Dynamic Changes in Renal Function Are Associated With Major Cardiovascular Events in Patients With Type 2 Diabetes

Diabetes Care 2016;39:1259–1266 | DOI: 10.2337/dc15-2607

Stéphanie Ragot,[1–3] Pierre-Jean Saulnier,[1–3] Gilberto Velho,[4,5] Elise Gand,[6] Astrid de Hauteclocque,[1] Yousri Slaoui,[7] Louis Potier,[4,5] Philippe Sosner,[8,9] Jean-Michel Halimi,[10,11] Philippe Zaoui,[12,13] Vincent Rigalleau,[14,15] Frederic Fumeron,[4,5] Ronan Roussel,[4,5] Michel Marre,[4,5] and Samy Hadjadj,[1,2,3,16] on behalf of the SURDIAGENE and DIABHYCAR study groups

OBJECTIVE

The pattern of renal function decline prior to cardiovascular (CV) events in type 2 diabetes is not well known. Our aim was to describe the association between renal function trajectories and the occurrence of a CV event.

RESEARCH DESIGN AND METHODS

We considered patients with type 2 diabetes from the SURDIAGENE (Survie, Diabete de type 2 et Genetique) study (discovery cohort) and the DIABHYCAR (Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril) study (replication cohort). Global patterns of estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI]) and serum creatinine (SCr) prior to a major CV event (MACE) or last update were determined using a linear mixed-effects model and annual individual slopes computed by simple linear regression.

RESULTS

In the 1,040 participants of the discovery cohort, establishment of global patterns including 22,227 SCr over 6.3 years of follow-up showed an annual eGFR decline and an annual SCr increase that were significantly greater in patients with MACE compared with patients without (−3.0 and −1.7 mL/min/1.73 m^2/year and +10.7 and +4.0 μmol/L/year, respectively; $P < 0.0001$ for both). Median annual individual slopes were also significantly steeper in patients with MACE, and adjusted risk of MACE was 4.11 times higher (3.09–5.45) in patients with rapid decline in eGFR (change less than −5 mL/min/1.73 m^2/year). Consideration of renal function trajectories provided significant additive information helping to explain the occurrence of MACE for both SCr and eGFR ($P_{IDI} < 0.0001$ and $P = 0.0005$, respectively). These results were confirmed in the replication cohort.

CONCLUSIONS

Renal function decline was associated with a higher risk of MACE. The pattern of renal function decline, beyond baseline kidney function, is an independent factor of CV risk.

Diabetes is considered a global nontransmissible epidemic, of which the prevalence has been increasing worldwide. Interestingly, cardiovascular (CV) disease is the first cause of death in people with diabetes (1). In addition to traditional risk factors, such as lipids or smoking, kidney disease is an important contributor to CV disease (2).

[1]*INSERM CIC 1402, Poitiers, France*
[2]*UFR Médecine Pharmacie, Université de Poitiers, Poitiers, France*
[3]*Centre d'Investigation Clinique, CHU de Poitiers, Poitiers, France*
[4]*INSERM UMRS1138, Centre de Recherche des Cordeliers, Paris, France*
[5]*Département d'Endocrinologie, Diabétologie, et Nutrition, DHU FIRE, Hôpital Bichat, AP-HP, Paris, France*
[6]*Pôle DUNE, CHU de Poitiers, Poitiers, France*
[7]*Laboratoire de Mathématiques et Applications, Université de Poitiers, Poitiers, France*
[8]*Complexe Médico-Sportif Mon Stade, Paris, France*
[9]*Laboratoire MOVE (EA 6314), Université de Poitiers, Poitiers, France*
[10]*Service Néphrologie Immunologie Clinique, CHU de Tours, Tours, France*
[11]*Cellules Dendritiques, Immunomodulation, et Greffes (EA 4245), Université François Rabelais, Tours, France*
[12]*Service Néphrologie, Dialyse, et Transplantation, CHU de Grenoble, Grenoble, France*
[13]*Faculté de Médecine, Université Joseph Fournier, Grenoble, France*
[14]*Service Nutrition-Diabétologie, CHU Haut-Lévêque, Pessac, France*
[15]*Faculté de Médecine, Université Victor Segalen, Bordeaux, France*
[16]*INSERM U1082 IRTOMIT, Poitiers, France*

Corresponding author: Stéphanie Ragot, stephanie.ragot@univ-poitiers.fr.

Received 2 December 2015 and accepted 18 April 2016.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc15-2607/-/DC1.

Indeed, numerous studies have established that kidney disease was associated with CV hard end points (3), both in the general population and in secondary prevention of CV disease.

Due to its association with kidney and CV diseases on the one hand and to recommended monitoring of serum creatinine (SCr) on the other hand, diabetes is an excellent model for study of the temporal relationship between SCr trajectories and CV outcomes. One key question in this context is whether the dynamic process of renal function decline is a contributor to CV disease beyond baseline kidney function.

The relationship between estimated glomerular filtration rate (eGFR) slope and major CV outcomes is a recent finding, established in studies on large populations. It has consequently been suggested that eGFR slope can be of prognostic interest. However, some of these studies were retrospective (4), and no study has tried to determine whether this was true in patients with type 2 diabetes (5,6). That is why we aimed to study the association between renal function patterns and the occurrence of CV events in a cohort study of patients with type 2 diabetes, using a complementary replication cohort to validate our findings.

RESEARCH DESIGN AND METHODS

Discovery Cohort Patients

Data are from the SURDIAGENE (Survie, Diabete de type 2 et Genetique) study, a prospective monocentric cohort of 1,468 patients with type 2 diabetes recruited and followed at the University Hospital of Poitiers (France) between 2002 and 2012. A description of the cohort has been presented elsewhere (7). The study protocol received ethics approval (Comité de Protection des Personnes Ouest III), and written informed consent was given by each participant.

To be considered in the present analysis, patients had to fulfill the following criteria: free of renal replacement therapy at entry in the cohort, normal to moderately reduced kidney function (eGFR estimated by the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula; $\geq$30 mL/min/1.73 m^2), and at least three SCr determinations during follow-up.

Variables and Their Measurement in the Discovery Cohort

Baseline data used for the analysis included demographic information, diabetes duration, smoking status, systolic and diastolic blood pressure, HbA_{1c}, SCr, and comorbid conditions. The SCr determinations included in this study were all available determinations recorded in the Poitiers hospital biological database. We deleted values determined after an occurrence of end-stage renal disease requiring renal replacement therapy or after the first study outcome. A distinction was made between determinations performed during an overnight hospital stay (in-hospital determinations) and determinations performed during consultations (outpatient determinations). SCr was measured by nephelometry using a MODULAR System P (Roche Diagnostics GmbH, Mannheim, Germany).

The eGFR was calculated using the CKD-EPI equation (8). HbA_{1c} was determined using a high-performance liquid chromatography method performed with an ADAMS A1c HA-8160 analyzer (normal values 4.0–6.0%; Menarini, Florence, Italy).

The study outcome was the occurrence of a major CV event (MACE), a composite criterion combining CV mortality, nonfatal myocardial infarction, and nonfatal stroke, as is widely used (9). Living status and CV end points were determined from patients' hospital records and interviews of their general practitioners, every 2nd year since 2007. The present analysis takes into account data of the last updating performed at the end of 2013. All events were adjudicated by an independent adjudication committee (see composition in ACKNOWLEDGMENTS). Cardiovascular death was defined as death due to causes listed in the World Health Organization ICD-10, chapter IX (diseases of the circulatory system) (2007).

Replication Cohort Patients

DIABHYCAR (Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril) is a clinical trial conducted in people with type 2 diabetes selected on the basis of persistent microalbuminuria (urinary albumin concentration [UAC] in the range 20–200 mg/L) or macroalbuminuria (UAC $>$200 mg/L) without renal failure (plasma creatinine $<$150 μmol/L) at baseline (10). The trial tested the effect of a low dose of ramipril, an ACE inhibitor (ACEI), on the incidence of CV and/or renal events. The median duration of follow-up was 4.7 years. Results were negative regarding ramipril and were published previously (11). Participants gave written informed consent, and the ethics committee of Angers University Hospital approved the study protocols.

We included in our analysis French patients with type 2 diabetes with three or more SCr determinations during follow-up. SCr determinations were performed locally. HbA_{1c} was determined using a high-performance liquid chromatography method performed using a DIAMAT analyzer (normal values 4.0–5.6%; Bio-Rad, Richmond, CA)

Statistical Analysis

Analyses were conducted in SAS for windows, version 9.3 (SAS Institute, Cary, NC). Statistical significance was set at a P value $<$0.05.

Characteristics of patients are presented as frequency and percentage, means and SDs, or medians (25th–75th percentiles). Patients with MACE and without MACE were compared with the χ^2 test for categorical variables and the Student t test or the Mann-Whitney U test for continuous variables.

To describe renal function patterns, all determinations recorded during the window period (in-hospital plus outpatient determinations) were considered for the main analysis, and determinations exclusively recorded in the outpatient setting were taken into account in a second analysis.

Trajectories for creatinine and for eGFR were studied in patients with MACE during follow-up and in patients without MACE. Both global patterns and individual patterns for these renal markers were established. A population approach determined global patterns using the linear mixed-effects model, where random intercepts and random coefficients (slopes) were calculated and tested using the likelihood ratio test. Trajectories were calculated using the fixed-portion linear predictor plus the value corresponding to the predictor random effects. Differences in slopes between groups were evaluated in the linear mixed-effects model. The observation period started at the date of the

first event of the composite outcome for the patients having experienced an event and at the last screening or consultation date for patients without event (right-justified data). Patients were then traced backward to the date of entry in the cohort, so that creatinine and eGFR trajectories reflected the series of determinations recorded before the event.

Individual patterns (slope) were established calculating the absolute annual change in creatinine and eGFR for each patient using the simple linear regression coefficient. eGFR slope was recoded in a binary variable according to a threshold proposed in the literature (−5 mL/min/1.73 m^2/year) (12). The cutoff value for creatinine slope was estimated from simple linear regression between eGFR slope and creatinine slope, as there was no advocated threshold value in the literature for creatinine slope. Survival curves were built by the Kaplan-Meier method and compared using a log-rank test.

Univariate and multivariate stepwise Cox proportional hazard regression analyses were performed to identify factors associated with MACE. Regarding multivariate analysis, we used a backward manual procedure performed on a maximal model including all factors that were associated with MACE with $P < 0.20$ in univariate Cox analysis. Results are given as hazard ratios with 95% CIs.

The improvement in Cox model performance given by adding creatinine or eGFR slope was calculated using the integrated discrimination improvement (IDI) index. Results are given as *P* values of the IDI, which indicate significance of the improvement.

RESULTS

Characteristics of the Study Populations

Discovery Cohort

Of the 1,468 patients enrolled in the SURDIAGENE cohort, 1,140 patients were considered in the present analysis of the discovery cohort and yielded 22,227 creatinine determinations over a period of 6.3 (3.6–8.9) years (Fig. 1*A*). The composite outcome occurred in 218 patients (30.64 per 1,000 person-years [95% CI 26.57–34.71]), with 41 patients presenting a nonfatal stroke, 62 patients a nonfatal myocardial infarction, and 115 a CV death. A total of 154 CV deaths (21.13 per 1,000 person-years [95% CI 17.79–24.47]) and 282 all-cause deaths (38.69 per 1,000 person-years [95% CI 34.17–43.20]) were observed.

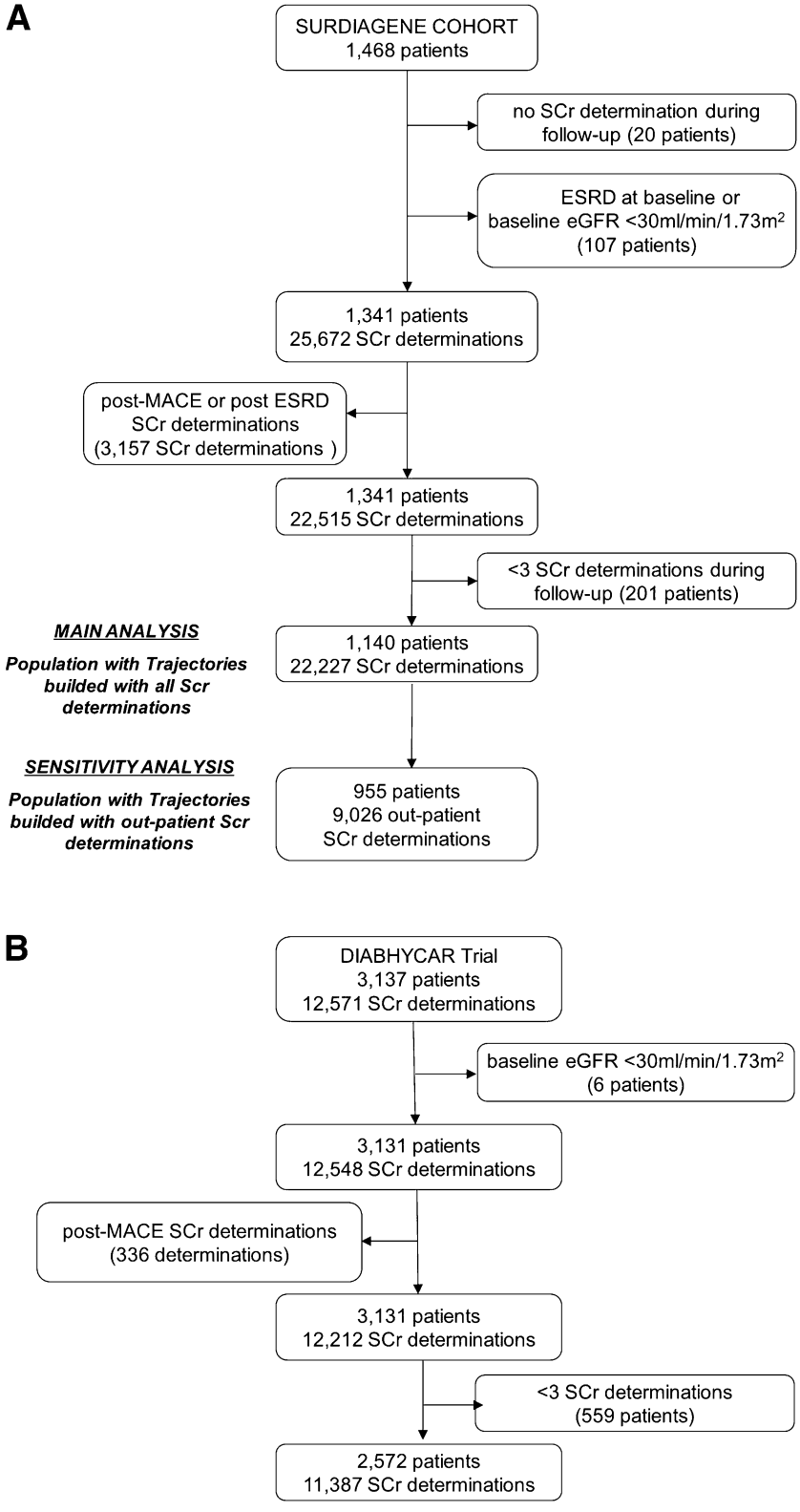

Figure 1—Analyzed populations from SURDIAGENE cohort (*A*) and DIABHYCAR trial (*B*). ESRD, end-stage renal disease.

Replication Cohort

Regarding the replication cohort, 2,572 patients of the 3,137 French patients included in the DIABHYCAR trial were considered for analysis, yielding 11,387

creatinine determinations (Fig. 1*B*). MACE events occurred in 180 patients (14.76 per 1,000 person-years [95% CI 12.60–16.92]), with 46 patients presenting a nonfatal stroke, 48 patients a nonfatal myocardial infarction, and 86 a CV death. A total of 97 CV deaths (7.87 per 1,000 person-years [95% CI 6.30–9.43]) and 235 all-cause deaths (19.06 per 1,000 person-years [95% CI 16.62–21.50]) occurred during follow-up.

Baseline characteristics according to the occurrence of MACE are described in Table 1 for both cohorts. Of note, the studied treatment allocated by randomization was not associated with MACE.

Global Patterns of Renal Markers

Discovery Cohort

Global patterns of SCr and eGFR established using linear mixed-effect models showed an SCr annual increase greater in patients with a MACE event compared with patients without (10.7 and 4.0 μmol/L/year, respectively; $P < 0.0001$). Similarly, eGFR annual decline was greater in patients with MACE than in those without (−3.0 in patients with MACE and −1.7 mL/min/1.73 m^2/year in those without; $P < 0.0001$).

When considering outpatient determinations only, in a sensitivity analysis made on 9,026 determinations, SCr annual increase and eGFR annual decline were also greater in patients with MACE compared with patients without (SCr annual increase: 7.4 vs. 3.1 μmol/L/year; eGFR annual decline: −2.5 vs. −1.5 mL/min/1.73 m^2/year, respectively, in patients with and without event; $P = 0.0003$ and 0.0002, respectively).

Replication Cohort

In the DIABHYCAR cohort, mixed-effect models showed, as in the discovery cohort, a greater SCr annual increase in patients with MACE event compared with patients free of event (5.1 and 1.8 μmol/L/year, respectively; $P < 0.0001$). Regarding eGFR trajectory, a greater eGFR annual decline was found in patients with MACE (−2.6 mL/min/1.73 m^2/year) than in patients without an event (−1.1 mL/min/1.73 m^2/year; $P < 0.0001$).

Individual Patterns of Renal Markers

Discovery Cohort

Dichotomization of annual change in SCr was made according to the result of simple linear regression between eGFR change and SCr change, translating an annual change of −5 mL/min/1.73

Table 1—Baseline characteristics according to the occurrence of MACE in discovery and replication cohorts

	Discovery cohort (SURDIAGENE)				Replication cohort (DIABHYCAR)			
	All *n* = 1,140	Event *n* = 218	No event *n* = 922	*P* value	All *n* = 2,572	Event *n* = 180	No event *n* = 2,392	*P* value
Sex: men/women, *n* (%)	657/483 (58%/42%)	145/73 (67%/33%)	512/410 (56%/44%)	0.003	1,888/684 (73%/27%)	140/40 (78%/22%)	1,748/644 (73%/27%)	0.17
Age (years)	65 ± 11	69 ± 10	64 ± 11	<0.0001	65 ± 8	68 ± 8	65 ± 8	<0.0001
Known diabetes duration (years)	14 ± 10	17 ± 10	13 ± 10	<0.0001	10 ± 8	11 ± 8	10 ± 8	0.04
BMI (kg/m^2)	31 ± 6	31 ± 6	32 ± 6	0.09	29 ± 5	29 ± 4	29 ± 5	0.22
Active smoking: *n* (%)	122 (11%)	21 (10%)	101 (11%)	0.56	369 (17%)	22 (14%)	347 (17%)	0.31
Systolic blood pressure (mmHg)	131 ± 17	135 ± 19	131 ± 17	0.004	145 ± 14	147 ± 12	147 ± 14	0.06
Diastolic blood pressure (mmHg)	72 ± 11	72 ± 11	72 ± 11	0.78	82 ± 8	83 ± 8	82 ± 8	0.36
History of CV disease*: *n* (%)	210 (18%)	71 (33%)	139 (15%)	<0.0001	208 (8%)	31 (17%)	177 (7%)	<0.0001
Myocardial infarction	163 (14%)	57 (26%)	106 (11%)	<0.0001	130 (5%)	18 (10%)	112 (5%)	0.002
Stroke	62 (5%)	21 (10%)	41 (4%)	0.002	88 (3%)	18 (10%)	70 (3%)	<0.0001
HbA_{1c} (%)	7.83 ± 1.54	8.06 ± 1.45	7.77 ± 1.56	0.02	7.83 ± 1.73	8.16 ± 1.88	7.81 ± 1.71	0.008
HbA_{1c} (mmol/mol)	62.05 ± 16.83	64.55 ± 15.89	61.46 ± 17.00	0.02	62.13 ± 18.86	65.72 ± 20.57	61.85 ± 18.70	0.008
UAC (mg/L)	22 (8–79)	51 (12–256)	19 (8–66)	<0.0001	72 (39–172)	90 (42–298)	71 (39–166)	0.003
SCr (μmol/L)	86.20 ± 26.04	96.08 ± 30.28	83.87 ± 24.37	<0.0001	88.73 ± 19.26	93.44 ± 19.87	88.38 ± 19.17	0.0007
eGFR (mL/min/1.73 m^2)	76.48 ± 20.67	68.17 ± 21.89	78.45 ± 19.88	<0.0001	74.98 ± 16.98	70.11 ± 15.93	75.35 ± 17.00	<0.0001
Drugs: *n* (%)								
Insulin	681 (60%)	161 (74%)	520 (57%)	<0.0001	0	0	0	
ACEIs or ARBs	710 (60%)	159 (73%)	551 (60%)	0.0003	151 (6%)	14 (8%)	137 (6%)	0.26
Diuretics	506 (44%)	123 (56%)	383 (42%)	<0.0001	554 (21%)	42 (23%)	512 (21%)	0.54
Calcium antagonists	342 (30%)	82 (38%)	260 (28%)	0.007	762 (30%)	73 (41%)	689 (29%)	0.0009
β-Blockers	387 (34%)	85 (39%)	302 (33%)	0.09	480 (19%)	40 (22%)	440 (18%)	0.21
Statins	523 (46%)	105 (48%)	418 (45%)	0.47	932 (36%)¶	64 (36%)¶	868 (36%)¶	0.84
Fibrates	131 (11%)	18 (8%)	113 (12%)	0.09				

Values for continuous variables are given as mean ± SD or median [25th–75th percentile]. Event was defined as MACE (CV death, nonfatal myocardial infarction, or nonfatal stroke). ARB, angiotensin receptor blocker. *History of myocardial infarction and/or history of stroke. ¶In DIABHYCAR study, the distinction between fibrates and statins was not available.

m^2/year for eGFR to 14.0 μmol/L/year for SCr.

Determination of individual patterns showed median individual SCr slopes significantly steeper in patients with a MACE compared with patients free of MACE (5.5 μmol/L/year [0.9–18.9] vs. 1.0 μmol/L/year [−1.0 to −4.7], respectively; $P < 0.0001$) (Supplementary Table 1) and median eGFR slopes significantly greater in patients with a MACE (−3.3 mL/min/1.73 m^2/year [−7.5 to −0.6] vs. −1.4 mL/min/1.73 m^2/year [−3.7 to 0.2] in patients without MACE; $P < 0.0001$). Distribution of these annual rates of change in SCr and eGFR are shown in Supplementary Fig. 1.

Patients with an annual increase of SCr >14.0 μmol/L/year were significantly more likely to develop MACE than patients with a lower change (*P* log-rank <0.0001) (Fig. 2*A*). In the same manner, an absolute annual change in eGFR less than −5 mL/min/1.73 m^2/year was associated with a higher risk of MACE (*P* log-rank <0.0001) (Fig. 2*B*). Of note, these associations between renal function pattern and risk of MACE were consistent in all quartiles of baseline creatinine ($P < 0.001$ for all) (Supplementary Fig. 2). Moreover, when stratifying on the personal history of CV disease, the association remained significant ($P < 0.001$ in both subgroups).

After adjustment on baseline renal function, CV disease history, and other prognostic factors, the risk of MACE was 3.15 times higher (2.25–4.41) in patients with an increase in SCr >14.0 μmol/L/year and 4.11 times higher (3.09–5.45) in patients with rapid renal function decline (change in eGFR less than −5 mL/min/1.73 m^2/year) (Table 2). Using renal pattern as a dependent variable in Cox models significantly improved the performance of the models ($P < 0.0001$ with SCr slope; $P = 0.0005$ with eGFR slope). These results were unchanged when only out determinations were taken into account to build individual renal patterns.

Replication Cohort

The analysis made on the DIABHYCAR cohort confirmed that patients with an SCr change >14.0 μmol/L/year or an eGFR change less than −5 mL/min/1.73 m^2/year were at higher risk of MACE even after adjustment on the other contributory factors (Table 2). Cox model performance was significantly improved by adding renal function decline as a dependent variable ($P < 0.0001$ with SCr slope; $P < 0.002$ with eGFR slope).

CONCLUSIONS

In our discovery cohort, we found that creatinine and eGFR trajectories were significantly associated with the occurrence of a MACE in type 2 diabetes; a more rapid renal function decline was associated with a higher risk of occurrence of a MACE. This finding was replicated using another cohort from the same geographical origin. It was also supported by different sensitivity analyses taking into consideration both the whole discovery cohort and outpatient SCr determinations.

Whereas most of the studies evaluating dynamic changes of renal function report eGFR trajectories, the analyses we performed assessed both the pattern of SCr and estimated GFR. We believe that SCr is a good clinical biomarker, as its validity is not influenced by the validity of the CKD-EPI formula. In addition, consideration of SCr instead of estimated GFR rules out the effect of age change during follow-up. Last, whereas the CKD-EPI formula proved to be well correlated with renal function, its value for repeated measures proved to be lesser, rendering SCr an interesting biomarker to evaluate follow-up changes (13–15). Consequently, not only eGFR trajectory but also SCr trajectory should be considered as a means of capturing the dynamics of renal function modifications with regard to CV diseases.

Our results proved to be consistent in the two studied cohorts: SURDIAGENE as a discovery cohort and DIABHYCAR as a replication cohort. In both studies, adjudication of outcomes rendered our findings more reliable. Even though both cohorts are composed of French patients with type 2 diabetes, they are actually rather dissimilar; whereas SURDIAGENE is a single-center hospital-based cohort, patients from DIABHYCAR were recruited on the occasion of a clinical trial managed by their general practitioners. The determinations of SCr during follow-up were correspondingly different; in the SURDIAGENE cohort, as in real-life situations, frequency of SCr determinations and their timing and follow-up time can largely vary, whereas in clinical trials such as DIABHYCAR, the determinations are preplanned and controlled. In addition, the SURDIAGENE and DIABHYCAR populations were different with regard to diabetes treatment and renal function; whereas SURDIAGENE

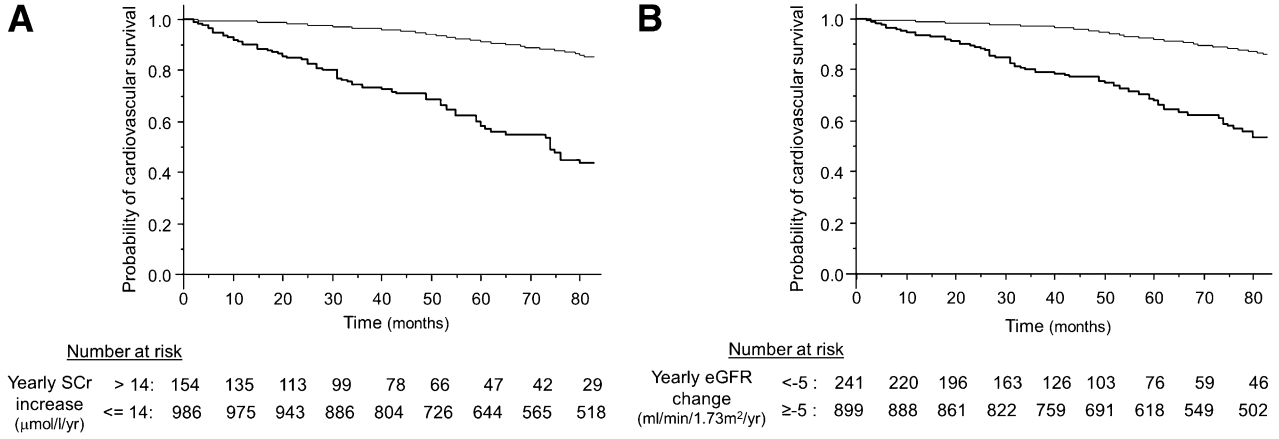

Figure 2—Kaplan–Meier plot of the probability of CV survival according to yearly SCr change (*A*) and yearly eGFR change (*B*). Thick lines represent patients with rapid renal function decline (>14 mmol/L/year for SCr increase and less than −5 mL/min/1.73 m^2/year for eGFR change) and thin lines represent the other patients.

Table 2—Risk of MACE by annual percentage change in eGFR or in SCr adjusted for baseline covariates

Variable	Hazard ratio	95% CI	*P* value	P_{IDI}
Renal function pattern: SCr slope				
SURDIAGENE cohort				
Model 1[a]				
History of CV disease	1.85	(1.39–2.44)	<0.0001	
Age at baseline (years)	1.05	(1.04–1.07)	<0.0001	
Female sex	0.73	(0.54–0.98)	0.04	
Diuretics at baseline	1.45	(1.10–1.92)	0.008	
Baseline HbA_{1c} (%)	1.10	(1.01–1.20)	0.04	
Baseline UAC[e] (mg/L)	1.24	(1.04–1.49)	0.02	
SCr slope >14 μmol/L	3.15	(2.25–4.41)	<0.0001	<0.0001
DIABHYCAR cohort				
Model 2[b]				
History of CV disease	2.23	(1.50–3.30)	<0.0001	
Age at baseline (years)	1.06	(1.04–1.08)	<0.0001	
Baseline HbA_{1c} (%)	1.14	(1.04–1.24)	0.003	
Baseline UAC[e] (mg/L)	1.42	(1.05–1.91)	0.02	
SCr slope >14 μmol/L	1.66	(1.00–2.76)	0.049	<0.0001
Renal function pattern: eGFR slope				
SURDIAGENE cohort				
Model 3[c]				
History of CV disease	2.20	(1.67–2.90)	<0.0001	
Known diabetes duration (years)	1.02	(1.00–1.03)	0.009	
Diuretics at baseline	1.47	(1.12–1.94)	0.006	
Baseline eGFR (mL/min/1.73 m^2)	0.98	(0.98–0.99)	<0.0001	
eGFR slope less than −5 mL/min/1.73 m^2	4.11	(3.09–5.45)	<0.0001	0.0005
DIABHYCAR cohort				
Model 4[d]				
History of CV disease	2.43	(1.64–3.59)	<0.0001	
Baseline HbA_{1c} (%)	1.11	(1.02–1.20)	0.02	
Baseline eGFR (mL/min/1.73 m^2)	0.98	(0.97–0.99)	<0.0001	
eGFR slope less than −5 mL/min/1.73 m^2	2.24	(1.59–3.15)	<0.0001	0.002

IDI evaluated the additive information of eGFR slope (or SCr slope) for risk of MACE. [a]Best fit model obtained from a maximal model containing the following: sex, age, known diabetes duration (years), BMI (kg/m^2), systolic blood pressure (mmHg), history of CV disease, insulin, ACEIs or angiotensin receptor blockers (ARBs), diuretics, calcium antagonists, β-blockers, fibrates, HbA_{1c} (%), log UAC (mg/L), SCr (μmol/L) measured at baseline, and SCr slope (>14 μmol/L vs. ≤14 μmol/L). [b]Best fit model obtained from a maximal model containing the following: sex, age, known diabetes duration (years), systolic blood pressure (mmHg), history of CV disease, calcium antagonists, HbA_{1c} (%), log UAC (mg/L), SCr (μmol/L) measured at baseline, and SCr slope (>14 μmol/L vs. ≤14 μmol/L). [c]Best fit model obtained from a maximal model containing the following: known diabetes duration (years), BMI (kg/m^2), systolic blood pressure (mmHg), history of CV disease, insulin, ACEIs or ARBs, diuretics, calcium antagonists, β-blockers, fibrates, HbA_{1c} (%), log UAC (mg/L), eGFR (mL/min/1.73 m^2) measured at baseline, and eGFR slope (less than −5 mL/min/1.73 m^2 vs. ≥5 mL/min/1.73 m^2). [d]Best fit model obtained from a maximal model containing the following: known diabetes duration (years), systolic blood pressure (mmHg), history of CV disease, calcium antagonists, HbA_{1c} (%), log UAC (mg/L), eGFR (mL/min/1.73 m^2) measured at baseline, and eGFR slope (less than −5 mL/min/1.73 m^2 vs. ≥5 mL/min/1.73 m^2). In models 3 and 4, age and sex were not included in the maximal model because they were already taken into account in the eGFR calculation. [e]Log-transformed data.

participants were recruited regardless of renal function and diabetes treatment, participants in the DIABHYCAR study were recruited with SCr <150 μmol/L and were treated with oral antidiabetic drugs only without insulin. The consistency of the results in both cohorts strongly supports the generalization of our results. Last, our sensitivity analysis proved that when focusing on SCr determinations from outpatients only, the data were unchanged.

Analysis of decline in renal function for diagnosis of clinical outcomes has previously been used. In type 1 diabetes, Skupien et al. (16) established the prognostic role of eGFR changes for the prognosis of end-stage renal disease, and it has been confirmed in the general population (6). In coronary artery disease patients, the eGFR pattern likewise proved to be prognostic for vascular events (17). This was also suggested in a Japanese population, in spite of the fact that the precise pattern of eGFR previous to CV outcome could not be ascertained, leaving some doubt as to whether eGFR decline was the cause or the consequence of CV events (18). Interestingly, the just-mentioned studies were not performed in specific populations with diabetes. The current study has established the value of decline of kidney function beyond baseline SCr value, in accordance with the Atherosclerosis Risk in Communities (ARIC) study focusing on patients with CKD stage 3 (19).

We used a minimal number of three SCr determinations at variance with the data from the CKD consortium involving two SCr determinations in 1–3 years (6). However, our findings proved to be very consistent with their results. The magnitude of the effect in our two cohorts was much greater than in a general Canadian population (6), a finding that may be related to the high CV risk of patients with type 2 diabetes.

It is possible to speculate about the relevance of the decline of renal function beyond baseline value. We can imagine that the clearance of a deleterious factor is affected by the dynamic

change in renal function rather than by its value per se. Whether this is related to renal clearance or to other metabolic clearance pathways influenced by renal function is not clearly understood. If some deleterious factors have a greater concentration in people with rapid renal function decline, then the search for such biomarkers should be a key point for future work in this field. Our results support a search for biomarkers in patients with the same renal function, comparing those with a sharp increase in SCr and those with a more stable profile. If specific targets were to emerge in patients recording significant changes, this could be of great interest and would help to open new therapeutic avenues.

Some epidemiological associations can be reminded to explain the CV impact of the decline of renal function beyond baseline value. Renal function has been shown to be associated with many different changes, such as lipids (20–22), blood pressure (23–26), insulin resistance (27,28), or low-grade inflammation (29–31). Unfortunately, it was not feasible to take such changes into account as long-term serial determinations of these variables were unavailable in most of the patients considered in our analysis.

Some limitations in our study must be noted. Renal function decline can be impacted by many drugs such as ACEIs (32). Our cohort was not designed to take drug modifications during follow-up into account. However our primary aim was to evaluate the association between renal function decline and occurrence of MACE rather than the determinants of renal function decline, such as drugs or comorbidities

In the SURDIAGENE cohort, all determinations were performed in the same laboratory but with no prespecified time frame. However, use of the mixed linear model helped to take this into account as this model does not require a specific time lapse between determinations. The dynamic process we were dealing with was not always linear, which might blur interpretation of the dynamic changes, particularly when considering eGFR or Scr individual slopes. Exclusion of nonlinear trajectories (n = 319 [i.e., 28%] and n = 255 [i.e., 22%] regarding trajectories of SCr and eGFR built with all-determinations in SURDIAGENE cohort) did not induce any modification of our conclusion (data not shown).

In the DIABHYCAR study, longitudinal SCr determinations were determined locally, possibly entailing some heterogeneity, but the results were satisfactorily robust. It is worth recalling that as we used SCr, our findings should be interpreted cautiously. It would be extremely interesting to consider another marker, such as cystatin C, which has proved to be of higher value compared with SCr, for the prognosis of severe outcomes (33).

Analysis with the IDI index showed that the trajectory of the renal function adds significant information to baseline creatinine. This result suggests that the dynamic process of renal function could be used as a prognostic marker of MACE, as it could easily be integrated in clinical practice.

In conclusion, the consideration of a simple and inexpensive biomarker, analyzed using a dynamic pattern, proved to be of prognostic value for CV outcomes in two complementary cohorts of patients with type 2 diabetes. Our data strongly support the systematic use of serial measurements of SCr and/or eGFR for fine tuning the prognosis of patients with type 2 diabetes. They should be carried out with adequate computing tools or web application (see eGFR calculator of renal function decline at http://www.sfdiabete.org/renalfunctiondeclinecalculator).

Acknowledgments. The authors warmly thank all patients included and followed in the cohort study for their kind participation in this research. Their general practitioners are acknowledged for their help in collecting clinical information. The authors acknowledge the following recruiting physicians: Frédérique Duengler, Louis Labbé, Aurélie Miot, Xavier Piguel, Florence Torremocha, Pierre-Jean Saulnier, and Richard Maréchaud (CHU de Poitiers). The following individuals provided secretarial and technical assistance: Vanessa Le Berre (CHU de Poitiers; Pôle DUNE; editorial assistance), all the staff from the Department of Endocrinology and Diabetology, CHU de Poitiers (recruitment), and Sonia Brishoual and the staff of the INSERM CIC 1402, CHU de Poitiers (biobanking and data management). Gérard Mauco (Department of Biochemistry, CHU de Poitiers) and Thierry Hauet (INSERM U1082, CHU de Poitiers) are acknowledged for helping in biological determinations. Marie Claire Pasquier and Alexandre Pavy (DSIO, CHU de Poitiers) actively contributed to the collection of data in the SURDIAGENE cohort. Jeffrey Arsham (CHU de Poitiers) edited the English of the manuscript. All patient records were reviewed to ascertain the following points: type 2 diabetes, diabetic kidney disease, diabetic retinopathy, and CV disease. The authors warmly thank the clinicians involved in this process: Daniel Herpin and Philippe Sosner (CHU de Poitiers; cardiology), Frank Bridoux (CHU de Poitiers; nephrology), and Helene Manic (CHU de Poitiers; ophthalmology). The following individuals assisted with the adjudication procedure: case inquiry, Sonia Brishoual, Céline Divoy, Cécile Demer, Aurélie Miot, Xavier Piguel, Florence Torremocha, Nathalie Fauvergue, Séverin Carasson, Pierre-Jean Saulnier, and Philippe Sosner (CHU de Poitiers); local coordination (CHU de Poitiers), Stéphanie Ragot (coordinator and biostatistician) and Fabrice Lebel (data manager); adjudication committee, Jean-Michel Halimi (chairman, Tours), Gregory Ducrocq (Paris Bichat), Charlotte Hulin (Poitiers), Pierre Llatty (Poitiers), David Montaigne (Lille), Vincent Rigalleau (Bordeaux), Ronan Roussel (Paris Bichat), Philippe Zaoui (Grenoble); and quality control (INSERM CIC 1402, CHU de Poitiers), Pierre-Jean Saulnier, Astrid de Hautecloque, Frederike Limousi, Nathalie Fauvergue, Sofia Hermann, and Sonia Brishoual.

Funding. The SURDIAGENE cohort was supported by grants from the French Ministry of Social Affairs and Health (Programme Hospitalier de Recherche Clinique [PHRC] 2004 [Poitiers] and PHRC IR 2008 [Grand Ouest]), Association Française des Diabétiques (AFD) (Research Grant 2003), and Groupement pour l'Étude des Maladies Métaboliques et Systémiques (Poitiers, France). The original DIABHYCAR trial was supported by grants from Sanofi (France), the French Ministry of Social Affairs and Health (PHRC 1996 [Angers]), the AFD (Research Grant 2004), and Association Diabète Risque Vasculaire (Paris, France).

Duality of Interest. P.-J.S. received travel grants from Servier, Novo Nordisk, and Roche Diagnostics. L.P. reports personal fees from Novo Nordisk, Sanofi, and Servier and grants from Sanofi outside the submitted work. V.R. has received research grants from Servier, Roche, and Merck Lipha Santé and has received travel grants from AstraZeneca, Bayer, GlaxoSmithKline, Janssen, Eli Lilly and Company, Merck, Novartis, Novo Nordisk, Pfizer, Schering-Plough, and Takeda. R.R. has served as a consultant and/or on advisory panels for AstraZeneca/Bristol-Myers Squibb, Novo Nordisk, Sanofi, Merck, Janssen, and AbbVie; has received honorarium or speaking fees from AstraZeneca/Bristol-Myers Squibb, AbbVie, Boehringer Ingelheim, Janssen, Merck, Novartis, Novo Nordisk, and Sanofi; has received research grants from Sanofi and Janssen; and has received travel grants from Janssen, AstraZeneca/Bristol-Myers Squibb, Sanofi, and Janssen. M.M. has served as a consultant and/or on advisory panels for Abbott, Merck, Novo Nordisk, Sanofi, and Servier; has received honorarium or speaking fees from Abbott, Eli Lilly and Company, Merck, Novo Nordisk, Sanofi, Servier, and Takeda; and has received research grants from Abbott, Merck, Novartis, Novo Nordisk, Sanofi, and Servier. S.H. has served as a consultant and/or on advisory panels for AstraZeneca/Bristol-Myers Squibb; has received honorarium or speaking fees from AstraZeneca/Bristol-Myers Squibb, Abbott, Boehringer Ingelheim, Eli Lilly and Company, Janssen, Merck, Novartis, Novo Nordisk, Sanofi, Servier, and Takeda; has received research grants from Abbott and Takeda; and has received travel grants from Janssen, AstraZeneca/Bristol-Myers Squibb, Merck, and Sanofi. No other potential

conflicts of interest relevant to this article were reported.

The analysis and interpretation of the data was performed without the participation of any of these organizations and companies.

Author Contributions. S.R. researched data, performed statistical analysis, contributed to the discussion, and wrote the manuscript. P.-J.S., G.V., E.G., A.d.H., and Y.S. researched data, performed statistical analysis, contributed to the discussion, and wrote the manuscript. L.P., P.S., J.-M.H., P.Z., V.R., F.F., and R.R. contributed to the discussion and edited the manuscript. M.M. designed the study, researched data, contributed to the discussion, and edited the manuscript. S.H. designed the study, researched data, contributed to the discussion, and wrote the manuscript. S.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Seshasai SR, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–841
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305
3. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285–1295
4. Perkins RM, Tang X, Bengier AC, Kirchner HL, Bucaloiu ID. Variability in estimated glomerular filtration rate is an independent risk factor for death among patients with stage 3 chronic kidney disease. Kidney Int 2012;82:1332–1338
5. Turin TC, Coresh J, Tonelli M, et al. Change in the estimated glomerular filtration rate over time and risk of all-cause mortality. Kidney Int 2013;83:684–691
6. Coresh J, Turin TC, Matsushita K, et al.; CKD Prognosis Consortium. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA 2014;311:2518–2531
7. Hadjadj S, Fumeron F, Roussel R, et al.; DIABHYCAR Study Group; DIAB2NEPHROGENE Study Group; SURDIAGENE Study Group. Prognostic value of the insertion/deletion polymorphism of the ACE gene in type 2 diabetic subjects: results from the Non-insulin-dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR), Diabete de type 2, Nephropathie et Genetique (DIAB2NEPHROGENE), and Survie, Diabete de type 2 et Genetique (SURDIAGENE) studies. Diabetes Care 2008;31:1847–1852
8. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150:604–612
9. The HOPE (Heart Outcomes Prevention Evaluation) Study: the design of a large, simple randomized trial of an angiotensin-converting enzyme inhibitor (ramipril) and vitamin E in patients at high risk of cardiovascular events. The HOPE study investigators. Can J Cardiol 1996;12: 127–137
10. Lièvre M, Marre M, Chatellier G, et al.; DIABHYCAR Study Group. The non-insulin-dependent diabetes, hypertension, microalbuminuria or proteinuria, cardiovascular events, and ramipril (DIABHYCAR) study: design, organization, and patient recruitment. Control Clin Trials 2000;21:383–396
11. Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Ménard J; DIABHYCAR Study Investigators. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). BMJ 2004; 328:495
12. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int 2014;85:49–61
13. Perkins BA, Nelson RG, Ostrander BE, et al. Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. J Am Soc Nephrol 2005;16:1404–1412
14. Rossing P, Rossing K, Gaede P, Pedersen O, Parving HH. Monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy. Diabetes Care 2006;29: 1024–1030
15. Gaspari F, Ruggenenti P, Porrini E, et al.; GFR Study Investigators. The GFR and GFR decline cannot be accurately estimated in type 2 diabetics. Kidney Int 2013;84:164–173
16. Skupien J, Warram JH, Smiles AM, et al. The early decline in renal function in patients with type 1 diabetes and proteinuria predicts the risk of end-stage renal disease. Kidney Int 2012;82: 589–597
17. Rein P, Saely CH, Muendlein A, Vonbank A, Drexel H. Serial decline of kidney function as a novel biomarker for the progression of atherothrombotic disease. Atherosclerosis 2010;211:348–352
18. Nagai K, Yamagata K, Ohkubo R, et al. Annual decline in estimated glomerular filtration rate is a risk factor for cardiovascular events independent of proteinuria. Nephrology (Carlton) 2014;19:574–580
19. Matsushita K, Selvin E, Bash LD, Franceschini N, Astor BC, Coresh J. Change in estimated GFR associates with coronary heart disease and mortality. J Am Soc Nephrol 2009;20:2617–2624
20. Gröne EF, Walli AK, Gröne HJ, Miller B, Seidel D. The role of lipids in nephrosclerosis and glomerulosclerosis. Atherosclerosis 1994; 107:1–13
21. Bonnet F, Cooper ME. Potential influence of lipids in diabetic nephropathy: insights from experimental data and clinical studies. Diabetes Metab 2000;26:254–264
22. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the Atherosclerosis Risk in Communities study. Kidney Int 2000;58:293–301
23. Barzilay J, Warram JH, Bak M, Laffel LM, Canessa M, Krolewski AS. Predisposition to hypertension: risk factor for nephropathy and hypertension in IDDM. Kidney Int 1992;41: 723–730
24. de Galan BE, Perkovic V, Ninomiya T, et al.; ADVANCE Collaborative Group. Lowering blood pressure reduces renal events in type 2 diabetes. J Am Soc Nephrol 2009;20:883–892
25. Jerums G, Allen TJ, Tsalamandris C, et al. Relationship of progressively increasing albuminuria to apoprotein(a) and blood pressure in type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetic patients. Diabetologia 1993; 36:1037–1044
26. Nelson RG, Pettitt DJ, de Courten MP, Hanson RL, Knowler WC, Bennett PH. Parental hypertension and proteinuria in Pima Indians with NIDDM. Diabetologia 1996;39:433–438
27. Thorn LM, Forsblom C, Fagerudd J, et al.; FinnDiane Study Group. Metabolic syndrome in type 1 diabetes: association with diabetic nephropathy and glycemic control (the FinnDiane study). Diabetes Care 2005;28:2019–2024
28. Yip J, Mattock MB, Morocutti A, Sethi M, Trevisan R, Viberti G. Insulin resistance in insulin-dependent diabetic patients with microalbuminuria. Lancet 1993;342:883–887
29. Clausen P, Jacobsen P, Rossing K, Jensen JS, Parving HH, Feldt-Rasmussen B. Plasma concentrations of VCAM-1 and ICAM-1 are elevated in patients with type 1 diabetes mellitus with microalbuminuria and overt nephropathy. Diabet Med 2000;17:644–649
30. Lim AK, Tesch GH. Inflammation in diabetic nephropathy. Mediators Inflamm 2012;2012: 146154
31. Navarro-González JF, Mora-Fernández C, Muros de Fuentes M, García-Pérez J. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nat Rev Nephrol 2011;7:327–340
32. Apperloo AJ, de Zeeuw D, de Jong PE. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney Int 1997;51:793–797
33. Shlipak MG, Matsushita K, Ärnlöv J, et al.; CKD Prognosis Consortium. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med 2013;369:932–943