Q J Med 2014; **107**:545–555
doi:10.1093/qjmed/hcu043 Advance Access Publication 24 February 2014

Survival of patients with ANCA-associated vasculitis on chronic dialysis: data from the French REIN registry from 2002 to 2011

M. ROMEU[1], C. COUCHOUD[2], J.-C. DELAROZIÈRE[3], S. BURTEY[1], L. CHICHE[4], J.-R. HARLÉ[4], B. GONDOUIN[1], P. BRUNET[1], Y. BERLAND[1] and N. JOURDE-CHICHE[1]

From the [1]Department of Nephrology, Hopital Conception, AP-HM, Aix-Marseille Université, 147 Bd Baille, 13385 Marseille Cedex 5, [2]Agence de la Biomédecine, Registre REIN, 1 avenue du Stade de France, 93212 Saint-Denis-La Plaine, France, [3]Department of Public Health, Hopital Timone, AP-HM, Aix-Marseille Université, 27 Bd Jean Moulin, 13385 Marseille Cedex 5 and [4]Department of Internal Medicine, Hopital Conception, AP-HM, Aix-Marseille Université, 147 Bd Baille, 13385 Marseille Cedex 5, France

Address correspondence to Dr N. Jourde-Chiche, Service de Néphrologie, Hôpital de la Conception, 147 Bd Baille, 13385 Marseille Cedex 5, France. email: noemie.jourde@ap-hm.fr

This work was presented as a poster at the ACR/ARHP Annual Meeting in San Diego, CA on 27 October 2013.

Received 19 November 2013 and in revised form 11 February 2014

Summary

Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) can lead to end-stage renal disease in patients with renal involvement.

Objective: This study evaluated the survival of AAV patients on chronic dialysis in France.

Methods: Between 2002 and 2011, a total of 425 AAV patients started chronic dialysis and were registered in the Renal Epidemiology and Information Network. We analysed survival censored for renal transplantation, recovery of renal function and loss to follow-up. AAV patients were compared with 794 matched non-AAV patients on chronic dialysis.

Results: A total of 166 (39%) patients with microscopic polyangiitis and 259 (61%) patients with granulomatosis with polyangiitis were registered. Within a median follow-up of 23 months, 58 (14%) patients received a renal allograft and 19 (4%) recovered renal function. Median survival on dialysis was 5.35 years (95% CI, 4.4–6.3) and survival rates at 3 months, 1, 3 and 5 years were 96%, 85%, 68% and 53%, respectively. A total of 143 (41%) patients died after a median of 16 months. Causes of death were cardiovascular (29%), infections (20%), malnutrition (13%), malignancies (4%), AAV relapse (2%), miscellaneous (14%) and unknown (18%). Multivariate logistic regression identified three independent risk factors associated with AAV patients' mortality: age (HR = 1.05/year, $P < 0.001$), peripheral artery disease (HR = 2.62, $P = 0.003$) and frailty (HR = 2.43, $P < 0.001$). Survival of AAV patients did not differ from non-AAV controls, but infectious mortality was higher in AAV patients (20% vs. 8%, $P < 0.001$).

Conclusion: Survival of AAV patients in chronic dialysis, although poor, was comparable to survival of non-AAV controls on dialysis. There was a similar burden of cardiovascular mortality, but higher infectious mortality.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are small-vessel vasculitides, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA.[1] The incidence of AAV in Europe is 10–20/million/year and occurs at a peak age of 65–74 years.[2]

Renal vasculitis is a frequent severe manifestations of AAV,[3] occurring in 50% of patients at presentation, and up to 70–85% of patients with GPA or MPA during the course of their disease.[4] Historically, left untreated, active AAV resulted in a 1-year mortality >80%.[4] Although immunosuppressive drugs have dramatically improved the survival of AAV patients,[5,6] end-stage renal disease (ESRD) has remained common and chronic renal-replacement therapy (RRT) is needed for up to 30% of patients with moderate to severe renal disease at diagnosis.[4,7,8]

Severe renal failure at presentation is associated with poor survival in AAV patients.[8–10] Renal function may eventually recover (49–69% following induction treatment[11]), with or without residual chronic kidney disease, or RRT may be needed.

In Europe, median survival on chronic dialysis is 3–6 years (5 years in France[12]) and the main cause of mortality is cardiovascular disease (CVD), followed by infections and malignancy.[13,14] The specific survival rates and outcomes for AAV patients after initiation of RRT have only been described in small cohorts of patients in Europe.[15–17]

The objective of this study was to evaluate the survival of incident AAV patients on chronic dialysis in France using data from the Renal Epidemiology and Information Network (REIN) registry.

Subjects and methods

Patient population, data collection and definitions

All patients with ESRD secondary to AAV (as a primary or associated diagnosis declared by the attending nephrologist), registered in REIN between 1 January 2002 and 31 December 2011, were included. REIN was founded in 2001 as a tool to provide support, evaluation and research on public health.[18] It has progressively covered the French territory between 2002 and 2011, with a 100% uptake of patients starting RRT in each participating region. Data are collected prospectively at the initiation of RRT (i.e. hemodialysis, peritoneal dialysis or transplantation) for all patients in France with renal failure considered irreversible by the attending nephrologists, who provide clinical and demographic information, updated annually by a team of 36 clinical research assistants dedicated to REIN. Patients requiring RRT for acute renal failure are not registered in REIN. Six types of events are reported in REIN from the first day of RRT: (i) renal transplantation, (ii) registration on the kidney-transplantation waiting list, (iii) changes in dialysis setting, (iv) changes in type of dialysis, (v) transient recovery of renal function and (vi) death. If a death occurs, the main cause of mortality is recorded. The national ethics committee (Commission Nationale de l'Informatique et des Libertés) approved the data collection conducted by REIN, and this study was approved by the scientific committee of REIN.

Baseline information included age at the start of dialysis, gender, primary renal disease, body-mass index (BMI) and serum albumin. We studied the following comorbidities: diabetes, hypertension, congestive heart failure, peripheral vascular disease, coronary heart disease, cerebrovascular disease, chronic respiratory disease, active malignancy, mobility status and smoking.[18] The initial dialysis modality was studied in three categories: hemodialysis in the hospital center, other hemodialysis and peritoneal dialysis. Patients who recovered renal function before 45 days on dialysis were excluded.

Malnutrition was defined as a serum-albumin level of <3 g/dl and/or a BMI of <20 kg/m^2.[19–21] Frailty was defined by an inability to walk without help.[19,22,23] Primary renal diseases were coded according to the thesaurus of the French Society of Nephrology.[18] Dialysis started in an emergency was defined as a life-threatening circumstance that required dialysis within 24 h.

Any deaths were registered from the first day of dialysis up to the study's end-point on 31 December 2011.

Aims of the study

The main objective of this study was to evaluate the survival of AAV patients in chronic dialysis. Additional objectives were to identify the causes of mortality as well as the predictors for mortality in this population.

Two approaches were used. First, analyses were only performed among AAV patients identified in REIN. The primary outcome examined was the survival of patients, censored for recovery of renal function, renal transplantation, loss to follow-up, or the end of the study. To indicate the global prognosis of AAV patients in RRT, a survival analysis was also performed without censoring for renal transplantation. We then performed the same analyses to

compare AAV patients with non-AAV patients in dialysis, who were matched (1:2) for the following characteristics: age (±2 years), gender, diabetes, dialysis start in an emergency, chronic lung disease, malnutrition, frailty, dialysis modality (hemodialysis or peritoneal dialysis) and CVD (defined as $\geqslant 1$ of the following: coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease). Comparisons were also performed among AAV patients between MPA and GPA.

Statistical analyses

For descriptive factors, results were expressed as frequencies and percentages for categorical variables. Means and standard deviations or medians and interquartile ranges (IQRs) were used for continuous variables with asymmetrical distributions. Survival probabilities from the initiation of RRT were estimated using the Kaplan–Meier method and compared using the log-rank test for equality of the survival curves. Survival probabilities of AAV patients were also compared using the log-rank test between two periods, from 2002 to 2006 and from 2007 to 2011. Univariate survival analyses were performed using the log-rank test. Multivariate analyses of AAV patients' survival used Cox's regression model: parameters with a log-rank $P < 0.25$ in the Kaplan–Meier univariate analysis were entered into multivariate analyses, as well as age. The variables that did not affect survival significantly were removed by a backwards stepwise procedure according to a likelihood ratio. A P-value of $\leqslant 0.05$ was considered statistically significant. The analyses were conducted using SPSS19 and SAS9.3 softwares. We also performed a competing risk analysis for the estimation of AAV patients' survival, considering recovery of renal function and renal transplantation as competing risks (macro %cuminc, SAS software).

Results

Characteristics of AAV patients at the initiation of RRT

Between 2002 and 2011, a total of 425 AAV patients starting RRT were registered in REIN: 259 (61%) with GPA and 166 (39%) with MPA. Most patients (75%) had biopsy-proven AAV nephropathy. These patients represented 0.7% of the 63 311 patients incident in RRT in France during this period.

Demographics and baseline characteristics are described in Table 1. The gender ratio was 1.4 (249 male, 176 female). The median age at the initiation of dialysis was 70 years (range: 7–93 years, IQR 60–78), with four pediatric patients (aged 7–12 years old). Dialysis was initiated as an emergency for 174 (44%) patients, and 279 (66%) patients started hemodialysis on a central venous catheter. As first treatment modality, most patients (94%) were treated with hemodialysis, mainly in hospital centers (90%), whereas only 27 (6%) were treated with peritoneal dialysis.

Comorbid conditions of the AAV patients when dialysis was initiated were hypertension (64%), malnutrition (44%), chronic lung disease (16%), congestive heart failure (15%), diabetes mellitus (14%), coronary artery disease (12%), cerebrovascular disease (11%), peripheral vascular disease (5%) and malignancy (5%). Frailty was reported in 55 (13%) patients. Baseline characteristics were similar between MPA and GPA patients (Table 1), except for chronic lung disease, which was more frequent in MPA patients (23% vs. 11%, $P = 0.01$), and progressive malignancy, which was more frequent in GPA patients (7% vs. 2%, $P = 0.02$).

During the study period (Figure 1), 45 (11%) patients (16 MPA and 29 GPA) partially recovered renal function, which allowed RRT withdrawal after a median duration of 5 months (IQR 3–11). Among them, 19 remained dialysis-free at the last follow-up, whereas 26 recommenced dialysis after a median dialysis-free period of 14 months (IQR 2–24). Eighty-six (20%) AAV patients were listed on the kidney-transplantation waiting list, and 58 (14%) patients (19 MPA and 39 GPA) received a renal allograft after a median duration of 23 (IQR 12–35) months on dialysis (no preemptive transplantation, 55 deceased donors and 3 living donors). Graft function was lost in five (9%) allograft recipients (two primary graft failures; three graft failures after 7, 39 and 72 months), and two (3%) patients died with a functioning allograft after 8 months and 5 years. The 51 remaining patients had a functional allograft after a median follow-up of 13 (IQR 1.5–50) months.

Survival of AAV patients in chronic dialysis

The median follow-up period for AAV patients was 23 months (IQR 8–44). During this time (Figure 1), 348 patients remained on dialysis or returned to dialysis after a temporary recovery, of which 143 (41%) died after a median dialysis duration of 16 months (IQR 6–41): 87 (61%) GPA and 56 (39%) MPA patients. The median survival time was 5.35 years (95% CI, 4.4–6.3). Survival rates at 3 months, 1, 3 and 5 years were, respectively, 96%, 85%, 68% and 53% with no significant difference between GPA and MPA. Median survival was 5.6 years (95% CI, 4.4–6.8) for GPA and 4.7 years for MPA (95% CI,

Table 1 Baseline characteristics of AAV patients at the initiation of RRT in France between 2002 and 2011

	AAV ($n=425$)	MPA ($n=166$)	GPA ($n=259$)	P
Gender ratio (M/F)	1.4	1.3	1.5	NS
Median age at the start of dialysis (IQR)	70 (60–78)	71 (62–77)	69 (59–77)	NS
Renal allograft, *n* (%)	58 (14)	19 (11)	39 (15)	NS
Median graft delay, months (IQR)	24 (14–43)	23 (12–45)	26 (16–39)	NS
First treatment modality				NS
Hemodialysis in hospital center	380 (90)	144 (87)	236 (91)	
Hemodialysis, other	18 (4)	8 (5)	10 (4)	
Peritoneal dialysis	27 (6)	14 (8)	13 (5)	
Renal biopsy performed, *n* (%)	307 (75)	116 (72)	191 (77)	NS
Missing	16 (4)	4 (2)	12 (5)	
Dialysis started in an emergency, *n* (%)	174 (44)	69 (44)	105 (44)	NS
Missing data	28 (7)	8 (5)	20 (8)	
Hypertension, *n* (%)	250 (64)	100 (64)	150 (63)	NS
Missing data	33 (8)	11 (7)	22 (8)	
Diabetes mellitus, *n* (%)	54 (14)	21 (13)	33 (14)	NS
Missing data	33 (8)	9 (5)	24 (9)	
Coronary artery disease, *n* (%)	47 (12)	23 (15)	24 (10)	NS
Missing data	37 (9)	11 (7)	26 (10)	
Myocardial infarction, *n* (%)	26 (7)	12 (8)	14 (6)	NS
Missing data	37 (9)	11 (7)	26 (10)	
Congestive heart failure, *n* (%)	57 (15)	25 (16)	32 (14)	NS
Missing data	40 (9)	13 (8)	27 (10)	
Peripheral vascular disease, n (%)	21 (5)	7 (5)	14 (6)	NS
Missing data	38 (9)	14 (8)	24 (9)	
Cerebrovascular disease, *n* (%)	42 (11)	17 (11)	25 (11)	NS
Missing data	43 (10)	15 (9)	28 (11)	
Smoking				NS
Never	199 (62)	82 (61)	117 (62)	
Stopped	82 (25)	33 (25)	49 (26)	
Current	40 (12)	19 (14)	22 (12)	
Missing data	*103* (*24*)	*32* (*19*)	*71* (*27*)	
Chronic lung disease, *n* (%)	62 (16)	36 (23)	26 (11)	0.01
Missing data	33 (8)	11 (7)	22 (8)	
Oxygen-therapy, *n* (%)	7 (2)	5 (3)	2 (0.8)	NS
Missing data	34 (8)	10 (6)	24 (9)	
Active malignancy, *n* (%)	20 (5)	3 (2)	17 (7)	0.02
Missing data	38 (9)	14 (8)	24 (9)	
Serum albumin < 3 g/dl, *n* (%)	139 (54)	54 (49)	85 (58)	NS
Serum albumin, mean (SD)	3 (0.5)	3.1 (0.6)	2.9 (0.6)	NS
Missing data	167 (39)	55 (33)	112 (43)	
BMI < 20 kg/m^2, *n* (%)	63 (20)	25 (19)	38 (20)	NS
BMI, mean (SD)	24 (4)	24 (4)	24 (4)	NS
Missing data	111 (26)	36 (22)	75 (29)	
Malnutrition, *n* (%)	161 (44)	61 (41)	100 (46)	NS
Missing data	59 (14)	16 (10)	43 (17)	
Frailty, *n* (%)	55 (13)	19 (11)	36 (14)	NS
Missing data	77 (18)	23 (14)	54 (21)	

NS, not significant.

3.2–6.0) patients ($P=0.59$) (Figure 2). Survival rates at 3 months, 1, 3 and 5 years were, respectively, 97%, 86%, 68% and 56% for GPA and 95%, 84%, 69% and 48% for MPA. Similar results were obtained with competing risk analysis (Supplementary Figure S1). Global survival of AAV patients in RRT without censoring at the time of renal transplantation was 5.8 years (95% CI, 5.1–7.4), which was not statistically different from survival on dialysis, with no difference between

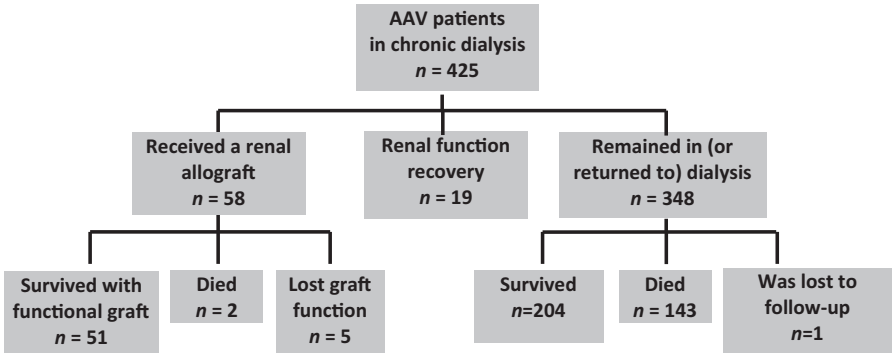
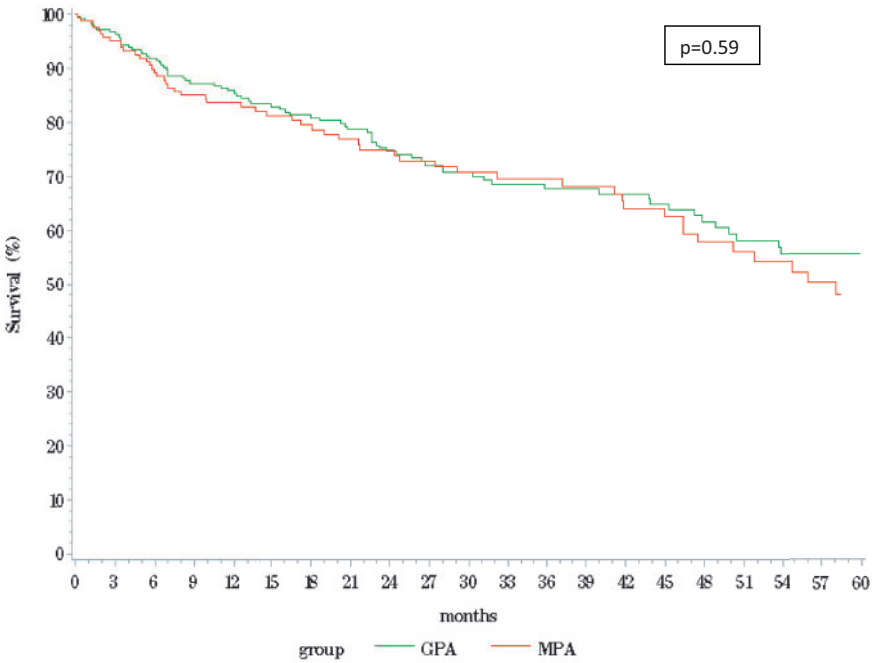


Figure 1. Flowchart of AAV patients starting RRT in France between 2002 and 2011. A total of 425 patients started chronic dialysis (no preemptive transplantation).



		3 months	1 year	3 years	5 years
GPA (n=259)	Number at risk	240	179	78	32
	% survival	96.9	85.9	67.7	55.7
	95%CI	[94.7-99.0]	[81.5-90.3]	[60.9-74.4]	[47.2-64.3]
MPA (n=166)	Number at risk	152	107	54	21
	% survival	95.1	83.6	69.5	48.0
	95%CI	[91.8-98.4]	[77.7-89.5]	[61.3-77.7]	[36.5-59.5]

Figure 2. Kaplan–Meier survival curves (censored for recovery of renal function, renal transplantation and loss to follow-up) in AAV patients on chronic dialysis, with GPA or MPA.

Table 2 Causes of death for AAV and non-AAV patients in chronic dialysis

	MPA ($n=56$)	GPA ($n=87$)	P	AAV ($n=143$)	Non-AAV ($n=270$)	P
Cardiovascular	20 (36)	22 (25)	NS	42 (29)	74 (27)	NS
Infectious	10 (18)	19 (22)	NS	29 (20)	23 (8)	<0.001
Malnutrition	8 (14)	10 (12)	NS	18 (13)	19 (7)	NS
Malignancy	5 (9)	1 (1)	0.02	6 (4)	40 (15)	0.001
AAV relapse	0 (0)	3 (3)	NS	3 (2)	—	—
Other	7 (12)	14 (16)	NS	21 (15)	56 (21)	NS
Unknown	6 (11)	18 (21)	NS	24 (17)	58 (22)	NS

MPA patients are compared with GPA patients, and all AAV patients with non-AAV patients. Values are represented as *n* (%). NS, not significant.

MPA and GPA (Figure 4). There was no difference in survival of AAV patients on dialysis between the two study periods (2002–06 and 2007–11, log-rank $P=0.19$).

Principal causes of mortality in AAV patients in chronic dialysis

The causes of death for the 143 AAV patients were cardiovascular events (42: 29%), bacterial or viral infection (29: 20%), malnutrition (18: 13%), malignancy (6: 4%), AAV relapse (3: 2%) and other miscellaneous (20: 14%). Data were missing for 25 patients (18%). For 20 patients (14%), death occurred after withdrawal of dialysis. There was no significant difference in mortality causes between GPA and MPA, except for malignancy, which was more frequent in patients with MPA (9% vs. 1%, $P=0.02$) (Table 2).

Predictors of mortality in AAV patients in chronic dialysis

Six parameters were significantly associated with mortality in univariate survival analysis (Table 3): malignancy, chronic lung disease, cerebrovascular disease, coronary artery disease, peripheral vascular disease and frailty. Frailty was the most significant risk factor associated with mortality.

Nine parameters (malnutrition, frailty, coronary artery disease, chronic lung disease, cerebrovascular disease, malignancy, peripheral vascular disease, myocardial infarction and congestive heart failure), as well as age, were entered in the multivariate logistic Cox's regression analyses. Dialysis modality was excluded because of the unbalanced distribution of modalities. After a backward stepwise procedure that comprised nine steps, three risk factors were independently associated with mortality in AAV patients: age (HR = 1.05 per year; 95% CI, 1.02–1.07; $P<0.001$), peripheral vascular disease (HR = 2.62; 95% CI, 1.38–4.98; $P=0.003$) and frailty (HR = 2.43; 95% CI, 1.48–3.99; $P<0.001$).

Comparison of survival rates between AAV patients and matched control dialysis patients

Matching between AAV and non-AAV patients was performed randomly from the REIN database on a 2:1 basis. For some AAV patients, only one matched control could be found. The non-AAV matched dialysis control group thus comprised 794 patients. Causes of ESRD (Supplementary Table S1) were vascular disease (28%), glomerular disease (27%), unknown (17%), tubulo-interstitial nephritis (15%), hereditary (9%) and other (4%). AAV and non-AAV patients were comparable for non-matched characteristics except for the initiation of dialysis via a central venous catheter, which was more frequent in AAV patients (66% vs. 53%, $P<0.0001$), and hypertension, less frequent in AAV patients (64% vs. 77%, $P<0.0001$). Of note, although patients were matched for CVD in general, cerebrovascular disease was more frequent (11% vs. 5%, $P<0.0001$) and peripheral vascular disease less frequent (5% vs. 14%, $P<0.0001$) in AAV patients (Supplementary Table S1). As expected, a renal biopsy had been performed more frequently in AAV patients (75% vs. 22%, $P<0.0001$).

The median follow-up time for non-AAV patients was 18 (IQR 8–37) months. Recovery of renal function was observed in 40 (5%) patients, of which 19 remained dialysis-free at the last follow-up, and 134 (17%) received a renal allograft. There was no significant difference between AAV and non-AAV patients concerning inscription on a kidney-transplantation waiting list or the incidence of renal transplantation. During the follow-up period, 270 (42%) non-AAV patients on dialysis died. Median survival time was 5 years for non-AAV

Table 3 Univariate Kaplan–Meier survival analysis: risk factors for mortality of patients with AAV in chronic dialysis

	Median survival	95% CI	Log-rank: *P*-value
Gender			
Male	5.45	4.40–6.50	0.405
Female	4.31	2.93–5.70	
AAV type			
MPA	4.67	3.28–6.06	0.533
GPA	5.62	4.44–6.79	
Dialysis via a central venous catheter	5.46	4.25–6.66	
No catheter	4.31	3.02–5.61	0.837
Start of dialysis in an emergency	5.74	4.50–6.98	
No emergency	4.48	3.33–5.63	0.519
Malignancy	2.78	0.81–4.75	
No malignancy	4.84	3.87–5.80	**0.023**
Chronic lung disease	3.48	2.18–4.79	
No chronic lung disease	4.84	3.76–5.91	**0.035**
Current smoker	3.99	3.27–4.70	
Not a current smoker	4.57	3.45–5.69	0.550
Cerebrovascular disease	2.34	1.46–3.21	
No cerebrovascular disease	4.84	3.77–5.91	**0.017**
Congestive heart failure	3.48	2.52–4.43	
No congestive heart failure	4.67	3.76–5.58	0.055
Myocardial infarction	3.33	1.53–5.13	
No myocardial infarction	4.57	3.67–5.47	0.241
Coronary artery disease	3.10	2.08–4.12	
No coronary artery disease	4.67	3.77–5.56	**0.033**
Peripheral vascular disease	2.59	0–5.30	
No peripheral vascular disease	4.67	3.80–5.53	**0.014**
Malnutrition	5.46	3.88–7.03	
No malnutrition	5.64	4.20–7.08	0.058
Frailty	1.72	1.10–2.34	
No frailty	5.62	5.25–5.99	**<0.001**

patients (95% CI, 4.2–6.1). Survival rates at 3 months, 1, 3 and 5 years were 95%, 84%, 67% and 48% for non-AAV patients (Figure 3). Kaplan–Meier survival analysis showed that there was no significant difference between survival of AAV and non-AAV patients, whether renal transplantation was censored ($P = 0.94$) or not (Figure 4).

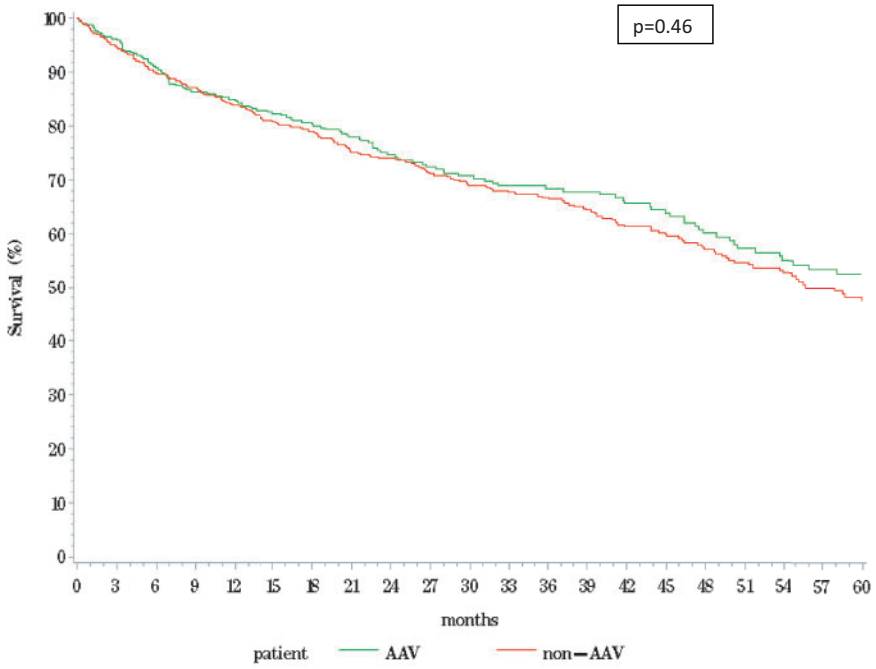
Comparison of causes of mortality between AAV and the matched dialysis controls

Although survival did not differ between AAV and non-AAV patients, the causes of mortality were different (Table 2). Indeed, more AAV patients died from infectious causes (20% vs. 8%, $P < 0.001$), but there were less deaths by malignancy than for the matched controls (4% vs. 15%, $P = 0.001$).

Discussion

To our knowledge, to date, this is the largest national cohort study that has evaluated the survival of AAV patients in RRT in a European country. AAV patients accounted for 0.7% of all incident patients registered in REIN, which is the comprehensive registry of all incident patients in RRT in France. The median age at the initiation of dialysis was 70 years for AAV patients, which is close to the median age of starting dialysis in France (71 years in 2010[12]). After a median follow-up of 23 months, the mortality rate in our cohort was 41%, which corresponded to a median survival time of 5.35 years that did not differ between MPA and GPA.

Three studies in the last decade have specifically reported on the outcomes of AAV patients on chronic dialysis. Weidanz *et al.*[16] reported on 46 AAV patients with ESRD from a referral center in the UK between 1971 and 2004. Lionaki *et al.*[24]



		3 months	1 year	3 years	5 years
AAV (n=425)	Number at risk	392	286	132	53
	% survival	96.2	85.0	68.4	52.6
	95%CI	[94.3-98.0]	[81.5-88.6]	[63.1-73.6]	[45.6-59.5]
non-AAV (n=794)	Number at risk	716	539	242	75
	% survival	94.7	84.0	66.7	47.6
	95%CI	[93.1-96.3]	[81.3-86.6]	[62.8-70.6]	[42.0-53.2]

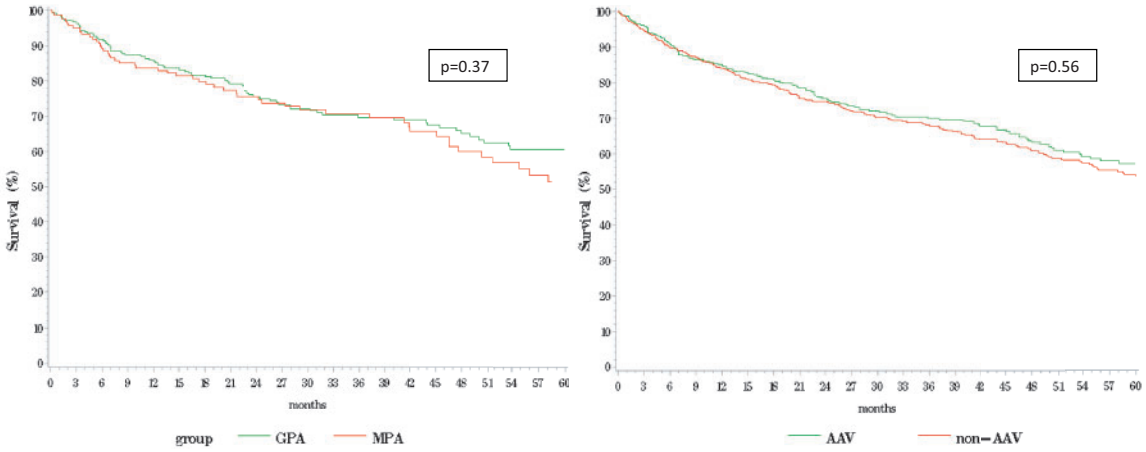
Figure 3. Kaplan–Meier survival curves (censored for recovery of renal function, renal transplantation and loss to follow-up) for AAV patients and matched controls on chronic dialysis.

reported on 93 AAV patients in dialysis between 1986 and 2007, using data from the Chapell Hill registry. Finally, Tang *et al.*[25] have recently published a large cohort study and report data from 449 AAV patients within the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry of Australia and New Zealand.

The survival rates of AAV patients on chronic dialysis in our cohort were 85%, 68% and 53% at 1, 3 and 5 years, respectively. In comparison, the 1-year survival rate was higher in the ANZDATA cohort (92% for MPA and 89% for GPA),[25] but the 5-year survival rate was similar. Survival rates at 1 and 5 years were 77% and 28% in the Chapell Hill registry,[24] and were 82% and 55% in the UK cohort.[16]

In our cohort, the main causes of death were CVD (29%), followed by infections (20%). Although infections have been the main cause of mortality (15–58% of deaths) in smaller cohorts of AAV patients,[7,16,17,24] CVD was the leading cause of death in the ANZDATA cohort,[25] with cardiac and vascular deaths accounting together for 23–25% of deaths, whereas infectious mortality was only 6–8%. In our cohort, as in the ANZDATA cohort, the type of AAV (MPA or GPA) was not associated with mortality. Of note, AAV relapses accounted for only 2% of deaths, which is in accordance with the recent study on the long-term follow-up of patients with severe AAV from the MEPEX study,[26] where only 3% of deaths were due to active vasculitis. Cancer was the cause of death in fewer AAV patients than we expected in this immunocompromised population, possibly because of the short follow-up duration.

Independent risk factors of mortality for AAV patients on dialysis were age, peripheral artery disease and frailty. The absence of autonomy (inability to



		3 months	1 year	3 years	5 years
GPA (n=259)	N at risk	241	185	104	51
	% survival	96.9	86.0	69.6	60.5
	95%CI	[94.7-99.0]	[81.6-90.4]	[63.3-76.0]	[53.1-68.0]
MPA (n=166)	N at risk	152	111	60	25
	% survival	95.1	83.7	70.7	51.3
	95%CI	[91.8-98.4]	[77.9-89.6]	[62.8-78.6]	[40.5-62.1]

		3 months	1 year	3 years	5 years
AAV (n=425)	N at risk	393	296	164	76
	% survival	96.2	85.1	70.0	57.2
	95%CI	[94.3-98.0]	[81.6-88.6]	[65.1-74.9]	[50.9-63.4]
non-AAV (n=794)	N at risk	721	564	296	115
	% survival	94.7	84.1	68.2	53.5
	95%CI	[93.2-96.3]	[81.4-86.7]	[64.5-71.9]	[48.7-58.3]

Figure 4. Kaplan–Meier survival curves censored only for recovery of renal function and loss to follow-up, not for renal transplantation, in (**A**) GPA and MPA patients and (**B**) AAV and non-AAV patients.

walk, even with help) has been previously reported to be an independent risk factor for mortality (OR = 2.3, $P < 0.0001$) in a large cohort ($n = 1642$) of elderly French patients in dialysis.[19] The inability to walk without help, which was registered in the REIN at inclusion, was chosen here to define frailty (as could have gait speed).[23] There was no criterion for frailty in the ANZDATA registry: only age (HR = 1.47 per decade, $P < 0.001$) and initiation of dialysis at an earlier time ($P = 0.02$) were independent predictors of death.

To our knowledge, to date, only two studies have compared the survival rates and causes of mortality of AAV patients with non-AAV patients on dialysis.[25,27] The control groups comprised all non-AAV dialysis patients, with different baseline characteristics (such as diabetes), and used adjusted models to correct for the different risk factors for death. After adjustment, no difference was found in the survival rates of AAV and non-AAV patients. In order to limit the confusion bias in this comparison, we closely matched our control dialysis population.

The main causes of mortality in the general dialysis population are CVD and infections. Low serum-albumin level and the use of a central venous catheter have also been described as important predictors of mortality.[28–30]

In our study, two matched controls from the entire REIN registry were randomly assigned to each AAV patient. Thus, the non-AAV dialysis group was not representative of the general dialysis population in France (e.g. only 8% diabetic patients), but corresponded closely to AAV patients. We observed no significant difference in the global survival rates of AAV and non-AAV patients: this suggests that, for patients with severe AAV and renal involvement, vasculitis itself is not an additional risk factor for mortality on chronic dialysis.

Although survival rates were similar, causes of death differed between AAV and non-AAV patients. Indeed, although CVD was the leading cause of death in both groups, AAV patients had a higher rate of infectious mortality. This over-representation of infectious mortality may be the consequence of past or current immunosuppression in AAV patients,[9] and claims for preventive measures, such as pneumococcal vaccination. The frequent initiation of hemodialysis on a central catheter in patients with sudden onset of ESRD may also participate in this infectious mortality.[31]

Although one could have expected a lower rate of cardiovascular mortality in AAV patients compared with patients with a longer history of chronic kidney disease and cardiovascular burden associated with

it, the preeminent incidence of cardiovascular mortality we observed in our AAV patients, as in all dialysis patients, calls for additional preventative measures to be taken for this population.

The major strengths of this study include the large number and relevance of the recorded variables as well as the unselected nature of the population. Our findings, however, should be interpreted in the light of the following limitations. First, although data were collected prospectively in REIN, significant proportion of data is missing for some parameters (such as smoking histories and serum-albumin values). Second, the few patients with persistent renal function recovery after 45 days on dialysis were not excluded. Although they were considered by the attending nephrologist as having chronic ESRD, and thus were included in REIN, these 19 patients (4% of the cohort) may be considered a posteriori as having acute renal failure. We chose not to include only patients who survived a minimum of 3 months on dialysis, in order to record all deaths from the first day on dialysis, in patients clinically considered as 'chronic' by the attending nephrologist. Then, all patients in chronic dialysis with a primary or associated diagnosis of AAV were included and, although most patients had biopsy-proven nephropathy, we cannot rule out that AAV might not have been the cause of ESRD for a small proportion of them. Finally, REIN registry is not specific to AAV, and specific scores for activity or organ involvement, as well as vasculitis vintage, immunosuppressive therapies and non-fatal relapses, were not recorded.

In summary, the survival of AAV patients on chronic dialysis, although poor, is acceptable with regards to the survival of matched patients with other causes of ESRD. Although it exposes patients to a higher rate of infectious mortality, which claims for monitoring of vaccination status in this population, AAV itself is not a risk factor for mortality on dialysis. Importantly, on chronic dialysis, AAV patients share the same cardiovascular burden as non-AAV patients and could benefit from cardiovascular monitoring.

Supplementary material

Supplementary material is available at *QJMED* online.

Acknowledgement

The authors thank all REIN registry participants, especially the nephrologists and professionals who collected the data and conducted the quality control. Dr N.J.-C. declares that she had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest: The authors declare that there is no financial conflict of interest, related or unrelated to this study, for any of the contributing authors.

References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, *et al.* 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65**:1–11.
2. Booth AD, Pusey CD, Jayne DR. Renal vasculitis—an update in 2004. *Nephrol Dial Transplant* 2004; **19**:1964–8.
3. Jennette JC. Rapidly progressive crescentic glomerulonephritis. *Kidney Int* 2003; **63**:1164–77.
4. Booth AD, Almond MK, Burns A, Ellis P, Gaskin G, Neild GH, *et al.* Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study. *Am J Kidney Dis* 2003; **41**:776.
5. Jayne D, Rasmussen N, Andrassy K, Bacon P, Tervaert JW, Dadoniené J, *et al.* A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *N Engl J Med* 2003; **349**:36–44.
6. Nachman PH, Hogan SL, Jennette JC, Falk RJ. Treatment response and relapse in antineutrophil cytoplasmic autoantibody-associated microscopic polyangiitis and glomerulonephritis. *J Am Soc Nephrol* 1996; **7**:33–9.
7. de Lind van Wijngaarden RA, Hauer HA, Wolterbeek R, Jayne DR, Gaskin G, Rasmussen N, *et al.* Clinical and histologic determinants of renal outcome in ANCA-associated vasculitis: a prospective analysis of 100 patients with severe renal involvement. *J Am Soc Nephrol* 2006; **17**:2264–74.
8. Weidner S, Geuss S, Hafezi-Rachti S, Wonka A, Rupprecht HD. ANCA-associated vasculitis with renal involvement: an outcome analysis. *Nephrol Dial Transplant* 2004; **19**:1403–11.
9. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, *et al.* Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis* 2011; **70**:488–94.
10. Slot MC, Tervaert JW, Franssen CF, Stegeman CA. Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement. *Kidney Int* 2003; **63**:670–7.
11. Jayne DR, Gaskin G, Rasmussen N, Abramowicz D, Ferrario F, Guillevin L, *et al.* Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. *J Am Soc Nephrol* 2007; **18**:2180–8.
12. Réseau Epidémiologie et Information en Néphrologie: Rapport REIN 2010. *Nephrol Thér* 2012; **1**:1–218.
13. Canaud B, Tong L, Tentori F, Akiba T, Karaboyas A, Gillespie B, *et al.* Clinical practices and outcomes in elderly hemodialysis patients: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2011; **6**:1651–62.

14. de Jager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, *et al.* Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* 2009; **302**:1782–9.

15. Merino JL, Galeano C, Espejo B, Rivera M, Fernández-Lucas M, Caldés S, *et al.* A retrospective study on outcome of microscopic polyangiitis in chronic renal replacement therapy. *Nephrol Dial Transplant* 2011; **26**:1360–6.

16. Weidanz F, Day CJ, Hewins P, Savage CO, Harper L. Recurrences and infections during continuous immunosuppressive therapy after beginning dialysis in ANCA-associated vasculitis. *Am J Kidney Dis* 2007; **50**:36–46.

17. Allen A, Pusey C, Gaskin G. Outcome of renal replacement therapy in antineutrophil cytoplasmic antibody-associated systemic vasculitis. *J Am Soc Nephrol* 1998; **9**:1258–63.

18. Couchoud C, Stengel B, Landais P, Aldigier JC, de Cornelissen F, Dabot C, *et al.* The renal epidemiology and information network (REIN): a new registry for end-stage renal disease in France. *Nephrol Dial Transplant* 2006; **21**:411–8.

19. Couchoud C, Labeeuw M, Moranne O, Allot V, Esnault V, Frimat L, *et al.* Registry FREaINR: a clinical score to predict 6-month prognosis in elderly patients starting dialysis for end-stage renal disease. *Nephrol Dial Transplant* 2009; **24**:1553–61.

20. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA* 2006; **295**:801–8.

21. *Stratégie de prise en charge en cas de dénutrition protéino-énergétique chez la personne âgée—recommandation HAS avril 2007.* http://www.has-sante.fr/portail/upload/docs/application/pdf/denutrition_personne_agee_2007_-_argumentaire.pdf.

22. Roshanravan B, Robinson-Cohen C, Patel KV, Ayers E, Littman AJ, de Boer IH, *et al.* Association between physical performance and all-cause mortality in CKD. *J Am Soc Nephrol* 2013; **24**:822–30.

23. Studenski S, Perera S, Patel K, Rosano C, Faulkner K, Inzitari M, *et al.* Gait speed and survival in older adults. *JAMA* 2011; **305**:50–8.

24. Lionaki S, Hogan SL, Jennette CE, Hu Y, Hamra JB, Jennette JC, *et al.* The clinical course of ANCA small-vessel vasculitis on chronic dialysis. *Kidney Int* 2009; **76**:644–51.

25. Tang W, Bose B, McDonald SP, Hawley CM, Badve SV, Boudville N, *et al.* The outcomes of patients with ESRD and ANCA-associated vasculitis in Australia and New Zealand. *Clin J Am Soc Nephrol* 2013; **8**:773–80.

26. Walsh M, Casian A, Flossmann O, Westman K, Höglund P, Pusey C, *et al.* Long-term follow-up of patients with severe ANCA-associated vasculitis comparing plasma exchange to intravenous methylprednisolone treatment is unclear. *Kidney Int* 2013; **84**:397–402.

27. Nissenson AR, Port FK. Outcome of end-stage renal disease in patients with rare causes of renal failure. III. Systemic/vascular disorders. *Q J Med* 1990; **74**:63–74.

28. Lukowsky LR, Kheifets L, Arah OA, Nissenson AR, Kalantar-Zadeh K. Patterns and predictors of early mortality in incident hemodialysis patients: new insights. *Am J Nephrol* 2012; **35**:548–58.

29. Bradbury BD, Fissell RB, Albert JM, Anthony MS, Critchlow CW, Pisoni RL, *et al.* Predictors of early mortality among incident US hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Clin J Am Soc Nephrol* 2007; **2**:89–99.

30. Collins AJ, Foley RN, Gilbertson DT, Chen SC. The state of chronic kidney disease, ESRD, and morbidity and mortality in the first year of dialysis. *Clin J Am Soc Nephrol* 2009; **4(Suppl. 1)**:S5–11.

31. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J Am Soc Nephrol* 1998; **9**:869–76.