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ORIGINAL ARTICLE

Stroke risk in ADPKD patients treated by dialysis: a retrospective study

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ABSTRACT

Background and hypothesis. The risk of ischaemic or haemorrhagic strokes in patients living with end-stage renal disease and receiving replacement therapy is more than double that of non-dialysed individuals. Autosomal dominant polycystic kidney disease (ADPKD) is an inherited systemic disorder associated with renal and non-renal manifestations, including intracerebral aneurysms. The role of underlying nephropathy in determining the onset of the stroke is unclear.
Methods. All patients who started dialysis between 1 January 2015 and 31 December 2019 were included in the analysis. Data were retrieved from the REIN registry and the French national Health Data System (SNDS). Cases of stroke were extracted from the SNDS by using ICD-10 codes. The first stroke observed during the follow-up, irrespective of its nature, was considered as the event of the main analysis, based on a semi-parametric survival model.
Results. The analysis included 40 980 patients on dialysis. Overall, 1549 patients experienced stroke during the follow-up. The first stroke was ischaemic in 1148 (74.1%) and haemorrhagic in the remaining 281 patients. The cumulative incidence of stroke on dialysis was 1.58 per 100 person-years (95% CI = 1.51, 1.70). Among 2182 ADPKD patients, only 44 (2%) experienced stroke. ADPKD was not significantly associated with an increased risk of all types of stroke, after considering major risk factors.
Conclusions. We found no increase in the risk of stroke in ADPKD patients under dialysis. We believe that the findings of our study support a similar screening strategy in ADPKD patients on dialysis compared with patients not on dialysis.

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GRAPHICAL ABSTRACT

Clinical Kidney Journal

Stroke risk in ADPKD patients treated by dialysis: a retrospective study

The role of underlying nephropathy in the risk of stroke is poorly known. Autosomal dominant polycystic kidney disease (ADPKD) is associated with renal and non-renal manifestations, that may lead to haemorrhagic or ischaemic stroke.

Methods

Retrospective nationwide cohort study

Dialysed patients
Jan 1 2015–Dec 31 2019

REIN + SNDS
N = 40,980

SNDS

ADPKD+
N = 2182

ADPKD–
N = 38,798

STROKE–
N = 2138

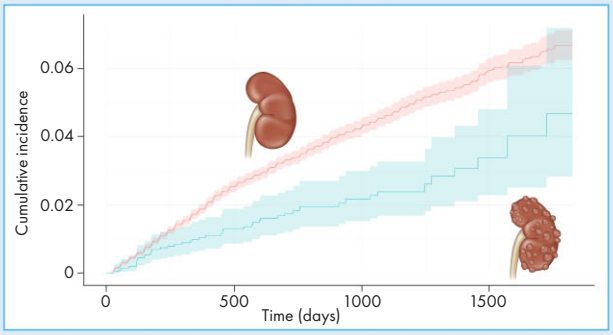
STROKE+
N = 44

STROKE+
N = 1505

STROKE–
N = 37,293

REIN: Dialysis registry
SNDS: French Health Insurance System Database

Results



Incidence rate (95% CI) per 100 PY of stroke (all types)
Non-ADPKD: 1.62 (1.54; 1.70)
ADPKD: 0.89 (0.65; 1.19)

AVC type	aHR (95% CI)
Ischaemic	0.65 (0.46; 0.96)
Haemorrhagic	1.40 (0.85; 2.29)

Conclusion: ADPKD does not carry an increased risk of ischaemic or haemorrhagic stroke compared to other nephropathies, even after adjusting for major confounding factors and dialysis treatment (peritoneal or haemodialysis).

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Keywords: autosomal dominant polycystic kidney disease, dialysis, haemorrhagic stroke, ischaemic stroke, renal replacement therapy

KEY LEARNING POINTS

What was known:

- The risk of stroke in patients living with end-stage renal disease, receiving renal replacement therapy, is more than double that of non-dialysed individuals. While the role of modifiable risk factors is well established, there is a lack of data regarding the role of underlying nephropathy in the risk of stroke.
- Autosomal dominant polycystic kidney disease (ADPKD) is an inherited systemic disorder associated with renal and non-renal manifestations, including intracerebral aneurysms (ICAs), whose rupture may result in subarachnoid haemorrhage or intracranial haemorrhage. ADPKD patients tend to experience ICA ruptures one decade earlier than other ICA patients.
- Hypertensive intracranial haemorrhage and ischaemic stroke represent one of the leading causes of death among ADPKD patients.

This study adds:

- ADPKD is a rare disease. Our study, carried out on national administrative databases, has sufficient power to study risk factors associated with events, like stroke, observed in this population.
- We estimated the incidence and risk of stroke (ischaemic or haemorrhagic) after adjustment for main risk factors, including age, sex, comorbidities and past medical history, and we also considered common modifiable factors.

Potential impact:

- ADPKD patients have no increased risk of stroke compared with patients with other nephropathies.
- The findings of our study support the practice of a similar screening strategy in ADPKD patients on dialysis compared with patients not on dialysis.
- Dialysis treatment (peritoneal or haemodialysis) does not seem associated with a greater risk of stroke for ADPKD patients and treatment choice should not induce screening for ICA in ADPKD patients.

INTRODUCTION

The risk of ischaemic or haemorrhagic stroke in patients living with end-stage renal disease (ESRD) and receiving renal replacement therapy is more than double that of non-dialysed individuals [1], and it is characterized by an earlier onset [2]. The modifiable risk factors associated with stroke in dialysed patients are similar to those identified in the general population. Tobacco consumption and diabetes mellitus are associated with ischaemic stroke [3, 4]. Hypertension is a risk factor for both ischaemic and haemorrhagic strokes [5].

There is a lack of data regarding the role of underlying nephropathy in the risk of stroke. Autosomal dominant polycystic kidney disease (ADPKD) is an inherited systemic disorder due to mutations in two main genes, *PKD1* and *PKD2* [6]. In ADPKD, the kidney is affected by the progressive onset and growth of tubular cysts, often leading to renal failure [7]. ADPKD is the fourth most common cause of initiation of dialysis worldwide [7, 8].

The association of intracerebral aneurysms (ICAs) with ADPKD has been mainly attributed to the direct consequences of mutations in *PKD1* or *PKD2* in the arteries rather than to hypertension [9, 10]. Polycystins 1 and 2 (PC1/PC2) are detected in both vascular smooth muscle cells and endothelial cells of all major vessels, including intracranial arteries [11]. Approximately 11% of ADPKD patients harbour an unruptured ICA [12], with an estimated rupture rate of ∼10 000 person-years [13], similar to that of the general population with ICA [14, 15]. However, due to the high prevalence of ICA in ADPKD, these patients are at increased risk of ICA rupture [16]. A ruptured ICA is a potentially life-threatening complication of ADPKD, and it may result in subarachnoid haemorrhage (SAH) or intracranial haemorrhage (ICH). The average age of patients who experience ICA rupture has been reported to be close to that of patients with other familiar forms of intracranial aneurysm [17] but a decade lower than that of patients with the reported sporadic form. Independent of ADPKD status, rupture is associated with considerable morbidity and mortality [18–21]. An early review [22] analysing the causes of death among ADPKD patients revealed that 6% of patients were affected by the rupture of an intracranial aneurysm, 5% by hypertensive intracranial haemorrhage, and 1% by ischaemic stroke. At the same time, other risk factors, such as hypertension, which is highly prevalent in ADPKD, may increase the risk of stroke in this population.

Indeed, most acute neurological events affecting patients with ADPKD do not result from ICA rupture but from primary hypertensive intracranial haemorrhage or ischaemic stroke [23]. Haemorrhagic strokes, when not associated with ICA rupture, are mostly due to hypertension and represent one of the leading causes of death in this population of patients [24]. In addition to thrombosis and embolisms, which are often associated with new-onset atrial fibrillation [25], ischaemic stroke can be caused by intracranial arterial dolichoectasia [26], and the prevalence of microbleeds is approximately one-fourth that in ADPKD patients compared with non-ADPKD patients, indicating the fragility of cerebral vessels [27]. However, few studies have investigated the association between brain ischaemia and ADPKD.

The objective of the study was to estimate whether ADPKD, compared with other causes of ESRD, was a risk factor for stroke in patients treated with dialysis.

MATERIALS AND METHODS

Databases

This retrospective study used data prospectively retrieved from the Renal Epidemiology and Information Network (REIN) registry and the French National Health Data System (Système National des Données de Santé, SNDS).

The French REIN registry is a national database that includes all ESRD patients who have undergone dialysis since 2003 [28]. The SNDS is the central administrative database of the French healthcare system [29]. All outpatient reimbursed health care expenditures and inpatient hospital discharge data were included.

A deterministic iterative approach was used to link the REIN registry and the SNDS [30]. Biological and clinical data are systematically collected by the registry when the patient starts renal replacement treatment (RRT). Information about stroke events was retrieved from the hospitalization data provided by the SNDS.

Selection of participants

All patients aged 18 years and older who started dialysis between 1 January 2015 and 31 December 2019 were included in the analysis.

Data collection and variables

The following four types of variables were included in the descriptive analysis: (i) demographic data—age and sex; (ii) biological and clinical data at dialysis initiation—comorbidities such as diabetes and cardiovascular disease (heart failure, coronary artery disease, myocardial infarction, arrhythmias, and abdominal aortic aneurysm); tobacco consumption (current versus former or never smoking); serological status for HBV, HCV, and HIV; body mass index (BMI), categorized as $<$18.5, 18.5–25, 25–30 and $>$30 kg/m^2; and aetiology of RRT (ADPKD versus others); (iii) date and type of RRT at inclusion (peritoneal dialysis or haemodialysis); and (iv) death and date of death.

Events of interest

All cases of ischaemic and haemorrhagic cerebral events that occurred after dialysis initiation until December 2019 were extracted from the SNDS. Each hospital stay is described in the Uniform Hospital Discharge Data Set Database (PMSI) by specifying diseases treated using codes from the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10); a first code is used to identify the main diagnosed pathology, and a second one for the associated pathologies. Only the main diagnosis codes were used to identify incident events.

Haemorrhagic strokes were identified using the I60 (subarachnoid haemorrhage) and I61 (non-traumatic intracerebral haemorrhage) ICD-10 codes. Ischaemic strokes were identified using the G45 (transient ischaemic stroke and related syndromes), G46 (cerebrovascular syndromes in the course of cerebrovascular diseases), and I63 (cerebral infarction) ICD-10 codes. Only the first hospitalization associated with each event type (ischaemic, haemorrhagic, or undefined) was considered

in the analysis, and the date of stroke onset was considered the date of hospital admission.

The death status and date were reported in the REIN database.

Statistical analysis

The end date of the study was 31 December 2019. For the main analysis, only the first stroke observed during follow-up, irrespective of its nature (ischaemic, haemorrhagic), was considered. Patients were censored at the time of transplantation, death, or the end of follow-up. The participation time of each patient was calculated as the time between dialysis initiation and the first event between stroke, transplantation, death, and the end of follow-up.

Incidence of stroke of all types, ischaemic or haemorrhagic, were calculated as new events during the follow-up per 100 person-years.

Two complementary analyses were also performed, each focusing on one type of stroke (ischaemic or haemorrhagic) separately. In these complementary analyses, the first event of the selected type of stroke was considered an outcome, irrespective of the occurrence of any other type of stroke occurring earlier during the follow-up. Hence, a patient experiencing two types of strokes during follow-up contributed differently to the three analyses.

Missing data (up to 14%) followed a missing at random (MAR) pattern, allowing a multiple imputation procedure to provide unbiased and valid estimates of the associations. Ten iterations were used. Each Cox model, bivariate or multivariate, was performed on 20 imputed datasets, and their results were pooled by Rubin's rules. The hypothesis of the linear association between event indicators and times was tested by replacing event time by its non-linear function, the cumulative baseline hazard [31], in the imputation model.

The Cox proportional hazard risk model was used in both bivariate and multivariate analyses to estimate hazard ratios (HRs) and their 95% confidence intervals (95% CIs). The main analysis focused on cerebrovascular events, irrespective of aetiology. Secondary analyses were performed for both ischaemic (G45, G46 or I63) and haemorrhagic (I60 or I61) events separately. These models were mutually blind to the occurrence of events of opposite aetiologies, meaning that only the first event, ischaemic or haemorrhagic, irrespective of previous events of different aetiologies, was considered for the analysis. This may have led to different event counts and follow-up times. In the haemorrhage event analysis, time to event was calculated as the time between inclusion and cerebral haemorrhage, despite the possibility that patients might have experienced an ischaemic event before. We applied the same strategy for ischaemic event analysis. A P value <0.05 was considered to indicate statistical significance. All analyses were run in R 4.3.1 (The R Foundation for Statistical Computing) and RStudio 2023.06.1 build 524 (Posit Software, PBC).

Sensitivity analysis

Sensitivity analyses for the occurrence of a first ischaemic or haemorrhagic event and for first ischaemic and haemorrhagic events alone were performed by excluding all patients affected by diabetes, which was intended to be a comorbidity or aetiological cause of nephropathy.

As stroke could lead to death without hospitalization, a sensitivity analysis for the composite endpoint of first cerebral event (SNDS) or cerebrovascular-related death (REIN), was performed.

Ethics approval and consent to participate

This French REIN registry received approval from the National Committee for Civil Liberties and Data Protection, CNIL (approval no. 903 188). This study was conducted within the framework of this authorization.

Data from the SNDS are linked to the registry through an iterative algorithm that guarantees its anonymity. Both data sources are provided by the Agence de la Biomédecine.

RESULTS

Patient characteristics

Between 2015 and 2019, 40 980 patients aged over 18 years who were on dialysis and successfully linked to the SNDS were identified (Fig. 1 and Table 1). The patients' mean age at the beginning the treatment was 68 ± 15 years. Approximately 5% of patients had ADPKD. Among other causes of ESRD, diabetic and so-called hypertensive nephropathies were the most represented, accounting for 23.3% and 25.8%, respectively. Patients affected by ADPKD were significantly younger than patients affected by other nephropathies (59.6 ± 12.8 versus 69.1 ± 14.8), were more likely to be women, were less likely to be exposed to active smoking and to have a BMI ≥30. Cardiovascular disease and diabetes were also less common in the ADPKD population (26.7% versus 52.4% and 9.2% versus 48.3%, respectively).

At the end of follow-up, 12 861 (31.4%) patients had died on dialysis, and 4993 (12.2%) had undergone transplantation. The mean follow-up time was 2.39 years.

Ischaemic or haemorrhagic stroke (all events)

Overall, 1549 patients experienced stroke during follow-up; the first stroke was ischaemic in 1148 (74.1%) patients and haemorrhagic in the remaining 281 patients. The cumulative incidence of stroke on dialysis was 1.58 per 100 person-years (95% CI = 1.51, 1.70) in the cohort, and 0.89 per 100 person-years (95% CI = 0.65, 1.19) and 1.62 per 100 person-years (95% CI = 1.54, 1.70) in ADPKD and other ESRD patients, respectively (Fig. 2). Among the 2182 ADPKD patients, only 44 (2%) experienced stroke. They were more frequently ischaemic (35%) than haemorrhagic, subarachnoid, or intracerebral (7.1 and 28.6%, respectively). Transient ischaemic attack rate was 28.6%.

According to the bivariate analysis, ADKPD patients were less likely to develop ischaemic or haemorrhagic stroke (HR, 0.54; 95% CI = 0.40, 0.73). The risk of stroke increased with age (HR = 1.03, 95% CI = 1.02, 1.03), in diabetic patients (HR = 1.30; 95% CI = 1.17, 1.44), and in those with a history of cardiovascular disease (HR = 2.23, 95% CI = 1.99, 2.49). Women had an increased risk of stroke (HR = 1.16, 95% CI = 1.05, 1.28), and the risk of stroke tended to decrease with increasing BMI.

In the multivariate analysis, after adjustment for sex, age, active smoking status, cardiovascular disease history, and diabetes status, the association between ADPKD and the risk of stroke decreased but remained close to significant (HR = 0.77, 95% CI = 0.57, 1.43; P = 0.08) (Table 2). When the event of interest was defined as either stroke-related hospitalisation (SNDS database) or death due to cerebrovascular causes (REIN registry, which adds 177 additional events to the SNDS data), there were

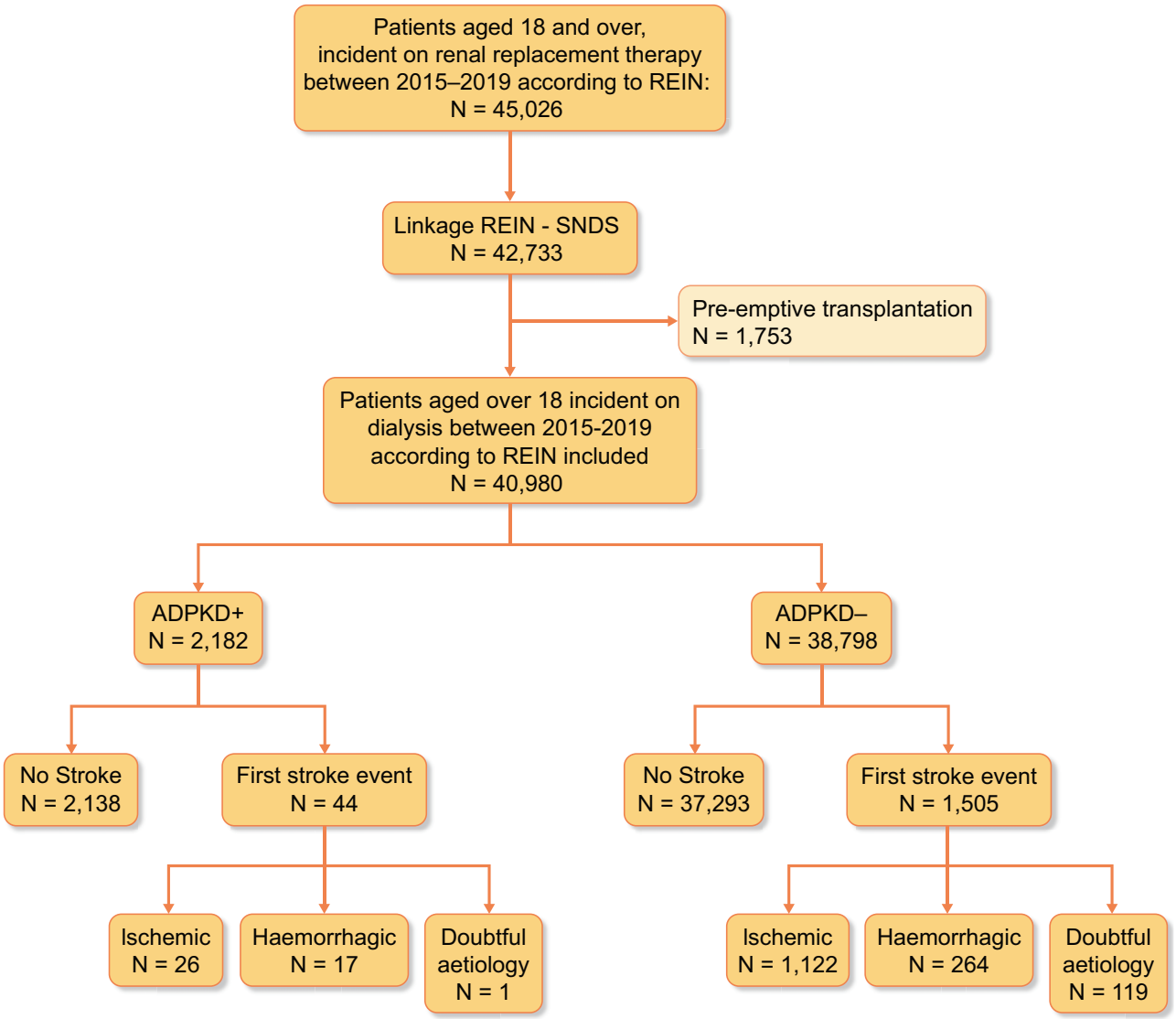

Figure 1: Flow chart of the population.

no differences in the statistical significance of the results (not shown).

A sensitivity analysis excluding diabetic patients revealed no significant difference in the risk of stroke between ADPKD patients and non-diabetic ESRD patients in the multivariate analysis (Fig. 3 and Table 3). The risk of stroke was increased in patients who underwent peritoneal dialysis in the main analysis but not when the analysis was restricted to non-diabetic ESRD patients.

Ischaemic stroke

Overall, 1 172 patients experienced at least one ischaemic stroke (Table 4) during follow-up. The risk of ischaemic stroke increased with age, female sex, and history of cardiovascular disease. A weak instantaneous risk of ischaemic stroke [adjusted HR (aHR) = 1.29, 95% CI = 1.07, 1.54] was observed for patients treated by peritoneal dialysis compared with patients treated by haemodialysis. Patients affected by ADPKD had a 45% lower risk of experiencing an ischaemic event than patients affected by other nephropathies (HR = 0.65, 95% CI = 0.45, 0.96). Sensitivity analysis excluding diabetic patients (Table 5) revealed similar results, with a greater risk of ischaemic events among older patients and those with a history of cardiovascular disease (aHR = 2.37, 95% CI = 1.91, 2.93). ADPKD was not associated with stroke (aHR = 1.11, 95% CI = 0.85, 1.45) in the non-diabetic population.

Haemorrhagic stroke

Overall, 297 patients experienced at least one haemorrhagic stroke during follow-up (Table 6). Only diabetes (HR = 1.44, 95% CI = 1.08, 1.81) and history of cardiovascular disease (HR = 1.41, 95% CI = 1.08, 1.83) were significantly associated with an increased risk of stroke, while high BMI lowered it (HR = 0.34, 95% CI = 0.22, 0.87). The hazard ratios for ADPKD were 1.40 (95%

Table 1: Sociodemographic and clinical characteristics of the population.

	N = 40 980	ADPKD (−) (n = 38 798)	ADPKD (+) (n = 2182)	P-value
Sociodemographic characteristics				
Age, mean (SD)	68.62 (14.86)	69.13 (14.80)	59.61 (12.83)	<0.001
Sex				<0.001
Male	26 414 (64.5)	25 270 (65.1)	1144 (52.4)	
Female	14 566 (35.5)	13 528 (34.9)	1038 (47.6)	
BMI				<0.001
<18.5	1436 (4.1)	1378 (4.2)	58 (3.0)	
18.5–25	13 617 (39.0)	12 738 (38.7)	879 (45.2)	
25–30	11 081 (31.8)	10 429 (31.6)	652 (33.6)	
≥30	8762 (25.1)	8408 (25.5)	354 (18.2)	
Missing	*6084*	*5845*	*239*	
Active smoking				<0.001
No	19 359 (56.7)	18 182 (56.4)	1177 (62.3)	
Yes	14 770 (43.3)	14 057 (43.6)	713 (37.7)	
Missing	*6851*	*6559*	*292*	
Nephropathy and dialysis				
Nephropathy				
ADPKD	2182 (5.3)			
Diabetes	9560 (23.3)			
Primitive glomerulonephritis	4537 (11.1)			
Hypertension	10 578 (25.8)			
Unknown	6619 (16.2)			
Pyelonephritis	1750 (4.3)			
Vascular	288 (0.7)			
Other	5466 (13.3)			
Dialysis type				<0.001
Haemodialysis	36 682 (89.5)	34 789 (89.7)	1893 (86.8)	
Peritoneal dialysis	4298 (10.5)	4009 (10.3)	289 (13.2)	
Emergency first treatment				<0.001
No	28 146 (72.1)	26 280 (71.1)	1866 (88.6)	
Yes	10 913 (27.9)	10 672 (28.9)	241 (11.4)	
Missing	*1921*	*1846*	*75*	
First haemodialysis on catheter				<0.001
No	17 331 (45.9)	15 893 (44.4)	1438 (72.1)	
Yes	20 458 (54.1)	19 901 (55.6)	557 (27.9)	
Missing	*3191*	*3004*	*187*	
Erythropoietin				0.256
No	18 266 (52.5)	17 259 (52.5)	1007 (53.9)	
Yes	16 497 (47.5)	15 634 (47.5)	863 (46.1)	
Missing	*6217*	*5905*	*312*	
Treatment method				<0.001
Haemodialysis	29 149 (71.1)	27 623 (71.2)	1526 (69.9)	
Haemofiltration	63 (0.2)	63 (0.2)	0 (0.0)	
Haemodiafiltration	7424 (18.1)	7062 (18.2)	362 (16.6)	
Automated peritoneal dialysis	958 (2.3)	838 (2.2)	120 (5.5)	
Outpatient continuous peritoneal dialysis	3336 (8.1)	3167 (8.2)	169 (7.7)	
Acetate-free haemodialysis	28 (0.1)	27 (0.1)	1 (0.0)	
Intermittent peritoneal dialysis	4 (0.0)	4 (0.0)	0 (0.0)	
Low-flow daily haemodialysis	18 (0.0)	14 (0.0)	4 (0.2)	
Vascular access				<0.001
Native arteriovenous fistula	16 732 (45.9)	15 389 (44.5)	1343 (71.2)	
Tunnelled catheter	17 038 (46.7)	16 591 (47.9)	447 (23.7)	
Bridging	480 (1.3)	442 (1.3)	38 (2.0)	
Other	2239 (6.1)	2181 (6.3)	58 (3.1)	
Missing	*4491*	*4195*	*296*	
Comorbidities				
Diabetes				<0.001
No	21 804 (53.8)	19 829 (51.7)	1975 (90.8)	
Yes	18 751 (46.2)	18 551 (48.3)	200 (9.2)	
Missing	*425*	*418*	*7*	

Table 1: Continued

	N = 40 980	ADPKD (−) (n = 38 798)	ADPKD (+) (n = 2182)	P-value
History of cardiovascular disease				<0.001
No	18 614 (49.0)	17 087 (47.6)	1527 (73.3)	
Yes	19 374 (51.0)	18 819 (52.4)	555 (26.7)	
Missing	*2992*	*2892*	*100*	
Chronic respiratory failure				<0.001
No	34 265 (86.3)	32 239 (85.8)	2026 (94.9)	
Yes	5451 (13.7)	5341 (14.2)	110 (5.1)	
Missing	*1264*	*1218*	*46*	
Cardiac failure				<0.001
No	29 487 (74.0)	27 534 (73.0)	1953 (91.5)	
Yes	10 361 (26.0)	10 179 (27.0)	182 (8.5)	
Missing	*1132*	*1085*	*47*	
Coronary failure				<0.001
No	29 754 (74.9)	27 815 (74.0)	1939 (90.7)	
Yes	9994 (25.1)	9795 (26.0)	199 (9.3)	
Missing	*1232*	*1188*	*44*	
Myocardial stroke				<0.001
No	35 465 (89.2)	33 414 (88.8)	2051 (95.9)	
Yes	4286 (10.8)	4199 (11.2)	87 (4.1)	
Missing	*1229*	*1185*	*44*	
Arrhythmias				<0.001
No	30 489 (76.4)	28 555 (75.6)	1934 (90.4)	
Yes	9419 (23.6)	9213 (24.4)	206 (9.6)	
Missing	*1072*	*1030*	*42*	
Abdominal aorta aneurysm				<0.001
No	37 484 (96.2)	35 417 (96.1)	2067 (98.1)	
Yes	1493 (3.8)	1452 (3.9)	41 (1.9)	
Missing	*2003*	*1929*	*74*	
Lower limb arteritis				<0.001
No	31 219 (79.7)	29 217 (78.8)	2002 (94.4)	
Yes	7969 (20.3)	7851 (21.2)	118 (5.6)	
Missing	*1792*	*1730*	*62*	
Stroke and transient ischaemic attack				<0.001
No	35 276 (88.4)	33 328 (88.3)	1948 (90.9)	
Yes	4626 (11.6)	4432 (11.7)	194 (9.1)	
Missing	*1078*	*1038*	*40*	
Cancer				<0.001
No	35 570 (89.1)	33 520 (88.7)	2050 (95.8)	
Yes	4372 (10.9)	4283 (11.3)	89 (4.2)	
Missing	*1038*	*995*	*43*	
Impairment (physical or intellectual)				<0.001
No	32 892 (85.0)	30 937 (84.5)	1955 (93.9)	
Yes	5808 (15.0)	5680 (15.5)	128 (6.1)	
Missing	*2280*	*2181*	*99*	
Paraplegia or hemiplegia				<0.001
No	37 032 (98.3)	34 994 (98.3)	2038 (99.0)	
Yes	633 (1.7)	612 (1.7)	21 (1.0)	
Missing	*3315*	*3192*	*123*	
Blindness				<0.001
No	36 336 (96.4)	34 295 (96.2)	2041 (99.3)	
Yes	1375 (3.6)	1360 (3.8)	15 (0.7)	
Missing	*3269*	*3143*	*126*	
Follow-up and event				
Last follow-up status				<0.001
Death	12 861 (31.4)	12 640 (32.6)	221 (10.1)	
Dialysis	22 001 (53.7)	20 911 (53.9)	1090 (50.0)	
Transplantation	4993 (12.2)	4140 (10.7)	853 (39.1)	
Lost to follow-up	365 (0.9)	357 (0.9)	8 (0.4)	
Withdrawal	760 (1.9)	750 (1.9)	10 (0.5)	
Mean follow-up time (days), mean (SD)	871.53 (508.7)	874.01 (509.7)	827.54 (490.3)	<0.001
Ischaemic or haemorrhagic event				<0.001
No	39 431 (96.2)	37 293 (96.1)	2138 (98.0)	
Yes	1549 (3.8)	1505 (3.9)	44 (2.0)	

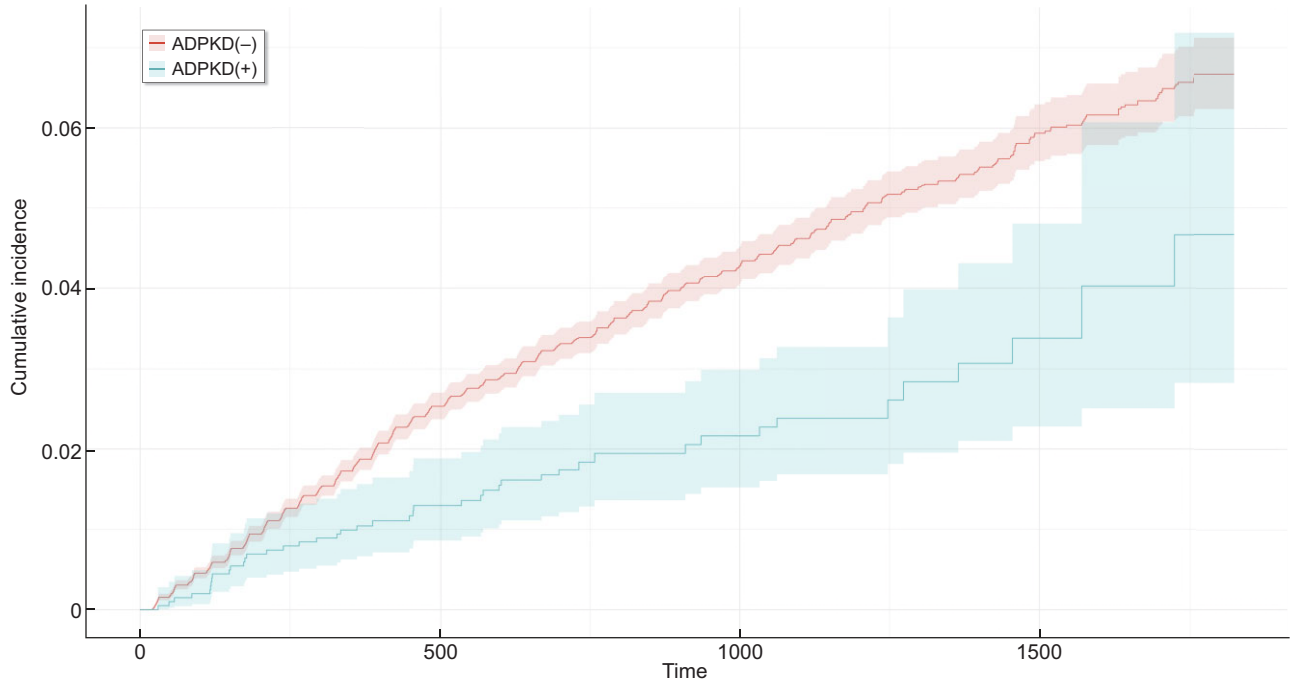

Figure 2: Cumulative incidence of ischaemic or haemorrhagic events according to ADPKD status.

Table 2: First ischaemic or haemorrhagic event ($n = 1549$) in the whole population ($N = 40\,980$).

		Unadjusted HR	P-value	Adjusted HR	P-value
Age		1.03 (1.02, 1.03)	<0.001	1.01 (1.01, 1.02)	<0.001
Sex, female	616	1.16 (1.05, 1.28)	0.004	1.27 (1.13, 1.41)	<0.001
BMI			<0.001		<0.001
18.5–25	541	0.91 (0.71, 1.19)		0.81 (0.62, 1.05)	
25–30	407	0.81 (0.62, 1.06)		0.66 (0.50, 0.87)	
>30	293	0.68 (0.52, 0.91)		0.54 (0.41, 0.72)	
Active smoking	545	0.95 (0.85, 1.07)	0.39	0.97 (0.86, 1.10)	0.69
Diabetes	826	1.30 (1.17, 1.44)		1.25 (1.13, 1.41)	<0.001
History of cardiovascular disease	971	2.23 (1.99, 2.49)	<0.001	1.96 (1.74, 2.22)	<0.001
Peritoneal dialysis	171	1.18 (1.00, 1.38)	0.05	1.20 (1.02, 1.41)	0.02
ADPKD	44	0.54 (0.40, 0.73)	<0.001	0.77 (0.57, 1.43)	0.08

CI = 0.85, 2.29) and 1.54 (95% CI = 0.92, 2.60) when diabetic patients were excluded from the analysis (Table 7), which could be explained by a loss of power in the analysis.

DISCUSSION

In our large retrospective study of the French population of ESRD patients on dialysis between 2015 and 2019, we did not observe a substantial difference in the instantaneous risk of stroke between ADPKD patients and non-ADPKD patients. However, in ADPKD patients who presented with at least one first stroke while on dialysis, the aetiology of this event was more frequently haemorrhagic than in non-ADPKD patients (38.6% versus 17%).

When considering the risk of ischaemic events, compared with other nephropathies, ADPKD was associated with a decreased risk of stroke in the multivariate analysis. Since atrial fibrillation is a main driver of ischaemic stroke and previous studies have suggested that the risk of atrial fibrillation is greater in ADPKD than in other nephropathies [32, 33], we could have expected a greater risk of ischaemic events in our ADPKD population than in patients affected by other nephropathies. Age is also an important risk factor for ischaemic stroke. The median age was lower in the ADPKD group than in the non-ADPKD group. However, a lower risk of ischaemic events in ADPKD patients persisted after adjustment for age.

Because of the higher incidence of ICA rupture in this population [16], the high prevalence of hypertension [34] and the use of anticoagulation during haemodialysis, we could have expected an association between ADPKD and haemorrhagic stroke. However, ADPKD was not significantly associated with an increase in the risk of haemorrhagic events in our study. ICA rupture is a rare event, and this result could be explained by the lack of statistical power in this analysis or by an insufficient duration of follow-up,

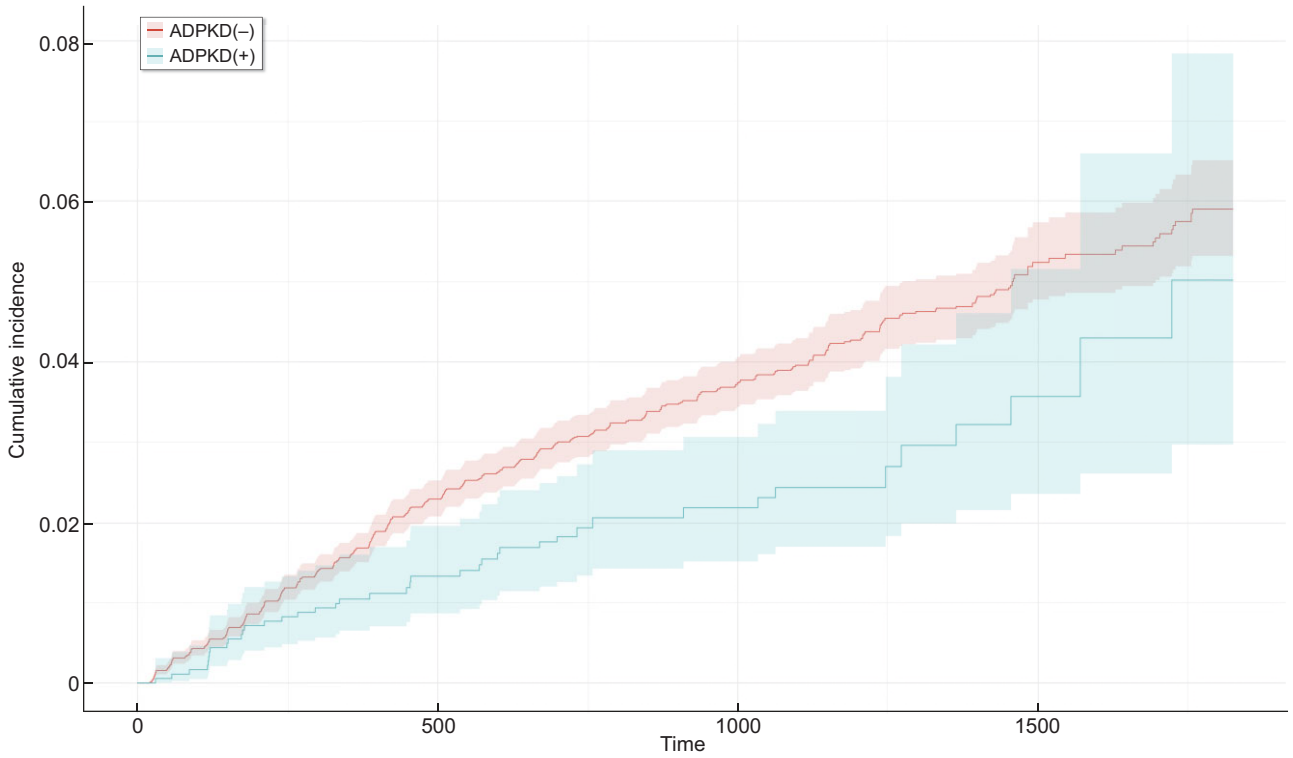

Figure 3. Cumulative incidence of ischaemic or haemorrhagic events according to ADPKD status in non-diabetic patients.

Table 3: First ischaemic or haemorrhagic event ($n = 706$) in the non-diabetic population ($N = 21\,804$).

		Unadjusted HR	*P*-value	Adjusted HR	*P*-value
Age		1.03 (1.02, 1.04)	*<0.001*	1.02 (1.01, 1.03)	*<0.001*
Sex, female	269	1.10 (0.93, 1.27)	*0.28*	1.20 (1.02, 1.42)	*0.03*
BMI			*<0.001*		*<0.001*
18.5–25	328	0.89 (0.66, 1.23)		0.82 (0.60, 1.14)	
25–30	163	0.71 (0.51, 0.99)		0.65 (0.46, 0.91)	
>30	58	0.47 (0.31, 0.71)		0.47 (0.33, 0.71)	
Active smoking	115	0.97 (0.82, 1.13)	*0.66*	0.94 (0.79, 1.04)	*0.40*
History of cardiovascular disease	425	2.58 (2.20, 3.02)	*<0.001*	2.13 (1.80, 2.54)	*<0.001*
Peritoneal dialysis	73	0.97 (0.75, 1.23)	*0.77*	0.97 (0.76, 1.24)	*0.82*
ADPKD	41	0.64 (0.46, 0.88)	*0.009*	0.88 (0.64, 1.21)	*0.41*

since in a previous study an increased risk was detected only after 3 years on dialysis. Another explanation could be the differences in ICA screening habits between ADPKD patients and the general population of patients with ESRD. At the time of the study the Kidney Disease Improving Global Outcomes (KDIGO) expert panel indeed recommended screening for an intracranial aneurysm in selected ADPKD patients, especially in the case of a family history of ICA rupture [35]. Finally, in our study, dialysis was initiated in ADPKD patients long after the median age of ICA rupture [36, 37] observed in ADPKD, when the adjusted excess of cerebrovascular risk compared with that in the non-ADPKD population is lower [38], suggesting the possibility of an immortality bias that could affect the ability to make evidence-based conclusions in clinical scenarios [39].

Dialysis type has long been considered a potential risk factor for stroke events. In contrast to other studies, we did not find an increased risk of haemorrhagic stroke in haemodialysed patients [40], compared with patients treated by peritoneal dialysis. The increased risk of ischaemic stroke in patients on peritoneal dialysisis consistent with studies conducted in non-Asian countries [41].

Longitudinal epidemiological studies on large populations are essential for obtaining a comprehensive view of a medical issue. Administrative databases, matched with registries, can provide validated epidemiological data [40, 41].

Limitations

Our study has several limitations. First, the relatively short follow-up and lack of data after transplantation. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was used for diagnosis, limiting the identification of stroke events only to hospitalizations. However, this kind of event leads to hospitalization

Table 4: First ischaemic event ($n = 1172$) in the whole population ($N = 40\,980$). Multiple imputation.

		Unadjusted HR	P-value	Adjusted HR	P-value
Age		1.03 (1.03, 1.04)	<0.001	1.03 (1.02, 1.03)	<0.001
Sex, female	485	1.24 (1.11, 1.40)	<0.001	1.38 (1.21, 1.57)	<0.001
BMI			0.11		0.004
18.5–25	398	0.97 (0.71, 1.32)		0.85 (0.62, 1.16)	
25–30	322	0.94 (0.68, 1.29)		0.77 (0.55, 1.05)	
>30	237	0.81 (0.58, 1.12)		0.64 (0.46, 0.90)	
Active smoking	417	0.95 (0.84, 1.08)	0.49	1.01 (0.87, 1.17)	0.91
Diabetes	632	1.33 (1.19, 1.50)	<0.001	1.23 (1.08, 1.40)	0.001
History of cardiovascular disease	761	2.46 (2.15, 3.82)	<0.001	2.09 (1.81, 2.41)	<0.001
Peritoneal dialysis	139	1.27 (1.07, 1.52)	0.007	1.29 (1.07, 1.54)	0.005
ADPKD	27	0.44 (0.30, 064)	<0.001	0.65 (0.45, 0.96)	0.03

Table 5: First ischaemic event ($n = 527$) in the non-diabetic population ($N = 21\,804$). Multiple imputation.

		Unadjusted HR	P-value	Adjusted HR	P-value
Age		1.04 (1.03, 1.05)	<0.001	1.03 (1.02, 1.03)	<0.001
Sex, female	202	1.10 (0.92, 1.31)	0.20	1.26 (1.04, 1.54)	0.02
BMI			0.012		0.02
18.5–25	248	0.94 (0.61, 1.44)		0.84 (0.55, 1.28)	
25–30	123	0.74 (0.46, 1.19)		0.66 (0.41, 1.04)	
>30	50	0.56 (0.34, 0.94)		0.57 (0.34, 0.93)	
Active smoking	190	1.01 (0.84, 1.21)	0.90	1.02 (0.83, 1.24)	0.84
History of cardiovascular disease	337	3.12 (2.52, 3.80)	<0.001	2.37 (1.91, 2.93)	<0.001
Peritoneal dialysis	61	1.09 (0.84, 1.42)	0.53	1.11 (0.85, 1.45)	0.46
ADPKD	24	0.50 (0.33, 0.77)	<0.001	0.74 (0.49, 1.13)	0.16

Table 6: First haemorrhagic event ($n = 297$) in the whole population ($N = 40\,980$). Multiple imputation.

		Unadjusted HR	P-value	Adjusted HR	P-value
Age		0.99 (0.99, 1.01)	0.99	0.99 (0.98, 1.00)	0.29
Sex, female	99	0.87 (0.69, 1.11)	0.27	0.88 (0.68, 1.15)	0.35
BMI			<0.001		<0.001
18.5–25	118	1.16 (0.63, 2.13)		1.07 (0.58, 1.98)	
25–30	69	0.79 (0.43, 1.47)		0.68 (0.36, 1.28)	
>30	41	0.54 (0.28, 1.05)		0.34 (0.22, 0.87)	
Active smoking	101	0.94 (0.73, 1.20)	0.61	0.83 (0.64, 1.09)	0.16
Diabetes	152	1.19 (0.94, 1.50)	0.15	1.44 (1.12, 1.86)	0.005
History of cardiovascular disease	157	1.35 (1.07, 1.72)	0.01	1.41 (1.08, 1.83)	0.01
Peritoneal dialysis	26	0.92 (0.61, 1.38)	0.67	0.93 (0.62, 1.40)	0.71
ADPKD	18	1.22 (0.76, 1.96)	0.42	1.40 (0.85, 2.29)	0.18

in most cases. Another limitation of our study is the unavailability of drug therapy as a potential confounding factor. Although intracranial bleeding might be a complication of anticoagulant treatment [42], we were not able to adjust for this factor. Moreover, heparin is regularly administered to ESRD patients on haemodialysis to prevent clotting in the extracorporeal circuit [32], but information on doses was not available in the registry. The selection of a population of patients due to dialysis eligibility could have induced the selection of ADPKD patients with a lower risk of ICA rupture, as ADPKD patients with ICA rupture could have died before reaching ESRD. Information on previous screening and treatment of ICA was not available. Finally, the number of events in the ADPKD population, which is younger than the non-ADPKD one, may be considered relatively small.

Strengths

Despite some limitations, our study has major strengths. This is the first longitudinal epidemiological study with an analysis of the association between ADPKD and the occurrence of stroke in a nationwide population of dialysed patients followed up through registry and administrative data, with a prospective

Table 7: First haemorrhagic event ($n = 141$) in the non-diabetic population ($N = 21\,804$). Multiple imputation.

		Unadjusted HR	P-value	Adjusted HR	P-value
Age		0.99 (0.98, 1.00)	0.84	0.99 (0.98, 1.01)	0.51
Sex, female	48	0.91 (0.64, 1.29)	0.60	0.90 (0.62, 1.31)	0.59
BMI			0.06		0.05
18.5–25	67	0.85 (0.40, 1.81)		0.83 (0.38, 1.79)	
25–30	32	0.65 (0.27, 1.49)		0.63 (0.27, 1.48)	
>30	8	0.30 (0.10, 0.89)		0.29 (0.09, 0.87)	
Active smoking	47	0.95 (0.65, 1.37)	0.66	0.87 (0.58, 1.29)	0.47
History of cardiovascular disease	63	1.25 (0.89, 1.75)	0.20	1.34 (0.93, 1.97)	0.12
Peritoneal dialysis	8	0.50 (0.28, 1.04)	0.06	0.51 (0.25, 1.04)	0.06
ADPKD	17	1.45 (0.87, 2.42)	0.15	1.54 (0.92, 2.60)	0.10

registration of events. The analysis is then exhaustive of the whole French population hospitalized for the events of interest. Registry data have allowed us to consider major risk factors, such as previous cardiovascular disease, diabetes, active smoking, and type of dialysis, which would not be available otherwise if the analyses were based on only administrative data.

CONCLUSION

We found no increase in the risk of ischaemic or haemorrhagic events in ADPKD patients under dialysis, regardless of the modality of renal replacement therapy, after considering major risk factors. We believe that the findings of our study support a similar screening strategy in ADPKD patients on dialysis compared to patients not on dialysis.

SUPPLEMENTARY DATA

Supplementary data are available at *Clinical Kidney Journal* online.

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AUTHORS' CONTRIBUTIONS

Study conception: D.C., C.B., L.G.; study design: D.C., C.B., L.G.; data acquisition: C.C.; data analysis: D.C.; data interpretation: D.C., C.B., L.G.; critical intellectual input: D.C., C.B., L.G., T.L.; drafting the article: D.C., C.B., L.G.; critical revision of the article: D.C., C.B., L.G.; C.C., D.G.; D.T.-R., T.L, R.M., F.T.-D., H.V.-C.

DATA AVAILABILITY STATEMENT

Public posting of individual level participant data is not covered by CNIL approval for the REIN registry. An anonymous dataset containing data from REIN registry paired with SNDS can be obtained by collaborating scientists upon approval of a scientific project proposal by the steering committee of the Agence de la Biomédecine.

CONFLICT OF INTEREST STATEMENT

The authors have nothing to declare. The results presented in this paper have not been published previously in whole or part.

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