Postprandial Blood Glucose Predicts Cardiovascular Events and All-Cause Mortality in Type 2 Diabetes in a 14-Year Follow-Up

Lessons from the San Luigi Gonzaga Diabetes Study

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OBJECTIVE—To evaluate whether postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a long-term follow-up taking into account A1C and the main cardiovascular risk factors.

RESEARCH DESIGN AND METHODS—Consecutive type 2 diabetic patients (n = 505) followed up at our diabetes clinic were evaluated at baseline (1995) for the main cardiovascular risk factors and for five glycemic control parameters (fasting blood glucose, blood glucose 2 h after breakfast, blood glucose 2 h after lunch, blood glucose before dinner, and A1C); all-cause mortality and the first cardiovascular events occurring during the 14-year follow-up were measured.

RESULTS—We observed 172 cardiovascular events (34.1% of the population) and 147 deaths (29.1% of the population). Using the Cox analysis with the backward method, we categorized the variables according to the therapeutic targets of the American Diabetes Association. Our observations were as follows. When the five glycemic control parameters were considered together, the predictors were *1*) for cardiovascular events, blood glucose 2 h after lunch (hazard ratio 1.507, P = 0.010) and A1C (1.792, P = 0.002); and 2) for mortality, blood glucose 2 h after lunch (1.885, $P < 0.0001$) and A1C (1.907, P = 0.002). When blood glucose 2 h after lunch and A1C were considered together with the main cardiovascular risk factors, the following glycemic control parameters were predictors: *1*) for cardiovascular events, blood glucose 2 h after lunch (1.452, P = 0.021) and A1C (1.732, P = 0.004); and 2) for mortality, blood glucose 2 h after lunch (1.846, P = 0.001) and A1C (1.896, P = 0.004).

CONCLUSIONS—In type 2 diabetes, both postprandial blood glucose and A1C predict cardiovascular events and all-cause mortality in a long-term follow-up.

Diabetes Care 34:2237–2243, 2011

The relationships between the parameters of blood glucose control, cardiovascular events, and all-cause mortality are controversial. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) reported that blood glucose concentrations at 2 h of an oral glucose tolerance test (OGTT) (i.e., postchallenge blood glucose) are better predictors of cardiovascular events and of all-cause mortality than fasting blood glucose (FBG) (1). Similarly, in the Framingham Offspring Study, 2-h postchallenge blood glucose predicted cardiovascular events better than did A1C (2).

Furthermore, a meta-analysis of 38 prospective studies carried out in nondiabetic subjects confirmed a strong association between 2-h postchallenge blood glucose with fatal and nonfatal cardiovascular events (3), and a linear relationship between this parameter and the risk of cardiovascular death has been observed (4).

In the studies mentioned above, the subjects were tested with an OGTT; the concern has been raised that OGTT is not a composite meal and that postchallenge hyperglycemia is only a surrogate marker of postmeal hyperglycemia. Thus, the last one should be directly measured to evaluate the risk conferred by postprandial hyperglycemia. A large body of evidence shows a relationship between postprandial hyperglycemia and factors causally related to atherosclerosis, such as oxidative stress (5), or markers of the atherosclerotic process, such as endothelial dysfunction (6) and carotid intima-media thickness (7). However, it has also been shown that mean blood glucose and A1C show stronger associations with cardiovascular risk factors than does postprandial blood glucose (8).

Only two studies have investigated the predictive power of postprandial blood glucose on cardiovascular events: the Diabetes Intervention Study (DIS) (9) and the San Luigi Gonzaga Diabetes Study (10). The DIS (9) is a pioneering investigation carried out in relatively young, newly diagnosed type 2 diabetic patients followed up for 11 years; it showed for the first time that postprandial blood glucose predicts myocardial infarction and mortality, but the study did not consider A1C. Thus, as far as we know, the only results demonstrating the independent predictive power of postprandial blood glucose on cardiovascular events after correction for A1C are the 5-year follow-up of the San Luigi Gonzaga Diabetes Study (10). We carried out this investigation in patients attending our diabetes clinic

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Received 22 December 2010 and accepted 6 July 2011.
DOI: 10.2337/dc10-2414

See accompanying editorial, p. 2333.

with a mean diabetes duration of about 9 years; the short-term follow-up, however, did not allow us to draw conclusions about mortality (10). For this reason, we carried out a long-term follow-up of the same study to evaluate whether *1*) the predictive role of postprandial blood glucose on cardiovascular events that we demonstrated after 5 years lasted up to 14 years; *2*) postprandial blood glucose also predicts all-cause mortality, even when A1C and the main nonglycemic cardiovascular risk factors are taken into account; and *3*) the predictive power of postprandial blood glucose and A1C could be demonstrated when these variables are categorized according to the therapeutic targets stated by the American Diabetes Association (11).

RESEARCH DESIGN AND METHODS

—In 1995, we started a prospective investigation aiming to evaluate the impact of cardiovascular risk factors on cardiovascular events and mortality in type 2 diabetes. The methodological details of the part the study including blood glucose profile evaluation have previously been extensively described (10) and are briefly summarized below.

From a population of approximately 5,000 outpatients affected by type 2 diabetes, we enrolled for a longitudinal study 529 consecutive patients in whom blood glucose values before and after breakfast, after lunch, and before dinner were measured together with A1C and the main nonglycemic cardiovascular risk factors. Exclusion criteria were history of cancer, liver, and pancreatic diseases or insulin treatment within 2 years of diagnosis.

At baseline, we evaluated age; sex; known diabetes duration; previous cardiovascular events; type of therapy; smoking habit; BMI; systolic and diastolic blood pressure; total, LDL, and HDL cholesterol; triglycerides; creatinine; albumin excretion rate (AER); A1C; and blood glucose profiles in which FBG and blood glucose 2 h after breakfast, 2 h after lunch, and before dinner were measured in the same day. Patients enrolled in the study were treated as all the other patients attending our outpatient diabetes clinic at that time. A1C was evaluated in our laboratory by high-performance liquid chromatography (Diamat; Bio-Rad Laboratories, Milan, Italy) (normal range 3.8–5.9%); blood glucose profiles were measured as part of the clinical routine and were carried out either at the hospital by trained nurses on the day of the scheduled visits or at home by self-monitoring of blood glucose (SMBG). Patients on SMBG were asked to perform one blood glucose profile in a day very close to the scheduled visit, when the other laboratory parameters were also evaluated. Both in the hospital and at home, blood glucose was determined utilizing the glucometer Reflolux II (Roche, Mannheim, Germany). The other laboratory parameters were determined at the San Luigi Gonzaga Central Laboratory, which participates in a Regional Quality Control Program. The patient cohort was followed up by evaluation of cardiovascular events and mortality. The follow-up was completed up to the 14th year in all the patients alive. We considered as outcomes the following events: *1*) the first cardiovascular event occurring after enrolment in the study (obviously, only one per patient), i.e., myocardial infarction, unstable angina, stroke, transient ischemic attacks, lower-limb amputation of any extent associated with ischemia, revascularization procedures at any site, and sudden death or death occurring before access to the hospital for coronary and cerebrovascular events and *2*) all-cause mortality. The methods used to ascertain the outcomes have previously been described (10). From the original cohort of 529 patients, 24 (4.5%) were considered lost to follow-up because no information could be obtained concerning cardiovascular events or death; 22 of these patients were already lost at the 5-year follow-up. In most cases, the lack of information was due to change of region of residence.

Statistical analysis

Data are reported as means ± SD. Categorical variables in different groups were compared, when applicable, by χ^2 test. The correlation between A1C and both FBG and blood glucose 2 h after lunch was evaluated by the Pearson method. Cox proportional hazards models were used to evaluate the predictive role of each parameter on cardiovascular events and mortality.

In model 1, FBG, blood glucose 2 h after breakfast, blood glucose 2 h after lunch, blood glucose before dinner, and A1C were introduced in the analysis separately as individual predictors. In model 2, the Cox analysis was performed with the backward method by introducing simultaneously in the analysis all five glycemic control parameters mentioned above. In model 3, the Cox analysis was performed with the backward method by introducing sex, age, known diabetes duration, smoking habit, BMI, systolic and diastolic blood pressure, LDL cholesterol, HDL cholesterol, triglycerides, creatinine, AER, and the glycemic control parameters identified as significant predictors in model 2 (i.e., blood glucose 2 h after lunch and A1C). The predictors were categorized in three different ways (models A, B, and C).

In model A, the variables were categorized as "good" and "bad" according to the American Diabetes Association "Standards of Medical Care in Diabetes—2010" (11), which identifies as "good" fasting or preprandial blood glucose 70–130 mg/dL (i.e., 3.9–7.2 mmol/L); postprandial blood glucose <180 mg/dL (<10 mmol/L); A1C <7%; systolic and diastolic blood pressure <130 and <80 mmHg, respectively; LDL cholesterol <100 mg/dL (<2.6 mmol/L); HDL cholesterol >40 mg/dL (>1 mmol/L) in men and >50 mg/dL (>1.3 mmol/L) in women; and triglycerides <150 mg/dL (<1.7 mmol/L). In model A, we also considered as "good" BMI ≤27 kg/m^2, AER <20 μg/min, and creatinine ≤1.2 mg/dL. In model B, the variables were used as continuous variables. In model C, the variables were categorized into tertiles and introduced by the creation of dummy variables; the worst tertile (i.e., the highest tertile, with the exception of HDL cholesterol, in which the first tertile was considered as the worst) was compared with the other two tertiles combined. This kind of categorization was the same as that used in the 5-year follow-up (10).

Age and known diabetes duration were categorized in models A and C as dichotomic variables by the median. Model 3A was also built by entering age and diabetes duration, which are not therapeutic targets, as continuous variables.

Collinearities were taken into consideration by introducing in the models artificial variables computed by multiplying the values of individual predictors. The added value given by postprandial blood glucose in the prediction of cardiovascular events and mortality evaluated by the Cox analysis was tested with Harrell *c*-statistic, computed before and after the introduction of postprandial blood glucose in model 3A, which included A1C. To clarify the occurrence of a U-shaped association between A1C and outcomes, Cox analysis with the

backward method was carried out by introducing A1C categorized into deciles together with all the nonglycemic cardiovascular risk factors introduced in model 3, codified as continuous variables.

The a posteriori power calculation of our study concerning the predictive value of postprandial blood glucose and A1C—fixing the CI for statistical significance at 95%—was calculated by the log-rank test in models 2A and 3A. All analyses were performed using SPSS software (version 7; SPSS, Chicago, IL).

RESULTS—Table 1 shows the characteristics at baseline of the 505 patients who completed the follow-up, with the percentages of achievement of the therapeutic targets described in RESEARCH DESIGN AND METHODS.

Of the patients, 16.8% had history of cardiovascular events at baseline. Patients on diet alone, oral agents, oral agents + insulin, or insulin alone were 44.6, 43.0, 7.3, and 5.1%, respectively.

During the 14-year follow-up, we observed the following: *1*)172 first cardiovascular events (34.1% of the population): 96 (55.8%) were coronary (36 myocardial infarctions, 45 revascularization procedures, 6 unstable anginas, and 9 sudden deaths), 55 (31.9%) cerebrovascular (25 transient ischemic attacks, 20 strokes, and 10 carotid thrombo-endoarterectomies), and 21 (12.2%) peripheral (16 lower-limb revascularizations, 2 operations for aortic aneurisms, and 3 amputations for lower-limb ischemia) and 2)147 deaths (29.1% of the population). The predictive role of the glycemic variables on cardiovascular events and all-cause mortality in model A is shown in Table 2.

When we evaluated with Cox models the predictive role on cardiovascular events and all-cause mortality of each of the five glycemic control parameters considered separately (model 1A [Table 2]), we observed that blood glucose 2 h after lunch and A1C, but not FBG, predicted both the first cardiovascular events and all-cause mortality. The correlations of A1C with FBG and with blood glucose 2 h after lunch were similar ($r = 0.446$, $P = 0.0001$, for FBG and $r = 0.475$, $P = 0.0001$, for blood glucose 2 h after lunch).

When the five glycemic control parameters were considered together in the Cox analysis with the backward method (model 2A [Table 2]), the parameters that remained significant in the final step were blood glucose 2 h after lunch and A1C both for cardiovascular events and for all-cause mortality. The standardized coefficients of the five glycemic parameters in model 2A were as follows: *1*) for cardiovascular events, FBG −0.077 ± 0.191, blood glucose 2 h after breakfast 0.100 ± 0.192, blood glucose 2 h after lunch 0.414 ± 0.181, blood glucose before dinner −0.060 ± 0.173, and A1C 0.599 ± 0.194; and 2) for all-cause mortality, FBG −0.117 ± 0.208, blood glucose 2 h after breakfast −0.116 ± 0.206, blood glucose 2 h after lunch 0.665 ± 0.191, blood glucose before dinner 0.103 ± 0.188, and A1C 0.670 ± 0.220.

Finally, when the two glycemic control parameters that were significant in model 2, i.e., blood glucose 2 h after lunch and A1C, were considered together with the nonglycemic cardiovascular risk factors (model 3A [Table 2]), they remained significant. The two parameters also remained significant when, in model 3A, age and diabetes duration were considered as continuous variables; in particular, the hazard ratios (HRs) for cardiovascular events were 1.455 (95% CI 1.060–1.998, $P = 0.020$) for blood glucose 2 h after lunch and 1.919 (1.327–2.774, $P = 0.001$) for A1C and for all-cause mortality were 1.888 (1.332–2.676, $P < 0.0001$) for blood glucose 2 h after lunch and 1.887 (1.228–2.901, $P = 0.004$) for A1C.

We then considered the influence of the collinearity between blood glucose 2 h after lunch and A1C by introducing in model 3A an artificial variable computed by multiplying values of A1C and blood glucose 2 h after lunch. Also, after the introduction of this artificial variable, A1C and blood glucose 2 h after lunch continued to predict both cardiovascular events and all-cause mortality without changes in their HRs because the artificial variable was not significant and therefore did not survive until the final step of the model.

We also evaluated the influence of sex on the predictive power of both A1C and blood glucose 2 h after lunch on cardiovascular events and all-cause mortality. The introduction of the artificial variables computed by multiplying the sex dummy and A1C or blood glucose 2 h after lunch in model 3 did not show significant sex-related differences.

Table 1—*Characteristics of the population at baseline (1995)*

	Values	Targets	At target (%)
n	505		
Women/men (%)	46.9/53.1		
Age (years)	62.2 ± 9.6		
Known diabetes duration (years)	9.4 ± 8.0		
Smoking habit (never vs. previous/present) (%)	52.5/47.5		
BMI (kg/m^2)	29.2 ± 4.96	<27	38.2
Systolic blood pressure (mmHg)	146.5 ± 18.1	<130	12.7
Diastolic blood pressure (mmHg)	84.5 ± 8.2	<80	11.7
HDL cholesterol (mg/dL)	48.9 ± 15.0	>40 M, >50 F	57.7
HDL cholesterol (mmol/L)	1.26 ± 0.39	>1.0 M, >1.3 F	
Triglycerides (mg/dL)	143.2 ± 87.0	<150	66.3
Triglycerides (mmol/L)	1.62 ± 0.98	<1.7	
LDL cholesterol (mg/dL)	140.2 ± 35.8	<100	12.9
LDL cholesterol (mmol/L)	3.62 ± 0.92	<2.6	
A1C (%)	7.61 ± 1.32	<7.0	34.1
Creatinine (mg/dL)	0.87 ± 0.26	<1.2	95.6
AER (μg/min)	45.3 ± 165.0	<20	70.7
FBG (mg/dL)	158.0 ± 47.1	70–130	31.7
FBG (mmol/L)	8.77 ± 2.62	3.9–7.2	
Blood glucose 2 h after breakfast (mg/dL)	150.8 ± 48.4	<180	73.5
Blood glucose 2 h after breakfast (mmol/L)	8.37 ± 2.68	<10.0	
Blood glucose 2 h after lunch (mg/dL)	158.7 ± 57.0	<180	66.3
Blood glucose 2 h after lunch (mmol/L)	8.82 ± 3.16	<10.0	
Blood glucose before dinner (mg/dL)	133.4 ± 50.4	70–130	51.9
Blood glucose before dinner (mmol/L)	7.41 ± 2.80	3.9–7.2	

Data are mean ± SD unless otherwise indicated. Targets are American Diabetes Association 2010 therapeutic targets (11).

Table 2—*HRs for cardiovascular events and all-cause mortality conferred by blood glucose control parameters*

	Model A			Model B		
	HR	95% CI	*P*	HR	95% CI	*P*
Model 1						
Cardiovascular events						
FBG	1.307	(0.939–1.820)	ns	1.042	(0.985–1.101)	ns
Blood glucose 2 h after breakfast	1.467	(1.066–2.017)	0.019	1.046	(0.989–1.106)	ns
Blood glucose 2 h after lunch	1.768	(1.307–2.392)	<0.0001	1.094	(1.047–1.144)	<0.0001
Blood glucose before dinner	1.286	(0.954–1.733)	ns	1.068	(1.015–1.124)	0.012
A1C	2.023	(1.424–2.874)	<0.0001	1.223	(1.103–1.356)	<0.0001
All-cause mortality						
FBG	1.318	(0.916–1.896)	ns	1.068	(1.008–1.133)	0.026
Blood glucose 2 h after breakfast	1.400	(0.992–1.976)	0.056	1.110	(1.049–1.176)	<0.0001
Blood glucose 2 h after lunch	2.234	(1.616–3.088)	<0.0001	1.122	(1.071–1.175)	<0.0001
Blood glucose before dinner	1.552	(1.119–2.152)	0.008	1.096	(1.040–1.155)	0.001
A1C	2.322	(1.554–3.470)	<0.0001	1.314	(1.184–1.459)	<0.0001
Model 2						
Cardiovascular events						
Blood glucose 2 h after lunch	1.507	(1.101–2.064)	0.010	1.064	(1.009–1.121)	0.021
A1C	1.792	(1.244–2.582)	0.002	1.134	(1.002–1.283)	0.046
All-cause mortality						
Blood glucose 2 h after lunch	1.885	(1.346–2.639)	<0.0001	1.076	(1.019–1.137)	0.008
A1C	1.907	(1.256–2.897)	0.002	1.209	(1.067–1.369)	0.003
Model 3						
Cardiovascular events						
Sex	2.172	(1.584–2.980)	<0.0001	1.921	(1.305–2.826)	0.001
Age	1.682	(1.208–2.343)	0.002	1.041	(1.024–1.059)	<0.0001
Known diabetes duration	1.483	(1.053–2.088)	0.024			
Systolic blood pressure	1.685	(0.987–2.875)	0.056			
Blood glucose 2 h after lunch	1.452	(1.057–1.994)	0.021	1.059	(1.004–1.118)	0.037
A1C	1.732	(1.187–2.526)	0.004	1.201	(1.052–1.371)	0.007
All-cause mortality						
Age	5.723	(3.436–9.532)	<0.0001	1.116	(1.094–1.139)	<0.0001
Sex				1.610	(1.143–2.266)	0.006
Creatinine	2.470	(1.409–4.333)	0.002			
AER	1.794	(1.280–2.515)	0.001	1.001	(1.001–1.002)	<0.0001
Systolic blood pressure	2.525	(1.105–5.773)	0.028			
Triglycerides				1.212	(1.031–1.424)	0.020
Blood glucose 2 h after lunch	1.846	(1.306–2.610)	0.001	1.057	(1.000–1.118)	0.054
A1C	1.896	(1.230–2.922)	0.004	1.263	(1.105–1.442)	0.001

In model A, blood glucose control parameters were categorized according to achievement of American Diabetes Association 2010 therapeutic targets (11), and in model B they were considered as continuous variables. In model 1, the five blood glucose parameters were considered independently. In model 2 they were considered together; the table shows the two independent predictors. In model 3, the two blood glucose parameters identified as independent predictors in model 2 were considered together with the nonglycemic variables, i.e., sex, age, diabetes duration, BMI, smoking habit, systolic and diastolic blood pressure, LDL and HDL cholesterol, triglycerides, creatinine, and AER. Cox analysis was applied, in models 2 and 3, with the backward method. In model B, HRs were referred to each unitary variation according to the unit of measure used (years for time, micrograms/min for AER, millimoles per liter for triglycerides and blood glucose, and % for A1C). ns, not significant.

The added value given by postprandial blood glucose in the prediction of cardiovascular events and mortality in a model where A1C is included was evaluated by comparing Harrell *c*-statistic computed on the output of Cox model 3A before and after the introduction of postprandial blood glucose. The addition of blood glucose 2 h after lunch significantly increased the *c*-statistic: *1*) for cardiovascular events, from 0.656 ± 0.001 to 0.682 ± 0.001 ($P < 0.0001$); *2*) for all-cause mortality, from 0.761 ± 0.001 to 0.790 ± 0.001 ($P < 0.0001$).

To clarify whether in our cohort the association of A1C with outcomes is U-shaped, we evaluated the HR conferred by the different A1C deciles for cardiovascular events and all-cause mortality. We observed that *1*) the lowest risk for cardiovascular events and all-cause mortality was conferred by the first decile (i.e., A1C ≤6.10%) and that *2*) the HR became significantly different from that of the first decile starting from the fourth decile (A1C >7.0%). In particular, *1*) HR conferred by A1C range 7.01–7.40% (i.e., the fourth decile) was 2.176 (95% CI 1.028–4.605, $P = 0.042$) for cardiovascular events and 2.532 (1.004–6.386, $P = 0.049$) for all-cause mortality, and *2*) the highest risk was conferred by the tenth decile (i.e., A1C >9.8%), with an HR of

4.259 (1.870–9.696, $P = 0.001$) for cardiovascular events and 5.012(1.909–13.158, $P = 0.001$) for all-cause mortality.

The percentage of patients on diet alone in the first A1C decile was 92.2%. Thus, the lowest A1C values were recorded in patients without hypoglycemic risk.

In our study, the a posteriori power calculation for the predictive value of a blood glucose 2 h after lunch value ≥180 mg/dL and of an A1C value ≥7% measured in models 2A and 3A (i.e., when the two parameters were simultaneously considered), was *1*) for postprandial blood glucose, in model 2A, 82% for cardiovascular events and 98% for all-cause mortality, and in model 3A, 75% for cardiovascular events and 95% for all-cause mortality; and *2*) for A1C, in model 2A, 98% both for cardiovascular events and for all-cause mortality and in model 3A, 96% for cardiovascular events and 98% for all-cause mortality.

The results of model B, where the parameters were considered—except for sex and smoking habit—as continuous variables, are reported in Table 2. They confirm the predictive role of blood glucose 2 h after lunch and A1C on the outcomes.

Also, in model C, where the parameters were categorized in tertiles, blood glucose 2 h after lunch predicted both cardiovascular events and all-cause mortality; in particular, in model 3C the HR was 1.464 (95% CI 1.074–1.996, $P = 0.016$) for cardiovascular events and 1.863 (1.313–2.644, $P < 0.0001$) for all-cause mortality. Note that the third tertile of blood glucose 2 h after lunch showed values ≥181 mg/dL.

CONCLUSIONS—The main finding of the current study, carried out in patients affected by type 2 diabetes with a 14-year follow-up, is that A1C and blood glucose 2 h after lunch—but not FBG—predict cardiovascular events and all-cause mortality also when considered simultaneously with the main nonglycemic cardiovascular risk factors. Note that, as previously discussed (10), in our population the blood glucose value 2 h after lunch is more representative of the postprandial state than blood glucose 2 h after breakfast because when the study was initiated, breakfast in Piedmont frequently consisted only of a cup of coffee with, sometimes, a small piece of bread.

The lack of a blood glucose peak after breakfast is also attributable to the fact that oral agents are mainly administered in the morning before this small breakfast. Furthermore, this study confirms our previous observation that blood glucose before dinner is the lowest blood glucose value of the profile (12,13). This phenomenon is attributable to the fact that in type 2 diabetes the glycemic baseline on which postmeal peaks are superimposed (the so-called "pre-prandial baseline") is not stable but declines from morning to evening even in patients on diet alone, likely because of waning of the early-morning increase in counterregulatory hormones (12). Not surprisingly, in patients on oral agents hypoglycemia is frequent in the late afternoon (14).

In the first 5 years' follow-up of the San Luigi Gonzaga Diabetes Study, we already demonstrated that blood glucose 2 h after lunch (referred to from here on as "postprandial blood glucose") predicts cardiovascular events in type 2 diabetes after adjustment not only for the main nonglycemic cardiovascular risk factors but also for A1C (10). We are now showing that this predictive power persists in the 14-year follow-up.

Furthermore, this long-term follow-up also allows estimation of the high predictive power of postprandial blood glucose on all-cause mortality when the effect of A1C is simultaneously considered; as far as we know, this is the first demonstration of this phenomenon. It should be emphasized that in model 3A the strength of prediction is similar for A1C and postprandial blood glucose, demonstrating that postprandial hyperglycemia predicts all-cause mortality per se and not only as a component of A1C.

Interestingly, in this 14-year follow-up of the San Luigi Gonzaga Diabetes Study, FBG did not predict cardiovascular events or all-cause mortality. Our study, therefore, confirms that which has been observed in the 11-year follow-up of the DIS concerning FBG (9).

In the current study, the variables were also categorized according to the achievement of American Diabetes Association 2010 therapeutic targets (11); it is not surprising that these targets were largely unfulfilled in 1995 in the San Luigi Gonzaga Diabetes Study cohort, given that at that time targets were much less tight. On the other hand, achievement of targets for the prevention of cardiovascular risk is also low in cohorts evaluated more recently, as shown by Multifactorial INtervention in Type 2 Diabetes–Italy (MIND-IT), a multicenter Italian investigation undertaken in 2004–2006 (15).

The epidemiological nature of our study does not allow for the statement that postprandial blood glucose is not only a predictor but also a risk factor for cardiovascular events and death. Further intervention studies showing that correction of postprandial hyperglycemia reduces these outcomes are needed to clarify this point.

It has been shown that reduction of hyperglycemia prevents diabetes macrovascular disease; in particular, a meta-analysis of randomized controlled trials evaluating the effects on cardiovascular outcomes and mortality of intensive blood glucose control policies targeting A1C showed a beneficial effect on coronary events without increasing the death risk (16). The specific effect of postprandial blood glucose correction, however, is far less clarified. The following evidence is available: *1*) a meta-analysis of seven randomized controlled trials in type 2 diabetes indicates that acarbose, a drug that corrects postprandial hyperglycemia by impairing carbohydrate absorption, reduces the occurrence of cardiovascular events; this effect has also been described in patients affected by impaired glucose tolerance in Study to Prevent NIDDM (STOP-NIDDM) (17); *2*) nateglinide, a drug administered to correct postprandial hyperglycemia by increasing insulin secretion, was unable in the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial to reduce cardiovascular events in a high-risk impaired glucose tolerance population; quite surprisingly, however, patients on nateglinide showed an increase of 2-h postchallenge blood glucose (18); and *3*) the Hyperglycemia and its Effect after Acute Myocardial infarction on cardiovascular outcomes in patients with Type 2 Diabetes mellitus (HEART2D) trial was carried out in type 2 diabetic patients after a myocardial infarction to compare the effects on cardiovascular mortality and morbidity of two different insulin regimens. The first aimed to correct postprandial blood glucose by premeal insulin lispro, and the second aimed to correct fasting blood glucose by basal NPH or insulin glargine. This trial was unable to confirm the superiority of postprandial blood glucose correction, even if the magnitude of the differences in postprandial glycemia was less than expected (19). Thus, it is not surprising that the role of postprandial blood glucose as a contributor to diabetes macrovascular complications and its relevance as a

treatment target is debated (20,21). In this context, our study encourages further efforts to design intervention studies able to give definite answers; actually, it demonstrates for the first time the predictive power of postprandial blood glucose on cardiovascular events and mortality in type 2 diabetes when A1C is also considered.

Intervention studies should be carried out in type 2 diabetic subjects with an average cardiovascular risk. In fact, patients of the HEART2D trial were not representative of the whole type 2 diabetic population, being a subset of very-high-risk patients randomized within 21 days after a myocardial infarction (19).

The San Luigi Gonzaga Diabetes Study identifies postprandial blood glucose as a predictor of cardiovascular events and death. Thus, it induces consideration of postprandial blood glucose not only as an essential component of A1C but also as a tool in risk stratification.

The specific contribution of FBG and postprandial blood glucose to A1C was considered in detail elsewhere (22,23); in our study, the correlation of these two variables with A1C is similar. The interrelationships among glycemic variables justify the fact that any intervention reducing preprandial blood glucose also reduces postprandial blood glucose because it lowers the baseline on which postprandial peaks are superimposed, as we have recently described (13). This is the rationale of therapeutic approaches targeting postprandial blood glucose after correction of preprandial values. The mechanisms involved in the association between postprandial blood glucose and cardiovascular events have previously been described (4,20).

Note that in our study, we did not observe the recently described U-shape in the association between A1C and mortality (24); actually, in our cohort the lowest risk for both cardiovascular events and all-cause mortality was conferred by the first A1C decile (≤6.10%) and the highest risk by the tenth decile (>9.8%). Those who observed the U-shaped association between A1C and death discussed the possible deleterious role of hypoglycemia (24). Note also that all patients considered in that study were on hypoglycemic treatment (24): either combination oral regimen with a sulphonylurea plus metformin or insulin, with or without concomitant oral agents; thus, they were at hypoglycemic risk. The absence of a U-shaped association in our cohort could be explained by the great attention we always paid to avoid hypoglycemia and also by considering the results of blood glucose profiles (13,14); in particular, because 92.2% of patients in the first A1C decile were on diet alone and therefore not at hypoglycemic risk, we can exclude that low A1C values were due to hypoglycemic episodes.

Thus, targeting A1C should be made without forgetting that it is an integrate measure of blood glucose values and is protective only if it mirrors the simultaneous avoidance of both hypo- and hyperglycemia. In conclusion, the 14-year follow-up of the San Luigi Gonzaga Diabetes Study strongly supports the predictive role for cardiovascular events and all-cause mortality not only of the overall blood glucose control evaluated by A1C but also of postprandial hyperglycemia, which is also reported to occur in type 2 diabetic patients when A1C is adequate (25).

Acknowledgments—This study was partly funded by Piedmont Region grants 908/2006 and 2303/2007 of the "Ricerca Sanitaria Finalizzata" to M.T. and F.C., respectively.

No potential conflicts of interest relevant to this article were reported.

F.C. designed the study, researched data, contributed to discussion, and wrote the manuscript. A.P. researched data, performed the statistical elaboration, and contributed to discussion. M.V., L.D.M., and K.B. researched data and contributed to discussion. P.M. and G.A. contributed to discussion. M.T. designed the study, contributed to discussion, and wrote the manuscript.

The authors thank the nurses of their Diabetes Outpatient Clinic for the wonderful job of patient care in the 14 years of follow-up of the San Luigi Gonzaga Diabetes Study. The authors also thank Dr. Michela Viretto, Department of Clinical and Biological Sciences, Turin University, for the revision of the English language.

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