DE GRUYTER OPEN

http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **22**(2):141-149
doi: 10.1515/rjdnmd-2015-0018

THE ROLE OF ELEVATED NT-PROBNP AND ALBUMINURIA AS CARDIO-VASCULAR RISK FACTORS IN TYPE 2 DIABETES MELLITUS PATIENTS AFTER ACUTE CORONARY SYNDROME

Johann Trutz [1], ***Aurel Babeș*** [2,✉], ***Katalin Babeș*** [2,3]

[1] Praxis fur Allgemeine Medizin Dr. Med. S. Hoppe, Darmstadt, Germany
[2] Faculty of Medicine and Pharmacy, Oradea University, Oradea, Romania
[3] Coronary Intensive Care Unit, Cardiology Clinic, Bihor County Emergency Clinical Hospital, Oradea, Romania

received: March 25, 2015 *accepted*: May 22, 2015
available online: June 15, 2015

Abstract

Background and Aims. *The identification of type 2 diabetes mellitus (T2DM) patients with high cardio-vascular risk became more crucial, especially in patients with known coronary artery disease (CAD). Our study is focusing on T2DM patients who suffered recently an acute coronary syndrome (ACS), and evaluates the importance of albuminuria and NT-proBNP level as risk factors for short-term recurrence.* ***Material and methods.*** *221 T2DM patients with recent ACS were evaluated 1 month after discharge, assessing NT-proBNP and albuminuria level and followed for 12 months for major adverse cardiac events (MACE).* ***Results.*** *Patients who reached the endpoint (33%) presented significantly higher levels of NT-proBNP (458.5 vs. 207.4 pg/ml, p<0.0001) and urinary albumin/creatinine ratio (80 vs. 27 mg/g, p<0.0001) than those who did not present a MACE in the follow-up period. Comparison of the MACE-free survival curves revealed that NT-proBNP has a better power than albuminuria in the prediction of the short-term outcome: hazard ratio (HR)=1.6176 (95%CI: 1.0047-2.6044), p=0.0433 vs. HR=1.4813 (95%CI: 0.8497-2.5824), p=0.1921. Only the NT-proBNP level entered the multivariable regression model besides age and represents an independent risk factor (HR=1.0025, 95%CI: 1.0014-1.0035, p=0.0036).* ***Conclusion.*** *NT-proBNP provides excellent prognostic information in patients with diabetes mellitus who recently suffered an ACS. Albuminuria wasn't an independent risk factor in this cohort.*

key words: *acute coronary syndrome, type 2 diabetes mellitus, albuminuria, NT-proBNP, major adverse cardiac events.*

Background and Aims

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease widespread through the world which has provoked considerable worrisome for public health care workers. Despite the fact that major progresses were recorded in the treatment of this disease, the prevalence and complications of T2DM are increasing [1]. Cardiovascular disease is the major cause of death in T2DM patients [2]. Many of diabetic patients with coronary artery disease (CAD) don't have any other classic risk factor for coronary disease and half of them have

✉ Str. General Henri Matthias Berthelot nr.21, 410050 Oradea Romania; Phone number: +40744793185; *corresponding author e-mail*: piszekati@yahoo.co.uk

normal lipid profiles [3]. This is why researchers in this field are looking for new risk factors to identify patients who are prone to CAD.

Albuminuria is present in about 30% of middle-aged patients with either type 1 or type 2 diabetes mellitus [4]. Albuminuria is a marker of endothelial dysfunction and vascular damage which could be a predictor for coronary artery atherosclerosis [5,6] and early mortality in patients with T2DM, independent of renal function [7]. Numerous studies have dealt with the importance of albuminuria in predicting long term (5-12 years) cardiovascular risk in patients with diabetes mellitus [8,9], and since the early 1980's albuminuria has been considered the gold standard for predicting cardiovascular events [10,11]. Recent data even indicated its importance in patients with established cardiac disease [12].

A better understanding of the pathophysiological mechanisms underlying cardio-vascular diseases has led to the discovery of numerous relevant markers [13]. Of those, N-terminal of the prohormone brain natriuretic peptide (NT-proBNP) is regarded as the most important risk-marker in cardiac disease [14]. The predictive value of neurohormones and especially NT-proBNP in patients with diabetes mellitus has been the subject of a limited number of studies [15-17].

Selection of T2DM patients for intensified treatment appears to be a new challenge in the era of limited resources on one hand and due to the questionable benefit of these interventions in distinct patient groups on the other. In recent megatrials examining patients with a long duration of diabetes, no beneficial effects of intensified antihyperglycemic therapy on cardiovascular outcome was seen [18-20]. Similar findings were presented for an aggressive lipid modulation in which addition of fibrates to statin therapy did not add any benefit to cardiovascular (CV) events prevention [21] or intensified blood pressure control [22]. Taken individually, these findings are quite different from the earlier results of the Steno 2 study, which investigated the influence of an intensive but multifactorial therapy on the incidence of cardiovascular events in a high-risk population of diabetic patients [23]. In this study including a highly selected population of albuminuric patients, significant treatment effects were noted despite the small number of patients included, proving the importance of multifactorial intervention in T2DM patients for the prevention of CV events.

According to these studies results, the selection of T2DM patients with high cardio-vascular risk became more crucial, especially in patients with known CAD. Our study is focusing on the T2DM patients who suffered recently an acute coronary syndrome (ACS), and evaluates the importance of albuminuria and NT-proBNP level, measured one month after the hospitalization, as risk factors for the short-term recurrence of CV events. We also aimed to determine the approximate cut-off values for each risk factor for the best prediction of adverse cardiac events in the follow-up period.

Material and Methods

Our study included 221 T2DM patients who were admitted in hospital in the last month for an ACS (unstable angina, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction). The selected patients were treated in Bihor County Emergency Clinical Hospital, Oradea, Romania and 6 Hospitals in the region of Darmstadt, Germany between 01.01.2013 and 31.12.2013. The diagnosis of ACS has been based on the American College of Cardiology (ACC) / American Heart Association (AHA) guidelines [24]. Inclusion criteria were: previous diagnosis

of T2DM, proved by either medical records or past laboratory results compatible with the diagnosis of T2DM, according to the American Diabetes Association (ADA) 2010 Revised Clinical Practice Guidelines for diabetes diagnosis [25]. All patients gave written informed consent prior to inclusion, according to the Helsinki II declaration.

The cohort study design was observational and prospective. We recorded the patient's age, gender, body-mass index (BMI), laboratory tests (including HbA1c level at discharge) and the type of the reperfusion therapy from the clinical records. The NT-proBNP level and the extent of albuminuria was determined 1 month after the discharge from the hospital.

After the patients had been at rest for at least 20 min in the supine position, venous blood samples for analysis of plasma NT-proBNP were collected. Plasma concentrations of NT-proBNP were measured by a sandwich immunoassay method in both countries.

Urinary albumin and creatinine were measured from a fresh morning spot urine sample stored at 4°C for <1 week. Urinary albumin was measured with immunoturbidimetric tests. Urinary creatinine was measured with Jaffe's kinetic method. The urinary albumin-to-creatinine ratio (UAC) was calculated to determine the categories for different levels of albuminuria: under 30 mg/g – normoalbuminuria, 30-300 mg/g – microalbuminuria, over 300 mg/g – macroalbuminuria.

The endpoint of this study was the rate of major adverse cardiac events (MACE) at 12 months. MACE included cardio-vascular mortality, myocardial infarction (MI), malignant arrhythmia, cardiac arrest, cardiogenic shock, congestive heart failure (CHF), hospitalisation for angina, and hospitalisation for heart failure. Cardiogenic shock was defined as systolic blood pressure <90 mm Hg or a drop of mean arterial pressure >30 mm Hg with a pulse >60 beats per minute (to exclude shock secondary to bradycardia) and/or low urine output (<0.5 mL/kg/h) with or without evidence of organ congestion [26]. Malignant arrhythmia was defined as symptomatic sustained ventricular tachycardia and also ventricular fibrillation, irrespective of symptoms or hemodynamic stability.

The follow-up was made by telephone monthly for 1 year after the inclusion in the study to exclude bias from losing data regarding the endpoint.

Statistical analysis. We used MedCalc version 12.5.0.0 (MedCalc Software, Mariakerke, Belgium) for statistical analysis. The Kolmogorov-Smirnov test was applied to examine normal distribution. Continuous variables with normal distribution were presented as mean and standard deviation – SD (in brackets); those with normal distribution after logarithmic transformation as geometric mean and 95% confidence interval (CI) (in brackets); those with skewed distribution as median and interquartile range (in brackets). Categorical variables were presented as number of patients and percentage. Baseline characteristics of the 2 groups were compared using the χ^2 test or the Fisher exact test for categorical variables, the Student unpaired t test for continuous variables with normal distribution and the Mann-Whitney test for those with skewed distribution, as appropriate. The dates of CV-related death, and MACE were recorded. The Receiver Operating Characteristic (ROC) curves with the highest Youden index were used to determine the best cut-off values. Twelve-month event-free survival was estimated by the Kaplan-Meier method and was compared with the log-rank test. Logistic regression with stepwise introduction method was used to select the independent risk factors and odds ratios. A $p< 0.05$ was considered statistically significant.

Results

From the originally included 221 patients 15 were lost (no response to follow-up phone calls). A number of 68 patients (33.0%) reached the endpoint (presented a major cardiac adverse event in the follow-up period). The geometric mean of the measured NT-proBNP at 1 month after discharge was 269.5 pg/ml (95% CI: 238.5-304.4 pg/ml). 97 patients (47.1%) presented microalbuminuria, 12 reached the limit of macroalbuminuria (5.8%) and 97 patients (47.1%) were detected with UAC ratio under 30 mg/g (normoalbuminuria).

The baseline characteristics of the study group divided according to the endpoint of the study occurrence are shown in Table 1.

Table 1. Patient baseline characteristics.

Variable	Without MACE n=138	With MACE n=68	p value
Demographics			
Age (years), Mean (SD)	60.5 (9.1)	66.8 (12.5)	0.0001
Male, n (%)	74 (53.6%)	34 (50.0%)	0.7329
BMI (kg/m^2) Median (interquartile range)	29.4 (25.7-35.44)	28.2 (25.7-33.9)	0.6817
Lab results			
HbA1c (%) Median (interquartile range)	6.5 (5.9-7.9)	6.9 (6.2-8.0)	0.1888
Total cholesterol (mg/dl) Median (interquartile range)	211 (184-242)	219 (184-244)	0.7148
Triglycerides (mg/dl) Median (interquartile range)	160.5 (101-222)	177.5 (105-218)	0.6817
Serum Creatinine (mg/dl) Mean (SD)	0.97 (0.21)	1.27 (0.5)	<0.0001
Type of ACS			
Unstable angina, n (%)	48 (34.8%)	17 (25.0%)	0.2702
NSTEMI, n (%)	66 (47.8%)	31 (45.6%)	0.8775
STEMI, n (%)	24 (17.4%)	20 (29.4%)	0.0721
Treatment modality			
Conservative, n (%)	64 (46.4%)	21 (30.9%)	0.0362
PCI, n (%)	70 (50.7%)	43 (63.2%)	0.1025
CABG, n (%)	4 (2.9%)	4 (5.8%)	0.4436

Abbreviations: MACE, major adverse cardiac events; BMI, Body-mass index; HbA1c, glycosylated haemoglobin; SD, standard deviation; ACS, acute coronary syndrome; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

No significant differences were found between the 2 groups, except for some known cardio-vascular risk factors: age, renal impairment. Regarding to the type of ACS and treatment modality we noticed a higher rate of STEMI and PCI in the worse outcome group, but without significant statistical difference. The only remarkable inequality appeared in the rate of conservative treatment modality, which was lower in the MACE group.

Analysing the results of the laboratory tests recorded at 1 month after discharge, we observed significant difference between the two groups of T2DM patients for both NT-proBNP and UAC as shown in Table 2.

Table 2. NT-proBNP and UAC ratio at 1 month after discharge.

Variable	Without MACE n=138	With MACE n=68	p value
NT-proBNP (pg/ml) Geometric mean (95% CI)	207.4 (179.9-239.0)	458.5 (384.6-546.6)	<0.0001
UAC ratio, mg/g Median (interquartile range)	27 (19-94)	80 (47.5-174)	<0.0001

Abbreviations: MACE, major adverse cardiac events; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; 95% CI, 95% confidence interval; UAC ratio, urinary albumin creatinine ratio.

With the help of the Receiver Operating Characteristic (ROC) curve analyses we

established the best cut-off points for the two variables (Figure 1): 400 pg/ml (rounded up from 385 pg/ml) for NT-proBNP and 30 mg/g for UAC ratio. Comparing the area under the curve (AUC) for the two risk factors we can observe that NT-proBNP has better prognostic value than UAC ratio in this group of T2DM patients (0.777 vs. 0.699, p=0.0735).

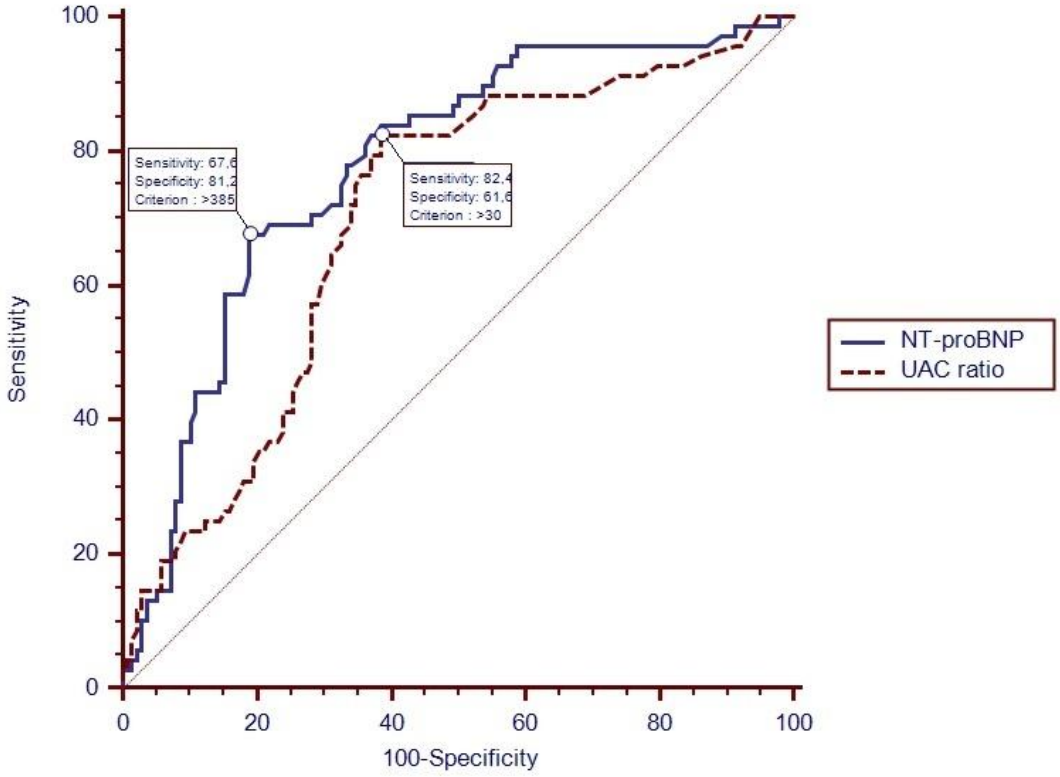

Figure 1. *ROC curve for NT-proBNP and UAC ratio regarding to the primary endpoint (MACE in 12 month).*

Using these cut-off levels we have calculated the corresponding odds ratios in univariate analysis that are given in Table 3.

Table 3. Odds ratios for the endpoint in the two subgroups depending on NT-proBNP and UAC ratio level.

	Odds ratio (CI 95%)	p value
NT-proBNP over 400 pg/ml	6.4571 (3.375-12.353)	<0.0001
UAC ratio over 30 mg/g	7.4843 (3.673-15.247)	<0.0001

For the purpose of multivariate analysis we introduced in the stepwise logistic regression model all registered variables that can predict the outcome (age, gender, BMI, HbA1c, cholesterol, triglycerides, creatinine, NT-proBNP level, UAC ratio). The result of this revealed that only the age and the level of NT-proBNP constitute independent risk factors for the endpoint in this group of patients. The multivariate odds ratios for these variables were: 1.0025 (95% CI: 1.0014-1.0035, p=0.0036) for NT-proBNP and 1.0490 (95% CI: 1.0217–1.0711, p=0.001) for age.

The MACE-free Kaplan-Meier survival curves also demonstrate significant differences between the 2 variables: for patients with NT-proBNP under 400 pg/ml the survival curve shows significantly better prognosis than for those with this cardiac biomarker over 400 pg/ml – logrank test: hazard ratio (HR)=1.6176, 95% CI: 1.0047-2.6044, p=0.0433 (Figure 2); in the same time this difference is not so remarkable in albuminuric patients compared to non-albuminuric patients – logrank test: HR=1.4813, 95%CI: 0.8497-2.5842, p=0.1921 (Figure 3).

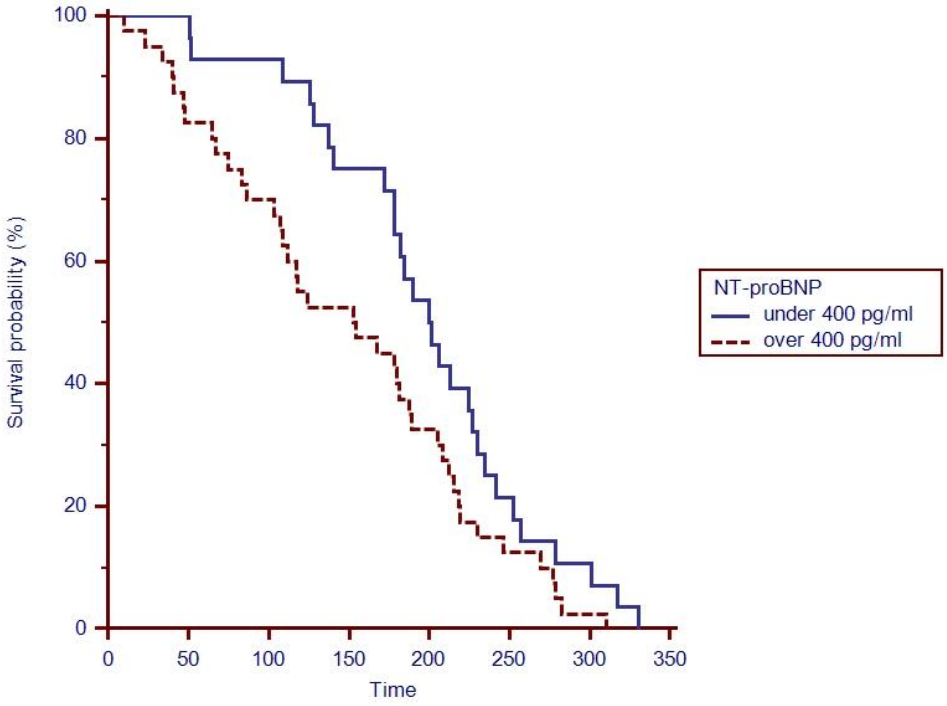

Figure 2. *MACE free Kaplan-Meier survival curves for patients with NT-proBNP over 400 pg/ml and under 400 pg/ml.*

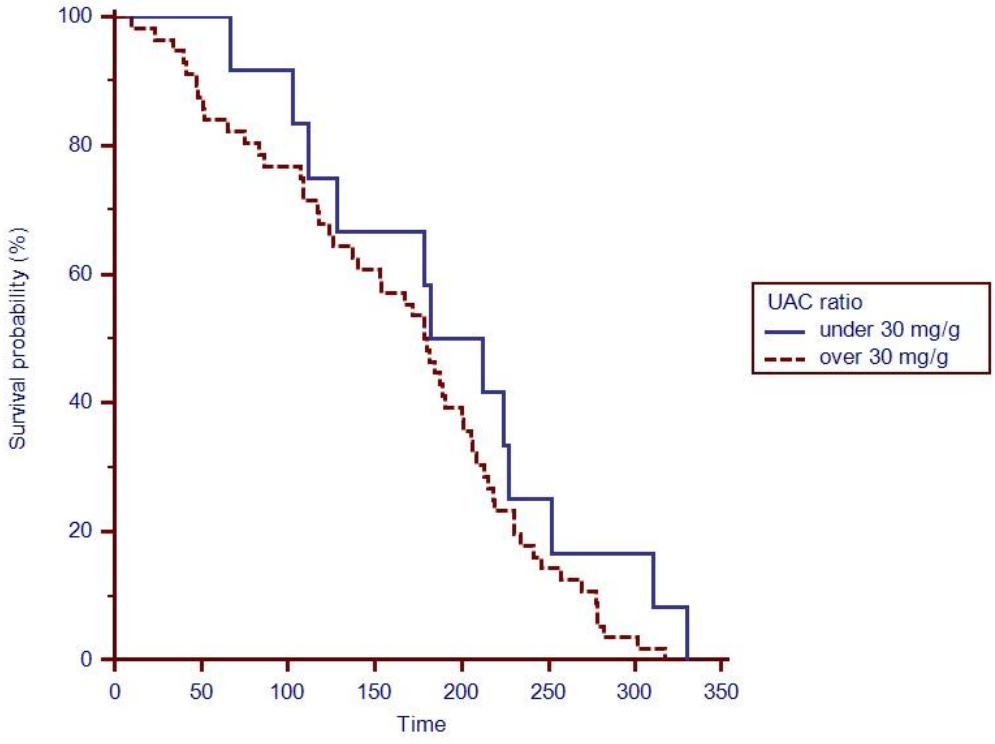

Figure 3. *MACE free Kaplan-Meier survival curves for patients with UAC ratio over 30 mg/g and under 30 mg/g.*

Discussion

To our knowledge this is the first study directly comparing albuminuria to NT-proBNP level in order to predict short-term outcome in known CAD patients with diabetes.

There are numerous established CV risk-markers for patients with diabetes mellitus to

determine the patient's CV risk profile. Albuminuria is most commonly used as the predictor of choice for CV risk [10]. Recommendations state that patients with albuminuria or advanced age should be more aggressively treated in regard to CV prevention. Albuminuria reflects vascular injury in the kidney, and is thereby a marker for secondary morphologic organ damage. Quite differently, NT-proBNP is directly linked to the function of the heart, as it is secreted by the ventricles in response to cardiac stress. Thus, NT-proBNP levels are elevated early in the course of disease, at the stage of functional impairment of the CV system. NT-proBNP is partly cleared by the kidneys and increases with the severity of renal dysfunction. This implies that peripheral organ damage is also reflected by increased levels of NT-proBNP [27]. The increased cardiac NT-proBNP release and reduced degradation by the kidneys add independent information to risk profiling. Looking at this as a whole, this might explain the superiority of NT-proBNP to albuminuria.

Gaede et al showed that stratifying the STENO population into those with high or low NT-proBNP, unmasks two distinct populations [15]. In the group of patients with low NT-proBNP concentrations, no treatment effect could be demonstrated, since this group did not experience significant adverse events, regardless of their randomization into the treatment arm or control arm. In the high NT-proBNP group, the event rate showed a five-fold increase. Therefore, treatment effects seem to be relevant only in this population. If NT-proBNP were used as a risk marker, we could safely focus our attention on a smaller group of high-risk patients.

Study limitations. The power of the study can be inadequate to detect a slight difference in clinical outcomes due to the relatively small study population. Therefore, it will be more informative if a larger sample size is studied. In addition, there are some risk factors that were not evaluated related to the endpoints because the lack of data: low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C) profiles, median values of blood pressure during the follow-up period, compliance to the recommended cardiologic treatment. These can constitute limitations for the present study. The lost 15 patients from the originally included cases can represent possible bias if they contain more patients with MACE in the follow-up period.

Conclusions

Similar to its prognostic power in cardiac disease, NT-proBNP provides excellent prognostic information in patients with diabetes mellitus who recently suffered an ACS. Albuminuria was not proven to be an independent risk factor in this cohort. Our data helps to select the target populations for tertiary CV prevention in patients with T2DM following an ACS.

Acknowledgements – none.

Duality of interest – no conflicts of interest.

REFERENCES

1. **Wild S, Roglic G, Green A, Sicree R, King H.** Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27: 1047-1053, 2004.

2. **Panzram G.** Mortality and survival in type 2 (non-insulindependent) diabetes mellitus. *Diabetologia* 30: 123-131, 1987.

3. **Pahor M, Elam MB, Garrison RJ, Kritchevsky SB, Applegate WB.** Emerging noninvasive biochemical

measures to predict cardiovascular risk. *Arch Intern Med* 159: 237-245, 1999.

4. Gerstein HC, Mann JF, Pogue J et al. Prevalence and determinants of microalbuminuria in high‐risk diabetic and nondiabetic patients in the Heart Outcomes Prevention Evaluation Study. The HOPE Study Investigators. *Diabetes Care 23[Suppl 2]: B35-B39*, 2000.

5. Stehouwer CD, Henry RM, Dekker JM, Nijpels G, Heine RJ, Bouter LM. Microalbuminuria is associated with impaired brachial artery, flow-mediated vasodilation in elderly individuals without and with diabetes: further evidence for a link between microalbuminuria and endothelial dysfunction - the Hoorn Study. *Kidney Int Suppl* (92): S42-S44, 2004.

6. Quyyumi AA. Prognostic value of endothelial function. *Am J Cardiol* 91(12A): 19H-24H, 2003.

7. Adler AI, Boyko EJ, Ahroni JH, Smith DG. Lower extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. *Diabetes Care* 22: 1029-1035, 1999.

8. Valmadrid CT, Klein R, Moss SE, Klein BE. The risk of cardiovascular disease mortality associated with microalbuminuria and gross proteinuria in persons with older-onset diabetes mellitus. *Arch Intern Med* 160: 1093-1100, 2000.

9. Mattock MB, Barnes DJ, Viberti G et al. Microalbuminuria and coronary heart disease in NIDDM: an incidence study. *Diabetes* 47: 1786-1792, 1998.

10. Gerstein HC, Mann JF, Yi Q et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. *JAMA* 286: 421-426, 2001.

11. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. *N Engl J Med* 310: 356-360, 1984.

12. Jackson CE, Solomon SD, Gerstein HC et al. Albuminuria in chronic heart failure: prevalence and prognostic importance. *Lancet* 374(9689):543-550, 2009.

13. Omland T, de Lemos JA, Sabatine MS et al. A sensitive cardiac troponin T assay in stable coronary artery disease. *N Engl J Med* 361: 2538-2547, 2009.

14. Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 50: 2357-2368, 2007.

15. 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.

16. 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* 293: 1609-1616, 2005.

17. Tarnow L, Gall MA, Hansen BV, Hovind P, Parving HH. Plasma N-terminal pro‐B‐type natriuretic peptide and mortality in type 2 diabetes. *Diabetologia* 49: 2256-2262, 2006.

18. ADVANCE Collaborative Group, Patel A, MacMahon S et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358: 2560-2572, 2008.

19. ACCORD Study Group, Gerstein HC, Miller ME et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358: 2545-2559, 2008.

20. Duckworth W, Abraira C, Moritz T et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 360: 129-139, 2009.

21. ACCORD Study Group, Ginsberg HN, Elam MB et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 362: 1563-1574, 2010.

22. ACCORD Study Group, Cushman WC, Evans GW et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 362: 1575-1585, 2010.

23. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348: 383-393, 2003.

24. Amsterdam EA, Wenger NK, Brindis RG et al. 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines *J Am Coll Cardiol* 64: e139-e228, 2014.

25. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 33[Suppl. 1]: S62–S69, 2010.

26. Lavi S, Kapeliovich M, Gruberg L et al. Hyperglycemia during acute myocardial infarction in patients who are treated by primary percutaneous coronary

intervention: impact on long-term prognosis. *Int J Cardiol* 123: 117–122, 2008.

27. 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.

1