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ARTICLE

Trends in the epidemiology and care of diabetes mellitus-related end-stage renal disease in France, 2007–2011

Frank G. A. Assogba · Cécile Couchoud · Thierry Hannedouche · Emmanuel Villar · Luc Frimat · Anne Fagot-Campagna · Christian Jacquelinet · Bénédicte Stengel · on behalf of the French Renal Epidemiology and Information Network (REIN) Registry

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Abstract
Aims/hypothesis The aim was to study geographic variations and recent trends in the incidence of end-stage renal disease (ESRD) by diabetes status and type, and in patient condition and modalities of care at initiation of renal replacement therapy.
Methods Data from the French population-based dialysis and transplantation registry of all ESRD patients were used to study geographic variations in 5,857 patients without diabetes mellitus, 227 with type 1 diabetes mellitus, and 3,410 with type 2. Trends in incidence and patient care from 2007 to 2011 were estimated.
Results Age- and sex-adjusted incidence rates were higher in the overseas territories than in continental France for ESRD unrelated to diabetes and related to type 2 diabetes, but quite similar for type 1 diabetes-related ESRD. ESRD incidence decreased significantly over time for patients with type 1 diabetes (−10% annually) and not significantly for non-diabetic patients (0.2%), but increased significantly for patients with type 2 diabetes (+7% annually until 2009 and seemingly stabilised thereafter). In type 2 diabetes, the net change in the absolute number was +21%, of which +3% can be attributed to population ageing, +2% to population growth and +16% to the residual effect of the disease. Patients with type 2 diabetes more often started dialysis as an emergency (32%) than those with type 1 (20%) or no diabetes.
Conclusions/interpretation The major impact of diabetes on ESRD incidence is due to type 2 diabetes mellitus. Our data demonstrate the need to reinforce strategies for optimal management of patients with diabetes to improve prevention, or

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F. G. A. Assogba · C. Couchoud · C. Jacquelinet
The French REIN Registry, Biomedicine Agency,
Saint Denis La Plaine, France

F. G. A. Assogba (✉)
Department of Chronic Diseases and Injuries, French Institute for Public Health Surveillance, 12 rue du Val d'Osne,
94415 Saint-Maurice Cedex, France
e-mail: f.assogba@invs.sante.fr

T. Hannedouche
Department of Nephrology, School of Medicine,
University Hospital, Strasbourg, France

E. Villar
Department of Nephrology, St Joseph St Luc Hospital, Lyon, France

E. Villar
Biostatistics Health Laboratory, CNRS, UMR 5558,
University Claude Bernard Lyon 1, Villeurbanne, France

L. Frimat
Clinical Epidemiology, School of Medicine,
University Hospital, Inserm CIC-EC, Vandoeuvre-lès-Nancy, France

L. Frimat
Department of Nephrology, School of Medicine,
University Hospital, Vandoeuvre-lès-Nancy, France

A. Fagot-Campagna
Department of studies on diseases and patients,
French National Health Insurance Fund for Salaried Workers,
Paris, France

B. Stengel
Centre for Research in Epidemiology and Population Health,
Diabetes, Obesity, and Chronic Kidney Disease Epidemiology Team,
Inserm U1018, Villejuif, France

B. Stengel
Paris-Sud University, UMRS 1018, 94807 Villejuif, France

delay the onset, of diabetic nephropathy, ESRD and cardiovascular comorbidities, and to reduce the rate of emergency dialysis.

Keywords Care · Diabetes mellitus · End-stage renal disease · Epidemiology · Incidence · Type 1 diabetes mellitus · Type 2 diabetes mellitus

Abbreviations

eGFR	Estimated GFR
ERBP	European Renal Best Practice
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
CKD	Chronic kidney disease
HD	Haemodialysis
PD	Peritoneal dialysis
pmp	Per million population
REIN	Renal Epidemiology and Information Network
RRT	Renal replacement therapy

Introduction

Sharply rising overall incidence rates of end-stage renal disease (ESRD) worldwide began to stabilise or even fall in the early 2000s in several European countries [1] and in New Zealand [2], although they continue to increase in the USA [3, 4], Canada [5], the UK [6], Taiwan and Japan [4]. Similarly, recent trends in diabetes-related ESRD incidence vary substantially according to geography. This rate has almost doubled in the UK over the past 10 years [6], while it has been stable since the end of the 2000s in the USA [4] and decreased in Denmark [7], Australia and New Zealand [2].

In France, 40% of the patients who started renal replacement therapy (RRT) in 2010 had diabetes, 94% of them type 2 diabetes mellitus [8]. The total cost of RRT to the national health insurance system was estimated to be 4 billion euros, 77% of it for haemodialysis (HD) alone [9]. In a previous study, we showed that 29–47% (high hypothesis) of people with type 2 diabetes in France have chronic kidney disease (CKD) [10]. We also reported that clinical guidelines [11] recommending CKD screening and renoprotective care in patients with type 2 diabetes have had a moderate effect, while the prevalence of diabetes is increasing steadily in France [12]. Another concern is the management of the transition from advanced CKD to ESRD. More than 30% of patients with ESRD started dialysis on an emergency basis, a circumstance that has major negative effects on both outcome and cost [8]. Little is known, however, about the differences in trends over time in diabetes-related compared with non-diabetes-related ESRD incidence or about the differences in patient clinical condition and care at RRT onset in the years after the wide dissemination of guidelines for diabetes and CKD [11, 13].

We therefore used data from the French Renal Epidemiology and Information Network (REIN) registry to study geographic variations in 2011 and trends in ESRD incidence from 2007 to 2011 according to diabetes status. We also analysed changes in patient condition and modalities of care at RRT onset over this period. Because of expected differences in epidemiological characteristics and patient condition between type 1 and type 2 diabetes [14], all analyses were conducted by diabetes type.

Methods

Population

The REIN registry is a national population-based registry, which started in 2002 in four pilot regions, and progressively spread throughout the country; it now covers the whole population. The details of its organisation principles and methods have been described previously [15]. To study patient characteristics and geographical variations, we included all patients with ESRD who started an initial RRT from 1 January to 31 December 2011, and living in any French region except the West Indies island of Martinique, because of incomplete registration.

We studied the trends in patients' characteristics and care over time from data for all incident ESRD cases first recorded from 1 January 2007 to 31 December 2011, who lived in 18 of 22 continental regions that contributed to the registry over the last 5 years, i.e. 82% of the French population.

Information

Data collected included patient demographics, primary renal disease, comorbidities including type 1 and type 2 diabetes, cardiovascular diseases, disabilities, estimated GFR (eGFR) by the simplified Modification of Diet in Renal Disease Study equation, haemoglobin level in the month before dialysis began, and predialysis use of erythropoiesis-stimulating agent (ESA). First RRT modalities (HD; peritoneal dialysis (PD); and pre-emptive transplantation) were recorded, as well as whether or not dialysis started as an emergency or with a central venous catheter. Detailed information on comorbidities was not available for 3% of the patients who received pre-emptive transplants. Primary renal diseases were categorised according to the European Renal Association – European Dialysis and Transplant Association coding systems [16]. All patients with either diabetic nephropathy or diabetes recorded as a comorbid condition were classified as having diabetes.

In the REIN registry, the type of diabetes is based on the patient's historical medical record made available by the nephrologist. However, an epidemiological algorithm based on age at diagnosis of diabetes (threshold 45 years), the existence of an insulin delivery, and time to insulin treatment after diagnosis of diabetes (threshold 2 years) is also available and used to classify the type of diabetes.

Ethics permission

The French dialysis and transplantation registry has the approval of the French national ethics committee 'Commission nationale de l'informatique et des libertés'. This study took place within the framework of this authorisation.

Statistical analysis

Of 40,397 patients with ESRD who started RRT in the regions and periods described above, we excluded eight (0.02%) with missing data for primary renal disease and 435 (3%) with missing type of diabetes. Data analysis for 2011 thus included 9,494 patients, and the 5-year trend analysis included 38,247 patients.

We first calculated 2011 crude incidence rates of ESRD by diabetes status for each region as the number of new cases of ESRD in each diabetes-status group divided by the region's mid-year population. To estimate age- and sex-adjusted ESRD incidence rates by region, we classified patients by sex and by 5-year age groups and performed direct standardisation with the total mid-2011 French population as the reference. We also estimated the ratio of the two incidence rates to compare morbidity using overall incidence as the reference. Next we estimated age- and sex-adjusted ESRD incidence rates by diabetes status and year from 2007 to 2011. To assess trends over this period, we estimated the average annual percentage changes in age- and sex-adjusted incidence rates and their 95% CIs by Poisson regression, with person-years as an offset, e.g. $[\exp(\beta)-1]\times 100$, where β denotes the regression coefficient of time (change per year). When trends were not linear, a segmented regression analysis was performed to estimate trends for each time interval. To explain changes over time in the number of patients, we used a method for partitioning the difference in the total number of cases into three components [17]:

- difference due to the population structure by age;
- difference due to the population size;
- difference due to the residual effect, i.e. due to a true increase in risk.

We then compared patient characteristics in 2011 for three groups according to diabetes status and type: no diabetes (n=5,857), type 1 diabetes (n=227), and type 2 diabetes (n=3,410). Differences between groups were tested after adjustment for age and sex with logistic regression or analysis of variance, as appropriate.

Finally, we compared patients' baseline characteristics and care for each year of the study period by diabetes status and type, both before and after adjustment for age. When these differences were significant, we used the Cochran–Armitage trend test to assess linear trends in each group. Five-year percentage changes were then estimated for categorical variables using the ratio of the difference between the values for 2011 and 2007 divided by the 2007 value, and for continuous variables using the difference in mean values between 2011 and 2007.

Two-sided p values <0.05 were considered significant. Statistical analyses were performed with SAS V9.2 software (SAS institute, Cary, NC, USA), and maps were drawn with Philcarto V5.

Results

Geographic variations and trends in ESRD incidence rates by diabetes status

The overall age- and sex-adjusted incidence rates were 3.5 (95% CI 3.1, 4.0) per million population (pmp) for type 1 diabetes-related ESRD (3.5 [95% CI 3.0, 3.9] for continental France vs 5.4 [95% CI 0.4, 10.4] for overseas territories), 53.0 (95% CI 51.2, 54.8) for type 2 diabetes mellitus-related ESRD (50.7 [95% CI 48.9, 52.4] vs 198.4 [95% CI 170.0, 226.9], respectively), and 91.0 (95% CI 88.7, 93.4) for non-diabetes-related ESRD (90.0 [95% CI 87.6, 92.3] vs 114.5 [95% CI 121.2, 167.8]). For type 2 diabetes, incidence rates were three to four times higher in the overseas territories than the national average; in continental France, they showed a gradient that decreased from northeast to southwest (Fig. 1b), similar to the gradient for diabetes prevalence (Fig. 1a). For type 1 diabetes, the highest rates were observed in southern France (Fig. 1c).

Trends in ESRD incidence rates by diabetes status Over the past 5 years, age- and sex-adjusted ESRD incidence rates decreased significantly by 10.4% (95% CI −12.8, −7.9, p<0.0001) per year, from 5.3 to 3.4 pmp for patients with type 1 diabetes, and non-significantly from 93 to 92 pmp (−0.2%, 95% CI −0.9, 0.4), p=0.5) for those without diabetes. In contrast, after a steep rise of 6.9% (95% CI 4.8, 9.1, p<0.0001) per year until 2009, the incidence of type 2 diabetes-related ESRD appeared to stabilise thereafter (0%, 95% CI −2.1, 2.2).

Trends in ESRD incidence rates by diabetes status according to age and sex Age-adjusted type 2 diabetes-related ESRD incidence rates were higher in men than women at all ages. In

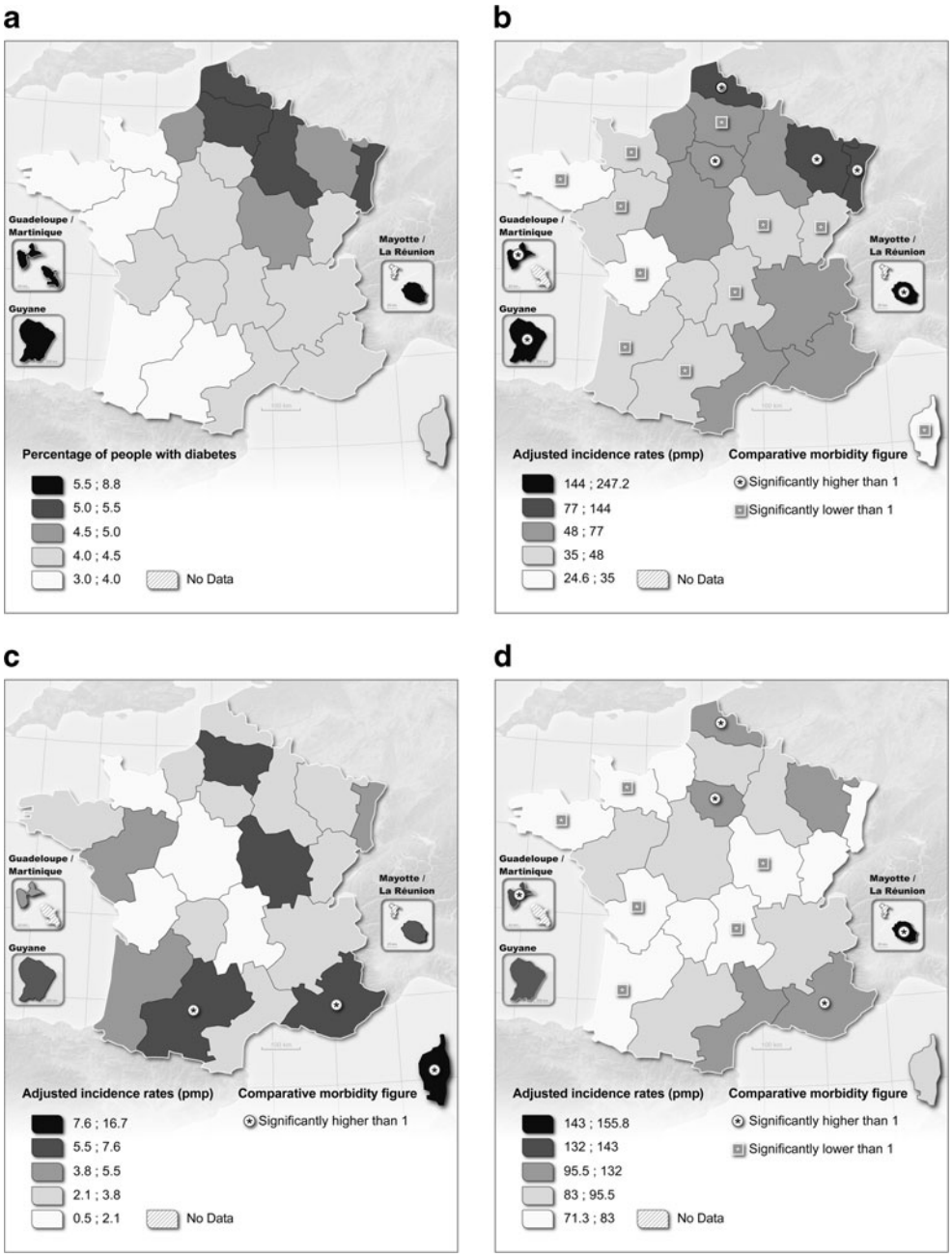

Fig. 1 Age- and sex-adjusted diabetes mellitus prevalence in the general population (**a**) and age- and sex-adjusted ESRD incidence rates associated with type 2 diabetes (**b**), type 1 diabetes (**c**), and not associated with diabetes (**d**), and by region, France 2011. The numbers listed for percentage/incident rate for each category in the key are the range values. Sources: the 2009 prevalence data used for (**a**) was provided by the Caisse Nationale d'Assurance Maladie des Travailleurs Salariés (CNAM-TS; the principal French health insurance fund); (**b**, **c**, **d**): Agence de la biomédecine, REIN 2013 CIAT-CSI (SRTM http://srtm.csi.cgiar.org) 2010

men, incidence increased consistently by 8.7% (95% CI 7.6, 9.8, $p<0.0001$) per year from 2007 to 2009 from 56.7 to 68.2 pmp, and decreased thereafter to 65.2 pmp in 2011, a decrease of 2.7% (95% CI −3.0, −2.4, $p<0.0001$) per year. In women, it increased from 2007 to 2010, an overall increase of 4.3% (95% CI 3.9, 4.6, $p<0.0001$), with a trend towards stabilisation thereafter. Over the study period, the ESRD incidence rates associated with type 2 diabetes mellitus were quite similar in women aged 65–74 years and those 75 years and older, but differed greatly for men in those age groups. In the oldest category of men, ESRD incidence rates increased consistently by 7.7% (95% CI 4.3, 11.3, $p<0.001$) per year between 2007 and 2010 and stabilised thereafter with no further significant change (Fig. 2a). For the corresponding women, the rate increased steadily by 4.1% (95% CI 2.7, 5.5, $p<0.0001$) per year over the 5-year study period (Fig. 2b).

Net growth of the absolute number of patients with ESRD by diabetes status and by sex

Over 2007–2011, the absolute number of patients with non-diabetes-related ESRD increased from 4,685 to 4,862 (i.e. +4%): +2% (89 patients) was due to population growth, +3% (141 patients) to population ageing, and −1%

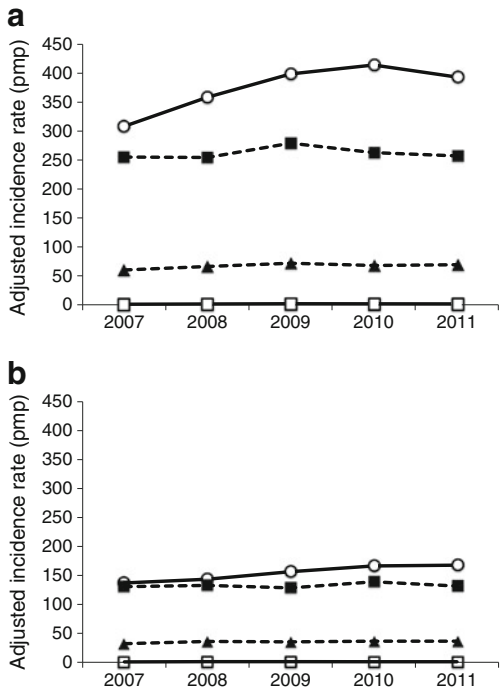

Fig. 2 Trends in age-adjusted type 2 diabetes-related ESRD incidence rates and percentage change over 2007–2011 in 18 French regions, by age and sex: (**a**) for men; (**b**) for women. White circles, ≥75 years; black squares, 65–74 years; black triangles, 45–64 years; white squares, 0–44 years

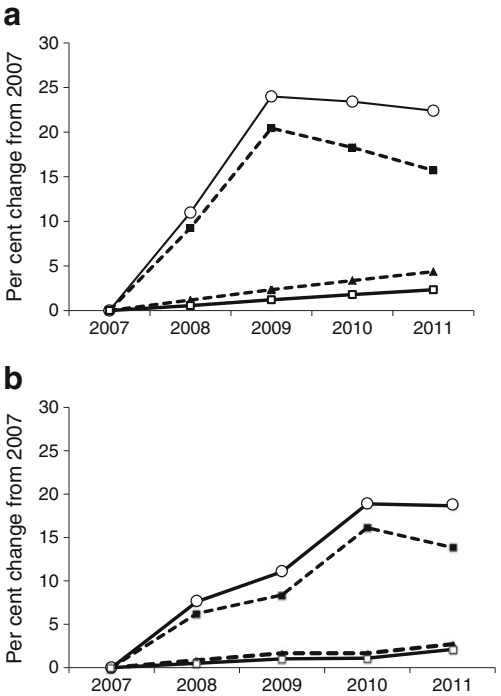

Fig. 3 Changes in the total number of patients with type 2 diabetes-related ESRD due to population growth or ageing and to a true increase in the disease over 2007–2011, in 18 French regions: (**a**) for men; (**b**) for women. White circles, net change in the number with type 2 diabetes-related ESRD; black squares, changes due to the residual effect; black triangles, changes due to population structure by age; white squares, changes due to the population size

(−53 patients) to a true decrease in non-diabetes-related ESRD. In contrast, the number of patients with type 2 diabetes-related ESRD increased from 2,270 to 2,745 (i.e. +21%): +2% (50 patients) was due to population growth, +3% (76 patients) to population ageing, and +16% (349 patients) to a true increase in type 2 diabetes-related ESRD. The last increase—due to a true rise—was higher in men than women: +16% (216 men) vs +14% (124 women) (Fig. 3a and b, respectively).

Patient characteristics at start of RRT according to diabetes status

In 2011, 36% of incident ESRD patients had type 2 diabetes and 2% had type 1 (Table 1). Those with type 2 diabetes were older than those with type 1 or without diabetes. The sex ratios (men/women) were 1.7 for patients without diabetes, 1.3 for those with type 1, and 1.6 for those with type 2 diabetes. Patients without diabetes were twice as likely to have a renal biopsy than those with diabetes. More than 80% of the patients with type 1 diabetes, but only 54% of those with type 2, were classified as having diabetic nephropathy. In patients with type 2 diabetes, the most common other primary renal disease was hypertensive or vascular nephropathy. Comorbidities and disabilities were common in all patients, but even more so in those with than without diabetes. After adjustment for age, the percentages of cardiovascular disease due to atherosclerosis did not differ significantly between patients with type 1 and type 2 diabetes. Patients with type 2 diabetes had higher rates of heart failure and obesity and lower rates of severe vision impairment than those with type 1. The latter were more often current smokers, whereas patients with type 2 diabetes were more often former smokers.

Trends in characteristics of patients at start of RRT according to diabetes status

Very minor changes were observed in patient characteristics over the 2007 period (electronic supplementary material [ESM] Tables 1–3). Patients with type 2 diabetes were slightly older and had higher BMIs than patients with type 1, who tended to be younger over time. There was a trend towards a higher renal biopsy rate in patients without diabetes and those with type 2 diabetes.

Patient condition and care at start of RRT according to diabetes status

Mean haemoglobin was similar in all groups (Table 1). Although almost half the patients were receiving ESA before dialysis, regardless of diabetes status, most failed to achieve the current European Renal Best Practice (ERBP) targets [18]. Patients with diabetes generally required more ESA than those

Table 1 Patient characteristics and medical care at start of RRT according to diabetes status in 2011 in France

Characteristic	All patients (*n*=9,494)	No diabetes (*n*=5,857)	Type 1 diabetes (*n*=227)	Type 2 diabetes (*n*=3,410)	*p* value[a]
Age (years), mean ± SD	67.0±16.5	65.0±18.6	54.4±15.6	71.2±10.7	<0.0001
Men, %	62.5	63.5	56.4	61.1	0.01
Renal biopsy, %	18.5	23.1	12.1	11.3	<0.0001
Primary renal disease, %					
Diabetic nephropathy	21.4	n/a	81.9	54.2	
Vascular or hypertensive nephropathy	25.5	29.4	5.3	20.3	
Glomerulonephritis	11.1	15.5	1.3	4.0	
Other	26.6	36.9	6.2	10.3	
Unknown	15.4	18.3	5.3	11.2	
Comorbidities[b], %	65.5	58.0	60.7	77.4	<0.0001
Cardiovascular disease	55.7	46.1	56.3	70.5	<0.0001
Heart failure	26.1	21.5	18.5	33.8	<0.0001
Coronary heart disease	25.2	18.4	25.8	35.8	<0.0001
Myocardial infarction	10.2	7.8	12.6	13.9	<0.0001
Dysrhythmia	21.4	19.2	11.2	25.3	<0.0001
Peripheral vascular disease	20.0	12.3	30.0	31.6	<0.0001
Cerebrovascular disease	10.9	8.8	12.2	14.2	<0.0001
Respiratory failure	14.2	11.4	8.4	18.9	<0.0001
Malignancy	11.8	13.8	3.2	9.1	<0.0001
Liver disease[c]	3.9	3.8	3.7	4.1	NS
HIV infection or AIDS	0.9	1.1	1.1	0.6	NS
Disability[d] ,%	8.3	5.0	22.6	12.8	<0.0001
Severe vision impairment	2.8	1.0	12.9	5.0	<0.0001
Hemiplegia or paraplegia	1.4	1.2	1.9	1.8	0.05
Amputation	1.9	0.5	7.9	3.9	<0.0001
Severe behavioural disorders	3.0	2.7	2.5	3.6	0.1
Smoking status, %					
Non-smoker	60.2	61.7	59.1	58.0	<0.0001
Current smoker	11.4	12.4	21.6	9.2	
Former smoker	28.4	26.0	19.3	32.8	
Body mass index (kg/m^2), %					
<18.5	5.5	7.7	6.1	2.0	<0.0001
18.5–22	25.6	32.8	26.4	14.4	
23–24	16.9	19.0	19.6	13.4	
25–29	29.5	28.1	24.3	31.9	
≥30	22.5	12.4	23.7	38.3	
Serum haemoglobin (g/l), mean ± SD	101.2±17.3	100.9±17.9	104.1±16.5	101.5±16.3	NS
Predialysis ESA treatment, %	46.7	45.1	54.5	48.9	0.006
Haemoglobin <100 g/l without predialysis ESA treatment, %	55.9	58.6	45.1	51.9	0.009
eGFR (ml min^{-1}1.73 m^{-2})					
Mean ± SD	9.9±8.0	9.7±9.1	9.6±3.7	10.3±6.0	NS
≥10, %	36.7	33.7	38.9	41.3	<0.0001
First RRT modality, %					
HD	86.9	84.8	76.7	91.2	<0.0001
PD	9.6	10.4	11.0	8.2	
Pre-emptive transplant	3.5	4.9	12.3	0.6	
First dialysis started emergently, %	29.8	28.9	20.5	31.7	0.0005
First HD on catheter, %	53.6	52.5	40.9	55.9	0.0004

Table 1 (continued)

Characteristic	All patients (*n*=9,494)	No diabetes (*n*=5,857)	Type 1 diabetes (*n*=227)	Type 2 diabetes (*n*=3,410)	*p* value[a]
Number of nephrologist consultations during the year before the start of dialysis[e], %					
0	40.6	50.3	33.3	28.1	<0.0001
1–3	34.8	32.0	16.7	39.4	
4–5	11.3	8.8	16.7	14.5	
≥6	13.2	9.0	33.3	18.0	

[a] Overall *p* value across the three diabetes status groups adjusted for age and sex

[b] Includes heart failure, coronary heart disease, dysrhythmia, peripheral vascular disease, cerebrovascular disease, chronic respiratory disease, malignancy, cirrhosis, viral hepatitis, HIV infection or AIDS

[c] Includes cirrhosis or viral hepatitis

[d] Includes severe vision impairment, hemiplegia, paraplegia, amputation and severe behavioural disorders

[e] For subsample of 20 regions with >30% of missing data

HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; n/a, not applicable

without diabetes. Mean eGFR did not significantly differ between the three groups, but patients with diabetes were more likely to start dialysis with an eGFR ≥10 ml min^{-1} 1.73 m^{-2} than those without diabetes. Haemodialysis was the most common treatment modality at RRT onset in all groups. More than 10% of the patients with type 1 diabetes had pre-emptive transplantation, but less than 1% of those with type 2. Patients with type 2 diabetes were more likely to start dialysis as an emergency or with a catheter than those in the other two groups.

Trends in patient condition and care at start of RRT, according to diabetes status

From 2007 to 2011, mean haemoglobin decreased significantly, by 2 g/l in patients without diabetes and by 1 g/l in those with type 2 diabetes (Table 2). Mean eGFR at initiation increased significantly by 0.6 ml min^{-1} 1.73 m^{-2} in patients without diabetes, while no significant change was seen in the other two groups. In patients with type 2 diabetes and those without diabetes, there was a similar downward trend of the yearly proportion of PD in favour of increased HD and, to a lesser extent, pre-emptive kidney transplantation. In contrast, in those with type 1 diabetes, an upward trend was seen in both pre-emptive kidney transplantation and PD, both replacing HD. No significant improvement in the proportion of emergency dialysis has been observed since 2007, but there was a trend towards higher rates of first HD by catheter in patients without diabetes and in those with type 2 diabetes.

Discussion

Incidence rates of ESRD in 2011 varied considerably between European countries, from 85 pmp in Finland to 226 pmp in Portugal. In France, the rate remains relatively high (149 pmp). However, the highest rates were reported in the USA and Jalisco (Mexico) (362 and 527 pmp, respectively) [19].

An important finding of this study is that the overall increase in the incidence of treated ESRD in recent years in France is due solely to type 2 diabetes. While the incidence rates of ESRD related to type 1 diabetes have decreased slightly and remained stable for ESRD unrelated to diabetes, the incidence rates of type 2-related ESRD have continued to rise, mainly in the elderly. One of the most important findings of the REIN registry is the persistently high percentage of patients with diabetes starting dialysis on an emergency basis. This result is important for determining priorities for secondary prevention in CKD, particularly at transition to ESRD.

We also documented a gradient of type 2 diabetes-related ESRD that decreased from the northeast to the southwest. This geographical variation has previously been shown to be related to geographic differences in the prevalence of diabetes in the background population—which displays a similar northeast to southwest gradient [12]—as well as in socioeconomic status and prevalence of obesity [20, 21]. Incidence in overseas territories is also dramatically higher for reasons related to specific epidemiological, dietary and sociocultural characteristics, and different genetic backgrounds.

We found that the overall ESRD related to type 2 diabetes increased sharply over the past 5 years, with a trend towards stabilisation since 2010 (to be confirmed in years to come). Similar trends in ESRD related to type 2 diabetes have been observed throughout the world, described as a rising tide. In France, this rise is related in part to the parallel increase in the prevalence of treated diabetes—from 2.6% to 4.4% in the background population [12]. Although population growth and ageing both play a role in this increased incidence of diabetes-related ESRD, our results show that most of it is

Table 2 Trends in the medical care of patients with ESRD at start of RRT according to diabetes status in 18 French regions, from 2007 to 2011

	2007	2008	2009	2010	2011	*p* value[a]	*p* value[b]
No diabetes, *n*	4,685	4,802	4,859	4,903	4,862		
Serum haemoglobin (g/l), mean ± SD	103.3±18.3	102.7±179	102 .4±17.9	102.4±17.7	101.1±17.6	<0.0001	<0.0001
Predialysis ESA treatment, %	46.9	47.1	49.2	47.6	44.6	0.003	NS
Haemoglobin <100 g/l without predialysis ESA treatment, %	59.3	56.6	55.5	56.5	59.2	NS	
eGFR (ml min^{-1} 1.73 m^{-2}), mean ± SD	9.3±7.3	9.2±5.8	10.0±15.9	10.1±11.8	9.9±9.6	<0.0001	0.0002
First RRT modality (%)							
HD	84.5	84.1	84.4	84.6	85.5	NS	
PD	11.7	11.6	11.4	11.2	10.2		
Pre-emptive transplant	3.8	4.3	4.2	4.2	4.3		
First dialysis started emergently, %	27.7	26.7	28.7	28.8	27.9	NS	NS
First HD by catheter, %	45.9	45.3	50.4	48.8	51.5	<0.0001	<0.0001
Type 1 diabetes mellitus, *n*	275	265	241	211	180		
Serum haemoglobin (g/l), mean ± SD	102.5±16.5	103.3±17.5	101.4±17.1	103.2±16.8	104.0±16.4	NS	NS
Predialysis ESA treatment (%)	51.0	44.2	57.1	54.8	55.0	NS	NS
Haemoglobin <100 g/l without predialysis ESA treatment, %	57.7	58.3	43.4	56.7	44.2	NS	
eGFR (ml min^{-1} 1.73 m^{-2}), mean ± SD	9.9±7.4	10.9±11.7	9.2±3.7	9.8±4.2	9.3±3.6	NS	NS
First RRT modality (%)							
HD	81.5	78.1	80.5	75.8	76.1	NS	
PD	8.7	12.5	10.8	11.9	11.1		
Pre-emptive transplant	9.8	9.4	8.7	12.3	12.8		
First dialysis started emergently, %	25.2	26.6	23.9	27.1	21.4	NS	NS
First HD by catheter, %	50.0	49.8	44.6	51.2	39.6	NS	NS
Type 2 diabetes mellitus, *n*	2,270	2,489	2,699	2,761	2,745		
Serum haemoglobin (g/l), mean ± SD	103.3±16.3	103.1±16.8	102.2±16.1	102.0±16.0	101.8±16.1	0.004	0.0002
Predialysis ESA treatment, %	50.6	49.8	55.4	52.5	48.0	<0.0001	0.4
Haemoglobin <100 g/l without predialysis ESA treatment, %	55.3	49.7	48.0	50.2	52.4	NS	
eGFR (ml min^{-1} 1.73 m^{-2}), mean ± SD							
All ages	10.1±5.4	10.3±5.9	10.2±5.1	10.7±8.4	10.3±5.5	NS	NS
Age <75 years	9.7±5.5	9.9±6.2	9.8±5.0	10.3±9.9	9.7±4.9	NS	
Age ≥75 years	10.8±5.0	11.0±5.4	10.7±5.2	11.2±5.9	11.1±6.2	NS	
First RRT modality, %							
HD	89.1	90.3	90.3	91.4	91.3	0.02	
PD	10.6	9.1	9.2	8.1	8.1		
Pre-emptive transplant	0.3	0.6	0.5	0.5	0.6		
First dialysis started as emergency, %	33.8	31.2	30.9	33.4	30.9	0.07	NS
First HD by catheter, %	51.8	50.6	51.7	55.2	55.2	0.001	0.0003

[a] Overall *p* value adjusted for age

[b] Cochran–Armitage trend test

attributable to a true increase in new cases. Improved life expectancy of patients with diabetes, due to widespread statin use and improved cardiovascular prevention, may explain this trend. An alternative explanation is the improved access of patients with diabetes to RRT [22–24], which began at a relatively higher residual renal function [25] in competition with cardiac mortality.

We also, however, found a trend towards stabilisation in the youngest age groups and—since 2010 (to be confirmed in years to come)—in men 75 years and older. Potential reasons for this trend are early detection and management of kidney disease, improved diabetes care, and better control of ESRD risk factors, especially blood pressure and glycaemic control [26–30]. These observations not only suggest the existence of

better practice, they also highlight the need to strengthen strategies to prevent or delay the onset of diabetes [31] and diabetic nephropathy [28, 32], especially among groups at high risk, including those older than 75 years.

Diabetes may be the cause of a primary renal disease, defined as diabetic nephropathy, but it can also aggravate the progression of any primary renal disease, so-called diabetes as comorbidity [33]. In the present study, diabetes was considered the primary renal disease in 82% of patients with type 1 diabetes and 54% of those with type 2. These findings must be interpreted cautiously for international comparisons because most diabetic nephropathies are presumptive diagnoses—only 12% of patients with type 1 or type 2 diabetes in our study had had a renal biopsy—and may vary with medical coding practices in the absence of an international operational definition for classifying patients. Furthermore, almost a quarter of patients with type 1 diabetes were obese, which indicates that this group may include some patients with type 2 diabetes.

Our study showed that all comorbidities and disabilities were more common at RRT onset in patients with both types of diabetes. Patients with type 1 diabetes were increasingly younger when RRT started, and those with type 2 increasingly older. However, the proportion of comorbidities remained stable over time in both types of diabetes. The high prevalence of comorbidities may partly explain their poorer prognosis on dialysis and the poorer access to kidney transplantation for patients with type 2 diabetes than for those without [24, 34].

There was no statistically significant difference in the proportions of comorbidities due to atherosclerosis between the two types of diabetes after adjustment for age. Although patients with type 1 diabetes were relatively young, they presumably had a long duration of diabetes and CKD increases the risk of cardiovascular disease. This finding indicates the existence of severe macroangiopathic vascular disease in type 1 diabetes with ESRD. A significant proportion (24%) of patients with type 1 diabetes was obese. Although it cannot be formally proven, this group is likely to include patients with type 2 diabetes. In the latter, these comorbidities coexist with a high proportion of heart failure and dysrhythmias. These conditions, combined with the older age of patients with type 2 diabetes, presumably influenced clinical decisions to start dialysis earlier (eGFR $\geq$10 ml min^{-1} 1.73 m^{-2}) in patients with both types of diabetes [35]. Of note, those with type 2 diabetes begin dialysis earlier, more often on an emergency basis, and have more comorbidities, especially cardiovascular comorbidities. These findings suggest late referral and either poor preparation for dialysis or rapid decompensation of their cardiopathy. In contrast, patients with type 1 diabetes are less likely to start dialysis as an emergency, probably because they are already part of the healthcare system and, indeed, accustomed to close follow-up.

In contrast with other studies [36, 37], but confirming a previous report in France [38], we found no association between predialysis haemoglobin levels and diabetes status. In its latest guideline update in 2010, the ERBP group [18] proposed a haemoglobin target of 110–120 g/l in patients with CKD not on dialysis. Although a significant proportion (~50%) of patients, with or without diabetes, receive ESA before dialysis, most fail to achieve the current recommended goal. This fact is generally viewed as an indicator of suboptimal predialysis care. Low haemoglobin levels might also, however, be a proxy for chronic inflammation and/or ESA resistance, which has been associated with poor outcomes in prospective trials [39, 40].

We showed that treatment modalities have not changed significantly since 2007. Patients with type 1 diabetes remain more likely to receive pre-emptive kidney transplants or to start with PD than those with type 2 or without diabetes. No evidence-based results favour HD or PD in patients with or without diabetes. The choice of one technique over another is usually based on the indications and contraindications of each treatment technique after taking into account the patient's preference, geographic distance from an HD unit, and patient education. However, PD is more often the first-choice modality for patients who are expected to be transplanted quickly, in particular, those with type 1 diabetes, who are likely to be transplanted in France because of a national priority for combined kidney/pancreas recipients. Conversely, patients with type 2 diabetes are increasingly older, obese, and have multiple cardiovascular comorbidities (~70% per year; see ESM Table 3), factors that discourage doctors and patients from choosing PD rather than HD.

Major strengths of this study include the nationwide design of the REIN registry, which now covers 25 regions and more than 65 million people—98% of the French population. Another significant strength is that this analysis takes both diabetic nephropathy and comorbidities into account for documenting diabetes. It also differentiates between the two types of diabetes mellitus, which has the advantage of highlighting the specificities of each type.

This national population-based dialysis and transplantation registry cannot be used to determine anything directly about the risk of ESRD in cohorts of type 1 and type 2 diabetes. Other limitations of this study include not having details on ethnicity or the duration of diabetes and our inability to differentiate accurately between diabetic nephropathy and other types of nephropathy because of the low rate of renal biopsy in France. This disadvantage is inherent in most countries, as routine biopsies are invasive and not medically useful. Furthermore, because registry coverage has expanded progressively, incidence trends are available only for continental France. Therefore, these trends may not be representative of those in the French overseas territories, where the incidence of ESRD and the prevalence of diabetes are very high. However, we believe that this study provides an accurate estimation of the burden and trends in care for patients treated for ESRD

associated with either type 1 or type 2 diabetes or not associated with diabetes over the past 5 years.

In summary, the skyrocketing incidence of ESRD in France and probably in other Western countries was found to be due exclusively to an actual increase in that related to type 2 diabetes, especially in elderly patients. There remain, however, wide regional disparities in incidence according to the background population characteristics and medical practices. Our data demonstrate the need to reinforce strategies for optimal management of patients with diabetes to improve prevention, or delay the onset, of diabetic nephropathy, ESRD and cardiovascular comorbidities, and to reduce the rate of emergency dialysis. This would aid significantly in reducing costs and improving the survival and quality of life of these patients.

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Contribution statement FGAA designed the study, acquired data, carried out statistical analyses, interpreted data and drafted the manuscript. BS, CC, TH, EV, AF-C, CJ and LF contributed to the conception and design of the study and interpretation of data. All authors critically revised earlier drafts of the manuscript and approved the final version of the manuscript.

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