

## **Insufficient control of blood pressure and incident diabetes**

*Diabetes and blood pressure control*

Short title:

Raffaele Izzo<sup>a</sup>, MD, PhD  
Giovanni de Simone<sup>b</sup>, MD  
Marcello Chinali<sup>b</sup>, MD, PhD  
Guido Iaccarino<sup>a</sup>, MD, PhD  
Valentina Trimarco<sup>c</sup>, PhD  
Francesco Rozza<sup>a</sup>, MD, PhD  
Renata Giudice<sup>a</sup>, MD  
Bruno Trimarco<sup>a</sup>, MD  
Nicola De Luca<sup>a</sup>, MD

<sup>a</sup>Department of Clinical Medicine, Cardiovascular and Immunological Sciences;

<sup>b</sup>Department of Clinical and Experimental Medicine,

<sup>c</sup>Department of Neuroscience. Federico II University, Naples, Italy.

### **Address for correspondence:**

Bruno Trimarco, MD

e-mail: [trimarco@unina.it](mailto:trimarco@unina.it); [simogi@unina.it](mailto:simogi@unina.it)

Submitted 23 October 2008 and accepted 3 February 2009.

This is an uncopyedited electronic version of an article accepted for publication in *Diabetes Care*. The American Diabetes Association, publisher of *Diabetes Care*, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of *Diabetes Care* in print and online at <http://care.diabetesjournals.org>.

*Objectives:* Incidence of type 2 diabetes might be associated with preexisting hypertension. There is no information on whether incident diabetes is predicted by blood pressure (BP) control. We evaluated the hazard of diabetes in relation to BP control in treated hypertensive patients.

*Research design and Methods:* Non-diabetic, otherwise healthy, hypertensive patients (n=1754, age 52±11yrs, 43% women) participated in a network over 3.4±1yr follow-up. BP was considered uncontrolled when systolic  $\geq 140$ mmHg or/and diastolic  $\geq 90$ mmHg at last outpatient visit. Diabetes was defined according to ADA guidelines.

*Results:* Uncontrolled BP despite antihypertensive treatment was found in 712 patients (41%). At baseline, patients with uncontrolled BP were slightly younger than patients with controlled BP (51±11 vs 53±12yrs;  $p < 0.001$ ) with no differences in gender distribution, body mass index, duration of hypertension, baseline BP, fasting glucose, serum creatinine and potassium, lipid profile or prevalence of metabolic syndrome. During follow-up, 109 subjects developed diabetes. Incidence of diabetes was significantly higher in patients with uncontrolled BP (8%) than in those with controlled BP (4 %; OR= 2.08;  $p < 0.0001$ ). In Cox analysis, controlling for baseline systolic BP and body mass index, *familiarity and physical activity*, uncontrolled BP doubled risk of incident diabetes (HR= 2.10;  $p < 0.001$ ), independently of significant effect of age (HR= 1.02/yr;  $p = 0.03$ ) and baseline fasting glucose (HR=1.10/mg×dL<sup>-1</sup>;  $p < 0.001$ ).

*Conclusion:* In a large sample of treated non-diabetic hypertensive subjects, uncontrolled BP is associated with 2-fold increased risk of incident diabetes independently of age, body max index, baseline BP and fasting glucose.

**A**rterial hypertension is common in patients with type 2 diabetes. A survey of over 1,500 patients with diabetes, conducted between 1988 and 1994, determined that 60–80% had blood pressure higher than 130/85 mmHg or had been prescribed antihypertensive medication (1). Results from the MRFIT study indicated that diabetes confers greater cardiovascular risk for comparable levels of other cardiovascular risk factors, suggesting that blood pressure (BP) control should be more rigorous in the presence of diabetes (2). However, there is no clearly defined temporal relationship between diabetes and hypertension.

Incidence of type 2 diabetes, in fact, also increases with increased baseline BP in women without prevalent diabetes, based on modified categories of BP from ESH/ESC 2007 guidelines (3). There is increasing evidence of a substantial interplay of metabolic factors with arterial hypertension (4; 5). We have recently shown that optimal control of BP is blunted by coexisting metabolic risk factors, clustering the phenotype of metabolic syndrome (4). There is no information about whether a suboptimal control of BP might be also associated with incident diabetes, independently of confounders. Accordingly, we tested the hypothesis that insufficient control of BP is an independent risk factor for diabetes in a cohort of hypertensive patients with initial normal fasting plasma glucose.

## **METHODS**

**Population study:** As previously reported (6), beginning in 1997 we generated a network among the Hypertension Center of the Federico II University Hospital (Naples, Italy), 23 Community Hospital-based Hypertension Clinics and 60 General Practitioners from our district area

(CampaniaSalute Network) including over 12,000 cardiovascular patients, of whom 10,254 had arterial hypertension. Among hypertensive subjects, 7,422 were initially free of prevalent cardiovascular disease (6). Prevalent cardiovascular disease was defined at the first examination in our outpatient clinic, and included previous myocardial infarction or angina or procedures of coronary revascularization, stroke or transitory ischemic attack or congestive heart failure. Prevalent cardiovascular disease was excluded by the Committee for Event Adjudication in the Hypertension Center, and was based on patients' history, contact with the reference general practitioner and clinical records documenting the occurrence of disease.

Criteria for selection in the present study included the availability of a follow-up of at least 2 years, and absence of diabetes at the time of the first visit. According to these criteria, we excluded 5,668 patients: 4,957 with follow up less than 2 years (3,258 due to enrolment in the past 2 years and 1,699 lost to follow-up), 386 with prevalent diabetes and 325 with reported impaired fasting glucose at the time of the first visit. Thus, we analyzed 1,754 Caucasian hypertensive patients (43% women, age  $52 \pm 11$  years), with normal fasting glucose, who had been followed up for  $3.5 \pm 1.8$  years. All eligible participants underwent at least 2 control visits after the first examination.

The data-base generation of the CampaniaSalute Network was approved by the Federico II University Hospital Ethic Committee. Signed informed consent for the possibility of using data for scientific purposes was obtained.

**Laboratory tests and definitions:** Fasting plasma glucose and lipid profiles were measured by standard methods. Glomerular filtration rate was estimated from

serum creatinine by the modified MDRD equation (7).

*According to a questionnaire, patients were asked to classify their life style as sedentary or non-sedentary. This information was used in the analysis as a raw indicator of physical activity.*

Systolic and diastolic blood pressures were measured at each visit by standard sphygmomanometer after 5 min in sitting position, according to the guidelines of the European Society of Hypertension/European Society of Cardiology (8). Three blood pressure measurements were always obtained in the sitting position at 2-min intervals. The average of these measurements was used for the analysis (8).

Body mass index (BMI) was calculated at each visit. *When  $BMI \geq 30 \text{ kg/m}^2$ , patients were classified as obese and were assumed to have central fat distribution (9).* Diagnosis of metabolic syndrome was, therefore, issued according to modified ATP III criteria (4; 5), and included at least two metabolic risk factors among plasma triglycerides  $\geq 150 \text{ mg/dl}$ , fasting plasma glucose  $\geq 110 \text{ mg/dl}$ , high-density lipoprotein (HDL)-cholesterol  $\leq 40 \text{ mg/dl}$  for men or  $\leq 50 \text{ mg/dl}$  for women,  $BMI \geq 30 \text{ kg/m}^2$  (as a surrogate of increased waist girth). Non-HDL cholesterol was also calculated as the difference between total and HDL cholesterol.

The number of antihypertensive medications used at the time of each visit was also evaluated. Blood pressure was considered controlled when  $< 140/90 \text{ mmHg}$ , otherwise it was classified as uncontrolled. Reported medical diagnostic codes for diabetes and prescriptions of oral hypoglycaemic drugs or insulin were used to identify prevalent and incident cases of diabetes. Prevalent and incident diabetes was also diagnosed when fasting plasma glucose was  $> 125 \text{ mg/dL}$ , according to ADA guidelines (10).

**Statistical Analysis:** Data were analyzed using SPSS (version 12.0; SPSS, Chicago, IL) and expressed as means  $\pm 1SD$ . All variables deviating from normal distribution were log-transformed before parametric statistics. Descriptive statistics were performed using ANOVA or chi-square distribution, using MonteCarlo simulation to generate exact p-values.

The last available value of BP was used to classify controlled or uncontrolled patients. For patients developing diabetes, we used the last available BP control before diabetes was diagnosed. Incidence of diabetes in relation to controlled or uncontrolled BP was evaluated using Cox regression, by enter procedure, controlling for baseline values of age (years), sex, BMI, fasting plasma glucose, familiarity for diabetes, BP at the time of the first visit, and *sedentary or non sedentary life style. Alternative models were also computed using the last available BP value instead of categories of controlled/uncontrolled BP.*

To account for by therapy in the Cox model, single classes of medications, including anti renin-angiotensin system (RAS: ACE inhibitors and/or AT1 receptor antagonists), calcium-channel blockers (CCB),  $\beta$ -blockers, thiazide diuretics, were dichotomized according to their overall use during the individual follow-up, based on the frequency of prescription during the control visits. Thus, all medications used for more than 50% of control visits were considered as covariates in a new proportional hazard analysis. In this Cox model we used a hierarchical model with a 1<sup>st</sup> step in which all covariates used in the previous Cox analysis were entered by a backward model building procedure (p-to-enter  $< 0.05$ , p-to-remove  $\geq 0.15$ ), and a 2<sup>nd</sup> step in which the classes of medications were thereafter forced into the model.

## RESULTS

Uncontrolled BP despite therapy was found in 712 patients (41% of population). Baseline characteristics in relation to control of blood pressure are shown in Table 1. At baseline, patients with subsequent uncontrolled BP were younger ( $p<0.001$ ) and had higher heart rate ( $p<0.02$ ) than patients with controlled BP, with no differences in gender distribution, BMI, reported duration of hypertension, baseline BP values, metabolic profile (glucose, uric acid and lipids), serum creatinine and electrolytes, GFR, and prevalence of metabolic syndrome. Uncontrolled BP was also associated with a slightly reduced number of control visits over the follow-up period ( $p=0.05$ ).

During follow-up, 109 patients (6% of population, 41% women) developed diabetes. At baseline, patients with subsequent diabetes were older ( $56.2 \pm 9.7$  vs  $51.6 \pm 11.6$  years) and had greater BMI ( $29.2 \pm 4$  vs  $27.3 \pm 4$  Kg/m<sup>2</sup>), fasting glucose ( $107.9 \pm 10$  vs  $92.5 \pm 11.6$  mg/dl), uric acid ( $5.7 \pm 1.8$  vs  $5.0 \pm 1.5$  mg/dl), plasma triglycerides ( $169.4 \pm 112.7$  vs  $126.5 \pm 68.4$  mg/dl) and prevalence of metabolic syndrome (60.7% vs 21.4%) than patients without incident diabetes (all  $p<0.001$ ). *In univariate cross tabulation, incident diabetes was 35% less in non-sedentary than in sedentary participants ( $p = 0.041$ ; OR = 0.65; 95% of CI = 0.44 – 0.97).* Reported duration of hypertension was also longer ( $8.7 \pm 7.5$  vs  $6.8 \pm 6.7$  years,  $p = 0.013$ ) and familiarity for diabetes more frequent (8.2% vs 5.1%,  $p=0.017$ ). *In univariate cross tabulation, incident diabetes was 2.45 fold higher in participants with BMI  $\geq 30$  kg/m<sup>2</sup> ( $p < 0.0001$ ; OR = 2.45; 95% of CI = 1.62 – 3.71).* No differences were found in gender distribution, number of visit/year, baseline BP values and heart rate, serum creatinine and electrolytes, GFR, cholesterol, HDL, and uric acid. There was no significant variation of BMI over time in both groups.

**Prediction of Incident Diabetes and BP control:** Risk of incident diabetes was significantly higher in patients with uncontrolled BP (8%) than in those with controlled BP (4 %; OR=2.08;  $p<0.0001$ ). In Cox analysis, controlling for age at the time of the first visit, sex, baseline values of systolic BP, family history of diabetes, fasting glucose, BMI and reported physical activity, incident diabetes remained more than 2-fold higher in patients with uncontrolled BP than in those with controlled BP ( $HR=2.1$ ,  $95\%CI=1.41-3.12$ ,  $p<0.0003$ ), with additional significant effect for higher baseline fasting glucose ( $HR=1.1$ ,  $95\%CI=1.08-1.13$ ,  $p<0.0001$ ), and older age ( $HR=1.02$ ,  $95\%CI=1.00-1.04$ ,  $<0.03$ ), and no detectable effect for the other covariates. Wald statistics suggests that fasting plasma glucose was the strongest predictor of incident diabetes and that suboptimal control of BP was the second strongest predictor.

*Alternative Cox models were generated using BP as continuous variable instead of dichotomizing controlled and uncontrolled BP. In these alternative models, either systolic (not diastolic) BP ( $HR=1.02/mmHg$ ;  $95\%CI=1.01-1.03$ ,  $p<0.01$ ) or mean BP ( $HR=1.03/mmHg$ ;  $95\%CI=1.01-1.06$ ,  $p<0.01$ ) were significant, independent predictors of incident diabetes.*

In another Cox model, using modified ATP III definition of metabolic syndrome instead of fasting plasma glucose and BMI, together with the risk of incident diabetes associated with metabolic syndrome ( $HR=4.4$  [2.9-6.7]), uncontrolled BP maintained or even increased its predictive value ( $HR=2.7$  [1.7-4.1], both  $p<0.0001$ ).

**Antihypertensive Therapy:** During follow-up, slightly more antihypertensive medications were prescribed in patients with controlled BP than in those with uncontrolled BP ( $1.57 \pm 0.94$  vs  $1.47 \pm 0.90$  drugs;  $p<0.03$ ). Single classes of antihypertensive

medications were, therefore, examined in relation to incident diabetes, considering the frequency of use over the entire follow-up time in censored and uncensored observations. We arbitrarily evaluated medications prescribed in more than 50% of available visits. Due to potential pharmacologic interaction favouring development of diabetes, the association between thiazides and  $\beta$ -blockers was also specifically examined.

*Thus, classes of antihypertensive medications analyzed were: thiazides,  $\beta$ -blockers, anti-RAS, CCB and combination of thiazides and  $\beta$ -blockers.*

*Frequency of prescription of  $\beta$ -blockers was 2-fold higher in patients with incident diabetes than in those without incident diabetes (HR=2.04, 95%CI=1.36-3.07;  $p<0.0008$ ). Similarly, combination of thiazides and  $\beta$ -blockers was 3-fold more frequent in patients with than in those without incident diabetes (HR=3.00, 95%CI=1.72-5.26;  $p<0.0002$ ). There was no difference in prescriptions for thiazides without  $\beta$ -blockers, anti-RAS and CCB.*

Another Cox model was, therefore, generated, including also classes of antihypertensive medications, in addition to the covariates used in the previous Cox model. Table 2 shows that uncontrolled BP retained a near 2-fold higher probability to be associated with incident diabetes, independently of all covariates also including treatment. In this model, additional significant predictors were older age, higher baseline fasting glucose, higher BMI, and therapy with  $\beta$ -blockers (table 2).

## DISCUSSION

In this study, for the first time we demonstrate that suboptimal control of BP is a strong predictor of incident type 2 diabetes in initially normo-glycemic, hypertensive

individuals after a follow-up of at least 2 years on antihypertensive treatment. This effect is independent of age, baseline fasting glucose, presence of metabolic syndrome and type of antihypertensive therapy. Prescription of  $\beta$ -blockers, but not of thiazides, is also strongly and independently associated with new onset of diabetes.

Our findings extend previous observations indicating that incident type 2 diabetes is more frequent in hypertensive than in normotensive subjects (3; 11). In particular, Conen et al. (3) recently reported a clear correlation between higher incidence of type 2 diabetes and BP levels in a large population of women, based on modified categories from ESH/ESC 2007 guidelines.

The relation between suboptimal control of BP and incident diabetes paralleled also evidence of different follow-up profiles in censored and uncensored individuals. Patients with incident diabetes underwent fewer visits each year, assumed a smaller number of medications and presented with a larger BMI. It is possible that a less attentive adherence to the suggestions of the specialist both in terms of compliance to the treatment and changes in life style could be at least in part associated with the increased risk of developing diabetes. However, this possibility was partly contradicted by our previous demonstration that the phenotype of metabolic syndrome, a potent risk factor for diabetes also in our analysis, is associated with high likelihood of uncontrolled blood pressure, despite the greater number of prescribed medications.

The other interesting aspect emerging from our analysis is the evidence of the independent relation of  $\beta$ -blocker therapy to the incidence of diabetes, which was consistent with recent literature (12). In contrast, diuretic therapy did not independently predict diabetes, a finding that was inconsistent with some (13), but not all

studies (11; 14). Gress et al. (11) have shown no significant, independent effect of thiazides in their population-based study, once demographic, environmental and metabolic co-factors were taken into account. In the ALLHAT study, clorthalidone, increased risk of diabetes after 2 and 4 years (14), but no multivariate adjustment comparable with the model used in this study was attempted to verify whether or not this effect was independent of confounders. In addition, while in the ALLHAT study design diuretic therapy was not associated with any anti-RAS medication (and in fact,  $K^+$  levels were significantly lower in the group on diuretic), in all analyzed patients in this study thiazides were associated with other medications and  $K^+$  levels were indistinguishable between the groups. Another characteristic to consider in our population is that thiazides were used at very low doses. There is some evidence that thiazides may also produce or increase hepatic insulin resistance, but this effect is dose-dependent and associated with hypokalaemia (15).

The two main findings in our study (i.e. relation of uncontrolled BP and use of  $\beta$ -blockers to incident diabetes) are biologically plausible and fitting with most recent findings suggesting that microvascular alterations might precede development of diabetes (16). Because the goal of our study was to assess the risk of incident diabetes in poorly controlled hypertensive patients, independent of the therapeutic aggressiveness (and therefore also including patients with possible suboptimal therapy at the time of censoring), these findings suggest that timing of achieving target BP values might be substantially relevant also to prevent diabetes, a possibility that should be tested in ad hoc clinical trials.

The temporal sequence observed in our study opens to some possibilities to be explored in future research. First, both

hypertension and diabetes might share a common abnormality of microvascular function that might be corrected or not by antihypertensive therapy. When generalized, dysfunction is more easily detectable with increased blood pressure than with metabolic alterations preceding diabetes, which provides explanation of why hypertension appears before diabetes. This hypothesis is supported by the increasing evidence that microvascular dysfunction might be the background abnormality in experimental diabetes (17). However, although vascular rarefaction has been generally suggested to contribute to insulin resistance (17), cause and effect relationship has not been demonstrated. Another possibility is that the lack of effective control of BP parallels persistent neurohormonal abnormalities that in the long run participate in the precipitation of diabetes, including sympathetic system (18) or/and RAS activity (19).

The unfavourable metabolic consequence of  $\beta$ -blockade are likely due to both decreased insulin sensitivity also demonstrated in hypertensive patients (20), associated with insulin-related metabolic features (21), and deleterious effects on insulin secretion (22). As widely reported, insulin-resistance evolves into diabetes once  $\beta$ -cell failure occurs (23). In addition to this mechanism,  $\beta$ -receptors blockade might favour enhancement of hepatic glucose output, which has been demonstrated in rats but not in humans (24).

**Limitations of the study:** A potential limitation of this study is the absence of direct information on body fat distribution. Due to this limitation, in addition to use BMI as a continuous variable, we also used cut-point of BMI to categorize obesity. The cut-point of BMI for obesity has been previously used as a surrogate of waist girth in studies on metabolic syndrome and the International Diabetes Federation indicates that when BMI

is in the range of obesity, a central fat distribution can be assumed. In addition, at least in terms of prediction of diabetes, BMI has been shown to be as informative as waist circumference, waist/hip ratio or direct visceral fat measured by computed tomography (25). Finally, the prevalence of obesity in this population is likely affected by our initial selection, excluding subjects with type 2 diabetes or impaired fasting glucose at baseline examination.

Another potential limitation of this study is the unavailability of albuminuria, because the data collection was initiated at a time when albuminuria was not yet required as a primary work-up test in all outpatients. According to selection criteria in the present study, we included relatively healthy patients who did not require assessment of albuminuria.

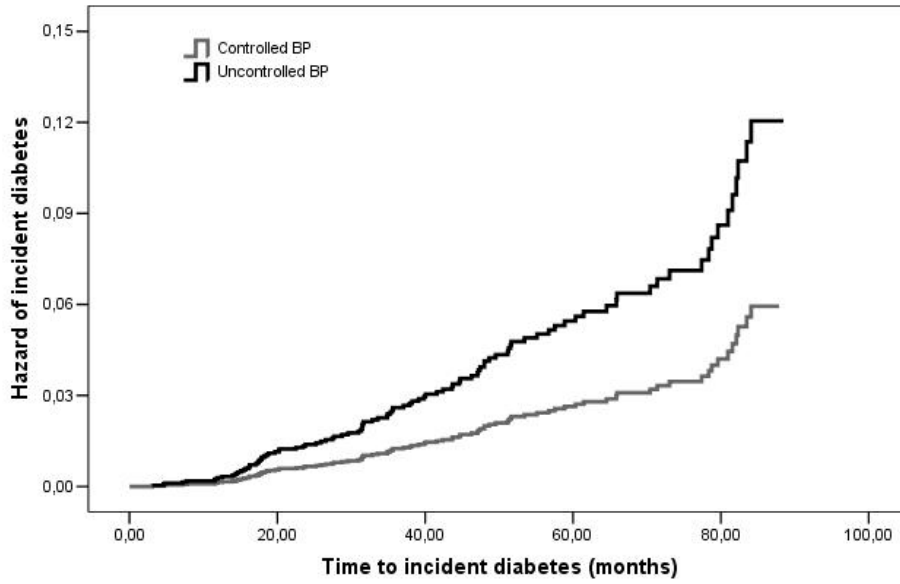


## REFERENCES

1. Geiss LS, Rolka DB, Engelgau MM: Elevated blood pressure among U.S. adults with diabetes, 1988-1994. *Am J Prev Med* 22:42-48, 2002
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434-444, 1993
3. Conen D, Ridker PM, Mora S, Buring JE, Glynn RJ: Blood pressure and risk of developing type 2 diabetes mellitus: the Women's Health Study. *Eur Heart J* 28:2937-2943, 2007
4. Arcucci O, de Simone G, Izzo R, Rozza F, Chinali M, Rao MA, Bodenizza C, De Luca N, Trimarco B: Association of suboptimal blood pressure control with body size and metabolic abnormalities. *J Hypertens* 25:2296-2300, 2007
5. de Simone G, Olsen MH, Wachtell K, Hille DA, Dahlof B, Ibsen H, Kjeldsen SE, Lyle PA, Devereux RB: Clusters of metabolic risk factors predict cardiovascular events in hypertension with target-organ damage: the LIFE study. *J Hum Hypertens* 21:625-632, 2007
6. De Luca N, Izzo R, Iaccarino G, Malini PL, Morisco C, Rozza F, Iovino GL, Rao MA, Bodenizza C, Lanni F, Guerrera L, Arcucci O, Trimarco B: The use of a telematic connection for the follow-up of hypertensive patients improves the cardiovascular prognosis. *J Hypertens* 23:1417-1423, 2005
7. Hallan S, Asberg A, Lindberg M, Johnsen H: Validation of the Modification of Diet in Renal Disease formula for estimating GFR with special emphasis on calibration of the serum creatinine assay. *Am J Kidney Dis* 44:84-93, 2004
8. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellems I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Viigimaa M, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B: 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 25:1105-1187, 2007
9. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome--a new worldwide definition. *Lancet* 366:1059-1062, 2005
10. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997
11. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL: Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 342:905-912, 2000
12. Almgren T, Wilhelmsen L, Samuelsson O, Himmelmann A, Rosengren A, Andersson OK: Diabetes in treated hypertension is common and carries a high cardiovascular risk: results from a 28-year follow-up. *J Hypertens* 25:1311-1317, 2007
13. Verdecchia P, Angeli F, Reboldi G: New-onset diabetes, antihypertensive treatment, and outcome. *Hypertension* 50:459-460, 2007

14. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Jama* 288:2981-2997, 2002
15. Harper R, Ennis CN, Heaney AP, Sheridan B, Gormley M, Atkinson AB, Johnston GD, Bell PM: A comparison of the effects of low- and conventional-dose thiazide diuretic on insulin action in hypertensive patients with NIDDM. *Diabetologia* 38:853-859, 1995
16. Nguyen TT, Wang JJ, Islam FM, Mitchell P, Tapp RJ, Zimmet PZ, Simpson R, Shaw J, Wong TY: Retinal arteriolar narrowing predicts incidence of diabetes: the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study. *Diabetes* 57:536-539, 2008
17. Anneren C, Welsh M, Jansson L: Glucose intolerance and reduced islet blood flow in transgenic mice expressing the FRK tyrosine kinase under the control of the rat insulin promoter. *Am J Physiol Endocrinol Metab* 292:E1183-1190, 2007
18. Lembo G, Napoli R, Capaldo B, Rendina V, Iaccarino G, Volpe M, Trimarco B, Sacca L: Abnormal sympathetic overactivity evoked by insulin in the skeletal muscle of patients with essential hypertension. *J Clin Invest* 90:24-29, 1992
19. Ogihara T, Asano T, Ando K, Chiba Y, Sakoda H, Anai M, Shojima N, Ono H, Onishi Y, Fujishiro M, Katagiri H, Fukushima Y, Kikuchi M, Noguchi N, Aburatani H, Komuro I, Fujita T: Angiotensin II-induced insulin resistance is associated with enhanced insulin signaling. *Hypertension* 40:872-879, 2002
20. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JT, Jr., Oakes R, Lukas MA, Anderson KM, Bell DS: Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *Jama* 292:2227-2236, 2004
21. Iaccarino G, Trimarco V, Lanni F, Cipolletta E, Izzo R, Arcucci O, De Luca N, Di Renzo G: beta-Blockade and increased dyslipidemia in patients bearing Glu27 variant of beta2 adrenergic receptor gene. *Pharmacogenomics J* 5:292-297, 2005
22. Struthers AD, Murphy MB, Dollery CT: Glucose tolerance during antihypertensive therapy in patients with diabetes mellitus. *Hypertension* 7:II95-101, 1985
23. Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA: beta-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J Clin Endocrinol Metab* 90:493-500, 2005
24. Sarafidis PA, Bakris GL: Antihypertensive treatment with beta-blockers and the spectrum of glycaemic control. *QJM* 99:431-436, 2006
25. Bray GA, Jablonski KA, Fujimoto WY, Barrett-Connor E, Haffner S, Hanson RL, Hill JO, Hubbard V, Kriska A, Stamm E, Pi-Sunyer FX: Relation of central adiposity and body mass index to the development of diabetes in the Diabetes Prevention Program. *Am J Clin Nutr* 87:1212-1218, 2008

**Figure 1: Cumulative hazard of incident diabetes in non-diabetic, hypertensive patients, under antihypertensive therapy, in relation to BP control, after adjusting for age, sex, systolic BP, familiarity for diabetes, BMI and plasma glucose at baseline (see text for explanation).**



**Table 1.** Demographic, clinical and laboratory characteristics of the study population. Data are expressed as mean  $\pm$  SD or percentage of the relevant group of patients.

	<b>BP controlled</b>	<b>BP uncontrolled</b>	<b>p <math>\leq</math></b>
	<b>n = 1042</b>	<b>n = 712</b>	
Age (years)	52.7 $\pm$ 11.6	50.6 $\pm$ 11.3	0.0001
Gender (M/F %)	58/42	56/44	NS
BMI (Kg/m <sup>2</sup> )	27.3 $\pm$ 3.9	27.6 $\pm$ 4.1	NS
Reported duration of hypertension (years)	7.2 $\pm$ 7.1	6.5 $\pm$ 6.3	NS
Number of visit/year	2.34 $\pm$ 1.03	2.25 $\pm$ 1.02	0.047
Systolic BP (mmHg)	159.8 $\pm$ 21.8	158.0 $\pm$ 19.2	NS
Diastolic BP (mmHg)	99.6 $\pm$ 10.8	99.6 $\pm$ 10.2	NS
Heart rate (bpm)	71.87 $\pm$ 11.29	73.16 $\pm$ 12.58	0.028
Fasting glucose (mg/dl)	93.5 $\pm$ 12.2	93.2 $\pm$ 12.0	NS
Uric acid (mg/dl)	5.1 $\pm$ 1.4	5.1 $\pm$ 1.7	NS
Blood urea nitrogen (mg/dl)	37.6 $\pm$ 10.1	36.3 $\pm$ 11.8	NS
Serum creatinine (mg/dl)	0.94 $\pm$ 0.2	0.93 $\pm$ 0.2	NS
GFR (ml/min)	82.7 $\pm$ 19.9	83.7 $\pm$ 19.1	NS
K <sup>+</sup> (mEq/l)	4.4 $\pm$ 0.4	4.4 $\pm$ 0.4	NS
Na <sup>+</sup> (mEq/l)	141.2 $\pm$ 3.3	141.3 $\pm$ 3.1	NS
Cholesterol (mg/dl)	206.5 $\pm$ 38.6	207.2 $\pm$ 37.4	NS
HDL cholesterol (mg/dl)	50.2 $\pm$ 12.3	50.7 $\pm$ 12.7	NS
Non-HDL cholesterolemia (mg/dl)	156.5 $\pm$ 37.9	156.7 $\pm$ 37.7	NS
Triglycerides (mg/dl)	129.2 $\pm$ 67.7	128.8 $\pm$ 79.0	NS
Metabolic syndrome (%)	24.2	23.6	NS

**Table 2.** Hazard of incident diabetes in non-diabetic, treated hypertensive patients, including classes of antihypertensive medications.

	B	Wald	p $\leq$	HR	95.0% CI for Exp(B)	
					Lower	Upper
Fasting glucose (mg/dl)	0.10	<b>84.56</b>	<b>0.0001</b>	<b>1.10</b>	1.07	1.12
BMI (Kg/m <sup>2</sup> )	0.03	<b>7.09</b>	<b>0.01</b>	<b>1.08</b>	1.02	1.14
Age (years)	0.03	<b>6.33</b>	<b>0.014</b>	<b>1.03</b>	1.01	1.05
Gender (M/F)	0.03	0.02	0.9	1.03	.67	1.60
Thiazide diuretics	-0.28	1.73	0.21	0.75	0.48	1.18
Beta-blockers	0.77	<b>13.05</b>	<b>0.0001</b>	<b>2.17</b>	1.41	3.34
Anti RAS	0.12	0.19	0.65	1.12	0.68	1.86
Suboptimal BP control	0.63	<b>7.58</b>	<b>0.004</b>	<b>1.88</b>	1.23	2.88

BMI = Body mass index

BP = Blood pressure