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Risk for Cardiovascular Disease Early and Late After a Diagnosis of Giant-Cell Arteritis:

A Cohort Study

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Abstract

Background—Involvement of large arteries is well-documented in giant-cell arteritis (GCA), but the risk for cardiovascular events is not well-understood.

Objective—To evaluate the risks for incident myocardial infarction (MI), cerebrovascular accident (CVA), and peripheral vascular disease (PVD) in individuals with incident GCA in a general population context.

Design—Observational cohort study.

Setting—U.K. primary care database.

Patients—3408 patients with incident GCA and 17 027 age- and sex-matched reference participants without baseline cardiovascular disease (MI, CVA, or PVD).

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Measurements—Diagnoses of GCA, outcomes, and cardiovascular risk factors were identified from electronic medical records. One combined and 3 separate cohort analyses were conducted for the outcomes of MI, CVA, and PVD. The association of GCA with study outcomes is expressed with hazard ratios (HRs) with 95% CIs after adjustment for potential cardiovascular risk factors.

Results—Among 3408 patients with GCA (73% female; mean age, 73 years), the incidence rates of MI, CVA, and PVD were 10.0, 8.0, and 4.2 events per 1000 person-years, respectively, versus 4.9, 6.3, and 2.0 events per 1000 person-years, respectively, among reference participants. The HRs were 1.70 (95% CI, 1.51 to 1.91) for the combined outcome, 2.06 (CI, 1.72 to 2.46) for MI, 1.28 (CI, 1.06 to 1.54) for CVA, and 2.13 (CI, 1.61 to 2.81) for PVD. The HRs were more pronounced in the first month after GCA diagnosis (combined HR, 4.92 [CI, 2.59 to 9.34]; HR for MI, 11.89 [CI, 2.40 to 59.00]; HR for CVA, 3.93 [CI, 1.76 to 8.79]; HR for PVD, 3.86 [CI, 0.78 to 19.17]).

Limitation—Information on temporal arterial biopsies was not available, and there was a substantial amount of missing data on cardiovascular risk factors.

Conclusion—Giant-cell arteritis is associated with increased risks for MI, CVA, and PVD.

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Giant-cell arteritis (GCA) is a large-vessel vasculitis that has predilection for large and medium-sized arteries (1, 2). It can result in ischemic blindness (3, 4), and the mainstay of treatment is high doses of glucocorticoids for substantial periods. Imaging studies have described a high prevalence of large-artery stenoses and aneurysms in cohorts of patients with GCA (5, 6), but studies exploring the association of GCA with clinically important cardiovascular events have provided conflicting results (7, 8). A large population study from Canada of 1100 patients with GCA showed an increase in vascular events (coronary heart disease, stroke, peripheral artery disease, aneurysm, and dissection) compared with randomly selected reference participants from the same population (hazard ratio [HR], 2.1 [95% CI, 1.5 to 3.0] after limited adjustment for potential risk factors [medication use for hypertension and hyperlipidemia]) (7). In contrast, a preliminary report from a large cohort study in the United States using hospital discharge diagnoses of GCA in 4807 patients found an increase in thoracic aortic aneurysms (HR, 5.2 [95% CI, 1.5 to 9.0]) and a minimally increased risk for strokes (HR, 1.29 [CI, 1.15 to 1.45]), but not for other atherosclerotic disease (coronary heart disease, peripheral artery disease, or aortic abdominal aneurysm) compared with 19 228 reference participants (8), with limited adjustment for cardiovascular risk factors. A few studies have suggested that traditional cardiovascular risk factors are associated with occurrence and complications of GCA (9 –12). Therefore, information on cardiovascular risk factors is important when the association of GCA with cardiovascular disease is explored.

The objective of this study was to determine the association between GCA and incident cardiovascular disease, defined as myocardial infarction (MI), cerebrovascular accident (CVA), or peripheral vascular disease (PVD), in an unselected population cohort with information on risk factors for cardiovascular disease.

Methods

Data Source

Data were obtained from The Health Improvement Network (THIN), an electronic database derived from general practices in the United Kingdom that includes data on approximately 7.3 million patients (13). Database elements are obtained from visits with general practitioners, specialists, and from hospitalizations. Data on diagnoses (14), prescription medications, height, weight, smoking status, vaccinations, and other variables are entered into the THIN database by primary care physicians during clinical visits. This study was judged to be exempt from review by the Institutional Review Board at Boston University Medical Center and was approved by the THIN Scientific Review Committee.

Study Design

We performed a matched cohort study to examine the relation of patient with incident GCA to risk for MI, CVA, and PVD. Specifically, for each GCA, we selected up to 5 individuals without GCA at the time that the patient with GCA was diagnosed, matched by age, sex, and time of entry into the THIN database. Patients with cardiovascular disease (MI, CVA, or PVD) at baseline were excluded.

GCA Definition

Patients with GCA were those who had a diagnosis of GCA, temporal arteritis, or Horton disease that appeared at least 1 year after the patient was entered into the THIN database and who received and used a prescription for glucocorticoids. We defined glucocorticoid use as 2 prescriptions for oral glucocorticoids, the first within 6 months of the date of GCA diagnosis and the second within 6 months of the first prescription. The database used for analysis was compiled in 2012. Because historical diagnoses may be erroneously recorded as having occurred on the date of patient enrollment or the date when a general practice begins to use the database software, patients with incident cases were included only if GCA was first diagnosed at least 12 months after their records were computerized. Because GCA is exceptionally rare among persons younger than 50 years, we excluded persons in this age group from the analysis. In a supplemental analysis, we used a more stringent definition of GCA that required 10 or more prescriptions of glucocorticoids.

Covariate Assessment

We obtained information on cardiovascular risk factors as follows. Information on *smoking status* was obtained from the codes for smoking and smoking history. A categorical variable with the values “current smoker,” “former smoker,” or “never smoker” was created. *Hypertension* was handled as a dichotomous variable defined as the presence or absence of any of the following diagnoses: hypertension, essential hypertension, high blood pressure, malignant essential hypertension, benign essential hypertension, systolic hypertension, or diastolic hypertension. We obtained data on *total cholesterol level* in millimoles per liter and used this as a continuous variable. *Diabetes mellitus* was handled as a dichotomous variable defined as a diagnosis of diabetes mellitus or any of its subcodes or an outpatient prescription code for any form of insulin, sulfonylureas, or other drugs used to treat diabetes

(excluding biguanides). *Body mass index* (BMI) was obtained from a corresponding code in the medical record. Only data on covariates that were recorded in the THIN database before patients' contribution of follow-up time were included in the analysis.

Assessment of Medications Used for Cardiovascular Disease

We assessed baseline use of the following medications commonly prescribed to treat cardiovascular disease: antiplatelet agents, β-blockers, nitrates, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). We defined medication use as 1 or more outpatient prescription codes for one of these medications.

Follow-up and Outcomes Definitions

Data collected from 1 January 1990 through 1 June 2010 were used for this study. We followed patients with GCA from the date of diagnosis and reference participants from the matched (index) date until occurrence of any cardiovascular event, death, migration of the THIN database, or 1 June 2010, whichever came first. Incident MI was defined as the presence of any of several diagnostic codes pertaining to MI, including myocardial infarction, heart attack, and codes pertaining to a specific anatomical site of the myocardium or specified pattern on an electrocardiogram. Incident PVD was defined as any of the following diagnoses: peripheral ischemic vascular disease, other specified peripheral vascular disease NOS, other peripheral vascular disease, or peripheral vascular disease. Incident CVA was defined as the first appearance of any of the following diagnoses: CVA unspecified, stroke unspecified, cerebrovascular accident unspecified, middle cerebral artery syndrome, anterior cerebral artery syndrome, posterior cerebral artery syndrome, brainstem stroke syndrome, cerebellar stroke syndrome, pure motor lacunar syndrome, pure sensory lacunar syndrome, or left- or right-sided CVA. Patients who had 1 type of cardiovascular event were censored in the analyses for the other types.

Statistical Analysis

We compared the characteristics of patients with GCA and reference participants by using the *t* test for continuous variables and a chi-square test for categorical variables. Person-years of follow-up for each patient were computed as the time from the index date to the end of follow-up. We calculated incidence rates of each outcome event for each group by dividing the number of cases of each outcome variable by the number of person-years. The associations between GCA and study outcomes are expressed as incidence rate ratios with 95% CIs. We plotted the cumulative incidence rate of each outcome variable for individuals with and without GCA and accounted for the competing risk for the other outcomes.

We used the Markov-chain Monte Carlo method (15) to impute missing data on BMI, cholesterol level, and smoking status under the assumption that data were missing at random (MAR). Because there was a substantial amount of missing data on cholesterol level (>50%), 50 data sets with imputed data were created and data for the following variables were used for imputation of missing variables: age, sex, GCA status, smoking status, hypertension, diabetes mellitus, cholesterol level, BMI, and outcome. Because the MAR assumption was unverifiable, we performed the analysis using both the imputed data sets and those restricted to patients with complete data.

We fitted Cox proportional hazards models to separately determine the relation of GCA to cardiovascular disease (MI, CVA, or PVD). In the multivariate Cox proportional hazards models, we adjusted for age, sex, smoking, hypertension, diabetes mellitus, BMI, and total cholesterol level. In the adjusted analysis, the effect of GCA on study outcomes is expressed with HRs with 95% CIs. The assumption of proportional hazards between patients with and without GCA was evaluated by a visual inspection of a diagnostic plot of the log of the minus log survival against log time and by testing an interaction term between time and GCA status for statistical significance, with a 2-sided *P* value less than 0.05 indicating statistical significance. In cases where the proportional hazards assumption was violated, series of average HRs for increasingly longer periods of follow-up are presented (16). We conducted 3 sensitivity analyses. First, to account for the effect of the competing event of death and the other cardiovascular events on the study outcome of interest, we conducted a competing risk analysis according to the Fine and Gray method (17) and expressed results as subdistribution HRs with 95% CIs. Second, we used a stricter definition of GCA limited to patients with the disease and 10 or more outpatient prescriptions for glucocorticoids. Third, we conducted an analysis restricted to patients who had no prescriptions for medications for treatment of cardiovascular disease. In all supplemental analyses, measures of association were adjusted for age and sex but not for cardiovascular risk factors.

We used SAS, version 9.2 (SAS Institute, Cary, North Carolina), for statistical analyses. Specifically, we used PROC MI to impute missing data, PROC PHREG for the survival analysis, and PROC MIANALYZE to estimate the effect over the 50 imputed data sets. For generation of cumulative incidence curves and competing risks calculations, the statistical package R (www.r-project.org) was used, specifically the crr and cuminc functions in the cm-prsk package.

Role of the Funding Source

The funding sources had no role in the design, conduct, or reporting of the study or the decision to submit the manuscript for publication.

Results

Baseline Characteristics

We included 3408 patients with a diagnosis of GCA and 17 027 reference participants in the analysis. Table 1 shows the baseline characteristics of patients in both groups. Tobacco use and hypertension were slightly more common among patients with GCA. There was a substantial amount of missing data on smoking status and hypercholesterolemia, and these data were more often missing among the reference participants.

Association of a Diagnosis of GCA With Incident Cardiovascular Disease

Median follow-up was 3.9 years (interquartile range, 1.5 to 7.2 years) among patients with GCA and 4.2 years (interquartile range, 1.8 to 7.5 years) among reference participants. Giant-cell arteritis was associated with a substantially increased risk for cardiovascular disease and statistically significantly increased risks for MI, PVD, and CVA (Table 2). Three hundred sixty-seven patients with GCA had cardiovascular events during 16 553

person-years of follow-up versus 1155 in the reference group during 87 504 person-years of follow-up (incidence rate ratio, 1.68 [95% CI, 1.49 to 1.89]). The Figure shows cumulative incidence of cardiovascular events among patients with GCA and reference participants.

In a multivariate proportional hazards analysis, the measure of association between traditional risk factors and cardiovascular outcomes was in the expected direction but was not statistically significant for all risk factors for each cardiovascular outcome. Visual inspection of diagnostic plots suggested violation of the proportional hazards assumption in the analyses for combined cardiovascular events, CVA, and MI but not for PVD. In models with interaction terms between time and GCA, those interaction terms were statistically significant ($P < 0.05$) in the analyses for cardiovascular disease and CVA. The plots and interactions between time and GCA indicate that the hazards of the outcome varied over time for persons with GCA compared with those without it. This violation of the proportional hazards assumption precluded us from expressing the relative risk among patients with GCA for cardiovascular disease, CVA, or MI with a single HR for the entire follow-up period. The associations between GCA and study outcomes were generally stronger among patients with complete data on cardiovascular risk factors. Adjustment for cardiovascular risk factors did not attenuate the association between GCA and study outcomes (Table 3).

Association Between GCA and Cardiovascular Disease Early and Late After Diagnosis

The series of average HRs for increasingly longer periods of follow-up (Table 3) suggests that the association of GCA with cardiovascular disease was stronger soon after the diagnosis of GCA. The HRs for the combined outcome of cardiovascular disease were 4.92 (CI, 2.59 to 9.34) at 1 month after diagnosis of GCA and 1.70 (CI, 1.51 to 1.91) during the total follow-up time. We saw similar patterns for the individual outcomes of cardiovascular disease, except for PVD.

Supplemental Analysis

Subdistribution HRs from analysis of the association between GCA and study outcomes that accounted for the competing event of death and other cardiovascular events gave estimates almost identical to those obtained from the regular proportional hazards regression analysis (Table 4). Of the 3408 patients who met the criteria for GCA, 1956 (57.4%) had 10 or more prescriptions for glucocorticoids; analysis restricted to this group and matched reference participants gave similar effect estimates, although CIs were wider because of smaller sample sizes (Table 4). In a sensitivity analysis restricted to patients with no history of prescription for medications to treat cardiovascular disease (1635 patients with GCA and 9664 reference participants), we found measures of association similar to those in the primary analysis but with wider CIs (Table 4).

Discussion

This large population study not only shows substantially elevated risks for MI, PVD, CVA, and the combined outcome of cardiovascular disease among patients with GCA but also

suggests that there may be a period immediately after diagnosis of GCA associated with an especially high relative risk for cardiovascular disease.

Our findings are consistent with those studies of GCA reporting an increased risk for blindness—also an ischemic vascular event— occurring early in the disease (12, 18, 19). A diagnosis of GCA represents a clinically significant event for elderly adults, and there are several mechanistic pathways that could mediate the increased risk for GCA on cardiovascular disease in the period immediately after diagnosis. Treatment with high doses of glucocorticoids is the standard of care for GCA and has well-documented proatherosclerotic effects (20). The diagnosis of GCA is most often established by obtaining a temporal artery biopsy, a procedure that may require temporary interruption of antiplatelet and anticoagulation agents. Finally, psychological stress associated with the diagnosis and fear of blindness could also contribute to the risk for cardiovascular events immediately after diagnosis, as has been observed for other diseases (21).

This analysis has important strengths. Disease criteria were limited to patients with incident GCA to better capture the entire span of the natural history of the disease as it relates to development of cardiovascular disease. The study cohort of incident cases of GCA is large (>3000 patients) compared with other cohort studies in this disease. The large size of the THIN database results in excellent statistical power to study a rare disease, including the ability to study subgroups of importance and examine risk estimates for different intervals of the follow-up period. One of the primary assumptions in Cox proportional hazards regression is that the relative risk associated with the condition of interest can be described with a single number—the ratio of hazards between patients with and without the condition —that stays constant for the total duration of follow-up (proportional hazards assumption). Although the finding of violation of the proportional hazards assumption results in effect estimates that are difficult to interpret, it is advantageous to be able to identify periods when hazards are increased the most.

This analysis also has limitations. The diagnoses of GCA have not been fully validated in the THIN cohort. This would be a difficult task to complete without information on temporal artery biopsies because American College of Rheumatology classification criteria for GCA (1) are not useful for detecting the disease in the general population but were developed to separate patients with GCA from those with other types of vasculitis. Therefore, we included the requirement of 2 prescriptions of glucocorticoids after diagnosis of GCA in the disease definition. In a sensitivity analysis limited to patients with 10 or more prescriptions of glucocorticoids, similar effect estimates were obtained. However, we acknowledge that some patients with GCA may not have had truly incident disease because they had relapsing disease requiring retreatment. In addition, information on the type and location of CVAs was not available. Although we did not include codes for hemorrhagic strokes, we used the codes “stroke unspecified” and “CVA unspecified” and some hemorrhagic strokes could have been included in the analysis. Within the THIN cohort, there is no continuous surveillance for cardiovascular or other disease, and the absence of diagnostic codes for those diseases probably does not fully exclude all patients with prevalent cardiovascular disease at baseline. However, it is unlikely that our findings were driven by the effect of cardiovascular disease at baseline. In a sensitivity analysis restricted to patients who had

never received an outpatient prescription for medications commonly used to treat cardiovascular disease, similar effect estimates were obtained. There was a considerable amount of missing data on some cardiovascular risk factors, and the missingness was inversely associated with GCA status in this cohort, which raises concerns that outcome assessment and assessment for hypertension and diabetes mellitus might also depend on GCA status. We address the issue of missing data by multiple imputation. These methods rely on the MAR assumption—that is, missingness is not dependent on the true nonobserved value but can be associated with other variables. This assumption cannot be verified, but it should be pointed out that calculating effect estimates in an analysis restricted to patients with complete data involves assuming that missingness occurs completely at random, which is an even stronger assumption violated in this data set (missingness is associated with GCA status). We saw similar effect estimates with both of these approaches and consider it unlikely that the associations of GCA with the observed study outcomes are driven by bias resulting from missing data on covariates. It is also reassuring that estimated risks from traditional cardiovascular risk factors were of expected direction (22) and magnitude in this analysis. Although the amount of missing data is statistically significantly different between individuals with and without GCA, the absolute and relative differences are small and the potential resulting biases probably do not completely offset the high effect estimates observed.

These results are consistent with growing evidence that some chronic inflammatory diseases, especially rheumatoid arthritis, systemic lupus erythematosus, and some forms of vasculitis, are associated with increased rates of cardiovascular disease (23–25). Rheumatoid arthritis and lupus have consistently been found to put patients at risk for accelerated atherosclerosis. Whether common pathophysiologic processes leading to cardiovascular disease are involved in these diseases and GCA remains to be determined.

The finding of increased cardiovascular disease among patients with GCA could have important implications for clinical care both immediately after a diagnosis of GCA and in long-term treatment. Our findings imply that a diagnosis of GCA should alert clinicians to be mindful of possible acute cardiovascular events, particularly in the period soon after diagnosis. Treatment of patients with GCA with low-dose aspirin is already routine practice to prevent ischemic events; these data could be considered indirectly supportive of aspirin therapy in these patients. The relative contributions of active vasculitis and treatment with glucocorticoids to the risks for MI, CVA, and PVD would be an interesting focus of future investigation in GCA.

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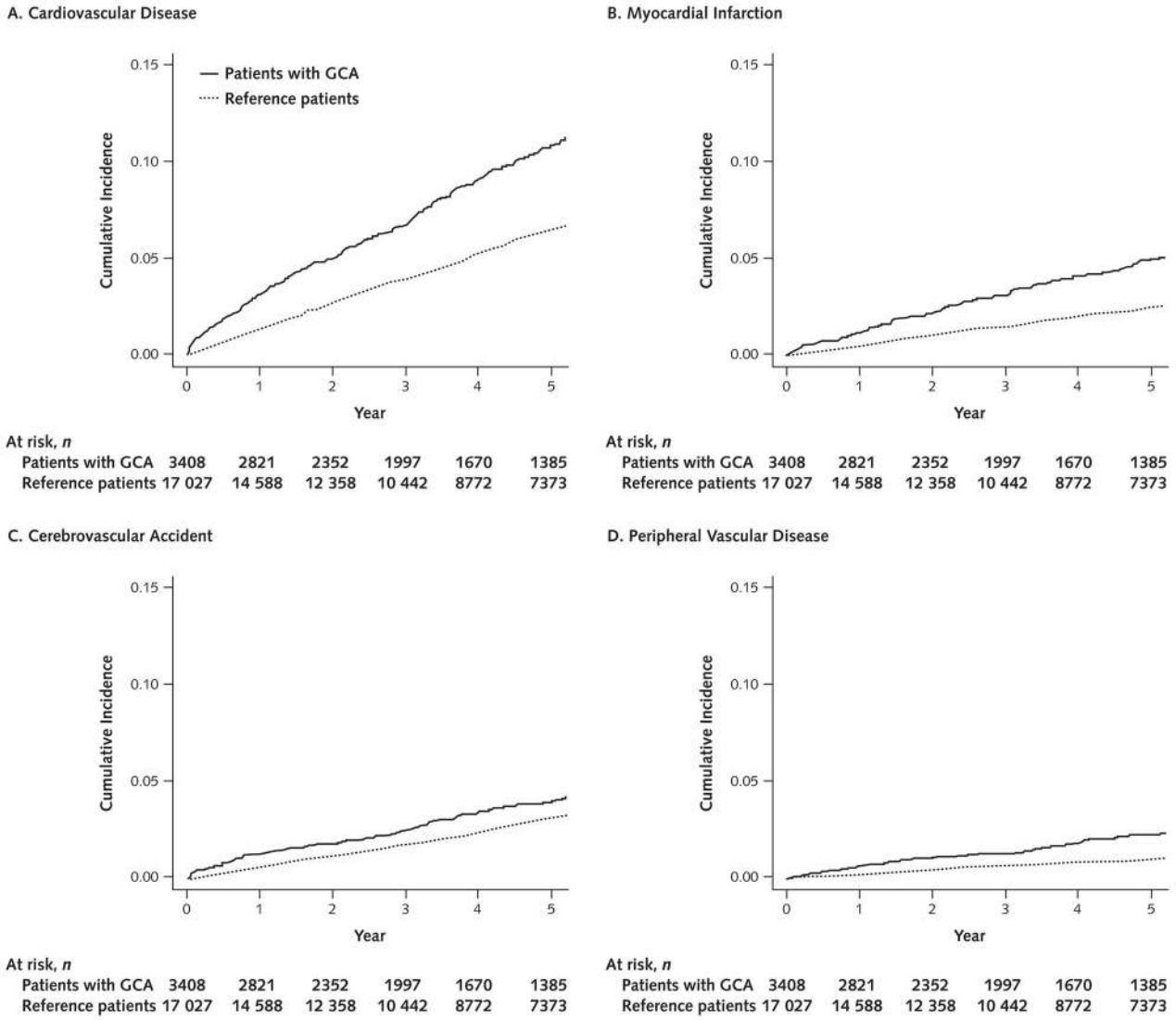

Figure.

Cumulative incidence in the 3408 patients with incident GCA and age-, sex-, and entry time–matched reference participants.

Because patients were censored when they sustained the competing event, the number "at risk" at each time is identical for the 4 outcomes. GCA = giant-cell arteritis.

Table 1

Baseline Characteristics

Variable	Patients With GCA (*n* = 3408)	Reference Participants (*n* = 17 027)	*P* Value
Mean age (SD), *y*	73.1 (10.0)	73.1 (9.0)	–
Female, *n (%)*	2495 (73.2)	12 457 (73.2)	–
Mean BMI (SD), kg/m^2	26.1 (4.5)	26.1 (4.5)	0.81
Smoking, *n (%)*	–	–	<0.001
Never	1903 (55.8)	9549 (56.1)	–
Former	392 (11.5)	1848 (10.9)	–
Current	720 (21.1)	2764 (16.2)	–
Unknown	393 (11.5)	2866 (16.8)	–
Hypertension, *n (%)*	1019 (29.9)	4669 (27.4)	0.003
Diabetes mellitus, *n (%)*	264 (7.7)	1303 (7.7)	0.86
Mean total cholesterol level (SD)	–	–	0.133
mmol/L	6.1 (1.2)	6.0 (1.2)	–
mg/dL	233.9 (47.5)	232 (46.6)	–
Missing cholesterol data, *n (%)*	1783 (52.3)	10 055 (59.1)	<0.001
Medication use, *n (%)*			
Antiplatelet agents	954 (28.0)	3801 (22.3)	<0.001
β-Blockers	1052 (30.9)	4518 (26.5)	<0.001
Statins	651 (19.1)	2744 (16.1)	<0.001
Nitrates	565 (16.6)	1907 (11.2)	<0.001
Complete data, *n (%)*[*]	1476 (43.3)	6346 (37.3)	<0.001

BMI = body mass index; GCA = giant-cell arteritis.

[*] No missing data on smoking status, BMI, or total cholesterol level.

Table 2

Occurrence of Cardiovascular Events During Follow-up

Event	Patients With GCA (n = 3408)		Reference Participants (n = 17 027)		Incidence Rate Ratio (95% CI)
	Events, n*	Incidence Rate, *events per 1000 person-years*	Events, n†	Incidence Rate, *events per 1000 person-years*	
CVD‡	367	22.17	1155	13.20	1.68 (1.49–1.89)
MI	165	9.97	430	4.91	2.03 (1.70–2.43)
CVA	132	7.97	550	6.28	1.27 (1.05–1.53)
PVD	70	4.23	175	2.00	2.12 (1.60–2.79)

CVA = cerebrovascular accident; CVD = cardiovascular disease; GCA = giant-cell arteritis; MI = myocardial infarction; PVD = peripheral vascular disease.

*During 16 553 person-years of follow-up.

†During 87 504 person-years of follow-up.

‡Composite outcome of MI, CVA, and PVD.

Table 3

Risk for Giant-Cell Arteritis on Study Outcomes After Diagnosis, With and Without Adjustment for Cardiovascular Risk Factors, by Average HR (95% CI)*

Time After Diagnosis	Total Cohort (n = 20 435)		Patients With Complete Data on CVD Risk Factors (n = 7822)	
	Adjusted for Age and Sex	Adjusted for Age, Sex, and CVD Risk Factors*	Adjusted for Age and Sex	Adjusted for Age, Sex, and CVD Risk Factors
CVD				
1 mo	4.92 (2.59–9.34)	5.57 (2.74–11.34)	_†	_†
3 mo	2.56 (1.70–3.88)	2.71 (1.79–4.09)	_†	_†
6 mo	2.26 (1.66–3.09)	2.16 (1.58–2.96)	2.67 (1.71–4.17)	2.81 (1.79–4.40)
2 y	1.81 (1.50–2.18)	1.74 (1.44–2.11)	2.05 (1.53–2.73)	2.05 (1.54–2.74)
Total follow-up	1.70 (1.51–1.91)	1.66 (1.47–1.86)	2.01 (1.62–2.48)	2.04 (1.65–2.53)
MI				
1 mo	11.89 (2.40–59.00)	13.24 (2.30–76.15)	_†	_†
3 mo	4.13 (2.05–8.35)	3.70 (1.83–7.46)	_†	_†
6 mo	2.86 (1.69–4.83)	2.77 (1.63–4.71)	2.62 (1.10–6.25)	2.95 (1.21–7.15)
2 y	2.01 (1.50–2.70)	1.93 (1.44–2.59)	1.90 (1.20–3.00)	1.88 (1.18–2.99)
Total follow-up	2.06 (1.72–2.46)	2.00 (1.67–2.40)	1.94 (1.39–2.70)	1.97 (1.42–2.75)
CVA				
1 mo	3.93 (1.76–8.79)	5.60 (2.30–13.64)	_†	_†
3 mo	2.30 (1.25–4.22)	2.51 (1.36–4.62)	_†	_†
6 mo	1.91 (1.21–3.03)	1.78 (1.11–2.83)	2.36 (1.23–4.50)	2.40 (1.24–4.62)
2 y	1.51 (1.11–2.04)	1.49 (1.10–2.02)	1.94 (1.21–3.11)	2.00 (1.24–3.21)
Total follow-up	1.28 (1.06–1.54)	1.27 (1.05–1.54)	1.73 (1.21–2.47)	1.77 (1.24–2.53)
PVD				
1 mo	3.86 (0.78–19.17)	1.75 (0.23–13.06)	_†	_†
3 mo	1.57 (0.58–4.24)	1.91 (0.71–5.17)	_†	_†
6 mo	2.33 (1.14–4.77)	2.34 (1.13–4.83)	3.48 (1.44–8.38)	3.91 (1.59–9.62)
2 y	2.10 (1.37–3.21)	1.93 (1.26–2.96)	2.59 (1.42–4.70)	2.55 (1.40–4.65)
Total follow-up	2.13 (1.61–2.81)	1.98 (1.50–2.62)	2.75 (1.75–4.33)	2.76 (1.75–4.36)

CVA = cerebrovascular accident; CVD = cardiovascular disease; HR = hazard ratio; MI = myocardial infarction; PVD = peripheral vascular disease.

*Data imputed for missing values.

†Too few events to obtain stable effect estimates.

Table 4

Supplemental Analyses, by Average HR (95% CI)*

Event	Primary Analysis	Supplemental Analysis 1† (*n* = 20 435)	Supplemental Analysis 2‡ (*n* = 11 693)	Supplemental Analysis 3§ (*n* = 11 299)
CVD	1.70 (1.51–1.91)	1.68 (1.49–1.89)‖	1.73 (1.48–2.04)	1.70 (1.44–2.02)
MI	2.06 (1.72–2.46)	1.99 (1.66–2.38)‖	2.27 (1.78–2.91)	2.38 (1.85–3.05)
CVA	1.28 (1.06–1.54)	1.23 (1.02–1.49)‖	1.17 (0.90–1.52)	1.24 (0.95–1.64)
PVD	2.13 (1.61–2.81)	2.05 (1.55–1.70)‖	2.27 (1.61–3.22)	1.59 (1.03–2.47)

CVA = cerebrovascular accident; CVD = cardiovascular disease; HR = hazard ratio; MI = myocardial infarction; PVD = peripheral vascular disease.

*Adjusted for age and sex.

†Accounts for competing risks for death and other cardiovascular events.

‡Giant-cell arteritis definition restricted to patients with ≥10 prescriptions for glucocorticoids.

§Restricted to patients not receiving statins, antiplatelet agents, β-blockers, or nitrates before start of follow-up.

‖Subdistribution HR and 95% CI.