Rate of Comorbidities in Giant Cell Arteritis: A Population-based Study

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ABSTRACT. ***Objective.*** 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 included a population-based cohort of biopsy-proven GCA cases diagnosed between 1998 and 2010 from the Skåne region in Southern Sweden (population: 1.2 million). For each patient, 4 reference subjects were identified from the general population and 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 GCA onset were identified. The rate of the first occurrence of each comorbidity was the result of dividing the number of subjects with a given comorbidity by the person-years of followup. The rate ratio (RR; GCA:reference population) was also calculated.

Results. There were 768 patients (571 women) with GCA and 3066 reference persons included in the study. The RR were significantly elevated for osteoporosis (2.81, 95% CI 2.33–3.37), followed by venous thromboembolic 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).

Conclusion. Patients with GCA have 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. (J Rheumatol First Release November 1, 2016; doi:10.3899/jrheum.160249)

Key Indexing Terms:
GIANT CELL ARTERITIS
OSTEOPOROSIS
CARDIOVASCULAR DISEASES
INFECTIONS

Giant cell arteritis (GCA) is a large-vessel vasculitis that 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 because of cardiovascular disease (CVD), especially ischemic heart disease (IHD), 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[5,6,7]. Infections, osteoporosis, diabetes mellitus (DM), and hypertension (HTN) are

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Supported by research grants from The Faculty of Medicine, Lund University, Governmental Funding of Clinical Research within National Health Service, and the Swedish Rheumatism Association (Reumatikerförbundet).

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Accepted for publication September 22, 2016.

examples of common side effects and longterm 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 healthcare registries are of vital importance for such studies.

In our 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.

MATERIALS AND METHODS

The study area and patients. The study area included the Skåne region, the southernmost region in Sweden, with a total population of 1.2 million people (36% older than 50 yrs). 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 10 public hospitals; each provides 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 diagnosis 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 to the SHR[9]. Since 1998, diagnoses have been classified according to the International Classification of Diseases, 10 ed (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 our analysis. The cohort consisted 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 1 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 2 investigators (AJM and CT), and the final judgment was based on consensus.

In our study, the general population from the study area seeking healthcare was referred to as the "reference population." The inclusion criteria and selection of the reference population were described elsewhere[10]. All reference subjects had at least 1 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, 4 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 GCA diagnosis 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 our study, only the first occurrence of the physician's diagnostic code of a given comorbidity registered in the SHR after the date of the GCA diagnosis for cases and the corresponding index date for reference subjects were counted. These consultation rates are referred to in our study as "comorbidity rates." The ICD codes searched are listed in Table 1 and Table 2. IHD refer to any, single or combination, of the following: angina pectoris, myocardial infarction (MI; or reinfarction), and chronic IHD. Cerebrovascular accidents (CVA) included any condition leading to stroke, such as cerebral infarct or bleeding, subarachnoid bleeding, or any cerebrovascular abnormalities that result in stroke. The venous thromboembolic diseases (VTE) in our study included deep vein thrombosis (DVT) and/or pulmonary embolism. Also studied were a selected number of common osteoporosis-related fractures in the clavicle, spine, femur, and radius. Severe infections were defined as those requiring hospitalization. To increase the reliability of the diagnosis for IHD, CVA, severe infections, and VTE, only diagnosis codes assigned at hospital discharge were included in our 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 followup. 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 followup, as described[10]. The followup 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 (RR) was calculated by dividing the morbidity rate for patients with GCA by that of the reference population. An RR of > 1 indicates a higher morbidity rate in the GCA cohort compared with the reference population, whereas an RR of < 1 indicates a lower morbidity rate in the GCA cohort than in the reference population.

The Regional Ethical Review Board for Southern Sweden approved the study protocol (301-2007 and 2010/517).

RESULTS

Patients with GCA and the 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 years [interquartile range (IQR) 69.9–81.3], and was the same for women (IQR 70.0–81.2) and for men (IQR 69.4–81.6). In a substudy using the same cohort, the classification of cases was checked against the 1990 American College of Rheumatology (ACR) Classification criteria for GCA[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

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

Comorbidity	ICD-10 Codes	GCA, n = 768	GCA, Person-yrs	Rate	Reference, n = 3066	Reference, Person-yrs	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

[1] Only inpatient diagnoses; all other diagnoses are for both inpatient and outpatient diagnoses. GCA: giant cell arteritis; ICD-10: International Classification of Diseases, 10th ed; VTE: venous thromboembolic 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 GCA (cases) and reference subjects (reference) matched for age, sex, and date of diagnosis.

Variables	ICD-10 Codes	GCA, n = 768	Cases, Person-yrs	Rate	Reference, n = 3066	Reference, Person-yrs	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

GCA: giant cell arteritis; ICD-10: International Classification of Diseases, 10th ed; URTI: upper respiratory tract infections.

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 followup from the date of GCA diagnosis (or index date for reference persons) to the occurrence of first comorbidity is shown in Appendix 1.

CVD. The RR was increased among patients with GCA compared with the reference population for CVA (RR 1.40, 95% CI 1.12–1.74), and to a lesser extent and not reaching statistical significance, for IHD (RR 1.20, 95% CI 1.00–1.44). Similarly, significantly higher rates for HTN and DM, but not for dyslipoproteinemias, were found in patients with GCA (Table 1).

VTE. The RR was significantly increased among patients with GCA compared with the reference population (RR 2.36, 95% CI 1.61–3.40). In a separate analysis of events of pulmonary embolism, the RR 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 DVT (RR 1.65, 95% CI 1.17–2.28).

Osteoporosis and related fractures. The RR for osteoporosis was significantly increased among patients with GCA compared with the reference population (2.81, 95% CI 2.33–3.37; Table 1). 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 they were accompanied by a diagnosis of osteoporosis. The RR 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 RR was 1.85 (95% CI 1.57–2.18) for severe infections and 1.83 (95% CI 1.27-2.60) for septicemia. 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 (RR 1.64, 95% CI 0.88–2.91).

Other comorbidities. The RR 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 RR are shown in Table 3 and Table 4. There were some differences in the rates and RR of a number of comorbidities when the cohort was stratified by sex. Among male patients, the highest RR was obtained for VTE, followed by osteoporosis and CVA. Among women, the highest RR was obtained for osteoporosis, followed by VTE, fractures, thyroid diseases, DM, and HTN. 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 subanalyses of male subjects (Table 4).

DISCUSSION

Our 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 experience a high rate of comorbidities. In terms of an absolute rate, our study found that 1 patient in every 5 developed at least 1 event of IHD and 1 in every 7 patients developed a CVA. Further, more than 50% of the patients were diagnosed with HTN, and 1 in 4 experienced at least 1 osteoporosis-related fracture.

Importantly, patients with GCA had higher rates of CVD. These results are similar to those of previously reported increased rates of stroke, MI, and peripheral vascular disease among patients with GCA in a large UK-based population[13]. Our study showed quite similar results to those in the recently published data from Amiri, *et al* on the rate of IHD and CVA among patients with GCA[14]. However, the RR compared with the reference population were higher in the Canadian

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

Comorbidity	GCA, n = 571	Cases, Person-yrs	Rate	Reference, n = 2284	Reference, Person-yrs	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

[1] Only inpatient diagnoses; all other diagnoses are for both inpatient and outpatient diagnoses. GCA: giant cell arteritis; VTE: venous thromboembolic diseases: pulmonary embolus and/or deep vein thrombosis.

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

Comorbidity	GCA, n = 197	Cases, Person-yrs	Rate	Reference, n = 782	Reference, Person-yrs	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

[1] Only inpatient diagnoses; all other diagnoses are for both inpatient and outpatient diagnoses. GCA: giant cell arteritis; VTE: venous thromboembolic diseases: pulmonary embolus and/or deep vein thrombosis.

study. Udayakumar, *et al* demonstrated no overall increase 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[13,14,15]. 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.

Our study found significantly higher rates of osteoporosis and related fractures (irrespective of whether 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 subclinical osteoporosis. The higher rates of osteoporosis and related fractures among the group with GCA further highlight the increased risk of this likely treatment-related morbidity.

We found a higher rate of thyroid disease among patients with GCA compared with the reference population, which is consistent with 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 experiencing recurrence of nonspecific symptoms such as fatigue, myalgia, and arthralgia. Outcomes in patients with GCA and thyroid disease warrant further studies.

The risks of infections and related morbidity are among the major concerns when treating older people with immunosuppressive drugs, including high-dose glucocorticoids. In our study, significant increases in rates of severe infections and septicemia were found among patients with GCA compared with reference subjects. However, in a 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[23]. The difference between these results and those of our current study may relate to differences in case definition; our current study only included first episodes of infection. 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 VTE 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[25,26,27,28]. The reason for the association between GCA and the high rate of VTE is not clear. The hypercoagulability associated with vascular inflammation is a possible explanation because VTE are among direct consequences of inflammatory vessel diseases as in other autoimmune diseases[27].

The sex-specific RR 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 RR were obtained for thyroid diseases among female patients. Because of the limited number of male patients with GCA, the estimated rates and RR are less precise for these subanalyses in men compared with women.

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

Our 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% and 95%[29]. Because the inpatient codes included in the SHR are reported to the national register, these figures should be applicable to hospitalization with comorbidities in our present study.

By only including the first event that occurred after the GCA diagnosis 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 our 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 our study do not apply to patients with GCA with negative temporal artery biopsies.

Our study demonstrated that patients with biopsy-proven GCA 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 improved disease control in this context.

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APPENDIX 1. The average time (person-year) of followup from diagnosis of giant cell arteritis (or index date for reference population) to the occurrence of first comorbidity.

Comorbidity	No. Pts. with Comorbidity, GCA	Average Time of Followup (person-year; GCA)	No. Pts. with Comorbidity, Reference	Average Time of Followup (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; VTE: venous thrombotic event; URTI: upper respiratory tract infection.