Metabolic Syndrome as a Predictor of All-Cause and Cardiovascular Mortality in Type 2 Diabetes

The Casale Monferrato Study

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OBJECTIVE — The aim of this study was to assess in an 11-year survival follow-up of a population-based cohort of type 2 diabetes the predictive role of World Health Organization–defined metabolic syndrome, independent of conventional cardiovascular risk factors.

RESEARCH DESIGN AND METHODS — During the follow-up (1991–2001), 1,565 patients were regularly examined with centralized measurements of HbA_{1c}. The independent role of the metabolic syndrome as a predictor of all-cause and cardiovascular mortality was assessed with multivariate Cox proportional hazards modeling.

RESULTS — At baseline, the prevalence of the metabolic syndrome was 75.6% (95% CI 73.6–77.9). Results are based on 685 deaths (520 with the metabolic syndrome and 165 without it) in 10,890.2 person-years of observations. With respect to subjects without the metabolic syndrome, those with the metabolic syndrome had a similar hazard ratio (HR) of cardiovascular mortality after adjustment for age, sex, smoking, total cholesterol level, and coronary heart disease. In contrast, relative to subjects with diabetes only, the HR of subjects with only one component of the syndrome was 2.92 (1.16–7.33), independent of other risk factors.

CONCLUSIONS — We found that *1*) the prevalence of the metabolic syndrome in a population-based cohort of type 2 diabetes is high (75.6%); *2*) the metabolic syndrome is not a predictor of 11-year all-cause and cardiovascular mortality; and *3*) more than twofold higher cardiovascular risk, independent of conventional risk factors, is evident in diabetic subjects with only one component of the syndrome compared with those with diabetes only. Categorizing type 2 diabetic subjects as having or not having the metabolic syndrome does not provide further prediction compared with the knowledge of its single components.

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Subjects with type 2 diabetes have higher cardiovascular risk than nondiabetic subjects, independent of conventional risk factors such as smoking, hypertension, and hypercholesterolemia (1). This finding, which is evident even at the time of diagnosis of diabetes, has suggested the hypothesis of a common antecedent for diabetes and atherosclerosis (2). The underlying abnormality could be insulin resistance, which is characterized by clustering of hyperglycemia, hypertension, dyslipidemia, and albuminuria (3). Recently, the definition of metabolic syndrome with internationally defined criteria has been preferred, allowing comparison of rates among different studies (4,5). Prevalence ranging between 20 and 30% in nondiabetic subjects and between 70 and 80% in diabetic subjects has been estimated in studies using either National Cholesterol Education Program III (NCEP-III) or World Health Organization (WHO) criteria (6–9). Although the former provide a more clinically oriented set of criteria, the WHO definition has higher likelihood of identifying individuals with low insulin sensitivity (10). From a clinical point of view, however, it has not yet been clarified whether the identification of the metabolic syndrome confers a clinical advantage over identification and treatment of its single components, i.e., whether identification of diabetic and nondiabetic subjects as having the metabolic syndrome improves the prediction of cardiovascular events (11). Indeed, the few studies exploring this issue have provided conflicting results (12–16).

The aim of this study was to assess, in a 11-year follow-up of type 2 diabetic subjects of the Casale Monferrato cohort (17–19), the predictive role on all-cause and cardiovascular mortality of WHO-defined metabolic syndrome, independent of conventional cardiovascular risk factors.

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Abbreviations: AER, albumin excretion rate; CHD, coronary heart disease; NCEP-III, National Cholesterol Education Program III; WHO, World Health Organization.

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

Table 1 —*Distribution of variables defying the metabolic syndrome in the Casale Monferrato cohort of type 2 diabetes*

	Total
N	1,565
Four factors ($n = 169$)	
Obesity + hypertension + dyslipidemia + elevated AER	169 (10.8)
Three factors ($n = 468$)	
Obesity + hypertension + elevated AER	166 (10.6)
Obesity + hypertension + dyslipidemia	160 (10.2)
Hypertension + dyslipidemia + elevated AER	127 (8.1)
Obesity + dyslipidemia + elevated AER	15 (1.0)
Two factors ($n = 549$)	
Hypertension + obesity	204 (13.0)
Hypertension + elevated AER	187 (11.9)
Hypertension + dyslipidemia	94 (6.0)
Obesity + dyslipidemia	21 (1.3)
Obesity + elevated AER	20 (1.3)
Dyslipidemia + elevated AER	23 (1.5)
One factor ($n = 304$)	
Hypertension	202 (12.9)
Elevated AER	46 (2.9)
Obesity	28 (1.8)
Dyslipidemia	28 (1.8)
Diabetes only ($n = 75$)	75 (4.8)

Data are *n* (%).

RESEARCH DESIGN AND METHODS

— The study base comprised 1,565 patients with known type 2 diabetes, residents in 1988 of the town of Casale Monferrato, in northwestern Italy (93,477 inhabitants), who were invited to undergo baseline examination in 1991–1992 to assess the prevalence of micro- and macroalbuminuria and cardiovascular risk factors. These patients were followed to 31 December 2001 (17–19).

As described in detail elsewhere, at baseline all patients were interviewed and examined by trained investigators (17). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or treatment with antihypertensive drugs. Venous blood samples were collected in the fasting state for determinations of triglyceride, total cholesterol, and HDL cholesterol levels (enzymatic-colorimetric method, after precipitation with Mn^{2+}) as well as HbA_{1c} (high-performance liquid chromatography; Daiichi, Menarini, Japan; laboratory reference range 3.8–5.5%). LDL cholesterol was calculated with Friedewald's formula in all subjects of the cohort, except for 43 patients in whom triglyceride levels were >400 mg/dl. All laboratory determinations were centralized. The albumin excretion rate (AER) was calculated on the basis of urinary albumin concentration measured on a single timed overnight urine collection by the nephelometric method (Behring Nephelometer Analyzer; Behring Institute, Marburg, Germany), after having excluded urinary tract infection, congestive heart failure, or other known causes of nondiabetic renal diseases. Smoking habit was classified into one of three categories: never smoker, ex-smoker if the patient stopped smoking at least 1 month before the visit, and smoker. For all patients enrolled, the date of diagnosis was retrieved and recorded. The Casale Monferrato Study database does not contain information about previous coronary heart disease (CHD); therefore, CHD was defined by electrocardiographic abnormalities according to the Minnesota code, as previously described (19). Metabolic syndrome was defined, according to the WHO definition, as the presence of two or more of the following risk factors: *1*) arterial blood pressure ≥140/90 mmHg or antihypertensive treatment; *2*) triglyceride level ≥150 mg/dl and/or HDL cholesterol level <35 mg/dl (men) or <39 mg/dl (women); *3*) waist-to-hip ratio >0.9 (men) or >0.85 (women) or BMI >30 kg/m^2; and *4*) AER ≥20 μg/min (4).

During the follow-up period (1991–2001), patients were regularly examined, either at the diabetes clinic or by general practitioners, three to four times per year depending on the severity of the disease, with centralized measurements of HbA_{1c}. Cumulative individual averages of HbA_{1c} during follow-up were calculated.

The relevant time scale for the analysis was time since diagnosis of diabetes to death or to 31 December 2001. The data in analyses are left-censored because subjects entered follow-up at various times after initial diagnosis. Information regarding which subjects had died was obtained from the demographic files of towns of residence, hospital discharges, and autopsy records. Only one patient was lost to follow-up. Underlying causes of death were derived and coded by two authors, according to the International Classification of Diseases, 9th Revision (ICD-9) (20). Mortality rates were calculated dividing the number of deaths occurring during the study period by the number of person-years of observation.

Analyses were performed using baseline variables. HbA_{1c} values were measured both at baseline and during follow-up and were included in models using their cumulative individual average as the time-dependent variable. All continuous variables were categorized in quartiles of distribution, except age, which was categorized in 5-year age-groups (<60, 60–64, 65–69, 70–74, 75–79, and >79 years).

Unconditional logistic regression analysis was performed to assess the independent association of baseline CHD (dependent variable) with metabolic syndrome, independent of age, sex, smoking, and total cholesterol level. Odds ratios (ORs) and 95% CIs were calculated as estimates of the associations. The likelihood ratio test was used to assess statistical significance.

Mortality analyses of the cohort were then performed using multivariate Cox proportional hazards modeling to assess the role of the metabolic syndrome as a predictor of cardiovascular and all-cause mortality, independent of age, sex, smoking, total cholesterol level, CHD, and HbA_{1c} cumulative individual average during follow-up. Age- and sex-adjusted

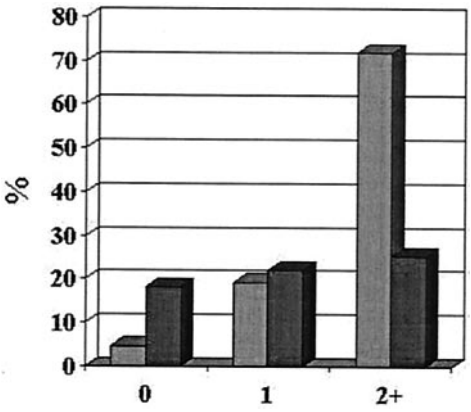

Figure 1—*Prevalence of subjects with 0, 1, and 2 or more components of the metabolic syndrome (▨) and of CHD (■) at the baseline examination in the Casale Monferrato cohort of type 2 diabetes.*

hazard rate ratios (HRs) as estimates of associations are shown in Tables 1 and 2. *P* values for trend in HRs for severity of disease were estimated according to the Mantel-Haenszel procedure (21). The proportional hazard assumptions of explanatory variables were assessed based on Schoenfeld residuals. The likelihood ratio test was used to assess the significance of variables. We tested for linear trend across categorical variables by entering a single ordinal term in the Cox regression model.

The *P* value was two sided; $P < 0.05$ was considered to indicate statistical significance. All analyses were performed using Stata software (Stata Release 8.0; Stata Corporation, College Station, TX).

RESULTS — At the baseline examination, most of diabetic subjects were elderly; 979 of 1,565 (56.2%) subjects were ≥65 years at recruitment. Mean age and mean duration of diabetes (± SD) of diabetic subjects were 68.9 ± 10.7 and 10.8 ± 7.0 years, respectively. As previously described (17), the prevalences of hypertension, microalbuminuria, and macroalbuminuria was 84.5, 32.1, and 17.6%, respectively. Of the cohort, 23.7% of subjects were treated exclusively by their general practitioners. Frequencies of treatment with diet, oral hypoglycemic drugs, and insulin were 12.2, 70.9, and 16.9%, respectively.

At baseline, 1,186 of 1,565 diabetic subjects were defined as having the metabolic syndrome, representing a prevalence of 75.6% (95% CI 73.6–77.9). The highest proportion was that of subjects with two components of the metabolic syndrome (32.3%). Only 10.8% of subjects had four components, whereas the more common associations were those including hypertension (Table 1).

Baseline prevalence of CHD was 24.4%, and there was an increasing but no significant trend across the number of components of the metabolic syndrome: 18.3% in subjects with diabetes only and 22.2, 22.9, 27.5% in those with one, two, and three or more components of the metabolic syndrome, respectively ($P = 0.30$) (Fig. 1). In logistic regression analysis, ORs of baseline CHD in subjects with one component of the metabolic syndrome and in those with two or more components were 1.16 (0.55–2.43) and 1.17 (0.58–2.33), respectively (reference, diabetes only), independent of age, sex, smoking, and total cholesterol level.

During the 11-year follow-up period (median 8.21 years, range 0.1–11.1 years), 520 diabetic subjects with the metabolic syndrome and 165 without it died, resulting in all-cause mortality rates per 1,000 person-years of 63.0 (57.8–68.6) and 64.7 (55.6–75.4), respectively. Cardiovascular mortality (ICD-9 codes 390–459) accounted for 256 of 520 (49.2%) deaths among subjects with the metabolic syndrome (rate 31.0/1,000 person-years [27.4–35.0]) and 85 of 165 (51.5%) deaths among subjects without it (rate 33.4/100,000 person-years, [27.0–41.3]).

Table 2 shows that adjusted risks of all-cause and cardiovascular mortality in the cohort were only slightly higher in subjects with the metabolic syndrome than in those without it. However, when HRs across strata of subjects with increasing numbers of its components were compared with subjects with diabetes only, increased all-cause and cardiovascular mortality rates, even in subjects with only one component of the syndrome, were evident. This effect was particularly evident for cardiovascular mortality, with HR in subjects with only one component of the metabolic syndrome of 2.92 (1.16–7.33), even after adjustment for age, sex, smoking, total cholesterol level, and CHD. Results were also similar when the model included smoking, total cholesterol level, and CHD one at a time. This mortality excess, however, was masked when subjects with less than two components were grouped together as a reference category, thus determining similar mortality risks in subjects with and without the metabolic syndrome. HRs were only slightly reduced by further adjustment for HbA_{1c} cumulative average during follow-up. Because total cholesterol was correlated with both HDL (correlation coefficient 0.20, $P < 0.0001$) and triglycerides (0.30, $P < 0.0001$), a full-adjusted model was also performed after replacement of total cholesterol with LDL cholesterol, obtaining similar results (HRs 2.72, 2.15, and 2.36).

When the metabolic syndrome was replaced in the model by the simultaneous inclusion of all of its individual components, results were as follows: HR 1.34 (0.89–2.00) for hypertension, 0.47 (0.36–0.62) for obesity, 1.34 (1.03–1.75) for dyslipidemia, and 1.37 (1.05–1.78) for elevated AER.

CONCLUSIONS — The results of this population-based study indicate that the metabolic syndrome is common in subjects with type 2 diabetes; 76% of this cohort had at least two components of the syndrome (hypertension, dyslipidemia, increased AER, and obesity), as defined by the WHO criteria. From a clinical point of view, however, its identification does not add further information on the individual mortality risk beyond knowledge of patient's conventional risk factors. Indeed, diabetic subjects with the metabolic syndrome were not characterized by an increased 11-year cardiovascular or all-cause mortality risk compared with subjects without it. Our findings indicate that diabetic subjects with even only one component of the syndrome have more than twofold higher risk of cardiovascular mortality than subjects with diabetes only, independent of age, sex, smoking, total cholesterol level, CHD, and cumulative HbA_{1c}. This finding, however, was masked when subjects with one component and those with diabetes only were grouped as a reference category and compared with subjects with the metabolic syndrome.

Table 2 —*All-cause and cardiovascular mortality rates in the Casale Monferrato cohort of type 2 diabetes by metabolic syndrome at baseline examination (1991–1992)*

	All-cause mortality				Cardiovascular mortality			
	n deaths (rate/1,000 person-years)	HR*	HR†	HR‡	*n* deaths (rate/1,000 person-years)	HR*	HR†	HR‡
Metabolic syndrome								
No	165 (64.7)	1.00	1.00	1.00	85 (33.4)	1.00	1.00	1.00
Yes	520 (63.0)	1.05(0.88–1.25)	1.04(0.86–1.26)	1.06(0.86–1.30)	256 (31.0)	1.01(0.78–1.28)	1.04(0.78–1.39)	0.95(0.71–1.28)
Number of components								
0	30 (58.7)	1.00	1.00	1.00	11 (21.5)	1.00	1.00	1.00
1	135 (66.2)	1.19(0.76–1.86)	1.41(0.86–2.31)	1.37(0.83–2.25)	74 (36.3)	2.39(1.09–5.22)	2.92(1.16–7.33)	2.80(1.11–7.11)
2	249 (68.3)	1.17(0.76–1.81)	1.48(0.90–2.33)	1.36(0.85–2.21)	116 (31.8)	1.83(0.85–3.97)	2.44(0.99–6.06)	2.21(0.89–5.49)
>2	271 (58.8)	1.07(0.70–1.65)	1.36(0.85–2.19)	1.25(0.78–2.02)	140 (30.4)	2.10(0.98–4.52)	2.80(1.14–6.92)	2.46(0.99–6.07)
P value for trend		0.62	0.35	0.93		0.12	0.69	0.40

Data are hazard ratios (HRs) (95% CI) unless otherwise indicated. *Adjusted for age and sex; †adjusted for age, sex, smoking, total cholesterol, and CHD; ‡adjusted for age, sex, smoking, total cholesterol, CHD, and HbA_{1c} cumulative average.

Recent studies have examined the question of whether the metabolic syndrome adds to prediction of CHD beyond knowledge of conventional risk factors, providing conflicting results (12–16). This point is relevant because clinicians are interested in knowing what is gained and what is lost by categorizing individuals as having the metabolic syndrome compared with assessing their cardiovascular risk on the basis of combinations of individual risk factors (11). From a statistical point of view, this issue is examined by modeling the metabolic syndrome as a predictor of cardiovascular disease, with its individual components (increased waist circumference, low HDL cholesterol, hypertension, and microalbuminuria) being replaced by the binary metabolic syndrome variable. A fourfold higher incidence of cardiovascular disease and a 15% higher cardiovascular mortality, although not significant, have been found in diabetic subjects in the Verona Study (12) and in Finland (13), respectively. Both studies, however, used logistic regression rather than survival methods of analysis, thus not taking into account the individual length of follow-up. The prevalence of CHD in diabetic subjects of the National Health and Nutrition Examination Survey (NHANES) III Study increases with the number of the components of the metabolic syndrome (NCEP-III criteria) (6). In nondiabetic Finnish men aged 42–60 years without cardiovascular disease at baseline, the metabolic syndrome (based on WHO criteria) was associated with an almost threefold higher risk of cardiovascular mortality, after adjustment for conventional risk factors not included in the definition of the syndrome (smoking, LDL cholesterol, and family history of CHD) (14). In nondiabetic subjects of the Strong Heart Study, however, 8-year incidence of cardiovascular disease was not predicted by either baseline homeostasis model assessment or the metabolic syndrome (NCEP-III criteria) (10). In the West of Scotland Coronary Prevention Study, the metabolic syndrome (NCEP-III criteria) was associated with a 30% increased risk of 5-year CHD in middle-aged men, even after adjusting for smoking, cholesterol–to–HDL cholesterol ratio, and systolic blood pressure (15). However, the metabolic syndrome did not improve the prediction of CHD events compared with the predictive

value of its components. Differences in age of recruited subjects could at least partially explain different results. The Casale Monferrato Study recruited mainly elderly subjects (mean age at baseline 69 years) with a mean duration of disease of 10 years, who were representative of prevalent Italian diabetic populations. Moreover, in Italy diabetic subjects show only a 30% higher mortality risk compared with the general population (22,23), probably reflecting better glycemic control and later age at onset than those recruited in Northern European countries and in the U.S. However, the present study provides evidence that most diabetic subjects (95%) have at least another cardiovascular risk factor and, therefore, according to the HOPE Study (24), would probably benefit further from extended therapy with ACE inhibitors, which at baseline was prescribed in only 18% of this cohort. The negative relationship between obesity and cardiovascular mortality in our analysis is consistent with results of Verona Study, pointing out that elderly lean diabetic subjects may be at higher risk of death than obese diabetic subjects (25).

In conclusion, this study points out that *1*) the prevalence of the metabolic syndrome (WHO criteria) in a population-based cohort of mainly elderly type 2 diabetic subjects is high (76%); *2*) the metabolic syndrome is not a predictor of 11-year all-cause and cardiovascular mortality; and *3*) more than twofold higher cardiovascular risk, independent of conventional risk factors, is evident in diabetic subjects with only one component of the syndrome compared with those with diabetes only. Therefore, categorizing type 2 diabetic subjects as having or not having the metabolic syndrome does not provide further prediction of all-cause and cardiovascular mortality compared with the knowledge of its single components.

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References

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-year cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial (MRFIT). *Diabetes Care* 16:434–444, 1993
2. Haffner SM, Stern PM, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–2898, 1990
3. Haffner SM, D'Agostino J Jr, Mykkanen L, Tracy R, Howard B, Rewers M, Selby J, Savage PJ, Saad MF: Insulin sensitivity in subjects with type 2 diabetes: relationship to cardiovascular risk factors: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 22:562–568, 1999
4. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Org., 1999
5. National Institutes of Health: Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary. Washington, DC, U.S. Govt. Printing Office, 2001 (NIH publ. no. 01–3670)
6. Alexander CM, Landsman PB, Teutsch SM, Haffner SM: NCEP-defined metabolic syndrome, diabetes, and the prevalence of coronary heart disease among NHANES III participants age 50 years and older. *Diabetes Care* 52:1210–1214, 2003
7. Meigs JB, Wilson PWF, Nathan DM, D'Agostino RB, Williams K, Haffner SM: Prevalence and characteristics of the metabolic syndrome in the San Antonio Heart and Framingham Offspring studies. *Diabetes* 52:2160–2167, 2003
8. Ford ES, Giles WH: A comparison of the prevalence of the metabolic syndrome using two proposed definitions. *Diabetes Care* 26:575–581, 2003
9. Hanley AJG, Wagenknecht LE, D'Agostino RB, Zinman B, Haffner SM: Identification of subjects with insulin resistance and β-cell dysfunction using alternative definitions of the metabolic syndrome. *Diabetes* 52:2740–2747, 2003
10. Resnick HE, Jones K, Ruotolo G, Jain AK, Henderson J, Lu W, Howard BV: Insulin resistance, the metabolic syndrome, and the risk of incident cardiovascular disease in nondiabetic American Indians: the Strong Heart Study. *Diabetes Care* 26: 861–867, 2003
11. Meigs JB: The metabolic syndrome may be a guidepost or detour to preventing type 2 diabetes and cardiovascular disease? *BMJ* 327:61–62, 2003
12. Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, Taskinen M-R, Groop L: Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 24:683–689, 2001
13. Bonora E, Targher G, Fomentini G, Calcaterra F, Lombardi S, Marini F, Zenari L, Saggiani F, Poli M, Perbellini S, Raffaelli A, Gemma L, Santi L, Bonadonna RC, Muggeo M: The metabolic syndrome is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. *Diabet Med* 21:52–58, 2004
14. Lakka H-M, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, Salonen JT: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA* 288: 2709–2716, 2002
15. Sattar N, Gaw A, Scherbakova O, Ford I, O'Reilly DS, Haffner SM, Isles C, Macfarlane PW, Packard CJ, Cobbe SM, Sheperd J: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation* 108:414–419, 2003
16. Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM: The metabolic syndrome as predictor of type 2 diabetes: the San Antonio Heart Study. *Diabetes Care* 26: 3135–3159, 2003
17. Bruno G, Cavallo-Perin P, Bargero G, Borra M, Calvi V, D'Errico N, Deambrogio P, Pagano G: Prevalence and risk factors for micro- and macroalbuminuria in an Italian population-based cohort of non-insulin-dependent diabetic subjects. *Diabetes Care* 19:43–47, 1996
18. Bruno G, Cavallo-Perin P, Bargero G, Borra M, D'Errico N, Pagano G: The associations of fibrinogen with glycemic control and albumin excretion rate in patients with non-insulin-dependent diabetes. *Ann Intern Med* 125:653–657, 1996
19. Bruno G, Biggeri A, Merletti F, Bargero G, Ferrero S, Pagano G, Cavallo Perin P: Low incidence of end-stage renal disease and chronic renal failure in type 2 diabetes: a 10-year prospective study. *Diabetes Care* 26:2353–2358, 2003
20. World Health Organization: *International Classification of Diseases*. Vol. 1–2, 9th ed. Geneva, World Health Org., 1977
21. Mantel N: Chi-square tests with one degree of freedom: extension of the Mantel-Haenszel procedure. *J Am Stat Assoc* 58: 690–700, 1963
22. Bruno G, Merletti F, Boffetta P, Cavallo-

Perin P, Bargero G, Gallone G, Pagano G: Impact of glycemic control, hypertension and insulin-treatment on general and cause-specific mortality: an Italian population-based cohort of type 2 diabetes. *Diabetologia* 42:297–301, 1999
23. Muggeo M, Verlato G, Bonora E, Bressan F, Girotto S, Corbellini M, Gemma ML, Moghetti P, Zenere M, Cacciatori V, Zoppini G, de Marco R: The Verona Diabetes Study: a population-based survey on known diabetes mellitus prevalence and 5-year all-cause mortality. *Diabetologia* 38:318–325, 1995
24. Gerstein HC: Reduction of cardiovascular events and microvascular complications in diabetes with ACE inhibitor treatment: HOPE and MICRO-HOPE. *Diabete Metab Res Rev* 18 (Suppl. 3):S82–S85, 2002
25. Zoppini G, Verlato G, Leuzinger C, Zamboni C, Brun E, Bonora E, Muggeo M: Body mass index and the risk of mortality in type II diabetic patients from Verona. *Int J Obes Relat Metab Disord* 27:281–285, 2003