



Universiteit
Leiden
The Netherlands

Proteinuria and hematuria after remission induction are associated with outcome in ANCA-associated vasculitis

Benichou, N.; Charles, P.; Terrier, B.; Jones, R.B.; Hiemstra, T.; Mouthon, L.; ... ; European Vasculitis Soc Euvas Inv

Citation

Benichou, N., Charles, P., Terrier, B., Jones, R. B., Hiemstra, T., Mouthon, L., ... Karras, A. (2023). Proteinuria and hematuria after remission induction are associated with outcome in ANCA-associated vasculitis. *Kidney International*, 103(6), 1144-1155.
doi:10.1016/j.kint.2023.02.029

Version: Publisher's Version
License: [Creative Commons CC BY 4.0 license](#)
Downloaded from: <https://hdl.handle.net/1887/3764073>

Note: To cite this publication please use the final published version (if applicable).

Proteinuria and hematuria after remission induction are associated with outcome in ANCA-associated vasculitis



Nicolas Benichou^{1,2}, Pierre Charles³, Benjamin Terrier^{2,4}, Rachel B. Jones^{5,6}, Thomas Hiemstra⁶, Luc Mouthon^{2,4}, Ingeborg Bajema^{7,8}, Annelies Berden⁹, Eric Thervet^{1,2}, Loïc Guillevin^{2,4}, David Jayne^{5,6} and Alexandre Karras^{1,2}; on behalf of French Vasculitis Study Group (FVSG) and European Vasculitis Society (EUVAS) investigators

¹Department of Nephrology, Hôpital Européen Georges Pompidou, Assistance Publique – Hôpitaux de Paris, Paris, France; ²Department of Medicine, Université de Paris, Paris, France; ³Department of Internal Medicine, Institut Mutualiste Montsouris, Paris, France; ⁴Department of Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, Paris, France; ⁵Lupus and Vasculitis Clinic, Department of Renal Medicine, Addenbrooke's Hospital, Cambridge, UK; ⁶Department of Medicine, University of Cambridge, Cambridge, UK; ⁷Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands; ⁸Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, The Netherlands; and ⁹Department of Rheumatology and Clinical Immunology, Maastricht Hospital, Rotterdam, The Netherlands

In anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), hematuria and proteinuria are biomarkers reflecting kidney involvement at diagnosis. Yet, the prognostic value of their persistence after immunosuppressive induction therapy, reflecting kidney damage or persistent disease, remains uncertain. To study this, our post hoc analysis included participants of five European randomized clinical trials on AAV (MAINRITSAN, MAINRITSAN2, RITUXVAS, MYCYC, IMPROVE). Urine protein-creatinine ratio (UPCR) and hematuria of spot urine samples collected at the end of induction therapy (four-six months after treatment initiation) were correlated with the occurrence of a combined end point of death and/or kidney failure, or relapses during follow-up. Among 571 patients (59% men, median age 60), 60% had anti-proteinase 3-ANCA and 35% had anti-myeloperoxidase-ANCA, while 77% had kidney involvement. After induction therapy, 157/526 (29.8%) had persistent hematuria and 165/481 (34.3%) had UPCR of 0.05 g/mmol or more. After a median follow-up of 28 months (interquartile range 18–42), and adjustment for age, ANCA type, maintenance therapy, serum creatinine and persistent hematuria after induction, a UPCR of 0.05 g/mmol or more after induction was associated with significant risk of death/kidney failure (adjusted Hazard Ratio [HR] 3.06, 95% confidence interval 1.09–8.59) and kidney relapse (adjusted subdistribution HR 2.22, 1.16–4.24). Persistent hematuria was associated with significant kidney relapse (adjusted subdistribution HR 2.16, 1.13–4.11) but not with relapse affecting any organ nor with

death/kidney failure. Thus, in this large cohort of patients with AAV, persistent proteinuria after induction therapy was associated with death/kidney failure and kidney relapse, whereas persistent hematuria was an independent predictor of kidney relapse. Hence, these parameters must be considered to assess long-term kidney prognosis of patients with AAV.

Kidney International (2023) **103**, 1144–1155; <https://doi.org/10.1016/j.kint.2023.02.029>

KEYWORDS: ANCA-associated vasculitis; chronic kidney disease; hematuria; kidney failure; proteinuria; relapse

Copyright © 2023, International Society of Nephrology. Published by Elsevier Inc. All rights reserved.

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAVs) are a group of small vessel necrotizing vasculitis syndromes with multisystemic involvement, including the kidney.¹ Notwithstanding the significant progress achieved during these last decades regarding induction and maintenance immunosuppressive therapy,^{2–5} severe organ damage due to delayed diagnosis⁶ remains a major concern for patients with AAV.

Kidney involvement in AAV is characterized by pauci-immune necrotizing crescentic glomerulonephritis. The occurrence of glomerulonephritis is particularly frequent in microscopic polyangiitis and granulomatosis with polyangiitis, affecting >50% of all patients at diagnosis or during follow-up and sometimes leading to chronic kidney disease (CKD), which is independently associated with poor survival.^{7,8} Kidney failure can result from irreversible initial acute kidney disease or occur years later because of the nonspecific progression of CKD or to vasculitis relapses.⁹

At AAV diagnosis, hematuria and proteinuria are considered as biomarkers reflecting kidney involvement.¹⁰ Yet, the prognostic value of their persistence after the induction of remission by immunosuppressive therapy remains uncertain,

Correspondence: Nicolas Benichou, Department of Nephrology, Hôpital Européen Georges Pompidou, Assistance Publique – Hôpitaux de Paris, 20 rue Leblanc, 75015 Paris, France. E-mail: nico.benichou@gmail.com

Received 9 May 2022; revised 7 February 2023; accepted 16 February 2023; published online 20 March 2023

Lay Summary

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides are small vessels necrotizing diseases with multisystemic involvement, including the kidney. Hematuria and proteinuria are biomarkers reflecting kidney involvement at diagnosis. Yet, the prognostic value of their persistence after immunosuppressive induction therapy, reflecting either kidney damage or persistent disease, remains uncertain. In this *post hoc* study including 571 participants (77% of whom had kidney involvement) of 5 European randomized clinical trials on ANCA-associated vasculitis, the prognostic value of urine protein-creatinine ratio (UPCR) and hematuria of spot urine samples collected at the end of induction therapy was studied. After induction therapy, 29.8% of patients had persistent hematuria and 34.3% had $\text{UPCR} \geq 0.05$ g/mmol. After a median follow-up of 28 months and adjustment for age, ANCA type, maintenance therapy, serum creatinine, proteinuria and hematuria, persistence of a $\text{UPCR} \geq 0.05$ g/mmol after induction therapy was associated with poorer kidney survival and increased risk of kidney relapse whereas persistent hematuria was an independent predictor of kidney relapse. These parameters must be taken into account to assess the long-term renal prognosis of patients with ANCA-associated vasculitis.

although it could reflect either kidney damage or persistent active disease.

Albuminuria excretion rate,^{11–13} and by extension proteinuria excretion rate,^{14,15} is a well-recognized predictive factor for kidney failure in the general population and especially in patients with glomerular diseases.^{16,17} However, in AAV, its persistence after induction therapy has seldom been investigated, and no study has demonstrated a prognostic value for this simple biomarker. In contrast, a recent study has suggested that persistent hematuria during the remission phase of AAV is associated with the subsequent risk of kidney relapse but not with the risk of progression to kidney failure.¹⁸

The aim of this study was to evaluate the prognostic value of persistent proteinuria and/or hematuria after induction therapy in a large population of patients with AAVs by using pooled individual participant data from 5 large randomized controlled trials.

METHODS

Setting/participants

This study was a *post hoc* individual patient data analysis from 5 international multicenter randomized controlled trials on AAV published between 2010 and 2019. The Efficacy Study of Two Treatments in the Remission of Vasculitis (MAINRITSAN) and Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis (MAINRITSAN2) trials were coordinated by the French Vasculitis Study group, whereas RITUXVAS (An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine

based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis), Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC), and Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in ANCA Associated Systemic Vasculitis (IMPROVE) were performed by the European Vasculitis Society network. Rationale, study design, and results of these studies have been published elsewhere,^{3,19–22} and their main characteristics are presented in [Supplementary Tables S1 and S2](#). All 5 trials included either newly diagnosed or relapsing patients with granulomatosis with polyangiitis or microscopic polyangiitis (defined by 1994 Chapel Hill nomenclature)²³ and compared different induction or maintenance immunosuppressive therapy schemes. Local ethics committees approved each of the studies, and all patients gave written informed consent for participation.

All adult patients included in these trials were eligible for this study. Patients were excluded from the analysis if death or kidney failure had occurred during induction therapy or if no serum creatinine (sCreat) measurement was available after the end of induction therapy.

Data sources

For patients included in the MAINRITSAN study, we retrospectively contacted investigators to request proteinuria data after induction therapy from individual patient medical file. For the other studies, data were prospectively collected and retrieved in electronic data sets.

We reviewed the individual study protocols, template case report forms, and database dictionaries to harmonize study databases. We updated each database with unified coding across trials and merged them into a single database.

Exposure/definitions

The 2 main variables of interest were (i) proteinuria and (ii) hematuria, collected in a single measurement at the end of induction therapy, that is, between 4 and 6 months after treatment initiation for active disease (onset or flare; details in [Supplementary Table S2](#)). Proteinuria was quantitatively measured in either 24-hour urine samples or random spot urine samples, together with urinary creatinine level. Throughout this article, *proteinuria excretion rate* is defined and expressed as urine protein-creatinine ratio (UPCR) in grams per millimole. *Hematuria* was defined by the presence of ≥ 10 red blood cells per mm^3 in cytological examination of the urine. If cytological urine data were missing, blood by dipstick was used to identify hematuria.

Covariates and definitions

Baseline clinical characteristics (age, sex, ANCA, and AAV type), immunosuppressive therapies, and clinical, biological, and histological data prospectively collected during follow-up visits were analyzed. *Remission* was defined as a Birmingham Vasculitis Activity Score of 0.

Kidney involvement was defined as ≥ 1 kidney Birmingham Vasculitis Activity Score items present at entry or relapse, excluding hypertension alone (i.e., new or worsening hematuria, red blood cell casts, or new rise in sCreat $\geq 30\%$). Kidney function was assessed using sCreat and estimated glomerular filtration rate (eGFR), calculated using the Modified Diet in Renal Disease equation. Histological data, when available, were analyzed by a kidney pathologist at each center, with centralized review for biopsies from the RITUXVAS trial, and Berden classification²⁴ was retrospectively established.

End points

The main outcomes were time from the end of induction therapy to (i) a composite end point of death or incident kidney failure, whichever occurred first; (ii) first relapse; and (iii) first kidney relapse during follow-up. The secondary outcome included time from the end of induction therapy to (i) a composite end point of death or severe CKD, (ii) incident kidney failure, and (iii) severe CKD.

Incident kidney failure was defined as dialysis dependence at 2 consecutive visits at least 1 month apart or kidney transplantation. *Severe CKD* was defined as eGFR <30 ml/min per 1.73 m² (Kidney Disease: Improving Global Outcomes GFR categories G4 or G5) at ≥2 consecutive visits and included kidney failure. *Relapses* were defined as the recurrence or new appearance of any disease activity reflected by a Birmingham Vasculitis Activity Score of >0. *Kidney relapses* were defined as relapses with kidney involvement as defined above.

Statistical analysis

Categorical variables were summarized as number (percentage), and continuous variables were expressed as median (interquartile range [IQR]). To ensure a clear and simple clinical message, UPCR was coded as a binary variable (<0.05 or ≥0.05 g/mmol). The cumulative incidence of the composite outcome of death or kidney failure according to UPCR after induction therapy was determined using the Kaplan-Meier method with the use of the log-rank test. Cox proportional hazards regression models were used to estimate bivariate associations between patients' characteristics (at baseline and after induction therapy) and time to death/kidney failure. In multivariable Cox regression models, the effect of UPCR and hematuria after induction therapy on the composite end points of death or kidney failure and death or severe CKD, were adjusted for age, ANCA type, maintenance therapy, sCreat, UPCR, and hematuria after induction therapy. Patients without the occurrence of the end point were censored at the end of follow-up. Proportional hazards assumptions were graphically tested with Schoenfeld residuals.

For the outcomes of kidney relapse and relapse affecting any organ, incident kidney failure, and severe CKD, competing risk regression was performed.²⁵ For the outcome of kidney relapse, occurrence of death, kidney failure, and non-kidney relapse were considered competing events. For the outcome of relapse affecting any organ, death and kidney failure were considered competing events. For the outcomes of incident kidney failure and severe CKD, death was considered a competing event. Patients without the occurrence of the end point or any competing event were censored at the end of follow-up. The cumulative incidence of outcomes according to hematuria or UPCR was estimated, and adjusted analyses were performed accounting for age, ANCA type, maintenance therapy, sCreat, and hematuria or UPCR after induction therapy.

The association between risk factors and outcome was expressed as subdistribution hazard ratio (sHR) or hazard ratio (HR) with 95% confidence interval (95% CI). Covariates included in multivariable analyses were selected from among those with $P < 0.05$ in bivariate analyses or those with a known prognostic impact in the literature.

Statistical significance was set at 2-sided $P < 0.05$. Analyses were performed with R Studio software version 1.2.5033 (R Project for Statistical Computing, R Foundation).

Subgroups, sensitivity analysis, and missing data handling

Subgroup analysis including (i) only patients with kidney involvement at baseline, (ii) patients with myeloperoxidase (MPO)–ANCA

antibodies, (iii) patients with proteinase 3 (PR3)–ANCA antibodies, and (iv) patients with kidney pathology available at induction therapy initiation was performed.

The complete case method was adopted in the primary statistical analysis. To address missing data, the analysis assessing the time from the end of induction therapy to the composite end point of death or kidney failure was repeated with the entire cohort using the technique of multiple imputations by chained equations. The variables with missing data were imputed using all covariates of interest except those with >20% missing data. Using the “mice” package in R Studio,²⁶ 5 imputations were performed with 5 iterations per imputation.

Sensitivity analyses were performed using sCreat at induction therapy initiation and delta sCreat (sCreat before minus sCreat after induction) instead of sCreat after induction in the kidney survival models. An additional analysis was performed including ANCA persistence after induction therapy as an additional covariate for relapse-related outcomes. At last, sensitivity analyses with UPCR coded as a continuous variable were implemented.

RESULTS

Study population

Of the 617 patients enrolled in the 5 trials (MAINRITSAN, MAINRITSAN2, RITUXVAS, MYCYC, and IMPROVE),^{3,19–22} data were available for 614. After exclusion of 43 participants, 571 were included in the present study (Figure 1).

Baseline characteristics, clinical data, and biological data at the initiation of and after induction therapy are detailed for these 571 patients in Table 1. Briefly, there were 59% men, the median age was 60 years (IQR 50–68 years), 60% had anti-PR3-ANCA, 35% had anti-MPO-ANCA, and 77% had kidney involvement with a median sCreat of 133 μmol/l (IQR 84.3–241.8 μmol/l) at induction therapy initiation. Cyclophosphamide was used for the induction of remission in 75% of cases (63% i.v., 12% orally), rituximab for 15%, and mycophenolate mofetil for 10%. Rituximab and azathioprine were used as maintenance therapy in 37% and 46% of cases, respectively.

At the end of induction therapy, the median UPCR was 0.025 g/mmol (IQR 0.007–0.081 g/mmol), with 34.3% of patients (165 of 481) displaying UPCR ≥0.05 g/mmol. At this time point, persistent hematuria was noted in 29.8% of cases (157 of 526).

Death or kidney failure

After a median follow-up of 28 months (IQR 18–42 months) from the end of induction therapy, the composite outcome of death or kidney failure occurred in 5.1% of patients (29 of 571), including 2.3% of deaths (13 of 571) and 2.8% of incident kidney failure cases (16 of 571).

Factors associated with this outcome in bivariate and multivariable analysis are listed in Table 2. In multivariable analysis, the only factors independently associated with the occurrence of this end point were higher sCreat and UPCR ≥0.05 g/mmol after induction therapy (vs. <0.05 g/mmol: HR 3.06; 95% CI 1.09–8.59; $P = 0.034$; Kaplan-Meier survival curve shown in Figure 2) whereas persistent hematuria was not. UPCR after induction therapy was also

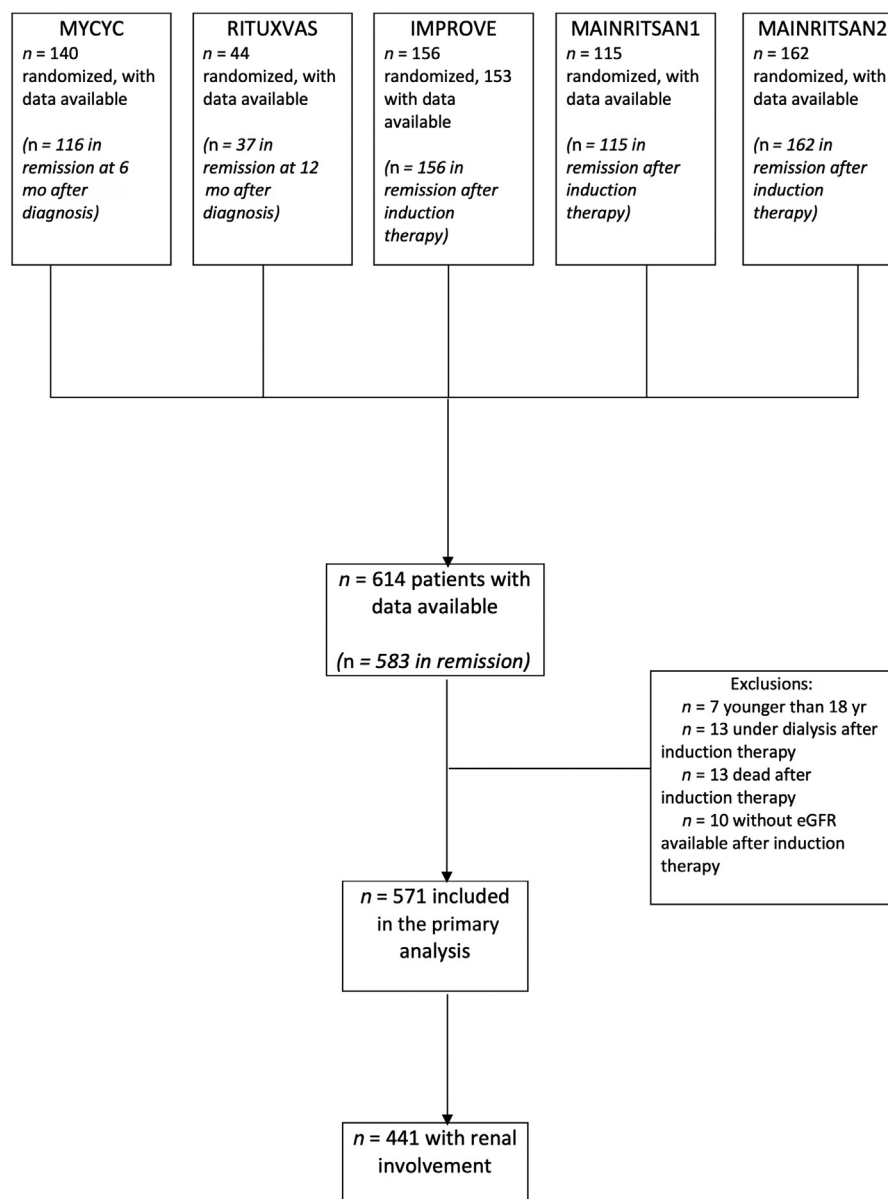


Figure 1 | Flowchart. eGFR, estimated glomerular filtration rate; IMPROVE, Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in ANCA Associated Systemic Vasculitis¹⁹; MAINRITSAN, Efficacy Study of Two Treatments in the Remission of Vasculitis²⁰; MAINRITSAN2, Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis²¹; MYCYC, Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis²²; RITUXVAS, An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis.³

independently associated with this outcome when sCreat after induction therapy was replaced by sCreat at induction therapy initiation and by delta sCreat. Overall, there were 12.1% of deaths/kidney failure cases (20 of 165) among patients with UPCR ≥ 0.05 g/mmol versus 1.6% (5 of 316) among those with UPCR < 0.05 g/mmol.

When considering death as a competing event, incident kidney failure occurred more often when UPCR was ≥ 0.05 g/mmol ($n = 13$ of 165 [7.9%]) than when UPCR was < 0.05 g/mmol ($n = 1$ of 316 [0.3%]; cumulative incidence in [Supplementary Figure S1](#)).

Death or severe CKD (eGFR < 30 ml/min per 1.73 m^2)

The composite outcome of death or severe CKD occurred in 13.7% of patients (78 of 571) after a median follow-up of 28 months (IQR 12–42 months).

In multivariable analysis ([Supplementary Table S3](#)), factors associated with this outcome were age, higher sCreat, and UPCR after induction therapy ≥ 0.05 g/mmol (vs. < 0.05 g/mmol: HR 3.85; 95% CI 1.96–7.58; $P < 0.001$).

When considering death as a competing event, severe CKD occurred more often when UPCR was ≥ 0.05 g/mmol ($n = 46$ of 165 [27.9%]) versus than when UPCR was < 0.05 g/mmol

Table 1 | Characteristics at the initiation of and after induction therapy (N = 571)

Characteristic	Value
Male sex	336/571 (58.8)
Age, yr	60 (50–68)
ANCA type (ELISA)	
Proteinase 3	318/532 (59.8)
Myeloperoxidase	185/532 (34.8)
Negative	29/532 (5.5)
AAV type	
Granulomatosis with polyangiitis	386/571 (67.6)
Microscopic polyangiitis	185/571 (32.4)
Induction therapy	
i.v. cyclophosphamide	359/571 (62.9)
p.o. cyclophosphamide	70/571 (12.3)
Rituximab	84/571 (14.7)
Mycophenolate mofetil	57/571 (10.0)
Methotrexate	1/571 (0.2)
Maintenance therapy	
Rituximab	212/571 (37.1)
Azathioprine	261/571 (45.7)
Mycophenolate mofetil	71/571 (12.4)
None	27/571 (4.7)
Kidney involvement	441/571 (77.2)
De novo AAV flare (vs. relapse)	495/571 (86.7)
Data at induction therapy initiation	
Serum creatinine, $\mu\text{mol/l}$ ^a	133 (84.8–246.3)
eGFR, ml/min per 1.73 m ^{2b}	45 (21–77)
UPCR, g/mmol ^c	0.082 (0.022–0.175)
Hematuria	153/269 (56.9)
Pulmonary involvement	141/270 (52.2)
Intra-alveolar hemorrhage	47/269 (17.5)
Data at the end of induction therapy	
Serum creatinine, $\mu\text{mol/l}$	105 (88–142)
eGFR, ml/min per 1.73 m ²	58 (40–77)
ANCA positivity	313/534 (58.6)
Hematuria	157/526 (29.8)
UPCR, g/mmol ^d	0.025 (0.007–0.081)
UPCR <0.03 g/mmol ^d	262/480 (54.6)
UPCR 0.03–0.1 g/mmol ^d	117/480 (24.4)
UPCR >0.1 g/mmol ^d	101/480 (21.0)
UPCR <0.05 g/mmol ^d	316/481 (65.7)
UPCR $\geq$ 0.05 g/mmol ^d	165/481 (34.3)

AAV, anti-neutrophil cytoplasmic autoantibody-associated vasculitis; ANCA, anti-neutrophil cytoplasmic autoantibody; eGFR, estimated glomerular filtration rate (Modified Diet in Renal Disease equation); ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; UPCR, urine protein-creatinine ratio.

^aSerum creatinine at induction therapy initiation replaced by 800 $\mu\text{mol/l}$ for 2 patients under renal replacement therapy; 3 missing values.

^beGFR at induction therapy initiation replaced by 5 ml/min per 1.73 m² for 2 patients under renal replacement therapy; 3 missing values.

^c226 missing values for UPCR at induction therapy initiation.

^d90 missing values for UPCR after induction therapy.

Quantitative values are given as median (IQR), and qualitative values are given as *n*/total *n* (%).

(*n* = 9 of 316 [2.8%]) (adjusted sHR 4.62; 95% CI 2.08–10.28; *P* < 0.001) (cumulative incidence in [Supplementary Figure S2](#)). The only other factor associated with this outcome in multivariable analysis was higher sCreat after induction therapy ([Supplementary Table S4](#)).

Relapse and kidney relapse

During follow-up, 196 of the 571 patients (34.3%) experienced a subsequent relapse, of whom 42 had kidney relapses (7.4%). Thirteen patients developed kidney failure

and 8 died before relapse occurrence. The median time from the end of induction to relapse, kidney failure, or death was 28 months (IQR 12–42 months).

In adjusted analysis for confounders with death and kidney failure as competing events, PR3-ANCA (vs. MPO-ANCA), maintenance therapies other than rituximab, and lower sCreat after induction therapy were the only factors associated with the overall risk of relapse ([Table 3](#)). Regarding the risk of kidney relapse, in adjusted analysis including non-kidney relapses as competing events, maintenance therapies other than rituximab, persistent hematuria, and UPCR $\geq$ 0.05 g/mmol after induction therapy were the sole significant prognostic factors identified (sHR 2.16; 95% CI 1.13–4.11; *P* = 0.020 and sHR 2.22; 95% CI 1.16–4.24; *P* = 0.016, respectively; [Table 3](#)). The results were similar after adjusting for ANCA persistence after induction therapy. ANCA persistence at this time point was not associated with the subsequent occurrence of any relapse, nor with kidney relapse. The cumulative incidence of kidney relapse according to persistent hematuria and UPCR is shown in [Figures 3](#) and [4](#).

Subgroup analyses

In the subgroup of patients with kidney involvement at induction therapy initiation (*n* = 441 patients), the results were identical ([Supplementary Figure S3](#) and [Supplementary Tables S5](#) and [S6](#)).

In both subgroups of patients with MPO-ANCA and PR3-ANCA, death/kidney failure (observed in 14 of 185 and 12 of 318 cases, respectively) occurred more often in patients with UPCR $\geq$ 0.05 than in those with UPCR <0.05 g/mmol ([Supplementary Table S7](#) and [Supplementary Figures S4](#) and [S5](#)). For patients with PR3-ANCA, kidney relapses were more common in patients with UPCR $\geq$ 0.05 g/mmol. No other significant relationship between UPCR and hematuria after induction therapy and outcomes were found across MPO-ANCA and PR3-ANCA subgroups ([Supplementary Table S7](#)). ANCA persistence after induction was not associated with the subsequent occurrence of any relapse or kidney relapse within each subgroup.

Subgroup with kidney pathology

Initial kidney pathology data could be retrospectively collected for 65 patients included either in the RITUXVAS or the MAINRITSAN and MAINRITSAN2 trials and reclassified according to the glomerular histopathological classification currently used in AAV.²⁴ In this subgroup of patients with kidney involvement and available kidney biopsy results (detailed in [Table 4](#)), the focal subtype was the most frequently observed (23 of 65 [35%]) whereas the sclerotic subclass was less common (9 of 65 [14%]). The latest category was associated with more severely decreased GFR at the initial presentation and after the induction of remission as well as with higher UPCR levels at the end of induction therapy, but also with poor kidney prognosis, as almost

Table 2 | Bivariate and multivariable Cox regression analysis of factors associated with death or kidney failure

Variable	Bivariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	P	Adjusted hazard ratio (95% CI)	P
Male sex	0.86 (0.41–1.78)	0.67		
Older age (per 1-yr increase)	1.04 (1.01–1.08)	0.009	1.04 (1.00–1.07)	0.056
AAV type: MPA (vs. GPA)	3.10 (1.45–6.66)	0.004		
ANCA type (reference: PR3)				
MPO	2.36 (1.08–5.12)	0.030	1.09 (0.42–2.86)	0.107
Negative	1.53 (0.34–6.85)	0.578	0.85 (0.11–6.74)	0.877
Relapse (vs. <i>de novo</i> AAV flare)	0.62 (0.19–2.07)	0.441		
Kidney involvement	9.34 (1.27–68.68)	0.028		
Pulmonary involvement	0.32 (0.12–0.81)	0.017		
Intra-alveolar hemorrhage	1.08 (0.36–3.20)	0.894		
sCreat at induction therapy initiation (per 10 μ mol/l) ^a	1.02 (1.01–1.03)	<0.001		
sCreat after induction therapy (per 10 μ mol/l)	1.10 (1.08–1.13)	<0.001	1.11 (1.07–1.16)	<0.001
ANCA positive after induction therapy	0.85 (0.40–1.83)	0.683		
Maintenance therapy: other (vs. RTX) ^b	0.87 (0.42–1.83)	0.718	0.79 (0.32–1.97)	0.611
Hematuria after induction therapy	2.13 (1.01–4.49)	0.041	1.50 (0.62–3.62)	0.369
UPCR after induction therapy ≥ 0.05 g/mmol	7.91 (2.97–21.09)	<0.001	3.06 (1.09–8.59)	0.034
UPCR after induction therapy (per 0.1 g/mmol)	1.93 (1.61–2.30)	<0.001		

AAV, anti-neutrophil cytoplasmic autoantibody-associated vasculitis; ANCA, anti-neutrophil cytoplasmic autoantibody; CI, confidence interval; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; RTX, rituximab; sCreat, serum creatinine; UPCR, urine protein-creatinine ratio.

^asCreat at induction therapy initiation replaced by 800 μ mol/l for 2 patients under renal replacement therapy.

^bOther maintenance therapies: azathioprine ($n = 261$), mycophenolate mofetil ($n = 71$), none ($n = 27$).

Bivariate analysis: hazard ratios were obtained using the Cox proportional hazards model. Number of events: 29 (13 deaths, 16 kidney failure) in 571 patients.

Multivariable analysis: hazard ratios were obtained using the Cox proportional hazards model after adjustment for age, ANCA type, maintenance therapy, sCreat after induction therapy, hematuria, and UPCR ≥ 0.05 g/mmol after induction therapy. In the 417 patients included in this analysis, there were 24 events (death or kidney failure).

half of them met the composite death/kidney failure end point during follow-up. In contrast, patients with the focal subtype had very low levels of proteinuria and mildly decreased GFR after induction therapy, with an excellent prognosis, as only 4.3% of them reached the death/kidney failure end point.

The number of patients with available kidney pathology was too small to perform a multivariable analysis including both the glomerular classification and proteinuria. Nevertheless, after adjustment for the percentage of normal glomeruli, persistence of UPCR ≥ 0.05 g/mmol after induction therapy was still associated with the risk of death/severe CKD (HR 3.99; 95% CI 1.04–15.24; $P = 0.043$).

Other sensitivity analyses

A total of 3 variables included in the primary regression models had missing data (Supplementary Table S8). UPCR after induction therapy, the variable that had the largest amount of missing data, had 90 missing values (15.8%).

Multiple imputation was performed, and the imputed cohort included all 154 patients (27%) who were excluded because of missing values in any of the variables used in the regression models. The model estimate of UPCR ≥ 0.05 g/mmol for the risk of death/kidney failure from the imputed data set was consistent with the complete case cohort (vs. <0.05 g/mmol: adjusted HR 4.99; 95% CI 1.76–14.17; $P = 0.002$). However, missing data for UPCR and hematuria after induction therapy may not have been missing at random, a hypothesis that could limit the accuracy of this analysis.

In analyses with UPCR coded as a continuous variable, the prognostic value of persistent proteinuria was confirmed in multivariable analyses (Supplementary Table S9).

DISCUSSION

In this large cohort of 571 patients with AAVs, persistence of proteinuria after the induction of remission was an independent predictor of death/kidney failure whereas persistent hematuria or proteinuria after induction therapy were independent predictors of kidney relapse. On the basis of the individual patient data of 5 recent randomized controlled trials on AAV, this study is, to our knowledge, the largest one to investigate the prognostic value of persistence of proteinuria and hematuria after the induction of remission in this disease.

The long-term consequences of kidney involvement are a major concern in AAV. The severity of chronic kidney damage has mainly been associated with the level of sCreat/eGFR at diagnosis, reflecting the severity of the initial kidney insult and sometimes the diagnostic delay, which is necessary before therapy is initiated. Kidney survival can also be predicted by initial kidney pathology, and several studies have shown that both the percentage of sclerotic glomeruli and the degree of interstitial fibrosis/tubular atrophy are strongly associated with long-term kidney prognosis.^{24,27,28}

Although the level of proteinuria at diagnosis has been associated with the presence of chronic glomerular lesions and unfavorable kidney outcome in unadjusted analyses,^{29,30} little is known about the significance of persistent proteinuria at the end of induction therapy in AAV, in contrast to

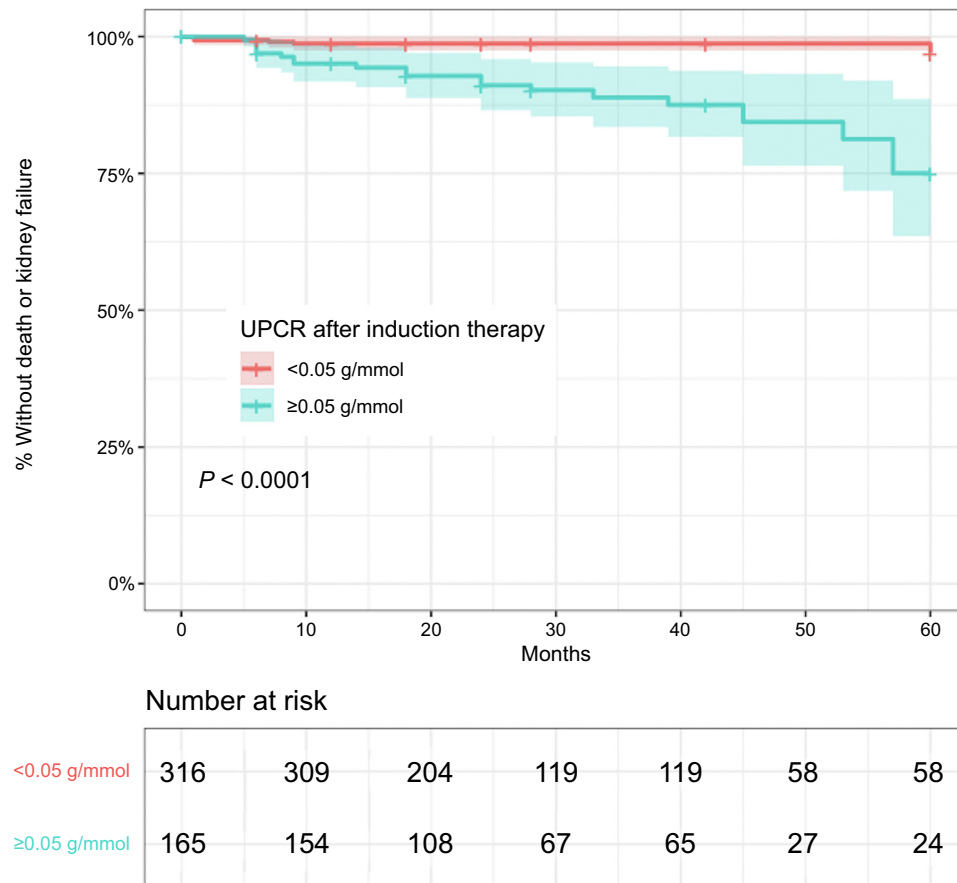


Figure 2 | Kaplan-Meier analysis of the composite outcome of death or kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] ≥ 0.05 or < 0.05 g/mmol).

data observed in other glomerular diseases^{16,17,31} as well as in cohorts with CKD.¹⁴ Although patients with poor kidney outcome displayed higher proteinuria during follow-up in a small analysis of 21 patients with MPO-ANCA,³² this result was not confirmed by de Joode *et al.*,⁶ who analyzed 212 kidney AAVs and found no association between baseline or 6-month proteinuria and kidney failure. In their *post hoc* study

of 149 patients extracted from the Wegener's Granulomatosis Etanercept Trial (WGET) and Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis (RAVE) trial,¹⁸ Rhee *et al.* observed no significant effect of proteinuria at remission (assessed with a urine dipstick test) on eGFR slopes nor on the risk of subsequent relapse. Hence, our study is the first to demonstrate that UPCR ≥ 0.05 g/

Table 3 | Competing risk regression multivariable analysis of factors associated with any relapse and kidney relapse

Variable	Any relapse			Kidney relapse		
	Adjusted sHR	95% CI	P	Adjusted sHR	95% CI	P
Older age (per 1-yr increase)	0.99	0.98–1.00	0.070	1.02	0.99–1.04	0.170
ANCA type (reference: MPO)						
Negative	1.51	0.77–2.93	0.230	1.27	0.32–4.95	0.730
PR3	1.67	1.15–2.43	0.007	1.40	0.68–2.88	0.360
Maintenance therapy: other (vs. RTX)	3.80	2.44–5.91	<0.001	7.11	2.15–23.52	0.001
sCreat after induction therapy (per 10 μ mol/l)	0.94	0.89–0.99	0.013	0.98	0.94–1.03	0.490
Hematuria after induction therapy	1.01	0.70–1.45	0.970	2.16	1.13–4.11	0.020
UPCR after induction therapy ≥ 0.05 g/mmol	1.06	0.73–1.54	0.750	2.22	1.16–4.24	0.016

ANCA, anti-neutrophil cytoplasmic autoantibody; CI, confidence interval; MPO, myeloperoxidase; PR3, proteinase 3; RTX, rituximab; sCreat, serum creatinine; sHR, sub-distribution hazard ratio; UPCR, urine protein-creatinine ratio.

sHRs were obtained using Fine and Gray competing risk regression after adjustment for each of the variables presented in this table. Sensitivity analyses also adjusted for ANCA persistence after induction therapy did not change the results. Of the 417 patients included in these analyses, 141 underwent relapses, 36 underwent kidney relapses, and 17 had a competing event occurring before relapse (11 kidney failure, 6 deaths). For kidney relapse analysis, non-kidney relapses were also considered as competing events.

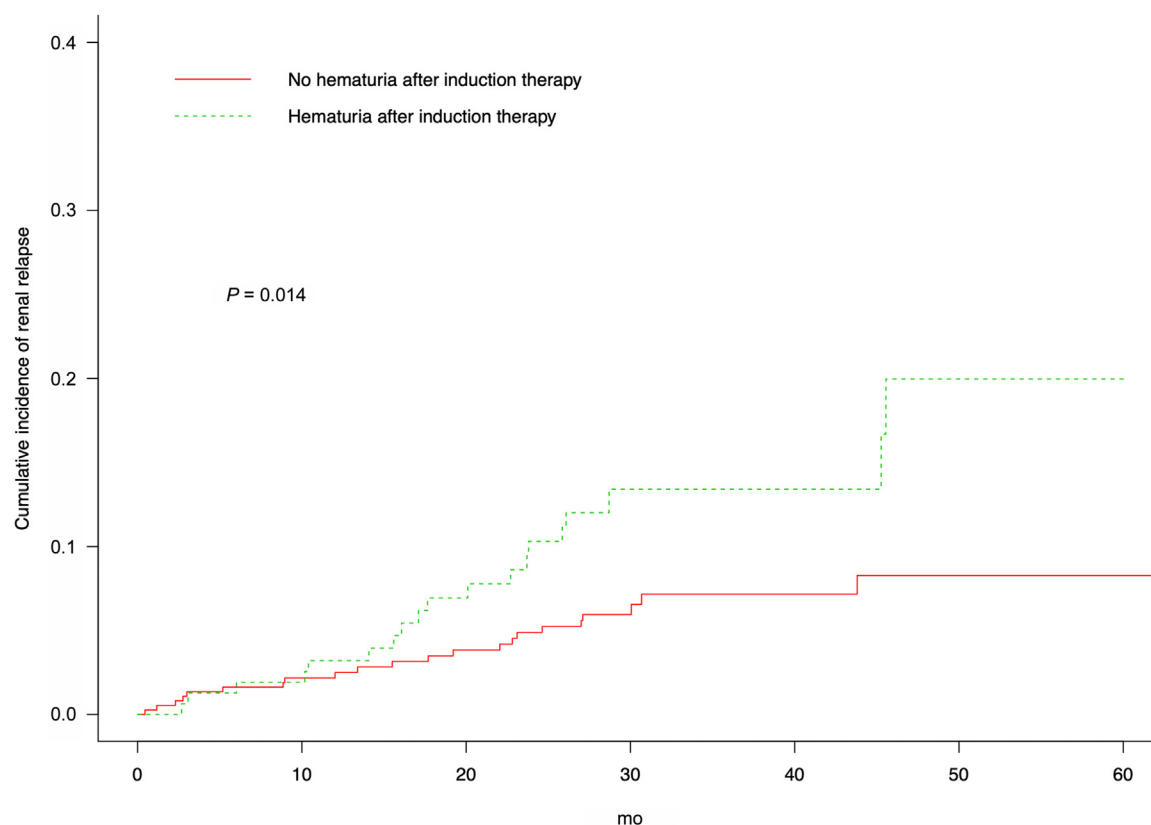


Figure 3 | Cumulative incidence of kidney relapse according to persistent hematuria after induction therapy. Competing risk survival model: the event of interest was kidney relapse, and the competing events were death and non-kidney relapses.

mmol after induction therapy is a strong predictor (HR 3) for the clinically meaningful composite outcome of death or kidney failure even after adjustment for age, ANCA type, type of maintenance therapy, and kidney function after induction. This association was found in all subgroups of patients and was consistent in sensitivity analyses, including multiple imputation for missing data. The precise significance of persistent proteinuria remains unclear as it might be associated either with resistant and still active glomerulonephritis or with chronic kidney damage due to glomerular scarring, such as fibrotic crescents and sclerotic glomeruli.^{33,34} Nevertheless, the fact that persistent proteinuria after induction therapy was also associated with the occurrence of subsequent kidney relapse (sHR 2.22 in adjusted analyses) supports the hypothesis that proteinuria may reflect the ongoing inflammatory activity. Data from studies evaluating the anti-inflammatory complement inhibitor avacopan in AAV are consistent with this hypothesis, as proteinuria excretion rate fell more quickly than in standard-of-care treated patients, and this was associated with higher subsequent GFR.³⁵ Although the prognostic value of the initial kidney biopsy is well established in AAV,^{24,27} a systematic assessment of repeat biopsies to detect ongoing glomerular inflammation and guide clinical management is currently lacking. Considering the poor clinical-pathological correlation recently underlined in lupus nephritis,^{36,37} similar studies would be of special

interest in AAV, especially in patients with persistence of proteinuria and/or hematuria, after induction therapy is achieved.

In addition, our data indicate that the presence of hematuria after induction therapy was an independent predictive factor for the risk of kidney relapse (sHR 2.16) and confirm the findings of 2 recent studies. In the analysis by Rhee *et al.*,¹⁸ an increase in hematuria extent was associated with a higher 12-month risk of kidney relapse. In a retrospective French study of 86 patients,³⁸ hematuria at remission was associated with an increased kidney relapse risk within 44 months. Again, the pathophysiological significance of the persistence of isolated hematuria in patients otherwise in clinical remission is uncertain. Histopathological data of patients in such situations are scarce, and the only small series of repeat kidney biopsies published to date did not find correlations between hematuria and histological activity.^{38–41} Of note, our data suggest that the overall—kidney and extra-kidney—relapse risk was not predicted by urinalysis but was higher in patients with PR3-ANCA, in those with better kidney function, and in those who did not receive rituximab as maintenance therapy, as previously described.^{42–45} Pulmonary involvement and ANCA persistence after induction therapy, previously identified as risk factors for relapses,^{43,46} were not highlighted as such in our multivariable analysis. Although there was an association between persistent hematuria and

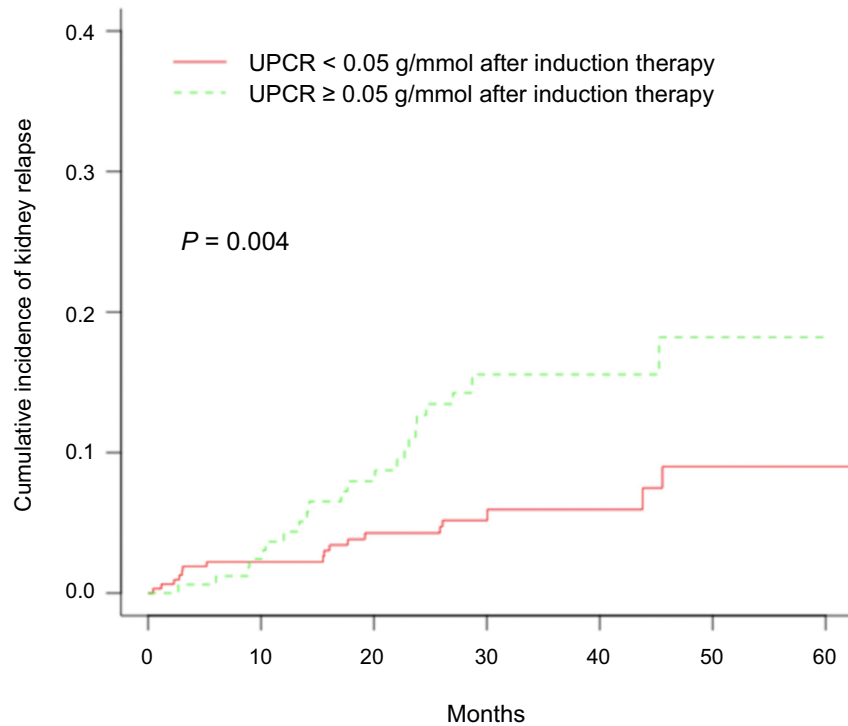


Figure 4 | Cumulative incidence of kidney relapse according to persistent urine protein-creatinine ratio (UPCR) ≥ 0.05 g/mmol after induction therapy. Competing risk survival model: the event of interest was kidney relapse, and the competing events were death and non-kidney relapses.

risk of death/kidney failure in bivariate analysis, this relationship was not significant after adjusting for confounders. Similarly, maintenance therapy with rituximab, which was

clearly associated with a reduced risk of kidney (and overall) relapse, was not predictive of kidney survival, perhaps owing to a lack of power.

Table 4 | Characteristics at induction therapy initiation and after induction therapy and outcomes according to initial kidney biopsy (Berdén classification²⁴)

Variable	Focal (n = 23)	Crescentic (n = 16)	Mixed (n = 17)	Sclerotic (n = 9)	Total (n = 65)
Age, yr	61 (53–71)	58 (52–64)	67 (60–74)	54 (48–61)	61 (52–69)
MPO vs. PR3	8 vs. 15	3 vs. 13	11 vs. 6	6 vs. 3	28 vs. 37
sCreat at induction therapy initiation ^a	111 (94–194)	406 (318–555)	187 (128–275)	388 (317–464)	243 (115–388)
sCreat after induction	106 (95–117)	131 (113–173)	135 (108–200)	228 (168–286)	124 (105–180)
UPCR after induction (g/mmol)	0.029 (0.004–0.044)	0.130 (0.042–0.200)	0.067 (0.030–0.110)	0.129 (0.099–0.195)	0.051 (0.021–0.130)
UPCR after induction ≥ 0.05 g/mmol	5/22 (22.7)	11/15 (73.3)	9/17 (52.9)	8/9 (88.9)	33/63 (52.4)
Hematuria after induction	7/22 (31.8)	7/16 (43.8)	9/17 (52.9)	2/7 (28.6)	25/62 (40.3)
Death or kidney failure	1/23 (4.3)	1/16 (6.3)	3/17 (17.6)	4/9 (44.4)	9/65 (5.1)
	Reference	HR 1.58 (95% CI 0.09–25.20)	HR 5.27 (95% CI 0.54–51.10)	HR 9.21 (95% CI 1.02–82.71)	
Death or severe CKD ^b	3/23 (13.0)	1/16 (6.3)	6/17 (35.3)	7/9 (77.8)	17/65 (26.2)
	Reference	HR 0.50 (95% CI 0.05–4.79)	HR 3.60 (95% CI 0.89–14.49)	HR 6.48 (95% CI 1.67–25.18)	
Any relapse	10/23 (43.5)	5/16 (31.3)	5/17 (29.4)	2/9 (22.2)	22/65 (33.8)
	Reference	sHR 0.64 (95% CI 0.21–1.91)	sHR 0.86 (95% CI 0.30–2.46)	sHR 0.30 (95% CI 0.07–1.28)	
Kidney relapse	0/23 (0)	3/16 (18.8)	3/17 (17.6)	1/9 (11.1)	7/65 (10.8)

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IQR, interquartile range; MPO, myeloperoxidase; PR3, proteinase 3; sCreat, serum creatinine; sHR, subdistribution hazard ratio; UPCR, urine protein-creatinine ratio.

^asCreat at induction therapy initiation replaced by 800 μ mol/l for 1 patient under renal replacement therapy.

^bSevere CKD: eGFR < 30 ml/min per 1.73 m².

Quantitative values are given as median (IQR), and qualitative values are given as n/total n (%).

HRs were obtained using the Cox unadjusted proportional hazards model.

sHRs were obtained using unadjusted Fine and Gray competing risk regression.

Our study has several limitations. First, kidney involvement was not present in all patients, and one could argue that persistent proteinuria is just the reflection of unspecific kidney disease at presentation, a condition known to be associated with a long-term kidney failure risk. Nevertheless, when focusing on patients with kidney vasculitis, our results were not modified, meaning that persistent proteinuria allows differentiation between patients with low- and high-risk kidney AAVs. Second, our results cannot be applied to all patients with AAV. Indeed, patients included in this study were mostly of European ancestry, and only a minority of them received rituximab (15% for induction, 37% for maintenance), an immunosuppressive drug that is now considered as standard-of-care therapy in AAV. Third, we performed *post hoc* analyses of heterogeneous randomized controlled trials with different induction/maintenance immunosuppressive schemes, inclusion criteria, and end points. However, data, including outcome assessment, were prospectively collected, with the exception of proteinuria, obtained retrospectively in the MAINRITSAN trial. Fourth, proteinuria and hematuria evaluations relied on single measurement—fluctuations in urine findings might occur between several samples—and 24-hour proteinuria or spot UPCR was used indistinctly to estimate proteinuria (converted in UPCR for all). However, potential misclassification induced bias would probably not be differential. In addition, the glomerular origin of hematuria could not be certified as the presence of urinary casts or acanthocytes was not available, nor was the intensity of hematuria. Finally, we could not include in our models important missing covariates such as prescription of renin-angiotensin-system blockers, which can modify both the level of proteinuria and kidney prognosis, as well as initial kidney biopsy results, which could only be retrospectively obtained for a small proportion of our study population. However, our data suggest that persistence of proteinuria after induction therapy was particularly elevated in patients with the sclerotic subtype of the glomerular AAV classification, which is also known to have worse long-term kidney prognosis. Furthermore, persistent proteinuria was predictive of kidney outcome, irrespective of the initial percentage of normal glomeruli.

Our results have important implication for clinical research, as they suggest that persistent proteinuria could be considered as a target in future AAV studies. Nevertheless, further studies are needed to demonstrate that resolution of proteinuria can be used as a short-term surrogate marker. Indeed, the identification of a strong but simple prognostic factor assessed after induction therapy could provide a valuable surrogate end point to evaluate future therapies. Despite validation of surrogate end points based on proteinuria reduction in different types of glomerulonephritis,^{47,48} this approach has never been validated in AAV.⁴⁹ Although we know that a significant proportion of patients with AAV reaching kidney failure have slowly progressive CKD without active vasculitis,⁵⁰ no specific study has been performed to demonstrate that

nephroprotection with antiproteinuric treatments such as renin-angiotensin-system inhibitors can modify kidney prognosis in AAV-related nephropathy.

We believe that our findings can be useful for guiding clinical care of patients with AAV. Individualized management could embed closer follow-up and longer duration of maintenance therapy for patients at a higher risk of relapse, including those with PR3-ANCA, persistent ANCA positivity, or persistent hematuria/proteinuria. Pending for more accurate insight into the significance of persistent proteinuria, increased kidney risk in this subgroup of patients emphasizes the need for careful nephroprotective measures such as renin-angiotensin-system blockers or sodium-glucose-transporter 2 inhibitors prescription, therapeutic interventions that has been proven particularly useful in other glomerulopathies.^{51–53}

Precision medicine relying on individual characteristics is currently revolutionizing patient management in many fields of medicine. Awaiting for the development and validation of novel biomarkers,⁵⁴ simple, noninvasive, and costless assessment of proteinuria and hematuria should be used for the management of AAV glomerulonephritis, especially to assess the long-term kidney prognosis of these patients.

DISCLOSURE

PC reports grants from Hoffmann-La Roche during the conduct of the Comparison Between a Long Term and a Conventional Maintenance Treatment With Rituximab (MAINRITSAN3) study. BT has received consulting fees from GSK, Vifor Pharma, AstraZeneca, Pfizer, and Boehringer Ingelheim. DJ and RBJ received grant support paid to the Cambridge University Hospitals National Health Service (NHS) foundation Trust from Roche for the RITUXVAS (An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis) trial and from Vifor Pharma for the Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC). DJ has received consulting or lecture fees from Amgen, AstraZeneca, Chemo-Centryx, GSK, Novartis, Roche, Takeda, and Vifor Pharma; has stock or stock options in Aurinia; and has received research grants from National Institute for Health and Care Research (NIHR) (UK), UK Research and Innovation (UK), and GSK. He is also supported by the Cambridge NIHR Biomedical Centre. AK has received consulting or lecture fees from Novartis, Boehringer Ingelheim, Otsuka, Vifor Pharma, GSK, and AstraZeneca. IB has received consulting fees from Boehringer Ingelheim, GSK, Aurinia, Novartis, Toleranzia, Catalyst Biosciences, and Hansa Biopharma. She is the owner of BiPath (Bajema Institute of Pathology). She is on consultancy boards of Glomerular Disease Council (Vifor Pharma) and C3G Adviesraad (Novartis). All the other authors declared no competing interests.

ACKNOWLEDGMENTS

The authors thank all investigators, trial teams, and patients for their participation in the trials: Efficacy Study of Two Treatments in the Remission of Vasculitis (MAINRITSAN),²⁰ Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis

(MAINRITSAN2),²¹ RITUXVAS (An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis),³ Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC),²² and Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in ANCA Associated Systemic Vasculitis (IMPROVE).¹⁹ In particular, the authors thank Christian Pagnoux, Chahera Kouatra, Olivier Aumaitre, Pascal Cohen, François Maurier, Olivier Decaux, Jacques Ninet, Pierre Gobert, Thomas Quémeneur, Claire Blanchard-Delaunay, Pascal Godmer, Xavier Puéchal, Pierre-Louis Carron, Pierre-Yves Hatron, Nicolas Limal, Mohamed Hamidou, Maïze Ducret, Eric Daugas, Thomas Papo, Bernard Bonnotte, Alfred Mahr, and Philippe Ravaud; Elodie Perrodeau, Stanislas Faguer, Antoine Huart, Christian Agard, Maxime Samson, Noémie Jourde-Chiche, François Lifermann, Catherine Hanrotel-Saliou, Nicolas Martin-Silva, Grégory Pignet, Marie Matignon, Jean-François Viallard, François Maurier, Nadine Meaux-Ruault, Sophie Rivière, and Jean Sibilia; Michael Walsh, Caroline O. Savage, Kirsten de Groot, Lorraine Harper, Thomas Hauser, Irmgard Neumann, Vladimir Tesar, Karl-Martin Wissing, and Wilhelm Schmitt; Jose Ballarin, Daniel Engelbert Blockmans, Paul Brogan, Annette Bruchfeld, Maria C. Cid, Karen Dahlsveen, Janak de Zoysa, Georgina Espigol-Frigolé, Peter Lanyon, Chen Au Peh, Augusto Vaglio, Dorothy Walsh, and Giles Walters; and Jan Willem Cohen Tervaert, Raashid Luqmani, Matthew D. Morgan, Marten Segelmark, Pieter van Paassen, and Kerstin Westman. The author also thank the French Vasculitis Study Group (FVSG) and European Vasculitis Society (EUVAS) for their support.

The present *post hoc* study did not receive any specific funding. The MAINRITSAN trial received funding from the French Ministry of Health (grant PHRC 2008-002846-51). The MAINRITSAN2 trial received funding from the French Ministry of Health (grant PHRC 2011 AOM11145). The IMPROVE trial received funding from the Cambridge Biomedical Research Centre, the French Ministry of Health (PHRC régional 2011), and Hoffman-La Roche Ltd. The RITUXVAS trial was supported by the Cambridge University Hospitals National Health Service Foundation Trust, a research grant from F. Hoffmann–La Roche, a Kidney Research Scientist Core Education and National Training Program award from the Canadian Institute of Health Research, grants from the Kidney Foundation of Canada and the Canadian Society of Nephrology, and a Clinical Fellowship Award from the Alberta Heritage Foundation for Medical Research. The MYCYC trial was supported by the Cambridge University Hospitals NHS Foundation Trust and Vifor Pharma.

SUPPLEMENTARY MATERIAL

[Supplementary File \(Word\)](#)

Supplementary Table S1. Studies' characteristics.

Supplementary Table S2. Characteristics at the initiation of and after induction therapy according to trial (for the 571 patients included).

Supplementary Table S3. Multivariable Cox regression analysis of factors associated with the composite outcome of death or severe chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <30 ml/min per 1.73 m²).

Supplementary Table S4. Competing risk regression analysis of factors associated with severe chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <30 ml/min per 1.73 m²), with death as a competing event.

Supplementary Table S5. Multivariable Cox regression analysis of factors associated with the composite outcome of death or kidney failure in patients with kidney involvement.

Supplementary Table S6. Competing risk regression analysis of factors associated with any relapse and kidney relapse in patients with kidney involvement.

Supplementary Table S7. Outcomes according to urine protein-creatinine ratio (UPCR) and hematuria after induction therapy across myeloperoxidase (MPO)–anti-neutrophil cytoplasmic antibody (ANCA) and proteinase 3 (PR3)–ANCA subgroups in unadjusted analyses.

Supplementary Table S8. Description of the variables with missing data.

Supplementary Table S9. Multivariable Cox regression analysis of factors associated with death or kidney failure, with urine protein-creatinine ratio (UPCR) after induction therapy as a continuous variable.

Supplementary Figure S1. Cumulative incidence curves for kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] ≥0.05 or <0.05 g/mmol). Competing risk survival model: the event of interest was kidney failure, and the competing event was death.

Supplementary Figure S2. Cumulative incidence curves for severe chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <30 ml/min per 1.73 m²) according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] ≥0.05 or <0.05 g/mmol). Competing risk survival model: the event of interest was incident eGFR <30 ml/min per 1.73 m² (including kidney failure), and the competing event was death.

Supplementary Figure S3. Kaplan-Meier analysis of the composite outcome of death or kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] ≥0.05 or <0.05 g/mmol) in patients with kidney involvement.

Supplementary Figure S4. Kaplan-Meier analysis of the composite outcome of death or kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] ≥0.5 or <0.05 g/mmol) in patients with myeloperoxidase (MPO)–anti-neutrophil cytoplasmic antibody (ANCA).

Supplementary Figure S5. Kaplan-Meier analysis of the composite outcome of death or kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] ≥0.05 or <0.05 g/mmol) in patients with proteinase 3 (PR3)–anti-neutrophil cytoplasmic antibody (ANCA).

REFERENCES

- Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum.* 2013;65:1–11.
- de Groot K, Harper L, Jayne DRW, et al. Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized trial. *Ann Intern Med.* 2009;150:670–680.
- Jones RB, Tervaert JWC, Hauser T, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. *N Engl J Med.* 2010;363:211–220.
- Stone JH, Merkel PA, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. *N Engl J Med.* 2010;363:221–232.
- Flossmann O, Berden A, de Groot K, et al. Long-term patient survival in ANCA-associated vasculitis. *Ann Rheum Dis.* 2011;70:488–494.
- de Jode AAE, Sanders JSF, Stegeman CA. Renal survival in proteinase 3 and myeloperoxidase ANCA-associated systemic vasculitis. *Clin J Am Soc Nephrol.* 2013;8:1709–1717.
- Robson J, Doll H, Suppiah R, et al. Damage in the ANCA-associated vasculitides: long-term data from the European vasculitis study group (EUVAS) therapeutic trials. *Ann Rheum Dis.* 2015;74:177–184.
- Rhee RL, Hogan SL, Poulton CJ, et al. Trends in long-term outcomes among patients with antineutrophil cytoplasmic antibody-associated vasculitis with renal disease. *Arthritis Rheumatol.* 2016;68:1711–1720.

9. Wester Trejo MAC, Floßmann O, Westman KW, et al. Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: unpredictable, but predictive of renal outcome. *Rheumatology*. 2019;58:103–109.
10. Jennette JC. Rapidly progressive crescentic glomerulonephritis. *Kidney Int*. 2003;63:1164–1177.
11. Iseki K, Ikemiya Y, Iseki C, Takishita S. Proteinuria and the risk of developing end-stage renal disease. *Kidney Int*. 2003;63:1468–1474.
12. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:2073–2081.
13. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. *JAMA*. 2010;303:423–429.
14. Ruggerenti P, Perna A, Mosconi L, et al; “Gruppo Italiano di Studi Epidemiologici in Nefrologia” (GISEN). Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. *Kidney Int*. 1998;53:1209–1216.
15. Sumida K, Nadkarni GN, Grams ME, et al. Conversion of urine protein-creatinine ratio or urine dipstick protein to urine albumin-creatinine ratio for use in chronic kidney disease screening and prognosis: an individual participant-based meta-analysis. *Ann Intern Med*. 2020;173:426–435.
16. Reich HN, Troyanov S, Scholey JW, Cattran DC; Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol*. 2007;18:3177–3183.
17. Moroni G, Gatto M, Tamborini F, et al. Lack of EULAR/ERA-EDTA response at 1 year predicts poor long-term renal outcome in patients with lupus nephritis. *Ann Rheum Dis*. 2020;79:1077–1083.
18. Rhee RL, Davis JC, Ding L, et al. The utility of urinalysis in determining the risk of renal relapse in ANCA-associated vasculitis. *Clin J Am Soc Nephrol*. 2018;13:251–257.
19. Hiemstra TF, Walsh M, Mahr A, et al. Mycophenolate mofetil vs azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis: a randomized controlled trial. *JAMA*. 2010;304:2381–2388.
20. Guillevin L, Pagnoux C, Karras A, et al. Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis. *N Engl J Med*. 2014;371:1771–1780.
21. Charles P, Terrier B, Perrodeau É, et al. Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomised controlled, phase III trial (MAINRITSAN2). *Ann Rheum Dis*. 2018;77:1143–1149.
22. Jones RB, Hiemstra TF, Ballarin J, et al. Mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis: a randomised, non-inferiority trial. *Ann Rheum Dis*. 2019;78:399–405.
23. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. *Arthritis Rheum*. 1994;37:187–192.
24. Berden AE, Ferrario F, Hagen EC, et al. Histopathologic classification of ANCA-associated glomerulonephritis. *J Am Soc Nephrol*. 2010;21:1628–1636.
25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
26. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. *J Stat Softw*. 2011;45:1–67.
27. Brix SR, Noriega M, Tennstedt P, et al. Development and validation of a renal risk score in ANCA-associated glomerulonephritis. *Kidney Int*. 2018;94:1177–1188.
28. Bajema IM, Hagen EC, Hermans J, et al. Kidney biopsy as a predictor for renal outcome in ANCA-associated necrotizing glomerulonephritis. *Kidney Int*. 1999;56:1751–1758.
29. Neumann I, Kain R, Regele H, et al. Histological and clinical predictors of early and late renal outcome in ANCA-associated vasculitis. *Nephrol Dial Transplant*. 2005;20:96–104.
30. Xu PC, Chen T, Gao S, et al. Clinical and pathologic characteristics of pauci-immune anti-myeloperoxidase antibody associated glomerulonephritis with nephrotic range proteinuria. *Ren Fail*. 2018;40:554–560.
31. Rovin BH, Caster DJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2019;95:281–295.
32. Franssen CF, Stegeman CA, Oost-Kort WW, et al. Determinants of renal outcome in anti-myeloperoxidase-associated necrotizing crescentic glomerulonephritis. *J Am Soc Nephrol*. 1998;9:1915–1923.
33. Hauer HA, Bajema IM, Hagen EC, et al. Long-term renal injury in ANCA-associated vasculitis: an analysis of 31 patients with follow-up biopsies. *Nephrol Dial Transplant*. 2002;17:587–596.
34. Hruskova Z, Honsova E, Berden AE, et al. Repeat protocol renal biopsy in ANCA-associated renal vasculitis. *Nephrol Dial Transplant*. 2014;29:1728–1732.
35. Jayne DRW, Merkel PA, Schall TJ, Bekker P. Avacopan for the treatment of ANCA-associated vasculitis. *N Engl J Med*. 2021;384:599–609.
36. De Rosa M, Azzato F, Toblli JE, et al. A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. *Kidney Int*. 2018;94:788–794.
37. Malvar A, Alberton V, Lococo B, et al. Kidney biopsy-based management of maintenance immunosuppression is safe and may ameliorate flare rate in lupus nephritis. *Kidney Int*. 2020;97:156–162.
38. Vandenbussche C, Bitton L, Bataille P, et al. Prognostic value of microscopic hematuria after induction of remission in antineutrophil cytoplasmic antibodies-associated vasculitis. *Am J Nephrol*. 2019;49:479–486.
39. Lv L, Chang DY, Li ZY, et al. Persistent hematuria in patients with antineutrophil cytoplasmic antibody-associated vasculitis during clinical remission: chronic glomerular lesion or low-grade active renal vasculitis? *BMC Nephrol*. 2017;18:354.
40. Geetha D, Seo P, Ellis C, et al. Persistent or new onset microscopic hematuria in patients with small vessel vasculitis in remission: findings on renal biopsy. *J Rheumatol*. 2012;39:1413–1417.
41. Chapman GB, Farrah TE, Chapman FA, et al. Utility of interval kidney biopsy in ANCA-associated vasculitis. *Rheumatology (Oxford)*. 2022;61:1966–1974.
42. Hogan SL, Falk RJ, Chin H, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. *Ann Intern Med*. 2005;143:621–631.
43. Pagnoux C, Hogan SL, Chin H, et al. Predictors of treatment resistance and relapse in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis: comparison of two independent cohorts. *Arthritis Rheum*. 2008;58:2908–2918.
44. Walsh M, Flossmann O, Berden A, et al. Risk factors for relapse of antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheum*. 2012;64:542–548.
45. King C, Druce KL, Nightingale P, et al. Predicting relapse in antineutrophil cytoplasmic antibody-associated vasculitis: a systematic review and meta-analysis. *Rheumatol Adv Pract*. 2021;5:rkab018.
46. Karras A, Pagnoux C, Haubitz M, et al. Randomised controlled trial of prolonged treatment in the remission phase of ANCA-associated vasculitis. *Ann Rheum Dis*. 2017;76:1662–1668.
47. Mackay M, Dall'Era M, Fishbein J, et al. Establishing surrogate kidney end points for lupus nephritis clinical trials: development and validation of a novel approach to predict future kidney outcomes. *Arthritis Rheumatol*. 2019;71:411–419.
48. Barratt J, Rovin B, Diva U, et al. Implementing the kidney health initiative surrogate efficacy endpoint in patients with IgA nephropathy (the PROTECT Trial). *Kidney Int Rep*. 2019;4:1633–1637.
49. Walsh M, Tonelli M, Jayne D, Manns B. Surrogate end points in clinical trials: the case of anti-neutrophil cytoplasm antibody-associated vasculitis. *J Nephrol*. 2007;20:119–129.
50. Lionaki S, Hogan SL, Jennette CE, et al. The clinical course of ANCA small-vessel vasculitis on chronic dialysis. *Kidney Int*. 2009;76:644–651.
51. Praga M, Gutiérrez E, González E, et al. Treatment of IgA nephropathy with ACE inhibitors: a randomized and controlled trial. *J Am Soc Nephrol*. 2003;14:1578–1583.
52. D’Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med*. 2011;365:2398–2411.
53. Wheeler DC, Toto RD, Stefánsson BV, et al. A pre-specified analysis of the DAPA-CKD trial demonstrates the effects of dapagliflozin on major adverse kidney events in patients with IgA nephropathy. *Kidney Int*. 2021;100:215–224.
54. Moran SM, Monach PA, Zgaga L, et al. Urinary soluble CD163 and monocyte chemoattractant protein-1 in the identification of subtle renal flare in anti-neutrophil cytoplasmic antibody-associated vasculitis. *Nephrol Dial Transplant*. 2020;35:283–291.