The Importance of Demographic and Geographical Factors on the Incidence and Outcome of Systemic Small Vessel Vasculitis Associated with Anti-Neutrophil Cytoplasmic Antibodies

Maria Weiner

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Factors on the Incidence and Outcome of
Systemic Small Vessel Vasculitis Associated with
Anti-Neutrophil Cytoplasmic Antibodies

Maria Weiner

Department of Nephrology and
Department of Medical and Health Sciences
Linköping University, Sweden
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Till Signe och Astrid

Solskensöga ser på dig, solskensfamn dig vagnar
- Ur *Videvisan*, Zacharias Topelius 1869

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ABSTRACT

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) comprise microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Two serotypes are recognized: myeloperoxidase (MPO)-ANCA and proteinase 3 (PR3)-ANCA. Renal involvement is a common and severe manifestation associated with increased mortality. The incidence varies geographically, but studies are difficult to compare due to heterogeneous methodology and inclusion criteria. AAV is commonly found in the elderly, but there are little data on outcome and optimal treatment in the highest age groups. This thesis focuses on the epidemiology of AAV: incidence, geographical distribution, and outcome.

In *Paper I* annual incidence rates and outcome were compared between nephritis in AAV and nephritis in systemic lupus erythematosus (SLE) in two geographically defined populations in Sweden. Even though SLE is twice as common as AAV, ANCA-associated nephritis outnumbered lupus nephritis by three to one, and was significantly more severe in terms of mortality and development of end stage renal disease.

In *Paper II* associations between ANCA serotype and geographical and demographic factors were investigated in a large multi-centre study of 1408 patients with renal biopsy-proven AAV. PR3-ANCA was associated with male gender, younger age and higher glomerular filtration rate. PR3-ANCA was also associated with higher latitude and lower ultraviolet radiation levels, but analyses of subgroups suggested that genetic rather than environmental explanations might be more important for this geographical gradient.

In *Paper III* a consecutive cohort of 151 elderly patients with MPA and GPA was studied with a focus on treatment, mortality and renal survival. Patients who had received immunosuppressive treatment with cyclophosphamide or rituximab had better survival rates compared to less intensively treated or untreated patients. Severely impaired renal function at diagnosis was associated with worse outcome in terms of both patient and renal survival.

In *Paper IV* the elderly cohort was extended to 202 patients. In this study we found that treatment with cyclophosphamide or rituximab was associated with the development of less permanent organ damage, and not with higher utilization of in-hospital care. However, high doses of glucocorticoids were associated with fatal infections and treatment-related damage.

SAMMANFATTNING

I denna avhandling har vi studerat en grupp sjukdomar som kallas för ANCA-vaskulit. 'Vaskulit' betyder inflammation i blodkärl och ANCA är en förkortning för en speciell typ av antikropp som är typisk vid dessa sjukdomar. Det finns två sorters antikroppar: PR3-ANCA och MPO-ANCA. ANCA-vaskulit är en autoimmun sjukdom där immunförsvaret riktas mot den egna kroppen; i det här fallet angrips små blodkärl vilket leder till att i stort sett alla kroppens organ kan drabbas. Njurarna är ett av de organ som innehåller flest små blodkärl och ett av de vanligaste symptomen är inflammation i njurarna.

Delarbete I: SLE och ANCA-vaskulit är två olika autoimmuna sjukdomar som kan drabba i stort sett alla organ i kroppen men där njurinflammation är en speciellt fruktad komplikation. Trots att SLE är en dubbelt så vanlig sjukdom fann vi att ANCA-vaskulit med njurinflammation var tre gånger vanligare än SLE med njurinflammation och att risken att dö eller hamna i dialys var betydligt högre. Resultaten är viktiga eftersom SLE är en mer välkänd sjukdom som ofta upptäcks i ett tidigare stadium än ANCA-vaskulit. Med denna studie hoppas vi kunna öka uppmärksamheten kring ANCA-vaskulit så att den kan upptäckas och behandlas tidigare.

Delarbete II: Det är inte klarlagt hur stor betydelse arv respektive miljö har för uppkomsten av ANCA-vaskulit. I denna studie jämförde vi förekomsten av de två ANCA-typerna på flera platser i Europa och USA och fann att PR3-ANCA var vanligare längre norrut där UV-strålningen är lägre. När vi analyserade norra och centrala Europa separat såg vi dock inget sådant samband. Detta skulle kunna tala för att genetiskt arv spelar större roll än omgivningsfaktorer för ANCA-typ eftersom skillnaderna i UV-strålning var stor mellan de platser vi analyserade, medan de genetiska skillnaderna sannolikt inte är så stora i norra och centrala Europa som mellan norra och södra Europa.

Delarbete III: ANCA-vaskulit drabbar främst äldre patienter, men trots det har få patienter över 75 år deltagit i de läkemedelsstudier som dagens behandlingsrekommendationer grundar sig på. I denna studie fann vi att dödligheten hos patienter över 75 år med ANCA-vaskulit var nästan fyra gånger högre jämfört med personer i samma ålder i Sverige. Viktigt var också att vi fann att de patienter som fått behandling med kraftigt immundämpande läkemedel enligt riktlinjer utarbetade för en yngre population hade bättre överlevnad än de som fick mindre behandling eller ingen behandling alls.

Delarbete IV: En fråga som väcktes av resultaten i delarbete III var om den högre överlevnaden hos behandlade skedde till priset av komplikationer med kroniska skador och större behov av sjukhusvård. Tvärt emot vad man kanske kunde väntat sig fann vi att de äldre patienter som fått ordentlig behandling utvecklade mindre kroniska skador och att de inte hade längre vårdtider eller fler återinläggningar på sjukhus. Vi fann dock ett samband mellan höga kortisondoser och risken för dödliga infektioner och biverkningar som benskörhet och diabetes.

LIST OF PAPERS

Paper I

Incidence and disease severity of anti-neutrophil cytoplasmic antibody-associated nephritis are higher than in lupus nephritis in Sweden. Mohammad A, Weiner M, Sjöwall C, Johansson M, Bengtsson A, Ståhl-Hallengren C, Nived O, Eriksson P, Sturfelt G, Segelmark M. *Nephrol Dial Transplant* 2015; 30:i23-30.

Paper II

Proteinase-3 and myeloperoxidase serotype in relation to demographic factors and geographic distribution in anti-neutrophil cytoplasmic antibody-associated glomerulonephritis. Weiner M, Bjørneklett R, Hrušková Z, Mackinnon B, Poulton CJ, Sindelar L, Mohammad AJ, Eriksson P, Gesualdo L, Geetha D, Crnogorac M, Jayne D, Hogan SL, Geddes C, Tesar V, Aasarød K, Segelmark M. *Nephrol Dial Transplant* 2019; 34:301-308.

Paper III

Outcome and Treatment of Elderly Patients with ANCA-Associated Vasculitis. Weiner M, Goh S, Mohammad A, Hruskova Z, Tanna A, Bruchfeld A, Selga D, Chocova Z, Westman K, Eriksson P, Pusey C, Tesar V, Salama A, Segelmark M. *Clin J Am Soc Nephrol* 2015; 10:1128-35.

Paper IV

Impact of treatment on damage and hospitalization in elderly patients with microscopic polyangiitis and granulomatosis with polyangiitis. Weiner M, Goh SM, Mohammad AJ, Hrušková Z, Tanna A, Sharp P, Kang A, Bruchfeld A, Selga D, Chocová Z, Westman K, Eriksson P, Harper L, Pusey CD, Tesar V, Salama AD, Segelmark M. *J Rheumatol* 2019, doi: 10.3899/jrheum.190019. [Epub ahead of print]

ABBREVIATIONS

AAN	ANCA-associated nephritis
AAV	ANCA-associated vasculitis
ACR	American College of Rheumatology
ANA	anti-nuclear antibody
ANCA	anti-neutrophil cytoplasmic antibody
Anti-GBM	anti-glomerular basement membrane
AZA	azathioprine
BPI	bactericidal/permeability-increasing protein
BVAS	Birmingham Vasculitis Activity Score
C-ANCA	cytoplasmic ANCA
CHCC	Chapel Hill Consensus Conference
CI	confidence interval
CRP	C-reactive protein
CSS	Churg-Strauss syndrome
CYC	cyclophosphamide
DCVAS	diagnostic and classification criteria in vasculitis
eGFR	estimated glomerular filtration rate
EGPA	eosinophilic granulomatosis with polyangiitis
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ENT	ear-nose-throat
ESR	erythrocyte sedimentation rate
ESRD	end stage renal disease
EUVAS	European Vasculitis Society
GC	glucocorticoids
GDCN	Glomerular Disease Collaborative Network
GPA	granulomatosis with polyangiitis
GWAS	genome-wide association study

HR	hazard ratio
ICD	International Classification of Diseases
IIF	indirect immunofluorescence
IQR	interquartile range
ISN/RPS	International Society of Nephrology/Renal Pathology Society
MHC	major histocompatibility complex
MMF	mycophenolate mofetil
MPA	microscopic polyangiitis
MPO	myeloperoxidase
MTX	methotrexate
OR	odds ratio
PAN	polyarteritis nodosa
P-ANCA	perinuclear ANCA
PLEX	plasma exchange
PMN	polymorphonuclear
PR3	proteinase-3
RTX	rituximab
SD	standard deviation
SLE	systemic lupus erythematosus
SLEDAI	SLE disease activity index
SMR	standardized mortality ratio
SPSS	Statistical Package for the Social Sciences
SVV	small vessel vasculitis
UV	ultraviolet
VDI	Vasculitis Damage Index
WBC	white blood cell count
WG	Wegener's granulomatosis

INTRODUCTION

The word ‘vasculitis’ means inflammation of blood vessels, but it is also the common term for a group of inflammatory diseases with vascular inflammation as a defining feature. Vasculitis can be caused by an underlying infectious, rheumatic or malignant disease, and is then referred to as secondary vasculitis. If there is no known underlying disease, the vasculitis is referred to as primary.

The primary vasculitides are categorized based on the size of the predominant vessels involved: large vessel vasculitis, medium vessel vasculitis and small vessel vasculitis [1], as shown in Figure 1. The small vessel vasculitides (SVV) are further divided into those associated with deposition of immune complexes in the vessel walls, and those without such depositions, called pauci-immune.

This thesis focuses on the pauci-immune SVV, or the preferred name anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). These are histologically characterized by necrotizing inflammation of vessel walls with few or no immune deposits, and associated with the presence of ANCA in the circulation. The AAV group is further divided into three different disease entities: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, previously Wegener’s granulomatosis) and eosinophilic granulomatosis with polyangiitis (EGPA, previously Churg-Strauss syndrome) [1].

Figure 1. Vessel involvement

Reproduced from Jennette *et al.* [1] with permission from John Wiley & Sons.

Definitions, diagnosis and classification

The different vasculitides vary in underlying pathogenesis, clinical presentation and outcome. However, they also share overlapping findings and within one disease entity, presentation may vary. This makes diagnosis challenging. There is no single test that can demonstrate that a patient has vasculitis, thereby giving rise to a need for diagnostic and classification criteria. There is an important distinction between classification criteria that are used to group patients in a reproducible way for research purposes, and diagnostic criteria that are used to help clinicians to correctly diagnose individual patients and guide clinical management and treatment. Nomenclature systems are also described below. Such systems specify the name that should be used for a defined disease process, and are neither classification, nor diagnostic criteria.

American College of Rheumatology classification criteria

In 1990, the American College of Rheumatology (ACR) published classification criteria for seven vasculitis diseases: polyarteritis nodosa (PAN), Churg-Strauss syndrome (CSS), Wegener's granulomatosis (WG), hypersensitivity vasculitis, Henoch-Schönlein purpura, giant cell arteritis and Takayasu arteritis. The criteria were developed by comparing patients who had the particular vasculitis with the remaining vasculitis patients [2-9].

The ACR criteria were developed to help distinguish different vasculitis types from others for use in clinical studies, and to allow for comparisons between studies. The ACR criteria were not intended to be used for diagnosing vasculitis in individual patients, and have been shown to function poorly for this purpose [10]. The ACR criteria for WG and CSS are shown in Tables 1 and 2, respectively.

Table 1. ACR criteria for WG

Criterion	Definition
<i>Nasal or oral inflammation</i>	Development of oral ulcers or purulent/bloody nasal discharge.
<i>Abnormal chest radiograph</i>	Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities.
<i>Urinary sediment</i>	Microhematuria or red cell casts in urine sediment.
<i>Granulomatous inflammation on biopsy</i>	Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole).

At least 2 of 4 criteria need to be present to classify a patient as having WG. Adapted from Leavitt *et al.* [3]

Table 2. ACR criteria for CSS

Criterion	Definition
<i>Asthma</i>	History of wheezing or diffuse high-pitched rales on expiration.
<i>Eosinophilia</i>	Eosinophilia >10% on white blood cell differential count.
<i>Mononeuropathy or polyneuropathy</i>	Development of mononeuropathy, multiple mononeuropathies, or polyneuropathy attributable to a systemic vasculitis.
<i>Pulmonary infiltrates, non-fixed</i>	Migratory or transitory pulmonary infiltrates on radiographs attributable to a systemic vasculitis.
<i>Paranasal sinus abnormality</i>	History of acute or chronic paranasal sinus pain or tenderness or radiographic opacification of the paranasal sinuses.
<i>Extravascular eosinophils</i>	Biopsy including artery, arteriole, or venule, showing accumulations of eosinophils in extravascular areas.

At least 4 of 6 criteria need to be present to classify a patient as having CSS. Adapted from Masi *et al.* [8]

Chapel Hill Consensus Conference nomenclature

The first International Chapel Hill Consensus Conference (CHCC) nomenclature was published in 1994. The aim of the conference was to reach a consensus on the names and definitions of the vasculitides [11]. The CHCC is a nomenclature system, and it does not provide classification or diagnostic criteria. Importantly, even though the definitions might include histopathologic terms, this does not imply that the diagnosis can only be made if a biopsy has been carried out.

One of the most important proposals in the original document was the separation between microscopic and classical polyarteritis, which had previously been grouped together. According to the CHCC, classical PAN is a disease of medium-sized and small arteries, and glomerulonephritis is not a feature of PAN. Microscopic polyarteritis, or the preferred name microscopic polyangiitis, is on the contrary defined by necrotizing vasculitis in small vessels (capillaries, venules, arterioles) and glomerulonephritis is commonly seen.

In 2012 the nomenclature was revised with changes of names and definitions and addition of categories that were not included in the original consensus document. An important change in the revised version was that the SVV group now was divided into two categories: AAV and immune complex associated SVV. This reflected the increased recognition that ANCA are of pathogenic importance in AAV. Also, in line with advances in the understanding of the aetiology and pathogenesis of vasculitis, names of several diseases were changed in an attempt to move away from eponyms and instead towards names reflecting aetiopathogenesis. Hence, the eponyms Wegener's granulomatosis, Churg-Strauss syndrome, and Henoch-Schönlein purpura were replaced by GPA, EGPA and IgA-vasculitis, respectively [1]. Table 3 shows definitions of the AAV according to the CHCC.

Table 3. Definitions of AAV according to the CHCC

Name	Definition
<i>Granulomatosis with polyangiitis (GPA)</i>	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels. Necrotizing glomerulonephritis is common.
<i>Microscopic polyangiitis (MPA)</i>	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels. Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.
<i>Eosinophilic granulomatosis with polyangiitis (EGPA)</i>	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia.

Adapted from Jennette *et al.* [1]

European Medicines Agency algorithm

The ACR criteria and the CHCC definitions are widely used in epidemiological research to classify patients. However, limitations in their use include that there are no ACR criteria for MPA and that the CHCC nomenclature was not intended to be used as classification criteria. In addition, neither ACR nor the original CHCC nomenclature included ANCA in their respective classification criteria and definitions.

The European Medicines Agency (EMA) algorithm was developed as a consensus on how to use the available CHCC definitions and ACR classification criteria for PAN and AAV in epidemiological studies to facilitate comparisons between different studies without confounding by classification [12]. In this algorithm, the ACR criteria for CSS [8] and WG [3], the Lanham criteria for CSS [13] and the CHCC definitions [11] are used in a stepwise, hierarchic manner, to enable each patient to be classified into one single category with a minimum of unclassified patients. Surrogate markers for GPA and renal vasculitis and ANCA are incorporated into the algorithm in addition to the existing criteria/definitions. Before applying the algorithm for classification, the patients must have a clinical diagnosis of AAV or PAN and the following criteria must be met: clinical features compatible or characteristic for AAV or PAN; objective diagnostic measures supporting diagnosis (histopathology, ANCA serology, investigations strongly suggesting vasculitis/granuloma); no other diagnosis more likely to account for the signs/symptoms. Figure 2 shows the EMA classification algorithm and surrogate markers for GPA and renal vasculitis.

The initial validation showed good agreement between the classification algorithm and the clinical diagnosis, and it has since also been evaluated in Chinese and Turkish populations [14, 15]. The changes introduced in the 2012 revised CHCC nomenclature was shown not to affect the performance of the algorithm [16].

Surrogate markers for GPA

- X-ray evidence of fixed pulmonary infiltrates/nodules/cavitations present for >1 month
- Bloody nasal discharge and crusting for >1 month, or nasal ulceration
- Chronic sinusitis, otitis media or mastoiditis for >3 months
- Retro-orbital mass or inflammation
- Saddle nose deformity/destructive sinonasal disease
- Bronchial stenosis
- Subglottic stenosis

Surrogate markers for renal vasculitis

- Red cell casts or >10% dysmorphic erythrocytes
- 2+ hematuria and 2+ proteinuria on urinalysis

Figure 2. EMA classification algorithm and surrogate markers

Reproduced from Watts *et al.* [12] with permission from BMJ Publishing Group Ltd.

Future developments

There are no validated diagnostic criteria for vasculitis, and as described above, the currently available classification criteria are imperfect. This is the rationale behind the diagnosis and classification of vasculitis study (DCVAS), a multinational, observational study that aims to develop diagnostic criteria and update and validate classification criteria in vasculitis [17].

Disease entities

Granulomatosis with polyangiitis

Characteristic for GPA is granulomatous inflammation of the upper and lower respiratory tract in combination with necrotizing small vessel vasculitis [1]. The type of ANCA usually associated with GPA is proteinase 3 (PR3)-ANCA [18], but 10-15% in Europe have myeloperoxidase (MPO)-ANCA [19-21].

The most typical manifestation is involvement of the ear-nose-throat (ENT) region with symptoms like epistaxis, nasal crusting, sinusitis, otitis media, and chronic changes including saddle nose deformity and subglottic stenosis. Involvement of the lower respiratory tract with lung nodules and alveolar haemorrhage is seen in 50-90% [22]. Renal disease is also common and associated with worse prognosis [23, 24]. Gastrointestinal manifestations have been reported in 5-10% of patients and cardiac involvement such as heart failure, pericarditis and valvular heart disease in 10-20% [24-26]. In a study by Mahr *et al.*, patients with gastrointestinal and cardiac involvement had the worst prognosis in a cohort of patients with both MPA and GPA [27].

In the majority of cases GPA is a systemic disease, but a persistent localized disease of the respiratory tract with no signs of systemic involvement has been described in 5% of patients with GPA. In these cases ANCA positivity is seen in about half of patients, long-term survival is good, but permanent damage such as septal perforation and saddle nose deformity is common [28].

Microscopic polyangiitis

In MPA, the defining feature is necrotizing vasculitis of small vessels, while granulomatous inflammation is not present [1]. Most patients with MPA are MPO-ANCA positive at diagnosis [18], but 15-30% are PR3-ANCA positive [19-21] and a small number of patients are ANCA negative [29].

The most common manifestation is glomerulonephritis, present in about 90% and sometimes being the only manifestation of the disease [30]. Lung involvement with pulmonary capillaritis occurs, in the most severe cases in the form of massive lung bleedings. MPA is also associated with pulmonary fibrosis [31]. Skin manifestations and involvement of peripheral nerves have

been reported in up to 60% of patients [32]. Patients with MPA are often older compared to patients with GPA, and mortality rates are higher [19, 33].

Eosinophilic granulomatosis with polyangiitis

In EGPA, asthma, eosinophilia and granulomatous inflammation are the characteristic findings [1]. Although the majority of patients are ANCA negative, EGPA is classified as an AAV and MPO-ANCA is seen in 30-40% of patients [34, 35].

Cardiac, skin and gastrointestinal manifestations, and involvement of the peripheral nervous system are common [36]. Due to its differing clinical presentation and outcome, EGPA is often studied separately from GPA and MPA.

Anti-neutrophil cytoplasmic antibodies

Anti-neutrophil cytoplasmic antibodies (ANCA) are autoantibodies reacting with proteins that are predominantly expressed in the cytoplasmic granules of polymorphonuclear neutrophil granulocytes (PMNs) and lysosomes of monocytes. With indirect immunofluorescence (IIF), two main patterns are recognized: perinuclear ANCA (P-ANCA) and cytoplasmic ANCA (C-ANCA) [37]. Today, the use of antigen-specific immunoassays such as enzyme-linked immunosorbent assay (ELISA) is preferred to increase specificity [18]. In recent years, novel automated techniques have been introduced, and assays have developed with second generation capture ELISA and third generation anchor ELISA [18, 38].

The ANCA associated with AAV have two main antigens, myeloperoxidase (MPO) [39] and proteinase-3 (PR3) [40], which are both expressed in the granules of PMNs and monocytes. Autoantibodies against MPO are referred to as MPO-ANCA and those against PR3 as PR3-ANCA. The C-ANCA pattern is usually caused by PR3-ANCA, but in some cases by reactivity with MPO or bactericidal/permeability-increasing protein (BPI) [41]. The P-ANCA pattern can be caused by antibodies against MPO, but also against elastase [42], lactoferrin [43], cathepsin G [44] and BPI [41], and is thus less specific.

Clinical importance

Although ANCA are characteristic for AAV, they are neither required for diagnosis nor specific. Especially when detected by IIF, ANCA can also be seen in other diseases with varying frequency, such as anti-glomerular basement membrane (anti-GBM) disease [45], inflammatory bowel disease [46], rheumatoid arthritis [47], systemic lupus erythematosus (SLE) [48], infections [49-51] and haematological malignancies [52, 53].

A role for ANCA in disease development is supported by the fact that the majority of AAV patients are ANCA positive and that titres often rise in active disease [54]. Patients who become ANCA negative after induction treatment have a lower risk of relapse [55], but serial measurements of ANCA during remission are only modestly predictive of relapses and cannot

be used alone to guide treatment decisions [56]. Several studies have shown that ANCA serotype is important in predicting outcome in terms of treatment response [57], risk of relapse, renal survival and mortality [27, 58, 59], and it has been suggested that classification according to ANCA serotype (PR3-AAV vs MPO-AAV) is to be preferred or used in addition to the traditional dichotomization based on clinical diagnosis (GPA vs MPA).

Pathogenic importance

Further support for a pathogenic role for ANCA can be found in animal models. There are several different mouse and rat models in which an immune response to MPO is induced resulting in necrotizing pauci-immune glomerulonephritis and pulmonary capillaritis, thus mimicking MPO-AAV in humans. Similar rodent models have been developed in efforts to study PR3-ANCA related disease, but have so far failed in inducing granulomatous disease. This is likely in part attributed to differences between human and rodent PR3 [60-62].

In vitro studies have demonstrated that PR3- and MPO-ANCA can activate neutrophils, leading to the production of reactive oxygen species and proteolytic enzymes with subsequent endothelial damage and inflammation of the vessel walls [63, 64]. Additional work have demonstrated that ANCA can stimulate neutrophils to produce pro-inflammatory mediators such as IL-1 β [65], neutrophil extracellular traps [66], and factors that activate complement via the alternative pathway [67, 68]. The latter and other discoveries regarding the importance of the complement system in the pathogenesis of AAV have led to the development of complement-targeted therapies that are now being tested as part of the treatment arsenal in AAV [69, 70].

Epidemiology

Incidence

Overall incidence numbers for AAV vary between countries and regions (Table 4). In Europe, incidence rates range between 10 and 20 per million. Studies from Australia and New Zealand show similar incidence rates to those found in Europe [71], while the incidence found in Minnesota in the USA is the highest reported so far [72].

Reasons for differences in incidence estimates could be found in the methodology used: the classification criteria and case recruitment, adjustments for age and gender, and choice of population used as the denominator. Other likely contributing factors are differences in population demographics and genetics, environmental factors and health care access.

Several studies have shown an increase in the incidence of GPA and MPA since the 1980s [73, 74]. Naturally, this observation could be the result of a true increase in the number of patients developing the diseases due to unidentified environmental factors. However, the widespread introduction of ANCA testing in routine clinical practice in the 1990s and the

subsequent increased detection and awareness of AAV have most likely played an important role, as more recent studies on the incidence of AAV have found stable figures [72, 75].

Most studies show a fairly equal gender distribution for the AAV group as a whole. Age-specific incidence numbers show an increase with age, with peak incidence numbers reported in the age groups 55-64 years [76], 65-74 years [77] and above 75 years [21, 72].

Prevalence

Prevalence numbers also vary between studies, and have increased with time [23, 78, 79]. This reflects the increased incidence followed by the introduction of ANCA in clinical practice as discussed above, but also increased survival in AAV patients in recent decades due to earlier detection and improvements in the treatment and management of patients.

The prevalence estimates for MPA in Europe range between 25 and 94 per million and for GPA between 24 and 160 per million [23, 79-83]. In Australia and New Zealand prevalence numbers are around 95 per million for GPA and 39 per million for MPA [71, 84], and in Japan 2 per million for GPA and 14 per million for MPA [85]. The highest prevalence estimates reported are from the USA, at 218 per million for GPA and 184 per million for MPA [72].

Prevalence figures are generally lower for MPA compared to GPA. This mirrors the lower incidence found in many areas, but is also seen in areas in which incidence numbers are equal [72, 80], conceivably reflecting the higher mortality in patients with MPA.

Table 4. Selected studies on the incidence of MPA and GPA

Study area	Criteria	Case recruitment	Time period	Population	Incidence GPA	Incidence MPA	Reference
<i>Greece</i>	ACR CHCC	Referral centre	1995-2003	369 430	6.6	10.2	Panagiotakis [86]
<i>Turkey</i>	ACR CHCC	Hospital + immunology lab register	2004-2014	620 450	4.8	2.4	Pamuk [87]
<i>Spain</i>	CHCC	Referral centre	1988-2001	208 270	3.0	7.9	Gonzalez-Gay [76]
<i>Italy</i>	EMA	Hospital + pathology + immunology lab register + private specialists	1995-2009	475 000	2.8		Catanoso [83]
<i>Germany</i>	CHCC	Hospital + pathology + immunology lab register	1998-2002	2 777 275	8.6	2.7	Reinhold-Keller [75]
<i>United Kingdom</i>	ACR CHCC	Hospital + pathology register	1988-1997	413 500	9.7	8.0	Watts [88]
<i>United Kingdom</i>	ACR CHCC	Hospital register	2005-2009	459 000	14.3	6.5	Fujimoto [89]
<i>Sweden</i>	ACR CHCC	Hospital + immunology lab register	1997-2006	641 760	9.8	10.1	Mohammad [21]
<i>Sweden</i>	ICD	National inpatient register	1991-2001	8 000 000	11.9		Knight [74]
<i>Finland</i>	ICD	National inpatient register	1996-2000	4 200 000	9.3		Takala [90]
<i>Norway</i>	ACR	Hospital discharge records + pathology register + private specialists	1994-1998	374 280	14.4		Koldingsnes [23]
<i>USA</i>	EMA	Hospital + immunology lab register	1996-2015	107 750	13	16	Berti [72]
<i>Australia</i>	ACR CHCC	Hospital register	2000-2004	360 000	8.4	5.0	Ormerod [71]
<i>New Zealand (Upper North Island)</i>	ICD	National inpatient register	1999-2003		5.8		O'Donnell [91]
<i>New Zealand (Lower South Island)</i>	ICD	National inpatient register	1999-2003		15		O'Donnell [91]
<i>Japan</i>	EMA	Hospital register	2005-2009	759 000	2.1	18.2	Fujimoto [89]

Incidence is presented per million inhabitants and year. ICD, International Classification of Diseases

Geographical differences

A north-south gradient in the distribution of AAV has been proposed based on an observation that GPA is more common in the north of Europe compared to the south, with the opposite for MPA (Table 4). A reciprocal gradient has been reported from the southern hemisphere [91]. Nevertheless, there are studies from Sweden, the United Kingdom and the USA showing fairly equal incidence of MPA and GPA [21, 72, 88], and simply comparing incidence figures derived from different epidemiological studies with heterogeneous inclusion criteria and case retrieval is not easily done. In a study by Watts *et al.* the same methodology was therefore applied in three different areas: in Spain, the United Kingdom and Norway. The annual incidence of GPA was lower in Spain compared to the United Kingdom and Norway, while the incidence of MPA was lower in Norway compared to the United Kingdom and Spain [92]. This study has however not yet been replicated.

In addition to the proposed north-south axis, there are other differences in the geographic and ethnic distribution of AAV that could suggest both environmental and genetic factors. The overall incidence of AAV is similar in the United Kingdom, Scandinavia and Japan, but the relative distribution of the different serotypes and clinical diagnoses varies greatly [21, 89, 92]. MPO-ANCA and MPA is strongly predominant over PR3-ANCA and GPA in Asian countries [85, 93]. In a study from a multi-ethnic population in Paris, GPA was reported to be less common in patients of non-European origin [82], and similarly PR3-ANCA positivity was more uncommon in African-Americans compared to Caucasians in a study from the USA [94]. The incidence of GPA is higher in Caucasians compared to individuals of Maori or Asian origin in New Zealand [91] and the Inuit in Greenland [95].

There are also studies investigating the influence of living in rural versus urban areas. The incidence of AAV was significantly higher in rural areas compared to urban areas in studies from Australia and Canada [71, 96], while such a pattern was not seen for MPA and GPA in a Spanish study [76].

Seasonal differences

Seasonal variations in the onset of vasculitis have been discussed and studied for many years, although such an association has not been established. There are some studies showing peak onset during winter [97, 98] and some showing peak onset during summer [99]. Other studies have not been able to confirm these findings [23, 100]. In a study from the United Kingdom, GPA was found to follow a cyclical pattern of occurrence with a periodicity of 7.6 years. A similar cyclical pattern was not evident for MPA [81].

Aetiology

Epidemiological data may reveal clues to the aetiology of disease. The ethnic differences suggest that genetic factors play an important role, although geographic differences in the incidence and prevalence of AAV and the relative distribution of different serotypes and clinical phenotypes could also be due to environmental factors. Among the environmental factors that have been associated with AAV are different infectious agents, silica and ultraviolet (UV) radiation.

Infections

The observed seasonal and cyclical variations in the onset of symptoms have led to hypotheses of an infectious trigger of disease. There are several smaller studies and case reports implicating different infectious agents, but the best studied association is between chronic carriage of *Staphylococcus aureus* in the nose and development and relapse of GPA [101, 102]. The finding that treatment with trimethoprim-sulfamethoxazole reduced the risk of relapse in patients with GPA in remission supports a causal relationship [103]. However, this could also be due to the immunomodulatory effects of trimethoprim-sulfamethoxazole and a pathogenic mechanism behind the association has not been fully elucidated [104].

Silica

An increased frequency of ANCA positivity in individuals occupationally exposed to silica was described in the 1990s [105]. Silica has been shown to activate T-cells and cause dysregulation of the immune response [106, 107]. It has also been suggested that apoptosis induced by silica exposes antigens leading to the production of autoantibodies [108]. Silica has been implicated in several other autoimmune diseases, such as rheumatoid arthritis [109], SLE [110] and systemic sclerosis [111]. In a meta-analysis of six case-control studies, the overall odds ratio for developing AAV after exposure for silica was found to be 2.56 (95% CI 1.51-4.36), with a latency between the exposure and diagnosis of around 25 years [112].

Ultraviolet radiation

Another environmental factor that has been implicated in AAV is exposure to UV radiation, and this has been suggested as the underlying mechanism behind the latitudinal gradient described above. In other autoimmune diseases such as type 1 diabetes and multiple sclerosis, UV radiation has been studied more extensively [113-115].

Gatenby *et al.* investigated this possible relationship in AAV and found an increase in the incidence of GPA with increasing latitude and decreasing UV radiation levels, while no latitudinal variation in MPA incidence was found [116]. This study was based on previously published incidence studies from different continents (Asia, South America, North America,

Europe and Australia), and the authors acknowledge that genetic variations between the studied populations were not controlled for and might play a role.

The proposed mechanism behind the effect of UV radiation on autoimmune diseases is the effect of vitamin D on the immune system. Sun exposure of the skin is the main source of vitamin D in humans [117]. The active form of vitamin D, 1,25-dihydroxyvitamin D₃, has the ability to suppress Th1 cell proliferation and cytokine production, as well as Th17 cell responses [118]. Th1/Th17 cells have been implicated in the pathogenesis of GPA and PR3-ANCA mediated disease [119].

Genetic factors

Genetic factors are thought to play a role in the development of AAV, and there are numerous studies on genetic susceptibility focusing on genes involved in immune responses and in the expression of target antigens [120]. Many of the genetic studies are small, and not all associations have been replicated. Familial cases of AAV have been described [121, 122], although the risk of disease among close relatives has been shown to be lower compared to that in several other autoimmune diseases [123].

In a large meta-analysis the pooled effects of genetic variants investigated in at least two studies were assessed. The majority of the genetic variants were in the major histocompatibility complex (MHC) region. The strongest contributors to an increased risk of AAV were the *SERPINA1* Z allele and *HLA-DPBI**0401 allele, while the strongest protective effect was found for *HLA-DPA1* rs9277341 [124]. Associations were also found for *PTNP22* and *CTLA-4*, which are implicated in several other autoimmune diseases such as rheumatoid arthritis, type 1 diabetes, SLE and giant cell arteritis [124].

In a large genome-wide association study (GWAS) conducted in Europe, a genetic association between *HLA-DP*, *SERPINA1* and *PRTN3* (the gene encoding PR3) and PR3-ANCA was found, while *HLA-DQ* was associated with MPO-ANCA. In this GWAS, the strongest genetic association was seen for ANCA serotype and not for the clinical diagnosis [20]. Such a division was also supported in the meta-analysis mentioned above, in which the genetic associations differed for MPA/GPA and for MPO-ANCA/PR3-ANCA, but odds ratios were higher for ANCA serotype than for clinical diagnosis. An association between *HLA-DPBI**0401 and GPA was confirmed in another GWAS in patients of European descent in North America [125].

The serpin A1 gene (*SERPINA1*) encodes the serine protease inhibitor alpha-1-antitrypsin which has PR3 as one of its substrates. Studies of its global distribution show that it is more common in Scandinavia, Western and Central Europe and countries colonized by Europeans [126]. The *HLA-DPBI**0401 allele also varies geographically, and is more common in Europe compared to Japan, China and African Americans in the USA [127].

Treatment

Treatment of AAV is aimed at inducing remission, preventing relapses and avoiding permanent organ damage caused by the vasculitis disease and the treatment.

Induction therapy

Treatment with cyclophosphamide in combination with corticosteroids has dramatically improved survival and has been the first choice of treatment for AAV for decades [128]. Although effective in achieving remission, the use of cyclophosphamide is associated with adverse effects such as leukopenia, infections, infertility and malignancies [29]. The search for less toxic treatment alternatives has resulted in several trials aiming at reducing the use of cyclophosphamide. Intravenous pulse cyclophosphamide is now preferentially used over daily oral cyclophosphamide, since it results in similar rates of remission, but a lower cumulative dose of cyclophosphamide and a lower rate of leukopenia [129].

The RAVE trial showed that rituximab, a monoclonal anti-CD20 antibody resulting in B-cell depletion, was as effective as cyclophosphamide for inducing remission in AAV, and it was even more effective in relapsing disease. Rituximab was also as effective as cyclophosphamide among patients with renal disease or alveolar haemorrhage [130, 131]. In the RITUXIVAS trial, a rituximab-based regimen was found to be equally effective as cyclophosphamide in inducing remission in AAV with renal involvement [132]. After two years, relapse rates and mortality rates did not differ between the two arms [133]. Nevertheless, the rituximab-based regimens have not been associated with lower rates of adverse events compared to standard cyclophosphamide therapy in these trials [130, 132]. A combination of glucocorticoids and cyclophosphamide or rituximab is currently recommended in guidelines for induction of organ- or life-threatening disease [134, 135].

For patients with severe renal disease due to rapidly progressive glomerulonephritis and patients with diffuse alveolar haemorrhage, plasma exchange should be considered [135]. Plasma exchange was shown to decrease the risk of end stage renal disease (ESRD) and death at three months in the MEPEX trial [136], although the long-term results are unclear [19]. PEXIVAS is a randomized trial aimed at evaluating the effect of plasma exchange on mortality and ESRD and comparing a low-dose glucocorticoid regimen with standard dosing [137]. Preliminary results have shown that the use of plasma exchange did not reduce the risk of death or ESRD. Importantly, the reduced dose glucocorticoid regimen was associated with fewer serious infections without increasing the risk of adverse outcome [138].

For non-organ-threatening disease, both methotrexate and mycophenolate mofetil (MMF) have been shown to be non-inferior to cyclophosphamide in inducing remission [139, 140]. However, long-term disease control seems to be less effective [140, 141].

The use of prophylaxis against infection with *Pneumocystis jiroveci* with trimethoprim-sulfamethoxazole is recommended during induction treatment [134, 135]. A treatment algorithm based on current guidelines is shown in Figure 3.

Figure 3. Treatment algorithm.

Adapted from Yates *et al.* [135] and Ntatsaki *et al.* [134]. GC, glucocorticoids; MTX, methotrexate; MMF, mycophenolate mofetil; CYC, cyclophosphamide; RTX, rituximab; PLEX, plasma exchange; AZA, azathioprine

Maintenance therapy

After induction therapy, maintenance therapy with low-dose glucocorticoids in combination with azathioprine, methotrexate, rituximab or MMF is initiated [134, 135]. Azathioprine was the first immunosuppressive agent shown to be an equal alternative to cyclophosphamide as maintenance therapy. In CYCAZAREM, it was shown that the standard therapy with 12 months of oral cyclophosphamide could be replaced by azathioprine once patients had achieved remission, without increasing the risk of relapses [142]. If azathioprine is used after cyclophosphamide induction, relapse rates are lower if treatment is continued for 48 months as opposed to 24 months [143]. Methotrexate can be used for maintenance after cyclophosphamide induction in patients without severely impaired renal function and has been shown to be equivalent to azathioprine [144]. MMF is an alternative, but azathioprine is preferred due to a higher relapse rate in patients treated with MMF [145].

In MAINRITSAN, low-dose rituximab given at fixed intervals was shown to be associated with lower relapse rates at 28 months compared to standard-of-care with azathioprine [146]. In a recently published phase III trial, rituximab given at similar fixed intervals was compared with an individually tailored regimen with rituximab given only at the reappearance of CD19+ B-cells or ANCA, or marked rise in ANCA titre. The relapse rate did not differ significantly between arms, even though there was a trend towards more relapses in the patients receiving the tailored regimen. Monitoring ANCA and B-cells could not predict relapses, but resulted in fewer rituximab infusions [147].

Disease assessment tools

Chronic diseases such as AAV can be described in terms of both disease activity and damage, respectively representing the reversible and irreversible aspects of the disease process [148]. For the purpose of quantifying the information collected during clinical evaluation of patients, scoring systems recording both disease activity and permanent damage have been developed, the most widely used being the Birmingham Vasculitis Activity Score (BVAS) and the Vasculitis Damage Index (VDI).

Birmingham Vasculitis Activity Score

The Birmingham Vasculitis Activity Score (BVAS) is a clinical tool for assessing disease activity in systemic vasculitis, first published in 1994 [149]. It was designed to document the presence of new or worsening active vasculitis that requires institution or intensification of immunosuppressive treatment.

The most important principle when recording disease activity is that a symptom can only be recorded if it is attributed to active vasculitis, after exclusion of other causes such as infections or permanent damage. The second principle is the intention-to-treat principle. If a symptom is scored this should give an indication to act on that item and intensify treatment [150].

The current version consists of a wide variety of clinical features grouped in nine different organ systems. Each item has a numerical value reflecting its clinical relevance and there is a maximum score for each organ system. The issue of low-grade activity not requiring intensification of treatment is addressed in the latest version of BVAS by the opportunity to record “persistent disease only” if all items scored are due to active disease that is not new or worse within the last three months. This situation would normally not require intensification of treatment. However, if a patient has a mixture of persistent and new or worse disease, all items will be scored as new or worse and warrant increased therapy according to the intention-to-treat principle [150].

The BVAS score has become the standard disease activity measure in vasculitis [148], used in a large number of clinical trials to assess disease activity at diagnosis, and during follow-up to define remission and relapse [150]. It has also been shown to have prognostic value [19, 149].

Vasculitis Damage Index

Damage is defined as a non-healing scar that is not responsive to immunosuppressive treatment. The distinction between activity that calls for intensification of therapy and permanent damage that does not warrant immunosuppression is not always easy, but is important in order to avoid over-treatment [148]. Generally, if a sign or symptom does not respond to treatment over time, it should be considered as damage.

The Vasculitis Damage Index (VDI) was developed to reflect damage items common in patients with vasculitis and comprises items of damage in 11 categories. If an item occurred after the onset of vasculitis and has lasted for at least three months it can be recorded as damage. Importantly, items are scored regardless of attribution, and damage items can thus reflect both the effects of the vasculitis disease and the effects of therapy. Since items are considered permanent, the VDI score can only increase or remain stable over time [151].

Treatment-related damage refers to VDI items attributable in major part to drug toxicity rather than the vasculitis process itself and includes osteoporosis, avascular necrosis, osteomyelitis, cataract, gonadal failure, marrow failure, chemical cystitis, diabetes mellitus and malignancy [152]. Critical damage (items consistent with organ failure) and major vascular damage (damage to major blood vessels) are also described in the original publication [152].

Damage is an important outcome in AAV both as a reflection of cumulative disease activity and treatment toxicity [153], and as a predictor of subsequent mortality [24, 152]. The VDI is therefore recommended as one of the key outcome measures in clinical trials in AAV [148].

Outcome

Patient survival

If not treated, mortality rates are up to 80-90% in a few months, mainly caused by renal failure and lung bleedings [154, 155]. The introduction of immunosuppressive therapy has dramatically improved this poor survival rate. Although still accounting for significant mortality, the AAV have changed into chronic diseases with a relapsing course associated with accumulation of permanent organ damage over time.

Survival at 1, 2 and 5 years in four randomized multi-centre trials conducted by the European Vasculitis Society (EUVAS) between 1995 and 2002 was 88%, 85% and 78% respectively [19]. These studies have often excluded the oldest and most severely ill patients, and descriptive cohort studies are important in describing outcome in the clinical setting. In a Swedish cohort of patients with renal AAV, survival was 85% at 1 year, 82% at 2 years, 74% at 5 years and 52% at 10 years [156], similar to survival rates found in the United Kingdom [157]. In a population-based study from the USA including all known AAV cases 2-, 5- and 10-year survival was 91%, 81% and 64% [72]. Compared to the general population, mortality in patients with AAV is increased two to three times [19, 21, 72].

A number of risk factors have been associated with increased mortality, the most well-established being higher age and worse renal function [19, 24, 29, 156, 158-161]. Other risk

factors described include high levels of PR3-ANCA [156], high BVAS at diagnosis [19, 158], low serum albumin [33, 162], lower haemoglobin [19] and development of permanent organ damage [24, 151].

Causes of death

Most deaths occur during the first year, and in particular during the first three months, corresponding to the time frame when both immunosuppression and vasculitis activity is most intensive [19, 163]. Early mortality is mainly caused by infections and active vasculitis, with infections being the leading cause of death during the first year after diagnosis [163]. Long-term risks include malignancies and increased cardiovascular risk [19, 164, 165].

Older studies showed that the cancer incidence in patients with AAV was increased about two times compared to the general population, with the highest risk observed for bladder cancer, non-melanoma skin cancer, leukaemia and lymphoma [166, 167]. A more recent EUVAS follow-up study found a lower incidence ratio, and non-melanoma skin cancer was the only cancer site with a statistically significantly increased incidence [164]. In a German study, there was no increased incidence of malignancies in vasculitis patients [168]. These recent findings might reflect advances in reducing the toxicity of treatment, with less cyclophosphamide exposure, but it is also possible that follow-up needs to be longer to detect a significant increase in cancer incidence [169].

Compared with controls, patients with AAV have a two- to threefold increased risk of cardiovascular events [165, 170]. Long-term data have shown that 14% of patients with AAV suffered from cardiovascular events within five years from diagnosis [171]. The increased cardiovascular risk is probably multifactorial, including endothelial dysfunction, renal impairment, chronic inflammation and corticosteroid use causing accelerated development of hypertension, hyperlipidaemia and diabetes [165].

Renal survival

Development of ESRD is seen in 20 to 40% of patients during long-term follow-up [24, 156, 157, 172]. These numbers vary depending on the characteristics of the patients studied (e.g., age, renal involvement at diagnosis or not, renal function at presentation, ANCA type). Dialysis dependency at diagnosis and initial creatinine level have been associated with increased risk of subsequent ESRD in several studies [162, 173]. Increasing age is another risk factor [162]. MPO-ANCA positivity has been associated with increased risk of developing ESRD compared to PR3-ANCA positivity [58, 173], possibly due to the presence of more chronic renal lesions such as glomerulosclerosis, tubular atrophy and interstitial fibrosis [174, 175]. However, these results are not consistent, and others have found no significant differences in renal outcome with relation to ANCA specificity [174, 176].

Development of ESRD is associated with increased mortality, while relapse rates are lower compared to patients with preserved renal function [177]. In patients with dialysis dependency

at diagnosis, 23% died within 6 months, and of those surviving 29% remained dialysis dependent [173].

Permanent organ damage

As survival has improved, other outcome measures have become more important. The majority of patients with AAV develop some degree of permanent organ damage during follow-up. Development of higher total VDI scores is associated with increased mortality [152]. Patients with severe fatal disease were more likely to have major vascular damage and critical damage, while there was no association between treatment-related damage and fatal disease in the study by Exley *et al.* [152].

In a cross-sectional study of vasculitis patients in Sweden, the median VDI score was 3 after a median disease duration of 9 years. Severe damage (≥ 5 items) was seen in 56% of the patients included and only 9% had no items of damage. Cardiovascular and renal damage were most common, and the single most prevalent item was hypertension [178].

The type of damage developing over time differs between the two clinical diagnoses GPA and MPA. In patients with GPA, the most common damage items are found in the ENT domain, while renal damage is more frequently seen in MPA [153, 178, 179]. Interestingly, in the Swedish study there was almost complete separation between ENT damage and cardiac and renal damage in GPA patients, underscoring the differences in terms of organ involvement and prognosis that are present within this group [178].

Remission and relapse

Remission is achieved in the majority of patients, but relapses are common and up to 60% of patients relapse during long-term follow-up [29]. Remission rates in the large randomized clinical trials range from 60% to 90% depending on the definition of remission (i.e., absence of new or worse clinical disease activity but allowing minor persistent disease activity, or complete absence of disease activity at six months and adherence to the prednisolone taper scheme) [130, 139].

A clinical diagnosis of GPA and PR3-ANCA positivity is associated with a greater risk of relapse compared to patients with MPA and MPO-ANCA positivity [142, 157, 180]. Other factors associated with increased risk of relapse include chronic nasal carriage of *Staphylococcus aureus* [101], cardiac involvement [181], respiratory tract involvement [182] and preserved renal function [101].

ANCA-associated vasculitis in older patients

The AAV can affect patients of any age, but are mainly diseases of older patients with incidence rates increasing with age as described above. A large study of patients with ANCA-associated glomerulonephritis identified through the Norwegian Kidney Biopsy Registry found that 27% of the patients were 75 years or older at the time of biopsy [183]. In the Swedish Renal Biopsy Registry, AAV was the most common diagnosis in patients aged 75 years or more, accounting for 18% of the biopsies [184], and in patients aged 80 years or more, pauci-immune glomerulonephritis accounted for about 30% in patients biopsied for acute kidney injury in the USA [185].

Clinical features

With increasing age, the proportion of MPO-ANCA positivity and a clinical diagnosis of MPA increases compared to PR3-ANCA positivity and GPA [33, 158, 161]. In line with this, the majority of older patients with AAV have renal involvement, while ENT symptoms are less common [158, 186, 187]. Some studies have also described more pulmonary involvement in the elderly [86, 161], although this is not evident in other studies [188]. Renal impairment is often severe, with dialysis dependency more frequently seen when comparing older and younger patients [33, 189]. Nevertheless, in studies describing renal histology, no significant differences have been found with regard to the percentage of normal glomeruli and percentage of crescents in renal biopsy specimens [161, 188].

Outcome

The response to immunosuppressive treatment is described as equal in some [33, 186], but not all [161] studies comparing older and younger patients. Regarding relapses, rates are similar to or lower than those found in younger patients [33, 161, 187]. PR3-ANCA positivity is a well-established risk factor for relapses, and this is also evident in older patients. While PR3-ANCA positivity increases the risk of relapse, impaired renal function decreases the risk and the seemingly lower overall relapse risk in the elderly might be due to the lower frequency of PR3-ANCA and the high frequency of renal involvement [190].

As described above, age is one of the best-established risk factors for death. Older patients are at a higher risk of death due to comorbidities such as cardiovascular disease [186], but are also more susceptible to infections [33, 189] and adverse events [163, 178], due to impaired renal function and possibly also to changes in the immune system [191].

Despite the fact that a large and growing proportion of patients with AAV are older, and that age has consistently been shown to be a risk factor for poor outcome, the mean age in a majority of the large vasculitis trials conducted to date is around 60 years and many of the clinical trials on which current guidelines are based have excluded patients over the age of 75 years [136, 139, 142].

Lupus nephritis

Often described as the prototype of a systemic autoimmune disease, SLE is characterized by the production of a number of different autoantibodies and a broad range of clinical manifestations, including muco-cutaneous, musculoskeletal, neurologic, haematological, pulmonary, cardiac, gastrointestinal and renal involvement.

Renal disease with lupus nephritis (LN) develops in 20 to 45% of Caucasian SLE populations [192-195] and in up to 70% of African American, Asian and Hispanic populations [194, 196]. Some patients present with renal involvement, but it occurs most commonly after the diagnosis of SLE has been made [197].

Epidemiology

Incidence rates for SLE vary around the world, ranging from 10 to 49 per million in Europe to 10 to 76 per million in North America, 46 to 63 per million in Central America, 48 to 87 per million in South America, 110 per million in Australia, and 12 to 84 per million in Asia [198]. As in AAV, there may be true differences in the incidence of SLE around the world. However, the large differences found between studies from the same geographical area suggest that factors such as case retrieval strategy and classification are also of importance.

Peak incidence is seen in middle-aged adults and SLE is more common in women than in men, with a ratio ranging from 2:1 to 15:1 [198]. This is seen across all age groups, but particularly during childbearing age [199]. SLE more frequently affects African-Americans, Hispanics and Asians than Caucasians in the USA, suggesting that genetic factors play a role [200]. Renal involvement with LN is also more common in patients of African-American and Hispanic ethnicity compared to Caucasians [201].

Incidence numbers for LN in Caucasian populations range from 4 to 7 per million [202-206]. There are conflicting data on trends in the incidence of LN over the years. In Norway, the incidence decreased from 7 per million in the years 1978-1995 to 4.5 per million in 1996-2006 [204]. Contrary to these findings, the incidence in Germany increased from 2 per million in 1990-1997 to 4 per million in 2006-2013 [207]. Reported incidence figures from the USA were stable over a period of 30 years [203].

Aetiology

In SLE, inadequate removal of apoptotic cells exposing immune cells to nuclear and cell membrane components and loss of self-tolerance ultimately lead to the production of autoantibodies. Autoantibodies binding to circulating antigens or antigens deposited in the glomeruli form immune complexes. Subsequent inflammation and cytotoxicity mediated by complement and Fc receptor binding causes damage to the glomeruli [197].

The best-studied autoantibodies associated with LN are anti-dsDNA antibodies and anti-C1q-antibodies. Both are seen more frequently in SLE patients with renal involvement

compared to those without [197]. A number of different genes have been associated with SLE and LN, and as in several other autoimmune diseases many of the genetic variants are found in the MHC region [208].

Environmental risk factors associated with SLE include exposure to silica, solvents, pesticides [209], oral contraceptives and hormone replacement therapy [210, 211]. Current, but not past, cigarette smoking increases the risk [212, 213], while there is an inverse relationship between moderate alcohol intake and risk of SLE [214]. Exposure to UV radiation can exacerbate symptoms, but it remains to be determined if UV radiation is also a risk factor for developing disease [215].

Treatment

Treatment of LN, as with AAV, is divided into an induction phase to achieve remission, and a maintenance phase to prevent relapses. The ultimate goal of treatment is to prevent chronic kidney disease and ESRD. For induction, glucocorticoids in combination with intravenous cyclophosphamide or MMF are recommended, and for maintenance MMF or azathioprine are first-line choices. In severe nephrotic syndrome or incomplete renal response, MMF may be combined with a calcineurin inhibitor [216]. Hydroxychloroquine is recommended for all patients with SLE [216] due to its effect on disease activity, organ damage and survival [217].

In a randomized trial comparing MMF with standard-dose intravenous cyclophosphamide, renal response rates at 6 months were similar in the two treatment arms [218]. Low-dose cyclophosphamide has been shown to be equivalent to standard-dose cyclophosphamide, for both induction of remission and long-term kidney preservation [219, 220]. For maintenance, MMF has been shown to be superior to azathioprine in maintaining renal remission and preventing flares [221].

A combination of MMF and a calcineurin inhibitor has been studied in LN as induction therapy [222], as maintenance therapy [223] and in patients not responding to standard therapy [224, 225]. The great majority of these studies have been performed in Asian populations, but recently a phase II trial in 20 countries in America, Europe and Asia evaluated addition of the calcineurin inhibitor voclosporin to background MMF and corticosteroids for induction treatment of LN. Renal response was higher in the voclosporin group, but also adverse events including deaths [226]. Rituximab can be considered following failure of the first-line treatment or in relapsing disease [216, 227].

Outcome

Survival rates at 5, 10, 15 and 20 years are 95%, 91%, 85% and 78% respectively in a mixed North American SLE population [228]. The most common causes of death are infections and cardiovascular disease [229]. Outcome is generally worse in African-American and Hispanic patients, with regard to both development of ESRD and death [230, 231].

Development of LN is associated with worse outcome in terms of both morbidity and mortality. The standardized mortality ratio (SMR) in patients with SLE is 1.5-3.0 [195, 232-234], and in patients with LN it is 5.9-6.6 [235, 236]. In a population-based Norwegian SLE cohort, the SMR was 3.8 in LN patients compared with 1.7 in non-LN patients. ESRD developed in 6% of the entire cohort and in 20% of LN patients [195]. Overall, 22% of patients with LN in developed countries reached ESRD within 15 years, and in patients with class IV LN the corresponding figure was 44% of patients [237].

Renal biopsy

Renal biopsies are performed in order to establish a histological diagnosis in various renal diseases, and are recommended in current guidelines for both AAV and SLE [135, 216].

ANCA-associated glomerulonephritis

Pauci-immune necrotizing and crescentic glomerulonephritis is the characteristic histologic finding in AAV with renal involvement [1]. A renal biopsy is useful not only for confirming a new diagnosis or relapse of AAV, but also for histopathological classification and predicting prognosis. Lesions are classified as focal (predominance of normal glomeruli), crescentic (predominance of crescentic glomeruli), sclerotic (predominance of sclerotic glomeruli) or mixed (none of the aforementioned features is predominant). This classification has prognostic value on renal outcome, with the best renal survival seen in the focal class and the worst seen in the sclerotic class [238, 239].

When extra-renal involvement is present, a histological diagnosis can also be made with biopsies from other organs such as nasal mucosa, skin, lung tissue, muscle and nerves [240-242]. Reasons for not performing a renal biopsy in AAV include the presence of absolute or relative contraindications such as increased bleeding risk, uncontrolled hypertension and solitary kidney [243], or that a histological diagnosis has already been obtained by biopsy of another organ.

In a report from the Spanish Registry of Glomerulonephritis, vasculitis accounted for 4.5% of all biopsies, but in the elderly it accounted for 18.3% [205]. In the Czech Republic, necrotizing vasculitis accounted for 5.7% of renal biopsies [206]. Pauci-immune glomerulonephritis accounted for 4.9% and 9.4% of the biopsies performed in patients <65 years and ≥65 years respectively in Poland [244].

Lupus nephritis

If there is clinical evidence of renal involvement in SLE, a renal biopsy should be performed to establish a histological diagnosis in order to guide treatment and for prognostic information. Immune-complex-mediated glomerulonephritis is the most common cause of renal disease in SLE, but tubulointerstitial disease, podocytopathy and thrombotic microangiopathy also occur [245]. The lesions found are classified according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN [246] (Table 5).

Table 5. ISN/RPS 2003 classification of LN

Class I	Minimal mesangial lupus nephritis Normal glomeruli by light microscopy, mesangial immune deposits by immunofluorescence.
Class II	Mesangial proliferative lupus nephritis Mesangial hypercellularity or mesangial matrix expansion, with mesangial immune deposits.
Class III	Focal lupus nephritis Focal, segmental or global endocapillary or extracapillary glomerulonephritis involving <50% of glomeruli. Active (A) or chronic (C) lesions.
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis Diffuse, segmental or global endocapillary or extracapillary glomerulonephritis involving ≥50% of glomeruli. Active (A) or chronic (C) lesions.
Class V	Membranous lupus nephritis Global or segmental subepithelial immune deposits or their morphologic sequelae.
Class VI	Advanced sclerosing lupus nephritis ≥90% of glomeruli globally sclerosed.

Adapted from Weening *et al.* [246]

Immunosuppressive treatment for renal disease is used in proliferative LN (classes III and IV), and in membranous LN (class V) with nephrotic range proteinuria. During the course of disease, patients with LN can change ISN/RPS class, and repeat biopsy in the setting of worsening renal function or persistence/worsening of proteinuria can thus be indicated and support changes in treatment strategy [245].

When reporting on the frequency and incidence of LN, it is crucial to exclude re-biopsies in order to obtain correct estimates. Data from renal biopsy registries in Europe report that LN constitutes 5-10% of all biopsy diagnoses [205-207, 244].

RATIONALE AND AIM

Although great progress has been made in the understanding, diagnosis and treatment of AAV, much remains to be elucidated regarding aetiology and further improvement is needed in the management and treatment of patients. Epidemiologic studies are important in this sense, allowing for both descriptive and analytic studies in large populations and in a real-world setting.

The descriptive epidemiology of both AAV and SLE has been studied for many years, but the incidence and outcome of renal disease in the two conditions has not previously been studied simultaneously in the same geographic area with similar inclusion criteria allowing for head-to-head comparison.

There are geographical differences in the occurrence of AAV. Data available from different studies can however not be readily compared, and there is need for larger studies in a more homogeneous population. UV radiation is one environmental factor associated with geographical location that has been studied extensively in other autoimmune diseases, but the data in AAV are scarce.

The elderly constitute a large and growing proportion of patients with AAV. Despite this, most studies on the elderly define this as an age above 60-65 years and data on clinical presentation and outcome in patients above 75 years are insufficient. In addition, many of the large randomized trials on treatment of AAV have excluded this patient population, and there is uncertainty regarding treatment of elderly patients.

The overall aim of the work presented in this thesis was to learn more about the epidemiology of AAV: incidence and distribution, factors potentially underlying the development of disease and factors influencing outcome. In the four studies we have used different epidemiological approaches, making comparisons with another inflammatory disease, between geographic regions and with a focus on a specific age group.

Specific aims

1. To compare annual incidence rates of biopsy-proven lupus nephritis and ANCA-associated nephritis in two geographically defined populations in Sweden and to compare renal and patient survival between these two groups.
2. To investigate associations between ANCA serotype and geographical latitude and ultraviolet radiation levels in a population of patients with biopsy-proven ANCA-associated glomerulonephritis in Europe and North America.
3. To study associations between demographic factors, treatment and outcome in terms of patient survival and renal survival in patients aged 75 years or more with MPA and GPA.
4. To investigate whether immunosuppressive treatment in elderly patients aged 75 years or more with MPA and GPA is associated with development of permanent organ damage and increased need for in-hospital care, and to study causes of death.

METHODS

Study population and patient retrieval

Paper I

Two geographically defined areas in Sweden were studied: a health care district in the county of Skåne and one in the county of Östergötland. Patients were identified from local registries based at Skåne University Hospital in Lund and the University Hospital in Linköping.

Inclusion criteria were residence within the study area, a clinical diagnosis of AAV or SLE and a first flare of biopsy-proven nephritis during the period 1997 to 2008. Only biopsy-verified nephritis cases were included to ensure that all were incident during the study period and that no prevalent nephritis cases before the study period were included.

Paper II

Patients with renal biopsy-proven AAV were identified from national and regional renal biopsy registries and vasculitis registries in seven countries in Europe and the USA: the Norwegian renal biopsy registry, the Scottish renal biopsy registry, the Italian Registry of Renal Biopsies, the renal biopsy registry at Dubrava University Hospital in Croatia, the Vasculitis registry in the Czech Republic, the vasculitis registries in Östergötland and Skåne, the vasculitis registry in Cambridge, the Glomerular Disease Collaborative Network (GDCN) registry in North Carolina and the Johns Hopkins Vasculitis database in Maryland.

Only registries including consecutive patients from a defined geographic area were included. Inclusion criteria were a clinical diagnosis of AAV verified by renal biopsy during the period 2000 to 2013, ANCA positivity verified by ELISA and age 18 years or above.

Papers III and IV

Consecutive patients were included from Linköping University Hospital, Skåne University Hospital and Karolinska University Hospital in Sweden; Imperial College London and Royal Free Hospital in the United Kingdom; and General University Hospital in the Czech Republic. In Paper IV, a centre at Queen Elizabeth Hospital in Birmingham was also involved.

Patients were included if they were aged 75 years or more at diagnosis and had a clinical diagnosis of MPA and GPA. The study periods were 1997 to 2009 for Paper III and 1997 to 2013 for Paper IV.

The vasculitis and SLE registries in Östergötland and Skåne

All patients diagnosed with systemic vasculitis and SLE in the county of Östergötland are referred to the Nephrology and Rheumatology departments at Linköping University Hospital. Since 1997, all patients with AAV are registered in a local vasculitis registry. The database includes all incident cases since 1997 and all prevalent cases at the time of the start of the registry. A clinical SLE registry was started at the Department of Rheumatology in Linköping in 2008 and includes both incident and prevalent cases.

A local vasculitis registry was started in the county of Skåne in 2002, including all cases of AAV since 1997 and covering the health care district surrounding Skåne University Hospital in Lund and Malmö. Using a capture-recapture technique, the completeness of the database has been shown to be >95% [80]. All diagnosed cases of SLE at the Department of Rheumatology in Lund have been included in a longitudinal cohort since 1981. The retrieval of patients has been analysed by capture-recapture methodology [247].

Data collection

Data were collected from registries/databases and patients' medical records. Baseline demographic data and clinical and laboratory data were collected from the time of diagnosis or renal biopsy as described below.

Paper I

Baseline data were collected on age, gender, creatinine, haemoglobin, white blood cell count (WBC), platelet count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and organ involvement at the time of biopsy. For LN data were also collected on anti-nuclear antibodies (ANA), anti-dsDNA and complement consumption. Data on outcome included death, ESRD and creatinine at last follow-up.

Biopsy rate was calculated by dividing the number of patients with biopsy-proven nephritis with the number of patients who were judged to have active nephritis by clinical assessment. For AAV this corresponded to a score ≥ 1 in the BVAS renal domain and for SLE the presence of haematuria and proteinuria according to SLE disease activity index (SLEDAI) [248].

Paper II

Data were only collected from the time of biopsy and included age, gender, ANCA serotype (according to antigen-specific ELISA) and estimated glomerular filtration rate (eGFR) according to the Modification of Diet in Renal Disease equation [249]. Biopsy rate was calculated as described for Paper I.

Data on mean monthly erythemally weighted UV radiation levels in Europe were extracted from the STRÅNG database provided by the Swedish Meteorological and Hydrological Institute [250]. Historical data can be extracted from the database with yearly, monthly, daily or hourly radiation data by defining the latitude and longitude for the location of interest and the dates defining the time period of interest. The World Geodetic System 84 coordinate reference system was used for the latitude and longitude coordinates of the participating centres (in the USA the capital city of participating states).

Papers III and IV

Demographic and clinical data at the time of diagnosis included: date of diagnosis, age, gender, diagnosis type (MPA/GPA), ANCA specificity (according to IIF or ELISA), CRP, creatinine, dialysis dependency, BVAS and major comorbidities. Data on outcome up to two years from diagnosis included: date of death, cause of death, date of ESRD, accumulated organ damage according to VDI at one and two years, and hospitalization during the first year. Treatment data included: cumulative dose of intravenous pulsed methylprednisolone, oral prednisolone and intravenous/oral cyclophosphamide; treatment with rituximab, MMF, azathioprine or methotrexate; and use of plasma exchange.

A comorbidity score was calculated as described by Davies *et al.* [251] with one point awarded each for malignancy, ischemic heart disease, peripheral vascular disease, heart failure, diabetes, systemic inflammatory disease (excluding AAV), pulmonary disease and cirrhosis.

Diagnosis and classification

Patients with a clinical diagnosis of AAV were eligible for inclusion in all four studies in this thesis. Classification of patients as having GPA, MPA or EGPA was made according to the EMA algorithm. Only primary AAV was included, excluding PAN, anti-GBM disease, secondary vasculitis and drug-induced vasculitis.

All SLE patients fulfilled the 1982 ACR classification criteria [252]. Histopathology classifications were performed according to the ISN/RPS 2003 classification of LN.

In Paper I, patients with EGPA were included in the estimation of annual incidence. In the remaining papers, patients with EGPA were excluded based on the differing clinical picture and outcome. In Papers I and II, only patients with renal involvement were included and the diagnosis was confirmed by renal biopsy in all cases.

Statistical methods

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Statistics for Windows versions 21-24 (IBM, Armonk, NY, USA). P values <0.05 were considered significant and all analyses were two-sided. For hazard ratios (HR), odds ratios (OR), β -coefficients, SMR and incidence rates, 95% confidence intervals (CI) were calculated.

Continuous variables were described as mean with standard deviation (SD) when normally distributed and as median with interquartile range (IQR) when non-normally distributed. Categorical variables were described as frequencies. Differences between groups were analysed using the Mann-Whitney or Kruskal-Wallis test for non-normally distributed or nonparametric data, the Student's t-test for normally distributed data and the chi-square test or Fisher's exact test for categorical data. An overview of the statistical methods used is shown in Table 6.

Table 6. Overview of statistical methods

Statistical method	Paper I	Paper II	Paper III	Paper IV
<i>Descriptive statistics</i>				
Mean with standard deviation (SD)	X			
Median with interquartile range (IQR)	X	X	X	X
Frequency	X	X	X	X
Annual incidence rates	X			
<i>Analytic statistics</i>				
Student's t-test	X			
Mann-Whitney/Kruskal-Wallis test	X	X	X	X
Chi-square/Fisher's exact test	X	X	X	X
<i>Regression analysis</i>				
Binary logistic regression with odds ratios (OR)		X		X
Linear regression with β -coefficient				X
<i>Survival analysis</i>				
Kaplan-Meier analysis with log-rank test	X		X	
Cox regression with hazard ratios (HR)			X	X

Paper I

Annual incidence rates were calculated using the number of cases as the numerator and the mean population between 1997 and 2008 in the two geographical areas as the denominator. The Kaplan-Meier method was used to estimate patient and renal survival and the log-rank test to evaluate differences in survival between ANCA-associated nephritis (AAN) and LN.

Paper II

Univariable and multivariable logistic regression analysis was used to assess associations between ANCA serotype (PR3-ANCA) and the variables gender, age, eGFR, latitude, longitude

and UV radiation levels. Latitude and UV radiation were not entered in multivariable analysis simultaneously due to strong correlation.

Paper III

The Kaplan-Meier method was used to estimate overall and renal survival and the log-rank test to evaluate differences in survival between groups. Cox proportional hazards models were used to analyse time-dependent variables (time to death and time to ESRD). The proportional hazards assumption was checked using visual examination of the Kaplan-Meier curves and by investigating interaction terms. Censoring was performed at the day of loss to follow-up or completion of follow-up. Estimates of renal survival were censored for death. In analysis of treatment, patients who died within 30 days of diagnosis were excluded.

Both univariable and multivariable analyses were performed. The variables entered were chosen to reflect patient characteristics (age, gender and comorbidity score), disease severity (BVAS, CRP and creatinine), disease type (ANCA serotype) and treatment (cyclophosphamide or rituximab) based on previous studies and theoretical reasoning.

The SMR was calculated by dividing the observed death rates in the Swedish cohort with expected death rates in the general Swedish population matched for age and calendar year using life tables provided by Statistics Sweden.

Paper IV

Binary logistic regression analysis was used to analyse binary variables (readmission, treatment-related damage), linear regression analysis to analyse continuous variables (VDI score, total hospital time) and Cox regression analysis to analyse time-dependent variables (time to death caused by infection). Scatter plots and residual plots were examined to determine whether the assumption for linear regression was met. In addition to the variables described above for Paper III, cumulative oral and intravenous glucocorticoid dose were included.

Ethical approval

The collection of data on vasculitis patients in Skåne and Östergötland was approved by the Regional Ethical Review Board in Lund (numbers 2010/517, 2012/252). For Paper I, the collection of data on SLE patients was approved by the Regional Ethical Review Boards in Lund (number 2010/668) and Linköping (number M75-08/2008). For the remaining centres, the applicable ethical permits have been obtained according to national regulations.

RESULTS AND DISCUSSION

Paper I

Incidence

The major finding in Paper I was that the incidence of biopsy-verified AAN was three times higher than the incidence of LN. The annual incidence rate per million adults in the two areas combined was estimated to be 13.2 (95% CI 10.4-16.1) for AAN and 4.3 (95% CI 2.7-6.0) for LN ($P<0.001$) (Table 7). The biopsy rate was 88% for LN and 67.9% for AAN, showing that the higher incidence of AAN cannot be explained by differences in the biopsy rate.

The incidence of AAN differed significantly between the two areas ($P=0.001$), mainly driven by a difference in MPA incidence. The reason for this discrepancy could be a true lower incidence in Östergötland, or lower completeness in the case retrieval. Capture-recapture analysis has been carried out on the case retrieval strategy in the Skåne area, but not in Östergötland. There is an established collaboration between the vasculitis registry in Linköping and the nephrology unit at a referring hospital, but it is possible that diagnosis of renal limited MPA cases in this part of the county was lower during the first part of the study period. It should also be noted that the incidence of MPA was lower in the Malmö area compared with the Lund area in a previous publication by our group [21].

Table 7. Annual incidence rate of biopsy-proven AAN and LN

	AAN	MPA	GPA	EGPA	LN
<i>All</i>	13.2 (10.4-16.1)	9.7 (7.2-12.1)	3.4 (1.9-4.8)	0.2 (0-0.5)	4.3 (2.7-6.0)
<i>Skåne area</i>	19.5 (13.7-25.2)	15.0 (10.0-20.1)	4.0 (1.4-6.6)	0.4 (0-1.3)	5.7 (2.6-8.9)
<i>Östergötland area</i>	9.6 (6.6-12.7)	6.6 (4.1-9.1)	3.0 (1.3-4.8)	0 (0-0)	3.5 (1.7-5.4)

Incidence is presented per million inhabitants and year. Values between parentheses are 95% confidence intervals.

The incidence figures for renal AAV found in this study are similar to the incidence of 14.8 per million found in Japan [85] and 12.2 per million found in the United Kingdom [253]. Incidence numbers for LN described previously range from 4 per million in the United Kingdom and the Czech Republic [202, 206] to 4.5 per million in Norway [204], 5.6 per million in Spain [205] and 7 per million in the USA [203]. Since the incidence figures in this study are similar to previously published data, it is likely that AAN is also more common than LN in other Caucasian populations. As described in the introduction, LN is less common in Caucasians compared to other ethnic groups, and therefore our findings cannot readily be generalized to other parts of the world.

Previous studies from the same area in Sweden found an annual incidence of SLE of 48 per million [254], while the incidence of AAV was 21 per million [21]. The higher incidence of AAN compared to LN is thus most likely due to a lower occurrence of nephritis in SLE patients compared to AAV patients in this and other Caucasian populations.

Survival

Mortality rates were significantly higher for the patients with AAN compared to LN ($P=0.001$). The 1-, 5- and 10-year survival for patients with AAN was 85.4%, 71.8% and 48.3% respectively. The corresponding figures for LN were 100%, 96.3% and 96.3% (Figure 4).

Figure 4. Renal and patient survival

Kaplan-Meier curves showing renal (A) and patient (B) survival in AAN and LN. P values derived from the log-rank test.

Survival rates for AAN are comparable to previously described cohorts in the United Kingdom and Sweden [156, 157]. The survival rates in the LN group are comparable to or better than other published data from SLE populations in Sweden and the USA [228, 254], and thus show a good prognosis despite renal involvement.

The worse survival seen in AAN was not surprising given the fact that age and severity of renal disease are associated with worse prognosis in both SLE and AAV [19, 230, 255]. Mean age at diagnosis was 65.5 years ($SD \pm 13.9$) in patients with AAN and 38.6 years ($SD \pm 15.1$) in patients with LN. Renal function at the time of biopsy was more severely impaired in AAN with a median creatinine at diagnosis of 249 $\mu\text{mol/L}$ (IQR 161-392) compared to 77 $\mu\text{mol/L}$ (IQR 64-100) in LN.

Due to the low number of deaths in the LN group, it was not possible to perform any analyses of predictors of mortality or further determine the relative contribution of age and renal function

to the survival difference observed. Nor did we have very long-term data on the survival of LN patients. Whether or not mortality rates will be similar in the LN patients when they reach above 60-70 years to those observed in the AAN patients remains to be determined.

Renal survival

Renal survival was significantly worse for patients with AAN compared to patients with LN, and 19 of 20 patients who developed ESRD had AAN ($P=0.02$) (Figure 4). The proportion of patients who developed ESRD was 23.2% for AAN and 3.7% for LN during a mean follow-up period of 6.4 years. The frequency of AAV patients developing ESRD is similar to previously published numbers ranging from 20% to 40% [157, 162, 183, 256, 257].

The favourable renal outcome in LN described in this cohort is in line with the results from the long-term follow-up of the Euro-Lupus Nephritis Trial, in which 7% developed ESRD [220]. In a Norwegian population-based study of LN conducted during a similar time period to Paper I, the frequency of ESRD was 20% during a mean follow-up of 18 years [195]. In another Norwegian study renal outcome improved over time, with 11% developing ESRD in the early cohort (1978-1995) during a 10-year follow-up period, while there were no cases of ESRD in the more recent cohort (1996-2006). The use of hydroxychloroquine, pulse methylprednisolone, anticoagulants and anti-hypertensive treatment increased significantly in the more recent cohort, and the authors speculate that the lower incidence and more favourable renal outcome might be due to earlier institution of immunosuppressive, anticoagulant and antihypertensive therapies [204]. Among the patients with LN in our study, 63% had a diagnosis of SLE established before the onset of nephritis, with a median time from diagnosis of SLE to diagnosis of nephritis of 50 months (IQR 16.5-186.5). All the AAN patients had renal involvement at the time of diagnosis. The latency between diagnosis of SLE and onset of nephritis allows for the initiation of therapy as described above, and this could affect renal outcome in a positive direction. This view is further supported by a meta-analysis of both prospective and retrospective studies as well as clinical trials in LN, showing a decreased risk of ESRD paralleled by an increased use of immunosuppressive treatment [237].

Success in terms of increased awareness, earlier diagnosis and treatment are probably key reasons behind the favourable prognosis observed in LN in Paper I. Since impaired renal function at diagnosis has consistently been shown to be associated with poor prognosis in AAV, these factors are most likely key elements in improving results in AAN as well. A recently published study on renal AAV showed better renal survival in a cohort of patients diagnosed in 2000-2010 compared to an older cohort diagnosed in 1988-1999 and significantly lower creatinine levels at diagnosis in the recent cohort, supporting this assumption [258]. Similar findings with improved renal survival paralleled by better renal function at diagnosis, indicating shorter diagnostic delay, have been reported also in ANCA-associated glomerulonephritis [183, 259].

Paper II

Geographical pattern

The latitude of the participating centres spanned a large distance, between 35.8°N and 69.6°N and the UV radiation levels varied between 5246 mWh/m² in the northernmost centre and 14 565 mWh/m² in the southernmost centre in Europe. Table 8 shows demographic and geographical factors at the time of biopsy.

Table 8. Demographic and geographical factors

Centre	N	ANCA % PR3/MPO	Gender % M/F	Age	eGFR ¹	Latitude	UVR
<i>Tromsø</i>	21	57.1/42.9	52.4/47.6	60 (51-69)	17 (7-25)	69.6°N	5246
<i>Trondheim</i>	62	53.2/46.8	45.2/54.8	68 (58-76)	20 (8-38)	63.4°N	6616
<i>Bergen</i>	88	44.3/55.7	52.3/47.7	62 (49-75)	27 (15-54)	60.4°N	7082
<i>Oslo</i>	140	48.6/51.4	54.3/45.7	65 (53-74)	19 (10-40)	59.9°N	7623
<i>Linköping</i>	49	30.6/69.4	61.2/38.8	70 (61-75)	26 (18-37)	58.4°N	9398
<i>Glasgow</i>	238	43.7/56.3	45.8/54.2	67 (59-75)	15 (9-27)	55.9°N	8086
<i>Lund</i>	72	48.6/51.4	51.4/48.6	66 (54-75)	24 (13-44)	55.7°N	10087
<i>Cambridge</i>	54	40.7/59.3	57.4/42.6	64 (58-73)	20 (10-43)	52.2°N	9851
<i>Prague</i>	305	52.5/47.5	53.4/46.6	59 (52-67)	23 (13-47)	50.1°N	12262
<i>Zagreb</i>	42	28.6/71.4	45.2/54.8	64 (47-70)	12 (7-20)	45.8°N	14395
<i>Milan</i>	71	39.4/60.6	46.5/53.5	68 (61-74)	15 (8-25)	45.5°N	13874
<i>Rome</i>	25	36.0/64.0	60.0/40.0	65 (56-70)	8 (6-21)	41.9°N	14565
<i>Maryland</i>	71	42.3/57.7	43.7/56.3	63 (55-72)	18 (10-29)	39.0°N	
<i>North Carolina</i>	170	40.6/59.4	55.3/44.7	59 (49-72)	18 (10-36)	35.8°N	

Data are expressed as % or median (IQR). ¹Data missing in 84 patients. UV radiation (UVR) levels in mWh/m²; eGFR in ml/min/1.73 m².

Increasing age was associated with lower odds of PR3-ANCA positivity, while increasing eGFR and male gender were associated with higher odds of PR3-ANCA positivity (Table 9). The association was seen in both univariable and multivariable analysis, and both when analysing the entire study population and when restricting the analysis to the European patients. Our results support the view that patients with PR3-ANCA positivity are in general younger and have better renal function at diagnosis compared to patients with MPO-ANCA positivity [27, 173]. Higher proportion of PR3-ANCA positivity in men has also been reported in previous studies [19, 173]. In multivariable analysis, higher latitude was associated with higher odds of PR3-ANCA positivity (Table 9). When analysing the European patients separately, the results remained essentially the same. For UV radiation levels an opposite association was found with

lower odds of PR3-ANCA positivity with increasing UV radiation levels (OR per Wh/m² 0.94; 95% CI 0.89-0.99; P=0.038).

Table 9. Analysis of ANCA serotype

Variables	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
<i>Age (per year)</i>	0.97 (0.96-0.98)	<0.001	0.97 (0.97-0.98)	<0.001
<i>Gender (male)</i>	2.12 (1.71-2.62)	<0.001	1.98 (1.58-2.49)	<0.001
<i>eGFR (per ml/min/1.73 m²)</i>	1.01 (1.01-1.02)	<0.001	1.01 (1.00-1.01)	0.012
<i>Latitude (per 10 units)</i>	1.12 (0.99-1.27)	0.071	1.29 (1.05-1.58)	0.016
<i>Longitude (per 10 units)</i>	1.03 (0.99-1.06)	0.11	0.98 (0.93-1.03)	0.34

The OR refers to the probability of being PR3-ANCA positive.

Previous studies on the geographical distribution of AAV have mainly been focused on the clinical entities MPA and GPA, while associations between latitude and ANCA serotype have not previously been explored. Our selection of patients is in line with the suggested clustering of AAV patients into non-renal AAV and renal AAV and further into PR3-ANCA positive and PR3-ANCA negative renal AAV [27].

The association between PR3-ANCA and latitude observed is consistent with the hypothesis that GPA/PR3-ANCA is more common at northern latitudes and lower UV radiation levels [92, 116]. However, it was only significant in multivariable analysis when adjusting for age, gender and renal function. Previous epidemiological studies have shown large differences in the incidence of GPA in different regions in Europe, from 2.8 per million inhabitants in Italy [83] to 14.4 per million in Norway [23].

In renal AAV, the proportion of MPO-ANCA and PR3-ANCA positivity is more equal compared to non-renal AAV in which PR3-ANCA and GPA predominate [27, 173]. ANCA negativity is more common in limited and localized forms of GPA [28, 260], and it has been suggested that the underlying pathogenesis is different with localized forms being caused by granulomatous inflammation and a more predominant Th1 response [22]. Since we only included patients with renal biopsy-proven glomerulonephritis, patients with GPA limited to the upper airways were excluded and whether this disease type is more common at northern latitudes and contribute to the described north-south gradient in the occurrence of GPA remains to be determined.

There are genetic differences between populations in the north and south of Europe [261], and most likely also in the populations in North Carolina and Maryland given their mixed origins from Latin America, Africa and Europe. When limiting the analysis to northern and central Europe, our aim was to analyse a more genetically homogeneous population. Interestingly, the association between ANCA serotype and latitude and UV radiation level was lost in this sub-analysis (Table 10).

Given the large difference in UV radiation levels between the centres included, the paucity of a significant association between serotype and UV radiation could speak in favour of genetic differences along a latitudinal gradient rather than environmental factors such as UV radiation. This is supported by a study from Europe showing that the association between GPA incidence and latitude was due to the distribution of *HLA-DPB*0401* allele frequency [127], a gene variant associated with PR3-ANCA positivity. Further support for this hypothesis comes from a recent analysis of data from several rheumatology units, in which an increased chance of MPO-ANCA positivity (compared with PR3-ANCA) was found in Caucasian Americans and southern Europeans compared with northern Europeans, although the latter did not reach statistical significance [262].

Table 10. Analysis of ANCA serotype in northern and central Europe

Variables	OR (95% CI)	P value
Age (per year)	0.98 (0.97-0.99)	<0.001
Gender (male)	2.01 (1.54-2.63)	<0.001
eGFR (per ml/min/1.73 m ²)	1.01 (1.00-1.01)	0.021
Latitude (per 10 units)	1.14 (0.85-1.52)	0.38
Longitude (per 10 units)	1.00 (0.84-1.19)	0.99

The OR refers to the probability of being PR3-ANCA positive. Showing results from multivariable analysis.

Biopsy rate

Since the study only included biopsy-proven cases of nephritis, a comparison was made between biopsied and non-biopsied cases with AAV and renal involvement at the Linköping, Lund and Cambridge centres. The overall biopsy rate was 68.9%. In Linköping the figure was 71%, which can be compared to the biopsy rate of 67.9% found in Paper I. Biopsied patients were significantly younger (67 years vs 74 years; $P=0.002$) and more often MPO-ANCA positive (58.9% vs 43.0%; $P=0.019$) compared to non-biopsied patients, which would underestimate the number of PR3-ANCA positive patients in the study. The reasons for this difference could be that PR3-ANCA positive patients have more extra-renal manifestations and that diagnosis is confirmed by biopsy of another organ, or that MPO-ANCA positive patients have more severe renal disease strengthening the indication for renal biopsy.

It is not possible to rule out the possibility that there are differences in biopsy policies between the centres, and this is important to consider when interpreting the results. However, it is not likely that minor differences in the tendency to perform renal biopsy in patients with a clinical diagnosis of AAV and renal involvement would have altered the main findings of the study.

Paper III

Demographics

Renal involvement was seen in 92% of the patients, while ENT involvement was only present in 15% at diagnosis. This is in line with the observation that older patients with AAV have more renal and less ENT involvement [263]. The majority of the patients had MPA and were MPO/P-ANCA positive, which is consistent with the findings in other studies of older patients [158, 161]. Demographic and clinical factors at the time of diagnosis are shown in Table 11.

Table 11. Demographic and clinical factors

Variables	All (n=151)	MPA (n=105)	GPA (n=46)	P value
<i>Female gender</i>	50% (75)	53% (56)	41% (19)	0.17
<i>Age</i>	79 (77-82)	79 (77-82)	78 (76-81)	0.16
<i>ANCA¹</i>				
MPO/P-ANCA	60% (89)	75% (78)	24% (11)	<0.001
PR3/C-ANCA	36% (53)	18% (19)	76% (34)	<0.001
Double-positive	1% (2)	2% (2)	0% (0)	>0.99
Negative	3% (5)	5% (5)	0% (0)	0.32
<i>Creatinine $\mu\text{mol/L}$²</i>	283 (152-458)	332 (201-503)	180 (86-287)	<0.001
<i>CRP mg/L³</i>	75 (18-134)	62 (15-123)	119 (50-156)	<0.001
<i>BVAS⁴</i>	15 (12-19)	14 (12-18)	17 (13-21)	0.02
<i>Organ involvement⁵</i>				
General	63% (82)	62% (56)	65% (26)	0.71
Cutaneous	9% (12)	10% (9)	8% (3)	0.76
Mucous/eyes	5% (7)	0% (0)	18% (7)	<0.001
ENT	15% (20)	3% (3)	43% (17)	<0.001
Chest	34% (44)	25% (23)	53% (21)	0.002
Cardiovascular	5% (7)	4% (4)	8% (3)	0.44
Abdominal	3% (4)	3% (3)	3% (1)	>0.99
Renal	92% (121)	98% (89)	80% (32)	<0.001
Nervous system	16% (21)	15% (14)	18% (7)	0.76
<i>Dialysis dependency⁶</i>	31% (45)	34% (35)	22% (10)	0.14
<i>Comorbidity score</i>				
0	40% (61)	36% (38)	50% (23)	0.11
1	35% (53)	35% (37)	35% (16)	0.96
2	19% (29)	22% (23)	13% (6)	0.20
3-4	5% (8)	7% (7)	2% (1)	0.44
<i>Comorbidities</i>				
Hypertension	46% (70)	49% (51)	41% (19)	0.41
Heart failure	8% (12)	10% (11)	2% (1)	0.11
Diabetes	15% (22)	14% (15)	15% (7)	0.88
Ischemic heart disease	19% (28)	23% (24)	9% (4)	0.04
Stroke	13% (20)	14% (15)	11% (5)	0.57
Malignancy	15% (22)	12% (13)	20% (9)	0.25
Pulmonary disease	12% (18)	16% (17)	2% (1)	0.01

Values are presented as % (n) or median (interquartile range) and exclude missing data. ¹Data missing for two patients; ²data missing for nine patients; ³data missing for six patients; ⁴data missing for four patients; ⁵data missing for 20 patients; ⁶data missing for four patients.

Comorbidities were common, with 60% of the patients having some degree of comorbidity according to the modified version of the Davies score. In addition to this, 46% had hypertension prior to the diagnosis of AAV.

Treatment

Complete treatment data for patients alive 30 days after diagnosis were available for 130 patients. These were divided into six groups as shown in Table 12. In total, 78.5% had received cyclophosphamide or rituximab. The cut-off for cyclophosphamide dose was chosen to reflect the minimum dose that would have been administered if there was an intention to treat the patient, reasoning that three intravenous pulses or 30 days of continuous oral cyclophosphamide would have been given to patients surviving the first month.

Table 12. Treatment groups

Treatment group	Description	N (%)
<i>Oral cyclophosphamide</i>	≥2000 mg during first three months	46 (35.4%)
<i>Intravenous cyclophosphamide</i>	≥1500 mg during first three months	40 (30.8%)
<i>Rituximab</i>	Any dose of rituximab	16 (12.3%)
<i>Steroids</i>	≥30 mg prednisolone/day	2 (1.5%)
<i>Other</i>	Azathioprine, methotrexate, MMF, low dose cyclophosphamide	19 (14.6%)
<i>Untreated</i>	<30 mg prednisolone/day, no other immunosuppressive therapy	7 (5.4%)

When comparing the patients who had received cyclophosphamide or rituximab with those who had not received such therapy (other, steroids and untreated groups), there were no significant differences with regard to creatinine level, BVAS, dialysis dependency or comorbidities at diagnosis, showing that at the group level they were comparable in terms of disease severity and comorbidity. As a group, the patients in Paper III did not present with mild disease that could motivate less intensive treatment than what is recommended in current guidelines for organ- or life-threatening disease [135]. Rather, renal involvement was seen in a great majority of the patients, median creatinine at diagnosis was 283 µmol/L (IQR 152-458) and median BVAS was 15 (IQR 12-19).

Survival

The overall 1- and 2-year survival in patients aged 75 years or more was 71.5% and 64.6%. These survival figures are, not surprisingly, lower than previously reported in younger patients [19, 157], but largely similar to other cohorts of older patients in which the reported 1-year mortality has varied between 20% and 40% [33, 186, 190, 239]. Older age, higher creatinine and lower BVAS were all associated with mortality when analysing the entire cohort (Figure 5).

Figure 5. Patient survival

Kaplan-Meier curves showing patient survival according to age (A), creatinine (B), BVAS (C) and treatment (D). P values derived from the log-rank test.

Higher age and worse renal function have been shown to predict mortality in a number of studies, in both older and younger patients [19, 29, 158], while previous studies have found an association between higher BVAS and higher mortality [19, 158], contrary to our results. We speculate that the reverse association between BVAS and mortality could be due to patients

with few extra-renal symptoms being diagnosed at a later stage with more irreversible renal damage and higher mortality. Median BVAS in patients with renal-limited disease was 12 (IQR 9-12) compared to 16 (IQR 13-19) in patients with more than one organ system involved ($P<0.001$).

In analysis of treatment, patients in the intravenous/oral cyclophosphamide and rituximab groups were compared with the remaining patients. Mortality was significantly higher in those patients who had not been treated with cyclophosphamide or rituximab (Table 13, Figure 5). When treatment was included in the multivariable analysis, age and creatinine level remained significant predictors of mortality, while BVAS lost its significance. Two-year survival was 72.9% for patients treated with oral cyclophosphamide, 72.5% for intravenous cyclophosphamide, 81.3% for rituximab and 45.0% for no/other treatment. Also when considering all cyclophosphamide doses as standard therapy, there was a clear survival benefit in the treatment group. Our findings are in line with the study by Bomback *et al.* showing better survival for elderly patients above 80 years of age treated with immunosuppressive therapy [264].

Table 13. Analysis of mortality at two years

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (per year)	1.15 (1.07-1.25)	<0.001	1.13 (1.04-1.23)	0.003
Male gender	1.17 (0.63-2.15)	0.62	1.37 (0.69-2.73)	0.37
BVAS (per point) ¹	0.94 (0.89-0.99)	0.05	0.94 (0.88-1.01)	0.09
MPO/P-ANCA ¹	0.88 (0.47-1.67)	0.71	0.74 (0.36-1.51)	0.41
CRP (per quartile) ²	1.01 (0.77-1.33)	0.94	1.01 (0.72-1.42)	0.95
Creatinine (per quartile) ³	1.47 (1.08-2.00)	0.01	1.40 (1.02-1.92)	0.04
Comorbidity score (per point)	1.32 (0.90-1.93)	0.16	1.48 (0.97-2.26)	0.07
Cyclophosphamide/rituximab	0.35 (0.18-0.66)	0.001	0.40 (0.19-0.87)	0.02

Analysis of 130 patients with complete treatment data. Multivariable analysis performed on 119 patients.

¹Data missing for one patient; ²data missing for four patients; ³data missing for six patients.

Standardized mortality ratio

There are several studies comparing the mortality rate in AAV patients with that in the normal population. In a meta-analysis including a total number of 3338 patients with AAV included in observational studies between 1966 and 2009, the meta-SMR was 2.71 (95% CI 2.26-3.24), with a non-significant trend towards lower SMR in the more recent cohorts [265].

The SMR for the Swedish cohort aged 75-84 years in Paper III was 3.69 (95% CI 2.45-5.55). In the first year it was 5.04 (95% CI 3.13-8.11), while it was not significantly increased in the second year (SMR 1.86; 95% CI 0.77-4.47). In comparison, the SMR in a cohort of patients

with ANCA-associated glomerulonephritis retrieved from the Norwegian Kidney Biopsy Registry was 2.8 (95% CI 2.4-3.3), and during the first year after diagnosis it was 10.8 (95% CI 8.6-13.5). Similar to our findings, the mortality rate in patients surviving the first year without ESRD was not increased compared to the general population [183].

In a recent study based on the Norwegian systemic connective tissue disease and vasculitis registry (NOSVAR) based at the Rheumatology Department in Oslo, the SMR for AAV was found to be 1.5 (95% CI 1.0-2.1) [234]. The reason for the discrepancy between this result and the results in Paper III and the study from the Norwegian Kidney Biopsy Registry is probably that fewer of the patients in NOSVAR had severe renal involvement. This is supported by a previous study by our group showing an SMR of 3.22 (95% CI 2.21-4.23) in patients with primary systemic vasculitis and renal involvement compared to 1.46 (95% CI 0.29-2.62) in patients without renal involvement [21].

Renal survival

Dialysis dependency at presentation was seen in 30.6% of the patients. By the end of the first year, 37 patients (24.5%) had developed ESRD (need for dialysis >90 days), which is similar to previous studies on elderly patients [86, 186, 187, 190, 239]. Renal survival censored for death at two years was 74.8%.

Creatinine level at diagnosis was the only significant predictor of ESRD (HR 4.10 per quartile; 95% CI 2.25-7.49; $P < 0.001$) (Figure 6), indicating that early recognition before severe renal impairment has developed is important for improving renal survival in elderly patients.

Figure 6. Renal survival

Kaplan-Meier curve depicting renal survival censored for death divided according to serum creatinine at diagnosis (1st quartile 61-153 $\mu\text{mol/L}$, 2nd quartile 154-295 $\mu\text{mol/L}$, 3rd quartile 296-501 $\mu\text{mol/L}$, 4th quartile 502 $\mu\text{mol/L}$ -dialysis dependency). P value derived from the log-rank test.

Censoring the analysis for death decreases the number of individuals at risk of ESRD and overestimates the probability of the event compared to analyses in which death is treated as a competing risk. However, we were indeed interested in the risk of ESRD in those patients who did not die, and found a fairly favourable outcome in patients surviving the first year with no new cases of ESRD occurring during the second year after diagnosis.

Treatment with cyclophosphamide or rituximab was not associated with the risk of ESRD (HR 1.88; 95% CI 0.61-5.77; $P=0.27$). This differs from the results of Bomback *et al.*, who showed that renal survival was better in patients treated with immunosuppressive therapy [264]. Many of the patients reaching ESRD in Paper III were dialysis dependent at the time of diagnosis, and presumably already had renal damage that was not reversible despite immunosuppressive therapy. Still, 26.7% of the patients who presented with dialysis-dependency recovered independent renal function. Among these, a larger proportion had received plasma exchange (81.8%) compared to those who did not recover renal function (53.8%), although this was not statistically significant ($P=0.15$). Interestingly, Lee *et al.* have presented a model in which the likelihood of treatment response (defined as dialysis independency and no signs of active vasculitis) was seen in >14% of patients even with severely impaired renal function at diagnosis and a high chronicity score on renal biopsy, arguing that there is no threshold below which there is no chance for renal recovery [266]. In a study of patients with AAV requiring dialysis at presentation 43% had ESRD three months after diagnosis, with a statistically similar proportion in the older cohort aged above 60 years compared to the younger cohort (50% vs 33%; $P=0.37$) [188].

Paper IV

Treatment

Complete data on treatment in patients alive after 30 days from diagnosis were available for 167 patients. These were divided up as described for Paper III, and further into three groups: CYC (intravenous or oral cyclophosphamide; n=112), RTX (any dose of rituximab; n=24) and no/other treatment (low dose cyclophosphamide, azathioprine, MMF, methotrexate, steroids only, no treatment; n=31). Intravenous methylprednisolone was given in 45.5% of the patients.

Damage

Two years after diagnosis, the median VDI score was 2 (IQR 1-3) in patients surviving to that point. Almost all patients developed some degree of permanent damage during follow-up. Only 3.7% had no damage item at two years, even though five or more items was only seen in 6.5% of the patients. This can be compared to the data from long-term follow-up of several randomized trials in Europe conducted by the EUVAS and a population-based study from Sweden in which 8% and 9% of patients had no items of damage and 34% and 56% had five or more items [153, 178]. It is important to remember that the damage items in Paper IV were recorded in patients alive at one and two years, and that severe damage might have been overrepresented in those who died, as shown by Exley *et al.* [152].

The pattern of damage is largely dependent on the organ involvement at diagnosis, and differs depending on the studied population. In studies of damage in GPA patients, ENT damage is far more common [24, 179] compared to the frequency found in this elderly population with predominance of MPA. Instead, renal damage predominated (Figure 7). Renal and cardiovascular damage were most common in the follow-up of the EUVAS trials, although ENT damage was also seen more frequently [153]. In the Swedish study, cardiovascular damage was most common, followed by renal damage. In patients aged above 65 years renal damage was most frequent, similar to our results [178].

When comparing damage items with those found in younger cohorts, it is important to bear in mind that items can only be scored if they occurred after the onset of vasculitis. Comorbidities present at diagnosis can thus not be recorded in the VDI. Since almost half the patients had hypertension at presentation, cardiovascular damage is underestimated in the elderly patients in Paper IV. This inherent restriction of the damage score would however not affect the comparison between treated and untreated patients since the presence of comorbidities did not differ.

Figure 7. Vasculitis Damage Index items

Frequency of damage items at one and two years in patients surviving two years (N=108).

In multivariable analysis, BVAS was positively associated with VDI score at two years, while there was a negative association with treatment with cyclophosphamide or rituximab (Table 14). Patients treated with cyclophosphamide or rituximab had a median VDI of 2 (IQR 1-3) at two years, which can be compared to a median VDI of 3 (IQR 2-4) in patients not given such treatment ($P=0.09$).

The starting point for the study was the question of whether the increased survival seen in treated patients in Paper III was accompanied by an increase in permanent organ damage. Instead, the opposite was found, suggesting that treatment can halt the disease process leading to development of permanent organ damage. In a previous study on damage development in GPA patients, the cumulative dose of cyclophosphamide was associated with increasing VDI score during follow-up. However, treatment with cyclophosphamide during the first six months and pulsed intravenous compared to daily oral cyclophosphamide were associated with reduced VDI score. The authors suggested that this is because cyclophosphamide has an effect on initial disease activity, while long-term high cumulative doses increase the risk of damage development [24]. This hypothesis is supported by our results of an inverse association between induction treatment with cyclophosphamide/rituximab and permanent damage.

Table 14. Vasculitis Damage Index at two years

Variable	Univariable analysis		Multivariable analysis	
	β (95% CI)	P value	β (95% CI)	P value
Age (per year)	0.008 (-0.08-0.095)	0.86	0.026 (-0.065-0.12)	0.57
Male gender	-0.29 (-0.85-0.27)	0.31	-0.32 (-0.89-0.25)	0.26
BVAS (per point) ¹	0.076 (0.027-0.13)	0.002	0.096 (0.037-0.16)	0.002
MPO/P-ANCA	-0.45 (-1.03-0.13)	0.13	-0.072 (-0.72-0.57)	0.82
CRP (per percentile) ²	-0.038 (-0.21-0.13)	0.66	-0.18 (-0.34-0.007)	0.059
Creatinine (per percentile) ³	0.023 (-0.16-0.21)	0.81	-0.068 (-0.26-0.12)	0.48
Comorbidity score (per point)	0.19 (-0.17-0.55)	0.29	0.12 (-0.24-0.48)	0.52
Cyclophosphamide/rituximab	-0.82 (-1.66-0.022)	0.056	-1.16 (-2.09- -0.23)	0.015
Prednisolone dose (per percentile)	-0.002 (-0.18-0.17)	0.98	0.005 (-0.19-0.20)	0.96
Methylprednisolone dose (per 250 mg)	-0.004 (-0.11-0.11)	0.95	0.059 (-0.064-0.18)	0.34
Year of diagnosis (per year from 1997)	-0.09 (-0.15--0.025)	0.007	-0.046 (-0.12-0.025)	0.20

Analysis of 108 patients with complete treatment data and data on VDI at two years. Multivariable analysis performed on 100 patients. ¹Data missing for two patients; ²data missing for five patients; ³data missing for two patients.

Treatment-related damage was seen in 26.9% of the patients alive at two years. This is lower than the frequency of 58% reported for patients aged above 65 years in a previous study with longer follow-up [178], but higher than the frequency of 15% described from the WGET trial [179]. Cumulative methylprednisolone dose during the first three months was associated with higher odds of treatment-related damage at two years (OR per 250 mg 1.25; 95% CI 1.01-1.55; $P=0.043$), while oral prednisolone dose and treatment with cyclophosphamide/rituximab were not. Similar results were seen at one year, both in univariable and multivariable analysis. Previous studies have found associations between long duration of glucocorticoid use, especially in higher doses, and total organ damage [24, 267]. Associations have also been reported between duration of glucocorticoids and cataract [267], and between treatment with intravenous methylprednisolone and development of diabetes mellitus [268, 269].

Hospitalization

The readmission rate was high during the first year after diagnosis; 69.1% of the patients were readmitted to hospital, and 24.2% had two or more readmissions. The total hospital stay during the first year was 31 days (IQR 17-50). This is substantially higher than the median stay of six days found in a previous study of patients hospitalized with a principal diagnosis of GPA [270]. However, the numbers are not entirely comparable since the hospitalizations recorded in Paper

IV were of any cause and did not necessarily have AAV as the principal diagnosis. Compared to the general population in Sweden aged above 75 years, the median total hospital stay in elderly patients with AAV was almost five times higher [271].

Higher creatinine at presentation was associated with higher odds of readmission, while MPO/P-ANCA positivity was associated with lower odds. Treatment with cyclophosphamide/rituximab or glucocorticoids was not associated with readmission to hospital during the first year after diagnosis (Table 15).

Table 15. Rehospitalization during the first year after diagnosis

Variable	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per year)	0.99 (0.91-1.09)	0.89	0.99 (0.89-1.10)	0.82
Male gender	0.73 (0.37-1.41)	0.34	0.50 (0.24-1.06)	0.072
BVAS (per point) ¹	1.05 (0.98-1.11)	0.16	1.02 (0.95-1.10)	0.63
MPO/P-ANCA	0.56 (0.27-1.16)	0.12	0.36 (0.15-0.87)	0.024
CRP (per percentile) ²	1.02 (0.82-1.26)	0.89	1.02 (0.78-1.34)	0.87
Creatinine (per percentile) ³	1.22 (0.98-1.52)	0.072	1.34 (1.02-1.78)	0.039
Comorbidity score (per point)	1.18 (0.78-1.80)	0.43	1.23 (0.77-1.96)	0.39
Cyclophosphamide/rituximab	1.83 (0.82-4.09)	0.14	2.21 (0.82-5.94)	0.12
Prednisolone dose (per percentile)	1.05 (0.86-1.29)	0.62	0.99 (0.76-1.30)	0.96
Methylprednisolone dose (per 250 mg)	1.07 (0.93-1.23)	0.37	1.02 (0.86-1.20)	0.85

Analysis of 165 patients with complete treatment data and data on rehospitalization. Multivariable analysis performed on 148 patients. ¹Data missing for five patients; ²data missing for five patients; ³data missing for seven patients.

Higher creatinine was also the only significant factor associated with the length of the total hospital stay during the first year of diagnosis (β 5.04; 95% CI 0.67-9.41, $P=0.024$). Together with the association with both mortality and ESRD observed in Paper III, it is clear that renal involvement in elderly patients is of great clinical importance, and further stresses the need for early detection before advanced renal damage develops.

Information on the cause of readmission to hospital was available in 156 of the total number of 187 readmissions that occurred during the first year after diagnosis. The most common cause was infections (37.2%), followed by dialysis-related events (11.5%) and cardiovascular events (9.6%). Relapse was the cause of readmission in a minority of patients, only 5.1% of the known causes were due to relapses or active vasculitis.

Cause of death

During the two years of follow-up, 69 of 202 patients died (34.2%). The cause of death was known in 55 of these cases, with the most common causes being infections (34.5%), myocardial infarction (16.4%) and active vasculitis (14.5%). Infections have been shown to be the most common cause of death both in younger vasculitis patients [19, 163] and in other studies of older patients [158].

There was an association between cumulative oral prednisolone dose and death caused by infection both in univariable and multivariable Cox regression analysis (HR per percentile 1.57; 95% CI 1.06-2.32; $P=0.024$), and the median cumulative dose of oral prednisolone during the first three months was higher in the patients who died from infections compared to those who died from other causes or survived two years (3480 mg versus 2280 mg and 2290 mg respectively; $P=0.01$). The majority of infection-related deaths occurred after the first three months of treatment. Since we did not have data on treatment beyond three months, it is not possible to establish whether the observed association with fatal infections was due to a continued trend of higher prednisolone dose or whether higher doses during the induction phase also conferred an increased risk after the first months of treatment. It should also be noted that the number of events was rather low.

Previous studies have shown that longer use of glucocorticoids and steroid-induced diabetes are associated with increased risk of infections [269, 272]. In contrast to cyclophosphamide, in which the dose is normally adjusted for both age and renal function, glucocorticoids are generally only adjusted for body weight. The risks associated with both short- and long-term use of glucocorticoids have been increasingly acknowledged and alternatives have been suggested, including a prospective non-randomized study of rapid glucocorticoid withdrawal within two weeks [273], the low-dose glucocorticoid regimen studied in the PEXIVAS trial [137], and the C5a receptor inhibitor avacopan that has shown promising results in a phase II trial [69]. In a randomized trial of patients aged 65 years or more, lower dose of cyclophosphamide and faster tapering of glucocorticoids was found to decrease the risk of serious adverse events, while mortality, remission and relapse rates did not differ significantly [274]. The median cumulative dose of pulsed intravenous cyclophosphamide in Paper IV was 3000 mg (IQR 2100-4500), similar to the median dose of 2688 mg in the experimental arm in that study.

Severe infections pose a major threat to patients with AAV. Compared to population controls, the rate ratio for serious infections was 4.5 in a study from southern Sweden [275] and the risk of hospitalization due to infections was increased almost ten times in a study from Denmark [276]. Although the aim of Paper IV was not to study infections, we did find that it was the most common cause of both death and readmission, in line with the increased risk of infections in AAV, seen especially with higher age and renal impairment [269, 272, 275, 277].

Ethical considerations

In all observational and register-based research there are important ethical considerations. If participants are not subject to any intervention, sampling, interview or other contact with the investigator, informed consent is generally not required. However, when data are only obtained from available registries and medical records it is also important to safeguard individual privacy. This has to be balanced against the benefit that society will gain from the research conducted, and it could even be considered unethical not to carry out high quality epidemiological research [278].

This thesis is based on observational data retrieved from different registries, databases and patients' medical records. The identity of the individual participants has only been known to the researchers collecting data. Code lists have been stored at each participating centre separately from the coded material and have only been available to the local researcher designated to collect data. The data that have been shared and analysed have been completely anonymized. Since the data were anonymized and reported at group rather than individual level, it was judged that the participants would suffer no negative consequences despite not having consented to participation.

STRENGTHS AND LIMITATIONS

Paper I

The strength of Paper I is that the incidence estimates are population-based and retrieved from two geographically defined areas in Sweden with comprehensive and well-organized follow-up of patients. The completeness of the retrieval of LN and AAN cases in the Skåne area has been shown by capture-recapture methodology. Similar capture-recapture analysis has not been performed in the Östergötland area, but the clinical registries for SLE and AAV at the Rheumatology and Nephrology departments include all known cases in the region.

The study was limited to biopsy-proven nephritis. This ensures a correct diagnosis, but cases with clinical nephritis that are not biopsied are not included and the true incidence might be underestimated. A limitation related to this is the differences in biopsy rate, with a higher biopsy rate seen in SLE cases compared to AAV cases. However, this does not change the conclusion that AAN is more common than LN, but rather underestimate the number of AAN cases.

Another limitation of the study is that it was not possible to carry out meaningful analyses of factors associated with death and ESRD due to the low number of events among the LN patients. Although the follow-up was 6.5 years for AAN and 8.6 years for LN, with even longer follow-up outcomes in terms of death and ESRD in older patients with LN could have been analysed and compared to the outcomes in AAN.

Paper II

The large population studied is a strength compared to many other studies focusing on the geographic distribution of AAV. It is also the first study to focus on ANCA serotype instead of clinical phenotype in relation to geographical latitude, an approach that limits the risk of differences in classification and a division that is increasingly supported based on genetic susceptibility, treatment response and prediction of outcome.

Studying only renal biopsy-proven cases with a focus on serotype makes the population more homogeneous and was done with the aim to reduce differences in inclusion of patients between regions and units. However, it also limits the generalizability to patients with ANCA positive renal vasculitis and does not answer the question of whether the distribution of the different disease entities GPA and MPA vary with geographical latitude.

A limitation is that we did not have data on UV radiation from the USA. In addition, the use of latitude and mean UV radiation levels for one city in every region does not take into account the fact that there are differences in latitude and UV radiation within regions or migration from other regions. We did not have data on the distribution of genetic variants such as *SERPINA1* or *HLA-DPB1*0401*. Nor did we have data on vitamin D levels or dietary habits in the studied

populations, factors that could affect vitamin D status in addition to the exposure to UV radiation.

Papers III and IV

The patients studied in Paper III and Paper IV are, to our knowledge, the largest cohort of patients above 75 years with AAV that has been studied to date. Patients have been included from several centres, giving this large number and reflecting real-life data on treatment and outcome of elderly patients in different parts of Europe. A limitation is the fact that some of the centres are tertiary referral centres that almost exclusively see nephrology patients, including the most severely ill patients with dialysis-dependent renal failure, and the results might not be generalizable to populations seen mainly at rheumatology units.

The main limitations are that the data are retrospective and that patients have not been randomized to the treatment given. By excluding deaths during the first month and using an intention-to-treat approach, we have tried to reduce the risk of selection by prognosis. However, despite adjusting for markers of disease severity and comorbidities, we cannot rule out the possibility that some patients were perceived to be frail and not suitable for immunosuppressive therapy or that some patients developed adverse events due to therapy and that it was thus stopped. Such patients would likely have higher risks of both death and permanent damage. It is also possible that patients with severe disease received higher doses of glucocorticoids and that the underlying more aggressive disease made them more susceptible to adverse events and development of organ damage. Another limitation is the lack of data on glucocorticoid treatment beyond three months. As a result, we cannot establish whether the danger lies in using high doses during a short time period or a long duration of glucocorticoid treatment.

CONCLUSIONS AND FUTURE PERSPECTIVES

Paper I

The incidence of biopsy-verified AAN is about threefold higher than the incidence of LN in two geographically defined populations in Sweden. Previous studies by our group have shown that the incidence of SLE is higher than that found for AAV, and we therefore conclude that a lower occurrence of nephritis among SLE patients compared to AAV patients is the main explanation. Outcomes in terms of both patient and renal survival are considerably worse in AAN. The majority of the patients with LN had an established diagnosis of SLE at the time of the first renal flare, while none of the patients with AAN had a diagnosis of AAV before the onset of nephritis. Our data suggest that early diagnosis and treatment before the onset of nephritis is of pivotal importance for the good results seen in SLE with respect to ESRD and early deaths.

The remaining question is if similar improvement is possible to achieve in AAV and in SLE in other parts of the world. To investigate this further future studies should be aimed at studying changes in incidence of LN and AAN over time in defined areas and exploring treatment, diagnosis delay and outcome during the same time period. Since age differs substantially between patients with LN and patients with AAN, an interesting future project would be to calculate potential years of life lost for the two diseases, as well as for other glomerular diseases.

Paper II

There are clear differences between MPO-ANCA positive and PR3-ANCA positive biopsy-proven glomerulonephritis with regard to age, gender and renal function. There are also associations between PR3-ANCA and higher latitude and lower UV radiation levels, in line with the north-south hypothesis. With these results we add to the current knowledge by focusing on ANCA serotype and by studying renal AAV. However, the geographical differences in distribution of GPA and MPA seem to be greater than the differences between renal PR3-ANCA positive AAV and MPO-ANCA positive AAV. Given the loss of the associations between ANCA serotype and latitude and UV radiation level in the analysis of northern and central Europe, the contribution of genetic differences needs more attention.

To further elucidate the relative contribution of environmental and genetic factors to both serotype and phenotype it would be interesting to include centres in Norway, Sweden and Denmark, countries in which the populations have similar genetic inheritance, and to investigate differences in GPA/MPA, PR3-AAV/MPO-AAV and non-renal GPA/renal GPA in relation to different environmental exposures.

Papers III and IV

Elderly patients with AAV often present with significant renal involvement, predominance of MPO-ANCA positivity and a clinical MPA diagnosis. Patient survival is significantly better in patients treated with adequate doses of cyclophosphamide or rituximab compared to patients who are left untreated, or are treated with alternative regimens such as azathioprine, MMF, methotrexate or glucocorticoids alone. Although elderly patients are at higher risk of adverse events, treatment with cyclophosphamide and rituximab is not associated with development of more permanent organ damage and need for hospitalization when compared with no treatment or other treatment regimens. Rather, our results suggest that adequate treatment of the elderly can halt the disease process and lower the risk of organ damage. Our results support induction treatment of elderly patients with cyclophosphamide or rituximab, but raise concerns regarding the use of high doses of glucocorticoids in the elderly.

Future randomized trials of treatment in AAV should not exclude elderly patients, especially those aiming at reducing the use of glucocorticoids. Although our results suggest that patients who are treated with rituximab do well, too few patients were treated with this agent to allow for a comparison between rituximab and cyclophosphamide. Data on the use of rituximab in elderly patients are scarce, but the increasing use during the last years could allow for comparison with cyclophosphamide with respect to remission rates, mortality and adverse events. We would like to carry out a long-term follow-up of the elderly cohort with a focus on renal and patient survival. With longer follow-up it would also be possible to include data on maintenance therapy and relapse rates.

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Department of Nephrology and Department of Medical and Health Sciences

Linköping University
SE-581 83 Linköping, Sweden

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