# ANCA-associated vasculitis : towards patient-tailored therapy

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# PREDICTORS OF LONG-TERM (≥ 5 YEAR) RENAL SURVIVAL IN 535 PATIENTS WITH ANCA-ASSOCIATED VASCULITIS

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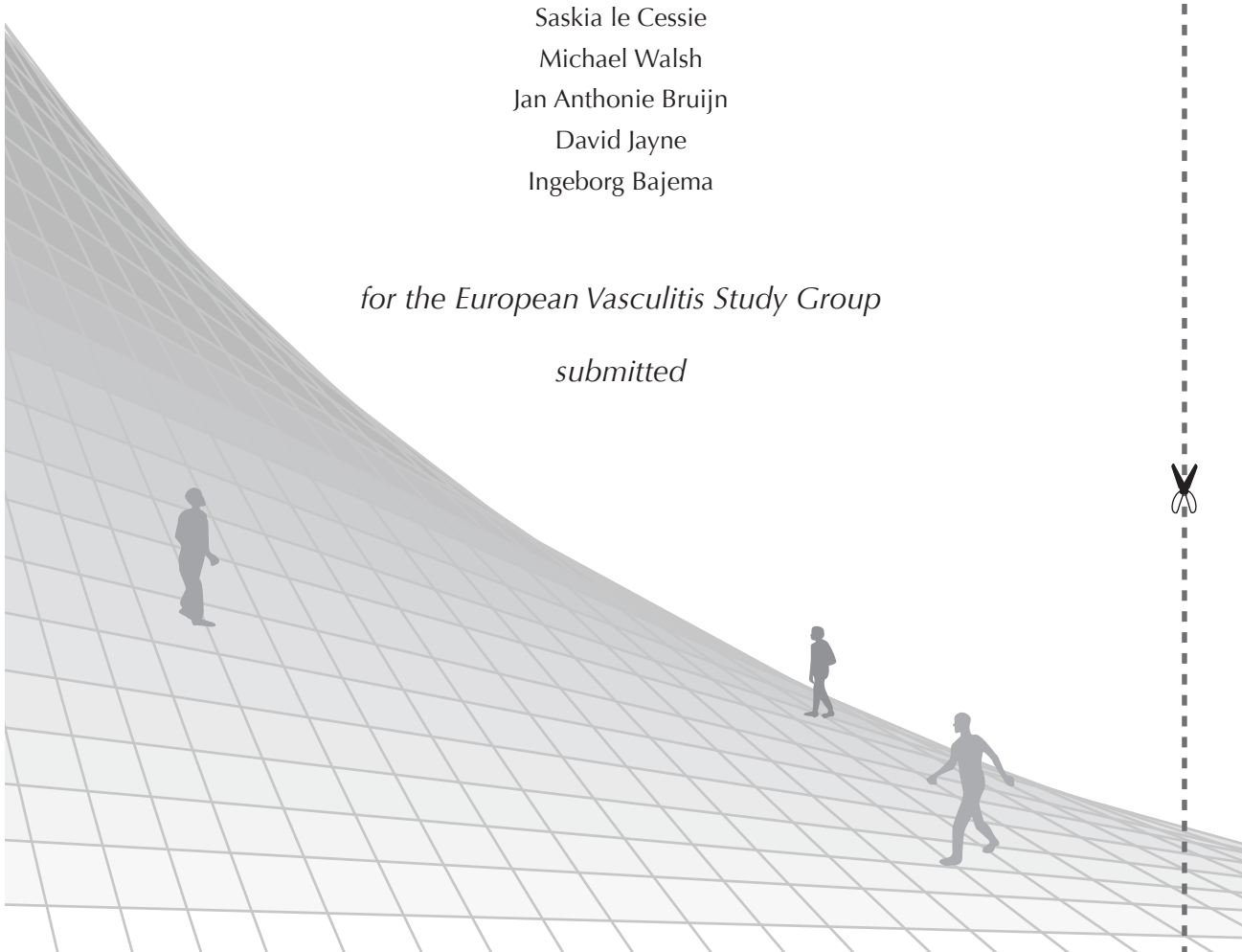

## ABSTRACT

In the ANCA-associated vasculitides end stage renal failure (ESRF) is an important factor with respect to patient morbidity and mortality. Data from four European Vasculitis Study Group randomized controlled trials were pooled to determine predictors of long-term renal survival. The respective trial inclusion criteria covered the entire spectrum of disease severity.

Baseline predictors for time to ESRF (primary endpoint) and time to the first renal relapse were assessed by Kaplan-Meier analysis, Cox proportional hazards regression and extended Cox modelling. For the secondary endpoint, estimated GFR at 5 years (eGFR5), linear regression analyses were performed.

535 patients participated; mean eGFR (± SD) at entry was 39.0 ± 33.6 mL/min/1.73 $m^2$ and 19.7% developed ESRF. Multivariable Cox regression demonstrated that anti-MPO antibodies ($p = 0.04$) and impaired baseline eGFR ($p < 0.001$) were independent risk factors for developing ESRF. Age ($p = 0.03$), baseline eGFR ($p < 0.001$), and systemic manifestations of vasculitis at baseline ($p = 0.02$) were independently associated with eGFR5. 101 patients experienced 1 or more renal relapse(s). Developing $\geq 1$ renal relapse was an independent risk factor for ESRF.

Entry eGFR is an important baseline determinant of long-term renal survival in ANCA-associated vasculitis, and remains so after correcting for within-trial therapy. Experiencing 1 or more renal relapse(s) increases chances on developing ESRF.

## INTRODUCTION

In the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) renal involvement is common[1] and end stage renal failure (ESRF) is an important factor with respect to morbidity and mortality.[2] Early reports from the 1950s reveal that without treatment average patient survival is approximately 5 months, the most frequent cause of death being renal failure.[3] With the introduction of cyclophosphamide and corticosteroid treatment, patient survival improved to 80% at 5 to 8 years follow-up.[4;5]



Given the great variety in clinical course of AAV combined with the great burden of cyclophosphamide and corticosteroid treatment with respect to morbidity and mortality,[6] patient-tailored therapy is what should be strived for. Patient profiling at the time of diagnosis is a prerequisite for this approach. Clinical, laboratory and histopathology findings form the basis for the establishment of a 'patient profile' with respect to outcome. In this paper, clinical and laboratory parameters are analyzed in relation to long-term renal outcome ($\geq$ 5 years), with the goal to identify those parameters that can be used to tailor therapy to individual patients. A detailed analysis of histopathology in relation to outcome in a representative portion of the same study population is described in a companion article (de Lind van Wijngaarden *et al.* submitted for publication).

Over the years, several studies were published on renal outcome in patients with AAV, but only a few of those fulfilled the selection criteria adopted in a recent systematic review investigating outcomes from studies of AAV.[2] Most studies took ESRF as an endpoint, which is a clear-cut and clinically relevant outcome. Consistent findings in these studies were the correlations of a number of clinical parameters, namely renal function, proteinuria, a fall in hemoglobin and an increase in age at entry, to renal outcome in terms of development of ESRF.[2] While providing valuable information, many of these studies were small, retrospective and from limited numbers of centers, thus jeopardizing power, precision and generalizability.

The current study describes predictors for long-term renal outcome in an international, multicenter, prospectively recruited patient cohort and is by our knowledge

the largest reported study on long-term renal outcome in AAV so far. Comparable to previous outcome studies ESRF is the primary endpoint. Predicting ESRF is important to identify potential modifiable risk factors and improve monitoring strategies, in order to minimize the need for permanent renal replacement therapies and reduce associated morbidity and mortality.



## CONCISE METHODS

### *Patients*

A total of 535 patients with a new diagnosis of Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) or renal limited vasculitis (RLV) were included in this study. EUVAS diagnostic criteria were adapted from the Chapel Hill Consensus Conference disease definitions.[21]

Ninety-five patients were originally entered in the NORAM trial, 155 patients in the CYCAZAREM trial, 137 patients in the MEPEX trial and 148 patients in the CYCLOPS trial.[22-25] The NORAM trial compared a remission induction regimen based on methotrexate to standard therapy with cyclophosphamide in patients with early, limited AAV; the CYCAZAREM trial compared remission maintenance therapy with azathioprine to standard therapy with cyclophosphamide in patients with generalized AAV; the MEPEX trial compared adjunctive therapy with intravenous methylprednisolone to plasma exchange in patients with severe renal vasculitis, and the CYCLOPS trial compared remission induction therapy with pulsed cyclophosphamide with daily oral cyclophosphamide in patients with generalized vasculitis.[22-25]

Patient recruitment for all trials took place between March 1995 and September 2002. Seventy centers in 15 countries (14 European countries and one Mexican center) collaborated in all respective trials. Inclusion criteria of the four trials were designed to cover the entire disease severity spectrum of AAV. Therefore, patients consecutively seen in each collaborating center could be included in any one of the four trials. All trials were performed in accordance with the Declaration of Helsinki.

### *Data collection*

All patient data were collected prospectively, starting from the date of trial-entry. Long-term follow-up data were acquired from a questionnaire filled in by the phy-

sicians who participated in the original trials. Disease assessments were performed regularly during trial (protocols at www.vasculitis.org/comptrials.htm), at 5 years follow-up and at the time the questionnaire was received. Data from the patients originally entered in the four trials were pooled to determine predictors of long-term renal survival after end of trial.



### *Treatment*

Patients were recruited at the time of diagnosis and randomized to receive different protocol treatment regimens, as described elsewhere.[22-25] The duration of trial follow-up was 12 months (MEPEX) and 18 months (NORAM, CYCAZAREM, CYCLOPS). After the end of each respective trial, patients reverted to the local standard of care treatments. Protocolized treatments received during the trial period were adjusted for in all regression analyses by including treatment limb as a covariate.

### *Entry parameters*

The baseline characteristics that were assessed were: patient age, sex, diagnosis, ANCA-subtype (proteinase 3 [PR3]-ANCA or myeloperoxidase [MPO]-ANCA), estimated glomerular filtration rate (eGFR), hemoglobin levels, white blood cell counts (WBC), platelet counts, C-reactive protein levels and the Birmingham Vasculitis Activity Score (BVAS).[26] No interactions were considered. These entry parameters were decided upon during a EUVAS consensus meeting. Regarding the entry parameter age, continuous values were used except for Kaplan-Meier analyses where 4 categories were made ($< 50$, 50-60, 60-70, $\geq 70$ years of age). ANCA positivity was an entry criterion for all four trials; however, 18 patients were reported to be ANCA-negative at the start of trial and 16 patients were positive for both PR3- and MPO-ANCA. These groups, however small, were regarded as separate entities. Baseline eGFR was calculated using the four-variable Modification of Diet in Renal Disease equation (MDRD).[27] Regarding the BVAS, we took into account the total score as well as separate subsets of the BVAS (presence/absence of disease activity in the following subsets: Systemic, Cutaneous, Mucous membranes/eyes, Ear-nose-throat [ENT], Chest, Cardiovascular, Abdominal, Nervous system). Renal involvement as scored on the BVAS was not a candidate predictor variable in this study, because entry eGFR was included in all analyses.

### *Renal relapse*

In addition to studying baseline clinical parameters, the effect of experiencing at least 1 renal relapse on the primary endpoint time to ESRF (defined as the need for permanent dialysis or receipt of a renal transplant) was assessed both during and subsequent to trial duration. A renal relapse was defined as a rise in serum creatinine of > 30% or a fall in eGFR > 25% and/or new hematuria or proteinuria (all attributable to active vasculitis) as indicated on the BVAS.

### *Study outcomes*

The primary outcome in this study was time to ESRF. Time to ESRF was calculated as time from date of entry until date of ESRF for patients who reached this endpoint. For patients who did not develop ESRF during follow-up, the follow-up time was date of entry until date of last visit (when the patient was last seen by the treating physician).

Two secondary outcomes were considered: eGFR at 5 years (eGFR5) and time to the first renal relapse. For the secondary outcome eGFR5, patients were included who were alive and followed up for 5 years. Patients who developed ESRF before 5 years of follow-up were regarded as having an eGFR of "0" mL/min/1.73 $m^2$ at 5 years. Those patients who were alive and followed up for 5 years, but had no eGFR measurements during long-term follow-up were not included in these analyses. The other secondary endpoint was the time to the first renal relapse. Time to the first renal relapse was calculated as time from date of entry until date of the first renal relapse for patients who reached this endpoint. Patients were censored at the time of ESRF, or the last time of ESRF-free survival in those that did not experience a renal relapse.

### *Statistical analysis*

Single imputation was done to capture missing values. Overall long-term renal survival was assessed using Kaplan-Meier survival analysis. The predefined set of entry parameters was entered in a multivariable Cox proportional hazards model to ascertain independent baseline predictors of time to ESRF. For assessment of the effect of experiencing 1 or more renal relapse(s) on time to ESRF, renal relapse was added to the multivariable Cox proportional hazards model as a time-dependent covariate (time to the first renal relapse*occurrence of a renal relapse), all baseline parameters were included in this model as fixed covariates. Reference categories for individual entry parameters were as follows: female sex, a diagnosis of WG, PR3-ANCA, and the

absence of organ involvement on the BVAS. Protocolized within-trial treatment was included in all multivariable regression analyses as a covariate; "standard treatment" with cyclophosphamide and azathioprine was set as the reference category (experimental limb CYCAZAREM trial). Patients with missing values for any of the risk variables and patients with ESRF at baseline were excluded during multivariable Cox regression analysis.



To distinguish independent predictors of eGFR5, the predefined set of entry parameters was entered in a multivariable linear regression model. For the endpoint time to the first renal relapse, the same analyses as described for the primary endpoint time to ESRF were performed.

Regarding all study endpoints, various prespecified subgroup sensitivity analyses were performed. Patients were classified *a priori* into subgroups based on baseline characteristics, as stated throughout the text. Block entry, in which all variables are entered into the analysis simultaneously, was used for all multivariable regression analyses. For multivariable Cox regression analyses hazard ratios (HR) and 95% confidence intervals (CI) are given. For multivariable linear regression analyses the standardized slope of the regression equation (β) is given. All statistical calculations were performed using SPSS software (version 16.0; SPSS Inc, Chicago, IL). A p-value $< 0.05$ was considered statistically significant.

## RESULTS

### *Patients*

A total of 535 patients with a new diagnosis of AAV were included in this study. Mean (± SD) age at presentation was 57.7 (± 14.3) years respectively (**Table 1**). Fifty-four percent of patients were male and 97% of patients tested positive for ANCA. Of the ANCA-positive patients, 288 (54%) patients were PR3-ANCA-positive, 205 (38%) patients were MPO-ANCA-positive and 16 (3%) patients were double positive for PR3- and MPO-ANCA. Most patients were diagnosed with WG (53%), 43% of patients had a diagnosis of MPA, and 4% had renal-limited disease at presentation. Mean eGFR (± SD) at entry was 39.0 ± 33.6 mL/min/1.73 $m^2$. Median time of follow-up in this study was 5.2 years.

### *Time to end stage renal failure*

During follow-up, 19.7% of patients developed ESRF. Renal survival was 89% at 1 year, 87% at 2 years and 83% at 5 years in this cohort (**Figure 1**). Of the patients who developed ESRF at any point in time, 63% had a baseline serum creatinine of > 500 µmol/L (patients originally entered in MEPEX trial) and 36% had a baseline serum creatinine between 200 and 500 µmol/L (patients originally entered in CYCAZAREM and CYCLOPS trials). There was one patient who had no manifest renal involvement at entry (patient originally entered in NORAM trial) and still developed ESRF just over 3 years after trial entry. Of the total of 535 patients, 104 had missing values for any of the risk variables and 11 had ESRF at baseline, and these patients were excluded from multivariable Cox regression analysis. The multivariable Cox model demonstrated that a lower baseline eGFR and MPO-ANCA were the only independent risk factors for developing ESRF (**Table 2**). These results were sustained when excluding NORAM patients in a prespecified sensitivity analysis.

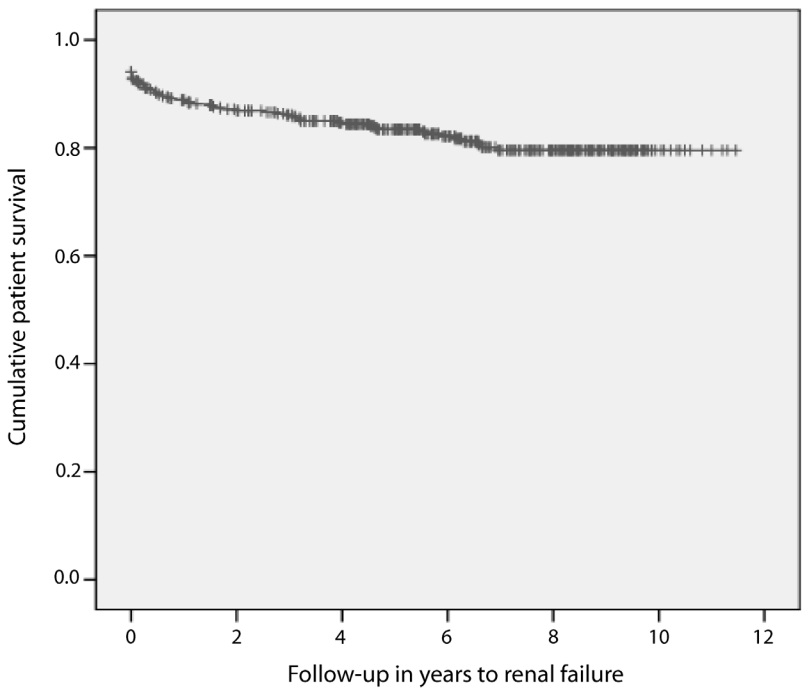


**Figure 1.** Overall renal survival. Renal survival is depicted according to the Kaplan-Meier method. During follow-up, 19.7% of patients developed ESRF. Renal survival was 89% at 1 year, 87% at 2 years and 83% at 5 years in this cohort.

**Table 1.** Patients and baseline characteristics

| Baseline characteristic | n (%), unless stated otherwise |
|---|---|
| Age (Mean ± SD) | 57.7 ± 14.3 |
| Sex | |
| female | 247 (46%) |
| male | 288 (54%) |
| ANCA | |
| PR3 | 288 (54%) |
| MPO | 205 (38%) |
| double positive | 16 (3%) |
| negative | 18 (3%) |
| Diagnosis | |
| WG | 281 (53%) |
| MPA | 232 (43%) |
| RLV | 22 (4%) |
| eGFR (Mean ± SD) | 39.0 ± 33.6 |

ANCA, antineutrophil cytoplasmic antibodies; PR3, proteinase 3; MPO, myeloperoxidase; WG, Wegener's granulomatosis; MPA, microscopic polyangiitis; RLV, renal-limited vasculitis.

**Table 2.** Time to end stage renal failure

| | | Multiple Cox regression analysis[b] | | |
|---|---|---|---|---|
| **Parameter** | **n** | **HR** | **95% CI** | **Adjusted p-value** |
| Age | 439 | 0.98 | 0.96 to 1.00 | NS |
| Sex | | | | |
| female[a] | 201 | 1 | | |
| male | 238 | 1.56 | 0.90 to 2.72 | NS |
| Diagnosis | | | | |
| WG[a] | 241 | 1 | | |
| MPA | 178 | 0.98 | 0.49 to 1.97 | NS |
| RLV | 20 | 0.99 | 0.23 to 4.19 | NS |

Table continues on next page. [a] Reference category; [b]multiple model is adjusted for within-trial therapy. MPA, microscopic polyangiits; RLV, renal-limited vasculitis; WG, Wegener's granulomatosis.

**Table 2.** Time to end stage renal failure *continued*

| | | Multiple Cox regression analysis[b] | | |
|---|---|---|---|---|
| **Parameter** | **n** | **HR** | **95% CI** | **Adjusted p-value** |
| ANCA | | | | |
| PR3[a] | 242 | 1 | | |
| MPO | 166 | 1.83 | 1.01 to 3.30 | 0.045 |
| double positive | 11 | 2.08 | 0.26 to 16.51 | NS |
| negative | 16 | 1.42 | 0.30 to 6.64 | NS |
| Entry eGFR | 439 | 0.92 | 0.88 to 0.95 | < 0.001 |
| Entry hemoglobin | 439 | 0.94 | 0.80 to 1.11 | NS |
| Entry WBC | 439 | 0.99 | 0.93 to 1.05 | NS |
| Entry platelets | 439 | 1.00 | 0.999 to 1.003 | NS |
| Entry CRP | 439 | 1.00 | 0.997 to 1.004 | NS |
| Entry BVAS | 439 | 0.99 | 0.93 to 1.05 | NS |
| BVAS systemic | | | | |
| No[a] | 33 | 1 | | |
| Yes | 389 | 1.06 | 0.36 to 3.16 | NS |
| BVAS cutaneous | | | | |
| No[a] | 318 | 1 | | |
| Yes | 104 | 0.79 | 0.38 to 1.63 | NS |
| BVAS mucous membranes/eyes | | | | |
| No[a] | 294 | 1 | | |
| Yes | 128 | 1.58 | 0.78 to 3.18 | NS |
| BVAS ear-nose-throat | | | | |
| No[a] | 190 | 1 | | |
| Yes | 232 | 0.81 | 0.41 to 1.62 | NS |
| BVAS chest | | | | |
| No[a] | 196 | 1 | | |
| Yes | 226 | 1.58 | 0.81 to 3.07 | NS |

Table continues on next page. [a] Reference category; [b] multiple model is adjusted for within-trial therapy. ANCA, antineutrophil cytoplasmic antibodies; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MPO, myeloperoxidase; PR3, proteinase 3; WBC, white blood cell count.

**Table 2.** Time to end stage renal failure *continued*

| | | Multiple Cox regression analysis[b] | | |
|---|---|---|---|---|
| **Parameter** | **n** | **HR** | **95% CI** | **Adjusted p-value** |
| BVAS cardiovascular | | | | |
| No[a] | 398 | 1 | | |
| Yes | 24 | 1.67 | 0.70 to 4.02 | NS |
| BVAS abdominal | | | | |
| No[a] | 404 | 1 | | |
| Yes | 18 | 2.07 | 0.73 to 5.85 | NS |
| BVAS nervous | | | | |
| No[a] | 339 | 1 | | |
| Yes | 83 | 0.81 | 0.33 to 1.98 | NS |

[a] Reference category; [b]multiple model is adjusted for within-trial therapy. BVAS, Birmingham Vasculitis Activity Score



Analyzing patient subgroups according to ANCA subtype demonstrated that baseline eGFR was still an independent predictor for time to ESRF. In the MPO-ANCA group (n = 157, 38 events, 119 censored, 42 missing values, 6 patients with ESRF at baseline) besides a lower baseline eGFR (HR = 0.92, 95% CI = 0.87-0.98; p = 0.007), abdominal involvement on the BVAS (HR = 9.57, 95% CI = 2.0-45.87; p = 0.005) was associated with an increased risk of developing ESRF. In the PR3-ANCA group (n = 236, 26 events, 210 censored, 48 missing values, 4 patients with ESRF at baseline), apart from a lower baseline eGFR (HR = 0.91; 95% CI = 0.85-0.98; p = 0.008), male sex was found to be an independent risk factor for developing ESRF (HR = 3.8; 95% CI = 1.2-12.2; p = 0.02).

### *eGFR at 5 years*

Data on eGFR5 were available for 209 patients. Mean eGFR5 (± SD) was 46.5 (± 30.0) mL/min/1.73 $m^2$. In a multivariable linear regression model, baseline eGFR, higher age and absence of BVAS systemic symptoms independently predicted a lower eGFR5 (**Table 3**). Analyses subgrouping patients according to ANCA-subtype underlined that entry eGFR is an important predictor for eGFR5 (MPO-ANCA group [n = 69] eGFR entry $\beta = 0.453$, $p = 0.03$; PR3-ANCA group [n = 122] eGFR entry $\beta = 0.562$, $p < 0.001$).

**Table 3.** Baseline predictors of eGFR5

| | | Multiple linear regression[b] | |
|---|---|---|---|
| **Parameter** | **n** | β[a] | **Adjusted p-value** |
| Age continuous | 209 | -0.12 | 0.03 |
| Sex | | | |
| female | 99 | | |
| male | 110 | -0.02 | NS |
| Diagnosis | | | |
| WG | 123 | | |
| MPA | 79 | 0.01 | NS |
| RLV | 7 | 0.003 | NS |
| ANCA | | | |
| PR3 | 124 | | |
| MPO | 70 | -0.02 | NS |
| double positive | 4 | -0.04 | NS |
| negative | 9 | 0.01 | NS |
| Entry eGFR | 209 | 0.54 | < 0.001 |
| Entry hemoglobin | 209 | 0.05 | NS |
| Entry WBC | 209 | 0.002 | NS |
| Entry platelets | 209 | 0.06 | NS |
| Entry CRP | 209 | -0.02 | NS |
| Entry BVAS | 209 | -0.01 | NS |
| BVAS systemic | | | |
| No | 14 | | |
| Yes | 191 | 0.13 | 0.02 |
| BVAS cutaneous | | | |
| No | 159 | | |
| Yes | 46 | -0.01 | NS |
| BVAS mucous membranes/eyes | | | |
| No | 143 | | |
| Yes | 62 | -0.01 | NS |

Table continues on next page. [a]Standardized regression coefficient β is given for continuous entry parameters; [b]multiple model is adjusted for within-trial therapy. ANCA, antineutrophil cytoplasmic antibodies; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MPA, microscopic polyangiits; MPO, myeloperoxidase; PR3, proteinase 3; RLV, renal-limited vasculitis; WG, Wegener's granulomatosis; WBC, white blood cell count.

**Table 3.** Baseline predictors of eGFR5 *continued*

| | | Multiple linear regression[b] | |
|---|---|---|---|
| **Parameter** | **n** | **β[a]** | **Adjusted p-value** |
| BVAS ear-nose-throat | | | |
| No | 88 | | |
| Yes | 117 | 0.07 | NS |
| BVAS chest | | | |
| No | 92 | | |
| Yes | 113 | -0.02 | NS |
| BVAS cardiovascular | | | |
| No | 198 | | |
| Yes | 7 | -0.05 | NS |
| BVAS abdominal | | | |
| No | 195 | | |
| Yes | 10 | 0.02 | NS |
| BVAS nervous | | | |
| No | 170 | | |
| Yes | 35 | 0.03 | NS |

[a]Standardized regression coefficient β is given for continuous entry parameters; [b]multiple model is adjusted for within-trial therapy. BVAS, Birmingham Vasculitis Activity Score.



### *Renal relapse*

Renal relapse and long-term renal survival data were available of 467 patients. A total of 101 of these patients (22%) experienced one or more renal relapse(s) during the entire follow-up period. At 1 year, 96% of patients had not experienced one or more renal relapses, at 2 years this percentage was 89%, at 5 years 76%, and at 10 years 63%.

Patients without clinical renal involvement at entry were nevertheless at risk of developing renal manifestations and experiencing one or more renal relapse(s) in the course of their disease. Data of 51 patients without manifest renal involvement at baseline, as recorded on the BVAS, were available for renal relapse analyses. These patients originally participated in the NORAM-trial, and 9 (18%) of them eventually experienced a renal relapse during follow-up.

Multiple Cox regression analysis investigating baseline predictors for time to the first renal relapse demonstrated that only baseline hemoglobin levels were independently associated with renal relapse (HR 1.20, p = 0.006; **Table 4**).

**Table 4.** Time to the first renal relapse

| | | Multiple Cox regression analysis[b] | | |
|---|---|---|---|---|
| **Parameter** | **n** | **HR** | **95% CI** | **Adjusted p-value** |
| Age | 424 | 1.01 | 0.99 to 1.03 | NS |
| Sex | | | | |
| female[a] | 192 | 1 | | |
| male | 232 | 1.32 | 0.84 to 2.09 | NS |
| Diagnosis | | | | |
| WG[a] | 234 | 1 | | |
| MPA | 170 | 0.71 | 0.36 to 1.41 | NS |
| RLV | 20 | 0.85 | 0.22 to 3.34 | NS |
| ANCA | | | | |
| PR3[ac] | 244 | 1 | | |
| MPO | 161 | 0.80 | 0.44 to 1.44 | NS |
| Entry eGFR | 424 | 0.99 | 0.98 to 1.00 | 0.08 |
| Entry hemoglobin | 424 | 1.20 | 1.05 to 1.36 | 0.006 |
| Entry WBC | 424 | 0.97 | 0.92 to 1.04 | NS |
| Entry platelets | 424 | 1.00 | 0.999 to 1.002 | NS |
| Entry CRP | 424 | 1.00 | 0.998 to 1.001 | NS |
| Entry BVAS | 424 | 1.04 | 1.00 to 1.08 | 0.07 |
| BVAS systemic | | | | |
| No[a] | 32 | 1 | | |
| Yes | 377 | 0.82 | 0.33 to 2.04 | NS |
| BVAS cutaneous | | | | |
| No[a] | 306 | 1 | | |
| Yes | 103 | 0.93 | 0.51 to 1.69 | NS |

Table continues on next page. [a] Reference category; [b]multiple model is adjusted for within-trial therapy; [c]eleven double positive patients were added to the PR3-ANCA group. None of 16 ANCA-negative patients relapsed. ANCA, antineutrophil cytoplasmic antibodies; BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MPA, microscopic polyangiits; MPO, myeloperoxidase; PR3, proteinase 3; RLV, renal-limited vasculitis; WG, Wegener's granulomatosis; WBC, white blood cell count.

**Table 4.** Time to the first renal relapse *continued*

| | | Multiple Cox regression analysis[b] | | |
|---|---|---|---|---|
| **Parameter** | **n** | **HR** | **95% CI** | **Adjusted p-value** |
| BVAS mucous membranes/eyes | | | | |
| No[a] | 284 | 1 | | |
| Yes | 125 | 0.98 | 0.58 to 1.64 | NS |
| BVAS ear-nose-throat | | | | |
| No[a] | 183 | 1 | | |
| Yes | 226 | 1.36 | 0.73 to 2.52 | NS |
| BVAS chest | | | | |
| No[a] | 195 | 1 | | |
| Yes | 214 | 0.90 | 0.54 to 1.49 | NS |
| BVAS cardiovascular | | | | |
| No[a] | 386 | 1 | | |
| Yes | 23 | 1.89 | 0.79 to 4.52 | NS |
| BVAS abdominal | | | | |
| No[a] | 394 | 1 | | |
| Yes | 15 | 0.54 | 0.13 to 2.29 | NS |
| BVAS nervous | | | | |
| No[a] | 328 | 1 | | |
| Yes | 81 | 0.68 | 0.36 to 1.30 | NS |

[a] Reference category; [b]multiple model is adjusted for within-trial therapy. BVAS, Birmingham Vasculitis Activity Score.

Patients who experienced at least 1 renal relapse were at an increased risk of developing ESRF: renal relapse proved an independent predictor of ESRF when it was added as a time-dependent covariate in our multivariable Cox model investigating time to ESRF (HR = 7.52, 95% CI = 3.19-17.72; $p < 0.001$) (**Table 5**). Among the patients who developed ESRF after experiencing one or more renal relapse(s), the time from renal relapse to development of ESRF varied from 13 days to over 4.5 years.

**Table 5.** Renal relapse and time to ESRF

| | | Multiple Cox regression analysis[b] | | |
|---|---|---|---|---|
| **Parameter** | **n** | **HR** | **95% CI** | **Adjusted p-value** |
| Entry eGFR | 404 | 0.91 | 0.88 to 0.95 | < 0.001 |
| ANCA | | | | |
| PR3[a] | 224 | 1 | | |
| MPO | 153 | 1.91 | 1.03 to 3.55 | 0.04 |
| double positive | 11 | 2.24 | 0.28 to 17.92 | NS |
| negative | 16 | 1.77 | 0.37 to 8.49 | NS |
| At least 1 renal relapse | | | | |
| No[a] | 313 | 1 | | |
| Yes[c] | 91 | 7.52 | 3.19 to 17.72 | < 0.001 |

[a] Reference category; [b]multiple model is adjusted for age, gender, diagnosis, hemoglobin, white blood cell count, platelets, C-reactive protein, Birmingham Vasculitis Activity Score total, systemic; cutaneous; mucous membranes/eyes; ear-nose-throat; chest; cardiovascular; abdominal and nervous Birmingham Vasculitis Activity Score subelements, and within-trial therapy; [c]renal involvement at the first relapse after trial was noted in 101 patients, however, the exact date of the first relapse was not recorded in 10 patients. ANCA, antineutrophil cytoplasmic antibodies; eGFR, estimated glomerular filtration rate; MPO, myeloperoxidase; PR3, proteinase 3.



## DISCUSSION

This study is to our knowledge the largest reported study of long-term renal outcome in AAV to date. The primary outcome was time to ESRF. Almost 20% of patients developed ESRF in the period under study, the median time of follow-up was 5.2 years. This percentage is comparable to previous studies which reported that ANCA-associated glomerulonephritis results in ESRF in 20-40% of patients (median time of follow-up range 3.4 years to ≥ 5 years).[7-12]

An impaired baseline eGFR and MPO-ANCA proved independent risk factors for developing ESRF. The distinction between MPO-ANCA- and PR3-ANCA-positive disease is still debatable; therefore we investigated potential risk factors for developing ESRF when regarding ANCA-subtype as given in prespecified subset analyses. In the subgroups, baseline eGFR remained an independent predictor for development of ESRF. This finding agrees well with other studies in which baseline serum creatinine or eGFR was (one of) the most important predictor(s) for renal outcome as well.[9-15] Franssen and co-workers described a cohort of patients with MPO-ANCA-associated

vasculitis wherein proteinuria at diagnosis and during follow-up was the most important risk factor for developing renal insufficiency at a later time point.[16] Due to lacking data on proteinuria in our study, we were unable to confirm these results.

The independent predictors for an impaired eGFR5 were an impaired baseline eGFR, and to a lesser extent higher age at entry and absence of systemic symptoms on the BVAS. The reduced risk associated with systemic symptoms might follow from a shorter patient delay, since constitutional symptoms might encourage patients to visit a physician. However, the number of patients investigated without systemic symptoms was very small.



This study furthermore demonstrated that patients who did not present with renal involvement at entry, and had so-called limited disease, could develop renal involvement at a later stage, and were at risk of experiencing a renal relapse. The independent association of hemoglobin levels with time to the first renal relapse that we demonstrated might be explained by the interrelation of higher hemoglobin levels with other factors that were univariately related to relapsing renal disease, namely a diagnosis of WG and ENT involvement (data not shown). Since a diagnosis of WG and ENT involvement fall out of the multivariable analysis, hemoglobin could be considered more proximal a causal event to relapse than e.g. ENT involvement. Such a relationship between hemoglobin levels and renal relapse, however, does not appear straightforward, and it cannot be completely ruled out that this is a chance finding or represents residual confounding from an unknown variable that we were not able to adjust for. Importantly, experiencing a renal relapse increased a patient's risk of developing ESRF. This is in agreement with other studies that reported an unfavorable relation between renal relapse and renal outcome as well.[9;17;18]

The current study has its limitations. Patients from this long-term follow-up study came from four different trials, which were originally designed to investigate therapeutic outcome. During long-term follow-up of these patients one problem was incomplete data return, for example we were unable to obtain data on the exact number of renal relapses each patient experienced, and although we present the largest reported study of AAV, the data on eGFR at 5 years are relatively limited.

Concluding, in this large population of patients with AAV, entry eGFR proved to be a consistent determinant of long-term renal survival, also after correcting for within-trial therapy. On a group level, presentation with very impaired renal function puts a patient at a high risk of becoming dialysis-dependent. In other aggressive forms of glomerulonephritis, namely Goodpasture's syndrome and lupus nephritis, the importance of entry serum creatinine as a long-term prognostic marker of renal outcome has been long since recognized.[19;20] Furthermore, experiencing 1 or more renal relapse(s) increased chances on developing ESRF. The predictive value of entry eGFR and renal relapse with respect to long-term renal survival reported in this study, underlines the importance of an early diagnosis and prompt initiation of therapy to stop the rapidly progressive loss of renal function at an as early a time point as possible. The results also highlight the need for efficacious remission maintenance therapy, and hereby support ongoing clinical trials investigating alternatives to standard therapy with the aim to prevent relapses, and hereby increase sustained remission rates.



## ACKNOWLEDGEMENTS

We would like to thank those who returned the questionnaires and the investigators of the included trials.

## DISCLOSURES

MW is supported by the Kidney Research Scientist Core Education National Training (KRESCENT) Program and by the Alberta Heritage Foundation for Medical Research. This study was presented in part at the 14th International Vasculitis & ANCA Workshop, June 6-9, 2009, Lund (Sweden) and Copenhagen (Denmark), and at the annual meeting of the American Society of Nephrology, October 27-November 1, 2009, San Diego, CA, USA; and has been published in part in abstract form.

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