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## ORIGINAL ARTICLE

# Specific impact of past and new major cardiovascular events on acute kidney injury and end-stage renal disease risks in diabetes: a dynamic view

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## ABSTRACT

**Background.** Interconnections between major cardiovascular events (MCVEs) and renal events are recognized in diabetes, however, the specific impact of atrial fibrillation (AF), heart failure (HF) and acute coronary syndrome (ACS) on the risk of end-stage renal disease (ESRD) on top of established renal risk factors is unclear in type 2 diabetes mellitus.

**Methods.** We conducted a retrospective study in 861 consecutive patients followed in a nephrology setting during the 2000–13 period.

**Results.** The mean age was  $70 \pm 10$  years, 65.1% were men and the estimated glomerular filtration rate (eGFR) was  $42.4 \pm 21.0$  mL/min/1.73 m<sup>2</sup>. During follow-up (median 59 months), 194 patients reached ESRD. A history of AF, HF or ACS was associated with an increased risk of reduced baseline eGFR. In turn, reduced baseline eGFR resulted in a greater risk of new MCVE (especially HF) during follow-up. Finally, all new MCVEs were risk factors for subsequent acute kidney injury (AKI) {HF: hazard ratio [HR] 8.99 [95% confidence interval (CI) 7.06–11.4]; AF: HR 5.42 (3.91–7.52); ACS: HR 8.82 (6.24–12.5); all  $P < 0.0001$ } and ESRD [HF: HR 5.52 (95% CI 4.01–7.60),  $P < 0.0001$ ; AF: HR 3.48 (2.30–5.21),  $P < 0.0001$ ; ACS: HR 2.31 (1.43–3.73),  $P = 0.0006$ ]. The AF- and HF-associated risks of ESRD were significant after adjustments on all renal risks of ESRD (gender, blood pressure, eGFR, albuminuria, renin-angiotensin blockers, retinopathy and AKI), but the association was less strong for ACS. Importantly, no association was noted between other major events such as stroke or infections and the risk of ESRD.

**Conclusions.** Past and new cardiovascular events (more HF and AF than ACS) have a strong, independent impact on the development of ESRD above and beyond established risk factors in diabetes.

**Keywords:** cardiovascular events, diabetes mellitus, end-stage renal disease, epidemiology, heart failure

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## INTRODUCTION

Diabetes is associated with a greater risk of major cardiovascular events [MCVEs, i.e. heart failure (HF), coronary artery disease (CAD) and atrial fibrillation (AF)], non-cardiovascular events (such as strokes or infections) and end-stage renal disease (ESRD) [1–3]. It has been shown that cardiovascular events are more frequent in patients with abnormal renal function and, conversely, that renal function deterioration may be precipitated by MCVEs [1–3].

Established risk factors for ESRD include baseline reduced glomerular filtration rate (GFR), high albuminuria, elevated systolic blood pressure (SBP), diabetic retinopathy, acute kidney injury (AKI), hyperlipidaemia, obesity, anaemia, bone metabolism disorders, acidosis, oxidative stress and inflammation [3–7]. Interestingly, major cardiac events may result in the development of AKI [8, 9] and may also lead to an increased risk of ESRD [9]. However, the interrelationships between cardiovascular events and the risk of ESRD or AKI are not well understood. It is presently unknown whether MCVEs such as AF, HF and acute coronary syndrome (ACS) convey the same renal risk. It is also unknown whether some cardiovascular events are more prone than others to lead to deleterious renal outcomes. It is unclear whether the effects of MCVEs on the risk of ESRD are specific or whether major non-cardiovascular events such as strokes or infections result to the same renal risk [6, 10–12].

The aim of the present retrospective study was to assess the impact of past and new cardiovascular events and the risk of ESRD and AKI in a large cohort of patients with type 2 diabetes followed in a nephrology setting. We also assessed the respective impact of AF, HF and ACS on the risk of AKI and ESRD. Finally, we tried to evaluate whether strokes and infections also constituted risks of ESRD.

## MATERIALS AND METHODS

### Study population

We consecutively included 861 patients with type 2 diabetes who were referred as outpatients to nephrologists in a four-hospital institution during the 2000–13 period (CHU Tours, Tours, France). The study was approved by the Ethics Committee of Human Research of our hospital (approval number 2016-21).

Type 2 diabetes was defined according to the American Diabetes Association criteria [13]. Data were individually retrieved from files at baseline and during follow-up. These included age, sex, ethnicity, comorbid conditions (hypertension, CAD, stroke, HF, peripheral arterial disease, AF, renal artery stenosis and diabetic retinopathy), smoking status and diabetes duration. At baseline, SBP, diastolic blood pressure and body mass index were measured. Information regarding the use of antihypertensive drugs [angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers, diuretics,  $\beta$ -blockers, spironolactone], glucose-lowering agents, statins, other lipid-lowering agents (and the presence of hypercholesterolaemia) and antiplatelet medications was also collected.

Baseline laboratory results (including serum creatinine and glycated haemoglobin) were obtained. Baseline albuminuria was defined based on urine dipstick or 24-h urine albumin; proteinuria was converted in albuminuria as described previously [14]. Albuminuria classes were defined as normoalbuminuria (albuminuria <30 mg/day, <30 mg/g or <20 mg/L), microalbuminuria

(albuminuria  $\geq 30$ –<300 mg/day, or  $\geq 30$ –<300 mg/g or  $\geq 20$ –<200 mg/L) or macroalbuminuria (albuminuria  $\geq 300$  mg/day,  $\geq 300$  mg/g or  $\geq 200$  mg/L).

GFR was estimated using the Modification of Diet in Renal Disease equation [15]. Haemoglobin, calcium, phosphorus and bicarbonate levels were noted.

Data were retrieved using hospital discharge reports, paper charts and electronic files and patients' files were individually analysed.

### Follow-up and outcomes

AKI during follow-up was diagnosed using the Kidney Disease: Improving Global Outcomes criteria [16]. Serum creatinine criteria were used to diagnose AKI (urinary output criteria were not available). For the diagnosis of AKI, the reference creatinine value was the lowest creatinine value, and we identified AKI by comparing the highest creatinine value found during hospitalization to this reference serum creatinine value. AKI was defined as a serum creatinine level of 150% or +0.3 mg/dL (+26.5  $\mu$ mol/L) versus the reference serum creatinine level.

Stroke was defined in patients with focal neurological abnormalities associated with ischaemic or haemorrhagic tissular lesions found on computed tomography scan and/or magnetic resonance imaging (diagnosis of stroke is usually supported by the result of neurological imaging in France). Transient ischaemic attacks were not considered as strokes. Amputation was defined by a lower limb amputation above the metatarsophalangeal joint. We also recorded revascularization of coronary arteries and of peripheral arteries (angioplasty or bypass of aortic or lower limb arteries).

We collected information regarding the development of ACS, AF and hospitalization for HF during follow-up, as well serious infections requiring hospitalization (serious infection was defined as either an infection leading to hospitalization or a major infection in a patient during hospitalization (pulmonary, cutaneous, urinary or bone infection)) and strokes. We chose not to collect information regarding cardiovascular mortality because our main goal was to assess the risk associated with AKI and ESRD following cardiovascular events.

Standard follow-up in our nephrology department includes outpatient visits every year in most patients when estimated GFR (eGFR) is  $>45$  mL/min/1.73 m<sup>2</sup>, every 6 months in most patients with GFR  $<45$  mL/min/1.73 m<sup>2</sup> or every 1–3 months in most patients with eGFR  $<20$  mL/min/1.73 m<sup>2</sup>. National guidelines regarding glycaemic and blood pressure control as well as the use of ACEIs and ARBs and cardiology referral are used by all nephrologists in our department.

Patients were followed up until death, ESRD (defined as initiation of chronic dialysis or pre-emptive renal transplantation) or the end of the study period (15 November 2015). The primary endpoint was to assess the risk of AKI and ESRD associated with MCVE during follow-up. Secondary endpoints were to assess (i) the specific risk of AKI and ESRD associated with HF, AF and ACS and (ii) the risk of AKI and ESRD associated with non-cardiovascular major events (infection and strokes leading to hospitalization). Deaths were identified using national death registers and medical records from our centre or primary care physicians.

### Statistical analyses

Results are reported as mean and standard deviation (SD) for continuous variables [or median and interquartile range (IQR)] and as percentages for categorical variables.

To assess the association between past MCVE and the risk of baseline reduced GFR, we performed univariate and multivariate logistic regressions. To assess the association between baseline reduced GFR and the risk of new MCVE during follow-up and the association between new MCVE and the risk of subsequent AKI and ESRD, we performed univariate and multivariate Cox models.

Sensitivity analyses restricted to patients who remained alive at the end of follow-up (i.e. patients who died during follow-up before ESRD were excluded from this analysis) were also conducted. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). P-values <0.05 were considered statistically significant.

## RESULTS

### Baseline characteristics

The study population included 861 patients (Table 1). The mean age was 70.3 years, most patients were men (65.1%) and the mean eGFR was  $42.4 \pm 21.0$  mL/min/1.73 m<sup>2</sup>. Diabetes duration was  $13.7 \pm 10.3$  years. Overall, 44.3% of patients had MCVE [including CAD (26.6%), HF (20.5%) and AF (20.2%)] (Table 1). Many patients had other cardiovascular complications [peripheral artery disease (19.2%), hypertension (93.5%), renal artery stenosis (3.4%)] or stroke (6.9%) (Table 1).

Despite a significant proportion of patients with chronic kidney disease (CKD), diabetic retinopathy was present in only 207 patients (24%). Most patients had albuminuria [either macroalbuminuria [385 (45.3%)] or microalbuminuria [276 (32.4%)]]. ACEIs and ARBs (72.3%) were used in most patients and 388 (45.5%) received insulin (Table 1).

### Association between past MCVE and baseline renal function

Overall, 381 (44.3%) patients had a history of MCVE (Table 1). These patients had a greater risk of reduced baseline eGFR (<30 mL/min/1.73 m<sup>2</sup> or <45 mL/min/1.73 m<sup>2</sup>) in univariate and multivariate analyses (Table 2). Specifically, a history of AF and HF were associated with renal dysfunction in univariate and multivariate analyses (Table 2). Of note, a history of stroke was not associated with a risk of renal dysfunction at baseline [odds ratio [OR] for eGFR <30: 0.96 [95% confidence interval (CI) 0.54–1.73], P=0.9017; OR for eGFR <45: 1.53 (0.51–4.63), P=0.4494] in multivariate analyses.

### Impact of baseline renal function on the risk of new MCVE during follow-up

During follow-up (median 59 months [IQR 4.5–193]), the cumulative incidence of MCVE was 27.9 and 40.5% at 5 and 10 years, respectively (AF occurred in 93 patients, hospitalization for HF in 220 patients and ACS in 67 patients). Expectedly, a history of MCVE at baseline was associated with a greater risk of new MCVE during follow-up [hazard ratio (HR) 2.43 (95% CI 1.87–3.16), P<0.0001].

Reduced eGFR was a significant risk factor for new MCVE in univariate and multivariate analyses (Table 3), mostly for the risk of new HF [HR for eGFR <30: 1.33 (95% CI 1.01–1.76), P=0.0473; HR for eGFR <45: 1.72 (1.27–2.33), P=0.0004] (Table 3).

Of note, the albuminuria category (macroalbuminuria versus microalbuminuria or microalbuminuria versus normoalbuminuria) was also associated with the risk of new MCVE in

univariate [HR 1.31 (95% CI 1.11–1.56), P=0.0015] and multivariate analysis [HR 1.36 (1.13–1.64), P=0.0013] (Table 3).

### Impact of baseline and new MCVE during follow-up on the subsequent risk of AKI and ESRD

**Risk of AKI.** During follow-up (median 59 months), 333 (38.7%) patients developed AKI. Baseline MCVEs were associated with a higher risk of AKI [HR 1.57 (95% CI 1.26–1.94), P<0.0001]; of note, all baseline MCVEs were risk factors of AKI [CAD: HR 1.50 (95% CI 1.20–1.89), P=0.0005; HF: HR 1.82 (1.43–2.31), P<0.0001; AF: HR 1.42 (1.10–1.83), P=0.0072].

New MCVEs during follow-up were powerful risk factors for AKI [HR 4.01 (95% CI 3.23–4.98), P<0.0001]. Specifically, all new MCVEs (AF, HF and ACS) during follow-up were risk factors for AKI in univariate and multivariate analysis (Table 4).

Coronary bypass or angioplasty was also significant in univariate and multivariate analyses [HR 4.48 (95% CI 3.16–6.34), P<0.0001 and 4.80 (3.25–7.11), P<0.0001, respectively].

Of note, stroke and hospitalization for serious infection occurred in 60 patients and 205 patients, respectively. Stroke [HR 1.08 (95% CI 0.71–1.64), P=0.7109 and HR 1.00 (0.64–1.55), P=0.9814, respectively] and hospitalization for serious infection [HR 2.98 (95% CI 0.42–21.4), P=0.2757 and HR 1.78 (0.25–12.9), P=0.5663, respectively] were not risk factors for AKI in univariate and multivariate analyses.

**Risk of ESRD.** During follow-up, 194 patients reached ESRD (dialysis, n=183; pre-emptive transplantation, n=11) and 180 patients died. The cumulative risk of ESRD was 19.2% at 5 years and 30.8% at 10 years. Among baseline MCVEs, only HF was associated with a higher risk of ESRD [HR 1.46 (95% CI 1.06–2.02), P=0.0203].

New HF, AF and ACS during follow-up were risk factors for subsequent ESRD in univariate analyses (Table 4). New HF and AF remained significant after multiple adjustments on established risk factors for ESRD (eGFR, albuminuria, diabetic retinopathy and SBP at baseline and AKI during follow-up) (Table 4). The relationship with ACS was less strong (Table 4).

When patients were stratified according to the development of AKI during follow-up, AF and HF remained risk factors for ESRD in patients who developed AKI and in those who did not, suggesting that the effects of these cardiovascular events on the risk of ESRD were not systematically mediated by AKI. Again, the relationship between ACS and ESRD was less strong both in patients with AKI and in those without (Table 4).

Importantly, hospitalization for serious infection [HR 4.97 (95% CI 0.69–35.9), P=0.1113 and 5.64 (0.76–41.9), P=0.0906 in univariate and multivariate analyses, respectively] and stroke [HR 1.09 (95% CI 0.64–1.84), P=0.7600 and 0.77 (0.40–1.50), P=0.4437 in univariate and multivariate analyses, respectively] were not significantly associated with the risk of ESRD.

**Sensitivity analyses.** When the analyses were restricted to patients who remained alive at the end of follow-up (i.e. patients who died during follow-up before ESRD were excluded from this analysis), the results were qualitatively unchanged. AF [univariate: HR 3.47 (95% CI 2.30–5.24), P<0.0001; multivariate: HR 2.35 (1.48–3.73), P=0.0003], HF [univariate: HR 8.24 (95% CI 6.03–11.27), P<0.0001; multivariate: HR 6.37 (4.43–9.16), P<0.0001] and ACS [univariate: HR 2.99 (95% CI 1.85–4.82), P<0.0001; multivariate: HR 2.12 (1.16–3.87), P<0.0151] remained significant risk factors for ESRD.

Table 1. Baseline characteristics (N = 861)

Clinical characteristics	
Age (years), mean ± SD	70.3 ± 10.0
Sex (male), %	65.1
BMI (kg/m <sup>2</sup> ), mean ± SD	30.7 ± 5.9
Systolic/diastolic arterial pressure (mmHg), mean ± SD	149 ± 23/78 ± 12
Diabetes duration (years), mean ± SD	13.7 ± 10.3
Main reason for first outpatient visit in nephrology ward, %	
CKD	54.3
Albuminuria	15.6
Hypertension	3.4
Other	26.7
Comorbid conditions, %	
Hypertension	93.5
CAD	26.6
Congestive HF	20.5
Peripheral artery disease	19.2
AF	20.2
MCVEs <sup>a</sup>	44.1
Stroke	6.9
Renal artery stenosis	3.4
Smoking (active/former)	8.2/33.1
Diabetic retinopathy	24.0
Biological data	
Serum creatinine (μmol/L), mean ± SD	176 ± 124
eGFR (mL/min/1.73 m <sup>2</sup> ) mean ± SD	42.4 ± 21
CKD stage <sup>b</sup> , %	
1 or 2	15.6
3a	19.7
3b	35.7
4	22.8
5	6.2
Albuminuria (mg/day or mg/g of urine creatinine), mean ± SD	722 ± 1090
Normoalbuminuria, %	22.3
Microalbuminuria, %	32.4
Macroalbuminuria, %	45.3
Haemoglobin (g/L)	120 ± 20
Calcium (mmol/L)	2.34 ± 0.21
Phosphorus (mmol/L)	1.27 ± 0.36
Bicarbonate (mmol/L)	24.4 ± 3.8
HbA1c (%), mean ± SD	7.25 ± 1.5
Antihypertensive therapy, %	
ACEI/ARB/both	33.5/42.5/3.7
Calcium channel blocker	50.4
Loop diuretic	39.0
Thiazide	23.5
β-blocker	46.0
Spironolactone	3.5
Others	22.1
Glucose-lowering therapy, %	
Insulin	45.5
Oral agents	53.0
Diet only	7.5
Other treatments, %	
Statin	57.7
Fibrate	8.8
Antiplatelet drug	51.0

Albuminuria: values after conversion of proteinuria in albuminuria when only proteinuria was available [14].

<sup>a</sup>MCVEs include HF, ACS and/or AF.

<sup>b</sup>CKD Stages 1–2: eGFR ≥ 60 mL/min/1.73 m<sup>2</sup>; 3a: 45–59.9 mL/min/1.73 m<sup>2</sup>; 3b: 30–44.9 mL/min/1.73 m<sup>2</sup>; 4: 15–29.9 mL/min/1.73 m<sup>2</sup>; 5: <15 mL/min/1.73 m<sup>2</sup>.

Table 2. Association between past MCVes and the risk of baseline renal dysfunction

Risk of baseline renal dysfunction associated with cardiac events	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Association with eGFR <30 mL/min/1.73 m <sup>2</sup>				
AF	1.67 (1.18–2.37)	0.0040	1.98 (1.03–3.82)	0.0412
Hospitalization for HF	2.10 (1.49–2.96)	<0.0001	3.55 (1.71–7.39)	0.0013
CAD	0.96 (0.69–1.34)	0.8007	1.09 (0.77–1.55)	0.6266
Association with eGFR <45 mL/min/1.73 m <sup>2</sup>				
AF	2.80 (1.86–4.21)	<0.0001	1.97 (1.02–3.80)	0.0421
Hospitalization for HF	3.26 (2.14–4.98)	<0.0001	3.56 (1.71–7.40)	<0.0001
CAD	1.24 (0.90–1.71)	0.1907	1.35 (0.96–1.88)	0.0881

Multivariate analysis: adjustments on age, gender, renin–angiotensin system blockade and diabetic retinopathy.

Table 3. Impact of baseline eGFR and albuminuria on the risk of new MCVes and HF

Risk of new cardiac events associated with baseline renal dysfunction	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>MCVes</b>				
eGFR (per 10 mL/min/1.73 m <sup>2</sup> )	1.25 (1.15–1.35)	<0.0001	1.19 (1.09–1.30)	<0.0001
eGFR <30 (versus ≥30 mL/min/1.73 m <sup>2</sup> )	1.77 (1.35–2.33)	<0.0001	1.40 (1.03–1.92)	0.0340
eGFR <45 (versus ≥45 mL/min/1.73 m <sup>2</sup> )	1.91 (1.43–2.54)	<0.0001	1.57 (1.15–2.15)	0.0050
Albuminuria category increment	1.31 (1.11–1.56)	0.0015	1.36 (1.13–1.64)	0.0013
Microalbuminuria versus normoalbuminuria	1.00 (0.68–1.48)	0.9942	1.14 (0.75–1.72)	0.5402
Macroalbuminuria versus normoalbuminuria	1.26 (1.06–1.49)	0.0078	1.30 (1.08–1.58)	0.0072
<b>HF</b>				
eGFR (per 10 mL/min/1.73 m <sup>2</sup> )	1.13 (1.05–1.21)	0.0007	1.12 (1.04–1.22)	0.0037
eGFR <30 (versus ≥30 mL/min/1.73 m <sup>2</sup> )	1.33 (1.01–1.33)	0.0473	1.31 (0.96–1.78)	0.0925
eGFR <45 (versus ≥45 mL/min/1.73 m <sup>2</sup> )	1.72 (1.27–1.33)	0.0004	1.64 (1.19–2.27)	0.0025
Albuminuria category increment	1.24 (1.04–1.48)	0.0153	1.28 (1.06–1.55)	0.0119
Microalbuminuria versus normoalbuminuria	0.99 (0.66–1.49)	0.9659	1.17 (0.76–1.80)	0.4858
Macroalbuminuria versus normoalbuminuria	1.20 (1.01–1.43)	0.0458	1.27 (1.04–1.55)	0.0176

MCVes defined as new AF, hospitalization for HF and/or ACS. Albuminuria category defined as macroalbuminuria versus microalbuminuria or microalbuminuria versus normoalbuminuria. Multivariate analyses: adjustments on age, gender, systolic arterial pressure, history of cardiovascular events, blockade of the renin system, diabetic retinopathy, eGFR and albuminuria.

Table 4. Impact of new MCVes on the risk of AKI and ESRD

Risk of AKI and ESRD associated with new cardiac events	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Risk of AKI</b>				
AF	5.42 (3.91–7.52)	<0.0001	5.88 (4.11–8.42)	<0.0001
Hospitalization for HF	8.99 (7.06–11.4)	<0.0001	9.05 (6.85–12.0)	<0.0001
ACS	8.82 (6.24–12.5)	<0.0001	9.08 (6.05–13.6)	<0.0001
<b>Risk of ESRD</b>				
Atrial fibrillation	3.48 (2.30–5.21)	<0.0001	2.31 (1.45–3.68)	0.0004
Hospitalization for heart failure	5.52 (4.01–7.60)	<0.0001	3.80 (2.56–5.63)	<0.0001
Acute coronary syndrome	2.31 (1.43–3.73)	0.0006	1.02 (0.56–1.87)	0.9475

Model: the effect of each parameter was adjusted on baseline parameters (eGFR, albuminuria, SBP, diabetic retinopathy, age and sex).

## DISCUSSION

In this study conducted in a large cohort of diabetic patients in a nephrology setting, a high proportion of patients developed MCVes, AKI and ESRD. We tried to describe the renal consequences of cardiac events over a long period of time in a cohort

of diabetic patients. Our results help us to better understand the interrelationship among cardiorenal syndrome subtypes—starting from past cardiovascular events leading to a higher risk of reduced GFR, reduced GFR at presentation leading to a higher risk of new cardiovascular events during follow-up and new cardiovascular events leading to an increased risk of AKI and an

increased risk of ESRD. Of note, new MCVEs constituted a risk factor for ESRD even in patients without AKI. HF and AF were associated with renal events to a greater extent than ACS. In marked contrast, this sequence of events was not observed for major non-cardiovascular events such as stroke or hospitalization for serious infection.

Specifically, we observed that HF, AF and ACS were associated with an increased risk of AKI and ESRD, but the cardiovascular risk of ESRD was not systematically mediated by AKI. It can be hypothesized that acute cardiac dysfunction such as ACS, AF and HF may lead to subtle renal dysfunction that is not always identified, as no immediate change of serum creatinine is detected. Acute worsening of cardiac function due to acute decompensated HF or ACS may lead to AKI [7]. Many parameters can be involved in the development of AKI, including hormonally mediated renal damage, contrast media, renin-angiotensin blockers or other drugs [17–21]. It has been shown that risk factors of AKI include previous HF episodes, diabetes mellitus, abnormal baseline serum creatinine and elevated SBP [9]. AKI may lead to an increased risk of ESRD, mostly among non-diabetic elderly patients [22]. AKI was associated with an increased risk to reach Stage 4 CKD during follow-up in diabetic subjects who sought ambulatory and inpatient care [23]. In this study, however, these patients were not followed up in a nephrology setting and the role of MCVEs was not studied [23].

In our cohort, stroke was not a risk factor of AKI or ESRD. Tsagalis et al. [24] indicated that low GFR at the time of stroke was a risk factor of major vascular events and mortality; however, 14.3% of these patients developed AKI in this report and the relationship between MCVEs and AKI was not analysed [24]. In another study from the same group, it was shown that AKI occurred in 27% of 2155 patients with stroke [12]; the relationship between AKI and ESRD was not studied [12]. However, only a quarter of these patients were diabetic. Other studies found that stroke was associated with an increased risk of AKI [25], but only 19.6% of these subjects had diabetes mellitus. Finally, whether the association between stroke and ESRD is independent is not settled in diabetic patients.

We found that the 10-year cumulative incidence of ESRD was 30% in our patients followed up in a nephrology setting. In a nationwide French study in 986 diabetic patients from 153 nephrologists, patients had similar ages and GFRs and the incidence of ESRD was comparable, suggesting that our population is representative of the diabetic population usually observed in nephrology settings in France [26]. In the Chronic Renal Insufficiency Cohort study, baseline GFR was comparable but the incidence of ESRD seemed higher in our cohort [27]. However, only half of these patients had diabetes mellitus and only half of them benefited from nephrology care [27]. Interestingly, the incidence of ESRD was greater than the incidence of death in our cohort. It was reported that the incidence of ESRD is lower than the incidence of death in patients with mild to moderate CKD [28]. Differences may stem from the fact that very few patients had nephrology care and they were mostly patients in unstable condition in this study [28].

Our study has several limitations. It is a monocentric study and therefore our findings need to be replicated; however, our cohort was large and the total observation period was important. Files were individually reviewed and we included consecutive patients. At baseline, brain natriuretic peptide was not measured. Although HF associated with high brain natriuretic peptides levels is associated with a more rapid progression towards ESRD in CKD patients [29], systematic use of B-type

natriuretic peptide in stable CKD patients is presently not recommended.

Our study also has some strengths. Multivariate analyses (and sensitivity analyses) were carefully designed to take into account potential confounders. We tried to identify the predictive value of MCVEs such as AF, HF and ACS during follow-up and identify which ones were specifically associated with the risk of AKI and ESRD. Patients were followed in the same centre and all treatments, hospitalizations and biochemical evaluations were available in our study; these data could be retrieved in all of them. It is obviously possible that AKI episodes remained undiagnosed in some of these patients; however, all creatinine values were retrieved during outpatient visits or after admission to the hospital for serious events. The likelihood that patients developed AKI in the absence of serious events is probably small. Whether the effects of undiagnosed and diagnosed AKI on the risk of ESRD are similar is unknown and, to our knowledge, has not been discussed in the literature.

The results of our study may be important with regard to the classification and understanding of cardiorenal syndromes. The current classification of cardiorenal syndromes includes five different subtypes (1: acute cardiorenal; 2: chronic cardiorenal; 3: acute renocardiac; 4: chronic renocardiac; 5: secondary cardiorenal syndromes) [7]. Some authors have proposed the concept of a ‘cardiorenal syndrome continuum’ [30]. Our own findings are consistent with this view: past cardiovascular events were associated with a higher risk of reduced GFR (i.e. type 2: chronic cardiorenal syndrome); low GFR was a risk factor for new cardiovascular events during follow-up (i.e. type 4: chronic renocardiac syndrome); new cardiovascular events were risk factors for AKI (i.e. type 1: acute cardiorenal syndrome) and faster degradation of renal function (i.e. type 2: chronic cardiorenal syndrome); and AKI was associated with a higher risk of new cardiovascular events (i.e. type 3: acute renocardiac syndrome). Acute and chronic cardiovascular events lead to acute and chronic renal events and, conversely, acute and chronic renal events lead to new cardiovascular events, at least in patients with diabetes mellitus, supporting the concept of a ‘single cardiorenal syndrome umbrella’ [30]. Of note, new MCVEs constituted a risk factor for ESRD even in patients without AKI. HF and AF were associated with renal events to a greater extent than ACS. The association between HF and renal outcome was well known. Our study also indicates that other MCVEs such as AF are a risk factor for AKI and ESRD [31, 32].

In conclusion, most past or new MCVEs constitute powerful risk factors for ESRD beyond established risk factors and AKI.

## CONFLICT OF INTEREST STATEMENT

None declared.

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