Diverging Association of Reduced Glomerular Filtration Rate and Albuminuria With Coronary and Noncoronary Events in Patients With Type 2 Diabetes

The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study

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OBJECTIVE—Although a reduced estimated glomerular filtration rate (eGFR) was shown to be a powerful independent predictor of cardiovascular disease (CVD), other studies suggested that it confers a much lower risk than albuminuria alone, whereas the combination of the two abnormalities is associated with multiplicative risk. This study aimed at assessing the independent association of previous CVD events, either total or by vascular bed, with eGFR and albuminuria and chronic kidney disease (CKD) phenotypes.

RESEARCH DESIGN AND METHODS—This cross-sectional study evaluated 15,773 patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study in 19 outpatient diabetes clinics in years 2007–2008. Albuminuria was assessed by immunonephelometry or immunoturbidimetry. GFR was estimated by the simplified Modification of Diet in Renal Disease Study and the Chronic Kidney Disease-Epidemiology Collaboration equation. CKD was defined as an eGFR <60 mL/min/1.73 m^2 or micro- or macroalbuminuria. Major acute CVD events were adjudicated based on hospital discharge records or specialist visits.

RESULTS—CVD risk increased linearly with eGFR decline and albuminuria and became significant for values <78 mL/min/1.73 m^2 and ≥ 10.5 mg/24 h, respectively. Beyond traditional CVD risk factors, total CVD showed an independent association with albuminuria alone (odds ratio 1.20 [95% CI 1.08–1.33]), reduced eGFR alone (1.52 [1.34–1.73]), and both abnormalities (1.90 [1.66–2.19]). However, coronary events were associated predominantly with reduced eGFR alone, whereas cerebrovascular and peripheral events showed a stronger correlation with the albuminuric CKD phenotypes.

CONCLUSIONS—These data, although cross-sectional, show that reduced eGFR, irrespective of albuminuria, is associated with significant CVD, particularly in the coronary district.

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A large body of evidence suggests that individuals with chronic kidney disease (CKD) are more likely to die, particularly from cardiovascular disease (CVD), than to progress to end-stage renal disease (ESRD) (1), although recent findings seem to favor progression (2). In fact, although CVD risk is particularly increased in patients with ESRD, where CVD mortality accounts for the vast majority of deaths (3), even mild-to-moderate renal impairment is associated with CVD, as shown in the general population (4) and in subjects with type 2 diabetes (5).

For clinical and epidemiologic purposes, CKD is currently classified into five stages, according to the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI). Classification is based on the presence or absence of kidney damage, as manifested by pathologic abnormalities or by disease markers such as micro- or macroalbuminuria, and glomerular filtration rate (GFR), as calculated by the use of estimating equations from serum creatinine measurements. Although stages 1–2 CKD are identified by evidence of kidney damage, stages 3–5 CKD are defined solely on the basis of estimated GFR (eGFR), irrespective of albuminuria (6). Because staging systems

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for disease classification should assign people with worse prognoses to more advanced stages, based on that introduced by the NKF KDOQI, subjects with an eGFR <60 mL/min/1.73 m^2 (i.e., stage ≥3 CKD) without albuminuria would carry the same CVD and renal risk as those with albuminuria but a lower risk than individuals with albuminuria and normal or subnormal eGFR, who are assigned to stages 1–2 CKD.

In the Third National Health and Nutrition Examination Survey (NHANES III) cohort, increased albuminuria and reduced eGFR were both associated with increased risk of CVD and all-cause mortality overall and within every eGFR and albuminuria category, respectively (7). A recent meta-analysis confirmed that albuminuria, with no threshold, and an eGFR <60 mL/min/1.73 m^2 are both independent predictors of death and indicated that these two abnormalities are multiplicatively associated with risk of death without evidence of interaction (8). However, in other samples of the general population, the eGFR cutoff point for optimal discrimination of CVD risk was higher (9,10), whereas more recent reports showed that individuals with reduced eGFR without albuminuria are at much lower CVD risk than subjects with albuminuria without reduced eGFR (11–13). Studies in patients with type 2 diabetes showed that albuminuria and reduced eGFR are associated to the same extent with total CVD events (14,15), whereas albuminuria predicts death from CVD better than reduced eGFR (8,16).

Thus, although the independent contribution of albuminuria appears to be relevant, it is unclear whether subnormal eGFR levels (i.e., 60–89 mL/min/1.73 m^2) and, particularly, reduced eGFR levels (i.e., <60 mL/min/1.73 m^2) in the absence of albuminuria are associated with significant CVD risk. This issue is particularly relevant in patients with type 2 diabetes, because reduced eGFR is more common than previously recognized in these individuals (17), and more importantly, it occurs in the absence of albuminuria in most of them (14,18,19).

This study assessed the independent association of previous CVD events, either total or by vascular bed, with eGFR and albuminuria as well as with nonalbuminuric CKD, as defined by an eGFR <60 mL/m/1.73 m^2 without albuminuria, compared with albuminuric CKD with either reduced (stage ≥3 CKD) or nonreduced (stages 1–2 CKD) eGFR, in a large Italian cohort of patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population

We used the data collected at the baseline visit for the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study (registered with ClinicalTrials.gov, NCT00715481; http://clinicaltrials.gov/ct2/show/NCT00715481), an observational, prospective cohort study on the effect of eGFR on CVD morbidity and mortality in type 2 diabetes.

The RIACE population consisted of 15,933 Caucasian patients with type 2 diabetes (defined by the American Diabetes Association criteria) attending consecutively 19 hospital-based diabetes clinics of the National Health Service throughout Italy (see Supplementary Data) between 2007 and 2008. Exclusion criteria were dialysis or renal transplantation. The study protocol was approved by the locally appointed ethics committees.

The quality and completeness of data were controlled, and 160 patients were excluded due to missing or implausible values. Data from the remaining 15,773 patients were subsequently analyzed.

Clinical determinations

All patients underwent a structured interview to collect the following information: age, smoking status, and known diabetes duration; current glucose-, blood pressure (BP), and lipid-lowering therapy, with indication of the class of drug; and previously documented major acute CVD events, including myocardial infarction, stroke, foot ulcer, gangrene or amputation; coronary, carotid, and lower limb revascularization; and surgery for aortic aneurysm. CVD events were adjudicated based on hospital discharge records or specialist visits by an ad hoc committee in each center.

At physical examination, weight and height were assessed, with calculation of BMI. BP was measured with a sphygmomanometer after a 5-min rest. The presence of retinopathy was assessed by an expert ophthalmologist by ophthalmoscopy or retinography and classified as absent, nonadvanced, or advanced, the latter comprising maculopathy, preproliferative and proliferative retinopathy or history of previous photocoagulation, and blindness (if less than 1/10 normal vision or 20/200 on the Snellen test).

Analytical determinations

Glycated hemoglobin (HbA_{1c}) was measured by high-performance liquid chromatography using Diabetes Control and Complications Trial–aligned methods; fasting levels of triglycerides and total and HDL cholesterol were determined by standard analytical methods; and LDL cholesterol was calculated by the Friedewald formula.

Albumin excretion rate (AER) was obtained from timed (24-h) urine collections or calculated from the albumin-to-creatinine ratio in early-morning, first-voided urine samples, in the absence of symptoms and signs of urinary tract infection or other interfering clinical conditions. A conversion formula developed in type 1 diabetes (20) and preliminarily validated in a subgroup from the RIACE cohort was used for AER calculation from the albumin-to-creatinine ratio. Albuminuria was measured in fresh urine samples by immunonephelometry or immunoturbidimetry (21). As recommended, the analytical coefficient of variation (CV) of both methods was largely <15% (i.e., 2.1–5.2% for immunonephelometry vs. 3.4–8.1% for immunoturbidimetry), with a detection limit of 1.7 and 3.0 mg/L, respectively.

To ensure an external quality control of urinary albumin assays, 50 samples from each center were reanalyzed at the reference laboratory of the coordinating center. Results showed that the CVs between the peripheral and central values were lower than 15% in 94% of samples included in the 15–500 mg/L interval. One to three measurements for each patient were obtained, and in case of multiple measurements, the geometric mean was used for analysis. In subjects with multiple measurements (4,062 with at least two and 2,310 with three values), concordance rate between the first value and the geometric mean of multiple measurements was >90% for all classes of albuminuria (21). Patients were then assigned to one of the following classes of albuminuria (mg/24 h): normoalbuminuria (AER <30), microalbuminuria (AER 30–299), or macroalbuminuria (AER ≥300). In addition, normoalbuminuric subjects were further classified as having normal (AER <10) or low albuminuria (AER 10–29), according to the recent definition of the NKF (22).

Serum (and urine) creatinine was measured by the modified Jaffe method. One to three measurements were obtained for each patient, and eGFR was calculated by the four-variable Modification of Diet in Renal Disease (MDRD) study equation (23) using the mean serum creatinine value in case of multiple measures. As recommended (24), one of two versions of this equation was used, depending on whether serum

creatinine methods had been calibrated to be traceable to an isotope dilution mass spectrometry (IDMS) reference method. GFR was also estimated using the recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which was found to be more accurate and to provide lower estimates of CKD prevalence than the MDRD study equation (25). To this end, non-IDMS serum creatinine values were standardized using the following equation: $-0.166 + 1.10 \times$ (measured serum creatinine [mg/dL]). To derive this equation, 201 frozen samples previously analyzed using a non-IDMS method were reassayed by an IDMS reference method. Patients were then assigned to one of the following classes of eGFR (mL/min/1.73 m^2): 1 (≥90), 2 (60–89), 3 (30–59), 4 (15–29), or 5 (<15).

Finally, subjects were classified as having no CKD (eGFR ≥60 mL/min/1.73 m^2 without micro- or macroalbuminuria) or stages 1–5 CKD, based on the presence or absence of micro- or macroalbuminuria and the value of eGFR according to the NKF KDOQI (5). Patients assigned to CKD stages (and GFR classes) 4 and 5 were pooled together.

Statistical analysis

Data are expressed as median and mean ± SD or number of cases and percentages. The Kolmogorov-Smirnov normality test, followed by Mann-Whitney test for continuous variables or Pearson χ^2 test for categorical variables, were applied.

Logistic regression analyses with stepwise variable selection were performed to identify factors independently associated with major acute CVD events, either total or by vascular bed; that is, coronary events, including myocardial infarction and/or coronary revascularization; cerebrovascular, including stroke and/or carotid revascularization; and peripheral, including ulcer/gangrene/amputation and/or lower limb revascularization. Separated analyses for events (myocardial infarction, stroke, and ulcer/gangrene/amputation) and revascularization procedures were also performed. Covariates were individual values, deciles, or categories of eGFR and albuminuria or CKD phenotypes, such as reduced eGFR (stage ≥3 CKD), with or without albuminuria (micro or macro), and albuminuria with nonreduced eGFR (stages 1–2 CKD), together with age, male sex, and smoking status, known diabetes duration, HbA_{1c}, hypertension, triglycerides, HDL and LDL cholesterol, lipid-lowering treatment, BMI, nonadvanced and advanced retinopathy, and when applicable, previous CVD event(s) in other vascular beds. Hypertension was defined by systolic BP ≥140 and/or diastolic BP ≥90 mmHg and/or antihypertensive treatment. Dyslipidemia was defined as high LDL cholesterol and/or lipid-lowering treatment, whereas high triglycerides and low HDL cholesterol were considered separately. Results of these analyses were expressed as odd ratios (ORs) with their 95% CI.

All P values were two-sided, and a P value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 13.0 software (SPSS Inc., Chicago, IL).

RESULTS—One or more major acute CVD events were adjudicated in 3,654 patients. Clinical characteristics of subjects with or without prior CVD event(s) are reported in Table 1. Compared with subjects without CVD, patients with prior event(s) were older, with a higher prevalence of men, a longer diabetes duration, and worse metabolic control; moreover, a significantly higher percentage was receiving insulin treatment. Concerning the other CVD risk factors, these patients had higher triglycerides and lower HDL cholesterol, but also lower LDL cholesterol and diastolic (but not systolic) BP levels. However, the percentage of patients treated for dyslipidemia and/or hypertension was higher among those with prior CVD event(s), who also showed a higher prevalence of retinal involvement. Finally, with regard to renal function, patients with prior CVD event(s) had higher serum creatinine and albuminuria levels and lower eGFR—whether by MDRD or CKD-EPI—than patients without. Correspondingly, the two groups differed for eGFR and albuminuria class and CKD stage distribution.

Multiple logistic regression indicated that age, male sex, diabetes duration, smoking status, and presence of dyslipidemia and hypertension were positively associated with total CVD, whereas HDL cholesterol levels were inversely correlated (Supplementary Table 1 and Table 2). Independent of these factors, pharmacologic treatment of diabetes and presence of retinal involvement were graded risk indicators (Supplementary Table 1 and Table 2). Compared with normal eGFR and albuminuria categories, subnormal eGFR and low albuminuria were nonsignificantly associated with total CVD, with the association becoming significant for eGFR <60 mL/min/1.73 m^2 (a 65% risk increase, which was only marginally greater for eGFR <30 mL/min/1.73 m^2) and micro- or macroalbuminuria (Supplementary Table 1). After accounting also for the use of angiotensin-converting enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs), association with CVD events remained significant at the same threshold values of eGFR and albuminuria (data not shown). Results were virtually identical when separate analyses were conducted for CVD events alone (with or without revascularization), whereas a significant association of revascularization procedures alone was found for eGFR but not albuminuria categories (data not shown).

When eGFR and albuminuria values were included as continuous variables, the age- and sex-adjusted risk for a CVD event increased by 6.8% for every 5 mL/min/1.73 m^2 eGFR decrease (OR 1.068 [95% CI 1.058–1.078]; $P < 0.0001$) and by 0.4% for every 10 mg/24 h albumin increase (1.004 [1.003–1.005]; $P < 0.0001$). The risk associated with albuminuria (1.006 [1.004–1.007]) and reduced eGFR (1.074 [1.064–1.085]) increased further if the other variable was excluded from the model. When deciles of eGFR and albuminuria were considered, age- and sex-adjusted risk for a CVD event increased linearly by 12% (1.12 [1.10–1.14]) for each decreasing decile of eGFR and by 9% (1.09 [1.08–1.10]) for each increasing decile of albuminuria. Excess risk was significant for eGFR values <78 mL/min/1.73 m^2 and albuminuria values ≥10.5 mg/24 h (Fig. 1); the eGFR cutoff became 84 mL/min/1.73 m^2, whereas that of albuminuria did not change when the two variables were included simultaneously.

When CKD phenotypes were introduced as covariates in the model, reduced eGFR without albuminuria was more strongly associated with events than normal eGFR with micro- or macroalbuminuria; however, the combination of reduced eGFR and albuminuria marked an increased risk of CVD events in an additive manner (Table 2).

When analysis was carried out separately for coronary events (Table 3), albuminuria alone was no longer an independent predictor, even after accounting for the use of ACEIs and/or ARBs (data not shown), and the association was stronger with nonalbuminuric than with albuminuric renal impairment. No association was observed between coronary events and retinopathy, whereas, as expected, the coexistence of a cerebrovascular or peripheral event carried additional quotas of risk. In contrast, the

Table 1—*Clinical characteristics of subjects with or without prior CVD event(s)*

Variable	Prior CVD event		*P**
	No	Yes	
Patients	12.119 (76.8)	3.654 (23.2)	
Age, years	65.1 ± 10.4	69.1 ± 9.3	<0.0001
Male sex	6,496 (53.6)	2,470 (67.6)	<0.0001
Smoking status			<0.0001
Never	7,174 (59.2)	1,754 (48.0)	
Former	3,042 (25.1)	1,389 (38.0)	
Current	1,903 (15.7)	511 (14.0)	
Diabetes duration, years	12.2 ± 9.8	16.4 ± 10.6	<0.0001
HbA_{1c}, %	7.5 ± 1.5	7.7 ± 1.6	<0.0001
Glucose-lowering treatment			<0.0001
Diet	1,830 (15.1)	295 (8.1)	
OHA	7,635 (63.0)	2,053 (56.2)	
Insulin + OHA	1,115 (9.2)	409 (11.2)	
Insulin	1,539 (12.7)	897 (24.5)	
Triglycerides, mmol/L	1.56 ± 0.99	1.62 ± 1.02	0.001
Cholesterol, mmol/L			
Total	4.87 ± 0.98	4.53 ± 0.98	<0.0001
HDL	1.30 ± 0.36	1.22 ± 0.24	<0.0001
LDL	2.85 ± 0.83	2.59 ± 0.83	<0.0001
Non-HDL	3.55 ± 0.96	3.32 ± 0.93	<0.0001
Lipid-lowering treatment	4,860 (40.1)	2,430 (66.5)	<0.0001
BP, mmHg			
Systolic	138 ± 18	138 ± 19	0.89
Diastolic	79 ± 9	77 ± 10	<0.0001
BP-lowering treatment	7,974 (65.8)	3,186 (87.2)	<0.0001
BMI, kg/m^2	29.0 ± 5.2	28.8 ± 4.8	0.57
Retinopathy			0.57
Absent	9,780 (80.7)	2,492 (68.2)	
Nonadvanced	1,345 (11.1)	629 (17.2)	
Advanced	994 (8.2)	533 (14.6)	
AER, mg/24 h	57 ± 239	124 ± 490	<0.0001
AER categories			<0.0001
Normal	4,945 (40.8)	1,074 (29.4)	
Low	4,302 (35.5)	1,210 (33.1)	
Micro	2,424 (20.0)	1,074 (29.4)	
Macro	448 (3.7)	296 (8.1)	
Serum creatinine, μmol/L	81.3 ± 30.9	95.5 ± 41.5	<0.0001
eGFR (MDRD), mL/min/1.73 m^2	81.5 ± 23.1	72.5 ± 24.3	<0.0001
eGFR (MDRD) categories			<0.0001
≥90 mL/min/1.73 m^2	3,890 (32.1)	771 (21.1)	
60–89 mL/min/1.73 m^2	6,375 (52.6)	1,777 (48.7)	
30–59 mL/min/1.73 m^2	1,721 (14.2)	986 (26.9)	
<30 mL/min/1.73 m^2	133 (1.1)	120 (3.3)	
eGFR (CKD-EPI), mL/min/1.73 m^2	82.9 ± 20.2	72.6 ± 22.2	<0.0001
eGFR (CKD-EPI) categories			<0.0001
≥90 mL/min/1.73 m^2	5,029 (41.5)	906 (24.8)	
60–89 mL/min/1.73 m^2	5,441 (44.9)	1,688 (46.2)	
30–59 mL/min/1.73 m^2	1,491 (12.3)	914 (25.0)	
<30 mL/min/1.73 m^2	158 (1.3)	146 (4.0)	
CKD phenotypes			<0.0001
No CKD	8,108 (66.9)	1,757 (48.1)	
Stages 1–2 CKD	2,155 (17.8)	794 (21.7)	
Nonalbuminuric stage ≥3 CKD	1,145 (9.4)	528 (14.4)	
Albuminuric stage ≥3 CKD	710 (5.9)	576 (15.8)	

Categorical variables are presented as *n* (%) and continuous variables as mean ± SD. OHA, oral hypoglycemic agent. *For continuous variables, the Mann-Whitney test was applied because the Kolmogorov-Smirnov normality test yielded highly significant *P* values (<0.0001) for all the variables investigated.

analysis of the relationship between cerebrovascular or peripheral events and CKD phenotypes (Table 3) showed that the association with nonalbuminuric CKD was somewhat weaker than that with the albuminuric forms. Again, a previous event in another vascular bed was an additional risk determinant, whereas the presence of retinopathy was an independent risk factor for peripheral events. A strong association of reduced eGFR with coronary events and a weak relation to cerebrovascular and peripheral disease also emerged when eGFR and albumin categories were introduced as covariates (Supplementary Tables 2–4).

CONCLUSIONS—Data from this large multicenter Italian cohort extends previous reports on the association of major acute CVD events with increased albuminuria and/or reduced eGFR in subjects with type 2 diabetes (14–16). Both markers of renal dysfunction, independent of each other and of the cluster of traditional CVD risk factors, were associated with CVD in a graded manner. Although total CVD was nonsignificantly associated with subnormal eGFR (i.e., 60–89 mL/min/1.73 m^2) and also with low albuminuria values (i.e., 10–29 mg/24 h), the analysis by deciles of eGFR and albuminuria showed "thresholds" within these ranges, consistent with the observation that an albuminuria cutoff of ~10 mg/24 h predicts all-cause and CVD mortality in the general population (8). Interestingly, in the presence of albuminuria, the eGFR cutoff for CVD risk almost reached the lower limit of the normal range, whereas that of albuminuria was not influenced by eGFR levels.

The weaker association of total CVD with albuminuria alone, compared with reduced eGFR alone, supports the assignment of subjects with increased albuminuria and normal or subnormal eGFR to earlier CKD stages than patients with reduced eGFR, irrespective of albuminuria. However, the significantly higher CVD burden associated with the combination of increased albuminuria and reduced eGFR suggests that subjects presenting with albuminuric stage ≥3 CKD should be considered at higher CVD risk than those with the nonalbuminuric phenotype of renal impairment, in keeping with recent reports from general population (7,8) and type 2 diabetes (14,15) cohorts. This would also imply that all stages of CKD should be stratified by the presence or absence of albuminuria, as recently suggested (26), for better prediction of both CVD

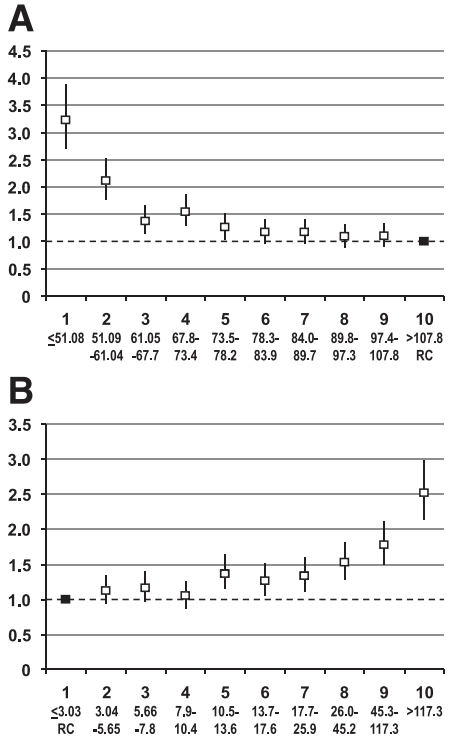

Figure 1—*Age- and sex-adjusted risk of major acute CVD events (OR [95% CI]) according to eGFR deciles (mL/min/1.73 m^2)* (A) *and albuminuria deciles (mg/24 h)* (B). □*, event;* ■*, reference category (RC).*

and renal outcome. More importantly, our data suggest that the relation of CVD with renal dysfunction is more complex and varies with the vascular bed affected, although a history of an event in one vascular bed is associated with a two- to threefold risk of event in another.

At variance with previous reports (15,27), albuminuria was weakly associated with coronary events. This might be only partly explained by a survivor or inclusion bias, due to the higher risk of CVD death and progression toward CKD associated with albuminuria than with reduced eGFR in subjects with type 2 diabetes (16). However, in the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) study, although the multivariable-adjusted hazard ratio (HR) for total CVD events was 2.48 for every 10-fold increase in baseline albuminuria and 2.20 for every halving of baseline eGFR, the HRs associated with microalbuminuria alone, macroalbuminuria alone, and reduced eGFR alone were 1.48, 1.18, and 1.33, respectively (14). On the other hand, the strong association of coronary events with reduced eGFR is in keeping with the finding that a moderate-to-severe reduction in eGFR is related to the number of narrowed coronary arteries in subjects undergoing coronary angiography for suspected coronary artery disease (CAD) (28).

Table 2—*Logistic regression analysis of all CVD events (N = 3,654) with CKD phenotypes as covariates*

Variable	OR	95% CI
Age (1 year)	1.030	1.025–1.035
Male sex	1.84	1.68–2.01
Smoking status		
Never	1.0	—
Former	1.55	1.42–1.70
Current	1.15	1.02–1.30
Diabetes duration (1 year)	1.017	1.012–1.021
Glucose-lowering treatment		
Diet	1.0	—
OHA	1.35	1.17–1.65
OHA + insulin	1.62	1.34–1.94
Insulin	2.46	2.09–2.90
Triglycerides (10 mg/dL)	0.995	0.989–1.000
HDL cholesterol (5 mg/dL)	0.925	0.909–0.941
Dyslipidemia	2.23	2.04–2.44
Hypertension	2.32	2.00–2.69
Retinopathy		
Absent	1.0	—
Nonadvanced	1.33	1.18–1.49
Advanced	1.39	1.22–1.58
CKD phenotype		
No CKD	1.0	—
Stages 1–2 CKD	1.20	1.08–1.33
Nonalbuminuric stage ≥3 CKD	1.52	1.34–1.73
Albuminuric stage ≥3 CKD	1.90	1.66–2.19

Variables excluded: HbA_{1c}, BMI. OHA, oral hypoglycemic agent.

A possible explanation of our finding is that patients with coronary events were treated more aggressively than subjects with cerebrovascular or peripheral events, with a higher use rate of drugs known to reduce albuminuria, such as ACEIs/ARBs (71.8% vs. 65.1%; $P < 0.0001$) and statins (71.2% vs. 48.1%; $P < 0.0001$). In this view, regression of micro- or macroalbuminuria to AER values within the normal range due to intensive treatment might have occurred in a percentage of subjects with a previous coronary event, although lack of association with albuminuria remained after accounting for ACEI/ARB use. Moreover, in a cross-sectional analysis, this powerful association between CAD and impaired eGFR might likely reflect the unique bidirectional nature of heart–kidney interactions in the context of the cardiorenal syndrome (29), with chronic cardiac dysfunction resulting from CAD causing progressive eGFR impairment or renal dysfunction favoring coronary atherosclerosis. The latter scenario is consistent with the role of renal dysfunction in promoting vascular calcification, the extent of which was inversely related to eGFR (30) and predicted CAD and death (31).

Finally, the stronger association of coronary events with reduced eGFR than with albuminuria may also reflect differences in renal pathology underlying the albuminuric and nonalbuminuric CKD phenotypes. In fact, microalbuminuria is considered a reliable biomarker of renal microvascular disease (32), although it may occur in the absence of significant kidney damage (33), whereas eGFR was inversely related with indexes of intrarenal as well as systemic atherosclerosis (34), although this association occurred independent of albuminuria (35). Thus, nonalbuminuric renal impairment, as a manifestation of prevailing renal macrovascular involvement, would be more frequently associated with coronary atherosclerosis than the albuminuric forms, which might conversely indicate the presence of microangiopathy. This interpretation is supported by the lack of association of coronary events with retinopathy.

At variance with reports from other large datasets of subjects with type 2 diabetes (14,15), our study also includes a separate analysis of cerebrovascular and peripheral events. Data showed that involvement of both vascular beds was associated more strongly with albuminuria than coronary events, with a weaker relation to nonalbuminuric CKD. This is consistent with reports that albuminuria, but not eGFR, is associated with maladaptive carotid artery remodeling (36) and that reduced eGFR is a risk factor for hemorrhagic but not ischemic stroke (37). This also in keeping with data from the NHANES III cohort showing a higher relation of peripheral artery disease with albuminuria than with reduced eGFR (38), although this was not the case in diabetic subjects (39). However, this might argue against the concept that the albuminuric phenotypes underlie predominantly microangiopathic lesions within the kidney and, therefore, should be less frequently associated with atherosclerosis. Indeed, events in noncoronary vascular beds, at variance with coronary events, were significantly related with retinopathy, even if no relation was

Table 3—*Logistic regression analysis of coronary (N = 2,405), cerebrovascular (N = 1,298), or peripheral (N = 894) events with CKD phenotypes as covariates*

Variable	Coronary events	Cerebrovascular events	Peripheral events
Age (1 year)	1.020 (1.014–1.026)	1.030 (1.022–1.038)	1.013 (1.004–1.021)
Male sex	2.129 (1.906–2.379)	1.16 (1.02–1.33)	1.23 (1.04–1.45)
Smoking status			
Never	1.0	—	1.0
Former	1.508 (1.355–1.678)	—	1.33 (1.13–1.57)
Current	1.065 (0.921–1.233)	—	1.38 (1.12–1.71)
Diabetes duration (1 year)	1.009 (1.004–1.014)	1.024 (1.017–1.030)	1.025 (1.017–1.033)
Glucose-lowering treatment			
Diet	1.0	1.0	1.0
OHA	1.268 (1.075–1.495)	1.20 (0.96–1.51)	1.38 (1.01–1.89)
OHA + insulin	1.743 (1.409–2.155)	0.86 (0.63–1.16)	1.52 (1.05–2.20)
Insulin	2.027 (1.674–2.455)	1.48 (1.15–1.91)	2.12 (1.52–2.86)
Triglycerides (10 mg/dL)	0.992 (0.986–0.998)	—	—
HDL cholesterol (5 mg/dL)	0.934 (0.916–0.954)	0.958 (0.936–0.982)	0.933 (0.905–0.961)
Dyslipidemia	2.730 (2.440–3.055)	1.52 (1.33–1.75)	—
Hypertension	3.050 (2.505–3.715)	1.42 (1.13–1.77)	—
Retinopathy			
Absent	—	1.0	1.0
Nonadvanced	—	1.37 (1.17–1.62)	1.71 (1.41–2.06)
Advanced	—	0.88 (0.72–1.08)	2.52 (2.07–3.07)
CKD phenotype			
No CKD	1.0	1.0	1.0
Stages 1–2 CKD	0.901 (0.794–1.022)	1.41 (1.20–1.65)	1.51 (1.25–1.82)
Nonalbuminuric stage ≥3 CKD	1.514 (1.304–1.757)	1.22 (1.01–1.48)	1.40 (1.11–1.76)
Albuminuric stage ≥3 CKD	1.270 (1.083–1.490)	1.69 (1.40–2.00)	1.88 (1.52–2.34)
Cerebrovascular events	2.472 (2.156–2.834)	2.51 (2.19–2.87)	2.77 (2.37–3.23)
Peripheral events	2.702 (2.306–3.167)	3.75 (3.17–4.44)	3.81 (3.21–4.51)

Results are presented as OR (95% CI). Variables excluded: HbA_{1c}, BMI. OHA, oral hypoglycemic agent.

found between cerebrovascular disease and advanced retinopathy.

The main limitation of this study is the cross-sectional design, which does not allow us to derive any cause–effect relationship, although data clearly indicate an association of reduced eGFR and/or albuminuria with CVD, with unique differences by vascular bed. Moreover, variability in laboratory measurements might have influenced the results. However, data did not change when analyzed separately by the method for measuring albuminuria (immunonephelometry vs. immunoturbidimetry) or serum creatinine (IDMS-traceable vs. non–IDMS-traceable).

In conclusion, this large-cohort study indicates that in subjects with type 2 diabetes, *1*) CVD is linearly associated with eGFR reduction and albuminuria; *2*) this association becomes significant for an eGFR <78 mL/min/1.73 m^2 and an albuminuria ≥10.5 mg/24 h; and *3*) the relation with reduced eGFR, independent of albuminuria, is stronger for coronary than for cerebrovascular or peripheral events, thus suggesting that nonalbuminuric renal impairment carries significant risk for CAD and vice versa. These observations also highlight the usefulness of CKD screening by GFR estimation, which was claimed to be effective in high-risk populations, such as subjects with type 2 diabetes, though not advisable in the general population (40). Even considering the above-reported limitations, our survey describes the relationship of CVD with renal dysfunction in the largest cohort of type 2 diabetic patients referring to outpatient diabetes clinics in Europe.

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