Is Statin Exposure Associated with Occurrence or Better Outcome in Giant Cell Arteritis? Results from a French Population-based Study

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ABSTRACT. ***Objective.*** To investigate the potential association between statin use and giant cell arteritis (GCA) course.

Methods. Using the French National Health Insurance system, we included patients with incident GCA from the Midi-Pyrenees region, southern France, from January 2005 to December 2008 and randomly selected 6 controls matched by age, sex, and date of diagnosis. Statin exposure was compared between patients with GCA and their controls before GCA occurrence with a logistic regression. Influence of statin exposure on prednisone requirements during GCA course was explored with a Cox model, considering statin exposure as a time-varying variable.

Results. The cohort included 103 patients (80 women, mean age 74.8 ± 9 yrs, mean followup 48.9 ± 14.8 mos), compared to 606 controls. Statin exposure (27.2% of patients with GCA and 23.4% of controls) was not associated with GCA occurrence (adjusted OR 1.2, 95% CI 0.76–1.96; p = 0.41). Diabetes mellitus was significantly associated to GCA occurrence (adjusted OR 0.38, 95% CI 0.11–0.72; p = 0.008). After diagnosis, exposure to statins up to 20 months was associated with maintenance while taking low prednisone doses (p = 0.01).

Conclusion. Statin exposure was not associated with GCA occurrence in the general population. However, exposure to statins up to 20 months may favor a quicker corticosteroid tapering. Based on those results, statin effect on GCA course should not be definitively ruled out. (J Rheumatol First Release Dec 15 2014; doi:10.3899/jrheum.140906)

Key Indexing Terms:
GIANT CELL ARTERITIS PREDNISONE STATINS

Statins are widely prescribed to lower blood cholesterol levels and to reduce the risk of cardiovascular ischemic events[1,2]. These drugs may also exert immunomodulatory and antiinflammatory effects, both *in vitro* and *in vivo* by promoting a shift from a Th1 to a Th2 immune response[3,4,5]. Some studies suggested that statin use was associated with an increased risk of Th2 type autoimmune diseases such as dermatomyositis[6] and systemic lupus erythematosus[7,8], whereas other studies found a decreased risk of rheumatoid arthritis (Th1-type autoimmune disease)[9], although this latter association remains in dispute[10].

Giant cell arteritis (GCA), an antigen-driven Th1 and Th17 disease[11], is the most frequent primary vasculitis in patients aged over 50 years[12,13]. Glucocorticosteroids (GC) are the only drugs that can prevent ischemic complications due to the vasculitic process. A recent study at the Mayo Clinic in Minnesota, USA, found that statin users may be less likely to develop GCA compared with nonusers[14]. However, the authors did not confirm their results when they restricted the analysis to the population-based subset of patients living in Olmsted County, Minnesota, possibly because of the small sample size. The authors found no effect of statins on the course of the disease, as reported in other studies[15,16]. The methodological pitfalls of these latter studies have been discussed[17], leading to the conclusion that further studies are necessary before definitively ruling out an effect of statins on GCA course.

Corticosteroid-treated patients including those with GCA are at increased risk of cardiovascular events[18,19,20,21,22]. Statins may reduce inflammation *in vivo* in patients with GCA[23]. Therefore, patients with GCA may be candidates for a liberal prescription of statins. We built up an exhaustive and population-based cohort to study GCA incident cases in

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the geographical area of Midi-Pyrenees, southern France (2.8 million inhabitants). This cohort was implemented through data systematically and prospectively collected in the French National Health Insurance system (FNHIS) database. The objectives of the present study were to investigate the potential association between statin exposure and GCA occurrence, and to evaluate the influence of statins on prednisone requirement after GCA diagnosis.

MATERIALS AND METHODS

Population source. The FNHIS covers more than 95% of the French population, whether they are treated in hospitals or by general practitioners (GP). Several pharmacoepidemiologic studies have been done during the last few years using the SNIIRAM (Système National d'Information Inter Régime de l'Assurance Maladie), the national database of the FNHIS[24,25,26,27,28,29]. The database contains demographic characteristics of patients (age, sex, vital status, and date of death); characteristics of health professionals; all chronic disabling longterm disease (LTD), and all reimbursement data (drug, laboratory, radiology, and medical procedures). LTD status is requested by the GP on behalf of the patient, by completing a standardized medical form with clinical, biological, and histological criteria of the corresponding disease. An FNHIS physician validates the diagnosis on the basis of this information and allocates a disease code according to the International Classification of Diseases, 10th ed (ICD-10), which is recorded in the database. This is a mandatory procedure to obtain the full reimbursement of medical expenditures for LTD. Concerning drugs, information about the date of dispensing, quantity dispensed, date of prescription, and qualification of the prescriber are available. All drugs are classified according to the Anatomical Therapeutic and Chemical system. The medical indication for outpatient reimbursement is not available, except for patients with a severe and costly chronic disabling LTD, who are fully reimbursed for most of their disease-related expenses. For research purposes, all these data are available anonymously regarding patients and health professionals.

When the current study was designed, only part of the SNIIRAM data was available, corresponding to that of the workers general insurance system, which covers 87% of the population. We used the data of the workers general insurance system from the Midi-Pyrenees County, southern France.

From January 2005 to December 2008, the database was searched every 6 months for patients with incident GCA. Once the cohort of incident patients was built, patients were followed until April 30, 2011.

Identification of patients with incident GCA. The first step was the extraction of all possible patients with GCA from January 2005 to December 2008 using the following criteria: (1) age ≥ 50 years, (2) LTD with an ICD-10 code M31, and (3) at least 1 prescription of GC including prednisone, prednisolone, or methylprednisolone. The second step consisted of the validation by the FNHIS physician (RB) of the diagnosis by a systematic review of the original medical form completed by the patient's GP to obtain the LTD status. Only patients with a diagnosis of GCA (M31.5 or M31.6 codes) that raised no doubt at this assessment were retained for further selection. Of note, because of French rules, we were not authorized to get clinical or biological information from these medical forms.

The third step aimed at identifying incident cases defined by (1) a continuous GC course defined by at least 4 prescriptions of prednisone, prednisolone, or methylprednisolone during a 6-month period, the date of first GC prescription defining the index date for followup; (2) first prescription corresponding to a prednisone equivalent dose between 5 and 150 mg/d; (3) no exposure to GC during the 6 months before the index date; and (4) GCA recorded as an LTD from 1 month before to 3 months after index date.

Selection of controls. For each incident case, we randomly selected 6 controls matched for sex and age at calendar year of diagnosis in the FNHIS database among patients who did not have GCA, polymyalgia rheumatica (PMR; code M35.3), or vasculitis. All controls exposed to at least 1 prednisone prescription during the 6 months before index date were excluded and replaced by another control. Each control was assigned the same index date as his/her corresponding case, and data collected were the same as for patients with GCA.

Drug exposure. Drug exposure relies on the drugs actually dispensed by pharmacists. We collected information on the drugs dispensed to patients with GCA until April 2011. These drugs were GC, hydroxychloroquine, immunosuppressants, statins, blood glucose–lowering drugs, antihypertensive drugs, platelet aggregation–inhibiting drugs, and antiarrhythmic drugs. GC dose was standardized in prednisone equivalent as follows: 1 mg of prednisone equivalent = 1 mg of prednisone = 1 mg of prednisolone = 0.8 mg of methylprednisolone.

For statins and GC, we collected the dose and number of pills in the box, with all prescription dates. Sustained statin exposure before index date was defined as at least 4 prescriptions in a 6-month period before index date, both for GCA cases and controls. Cumulative doses of GC were computed in grams and cumulative doses of statins were computed in defined daily doses (DDD; www.whocc.no/ddd/definition_and_general_considera/) by adding up all prescribed doses. These were calculated before index date, and then from index date to the date of entering maintenance with a low prednisone dose (LPD), and from index date to the end of the followup. We estimated the ongoing daily dose of prednisone equivalent at various timepoints by dividing the quantity of GC prescribed at this time by the number of days until next prescription.

Comorbidities. We also collected information on comorbidities recorded earlier than 1 month before index date using their respective chronic disabling LTD ICD-10 code. Diabetes mellitus (DM) was defined by the sustained prescription (i.e., at least 4 prescriptions during the 6 months before index date) of blood glucose–lowering drugs used as a proxy and its ICD-10 code. We speculated that the presence of cardiovascular comorbidities (stroke, coronary artery disease, heart failure, peripheral artery disease, hypertension, cardiac arrhythmias, or other cardiovascular comorbidities, essentially valvular or congenital cardiopathies) might influence the management of GC tapering by attending physicians. Therefore, we pooled these diseases to study their influence on time to reach maintenance while taking LPD.

Maintenance while taking LPD. Maintenance while taking LPD was defined as a daily dose of < 5 mg prednisone with no increase during 6 consecutive months. The 5-mg threshold was chosen because it is lower than that required for physiological replacement therapy (usually 5 to 7.5 mg/d) and has probably no significant antiinflammatory effect[30].

Statistical analysis. Descriptive statistics were used to summarize the data including percentage, mean with ± SD, and median with first and third quartiles of the distributions (IQR). Comparisons between patients with GCA and matched controls were done using the Fisher's exact test and the Wilcoxon signed-rank test. Association between statin exposure and the occurrence of GCA was analyzed with a conditional logistic regression model, allowing for adjustment on potential confounding variables. These were age, sex, cardiovascular comorbidities, DM, and exposure to drugs that reflect the presence of cardiovascular diseases (Table 1, Appendix 1). Variables with a p value < 0.25 in the univariate analysis were included in the multivariate conditional logistic regression model. We calculated OR and their 95% CI.

To evaluate the effect of statin exposure on GC requirement, we performed a survival analysis only on the cohort of patients with GCA. Time to maintenance with LPD was estimated with the Kaplan-Meier method. Statin users were compared to nonusers using the log-rank test. Patients were censored at the date of getting first maintenance with LPD, at the date of death or at the date of last drug prescription plus 30 days (patients lost to followup). For the other patients, followup ended April 30, 2011.

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Table 1. Population characteristics at index date.

Characteristics	GCA Patients, n = 103	Controls*, n = 606	p**
Age, yrs, mean, median (range)	74.8, 77 (51–91)	74.7, 77 (51–91)	0.97
Females, n (%)	80 (77.7)	469 (77.4)	1.0
Followup, mean (± SD), mos	48.9 (± 14.8)	48.0 (± 13.1)	0.56
GCA with PMR, n (%)	57 (55.3)	—	—
First prednisone dose, mean (± SD), mg/d	54.5 ± 27	—	—
Comorbidities, n (%)			
Cardiovascular diseases	11 (10.7)	88 (14.5)	0.63
Diabetes mellitus	5 (4.9)	90 (14.9)	0.004
Lung diseases	1 (1.0)	2 (0.3)	0.38
Cancer	10 (9.7)	48 (7.9)	0.56
Dementia	1 (1.0)	4 (0.7)	0.54
Psychiatric disorders	1 (1.0)	10 (1.7)	0.58
Other	0	24 (4.0)	0.05
Drugs exposure, n (%)			
Antihypertensives	57 (55.3)	303 (50.0)	0.39
Platelet aggregation inhibitors	19 (18.5)	103 (17.0)	0.78
Cardiac glycosides or antiarrhythmics	5 (4.9)	51 (8.4)	0.32
Statins, n (%)	28 (27.2)	142 (23.4)	0.45
Cumulative dose, median (range), DDD	70 (10–252)	84 (14–378)	0.10
Atorvastatin, n (%)	2 (1.9)	32 (5.3)	0.21
Cumulative dose, median (range), DDD	37 (14–60.7)	84 (14–378)	0.13
Fluvastatin, n (%)	3 (2.9)	10 (1.7)	0.42
Cumulative dose, median (range), DDD	37 (10–120)	112 (38.7–298.7)	0.15
Pravastatin, n (%)	11 (10.7)	47 (7.8)	0.33
Cumulative dose, median (range), DDD	93 (18.7–242.7)	93 (18.7–223.8)	0.71
Rosuvastatin, n (%)	0	14 (2.3)	0.24
Cumulative dose, median (range), DDD	—	91 (14–196)	—
Simvastatin, n (%)	12 (11.7)	39 (6.4)	0.05
Cumulative dose, median (range), DDD	65 (18.7–252)	89 (18.7–240)	0.31

* For 12 patients, only 5 accurately matched controls could be found in the database. ** p values > 0.05 not significant. DDD: defined daily dose; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

We then identified variables associated with maintenance with LPD using Cox models. We studied separately the effect of a sustained statin exposure at index date, statin exposure at the time of censoring events or April 30, 2011, and statin exposure after index date as a time-dependent covariate. For this latter purpose, statin exposure was divided into 4 classes, first according to the duration of exposure and then according to the cumulated prescribed doses, cutoff values being terciles of the respective distributions. Other explanatory variables are listed in Table 3. We planned to include variables associated with maintenance while taking LPD at a p value < 0.25 in multivariate, stepwise descendant models. Results were expressed as hazard ratios (HR) and their 95% CI.

All tests were 2-sided with a significance level of $p < 0.05$. Statistical analysis was performed using SAS software (version 9.3; SAS Institute).

Ethics/consent. We performed an observational study on anonymous data. Thus, according to French law, the study does not need to be approved by an ethics committee (French law on privacy: National Commission on Information Technology and Liberty, decision no. 89-117).

RESULTS

Patient selection. Among 268 patients with M31 code during the inclusion period, 103 were defined as patients with incident GCA (Figure 1). Mean age was 74.8 ± 9 years and 80 were women (77.7%). During the study period, 8 patients died (7.8%). Fifty-seven patients [presenting with "GCA with PMR" (M31.5 code; 55.3%)] did not differ from other patients with GCA regarding age, sex, comorbidities, cardiovascular drug exposure, or initial prednisone doses. No patients with GCA were taking methotrexate during the study.

Table 2. Time-dependent statin exposure during prednisone course in 103 patients with incident giant cell arteritis.

Statin Exposure from Index Date	Maintenance on Low Prednisone Dose, n (%)	
	Yes	No
No exposure	54 (52.4)	20 (19.4)
1 to 12 mos	9 (8.7)	0
12 to 20 mos	8 (7.8)	1 (0.97)
> 20 mos	10 (9.7)	1 (0.97)

Maintenance on low prednisone dose: < 5 mg/d for at least 6 months.

Case-control analysis for statin exposure and GCA occurrence. There was no significant difference between groups except for DM, which was more frequent among controls

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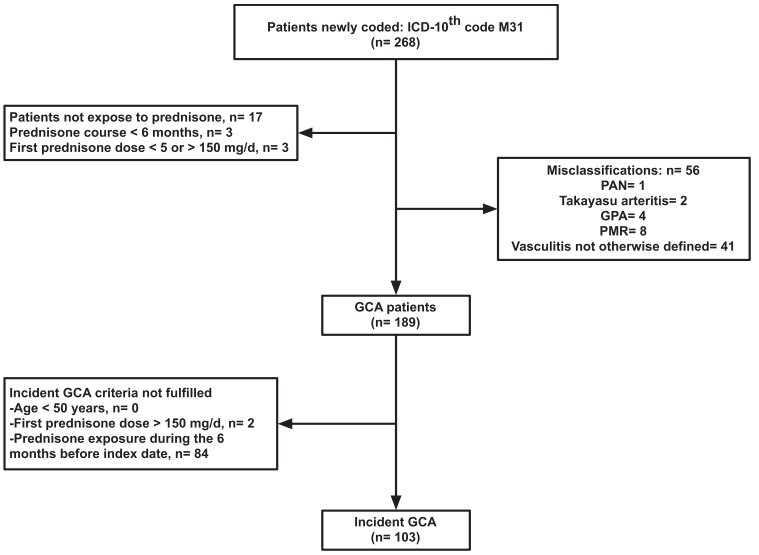

Figure 1. Flow diagram of GCA incident cases selected from the Midi-Pyrenees FNHIS database. FNHIS: French National Health Insurance System; ICD-10: International Classification of Diseases, 10th ed; PAN: polyarteritis nodosa; GPA: granulomatosis with polyangiitis; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

(4.9% vs 14.9%, p = 0.004; Table 1). Twenty-eight patients (27.2%) and 142 controls (23.4%) had a sustained statin exposure before index date, with a similar distribution between groups, simvastatin being the most frequently used (Table 1). Statin exposure was not associated with GCA occurrence (age-adjusted and sex-adjusted OR 1.2, 95% CI 0.76–1.96; p = 0.41). DM was associated with GCA (age-adjusted and sex-adjusted OR 0.38, 95% CI 0.11–0.72; p = 0.008). There was also no significant relationship between each statin studied separately and GCA occurrence: atorvastatin (adjusted OR 0.36, 95% CI 0.08–1.5; p = 0.17), simvastatin (adjusted OR 1.8, 95% CI 0.85–3.6; p = 0.13), and pravastatin (adjusted OR 1.6, 95% CI 0.77–3.2; p = 0.21). The overall cumulative statin dose in the 6 months before index date had no influence on GCA occurrence (adjusted OR 1.0, 95% CI 0.99 to 1.004; p = 0.28).

Statin exposure effect on GC course. Mean patient followup and initial prednisone-equivalent doses are presented in Table 1. Three patients who received a first prednisone dose lower than 20 mg/d then had an increase in dosage, leading to a mean daily prednisone dose above 20 mg during the first 3 months.

The rate of patients reaching maintenance with LPD was 48%, 70%, 85%, and 89% at 2, 3, 4, and 5 years of followup, respectively. Mean time to reach maintenance with LPD was 24.3 ± 11.2 months. At that time, the mean cumulative prednisone dose was 11.4 ± 6.1 g.

Among the 28 patients who had a sustained statin exposure before index date, 6 stopped statins at GCA diagnosis, and 7 began statins from index date to time of reaching LPD or to end of followup for those not reaching an LPD. Therefore, 29 statin-exposed patients were included in the survival analysis (Table 2). Mean duration of statin exposure after index date was 21.1 ± 14.4 months with a mean cumulative dose of 313.9 ± 280.0 DDD.

Maintenance with LPD was achieved more frequently in patients exposed to statins before index date (HR 1.9, 95% CI 1.16–3.15; p = 0.011; Table 3) and there was a trend toward a beneficial effect of statin exposure at the time of maintenance with LPD (HR 1.6, 95% CI 0.97–2.72; p = 0.067). Compared to no exposure, we found a protective effect of statins for exposures lasting for 1 to 12 months (HR 4.5, 95% CI 2.15–9.55; p < 0.0001) and for 12 to 20 months (HR 3.8, 95% CI 1.69–8.44; p = 0.00012), but not beyond 20 months (HR 0.8, 95% CI 0.41–1.61; p = 0.56). We did not perform the planned multivariate analysis because of the low level of association of all variables of interest with maintenance on LPD. The results were similar when statin exposure was expressed in cumulative doses. In patients exposed to statins after the index date, the cumulative prednisone dose required to reach maintenance with LPD tended to be lower (10.9 ± 7.3 g vs 12.1 ± 7.0 g; p = 0.25) and shorter (median 20 mos, IQR 15–27 vs 23.5, IQR 16 to 33; p = 0.34), but the differences were not significant.

In the confirmatory analyses of time to complete prednisone withdrawal, the results were consistent with the main analysis but did not achieve significance, perhaps owing to loss of power (data not shown).

DISCUSSION

In our study, we found no influence of exposure to statins on the occurrence of GCA in the general population. However,

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Table 3. Results of Cox proportional hazard regression model investigating the effect of statins and other variables on the probability of maintenance on a low prednisone dose (< 5 mg/day) during more than 6 months in giant cell arteritis.

Variables	Hazard Ratio (95% CI)	p
Age	1.0 (0.64–1.54)	0.98
Sex	0.95 (0.55–1.62)	0.83
GCA with PMR	0.84 (0.54–1.3)	0.43
First prednisone dose	1.0 (0.99–1.01)	0.98
Cardiovascular comorbidity	0.94 (0.6–1.47)	0.78
Diabetes mellitus	1.21 (0.38–3.85)	0.75
Platelet aggregation inhibitors	0.89 (1.0–1.76)	0.97
Antihypertensives	0.91 (0.58–1.42)	0.67
Statins at baseline	1.9 (1.16–3.15)	0.011
Statins at maintenance on low prednisone dose	1.6 (0.97–2.72)	0.067
Time-dependent statin exposure from index date		
No exposure	1	
1 to12 mos	4.5 (2.15–9.55)	< 0.0001
12 to 20 mos	3.8 (1.69–8.44)	0.00012
> 20 mos	0.8 (0.41–1.61)	0.56
Cumulative statin exposure from index date		
No exposure	1	
1 to 160 DDD	4.88 (2.32–10.28)	< 0.0001
160 to 261.1 DDD	2.36 (1.10–5.09)	0.027
> 261.1 DDD	0.89 (0.45–1.75)	0.73

The hazard ratios displayed are from the univariate analysis. DDD: defined daily dose; GCA: giant cell arteritis; PMR: polymyalgia rheumatica.

our results suggest that statins might favor corticosteroid tapering in a majority of patients with GCA.

We also found a large difference in the frequency of DM before GCA occurrence between patients and controls. This unexpected result has been reported in an American study and a French one[14,31]. We have no explanation, and these results must be confirmed in a larger and independent cohort to adjust the risk of potential confounders.

Regarding statin exposure as a time-dependent variable, the Cox analysis showed that there was a time interaction and this effect disappeared beyond 20 months. No association between any cardiovascular risk factor and GC course in GCA has yet been described. So it seems unlikely that statin use acted as a confounder for another risk factor. We hypothesize that this may be due to a specific reduced pharmacogenetic susceptibility. The immunoregulatory effects of biological statins are many. The main one is downregulation of inflammatory mediators, especially interleukin 17 (IL-17) and IL-6, which are key mediators in the GCA pathophysiological process[32]. Statins also reduce co-stimulation, especially by dendritic cells[33]. This hypothesis needs further validation in independent cohorts.

The strengths of our study are (1) the significant number of patients in our cohort considering the short period of inclusion (other population-based GCA cohorts included patients over 20 to 40 years[22,34]; however, our case series allowed for much more detailed information about diagnosis and flares[35]); (2) a prolonged followup from 34 to 69 months with a remarkably low attrition rate; (3) comprehensive information on drug exposure from 6 months before the index date; (4) accurate measurement of GC course duration and cumulative prednisone doses; and (5) the use of a survival analysis model, taking into account the variability of exposure to statins.

Some limitations of our study should be considered. First, because of French laws on privacy, we had no access to clinical and histological data to check the diagnosis of GCA using American College of Rheumatology criteria[36]; however, doubtful cases were excluded by the FNHIS physician. Of note, the profile of identified patients, the evolution of prednisone exposure over time (Appendix 2), as well as the rate of prednisone withdrawal were highly consistent with data from other studies[31,34,37]. Our method was not sensitive enough to identify disease flares requiring a small GC dosage increase. Flares requiring a GC dosage increase above 20 mg/d as well as disease recurrences were rare (data not shown).

We found no clear difference in the cumulative prednisone doses between statin-exposed and statin-unexposed patients. In fact, the largest part of the cumulative prednisone dose was supported by the higher doses required during the first year of treatment. Therefore, moderate reductions in the cumulative doses after the first year may not result in significant differences in the total cumulative dose.

Our method probably did not capture all patients with GCA in the region. Indeed, all patients exposed to corticosteroids at least once during the 6 months before the index date were excluded. These patients could not be included

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back in a complementary analysis because of the uncertainty on the accurate index date. Moreover, many patients were excluded from the study as a result of insufficient information to confirm GCA diagnosis. Some of them may have been patients with true GCA.

Finally, we lacked clinical data to adjust the risk of disease occurrence for some potential confounding factors such as smoking, which has previously been identified as an independent risk factor for GCA in French women[31]. However, smoking habits were not associated with the risk of GCA occurrence in 2 recent population-based studies[14,38].

We showed that sustained statin therapy during the 6 months preceding the diagnosis of GCA was not associated with GCA occurrence in the general population. However, exposure to statins up to 20 months was associated with a quicker corticosteroid tapering. Based on those results, statin effect on GCA course should not be definitively ruled out.

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APPENDIX 1. Detail of the "cardiovascular diseases" section of Table 1. Data are n (%).

Cardiovascular Diseases at Study Entry	GCA, n = 103	Controls, n = 606
Heart failure	2 (1.9)	15 (2.5)
Coronary artery disease	4 (3.9)	24 (4.0)
Peripheral artery disease	0	15 (2.5)
Cardiac arrhythmia	5 (4.9)	53 (8.8)
Stroke	0	8 (1.3)
Other cardiovascular disease	1 (1.0)	4 (0.7)

APPENDIX 2. Prednisone tapering during giant cell arteritis (GCA) course at 6-month intervals. In our incident GCA patient cohort, the prednisone course was comparable to what we prescribe in our clinical practice.

	M6	M12	M18	M24	M30	M36	M42	M48	M54
No. at risk	97	87	74	54	46	36	22	15	8
Prednisone, mg/d, mean ± SD	25.3 ± 17.7	16 ± 16.6	13.6 ± 13.4	12.9 ± 11	12.4 ± 11.4	13.4 ± 12	10 ± 9.2	10 ± 8.7	11 ± 11

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