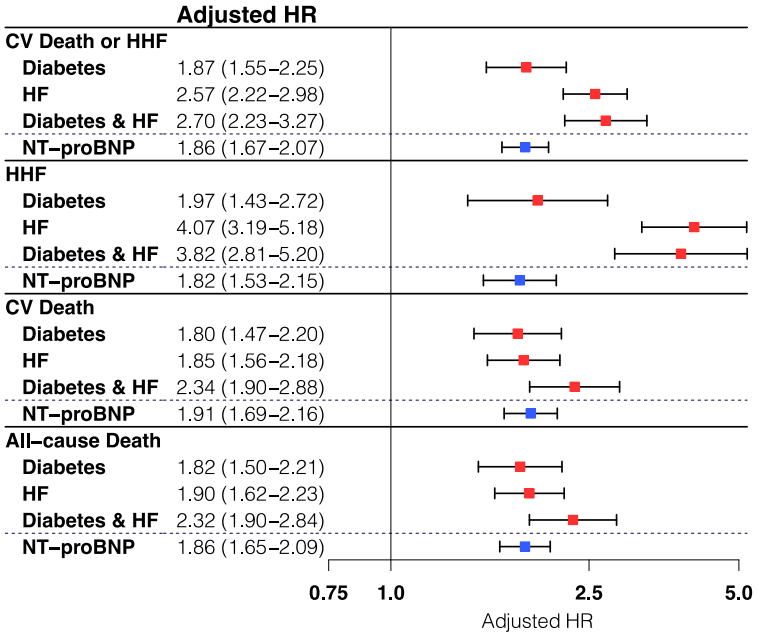


Figure 3 Kaplan–Meier curves and the corresponding 5-year Kaplan–Meier event rates for CV death/HHF stratified by quartiles of NT-proBNP. CV, cardiovascular; HHF, hospitalization for heart failure; Q, quartile.

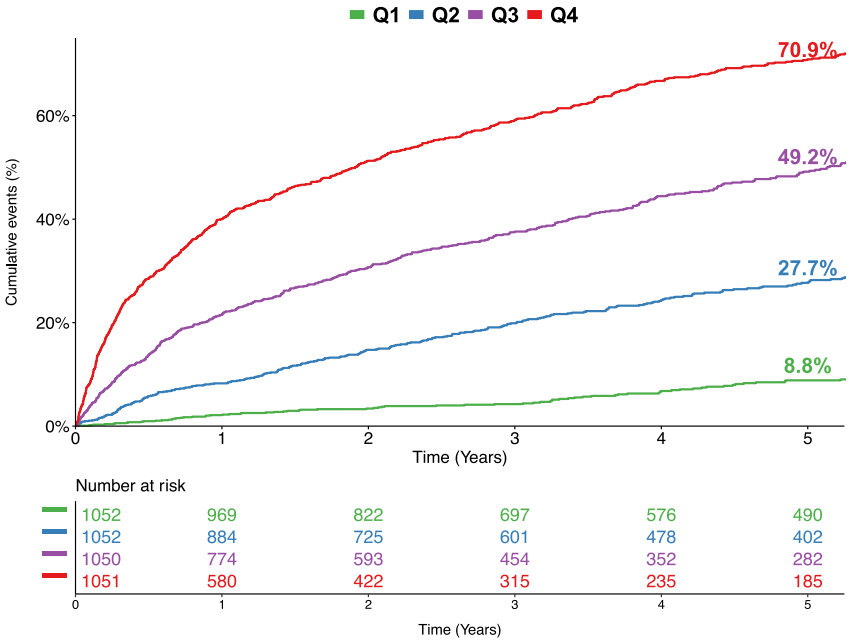
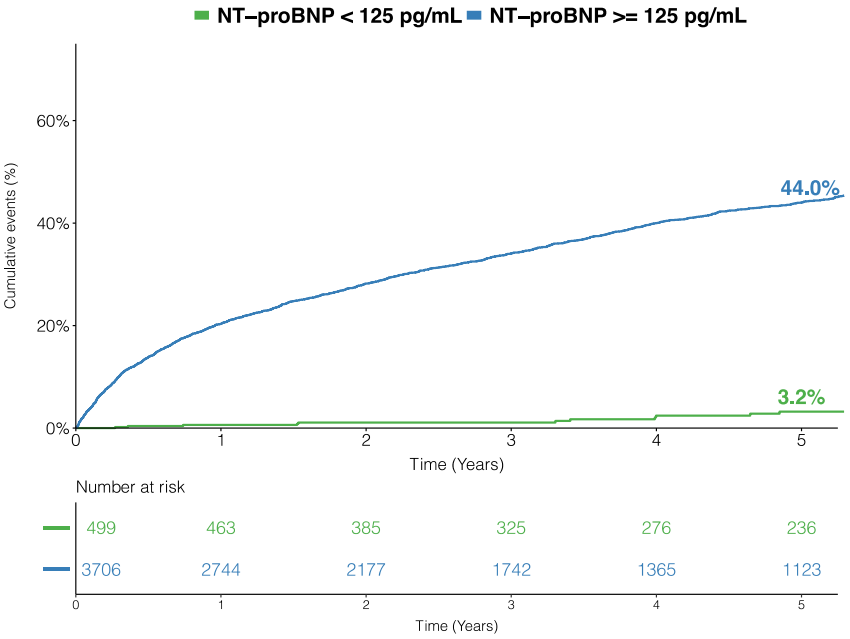


Figure 4 Kaplan–Meier curves and the corresponding 5-year Kaplan–Meier event rates for CV death/HHF stratified by an NT-proBNP cut-off of 125 pg/mL.



NT-proBNP, HF, and diabetes. In general comparable estimates were obtained from the standard maximum likelihood and the LASSO estimation approaches; with LASSO, the HR was 1.91 for NT-proBNP on a 1-SD increment scale in log-transformed biomarker, followed by an HR of 1.72 for HF, and an HR of 1.56 for diabetes.

Discriminatory performance and reclassification analyses

The diagnostic performance evaluated by receiver operating characteristic curve analysis indicated moderate to good performance of NT-proBNP and the clinical variables used for adjustment for the discrimination of CV death/HHF [area under the curve (AUC) for NT-proBNP 0.78, 95% CI 0.77 to 0.80, AUC for the clinical variables used for adjustment 0.78, 95% CI 0.76 to 0.80]. The addition of NT-proBNP to the covariates used for adjustment (including diabetes and HF) resulted in a significant AUC improvement (Δ = 0.04, *P*-value $<$0.001; *Table 2*). In addition, reclassification analyses indicated a significant improvement in risk discrimination (NRI at the event rate: 0.51, 95% CI 0.42 to 0.60, *P*-value $<$0.001; IDI: 0.06, 95% CI 0.05 to 0.07, *P*-value $<$0.001; *Table 2*; Supporting Information, *Figure S8*).

Discussion

In this retrospective study of 7412 patients, we found that a history of diabetes and HF, and NT-proBNP levels had the strongest associations with CV death/HHF in an unselected AF patient population. AF patients with either diabetes or HF were at high risk of developing subsequent HF and cardiovascular events during their lifetime. As expected, patients with HF were at higher risk of HHF than diabetes patients, while patients with diabetes and HF had a similar risk for CV death and all-cause death. The present results, thus, underscore the importance of preventing these two frequent and serious co-morbidities and point to the need to promote individualized care for this high-risk patient population. Moreover, natriuretic peptides were found to identify patients at the highest risk and, therefore, may hold promise to be helpful tools for risk stratification of these patients.

Diabetes and HF share several pathobiological mechanisms and have a bidirectional relationship in patients with and without AF as each condition independently increases the risk for the other.[14] Both diseases promote AF and are associated with an increased risk of stroke and systemic embolic events, HF, and death in patients with AF. Several pathobiological mechanisms have been proposed on how diabetes and HF are linked with AF, including structural, electromechanical, mechanical myocardial remodelling, and an imbalance in the sympathetic-parasympathetic tone.[15,16] Conversely, AF is also a significant risk factor for HF events in patients with diabetes and is assigned 1 point in the TIMI risk score for HF in diabetes.[17] The significance of diabetes and HF in patients with AF has also been highlighted in recent European guidelines. In its ABC ('*Atrial fibrillation Better Care*') pathway, the European Society of Cardiology endorses the need for appropriate management of these two co-morbidities to reduce adverse outcomes in AF patients.[18,19] Importantly, both conditions represent preventable and treatable diseases and optimum management can reduce the risks of cardiovascular complications in this vulnerable patient population.[20] Although neither American nor European AF guidelines elaborate on the use of sodium-glucose co-transporter 2 inhibitors (SGLT2i), this class of drugs has been shown to effectively reduce the risk of CV death and HF events in patients with diabetes and HF (irrespective of the presence or absence of AF).[21–24] Moreover, a secondary analysis of the *Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58* (DECLARE-TIMI 58) trial indicated that treatment with the SGLT2i dapagliflozin decreased the incidence of reported AF episodes in patients with type 2 diabetes,[25] a finding that has also been supported by an analysis of the Food and Drug Administration pharmacovigilance database.[26] Although these results require confirmation in a dedicated randomized controlled trial, several mechanisms have been suggested how SGLT2i may modify the risk of AF, including improved glucose control, lowering blood pressure and weight, modest diuretic effects, mitigation of inflammation and oxidative stress, enhanced myocardial efficiency and oxygen delivery, as well as a preserved kidney function.[27–29] Furthermore, a secondary analysis of the *Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction* (DAPA-HF) trial showed that dapagliflozin lowered the incidence of diabetes in patients with HF and reduced ejection fraction.[30] In addition to SGLT2i, catheter ablation emerged as another important prevention strategy for cardiovascular death and HHF in patients with AF. Catheter ablation was associated with significantly lower rates of HHF and death

Table 2 C-statistics and reclassification analyses for the composite outcome of cardiovascular death or hospitalization for heart failure

	C-statistic (95% CI)	ΔAUC	*P-value*	IDI (95% CI)	*P*-value	NRI at the event rate (95% CI)	*P*-value
Model A (incl. Variables used for adjustment)[a]	0.78 (0.76 to 0.80)						
Model A (incl. Variables used for adjustment)[a] + NT-proBNP	0.81 (0.80 to 0.83)	0.04	<0.001	0.06 (0.05 to 0.07)	<0.001	0.51 (0.42 to 0.60)	<0.001

IDI, integrated discrimination increment; NRI, net reclassification index.
NT-proBNP was included as a log-transformed variable. IDI and NRI and the corresponding *P*-values are reported for the comparisons between Model A and Model B with NT-proBNP.
[a]The model consists of age, sex, diabetes, heart failure, estimated glomerular filtration rate, body mass index, C-reactive protein, prior myocardial infarction, coronary artery disease, hypertension, low-density lipoprotein cholesterol, and smoking.

in patients with HF and an LVEF ≤35%.[31,32] Evidently, besides preventing and treating diabetes and HF, the reduction of thromboembolic risk and mitigation of risk factors for AF, including hypertension, hyperlipidaemia, obesity, sleep apnoea, and alcohol abstinence, are imperative.[33,34]

While oral anticoagulants effectively reduce the risk of stroke and systemic thromboembolic events, patients with AF have a disproportionate burden of HF and CV death.[33,35] As such, risk stratification of patients with AF should also consider the risk of HF. To date, several risk scores for assessment of risk for stroke and bleeding exist, but HF risk scores are scarce for this patient population.[36] Several important studies, including biomarker studies of the randomized non-vitamin K antagonist oral anticoagulants versus warfarin trials, found a significant relationship between NT-proBNP levels and the incidence of AF, stroke, bleeding events, and death,[37–39] but the predictive value of NT-proBNP for HF events in patients with AF has been less well studied and remains elusive. The present results suggest that NT-proBNP levels (with a proposed threshold of ~1250 pg/mL providing the largest discrimination of risk) may help identify AF patients at highest risk of CV death/HHF irrespective of the presence or absence of diabetes or HF.

In light of the present findings, the inclusion of NT-proBNP, as a marker of haemodynamic stress, thus, may aid clinical decision making.

Limitations

Despite the large patient population and extended follow-up, several limitations should be addressed. Firstly, patients were not followed using a standardized follow-up, and the available data set allows only limited information on the burden of AF and baseline medication. Moreover, clinical outcomes were not adjudicated and therefore inaccurate diagnoses as well as underreporting are possible. However, we found that the event rates were similar to those reported in a recently published contemporary study.[40] We also did not have echocardiographic assessment of the left atrial structure and function or information on medications for all patients.[41,42] Also, laboratory measurements were only available for a subset of patients introducing possible selection bias. Patients were included from a single tertiary academic site, and therefore, these results might not be generalizable to the general population. Finally, despite multivariable adjustment for clinical variables and biomarkers, residual confounding is possible.

Conclusion

These findings of this retrospective study suggest that AF patients with either diabetes or HF should be managed not only for their risk of stroke and systemic embolic events but also for CV death/HHF. NT-proBNP may provide improved risk assessment in an unselected AF patient population.

Conflict of interest

Dr. Hofer has no conflict of interest. Dipl. Ing. Pailer has no conflict of interest. Dr. Sulzgruber reports grants from Daiichi Sankyo, grants from AstraZeneca and grants from Boehringer-Ingelheim outside the submitted work. Dr. Gerges has received compensation for scientific symposia from Actelion, AOPOrphan Pharmaceuticals, AstraZeneca, and GlaxoSmithKline. Dr. Winter has no conflict of interest. Dr. Giugliano reports grant support from Anthos. Amgen, and Daiichi Sankyo to his institution, and honoraria for CME lectures and/or consulting from Amgen, Boeheringer-Ingelheim, Bristol Myers Squibb, CryoLife, Daiichi Sankyo, Janssen, Pfizer, SAJA, Servier, and St Lukes Hospital System of Kansas City. Dr. Gottsauner-Wolf reports no conflicts of interest for this study. Dr. Hülsmann reports consultant, speaker, and research support by Roche Diagnostics, consultant and speaker fee, by Boehringer, Astra Zeneca, Vifor, Novartis, Pfizer, Merck and Bayer. Dr. Kazem reports no conflict of interest. Dr. Koller reports no conflict of interest. Dr. Schönbauer reports no conflict of interest. Dr. Niessner reports personal fees from Bayer, personal fees from BMS, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Daiichi Sankyo and personal fees from Pfizer outside the submitted work. Dr. Hengstenberg reports no conflicts of interest for this study. Dr. Zelniker reports research grants from the Austrian Science Funds and the German Research Foundation, honoraria for serving on advisory boards from Boehringer Ingelheim, personal fees from AstraZeneca, Boehringer Ingelheim, and Sun Pharmaceutical Industries, and educational grants from Eli Lilly and Company.

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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: Baseline medication for patients included after 2012.

Table S2: Baseline characteristics of patients with diabetes, HF and both diabetes and HF.

Table S3: Baseline characteristics stratified by quartiles of NT-proBNP.

Table S4: Baseline characteristics of patients with available NT-proBNP values vs. patients without available NT-proBNP values.

Table S5: Relationship between quartiles of NT-proBNP and the risk of death and hospitalization for heart failure.

Figure S1: Distribution of NT-proBNP by presence or absence of diabetes and heart failure (HF).

Figure S2: Kaplan Meier curves and the corresponding 5-year Kaplan–Meier event rates for all-cause death stratified by presence of diabetes and/or heart failure.

Figure S3: Kaplan Meier curves and the corresponding 5-year Kaplan–Meier event rates for CV death/HHF stratified by presence of HF and LVEF ≤40%.

Figure S4: Kaplan Meier curves and the corresponding 5-year Kaplan–Meier event rates for CV death/HHF stratified by an NT-proBNP cut-off value of 450 pg/mL.

Figure S5: Kaplan Meier curves and the corresponding 5-year Kaplan–Meier event rates for CV death/HHF in low risk patients without diabetes or HF stratified by quartiles of NT-proBNP.

Figure S6: Top: Distribution of NT-proBNP concentrations according to the maximally selected logrank statistic; Bottom: Standardized logrank statistic across NT-proBNP levels.

Figure S7: Kaplan Meier curves and the corresponding 5-year Kaplan–Meier event rates for CV death/HHF in patients with A.) no diabetes and no HF, B.) diabetes (without HF), C.) HF (without diabetes), and D.) both, diabetes and HF stratified by NT-proBNP levels.

Figure S8: Calibration plot and the Hosmer–Lemeshow test for the calibration of the discriminatory performance of NT-proBNP in addition to the clinical covariates for CV death/HHF.

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