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

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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.

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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).

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. 1A). 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
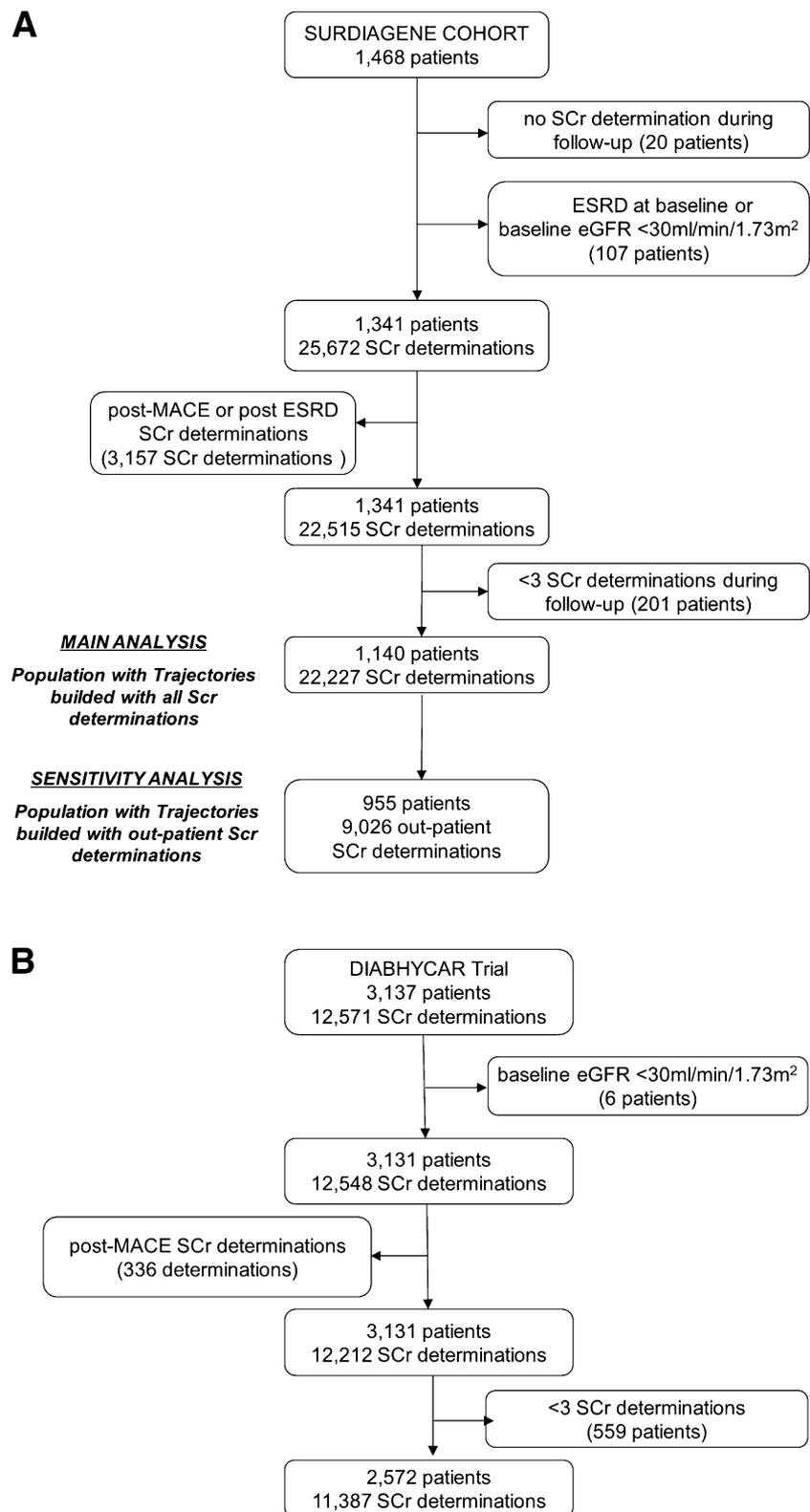

Figure 1—Analyzed populations from SURDIAGENE cohort (A) and DIABHYCAR trial (B). ESRD, end-stage renal disease.

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.

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. 1B). 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. 2A). 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. 2B). 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

A

Number at risk										
Yearly SCr increase (µmol/l/yr)	> 14:	154	135	113	99	78	66	47	42	29
	<= 14:	986	975	943	886	804	726	644	565	518

B

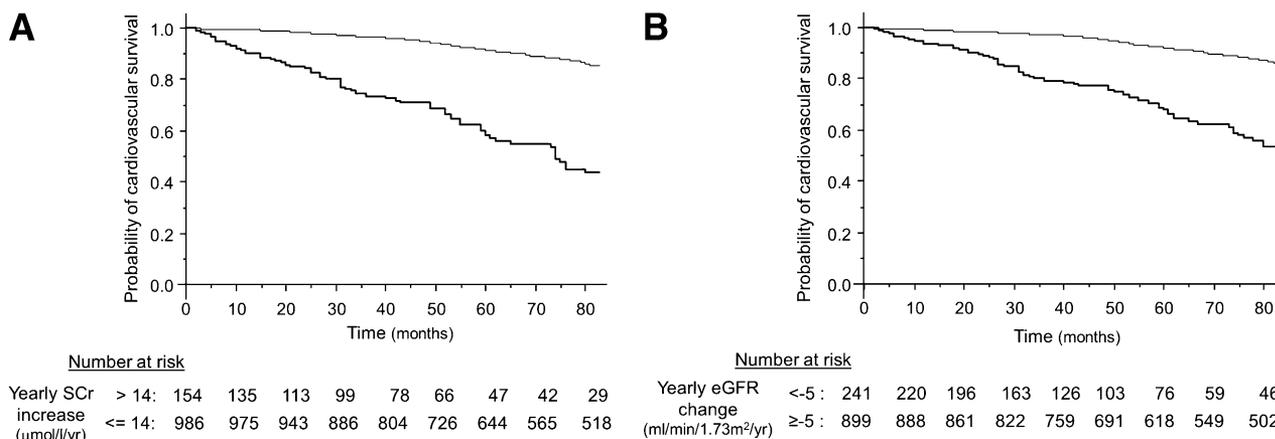| Number at risk										
Yearly eGFR change (ml/min/1.73m^2/yr)	<-5 :	241	220	196	163	126	103	76	59	46
	≥-5 :	899	888	861	822	759	691	618	549	502

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).

conflicts of interest relevant to this article were reported.

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