FACULTY OF HEALTH AND MEDICAL SCIENCES
UNIVERSITY OF COPENHAGEN

Doctoral dissertation

Mikkel Faurschou

Comorbidities in patients treated for granulomatosis with polyangiitis

Submitted: December 1, 2018

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Copenhagen 2018

The Faculty of Health and Medical Sciences at the University of Copenhagen has accepted this dissertation, which consists of the already published dissertations listed below, for public defence for the doctoral degree in Medicine.

Copenhagen, 18 December 2019.

Ulla Wewer, Head of Faculty.

The defence will take place on Friday 21 August 2020 at 2:00 p.m. via Zoom (virtual defence).

ISBN 978-87-971966-0-1

PUBLICATIONS

This thesis is based on the following papers referred to in the text by Roman numerals:

I. Faurschou M, Sørensen IJ, Mellemkjær L, Loft AG, Thomsen BS, Tvede N, Baslund B. Malignancies in Wegener's granulomatosis: Incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. Journal of Rheumatology, 35(1): 100-105, 2008.

II. Faurschou M, Mellemkjær L, Voss A, Keller KK, Hansen IT, Baslund B. Prolonged risk of specific malignancies following cyclophosphamide therapy among patients with granulomatosis with polyangiitis. Rheumatology, 54(8): 1345-1350, 2015.

III. Faurschou M, Mellemkjær L, Sørensen IJ, Thomsen BS, Dreyer L, Baslund B. Cancer preceding Wegener's granulomatosis: A case-control study. Rheumatology, 48(4): 421-424, 2009.

IV. Faurschou M, Mellemkjær L, Sørensen IJ, Thomsen BS, Dreyer L, Baslund B. Increased morbidity from ischemic heart disease in patients with Wegener's granulomatosis. Arthritis and Rheumatism, 60(4): 1187-1192, 2009.

V. Faurschou M, Obel N, Baslund B. High risk of pulmonary embolism and deep venous thrombosis but not of stroke in granulomatosis with polyangiitis (Wegener's). Arthritis Care and Research, 66(12): 1910-1914, 2014.

VI. Faurschou M, Baslund B, Obel N. Pronounced risk of fractures among elderly men affected by granulomatosis with polyangiitis. Journal of Rheumatology, 42(9): 1667-1671, 2015.

VII. Faurschou M, Ahlström M, Lindhardsen J, Obel N, Baslund B. Risk of diabetes mellitus among patients diagnosed with giant cell arteritis or granulomatosis with polyangiitis: comparison with the general population. Journal of Rheumatology, 44(1):78-83, 2017.

VIII. Faurschou M, Obel N, Baslund B. Long-term risk and outcome of infection-related hospitalization in granulomatosis with polyangiitis: a nationwide population-based cohort study. Scandinavian Journal of Rheumatology, epub ahead of print, 2018.

CONTENTS

1. PREFACE

The present thesis is based on scientific studies conducted at the Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Denmark during 2006-2018.

I wish to thank each of my co-authors for enthusiastic collaboration on the various papers that constitute the foundation of the thesis. I am very grateful to Lene Mellemkjær and her colleagues at the Danish Cancer Society Research Center for providing expert statistical assistance on several of the papers and to Magnus Ahlström for fruitful methodological discussions.

I want to thank Niels Obel for excellent scientific guidance and for many cheerful moments along the way. Finally, I thank Bo Baslund for introducing me to the world of vasculitis research, for inspiring academic mentoring, and for great friendship throughout the years.

Mikkel Faurschou, December 2018.

2. ABBREVIATIONS

AAV:	ANCA-associated vasculitis
ANCA:	Anti-neutrophil cytoplasmic antibody
CCI:	Charlson Comorbidity Index
CI:	Confidence interval
CRS:	Danish Civil Registration System
DM:	Diabetes mellitus
DVT:	Deep venous thrombosis
EGPA:	Eosinophilic granulomatosis with polyangiitis
GCA:	Giant cell arteritis
GPA:	Granulomatosis with polyangiitis
HR:	Hazard ratio
ICD:	International classification of diseases
IH:	Infection-related hospitalization
IHD:	Ischemic heart disease
IRR:	Incidence rate ratio
MI:	Myocardial infarction
MPA:	Microscopic polyangiitis
NHR:	Danish National Hospital Register
NIH:	US National Institutes of Health
NMSC:	Non-melanoma skin cancer
O:E ratio:	Standardized ratio of observed to expected events
OR:	Odds ratio
PE:	Pulmonary embolism
RR:	Rate ratio
SIR:	Standardized incidence ratio
VTE:	Venous thromboembolic event

3. INTRODUCTION

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a severe inflammatory disease of unknown etiology. At the histological level, the disease is characterized by necrotizing granulomatous inflammation and by necrotizing small-vessel vasculitis (1). Classical clinical features of GPA encompass inflammation in the airways and pauciimmune glomerulonephritis, but the inflammatory disease processes of GPA can involve and irreversibly damage any organ system of the body (2). Circulating anti-neutrophil cytoplasmic antibodies (ANCA) can be detected in the majority of patients (3-8), with antibodies directed against the neutrophil granule protein proteinase-3 being more common than antibodies with specificity towards the granule protein myeloperoxidase (9). The pathogenic significance of these auto-antibodies in GPA remains incompletely understood (10). ANCA are also present in many patients with microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), and GPA, MPA, and EGPA are collectively referred to as ANCA-associated vasculitides (1).

Before the development of cyclophosphamide-based treatment regimens, patients with GPA typically died within a few months of the vasculitis-diagnosis (11). In the 1970s, therapy with cyclophosphamide was shown to improve the prognosis of GPA patients dramatically. Landmark studies conducted at the US National Institutes of Health (NIH) demonstrated high remission rates in response to prolonged treatment with daily oral cyclophosphamide in combination with high cumulative doses of corticosteroids (12;13). The effectiveness of the NIH treatment regimen for remission induction in GPA was subsequently confirmed in a pivotal long-term follow-up study of 158 patients treated at the institution (2). Importantly, this study also shed light on shortcomings of the regimen with respect to relapse prevention and on safety problems related to the provided immunosuppressants. In the cohort, 75% of the patients obtained remission in response to treatment as per the NIH protocol, but remissions were followed by relapsing disease activity in 50% of cases, and severe forms of organ-damage induced by vasculitis activity were observed in 86% of the study-subjects. Moreover, comorbidities potentially related to carcinogenic effects of cyclophosphamide were observed in a high proportion of patients (hemorrhagic cystitis: 43%, bladder cancer: 2.8%, myelodysplasia: 2%), many patients developed comorbidities with a well-known association to corticosteroid-therapy (diabetes mellitus (DM): 8%, cataracts: 21%, fractures: 11%, aseptic necrosis: 3%), and 46% were hospitalized for severe infection during their disease course.

The high incidence of therapy-related comorbidities among GPA patients treated according to the NIH protocol sparked efforts to develop safer treatment regimens for GPA with a focus on cyclophosphamide-sparing strategies (14). Over the last decades, several cyclophosphamide-sparing regimens have been proven effective for remission induction in GPA (15-18), and treatment strategies involving the use of much lower cumulative cyclophosphamide-doses than dictated by the original NIH protocol are now widely

implemented in daily clinical practice. However, despite the implementation of novel treatment regimens, substantial challenges persist in the clinical management of patients with GPA. Thus, overall mortality rates remain 2-3 times higher among GPA patients than in the general population (9;19-21), and rates of vasculitis-induced organ damage continue to be high (22). With regard to comorbidities with a treatment-related or presumed multifactorial pathogenesis, large-scale cohort studies comparing the risk in GPA patients with that in the background population were limited in number prior to the publication of the first wave of papers included in the present thesis. The pattern of comorbidities associated with GPA and current therapies for the disease was therefore incompletely characterized.

During recent years, we and other groups have conducted a range of population-based cohort studies, which have provided information on the incidence of a broad spectrum of comorbidities among patients with GPA. These studies have contributed to a better understanding of the comorbidity risk of GPA patients during short- and long-term follow-up and have led to the identification of risk factors for comorbidities as outlined in the following sections.

4. AIM OF PAPERS INCLUDED IN THE THESIS

The aim of the papers included in the present thesis was to assess the risk of various comorbidities among patients with GPA. Based on the available literature concerning GPA and its treatment, we hypothesized that the risk of certain malignancies, certain cardiovascular diseases, DM, fractures, and infections is increased among GPA patients compared with the risk in the general population. This hypothesis was tested in eight cohort studies (paper I-VIII). The results of the studies are summarized in the thesis and discussed in the context of previous and subsequent publications on comorbidities and factors predisposing to comorbidity development in GPA.

5. DATA SOURCES, COHORTS, AND METHODS

5.1. Data sources

In Denmark, administrative registers with nationwide coverage have been in use for decades. The country thus constitutes an ideal society for epidemiological studies. In paper I-VIII, data were obtained from several Danish registers and used for construction and tracking of cohorts, collection of information concerning medication exposures, and identification of diagnoses. A description of the relevant registers is provided below.

5.1.1. The Danish Civil Registration System

The Danish Civil Registration System (CRS) was established in 1968. At this time point, information regarding all persons living in Denmark was reported to the system. Since then, every person born in Denmark or taking residence in the country has been registered. A registered individual is provided with a unique 10-digit personal identification number, which is assigned to the person on a permanent basis. From a scientific viewpoint, the personal identification number allows for linkage of individual-level data across the spectrum of Danish administrative registers. The CRS stores a variety of information concerning each resident of Denmark, including name, gender, date of birth, and constantly updated information on vital status (23).

5.1.2. The Danish National Hospital Register

The Danish National Hospital Register (NHR) has collected information on contacts to non-psychiatric hospital departments in Denmark since 1977. From 1995 onwards, data on visits to emergency rooms and outpatient clinics has also been collected. The coverage is estimated to be almost complete. A record in the NHR contains data concerning a specific hospital contact, encompassing the personal identification number of the patient, hospital- and department-codes, date of admission and date of discharge/start date and end date of outpatient treatment, and a primary diagnosis. If relevant for the contact, supplementary diagnoses are also listed. The diagnoses were coded according to a Danish version of the 8th Revision of the International Classification of Diseases (ICD-8) during 1977-1993 and have been coded according to the ICD-10 since 1994. Primary and supplementary diagnoses are selected by a physician at time of discharge/end of outpatient treatment (24;25).

5.1.3. The Danish Cancer Registry

The Danish Cancer Registry keeps information regarding incident cancers diagnosed in Denmark since 1943. The registry is provided with diagnostic information from multiple sources, and the coverage of cancers diagnosed in the Danish population is estimated to be close to 100%. A record in the registry is marked by the personal identification number of the patient and comprises information regarding the patient and the malignancy, including date of diagnosis and type of cancer (26;27).

5.1.4. The Danish National Prescription Registry

The Danish National Prescription Registry contains information regarding prescriptions claimed at Danish community pharmacies since 1995. The person for whom a given drug was prescribed can be identified in the registry on the basis of the personal identification number. Due to the existence of a national

reimbursement system for prescribed drugs, claimed prescriptions are systematically registered at Danish community pharmacies. Consequently, the Danish National Prescription Registry is assumed to provide more or less complete coverage of prescriptions claimed in the country (28).

5.1.5. The Danish National Pathology Registry

The Danish National Pathology Registry keeps records on all pathology specimens analyzed in Denmark since 1997. A record in the registry contains a multitude of data, including the personal identification number of the patient, a code for the requesting department/practicing physician, date of biopsy, information on specimen type, and histological diagnoses coded according to a Danish version of the Systematized Nomenclature of Medicine (29).

5.2. Vasculitis cohorts

We used various methodological approaches to construct the vasculitis cohorts described in paper I-VIII (Table 1). In all cohort constructions, measures were taken to reduce the risk of unintended inclusion of diagnostically misclassified patients.

Paper I-IV were based on the same nationwide cohort of GPA patients. To construct the cohort, we used the NHR to identify all patients discharged from Danish hospitals with a diagnosis of GPA during 1977-1999. From this group, we selected patients for whom 1) relevant medical files/sufficient clinical information could be retrieved, and 2) the GPA diagnosis was considered plausible after medical files review.

In paper V, a tertiary care centre cohort of patients diagnosed with GPA during 1993-2011 was constructed using 1) local hospital discharge lists to identify patients, 2) medical files review to confirm the GPA diagnoses, and 3) data from the NHR to exclude non-incident cases.

The same method for cohort construction was used to establish the monocentric GPA cohort described in paper VI, and patients included in the monocentric GPA cohort of paper VI were also included in the GPA cohort of paper V. The register-based GPA cohort of paper VI comprised patients who 1) were not a part of the monocentric cohort of the study, 2) were diagnosed with GPA in Denmark during 1995-2010, and 3) had at least one GPA-related hospital contact to a department of rheumatology between 1995 and 2010.

The nationwide GPA cohorts of papers VII and VIII were widely overlapping with respect to study-subjects. The cohorts were constructed using a previously developed search strategy for GPA patients in the NHR associated with a positive predictive value of 0.91 for the identified cases (30). Patients were considered eligible in case of 1) two or more GPA-related hospital contacts to Danish departments of rheumatology, and 2) no more than 18 months between first-ever hospital-contact for GPA and the second GPA-related contact to a rheumatology unit.

In paper VII, we also identified a nationwide cohort of patients with biopsy-proven giant cell arteritis (GCA) on the basis of hospital discharge diagnoses from the NHR and biopsy-data from the Danish National Pathology Registry.

Table 1. Vasculitis cohorts of paper I-VIII.

	Paper	Calendar-period of diagnosis	No.	Included patients	Validation of vasculitis diagnoses
GPA cohort 1	I-IV	1973-1999	293	Patients with a GPA diagnosis in the NHR and retrievable medical files	Medical files review
GPA cohort 2	V	1993-2011	180	Patients treated at tertiary care centre[1]	Medical files review
GPA cohort 3	VI	1995-2010	159	Patients treated at tertiary care centre[1]	Medical files review
GPA cohort 4	VI	1995-2010	402	Patients registered in the NHR with a first-time diagnosis of GPA and one or more GPA-related visits to a department of rheumatology (excluding patients of cohort 3) [1]	None
GPA cohort 5	VII	1997-2015	342	Patients registered in the NHR with a first-time diagnosis of GPA and two or more GPA-related visits to a department of rheumatology[1]	Validated search strategy (30)
GPA cohort 6	VIII	1995-2014	398	Patients registered in the NHR with a first-time diagnosis of GPA and two or more GPA-related visits to a department of rheumatology[1]	Validated search strategy (30)
GCA cohort	VII	1997-2015	1682	Patients with a first-time diagnosis of GCA in the NHR and a temporal artery biopsy, registered in the DNPR, showing giant cell inflammation[1]	Clinical diagnosis supported by characteristic biopsy findings in all cases

No: Number of patients. GPA: Granulomatosis with polyangiitis. NHR: National Hospital Register. GCA: Giant cell arteritis. DNPR: Danish National Pathology Registry. 1: See the paper for details regarding construction of the cohort/additional inclusion criteria.

5.3. Outcomes

Throughout study I-VIII, information regarding outcomes was collected from registers with nationwide coverage. In study I-III, malignancies were identified by linkage with the high-quality files of the Danish Cancer Registry (26). For study IV, V, VI, and VIII we collected information regarding comorbidity diagnoses from the NHR. In this register, high or moderately high validity had previously been demonstrated for each of the investigated diagnoses, including manifestations of ischemic heart disease (IHD), deep venous thrombosis (DVT), pulmonary embolism (PE), stroke, fracture, any infection, pneumonia, urinary tract infection, sepsis, and skin infection (31-40).

For the purposes of study VII, we considered patients with claimed prescription for anti-diabetic drugs as having DM. Data on claimed prescriptions for anti-diabetic drugs were collected from the Danish National

Prescription Registry, which is a trustworthy source of information regarding prescribed medications as outlined in section 5.1.4 (28).

Data on deaths, disappearances, and migrations was obtained from the CRS. The completeness of data kept in the CRS (23) allowed us to perform long-term follow-up of our study-subjects with precise tracking of their vital status and to calculate the mortality rate ratios presented in paper V and the mortality rates described in paper VIII.

5.4. Statistical analyses

Standardized incidence ratios (SIRs) for various cancers were calculated as the observed number of cancers divided with the expected number (paper I and II). In these analyses, the expected number of cancers was determined by multiplication of person-years under observation for the GPA patients by cancer incidence-rates in the general population of Denmark for men and women separately in 5-year age groups and 5-year calendar-periods. For IHD-related hospitalizations, standardized ratios of observed to expected (O:E) events were determined by means of a comparable methodology (paper IV). We used conditional logistic regression for matched sets to calculate prevalence odds ratios (ORs) for malignancies preceding GPA (paper III), while Cox proportional hazard models were used to calculate relative risk estimates for clinical events occurring after the diagnosis of GPA (papers V-VIII). Kaplan-Meier tables were computed to determine cumulative proportion with events at various time points (paper VIII) and to construct plots to illustrate time to first event (papers V and VI). In paper VII, the association between cumulative corticosteroid-dose and DM was studied using logistic regression analysis adjusted for age and gender. We used the chi-squared test or Fishers exact test to compare proportions (paper VII-VIII) and the Wilcoxon two-sample test to compare patient-groups with respect to cumulative cyclophosphamide-doses (paper I).

6. MALIGNANCIES IN GPA

6.1. Malignancies among patients treated for GPA.

The incidence of cancer among patients treated for ANCA-associated vasculitis (AAV) has been analyzed in a range of cohort studies encompassing patients diagnosed with vasculitis during different calendar-periods. In their important study from 1992, Hoffman et al reported a 2.4-times increased incidence of cancer at all sites among 158 GPA patients compared with the incidence in the general US population (2). Moreover, the incidence of bladder cancer was found to be 33 times increased, while the incidence of lymphoma was 11 times greater than expected. A decade later, Knight and co-workers published a register-based analysis of the incidence of malignancies among 1065 Swedish patients diagnosed with GPA during 1969-1994 (41). In this investigation, the incidence of any cancer among the GPA patients was found to be

twice as high as the incidence in the background population of Sweden. Significantly increased SIRs were calculated for bladder carcinoma (SIR: 4.8 (95% confidence interval (CI): 2.6-8.1)), leukemia (SIR: 5.7 (95% CI: 2.3-12)), non-melanoma skin cancer (NMSC; SIR: 7.3 (95% CI: 4.4-12)), lymphoma (SIR: 4.2 (95% CI: 1.8-8.3)), primary liver cancer (SIR: 3.8 (95% CI: 1.2-8.8)), and cancer of the brain (SIR: 3.9 (95% CI: 1.3-9.2)).
In a cohort of 293 Danish patients diagnosed with GPA during 1973-1999, we observed SIRs for cancer at all sites, bladder cancer, leukemia, and NMSC, which closely resembled those reported from Sweden (SIR for any cancer: 2.1 (95% CI: 1.5-2.7), SIR for bladder cancer: 3.6 (95% CI: 1.2-8.3), SIR for leukemia: 5.9 (95% CI: 1.2-17), SIR for NMSC: 4.7 (95% CI: 2.8-7.3)) (paper I). The occurrence of other cancer types was not increased in the cohort.

Table 2. Risk of cancer among patients diagnosed with GPA or other types of ANCA-associated vasculitis compared with the general population: Observations made in cohort studies.

Study	Calendar-period of diagnosis	Type	No./ PY	Any cancer SIR	Bladder SIR	Leukemia SIR	NMSC SIR	Other cancers
Hoffman (2)	1967-1990[1]	GPA	158/ 1229	2.4 (ND)	33 (ND)	ND	ND	Risk increased[2]
Westman (42)	1971-1993	GPA, MPA	123/ 944	1.6 (0.9-2.7)	4.8 (1-13.9)	None observed	10.4 (3.4-24.3)	Risk increased[3]
Knight (41)	1969-1994	GPA	1065/ 5708	2.0 (1.7-2.5)	4.8 (2.6-8.1)	5.7 (2.3-12)	7.3 (4.4-12)	Risk increased[4]
Faurschou (paper I)[5]	1973-1999	GPA	293/ 2121	2.1 (1.5-2.7)	3.6 (1.2-8.3)	5.9 (1.2-17)	4.7 (2.8-7.3)	Risk not increased
Holle (43)	1966-2002	GPA	445/ ND	0.82 (0.45-1.38)	ND	ND	ND	ND
Heijl (44)	1995-2002	GPA, MPA	535/ 2650	1.58 (1.17-2.08)	2.41 (0.66-6.17)	3.25 (0.39-11.65)	2.78 (1.56-4.59)	Risk not increased
Zycinska (45)	1990-2008	GPA	117/ ND	2.5 (1.2-2.9)	3.4 (1.6-5.2)	4.3 (2.1-11.2)[6]	5.2 (2.3-8.7)	Risk not increased
Rahmat-tulla (46)	1991-2013	GPA, MPA	138/ 1339	2.21 (1.64-2.92)	1.43 (0.04-7.96)	None observed	4.23 (2.76-6.19)	Risk not increased
van Daalen (47)	2000-2014	GPA, MPA, EGPA	323/ 1802	1.89 (1.38-2.53)	1.53 (0.04-8.57)	None Observed	4.58 (2.96-6.76)	Risk not increased

GPA: Granulomatosis with polyangiitis. ANCA: Anti-neutrophil cytoplasmic antibody. No.: Number of patients. PY: Person-years of observation. NMSC: Non-melanoma skin cancer. SIR: Standardized incidence ratio with 95% confidence interval. ND: No data provided. MPA: Microscopic polyangiitis. EGPA: Eosinophilic granulomatosis with polyangiitis. 1: Calendar-period estimated on the basis of data provided by Hoffman and Talar-Williams (2;48). 2: Lymphoma (SIR: 11 (ND)). 3: Testis (SIR: 45.7 (1.2-254.7)). 4: Primary liver (SIR: 3.8 (1.2-8.8)); brain (SIR: 3.9 (1.3-9.2)); lymphoma (SIR: 4.2 (1.8-8.3)). 5: Cancer risk during extended follow-up of this cohort is described in section 6.3 of this thesis and in paper II. 6: Acute myeloid leukemia.

The above-mentioned SIRs are summarized in Table 2, which also presents SIRs for malignancies calculated in other studies of patients with AAV. As shown, most authors have demonstrated a 1.5-2.5 times increased SIR for cancer at all sites (2;41;42;44-47) (paper I), and a substantially increased risk of NMSC was reported

in the majority of studies (41;42;44-47) (paper I). For bladder cancer and hematologic malignancies, increased SIRs were observed in some studies (2;41;42;45) (paper I), but not in three studies of patients diagnosed with AAV during recent calendar-periods (44;46;47).

6.2. Impact of cumulative cyclophosphamide-dose on malignancy risk in GPA

Exposure to cyclophosphamide was identified as a risk factor for the development of bladder cancer and myeloid malignancies in the 1970s (49-51). Subsequent cohort studies demonstrated a positive association between the cumulative cyclophosphamide-dose administered and the risk of these cancer types among patients treated for hematologic neoplasms (52-54). The ability of cyclophosphamide to induce myeloid malignancies is assumed to be a direct consequence of the alkylating properties of the drug, whereas the bladder toxicity of cyclophosphamide is believed to be mediated by its non-alkylating metabolite acrolein, which is excreted via the urinary tract (55;56).

In a retrospective analysis of GPA patients followed at the NIH between 1967 and 1993, neither the duration nor the cumulative dose of cyclophosphamide emerged as a predictor of bladder cancer in risk factor analyses (48). In contrast, a dose-response relationship between cumulative cyclophosphamide dose and risk of bladder cancer was found in a case-control study comprising a total of 36 GPA patients (57), and Westman et al observed excess occurrence of bladder cancer as well as increased incidence-rates for NMSC, testis cancer, and vulva cancer after prolonged cyclophosphamide-therapy in a cohort of 123 AAV patients (42).

In our first cohort study on cancer in GPA, we conducted a comprehensive analysis of the risk of various malignancies associated with different cumulative cyclophosphamide-doses among Danish GPA patients (paper I). As described above, incidence-rates for cancer at all sites, bladder cancer, leukemia, and NMSC, were significantly increased in the total cohort of 293 patients compared with those in the general population of Denmark. However, analyses stratified according to cumulative cyclophosphamide-dose revealed substantial differences in risk of malignancies across sub-groups of patients. In these analyses, we allocated patients treated with cumulative cyclophosphamide-doses of 1-36 gram, corresponding to therapy with 100 mg cyclophosphamide daily for up to 1 year, to a “low-dose cyclophosphamide” group and patients treated with higher cumulative cyclophosphamide-doses to a “high-dose cyclophosphamide” group. The SIR for cancer at all sites was 1.8 (95% CI: 1.1-2.9) in the “low-dose cyclophosphamide” group, but the only specific malignancy that occurred in excess in this group was NMSC (SIR: 3.9 (95% CI: 1.4-8.4)). Among patients in the “high-dose cyclophosphamide” group, increased SIRs were observed for cancer at all sites (SIR: 2.4 (95% CI: 1.4-3.7)), bladder cancer (SIR: 9.5 (95% CI: 2.6-24)), NMSC (SIR: 5.2 (95% CI: 2.1-11)), and acute myeloid leukemia (SIR: 59.0 (95% CI: 12-172)). The SIR for cancer at all sites was 0.9 (95% CI: 0.2-

2.5) among cyclophosphamide-naïve patients, who did not experience an increased number of any specific type of cancer.

In 2011, Le Guenno et al identified the cumulative cyclophosphamide-dose as a predictor of urinary tract cancer and/or hemorrhagic cystitis in a cohort of 467 patients with systemic necrotizing vasculitides (hazard ratio (HR) per 10 gram increase: 1.09 (95% CI: 1.01-1.17)), thus providing further evidence that the malignancy risk after cyclophosphamide-therapy for systemic vasculitis increases with the total dose administered over time (58).

6.3. Risk of early- and late-occurring malignancies in GPA

Prior to our analyses, studies of patients treated for hematologic diseases had demonstrated a substantial latency-period between exposure to cyclophosphamide and the occurrence of cyclophosphamide-induced cases of bladder cancer and myeloid leukemia (52;53). Among GPA patients, Knight at al had reported SIRs of 3.9 (95% CI: 1.7-7.6) and 11 (95% CI: 3.0-28) for bladder cancer diagnosed 1-9 years and ≥10 years after GPA, respectively, as well as a significantly increased incidence-rate for leukemia diagnosed 1-9 years after GPA (SIR: 4.6 (95% CI: 1.3-12)) (41).

In line with these observations, we observed a SIR of 4.6 (95% CI: 0.5-17) for bladder cancer diagnosed 5-9 years after GPA and a SIR of 12.9 (95% CI: 2.7-38) for bladder cancer diagnosed with a latency of ≥10 years (paper I). Furthermore, we calculated SIRs of 42.5 (95% CI: 5.1-153) and 32.8 (95% CI: 0.8-183) for acute myeloid leukemia diagnosed during year 5-9 years and ≥10 years after GPA, respectively. With regard to NMSC, Knight and co-workers reported a significantly increased occurrence during the first ten years of observation (41), while increased SIRs were detected in our cohort from the second year of follow-up onwards (paper I).

The incidence-rates for malignant diseases computed in paper I were based on a median follow-up period of 6.0 years among the patients under study. Since GPA patients frequently survive for much longer periods of time after conventional therapies (9), we found it relevant to conduct more detailed analyses of the cancer risk during very late follow-up periods in this patient-group with a focus on the long-term risk of cancer associated with different cumulative doses of cyclophosphamide. In paper II, we followed the above-mentioned cohort of Danish GPA patients throughout 2010, expanding the median follow-up time from 6.0 to 9.7 years and the total number of person-years of follow-up from 2121 to 2928. The analyses of the study demonstrated an increased risk of cancer at all sites among patients of the “high-dose cyclophosphamide” group (SIR: 2.3 (95% CI: 1.5-3.3)), whereas no significant increase in overall cancer risk was observed for patients of the “low-dose cyclophosphamide” group (SIR: 1.4 (95% CI: 0.8-2.1)) or for cyclophosphamide-naïve patients (SIR: 1.5 (95% CI: 0.6-3.0)). Importantly, a high risk of very late-occurring

bladder cancer was found in the cohort with SIRs of 5.3 (95% CI: 1.1-15), 14.4 (95% CI: 5.3-31), and 10.5 (95% CI: 1.2-38) obtained for cases diagnosed 5-9 years, 10-14 years, and 15-19 years after GPA, respectively. As in paper I, the increased risk of bladder cancer was confined to patients of the "high-dose cyclophosphamide" group. Among these patients, the SIR for bladder cancer was 2.8 (95% CI: 0.04-16) during year 0-9 and 29.0 (95% CI: 10-63) after ≥10 years of observation. Four cases of myeloid leukemia were diagnosed in the cohort. Three of these malignancies developed among patients of exposed to high cumulative cyclophosphamide-doses, yielding a SIR of 34.3 (95% CI: 3.9-124) for myeloid leukemia diagnosed 0-9 years after GPA and a SIR of 26.4 (95% CI: 0.3-147) for myeloid leukemia diagnosed during later follow-up periods in the "high-dose cyclophosphamide" group. Paper II also demonstrated substantially increased incidence-rates for NMSC during most follow-up periods, including a SIR of 7.0 (95% CI: 2.3-16) for NMSC diagnosed ≥20 years after GPA. The risk of NMSC was significantly increased in both groups of cyclophosphamide-treated patients, while the SIR for NMSC was 3.4 (95% CI: 0.7-10) among cyclophosphamide-naïve patients.

6.4. Malignancies preceding GPA

In 1999, an increased prevalence of malignancies preceding GPA was reported in a study of 477 GPA patients compared with 479 rheumatoid arthritis patients, with an OR of 8.73 (95% CI: 1.04-73.69) calculated for renal cell carcinoma preceding GPA and an OR of 18.00 (95% CI: 2.30-140.67) calculated for any malignant disease diagnosed within three months of GPA (59). In subsequent studies, Knight et al noticed that a history of bladder cancer was non-significantly 2.1 times as common as expected at time of vasculitis diagnosis among 1065 Swedish GPA patients (57), and Pankhurst et al reported a six-fold increased rate of preceding cancer among 200 British patients with AAV compared with the rate in the general population (60). On the basis of these findings, it was hypothesised that GPA may sometimes be triggered by an underlying malignancy (59). Moreover, it was proposed that malignancy should be considered a potential differential diagnosis in patients presenting with AAV (60) and that patients with new-onset GPA should be routinely screened for concomitant malignant disease (59;61).

To further examine the association between GPA and preceding cancer, we designed a case-control study comprising the same cohort of GPA patients as in paper I and II as well as a comparison cohort of 2930 age- and gender-matched population-controls (paper III). In the study, we did not observe an association between preceding cancer and GPA (OR for any cancer diagnosed before GPA: 1.4 (95% CI: 0.9-2.2)), and we did not observe an increased prevalence of cancer diagnosed <2 years (OR for any cancer: 1.6 (95% CI: 0.8-3.4)) or ≥2 years (OR for any cancer: 1.3 (95% CI: 0.8-2.2)) before GPA. Furthermore, we did not detect a statistically significant association between GPA and preceding renal cell carcinoma (OR: 5.2 (95% CI: 0.8-

32)) or an association between GPA and preceding bladder cancer (OR: 0.5 (95% CI: 0.1-3.7)). Among other types of cancer, we observed an increased OR for testis cancer diagnosed ≥2 years before GPA (OR: 9.5 (95% CI: 1.3-67)) based on 2 cases diagnosed >10 years before GPA. We also observed an increased OR for NMSC diagnosed <2 years prior to GPA (OR: 4.0 (95% CI: 1.4-12)) based on 5 cases of NMSC in the GPA cohort.

In a recent study from the Netherlands, the risk of preceding malignancies was analyzed in a cohort of 203 patients with AAV (62). Compared with the risk in the general population, the study did not reveal an increased risk of any preceding type of cancer among the vasculitis patients.

Table 3 presents important observations made in studies of the potential association between AAV and preceding cancer. As shown, three out of four studies did not demonstrate an increased overall occurrence of preceding malignancy among patients with AAV. Tatsis and co-workers calculated a high OR for cancer diagnosed within 3 months of GPA (59), whereas the occurrence of cancer diagnosed <2 years before AAV was not significantly increased in other cohorts (paper III) (62). The strong association between preceding renal cell carcinoma and GPA reported by Tatsis et al (59) was not observed in later analyses (paper III) (60;62), and statistically significant associations between other specific malignancies and GPA were only found in paper III of the present thesis suggesting the possibility of chance findings.

Table 3. Results obtained in studies of the potential association between ANCA-associated vasculitides and preceding cancer.

Study	Type	No.	Control-population	Any cancer diagnosed before AAV	Any cancer diagnosed <2 years before AAV	Any cancer diagnosed ≥2 years before AAV	Renal cell carcinoma diagnosed before AAV	Other cancers diagnosed before AAV
Tatsis (59)	GPA	477	479 RA patients	OR: 1.79 (0.92-3.48)[1]	ND	ND	OR: 8.73 (1.04-73.69)	No associations found
Pankhurst (60)	GPA, MPA	200	General population	RR: 6.02 (3.72-9.74)	ND	ND	No association found	ND
Faurschou (paper III)	GPA	293	2930 matched population-controls	OR: 1.4 (0.9-2.2)	OR: 1.6 (0.8-3.4)	OR: 1.3 (0.8-2.2)	OR: 5.2 (0.8-32)[2]	Associations found[3]
van Daalen (62)	GPA, MPA	203	General population	SIR: 0.96 (0.55-1.57)	SIR: 1.56 (0.57-3.40)	SIR: 0.78 (0.38-1.44)	SIR: 2.36 (0.06-13.13)	No associations found

ANCA: Anti-neutrophil cytoplasmic antibody. No.: Number of patients. AAV: ANCA-associated vasculitis. GPA: Granulomatosis with polyangiitis. RA: Rheumatoid arthritis. OR: Odds ratio with 95% confidence interval (CI). ND: No data provided. MPA: Microscopic polyangiitis. RR: Relative risk with 95% CI. SIR: Standardized incidence ratio with 95% CI. 1: OR for simultaneous occurrence of GPA and cancer: 18.0 (2.30-140.67). 2: No cases observed <3.2 years before date of vasculitis diagnosis among the GPA patients (paper III) or during the first year after this date (paper I). 3: OR for NMSC diagnosed <2 years before AAV: 4.0 (1.4-12); OR for testis cancer diagnosed ≥ 2 years before AAV: 9.5 (1.3-67).

In conclusion, the existing literature does not provide convincing evidence that a clinically relevant pathogenic link exists between AAV and cancer. The hypothesis that serious malignancy can sometimes trigger the development of GPA (59) is not substantiated by the results of paper III or by the findings of van Daalen et al (62), and the recommendation that patients with newly diagnosed GPA should be routinely screened for cancer (59;61) is not supported by these investigations.

6.5. Malignancies in GPA: Current status

The results obtained in paper I-III demonstrate that the risk of serious cancers among GPA patients treated according to conventional regimens depends upon the total dose of cyclophosphamide administered. Among patients exposed to cumulative cyclophosphamide-doses of more than 36 gram, we observed heavily increased SIRs for late-occurring bladder cancer and for myeloid leukemia. In contrast, we did not observe increased incidence-rates of these or other serious malignancies among patients treated with lower cumulative cyclophosphamide-doses or among patients never exposed to cyclophosphamide. From a clinical point of view, these observations have two important implications. First, they underscore that prolonged administration of cyclophosphamide to patients affected by GPA should be avoided. Second, they suggest that treatment with low cumulative cyclophosphamide-doses is not associated with a substantial risk of therapy-induced serious cancers among GPA patients.

Consistent with our observations, cohort studies published during recent years have shown a non-increased incidence of serious malignancies among AAV patients after limited exposure to cyclophosphamide (46;47). In a cohort of 138 Dutch patients treated for AAV during 1991-2013 and followed for a mean of 9.7 years, the authors reported a SIR for cancer at all sites of 2.21 (95% CI: 1.64-2.92) (46). The SIR for NMSC was 4.23 (95% CI: 2.76-6.19), whereas incidence-rates of other specific cancers were not significantly higher than those in the general population of the Netherlands. Of note, analyses stratified according to duration of cyclophosphamide-therapy did not reveal a significantly increased risk of any cancer type in the sub-group of patients treated with cyclophosphamide for less than a year. In a study from the UK, the authors analysed the cancer-incidence among 323 AAV patients diagnosed during 2000-2014 and treated according to cyclophosphamide-free regimens or with low cumulative cyclophosphamide-doses (mean cumulative cyclophosphamide-dose among patients exposed to cyclophosphamide but not to rituximab: 7.26 gram; mean cumulative cyclophosphamide among patients exposed to both cyclophosphamide and rituximab: 11.05 gram) (47). After a mean follow-up of 5.6 years, the SIR for cancer at all sites was 1.89 (95% CI: 1.38-2.53) in the cohort. A SIR of 4.58 (95% CI: 2.96-6.76) was calculated for NMSC, while incidence-rates of other cancers did not differ significantly from UK national incidence-rates. SIRs for NMSC of 4.89 (95% CI:

2.90-7.72) and 11.72 (95% CI: 2.42-34.25) were demonstrated among patients treated with a cumulative cyclophosphamide-dose of 0.1-20 gram (n=207) and >20 gram (n=16), respectively.

To some extent, the risk estimates for cancer observed in these studies bear resemblance to the SIRs obtained in the "low-dose cyclophosphamide" group of paper I and II. As emphasised in paper II, available data cannot be used to determine a threshold-dose of cyclophosphamide, below which therapy-related serious cancers are unlikely to develop. Accordingly, cyclophosphamide-treated GPA patients should be offered periodic urinalysis and thorough evaluation for bladder cancer in case of otherwise unexplained chronic hematuria. However, the results of paper I and II as well as those reported in the above-mentioned publications (46;47) indicate that the risk of serious cancers is low after short-term administration of cyclophosphamide as per modern-day recommendations for cyclophosphamide-based induction-therapy in AAV (63).

For NMSC, an increased risk was found among patients exposed to relatively low cumulative cyclophosphamide-doses in two large cohorts (paper I-II) (47). The excess occurrence of NMSC in these patient-groups probably reflects that some of the non-alkylating immunosuppressants administered to GPA patients have the potential to induce NMSC, including corticosteroids and azathioprine (64-67). Awareness of the increased risk of NMSC is therefore warranted among GPA patients treated with cyclophosphamide plus traditional disease-modifying antirheumatic drugs.

Data reported by van Daalen et al indicate that the risk of cancer at all sites and the risk of NMSC among AAV patients is similar to that in the general population after rituximab-based, cyclophosphamide-free therapy, even if rituximab-treated patients are also exposed to azathioprine (47), but further studies are needed to assess the risk of NMSC and other malignancies associated with rituximab-based therapeutic approaches to AAV.

7. CARDIOVASCULAR DISEASE IN GPA

Since 2005, the risk of cardiovascular events among patients with GPA and other types of AAV has been assessed in a number of cohort studies. Epidemiological data concerning the risk of IHD, PE, DVT, and stroke among GPA patients are outlined in sections 7.1-7.3, and a discussion of potential risk factors for cardiovascular comorbidity in GPA is provided in section 7.4.

7.1. Ischemic heart disease

Before the publication of paper IV of the present thesis, experimental studies had demonstrated a higher prevalence of markers of atherosclerosis among patients with GPA and other systemic vasculitides than among control-subjects, including an increased occurrence of endothelial dysfunction, increased mean

intima-media thickness, and a higher frequency of arterial plaques (68-72). However, no study had compared the risk of manifest IHD in GPA patients with that in matched population-controls.

In paper IV, we compared 293 GPA patients with age- and gender-matched persons of the general population of Denmark with respect to IHD-related hospitalizations registered after the diagnosis of vasculitis. During a total of 2482 persons-years of observation, significantly increased risks were observed in the GPA cohort for hospitalization due to any manifestation of IHD (O:E ratio: 1.9 (95% CI: 1.4-2.4)), hospitalizations due to myocardial infarction (MI) (O:E ratio: 2.5 (95% CI: 1.6-3.7)), and hospitalizations under IHD-related diagnoses other than MI and angina pectoris (O:E ratio: 1.9 (95% CI: 1.2-2.8)) (Table 4). Comparable or higher relative risk estimates for IHD-related hospitalizations were calculated in subsequent epidemiological studies encompassing patients diagnosed with AAV during 1964-2008 (73), 1996-2010 (74), 1998-2010 (75), and 1981-2015 (76), respectively. In contrast, a non-increased risk of manifestations of IHD was reported in two cohorts comprising patients diagnosed with AAV during 1990-2014 (77) and 1996-2015 (78) (Table 4).

Table 4. Risk of manifestations of ischemic heart disease among patients diagnosed with GPA or other types of ANCA-associated vasculitis compared with the general population: Observations made in cohort studies.

Study	Calendar-period of diagnosis	Type	No.	Any IHD-related diagnosis	MI	Angina pectoris	IHD-related diagnoses other than MI and angina pectoris
Faurschou (paper IV)	1973-1999	GPA	293	O:E ratio: 1.9 (1.4-2.4)	O:E ratio: 2.5 (1.6-3.7)	O:E ratio: 1.3 (0.7-2.1)	O:E ratio: 1.9 (1.2-2.8)
Zöller (73)	1964-2008	GPA	12670	SIR: 1.50 (1.46-1.55)	ND	ND	ND
Avina-Zubieta (74)	1996-2010	GPA	504	ND	HR: 1.86 (1.05-3.31)	ND	ND
Englund (75)	1998-2010	GPA, MPA, EGPA	186	HR: 1.5 (1.0-2.3)	HR: 2.0 (1.0-3.6)	ND	ND
Li (77)	1990-2014	GPA	527	HR: 0.91 (0.60-1.38)	ND	ND	ND
Berti (78)	1996-2015	GPA, MPA, EGPA	58	ND	HR: 0.87 (0.29-2.60)	ND	ND
Mourguet (76)	1981-2015	GPA, MPA	125	ND	CMF: 4.22 (1.52-11.68)	ND	ND

GPA: Granulomatosis with polyangiitis. ANCA: Anti-neutrophil cytoplasmic antibody. No.: Number of patients. IHD: Ischemic heart disease. MI: Myocardial infarction. O:E ratio: Standardized ratio of observed to expected events with 95% confidence interval (CI). SIR: Standardized incidence ratio with 95% CI. ND: No data provided. HR: Hazard ratio with 95% CI. MPA: Microscopic polyangiitis. EGPA: Eosinophilic granulomatosis with polyangiitis. CMF: Comparative morbidity figure with 95% CI.

Available analyses have not provided a clear picture of how the IHD risk develops over time among GPA patients. In paper IV, we observed an increased risk of IHD manifestations during year 0-4 after diagnosis of GPA (O:E ratio for IHD: 2.1 (95% CI: 1.4-3.0); O:E ratio for MI: 3.6 (95% CI: 2.0-5.9)) and ≥ 10 years after diagnosis of GPA (O:E ratio for IHD: 2.2 (95% CI: 1.3-3.4); O:E ratio for MI: 2.5 (95% CI: 0.9-5.5)). During year 5-9, the risk of IHD events was not increased in the GPA cohort (O:E ratio for IHD: 1.4 (95% CI: 0.8-2.3); O:E ratio for MI: 1.0 (95% CI: 0.2-2.9)). In a register-based study, Zöller et al detected a similar, but less pronounced biphasic risk pattern for IHD events among Swedish patients hospitalized under a GPA-related diagnosis during 1964-2008 (SIR during the first year of follow-up: 2.1 (95% CI: 1.98-2.46); SIR during year 1-5: 1.47 (95% CI: 1.39-1.55); SIR during year 5-10: 1.37 (95% CI: 1.30-1.45), SIR after ≥ 10 years: 1.54 (95% CI: 1.47-1.62)) (73). This analysis should, however, be interpreted with some caution, since the number of included patients (n=12670) seems much higher than would be expected from the size of the Swedish population during the calendar-period of study and the annual incidence-rate of GPA in Northern European countries of 6-12 per million (79-83). Avina-Zubieta and co-workers observed the highest relative risk of MI during the first year of follow-up in a register-based analysis comprising 504 GPA patients and 5222 matched population-controls (HR: 1.91 (95% CI: 0.68-5.34)) without separate risk estimates provided for follow-up periods beyond the fifth year of observation (74), while Li et al found a non-increased risk of hospitalization for IHD during early (< 3 years) as well as late (≥3 years) follow-up in their cohort of 527 GPA patients (77).

7.2. Venous thromboembolism

It has been repeatedly shown that patients with GPA suffer from increased morbidity due to venous thromboembolism (VTE) (75;77;78;84-88) (paper V). Merkel et al reported an incidence-rate for VTE of 7.0/100 person-years among 167 GPA patients enrolled in a clinical trial with 81% of cases observed in patients with active vasculitis (84). The authors did not perform a direct comparison of the VTE incidence-rate among their vasculitis patients with that among matched population-controls, but they noted that an incidence-rate of 0.31/100 person-years for VTE had previously been observed among healthy Swedish men, indicating a substantially increased risk in GPA (89). In a later cohort study of 105 AAV patients, a VTE incidence-rate of 4.3/100 person-years was found (85), while two studies of AAV patients demonstrated much higher incidence-rates for VTE during phases with active vasculitis than during phases with inactive vasculitis (incidence-rate for VTE during phases with active vasculitis: 7.26/100 person-years (87) and 6.7/100 person-years (86), respectively; incidence-rate for VTE during phases with inactive vasculitis: 1.84/100 person-years (87) and 1.0/100 person-years (86), respectively).

The risk of VTE among AAV patients was directly compared with that among age- and gender-matched population-controls in subsequent cohort studies (paper V) (75;77;78;88). As outlined in Table 5, a higher risk of VTE was observed in the vasculitis cohort than in the comparison cohort across the studies.

Table 5. Risk of venous thromboembolism among patients diagnosed with GPA or other types of ANCA-associated vasculitis compared with the general population: Observations made in cohort studies.

Study	Calendar-period of diagnosis	Type	No.	Any VTE (PE or DVT)	PE	DVT
Zöller (88)	1964-2008	GPA	15085	ND	SIR overall: 1.41 (1.31-1.50) SIR <1 year after GPA: 6.57 (5.66-7.58) SIR 1-5 years after GPA: 1.55 (1.37-1.75) SIR 5-10 years after GPA: 1.05 (0.90-1.21) SIR ≥10 years after GPA: 0.97 (0.85-1.10)	ND
Faurschou (paper V)	1993-2011	GPA	180	ND	IRR ≤2 years after GPA: 25.7 (6.9-96) IRR >2 years after GPA: 1.3 (0.2-9.6)	IRR ≤2 years after GPA: 20.2 (5.1-81) IRR >2 years after GPA: 4.5 (1.7-11.8)
Englund (75)	1998-2010	GPA, MPA, EGPA	186	RR: 4.0 (1.9-8.3)	ND	ND
Li (77)	1990-2014	GPA	554	HR <3 years after GPA: 5.24 (2.83-9.71) HR ≥3 years after GPA: 2.56 (1.44-4.54)	ND	ND
Berti (78)	1996-2015	GPA, MPA, EGPA	58	HR: 3.26 (0.84-12.60)	HR: 1.33 (0.23-7.54)	HR: 6.25 (1.16-33.60)

GPA: Granulomatosis with polyangiitis. ANCA: Anti-neutrophil cytoplasmic antibody. No.: Number of patients. VTE: Venous thromboembolism. PE: Pulmonary embolism. DVT: Deep venous thrombosis. ND: No data provided. SIR: Standardized incidence ratio with 95% confidence interval (CI). IRR: Incidence rate ratio with 95% CI. MPA: Microscopic polyangiitis. EGPA: Eosinophilic granulomatosis with polyangiitis. RR: Rate ratio with 95% CI. HR: Hazard ratio with 95% CI.

Zöller et al reported a significantly increased risk of PE during the first five years of follow-up but not during later periods of observation among 15085 patients registered with a GPA-related diagnosis in a nationwide Swedish database during 1964-2008 (88) (Table 5). However, the large number of patients included in this analysis suggests a substantial degree of diagnostic misclassification for reasons previously discussed in relation to the IHD study by the same group of authors (see section 7.1) (73).

In a monocentric cohort of 180 patients with a verified diagnosis of GPA, we observed a more than twenty times increased incidence of both PE and DVT during the first two years following the diagnosis of vasculitis (paper V) (Table 5). Importantly, we also observed a markedly increased risk of DVT during later follow-up periods in our GPA cohort, reflected by an incidence rate ratio (IRR) of 4.5 (95% CI: 1.7-11.8) for DVT diagnosed more than two years after first vasculitis-related hospitalization. As in other studies, we observed the majority of VTE events among patients with active vasculitis. In agreement with our findings, Li et al reported an increased risk of VTE during both early (<3 years) and late (≥ 3 years) follow-up among 554 GPA patients identified from a UK clinical database (77) (Table 5).

7.3. Stroke

Although GPA can involve the central nervous system and cause stroke-like manifestations due to cerebral vasculitis (90-92), most of the published epidemiological data on stroke in GPA suggest that GPA patients treated according to modern-day immunosuppressive regimens are not at substantially increased risk of being hospitalized for stroke compared with the general population (paper V) (74;75;77;93) (Table 6). However, an increased risk of stroke was reported in two studies (76;78) (Table 6).

In a register-based cohort of 1909 GPA patients, non-increased SIRs for ischemic and hemorrhagic stroke were observed during most follow-up periods (93). In this analysis, the only markedly increased risk estimate was calculated for hemorrhagic stroke diagnosed <1 year after GPA based on 6 cases of stroke registered among the vasculitis patients (Table 6). In paper V, we calculated incidence-rates for early and late-occurring stroke, which did not significantly exceed those observed among age- and gender-matched population-controls, and neither Avina-Zubieta et al (74), Englund et al (75) nor Li et al (77) reported an increased risk of stroke in relatively large cohorts of AAV patients (Table 6).

In contrast to the non-increased risk of stroke observed in these cohort studies, a 4.36-times increased risk of stroke was recently calculated for 58 US patients with AAV patients compared with 174 control-subjects (78) (Table 6). Considering the low number of study-subjects included in the investigation, the possibility of a chance finding cannot be ruled out. In a French study comprising 125 patients AAV patients, however, a 4.65-times increased risk of (ischemic) stroke was also observed (76) (Table 6). The patients of the study were diagnosed with vasculitis between 1981 and 2015, and the higher risk of stroke observed in the French cohort than in other cohorts (paper V) (74;75;77;93) could potentially reflect a decreasing risk of stroke from the early 1980s onwards among patients with AAV.

Table 6. Risk of stroke among patients diagnosed with GPA or other types of ANCA-associated vasculitis compared with the general population: Observations made in cohort studies.

Study	Calendar-period of diagnosis	Type	No.	Any stroke-related diagnosis	Ischemic stroke	Hemorrhagic stroke
Zöller (93)	1987-2008	GPA	1909	ND	SIR overall: 1.09 (0.83-1.40) SIR <1 year after GPA: 1.66 (0.82-2.98) SIR 1-5 years after GPA: 0.47 (0.24-0.83) SIR 5-10 years after GPA: 1.54 (1.0-2.25) SIR ≥10 years after GPA: 1.69 (0.87-2.96)	SIR overall: 1.47 (0.73-2.63) SIR <1 year after GPA: 5.83 (2.10-12.76) SIR 1-5 years after GPA: 0.9 (0.17-2.67) SIR 5-10 years after GPA: 1.08 (0.10-3.95) SIR ≥10 years after GPA: No cases
Faurschou (paper V)	1993-2011	GPA	180	IRR ≤2 years after GPA: 1.4 (0.3-5.7) IRR >2 years after GPA: 1.4 (0.6-3.3)	ND	ND
Avina-Zubieta (74)	1996-2010	GPA	504	ND	HR: 1.5 (0.78-2.89)	ND
Englund (75)	1998-2010	GPA, MPA, EGPA	186	RR: 1.1 (0.6-2.0)	ND	ND
Li (77)	1990-2014	GPA	549	HR: 1.08 (0.7-1.67)	ND	ND
Berti (78)	1996-2015	GPA, MPA, EGPA	58	HR: 4.36 (1.42-13.42)	ND	ND
Mourguet (76)	1981-2015	GPA, MPA	125	ND	CMF: 4.65 (4.06-5.31)	ND

GPA: Granulomatosis with polyangiitis. ANCA: Anti-neutrophil cytoplasmic antibody. No.: Number of patients. ND: No data provided. SIR: Standardized incidence ratio with 95% confidence interval (CI). IRR: Incidence rate ratio with 95% CI. HR: Hazard ratio with 95% CI. MPA: Microscopic polyangiitis. EGPA: Eosinophilic granulomatosis with polyangiitis. RR: Rate ratio with 95% CI. CMF: Comparative morbidity figure with 95% CI.

7.4. Risk factors for cardiovascular events in GPA

The factors promoting cardiovascular comorbidity in GPA are incompletely understood. In analyses stratified according to age and gender, we observed increased O:E ratios for IHD among GPA patients aged ≥50 years of age at GPA diagnosis and among male patients, but not among patients <50 years of age or female patients (paper IV). These observations indicate that the risk of IHD associated with male sex and older age in the general population (94) is somehow augmented among persons affected by GPA. Other traditional cardiovascular risk factors, including hypertension, (previous or current) smoking, impaired renal function, dyslipidemia, obesity, and DM (94) have also been identified as predictors of cardiovascular events within cohorts of patients with AAV (76;78;95;96).

In a recent study of 31 GPA patients with active disease, MRI abnormalities suggestive of myocardial inflammation was observed in 16%, and 6% had myocardial alterations compatible with ischemic lesions due to vasculitis (97). Moreover, it has been shown that vasculitis in cardiac vessels can cause a clinical picture of MI in GPA (98-100). As described in section 7.1, an increased risk of hospitalizations for MI during early follow-up periods has been observed in several GPA cohorts (paper IV) (73;74), and some of the IHD events diagnosed during the early treatment-phases in these cohorts may have been the clinical result of myocardial or coronary necrotizing inflammation.

It could also be speculated that exposure to high cumulative corticosteroid-doses is of importance for the increased risk of early-occurring IHD events observed among GPA patients, since high-dose corticosteroid therapy has been associated with an increased risk of MI among corticosteroid-users in general (101). Moreover, studies have demonstrated associations between markers of inflammation and vascular endothelial changes predisposing to atherosclerosis in GPA (68;70;71;102), and inflammation-induced accelerated atherosclerosis may be a contributing risk factor for development of overt IHD among patients affected by the disease.

For VTE, cohort studies have demonstrated an increased risk associated with traditional risk factors (94;103) in AAV patients. Thus, Allenbach et al identified increasing age, prior VTE, nephrotic range proteinuria, and stroke with motor deficits as predictors of VTE in a cohort of 1130 patients with small-vessel vasculitis (87), and Kronbichler et al described impaired renal function and cancer during follow-up as being associated with VTE development in a cohort of 417 patients with AAV (104). As described in section 7.2, several groups have demonstrated a high VTE risk among AAV patients during phases with active vasculitis (84;86;87) (paper V). In line with these observations, Kronbichler et al identified an association between the Birmingham Vasculitis Activity score and VTE in their cohort of AAV patients (104). An association between the C-reactive protein level and VTE was also observed in the study (104). These findings could reflect a VTE-promoting effect of factors related to the vasculitic disease and/or a VTE-promoting effect of the immunosuppressive agents used for remission-induction. The risk of VTE has been demonstrated to increase in a dose-dependent manner among persons taking corticosteroids (105). It is therefore tempting to hypothesise that high-dose corticosteroid-therapy could be an important predictor of VTE in GPA, but the impact of corticosteroid-therapy on VTE risk in GPA remains to be determined.

In summary, the risk of cardiovascular events among GPA patients is likely to be influenced by several factors in a manner, which has only been partially elucidated. Further studies are required to evaluate the interplay between traditional, vasculitis-induced, and treatment-related cardiovascular risk factors in GPA, and to clarify how the risk of cardiovascular comorbidity is modulated by such factors during early and late disease-phases.

7.5. Cardiovascular disease in GPA: Current status

Excess occurrence of cardiovascular events among GPA patients has been observed in a range of cohort studies published during recent years. An increased risk of VTE has been convincingly demonstrated across epidemiological analyses (paper V) (75;77;78;88), whereas an increased risk of IHD was only identified among AAV patients in some investigations (paper IV) (73;74;76). The majority of cohort studies indicate that the present-day risk of stroke among GPA patients is more or less the same as the risk in the general population (paper V) (74;75;77;93), but available data on stroke in GPA and other types of AAV are somewhat conflicting (76;78).

The literature suggests that the cardiovascular risk in GPA may be driven by both disease-related and traditional risk factors (paper IV-V) (68;70;71;76;78;87;95-97;101;102;104;105), and measures targeting modifiable traditional predictors of cardiovascular disease should probably be considered an important part of the therapeutic approach to patients with GPA. Prospective studies are, however, warranted to assess the extent to which the risk of cardiovascular events can be reduced in GPA by means of strict control of traditional cardiovascular risk factors.

In two cohort studies comprising patients diagnosed with AAV during 1990-2014 (77) and 1996-2015 (78), respectively, the authors calculated lower relative risk estimates for IHD than observed in other investigations (paper IV) (73-76). Additional epidemiological analyses are needed to evaluate whether these observations reflect a tendency towards improved IHD outcomes during recent calendar-periods. Furthermore, corticosteroid-therapy could constitute a risk factor for both IHD and VTE (101;105), but it remains to be determined whether lower incidence-rates for IHD and VTE can be achieved in GPA through implementation of immunosuppressive treatment-strategies involving a more restricted use of corticosteroids than dictated by conventional vasculitis protocols (106;107).

Importantly, the analyses of paper IV and V demonstrated an increased long-term risk of IHD and VTE among Danish GPA patients. Thus, interventions to reduce the risk of cardiovascular comorbidity should be prioritized among patients with GPA, even after prolonged follow-up.

8. FRACTURES IN GPA

Prior to the publication of paper VI of the present thesis, cohort studies with variable follow-up times had demonstrated fractures in 10-14% of patients treated for GPA or other types of AVV (2;22;108). However, fractures also occur with a high incidence-rate in the general population (109;110), and a direct comparison of the incidence of fractures among GPA patients with that among population-controls was required to assess the risk of fractures associated with GPA and current therapies for the disease.

In paper VI, we observed an IRR for fractures of 1.2 (95% CI: 0.7-2.0) among 159 patients treated for GPA at a tertiary care centre compared with 1113 age- and gender-matched population-controls. Analyses stratified according to age and gender revealed a significantly increased incidence-rate of fractures among male GPA patients aged ≥55 years at date of GPA diagnosis (IRR: 3.5 (95% CI: 1.6-7.6)), whereas incidence-rates of fractures were not significantly increased among men aged <55 years or women (Table 7). In a supplementary analysis, we examined the risk of fractures in a cohort of 402 patients who 1) were diagnosed with GPA in Denmark during 1995-2010, 2) had at least 1 GPA-related contact to a department of rheumatology during this period, and 3) were not included in the tertiary care centre cohort. In this patient-group, we also observed an overall risk of fractures, which was not significantly increased. As in the tertiary care centre cohort, excess occurrence of fractures was observed among male patients aged ≥55 years at date of GPA diagnosis, but not among younger men or among women (paper VI) (Table 7).

Table 7. Risk of fractures among patients diagnosed with GPA or other types of ANCA-associated vasculitis compared with the general population: Observations made in cohort studies.

Study	Calendar-period of diagnosis	Type	No.	Relative risk
Faurschou (paper VI)	1995-2010	GPA	159	IRR overall: 1.2 (0.7-2.0)[1] IRR for men <55 years at GPA diagnosis: 0.3 (0.04-2.1) IRR for men ≥55 years at GPA diagnosis: 3.5 (1.6-7.6) IRR for women <55 years at GPA diagnosis: 0.7 (0.2-2.4) IRR for women ≥55 years at GPA diagnosis: 1.0 (0.4-2.7)
Faurschou (paper VI)	1995-2010	GPA	402	IRR overall: 1.2 (0.9-1.7)[1] IRR for men <55 years at GPA diagnosis: 1.0 (0.4-2.3) IRR for men ≥55 years at GPA diagnosis: 2.0 (1.2-3.5) IRR for women <55 years at GPA diagnosis: 1.6 (0.7-3.6) IRR for women ≥55 years at GPA diagnosis: 0.9 (0.5-1.5)
Englund (75)	1998-2010	GPA, MPA, EGPA	186	RR: 1.1 (0.6-1.7)[2]

GPA: Granulomatosis with polyangiitis. ANCA: Anti-neutrophil cytoplasmic antibody. No.: Number of patients. IRR: Incidence rate ratio with 95% confidence interval (CI). MPA: Microscopic polyangiitis. EGPA: Eosinophilic granulomatosis with polyangiitis. RR: Rate ratio with 95% CI. 1: Any fracture-related diagnosis. 2: Fractures in clavicle, spine, radius, or femur.

The low relative risk of fractures observed in our GPA cohorts was a somewhat surprising finding, since the vast majority of patients with GPA are exposed to high-dose corticosteroid therapy during phases with active vasculitis (63), and since treatment with high doses of corticosteroids is an established risk factor for osteoporosis and fractures (111). In a subsequent study from Sweden, however, the authors observed a non-increased rate of osteoporosis-related fractures in a cohort of 186 AAV patients (Table 7), even though the rate of healthcare-contacts due to osteoporosis was markedly increased among the patients compared

with population-controls (rate ratio (RR) for osteoporosis: 4.6 (95% CI: 3.0-7.0)) (75). It could therefore be speculated that doctors following AAV patients in Denmark and Sweden are generally aware of diagnosing and treating corticosteroid-induced osteoporosis, resulting in a low incidence-rate of osteoporosis-related fractures among their patients.

8.1. Fractures in GPA: Current status

In conclusion, available cohort studies indicate that the overall incidence-rate of fractures is not significantly increased among GPA patients (paper VI) (75), but that the sub-group of elderly male patients have an increased risk of sustaining fractures (paper VI). The generalizability of these findings needs to be tested in other cohort studies, which should also attempt to characterize the fracture risk in GPA associated with various risk factors for fracture such as corticosteroid-therapy, vasculitis-related chronic nephropathy, and physical disability caused by other items of vasculitis-induced organ damage.

9. DIABETES MELLITUS IN GPA

As discussed in the sections above, conventional regimens for remission-induction in GPA involve high-dose corticosteroid-therapy during initial treatment-phases. Moreover, prolonged corticosteroid-treatment is frequently provided to obtain and maintain disease-control (63;112;113) (paper VII).

Corticosteroids can induce beta cell dysfunction and insulin resistance in skeletal muscles, adipose tissue, and the liver, and these metabolic effects predispose to development of DM (114). Before the publication of paper VII of the present thesis, DM had been reported in more than 10% of patients with AAV during long-term follow-up (115). Englund et al had reported a two-fold increased risk of DM among 186 AAV patients compared with population-controls (Table 8) (75), but more comprehensive analyses of the risk of DM associated with current therapies for AAV had not been published. The risk of DM during different treatment-phases as well as the relationship between corticosteroid-dosing and DM risk was therefore incompletely characterized.

In paper VII, we used data from the NHR to construct a nationwide cohort of 342 GPA patients and data from the NHR and the Danish National Pathology Registry to establish a cohort of 1682 patients with biopsy-proven GCA (see section 5.2 for methodological details). Moreover, we accessed the files of the Danish National Prescription Registry to collect information on claimed prescriptions for antidiabetic medications, prednisolone, and prednisone. Our analyses revealed a 10.4-fold increased risk of new-onset DM, defined on the basis of claimed prescriptions for antidiabetic drugs, among the GPA patients compared with age- and gender-matched population-controls during the first year after the diagnosis of vasculitis. During later follow-up periods, the risk of new-onset DM was not significantly higher among the GPA

patients than among the population-controls (Table 8). For the GCA patients, a markedly increased risk of new-onset DM was also observed during the first year of follow-up (IRR: 7.0 (95% CI: 5.2-9.3)), whereas no significant difference in risk of DM was observed between patients and population-controls during year 1-5 (IRR: 0.9 (95% CI: 0.6-1.3)) or after more than 5 years of follow-up (IRR: 0.7 (95% CI: 0.5-1.0)). In both vasculitis cohorts, higher relative risk estimates were observed for older patients than for younger patients during the first year (IRRs of 6.1 (95% CI: 1.01-36), 10.9 (95% CI: 3.7-32), 22.1 (95% CI: 2.0-245) for GPA patients aged <50 years, 50-70 years, and >70 years, respectively. IRRs of 3.6 (95% CI: 1.7-7.5) and 8.0 (95% CI: 5.9-11) for GCA patients aged 50-70 years and >70 years, respectively). No substantial differences in IRRs for DM were observed between male and female patients in either vasculitis cohort (paper VII).

Consistent with our findings, Li et al reported an increased risk of DM among British GPA patients <3 years after the diagnosis of vasculitis, while the risk of DM did not differ significantly between patients and population-controls beyond the third year of observation (Table 8) (77).

Table 8. Risk of diabetes mellitus among patients diagnosed with GPA or other types of ANCA-associated vasculitis compared with the general population: Observations made in cohort studies.

Study	Calendar-period of diagnosis	Type	No.	Relative risk
Englund (75)	1998-2010	GPA, MPA, EGPA	186	RR: 2.0 (1.3-2.9)
Faurschou (paper VII)	1997-2015	GPA	342	IRR <1 year after GPA: 10.4 (4.4-24) IRR 1-5 years after GPA: 1.6 (0.8-3.5) IRR >5 years after GPA: 1.3 (0.6- 2.5)
Li (77)	1990-2014	GPA	527	HR <3 years after GPA: 2.13 (1.36-3.32) HR≥ 3 years after GPA: 1.30 (0.81-2.09)

GPA: Granulomatosis with polyangiitis. ANCA: Anti-neutrophil cytoplasmic antibody. No.: Number of patients. MPA: Microscopic polyangiitis. EGPA: Eosinophilic granulomatosis with polyangiitis. RR: Rate ratio with 95% confidence interval (CI). IRR: Incidence rate ratio with 95% CI. HR: Hazard ratio with 95% CI.

9.1. Association between corticosteroid-dose and diabetes mellitus in GPA

In paper VII, we used data on claimed prescriptions for corticosteroids to calculate yearly doses of prednisolone/prednisone during the first ten years of observation for vasculitis-patients and their population-controls. Among study-subjects with claimed prescriptions for prednisolone/prednisone, the median yearly dose of these corticosteroids was 6.0 gram among the GPA patients, 5.6 gram among the GCA patients, and ≤1.5 gram among the population-controls during the first year. As expected, median yearly prednisolone/prednisone doses were markedly lower in both vasculitis cohorts during each of the

following 9 years of observation (≤2.5 gram per year among corticosteroid-exposed patients). Almost half of the GPA patients (45.7%) and more than a third of the GCA patients (37.4%) bought prednisolone or prednisone at community pharmacies ten years after the diagnosis of vasculitis (paper VII).

Within the first year of follow-up, a cumulative prednisolone/prednisone dose ≥5.6 gram was associated with new-onset DM among our vasculitis patients (OR: 1.6 (95% CI: 1.02-2.5)), and the OR for DM per 10-mg increase in average daily prednisolone/prednisone dose was 1.3 (95% CI: 1.01-1.8) during this time-interval (paper VII).

9.2. Diabetes mellitus in GPA: Current status

Existing cohort studies have demonstrated that GPA patients are at markedly increased risk of developing DM during early treatment-phases (paper VII) (77). Furthermore, the findings reported in paper VII indicate that the risk of new-onset DM rises with increasing doses of corticosteroids among vasculitis patients in the same way as previously reported for patients receiving corticosteroids due to other diseases (116-120).

It could be claimed that the possibility of a disease-driven pathogenesis underlying the increased DM risk in GPA was not ruled out by our findings, but the fact that we observed comparable relative risk estimates for DM among patients with GPA and GCA, i.e. vasculitic syndromes with dissimilar clinical and histological features (1), provides a strong argument against this possibility. The almost identical IRRs for DM observed in our vasculitis-cohorts also suggest that corticosteroid-treatment was the main therapeutic risk factor for DM, since monotherapy with corticosteroids constituted the recommended treatment for remission-induction in GCA during the calendar-period of study (121).

In the GPA cohort of paper VII, 11 out of 342 patients (3%) initiated antidiabetic medication due to incident DM within the first year of follow-up. Thus, DM is a common comorbidity among patients with newly diagnosed GPA, and systematic screening for DM should be considered in patients receiving high-dose corticosteroid therapy for the disease.

10. INFECTIONS IN GPA

Infections occur with high frequency and constitute a major cause of death among GPA patients. Serious infections were observed in 31-46% of GPA patients in some long-term follow-up studies, (2;122-125), and the cumulative proportion with infection-related hospitalization (IH) was 20%, 38%, and 52% after 1, 5, and 10 years, respectively, among the 398 GPA patients described in paper VIII of the present thesis (Figure 1).

In a long-term follow-up study of 535 AAV patients enrolled in clinical trials, 47% of deaths occurring <1 year after the diagnosis of vasculitis were infection-related, and 20% of deaths occurring >1 year after the

vasculitis diagnosis were caused by infection (9). From a clinical point of view, it is therefore reasonable to consider infection one of the most important comorbidities related to GPA and its treatment.

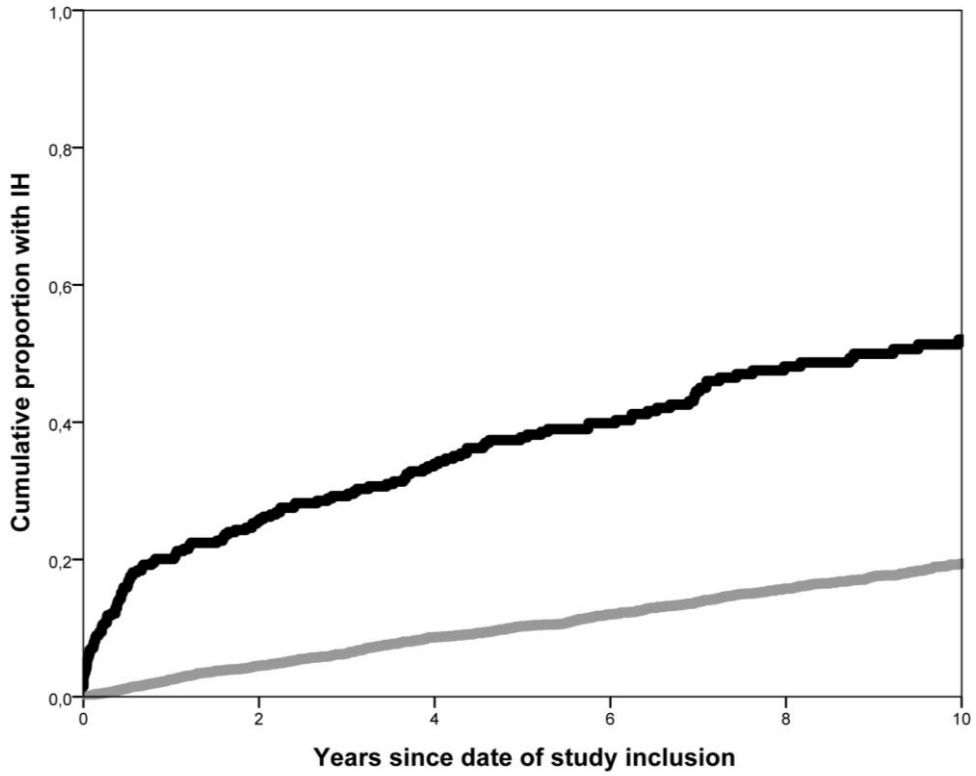

Figure 1. Cumulative proportion with infection-related hospitalization (IH) in a cohort of 398 patients diagnosed with GPA during 1995-2014 (black line) and in a cohort of 3980 age- and gender-matched population-controls (grey line). Previously unpublished figure based on data described in paper VIII of the present thesis.

10.1. Risk of early and late-occurring infections in GPA

Prior to the publication of paper VIII, a range of studies had demonstrated a higher incidence of infections during early treatment-phases than during later follow-up among patients with GPA (124-128). A 4.5 times increased overall rate of IH had been reported for 186 AAV patients compared with population-controls in a cohort study from Sweden (128), but no study had evaluated how the risk of IH changes over time among GPA patients compared with that in the general population.

In paper VIII, we conducted a comprehensive assessment of the short- and long-term risk of various serious infections in a cohort of patients diagnosed with GPA during 1995-2014. As described above and depicted in Figure 1, the cumulative proportion with any IH rose sharply in the cohort during the first year of follow-up (Figure 1). Compared with 3980 age- and gender-matched population controls, the risk of any IH was 9.5 times increased among the GPA patients during this time-interval (Table 9). A lower relative risk of IH was

observed beyond the first year, but even after 5-9 years of observation the risk of IH was 2.6 times higher in the GPA cohort than in the comparison cohort (Table 9). We observed increased short- and long-term risks for a variety of specific infections, including pneumonia (HR <1 year after GPA: 11.5 (95% CI: 7.4-18.0); HR year 1-4: 3.5 (95% CI: 2.4-5.4); HR year 5-9: 2.3 (95% CI: 1.4-3.9)); urinary tract infection (HR <1 year after GPA: 9.1 (95% CI: 4.2-19.8); HR year 1-4: 1.2 (95% CI: 0.5-2.7); HR year 5-9: 2.2 (95% CI: 1.01-5.0)); sepsis (HR <1 year after GPA: 11.6 (95% CI: 5.5-24.8); HR year 1-4: 3.6 (95% CI: 1.7-8.0); HR year 5-9: 3.3 (95% CI: 1.6-6.9)); and skin infection (HR <1 year after GPA: 4.8 (95% CI: 2.1-11.0); HR year 1-4: 3.2 (95% CI: 1.8-5.8); HR year 5-9: 2.9 (95% CI: 1.2-7.1)) (paper VIII).

Of note, mortality at 3 and 6 months after a first-time IH was 13% and 16%, respectively, among the GPA patients and 13% and 17%, respectively, among the population-controls (paper VIII). Thus, the mortality after IH was high in both cohorts, demonstrating that the excess occurrence of IH in the GPA group did not simply reflect an increased number of hospital-contacts due to trivial infections.

Table 9. Risk of infection-related hospitalization among patients diagnosed with GPA or other types of ANCA-associated vasculitis compared with the general population: Observations made in cohort studies.

Study	Calendar-period of diagnosis	Type	No.	Relative risk
Mohammad (128)	1998-2010	GPA, MPA, EGPA	186	RR overall: 4.53 (95% CI: 3.39-6.00) RR <1 year after AAV: 4.91 (95% CI: 2.68-8.86)[1]/5.65 (95% CI: 3.24-9.74)[2]
Faurschou (paper VIII)	1995-2014	GPA	398	HR <1 year after GPA: 9.5 (95% CI: 7.0-12.8) HR 1-4 years after GPA: 3.2 (95% CI: 2.4-4.3) HR 5-9 years after GPA: 2.6 (95% CI: 1.8-3.9)

GPA: Granulomatosis with polyangiitis. ANCA: Anti-neutrophil cytoplasmic antibody. No.: Number of patients. MPA: Microscopic polyangiitis. EGPA: Eosinophilic granulomatosis with polyangiitis. RR: Rate ratio with 95% confidence interval (CI). AAV: ANCA-associated vasculitis. HR: Hazard ratio with 95% CI. 1: Patients diagnosed with AAV during 1998-2003. 2: Patients diagnosed with AAV during 2004-2009.

10.2. Risk factors for infections in GPA

A spectrum of patient characteristics, treatment-related factors, and vasculitis manifestations has been identified as predictors of infection among patients with AAV. Advanced age (122;127-130), leukopenia (125;126;129;131), and compromised renal function (126-128;130) emerged as risk factors for infections in several cohorts, and Besada et al identified a high cumulative dose of cyclophosphamide as a predictor of severe infection in a cohort of 35 GPA patients (132). With regard to corticosteroids, higher daily doses (130), long-term therapy (126;133) and corticosteroid-related DM (127) predicted the occurrence of infection in various investigations.

Among AAV patients treated with rituximab, hypogammaglobulinemia has been identified as a predictor of infections (130;132), while prophylactic trimethoprim-sulfamethoxazole therapy has been associated with a reduced risk of IH (HR: 0.30 (95% CI: 0.13-0.69)) (130).

In paper VIII, we investigated the risk of IH associated with comorbidities developed before the onset of GPA using a previously validated methodology (134) to calculate Charlson Comorbidity Index (CCI) scores (135) for preceding chronic illnesses based on diagnoses extracted from the NHR. Among our GPA patients, a CCI score ≥1 at time of vasculitis diagnosis was identified as a significant risk factor for subsequent pneumonia (HR: 2.1 (95% CI: 1.3-3.5)) and urinary tract infection (HR: 4.0 (95% CI: 1.7-9.1)) but not for sepsis (HR: 1.2 (95% CI: 0.5-2.8)) or skin infection (HR: 1.5 (95% CI: 0.6-3.9)). Moreover, we observed a HR for pneumonia of 1.3 (95% CI: 1.1-1.5) per 1-point increase in CCI score and a HR for urinary tract infection of 1.5 (95% CI: 1.2-1.8) per 1-point increase in the score.

A significant influence of preceding chronic illnesses on risk of infection was also demonstrated in a more recent study comprising 192 patients diagnosed with AAV (130). In this study, chronic obstructive pulmonary disease (HR: 16.07 (95% CI: 4.41-58.49)), diabetes mellitus (HR: 2.35 (95% CI: 1.14-4.85)), and myocardial infarction/reduced left ventricular ejection fraction (HR: 2.21 (95% CI: 1.07-4.56)) were identified as baseline predictors of infection in univariate analyses.

10.3. Infections in GPA: Current status

Randomized trials conducted during the last decades demonstrated no differences in risk of infections between AAV patients treated according to cyclophosphamide-sparing regimens and patients receiving standard-of-care therapy (15-18). In agreement with these findings, population-based analyses revealed no decrease in risk of IH across recent decades among Scandinavian AAV patients despite the widespread implementation of cyclophosphamide-sparing therapies from the early 2000s onwards. Thus, a Swedish study did not demonstrate a lower overall rate of IH among patients diagnosed with AAV during 2004-2009 than among patients diagnosed during 1998-2003 (128), and we observed no differences in short- or long-term risk of IH between patients diagnosed with GPA in Denmark during 2005-2014 and 1995-2004, respectively (paper VIII). Furthermore, the analyses of paper VIII revealed no differences in mortality at 3 or 6 months after a first-time IH between patients diagnosed with GPA during 2005-2014 and those diagnosed with vasculitis during 1995-2004, indicating unchanged severity of infectious disease comorbidity across the decades of study.

Consistent with the above-mentioned trial results and real-world data, results of risk factor analyses suggest that the increased susceptibility to infections in GPA patients is driven by a number of factors in addition to cyclophosphamide-therapy (122;125-133). Among such factors, corticosteroid-therapy is likely

to be of great importance, since 1) corticosteroids are anchor drugs in current treatment-regimens for GPA (112), 2) GPA patients frequently receive corticosteroids for prolonged periods of time (paper VII), and 3) corticosteroid-therapy has been associated with a heightened risk of infections in patients with AAV (126;130;133) as well as in other patient-groups (136). In a pilot study, however, a lower rate of infections at 12 months was not unambiguously demonstrated for AAV patients exposed to extremely modest doses of corticosteroids during remission-induction than for patients enrolled in historic trials (107). Therefore, prospective studies with longer follow-up periods are required to assess whether the burden of infections in GPA can be diminished through implementation of corticosteroid-sparing treatment regimens.

Current recommendations for the management of patients with AAV support the use of trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* profylaxis in patients receiving cyclophosphamide (137). Since trimethoprim-sulfamethoxazole therapy was recently found to protect against serious infections among rituximab-treated AAV patients (130), trimethoprim-sulfamethoxazole prophylaxis is probably also relevant during cyclophosphamide-free induction-therapy for AAV.

Patients treated for GPA should be monitored closely for signs of infection, both during early and late follow-up periods. Attention must be paid to patients of older age, those with vasculitis-induced renal damage, and those with preceding comorbidities, as these patients are at particularly high risk of acquiring serious infections during their disease course.

11. STRENGTHS AND WEAKNESSES OF PAPER I-VIII

Paper I-VIII of the present thesis have methodological strengths and weaknesses. The high quality of data contained within the CRS (23) and the NHR (24;25) enabled us to identify our cohorts and to track GPA patients and population-controls with trustworthy coverage of their vital status during long-term follow-up. Cumulative doses of cyclophosphamide were determined on the basis of medical files review (paper I, II, and VI), while reliable data regarding prescribed antidiabetic agents and corticosteroids were obtained from The Danish National Prescription Registry (paper VII) (28). We followed the study-subjects for previously validated outcomes in Danish healthcare registers (paper I-VI and VIII) (26;31-40), and we used a validated methodological approach to calculate CCI scores for patients and controls (paper VIII) (134). Since data on comorbidity diagnoses were obtained from the same sources for patients and controls, diagnostic misclassification of comorbid conditions is likely to be nondifferential and without significant influence on the calculated relative risk estimates.

Some of the patients included in the GPA cohort of paper I-IV were diagnosed with vasculitis before the NHR was established in 1977. By allowing the inclusion of these patients, we introduced a risk of survival

bias in our analyses. However, only 4 of the 293 patients (1.3%) were diagnosed with GPA prior to 1977, and a significant impact of survival bias on the findings of paper I-IV is therefore improbable.

We constructed the GPA cohorts of paper VII and VIII by means of a search strategy in the NHR associated with a positive predictive value of 0.91 for the identified cases (30), implying that a small proportion of the included patients were diagnostically misclassified. Nevertheless, the risk estimates for DM calculated for the GPA patients are almost similar to those obtained for patients with biopsy-proven GCA (paper VII), and we observed an incidence of early-occurring IH among the GPA patients, which is comparable to the incidence reported in other AAV studies (paper VIII) (126-128;130). The findings reported in paper VII-VIII are therefore unlikely to be considerably influenced by misclassified cases of GPA.

Throughout papers I-VIII, we only had access to a limited amount of clinical information, and this prevented us from performing detailed risk factor analyses. For example, chronic nephropathy is a well-known risk factor for cardiovascular disease (94), but we were unable to assess the impact of chronic renal insufficiency on the risk of cardiovascular events due to lack of information concerning the renal status of our patients (paper IV and V). In paper VIII, we did not have access to information concerning non-steroidal immunosuppressive agents received by the patients and population-controls, and this precluded an evaluation of the infection risk associated with various immunosuppressive therapies.

In Denmark, GPA patients are typically followed closely at dedicated hospital-based clinics. For this reason, it cannot be excluded that some of our risk estimates were influenced by surveillance bias. With regard to serious diseases such as acute myeloid leukemia and MI, the risk of surveillance bias is probably limited because of the dramatic clinical features of the diseases and the absolute need for hospital-based therapy. In contrast, it is reasonable to assume that GPA patients are more prone to be hospitalized for infection than otherwise healthy persons. It is also possible that an increased number of hospital-contacts for NMSC and VTE occurs among GPA patients due to surveillance bias. However, the findings of paper I-VIII are compatible with observations made in other cohort studies as discussed in the previous sections, and surveillance bias is unlikely to have inflated our risk estimates substantially.

12. CONCLUSIONS AND PERSPECTIVES

GPA is an aggressive immune-inflammatory disorder, for which current treatment-options are suboptimal. Despite prolonged and intense immunosuppressive therapy, many patients are affected by debilitating organ-damage induced by necrotizing inflammation (22), and mortality-rates are increased among GPA patients compared with those in the general population (9;19;21). Furthermore, GPA patients are at increased risk of developing various comorbidities during early and late follow-up periods as demonstrated in paper I-VIII and discussed in the present thesis.

Epidemiological studies have shown that the risk of late-occurring bladder cancer and myeloid leukemia rises with increasing cumulative doses of cyclophosphamide among patients with GPA (paper I and II) (57;58). The long-term risk of NMSC is increased among patients treated with high cumulative cyclophosphamide-doses as well as patients exposed to low cumulative doses of the drug (paper I and II) (47), probably reflecting that the risk of NMSC is not just augmented by cyclophosphamide in this patient-group but also by non-alkylating immunosuppressants such as azathioprine and corticosteroids (64-67). Early reports of a pathogenic link between GPA and cancer (59;60) were not supported by subsequent investigations (paper III) (62), and routine screening for underlying cancer does not seem warranted in patients with new-onset GPA.

An increased incidence of IHD-related hospital-contacts has been reported for GPA patients in a number of population-based analyses (paper IV) (73;74;76), and the incidence of IHD was increased during both early and late observational periods in some cohorts (paper IV) (73). The long-term risk of VTE is substantially higher among patients with GPA than in the general population (paper V) (77;88), and the risk of this form of cardiovascular comorbidity is particularly high during phases with active vasculitis (paper V) (84;86;87). With regard to stroke, the majority of published studies suggest that the risk is not significantly increased among patients diagnosed with GPA during recent decades. (paper V) (74;75;77;93) The mechanisms responsible for the excess occurrence of IHD and VTE in GPA are not fully understood, but available data indicate that traditional cardiovascular risk factors (paper IV) (76;78;87;95;96;104), side effects of corticosteroids (101;105), and vasculitis-related factors (68;70;71;97-100;102;104) may all be of pathogenic importance.

Fractures do not constitute a major comorbidity problem among Scandinavian GPA patients (paper VI) (75). However, increased incidence-rates were observed among elderly male patients in two Danish cohorts (paper VI). Further studies are required to assess the incidence of fractures in non-Scandinavian cohorts and to analyse how the risk of fractures is modulated by various risk factors, including corticosteroids (111) and items of vasculitis-induced organ damage, in GPA.

The incidence of DM among GPA patients is markedly increased during early treatment-phases (paper VII) (77). An association between average daily corticosteroid-dose and DM has been observed (paper VII), strongly implying that the excess occurrence of DM in GPA is driven by the well-known diabetogenic effects of corticosteroids (114).

Infections represent a massive clinical problem in GPA (2;9;122-128). In a recent population-based cohort study, the risk of hospitalization due to severe infection was found to be approximately 10 times greater among GPA patients than among matched population-controls during initial treatment-periods and 2-3 times increased after several years of follow-up (paper VIII). A range of risk factors for infection has been

identified in GPA, including age (122;127-130), leukopenia (125;126;129;131), renal damage (126-128;130), cyclophosphamide-exposure (132), and corticosteroid-therapy (126;130;133). Moreover, GPA patients with preceding comorbidities are at higher risk of serious infections than GPA patients without preceding chronic illnesses (paper VIII) (130).

Since the etiology of GPA remains poorly understood, a therapy specifically targeting the cause of the disease is unlikely to be developed in the near future. Efforts should therefore be made to adjust the use of available immunosuppressive agents in a manner that reduces the risk of treatment-related comorbidities without loss of inflammatory disease control. To this end, further studies of corticosteroid-sparing regimens would probably be extremely relevant (106;107).

The observations reported in paper I-VIII and in other investigations underscore that monitoring for certain cancers, cardiovascular comorbidity, DM, and infections is required among GPA patients. Strict control of modifiable risk factors for cardiovascular disease, fractures, and DM appears reasonable despite lack of formal proof of the benefits of such interventions in the setting of GPA.

Over the past decades, therapeutic regimens for GPA have been modified considerably, and cyclophosphamide-sparing treatment regimens are now widely implemented. The risk of cyclophosphamide-induced malignancies has decreased due to a more restricted use of the drug, but the risk of other comorbidities continues to be markedly higher among GPA patients than in the general population. Thus, comorbidites induced by GPA and its treatment remain a major challenge in the clinical management of patients affected by the disease.

13. SUMMARY IN ENGLISH

The present thesis is based on epidemiological studies conducted at the Lupus and Vasculitis Clinic, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital, Rigshospitalet, Denmark during 2006-2018 and published as eight scientific papers (paper I-VIII). The aim of the papers was to assess the risk of various comorbidities among patients with granulomatosis with polyangiitis (GPA).

In paper I-II, the incidence of cancer among GPA patients was compared with the incidence in the general population. The studies revealed a pronounced long-term risk of bladder cancer and myeloid leukemia in the examined GPA cohort. However, analyses stratified according to cumulative cyclophosphamide-dose demonstrated that the risk of these malignancies was only increased among patients treated with high cumulative cyclophosphamide-doses. An increased long-term risk was also observed for non-melanoma skin cancer, and the risk of this cancer-type was increased among patients treated with high cumulative doses of cyclophosphamide as well as those exposed to low cumulative doses of the drug. Prior to our analyses, other studies had suggested that a pathogenic link might exist between cancer and GPA. We did

not observe a convincing association between preceding cancer and GPA (paper III). Thus, the findings of paper I-III indicate that the risk of malignancies in GPA is increased by the provided immunosuppressants and emphasise the relevance of restricting the use of cyclophosphamide as treatment for the disease (paper I-III).

In paper IV-V, an increased long-term risk of ischemic heart disease (paper IV) and venous thromboembolism (paper V) was demonstrated in cohorts of patients with GPA. In contrast, the risk of stroke was not significantly increased among GPA patients compared with population-controls (paper V). An increased relative risk of ischemic heart disease was observed for elderly patients and male patients (paper IV). More than half of the cases of venous thromboembolism were diagnosed in patients with active vasculitis (paper V).

We observed a non-increased overall risk of fractures in two GPA cohorts (paper VI). However, the occurrence of fractures was increased among elderly men in both cohorts.

In a nationwide GPA cohort, a substantially increased incidence of diabetes mellitus was observed during early treatment-phases (paper VII). An association between treatment with high corticosteroid-doses and diabetes mellitus was identified, indicating that the risk of diabetes mellitus in GPA is related to corticosteroid-therapy in a dose-dependent manner (paper VII).

The analyses of paper VIII demonstrated that GPA patients have a markedly increased long-term risk of being hospitalized for several types of infection. Furthermore, a Charlson Comorbidity Index score for preceding chronic illnesses ≥1 was identified as a risk factor for pneumonia and urinary tract infection in this patient-group.

The papers of the present thesis have contributed with information concerning the risk of comorbidities among GPA patients as described above. Together with observations made in other cohort studies, the findings reported in paper I-VIII underscore that novel treatment strategies are warranted to improve clinical outcomes in GPA.

14. SUMMARY IN DANISH

Denne afhandling er baseret på epidemiologiske studier gennemført ved Afsnit for Højt Specialiseret Reumatologi, Videncenter for Reumatologi og Rygsygdomme, Rigshospitalet, Danmark i perioden 2006-2018 og publiceret som otte videnskabelige artikler (artikel I-VIII). Formålet med studierne var at belyse risikoen for en række komorbiditeter blandt patienter med granulomatose med polyangiitis (GPA).

I artikel I og II sammenlignedes incidensen af cancer blandt GPA patienter med incidensen i baggrundsbefolkningen. Der påvistes en markant øget langtidsrisiko for blærecancer og myeloid leukæmi i den undersøgte GPA kohorte. Analyser stratificeret i henhold til kumuleret cyclophosphamid-dosis

demonstrerede dog, at risikoen for disse kræftsygdomme kun var øget blandt GPA patienter behandlet med høje kumulerede doser af cyclophosphamid. Der påvistes endvidere en øget langtidsrisiko for non-melanom hudkræft, og risikoen for denne kræftform var både øget blandt patienter behandlet med høje kumulerede cyclophosphamid-doser og patienter behandlet med lave kumulerede doser af præparatet. Forud for vore studier havde visse undersøgelser rejst mistanke om eksistensen af et patogenetisk link mellem cancer og GPA. Vi observerede ingen overbevisende association mellem forudgående cancer og GPA (artikel III). Fundene i artikel I-III indikerer med andre ord, at risikoen for cancer blandt GPA patienter øges af de anvendte immunosuppressive medikamina, og analyseresultaterne understreger vigtigheden af at begrænse brugen af cyclophosphamid i behandlingen af sygdommen.

I artikel IV og V påvistes en øget langtidsrisiko for iskæmisk hjertesygdom (artikel IV) og venøs tromboemboli (artikel V) blandt GPA patienter, mens risikoen for apopleksi ikke var øget i den undersøgte kohorte i forhold til risikoen blandt populations-kontroller (artikel V). En øget relativ risiko for iskæmisk hjertesygdom observeredes hos ældre patienter og mandlige patienter (artikel IV). Mere end halvdelen af de diagnosticerede tilfælde af venøs tromboemboli optrådte hos GPA patienter med aktiv vaskulitis (artikel V).

I to GPA kohorter konstateredes en overordnet incidens af frakturer, som ikke var signifikant øget i forhold til incidensen i baggrundsbefolkningen (artikel VI). Forekomsten af frakturer var dog øget i undergruppen af ældre mandlige patienter i begge kohorter.

I en landsdækkende GPA kohorte observeredes en markant øget incidens af diabetes mellitus gennem tidlige behandlingsfaser (artikel VII). Vi identificerede en association mellem behandling med høje kortikosteroid-doser og diabetes-udvikling, og vore observationer indikerer dermed, at risikoen for diabetes mellitus hos GPA patienter er relateret til kortikosteroid-behandling på dosis-afhængig vis.

Analyserne i artikel VIII demonstrerede, at GPA patienter har en markant øget langtidsrisiko for en række alvorlige infektioner. I artiklen påvistes desuden, at en Charlson Comorbidity Index score for forudbestående kroniske sygdomme ≥1 udgør en risikofaktor for pneumoni og urinvejsinfektion i denne patient-gruppe.

Artiklerne knyttet til denne afhandling har bidraget med viden om forekomsten af komorbiditeter blandt GPA patienter som beskrevet ovenfor. Sammenholdt med fundene i andre kohorte-studier understreger vore observationer behovet for nye terapeutiske strategier til forbedring af behandlingsresultaterne ved GPA.

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