Risk factors for the development of cardiovascular events within one year from the diagnosis of giant cell arteritis

Sirs,

Giant cell arteritis (GCA), a large-vessel vasculitis, may increase cardiovascular events (CVE) risk (1-3). However, not all studies report this risk (4). Methodological limitations in prior studies, including reliance on diagnostic codes and surrogates, may explain this discrepancy. Prior studies assessed risk over many decades of observation. With evolution of medical therapy, it is unclear whether CVE risk remains elevated. There is a paucity of data analysing risk at 1-year from diagnosis or risk factors (RF) within GCA. We assessed a well-characterised modern cohort of GCA patients meeting 1990 American College of Rheumatology classification criteria (ACRCC) (5) and identified RF for incident CVE within 1-year from diagnosis.

Retrospective chart review based on ICD-9 and 10 codes between 1/1/2010-12/31/2018 occurred at a tertiary medical centre. Inclusion criteria included ACRCC and ≥1-year follow-up. Additional exclusion occurred if GCA was not the final diagnosis. Detailed chart review occurred at diagnosis and time of a CVE.

Incident CVE included myocardial infarction (MI), stroke/transient ischaemic attack (CVA/TIA), acute peripheral arterial limb ischemia (PAI), new or exacerbation of congestive heart failure (CHF), development of aortic aneurysm (AA), new vision loss, venous thromboembolism (VTE), and death (1-4). Only the first event was analysed. Groups with and without CVE were compared. Univariate and multivariate logistic regression calculated odds ratios (OR). For regression, CRP tertiles were developed: 0-10 (reference value), 11-84, and ≥85 mg/L.

One hundred and forty-four patients with putative GCA diagnosis were identified. Eight-eight (61%) met criteria. Exclusions occurred for not meeting ACRCC (9), final diagnosis of another medical disease (29), or lack of 1-year follow-up (18).

Thirteen incident CVE occurred (event rate 14.8%/year). Mean time to CVE was 109±93 days (median: 62 days (IQR 44-169); range: 29-325 days). Events included: 5 CHF exacerbations (38.5%); 2 MI or VTE (15.4% each); 1 CVA/TIA, PAI, vision loss, or AA, (7.7% each).

At baseline (Table I), the CVE group had higher prevalence of diabetes mellitus (DM), coronary artery disease (CAD), MI, CVA/TIA, CHF, anticoagulation use, and C-reactive protein (CRP). Other comorbidities, medication use, including corticosteroids, symptoms of GCA, and artery biopsy positivity were similar.

Table I. Demographics, medical comorbidities, medication use, symptoms, and laboratory values at diagnosis of giant cell arteritis compared between groups.

Variable	No CVE Group n=75	CVE Group n=13	*p*
	Mean ± STD	Mean ± STD	
Age (years)	73.7 ± 8.6	74.6 ± 7.6	0.74
Height (cm)	164 ± 10	165 ± 12	0.6
Weight (kg)	73 ± 18	78 ± 19	0.36
BMI (kg/m^2)	27 ± 7	28 ± 5	0.59
	Count (%)	Count (%)	
Female Gender	51 (68)	7 (54)	0.4
Race			0.01
Caucasian	70 (93)	9 (69)	
African American	4 (5)	3 (23)	
Asian	1 (1)	0 (0)	
Native American	0 (0)	1 (8)	
Medical comorbidity			
Hypertension	51 (68)	11 (85)	0.23
Hyperlipidemia	41 (55)	8 (62)	0.65
Diabetes mellitus	15 (20)	6 (46)	0.04
Peripheral arterial disease	7 (9)	3 (23)	0.15
Aortic or peripheral aneurysm	2 (3)	0 (0)	0.68
Carotid stenosis	8 (11)	2 (15)	0.62
Peripheral arterial intervention	2 (3)	1 (8)	0.36
Coronary artery disease	7 (9)	5 (38)	0.005
Myocardial infarction	1 (1)	3 (23)	0.0005
Cardiac intervention	5 (7)	3 (23)	0.06
Arrhythmia	6 (8)	5 (38)	0.44
Congestive heart failure	1 (1)	7 (54)	<0.0001
Valvular heart disease	8 (11)	1 (8)	0.74
COPD	5 (7)	1 (8)	0.89
CVA/TIA	3 (4)	3 (23)	0.01
Venous thromboembolism	3 (4)	2 (15)	0.1
Chronic kidney disease	20 (27)	4 (31)	0.76
Malignancy	16 (21)	5 (38)	0.17
Smoking status:			0.44
Current	8 (11)	0 (0)	
Former	24 (32)	4 (31)	
Never	43 (57)	9 (69)	
Alcohol Use	29 (39)	4 (31)	0.59
Medication use			
Beta blocker	23 (31)	6 (46)	0.27
ACEi/ARB	30 (40)	3 (23)	0.24
Other anti-HTN	32 (43)	9 (69)	0.08
Statin	32 (43)	7 (54)	0.45
Antiplatelet	30 (40)	4 (31)	0.53
NSAID	18 (24)	2 (15)	0.49
Anticoagulation	7 (9)	5 (38)	0.005
GCA symptom			
Elevated temp >38C	6 (8)	2 (15)	0.4
Headache	62 (83)	11 (85)	0.86
Jaw claudication	45 (60)	6 (46)	0.35
Vision loss	22 (29)	3 (23)	0.64
Change in vision	43 (57)	6 (46)	0.45
Tender scalp	46 (61)	9 (69)	0.59
PMR	28 (37)	5 (38)	0.94
Lab value	Mean ± STD	Mean ± STD	
WBC (1000/μL)	10.0 ± 3.4	10.5 ± 2.9	0.28
Hgb (g/dL)	12.0 ± 1.7	11.3 ± 2.5	0.18
Plt (thousand/μL)	322.1 ± 127.1	298.3 ± 124.9	0.54
ESR (mm/hour)	69.2 ± 33.2	73.4 ± 28.5	0.68
CRP (mg/L)	75.6 ± 76.9	133.2 ± 83.2	0.02
sCr (mg/dL)	0.9 ± 0.3	1.1 ± 0.8	0.64
ALT (U/L)	33.4 ± 40.8	30.6 ± 29.8	0.99
AST (U/L)	30.1 ± 32.1	25.1 ± 13.6	0.94
AP (U/L)	92.7 ± 49.0	137.9 ± 72.7	0.06

CVE: cardiovascular event; STD: standard deviation; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CVA/TIA: cerebrovascular accident/transient ischaemic attack; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; HTN: hypertension; NSAID: non-steroidal anti-inflammatory drug; Temp: temperature; PMR: polymyalgia rheumatica; WBC: white blood cell count; Hbg: haemoglobin; Plt: platelet count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; sCr: serum creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; AP: alkaline phosphatase.

Univariate OR [95% confidence interval] were significant for baseline DM (3.4 [1.0–11.7), CAD (6.1 [1.6–23.7), MI (22.2 [2.1-234.5]), arrhythmia (7.2 [1.8–29.0]), CHF (86.3 [9.1–822.7]), CVA/TIA (7.2 [1.3–40.7]), anticoagulation use (6.1 [1.6–23.7]), African American race (5.8 [1.1–30.4]), or CRP >85mg/L at diagnosis (3.0 [1.4-–.6]). Multivariate model found CHF (165.7 [15.1–1812.8]) and CVA/TIA [23.7 [3.3–170.3] independent.

Many RF for CVE at 1-year from diagnosis are associated with cardiovascular disease. The African American racial difference is interesting, although the overall number was small, requiring further study. Highly elevated CRP also was a RF. CRP plays a role in atherogenesis, atherosclerotic plaque instability, and thrombus formation; thus, elevations in GCA may predispose patients to CVE (6, 7). Interleukin-6 has a pathophysiologic role in GCA, elevates CRP, and has been reported to have a deleterious effect in cardiovascular disease, including CHF and CVA/TIA (8, 9). This raises interest as to whether tocilizumab treatment could decrease CVE in GCA. Another possibility to consider is corticosteroids, the main treatment in GCA, are themselves associated with cardiovascular effects, including exacerbations of CHF, the most frequent event in our study. While initial corticosteroid treatment was similar between groups, cumulative dose was not able to be assessed. Further study to fully adjust for corticosteroid use is warranted.

The study's major strength is the detailed review and verification of all data in a modern cohort. Limitations include retrospective nature and overall small number of CVE.

In conclusion, we described RF for incident CVE within 1-year from diagnosis in a modern, well-characterised cohort of GCA patients.

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References

1. LI L, NEOGI T, JICK S: Giant cell arteritis and vascular disease-risk factors and outcomes: a cohort study using UK Clinical Practice Research Datalink. *Rheumatology* (Oxford) 2017; 56: 753-62.
2. RAY JG, MAMDANI MM, GEERTS WH: Giant cell arteritis and cardiovascular disease in older adults. *Heart* 2005; 91: 324-8.
3. TOMASSON G, PELOQUIN C, MOHAMMAD A *et al*.: Risk for cardiovascular disease early and late after a diagnosis of giant-cell arteritis: a cohort study. *Ann Intern Med* 2014; 160: 73-80.
4. PUJADES-RODRIGUEZ M, DUYX B, THOMAS SL, STOGIANNIS D, SMEETH L, HEMINGWAY H: Associations between polymyalgia rheumatica and giant cell arteritis and 12 cardiovascular diseases. *Heart* 2016; 102: 383-9.
5. HUNDER GG, BLOCH DA, MICHEL BA *et al*.: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum* 1990; 33: 1122-8.
6. STANCEL N, CHEN CC, KE LY *et al*.: Interplay between CRP, Atherogenic LDL, and LOX-1 and Its Potential Role in the Pathogenesis of Atherosclerosis. *Clin Chem* 2016; 62: 320-7.
7. BADIMON L, PENA E, ARDERIU G *et al*.: C-Reactive Protein in Atherothrombosis and Angiogenesis. *Front Immunol* 2018; 9: 430.
8. MARKOUSIS-MAVROGENIS G, TROMP J, OUWERKERK W *et al*.: The clinical significance of interleukin-6 in heart failure: results from the BIOSTAT-CHF study. *Eur J Heart Fail* 2019; 21: 965-73.
9. FROYSHOV HM, BJORNEREM A, ENGSTAD T, HALVORSEN DS: Elevated inflammatory markers predict mortality in long-term ischemic stroke-survivors: a population-based prospective study. *Aging Clin Exp Res* 2017; 29: 379-85.