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Biomarkers

PONTIAC (NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease)

A Prospective Randomized Controlled Trial

Martin Huelsmann, MD,* Stephanie Neuhold, MD,*† Michael Resl, MD,‡ Guido Strunk, PhD,§‖ Helmut Brath, MD,¶ Claudia Francesconi, MD,# Christopher Adlbrecht, MD,* Rudolf Prager, MD,** Anton Luger, MD,‡ Richard Pacher, MD,* Martin Clodi, MD‡

Vienna, Austria; and Dortmund, Germany

Objectives The study sought to assess the primary preventive effect of neurohumoral therapy in high-risk diabetic patients selected by N-terminal pro–B-type natriuretic peptide (NT-proBNP).

Background Few clinical trials have successfully demonstrated the prevention of cardiac events in patients with diabetes. One reason for this might be an inaccurate selection of patients. NT-proBNP has not been assessed in this context.

Methods A total of 300 patients with type 2 diabetes, elevated NT-proBNP (>125 pg/ml) but free of cardiac disease were randomized. The "control" group was cared for at 4 diabetes care units; the "intensified" group was additionally treated at a cardiac outpatient clinic for the up-titration of renin-angiotensin system (RAS) antagonists and beta-blockers. The primary endpoint was hospitalization/death due to cardiac disease after 2 years.

Results At baseline, the mean age of the patients was 67.5 ± 9 years, duration of diabetes was 15 ± 12 years, 37% were male, HbA_{1c} was 7 ± 1.1%, blood pressure was 151 ± 22 mm Hg, heart rate was 72 ± 11 beats/min, median NT-proBNP was 265.5 pg/ml (interquartile range: 180.8 to 401.8 pg/ml). After 12 months there was a significant difference between the number of patients treated with a RAS antagonist/beta-blocker and the dosage reached between groups ($p < 0.0001$). Blood pressure was significantly reduced in both ($p < 0.05$); heart rate was only reduced in the intensified group ($p = 0.004$). A significant reduction of the primary endpoint (hazard ratio: 0.351; 95% confidence interval: 0.127 to 0.975, $p = 0.044$) was visible in the intensified group. The same was true for other endpoints: all-cause hospitalization, unplanned cardiovascular hospitalizations/death ($p < 0.05$ for all).

Conclusions Accelerated up-titration of RAS antagonists and beta-blockers to maximum tolerated dosages is an effective and safe intervention for the primary prevention of cardiac events for diabetic patients pre-selected using NT-proBNP. (Nt-proBNP Guided Primary Prevention of CV Events in Diabetic Patients [PONTIAC]; NCT00562952) (J Am Coll Cardiol 2013;62:1365–72) © 2013 by the American College of Cardiology Foundation

Diabetes mellitus is considered one of the primary causes of cardiac disease. It is, therefore, remarkable that to date there have been no clinical trials conducted with diabetic patients focusing on the primary prevention of cardiac disease. Furthermore, most trials have failed to demonstrate a secondary preventive effect of treatment in patients with diabetes (1–4). Only 2 studies showed a reduction of cardiovascular events (5,6), and in some studies events even increased under therapy (7,8).

Surprisingly, during the ambitious recent trials cardiac events were less frequent than anticipated, even in pre-selected risk populations (1,7–9). The inclusion and exclusion criteria applied in these studies have been highlighted as one reason

From the *Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria; †Department of Anesthesia, Division of Cardio-Thoracic-Vascular Anesthesia and Intensive Care Medicine, Medical University of Vienna, Vienna, Austria; ‡Department of Internal Medicine III, Division of Endocrinology, Medical University of Vienna, Vienna, Austria; §University of Technology, Dortmund, Germany, ‖Complexity Research, Vienna, Austria; ¶Diabetes Outpatient Clinic, Health Centre South, Vienna, Austria; #Diabetes Outpatient Clinic, Health Centre Midtown, Vienna, Austria; and the **Third Department of Medicine, Hietzing Hospital Vienna, Austria. All authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Huelsmann and Neuhold contributed equally to this paper.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

eGFR = estimated glomerular filtration rate

NT-proBNP = N-terminal pro–B-type natriuretic peptide

RAS = renin-angiotensin system

why the studies have failed (10). In these trials, it appears that patient selection may have played a larger role in the disappointing results than treatment alone.

See page 1373

We have previously shown that N-terminal pro–B-type natriuretic peptide (NT-proBNP) has an excellent predictive value for both short- and intermediate-term cardiovascular events in patients with diabetes (11–13). Similarly, the authors of the STENO-2 (multifactorial intervention and cardiovascular disease in patients with type 2 diabetes) study, which is one of the rare studies that accomplished a substantial cardiovascular risk reduction, recognized that the pre-selection variable "microalbuminuria" was associated with a significant risk only if an increased NT-proBNP concentration was also found in patients (14).

The rationale of the prospective trial described in this report was based on 2 assumptions. First, that NT-proBNP was the best marker to identify diabetic patients at risk for cardiac disease in our prior studies. This biomarker can be considered an integral of the most important cardiac risk markers in diabetes mellitus, as this marker not only mirrors the presence but also the severity of the burden on the cardiovascular system. Second, renin-angiotensin system (RAS) antagonists and beta-blockers are two key therapies in cardiology and are well established for primary and secondary prevention of cardiac events.

We hypothesized accordingly that the up-titration of RAS antagonists such as ACE inhibitors or angiotensinogen II receptor blockers and beta-blockers would be most effective for the prevention of cardiac events in a pre-defined subgroup of diabetes mellitus patients with increased NT-proBNP concentrations at baseline.

Methods

Study design. Patients with diabetes mellitus type 2 were enrolled in the study between November 20, 2007, and January 12, 2010. The observation period continued until the last patient exited the study on January 12, 2012. Inclusion criteria were known type 2 diabetes for at least 6 months, age $\geq$18 years of age, NT-proBNP concentrations >125 pg/ml, and willingness to participate. The target value of 125 pg/ml was chosen as our prior data had shown that this is an excellent threshold for risk prediction in this population (11). Cardiac disease–based exclusion criteria were one or more of the following: history of cardiac disease; signs of cardiac disease in the electrocardiogram such as atrial fibrillation; ST-T-wave abnormalities or a bundle branch block; abnormal echocardiography (with the exception of diastolic dysfunction), defined as low ejection fraction; wall motion abnormalities, significant valve dysfunction, or other significant alteration. Other exclusion criteria were a disease other than diabetes lowering the patient's life expectancy to <1 year, chronic infections or malignancies, systemic treatment with cortisone, renal replacement therapy, and for women of childbearing age the absence of reliable contraception. For the patient flow diagram, see Figure 1.

An experienced study nurse screened consecutive patients from 4 specialized diabetes centers (see subsequent sections) for participation in the study. If eligible, patients were invited to the tertiary cardiac care unit for detailed information about the study protocol. Informed consent was obtained from participating patients. Three hundred patients were prospectively digitally randomized 1:1 into a control group that was cared for at 4 different specialized diabetes care units and an intensified group that was additionally treated at the cardiac outpatient clinic of the Medical University of Vienna. The diabetes care units were the diabetic care outpatient departments of the Medical University of Vienna and of Hietzing Hospital, as well as 2 centers run by the Vienna Health Insurance Fund (Wiener Gebietskrankenkasse). All 4 centers employ experienced staff, and therapy was given based on current guidelines. (15)

A detailed medical history was taken for each patient at the baseline visit in the cardiac outpatient clinic to obtain information about concomitant diseases and current treatment. A 12-lead electrocardiogram was recorded, and an echocardiogram was performed. Blood pressure was measured in the supine position after 20-min rest, and blood was drawn from every patient. NT-proBNP was determined by a commercially available point-of-care system (COBAS H232, Roche Diagnostics Rotkreuz, Switzerland). To measure additional risk markers for cardiovascular disease, cholesterol (especially low-density lipoprotein cholesterol) from fasting samples was measured and HbA_{1c} was determined. Kidney function was determined by measuring serum-creatinine; the estimated glomerular filtration rate (eGFR) was calculated using the MDRD (Modification of Diet in Renal Disease) formula. Albuminuria was determined as the albumin/creatinine ratio from spot urine.

All patients visited the clinics at baseline and after 3, 6, and 12 months. At that time the functional status of patients was assessed, current treatment was recorded, and lab-based parameters were measured. Data were collected by the diabetes unit (control group) and the cardiac care unit (intensified group) of the Medical University of Vienna at every scheduled visit and computerized by a cardiologist who was not involved in the patients' care. For all patients, guideline-based treatments were initiated if not yet established (15). Specifically, all patients received antiplatelet therapy and lipid lowering agents if appropriate, and antihyperglycemic therapy was optimized by a diabetologist.

Patients in the intensified group had additional individualized visits for the initiation and up-titration of RAS

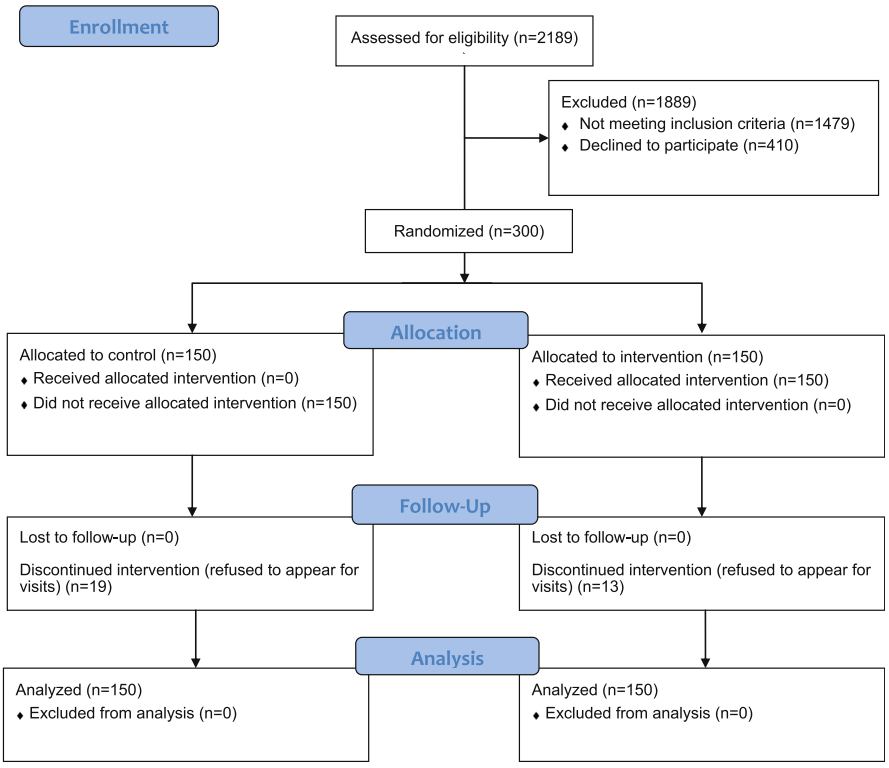

Figure 1 **Flow Diagram**

Enrollment, randomization, and follow-up of study participants.

antagonists and beta-blockers. In the intensified group, patients received a treatment logbook at their initial visit. In this logbook the physician noted the individual weekly titration steps, normally for the upcoming month. This way the dosage was increased very slowly (normally on a weekly basis) but steadily. Patients were instructed to measure blood pressure and heart rate at home and to record values. In case of hypotension (systolic blood pressure <100 mm Hg), bradycardia (heart rate <55 beats/min), or the onset of any new symptom before reaching the maximum dosage, they were advised to phone the outpatient unit. The physician then decided if the medication could be further up-titrated safely.

If the patient was already prescribed a RAS antagonist and a beta-blocker, these agents were titrated to the maximum recommended dosages. If the patient was not already prescribed a RAS antagonist, an ACE inhibitor was initiated. The same was true for beta-blockers. If the patient was not on any neurohumoral medication, the patient received an ACE inhibitor first; beta-blockers were prescribed in a second step.

Physicians increased the dosage of the medications until either NT-proBNP concentrations decreased by 50% or below normal values or a maximum recommended or tolerated dose was reached (see subsequent sections). Up-titration of therapy was scheduled within the first 3 months. The cardiologist was not involved in lifestyle recommendations or hospitalizations. Patients went for scheduled visits over a period of 1 year in the intensified group. The observation period for all patients was 2 years.

The study was conducted in accordance with the Helsinki II declaration and was approved by the ethics committee of the Medical University of Vienna. All participants gave written informed consent. The study was registered with clinical trial number NCT00562952.

Endpoints. The endpoints were assessed 2 years after the baseline visit of each patient. The primary endpoint was hospitalization or death due to cardiac disease.

Secondary endpoints were all-cause hospitalization, unplanned cardiovascular hospitalizations or death, and heart failure hospitalizations. A cardiovascular event was defined as any unplanned hospitalization or any death based on a cardiac or other macrovascular event. An additional secondary endpoint was a decrease of NT-proBNP concentrations after 1 year of intensified treatment.

Mortality data were obtained from the Austrian Central Office of Civil Registration (Zentrales Melderegister). Hospitalization information was obtained from the regional hospital data network (Krankenanstaltenverbund). The primary reasons for hospitalization were deduced from hospital files by a cardiologist who was not aware of the results at

the time of indexing or the randomization. The physician responsible was contacted for cases that were unclear.

Statistical analysis. The required sample size was calculated based on an expected event rate of 2% versus 9%, respectively, for the Fisher exact test, an alpha level at 0.05 and 1-beta = 0.80. Post hoc results revealed an actual power of 0.63 for the primary endpoint. Metric variables were presented as mean ± SD. Frequencies of categorical data were given by absolute numbers and percentages. Differences between groups were tested with the Student *t* test for metric variables, Fisher exact test for dichotomous variables, and the chi-square test for categorical data with more than 2 categories. Differences between baseline and follow-up were tested with respect to the data level either with paired-samples *t* test, the McNemar test, the Cochran's *Q* test, or the Wilcoxon matched-pairs signed rank test (for NT-proBNP after log-transformation).

Due to the nonlinear and nonnormal value distribution of NT-proBNP, this parameter was presented as the median and interquartile range. Differences in the value distribution between groups were tested with the nonparametric 2-sample Kolmogorov-Smirnov test.

We used the Kaplan-Meier method to estimate cumulative event-free survival functions and used a stratified log-rank test to compare the control and the intensified group. An additional Kaplan-Meier model was calculated including patients who did not participate in the study based on low (<125 pg/ml) NT-proBNP concentrations but who had given informed consent for further analysis.

We used unadjusted Cox regression models in order to test differences between the control and the intensified group. Additionally, we also calculated Cox models adjusted for age and log-transformed NT-proBNP concentrations at baseline for all endpoints. All results from the regression models were presented using hazard ratios EXP(B). Hazard ratios are given per unit increment. A p value of 0.05 was considered to indicate statistical significance for all tests. All analyses were performed with SPSS software (version 18.0.0, Chicago, Illinois).

Results

Patients' characteristics at baseline and after 1 year. Complete demographic data of the patients and differences between the parameters measured are described in Tables 1 and 2. For medication at baseline and target doses of medication for the entire cohort, see Online Table 1.

In the control group, 131 patients completed the study according to the study protocol, and 137 patients in the intensified group completed the study according to the protocol (Fig. 1).

After 12 months there was a significant difference between the control and intensified groups in both the number of patients treated with RAS antagonists and beta-blockers and in the dosage reached ($p < 0.0001$ for all). RAS antagonists were up-titrated to 100% of the recommended dosage in 79% of cases in the intensified group compared with 42% in the control group ($p < 0.0001$). Beta-blockers were up-titrated to 100% of the recommended dosage in 51% of cases in the intensified group and in only 10% of cases in the control group ($p < 0.0001$). A combination of 100% of the RAS antagonist and 100% of the beta-blocker recommended dosage was achieved in 46% of cases in the intensified group and in 5% of cases in the control group ($p < 0.0001$). Patients in the intensified group went to an average of 1.36 ± 0.96 additional visits. Reasons for not up-titrating to 100% of the recommended dosage were hypotension, bradycardia (<55 beats/min), nonadherence of the patient, or down-titration of medication by the primary care physician. Four patients in the intensified group were not up-titrated to the maximum dosage due to the development of normal NT-proBNP concentrations.

Blood pressure was significantly and similarly reduced in both groups after 12 months ($p = 0.003$ control group, $p = 0.002$ intensified group). Heart rate was reduced only in the intensified group ($p = 0.004$).

Changes in NT-proBNP. There was no significant decrease in NT-proBNP concentrations after 1 year in the intensified group. The control group NT-proBNP

Table 1 Baseline Characteristics

	Control (n = 150)	Intensified (n = 150)	p Value
Age, yrs	67.2 ± 9.6	67.8 ± 8.5	NS
Duration of diabetes, yrs	16 ± 12	15 ± 13	NS
Female	43.3	41.3	NS
History of hypertension	89	93	NS
History of nicotine use	44	40	NS
History of alcohol use	9	6	NS
Chronic obstructive lung disease	5	5	NS
Body mass index, kg/m^2	31 ± 7	30 ± 6	NS
Retinopathy (stage 0/1/2/3)	84/6/8/2	87/7/4/1	NS
Peripheral artery occlusive disease	15	13	NS
Peripheral artery occlusive disease (stage 0/1/2/3/4)	85/7/3/2/2	87/7/2/1/3	NS
Cerebral vascular disease	15	7	NS
Peripheral neuropathy	31	17	0.007

Values are mean ±SD or %.

Table 2 Baseline Characteristics and Follow-Up Values

	Control Baseline (n = 150)	Intensified Baseline (n = 150)	p Value	Control 12 Months (n = 131)	Intensified 12 Months (n = 137)	p Value
Blood pressure systolic, mm Hg	151 ± 22	151 ± 23	0.10	144 ± 22*	145 ± 22*	0.83
Heart rate, beats/min	72 ± 11	72 ± 12	0.78	72 ± 12	68 ± 11*	0.004
RAS antagonist, %	79	77	0.78	78	95*	0.0001
RAS % target dose	55 ± 40	57 ± 42	0.59	74 ± 31*	92 ± 30*	0.0001
Beta-blocker, %	45	54	0.13	44	85*	0.0001
Beta-blocker % target dose	24 ± 32	32 ± 35	0.05	54 ± 29*	80 ± 31*	0.0001
Statins	71 (47.3%)	72 (48.0%)	0.10	61 (40.7%)	70 (46.7%)	0.17
Aspirin	62 (41.3%)	63 (42.0%)	1.0	51 (34.0%)	63 (42.0%)	0.098
Oral antidiabetic drugs	68 (45.3%)	71 (47.3%)	0.62	61 (40.7%)	67 (44.7%)	0.62
Insulin	45 (30.0%)	42 (28.0%)	0.73	44 (29.3%)	35 (23.3%)	0.12
Triglycerides, mg/dl	154 ± 76	152 ± 70	0.83	146 ± 85	151 ± 85	0.63
LDL cholesterol, mg/dl	96 ± 33	94 ± 29	0.34	94 ± 32	89 ± 29*	0.21
eGFR, ml/min	81.5 ± 18.2	82.9 ± 18.2	0.51	82.2 ± 18.7	77 ± 17.6*	0.14
HbA_{1c}, %	6.9 ± 1	7.1 ± 1.1	0.27	7.1 ± 1.2*	7.1 ± 1	0.78
NT-proBNP, pg/ml	266 (181–402)	235 (169–343)	0.18	264 (167–394)	248 (169–433)	0.65

Values are mean ± SD, %, n (%), or median (interquartile range). *p < 0.05 baseline versus 12 months within a group. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for creatinine to micromoles per liter, multiply by 88.4.
eGFR = estimated glomerular filtration rate; NT-proBNP: N-terminal pro–B-type natriuretic peptide; RAS = renin-angiotensin system.

concentrations were comparable to concentrations in the intensified group after 1 year (Table 2). Among the patients that followed the scheduled visits (per protocol patients), 13 patients in each group developed normal concentrations of NT-proBNP (125 pg/ml). Of the 13 patients in the intensified group, 9 patients were treated with 100% of the RAS antagonist and beta-blocker dosage.

Safety. Potential side effects that would require hospitalization, such as hypotension, bradycardia, dizziness, hyperkalemia, or worsening kidney function, were not observed. One patient who experienced a cough under ACE inhibitor treatment was changed to an angiotensin II receptor blocker. Of note, there was a significant decrease of the estimated glomerular filtration rate overall in the intensified group (Table 2).

Outcome. Three patients in the intensified group and 5 patients in the control group died during the observation period. In the intensified group all witnessed deaths were noncardiac. One patient in this group died unwitnessed at home; this case was calculated as a cardiac death. In the control group, 3 of the 5 deaths were due to cardiac disease. Each patient who died due to a cardiac event had a cardiac hospitalization prior to death. For hospitalization data, see Table 3.

Kaplan-Meier analysis. The Kaplan-Meier analysis showed differences between the 2 groups for the primary endpoint. The difference was statistically significant (p = 0.035) (Fig. 2). The same was true for the endpoints: all cause hospitalization (p = 0.015), unplanned cardiovascular hospitalization/death due to cardiovascular disease (p = 0.046), and heart failure hospitalization (p = 0.031).

In the Kaplan-Meier model where we added the group of patients who did not enter the study solely based on low NT-proBNP (<125 pg/ml) there was a significant difference in the primary endpoint between the control group and the group with low NT-proBNP concentrations. There was no difference in survival between the intensified group and patients with low NT-proBNP concentrations (Online Fig. 1).

Cox regression models. Regarding the primary endpoint hospitalization or death due to cardiac disease, there was

Table 3 Reasons for Hospitalizations

Hospitalization Due to	All	Control	Intensified	p Value
Any reason	135 (45%)	77 (51%)	58 (39%)	0.02
Cardiovascular event	25 (8%)	18 (12%)	7 (5%)	0.02
Cardiac event	19 (6%)	14 (9%)	5 (3%)	0.03
Heart failure	8 (3%)	7 (5%)	1 (1%)	0.003

Values are n (%).

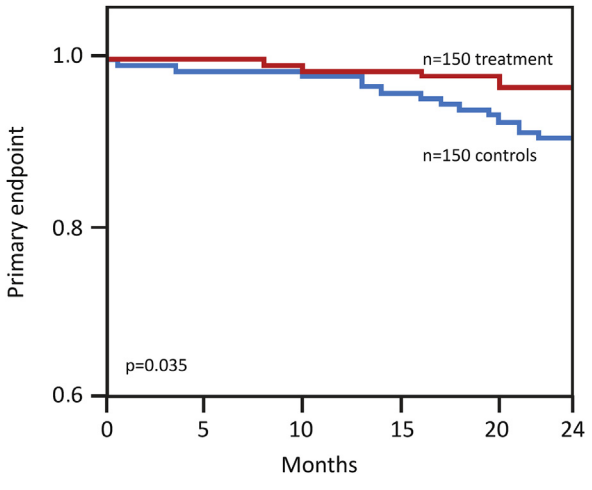

Figure 2 Kaplan-Meier Curves of the Primary Endpoint Hospitalization or Death Due to Cardiac Disease According to Treatment Strategy

Red line = intensified group. **Blue line** = control group. Log-rank test for overall difference, p = 0.035.

Table 4 Cox Regression Models (Unadjusted)

Endpoints	Hazard Ratio	95% Confidence Interval	p Value
Primary endpoint	0.351	0.127–0.975	0.04
All-cause hospitalizations	0.657	0.465–0.927	0.02
Unplanned cardiovascular hospitalizations or death	0.376	0.157–0.899	0.03
Heart failure hospitalizations	0.140	0.017–1.137	0.07

a significant difference between groups (hazard ratio: 0.351; 95% confidence interval: 0.127 to 0.975; $p = 0.044$).

A similar significant difference was seen for the secondary endpoints; see Table 4.

For all models adjusted for age and baseline log-transformed or absolute NT-proBNP, see Online Tables 2 and 3.

Changes in blood pressure between baseline and follow-up were not significant for any endpoint evaluated. Also, changes in heart rate did not influence outcome. Changes were calculated as absolute values and percentage of change.

Discussion

The PONTIAC (NT-proBNP Selected PreventiOn of cardiac eveNts in a populaTion of dIabetic patients without A history of Cardiac disease) study tested a primary preventive effect of combined neurohumoral therapy against hospitalization or death due to cardiac disease in patients with type 2 diabetes mellitus. Patient pre-selection using NT-proBNP concentration appears to identify diabetes patients who will benefit from neurohumoral therapy. The lack of any side effects requiring hospitalization during the study allows us to conclude that targeted blocking of neurohumoral activation in these patients is effective and safe. Remarkably, the preventive effect was already apparent after 2 years of observation, although the patients had an excellent background therapy concerning blood glucose and lipid goals.

Diabetes mellitus is a heterogeneous disease. It is well known from clinical practice that the cardiovascular risk of individual diabetes patients varies widely. Therefore, it seems possible that only certain subpopulations are at risk for the development of cardiac diseases (16). As outlined in the introduction, most studies with diabetes patients have failed to find a beneficial effect of standard therapy on cardiovascular outcome (1,2,7,8). Apart from the statistical weakness of low event rates in these studies, it can be argued that the reason for the disappointing study results might be not the drugs investigated but the wrong patient selection. This might also account for the contradictory results seen in the ONTARGET (ONgoing Telmirsatan Alone and in Combination with Ramipril Global Endpoint Trial) and ROADMAP (Randomized Olmesartan And Diabetes Microalbuminuria Prevention) studies, where the same class of drugs both decreased and increased cardiovascular events (8,17).

Previous studies demonstrated that NT-proBNP is an excellent predictor of long-term cardiac risk in patients with diabetes mellitus (14,18–20). Recently, we compared NT-proBNP with other important cardiac risk markers in diabetes and found that NT-proBNP has a greater predictive value in both the short and intermediate term (11,12). These factors strongly argue for the utility of NT-proBNP as the primary risk indicator for cardiac events.

The HOPE (Heart Outcomes Prevention Evaluation) and the STENO-2 trials were both successful studies using ACE inhibitors for the secondary prevention of cardiac events (6,21). As the majority of patients in both trials had a history of cardiovascular disease, the beneficial effect of both ACE inhibitor and angiotensin receptor blocker therapy is not surprising (22). What is more important in the context of the current study is that the authors tested post hoc the influence of NT-proBNP concentrations and found that it was primarily the patients with NT-proBNP concentrations above the median value who impacted the event rate (14).

The influence of beta-blockers on the primary or secondary prevention of cardiac disease in patients with diabetes mellitus is completely unknown, but from a pathophysiological perspective, counteracting the known overstimulated sympathetic nervous system is an interesting concept (23). As a means for secondary prevention in patients with cardiac disease, these agents have been established as an effective therapy for some time.

Unlike most previous studies in the field, we did not define traditional treatment goals regarding blood pressure, heart rate, or blood lipid values. Even the STENO-2 study failed to achieve those goals in most cases.

Changes in blood pressure and heart rate had no influence on outcome in our study. We found a similar decrease in blood pressure in both groups, despite the significant difference in our robust endpoints. Interestingly, the treatment effect was also independent of heart rate reduction. In our collective it appears that the statistically significant reduction of heart rate between baseline and follow-up in the intensified group indicates excellent adherence to the treatment, but seems to be only a surrogate of the depression of the sympathetic system.

The only treatment target in our study was a decrease in NT-proBNP concentrations. Contrary to our expectations, the allocation to a treatment group did not result in a significant decrease of this biomarker. Based on our experience that changes in NT-proBNP are predictive over time, we had hypothesized that the beneficial effect of neurohumoral therapy would, conversely, result in a subsequent decrease in concentration of the natriuretic peptides. In the STENO-2 trial and also in a recent analysis where we had tested the importance of changes in NT-proBNP on outcome, NT-proBNP levels actually increased over time (12,14). A separate study in a heart failure population demonstrated that long-term beta-blocker therapy was associated with decreased levels of plasma catecholamines but no decrease in the concentration of natriuretic peptides (24). Our data presented here do not allow us to draw a sound conclusion on why a decrease in risk by an

intervention did not result in a decrease of the biomarker. We therefore conclude that NT-proBNP is an excellent marker to select diabetic patients at risk of cardiac events, but more research is needed to guide the treatment using this biomarker, which has been proven to be effective in selected cohorts in heart failure (25,26).

The treatment combination seems safe, based on the lack of any adverse events requiring hospitalization during the study. Interestingly, the glycemic control achieved was significantly better in the intensified group. Although there was an aggressive up-titration of RAS antagonists and beta-blockers in an already well-treated population, there were no discontinuations of therapy or hospitalizations due to hypotensive symptoms or for worsening renal function. Among the reasons for this unexpected safety may be the individualized, slow but steady titration phase, which took up to 3 months. Another reason might have been the possibility to contact the outpatient department for advice if side effects emerged. It is worth noting that the glomerular filtration rate significantly decreased in the intensified group, which is a known and accepted effect of RAS inhibition (17,27).

Study limitations. A limitation of this trial was the absence of patient randomization for treatment, as withholding RAS antagonists is, at the very least, problematic based on the guidelines. However, data from previous studies in which patients were randomized for ACE inhibitor therapy argue that patient randomization for treatment would have increased the significance of our results. Second, the great majority of our patients were Caucasian; the results may not be the same in people of other races or ethnicities.

Finally, our statistical analysis was based on group comparisons without adjustment for additional covariates. Due to the low event rates, the validity of the adjusted models as shown in the appendix is limited and should be interpreted with caution. Also, adjusting for NT-proBNP is problematic as therapy and NT-proBNP are both functions of risk. The treatment provided is probably not able to surpass the risk mirrored by NT-proBNP. Therefore NT-proBNP remains a significant influencing factor superior to the treatment effect. This at least was true for log-transformed NT-proBNP (Online Table 3). The end-points remained significant, if NT-proBNP was included as an absolute value in the adjusted model (Online Table 3).

Conclusions

Our data suggest that accelerated up-titration of RAS antagonists and beta-blockers to maximum tolerated dosages is an effective and safe intervention for the primary prevention of cardiovascular events in a population of patients with diabetes pre-selected using NT-proBNP. Further study is required to validate these observations in larger populations. Especially patients with low NT-proBNP also have to be analyzed to test whether the treatment effect is exclusively present in patients with increased concentrations of NT-proBNP. We would expect that based on the low event rates in a population with low NT-proBNP the number to treat would be substantially higher than in the population presented in the PONTIAC trial.

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Reprint requests and correspondence: Dr. Richard Pacher, Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria. E-mail: richard.pacher@meduniwien.ac.at.

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Key Words: beta-blockers ▪ diabetes mellitus ▪ NT-BNP-selected ▪ primary prevention ▪ RAS antagonists.

APPENDIX

For a supplemental figure and tables, please see the online version of this article.