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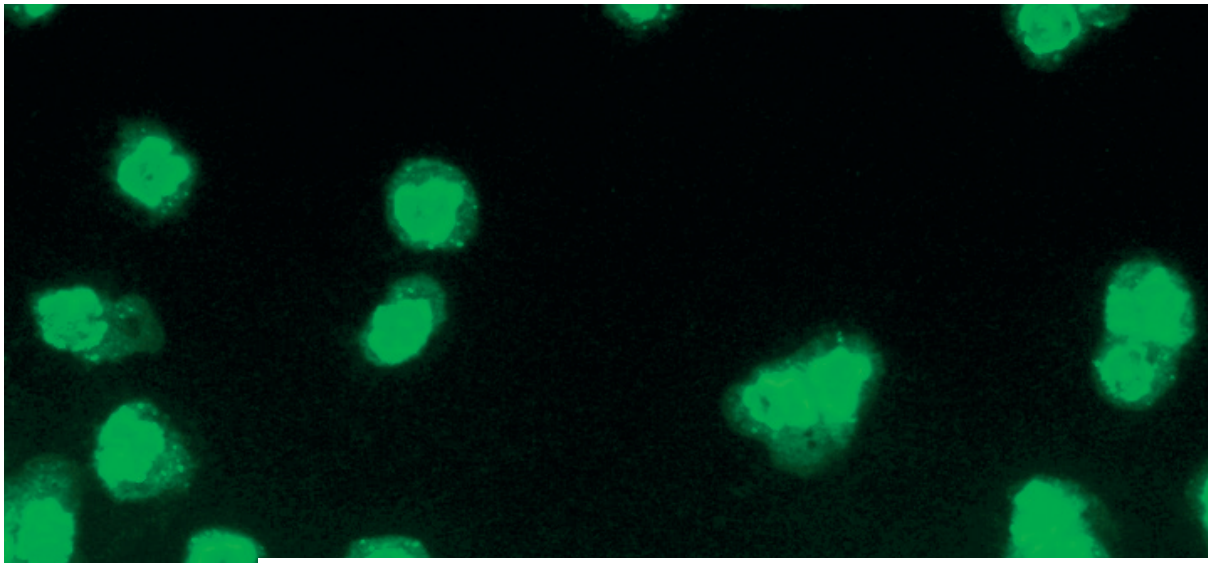

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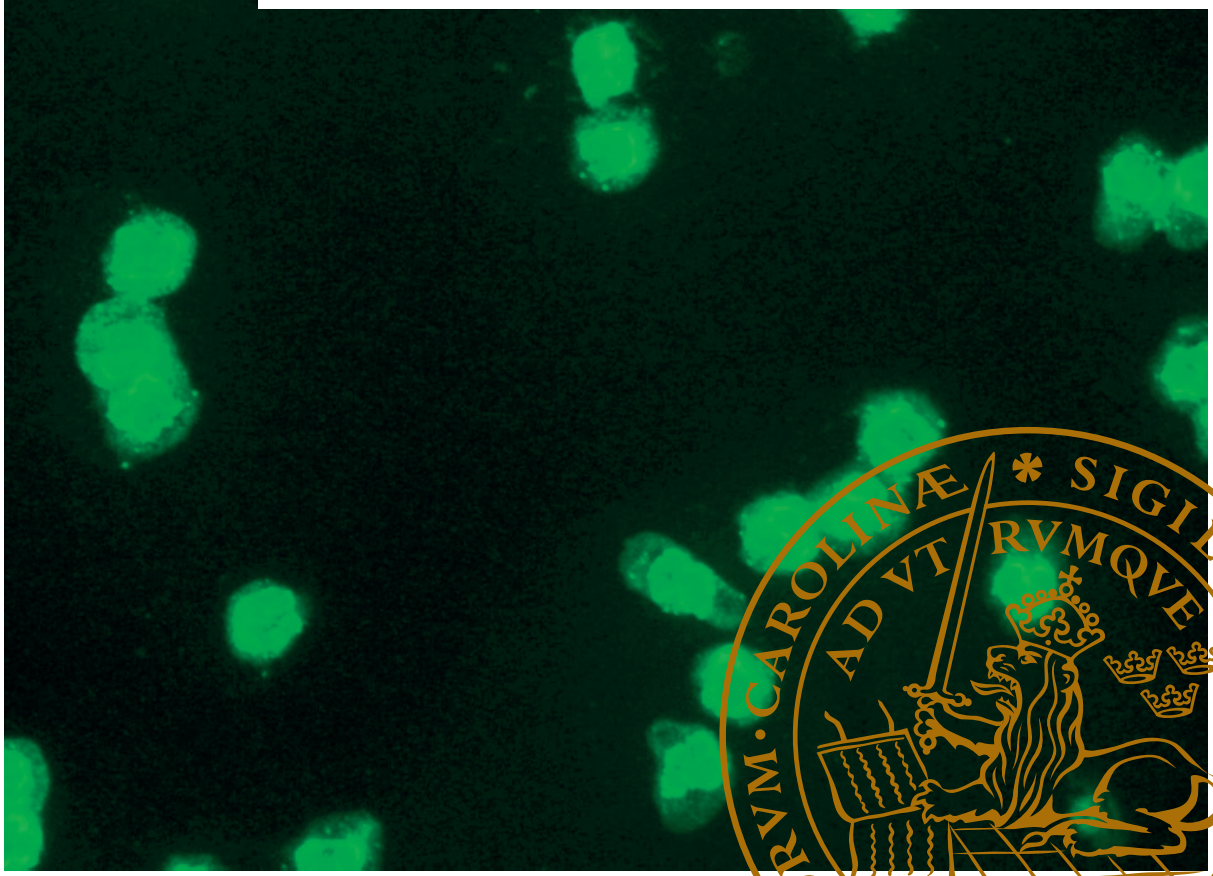
CAROLINE HEIJL
CLINICAL SCIENCES, LUND | LUND UNIVERSITY 2017



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som med vederbörligt tillstånd av medicinska fakulteten vid Lunds Universitet, för avläggande av doktorsexamen i medicinsk vetenskap, kommer att offentligen försvaras i Segerfalksalen, Biomedicinskt centrum (BMC), Sölvegatan 17, Lund.
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Title and subtitle

Long-term follow-up of patients with ANCA-associated vasculitis

This thesis is based on long-term follow-up results from two cohorts of patients with ANCA-associated vasculitis; one cohort with 535 patients originally included in four European randomized clinical trials (papers I and II) and one Swedish population-based cohort including 195 patients (papers III and IV). Two areas are covered in the two cohorts, respectively; the assessment of mortality, prognostic factors and causes of death (paper I and III) and the assessment of malignancy risk compared with a matched general population (papers II and IV).

Results

Paper I: 1-, 2-, and 5-year survival was 88%, 85% and 78%, respectively. Predictors of death were age, gender, kidney function and disease activity at presentation. Main causes of death were active vasculitis and infection during the first year, and after the first year, malignancy and cardiovascular disease.

Paper II: Higher risk for malignancy at all sites and for non-melanoma skin cancer.

Paper III: 1-, 2-, 5-, and 10-year survival was 87%, 82%, 70% and 55%, respectively. Predictors of death were age, gender, kidney function and organ involvement at diagnosis. Main causes of death were active vasculitis and infection during the first year, and after the first year, malignancy and cardiovascular disease.

Paper IV: Higher risk for malignancy at all sites, non-melanoma skin cancer, bladder cancer and pancreatic cancer.

Conclusions: The mortality and malignancy risk in patients treated for AAV with current treatment protocols are higher than in the general population. However, the mortality in the group of patients with AAV without gastrointestinal, cardiovascular, or renal involvement at presentation is not significantly increased compared with the general population.

Key words: ANCA-associated vasculitis, epidemiology, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis

Classification system and/or index terms (if any)

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Long-term follow-up of patients with ANCA-associated vasculitis

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"Att säga sannolikheten, hela sannolikheten
och ingenting annat än sannolikheten"

Tage Danielsson

Content

List of papers

This thesis is based on the following papers, referred to in the text by their Roman numerals. **Papers I** and **II** will be mentioned and integrated in the background knowledge because both papers, since their publications in 2011, have been widely cited and incorporated into meta-analyses that are mentioned in the introduction of this thesis.

Paper I: Floßmann O, Berden A, de Groot K, Hagen C, Harper L, **Heijl C**, Höglund P, Jayne D, Luqmani R, Mahr A, Mukhtyar C, Pusey C, Rasmussen N, Stegeman C, Walsh M, Westman K for the European Vasculitis Study Group. Long-term survival in ANCA-associated vasculitis. *Annals of the Rheumatic Diseases*. 2011;**70**:488-494.

Paper II: **Heijl C**, Harper L, Floßmann O, Stücker I, Scott DG, Watts RA, Höglund P, Westman K, Mahr A; European Vasculitis Study Group (EUVAS). Incidence of malignancy in patients treated for antineutrophil cytoplasm antibody-associated vasculitis: follow-up data from European Vasculitis Study Group clinical trials. *Annals of the Rheumatic Diseases*. 2011;**70**:760-763.

Paper III: **Heijl C**, Mohammad AJ, Westman K, Höglund P. Long-term patient survival in a Swedish population based cohort of patients with ANCA-associated vasculitis. *Under revision RMD Open.*

Paper IV: **Heijl C**, Westman K, Höglund P, Mohammad AJ. Malignancies in patients treated for ANCA-associated vasculitis in a Swedish population based cohort. *Manuscript*.

Thesis at a glance

		Patient cohort	
		EUVAS cohort from clinical trials 535 patients	Swedish population based cohort 195 patients
Aims	Assess mortality, prognostic factors and causes of death	**Paper I** 1-, 2- and 5-year survival; 88%, 85% and 78%. Predictors of death: age, gender, kidney function, disease activity Causes of death: active vasculitis, infection, cardiovascular disease, malignancy	**Paper III** 1-, 2- 5-, and 10-year survival; 87%, 82%, 70% and 55%. Predictors of death: age, gender, kidney function, organ involvement at diagnosis Causes of death: active vasculitis, infection, cardiovascular disease, malignancy
	Assess malignancy risk compared with general population	**Paper II** Higher risk for malignancy at all sites and non-melanoma skin cancer	**Paper IV** Higher risk for malignancy at all sites, non-melanoma skin cancer, bladder cancer and pancreatic cancer

Abbreviations

ANCA	Anti-Neutrophil Cytoplasmic Antibody
AAV	ANCA-Associated Vasculitis
GPA	Granulomatosis with Polyangiitis
MPA	Microscopic Polyangiitis
EGPA	Eosinophilic Granulomatosis with Polyangiitis
PAN	Polyarteritis Nodosa
IIF	Indirect Immunoflourescence
cANCA	cytoplasmic Anti-Neutrophil Cytoplasmic Antibody
pANCA	perinuclear Anti-Neutrophil Cytoplasmic Antibody
PR3	Proteinase 3
MPO	Myeloperoxidase
ELISA	Enzyme-Linked Immunosorbent Assay
ENT	Ear -Nose and Throat
CHCC	Chapel Hill Consensus Conference
ACR	American College of Rheumatology
EMA	European Medicines Agency
EULAR	European League Against Rheumatism
CYC	Cyclophosphamide
RTX	Rituximab
MTX	Methotrexate
AZA	Azathioprine
PE	Plasma Exchange
MetPred	Metylprednisolone
ATG	Anti-Thymocyte Globulin
MMF	Mycophenolate
BVAS	Birmingham Vasculitis Activity Score
VDI	Vasculitis Damage Index
FFS	Five Factor Score
eGFR	Estimated Glomerular Filtration rate
SIR	Standardized Incidence Ratio
EUVAS	European Vasculitis Study Group
NMSC	Non-Melanoma Skin Cancer

Introduction

Vasculitis is inflammation of blood vessel walls. This inflammation may be secondary to infection, medication, genetic disturbances, other systemic inflammatory conditions such as rheumatoid arthritis, or without known pathogenic factor (primary vasculitis). The primary vasculitides comprise a group of heterogenic diseases that have been categorized according to their primary target vessels into large vessel-, medium vessel,- and small vessel vasculitis (Jennette et al., 1994; 2013)(table 1).

Table 1

Large vessel vasculitis	Takayasu arteritis Giant Cell Arteritis
Medium vessel vasculitis	Polyarteritis nodosa Kawasaki disease
Small vessel vasculitis	Immune-complex mediated vasculitides 1. Anti-glomerular basement membrane disease 2. Cryoglobulinemic vasculitis 3. IgA vasculitis 4. Hypocomplementemic urticarial vasculitis ANCA-associated vasculitides 1. Microscopic polyangiitis 2. Granulomatosis with polyangiitis 3. Eosinophilic granulomatosis with polyangiitis

The small vessel vasculitides are divided into two groups; those with immune-complexes in the vessel wall (anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, IgA-vasculitis or hypocomplementemic urticarial vasculitis) or those without immune-complexes. The latter are often associated with circulating antibodies towards proteins in neutrophil granulae (antineutrophil cytoplasmic antibodies, ANCA) (van der Woude, Falk & Jennette, 1988; van der Woude et al., 1985) and have subsequently been named ANCA-associated vasculitides (AAV). The AAVs are pauci-immune i.e. without any detected, or possibly with minimal amount of immune-complex deposition on biopsy, and comprise three different diagnoses; GPA (granulomatosis with polyangiitis), MPA (microscopic polyangiitis) and EGPA (eosinophilic granulomatosis with polyangiitis).

The AAVs may present with various clinical symptoms and findings such as nephritic syndrome, pulmonary hemorrhage, pulmonary nodules or cavities, chronic destructive disease in the upper airways, nasal crusting, chronic sinusitis, hearing loss, purpura with systemic features, mononeuritis multiplex or retro-orbital mass (Savige et al., 1999). The AAV remain a persistent challenge to the medical profession and the etiology of the vasculitides is still unknown.

A brief history of ANCA-associated vasculitis

One of the first times the disease entity was mentioned in the literature was 1852 when Rokitansky wrote about aneurysms and necrotizing arteritis in a young patient (Rokitansky, 1852). Kussmaul and Maier were the first who used the term periarteritis nodosa, which then evolved into the more pathologically suitable name polyarteritis nodosa (PAN) (Kussmaul & Maier, 1866). This name was subsequently used for all patients with necrotizing arteritis until the middle of the 20th century when a type of small vessel vasculitis was singled out from the entity, separated from PAN and named "hypersensitivity angiitis" (Zeek, 1952). Two German pathologists, Klinger and Wegener, both described patients with necrotizing vasculitis and glomerulonephritis accompanied by necrotizing granulomatous inflammation of the respiratory tract (Klinger, 1932; Wegener, 1939). Goodman and Churg developed these distinctions in their widely cited work from 1954 and changed the name from "hypersensitivity angiitis" into "microscopic periarteritis" and further described two other features of the necrotizing arteritis; the syndrome previously described by Wegener (Churg and Strauss introduced the name of Wegener´s granulomatosis) and Churg-Strauss syndrome (Churg & Strauss, 1951). Already in this work they hypothesized that the diagnoses were related because the histology pattern seen in all of them were similar. A microscopic form of PAN was described by Davson *et al* in 1948 ("The Kidney in Periarteritis Nodosa," 1948) and in 1985 microscopic polyangiitis (MPA) was defined and separated from PAN (Savage, Winearls, Evans, Rees, & Lockwood, 1985). In the Chapel Hill Consensus Conference (CHCC) 1993, PAN was restricted to disease presenting with arteritis in medium-sized and small arteries but without involvement of smaller vessels such as arterioles, venules, or capillaries and without the presence of ANCA. This distinction excluded all patients with glomerulonephritis from the PAN entity (Jennette et al., 1994). A further change of naming of the AAVs was agreed upon 2010; Wegener´s granulomatosis was changed into granulomatosis with polyangiitis (GPA) and Churg-Strauss syndrome into eosinophil granulomatosis with polyangiitis (EGPA)(Jennette et al., 2013). The reason behind the change of name was in general the wish to avoid the use of eponyms but also, in the case of Wegener´s granulomatosis, that Friedrich Wegener was an active member of the Nazi party, stationed as pathologist in Lódz during the

Holocaust and even if there are no definitive evidences on that he actively took part in the genocide and experiments on humans this is regarded as likely (Lefrak & Matteson, 2007).

The discovery of ANCA

Antibodies towards neutrophil granulae can be detected using indirect immunofluorescence (IF) and in 1972 Wiik *et al* described a technique for detecting granulocyte-specific antinuclear antibodies (GS-ANA)(Wiik & Munthe, 1972) (Wiik, 1980). In a pivotal paper from 1985, antibodies reacting with the cytoplasm of ethanol-fixed neutrophils (anticytoplasmic antibodies, ACPA) were described in a patient with active GPA (van der Woude et al., 1985) and since then testing for these antibodies, subsequently called antineutrophil cytoplasmic antibodies (cANCAs), has become important in the diagnosis of GPA (Rasmussen, Wiik, Høier-Madsen, Borregaard, & van der Woude, 1988). Falk and Jennette *et al*, found that myeloperoxidase was the antigen giving rise to the GS-ANA perinuclear staining pattern (now called pANCA) and that they were linked to MPA (Falk & Jennette, 1988). The antigen behind the cANCA pattern in GPA was subsequently shown to be the granulae protein, proteinase 3 (PR3). There are other p- and cANCA antigens, but only PR3-ANCA and MPO-ANCA are important in the field of small vessel vasculitis (Kallenberg, 2016; Schultz & Tozman, 1995). The p- and cANCA patterns are actually caused by an artifact; when neutrophils are fixated with ethanol, myeloperoxidase (MPO) (positively charged) dissolves from its granulae and moves towards the cell nuclei (negatively charged) giving rise to a perinuclear staining pattern whereas PR3 stays in the cytoplasm (Falk & Jennette, 1988). Direct enzyme-linked immunosorbent assays (ELISA) have been developed to detect and quantify MPO- and PR3-ANCA, respectively (Hagen, 1995). Capture-ELISA, using a mouse-monoclonal antibody to present the antigen, has been shown to be more sensitive in detecting the PR3 autoantibodies (Baslund et al., 1995). International ANCA-meetings have been held since 1988 and several decisions on standardization of methods for ANCA-detection has been made throughout the years (Rasmussen, 1997; Savige et al., 1999). Indirect IF is not very specific and a pANCA pattern might be seen in various conditions such as cocaine abuse, endocarditis, inflammatory bowel disease among others (Kallenberg, 2016). The positive and negative predictive values of ANCA-testing are dependent on the pre-test likelihood in the tested population and should be used only when small vessel vasculitis might be suspected and in addition to biopsy of affected organ/organs.

Definitions and classification

Nomenclature

One important feature in the early research on AAV was the nomenclature and in 1993 a consensus conference was held in Chapel Hill where an international agreement was obtained (Jennette et al., 1994). This agreement was revised in 2012 and according to the CHCC the vasculitides are first categorized after type and distribution of blood vessels involved into three groups; large vessel vasculitis, medium-sized vessel vasculitis and small vessel vasculitis (Jennette et al., 1994; 2013). The small vessel vasculitides are then in turn divided into two groups; those with immune-complexes in the vessel wall (anti-glomerular basement membrane disease, IgA-vasculitis, cryoglobulinemic vasculitis or hypocomplementemic urticarial vasculitis) or those without immune-complexes. The ANCA-associated vasculitides are pauci-immune i.e. without any detected, or possibly with minimal amount of immune-complex deposition on biopsy. The CHCC system is on nomenclature and its purpose is to name and define types of vasculitis. The definitions explain the differences, for instance, between GPA, MPA and EGPA but was neither made to be used for diagnostic purposes in individual patients, nor for classification (Jennette et al., 1994; 2013).

Classification criteria

The American College of Rheumatology (ACR) published, in 1990, classification criteria for seven forms of systemic vasculitis (Hunder et al., 1990). The purpose of classification criteria is to identify patients with one condition and separate them from patients with similar conditions i.e. in this case to differentiate one type of vasculitis from another. Classification criteria cannot, unlike diagnostic criteria, differentiate vasculitis from other diseases, however the ACR criteria have erroneously been used for diagnosis (Hunder, 1998). One disadvantage with the ACR criteria is that neither the diagnosis MPA nor ANCA are included.

EMA Algorithm

An algorithm that merges the CHCC and ACR criteria regarding the nomenclature of primary vasculitides was agreed upon in 2007, by a group of physicians and researchers with special experience and interest in vasculitis epidemiology. The aim of the European Medicines Agency (EMA) algorithm was not to create new classification criteria but to reach a consensus on how to applicate the already

available nomenclature and classification criteria provided by CHCC and ACR in epidemiological studies (Watts et al., 2007).

The first step of the EMA criteria, before applying the algorithm, is to establish the diagnosis of AAV. Accordingly, all the following criteria (A+B+C) are required for the diagnosis of AAV.

A. Disease process compatible* or typical** with systemic vasculitis

B. Objective diagnostic measure supporting the diagnosis

1. Histology showing vasculitis
2. Positive ANCA serology
3. Other investigations indicating vasculitis (i.e. EMG) or granulomas (i.e. x-ray)

C. No other diagnosis more likely

* If B1 is present "compatible" is sufficient in A

** If B2 or B3 (and not B1) "typical" is required in A

Patients that have been diagnosed with AAV and who fulfill all the required criteria are entered in the EMA algorithm that is based on a stepwise application of the ACR classification of EGPA and GPA in combination with the CHCC definitions for MPA and PAN (Watts et al., 2007) (fig 1). The EMA algorithm have subsequently been validated in several epidemiological studies (Liu, Chen, Yu, Zhao, & Wang, 2008; Mohammad, Jacobsson, Mahr, Sturfelt, & Segelmark, 2007; Mohammad, Jacobsson, Westman, Sturfelt, & Segelmark, 2009).

Diagnostic criteria

The purpose of diagnostic criteria is to identify patients with similar conditions from unselected patients. For AAV there are no other diagnostic criteria than the EMA criteria, originally developed for epidemiologically purposes. There are ongoing efforts within ACR/EULAR (European League Against Rheumatism) to further develop a classification and diagnostic system for primary systemic vasculitis (Craven et al., 2013).

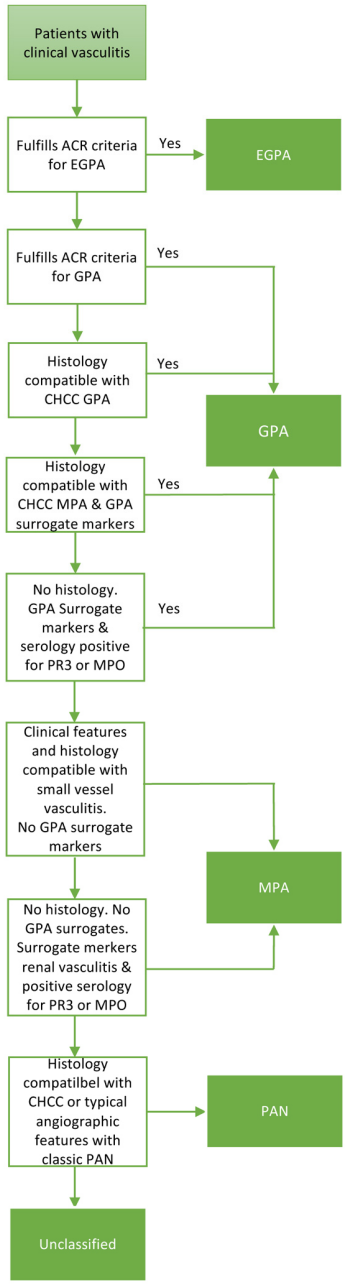

Fig 1.
The EMA algorithm

The ANCA-associated vasculitides

The ANCA-associated vasculitides all have one feature in common and that is a focal necrotizing inflammation of small vessels (Jennette & Falk, 1997). The glomerular pathology in these diseases is identical and consists of segmental fibrinoid necrosis, crescent formation and pauci-immunity (Berden et al., 2010; Jennette & Falk, 1997). AAV may affect medium sized vessels but they predominantly affect small vessels such as arterioles, venules or capillaries (Jennette et al., 2013). The symptoms vary according to the affected organ system but are almost always accompanied by multisystem symptoms as fever, arthralgia, myalgia and weight loss. A few patients are ANCA-negative and some cases exhibit both PR3- and MPO-ANCA positivity (Chen et al., 2007). In Europe, the overall yearly incidence of AAV is estimated to be in the range of 13 to 20 per million inhabitants (Watts et al., 2015). In Skåne (southern Sweden) the yearly incidence of AAV is approximately 20 per million inhabitants and 75% of the patients have renal involvement at diagnosis (Mohammad et al., 2009). The incidence of the AAVs seem to have geographical differences with an inverse relationship between GPA and MPA, at least in Europe, where GPA has been shown to be more common in the northern and MPA in the southern European countries (Watts et al., 2001). The AAVs have somewhat different features that distinguish them from each other but respond to the same treatment regimens, described more in detail in a subsequent section.

Granulomatosis with polyangiitis (GPA)

Formerly known as Wegener´s granulomatosis, GPA was first described in 1931 by Klinger *et al* (Klinger, 1932). GPA is characterized by granulomatous inflammation that predominantly affect the respiratory tract and/or the kidney (Comarmond & Cacoub, 2014). Involvement of ear, nose and throat (ENT) is present in 70 to 100% of patients at diagnosis. This involvement may consist of crusting rhinorrhea, sinusitis, chronic otitis media or damage to the nasal cartilage causing deformities such as saddle nose and perforation of the nasal septum. In localized forms of GPA, the ENT- involvement might be the only sign of disease (Trimarchi et al., 2013). The lungs are affected in 50 to 90% of patients (Aberle, Gamsu, & Lynch, 1990) (Daum et al., 1995; Hoffman et al., 1992). Reports of the frequency of renal involvement vary, depending on the cohort and has been observed in 40 to 100% of cases (Holle, Laudien, & Gross, 2010). The peripheral nervous system is affected in approximately 10-67% of cases with manifestations such as mononeuritis multiplex or sensimotor neuropathy (Fauci, Haynes, Katz, & Wolff, 1983; Pagnoux & Guillevin, 2005). The skin and mucous membranes might be involved, in most cases with purpura on the lower limbs (Comfere, Macaron, & Gibson, 2007). Ocular involvement may occur in

forms of episcleritis, scleritis, corneal ulceration or retinal vasculitis and in some cases as a granulomatous retro-orbital pseudo tumor causing exophthalmia (Pakrou, Selva, & Leibovitch, 2006). Urogenital (Dufour et al., 2012) and central nervous system involvement (Seror et al., 2006) has also been described in rare cases. Cardiac and gastrointestinal involvement are also rare in AAV, even though cardiac involvement has been shown to be more common than previously thought (Hazebroek et al., 2015) (Pagnoux, Mahr, Cohen, & Guillevin, 2005). PR3-ANCA is found in 85% of cases and MPO-ANCA in 10% (Kallenberg, Brouwer, Weening, & Tervaert, 1994). In a systematic review of 44 studies by Mukhtyar *et al* in 2008, the remission rates in GPA, after induction treatment, were shown to vary between 30 and 93%, the 5-year survival was 74-91% and relapses were common in the first 2 years with a varying frequency of 18 to 60%, and within 5 years > 50% of patients had relapsed (Mukhtyar et al., 2008). In a study from southern Sweden, the reported 1- and 5-year survival was 95% and 83%, respectively (Mohammad et al., 2009).

Microscopic polyangiitis (MPA)

MPA is characterized by necrotizing glomerulonephritis and pulmonary capillaritis. There are *in vivo* evidence that MPO-ANCA are sufficient to induce pulmonary capillaritis and glomerulonephritis in mouse models (Coughlan, Freeley, & Robson, 2012; Xiao et al., 2002). However, as in GPA and EGPA, there are patients diagnosed with MPA without detectable ANCA in serum. MPO-ANCA was found in 65% of cases and PR3-ANCA in 25% in a study from Kallenberg *et al* (Kallenberg et al., 1994). Renal involvement, in most cases presenting as a rapidly progressive glomerulonephritis, is reported in a range of 80-100% of patients (Guillevin et al., 1999; Savage et al., 1985). Pulmonary involvement might be seen in 25-55% of patients (Chung & Seo, 2010), classically as diffuse alveolar hemorrhage presenting with symptoms such as hemoptysis, dyspnea, cough and pleuritic chest pain (Collins & Quismorio, 2005; Franks & Koss, 2000). Skin lesions, most commonly with palpable purpura is seen in 30-60% of patients (Kluger, Pagnoux, Guillevin, Francès, French Vasculitis Study Group, 2008). Abdominal pain is rather common and gastrointestinal bleeding may occur (Pagnoux et al., 2005). Neurological involvement presents most commonly with peripheral neuropathy and mononeuritis multiplex and is present in 40–70% of patients (Guillevin et al., 1999; Zhang et al., 2009). Central nervous manifestations may also be seen (Zhang et al., 2009). Remission rates, after induction treatment, are 75-89% as reviewed by Mukhtyar *et al*, the 5-year survival 45-76% and relapse occurrence has a lower frequency than in the other AAVs with 8% during the first 2 years of follow-up (Mukhtyar et al., 2008). In a study from southern Sweden, the reported 1- and 5-year survival was 80% and 55%, respectively (Mohammad et al., 2009).

Eosinophilic granulomatosis with polyangiitis (EGPA)

EGPA is characterized by eosinophilic granulomatous inflammation of the respiratory tract, asthma or allergic rhinitis and peripheral blood eosinophilia. One major feature in EGPA is dysfunction of eosinophils with a massive proliferation and defect apoptosis (Chaigne, Dion, Guillevin, Mouthon, & Terrier, 2016). EGPA might involve any organ but exhibit the lowest frequency of renal involvement among the AAVs (less than 50%) but on the other hand higher frequencies of cardiomyopathy and polyneuropathy (Mouthon, Dunogue, & Guillevin, 2014). The leading cause of death in patients with EGPA is heart involvement and a small number of patients have received heart transplants (Groh et al., 2014). ANCAs are present in approximately 40% of patients with EGPA with PR3-ANCA in 5% and MPO-ANCA in 35% of cases (Sinico et al., 2005). Remission rates varied as reviewed by Mukhtyar *et al* from 81% to 91%, the 5-year survival was 60-97% and the relapse frequency during the first 2 years of follow-up was 35% (Mukhtyar et al., 2008).

European collaboration network

The initiation of a European collaboration network was tightly linked to the discovery of autoantibodies in vasculitis and the first ANCA-workshop was held in Copenhagen in 1988 (Rasmussen et al., 1988). The collaboration was at first focused on standardization of ANCA-testing and resulted in publications of recommendations on ANCA-testing (Hagen et al., 1993; 1998; Savige et al., 1999). The ECSYSVASTRIAL project, funded by the European Union, was launched in 1994 with the main goal of a standardization of treatment of GPA and MPA across 14 European centers. The diseases were subdivided into five subcategories by disease extent and severity (table 2) and a randomized controlled trial was developed for each category (table 3a). The results from these trials have had a substantial impact on how patients with AAV are currently treated and subsequent trials have been or are currently conducted (table 3b). The ECSYSVASTRIAL subsequently evolved into European Vasculitis Study Group (EUVAS) and again into the current European Vasculitis Society (EUVAS).

Table 2

Disease subgroup	Definition
Localized	Vasculitis confined to one organ system, no systemic disturbance.
Early systemic	Vasculitis in at least one organ system with systemic features *without* threatened vital organ function.
Generalized	Vasculitis in at least one organ system with systemic features *with* threatened vital organ function.
Severe	Vasculitis in at least one organ system with systemic features *and vital organ failure.*
Refractory	Failure of standard induction regimen.

Table 3a

Project	Trial question	Disease subgroup
NORAM (de Groot et al., 2005)	MTX or CYC for induction	Early systemic
CYCAZAREM (Jayne et al., 2003)	3 or 12 months CYC or AZA for remission maintenance	Generalised
MEPEX (Jayne et al., 2007)	Addition of PE or high-dose i.v. MetPred for induction	Severe renal
SOLUTION (Schmitt et al., 2004)	ATG for induction	Refractory
CYCLOPS (de Groot & Harper, 2009)	Pulsed i.v. or daily oral CYC for induction	Generalised
IMPROVE (Hiemstra et al., 2010)	MMF or AZA for relapse prevention after CYC induction.	Generalised
REMAIN	Long-term immunosuppression for relapse prevention.	Remission “generalised and severe renal”
Long-term follow-up (Flossmann et al., 2011) (**paper I**)	“5-year” follow-up of patients included in NORAM, CYCAZAREM, MEPEX, CYCLOPS.	

Table 3b

Project	Trial question	Disease subgroup
RITUXVAS(Jones, 2014)	RTX or CYC for induction.	Generalised and severe renal
MYCYC(Hiemstra et al., 2010)	MMF or CYC for induction	Early systemic and generalised
PEXIVAS (in progress)	PE and reduced CS for induction.	New onset or relapsing renal/ lung haemorrhage
RITAZAREM (in progress)	RTX or AZA for relapse prevention after rituximab induction.	Relapsing

MTX, methotrexate; CYC, cyclophosphamide; PE, plasma exchange; MetPred, metylprednisolon; ATG, anti-thymocyte globulin; MMF, mycophenolate; AZA, azathioprine; CS, corticosteroids..

Treatment

Before the introduction of immunosuppressive treatment 82% of the patients with GPA died during the first year after diagnosis and more than 90% died within two years (Walton, 1958). Corticosteroids were introduced in the 1950s and led to an improved outcome with 48% of patients diagnosed with polyarteritis nodosa surviving 5 years or more (Frohnert & Sheps, 1967). Corticosteroids were then combined with cyclophosphamide in the 1960s and patient survival increased dramatically to >80% at 2 years (Fauci, Wolff, & Johnson, 1971). The combination of daily oral cyclophosphamide (CYC) and corticosteroids became the standard of care for patients with AAV but had several adverse events such as the development of hemorrhagic cystitis, bladder cancer and lymphoproliferative malignancies (Hoffman et al., 1992). In order to prevent organ damage, decrease relapse rate and minimize the occurrence of adverse events, the first of the EUVAS clinical trials aimed to minimize the exposure of cyclophosphamide and to find optimal duration of maintenance treatment. Lately, rituximab (RTX) has been introduced as an alternative to CYC in the treatment of AAV.

Current treatment regimens

The current treatment regimens in AVV, based on results from the ECSYSVASTRIAL studies and others, are divided into three categories i.e. remission induction, remission maintenance and treatment of refractory disease (Holle & Gross, 2013; Mukhtyar et al., 2009; Smith, 2015).

Remission induction

The intensity of the induction treatment depends on the severity of the disease and the extent of organ involvement. The first line induction treatment in AAV consists of cyclophosphamide in combination with corticosteroids (de Groot et al., 2005) (Jayne et al., 2003) (de Groot & Harper, 2009). Cyclophosphamide is administered either intravenously in pulses or as continuous oral treatment and both treatment regimens have been shown to induce remission without significant differences (CYCLOPS study, de Groot & Harper, 2009). The main advantage of intravenous pulse treatment is that the cumulative dose of cyclophosphamide is lower, with probably lower risk for malignancy (de Groot, Adu, Savage, EUVAS (European vasculitis study group), 2001). In localized or early systemic disease methotrexate might be considered as induction treatment (the NORAM study, de Groot et al., 2005). Rituximab (RTX) has been introduced as an alternative to cyclophosphamide in the treatment of AAV and have been evaluated in two clinical trials (the EUVAS-study RITUXVAS and the American RAVE) showing that RTX is non inferior to

CYC in inducing remission in severe AAV and that it is superior to CYC in relapsing disease (Jones et al., 2010; Stone et al., 2010). Follow-up data did not show any significant differences in relapses in either of the two studies (Jones et al., 2015; Specks et al., 2013). Plasma exchange has been shown to have additional effect in renal recovery, but not in patient survival, in patients presenting with biopsy-proven AAV with creatinine > 500 μmol/L in the MEPEX study (Jayne et al., 2007).

Remission maintenance

The induction therapy is usually kept between 3 and 6 months and if remission is induced, cyclophosphamide is replaced by either azathioprine or methotrexate in combination with oral corticosteroids (the CYCAZAREM study, Jayne et al., 2003). Mycophenolate, leflunomide or rituximab may be used as alternatives to azathioprine/methotrexate (Guillevin et al., 2014; Hiemstra et al., 2010; Metzler et al., 2007). During maintenance corticosteroids are tapered to a maximum of prednisolone 15mg/day at 3 months, 10 mg/day at 6 months and 5 mg/day at 12-18 months (Mukhtyar et al., 2009). RTX has been shown to be superior to AZA in maintaining remission at 28 months (the French MAINRITSAN study, Guillevin et al., 2014) and Smith *et al* show in a retrospective study that routine re-treatment with RTX during 2 years after induction was associated with lower relapse rates compared with a single RTX course (Smith et al., 2012).

Refractory disease

When remission is not attained with full-dose cyclophosphamide and intravenous methylprednisolone (which is rare) alternative treatments might be considered. Rituximab has been used and evaluated and is considered a safe and effective alternative in refractory disease (Jones et al., 2009). Other options are intravenous immunoglobulin (Jayne et al., 2000), alemtuzumab (Walsh, Chaudhry, & Jayne, 2008), anti-tumor necrosis factor agents (Booth et al., 2004) and deoxyspergualin (Flossmann et al., 2009).

Long-term follow-up

Before the introduction of corticosteroids in the 50s and later cyclophosphamide in the treatment of AAV the mortality was high with less than 20% of patients surviving the first year after diagnosis (Walton, 1958). Follow-up of 158 GPA patients diagnosed between 1967 and 1990, where 85% received treatment of daily oral cyclophosphamide and corticosteroids, approximately 80% of the patients survived the first year. Almost all of the patients experienced morbidity from the vasculitis itself (86%) or side effect of treatment (40%), with for example infections and

malignancy, underlining the importance of finding other treatment options with less severe side effects (Hoffman et al., 1992). Several clinical trials have been conducted to evaluate the optimal treatment for the AAV, as described in previous sections. The prognosis for AAV patients with current treatment regimens has improved considerably and a number of recent studies highlight the improved outcome throughout the years (Hilhorst et al., 2013; Holle et al., 2011). However, the assessment of long-term mortality risk and morbidity might be difficult to interpret as the spectrum of the three diseases is varied and where clinical trials and follow-up studies have included different proportions of GPA, MPA and EGPA. Research tools to assess disease activity such as the Birmingham Vasculitis Activity Score (BVAS) (Luqmani et al., 1994), irreversible organ damage by the Vasculitis Damage Index (VDI) (Exley et al., 1997) and the mortality by the Five Factor Score (FFS)(Guillevin et al., 2011) are all used in different ways and might be of importance in comparing outcomes from different patient cohorts. BVAS is a clinical evaluation tool to assess ongoing activity in the disease, with a scoring sheet divided in nine organ systems (Appendix). The FFS is a prognostic score set, comprising 4 factors associated with poorer prognosis and 1 with better outcome (Appendix). VDI is used to record organ damage in patients with AAV that have occurred since the onset of the disease (Appendix).

Recently the OMERACT core set of outcome measures for use in clinical trials of AAV was launched (Merkel et al., 2011). The OMERACT defines a set of outcome parameters including disease activity, damage assessment, patient-reported outcomes and mortality with at least one validated outcome measure instrument available for each outcome parameter. Table 4 summarizes some of the long-term follow-up studies in AAV, highlighting the difficulties in comparison of the long-term follow-up studies; all studies differing in diagnoses included, time of inclusion, length of follow-up, type of trial and the statistics used to describe outcome.

Table 4

Author	**Flossman et al** (Flossmann et al., 2011)	**Hruskova et al** (Hruskova et al., 2013)	**Hilhorst et al** (Hilhorst et al., 2013)	**Holle et al** (Holle et al., 2011)	**Luqmani et al** (Luqmani et al., 2011)
Inclusion	1995-2002	1990-2011	Group I: 1979-1989 Group II: 1990-2000 GroupIII: 2001-2009	Group I: 1966-1993 Group II: 1994-1998 GroupIII: 1999-2002	1989-2004
Follow-up years	5.2 (median)	4.1 (mean)	Group I: 5.7 (median) Group II: 3.9 Group III: 3.1	Group I: 6.6 (median) Group II: 7.3 Group III: 3.9	6.4 (mean)
Cohort	Multicenter randomized clinical trials	Two tertiary referral centers retrospective	Monocenter retrospective	Tertiary referral center retrospective	General practice database
Results	SMR 2.6 (95% CI 2.2-3.1) 1-, 2-, and 5-year survival: 88%, 85%, 78%.	6 months survival: 82% 4- year survival: 58 %	Group I: HR 3.9 Group II: HR 2.9 Group III: comparator group All groups: 1-, 5-, and 10-year survival: 77%, 66%, 49%	Group I: SMR 2.1 Group II: SMR 1.41 Group III: SMR 1.03	Bimodal mortality pattern Year 0-1, HR=9.0; year 1-5 HR 4.0; year 5-10 HR 2.41; > 10 years HR 4.4. All compared with matched contols.
Patients	535	53	181 (34/49/98)	445 (114/102/40)	255
Diagnosis	MPA/GPA	MPA/GPA with severe alveolar haemorrhage	MPA/GPA	GPA	GPA
Country	Europe	Czech Republic	The Netherlands	Germany	UK
Main causes of death	<1 year: active vasculitis, infection > 1 year: cardiovascular, malignancy, infection	Infection 7 pts, cardiovascular 4 pts, gastrointestinal bleeding 1 pt, suicide 1 pt	< 1 year; sepsis, active vasculitis; > 1 year; cardiovascular, malignancy, kidney failure, infection	Not reported	<1 year; active vasculitis, infection, renal failure ; > 1 year infection

Predictors and causes of death

To evaluate what might predict a worse outcome is important when discussing how to tailor the immunosuppressive treatment in an optimal way. Advanced age, estimated glomerular filtration (eGFR) < 15 ml/min and high BVAS at entry are significant predictors of death as have been highlighted in several studies (Mahr, Girard, Agher, & Guillevin, 2001; Reinhold-Keller et al., 2000; Slot, Tervaert, Franssen, & Stegeman, 2003; Weidner, Geuss, Hafezi-Rachti, Wonka, & Rupprecht, 2004; Weiner et al., 2015; Westman, Selga, Isberg, Bladström, & Olsson, 2003). Other predictors of death in AAV, such as pulmonary involvement at diagnosis (Hruskova et al., 2013), low serum albumin (Aasarod et al., 2000) and high levels of PR3-ANCA in GPA measured by capture ELISA have been highlighted in other studies (Westman et al., 2003). The overall outcome for MPA is generally worse than for either GPA or EGPA, which probably reflect the older age and worse renal function at presentation (Lane, Watts, Shepstone, & Scott, 2005). In EGPA, the overall prognosis is influenced by the presence of neuropathy, renal involvement and cardiac involvement at presentation and might be predicted using the Five Factor Score (Guillevin et al., 1996). A new approach in assessing predictors of outcome in AAV with cluster analysis comes from Mahr *et al* (Mahr et al., 2013b). Cluster analysis is a statistical method where data, in this case individuals, are grouped together on basis of similarity. In medical research, cluster analysis has been used to identify phenotypes within certain diseases (McLachlan, 1992). Patients (n=715) with AAV that had participated in clinical trials (the EUVAS long-term follow-up study and the French MAINRITSAN study (Guillevin et al., 2014)) were grouped together in five different clusters based on their clinical similarities at presentation and the cluster affiliation correlated better with survival than the traditional way of dividing the AAV-group into the diagnoses of GPA, MPA or EGPA. The main causes of death during the first year of follow-up in the studies summarized in table 4 were infection or active vasculitis, whereas the main causes of death after 1 year was cardiovascular disease, malignancy or infection.

Malignancy in AAV

Increased risk for malignancy in AAV has been described since the introduction of effective immunosuppressive therapy i.e. when patients with AAV started to survive the first years after diagnosis (Hoffman et al., 1992) (Westman, Bygren, Olsson, Ranstam, & Wieslander, 1998) (Knight, Askling, & Ekbom, 2002). This increased risk for malignancy might have several explanations and it is difficult to

dissect the risk from the diseases themselves, with ongoing chronic immune stimulation, and the treatment given with possible direct oncogenicity and perhaps as a result from impaired immunosurveillance. Malignancy might also be a triggering factor of AAV (Pankhurst, Savage, Gordon, & Harper, 2004). Malignancy risk in other autoimmune diseases treated with immunosuppression such as rheumatoid arthritis and systemic lupus erythematosus have showed only a slightly increased standardized incidence ratio (SIR) for over-all malignancy, a markedly increased risk for lymphoma but on the other hand, a decreased risk for breast cancer, when compared with the general population (Bernatsky et al., 2013; Smitten, Simon, Hochberg, & Suissa, 2008).

Overall malignancy incidence

Several studies have assessed the overall malignancy incidence in AAV yielding standardized incidence ratios (SIRs) ranging between 0.8 and 2.5 (Knight et al., 2002; Westman et al., 1998) (Faurschou et al., 2008; Heijl et al., 2011(**paper II**)), but only the study from Holle *et al* showed reduced risk for malignancy among patients with AAV (Holle et al., 2011). SIRs compare the observed malignancies in a cohort with the expected numbers in the general population. In 2015 Shang *et al* conducted a meta-analysis of six studies assessing malignancy risk in AAV including three monocenter clinical cohorts (Holle et al., 2011; Westman et al., 1998; Zycinska, Kostrzewa-Janicka, Nitsch-Osuch, & Wardyn, 2013), two nationwide hospital discharge database studies (Faurschou et al., 2008; Knight et al., 2002) and one follow-up of multicenter clinical trials (Heijl et al., 2011). This meta-analysis showed a meta-analytical SIR for overall malignancy in AAV of 1.74 (95% CI 1.37-2.21) (Shang et al., 2015). The studies included in the meta-analysis had median follow-up times ranging from 4.58 to 7 years and several of the studies included patients that had been diagnosed already during the 1960s-1970s. One of the most recent publications by van Daalen *et al* shows interestingly that the patients in their cohort (at a tertiary vasculitis center, including all three diagnoses within the AAV spectrum) that were treated with rituximab and never with cyclophosphamide did not exhibit increased malignancy rates compared with the general population (van Daalen et al., 2016). This cohort consisted of patients diagnosed with AAV between 2000 and 2014 and the results might therefore better represent a current treatment regime and subsequent malignancy risk in patients with AAV. However, the follow-up time was relatively short with a mean time of 5.6 years. Another recent study by Rahmattulla *et al* assessing the malignancy risk in patients with GPA and MPA identified through the Dutch National Pathology Database, diagnosed between 1991 and 2013 and followed for a mean time of 10 years, show a SIR for overall malignancy of 2.21 (95% CI: 1.64-2.92) (Rahmattulla et al., 2015). Most of these studies included only patients with GPA, a few GPA and MPA, and only one

included all three diagnoses within the AAV spectrum. The follow-up study of the EUVAS clinical trials (Heijl et al., 2011(**paper II**)) showed a SIR for malignancy at all sites that were slightly higher in patients with GPA than MPA, but the confidence intervals overlapped and the corresponding RR was 1.6 (95% CI 0.90-2.86). The possible explanation of a higher malignancy incidence in patients with GPA is the higher relapse rate in GPA (Pagnoux et al., 2008) resulting in prolonged and repeated treatment with immunosuppressive drugs. The higher mortality seen in patients with MPA might insert death as a more prominent competing risk in this category (Lane et al., 2005).

Bladder Cancer

Early studies assessing malignancy risk in AAV highlighted an extreme risk for urinary tract cancer, especially bladder cancer with SIRs as high as 31-33 (Hoffman et al., 1992; Talar-Williams et al., 1996). These high risks have been associated with high cumulative doses of cyclophosphamide with a known dose-dependent urotoxicity (Pedersen-Bjergaard et al., 1988; Travis et al., 1995). With reduced doses of cyclophosphamide and the use of sodium 2-mercaptoethanesulfonate and hyper hydration to eliminate the metabolite acrolein that is excreted in urine and thought to be the main trigger for urinary tract cancer in cyclophosphamide treated patients, these high risks are no longer seen. More recent studies assessing malignancy risk in AAV have reported SIRs for bladder cancer ranging between 3.6-7.2 (Faurschou et al., 2008; Knight et al., 2002; Knight, Askling, Granath, Sparen, & Ekbom, 2004; Westman et al., 1998). In studies published after 2011, the SIRs for bladder cancer in AAV have not been significantly increased compared with the general population (Heijl et al., 2011(**paper II**)); Rahmattulla et al., 2015; van Daalen et al., 2016).

Leukemia

Leukemia, like urinary tract cancer, is a known potentially dose-dependent complication to treatment with cyclophosphamide (Baker et al., 1987) (Pedersen-Bjergaard et al., 1987). Two nationwide hospital discharge studies assessing malignancy risk in patients diagnosed with GPA show significantly increased SIRs for leukemia, 5.7 (95% CI: 2.3-12) (Knight et al., 2002) and 5.9 (95% CI: 1.2-17) (Faurschou et al., 2008) respectively; however, in both studies patients were diagnosed with GPA between approximately 1970 and 1999. In one recent study from Knight *et al* using the Swedish population-based patient registry, 21 cases of leukemia among all patients (n=3224) with GPA diagnosed between 1964 and 2012 were found (Knight et al., 2015) but no comparison with expected numbers were performed. The median time from diagnosis of vasculitis to diagnosis of leukemia was

8 years (range 5-21); all patients diagnosed with leukemia had severe, generalized GPA and had received high doses of cyclophosphamide (median cumulative dose 96.5g). Other recent studies, assessing malignancy risk in patients diagnosed after 1995, have not been able to detect any increased risk in leukemia among patients with AAV (Heijl et al., 2011(**paper II**); Rahmattulla et al., 2015; van Daalen et al., 2016). However, only the study from Rahmattulla *et al* had a median follow-up time of more than 8 years.

Lymphoma

The incidence of lymphoma in autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, Sjögren´s syndrome) evaluated in a meta-analysis, is increased compared with the general population (Zintzaras, Voulgarelis, & Moutsopoulos, 2005). In AAV the connection is more unclear, where earlier studies of GPA show a 4-fold to 11-fold increased risk (Hoffman et al., 1992; Knight et al., 2002), but more recent studies show no increased risk.

Non-melanoma skin cancer

The incidence of non-melanoma skin cancer (NMSC, in most cases including both basal cell carcinoma and squamous cell carcinoma) is increased in patients treated for AAV in most studies. Studies assessing malignancy risk in AAV diagnosed after 1991 has not been able to show an increased risk for any other specific malignancy than NMSC (Heijl et al., 2011(**paper II**); van Daalen et al., 2016) (Rahmattulla et al., 2015).

Aims

The aims of this thesis were to assess the long-term survival and malignancy risk in two different types of patient cohorts with ANCA-associated vasculitis; one large international multicenter cohort, prospectively recruited into four clinical trials conducted within the European Vasculitis Study group (EUVAS) and one smaller, population-based cohort in southern Sweden.

- To describe the long-term patient survival and possible prognostic factors at presentation in an international multicenter, prospectively recruited, representative patient cohort with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).
- To describe the long-term malignancy risk in an international multicenter, prospectively recruited, representative patient cohort with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).
- To describe the long-term patient survival and possible prognostic factors, including the validation of cluster affiliation as a prognostic factor, in a population-based cohort of patients, including all three diagnoses within the AAV spectrum, in southern Sweden.
- To describe the long-term malignancy risk in a population-based cohort of patients with ANCA-associated vasculitis, including all three diagnoses within the AAV spectrum, in southern Sweden.

Methods

This is a summary of the materials and methods used in the four papers, for more details see each individual paper.

Patient populations

In **papers I and II** we investigate the long-term survival and malignancy risk in patients with GPA and MPA, initially recruited into the four randomized clinical trials conducted within the EUVAS in 85 hospitals from 14 European countries (and Mexico).

In **papers III and IV** we investigate the long-term survival and malignancy risk in patients with AAV, including all three diagnoses within the AAV (i.e. GPA, MPA and EGPA), in a well-characterized population-based cohort in southern Sweden.

The EUVAS long-term follow-up cohort

EUVAS is a European network organization with the aim to carry out clinical trials in patients with ANCA-associated vasculitis. This European network is based on smaller working groups and regular whole group meetings. Between 1995 and 2002, four randomized clinical trials (CYCAZAREM, NORAM, MEPEX, CYCLOPS (de Groot et al., 2005; de Groot & Harper, 2009; Jayne et al., 2003; 2007)) were conducted within the EUVAS. Patients were included if they were diagnosed with GPA or MPA and the diagnosis was based on clinical presentation that was compatible with ANCA-associated vasculitis accompanied by a positive ANCA-serology and/or histology. Patients with coexisting multisystem autoimmune condition, active infection, pregnancy, previous malignancy diagnosis or age below 18 years were excluded. Patients who developed life-threatening pulmonary hemorrhage within 24 h were also excluded. Patients who have participated in the EUVAS-trials have been uniformly categorized and clinical and laboratory characteristics at entry and during 12-18 months of follow-up were registered.

The long-term follow-up was conducted as a 5-year follow-up study and during the period 2004-2007 questionnaires were sent out to the trial physicians in the different countries to gather data on the outcomes of the participants in the four different trials. The questionnaire was composed of 22 questions and data were collected on survival, cause of death, renal outcome, relapse and adverse events (including cardiovascular events and malignancy) that had occurred during the initial trial or during the follow-up period, as well as on type and duration of given immunosuppressive treatment (Appendix).

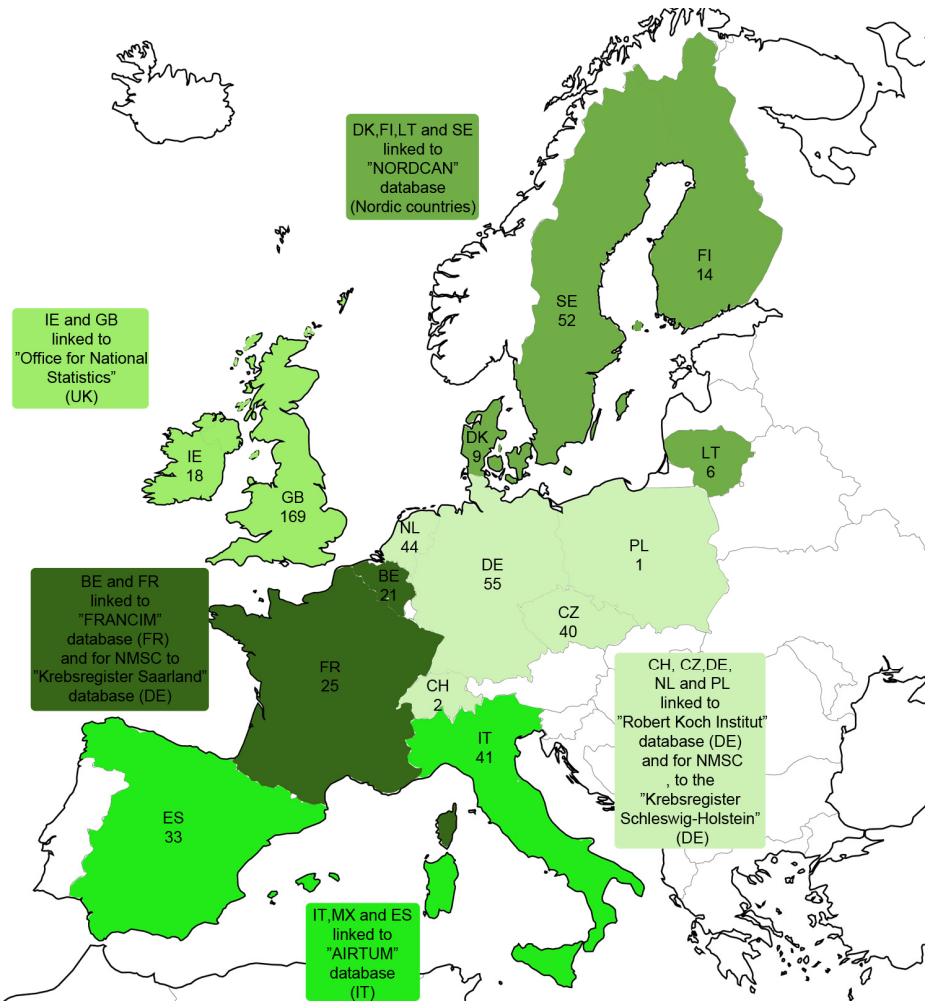

Fig 2.

Countries of residence of the 535 patients with AAV and their respective linkage to 5 cancer registries from the United Kingdom, Scandinavia, Germany, France and Italy. The values shown refer to the numbers of subjects per country; additional patients from Mexico are not shown in the map (linked to AIRTUM registry).

Assessment of malignancy

For each noted malignancy, additional information on the type of malignancy and its site and date of diagnosis were asked for. For participants for whom no follow-up data were available, a review of the trial adverse event report forms for possible additional malignancies was conducted. If more than one malignancy was noted, both first and subsequent malignancies were considered.

The population-based Swedish cohort

Case ascertainment

All cases with ANCA-associated small vessel vasculitis in a defined geographical area of approximately 0.7 million inhabitants in southern Sweden were included in the cohort (fig 3). Potential cases of AAV, diagnosed between 1997 and 2010, were identified through three different sources; clinical records, pathology records and ANCA serology databases (Mohammad et al., 2007; 2009) and were reviewed using case records. Patients were considered to have AAV if they had symptoms and signs compatible with small vessel vasculitis supported by histopathology, radiology or serological findings, and had been classified as having GPA, MPA, or EGPA according to the European Medicine Agency 2007 algorithm (Watts et al., 2007). Diagnoses were biopsy-proven in 172 of the 195 patients (88%).

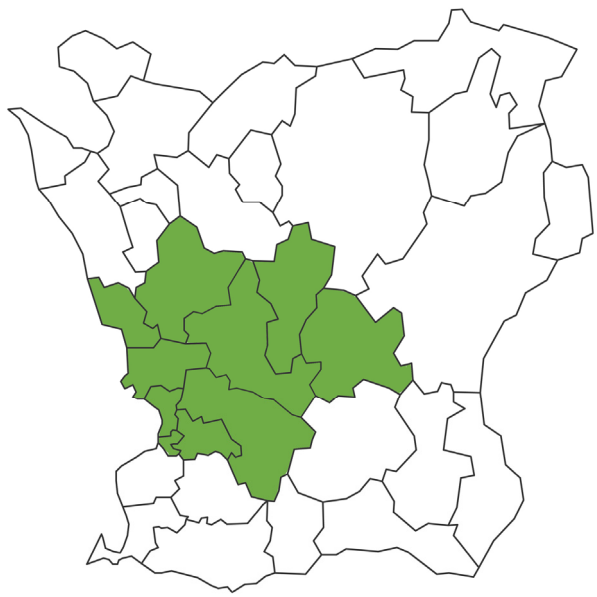

Fig 3.
Map showing the region of Skåne in southern Sweden and the study area (in green).

Assessment of malignancy

By review of each case record and pathology report for the 195 patients in the cohort, data of any malignancy occurring after the diagnosis of AAV were collected until December 31, 2015. If a patient developed several non-melanoma skin cancers (NMSC) only the first was reported. If a patient developed any malignancy type, excluding NMSC, only the first was reported in the assessment of overall malignancy. However, in the assessment of any specific malignancy, the malignancy was reported regardless of other malignancy diagnosis. If a patient developed both NMSC and any malignancy excluding NMSC, the first of either malignancy was reported, respectively. In the Swedish Cancer Registry, basal cell carcinoma has only been reported since 2004 and we did not include this diagnosis in the NMSC because of the lack of data for the general population.

General population

EUVAS long-term follow-up

Overall patient mortality was compared with a control cohort matched for age- sex, year and country. Official population statistics were searched for participating countries: Belgium, Czech Republic, Germany, Denmark, Spain, Finland, France, England and Wales, Italy, the Netherlands, Poland, Sweden and Scotland. For those few countries where information could not be obtained, data was retrieved from a neighboring country. For the patients from Mexico (n=5), data from Spain was used. The expected numbers of malignancies in the general population were obtained by pooling the patients into five geographical areas and linking each area to existing cancer registries from five large countries or areas, i.e. the UK, the Nordic countries (NORDCAN), Germany, France and Italy. Because NMSC were not recorded in the French and German national cancer registries, data from two regional German cancer registries were imputated into the French and German registries, respectively. For all the databases year 2000 was used, except for the Italian for which 2000-2003 data were used (Fig 3).

The population-based Swedish cohort

Overall patient mortality was compared with the general Swedish population using data from the Causes of Death Registry. The expected numbers of malignancies in the general population was calculated using data from the Swedish Cancer Registry webpage.

Statistical analyses

Papers I and III

Continuous variables in **paper I** are presented as medians with 25th and 75th centiles and in **paper III** with medians and interquartile ranges (IQR). Categorical variables are expressed as counts and frequencies. Survival was calculated using the Kaplan-Meier method. The log-rank test was used to compare the overall patient survival with that of the background populations matched for age, sex and calendar year, calculated with the Hakulinen method (Hakulinen, 1982).

In addition, in **paper III** we used cluster affiliation based on a cluster analysis in patients with AAV previously described by Mahr *et al* (Mahr et al., 2013b). Patients were grouped in five different clusters based on their clinical similarities at presentation and survival as well as comparison with the background population was calculated for each cluster (fig 4). In both papers we analyzed possible prognostic factors for death in multivariable Cox regressions (Thomas & Reyes, 2014).

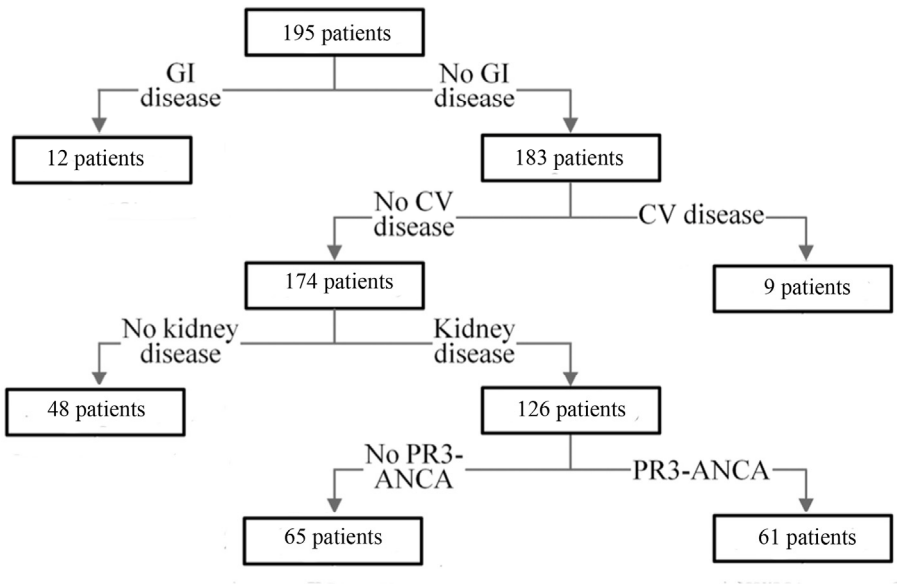

Fig 4.
Cluster affiliation

Papers II and IV

Cumulative incidence of malignancy, overall survival, and malignancy free survival, respectively, were calculated using the Kaplan–Meier method. Standardized incidence ratios (SIRs) were calculated to compare the observed malignancies in the cohorts with the expected numbers, calculated using malignancy registries from the corresponding countries (see methods). In **paper II** we matched for gender and 5-year age groups and in **paper IV** we matched for gender, 5-year age and 1-year calendar time period, i.e. for each year the patients grow older and, when appropriate, the corresponding 5-year age groups in the general population were changed. The expected numbers of malignancies of each kind were calculated by multiplying the number of person-years for each sex and age group by the corresponding incidence rates of malignancy in the background populations. SIRs were calculated for malignancies at all sites, for malignancies at all sites excluding NMSC and for each of the reported specific malignancies in the cohort. SIRs were stratified by subgroups and we performed Poisson regressions to generate relative risks (RR) for malignancy incidence in each subgroup. Continuous variables in **paper II** are presented as with 25th and 75th centiles medians and in **paper IV** with medians and interquartile ranges (IQR). Categorical variables are expressed as counts and frequencies. Comparisons of the baseline characteristics of patients diagnosed with malignancy and patients without malignancy were made using Mann-Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

Results

This is a summary of the results from the four papers, for more details see each individual paper.

Demographics

Main baseline characteristics of patients included in the EUVAS long-term follow-up and the Swedish population-based cohort is summarized in the table below.

Table 5

Main baseline characteristics		
	EUVAS (papers I+II)	**Skåne (papers III+IV)**
Number of patients	535	195
Male sex	288 (54%)	97 (50%)
Median age (Q1-Q3)	61 (49-69)	69 (55-77)
Median follow-up (ys)	5.16	8
MPA (n)	254 (47%)	90 (46%)
GPA (n)	281 (53%)	94 (48%)
EGPA (n)	0 (0%)	11 (6%)
eGFR ml/min	28 (10-65)	40 (15-80)
MPO-ANCA	174 (33%)	84 (43%)
PR3-ANCA	286 (53%)	100 (51%)
Negative	51 (10%)	11 (6%)
Missing	8 (1%)	0

MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA; eosinophilic granulomatosis with polyangiitis; eGFR (estimated glomerular filtration rate.

Five hundred and thirty-five patients with a median age of 61 years were included in the EUVAS long-term follow-up study (**papers I and II**). Patients with MPA were older than patients with GPA with a median age of 64 vs. 58 years. 254 of the patients were diagnosed with MPA (47%) and 281 with GPA (53%). 288 of the 535 patients were male (54%). The median time of follow-up was 5.16 years, ranging from 1 day to 11.46 years. Data on immunosuppression were available for 493

patients; 458 received cyclophosphamide and 331 received azathioprine, at some time during their treatment.

In the population-based Swedish cohort, 195 patients (98 female) with a median age of 69 years (IQR 55-77) at diagnosis fulfilled the inclusion criteria and were included in the study cohort (**papers III and IV**). Among these 90 (46%) were diagnosed with MPA, 94 (48%) with GPA and 11 (6%) with EGPA. The follow-up time ranged between 0.3 and 18 years with a median follow-up time of 8 years (IQR 4.0-11.9), and 98 (50%) of the patients died during follow-up.

Survival, causes of death and predictors of death

Survival and causes of death

During the follow-up period in the EUVAS long-term follow-up 133 deaths (25%) occurred (**paper I**). Survival at 1, 2 and 5 years was 88%, 85% and 78% respectively compared with that in the matched population that was 98%, 97% and 92% respectively. The overall mortality in the patient cohort was significantly increased compared with the general population. The overall mortality ratio among the patients compared with the controls was 2.6 (95% CI 2.2-3.1). The most common causes of death during the first year were infection or active vasculitis whereas the main causes of death after 1 year was cardiovascular disease, infection or malignancy. Fifty-nine deaths (44%) occurred during the first year.

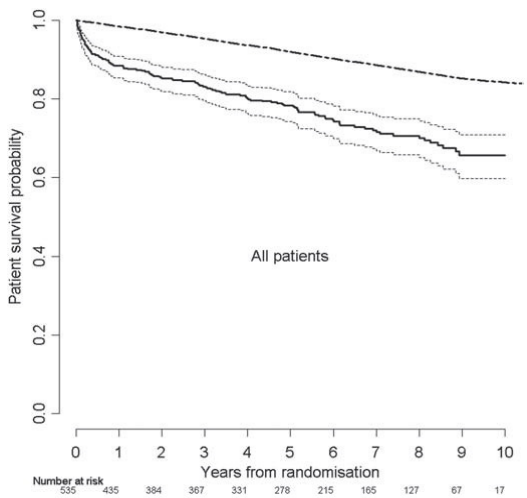

Fig 5.
Patient survival overall (solid line) with 95% CI (dashed lines) compared with a matched general population (dot/dash line).

In the Swedish population-based cohort a total of 98 deaths occurred during follow-up (50%) (**paper III**). Survival at 1, 2, 5 and 10 years was 87%, 82%, 70%, and 55%, respectively. In the AAV-cohort there was a significant increased mortality ratio compared with the age, sex, and calendar year matched general population. The overall mortality ratio among the patients compared with the controls was 2.4 (95% CI 2.0-3.0). The main causes of death during the first year of follow-up were active vasculitis and bacterial infection. After the first year of follow-up the main causes of death were malignancy, bacterial infection, and cardiovascular disease. Twenty-seven (28%) of the 98 deaths occurred during the first year after diagnosis.

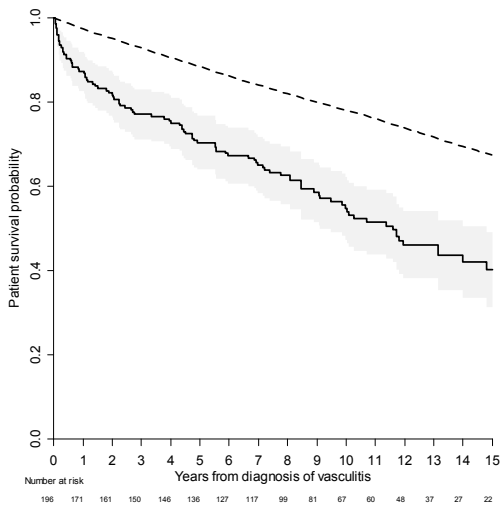

Fig 6.
Patient survival overall (solid line) with 95% CI (gray area) compared with a matched general population (dashed line).

Predictors of death

Predictors of death were calculated using Cox-regression. In the EUVAS long-term follow-up significant predictors of death were older age, eGFR <15 ml/min, higher BVAS, MPO-ANCA, a lower hemoglobin and higher white blood cell count at diagnosis. However, when using an age- sex- year- and country matched comparator group, younger age was associated with higher mortality.

Significant predictors of death in the Swedish population-based cohort were older age, gender, eGFR < 15 ml/min and cluster affiliation with the cardiovascular and gastrointestinal clusters exhibiting the highest mortality whereas the mortality in the non-renal cluster (i.e. patients without cardiovascular, gastrointestinal or renal

involvement at presentation) did not significantly differ from that in the general population.

Malignancies

During the observation period of approximately 2500 person-years in the EUVAS long-term follow-up, we found malignancies in 53 of the 535 patients (**paper II**). SIR (95% CI) was 1.58 (1.17-2.08) for malignancies at all sites, 1.30 (0.9-1.80) for all malignancies excluding non-melanoma skin cancers (NMSC), 2.78 (1.56-4.59) for NMSC and 2.41 (0.66-6.17) for bladder cancer. Subgroup analysis indicated higher SIR for malignancy at all sites in GPA than MPA patients (SIR 1.92 vs. 1.20) but the confidence intervals overlapped and the corresponding RR was 1.6 (95% CI 0.90-2.86).

During the approximately 1500 person-years observation period in the Swedish population-based cohort, we found malignancies in 52 of the 195 patients (**paper IV**). SIR (95% CI) was 2.8 (2.1-3.6) for malignancies at all sites, 1.8 (1.3-2.5) for all malignancies excluding NMSC, 12.9 (8.4 -18.8) for NMSC, 4.3 (1.4-10.0) for bladder cancer and 7.0 (1.4-20.5) for pancreatic cancer. Subgroup SIR showed a relative risk ratio of 3.96 (1.7-8.0) for patients with a malignancy diagnosis prior to the diagnosis of AAV.

Discussion

Survival and predictors of death *(papers I and III)*

Patients with AAV still exhibit an increased mortality compared with the general population even though there has been a tremendous improvement during the previous decades. The joint efforts resulting in several well-designed randomized clinical trials within the EUVAS have had a substantial impact on how patients with AAV currently are treated. However, there is no clear evidence on how the changes in treatment protocols affect long-term outcome. We show that the mortality in patients with AAV is still increased compared with a matched general population both in a European multicenter cohort as well as in a smaller population-based Swedish cohort.

Paper I

This study included a large cohort of patients initially treated within four clinical trials evaluating different treatment strategies in AAV. The follow-up study subsequently appertained patients with a variety of disease severity, treated according to different protocols but this mixture of disease severity and treatment regimens is a realistic picture on how cohorts of a rare and heterogenic disease like AAV are composed. We show in this study that patients with AAV have an increased mortality compared with a matched background population and that this increase is higher in younger patients, probably reflecting that older individuals, both in the AAV group and the general population, have more competing risk factors for mortality and morbidity than the younger. In consistency with other previous studies assessing the survival in AAV, we show that the mortality is high during the first year with the main causes of death being active vasculitis and infection (Ritchie, Reynolds, & Robson, 2016; Westman, Flossmann, & Gregorini, 2015), highlighting the difficulty in balancing the treatment between efficacy on one hand and adverse events such as infections on the other. In comparison with **paper III,** we show a higher incidence of fatal infections and this might reflect a less individualized immunosuppression in patients inside the protocols for clinical trials. The excess risk of mortality persists after the first year and the main causes of death after one year were malignancy, infection and cardiovascular disease. Consistent with other studies assessing predictors of death in AAV we show that advancing age and eGFR < 15 ml/min is associated with higher mortality (Mahr et al., 2001; Mohammad et al., 2015; Reinhold-Keller et al., 2000; Slot et al., 2003; Weidner et al., 2004; Weiner et al., 2015; Westman et al., 2003). Higher BVAS and lower hemoglobin was also associated with higher mortality. We did not analyze the relation between poor prognostic factors and

specific causes of death and can only speculate if factors such as eGFR< 15 ml/min and older age are associated with death from causes suggesting over- or undertreatment with immunosuppression.

The main strength of **paper I** is the large number of patients capturing almost the full range of disease severity in AAV. This is one of the biggest follow-up studies that have been conducted on patients with AAV. The follow-up time is however limited, with a median follow-up of 5.16 years and a longer follow-up might be needed to assess long-term morbidity and mortality in patients treated for AAV. Since **Paper I** is based on data from randomized clinical trials there are several exclusion and inclusion criteria that have to be taken into account before generalizing the results (Pagnoux et al., 2015). Even if we included a broad spectrum of patients with ANCA-associated vasculitis we excluded patients with EGPA, very elderly patients, those with severe lung hemorrhage at the time of diagnosis and those who had a known previous malignancy.

Paper III

This study is smaller, with 195 patients, carried out in a different setting within a well-defined, population-based cohort, including all patients within the AAV spectrum (GPA, MPA and EGPA). One of the advantages of a population based cohort, compared with hospital-based cohorts or cohorts originating from tertiary centers or clinical trials (such as in **paper I**) is the avoidance of selection or referral bias. We believe that the patients in our cohort in **paper III** are the better representatives for patients with AAV in ordinary practice.

Cumulative survival in **paper III** at 1, 2 and 5 years was slightly lower than in **paper I**, reflecting the higher age of the patients in this cohort (median age 69 years compared with 61 in **paper I**). However, the survival compared with the general population yielded similar SMRs at 2.6 and 2.4, respectively.

The long follow-up time, with a median of 4 years for the 98 patients that died during follow-up and 11 years for those alive at end of follow-up as well as the sound collection of data was major strengths with this study. We used cluster affiliation as a predictor of death in patients with AAV, showing that the patients in the cardiovascular and gastrointestinal clusters exhibited the highest mortality whereas the mortality in patients without cardiovascular, gastrointestinal or renal involvement at presentation did not differ from the general population.

Malignancy risk *(papers II and IV)*

When patients diagnosed with AAV tend to live longer the side effects of the immunosuppressive treatment have become a focus of interest and the development of malignancies is a major concern. Previous studies assessing malignancy risk in AAV

have reported SIR for overall malignancy of different ranges, and the relationship between malignancy and cumulative dose of cyclophosphamide has been highlighted. Up to a 33-fold risk for bladder cancer have been reported in earlier studies, but these risks are not seen with current treatment protocols (Hoffman et al., 1992). However, in more recent studies, the risk for malignancies of different types have not been fully consistent with SIRs for overall malignancy ranging from non-significant (Holle et al., 2011) to 3.76 (Faurschou et al., 2008; Heijl et al., 2011(**paper II**); Rahmattulla et al., 2015), the SIRs for bladder cancer ranging from non-significant to 3.6-fold increased, the SIRs for NMSC ranging between 2.8 and 4.7 and the SIRs for leukemia ranging from non-significant to 5.9-fold increased. Throughout the studies, there is an increased risk for NMSC. Interestingly, in a recent study the malignancy risk in patients treated with rituximab was not shown to be associated with an increased malignancy risk compared with the general population (van Daalen et al., 2016).

In our EUVAS-study (**paper II**) with a median follow-up of 5 years, as well as in another describing a cohort of 138 patients identified through a pathology database (Rahmattulla et al., 2015) and followed for a median of 10 years both stress that the malignancy risk in patients with AAV treated according to current protocols is increased but that this increase is solely driven by the increased risk for NMSC. The conclusions from these studies are that the increased malignancy risk has diminished as a direct consequence to lower cumulative doses of cyclophosphamide in current treatment protocols. However, the follow-up time in **paper I** was too short to detect late occurring malignancies and longer follow-up is warranted.

In **paper IV** the follow-up is longer, with a median of 8 years. In this study, we show a markedly increased risk for NMSC as well as for both bladder and pancreatic cancer. The increased risk for bladder cancer is in agreement with studies from 2002-2008 but pancreatic cancer has not been shown to be increased in other studies (Faurschou et al., 2008; Knight et al., 2002; 2004). In **paper IV** the median time of follow-up is 8 years, and 11 years for those patients who were alive at end of follow-up. We observed an increased risk for NMSC and bladder cancer already after 5-years follow-up, suggesting that even shorter studies assessing malignancy risk in AAV may be sufficient to evaluate the current risks.

The discrepancies between our two findings might have several explanations. The assessment of malignancies in Sweden is very thorough and each health care provider is obliged to send in a report the National Cancer Registry for every malignancy diagnosed at clinical, - morphological-, and other laboratory examinations as well as cases diagnosed at autopsy. Both the assessment of malignancies in our population-based cohort, as well as in the general population is reliable and the probability that any malignancy is missed is very low. This might explain why we see higher

malignancy risk in **paper IV** when compared with previous studies. Furthermore, in **paper IV** we included patients with previous malignancies and patients with renal transplants and in these groups the risk for additional malignancies is known to be higher (Hellström, Lorant, Döhler, Tufveson, & Enblad, 2016). In **paper IV**, patients with previous malignancy exhibited a significant higher risk for malignancy (RR 4.0: 95% CI 1.7-8.0) and so did renal transplant recipients even though this group was too small to reach a statistical significance (RR 1.7: 95% CI 0.50-4.1). In our Swedish population-based cohort the median age was also higher (median 67 years) compared with that in the EUVAS cohort (median 61 years).

Why is the malignancy risk increased in AAV?

There are of course several explanations; a possible underlying risk for malignancy development in general in systemic inflammatory diseases, an oncogenic effect from immunosuppressive drugs, an impaired immunsurveillance as an effect of immunosuppression or as a direct effect of a defect immune system (Mahr, **Heijl**, Le Guenno, & Faurschou, 2013a). The knowledge regarding malignancy risk in other autoimmune diseases treated with immunosuppression such as rheumatoid arthritis and systemic lupus erythematosus is of interest for comparison and studies have showed only a slightly increased SIR for overall malignancy and a markedly increased SIR for lymphoma (Bernatsky et al., 2013; Smitten et al., 2008). The general results in AAV are similar regarding overall malignancy but the risk for lymphoma is much lower, if at all increased. The risk for lymphoma is connected to defects in the immune system and with the lack of convincing evidence of increased risk for lymphoma in AAV the theory on defect immune system may seem to be less important in AAV.

The previous high risks for bladder cancer have been associated with high cumulative doses of cyclophosphamide with a known dose-dependent urotoxicity (Pedersen-Bjergaard et al., 1988; Travis et al., 1995). With reduced doses of cyclophosphamide and the use of sodium 2-mercaptoethanesulfonate and hyper hydration to eliminate the metabolite acrolein that is excreted in urine and thought to be the main trigger for urinary tract cancer in cyclophosphamide treated patients, these high risks are no longer seen but with the results from **paper IV,** the remaining risk even with current treatment protocols cannot be overseen. The results from van Daalen *et al* (van Daalen et al., 2016)where no increase in malignancy risk was seen in patients treated with rituximab and never with cyclophosphamide is interesting and strengthens the theory that the increased malignancy risk in AAV is mainly driven by cyclophosphamide exposure.

Conclusions

This thesis investigated the long-term risk of death and malignancy in patients with AAV within one large international, multicenter cohort, prospectively recruited into four clinical trials conducted within the European Vasculitis Study group (EUVAS) and one smaller, population-based cohort in southern Sweden and the following conclusions were drawn:

- Patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) treated with conventional regimens within four international clinical trials are at increased risk of death compared with an age- and sex-matched population.
- Patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) treated with conventional regimens within four international clinical trials are at increased risk of overall malignancy and non-melanoma skin cancer compared with an age- and sex-matched population.
- Patients with ANCA-associated vasculitis, including all three diagnoses within the AAV spectrum in a population-based cohort in southern Sweden, are at increased risk of death compared with an age-and sex-matched population if they have cardiovascular, gastrointestinal or renal involvement at presentation. Patients without cardiovascular, gastrointestinal or renal involvement at presentation do not exhibit an increased risk for death when compared with the general population.
- Patients with ANCA-associated vasculitis, including all three diagnoses within the AAV spectrum in a population-based cohort in southern Sweden, exhibit an increased risk for overall malignancy, for malignancy excluding non-melanoma skin cancer, for non-melanoma skin cancer, for bladder cancer and for pancreatic cancer.

Future aspects

The ANCA-associated vasculitides remain elusive; the pathogenesis is still unknown and has to be sought. In the meantime, the optimal treatment options have to be based on results from randomized clinical trials and their follow-up data. In the field of rare diseases, international multicenter collaboration is of course of crucial importance and the international vasculitis society is characterized of collegial collaboration.

Treatment

I am with interest looking forward to results from clinical trials such as RITAZAREM (evaluating rituximab compared with azathioprine for relapse prevention after rituximab induction) and PEXIVAS (evaluating plasmapheresis and reduced doses of corticosteroids for induction in new onset or relapsing renal disease and/or lung hemorrhage). In our Swedish cohort, we have observed preliminary indications that patients diagnosed during the periods after the international efforts to lower cyclophosphamide exposure and the introduction of rituximab, not only for refractory disease but also for induction treatment, exhibit an increase in mortality and this has to be further explored.

Prognostic factors

I am hoping to see a validation of the cluster analysis developed by Mahr *et al* in a large cohort. Our data from the Swedish population-based cohort support the importance of cluster affiliation as a prognostic factor but our cohort was not large enough for a formal validation. It would be interesting to investigate if there is a relationship between specific prognostic factors and causes of death, and if such a speculative connection may help in tailoring the intensity of treatment in individual patients.

Malignancy

The results from van Daalen *et al*, where no increase in malignancy in patients with AAV treated with rituximab could be seen, will be interesting to evaluate further in other cohorts and during longer follow-up. Rituximab might gain importance over cyclophosphamide in the treatment of patients at higher risk of developing malignancies.

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Populärvetenskaplig sammanfattning

Systemiska vaskulitsjukdomar karakteriseras av inflammation i och kring blodkärl och indelas efter vilken storlek av kärl de drabbar. ANCA (anti-neutrofila antikroppar) - associerad småkärlsvaskulit är en sjukdomsgrupp som engagerar små kärl och innefattar tre diagnoser; granulomatös polyangiit (GPA), mikroskopisk polyangiit (MPA) samt eosinofil granulomatös polyangiit. Dessa sjukdomar är i majoriteten av fallen associerade med antikroppar mot proteinerna proteinas 3 (PR3) eller myeloperoxidas (MPO) som finns i neutrofiler (vita blodkroppar). Sjukdomarna är kroniska och går ofta i skov.

Behandlingen innefattar kortison i kombination med annan immundämpande medicinering, oftast cyklofosfamid. Innan det fanns möjlighet till immunosuppressiv behandling dog 80% av de som insjuknade under första året efter diagnos. Med modern behandling har överlevnaden ökat markant men är fortfarande högre än hos normalbefolkningen. Med ökad överlevnad är biverkning till behandlingen ett problem med ökad risk för bland annat cancer. Vi har velat studera mortalitetsrisk samt cancerrisk hos patienter med ANCA-associerad småkärlsvaskulit både inom ramen för större europeiska behandlingsstudier samt i en mindre, men väl karaktäriserad, kohort patienter i Skåne.

Långtidsuppföljning av europeiska behandlingsstudier (delarbete I och II)

I dessa arbeten följs 535 patienter med nydiagnostiserad ANCA-associerad vaskulit från 15 länder upp 5 år efter inklusion i en av fyra behandlingsstudier, vilka genomförts i regi av European Vasculitis Society (EUVAS) mellan 1995 och 2002. Studierna baserar sig på data som samlats in under åren 2004 - 2007 via frågeformulär till de behandlande läkarna i respektive land.

I det första arbetet analyserades prognostiska överlevnadsfaktorer och jämfördes med bakgrundsdata från de deltagande länderna. Medianuppföljningstiden var 5,2 år och jämfört med en ålders- och könsmatchad bakgrundsbefolkning sågs en relativ dödlighet på 2.6 gånger den i normalbefolkningen. Kumulativ överlevnad var 88% efter 1 år, 85% efter 2 år och 78% efter 5 år. Högre dödlighet sågs hos de patienter som hade sämre njurfunktion, ökande ålder, högre aktivitet i sjukdomen, lägre hemoglobinnivåer, högre antal vita blodkroppar samt MPO-ANCA (antikroppar mot myeloperoxidas i vita blodkroppar).

I nästa arbete undersökte vi om det föreligger en ökad cancerrisk hos samma kohort. I de frågeformulär som skickades ut till behandlande läkare i respektive land efterfrågades även om de inkluderade patienterna hade fått cancerdiagnos. Under en uppföljningstid på 2650 personår diagnosticerades 50 fall av cancer hos 46 patienter. Vi drar slutsatsen att cancerrisken i denna kohort är generellt ökad jämfört med bakgrundsbefolkningen. Denna ökade risk ter sig i första hand orsakad av en ökad risk för hudcancer (undantaget malignt melanom). Jämfört med tidigare studier ses en lägre risk för cancer vilket kan vara orsakat av lägre doser cyklofosfamid i nuvarande behandlingsprotokoll. Vi konstaterar också att längre uppföljningstid krävs för att kunna uppskatta cancerrisk hos patienter med ANCA-associerad småkärlsvaskulit på längre sikt.

Långtidsuppföljning av skånska patienter (delarbete III och IV)

I dessa arbeten analyserades alla patienter som nyinsjuknat med ANCA-associerad småkärlsvaskulit i två sjukvårdsdistrikt i Skåne mellan 1997 och 2010. Patienterna följdes fram till död eller 31 december 2015. Dödsorsaker är kontrollerade via journalgenomgång och där uppgifter saknats har data kompletterats via Socialstyrelsens dödsorsaksregister. Uppgifter om cancersjukdom är insamlad via journaltext samt patologirapporter. 195 patienter med en medianålder på 68 år inkluderades i båda studierna. Uppföljningstiden var i median 4 år för de 98 patienter som dog under uppföljningstiden och 11 år för de som var i livet vid uppföljningstidens slut.

I det första arbetet beskrivs överlevnad och prognostiska faktorer. Kumulativ överlevnad var 87% efter 1 år, 82% efter 2 år, 70% efter 5 år samt 55% efter 10 år. Kohorten delades in i grupper (cluster) baserat på organengagemang vid insjuknandet enligt följande: gastrointestinalt, kardiovaskulärt, renalt med PR3 (njurengagemang med förekomst av PR3-ANCA), renalt utan PR3 (njurengagemang utan förekomst av PR3-ANCA) samt icke-renalt (dvs varken gastrointestinalt, kardiellt eller renalt engagemang) engagemang. De faktorer som hade prognostisk betydelse för överlevnad var ålder, kön, njurfunktion och clustertillhörighet. Mortaliteten för patienter med ANCA-associerad småkärlsvaskulit i denna kohort var signifikant ökad jämfört med en köns- och åldersmatchad bakgrundsbefolkning. Patienter tillhörande de gastrointestinala eller kardiovaskulära clustren uppvisade den högsta mortaliteten medan de patienter som tillhörde det icke-renala clustret inte uppvisade ökad mortalitet jämfört med bakgrundsbefolkningen.

I det andra arbetet analyserades cancerrisk i den skånska kohorten. Vi drar slutsatsen att cancerrisken, liksom i det europeiska arbetet, är generellt ökad jämfört med bakgrundsbefolkningen. Risken för hudcancer (undantaget malignt melanom) är högre än i tidigare arbeten. Vi ser även en ökad risk för urinblåsecancer och pancreascancer. I detta arbete, till skillnad från föregående, inkluderades patienter som hade haft cancer innan de fått sin vaskulitdiagnos. Förekomst av en tidigare

cancerdiagnos innebar en ökad risk för att på nytt insjukna i cancer även efter vaskulitdiagnosen.

Betydelse

Dessa forskningsstudier har stor klinisk betydelse för behandlingen av patienter med ANCA-associerad småkärlsvaskulit. EUVAS tidigare behandlingsstudier har haft stort genomslag i den kliniska praxisen i Europa. Resultaten från den skånska kohorten visar att de resultat vi ser från långtidsuppföljning av stora internationella, kliniska multicenterstudier kan upprepas i en mindre kohort som speglar den kliniska vardagen för de flesta läkare som tar hand om patienter med ANCA-associerad småkärlsvaskulit. Användning av clustertillhörighet som en ny och potentiellt viktig prognostisk faktor för överlevnad kan i framtiden vara till hjälp för att anpassa behandling till enskilda patienter. Ett positivt resultat med stor betydelse är att de patienter som inte har engagemang av hjärta, tarm eller njurar då diagnosen ställs inte uppvisar högre dödlighet än normalbefolkningen.

Vi visar i vårt skånska material att risken för att utveckla även andra cancerformer än hudcancer (undantaget malignt melanom) är fortsatt hög hos patienter som behandlas för ANCA-associerad vaskulit, i motsats till vad de senaste studierna kring cancerrisk hos dessa patienter visat och vad vi även såg i uppföljningen av de europeiska studierna. Dessa resultat kan förklaras med att kvaliteten av data är hög och inga cancerdiagnoser missas i det svenska materialet. En annan förklaring är att uppföljningstiden är relativt lång, i median 8 år, samt att vi inte exkluderat patienter som fått en cancerdiagnos vid något tillfälle före sin vaskulitdiagnos, vilket var fallet i den europiska långtidsuppföljningen.

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Appendix

Birmingham Vasculitis Activity Score (version 3)

Patient ID: **Date of birth:**

Total score:

Assessor: **Date of assessment**

Tick an item **only** if attributable to active vasculitis. If there are no abnormalities in a section, please tick 'None' for that organ-system.

If **all** abnormalities are due to persistent disease (active vasculitis which is not new/worse in the prior 4 weeks), tick the **PERSISTENT** box at the bottom right corner

Is this the patient's first assessment? **Yes** ○ **No** ○

	None	Active disease
1. General	○	
Myalgia		○
Arthralgia / arthritis		○
Fever ≥38° C		○
Weight loss ≥2 kg		○
2. Cutaneous	○	
Infarct		○
Purpura		○
Ulcer		○
Gangrene		○
Other skin vasculitis		○
3. Mucous membranes / eyes	○	
Mouth ulcers		○
Genital ulcers		○
Adnexal inflammation		○
Significant proptosis		○
Scleritis / Episcleritis		○
Conjunctivitis / Blepharitis / Keratitis		○
Blurred vision		○
Sudden visual loss		○
Uveitis		○
Retinal changes (vasculitis / thrombosis / exudate / haemorrhage)		○
4. ENT	○	
Bloody nasal discharge / crusts / ulcers / granulomata		○
Paranasal sinus involvement		○
Subglottic stenosis		○
Conductive hearing loss		○
Sensorineural hearing loss		○
5. Chest	○	
Wheeze		○
Nodules or cavities		○
Pleural effusion / pleurisy		○
Infiltrate		○
Endobronchial involvement		○
Massive haemoptysis / alveolar haemorrhage		○
Respiratory failure		○

	None	Active disease
6. Cardiovascular	○	
Loss of pulses		○
Valvular heart disease		○
Pericarditis		○
Ischaemic cardiac pain		○
Cardiomyopathy		○
Congestive cardiac failure		○
7. Abdominal	○	
Peritonitis		○
Bloody diarrhoea		○
Ischaemic abdominal pain		○
8. Renal	○	
Hypertension		○
Proteinuria >1+		○
Haematuria ≥10 RBCs/hpf		○
Serum creatinine 125-249 µmol/L*		○
Serum creatinine 250-499 µmol/L*		○
Serum creatinine ≥500 µmol/L*		○
Rise in serum creatinine >30% or fall in creatinine clearance >25%		○
***Can only be scored on the first assessment**		
9. Nervous system	○	
Headache		○
Meningitis		○
Organic confusion		○
Seizures (not hypertensive)		○
Cerebrovascular accident		○
Spinal cord lesion		○
Cranial nerve palsy		○
Sensory peripheral neuropathy		○
Mononeuritis multiplex		○
10. Other	○	
a.		○
b.		○
c.		○
d.		○
PERSISTENT DISEASE ONLY: (Tick here if **all** the abnormalities are due to persistent disease)		☐

References:

Version 1: Luqmani, RA, et al. (1994). "Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis." QJM **87**(11):671-8.

Version 2: Luqmani, RA, et al. (1997). "Disease assessment and management of the vasculitides." Baillieres Clin Rheumatol **11**(2): 423-46.

Version 3: Mukhtyar C, et al (2008). "Modification and validation of the Birmingham Vasculitis Activity Score (version 3) Ann Rheum Dis. 2008 Dec 3. [Epub ahead of print]

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Subject ID: ☐☐☐☐☐ Date form completed: ☐☐ / ☐☐ / ☐☐
Day Mon Year

Clinic ID: ☐☐☐☐☐ Investigator: ☐☐☐☐☐☐☐☐☐☐

FIVE-FACTOR SCORE (FFS)

1) Does the patient have a newly diagnosed vasculitis or is he/she experiencing a disease flare of previously diagnosed vasculitis?

O Yes → please go on to question 2

O No → please stop here *(FFS is not applicable)*

2) The FFS is based on the following 5 clinical items, with the presence of each being accorded 1 point for a maximum score of 5 (please tick the boxes)**:**

O Renal insufficency (serum creatinine >= 1.58 mg/dl [140 micro mol/1])
O Proteinuria >= 1g/day
O Central nervous system involvement
O Cardiomyopathy
O Severe gastrointestinal (GI) involvement (GI bleeding, infarction and/or pancreatitis

Total Score ☐☐

Important: *For patients experiencing a disease flare and not those with newly diagnosed vasculitis, the items should only be considered in the context of active renal disease. In particular, renal insufficiency >= 1.58 mg/l (140 µmol/l) and/or proteinuria >= 1 g/day present prior to the disease flare and considered to be a sequela of formerly active renal disease should not be scored.*

VASCULITIS DAMAGE INDEX (VDI)

This is for recording organ damage that has occurred in patients *since the onset of vasculitis*
Patients often have co-morbidity before they develop vasculitis, **which must not be scored**
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)
A new patient should ***usually have a VDI score of zero***, unless:
(a) they have had vasculitis for more than three months of onset of disease. **and**
(b) the damage has developed or become worse since the onset of vasculitis

1. Musculoskeletal	**No**	**Yes**
None	☐	
Significant muscle atrophy or weakness		○
Deforming/erosive arthritis		○
Osteoporosis/vertebral collapse		○
Avascular necrosis		○
Osteomyelitis		○
2. Skin/Mucous membranes		
None	☐	
Alopecia		○
Cutaneous ulcers		○
Mouth ulcers		○
3. Ocular		
None	☐	
Cataract		○
Retinal change		○
Optic atrophy		○
Visual impairment/diplopia		○
Blindness in one eye		○
Blindness in second eye		○
Orbital wall destruction		○
4. ENT		
None	☐	
Hearing loss		○
Nasal blockage/chronic discharge/crusting		○
Nasal bridge collapse/septal perforation		○
Chronic sinusitis/radiological damage		○
Subglottic stenosis (no surgery)		○
Subglottic stenosis (with surgey)		○
5. Pulmonary		
None	☐	
Pulmonary hypertention		○
Pulmonary fibrosis		○
Pulmonary infarction		○
Pleural fibrosis		○
Chronic asthma		○
Chronic breathlessness		○
Impaired lung function		○
6. Cardiovascular		
None	☐	
Angina angioplasty		○
Myocardial infarction		○
Subsequent myocardial infarction		○
Cardiomyopathy		○
Valvular disease		○
Pericaritis ≥ 3 mths or pericardectomy		○
Diastolic BP ≥ 95 or requiring antihypertensives		○

Name
Trial Number
Date
Centre

7. Peripheral vascular disease	**No**	**Yes**
None	☐	
Absent pulses in one limb		○
2nd episode of absent pulses in one limb		○
Major vessel stenosis		○
Claudication >3 mths		○
Minor tissue loss		○
Major tissue loss		○
Subsequent major tissue loss		○
Complicated venous thrombosis		○
8. Gastrointestinal		
None	☐	
Gut infarction/resection		○
Mesenteric insufficiency/pancreatitis		○
Chronic peritonitis		○
Oesophageal stricture/surgery		○
9. Renal		
None	☐	
Estimated/measured GFR ≤ 50%		○
Proteinuria ≥ 0.5g/24hr		○
End stage renal disease		○
10. Neuropsychiatric		
None	☐	
Cognitive impairment		○
Major psychosis		○
Seizures		○
Cerebrovascular accident		○
2nd cerebrovascular accident		○
Cranial nerve lesion		○
Peripheral neuropathy		○
Transverse myelitis		○
11. Other		
None	☐	
Gonadal failure		○
Marrow failure		○
Diabetes		○
Chemical cystitis		○
Malignancy		○
Other		○

Total VDI Score. Record the number of positive Items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage. ☐

VDI Modified from Exley AR, Bacon PA, Luqmani et al (1997) Development and initial validation of the VDI … Arthritis Rheum 40: 371-380

Questionnaire

Tick suitable boxes! **Please fill in VDI for the last available investigation!**

Patient ID number in the previous CRF (study- / site- / patient-number) [_ _][_ _ _ _][000 _ _ _]		Initials:
Clinical diagnosis	WG ○ MPA ○ RLV ○ CSS ○ Other… ○	Sex M ○ F ○
TRIAL	CHUSPAN ○ CYCAZAREM ○ CYCLOPS ○ MEPEX ○ NORAM ○ Entry date: *(dd/mm/yyyy)*……..	

1. Please write down the date on which you are completing this questionnaire (dd/mm/yyyy)			*Today's date:*
2. Is the patient alive as per today when filling in questionnaire?	Yes ○	No ○ *Date of death: (dd/mm/yyyy)* ……..	*Lost to follow-up* ○ *Date when last known to be alive (mm/yyyy)*
3. Date of the last available visit providing following information for question 4-9 (mm/yyyy)?			***Date:***
4. Had the patient developed end stage renal failure (start on dialysis, transplantation or terminal renal failure) at the last available visit?	Yes ○ Date of ESRF (mm/yyyy)……... Date of renal transplant (mm/yyyy).....	No ○	
5a. What was the serum creatinine at the last available visit? 5b. What was the serum creatinine at 5 years after inclusion in EUVAS-trial; mmm/yyyy?	……..µmol/L or ……mg/dL ……..µmol/L or ……mg/dL		
6. Has a **repeat renal biopsy** been performed?	Yes ○	No ○	

7. Any other severe organ failure (e.g. oxygen dependency, blindness) Please specify	Yes ○	No ○

8. Height of patient (cm)

9. Weight of patient (kg)	(mm/yyyy)? …….

10 a. Was the patient on immunosuppressive drugs at the last available visit?	Yes ○	No ○
10 b. Was the patient on corticosteroids at the last available visit?	Yes ○	No ○

11. Data on immunosuppressive therapy administered after end of EUVAS-trial:
Was the patient prescribed, any of the drugs below, during the time-periods respectively?
Please complete fill in all the cells in the table; indicate “Yes” or ,”NO” or “?”
Indicate “Yes”, even if the prescription was only during part of the time period Only if there is no information; sign with a “?”

Months **after start** of EUVAS-trial	13-18 (MEPEX only)	19-24	25-36	37-48	49-60
Corticosteroids	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○
Cyclophosphamide	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○
Azathioprine	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○
Methotrexate	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○
Mycophenolate mofetil	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○
Trimethoprim-sulphamethoxazole	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○
anti TNF - Please specify	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○
Other immunosuppr. Please specify	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○	Y ○ N ○ ? ○

12. Has the patient had any **relapse** after terminating the EUVAS-trial?	Yes ○ If YES, how many relapses? …… How many of those involved the kidneys?.....	No ○

13. Data of **first relapse after termination** in EUVAS-trial		
a. Date (mm/yyyy)	…….	
b. Organ involvement; tick all that apply	Kidney ○ Lungs ○ ENT ○ CNS ○ Skin ○ Eye ○ Other ○ specify	
c. Was the patient on immunosuppressive treatment at time of relapse	Yes ○ specify:……	No ○
d. Was the patient on corticosteroid treatment at time of relapse	Yes ○	No ○
e. Were the dosages of immunosuppressive treatment increased to deal with the relapse ?	Yes ○	No ○
f. Were the dosages of corticosteroid treatment increased to deal with the relapse ?	Yes ○	No ○
g. Was the immunosuppressive treatment changed to deal with the relapse?	Yes ○	No ○

14. Has the patient developed any malignancy, including basal cell carcinoma or myelodysplastic syndrome, after inclusion in the EUVAS-trial?	Yes ○		No ○ Missing data ○
	If YES Date of malignancy (yyyy):……	Type (histology) of malignancy ……..	Localization of malignancy ……
If several malignancies, please specify on last page			

Information on comorbidity factors. Please tick all suitable boxes for the problems occurring before inclusion in the EUVAS trial, at five year follow up, and currently, respectively									
Has/had the patient	Before start / inclusion in EUVAS trial			Up to five years follow-up after inclusion in EUVAS trial			Current follow-up after inclusion in EUVAS trial		
:	Yes	No	Not known	Yes	No	Not known	Yes	No	Not known
16. Diabetes mellitus (treated with diet, antidiabetics or insulin)?	○	○	○	○	○	○	○	○	○
17. Coronary heart disease (myocardial infarction, PTCA, coronary artery surgery)?	○	○	○	○	○	○	○	○	○
18. Stroke?	○	○	○	○	○	○	○	○	○
19. Deep venous thrombosis or embolism?	○	○	○	○	○	○	○	○	○
20. Any revascularization in the lower extremities?	○	○	○	○	○	○	○	○	○
21. Skeletal fracture?	○	○	○	○	○	○	○	○	○
22. Infectious disease requiring hospital stay or parenteral antibiotics?				○	○	○	○	○	○

23. Smoking history	Current ○	Previous ○	Never ○	Not known ○

24. Details of death	What was the cause of death (as indicated on the death certificate)?
	Which other conditions contributed to the death (in your opinion and/or on the death certificate)?
	In your opinion----------
	On the death certificate----------

We are very interested in your opinion on the relationship of the death to the vasculitis and/ or its treatment. Please circle all that apply:

	0 not related	1 unlikely	2 possible	3 probable	4 highly probable	5 definite
Was the death related to active vasculitis?	○	○	○	○	○	○
Was the death related to current immunosupression?	○	○	○	○	○	○
Was the death related to sepsis?	○	○	○	○	○	○

25. Other malignancies	Date of 2nd malignancy (yyyy):……	Type (histology) of 2nd malignancy	Localization of 2nd malignancy
	Date of 3rd malignancy (yyyy):……	Type (histology) of 3rd malignancy	Localization of 3rd malignancy

Other Remarks

PLEASE, COMPLETE THE VDI FORM FOR the time point closest to five year after inclusion!

THANK YOU VERY MUCH FOR YOUR CONTRIBUTION!

Please return the form to the address below. If you have any queries, please don't hesitate to get in touch
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This thesis is based on long-term follow-up results from two cohorts of patients with ANCA-associated vasculitis; one cohort with 535 patients originally included in four European randomized clinical trials (papers I and II) and one Swedish population-based cohort including 195 patients (papers III and IV). Two areas are covered in the two cohorts, respectively; the assessment of mortality, prognostic factors and causes of death (paper I and III) and the assessment of malignancy risk compared with a matched general population (papers II and IV).

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