Prognostic Value of NH_2-Terminal Pro B-Type Natriuretic Peptide in Patients With Diabetes and Stable Coronary Heart Disease

CHARLOTTE KRAGELUND, MD[1,2]
IDA GUSTAFSSON, MD, PHD[1]
TORBJØRN OMLAND, MD, PHD, MPH[2,3]
BJØRN GRØNNING, MD[1]
LARS KØBER, MD, DMSC[4]
JENS FABER, MD, DMSC[5]
SØREN STRANDE, MD[4]
ROLF STEFFENSEN, MD[6]
PER HILDEBRANDT, MD, DMSC[1]

Cardiovascular disease is the most frequent cause of death in patients with diabetes (1). It is difficult to evaluate the cardiovascular status of patients with diabetes because of complex symptomology, evidence of silent ischemia, and subclinical cardiac disease. Brain (B-type) natriuretic peptide (BNP) and the NH_2-terminal fragment of its prohormone (NT-proBNP) are novel biomarkers, which are released from cardiomyocytes in response to myocyte stretch. BNP and NT-proBNP both predict morbidity and mortality in the general population and in high-risk groups (2,3). In patients with diabetes, BNP is a promising screening marker for left-ventricular dysfunction, and both BNP and NT-proBNP are markers of increased risk (4–6). It is not known whether NT-proBNP is a useful risk marker in patients with diabetes and established coronary heart disease.

RESEARCH DESIGN AND METHODS

A total of 1,034 consenting patients with angina pectoris, or evidence of ischemia on exercise electrocardiography or myocardial radionuclide imaging, were included in this analysis. A detailed description of the study population has been reported previously (3). The Danish health authorities and regional ethics committee approved the study, and all participating subjects provided informed consent.

At baseline, selective coronary angiography and left ventriculography were performed in all patients. A thorough medical history of previous cardiovascular disease, diabetes, and smoking habits was recorded. Diabetes was defined as a history of diabetes, on antidiabetic treatment, or fasting plasma glucose (FPG) ≥7 mmol/l. Fasting blood samples were drawn for measurement of plasma glucose, lipids, creatinine, and NT-proBNP (Elecsys proBNP; Roche Diagnostics, Mannheim, Germany). Information on vital status was obtained from the Danish Central Person Registry by means of a computerized search performed on 1 August 2001. No patient was lost to follow-up.

Baseline characteristics, grouped according to NT-proBNP concentration above or below the median and diabetes status, were compared using the χ^2 test for discrete variables and the Wilcoxon or Kruskal-Wallis rank-sum test for continuous variables. Relative risks and 95% CIs were calculated as hazard ratios (HRs) derived from the Cox proportional-hazards regression analysis. The following covariates were considered potential confounders: age, sex, family history of ischemic heart disease, previous myocardial infarction, angina, hypertension, smoking, BMI, estimated glomerular filtration rate, plasma lipids, left-ventricular ejection fraction (LVEF), and severity of coronary disease at angiography. There was no interaction between NT-proBNP and diabetes status. Version 8.2 of the Statistical Analysis System (SAS Institute, Cary, NC) was used for all analyses.

RESULTS

A total of 197 patients (19%) had diabetes. Median (interquartile range) NT-proBNP level was increased in patients with diabetes (230 ng/l [78–632]) compared with patients without diabetes (161 ng/l [61–423]) (P = 0.015). Patients with supramedian NT-proBNP (>169 ng/l) were older, had a higher frequency of prior myocardial infarction, higher left-ventricular end-diastolic pressure, and lower LVEF and glomerular filtration rate, irrespective of diabetes status. Diabetic patients had higher frequency of history of hypertension, BMI, triglycerides, FPG, and insulin, and lower HDL cholesterol, irrespective of NT-proBNP level. Patients with both supramedian NT-proBNP and diabetes had more three-vessel disease and disease of the left main coronary artery. After a median follow up of 9.2 years, 288 (28%) patients had died, including 206 (25%) nondiabetic patients and 82 (43%) diabetic patients. Kaplan-Meier estimates of survival were made after dividing the subjects into four groups, as shown in Fig. 1. By multivariable Cox regression analysis, the HR was 1.8 (95% CI 1.1–3.0, P = 0.02) for the group of patients with low NT-proBNP levels and diabetes, 1.6 (1.2–2.3, P = 0.004) for the group of patients

From the [1]Department of Cardiology and Endocrinology, Frederiksberg University Hospital, Copenhagen, Denmark; the [2]Department of Medicine, Akershus University Hospital, Lørenskog, Norway; the [3]Faculty Division Akershus University Hospital, University of Oslo, Oslo, Norway; the [4]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark; the [5]Department of Endocrinology, Herlev University Hospital, Copenhagen, Denmark; and the [6]Department of Cardiology, Hillerød University Hospital, Hillerød, Denmark.

Address correspondence and reprint requests to Charlotte Kragelund, MD, Cardiology and Endocrinology, Frederiksberg University Hospital, Nordre Fasanvej 57, DK-2000 Frederiksberg, Denmark. E-mail: kragelund@dadlnet.dk.

Received for publication 27 January 2006 and accepted in revised form 23 February 2006.

C.K. has received honoraria from Roche. T.O. has received honoraria and grant/research support from Roche. P.H. has served on an advisory panel for and has received honoraria from Roche.

Abbreviations: BNP, brain (B-type) natriuretic peptide; FPG, fasting plasma glucose; LVEF, left-ventricular ejection fraction; NT-proBNP, NH_2-terminal fragment of BNP prohormone.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc06-0227

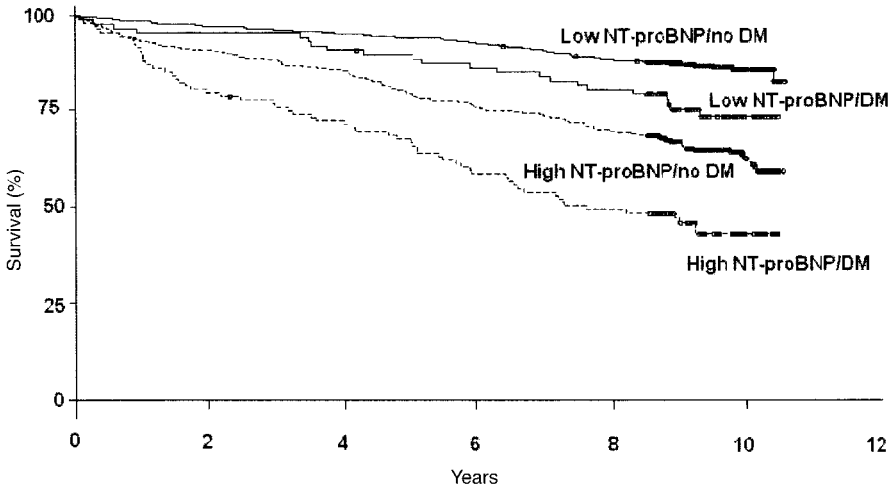

Figure 1—*Overall survival among patients with stable coronary disease, according to levels of NT-proBNP and diabetes status. P < 0.0001 by the log-rank test for overall comparison among the groups. Low NT-proBNP, NT-proBNP levels below median (<169 ng/l); High NT-proBNP, NT-proBNP levels equal to or above the median (≥169 ng/l); DM, diabetes mellitus.*

with high NT-proBNP without diabetes, and 2.8 (1.9–4.2, $P < 0.0001$) for the group of patients with high NT-proBNP and diabetes, as compared with patients with low NT-proBNP levels without diabetes. Other covariates independently associated with mortality were increasing age, smoking, and decreasing LVEF.

CONCLUSIONS — This study demonstrates that the combination of NT-proBNP and diabetes in patients with stable coronary heart disease provides independent prognostic information on all-cause mortality. Our results extend currently available information by showing that patients with diabetes and low NT-proBNP are at similar risk of death as patients with high NT-proBNP and no diabetes, and the combination of the two nearly tripled the risk.

Results from the EUROASPIRE surveys showed that patients with diabetes are currently not treated according to present guidelines (7). Identification of patients with diabetes at particularly high risk is clinically important because therapeutic agents to reduce morbidity and mortality in these patients are readily available. Previous studies investigating natriuretic peptide levels in patients with diabetes have shown conflicting results (5,8–15). Data from the Breathing Not Properly Multinational Study, investigating patients with acute dyspnea, failed to show any difference in levels of BNP between patients with and without diabetes, regardless of the presence of heart failure (16). However, this study may have excluded patients with more severe diabetes, as patients with advanced renal dysfunction were excluded.

Several different explanations for our findings are possible. Patients with diabetes may have a higher prevalence of diastolic dysfunction or have more peripheral and distal atherosclerotic changes in the coronary tree, which may be clinically important. Adjusting for these confounders in the multivariable models did not change the results. Nevertheless, the possibility remains that the increased risk of death in patients with high NT-proBNP and diabetes may be due to higher left-ventricular mass, left-ventricular hypertrophy, and fibrosis, as suggested by other investigators (17). The combination of diabetes and high NT-proBNP did not result in a superadditive effect on risk, even though patients with this combination may have had a longer duration of diabetes and be in a more dysmetabolic, insulin-resistant state. However, regardless of diabetes status, there was no difference in levels of FPG or insulin between patients with high versus low levels of NT-proBNP.

We conclude that NT-proBNP and diabetes are complementary independent risk factors of long-term mortality in patients with stable coronary disease. Combined assessment of these two readily obtainable risk factors provides risk stratification superior to that provided by either alone.

References

1. Butler R, MacDonald TM, Struthers AD, Morris AD: The clinical implications of diabetic heart disease. *Eur Heart J* 19:1617–1627, 1998
2. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, Wolf PA, Vasan RS: Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 350:655–663, 2004
3. 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* 352:666–675, 2005
4. Epshteyn V, Morrison K, Krishnaswamy P, Kazanegra R, Clopton P, Mudaliar S, Edelman S, Henry R, Maisel A: Utility of B-type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. *Diabetes Care* 26: 2081–2087, 2003
5. Tarnow L, Hildebrandt P, Hansen BV, Borch-Johnsen K, Parving HH: Plasma N-terminal pro-brain natriuretic peptide as an independent predictor of mortality in diabetic nephropathy. *Diabetologia* 48:149–155, 2005
6. Bhalla MA, Chiang A, Epshteyn VA, Kazanegra R, Bhalla V, Clopton P, Krishnaswamy P, Morrison LK, Chiu A, Gardetto N, Mudaliar S, Edelman SV, Henry RR, Maisel AS: Prognostic role of B-type natriuretic peptide levels in patients with type 2 diabetes mellitus. *J Am Coll Cardiol* 44:1047–1052, 2004
7. Pyorala K, Lehto S, De Bacquer D, De Sutter J, Sans S, Keil U, Wood D, De Backer G: Risk factor management in diabetic and non-diabetic patients with coronary heart disease: findings from the EUROASPIRE I AND II surveys. *Diabetologia* 47:1257–1265, 2004
8. Yano Y, Katsuki A, Gabazza EC, Ito K, Fujii M, Furuta M, Tuchihashi K, Goto H, Nakatani K, Hori Y, Sumida Y, Adachi Y: Plasma brain natriuretic peptide levels in normotensive noninsulin-dependent diabetic patients with microalbuminuria. *J Clin Endocrinol Metab* 84:2353–2356, 1999
9. Isotani H, Kameoka K, Sasaki I, Hida H, Kakutani S, Tasaki T: Plasma brain natriuretic peptide levels in normotensive type 2 diabetic patients without cardiac disease. *Diabetes Care* 23:859–860, 2000
10. Asakawa H, Fukui T, Tokunaga K,

Kawakami F: Plasma brain natriuretic peptide levels in normotensive type 2 diabetic patients without cardiac disease and macroalbuminuria. *J Diabetes Complications* 16:209–213, 2002
11. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Wilson PW, Vasan RS: Impact of obesity on plasma natriuretic peptide levels. *Circulation* 109:594–600, 2004
12. Magnusson M, Melander O, Israelsson B, Grubb A, Groop L, Jovinge S: Elevated plasma levels of Nt-proBNP in patients with type 2 diabetes without overt cardiovascular disease. *Diabetes Care* 27:1929–1935, 2004
13. Raymond I, Groenning BA, Hildebrandt PR, Nilsson JC, Baumann M, Trawinski J, Pedersen F: The influence of age, sex and other variables on the plasma level of N-terminal pro brain natriuretic peptide in a large sample of the general population. *Heart* 89:745–751, 2003
14. Gaede P, Hildebrandt P, Hess G, Parving HH, Pedersen O: Plasma N-terminal pro-brain natriuretic peptide as a major risk marker for cardiovascular disease in patients with type 2 diabetes and microalbuminuria. *Diabetologia* 48:156–163, 2005
15. Verges B, Zeller M, Desgres J, Dentan G, Laurent Y, Janin-Manificat L, L'huillier I, Rioufol G, Beer JC, Makki H, Rochette L, Gambert P, Cottin Y: High plasma N-terminal pro-brain natriuretic peptide level found in diabetic patients after myocardial infarction is associated with an increased risk of in-hospital mortality and cardiogenic shock. *Eur Heart J* 26:1734–1741, 2005
16. Wu AH, Omland T, Duc P, McCord J, Nowak RM, Hollander JE, Herrmann HC, Steg PG, Wold KC, Storrow AB, Abraham WT, Perez A, Kamin R, Clopton P, Maisel AS, McCullough PA: The effect of diabetes on B-Type natriuretic peptide concentrations in patients with acute dyspnea: an analysis from the Breathing Not Properly Multinational Study. *Diabetes Care* 27:2398–2404, 2004
17. Struthers AD, Morris AD: Screening for and treating left-ventricular abnormalities in diabetes mellitus: a new way of reducing cardiac deaths. *Lancet* 359:1430–1432, 2002