Early development of new cardiovascular risk factors in the systemic vasculitides

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ABSTRACT

Objective. *To analyse the frequency and predictors of new-onset cardiovascular (CV) risk factors in patients with anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) and giant cell arteritis (GCA).*

Methods. *We analysed the frequency and predictors of new-onset hypertension and/or diabetes mellitus (HTN/DM) amongst patients with AAV or GCA recruited in the Diagnostic and Classification of Vasculitis (DCVAS) study. Patients with pre-existing HTN/DM were excluded.*

Results. *We included 873 patients with AAV (506 GPA, 183 MPA, 184 EGPA), and 443 with GCA. Patients with GCA were more likely female (68% vs. 52%; p<0.001) and older (71.33±8.65 vs. 52.80±16.48; p<0.001) compared to patients with AAV. HTN/DM developed within 6 months of diagnosis in 9% of patients with AAV (6% in GPA, 21% in MPA, 3% in EGPA) and 6% of patients with GCA, p=0.15. Rise in creatinine/reduced glomerular filtration rate and/or anaemia (OR 3.98, 95% CI 2.09-7.59, p<0.001) and diagnosis (MPA: OR 2.42, 95%CI 1.52-3.83, p<0.001 and GCA: OR 2.12, 95%CI 1.34-3.38, p=0.001 vs. GPA) were significantly associated with the occurrence of HTN/DM after adjusting for age, sex, ethnicity, and smoking status. We developed and validated a predictive score to discriminate patients according to the risk of developing HTN/DM within 6 months from diagnosis.*

Conclusion. *Despite different epidemiological and clinical characteristics, new CV risk factors occur equally in the early stages of AAV and GCA. Renal function and type of diagnosis are associated with the occurrence of HTN/DM. We developed a simple predictive score for the risk-stratification of patients.*

Introduction

Despite major advances in the management and treatment options for systemic vasculitides, patients are still exposed to excessive cardiovascular (CV) risk and related morbidity and mortality (1, 2). Measures to reduce the risk of cardiovascular disease (CVD) should be part of the routine care of these patients. The mechanisms responsible for the increased prevalence of CVD and their relationship with disease activity and treatment in systemic vasculitis are still not well defined. Several hypotheses, including uncontrolled inflammation, endothelial dysfunction, and use of high dose glucocorticoids (GCs) have been proposed. (3) Moreover, the increased occurrence of traditional risk factors, both disease- and treatment-related, such as hypertension (HTN), diabetes mellitus (DM), impaired renal function, and dyslipidaemia may play a pivotal role. Damage accrual, including the new occurrence of CV risk factors, in patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) has been demonstrated to accumulate over time, but to be particularly relevant in the early stages of disease (4). Patients with giant cell arteritis (GCA), despite significant differences in epidemiology and clinical phenotype compared to patients with AAV, also experience significant CV burden over the course of disease (5, 6).

The aim of this study was to analyse and compare the onset and predictors of new CV risk factors (HTN and DM) amongst patients with AAV and GCA recruited into the Diagnostic and Classification of Vasculitis (DCVAS) study (7). Secondary aims were to assess the occurrence of other major CV events and CV mortality in this cohort.

Methods

DCVAS is an international observation-

al study of newly-diagnosed patients with vasculitis and diagnostic mimics of vasculitis, with the aim of developing and validating new classification and diagnostic criteria for several forms of systemic vasculitis (7). Patients were selected from those recruited in the DCVAS (February 24, 2011, until May 25, 2016). The University of Oxford is the sponsor of the DCVAS study with overall ethical approval given by the UK Berkshire Research Ethics 10/H0505/19, dated 7 May 2010. The study was performed in accordance with the 1964 Declaration of Helsinki and ethical approval was obtained by national and local ethics committees in accordance with national legislation. Participants consented to the study and access to their records was granted.

For the current study we selected patients with a confirmed final diagnosis of GCA or AAV [granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), or microscopic polyangiitis (MPA)]. Patients with comorbid HTN or DM preceding the diagnosis of vasculitis were excluded from the analysis. The following data was used for the analysis: age, sex, ethnicity, disease and symptoms duration, diagnostic delay from symptoms onset, organ systems involved at presentation, comorbid conditions, smoking status, body mass index (BMI), ANCA status (ANCA-PR3, ANCA-MPO, or negative), inflammatory markers, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), the presence of significant anaemia (haemoglobin level <10 g/dL), rise in creatinine values >30% or reduction of glomerular filtration rate (GFR) >25% at disease onset, proteinuria >1 g/24 hours, abnormal urinalysis (significant proteinuria on urine dipstick and/or haematuria on urine dipstick and/or the presence of red cell casts).

We determined the presence or absence of new CV risk factors (diastolic HTN and DM) from items recorded in the Vasculitis Damage Index (VDI) at the 6-month assessment. DM was defined according to internationally recognised definitions (8). We analysed the development of other major CV events as recorded in the VDI at 6 months as follows: myocardial infarction (MI), second MI, cerebrovascular event, second cerebrovascular event. We analysed survival and frequency of CV causes of death.

Statistical analysis

Analyses were performed with Stata 15 (StataCorp, College Station, TX, USA). A 2-sided p-value <0.05 was considered statistically significant. We applied the Bonferroni correction for post-hoc comparisons. We described presenting characteristics with mean and standard deviation (SD) or median and 25^{th}-75^{th} percentiles if continuous and with counts and percent if categorical. We compared diagnostic groups with the Kruskall Wallis test and Fisher's exact test.

We used logistic regression to assess the association of a series of candidate predictors with the development of HTN and/or DM (HTN/DM) at 6 months. We computed odds ratios and 95% confidence intervals (OR, 95%CI) to measure the strength of association. We calculated Huber-White robust standard errors while clustering on countries participating in the study. We included the following clinically-relevant predictors of HTN/DM in a multivariable model: age, sex, ethnicity, smoking status, creatinine rise by 30%/GFR reduction by 25%, anaemia, and diagnostic group. We computed the model's area under the receiver operating curve (AUC ROC) to assess discriminative ability. To generate a parsimonious predictive score for HTN/DM (with a minimum set of explanatory variables), we applied backward stepwise selection (p to remove 0.2) in a random sample representing 70% of the cohort. We validated the discriminative ability of this model in the remaining 30% of the cohort. Given the good discrimination (0.72 in the testing and 0.74 in the validation cohort), we collapsed both samples (AUC ROC 0.73; Supplementary Fig. 1). For score definition we computed the linear combination of the logistic regression coefficients (each multiplied by 100 to obtain integers). For practical use, we plotted in a nomogram the predicted probability of developing HTN/DM at 6 months given the score. We divided the score into tertiles that identified patients with low, intermediate and high risk and computed the associated probability (95%CI).

Results

At the cut-off date applied, the DCVAS dataset included 1278 patients with AAV (GPA 702, MPA 331, EGPA 245), and 895 patients with GCA, providing a total of 2173 patients. Of these, 857 patients were excluded from the analysis because they were recorded as having HTN or DM prior to the diagnosis of vasculitis. The final population analysed in the study included 873 patients with AAV (506 with GPA; 183 with MPA, 184 with EGPA), and 443 with GCA, giving a total of 1316 patients.

Demographics and general characteristics

Table I shows the general characteristics of the population. Significantly, more patients in the group with GCA were female (68%), older and Caucasian compared to all types of AAV (p<0.001 for all comparisons). Diagnostic delay from symptom onset was significantly greater in each form of AVV compared to GCA, (p<0.001).

At baseline, CV comorbidities other than HTN or DM, specifically coronary artery disease, heart failure, peripheral vascular disease, or stroke, were reported in a minority of patients with AAV (44 patients, 5%) or with GCA (35 patients, 7.9%), (p=0.028). Baseline dyslipidaemia was more frequent in GCA compared to AAV (10.8% vs. 4.9%; p<0.001).

Presenting clinical features

The prevalence of organ system involvement at disease onset in each group is presented in Table II. Systemic symptoms were more frequent in AAV (77.8%) compared to GCA (69.1%), p<0.001. Cardiac manifestations were equally distributed, occurring in 13% of cases both in GCA and in AAV.

Laboratory tests

Laboratory tests findings at disease onset are displayed in Table III. The proportion of patients with elevated CRP was significantly higher in GCA

Table I. Demographics and general characteristics of the study population.

	AAV n=873	GPA n=506	MPA n=183	EGPA n=184	GCA n=443	*p*-value	Post-hoc comparisons p-value
Female n (%)	454 (52)	258 (51)	104 (57)	92 (50)	304 (68)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GCA *vs*. GCA; EGPA *vs*. GCA) 0.036 (MPA *vs*. GCA)
Age (years ± SD) min-max	52.80±16.48 (18-89)	50.34±16.70 (18-88)	61.55±14.31 (20-89)	50.86±14.98 (18-85)	71.33±8.65 (45-90)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA *vs*. GCA; MPA *vs*. GCA; EGPA *vs*. GCA; MPA *vs*. GCA; MPA *vs*. EGPA)
Ethnicity: Caucasian (n;%)	622 (71.25)	369 (72.92)	109 (59.56)	144 (78.26)	424 (95.71)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA *vs*. GCA; MPA *vs*. GCA; EGPA *vs*. GCA; MPA *vs*. EGPA) 0.006 (GPA *vs*. MPA)
Symptoms duration (median; IQR)	9.95 (4.08;21.89)	9.51 (4.05; 21.48)	8.27 (3.88; 17.66)	14.28 (5.10; 26.86)	7.29 (2.93;14.34)	<0.001	<0.001 (AAV *vs*. GCA) 0.02 (MPA *vs*. EGPA); <0.001 (GPA *vs*. GCA); <0.001 (EGPA *vs*. GCA) 0.125 (GPA *vs*. EGPA);
Disease duration (median; IQR) months	2.53 (0.30; 10.10)	2.27 (0.23; 8.49)	3.45 (0.46; 11.05)	2.66 (0.36;12.66)	3.19 (0.23;10.07)	0.359	0.679 (AAV *vs*. GCA) 0.359 (GPA *vs*. MPA *vs*. EGPA *vs*. GCA)
Diagnostic delay (median; IQR) months	3.55 (1.55; 10)	3.65 (1.74; 9.51)	2.83 (1.28; 6.64)	4.69 (1.35; 15.81)	1.88 (0.86; 4.11)	<0.001	<0.001 (AAV *vs*. GCA) 0.034 (EGPA *vs*. MPA) <0.001 (GPA *vs*. GCA; EGPA *vs*. GCA; MPA *vs*. GCA) 0.12 MPA *vs*. GPA
BMI (mean ± SD)	25.49±5.27	26.3±5.58	24.65±4.78	24.40±4.63	25.15±4.64	0.002	0.462 (AAV *vs*. GCA) 0.024 (GPA *vs*. EGPA) 0.011 (MPA *vs*. GPA);
Cigarette smoking (n;%)							
never	517 (59.22)	291 (57.51)	102 (55.74)	124 (67.39)	227 (51.24)	<0.001	<0.0001 (AAV *vs*. GCA)
current	90 (10.31)	64 (12.65)	21 (11.48)	5 (2.72)	63 (14.22)		<0.001(GPA, MPA, EGPA *vs*. GCA; GPA *vs*. EGPA)
previous	251 (28.75)	144 (28.46)	55 (30.05)	52 (28.26)	124 (27.99)		0.024 (MPA *vs*. EGPA)
No comorbidities (n;%)	423 (48.45)	306 (60.47)	78 (42.62)	39 (21.20)	175 (39.50)	<0.001	0.002 (AAV *vs*. GCA) <0.001 (GPA *vs*. GCA; EGPA *vs*. GCA; GPA *vs*. EGPA; MPA *vs*. EGPA; GPA *vs*. MPA)
CV comorbidities* (n;%)	44 (5)	24 (4.74)	16 (8.74)	4 (2.17)	35 (7.9)	0.007	0.049 (AAV *vs*. GCA) 0.03 (EGPA *vs*. MPA; EGPA *vs*. GCA)
Dyslipidaemia[#] (n;%)	43 (4.93)	21 (4.15)	19 (10.38)	3 (1.63)	48 (10.84)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA *vs*. GCA; EGPA *vs*. GCA; MPA *vs*. EGPA) 0.003 (GPA *vs*. MPA)

AAV: anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis; GCA: giant cell arteritis; BMI: body max index; SD: standard deviation; IQR: interquartile range.
*CV: cardiovascular comorbidities prior to the diagnosis of vasculitis: coronary artery disease, heart failure, peripheral vascular disease, stroke.
[#]Dyslipidaemia defined by total cholesterol, LDL cholesterol or triglyceride levels above the upper normal laboratory limit.

(89.2%) compared to AAV (76.5%), $p<0.001$. The proportion of patients with raised ESR was significantly greater in GCA (91.2% *vs*. 68.0%), $p<0.001$. Anaemia was more frequent amongst patient with AAV than in GCA (32.4% *vs*. 13.5%; $p<0.001$). Renal function decreased by at least 25% in 26.7% of patients with AAV compared with 2% of patients with GCA.

Development of new cardiovascular risk factors: HTN and DM

Within 6 months from diagnosis, 104 patients (7.9%, 95%CI 6.5-9.5) developed HTN/DM. Forty-one (3.6%, 95%CI 2.7-4.8) patients developed DM, 56 (4.8%, 95%CI 3.7-6.1) HTN, 7 (0.5%, 95%CI 0.2-1.1) developed both. HTN/DM occurred in 76 (8.7%) of patients with AAV and in 28 (6.3%) with GCA, with no significant differences (Table IV). Within AAV, a diagnosis of MPA was associated with a 4-fold increase in risk of HTN/DM as compared to GPA (OR 4.01; 95%CI 2.90-5.56; $p<0.001$), while patients with EGPA had about half the risk of developing HTN/DM compared to GPA (OR 0.40; 95%CI 0.22-0.76; $p=0.007$).

Table II. Prevalence of organ system involvement at disease onset in each group.

N (%)	AAV n=873	GPA n=506	MPA n=183	EGPA n=184	GCA n=443	*p*-value	Post-hoc comparisons *p*-value
Systemic symptoms (n=985)	679 (77.78)	383 (76)	155 (85)	141 (77)	306 (69.07)	<0.001	0.001 (AAV *vs*. GCA) <0.001(GPA, MPA, EGPA *vs*. GCA)
Musculoskeletal symptoms (n=731)	495 (56.70)	308 (60.87)	91 (49.73)	96 (52.17)	236 (53.27)	0.017	0.241 (AAV *vs*. GCA) 0.102 (GPA, MPA, EGPA *vs*. GCA)
Cutaneous (n=339)	316 (36.20)	173 (34.19)	55 (30.05)	88 (47.83)	23 (5.19)	<0.001	<0.0001 (A *vs*. B) <0.001 (GPA *vs*. GCA); 0.006 (GPA *vs*. EGPA); 0.006 (MPA *vs*. EGPA)
Ocular (n=446)	254 (29.10)	204 (40.32)	28 (15.30)	22 (11.96)	192 (43.34)	<0.001	<0.001 (AAV *vs*. GCA) <0.0001 (GPA, MPA, EGPA *vs*. GCA; GPA *vs*. MPA)
ENT (n=466)	596 (68.27)	415 (82.02)	51 (27.87)	130 (70.65)	200 (45.15)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA, MPA, EGPA *vs*. GCA)
Gastrointestinal	618 (70.79%)	389 (76.88%)	129 (70.49%)	100 (54.35%)	128 (28.89%)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA, MPA, EGPA *vs*. GCA; GPA *vs*. EGPA) 0.012 (MPA *vs*. EGPA)
Jaw claudication	19 (2.18%)	10 (1.98%)	6 (3.28%)	3 (1.63%)	176 (39.73%)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA, MPA, EGPA *vs*. GCA)
Limb claudication	15 (1.72%)	6 (1.19%)	4 (2.19%)	5 (2.72%)	31 (7%)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA *vs*. GCA)
Pulmonary (n=699)	616 (70.56)	332 (65.61)	123 (67.21)	161 (87.50)	83 (19.74)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA, MPA, EGPA *vs*. GCA)
Any cardiac manifestation (n=171)	114 (13.06)	31 (6.13)	21 (11.48)	62 (33.70)	57 (12.87)	<0.001	1 (AAV *vs*. GCA) <0.001 (GPA, EGPA *vs*. GCA; GPA *vs*. EGPA; MPA *vs*. EGPA)
Cardiac failure (n=42)	42 (4.81)	4 (0.79)	5 (2.73)	33 (17.93)	0	<0.001	<0.001 (AAV *vs*. GCA) 0.006 (MPA *vs*. GCA) <0.001 (EGPA *vs*. GCA; GPA *vs*. EGPA; MPA *vs*. EGPA)
Myocardial infarction (n=31)	23 (2.63)	5 (0.99)	2 (1.09)	14 (8.70)	8 (1.81)	<0.001	0.443 (AAV *vs*. GCA) <0.001 (EGPA *vs*. GCA; GPA *vs*. EGPA) 0.006 (MPA *vs*. EGPA)
Arrhythmia* (n=269)	22 (2.52)	5 (0.99)	3 (1.64)	14 (7.61)	4 (0.9)	<0.001	0.058 (AAV *vs*. GCA) <0.001 (EGPA *vs*. GCA; GPA *vs*. EGPA)
Neurological (n=693)	344 (39.40)	156 (30.83)	69 (37.70)	119 (64.67)	349 (78.78)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA, MPA, EGPA *vs*. GCA; GPA *vs*. EGPA; MPA *vs*. EGPA)
TIA (n=13)	7 (0.8)	3 (0.59)	1 (0.55)	3 (1.63)	6 (1.35)	0.459	0.381 (AAV *vs*. GCA)
Stroke (n=11)	6 (0.69)	4 (0.79)	1 (0.55)	1 (0.54)	5 (1.13)	0.523	0.523 (AAV *vs*. GCA)
Peripheral nervous system (n=246)	235 (26.92)	84 (16.60)	49 (26.78)	102 (55.43)	11 (2.48)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA, MPA, EGPA *vs*. GCA; GPA *vs*. EGPA; MPA *vs*. EGPA) 0.024 (GPA *vs*. MPA)

AAV: anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis; GCA: giant cell arteritis; ENT: ear, nose, throat; TIA: transient ischaemic attack.
*Arrhytmia: any abnormal heart rhythm confirmed by altered diagnostic tests (*e.g.* electrocardiogram) or requiring treatment.

The correlation between type of diagnosis and development of a single new CV risk factor (either HTN or DM) was assessed. Among the 63 patients who developed HTN at 6 months, 53 (6.4%) had AAV as compared to 10 (2.2%) who had GCA (OR 0.36, 95% CI 0.16-0.81, p=0.014). Among the 48 patients who developed DM, 28 (3.2%) had AAV and 20 (4.5%) had GCA (OR 1.43, 95%CI 0.53-3.81, p=0.481).

Factors associated with HTN/DM

Age, sex, and BMI were not signifi-

Table III. Laboratory findings at disease onset in each group.

	AAV n=873	GPA n=506	MPA n=183	EGPA n=184	GCA n=443	*p*-value	Post-hoc comparisons *p*-value
CRP (mg/L) (median; IQR)	59 (17;138)	60.85 (19;147)	73 (19;144)	37.58 (11;92)	67 (31; 120)	<0.001	0.092 (AAV *vs*. GCA) <0.001 (EGPA *vs*. GCA) 0.002 (EGPA *vs*. GPA) 0.006 (EGPA *vs*. MPA)
High CRP (> 5 mg/L)* n (%)	668 (76.52)	396 (78.26)	145 (79.23)	127 (69.02)	395 (89.16)	<0.001	<0.001(AAV *vs*. GCA) <0.001 (GPA, EGPA *vs*. GCA) 0.006 (MPA *vs*. GCA)
ESR (mm/hour) (median; IQR)	59 (32;89)	60 (34;90)	77 (47;103)	39.50 (47;95)	72 (47;95)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (EGPA *vs*. GCA; EGPA *vs*. GPA; EGPA *vs*. MPA) 0.006 (MPA *vs*. GPA); 0.013 (GPA *vs*. GCA)
High ESR (> 15 mm/hour)* n (%)	594 (68.04)	351 (69.37)	132 (72.13)	111 (60.33)	404 (91.20)	<0.001	<0.0001 (AAV *vs*. GCA) <0.001 (GPA, MPA, EGPA *vs*. GCA)
At least one raised inflammatory marker n (%)	721 (95.62)	425 (95.94)	159 (97.55)	137 (92.57)	416 (98.11)	0.016	0.03 (AAV *vs*. GCA) 0.002 (EGPA *vs*. GCA)
Anaemia (< 10 g/L) n (%)	283 (32.42)	162 (32.02)	100 (54.94)	21 (11.41)	60 (13.54)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA, MPA *vs*. GCA; GPA *vs*. EGPA; MPA *vs*. EGPA; GPA *vs*. MPA)
c-ANCA (PR3) n (%)	318 (36)	306 (60.47)	11 (6.01)	1 (0.54)	1 (0.5)	<0.001	<0.0001 (A *vs*. B) <0.001 (GPA *vs*. EGPA, GPA *vs*. MPA) 0.018 (MPA *vs*. EGPA)
p-ANCA (MPO) n (%)	208 (24)	34 (6.72)	123 (67.21)	51 (27.72)	0	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA *vs*. EGPA; MPA *vs*. EGPA; GPA *vs*. MPA)
Rise in creatinine > 30% or GFR reduction > 25% n (%)	233 (26.69)	122 (24.11)	100 (54.64)	11 (5.98)	9 (2.03)	<0.001	<0.001(AAV *vs*. GCA) <0.001 (GPA, MPA *vs*. GCA); 0.002 (EGPA *vs*. GCA) <0.001 (GPA, MPA *vs*. EGPA; GPA *vs*. MPA) A1, A2 *vs*. A3); <0.001 (A1 *vs*. A2)
Abnormal urinalysis n (%)	459 (52.58)	279 (55.14)	138 (75.41)	42 (22.83)	86 (19.41)	<0.001	<0.001 (AAV *vs*. GCA) <0.001 (GPA, MPA *vs*. GCA; GPA *vs*. EGPA; MPA *vs*. EGPA; GPA *vs*. MPA)
24 hour urine protein excretion > 1 g n (%)	141 (16.15)	84 (16.60)	50 (27.32)	7 (3.80)	2 (0.45)	<0.001	<0.001(AAV *vs*. GCA) <0.001 (GPA, MPA, EGPA *vs*. GCA; GPA, MPA *vs*. EGPA)

AAV: anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis; GCA: giant cell arteritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range; GFR: glomerular filtration rate. *Data were categorised according to the specified cut-off.

cantly associated with the development of HTN/DM (Table IV). There was a higher frequency of HTN/DM within the first 6 months of disease (50.9% of patients developing HTN/DM) compared to 21.2% and 27.9% at 12 and 24 months from diagnosis, respectively (p=0.027). Ethnicity influenced the occurrence of HTN/DM; within the group of patients with HTN/DM 64.4% were Caucasian compared to 35% classified as other ethnicity (p<0.001).

The analysis of type of clinical presentation at disease onset did not demonstrate any association between specific organ involvement and the subsequent development of HTN/DM. None of the CV manifestations analysed in more detail were associated with HTN/DM (cardiac failure, MI, arrhythmia, pericarditis, transient ischaemic attack, stroke, gastrointestinal ischaemia, limb claudication). By contrast, anaemia conferred a 2-fold increase risk of developing HTN/DM: OR 2.09; 95%CI 1.07-4.10), p=0.005.

There was an association between an increase in creatinine values by 30% or decrease in GFR by 25% and the development of HTN (rather than any association with DM). Amongst patients with an increase in creatinine values, 17 (36%) had DM compared to 236 (19%) of those who did not have DM; however, the difference in association did not reach statistical significance (p=0.108). Creatinine rise/GFR reduction remained significantly associated with the subsequent development of diastolic HTN: 41 patients (67.2%) compared to 202 (17.7%); p<0.001. Rise in creatinine/GFR reduction conferred a significant risk for the development of HTN/DM: OR 5.55 (95%CI 2.42-12.75).

CRP levels were not associated with

Table IV. Univariable logistic regression analysis of factors associated with the development of HTN/DM at 6 months.

	HPT/ DIAB =1 (n=104)	HPT/ DIAB= 0 (n=1215)	OR	95%CI	*p*-value	Effect modification: *p* for interaction*
AAV			1			
GCA	28 (26.9%)	415 (34.2)	0.71	0.31-1.64	0.419	na
Diagnostic groups					<0.0001	
GPA	32 (31%)	474 (39%)	1			
MPA	39 (37%)	144 (12%)	4.01	2.90-5.56	<0.001	na
EGPA	5 (5%)	179 (15%)	0.40	0.22-0.76	0.007	
GCA	28 (27%)	415 (34%)	0.99	0.46-2.18	1.00	
Gender female (n=760)	53 (51%)	707 (58%)	0.75	0.43-1.31	0.179	0.306
Age (mean ± SD)	61.17±17.08	58.85±16.75	1	0.99-1.02	0.267	0.313
Disease duration					0.027	
6 months (n=830)	53 (50.96%)	777 (64%)	1			
12 months (n=209)	22 (21.15%)	187 (15.40%)	1.72	0.83-3.56	0.145	0.427
24 months (n=279)	29 (27.88%)	250 (20.59%)	1.70	0.70-4.12	0.240	
Symptoms duration before diagnosis (median; IQR)	2.34 (0.97; 5.90)	3.03 (1.18;7.43)	0.91	0.78-1.04	0.184	0.861
Ethnicity Caucasian (n=1049)	67 (64.42%)	982 (80.82%)	0.43	0.15-1.19	0.105	0.275
BMI (median; IQR)	24.36 (22;51)	24.80 (22;58)	0.99	0.93-1.07	0.988	0.970
Smoke					0.195	
Never (=744)	61 (58.65%)	683 (56.21%)	1			
Current (n=154)	11 (10.58%)	143 (11.77%)	0.86	0.56-1.32	0.557	0.167
Previous (n=377)	32 (30.77%)	345 (28.40%)	1.03	0.62-1.74	0.497	
Systemic symptoms (n=988)	79 (75.96%)	909 (74.81%)	1.06	0.58-1.94	0.840	0.043
Musculoskeletal symptoms (n=733)	53 (50.96%)	680 (55.97%)	0.82	0.60-1.11	0.192	0.06
Pulmonary (n=701)	59 (56.73%)	642 (52.84%)	0.42	0.58-2.37	0.663	0.002
Any cardiovascular manifestation (n=172)	7 (6.73%)	165 (13.58%)	0.20	0.19-1.08	0.075	0.464
Gastrointestinal (n=747)	61 (58.65%)	686 (56.46%)	1.09	0.53-2.24	0.806	0.008
Neurological any (n=696)	49 (47.12%)	647 (53.25%)	0.78	0.39-1.58	0.494	0.613
Anaemia (n=346)	43 (41.75%)	303 (25.51%)	2.09	1.07-4.10	0.001	0.003
CRP (mg/L); median (IQR)	52 (23;146)	62.90 (21;132)	1.02	0.72-1.46	0.892	0.917
ESR (mm/hour); median (IQR)	72 (48;104)	63 (37;90)	1.01	1.01-1.02	<0.001	0.728
Rise in creatinine >30% or GFR reduction > 25%	54 (53.57%)	189 (17.15%)	5.55	2.42-12.75	<0.001	0.041
c-ANCA (PR3) positive‡	22 (28.95)	296 (37.14)	0.69	0.44-1.09	0.112	na
p-ANCA (MPO) positive‡	36 (47.37)	172 (21.58)	3.27	2.08-5.15	<0.001	na

AAV: anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis; GCA: giant cell arteritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; BMI: body max index; SD: standard deviation; IQR: interquartile range; GFR: glomerular filtration rate.
*Test for interaction with diagnosis (AAV or GCA). ‡only tested in patients with a diagnosis of ANCA-associated vasculitis.

the occurrence of HTN/DM. MPO-ANCA was positive in 36 (47.4%) of patients with HTN/DM compared to 172 (21.6%) of those who did not develop HTN/DM, $p<0.001$. PR3-ANCA was not significantly associated (28.9% *vs*. 37.1%, $p=0.112$) with HTN/DM.

Multivariable logistic regression of factors influencing the development of HTN or DM

Multivariable logistic regression revealed that rise in creatinine or GFR reduction/anaemia at presentation and diagnosis (MPA and GCA) were significantly associated with the occurrence of HTN/DM within 6 months of the diagnosis of vasculitis, after adjusting for age, sex, ethnicity, and smoking status (Table V). A sensitivity analysis including or excluding the effect of BMI did not change these results.

Table V. Multivariable logistic regression of variables associated with the development of HTN/DM at 6 months. (Model $p<0.001$, AUC-ROC=0.77).

	OR	95% CI	*p*
Age	1.01	0.99-1.02	0.157
Gender			
Male	1		
Female	0.74	0.39-1.41	0.361
Ethnicity			
Other ethnicity	1		
Caucasian	0.51	0.23-1.13	0.099
Smoking status		0.70	
Never	1		
Current	0.88	0.53-1.45	0.614
Previous	0.88	0.57-1.34	0.545
Creatinine/anaemia		<0.001	
Both absent	1		
Only anaemia	0.51	0.23-1.14	0.103
Only creatinine rise*	4.21	1.97-9.01	<0.001
Both present	3.98	2.09-7.59	<0.001
Diagnosis		<0.001	
GPA	1		
MPA	2.42	1.52-3.83	<0.001
EGPA	0.66	0.35-1.27	0.218
GCA	2.12	1.34-3.38	0.001

*rise in creatinine > 30% or glomerular filtration rate reduction > 25%.
AAV: anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis; GPA: granulomatosis with polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis; MPA: microscopic polyangiitis; GCA: giant cell arteritis.

We derived a predictive score for the development of HTN/DM at 6 months, as described in the Methods section. The results are reported in Figure 1, including the coefficients for score computation, the score limits for the risk-stratification of patients, and the associated probability of developing HTN/DM. The discrimination ability of the predictive score was good (AUC-ROC 0.72) and the tertiles of its distribution allowed us to separate the corresponding probabilities of developing HPT or DM (Suppl. Fig. 1).

Development of major cardiovascular complications and cardiovascular mortality

MI or stroke developed within 6 months of diagnosis of vasculitis in 18 patients overall (1.4%): 5 patients had MI, 14 had a cerebrovascular event. Eleven of these cases (61% of all events, 1.3% of patients with AAV) were recorded amongst patients with AAV. The remaining 7 cases (39% of all events, 1.6% of GCA) occurred in patients with GCA, $p=0.628$. Overall there were 19 deaths (1.4%). A further twenty-six patients were lost to follow-up (1.9%). Median follow-up of the patients who died was 6.54 (5.82-8.09) months. There were 5 deaths related to CV causes (0.4% of all patients, 26% of all deaths). Two fatal cases were due to MI (0.15%) and 2 cases due to stroke (0.1%), all with a diagnosis of AAV, compared to no deaths due to CV causes in patients with GCA.

Discussion

In this large cohort of vasculitides there was a relevant risk of developing new CV risk factors within 6 months from diagnosis both in patients with AAV and GCA. This was the first study to analyse and compare the frequency and the predictors of new-onset HTN/DM between large-vessel and small-vessel vasculitis. We demonstrated that within the cohort of patients, the type of diagnosis (MPA or GCA, rather than GPA or EGPA) and the presence of worsening renal function and/or anaemia at disease onset significantly correlated with the development of HTN/DM. Identifying the predictors of new CV risk factors in vasculitides is pivotal to develop preventive strategies to improve future outcomes for patients with vasculitis. Suppiah *et al*. (9) proposed and validated a model to predict the 5-year CV risk in patients with newly-diagnosed GPA and MPA. In Suppiah's model, within 5 years of diagnosis, 14% of patients developed a CV event. Diastolic HTN was one of the major risk factors included in the score. By contrast, PR3-ANCA, appeared to have a protective role. In our study, we have found similar results, shifting the focus to an earlier phase of disease and to the investigation of CV risk factors rather than CV events. Interestingly, we demonstrated that MPO-ANCA, but not PR-ANCA, was associated with the occurrence of HTN/DM.

Our results suggest that increasing efforts should be directed towards more effective detection and management of CV risk in patients with MPO-ANCA positive MPA who have significant elevation of serum creatinine/GFR reduction, because this group of patients seems to be the more prone to developing CV risk factors, and subsequently suffering CV events in the following 5 years (9-11). We have developed a predictive score of early HTN/DM occurrence; neither sex nor ethnicity were associated with the development of new CV risk factors.

In our cohort followed for 6 months from diagnosis, HTN/DM occurred in 76 (9%) patients with AAV and in 28 (6%) with GCA without significant differences. Indeed, patients with GCA, despite being older, with higher rates of active smokers, higher inflammatory markers, and being more frequently female, seemed to have a comparable risk of developing new CV risk factors and a lower CV risk and related mortality compared to patients with AAV. A negative association of pre-existing DM on the occurrence of GCA, and a lower incidence of DM in patients with biopsy-proven GCA has been reported (12-14). In our study, the separate analysis on the risk of developing DM only did not show significant differences between AAV: 28 patients (3.2%) or GCA, 20 (4.5 %), $p=0.481$. Li *et al*. (15) investigated CV risk factors and outcomes

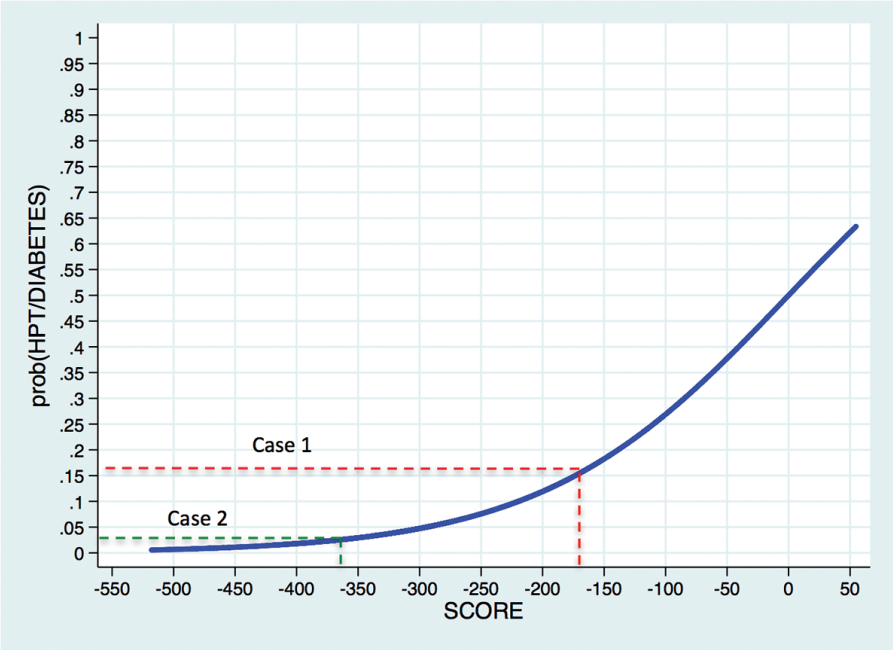
(1) Coefficients for score calculation

Variable	Coefficient
Age	-2*years
Female	-97
Caucasian	-79
Creatinine rise by 30%	109
GPA	0
MPA	103
EGPA	-89
GCA	102

(2) Categorization into risk groups

Risk Tertile	Score value	Probability of HPT/DIAB	95% CI
Low	-518 to -306	2.8	2.7-2.9
Intermediate	-307 to -226	6.0	5.8-6.1
High	-227 to 55	19.8	18.7-20.9

(3) Nomogram to derive the probability of hypertension/diabetes, given the score



(4) Simulated Examples

Case 1: Male, 70 years old, Caucasian, with GCA, normal renal function: -2*70 – 79 + 102 = -117
This corresponds to a high risk of developing HPT/DIAB within 6 months from diagnosis, with an expected probability for the high risk class around 20%. A probability of 15% for a score of -172 is derived from the plot (red dashed line).

Case 2: Female, 50 years old, Caucasian, with EGPA, normal renal function: -2*50 - 97 - 79 - 89 = -365.
This corresponds to a low risk of developing HPT/DIAB within 6 months from diagnosis, with a probability for the low risk class around 3%. A probability of 2.5% for a score of -365 is derived from the plot (green dashed line).

Fig. 1. Predictive score for the development of 6-months hypertension and/or diabetes.
(1) The score is computed using the coefficients from the upper left panel. (2) Then the category of risk is selected from the upper right panel (low/intermediate/high), where the expected probability of developing hypertension and/or diabetes can be read. (3) The probability of developing hypertension and or diabetes at 6 months, given the score, can also be read from the nomogram in the lower right panel. (4) The score is computed for 2 simulated cases in the lower left panel. The probability of hypertension/diabetes at 6 months can be read from the nomogram (Case 1: red dashed line; case 2: green dashed line).

on 9778 newly diagnosed patients with GCA and matched controls from UK-based Clinical Practice Research Datalink (CPRD). The authors identified a 1.4-fold increase risk of incident DM after the onset of GCA and a 24% increased risk of developing HTN. We (6) identified older age, male sex, and low socioeconomic status as risk factors for the development of CV disease in a study of 5800 patients with GCA and 37,000 matched controls.

We report a significant association between type of AAV, namely MPA, and development of HTN/DM. We found that MPA was mainly associated with the development of HTN (OR 4.53 (95% CI 2.63-7.81, $p<0.001$) rather than DM (OR 2.66 (95%CI 1.22-5.78, $p=0.013$). With multivariable analysis MPA remained significant after correcting for increased creatinine levels/reduced GFR. Our findings suggest that patients with MPA are at high risk of developing HTN regardless of renal function. A higher rate of HTN in MPA is in keeping with previous reports. Robson *et al*. (4) analysed data from several randomised controlled trials of MPA and GPA and reported HTN in 21.4% of patients with MPA within 6 months of diagnosis, compared to 15.2% with GPA. The association between AAV and increased CV events, even at the very early stages of disease, is well documented. A recent meta-analysis of observational studies on CV events in AAV comprising 14,000 patients reported an increase in CV risk in patients with AAV of 65%. (16) Of all cases of MI and stroke recorded in our cohort, 61% had a diagnosis of AAV. CV mortality is still one of the major issues affecting the prognosis of vasculitides. In our cohort, all cases of CV mortality occurred in patients with AAV. Despite the well-known CV risk associated with AAV, it has been reported that the management of associated factors, particularly HTN and dyslipidaemia is still suboptimal in clinical practice (17).

Our study has some limitations. Data regarding specific treatment with cardio-protective effects, including aspirin or statins were not available. Furthermore, information regarding remission-induction treatments for vasculitis, including data on GCs regimens were not available. The short period of observation related to the DCVAS study design might have led to an overestimation of the incidence of HTN/DM during the

acute phase of disease, whilst patients were being treated with the highest dosages of GCS. Nevertheless, the frequencies of HPT/DM that we report are in keeping with previous studies, if not lower. Moreover, it has been demonstrated that damage, whether it is treatment- or disease-related accumulates early; by 6 months, 82% of patients with AAV have accrued at least 1 VDI item of damage, with renal and CV features being the most represented (18), as confirmed by our study.

One of the main strengths of the current study is the large cohort with prospective data collection. Furthermore, the comparison between two types of systemic vasculitides with different size of vessels predominantly involved, clinical manifestations and epidemiologic characteristics allows for some interesting speculations on the common background factors leading to an increased probability of developing CV and metabolic complications that goes beyond the expected risk associated with traditional CV risk factors or treatment-related complications.

In conclusion, our study demonstrates that new-onset HTN/DM during the first few months from a diagnosis of vasculitis, particularly MPA and GCA, should represent a major concern in the management of these patients. We propose a simple score to identify patients with vasculitis who are most likely to be at risk of developing HTN or DM. Further efforts should be directed to finding measures to reduce the risk of CV disease, to be integrated early into the management of systemic vasculitides.

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Competing interests

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