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**Can NT-proBNP predict risk of cardiovascular mortality within 10 years?
Results from an epidemiological study of elderly patients with symptoms of
heart failure.**

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Abstract

Background

Heart failure has a serious prognosis. However, among elderly patients the panorama of concomitant diseases makes it difficult to implement the results from epidemiological studies. The aim of this study was to evaluate the influence of different clinical variables on cardiovascular mortality during a long-term follow-up.

Methods and Results

In all, 474 elderly patients (age 65-82 years) in primary health care were evaluated and followed during a 10 year period. All patients had symptoms associated with heart failure and were examined by a cardiologist. Blood samples including NT-proBNP were analyzed, and ECG and Doppler echocardiography were assessed. Both the systolic and diastolic function was evaluated. Functional capacity was evaluated according to the NYHA classification.

During the 10 years of follow-up those with the highest quartile of plasma concentration of NT-proBNP had almost four times increased risk of cardiovascular mortality. Impaired systolic function, diabetes and reduced functional capacity were all markers of increased risk of cardiovascular mortality. All variables were also evaluated after 5 years, with higher risk ratios for a majority of variables.

Conclusion

In this study 474 patients with symptoms of heart failure were followed during 10 years. High plasma concentration of NT-proBNP could predict almost four times increased risk of cardiovascular mortality up to 10 years. Also, impaired cardiac function according to echocardiography, and reduced functional capacity as well as diabetes all had influence on risk of cardiovascular mortality up to 10 years.

Background

It is known from the literature that heart failure (HF) is a condition with poor prognosis [1-3]. However, there is information indicating that the mortality in HF has decreased since the end of the 1970's [4, 5]. This could be the result of optimized treatment, but could also be the result of a more aggressive treatment of risk factors such as diabetes, influencing the development of HF [6].

The clinical use of natriuretic peptides has increased as tools giving information about the myocardial wall tension of patients with HF [7-9]. The usefulness of natriuretic peptides in patients with stable or unstable coronary syndromes has also been documented in the literature [10-12]. However, elderly patients in primary care with symptoms associated with HF are usually suffering from more than one disease. Thus the results of published studies are difficult to apply to the population as the complexity of the different diseases within the population is obvious. Therefore, we wanted to follow an elderly population with different risk factors during a longer time period than usual, and to evaluate the importance of the different risk factors concerning cardiovascular mortality.

Methods

Study population

All records of elderly patients who had symptoms associated with HF, that is shortness of breath, and /or peripheral oedema, and/or tiredness and who contacted the only primary health care centre in a municipality in southeast Sweden (population 10,300 inhabitants) during 1995-96 because of the symptoms were evaluated (n=1168). The inclusion into the study was completed in 1996. Those where HF as reason for the symptoms/signs could not be excluded from the record were invited to participate in the study (n=548). Out of these, 510 patients accepted to participate, as 38 patients decided not to because of incapacity, severe illness or

long transportation. All participants visited one cardiologist (UA) who recorded patient history, including drug treatment, and performed a clinical examination. An ECG and a chest x-ray were also performed in all participants. Also, the examining cardiologist classified all patients according to their NYHA functional classification.

The number of participants who accepted to attend the blood sampling procedure was 474, thus forming the final study population (Table 1). The design of the study is previously described in detail [13].

Diabetes mellitus was defined as a fasting blood glucose concentration ≥ 7.0 mmol/L, or ongoing treatment for diabetes (diet, oral therapy or insulin). Hypertension was defined as a blood pressure of more than 140/90 mm Hg measured in the right arm with the patient in the supine position after at least 30 minutes rest. Patients were also defined as hypertensive if they had been diagnosed with hypertension and were receiving antihypertensive medication. Ischemic heart disease was defined as a history of angina pectoris, treatment for angina pectoris and/or a previous myocardial infarction.

With regard to symptoms and signs, dyspnoea was defined from the patient history, whereas presence of peripheral oedema was defined from patient history and/or via clinical examination.

Cardiovascular mortality was defined as death caused by HF, and/or fatal arrhythmias, sudden death, ischemic heart disease or cerebrovascular death, and was decided from autopsy, or death certificate issued by the physician in charge of the patient. No patient was lost during follow-up. All death certificates have been analysed by the authors. All autopsies have been performed at the University Hospital of Linköping.

During the follow-up period all patients received standard treatment according to clinical routines.

Table 1. Basal characteristics of the elderly study population with symptoms associated with heart failure followed during 10 years.

Variable	Study population
Total, n	474
Mean (SD) age, years	72.6 (5.6)
M/F, n	246/228
NYHA classification, n (%)	
Class I	216 (46)
Class II	205 (43)
Class III	53 (11)
Mean (SD) blood pressure, mm Hg	
Systolic	155 (18)
Diastolic	84 (9)
History	
Hypertension, n (%)	415 (88)
Diabetes, n (%)	101 (21)
Ischemic heart disease, n (%)	157 (33)
Chronic obstructive pulmonary Disease, n (%)	36 (7.6)
Medication	
ACEI, n (%)	156 (33)
Diuretics, n (%)	207 (44)
β -Receptor blockers, n (%)	192 (41)
Digitalis, n (%)	48 (10)

Note: ACEI; ACE-inhibitors: M/F; Males/Females: NYHA classification: New York Heart Association functional class

Blood sampling procedure

Blood samples were obtained from fasting subjects after a resting period of 30 minutes. The samples were collected in pre-chilled plastic tubes, containing EDTA (Terumo EDTA K-3), placed on ice and centrifuged at 3000 g for 10 minutes at 4 °C. The samples were then immediately stored at -70 °C until further analysis. NT-proBNP was measured using an electrochemiluminiscence immunoassay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany) [14]. The analytical range was 5-35.000 ng/L (0.6- 4130 pmol/L). Total CV was 4.8% at the level of 217 ng/L (26 pmol/L) (n=70) and 2.1% at the level of 4261 ng/L (503 pmol/L) at our laboratory. All blood samples were stored at -70 °C, and none had been

thawed before analysis. All samples were analyzed within two weeks of inclusion in the study.

Doppler echocardiography

Doppler echocardiographic examinations (Accuson *XP-128c*) were performed with the patient in the supine left position. Both M-mode and 2D methodology were used. Values for systolic function, expressed as ejection fraction (EF) [15, 16], were categorized into 4 classes with interclass limits 30%, 40% and 50%. A semi quantitative method of assessment was used. Normal systolic function (normal SFN) was defined as $EF \geq 50\%$. Moderately impaired SFN was defined as $EF < 40\%$, whereas severely impaired SFN was defined as $EF < 30\%$. The diastolic function was analyzed evaluating the mitral E/A ratio and pulmonary venous flow pattern and compared with age-adjusted decision limits.

Statistics

The results were presented as percentage or mean and SD, or as median when values were not normally distributed. Survival analysis was conducted using Kaplan-Meier survival curve analysis. A Cox regression was performed to identify the weight of the individual risk variables for cardiovascular mortality. A p value less than 0.05 was considered statistically significant. All data analysis has been performed using a commercially available statistical analysis software package (Statistica v. 7.1, Statsoft Inc, Tulsa, OK, USA). The study protocol was approved by The Ethics Committee of the University Hospital of Linköping.

Results

The basal characteristics of the study population are presented in Table 1. An almost even distribution between males/females was found as seen in Table 1. The functional capacity as classified by the examining cardiologist using the NYHA classification show that only a small number of patients were severely impaired (NYHA class III), and no patient was classified as belonging to NYHA class IV. A vast majority of the included patients had a history of hypertension and 1/3 a history of ischemic heart disease (IHD). Less than ½ of the population were treated with β -receptor blockers, and 1/3 of the population was treated with ACE-inhibitors, as the patients were included into the study (Table 1). The result of a six-year follow-up of this study population is earlier presented [2, 17].

The total study population was followed during 10 years (median 3626 days, SD 1094), whereas those that survived during the follow-up period had a median observation of 3799 days (SD 120), and those that did not survive had a median follow-up period of 2066 days (SD 1067). During follow-up 206 patients suffered all cause mortality (40%) and 142 a cardiovascular mortality (28%).

Analyzing the difference in survival between the two genders, we found a significant longer survival rate ($\chi^2=4.1$; $p=0.04$) from all cause mortality for the females compared to the males. However no significant difference was found concerning survival from cardiovascular mortality.

NT-proBNP as prognostic indicator

The distribution of plasma concentration of NT-proBNP among survivors and non-survivors is presented in Table 2. At the inclusion of the participants NT-proBNP was drawn as part of the blood samples taken. Analyzing the prognostic capabilities of NT-proBNP, a Cox proportional hazard regression analysis has been performed first as a univariate regression, indicating an almost 6 times increased risk for those with a plasma concentration of NT-

proBNP in the 4th quartile. Then a multivariate regression was performed. Into that model other well-known variables were added that might have prognostic information (Table 3A). From the sole peptide sample, information concerning risk of cardiovascular mortality could be drawn up to ten years. Analyzing those with a plasma concentration higher than 496 ng/L (=4th quartile) against those with lower plasma concentrations we found a pronounced difference in survival during the ten years of follow-up. The Kaplan-Meier analysis also shows that the prognostic information persists after the first 5 years (Fig I).

Table 2. Plasma concentration of NT-proBNP in different groups of the study population with respect to 10-year mortality

	Range	NT-proBNP, ng/L	
		Median	IQR
Total study population	19-1870	217	391
Survivors	19-4717	170	246
Non-survivors	35-18713	378	830
Cardiovascular mortality	35-18713	544	1145
Other mortality	61-1716	257	340

Note; IQR: Interquartile range

From the multivariate analysis three variables apart from NT-proBNP were found to have significant prognostic information; Diabetes, EF<40%, and NYHA functional class III. As we wanted to evaluate the influence of a shorter observation period, the same type of regressions were performed from the same population using 5 years of observation as shown in Table 3B.

The relation between mortality, both all cause mortality and cardiovascular mortality and the plasma concentrations of NT-proBNP of the four quartiles are shown in Table 4. Both the cardiovascular and all cause mortality increases as the plasma concentration of NT-proBNP increases.

Table 3A regr. Multivariate Cox proportional hazard regression analysis of prognostic power concerning cardiovascular mortality during 10-years of follow-up

Variable	Hazard ratio	95% CI of HR	p-value
Hypertension	1.01	0.74-1.55	0.74
Diabetes	2.27	1.55-3.33	<0.0001
Male gender	1.28	0.88-1.10	0.20
IHD	0.82	0.56-1.21	0.32
EF<40%	1.66	1.04-2.68	0.035
NT-proBNP quartile 4	3.72	2.49-5.54	<0.0001
NYHA Class III	2.06	1.28-3.28	0.003

Note: CI: Confidence interval; EF: Ejection fraction; HR: Hazard ratio;
IHD: Ischemic heart disease; NYHA; New York Heart Association functional class

Table 3B. Multivariate Cox proportional hazard regression analysis of prognostic power concerning cardiovascular mortality during 5-years of follow-up

Variable	Hazard ratio	95% CI of HR	p-value
Hypertension	0.91	0.50-1.64	0.75
Diabetes	2.31	1.31-4.09	0.004
Male gender	1.70	0.93-3.11	0.09
IHD	0.74	0.41-1.33	0.32
EF<40%	2.50	1.30-4.81	0.006
NT-proBNP quartile 4	3.69	1.92-7.07	<0.0001
NYHA class III	2.44	1.28-4.64	0.007

Note: CI: Confidence interval; EF: Ejection fraction; HR: Hazard ratio;
IHD: Ischemic heart disease; NYHA: New York Heart Association functional class

Clinical parameters and cardiovascular mortality

The impact of pharmacological treatment on cardiovascular mortality was analyzed, and during the 10 years of follow-up there was a trend towards longer survival from cardiovascular mortality in those on treatment with beta blockers ($\chi^2= 3.8$; $p=0.051$). The positive effect of beta blockers is well documented in the literature [18].

Those on treatment with ACE-inhibitors have been analyzed as well during the 10 years of follow-up. From this analysis it was found that the patients on ACE-inhibitors had significantly better survival figures from cardiovascular mortality compared to those without

ACE-inhibitors ($\chi^2=6.6$; $p=0.010$). The result of treatment with ACE-inhibitors is also well documented in the literature [19].

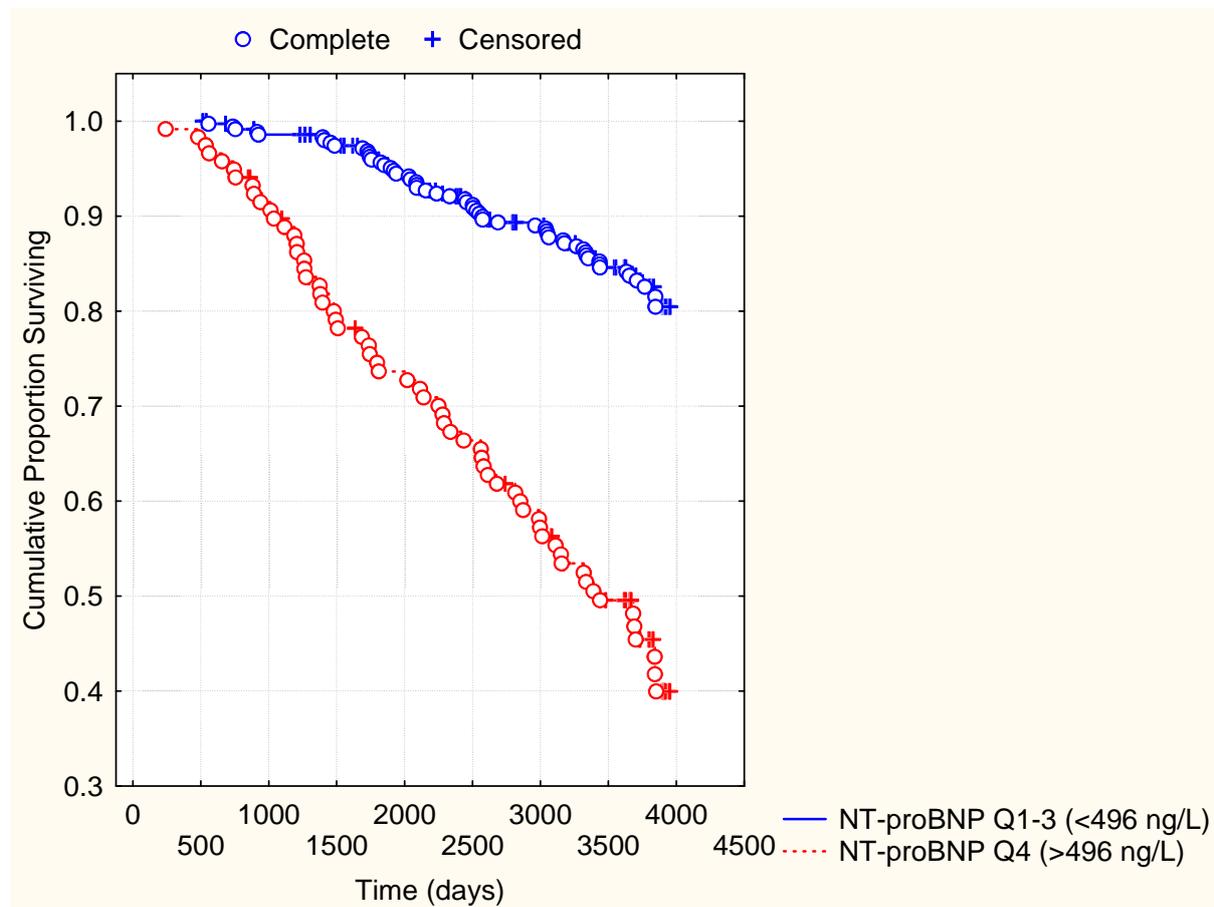


Fig I. Kaplan-Meier analysis comparing quartile 4 (<496ng/L) of NT-proBNP versus quartiles 1-3 (<496 ng/L) concerning cardiovascular mortality in the study population during 10 years of follow-up.

As shown in Table 3A those with diabetes had more than 2 times increased risk for cardiovascular mortality during the follow-up period of 10 years. The result of this increased risk is illustrated in Fig IIa. Analyzing those with an objective impairment of the cardiac function (EF<40%) plus diabetes in the study population regarding survival or not from cardiovascular mortality, the results are even more pronounced (Fig IIb). However, as the group sizes from this analysis are reduced, the results should be interpreted with caution.

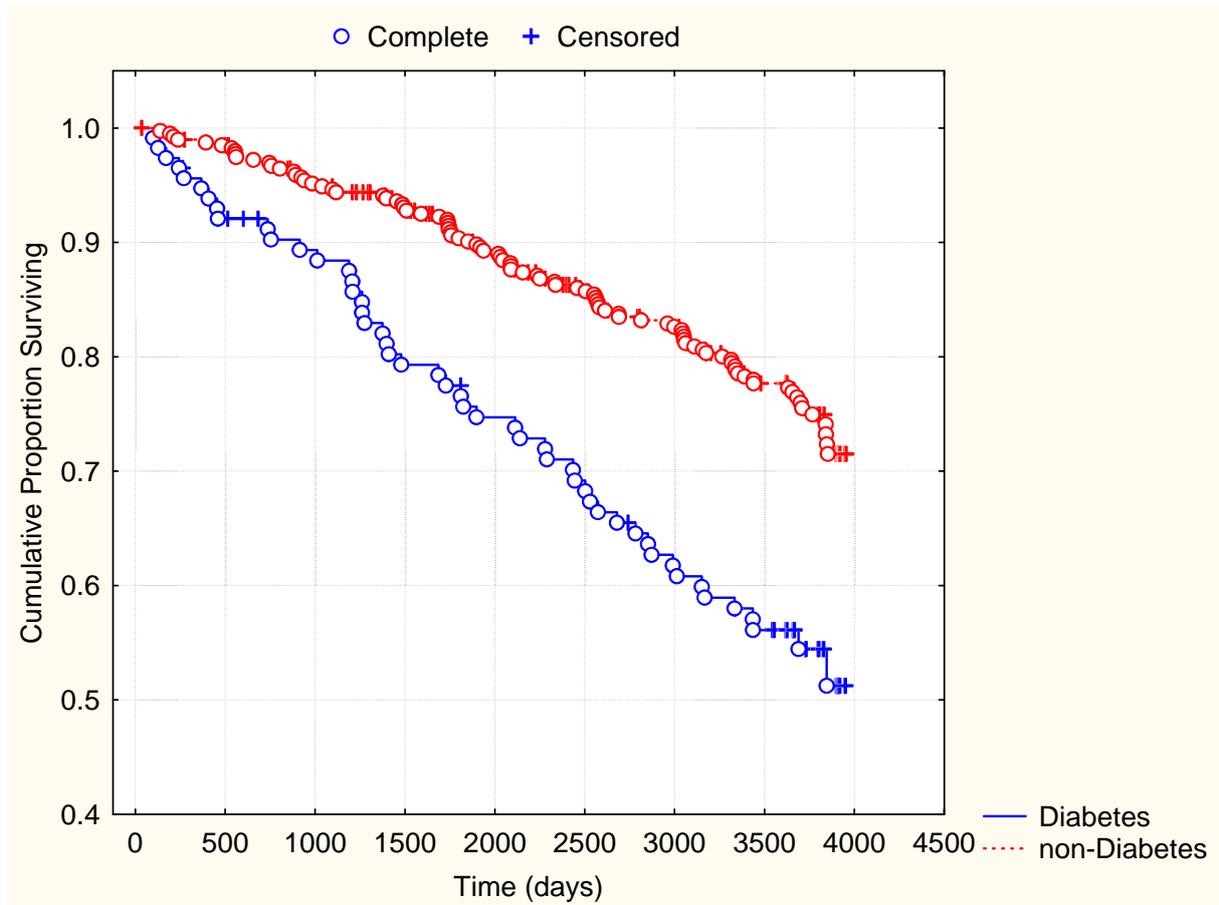


Fig IIa. Kaplan-Meier analysis comparing those with diabetes versus those not with diabetes concerning cardiovascular mortality in the study population during 10 years of follow-up.

The influence of the NYHA functional class as an indicator of severity of disease was also analyzed in the study (Table 5, Fig III). The increased risk of cardiovascular mortality (two times) in the group with NYHA classification III is presented in Table 3A.

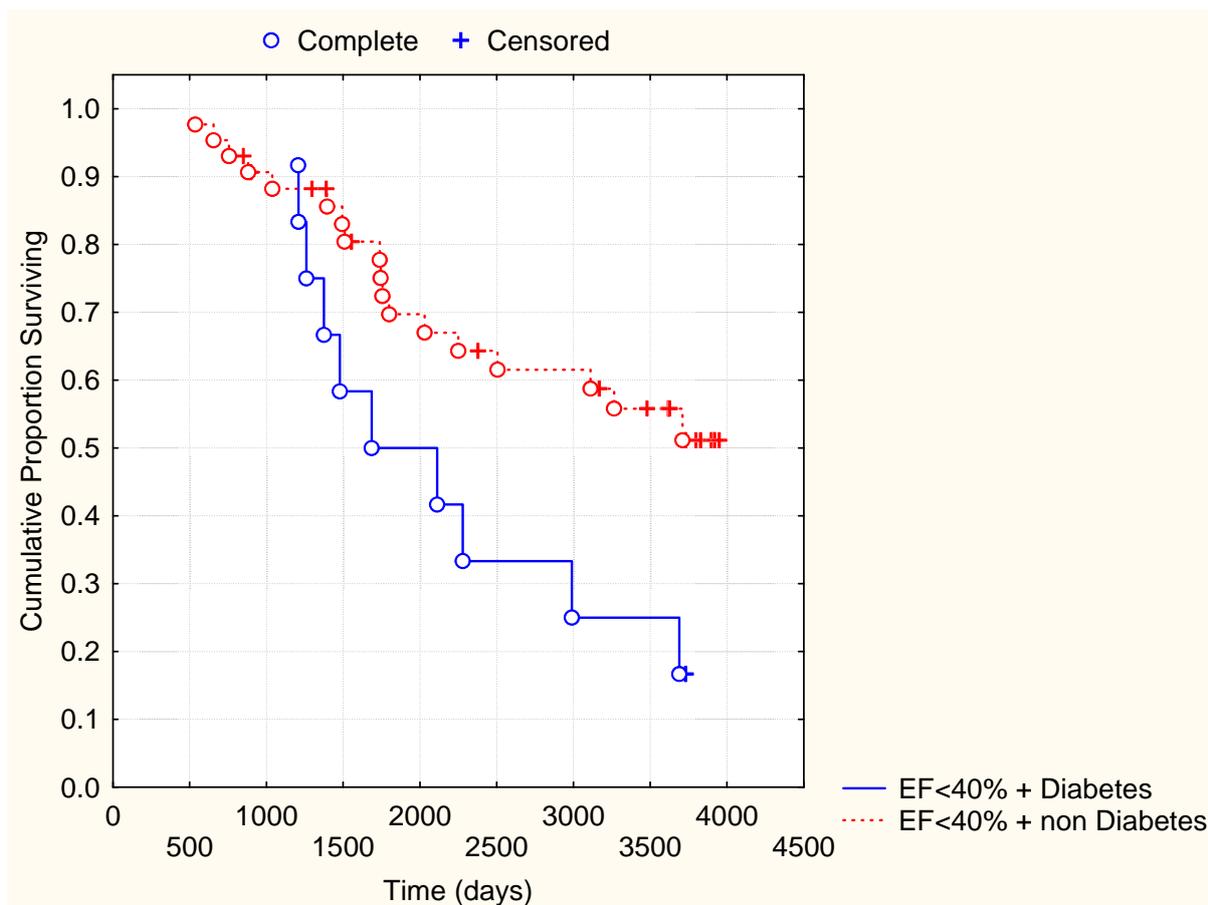


Fig IIb. Kaplan-Meier analysis comparing those with EF < 40% and diabetes versus those with EF < 40% and not diabetes concerning cardiovascular mortality in the study population during 10 years of follow-up.

Table 4. Analysis of mortality based on quartiles of plasma concentration of NT-proBNP in elderly patients (n=474) during a follow-up period of 10 years.

Quartile number	n	NT-proBNP, ng/L		Cardiovascular mortality (%)	All cause mortality (%)
		Range	Median (SD)		
1	118	1-109	65 (21.4)	12/118 (10)	22/118 (19)
2	118	109-216	155 (29.5)	20/118 (17)	36/118 (31)
3	120	216-496	301 (82.2)	25/120 (21)	43/120 (36)
4	118	>496	1008 (2035)	62/118 (53)	75/118 (64)

Echocardiographic parameters and cardiovascular mortality

All patients were evaluated with Doppler echocardiography concerning their systolic and diastolic function. According to the Doppler echocardiography, 48% of the patients showed evidence of impaired systolic and/or diastolic function. Abnormal diastolic function with preserved systolic function was found in 22%. Severely impaired systolic function (EF < 30%)

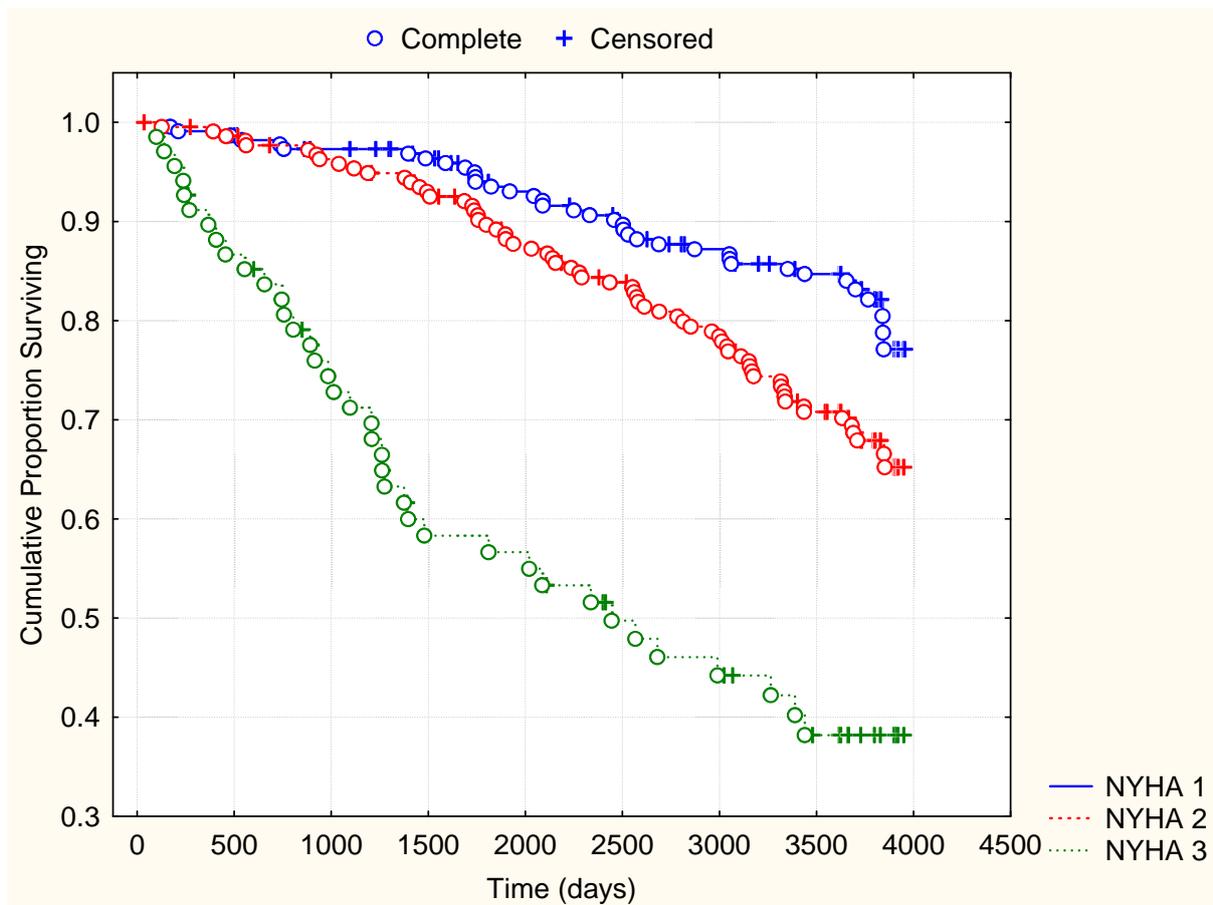


Fig III. Kaplan-Meier analysis comparing NYHA functional class I, II and III in the study population concerning cardiovascular mortality during 10 years of follow-up

was found in 9 patients. Moderately impaired systolic function (EF 30-39%) was found in 11%, slightly impaired systolic function (EF 40-49%) in 13%, and normal systolic and diastolic functions in 52%. From Table 5 it is obvious that the greater impairment of the systolic function, the higher mortality – both all cause and cardiovascular mortality. In the group with moderately impaired systolic function (EF<40%) the cardiovascular mortality is high during the follow-up period, more than 70%. In those with normal systolic function but with signs of relaxation abnormalities the part that diseased in cardiovascular mortality during the follow-up was 23%, as compared to almost 1/3 that suffered cardiovascular mortality in those patients with normal systolic but signs of a pseudonormal or restrictive filling pattern. However, the results from this last patient group should be interpreted with caution, as the group size is small. In the Cox proportional hazard regressions it was found that the patient

group that had EF<40% also had 2.5 times increased risk for cardiovascular mortality if followed during 5 years (Table 3B). The risk has decreased to 1.7 times as the observational time increased to 10 years (Table 3A).

Table 5 All cause mortality and cardiovascular mortality in different Doppler echocardiographic and functional classes during a follow-up period of 10 years

Variable	n	All cause mortality n (% of total number in each group)	Cardiovascular mortality n (% of total number in each group)
Doppler- echocardiography			
EF<30%	11	9 (82)	8 (73)
EF 30-39%	52	36 (69)	29 (56)
EF 40-49%	60	32 (53)	19 (32)
EF≥50% + NDFN	235	51 (22)	35 (15)
Isolated relaxation abnormalities + EF≥50%	83	30 (36)	19 (23)
Pseudonormal pattern + EF≥50%	13	6 (ca. 45)	4 (ca. 30)
Not possible to evaluate echocardiography, or did not attend echocardiography	56	42 (75)	28 (50)
NYHA class			
I	224	66 (29)	38 (17)
II	218	90 (41)	66 (30)
III	68	50 (74)	38 (56)

Note: EF: Ejection Fraction; NDFN: Normal diastolic function; NYHA New York Heart Association functional class

Discussion

Elderly patients with symptoms associated with HF are common for the general practitioner. Even though there are several risk factors for HF identified in the literature, information is still needed on which are the important risk factors for cardiovascular mortality for patients in primary health care that are many times multi diseased in the long perspective. As commented in an editorial there are few population based investigations, especially concerning the area of natriuretic peptides [20]. In the present study we have evaluated elderly patients in primary

health care with symptoms associated with HF with respect to some important variables, where the patients were followed during 10 years, an unusually long time of observation. Another of our goals was to identify specific risk factors for cardiovascular mortality in an elderly population in the community, and also evaluate what happens to this group of patients that are given routine treatment.

During the follow-up period no significant difference in cardiovascular mortality was found between the genders, probably as a result of the female part after menopause, catch up in risk compared to males and because the evaluated population had a range in age between 65 to 83 years.

NT-proBNP as prognostic indicator for cardiovascular mortality

It is well known that natriuretic peptides have a prognostic power concerning cardiovascular mortality [17, 21, 22]. In this study we have analyzed those within the 4th quartile of plasma NT-proBNP against the other three quartiles (Fig I). From this it is evident that the prognostic power from one blood sample is strong enough to give information 10 years after been drawn, as also can be seen in the multivariate Cox proportional regression analysis. In this analysis those within the 4th quartile of plasma concentration of NT-proBNP have almost four times the risk of cardiovascular mortality in spite of many other well known risk variables in the model (Table 3A). The high risk ratio after 10 years is surprising as the probability for a shift between groups is greater as the observation period is increasing. In addition, as observational time increases the chances of other factors influencing the patient increases. Therefore it is usually reported higher risk ratios after shorter observation periods [17]. The difference in risk ratios for the peptides are however not great in this study. The reason for this is probably that the natriuretic peptides have a central position in the total risk panorama of the patients with symptoms of HF.

It is also seen from the analysis of cardiovascular and all cause mortality divided into quartiles of plasma concentration of NT-proBNP, that the increase of mortality in the highest quartile is dramatic (Table 4). In the process where priority has to be given to those patients who have the highest risk, the analysis of natriuretic peptides is therefore a valuable tool for the clinician.

Echocardiographic parameters as prognostic indicators for cardiovascular mortality

One of the mainly used methods to objectively evaluate cardiac function is Doppler echocardiography. Patients with severely impaired systolic function as measured by low ejection fraction have a worse prognosis compared to those less impaired [2, 23-25]. In the present study population all patients have been evaluated both according to systolic and diastolic function. It is therefore possible to evaluate the long term prognosis of the different classes of impairment (Table 5). In the group of patients with $EF < 40\%$ more than 70% have suffered a cardiovascular mortality, whereas in those with normal systolic and diastolic function at inclusion into the study, only 20% suffered a cardiovascular death during the 10 years of observation. The result is stable during the follow-up period indicating that the cardiac impairment is an important factor that is not blunted in spite of long exposure for other risk factors.

It is also interesting to note that those with an isolated diastolic dysfunction had significantly less cardiovascular mortality compared to those with $EF < 40\%$. Unfortunately, the group size of those with pseudonormal or restrictive filling pattern are too small to allow further analysis, but it seems that this could be a more diseased group compared to those with an isolated relaxations abnormality (Table 5), in accordance with earlier published reports [26].

Clinical parameters as prognostic indicators for cardiovascular mortality

Functional capacity is a parameter that has well documented prognostic information, at least in the short perspective [17, 27, 28]. In this study, with an observational time of 10 years, we evaluated the patients according to NYHA functional class. From this information it is evident that the part suffering from cardiovascular mortality during the follow-up period increases as functional capacity decreases (Table 5).

Diabetes is a disease that influences a wide range of organ systems in the body. The consequences within the cardiovascular system are well known [6, 29, 30]. Elderly patients with diabetes have a worse prognosis compared to those without diabetes. The fact that those with diabetes are at higher risk of developing HF is well known [31]. We have analyzed those with diabetes in relation to cardiovascular mortality during the follow-up period as seen in Fig IIIa. We could based on the study results verify the severity of the disease. Even though the group size was reduced, the results concerning mortality that are presented in those with both an impaired cardiac function and diabetes in Fig IIb are dramatic. This illustrates that this patient group is at high risk that requires priority in the handling and optimizing of treatment.

Limitations

In a population based study the amount of patients that could be included is restricted if all patients are to be evaluated with blood samples, Doppler echocardiography evaluating both the systolic and the diastolic function, and clinical examination in contrast to register based studies. The limited size of groups in this study also limits the interpretation of results obtained. We have, however, tried not to push the conclusion too far.

The number of patients not participating in the blood sampling procedure or Doppler echocardiography is a problem as they could belong to the group that are most diseased, something that is indicated in table 5. However, in the study only 3 individuals declined to

participate in Doppler echocardiography. In another 53 patients it was not possible to evaluate the diastolic function, mainly because of atrial fibrillation or not acceptable image quality.

This group demonstrated a high mortality as a consequence of their disease. It is a limitation not to have complete information from this patient group. In the study 36 patients did not accept blood sampling, but on the other hand a majority of Doppler echocardiographic information was obtained from them.

We believe therefore, that the results obtained are representative of elderly patients with symptoms of heart failure in the community in Sweden.

Conclusion

Elderly patients in primary health care with symptoms associated with HF were examined according to plasma concentration of NT-proBNP, Doppler echocardiographic results, and functional capacity according to the NYHA functional classification. The patients were followed during almost 10 years, and all cardiovascular, as well as all cause mortality was registered. Those with a high plasma NT-proBNP had almost 4 times increased risk for cardiovascular mortality during the long time of follow-up. Impaired ejection fraction, reduced functional capacity and diabetes were other variables that increased risk for mortality in this group of elderly patients. This would indicate that patients belonging to these risk groups should be given priority in the handling of patients with possible HF.

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References

1. Kannel WB. Incidence and epidemiology of heart failure. *Heart Fail Rev* 2000 Jun;5(2):167-73.
2. Alehagen U, Lindstedt G, Levin LA, Dahlstrom U. The risk of cardiovascular death in elderly patients with possible heart failure. Results from a 6-year follow-up of a Swedish primary care population. *Int J Cardiol* 2005 Apr 8;100(1):17-27.
3. Shahar E, Lee S, Kim J, Duval S, Barber C, Luepker RV. Hospitalized heart failure: rates and long-term mortality. *J Card Fail* 2004 Oct;10(5):374-9.
4. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, et al. Trends in heart failure incidence and survival in a community-based population. *Jama* 2004 Jul 21;292(3):344-50.
5. Schaufelberger M, Swedberg K, Koster M, Rosen M, Rosengren A. Decreasing one-year mortality and hospitalization rates for heart failure in Sweden; Data from the Swedish Hospital Discharge Registry 1988 to 2000. *Eur Heart J* 2004 Feb;25(4):300-7.
6. Dirkali A, van der Ploeg T, Nangrahary M, Cornel JH, Umans VA. The impact of admission plasma glucose on long-term mortality after STEMI and NSTEMI myocardial infarction. *Int J Cardiol* 2007;121(2):215-217.
7. Rothenburger M, Wichter T, Schmid C, Stypmann J, Tjan TD, Berendes E, et al. Aminoterminal pro type B natriuretic peptide as a predictive and prognostic marker in patients with chronic heart failure. *J Heart Lung Transplant* 2004 Oct;23(10):1189-97.
8. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, Santalobal M, et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. *Eur Heart J* 2006 Feb;27(3):330-7.
9. Groenning BA, Raymond I, Hildebrandt PR, Nilsson JC, Baumann M, Pedersen F. Diagnostic and prognostic evaluation of left ventricular systolic heart failure by plasma N-terminal pro-brain natriuretic peptide concentrations in a large sample of the general population. *Heart* 2004 Mar;90(3):297-303.
10. Bibbins-Domingo K, Gupta R, Na B, Wu AH, Schiller NB, Whooley MA. N-terminal fragment of the prohormone brain-type natriuretic peptide (NT-proBNP), cardiovascular events, and mortality in patients with stable coronary heart disease. *Jama* 2007 Jan 10;297(2):169-76.
11. Galvani M, Ferrini D, Ottani F. Natriuretic peptides for risk stratification of patients with acute coronary syndromes. *Eur J Heart Fail* 2004 Mar 15;6(3):327-33.
12. James SK, Lindahl B, Siegbahn A, Stridsberg M, Venge P, Armstrong P, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003 Jul 22;108(3):275-81.
13. Alehagen U, Eriksson H, Nylander E, Dahlström U. Heart failure in the elderly. Characteristics of a Swedish primary health care population. *Heart Drug* 2002;2:211-20.
14. Karl J, Borgya A, Gallusser A, Huber E, Krueger K, Rollinger W, et al. Development of a novel, N-terminal-proBNP (NT-proBNP) assay with a low detection limit. *Scand J Clin Lab Invest Suppl* 1999;230:177-81.
15. Jensen-Urstad K, Bouvier F, Hojer J, Ruiz H, Hulting J, Samad B, et al. Comparison of different echocardiographic methods with radionuclide imaging for measuring left ventricular ejection fraction during acute myocardial infarction treated by thrombolytic therapy. *Am J*

Cardiol 1998 Mar 1;81(5):538-44.

16. van Royen N, Jaffe CC, Krumholz HM, Johnson KM, Lynch PJ, Natale D, et al. Comparison and reproducibility of visual echocardiographic and quantitative radionuclide left ventricular ejection fractions. *Am J Cardiol* 1996 Apr 15;77(10):843-50.
17. Alehagen U, Lindstedt G, Levin LA, Dahlstrom U. Risk of cardiovascular death in elderly patients with possible heart failure B-type natriuretic peptide (BNP) and the aminoterminal fragment of ProBNP (N-terminal proBNP) as prognostic indicators in a 6-year follow-up of a primary care population. *Int J Cardiol* 2005 Apr 8;100(1):125-33.
18. Jost A, Rauch B, Hochadel M, Winkler R, Schneider S, Jacobs M, et al. Beta-blocker treatment of chronic systolic heart failure improves prognosis even in patients meeting one or more exclusion criteria of the MERIT-HF study. *Eur Heart J* 2005 Dec;26(24):2689-97.
19. Swedberg K, Kjeksus J, Snapinn S. Long-term survival in severe heart failure in patients treated with enalapril. Ten year follow-up of CONSENSUS I. *Eur Heart J* 1999 Jan;20(2):136-9.
20. Schillinger M. Cardiovascular risk stratification in older patients: role of brain natriuretic peptide, C-reactive protein, and urinary albumin levels. *Jama* 2005 Apr 6;293(13):1667-9.
21. Kragelund C, Gronning B, Kober L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005 Feb 17;352(7):666-75.
22. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *Jama* 2005 Apr 6;293(13):1609-16.
23. Redfield MM, Jacobsen SJ, Burnett JC, Jr., Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *Jama* 2003 Jan 8;289(2):194-202.
24. McDonagh TA, Cunningham AD, Morrison CE, McMurray JJ, Ford I, Morton JJ, et al. Left ventricular dysfunction, natriuretic peptides, and mortality in an urban population. *Heart* 2001 Jul;86(1):21-6.
25. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation* 2003 Sep 26;108(8):977-82.
26. Whalley GA, Doughty RN, Gamble GD, Wright SP, Walsh HJ, Muncaster SA, et al. Pseudonormal mitral filling pattern predicts hospital re-admission in patients with congestive heart failure. *J Am Coll Cardiol* 2002 Jun 5;39(11):1787-95.
27. Formiga F, Chivite D, Manito N, Casas S, Riera A, Pujol R. Predictors of In-Hospital Mortality Present at Admission among Patients Hospitalised because of Decompensated Heart Failure. *Cardiology* 2006 Sep 25;108(2):73-8.
28. Ahmed A. A propensity matched study of New York Heart Association class and natural history end points in heart failure. *Am J Cardiol* 2007 Feb 15;99(4):549-53.
29. Sevil S, Janand-Delenne B, Avierinos JF, Habib G, Labastie N, Raccach D, et al. Six-year follow-up of a cohort of 203 patients with diabetes after screening for silent myocardial ischaemia. *Diabet Med* 2006 Nov;23(11):1186-91.
30. Estep JD, Aguilar D. Diabetes and heart failure in the post-myocardial infarction patient. *Current heart failure reports* 2006 Dec;3(4):164-9.
31. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol* 1974 Jul;34(1):29-34.