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ORIGINAL PAPER

Prognostic role of N-terminal pro-brain natriuretic peptide in asymptomatic hypertensive and diabetic patients in primary care: impact of age and gender

Results from the PROBE-HF study

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Abstract
Background The association between natriuretic peptides and clinical outcome in asymptomatic hypertensive and diabetic patients with no clinical evidence of heart failure (HF) is still unclear. We assessed the prognostic value of NT-pro BNP, and its interactions with age and gender, in a cohort of asymptomatic, stage A/B HF hypertensive and diabetic patients enrolled in primary care.
Methods NT-proBNP was measured in 1012 asymptomatic subjects with systemic hypertension and/or type-2 diabetes (age 66.6 ± 7.8 years, 48 % males) with no clinical evidence of HF. Patients were prospectively followed over 49.8 ± 6.7 months for the development of cardiac death, HF hospitalization, and nonfatal myocardial infarction.
Results Patients with NT-proBNP above the 80th age- and gender-specific percentile showed a threefold risk of events as compared to those with NT-proBNP under this cut-off [hazard ratio 3.2 (2.6–8.3), $p < 0.0001$]. In multivariable analysis, NT-proBNP added independent and incremental prognostic information to a predictive model including established risk factors ($p < 0.0001$). After stratification by age, increased NT-proBNP predicted outcome among patients in the second and third age tertiles, but not among those in the first tertile. Increased NT-proBNP was associated with a 3.6-fold risk in women and a 2.9-fold risk in men. Addition of the gender-NT-proBNP interaction to prognostic models further improved prediction of events ($p = 0.014$).
Conclusions NT-proBNP measurement adds independent and incremental information for the prediction of clinical outcome in asymptomatic, stage A-B HF hypertensive and diabetic patients taken from primary care. This prognostic value might be further evident in the elderly and among women.

Keywords Natriuretic peptide · Hypertension · Diabetes · Risk stratification · Primary care

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Introduction

Assessment of natriuretic peptide plasma concentrations plays a key role in the management of patients with chronic heart failure (HF). Evidences support their use as important diagnostic tools in primary care [1, 2], and as useful markers for cardiovascular risk stratification in subjects with established HF [3, 4]. A prognostic value of natriuretic peptides was also shown in the general population by large community-based analyses [5–8], and in a wide spectrum of pathophysiological cardiovascular conditions, some of which reflect preclinical stages of HF [9–12]. However, their prognostic value in the asymptomatic stages of sytemic hypertension and type-2 diabetes is still unknown. Moreover, an additional issue for their use in

clinical practice is related to the confounding effects of age and gender. Previous studies pointed out the importance of using age- and gender-specific cut-off values when using natriuretic peptides as diagnostic markers for the identification of cardiac dyspnoea or for the prediction of left ventricular systolic dysfunction [13, 14]. This raises the question of whether age and gender may affect not only the diagnostic performance, but also the prognostic value of natriuretic peptides. Nonetheless, few evidences exist regarding the impact of age and gender on the association between natriuretic peptides and risk of clinical events.

The aim of this study was to explore the prognostic role of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in a cohort of hypertensive and/or diabetic patients with stage A/B HF enrolled in a primary care setting. The impact of age and gender on the association between NT-proBNP and clinical outcome was also assessed.

Methods

Study population

Details on the PROBE-HF population have been reported elsewhere [15]. Briefly, 1012 asymptomatic subjects affected by arterial hypertension and/or type-2 diabetes mellitus, free from any other cardiovascular or systemic disease and with no clinical evidence of HF, were prospectively enrolled from a primary care population database involving 110 general practitioners for a population of about 130,000 citizens in the Florence area, Italy. To be considered for enrolment, diabetic patients had to be on treatment with antidiabetic medications at least for the last 6 months, whereas hypertensive patients had to be on treatment at least for the last 6 months with 2 or more antihypertensive agents. These patients could be considered at high risk of developing HF (stages A/B) on the basis of current ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure [16]. Systemic hypertension was diagnosed according to the European Society of Hypertension–European Society of Cardiology Guidelines [17] as systolic blood pressure $\geq$140 mmHg or diastolic blood pressure values $\geq$90 mmHg in multiple measurements, or as current antihypertensive therapy in the presence of documented history of hypertension. A documented history of fasting plasma glucose $\geq$126 mg/dl or 2-h plasma glucose $\geq$200 mg/dl was considered to confirm the diagnosis of type-2 diabetes mellitus, according to WHO Guidelines [18]. All patients underwent a targeted history, a physical examination, and an echocardiographic evaluation. For identification of stage B patients, left ventricular (LV) hypertrophy, LV enlargement, reduced LV ejection fraction (<55 %), LV diastolic dysfunction, and asymptomatic valve disease of at least moderate severity were defined according to current guidelines [19–22]. The study protocol complied with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and was approved by the Ethics Committee of the Local Health Authority of Florence (prot. 28/03). All subjects gave their written informed consent for participation into the study.

NT-proBNP assay

Blood was drawn from the antecubital vein into EDTA vacutainers. NT-proBNP concentrations were measured using a noncompetitive assay based on electrochemiluminescence detection and polyclonal antibodies (Elecsys Modular-E, Roche Diagnostic, Basel, Switzerland). High reproducibility of this assay has been reported [23]. NT-proBNP plasma concentration was considered both as a logarithmic continuous variable and a categorical variable. For the categorical analysis, participants were identified as having increased or normal NT-proBNP according to age- and gender-specific 80th percentile values of NT-proBNP plasma concentration, as previously suggested in several studies [24–26]. Additional event-free survival analyses were performed after categorization of patients in three groups according to age- and gender-independent cut-off values identified by NT-proBNP plasma concentration tertiles.

Follow-up

All patients were prospectively followed up for development of major adverse cardiovascular events. The predefined endpoint was a composite of cardiac death and hospitalization for HF or acute coronary syndrome. Information on mortality was obtained through the Florence Registry Office. For unambiguous identification of the causes of hospitalization, the following ICD-9 CM discharge codes provided by the Regional Hospital Discharge System were considered: 428 (heart failure), 410 and 411 (myocardial infarction and other coronary syndromes). Further information was obtained by chart review, hospital records, and phone interview of the referring physician and/or relatives. Only documented events were considered in the analysis.

Statistical analysis

Data were expressed as mean values $\pm$ SD for normal variables, and as median [interquartile range] for non-parametric variables. As the distribution of NT-proBNP plasma concentration was right-skewed and deviated from normality at the Kolmogorov–Smirnov test ($p < 0.0001$),

analyses were performed after logarithmic transformation ($p = 0.57$ for deviation of Log NT-proBNP from normal distribution). Comparisons were performed using the Student t test for normal variables, the Mann–Whitney U test for nonparametric variables, and the Chi-square test for categorical variables. For time-independent analysis, receiver-operating characteristic (ROC) analysis was performed to assess the performance of NT-proBNP for the prediction of the clinical endpoint. The areas under the curves (AUCs) obtained in different subsets were compared using the method of Hanley and McNeil. Logistic regression was used to explore the association of NT-proBNP with the probability of clinical events, expressed as odds ratio (OR). Relative risks (RRs) were calculated using 2×2 contingency tables by standard methods. Loglinear analysis using a three-dimensional $2 \times 2 \times 2$ table was performed to explore the interaction between NT-proBNP, age, and rate of events, and that between NT-proBNP, gender, and rate of events.

For time-dependent analysis, the association between NT-proBNP and risk of events was explored by Cox regression and expressed as hazard ratio (HR). A first multivariable model was obtained using the "Enter" procedure by considering all variables showing a p value of <0.10 at univariable Cox regression. To explore potential interactions between variables, a second analysis was performed by testing all possible two-way interaction terms as additional predictors over the first model. The proportionality assumption was checked using the Grambsch-Therneaus test. Two different methods were used to assess the incremental prognostic value of NT-proBNP in the study population when added to a multivariable model including established risk factors. First, the overall goodness-of-fit was compared between models by the likelihood ratio test. Second, we assessed discrimination for each model by determining Harrell's c-statistic at $t = 4$ years, corresponding to mean follow-up duration. The increase in c-statistic after addition of NT-proBNP to the model was taken as a measure of discrimination improvement, and its significance was tested using the method of DeLong. In addition, calibration was assessed for each model using a modified Hosmer–Lemeshow statistic, in which the observed outcome was compared to the event probabilities predicted by Cox models across ten groups given by the deciles of predicted probabilities. In this test, p values higher than 0.05 indicate good calibration. Kaplan–Meier curves and the log-rank test were used to compare survival probability between groups. For patients who had more than one event, only the first event was considered into the analysis. The significance level was set at 0.05. All statistical tests were two-tailed. All analyses were performed using SPSS for Windows release 13.0 (SPSS Inc., Chicago, IL).

Results

General characteristics

Table 1 shows the main characteristics of the study population and the comparison of variables between the groups with increased and normal NT-proBNP, as identified by the age- and gender-specific 80th percentile. Compared to patients with normal NT-proBNP, those with increased NT-proBNP showed lower LV ejection fraction, higher LV mass index and E/A ratio, and higher prevalence of stage B HF. Patients with increased NT-proBNP also had higher prevalence of use of betablockers and lower heart rate than those with normal NT-proBNP.

Median NT-proBNP plasma concentration in the overall population was 78.6 (43.8–141.8) pg/ml (range 5.0–3872.0). As expected, NT-proBNP showed a positive relationship with age (Fig. 1, top panel), and was higher in women than men [91.9 (51.2–173.9) vs 65.7 (35.9–119.9) pg/ml, $p < 0.0001$] (Fig. 1, middle panel). Age- and gender-specific 80th percentile values in the overall population are shown in Fig. 1, bottom panel. These values increased with age and were higher in women than men across all age strata, but remained below previously reported thresholds for HF diagnosis [24, 27].

Prognostic value of NT-proBNP in the overall population

During a follow-up of 49.8 ± 6.7 months, 128 events (four cardiac deaths, 45 hospitalizations for HF, and 79 acute coronary syndromes) occurred in 72 patients. Two patients (0.2 %) were lost to follow-up. Forty-three patients showed at least an episode of atrial fibrillation, which in 19 cases was observed during a hospitalization for HF. ROC analysis showed a good accuracy of NT-proBNP for the prediction of the clinical endpoint (Fig. 2, left panel). Logistic regression showed that Log NT-proBNP as a continuous variable was a predictor of outcome [OR 2.2 (1.7–2.8), $p < 0.0001$]. Considering NT-proBNP as a dichotomous variable, the rate of the endpoint was threefold higher among patients with increased NT-proBNP than those with normal NT-proBNP [3.7 vs 1.2 events per patient-years; RR 3.0 (1.9–4.6), $p < 0.0001$]. As a result of the relatively small event rate, the presence of an increased NT-proBNP showed a low positive predictive value (15.9 %) and a high negative predictive value (94.9 %).

In time-dependent analysis, univariable Cox regression confirmed that the logarithm of NT-proBNP plasma concentration as a continuous variable was a predictor of events [HR 2.7 (1.9–3.6), $p < 0.0001$]. Kaplan–Meier curves also confirmed that the risk of events in patients

Table 1 General characteristics in the overall population and in the groups with increased and normal NT-proBNP plasma concentration, as identified by the age- and gender-specific 80th percentile

	Overall population ($n = 1012$)	High NT-proBNP ($n = 205$)	Low NT-proBNP ($n = 807$)	p
Age (years)	66.6 ± 7.8	66.8 ± 7.8	66.6 ± 7.8	0.64
Male gender (*n*)	486 (48.1 %)	98 (48.0 %)	388 (48.1 %)	0.99
Body surface area (m^2)	1.84 ± 0.18	1.84 ± 0.19	1.84 ± 0.18	0.66
Body mass index (kg/m^2)	28.2 ± 4.5	27.9 ± 5.0	28.3 ± 4.3	0.24
Heart rate (bpm)	70.0 ± 11.0	67.0 ± 10.7	70.8 ± 10.9	<0.0001
Systolic blood pressure (mmHg)	141.4 ± 14.9	142.5 ± 15.5	141.2 ± 14.7	0.26
Diastolic blood pressure (mmHg)	82.3 ± 8.3	82.8 ± 9.2	82.2 ± 8.1	0.43
Hypertension (*n*)	927 (91.8 %)	188 (92.2 %)	739 (91.7 %)	0.94
Diabetes (*n*)	411 (40.7 %)	72 (35.3 %)	338 (41.9 %)	0.10
Hypercholesterolemia (*n*)	401 (39.7 %)	72 (35.3 %)	329 (40.8 %)	0.17
Cigarette smoking (*n*)	162 (16.0 %)	44 (21.6 %)	133 (16.5 %)	0.11
Stage B heart failure (*n*)	585 (57.8 %)	136 (66.3 %)	449 (55.6 %)	0.0071
Pharmacological agents				
ACE inhibitors (*n*)	525 (52.0 %)	100 (49.0 %)	425 (52.7 %)	0.39
Angiotensin II receptors antagonists (*n*)	143 (14.2 %)	34 (16.6 %)	109 (13.5 %)	0.30
Beta blockers (*n*)	284 (28.1 %)	101 (49.5 %)	183 (22.7 %)	<0.0001
Calcium antagonists (*n*)	234 (23.2 %)	46 (22.5 %)	188 (23.3 %)	0.89
Diuretics (*n*)	602 (59.6 %)	117 (57.4 %)	485 (60.2 %)	0.51
Statins (*n*)	114 (11.3 %)	26 (12.7 %)	88 (10.9 %)	0.54
Oral antidiabetics (n)	325 (32.2 %)	53 (26.0 %)	272 (33.7 %)	0.042
Insulin (*n*)	28 (2.8 %)	8 (3.9 %)	20 (2.5 %)	0.38
LV ejection fraction (%)	65.2 ± 4.9	63.8 ± 6.3	65.5 ± 4.5	<0.0001
Indexed LV mass (g/m^2)	105.1 ± 21.4	112.1 ± 26.3	103.4 ± 19.6	<0.0001
Relative wall thickness	0.44 ± 0.06	0.43 ± 0.06	0.44 ± 0.06	0.20
Mitral E/A ratio	0.84 ± 0.29	0.96 ± 0.44	0.82 ± 0.23	<0.0001
E wave deceleration time (ms)	231.1 ± 57.4	235.0 ± 62.9	230.2 ± 56.0	0.28
Isovolumic relaxation time (ms)	88.3 ± 18.9	88.9 ± 20.1	88.2 ± 18.5	0.61

LV left ventricular

with increased NT-proBNP was threefold higher than in those with normal NT-proBNP (Fig. 2, right panel). Notably, similar results were found using age- and gender-independent cut-offs, as identified by NT-proBNP plasma concentration tertiles. There was no difference in the risk of events between the first (<54.4 pg/ml) and the second tertile [54.4–115.6 pg/ml; HR 1.49 (0.61–3.65), $p = 0.38$], whereas a considerable increase was found in the third tertile [>115.6 pg/ml; HR 4.93 (2.30–10.56), $p < 0.0001$].

Impact of age on the prognostic value of NT-proBNP

The ROC performance of NT-proBNP for the prediction of the clinical endpoint improved for increasing age tertiles (Fig. 3, top panel). The subset with increased NT-proBNP showed a higher risk of events than that with normal NT-proBNP among patients in the third and second age tertile, whereas no significant difference was observed among patients in the first tertile (Fig. 3, bottom panel). Log-linear analysis confirmed a significant interaction between the presence of increased or normal NT-proBNP, age tertiles, and rate of events ($p < 0.0001$). All tertiles showed a low positive predictive value (<25 % for all) and a high negative predictive value (first, 97.2 %; second, 94.7 %; third, 93.1 %).

Univariable Cox regression showed that Log NT-proBNP was a predictor of the clinical endpoint among patients in the third and second age tertiles [HR 2.5 (1.7–3.5), $p < 0.0001$, and 1.7 (1.1–2.7), $p = 0.030$, respectively], but not among those in the first tertile [HR 1.5 (0.9–2.7), $p = 0.12$]. Kaplan–Meier curves also confirmed that increased NT-proBNP was associated with a

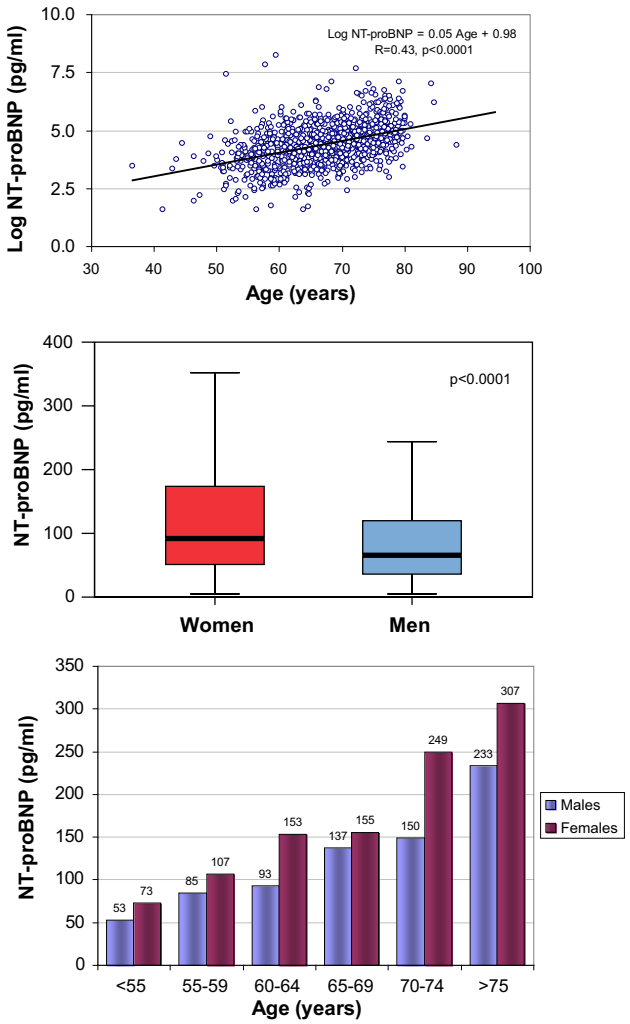

Fig. 1 *Top panel* relationship between age and NT-proBNP plasma concentration in the study population. *Middle panel* Comparison of NT-proBNP plasma concentration between women and men in the study population. *Box plots* show the median values (*horizontal thick lines*), the interquartile ranges (*colored boxes*) and the whiskers (*lines* extending out the *top* and *bottom* of the *box* to 1.5 times the interquartile range, excluding outliers and extreme values). *Bottom panel* Age- and gender-specific 80th percentiles of NT-proBNP distribution in the PROBE-HF population

fourfold risk increase among patients in the third age tertile and a nearly threefold risk increase among those in the second age tertile, whereas no significant impact on risk was found in the first tertile (Fig. 4).

Impact of gender

Gender-specific ROC curves showed that the performance of NT-proBNP for the prediction of the clinical endpoint was better in women than men (Fig. 5, top panel). The RR in patients with increased NT-proBNP as compared to those with normal NT-proBNP also tended to be higher in women than men (Fig. 5, bottom panel). Loglinear analysis confirmed a significant interaction between the presence of increased or normal NT-proBNP, gender, and rate of events ($p < 0.0001$). The positive predictive value was <20 % in both genders, whereas the negative predictive value was 93.6 % in men and 96.2 % in women.

Univariable Cox regression showed that Log NT-proBNP was a predictor of the endpoint in both women (HR 2.7, 95 % CI 1.9–3.6, $p < 0.0001$) and men (HR 1.9, 95 % CI 1.4–2.6, $p < 0.0001$). Despite a higher overall incidence of events in men than women, Kaplan–Meier curves showed that increased NT-proBNP was associated with a 3.6-fold risk increase in women and a 2.9-fold risk increase in men (Fig. 6).

Multivariable analysis

The results of multivariable Cox regression are shown in Table 2. In a model including established risk factors, NT-proBNP was the strongest independent predictor of clinical events. Compared to the model including the same variables except NT-proBNP, insertion of NT-proBNP yielded a significant improvement in both goodness-of-fit ($p < 0.0001$ by the likelihood ratio test) and discrimination (increase in c-statistic 0.05, $p < 0.0001$) for the prediction of events. In an additional analysis performed by considering all potential two-way interactions, only the Log NT-proBNP-gender interaction further improved both model goodness-of-fit ($p = 0.014$ by the likelihood ratio test) and discrimination (increase in c-statistic 0.02, $p = 0.035$), suggesting that the prognostic effect of NT-proBNP differed between women and men. All models were well calibrated ($p > 0.05$ for all by the Hosmer–Lemeshow test) and showed good stability by collinearity diagnostic.

Discussion

Main findings

Symptomatic HF is known to be associated with increased risk of recurrent cardiac hospitalizations and cardiac death [28, 29]. However, the ACCF/AHA classification of HF in four stages, as opposed to the traditional New York Heart Association classification, highlighted the clinical relevance of correctly identifying subjects at increased risk for HF who still have no symptoms of HF [16]. The rationale of this approach is based on the belief that early identification of increased risk and correct categorization of patients in the early stages of HF—such as those with hypertension or diabetes mellitus—may improve prevention and reduce the risk of HF progression. In this view, identification of prognosticators in the early stages of HF

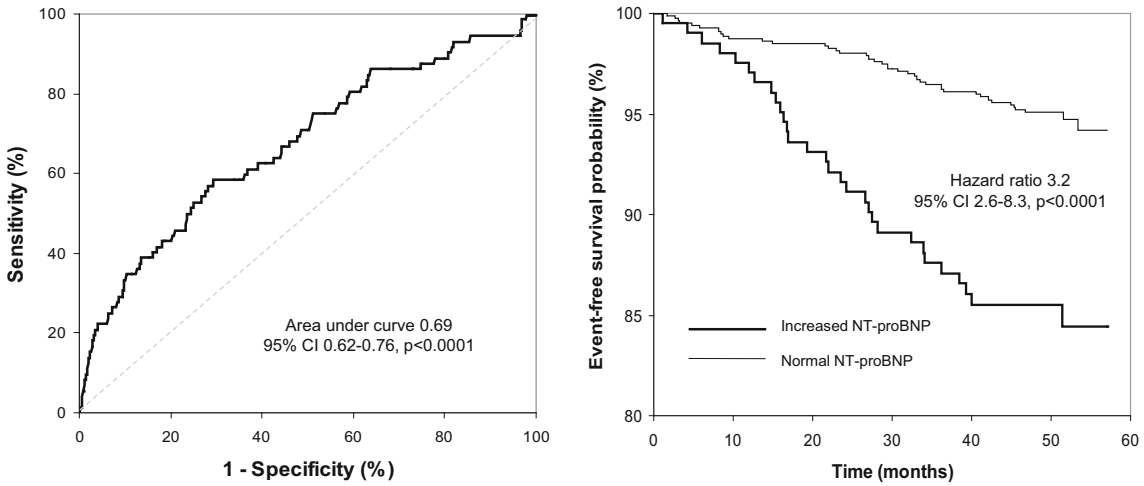

Fig. 2 *Left panel* receiver-operating characteristic curve showing the performance of NT-proBNP for the prediction of the clinical endpoint. *Right panel* Kaplan–Meier curves showing event-free survival probability in patients with increased and normal NT-proBNP plasma concentration. Increased NT-proBNP was defined as a value above the age- and gender-specific 80th percentile

could improve the clinical management of these patients. This study explored the association between NT-proBNP and risk of cardiac events in a population of asymptomatic, stage A–B hypertensive and/or diabetic patients enrolled in a primary care setting. We found that in these patients: (1) NT-proBNP adds independent and incremental prognostic information for the prediction of clinical outcome; (2) the prognostic value of NT-proBNP may increase with age and may be stronger in women than men.

NT-proBNP and clinical outcome

In our study, NT-proBNP plasma concentration was independently associated with the risk of cardiac death and cardiac events, and improved the prediction of clinical outcome when added to established cardiovascular risk factors such as age, gender, diabetes mellitus, HF stage, LV ejection fraction, indexed LV mass, and LV diastolic dysfunction degree. In particular, a high NT-proBNP—defined as a value above the age- and gender-specific 80th percentile—was associated with an overall threefold increase in the risk of clinical events. The finding of an association between NT-proBNP and clinical outcome in our population of asymptomatic hypertensive and diabetic patients taken from primary care extends previous evidences obtained in studies that enrolled hypertensive or diabetic patients in other settings regardless of symptoms and HF stage [11, 12], and is in accordance with data obtained in other pathophysiological conditions representing preclinical stages of HF [9, 10, 24, 30–32]. It is worthy of note that a considerable proportion of our population had values of NT-proBNP plasma concentration that were lower than previously reported age- and gender- reference cut-offs obtained in healthy individuals [33]. Also, about two-thirds of our patients had a value of NT-proBNP <125 pg/ml, which is commonly used as a partition value to rule out LV dysfunction in primary care [34]. These results might confirm previous evidences showing that a prognostic value of natriuretic peptide could exist even within physiological ranges of plasma concentration [2, 8].

Impact of age and gender

Our findings also support the hypothesis that the prognostic value of NT-proBNP in asymptomatic patients with hypertension and diabetes may be further evident in older subjects and in women. The confounding effect of age and gender on the diagnostic value of natriuretic peptide is established [13, 14, 34, 35], but few studies explored the impact of age and gender on the association between NT-proBNP and clinical outcome, providing inconsistent results. Older age was reported to reduce [36] or to have no effect [37] on the prognostic value of NT-proBNP in subjects with clinically established HF, whereas a stronger association with outcome after 70 years of age was observed among healthy individuals [38]. On the other hand, previous analyses found no gender differences in the prognostic value of NT-proBNP among patients with HF [39], whereas a better prediction of clinical events in women than men was reported in the general population [40]. Conflicting data on the effect of gender in this context were reported for BNP as well [41, 42]. It is likely that these inconsistent results could reflect not only differences in the clinical characteristics of the populations, but also discrepancies in clinical endpoints, duration of follow-up periods, and confounding variables considered in multivariable models.

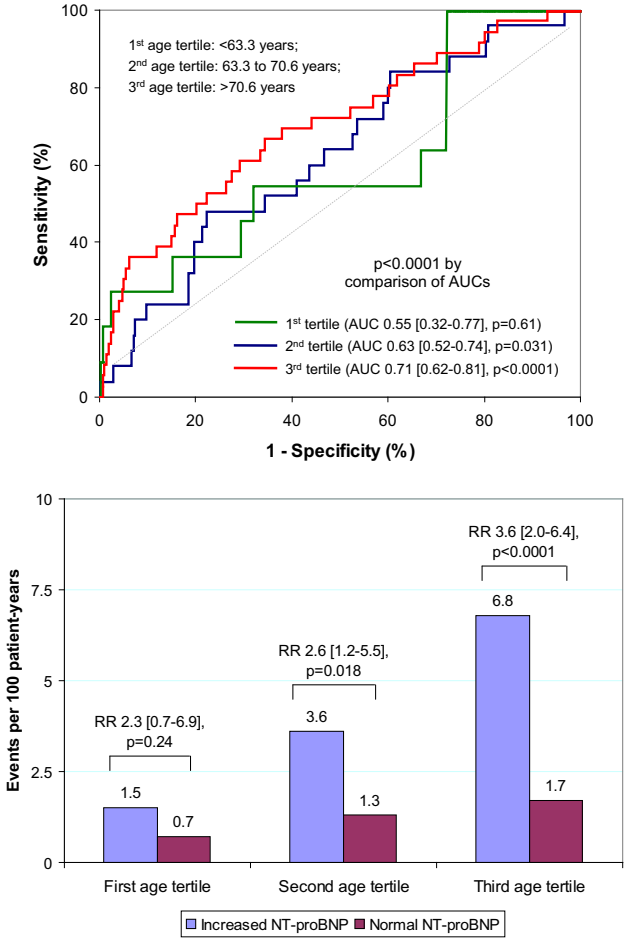

Fig. 3 *Top panel* receiver-operating characteristic curves showing increasing performance of NT-proBNP for the prediction of the clinical endpoint for increasing age tertiles. The best cut-offs were >76.7 pg/ml in the first tertile (54.5 % sensitivity and 68.3 % specificity), >132.7 pg/ml in the second tertile (48.0 % sensitivity and 78.5 % specificity), and >165.2 pg/ml in the third tertile (66.6 % sensitivity and 67.0 % specificity). *Bottom panel* Differences in event rate between patients with NT-proBNP above and below the age- and gender-specific 80th percentile after stratification by age tertiles. *AUC* area under the curve, *RR* relative risk

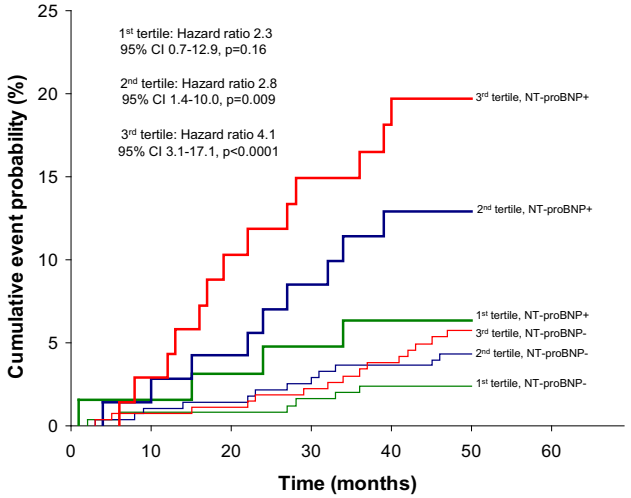

Fig. 4 Kaplan-Meier curves showing cumulative incidence of events in patients with NT-proBNP above and below the age- and gender-specific 80th percentile after stratification by age tertiles. *CI* confidence interval

To our knowledge, this study is the first to assess the impact of age and gender on the prognostic value of NT-proBNP in a population with stage A-B HF. In our cohort of asymptomatic hypertensive and diabetic patients, a NT-proBNP above the age- and gender-specific 80th percentile was not associated with clinical outcome among patients aged <63 years, but led to a threefold risk increase among those 63- to 71-year-old, and to a fourfold risk increase among those >71 year-old. Also, a NT-proBNP above the age- and gender-specific 80th percentile was associated with a 3- to 6-fold risk increase in women and a 2.9 risk increase in men, with evidence of a significant interaction between gender and NT-proBNP plasma concentration in multivariable survival analysis. The evidence of such interaction suggests that the prognostic effect of NT-proBNP could be better described in separate models for men and women, rather than in a single model for the overall population, and that might be more evident in women than men. Considering the relatively large confidence intervals and the potential drawbacks of comparing HRs derived from models obtained in different groups, caution is needed in interpreting these findings. However, it is possible that these differences reflect age- and gender-specific regulation of NT-proBNP release and formation or more complex interaction with other factors [36, 43–46]. It could also be postulated that enrollment of asymptomatic patients and exclusion of patients with significant comorbidities in our study population might have reduced the impact of age-related confounders potentially able to decrease NT-proBNP performance.

Clinical implications and study limitations

The findings of this study suggest that an elevated NT-proBNP plasma concentration in asymptomatic patients with hypertension and/or diabetes should alert physicians about an increased risk of cardiovascular events. In this subset, a more aggressive preventive treatment aimed at preventing the progression towards established HF might be reasonable [47]. This study also suggest that this risk increase might be even more evident among women and elderly patients, a finding that could be considered of further importance because female gender and advanced age are commonly associated with suboptimal quality of diabetes and hypertension management despite worse cardiovascular risk profile [48, 49]. However, whether a reduction of NT-proBNP

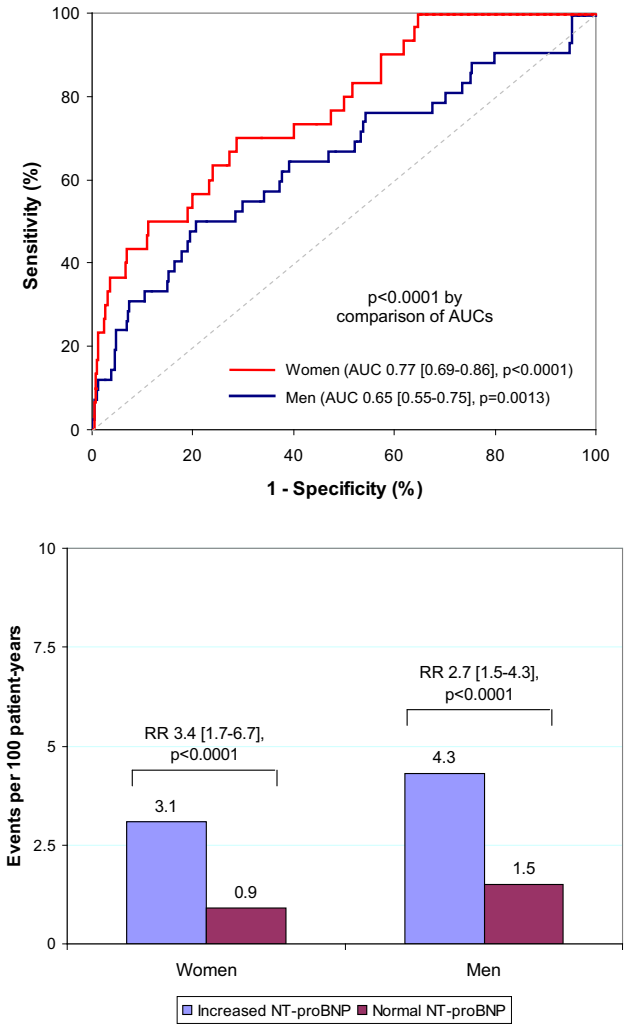

Fig. 5 *Top panel* receiver-operating characteristic curves showing better performance of NT-proBNP for the prediction of the clinical endpoint in women than men. The best cut-offs were >141.4 pg/ml in women (70.0 % sensitivity and 71.3 % specificity) and >128.9 pg/ml in men (50.0 % sensitivity and 79.3 % specificity). *Bottom panel* Differences in event rate between patients with NT-proBNP above and below the age- and gender-specific 80th percentile among men and women. *AUC* area under the curve, *RR* relative risk

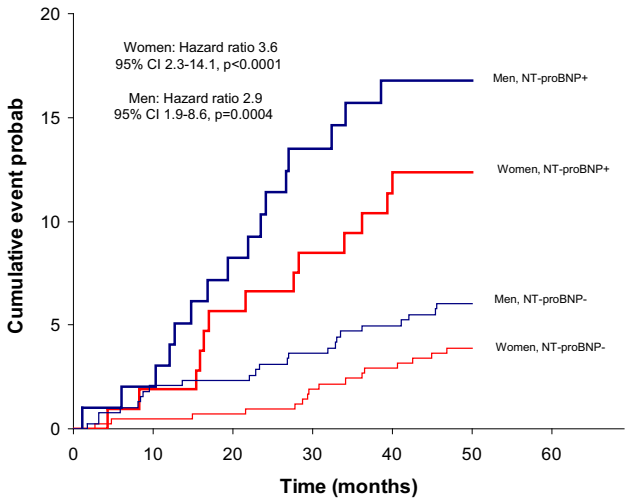

Fig. 6 Kaplan-Meier curves showing cumulative incidence of events in patients with NT-proBNP above and below the age- and gender-specific 80th percentile after stratification by gender. *AUC* area under the curve, *CI* confidence interval

by aggressive risk management could predict better outcomes in asymptomatic hypertesive and diabetic subjects, and more generally in stage A/B HF patients, remains to be demonstrated. In this regard, the AVANT GARDE-TIMI 43 trial showed no benefit of early initiation of renin–angiotensin system inhibitors in a high-risk population with elevated NT-proBNP levels and without clinical evidence of HF following acute coronary syndrome [50]. Our findings also suggest that, considering the high negative predictive value of a normal NT-proBNP plasma concentration observed in our population across all age tertiles and both genders—albeit affected by the relatively low event rate—a NT-proBNP below the age- and gender-specific 80th percentile in asymptomatic patients with hypertension and/or diabetes might suggest a low risk of events. It should also be emphasized that a considerable percentage of the incident events observed in this study were ischemic events. This may reflect the evidence that NT-proBNP plasma concentration is an early marker of significant coronary artery disease [51–53] and inducible myocardial ischemia [54, 55], and suggests that the prognostic value of natriuretic peptides may not be limited to the prediction of HF exacerbations alone [10]. In this view, appropriate tests for the detection of subclinical ischemia might be taken into account for the management of hypertensive and/or diabetic patients with increased NT-proBNP.

This study has some limitations. As the study population included diabetic and/or hypertensive patients, caution is needed in generalizing findings to other stage A/B HF populations. Most patients were assuming antihypertensive and/or antidiabetic medications at the time of enrollment. Even if pharmacological classes were considered in multivariable analysis, the confounding effect of therapy should be taken into account. In this regard, it is interesting to observe that patients with high NT-proBNP had a higher prevalence of use of betablockers than those with normal NT-proBNP. This finding may be in accordance with previous evidences showing that bradycardia induced by antihypertensive betablocker therapy in patients with no HF can increase natriuretic peptide levels because of increased cardiac wall tension [56–58]. In addition, considering that by design patients were asymptomatic and had no evidence of HF or angina, it can be hypothesized that in some cases the treatment with betablockers was driven by a previous history of palpitations, and that the potential

Table 2 Univariable and multivariable predictors of the clinical endpoint, as identified by Cox regression

	Univariable				Multivariable (model without interactions)				Multivariable (model with interactions)			
	HR	95 % CI	Wald	*p*	HR	95 % CI	Wald	*p*	HR	95 % CI	Wald	*p*
Log NT-proBNP	2.65	1.93–3.64	36.3	<0.0001	1.95	1.43–2.66	17.7	<0.0001	1.45	0.99–2.12	7.7	0.041
LV ejection fraction	0.91	0.88–0.94	31.0	<0.0001	0.96	0.93–0.99	4.1	0.044	0.96	0.92–0.99	6.2	0.013
Diabetes mellitus	2.87	1.77–4.66	18.1	<0.0001	2.89	1.74–4.80	16.8	<0.0001	2.87	1.73–4.77	16.5	<0.0001
Age	1.07	1.04–1.11	16.7	<0.0001	1.02	0.98–1.06	0.9	0.33	1.02	0.98–1.06	1.1	0.29
Diastolic dysfunction grade	1.78	1.34–2.37	15.8	<0.0001	0.92	0.58–1.44	0.1	0.71	0.90	0.58–1.42	0.2	0.66
Stage B heart failure	2.20	1.33–3.63	9.5	0.0021	1.63	0.80–3.33	1.8	0.18	1.76	0.85–3.63	2.3	0.13
Indexed LV mass	1.02	1.01–1.03	6.9	0.0087	1.00	0.99–1.01	0.4	0.51	1.00	0.98–1.01	0.6	0.44
Female gender	0.64	0.40–1.03	3.4	0.065	0.54	0.32–0.92	3.4	0.022	0.03	0.01–0.32	8.2	0.0041
Log NT–proBNP/female gender	–	–	–	–	–	–	–	–	1.82	1.13–2.93	6.1	0.014

The following variables were considered for inclusion in the model: age, gender, body surface area, body mass index, hypertension, diabetes, hypercholesterolemia, smoking, metabolic syndrome, systolic, diastolic, and mean blood pressure, heart rate, indexed left ventricular (LV) mass, relative wall thickness, LV ejection fraction, LV diastolic dysfunction degree, ≥grade 2 mitral regurgitation, HF stage, and use of single classes of pharmacological agents. Among these, only variables showing a *p* value of <0.10 at univariable analysis were finally included in the multivariable models shown in the table. The last variable is the interaction term between Log NT-proBNP and female gender

persistence of subclinical arrhythmic events despite beta-blocker therapy could have played a role in increasing NT-proBNP. The number of events in our population was relatively small. In particular, the lack of discrimination of NT-proBNP in the first age tertile could have been affected by the small numbers of events in these patients. The lack of an age- and gender-matched control group should also be considered. Lastly, a multimarker strategy has recently been shown to improve risk stratification in several settings [59–62]. In our population we did not assess whether the combination of natriuretic peptide and other biomarkers resulted in an improved risk prediction.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest in connection with this paper.

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