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Rate of comorbidities in giant cell arteritis - A population-based study

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Abstract

Objectives: To compare the rate of occurrence of comorbidities, including severe infections in a population-based cohort of patients with biopsy-proven giant cell arteritis (GCA) with a reference population in Southern Sweden.

Methods: The study includes a population-based cohort of biopsy-proven GCA diagnosed between 1998 and 2010 from the Skåne region in Southern Sweden (population: 1.2 million). For each patient four reference subjects were identified from the general population matched for age, sex, area of residence, and date of diagnosis of GCA. Using the Skåne Healthcare Register, comorbidities and severe infections (requiring hospitalization) diagnosed after onset of GCA were identified. The rate of first occurrence of each comorbidity was the result of dividing the number of subjects with a given comorbidity by the person-years of follow-up. The rate ratio (RR) (GCA:reference population) was also calculated.

Results: 768 patients (571 women) with GCA and 3066 reference persons were included in the study. The RRs were significantly elevated for osteoporosis (2.81, 95% CI 2.33-3.37), followed by venous thrombo-embolic diseases (2.36, 95% CI 1.61-3.40), severe infections (1.85, 95% CI 1.57-2.18), thyroid diseases (1.55, 95% CI 1.25-1.91), cerebrovascular accidents (1.40, 95% CI 1.12-1.74), and diabetes mellitus (1.29, 95% CI 1.05-1.56). The RR for ischemic heart disease was elevated but did not reach statistical significance (1.20, 95% CI 1.00-1.44).

Conclusions: Patients with GCA suffer higher rates of selected comorbidities including severe infections, compared with a reference population. Several of these

comorbidities may be related to treatment with glucocorticosteroids, emphasizing the unmet need to find alternative treatments for GCA.

Key words: Giant cell arteritis, cardiovascular diseases, osteoporosis, infections.

Running Head: Comorbidities in giant cell arteritis

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Introduction

Giant cell arteritis (GCA) is a large-vessel vasculitis, which affects persons older than 50 years and is more common among women (1). GCA is characterized by a wide range of cranial and systemic manifestations including headache, fever, polymyalgia rheumatica, and, in severe cases, a variety of ischemic symptoms of which the most important are visual disturbances (2). GCA is the most common primary systemic vasculitis, especially in Northern Europe and North America. The median age at diagnosis of GCA is around 75 years (3).

Glucocorticoids constitute the cornerstone of treatment of GCA. Immunosuppressive or cytotoxic drugs are sometimes prescribed for patients with especially severe ischemic manifestations or prolonged dependence on the use of glucocorticoids (2, 4). Increased mortality in GCA due to cardiovascular disease, especially ischemic heart disease, has been reported from a tertiary referral center (5). Treatment used in GCA, especially glucocorticoids, is associated with a wide range of drug toxicities and complications, and increased mortality (5-7). Infections, osteoporosis, diabetes mellitus, and hypertension are examples of common side-effects and long-term toxicities of treatment with glucocorticoids (8). Comorbidities and organ damage may also be the results of the disease itself. For health providers and public health officials it is important to assess the extent of problems of comorbidities among patients with systemic vasculitis. Large population-based cohorts as well as validated health care registries are of vital importance for such studies.

In this study, the rates of a number of common comorbidities and infections were assessed in a large population-based cohort of patients with biopsy-proven GCA, and compared with those of a background reference population in Southern Sweden.

Methods

The study area and patients

The study area includes the Skåne region, the southernmost region in Sweden, with a total population of 1.2 million people (36% older than 50 years). The study area and population have previously been described in detail (3). Women made up 50.4% of the study population, and the age distribution was as follows: 0–14 years, 18.8%; 15–54 years, 54.6%; and >55 years, 26.6% (www.scb.se). The healthcare system in Skåne consists of both public and private sectors. The Region Skåne, the administrative body, runs the public healthcare. Within the region there are ten public hospitals, each of which providing inpatient care at internal medicine and cardiology units.

The Skåne Healthcare Register (SHR)

The SHR is a central database to which all information on healthcare contacts and diagnoses codes is transferred. The SHR receives data from all levels of healthcare (the primary outpatient care, private clinics, and the highly specialized in-hospital care). Each single healthcare consultation (public and private) at any level (physicians or paramedics) generates data entries by the healthcare provider that are transferred the SHR (9). Since 1998, diagnoses are classified according to the International Classification of Diseases, tenth version (ICD-10) system. All inpatient care is public and about 30% of all outpatient healthcare contacts are made with private practitioners.

Patients and reference population

Patients with biopsy-proven GCA diagnosed within the Skåne region between 1998 and 2010 were included in this analysis. The cohort consists of 768 patients (571

women). GCA ascertainment and demographics have been previously described in detail (3). In short, the database of the Department of Pathology in Skåne was searched for all biopsies including 'artery', 'temporal artery' and 'artery in the head' between 1997 and 2010. All identified histopathology reports were reviewed by one of the authors (AJM) to verify the diagnosis of GCA. Patients were diagnosed as having GCA if the pathology report stated the diagnosis of 'giant cell arteritis', 'temporal arteritis', 'granulomatous arteritis', or unequivocally indicated infiltration of mononuclear cells into the arterial wall with or without giant cells. Borderline cases were reviewed by two investigators (AJM and CT), and the final judgment was based on consensus.

In this study, the general population from the study area seeking healthcare is referred to as the reference population. The inclusion criteria and selection of reference population were described elsewhere (10). All reference subjects had at least one registered healthcare contact during the study period in the Skåne region but had never been assigned any of the ICD codes for GCA. For each patient with GCA, four age- and sex-matched reference persons were randomly selected from the SHR database. The date of entry to the study was defined as the date of diagnosis of GCA for the cases. For the reference subjects, the corresponding date was the time of the first assigned diagnosis code in the index year. Reference subjects were chosen from the same civil parish if possible. If no reference person was found in the same civil parish then the next level to find a match in was the municipality. The population of the Skåne region is stable. During 1998-2010, the in-migration rate into Skåne was 2.7% and out-migration rate was 2.3% (Statistics Sweden: www.scb.se).

Linking of data sources

The cohort of the GCA and the reference populations were linked to the SHR to identify all healthcare visits and all assigned ICD codes. The time period searched was January 1998 to December 31, 2011. Information on all healthcare contacts for GCA and reference subjects since diagnosis (or index date) was extracted. The data included details concerning the type of contact (inpatient or outpatient), healthcare provider location (hospital and specialized ward), and all assigned ICD-10 diagnosis codes (up to maximum of 8 diagnosis codes at each healthcare contact).

The comorbidities

In this study, only the first occurrence of the physician's diagnostic code of a given comorbidity registered in the SHR after the date of the diagnosis of GCA for cases and the corresponding index date for reference subjects, were counted. These consultation rates are referred to in this study as comorbidity rates. The ICD codes searched are listed in **Table 1 and Table 2.** Ischemic heart diseases (IHD) refer to any, single or combination, of the following: angina pectoris, myocardial infarction (or re-infarction), and chronic ischemic heart diseases. Cerebrovascular accidents included any condition leading to stroke, including cerebral infarct or bleeding, subarachnoid bleeding, or any cerebrovascular abnormalities that result in stroke. The venous thrombo-embolic diseases in this study (VTEs) included deep vein thrombosis and/or pulmonary embolism. Also studied were a selected number of common osteoporosis related fractures in the following bones: clavicles, spine, femur, and radius. Severe infections were defined as those requiring hospitalization. To increase the reliability of the diagnosis for ischemic heart diseases, cerebrovascular accidents, severe infections, and venous thrombo-embolic diseases, only diagnosis codes assigned at hospital discharge were included in the analyses.

Statistical analyses

Morbidity rates were calculated by dividing the number of patients or reference subjects with the comorbidity of interest by the number of person-years of follow-up. The person-year period was defined as the number of days each person was followed from the date of the diagnosis for GCA or index date for a reference person to the end of follow-up, as previously described (10). The follow-up time was calculated from date of diagnosis or index date for reference until the earliest of the following: (1) date of occurrence of the comorbidity; (2) death; (3) the date when a case or reference person moved outside the study area; or (4) December 31, 2011. For a given comorbidity, patients and reference subjects stopped contributing to person-year when they developed a particular comorbidity (patients or subjects who developed this particular comorbidity were censored from that particular person-year calculation). The morbidity rate ratio was calculated by dividing the morbidity rate for patients with GCA by that of the reference population. A rate ratio of >1 indicates a higher morbidity rate in the GCA cohort compared with the reference population, whereas a rate ratio of <1 indicates a lower morbidity rate in the GCA cohort than in the reference population. The absolute morbidity rate difference was defined as the absolute difference of rates between patients and the reference population and was calculated to provide results of excess comorbidity on an absolute scale.

The Regional Ethical Review Board for Southern Sweden approved the study protocol.

Results

GCA patients and reference population: The GCA cohort included 768 patients (571 women) diagnosed with biopsy-proven GCA between 1998 and 2010 while they were living within the Skåne region. The median age at diagnosis for all cases was 76.1

year (IQR 69.9-81.3), for women 76.1 (IQR 70.0-81.2) and for men 76.1 (IQR 69.4-81.6). In a sub-study using the same cohort the classification of cases was checked against the 1990 American College of Rheumatology (ACR) Classification Criteria for giant cell arteritis (11). Out of 167 patients, 163 (98%) fulfilled ≥3 ACR criteria (12). A total of 3066 (2284 women) age- and sex-matched persons fulfilled the study criteria and were included as a reference population. All healthcare contacts that generated ICD codes were identified. The total time of observation for the patients with GCA was 4500 person-years and for the reference population was 18 526 person-years. The average time of follow-up from the date of diagnosis of GCA (or index-date for reference persons) to the occurrence of first comorbidity are shown in the Supplementary Table S1.

Cardiovascular diseases: The rate ratio was increased among patients with GCA compared with the reference population for cerebrovascular accidents (rate ratio 1.40; 95% CI 1.12-1.74) and, to a lesser extent and not reaching statistical significance, for ischemic heart diseases (rate ratio; 1.20; 95% CI 1.00-1.44). Similarly, significantly higher rates for hypertension and diabetes mellitus, but not for dyslipoproteinemias, were found in patients with GCA (**Table 1**).

Venous thrombo-embolic disease: The rate ratio was significantly increased among patients with GCA compared with the reference population (rate ratio 2.36; 95% CI 1.61-3.40). In a separate analysis of events of pulmonary embolism (PE), the rate ratio was significantly elevated among patients with GCA (2.82; 95% CI 1.79-4.38) and a similar, although somewhat weaker, association was observed for deep vein thrombosis (DVT), (rate ratio1.65 (95% CI 1.17-2.28).

Osteoporosis and related fractures: The rate ratio for osteoporosis was significantly increased among patients with GCA compared with the reference population (**Table 1**), 2.81 (95% CI 2.33-3.37). Similar results were obtained when in separate analyses including only hospital discharge diagnoses or only diagnoses from outpatient visits (data not shown). To reduce the possible effect of a bias in referring patients with GCA for bone mineral density measurement more frequently than the reference population, diagnoses of fractures were studied irrespective of whether or not they were accompanied by a diagnosis of osteoporosis. The rate ratios for fractures were also significantly elevated for patients with GCA compared with the reference population (**Table 1**).

The rate of severe infections: The rate of all severe infections, including septicemia, was significantly increased among patients with GCA compared with the reference population (**Table 2**). The rate ratio was 1.85 (95% CI 1.57-2.18) for severe infections and 1.83 (95% CI 1.27-2.60) for septicaemia. The rates of severe Clostridium difficile and acute upper respiratory tract infections were higher among patients with GCA, 2.07 (1.04-3.94) and 2.69 (1.45-4.83), respectively. There was a similar trend for skin infections, but it did not reach statistical significance (rate ratio 1.64;0.88-2.91).

Other comorbidities: The rate ratios for several other comorbidities were significantly increased among patients with GCA compared with the reference population, including those for thyroid diseases (1.55; 95% CI 1.25-1.91) and psychiatric diagnoses (1.28; 95% CI 1.12-1.46).

Sex-specific rates: The sex-specific comorbidity rates and rate ratios are shown in **Tables 3 and 4.** There are some differences in the rates and rate ratios of a number of comorbidities when the cohort was stratified by sex. Among male patients the highest

rate ratio was obtained for osteoporosis, followed by VTE and cerebrovascular accidents. Among women the highest rate ratio was obtained for osteoporosis, followed by VTE, fractures, thyroid diseases, diabetes mellitus, and hypertension. Rates of psychiatric diseases and fractures were lower among men with GCA compared with women, and not significantly different from the reference population in the sub-analyses of male subjects (Table 4). There were no sex-specific differences in the rate ratios for cerebrovascular accidents or ischemic heart diseases.

Discussion

This population-based study found significant differences in the rates of occurrence of a number of comorbidities between patients with biopsy-proven GCA and a reference population, thus demonstrating the added burden of disease that accompanies the development and treatment of this systemic vasculitis.

Patients with GCA suffer a high rate of comorbidities. In terms of absolute rate, this study found that one patient in every five developed at least one event of ischemic heart disease and one in every seven patients developed a cerebrovascular accident. Furthermore, more than 50% of the patients were diagnosed with hypertension, and one in four suffered at least one osteoporosis related fracture.

Importantly, patients with GCA had higher rates of cardiovascular diseases. These results are similar to those of previously reported increased rates of stroke, myocardial infarction, and peripheral vascular disease among patients with GCA in a large UK-based population (13). This study showed quite similar results to those in the recently published data from Amiri et al. on the rate of ischemic heart diseases and CVA among patients with GCA(14). However, the rate ratios compared with reference population were higher in the Canadian study. Udayakumar et al. demonstrated no

overall increased in the rate of acute coronary syndrome among patients with GCA(15). The association between GCA and coronary artery disease is unclear with varied findings among several population-based studies(13-15). Differences in case ascertainment of cases of GCA (study criteria vs. biopsy-proven GCA) may explain such variations. Increased atherosclerosis among patients with GCA, as a consequence of the chronic vascular inflammation and/or treatment with high cumulative doses of glucocorticoids, could explain the higher rate of cardiovascular events among patients with GCA. The use of aspirin, which has been shown to reduce the incidence of ischemic GCA complications such as CVA and visual loss (16, 17), to prevent comorbidities in patients with GCA should be further investigated.

This study found significantly higher rates of osteoporosis and related fractures (irrespective of whether or not they were accompanied by a diagnosis of osteoporosis) among patients with GCA compared with the reference population. Osteoporosis has been reported in up to 38% of patients with GCA and osteoporosis fractures in 9% (18). Interestingly, a recently published study by Petri et al., showed a 2.9-fold increased relative risk for osteoporosis among patients with GCA compared with matched controls (19). However, a previous study from Sweden found no reduction in the bone density of patients with GCA compared with the general population (20). Clinicians might order bone density testing more frequently for patients with GCA than for the reference population thus increasing the recognition of sub-clinical osteoporosis. The higher rates of osteoporosis and related fractures among the group with GCA, further highlights the increased risk of this likely treatment related morbidity.

This study found a higher rate of thyroid diseases among patients with GCA

compared with the reference population, which is consistent with findings of previous studies (21, 22). The mechanisms underlying the association between thyroid diseases and GCA are not known, but these data suggest that it may be appropriate for clinicians to be aware of this association and have a low threshold for assessing thyroid function in patients with GCA, especially those suffering recurrence of non-specific symptoms such as fatigue, myalgia, and arthralgia. Outcomes in patients with GCA and thyroid disease warrant further studies.

The risk of infections and related morbidity are among the major concerns when treating older people with immunosuppressive drugs, including high-dose glucocorticoids. In this study, significant increases in rates of severe infections and septicemia were found among patients with GCA compared with reference subjects. However, in a recently published population-based study from the Mayo Clinic, no increase in the rate of infections requiring hospitalization was found in a large cohort of patients with GCA. The difference between these results and those of the current study may relate to differences in case definition; the current study only included first episodes of infection (23). Patients with GCA were also found to have increased rates of mild-moderate infections diagnosed and treated at an outpatient visit and acute upper respiratory tract infections (data not shown). These data underline the risks for infection among patients with GCA, and the concerns for infection-related mortality (24).

The finding of higher rates of venous thrombo-embolic diseases (VTEs) among patients with GCA compared with the reference population is consistent with prior studies demonstrating increased rates of hypercoagulability among patients with GCA and other forms of vasculitis(25-28). The reason for the association between GCA and

high rate of VTEs is not clear. The hypercoagulability associated with vascular inflammation is a possible explanation as VTEs are among direct consequences of inflammatory vessel diseases as in other autoimmune diseases (27).

The sex-specific rate ratios of comorbidities showed some differences between male and female patients. The main difference is the significantly higher rate of CVA among male patients, while higher rate ratios were obtained for thyroid diseases among female patients. Due to the limited number of male GCA patients, the estimated rates and rate ratios are less precise for these sub-analyses in men compared with women.

The strengths of this study include the data source being a large and well-characterized cohort of patients with GCA, diagnostic confirmation through temporal artery biopsy, utilizing a well-established and validated diagnosis register database, and matched references from the background population.

This study also has a number of limitations. The diagnoses of comorbidities were not evaluated by medical records review. However, hospital discharge diagnoses in Sweden, included in the national Swedish inpatient register, have been validated for a number of diagnoses with a positive predictive value ranging between 85-95% (29). As the inpatient codes included in the SHR are reported to the national register, these figures should be applicable to hospitalization with comorbidities in the present study.

By only including the first event that occurred after the diagnosis of GCA or the index date for the reference population, the possibility remains that some of the comorbidities were prevalent before the diagnosis date of GCA or the index date. Another limitation of this study is that the analysis was restricted to patients with biopsy-proven GCA. While such patients make up the great majority of patients with

GCA, it is possible that the findings of this study do not apply to patients with GCA with negative temporal artery biopsies.

In conclusion, this study demonstrated that patients with biopsy-proven giant cell arteritis have higher rates of a number of important comorbidities including infections associated with hospitalization when compared with a reference population. Several of these problems known to be related to treatment with glucocorticoids and these findings highlight the need to find alternative treatments for GCA to allow for reduction in the dose and duration of glucocorticoids. The observed increase of some non-treatment related comorbidities may imply a GCA-related etiology, or shared risk factors. There is a need for better understanding of both the pathophysiology involved in such comorbidities and the role of improved disease control in this context.

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Table 1. Rate and rate ratio of selected comorbidities among 768 patients with giant cell arteritis and 3066 reference subjects, matched for age, sex, and date of diagnosis

Comorbidity	ICD-10 codes	GCA n=768	GCA person-years	Rate	Reference n=3066	Reference person-years	Rate	Rate ratio	95% CI	P
Ischemic heart disease[1]	I20-I25	150	4027	37.2	521	16 837	30.9	1.20	1.00-1.44	0.05
Cerebrovascular accident[1]	I60-I69	110	4147	26.5	333	17 636	18.8	1.40	1.12-1.74	0.005
Hypertension	I10-I15	407	2884	141	1421	13 155	108	1.31	1.17-1.46	<0.001
Diabetes mellitus	E10-E14	133	4006	33.2	431	16 716	25.7	1.29	1.05-1.56	0.01
VTE[1]		46	4364	10.5	82	18 339	4.47	2.36	1.61-3.40	<0.001
Thyroid diseases	E00-E07	122	3960	30.8	343	17 265	19.8	1.55	1.25-1.91	<0.001
Dyslipoproteinemias	E78	76	4252	17.8	323	17 495	18.4	0.97	0.74-1.24	0.7
Psychiatric diseases	F00-F99	290	3495	82.9	990	15 284	64.7	1.28	1.12-1.46	0.001
Osteoporosis	M80-M85	188	3722	50.5	313	17 429	17.9	2.81	2.33-3.37	<0.001
Fractures		185	3744	49.4	528	16 675	31.6	1.56	1.31-1.85	<0.001

GCA: giant cell arteritis; ICD: International Classification of Diseases;

[1]Only inpatient diagnoses; all other diagnoses are for both inpatient and outpatient diagnoses; CI: confidence interval

VTE: venous thrombo-embolic diseases: pulmonary embolus and /or deep vein thrombosis: I260-I269 and/or I800-I809

Fractures: M48.4, M48.5, S22.0-S22.3, S32.0-S32.8, S42.2, S42.3, S52.2-S52.6, S72.0-S72.9, S82.1-S82.6

Table 2. Rate and rate ratio of selected severe infections among patients with biopsy-proven giant cell arteritis (cases) and reference subjects (reference) matched for age, sex and date of diagnosis

	ICD-10 codes	GCA n=768	Cases Person-years	Rate	Reference n=3066	Reference Person-years	Rate	Rate ratio	95% CI	P
All severe infections		208	3842	54.1	501	17 150	29.2	1.85	1.57-2.18	<0.001
Septicemia	A419	46	4366	10.5	105	18 277	5.75	1.83	1.27-2.60	0.004
Clostridium difficile	A04.7	15	4455	3.37	30	18 450	1.63	2.07	1.04-3.94	0.05
Skin infections	L00-L08	17	4443	3.83	43	18 427	2.33	1.64	0.88-2.91	0.1
Acute URTI	J00-J06	20	4416	4.53	31	18 433	1.68	2.69	1.45-4.83	0.007
Influenza and pneumonias	J09-J18	123	4172	29.4	304	17 779	17.1	1.72	1.39-2.13	<0.001

ICD: International Classification of Diseases; GCA: giant cell arteritis; CI: confidence interval; URTI: upper respiratory tract infections

Table 3. Rate and rate ratio of selected comorbidities among 571 female patients with biopsy-proven giant cell arteritis (cases) and 2284 reference subjects (reference) matched for age, sex, and date of diagnosis

Comorbidity	GCA n=571	Cases Person-years	Rate	Reference n=2284	Reference Person-years	Rate	Rate ratio	95% CI	P
Ischemic heart disease[1]	94	3138	29.9	349	13 074	26.6	1.12	0.88-1.41	0.3
Cerebrovascular accidents[1]	72	3242	22.2	238	13 591	17.5	1.27	0.96-1.65	0.1
Hypertension	312	2179	143	1092	10 041	108	1.32	1.16-1.49	<0.001
Diabetes mellitus	94	3110	30.2	287	13 077	21.9	1.38	1.08-1.74	0.01
VTE[1]	31	3358	9.23	65	14 079	4.62	2.00	1.26-3.09	0.009
Thyroid disease	114	2946	38.6	316	13 059	24.2	1.60	1.28-1.98	<0.001
Dyslipoproteinemias	59	3256	18.1	245	13 480	18.1	1.00	0.74-1.33	0.9
Psychiatric diseases	237	2587	91.6	770	11 664	66.0	1.39	1.19-1.61	<0.001
Osteoporosis	171	2719	62.8	293	13 209	22.1	2.83	2.33-3.43	<0.001
Fractures	160	2778	57.5	445	12 632	35.2	1.63	1.36-1.96	<0.001

GCA: giant cell arteritis; VTE: venous thrombo-embolic diseases: pulmonary embolus and /or deep vein thrombosis,
[1]only in-patients diagnoses; all other diagnoses are for both inpatient and outpatient diagnoses

Table 4. Rate and rate ratio of selected comorbidities among 197 male patients with biopsy-proven giant cell arteritis (cases) and 782 of reference subjects (reference) matched for age, sex, and date of diagnosis

Comorbidity	GCA n=197	Cases Person-year	Rate	Reference n=782	Reference Person-year	Rate	Rate ratio	95% CI	P
Ischemic heart disease[1]	56	889	63.0	172	3763	45.7	1.38	1.00-1.87	0.05
Cerebrovascular accidents[1]	38	905	41.9	95	4045	23.4	1.79	1.19-2.61	0.01
Hypertension	95	705	135	329	3114	106	1.28	1.00-1.60	0.05
Diabetes mellitus	39	896	43.5	144	3640	39.5	1.10	0.75-1.57	0.6
VTE[1]	15	1006	14.9	17	4260	3.99	3.74	1.74-7.95	0.006
Thyroid disease	8	1014	7.89	27	4205	6.42	1.23	0.48-2.78	0.6
Dyslipoproteinemias	17	996	17.0	78	4016	19.4	0.88	0.49-1.49	0.6
Psychiatric disease	53	908	58.3	220	3620	60.7	0.96	0.70-1.30	0.7
Osteoporosis	17	1003	16.9	20	4220	4.74	3.58	1.76-7.15	0.004
Fractures	25	966	25.8	83	4043	20.5	1.26	0.77-1.98	0.3

GCA: giant cell arteritis; VTE: venous thrombo-embolic diseases: pulmonary embolus and /or deep vein thrombosis. [1]only in-patients diagnoses; all other diagnoses are for both inpatient and outpatient diagnoses

Supplementary Table S1

The average time (person-year) of follow-up from diagnosis of giant cell arteritis (or index-date for reference population) to the occurrence of first comorbidity

Comorbidity	Number of patients with comorbidity GCA	Average time of f-up (person-year) GCA	Number of patients with comorbidity Reference	Average time of f-up (person-year) Reference
IHD[1]	150	2.91	521	3.42
CVA[1]	110	3.14	333	4.16
Hypertension	407	2.28	1421	3.10
Diabetes mellitus	133	1.27	431	2.03
VTE[1]	46	2.45	82	4.42
Thyroid diseases	122	2.07	343	3.21
Dyslipoproteinemias	76	3.11	323	4.02
Psychiatric diseases	290	3.13	990	3.70
Osteoporosis	188	2.53	313	4.05
Fractures	185	3.45	528	4.05
All severe infections[1]	208	3.29	501	3.97
Septicemia[1]	46	3.08	105	4.07
Clostridium difficile[1]	15	3.53	30	3.93
Skin infections[1]	17	4.11	43	4.02
Acute URTI[1]	20	2.70	31	4.19
Influenza and pneumonias[1]	123	3.97	304	4.24

[1]Only inpatient diagnoses; GCA: giant cell arteritis; IHD: Ischemic heart disease, CVA: Cerebrovascular accident[1]; VTE: venous thrombotic event; URTI: upper respiratory tract infection