ANCA-associated vasculitis : towards patient-tailored therapy

Berden, A.E.

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LONG-TERM PATIENT SURVIVAL IN ANCA-ASSOCIATED VASCULITIS

Oliver Floßmann
Annelies Berden
Kirsten de Groot
Chris Hagen
Lorraine Harper
Caroline Heijl
Peter Höglund
David Jayne
Raashid Luqmani
Alfred Mahr
Chetan Mukhtyar
Charles Pusey
Niels Rasmussen
Coen Stegeman
Michael Walsh
Kerstin Westman

for the European Vasculitis Study Group

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ABSTRACT

Wegener's granulomatosis and microscopic polyangiitis are ANCA-associated vasculitides with significant morbidity and mortality. The long-term survival of patients with ANCA-associated vasculitis treated with current regimens is uncertain.

Outcome data were collected for 535 patients who had been recruited at the time of diagnosis to four randomized controlled trials between 1995 and 2002. Trial eligibility was defined by disease severity and extent, covered the spectrum of severity of ANCA-associated vasculitis, and used consistent diagnostic criteria. Demographic, clinical and laboratory parameters at trial entry were tested as potential prognostic factors in multivariable models.

The median duration of follow-up was 5.2 years and 133 (25%) deaths were recorded. Compared to an age- and sex-matched general population there was a mortality rate ratio of 2.6 (95% CI 2.2-3.1). Main causes of death within the first year were infection (48%) and active vasculitis (19%). After the first year, the major causes of death were cardiovascular disease (26%), malignancy (22%) and infection (20%). Multivariable analysis showed that estimated glomerular filtration rate less than 15 ml/min, advancing age, higher Birmingham Vasculitis Activity Score, lower hemoglobin and higher white cell count were significant negative prognostic factors for patient survival.

Patients with ANCA-associated vasculitis treated with conventional regimens are at increased risk of death compared to an age- and sex-matched population.

INTRODUCTION

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are primary vasculitides of unknown cause characterized by necrotizing inflammation involving predominantly small blood vessels, and the presence of circulating antineutrophil cytoplasmic antibodies (ANCA) in the majority of patients at diagnosis. They are often grouped as "ANCA-associated vasculitis" because of striking similarities in histology, absence of immune deposits, response to therapy and the likely contribution of ANCA to the pathogenesis.

The introduction of immunosuppression with cyclophosphamide and corticosteroids in the 1960's led to a dramatic improvement in prognosis with over 90% of patients achieving remission compared to a mortality of 80% at one year in untreated patients.[1;2] The addition of plasma exchange to immunosuppression showed promise in improving renal recovery in early small studies.[3] However, these advances were achieved at the cost of treatment-related toxicity such as hemorrhagic cystitis, bladder cancer, lymphoproliferative disease, myelodysplasia and infertility due to the cumulative exposure to cyclophosphamide.[4;5]

The European Vasculitis Study Group (EUVAS) standardized disease definitions, diagnostic criteria and disease assessment, and defined four disease stages according to severity and extent at presentation.[6] Four randomized controlled trials were launched to study treatment regimens tailored to different disease stages in newly diagnosed patients with ANCA-associated vasculitis.[7-10]

Despite advances in the treatment of ANCA-associated vasculitis, retrospective studies limited to patients with Wegener's granulomatosis suggest that there still is an excess mortality compared to the general population.[11;12]

This study aimed to describe the long-term patient survival and possible prognostic factors at presentation in an international, multicenter, prospectively recruited representative patient cohort, who were treated according to strictly defined protocols at presentation and included the full spectrum of ANCA-associated vasculitis disease severity.

METHODS

Study population

The patients were recruited into four randomized therapeutic multicenter trials organized by the European Vasculitis Study Group (EUVAS) in 70 general and university hospitals in 15 countries between 1995 and 2002.[7-10] All studies were approved by the local ethics committees and all patients gave written informed consent. The trials were conducted according to the 1964 Declaration of Helsinki and subsequent amendments.

Patients were eligible if they had a new diagnosis of Wegener's granulomatosis or microscopic polyangiitis according to criteria adapted from the 1994 Chapel Hill disease definitions.[13] The diagnosis was based on a clinical presentation compatible with ANCA-associated vasculitis, and substantiated by a positive ANCA serology and/or histology.[14] Patients were excluded if they had a coexistent multisystem autoimmune condition, concurrent malignancy, active infection, pregnancy or age below 18 or above 80 years. Entry into the different trials was dependent on the disease stage, as defined by severity subgroup.[14] Patients with life-threatening pulmonary hemorrhage within 24 hours of presentation were excluded. The protocols for the different trials are summarized in **Table 1**.

Table 1. Summary of trials

Trial	NORAM	CYCAZAREM	MEPEX	CYCLOPS
Disease stage	Early systemic	Mild – moderate renal	Severe renal	Mild – moderate renal
Remission induction	MTX + OCS vs poCYC + OCS	poCYC + OCS	ivMP + poCYC + OCS vs PE + poCYC + OCS	ivCYC + OCS vs poCYC + OCS
Remission maintenance	MTX + OCS vs poCYC + OCS	poCYC + OCS vs AZA + OCS	AZA + OCS	AZA + OCS

CYCAZAREM, randomized trial of cyclophosphamide versus azathioprine during remission in ANCA-associated vasculitis; CYCLOPS, randomized trial of daily oral versus pulsed cyclophosphamide for the treatment of ANCA-associated vasculitis; MEPEX, randomized trial of adjunctive therapy for severe glomerulonephritis in ANCA-associated systemic vasculitis, plasma exchange versus intravenous methylprednisolone; NORAM, efficacy of methotrexate versus cyclophosphamide in the treatment of 'non-renal' Wegener's granulomatosis. AZA, azathioprine; ivCYC, intravenous cyclophosphamide; poCYC, oral cyclophosphamide; ivMP, intravenous methylprednisolone; MTX, methotrexate; OCS, oral corticosteroids; PE, plasma exchange.

Baseline evaluation

Disease activity was assessed with the Birmingham Vasculitis Activity Score (BVAS).[15] Laboratory investigations included serum creatinine, full blood count, C-reactive protein and ANCA. Type of ANCA was categorized as proteinase 3 ANCA (PR3-ANCA) if there was positivity by PR3-ANCA ELISA or a cytoplasmic ANCA (cANCA) pattern by indirect immunofluorescence microscopy; as myeloperoxidase ANCA (MPO-ANCA) if there was positivity by MPO-ANCA ELISA or a perinuclear ANCA (pANCA) pattern on immunofluorescence microscopy, or as double positive if both PR3- and MPO-ANCA were detected. These data were recorded as baseline data at trial entry. The estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification of Diet in Renal Disease equation (MDRD).[16]

Questionnaire

This long-term follow-up was performed in accordance with the principles laid down in the 1964 Declaration of Helsinki and subsequent amendments, and ethical approval was obtained by national and local ethics committees in accordance with national legislation. In order to determine long-term survival a questionnaire was sent to participating physicians. Data collected were date of last physician visit, survival status and date of death. In cases of deaths the local investigators were asked to provide information regarding the cause of death and contributing factors, according to death certificate if available and in their own opinion. They were also asked to rate separately the likelihood that active vasculitis, immunosuppression or sepsis contributed to the death on a scale from 0 (not related) to 5 (definite).

Two authors (KW, OF) independently categorized the cause of death as being directly attributable or contributed to by vasculitis, infection, malignancy, cardiovascular, miscellaneous and unknown. In case of disagreement a third author (DJ) adjudicated. Replies were collected from September 2004 until January 2007.

Statistical analysis

Single imputation was done to capture missing values.[17] Continuous variables are expressed as median with 25th and 75th percentiles. Categorical variables are presented as percents and frequencies. Survival was calculated using the Kaplan-Meier method[18] and presented graphically for the whole cohort. The log-rank test was used to compare the overall patient mortality with that of a control cohort matched for age,

sex, year and country calculated by the Hakulinen method.[19] Sources for these controls were official vital statistics for participating countries: Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, England and Wales, Italy, the Netherlands, Poland, Sweden and Scotland. For a few countries from which we could not obtain information, data were retrieved from a neighbouring country. For each year and country we obtained the average number of inhabitants and death rates by age groups and gender for these groups. The following predetermined parameters were included in a multivariable Cox regression analysis: age at entry into clinical trial, sex, clinical diagnosis (WG, MPA), ANCA-type (PR3-, MPO-, double positive ANCA, negative), estimated glomerular filtration rate (MDRD), BVAS, hemoglobin (Hb), white cell count (WBC), platelets and C-reactive protein. Patients' estimated glomerular filtration rate was classified into stages 1-5 with the same cut-off points as chronic kidney disease stages.[20] For the analysis these were trichotomized into stages 1-2, 3-4 and 5, respectively. The proportional hazards assumption was tested by the weighted scaled Schoenfeld residuals test. We included interaction terms between hemoglobin, WBC and platelets and log time (subsequently referred to as 'time-dependent covariates') in order to satisfy the proportional hazards assumption. This model was applied to the patient material both without and with subtraction of general mortality in a control cohort matched for age, sex, year and country using the Hakulinen method.

Data were analyzed using SAS (SAS Institute, Cary, NC) version 8.2 and the R software (R foundation for Statistical Computing, Vienna, Austria) version 2.6.2. A two-tailed p-value of ≤ 0.05 was considered statistically significant.

RESULTS

Demography

Five hundred and thirty-five patients with a median (25th – 75th percentile) age of 61 (49-69) at diagnosis participated in the trials; 54% of whom were male. Of these patients 281 (52%) were diagnosed with Wegener's granulomatosis and 254 (48%) with microscopic polyangiitis. The duration of follow-up ranged from 1 day to 11.46 years, with a median length of follow-up of 5.16 years for all patients and a median of 5.95 years for patients alive at the last visit/end of follow-up. Further demographic data are summarized in **Table 2**.

Table 2. Descriptive statistics (median, lower and upper quartile) at baseline by dichotomized entry diagnosis Microscopic Polyangiitis (MPA) and Wegener's granulomatosis (WG)

Parameter	N (n)	MPA (N = 254)	WG (N = 281)	Combined (N = 535)	p-value
Sex	535				0.52[1]
male		52% (133)	55% (155)	54% (288)	
female		48% (121)	45% (126)	46% (247)	
Age (years)	535	54 **64** 70	43 **58** 66	49 **61** 69	< 0.001[2]
Age quartiles					< 0.001[1]
< 50 years		19% (48)	33% (93)	26% (141)	
50-60 years		18% (46)	24% (67)	21% (113)	
60-70 years		37% (94)	27% (76)	32% (170)	
> 70 years		26% (66)	16% (45)	21% (111)	
Serum creatinine (µmol/L)	535 (523)	174 **335** 654	82 **107** 292	97 **203** 498	< 0.001[2]
GFR (mL/min)		7.2 **14.7** 31.8	18.8 **59.2** 79.6	9.6 **27.9** 64.7	< 0.001[2]
GFR categorized as CKD stage					< 0.001[1]
1		2% (4)	15% (41)	8% (45)	
2		5% (13)	34% (95)	20% (108)	
3		20% (51)	17% (49)	19% (100)	
4		23% (58)	14% (38)	18% (96)	
5		50% (128)	21% (58)	35% (186)	
CKD stage trichotomized					< 0.001[1]
A		7% (17)	48% (136)	29% (153)	
B		43% (109)	31% (87)	37% (196)	
C		50% (128)	21% (58)	35% (186)	
Hb (g/dL)	535 (502)	8.6 **9.4** 10.7	8.7 **10.2** 11.9	8.6 **9.8** 11.5	< 0.001[2]
WBC (10^9/L)	535 (502)	8.1 **10.4** 13.1	8.8 **11.1** 14.3	8.4 **10.8** 13.7	< 0.021[2]
Platelets (10^9/L)	535 (501)	254 **330** 436	301 **400** 534	276 **364** 482	< 0.001[2]
CRP (mg/L)	535 (485)	13 **41** 98	21 **65** 142	18 **54** 118	< 0.001[2]

Table continues on next page.

Table 2. Descriptive statistics (median, lower and upper quartile) at baseline by dichotomized entry diagnosis MPA and WG *continued*

Parameter	N (n)	MPA (N = 254)	WG (N = 281)	Combined (N = 535)	p-value
ANCA ELISA only	535				< 0.001[1]
MPO		58% (148)	9% (26)	33% (174)	
PR3		25% (64)	79% (222)	53% (286)	
double positive		2% (4)	4% (12)	3% (16)	
negative		13% (32)	7% (19)	10% (51)	
missing		2% (6)	1% (2)	1% (8)	
ANCA ELISA or IIF	535				< 0.001[1]
MPO		67% (169)	13% (36)	38% (205)	
PR3		26% (65)	79% (223)	54% (288)	
double positive		2% (4)	4% (12)	3% (16)	
negative		4% (10)	3% (8)	3% (18)	
missing		2% (6)	1% (2)	1% (8)	
BVAS	535 (504)	13 **15** 21	12 **20** 26	12 **17** 23	< 0.001[2]
BVAS quartiles					< 0.001[1]
< 10		11% (28)	15% (42)	13% (70)	
10-18		53% (134)	23% (64)	37% (198)	
18-23		18% (46)	24% (67)	21% (113)	
> 23		18% (46)	38% (108)	29% (154)	

N, observations after single imputation; (n), observations before single imputation; [1]Pearson test; [2]Wilcoxon test. ANCA, antineutrophil cytoplasmic antibodies; BVAS, Birmingham Vasculitis Activity Score; CKD, chronic kidney disease; CRP, C-reactive protein; GFR, glomerular filtration rate; Hb, hemoglobin; IIF, indirect immunofluorescence; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; WBC, white blood cell count; WG, Wegener's granulomatosis.

Survival

Cumulative survival at 1, 2 and 5 years was 88% (95% CI 86-91), 85% (95% CI 82-88) and 78% (95% CI 75-82), respectively. The calculated survival in the matched population was 98%, 97% and 92%, respectively. The overall mortality rate ratio among the patients compared with the controls was 2.6 (95% CI 2.2-3.1) and was significant by log-rank test ($p < 0.0001$). Although the mortality rate ratio was highest in the first year, it was still significantly elevated for patients with ANCA-associated vasculitis in subsequent years with a ratio of 1.3 (95% CI 1.04-1.65) (**Figure 1**).

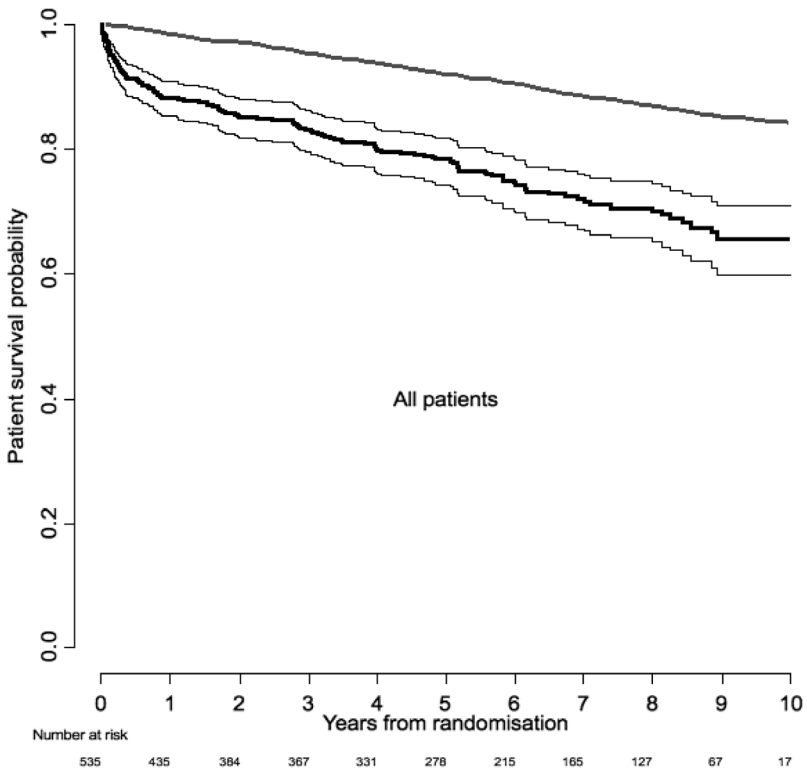

Figure 1. Patient survival overall (solid black line) with 95% CI (thin black lines) compared with a matched general population (solid grey line).

Cause of death

There were a total of 133 (25%) deaths during the observation period. The causes of death are summarized in **Table 3**.

Table 3. Causes of death within and after the first year of follow-up

Cause of death	< 1 year		> 1 year		Total (%)	
	Primary cause	Contributing factor	Primary cause	Contributing factor	Primary cause	Contributing factor
Active vasculitis	11 (18.6)	17 (28.8)	6 (8.1)	7 (9.5)	17 (12.8)	24 (18.0)
pulmonary hemorrhage	6		2		8	
Infection	28 (47.5)	31 (52.5)	15 (20.3)	23 (31.1)	43 (32.3)	54 (40.6)
pneumonia	15		8		23	
sepsis	8		7		15	
CMV	2				2	
PCP	3				3	
Cardiovascular	9 (15.3)	11 (18.6)	19 (25.7)	21 (28.4)	28 (21.1)	32 (24.1)
myocardial infarction	2		4		6	
cerebrovascular accident	2		2		4	
pulmonary embolus	2				2	
sudden death	1		3		4	
Malignancy	0 (0)		16 (21.6)	18 (24.3)	16 (12.0)	18 (13.5)
solid organ			12		12	
hematological			4		4	
Miscellanous	6 (10.2)		9 (12.2)		15 (11.3)	
pulmonary fibrosis	3		3		6	
Unknown	5 (8.5)		9 (12.2)		14 (10.5)	
Total	59		74		133	

Primary cause: number of patients where specific factor was main factor of death (% of total).
Contributing factor: all patients where specific factor contributed to death including primary cause (% of total).
CMV, cytomegalovirus infection; PCP, *Pneumocystis jiroveci* pneumonia.

Fifty-nine of the 133 deaths (44%) occurred within one year of enrolment. The cause of death differed between patients who died within the first year after enrolment compared with patients who died later (**Table 3**). In the first year, patients were most likely to die either of infection (48%) or active vasculitis (19%), whereas after one year patients died mostly of cardiovascular disease (26%), malignancy (22%) or infection (20%).

Predictors of death - multivariable analysis

In the multivariable Cox regression the following entry parameters were significant predictors of mortality: advancing age, an estimated glomerular filtration rate of < 15 ml/min, higher Birmingham Vasculitis Activity Score, lower hemoglobin and the time interaction for a higher white blood cell count (**Figure 2**).

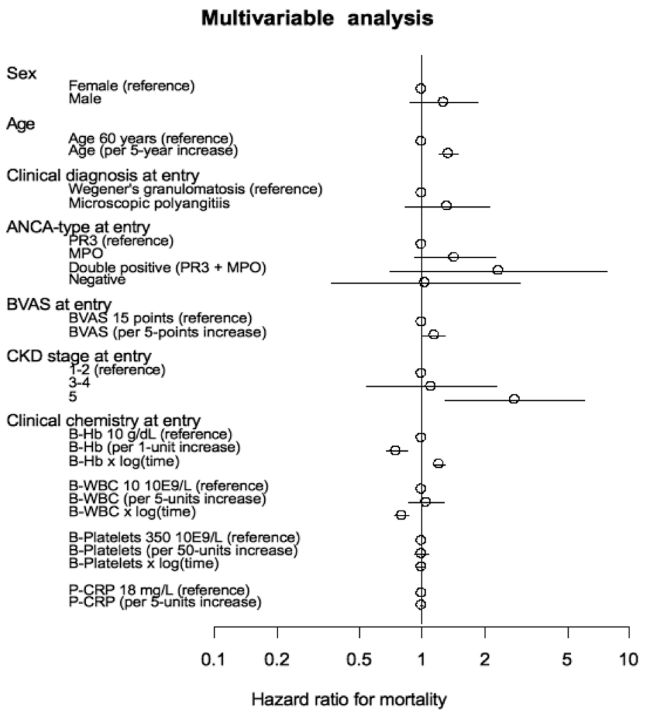

Figure 2. Multivariable analysis (Forrester plot). ANCA, antineutrophil cytoplasmic antibodies; BVAS, Birmingham Vasculitis Activity Score; CKD, chronic kidney disease; CRP, C-reactive protein; Hb, hemoglobin; MPO, myeloperoxidase; PR3, proteinase 3; WBC, white blood cell count.

In the multivariable Cox regression where the mortality of an age-, sex-, year- and country-matched cohort was used as comparator group the following entry parameters were significant predictors of reduced survival: younger age, an estimated glomerular filtration rate of < 15 ml/min, higher Birmingham Vasculitis Activity Score, MPO-ANCA, and lower hemoglobin, higher white blood cell count and their respective interaction terms for log time (data not shown). Patient survival according to ANCA-specificity, age, renal function as chronic kidney disease-stage and Birmingham Vasculitis Activity Score is presented in **Figure 3 A-D** as adjusted Cox curves.

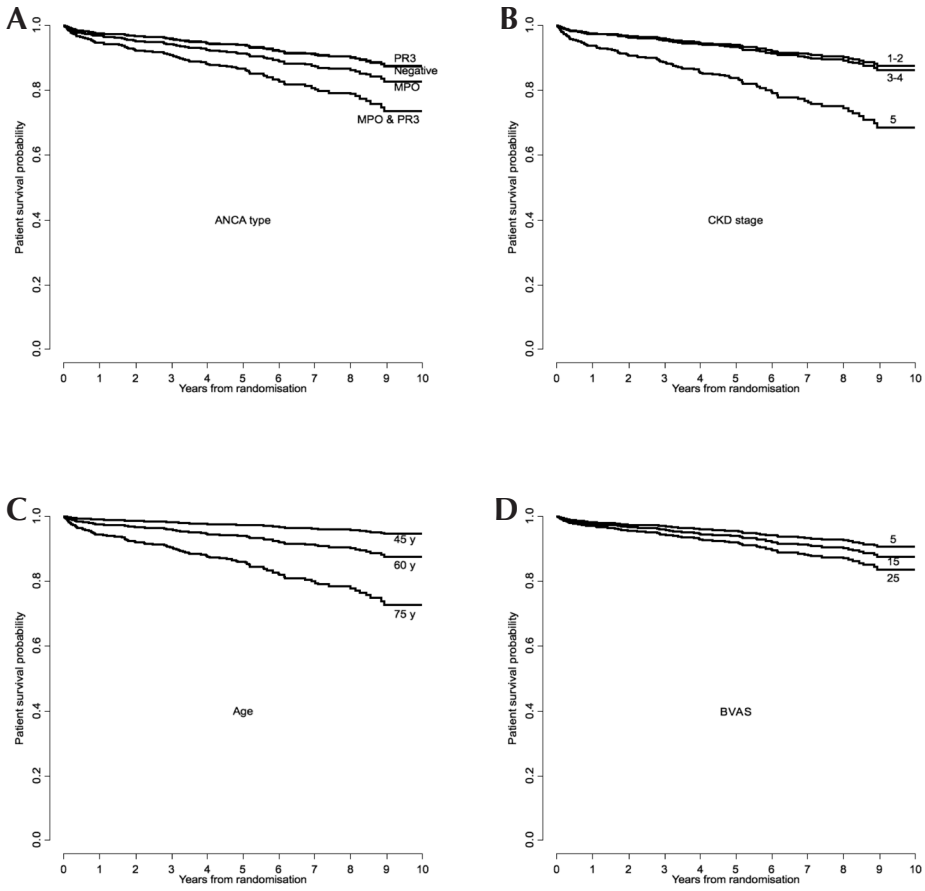

Figure 3. Calculated patient survival probability from the multivariable Cox regression. (A) Type of anti-neutrophil cytoplasm antibody (ANCA); proteinase 3 (PR3)-ANCA, myeloperoxidase (MPO)-ANCA, double positive and ANCA-negative; (B) renal function estimated as chronic kidney disease (CKD)-stage; stage 1 + 2, stage 3 + 4 and stage 5; (C) patient age at entry; age 60 years (reference) and 45 and 75 years; (D) Birmingham Vasculitis Activity Score (BVAS) which was set at 5, 15 (reference) and 25.

DISCUSSION

The last 20 years has seen the advent of randomized therapeutic trials in ANCA-associated vasculitis, which have substantially contributed to establishing modern treatment paradigms in these diseases.[21] This study assessed the long-term survival and factors predicting mortality in patients with ANCA-associated vasculitis who participated in four randomized trials organized by the European Vasculitis Study Group capturing almost the full range of disease severity.

The one, two and five year survival was 88%, 85% and 78%, respectively. The mortality rate ratio was 2.6 compared to the general population. The main predictors of poor outcome at presentation were advanced renal failure, increasing age, a high Birmingham Vasculitis Activity Score and white blood cell count and a low hemoglobin. Relative mortality was higher in younger patients when compared to a matched general population.

This study shows that patients with ANCA-associated vasculitis continue to have a substantially higher mortality compared to a matched general population despite advances in diagnosis and therapy in recent years. Mortality rates are high in the first year after diagnosis particularly for patients with severe renal impairment and advanced age. Disease- and therapy-related complications, in particular infections and active vasculitis, account for the majority of deaths within the first year. This emphasizes the need to strike the right balance between gaining rapid control of life-threatening disease manifestations without exposing the patients to undue risk of heavy immunosuppression. Improving the safety while at least maintaining current efficacy needs to be a focus for the further development of remission induction protocols.

The excess risk of mortality persists after the first year. The main causes of death, infections, cardiovascular causes and malignancies, are similar to the pattern seen in the general population. It is however noteworthy that death due to infection remains very prevalent. So far it is unclear whether there is an excess of cardiovascular and malignant death. It is interesting that, in the current study, most of the excess mortality compared to the general population occurred in the younger age group. This is an

important finding which has not been documented before and highlights the importance of comparing patient survival to the general population.

In our cohort increasing age, advanced renal impairment, higher disease activity and low hemoglobin were predictors of mortality. Advanced renal failure and higher age are independent risk factors for therapy-related toxicity, as previously shown by our group.[22] Although current therapy guidelines already make recommendations to modify cyclophosphamide dosing according to age and renal function,[21] further efforts are required to tailor therapy to individual patients taking into account the specific risk from disease manifestations and therapy toxicity. A timely diagnosis might help to prevent irreversible loss of kidney function, but this is hampered by the often silent nature of kidney disease. The identified adverse factors will be useful in the design of new therapeutic studies for risk stratification to address these questions.

Patient survival in our study was comparable to smaller previous studies, which have reported a survival of between 82-97% at one year, 45-91% at five years and 75-88% at ten years for patients with Wegener's granulomatosis and microscopic polyangiitis.[23] Several previous studies identified advancing age and various markers of impaired kidney function as predictors of early death,[5;24-27] in keeping with our findings. Disease activity as measured by the Birmingham Vasculitis Activity Score had a small, but statistically significant, effect on survival in the multivariable model. This is in keeping with some previous reports.[28] A low hemoglobin and high white blood cell count imparted an increased risk of death, possibly as markers of the severity of the systemic inflammation. In addition, the importance of neutrophils in particular in the pathogenesis of ANCA-associated vasculitis is well recognized.[29] A possible bias is, however, that patients with more severe disease may have been more likely to have received corticosteroids before enrolment, which would have increased their neutrophil count.

In contrast with several previous studies,[27;30;31] we did not find different survival in patients with either Wegener's granulomatosis or microscopic polyangiitis or patients with different ANCA specificities. The reported differences in previous studies are likely due to either reporting unadjusted mortality without correcting for the older age and more severe renal involvement of patients with microscopic polyangiitis and

anti-MPO-ANCA, underpowered multivariable analysis and/or inadequate case mix. The strengths of this study are that it is to our knowledge the largest study investigating survival in ANCA-associated vasculitis. The patients had a broad range of disease manifestations and were followed up for a median of 6 years for surviving patients.

However, there are some limitations to this study. This cohort was derived from four randomized controlled trials rather than a typical inception cohort. Although the proportions of patients with each severity of ANCA-associated vasculitis (limited, generalized, or severe) in our cohort may differ from an inception cohort, their characteristics are representative of the broader population of patients with ANCA-associated vasculitis. The relative magnitude of effect of each parameter in our multivariable model is therefore likely valid and representative of the broader population. Furthermore, most inception cohorts in ANCA-associated vasculitis are derived from a limited number of centers and geographic areas, while ours covers a large part of Europe further enhancing its generalizability. The ratio between Wegener's granulomatosis and microscopic polyangiitis patients varies geographically; the ratio in our study was typical for ratios found at middle European latitudes.[32] The overall mortality of ANCA-associated vasculitis may have been underestimated as our studies excluded very elderly patients and those with lung hemorrhage at the time of diagnosis. In addition, by necessity patients who died before they could be recruited are also not captured. Patients with only localized disease may be underrepresented as researchers could have been reluctant to enrol them into studies with possible exposure to cytotoxic medication. As such, it is difficult to generalize our results to those specific populations.

Despite recent advances in the therapy of ANCA-associated vasculitis, patients continue to have an excess mortality. This is particularly true for younger patients and patients with severe renal involvement. The increased risk persists after the initial acute presentation. Development of newer treatment strategies has the potential to reduce early deaths due to vasculitis and deaths consequent on the toxicity of current agents. It is unclear to what extent improved therapies will impact on later mortality.

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DISCLOSURES

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