Acute Kidney Injury Predicts Major Adverse Outcomes in Diabetes: Synergic Impact With Low Glomerular Filtration Rate and Albuminuria

Mathilde Monseu,[1,2,3,4] Elise Gand,[4] Pierre-Jean Saulnier,[1,2,3] Stéphanie Ragot,[1,2,3] Xavier Piguel,[4] Philippe Zaoui,[5,6] Vincent Rigalleau,[7] Richard Marechaud,[4,8] Ronan Roussel,[9,10] Samy Hadjadj,[1,2,3,4,8,11] and Jean-Michel Halimi,[12,13] for the SURDIAGENE Study Group

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OBJECTIVE

Subjects with diabetes are prone to the development of cardiovascular and noncardiovascular complications. In separate studies, acute kidney injury (AKI), albuminuria, and low estimated glomerular filtration rate (eGFR) were shown to predict adverse outcomes, but, when considered together, their respective prognostic value is unknown.

RESEARCH DESIGN AND METHODS

Patients with type 2 diabetes consecutively recruited in the SURDIAGENE cohort were prospectively followed up for major diabetes-related events, as adjudicated by an independent committee: death (with cause), major cardiovascular events (myocardial infarction, stroke, congestive heart failure, amputation, and arterial revascularization), and renal failure (i.e., sustained doubling of serum creatinine level or end-stage renal disease).

RESULTS

Intrahospital AKI occurred in 411 of 1,371 patients during the median follow-up period of 69 months. In multivariate analyses, AKI was significantly associated with cardiovascular and noncardiovascular death, including cancer-related death. In multivariate analyses, AKI was a powerful predictor of major adverse cardiovascular events, heart failure requiring hospitalization, myocardial infarction, stroke, lower-limb amputation or revascularization, and carotid artery revascularization. AKI, eGFR, and albuminuria, even when simultaneously considered in multivariate models, predicted all-cause and cardiovascular deaths. All three renal biomarkers were also prognostic of most adverse outcomes and of the risk of renal failure.

CONCLUSIONS

AKI, low eGFR, and elevated albuminuria, separately or together, are compelling biomarkers of major adverse outcomes and death in diabetes.

Patients with diabetes are prone to the development of cardiovascular and renal complications (1). In addition, it was shown that infections and cancers develop in patients with diabetes more frequently than patients without diabetes (2,3). Abnormal albuminuria and low estimated glomerular filtration rate (eGFR) are risk

[1]*Université de Poitiers, CIC1402, Poitiers, France*
[2]*Centre d'Investigation Clinique, CHU de Poitiers, Poitiers, France*
[3]*INSERM, CIC1402, Poitiers, France*
[4]*Service d'Endocrinologie, CHU de Poitiers, Pôle DUNE, Poitiers, France*
[5]*Service Néphrologie, Dialyse et Transplantation, CHU de Grenoble, La Tronche, France*
[6]*Faculté de Médecine, Domaine de la Merci, Université Joseph Fourrier, Grenoble, France*
[7]*Service d'Endocrinologie, Diabétologie, Maladies Métaboliques et Nutrition, CHU de Bordeaux, Pessac, France*
[8]*Faculté de Médecine et Pharmacie, Université de Poitiers, Poitiers, France*
[9]*Université Paris 7 Denis Diderot, U695, Paris, France*
[10]*Service d'Endocrinologie, Diabétologie, Nutrition, Groupe Hospitalier Bichat Claude Bernard, Assistance Public-Hôpitaux de Paris, Paris, France*
[11]*INSERM, U1082, Poitiers, France*
[12]*Service de Néphrologie, CHU de Tours, Tours, France*
[13]*Université François-Rabelais, EA4245, Faculté de Médecine, Tours, France*

Corresponding author: Jean-Michel Halimi, halimi@med.univ-tours.fr.

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factors for renal and cardiovascular complications (4,5). More recently, the development of acute kidney injury (AKI) was shown to predict subsequent renal failure and cardiovascular events in selected populations (6–8).

However, to date, our understanding of the actual prognostic value of AKI in subjects with diabetes is limited. There is no comprehensive evaluation of the prognostic value of AKI with regard to major complications in nonselected patients with diabetes. Moreover, our vision may be blurred by the fact that AKI occurs more frequently in patients with low eGFR and/or albuminuria, both of which are situations associated with deleterious outcome (9).

In the current study, we prospectively assessed the long-term prognostic value of in-hospital AKI in addition to albuminuria and low eGFR in a large population of patients with type 2 diabetes. We specifically analyzed whether AKI, low eGFR, and albuminuria, when considered alone or together, were global prognostic factors for death, major vascular events, or major renal events, and therefore whether these markers could be used as renal "sensors" of global outcome.

RESEARCH DESIGN AND METHODS

Study Protocols and Patient Selection

The present analyses include the subjects recruited in the SURDIAGENE (SURvie, DIAbete de type 2 et GENEtique) study (10). This French monocentric inception cohort of patients with type 2 diabetes regularly attending the Diabetes Department at Poitiers University Hospital, France, between 2002 and 2011 included patients with stable conditions whose diet was stable. Patients considered for the present analysis had a confirmed diagnosis of type 2 diabetes, and had not undergone renal replacement therapy (renal transplantation or dialysis) at study inclusion. Biopsy-proven IgA nephropathy (or other primary glomerular diseases) was an exclusion criterion in the SURDIAGENE cohort.

The design of this study was approved by the University Hospital Ethic Committee. All participants gave their written informed consent.

Clinical and Biological Measurements

Blood samples and second morning urine samples were obtained from patients after an overnight fast. Serum creatinine level was measured using the Jaffé method. Albuminuria was measured by nephelometry. Urinary albumin-to-creatinine ratio (uACR) was calculated. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula (11).

Albuminuria categories were defined as follows: normoalbuminuria (uACR <3 mg/mmol), microalbuminuria (uACR ≥ 3 to ≤ 30 mg/mmol), and macroalbuminuria (uACR >30 mg/mmol).

The following clinico-biological data, including personal medical history, were collected at baseline: myocardial infarction, stroke, peripheral artery revascularization and limb/thigh amputation, diabetes duration, smoking status, blood pressure, height, weight, and medications used. Heart rate was computed using a baseline patient electrocardiogram.

Definition of AKI

AKI (during follow-up) was diagnosed and staged using the KDIGO criteria (12). Only serum creatinine criteria were used to diagnose and stage AKI, and, therefore, urinary output criteria were omitted. We considered the lowest creatinine value found between the dates of hospital admission and discharge as the reference creatinine value. We identified and classified AKI by comparing the highest creatinine value found during full hospitalization to the reference serum creatinine value. AKI was defined as a serum creatinine level of $>150\%$ or ≥ 0.3 mg/dL (≥ 26.5 μmol/L) versus the reference serum creatinine level. AKI was further classified by stage according to this ratio (stage I 150–199%, stage II 200–299%, stage III $\geq 300\%$). Stage III AKI was also defined by a serum creatinine increase of ≥ 4.0 mg/dL (≥ 353.6 μmol/L). For each patient, we considered only the first episode of AKI.

We performed sensitivity analyses with two other definitions of AKI using different reference serum creatinine values (i.e., either the first serum creatinine value during hospitalization or the lowest serum creatinine value during the year before hospitalization). We also evaluated whether censoring the death events that occurred within 1 month after AKI would modify the results.

Clinical Outcomes

We studied all-cause, cardiovascular, and noncardiovascular (including cancer-related and infection-related) deaths, major cardiovascular and cerebrovascular events, and renal failure (i.e., sustained doubling of serum creatinine level or end-stage renal disease [ESRD]).

Cardiovascular death was defined as death due to causes listed in the World Health Organization ICD-10 (chapter IX). The cause of death was defined according to the death certificate or hospital record.

The diagnosis of stroke was adjudicated in patients with focal neurological abnormalities associated with ischemic or hemorrhagic tissular lesions found on computed tomography scan and/or MRI.

Amputation was defined by a lower-limb amputation above the metatarsophalangeal joint.

We also recorded revascularization of the carotid artery (i.e., angioplasty, bypass grafting, or endarterectomy of carotid artery), revascularization of coronary arteries (angioplasty, coronary artery bypass grafting, or coronary stent), and revascularization of peripheral arteries (angioplasty or bypass of aortic or lower-limb arteries).

Major adverse cardiac events (MACEs) were defined as a composite end point (e.g., first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke).

Serum creatinine level doubling was defined as a sustained (over 1 month) doubling of serum creatinine level compared with the baseline value. ESRD was defined by the need for long-term renal replacement therapy (dialysis or renal transplantation).

Adjudication Procedure

Living status, cardiovascular end points, cerebrovascular end points, renal failure, and the cause of death were individually determined from patients' hospital records, French death certificate registries, biochemical data, and interviews with their general practitioners, every second year since 2007. An independent adjudication committee reviewed every prospectively collected event (10). Each end point was reviewed by two independent physicians, and, in case of disagreement (11.1% of events), the end point was discussed by the whole committee until agreement was found.

Statistical Analyses

Quantitative data were expressed as the mean ± SD or median (interquartile range [IQR]). Qualitative variables are given as number (percentage) of patients. Comparisons were conducted using a *t* test or Wilcoxon test for normally and nonnormally distributed continuous variables, respectively. Comparisons for categorical variables were performed with χ^2 or Fisher exact tests.

Kaplan-Meier curves were plotted to assess survival. We analyzed data by Cox proportional hazards models. AKI was used as a time-dependent variable. A stepwise descending procedure was used to determine every final multivariate model, as follows. All conventional variables were included in the models, as follows: eGFR, smoking, albuminuria, history of myocardial infarction, stroke, peripheral vascular disease, amputation in addition to AKI, eGFR, and/or albuminuria. All univariate significant variables were included in a maximized multivariate model, then we determined an optimized model with a backward procedure.

Integrated discrimination improvement (IDI) was calculated to quantify improvement in model performance after the addition of AKI in the models (established with a multivariate model).

All hypotheses were tested at the 5% level of significance. Statistical analyses were carried out using the SAS version 9.3 software package (SAS Inc, Cary, NC).

RESULTS

Baseline Characteristics of the Population

Among the 1,468 patients with type 2 diabetes enrolled in the SURDIAGENE cohort, 1,371 participants (58% men) were considered for the present analysis. We excluded 97 patients because 22 had reached ESRD at baseline, and 75 patients had no creatinine measurement during the follow-up.

Baseline characteristics of the study population are shown in Table 1. During the observation period (2002–2011), full hospitalization occurred at least once in 984 patients, and the total number of hospitalizations was 3,660. Overall, 12,456 serum creatinine determinations were available during the follow-up.

Overall, 43%, 35%, and 22% of patients had normoalbuminuria, microalbuminuria, and macroalbuminuria, respectively; eGFR was >60 mL/min/1.73 m^2 in 73% of patients, between 30 and 59 mL/min/1.73 m^2 in 22% of patients, and <30 mL/min/1.73 m^2 in 5% of patients.

Table 1—Baseline characteristics of the study population

Variables	All (*N* = 1,371)	AKI (*n* = 411; 30%)	No AKI (*n* = 960; 70%)	*P* value
Sex, *n* (%)				0.0003
Men	794 (58)	268 (65)	526 (55)	
Women	577 (42)	143 (35)	434 (45)	
Age (years)	65.2 ± 10.6	69.1 ± 9.6	63.5 ± 10.6	<0.0001
African ethnicity, *n* (%)	31 (2)	8 (2)	23 (2)	0.6081
Follow-up duration (months)	57.3 ± 35.1	62.4 ± 31.2	55.1 ± 36.4	0.0004
BMI (kg/m^2)	31.4 ± 6.3	31.4 ± 6.7	31.4 ± 6.1	0.9994
Active smoking, *n* (%)	144 (11)	43 (11)	101 (11)	0.9141
Diabetes duration (years)	14.5 ± 10.0	17.4 ± 10.5	13.2 ± 9.6	<0.0001
HbA_{1c} (%)	7.8 ± 1.5	7.9 ± 1.5	7.7 ± 1.5	0.0197
HbA_{1c} (mmol/mol)	61.7 ± 16.4	62.8 ± 16.4	60.7 ± 16.4	0.0197
Serum creatinine (μmol/L)	82 (32)	94 (46)	79 (27)	<0.0001
eGFR (mL/min/1.73 m^2)	73.6 ± 23.9	64.0 ± 24.6	77.7 ± 22.4	<0.0001
uACR (mg/mmol)	3.0 (12.0)	7.7 (33.9)	2.3 (6.8)	<0.0001
Medical history at baseline, *n* (%)				
Myocardial infarction	210 (15)	82 (20)	128 (13)	0.0018
Stroke	79 (6)	31 (8)	48 (5)	0.0632
Peripheral artery disease	309 (23)	128 (31)	181 (19)	<0.0001
Amputation	69 (5)	38 (9)	31 (3)	<0.0001
Diabetic retinopathy	549 (41)	203 (50)	346 (37)	<0.0001
Systolic blood pressure (mmHg)	132.3 ± 17.7	135.7 ± 18.7	130.9 ± 17.0	<0.0001
Diastolic blood pressure (mmHg)	72.3 ± 11.2	72.7 ± 11.7	72.2 ± 10.9	0.4585
Total cholesterol (mmol/L)	4.8 ± 1.1	4.8 ± 1.1	4.7 ± 1.1	0.2897
Resting heart rate (bpm)	73.3 ± 13.4	73.4 ± 13.7	73.2 ± 13.3	0.8839
Treatments, *n* (%)				
Antiplatelet drugs	581 (43)	202 (49)	379 (40)	0.0011
Vitamin K antagonists	175 (13)	84 (20)	91 (10)	<0.0001
Antihypertensive drugs	1,144 (83)	378 (92)	766 (80)	<0.0001
Diuretics	633 (46)	223 (54)	410 (43)	0.0001
ARBs/ACEIs	871 (64)	283 (69)	588 (61)	0.0073
Antidiabetic agents	1,316 (96)	399 (97)	917 (96)	0.1776
Metformin	653 (48)	149 (36)	504 (53)	<0.0001
Sulfonylureas	550 (40)	136 (33)	414 (43)	0.0004
Glitazones	16 (1)	1 (0)	15 (2)	0.0505
Glycosidase inhibitors	79 (6)	18 (4)	61 (6)	0.1460
Insulin	820 (60)	296 (72)	524 (55)	<0.0001
NSAIDs	40 (3)	14 (3)	26 (3)	0.4897
Lipid-lowering drugs	807 (59)	253 (62)	554 (58)	0.1846

Quantitative variables are described by mean ± SD or median (IQR), unless otherwise indicated. ACEIs, ACE inhibitors; ARBs, angiotensin 2 receptor blockers; NSAID, nonsteroidal anti-inflammatory drug.

Median follow-up was 69 months (IQR 36–90). At least one AKI episode developed in 411 patients (total number 838 AKI episodes; stage I 80%; stage II 14%; stage III 6%). The median number of hospitalizations before the development of AKI was 2 (range 1–16, IQR 1–4) in the AKI group, and 2 (range 1–17, IQR 1–3) in the non-AKI group.

Compared with subjects without AKI (hospitalized or not), those in whom AKI developed were older and more frequently male, and had a longer duration of diabetes, a lower eGFR, a higher uACR, and a more frequent cardiovascular history (Table 1).

AKI as a Predictor of All-Cause, Cardiovascular, and Noncardiovascular Death

During follow-up, 281 (29%) patients died. Annual mortality was 43 (IQR 38–48) per 1,000 patient-years. The causes of death were adjudicated as follows: cardiovascular events (*n* = 157), cancer (*n* = 45), infection (*n* = 22), and other causes (*n* = 57).

Survival rate was significantly lower in patients with AKI than in those without

AKI (log rank = 92.5, $P < 0.0001$), and survival rates were significantly lower in patients with AKI stage II or stage III than in those with AKI stage I (Supplementary Fig. 1*A*). Similar results were found for cardiovascular and noncardiovascular death (Supplementary Fig. 1*B* and Fig. 1*C*).

Albuminuria, eGFR, AKI, and the Risk of All-Cause, Cardiovascular, and Noncardiovascular Death

When we considered AKI and eGFR together, we observed that both AKI and low eGFR increased the risk of all-cause death (Fig. 1*A*); the same held true for AKI and albuminuria when considered together (Fig. 1*B*). Similar findings were observed for cardiovascular death (Fig. 1*C* and *D*).

Baseline eGFR, albuminuria, and AKI were all significantly associated with the risk of all-cause and cardiovascular death in the univariate analysis and in multivariate models (Table 2). In the univariate analysis, AKI was associated with an increased risk of noncardiovascular death, including cancer-related or infection-related deaths (Table 2). Albuminuria was significantly associated with cancer-related death, whereas low eGFR was significantly associated with infection-related death during follow-up (Table 2).

In multivariate models, AKI and albuminuria remained significantly associated with noncardiovascular deaths. Only AKI remained significantly associated with cancer-related death after multiple adjustments (Table 2). For infection-related death, adjustments on AKI, albuminuria, and eGFR could not be adequately tested due to a lack of power.

Adding the presence of AKI to established risk factors in the multivariate model improved the prediction of all-cause mortality, as shown by the significant improvement of IDI (-0.02, $P < 0.0001$). Similarly, prognosis significantly improved for cardiovascular and noncardiovascular deaths (IDI = 0.02 [$P < 0.0001$] and IDI = 0.02 [$P = 0.0004$], respectively).

Sensitivity Analyses

When using alternate definitions of AKI, results were grossly unchanged (see Supplementary Data, Sensitivity analyses).

Of note, the median time from AKI to the event was 10 months (range 0–71 months) for all-cause death, 13 months (range 0–71) for cardiovascular death, and 10 months (range 0–67 months) for noncardiovascular death. Overall,

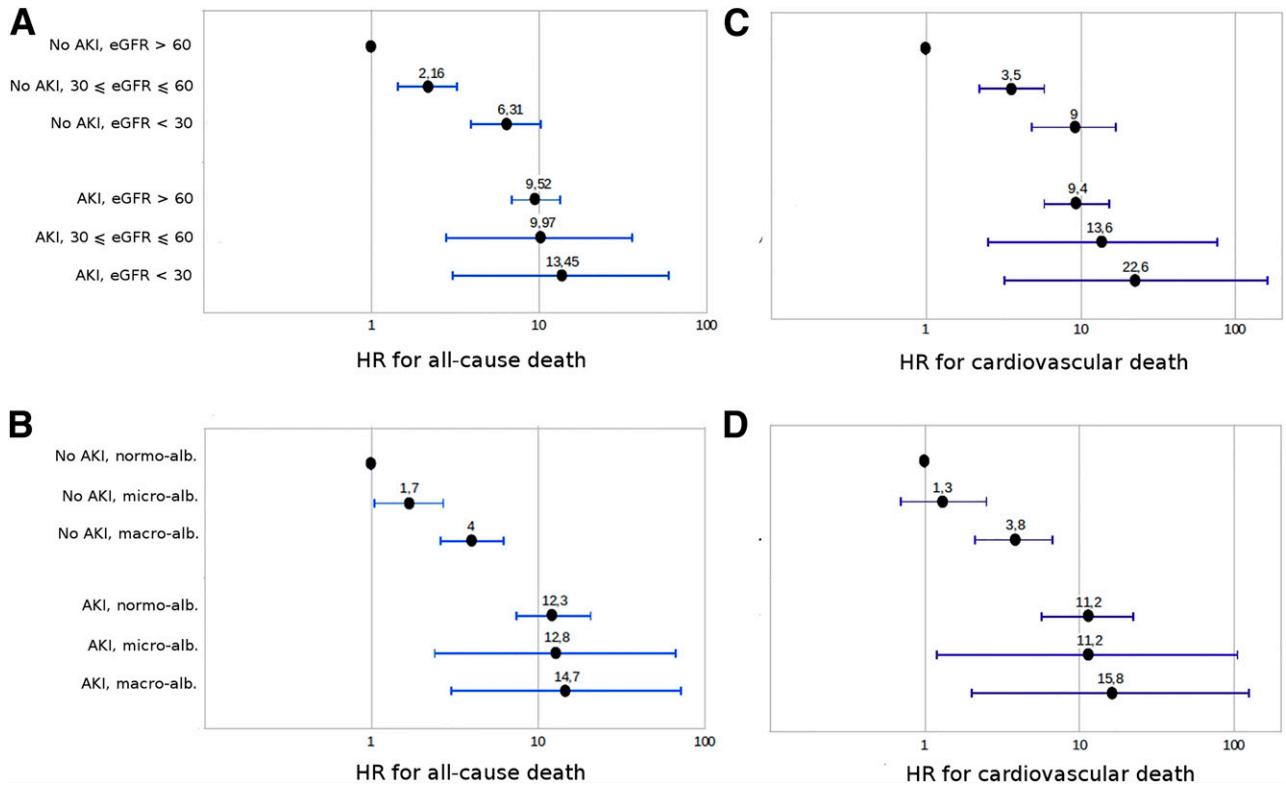

Figure 1—Combined risk of all-cause death and cardiovascular death associated with eGFR and development of AKI (*A* and *C*) and albuminuria and the development of AKI (*B* and *D*) considered together. Circle and lines indicate hazard ratio point estimates and 95% CIs. Labels on the lines represent hazard ratio estimates. AKI was diagnosed according to the KDIGO criteria as serum creatinine value increase >150% or ≥0.3 mg/dL (≥26.5 μmol/L) vs. baseline serum creatinine level. Albuminuria categories were defined as follows: normoalbuminuria, uACR <3 mg/mmol; microalbuminuria, uACR ≥3 and ≤ 30 mg/mmol; and macroalbuminuria, uACR >30 mg/mmol. Normoalbuminuria was present in 681 patients (50%), microalbuminuria was present in 467 patients (34%), and macroalbuminuria was present in 218 patients (16%). eGFR was >60 mL/min/1.73 m^2 for 998 patients (73%), between 30 and 60 mL/min/1.73 m^2 for 298 patients (22%), and <30 mL/min/1.73 m^2 for 75 patients (5%). The estimates were adjusted for baseline covariates, including smocking status and log uACR (*A*), smocking status and eGFR (*B*), and history of myocardial infarction and log uACR (*C*), and they were nonadjusted (*D*). All the parameters were significant as follows: for *A*: AKI ($P < 0.0001$), eGFR stages ($P < 0.0001$), and interaction between AKI and eGFR stages ($P < 0.0001$); for *B*: AKI ($P < 0.0001$), albuminuria categories ($P < 0.0001$), and interaction between AKI and albuminuria categories ($P = 0.0008$); for *C*: AKI ($P < 0.0001$), eGFR stages ($P < 0.0001$), and interaction between AKI and eGFR stages ($P = 0.0116$); and for *D*: AKI ($P < 0.0001$), albuminuria categories ($P < 0.0001$), and interaction between AKI and albuminuria categories ($P = 0.0354$). alb., albuminuria; HR, hazard ratio.

Table 2—AKI, eGFR, and albuminuria as predictors of death

	Univariate			Multivariate*		
	HR	95% CI	*P* value	HR	95% CI	*P* value
All-cause deaths						
AKI (yes vs. no)	7.38	5.76–9.46	<0.0001	5.53	4.24–7.21	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.80	0.77–0.84	<0.0001	0.92	0.87–0.97	0.0033
Albuminuria (log mg/mmol)	1.88	1.66–2.13	<0.0001	1.38	1.19–1.59	<0.0001
Cardiovascular deaths						
AKI (yes vs. no)	7.43	5.33–10.37	<0.0001	4.81	3.39–6.82	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.74	0.70–0.79	<0.0001	0.87	0.81–0.94	0.0002
Albuminuria (log mg/mmol)	2.13	1.80–2.52	<0.0001	1.46	1.20–1.77	0.0002
Noncardiovascular deaths						
AKI (yes vs. no)	7.31	5.03–10.63	<0.0001	6.43	4.35–9.51	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.89	0.83–0.96	0.0014			
Albuminuria (log mg/mmol)	1.60	1.32–1.94	<0.0001	1.28	1.05–1.57	0.0167
Cancer-related deaths						
AKI (yes vs. no)	5.85	3.13–10.93	<0.0001	5.80	3.08–10.90	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.96	0.85–1.09	0.5438			
Albuminuria (log mg/mmol)	1.43	1.03–1.99	0.0326			
Infection-related deaths						
AKI (yes vs. no)	9.98	4.06–24.53	<0.0001			
eGFR (per 10 mL/min/1.73 m^2)	0.79	0.67–0.94	0.0062			
Albuminuria (log mg/mmol)	1.46	0.91–2.35	0.1128			

During follow-up, 281 (29%) patients died: causes of death were cardiovascular (*n* = 157), cancer (*n* = 45), infection (*n* = 22), and other (*n* = 57). HR, hazard ratio. *A stepwise descending procedure was used to determine every final multivariate model: All-cause deaths, optimized model adjusted for AKI, eGFR, albuminuria, and smoking status; Cardiovascular deaths, optimized model adjusted for AKI, eGFR, albuminuria, and history of myocardial infarction; Noncardiovascular deaths, optimized model adjusted for AKI, albuminuria, and smoking status; Cancer-related deaths, optimized model adjusted for AKI and smoking status.

23 deaths (11 cardiovascular/12 noncardiovascular deaths) occurred within the first month after AKI: when these events were censored, the results were qualitatively unchanged (see Supplementary Data, Sensitivity analyses and Supplementary Table 1).

AKI, Albuminuria, eGFR, and Major Vascular Outcomes

During follow-up, vascular events were registered as follows: hospitalization for heart failure (*n* = 157, 16%), myocardial infarction (*n* = 81, 8%), stroke (*n* = 55, 6%), lower-limb amputation (*n* = 54, 6%), lower-limb revascularization (*n* = 60, 6%), coronary artery revascularization (*n* = 101, 10%), carotid artery revascularization (*n* = 25, 3%), and MACE (*n* = 238, 17%).

In univariate analysis, AKI, eGFR, and albuminuria were associated with MACE, hospitalization for heart failure, myocardial infarction, stroke, lower-limb amputation, lower-limb revascularization, and coronary artery revascularization during follow-up. Only AKI was significantly associated with carotid artery revascularization (Table 3).

Using multivariate analyses, AKI was associated with all of the major cardiovascular outcomes, whereas eGFR and albuminuria were inconstantly associated with these outcomes (Table 3).

AKI, Low eGFR, and Albuminuria as Predictors of Renal Risk

Renal failure (i.e., sustained doubling of serum creatinine level or ESRD) occurred in 79 patients (8%) during follow-up. Time to renal failure was significantly associated with AKI (log rank 19.2, $P < 0.0001$).

As expected, AKI, eGFR, and albuminuria were associated with renal failure in univariate and multivariate analyses when these three renal parameters were entered into the models (Table 3).

CONCLUSIONS

In the present prospective inception cohort, we adjudicated causes of death (cardiovascular, cancer, infection, or other causes) and major cardiovascular and renal events in subjects with type 2 diabetes. We carefully analyzed the prognostic value of AKI, low eGFR, and abnormal albuminuria alone or in combination on relevant diabetes-related events. The two major findings of the study were as follows: *1*) AKI was a powerful predictor of all-cause death, noncardiovascular and cardiovascular deaths, and all major cerebrovascular, cardiovascular, and renal events and *2*) AKI, low eGFR, and albuminuria remained predictors of all-cause and cardiovascular deaths, even when considered simultaneously.

In the current study, we observed for the first time that AKI predicted the risk of all-cause death and cardiovascular death in a cohort specifically dedicated to patients with type 2 diabetes. Similar data were observed in other populations, notably after myocardial infarction or coronary revascularization (13). To the best of our knowledge, our study is also the first to demonstrate a strong and robust relationship between AKI and noncardiovascular death. Surprisingly, we found that AKI was associated with cancer-related and infection-related death.

Furthermore, AKI predicted the risk of chronic nonfatal myocardial infarction, hospitalization for heart failure, lower-limb amputation and revascularization, carotid and coronary revascularization, nonfatal stroke, and renal failure. The risk of subsequent coronary events or stroke was increased in patients with AKI in most studies (8,14,15). A greater risk of hospitalization for heart failure after myocardial infarction or percutaneous coronary revascularization procedure was also noted (7,8). However, we were able to identify other major consequences of AKI such as lower-limb amputation and revascularization or carotid revascularization.

The results of our study extend the relationship between AKI and adverse outcomes even further to patients with diabetes and to all relevant major cardiovascular and noncardiovascular events that we have analyzed. These findings are important because the incidence of cardiovascular and cerebrovascular events remains greater in patients with diabetes compared with patients without diabetes, although the number of major complications declined from 1990 to 2010 (1). Moreover, patients with diabetes also have a greater risk of cancer and infection than subjects without diabetes (2,3).

The need for reliable and simple risk sensors is thus of outmost importance in diabetes. Importantly, AKI remained a significant marker of outcome regardless of

Table 3—AKI, eGFR, and albuminuria as predictors of major events

	Univariate			Multivariate*		
	HR	95% CI	*P* value	HR	95% CI	*P* value
MACE						
AKI (yes vs. no)	4.35	3.30–5.73	<0.0001	2.97	2.23–3.95	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.79	0.75–0.83	<0.0001	0.89	0.84–0.94	<0.0001
Albuminuria (log mg/mmol)	1.81	1.58–2.08	<0.0001	1.33	1.13–1.56	0.0005
Heart failure requiring hospitalization						
AKI (yes vs. no)	7.07	5.07–9.87	<0.0001	4.69	3.30–6.66	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.77	0.72–0.81	<0.0001	0.91	0.84–0.98	0.0086
Albuminuria (log mg/mmol)	2.06	1.74–2.44	<0.0001	1.49	1.22–1.82	0.0001
Myocardial infarction						
AKI (yes vs. no)	2.90	1.74–4.82	<0.0001	1.98	1.17–3.36	0.0116
eGFR (per 10 mL/min/1.73 m^2)	0.80	0.74–0.88	<0.0001	0.85	0.78–0.93	0.0002
Albuminuria (log mg/mmol)	1.70	1.34–2.15	<0.0001			
Stroke						
AKI (yes vs. no)	2.49	1.34–4.61	0.0039	2.35	1.26–4.38	0.0070
eGFR (per 10 mL/min/1.73 m^2)	0.87	0.78–0.97	0.0119			
Albuminuria (log mg/mmol)	1.40	1.03–1.88	0.0294			
Lower-limb amputation						
AKI (yes vs. no)	15.60	8.5–28.8	<0.0001	10.5	5.7–19.6	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.77	0.69–0.85	<0.0001			
Albuminuria (log mg/mmol)	2.45	1.84–3.25	<0.0001	1.65	1.21–2.25	0.0016
Peripheral artery revascularization						
AKI (yes vs. no)	4.93	2.80–8.67	<0.0001	3.56	1.98–6.43	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.86	0.78–0.96	0.0059			
Albuminuria (log mg/mmol)	1.81	1.37–2.38	<0.0001	1.49	1.11–2.00	0.0078
Carotid artery revascularization						
AKI (yes vs. no)	7.23	3.06–17.09	<0.0001	6.10	2.56–14.52	<0.0001
eGFR (per 10 mL/min/1.73 m^2)	0.90	0.76–1.05	0.1675			
Albuminuria (log mg/mmol)	1.37	0.88–2.13	0.1674			
Coronary artery revascularization						
AKI (yes vs. no)	2.30	1.40–3.80	0.0011	2.04	1.23–3.39	0.0055
eGFR (per 10 mL/min/1.73 m^2)	0.88	0.82–0.96	0.0022			
Albuminuria (log mg/mmol)	1.31	1.05–1.64	0.0166			
Doubling serum creatinine level/ESRD						
AKI (yes vs. no)	6.97	4.38–11.1	<0.0001	2.47	1.50–4.05	0.0004
eGFR (per 10 mL/min/1.73 m^2)	0.57	0.51–0.63	<0.0001	0.78	0.70–0.87	<0.0001
Albuminuria (log mg/mmol)	6.22	4.70–8.22	<0.0001	4.23	3.07–5.83	<0.0001

During follow-up, the following major events were noted: hospitalization for heart failure (n = 157), myocardial infarction (n = 81), stroke (n = 55), lower-limb amputation (n = 54), lower-limb revascularization (n = 60), coronary artery revascularization (n = 101), carotid artery revascularization (n = 25), and renal failure (i.e., sustained doubling of serum creatinine or ESRD) (n = 79). HR, hazard ratio. *A stepwise descending procedure was used to determine every final multivariate model: MACE, optimized model adjusted for AKI, eGFR, albuminuria, history of myocardial infarction, and amputation; Heart failure requiring hospitalization, optimized model adjusted for AKI, eGFR, albuminuria, history of myocardial infarction, and Peripheral artery arteriopathy; Myocardial infarction, optimized model adjusted for AKI, eGFR, and history of lower-limb arteriopathy; Stroke, optimized model adjusted for AKI and history of stroke; Lower-limb amputation, optimized model adjusted for AKI, albuminuria, and history of amputation; Peripheral artery revascularization, optimized model adjusted for AKI, albuminuria, and history of lower-limb arteriopathy; Carotid artery revascularization, optimized model adjusted for AKI and history of lower-limb arteriopathy; Coronary artery revascularization, optimized model adjusted for AKI and history of lower-limb arteriopathy; Doubling serum creatinine level/ESRD, optimized model adjusted for AKI, eGFR, and albuminuria.

its definition and severity. We used a well-accepted definition of AKI (12), and we performed sensitivity analyses using different definitions of AKI: our results remained qualitatively unchanged. We also assessed whether AKI severity modified our results: we observed a dose-effect relationship between the severity of AKI and the risk of all-cause and cardiovascular deaths, but not for the risk of renal failure, even though the smaller number of the latter outcomes might lead to inadequate statistical power.

The exact mechanisms explaining the association between AKI and subsequent major deleterious outcomes are unknown. AKI may be associated with systemic inflammation. Immediately after experimental AKI, alarmins, tumor necrosis factor-α, interleukin-1, and interleukin-6 are produced and lead to activation and proliferation of immune cells, deterioration of renal function through the development of interstitial fibrosis, tubular atrophy, and glomerular sclerosis. Production of these substances may also have systemic consequences, including reduced left ventricular fractional and myocardial cell apoptosis (9,16,17). Systemic production of proinflammatory cytokines associated with AKI may be responsible, at least in part, for the increased risk of renal, cardiovascular, and noncardiovascular events (16).

Alternatively, the occurrence of AKI may be a marker of renal and overall frailty in these patients with diabetes, since AKI was associated with age, duration of diabetes, blood pressure, and vascular diseases in our study and in the literature (18). This is supported by the association between AKI and noncardiovascular death such as cancer death or infection death.

The other major finding of our study, which may be one of the most salient ones, is the fact that AKI, eGFR, and albuminuria, even when simultaneously considered, remained significantly associated with all-cause and cardiovascular death and heart failure. It has been known for several years that eGFR and albuminuria considered together are powerful predictors of all-cause and cardiovascular deaths (19). In a recent study (20), albuminuria in addition to B-type natriuretic peptide emerged as a key biomarker predicting the risk of heart failure. In patients from the Atherosclerosis Risk in Communities (ARIC) study, cystatin C levels and elevated albuminuria were associated with a further risk of cardiovascular events, including heart failure (21). Interestingly, albuminuria was frequently observed and was a predictor of death in patients with heart failure in the GISSI-Heart Failure study (22). Our results indicate that all three renal markers have prognostic value in diabetes: AKI can be used alone

or in addition to eGFR and albuminuria to predict cardiovascular events, including heart failure. Taken together, these results suggest that the information regarding the risk of death or cardiovascular death conveyed by these renal markers is not redundant.

Interestingly, AKI was a predictor of renal failure and, when simultaneously considered, AKI, low eGFR, and albuminuria remained significant predictors and refined the estimation of the risk of renal failure in subjects with diabetes. Although low GFR and microalbuminuria/macroalbuminuria remained powerful predictors of all-cause death and cardiovascular death, even after adjustment for AKI, AKI seemed the most powerful biomarker of major events.

Admittedly, our study has several limits. We did not focus our analysis on the exact cause of AKI. However, most of our cases of AKI were stage I, which could result from many situations, including sepsis, dehydration, or use of nephrotoxic medications. It was not possible to assess whether the cause of AKI could play a role in our findings. Although our end points considered cardiovascular and renal outcomes, which are major in diabetes, other relevant diabetic microvascular end points, such as retinopathy or neuropathy, were not studied. In addition, only AKI in inpatients were considered. AKI in outpatients may have different predictive value on outcomes. However, to our knowledge, this type of analysis has not been performed in the literature.

Finally, the results of our monocentric study need to be replicated.

Our study has also some strengths. It is a relatively large prospective study with a long-term follow-up. Of note, 85% of studies reporting the long-term consequences of AKI were retrospective in a recent meta-analysis (13). In the present report, an independent committee adjudicated all events of interest, and records were individually handled and reviewed using hospital discharge summaries, interviews with general practitioners, and biochemical data. This point is probably crucial, although rarely performed in the literature: most studies only use administrative records to determine clinical outcomes, although this method was recently questioned (23,24).

To our knowledge, the current study is also the first to examine the risk for death, cardiovascular events, and noncardiovascular events in a comprehensive way in relation to AKI, albuminuria, and eGFR, considered separately or together, and the first one evaluating the long-term risk of AKI in consecutively recruited patients with diabetes.

In conclusion, AKI is a powerful predictor of major cerebrovascular, cardiovascular, and noncardiovascular events and deaths in individuals with type 2 diabetes. All three renal markers (AKI, eGFR, and albuminuria) alone or considered together are synergistically predictors of total and cardiovascular deaths, and renal outcomes.

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