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A Model to Predict Cardiovascular Events in Patients With Newly Diagnosed Wegener's Granulomatosis and Microscopic Polyangiitis

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Objective. **To create a prognostic tool to quantify the 5-year cardiovascular (CV) risk in patients with newly diagnosed Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) without premorbid CV disease.**

Methods. **We reviewed CV outcomes during the long-term followup of patients in the first 4 European Vasculitis Study Group (EUVAS) trials of WG and MPA. CV events were defined as CV death, stroke, myocardial infarction, coronary artery bypass graft, or percutaneous coronary intervention. Logistic regression was performed to create a model to predict the absolute risk of a CV event. The model was tested using the Wegener's Granulomatosis Etanercept Trial (WGET) cohort.**

Results. **Seventy-four (13.8%) of 535 patients with 5 years of followup from the EUVAS trials had at least 1 CV event: 33 (11.7%) of 281 WG versus 41 (16.1%) of 254 MPA. The independent determinants of CV outcomes were older age (odds ratio [OR] 1.45, 95% confidence interval [95% CI] 1.11–1.90), diastolic hypertension (OR 1.97, 95% CI 0.98–3.95), and positive proteinase 3 (PR3) antineutrophil cytoplasmic antibody (ANCA) status (OR 0.39, 95% CI 0.20–0.74). The model was validated using the WGET cohort (area under the receiver operating characteristic curve of 0.80).**

Conclusion. **Within 5 years of diagnosis of WG or MPA, 14% of patients will have a CV event. We have constructed and validated a tool to quantify the risk of a CV event based on age, diastolic hypertension, and PR3 ANCA status in patients without prior CV disease. In patients with vasculitis, PR3 ANCA is associated with a reduced CV risk compared to myeloperoxidase ANCA or negative ANCA status.**

INTRODUCTION

Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are the 2 most common types of small- and medium-vessel vasculitis, with an estimated combined prevalence of 49–254 per million in Europe and North America (1). Untreated these diseases are fatal, but modern therapy has dramatically improved survival (2–8). How-

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ever, patients continue to experience long-term morbidity and mortality from persistent low-grade activity and permanent damage caused by the acute phase of vasculitis or its treatment (9). An important component of this increased long-term morbidity and mortality is from cardiovascular (CV) disease, which was highlighted in a retrospective review of the Danish National Hospital Register, where patients with WG showed an increased rate of a myocardial infarction (MI) within the first 5 years after a diagnosis of WG compared to the general population (hazard ratio 3.6) (10). In addition, a retrospective study showed that patients with WG and MPA, when matched for renal function and other traditional risk factors, had double the rate of CV events (11). Theories for the increased CV events in vasculitis include systemic inflammation and endothelial dysfunction (12,13), factors associated with increased CV risk in other inflammatory diseases (14–16).

In 1995, the European Vasculitis Study Group (EUVAS) launched randomized controlled trials for the treatment of WG and MPA with unified trial protocols and data collection procedures; 4 of these trials have been published (4,6–8,17). Patient enrollment in the 4 trials was stratified by the degree of renal involvement. Subsequent to the completion of these trials, EUVAS has performed a long-term followup study on patients enrolled in these original trials. Together, this cohort represents the largest ever prospectively studied group of patients with WG and MPA.

The aims of this study were to 1) review the CV events in the first 5 years from the long-term followup of the 4 EUVAS trials, 2) use these data to create a prognostic tool aimed at predicting the 5-year risk of CV events in patients with newly diagnosed WG and MPA who have no CV disease at diagnosis, and 3) validate the tool in a second separate cohort of vasculitis patients.

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PATIENTS AND METHODS

The patients and methods of the first 4 EUVAS randomized controlled trials included in the long-term followup study have previously been described (4,6–8,17). In summary, all of the patients had a new diagnosis of WG, MPA, or renal-limited vasculitis. Patients were stratified into the 4 studies by the severity of renal involvement, listed here in order: 1) MEPEX: comparison of plasma exchange to methyl prednisone in patients with severe renal disease (creatinine level >500 mmoles/liter or requiring dialysis) (7), 2) CYCAZAREM: maintenance therapy with azathioprine versus cyclophosphamide in patients with a renal manifestation (creatinine level <500 mmoles/liter) or with generalized life-threatening disease (4), 3) CYCLOPS: induction therapy comparing daily oral cyclophosphamide with pulsed intravenous cyclophosphamide in patients with generalized disease (creatinine level <500 mmoles/liter) (8), and 4) NORAM: a comparison of methotrexate to cyclophosphamide for induction treatment in patients with a creatinine level <150 mmoles/liter and without critical organ-threatening disease (6). The study methods, data collection procedures, and disease scoring were consistent between the 4 trials.

For the validation set, we used anonymized data from patients enrolled in the Wegener's Granulomatosis Etanercept Trial (WGET), i.e., 180 patients with active WG who were randomized to receive etanercept or placebo in addition to standard maintenance therapy (18). Long-term followup of this cohort is now available, including CV events. Data from 136 patients without preexisting CV disease were available for testing our regression model. Sixteen of 136 patients in the WGET cohort had a CV event: 14 with a nonfatal cardiac event (MI, coronary artery bypass graft, or percutaneous coronary intervention), 1 nonfatal stroke, and 1 CV death. Baseline demographics for the EUVAS and WGET cohorts are shown in Table 1.

Ethics approval was obtained for each participating site as per local requirements. A questionnaire on vital status and CV events was completed on all eligible patients by clinical investigators at each participating site. Information was collected at 5 years from entry into the original study, and also at the last available followup. The databases containing baseline information for the 4 trials were merged with the long-term followup results. All patients with an entry diagnosis of renal-limited vasculitis were considered to have MPA for this analysis.

The primary outcome measure of interest in this subanalysis was a CV event within 5 years after enrollment into the original EUVAS trial. We defined a CV event as death from any CV cause, nonfatal stroke, nonfatal MI, and coronary artery bypass graft or percutaneous coronary intervention. The identification of CV death was based on the local investigator reporting death and cause of death. The cause of death was adjudicated by an independent panel. The observed CV death rate in the EUVAS trials was compared to the predicted CV death rate (adjusted for age and country of origin). The relevant European and Mexican CV death rates for the year 2002 based on the World Health Organization Statistical Information System database (online at http://www.who.int/whosis/en/) are pro-

Table 1. Baseline demographics in the EUVAS long-term followup and WGET cohorts*

	EUVAS (n = 535)	WGET (n = 180)	*P*†
Age, mean ± SD years	58 ± 14	47 ± 16	< 0.001
Male sex	288 (54)	108 (60)	0.17
WG	281 (53)	180 (100)	< 0.001
Microscopic polyangiitis	254 (47)	0 (0)	< 0.001
New diagnosis of vasculitis	535 (100)	80 (44)	< 0.001
Existing diagnoses of vasculitis	0 (0)	100 (56)	< 0.001
Serum creatinine, mean ± SD μmoles/liter	341 ± 321	153 ± 177	< 0.001
BVAS2 (new/worse) score, mean ± SD	16.9 ± 9.2	NA	–
BVAS/WG score, mean ± SD	NA	6.9 ± 3.4	–
MPO ANCA positive	190 (35.5)	21 (12)	< 0.001
PR3 ANCA positive	302 (56.5)	131 (73)	< 0.001
ESR, mean ± SD mm/hour	76 ± 36	NA	–
CRP level, mean ± SD mg/liter	88 ± 139	NA	–

* Values are the number (percentage) unless otherwise indicated. EUVAS = European Vasculitis Study Group; WGET = Wegener's Granulomatosis Etanercept Trial; WG = Wegener's granulomatosis; BVAS2 = Birmingham Vasculitis Activity Score, version 2; NA = not available; MPO = myeloperoxidase; ANCA = antineutrophil cytoplasmic antibody; PR3 = proteinase 3; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.
† Calculated using chi-square test of association for categorical variables and 2-sample *t*-test for continuous variables.

vided in Supplementary Appendix A (available in the online version of this article at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)2151-4658).

Determination of nonfatal MI required evidence of electrocardiogram changes or cardiac enzyme elevation. Nonfatal stroke was defined as a focal neurologic deficit present for at least 3 months (i.e., transient ischemic events were not included). All items recorded at baseline from entry into each trial such as patient demographics, clinical features, blood results, disease activity scores (Birmingham Vasculitis Activity Score [BVAS], versions 1 and 2]) (19), and disease damage scores (Vasculitis Damage Index) (20), including individual components of these instruments, were available as predictor variables. Hypertension in the development cohort (EUVAS trials) was defined as a diastolic blood pressure >95 mm Hg at the time of entry into the trial that was attributable to active vasculitis (irrespective of whether the patient had a previous history of hypertension or was receiving antihypertensive treatment). This definition of hypertension was chosen because of how the data were captured in the original trials (based on a BVAS item). For the validation sample (WGET cohort), hypertension was defined as a diastolic blood pressure >95 mm Hg at trial entry, irrespective of previous history of hypertension or antihypertensive therapy. Attribution of the diastolic hypertension to vasculitis in the WGET cohort was not included in the definition because it was not captured in the original trial.

A points-based Cox Framingham CV risk prediction tool (21) that uses body mass index (BMI) instead of total and high-density lipoprotein cholesterol was used to test how well a general population risk model performed in patients with vasculitis. We simplified systolic blood pressure to <140 mm Hg (0 points on the scoring system) versus ≥140 mm Hg (3 points for women, 2 points for men) because of the way in which hypertension was recorded in the data set.

We used 2 methods to validate our new regression model: 1) bootstrapping, an internal validation technique used to obtain a bias-corrected estimate in the development sample (22), and 2) testing the model in the validation cohort using receiver operator characteristics.

Data were analyzed using the statistical software package Stata, release 10.1. Univariate logistic regression modeling was used to examine the association between baseline variables and CV events. Fractional polynomial regression modeling was used to model nonlinear relationships for continuous variables. A multivariate logistic regression model was then fitted, including all predictor variables regardless whether or not they were statistically associated with a CV event in univariate analysis. Having fitted the full multivariate model, a backward selection process was used to exclude variables that did not improve model fit. Likelihood ratio tests were used to compare model fit. The results of complete case analyses can be biased because the cumulative effect of missing data in several variables often leads to exclusion of a substantial proportion of the original sample, causing a loss of precision and power (23). This bias can be overcome by using multiple imputation methods, which we did using the Imputation by Chained Equations procedure in Stata (23–26). For logistic regression, 10 times as many outcome events as predictor variables are required to avoid model over fit. Using clinical judgment, we initially created a model using traditional risk factors (age, sex, BMI, smoking status, hypertension, and diabetes mellitus), and then a model with only disease-specific items (BVAS, proteinase 3 [PR3] and myeloperoxidase [MPO] antineutrophil cytoplasmic antibody [ANCA] status, baseline estimated glomerular filtration rate [GFR], age, and sex). Regression diagnostics were performed to identify outlying data that may overly influence the model. Cholesterol measurements were not recorded at baseline, and therefore could not be included in the traditional risk factor model.

Performance of the predictive model was assessed in terms of calibration and discrimination. Calibration mea-

Table 2. Baseline variables for patients included in the development of the CV risk prediction model (n = 427)*

	Total no. of patients	No. (%) of patients with at least one CV event	Multiple imputation (n = 427), crude OR (95% CI)	*P*
Trial name				
CYCAZAREM	131	14 (10.7)	1.00	
CYCLOPS	107	14 (13.1)	1.26 (0.57–2.77)	0.57
MEPEX	99	18 (18.2)	1.86 (0.87–3.95)	0.11
NORAM	90	4 (4.4)	0.39 (0.12–1.22)	0.11
Diagnosis				
MPA	190	31 (16.3)	1.00	
WG	237	19 (8.0)	0.45 (0.24–0.82)	0.009
PR3 ANCA				
No	168	33 (19.6)	1.00	
Yes	257	17 (6.6)	0.29 (0.16–0.54)	< 0.001
MPO ANCA				
No	279	22 (7.9)	1.00	
Yes	146	28 (19.2)	2.78 (1.52–5.06)	0.001
Age			1.58 (1.22–2.06)	0.001
Sex				
Female	207	23 (11.1)	1.00	
Male	220	27 (12.3)	1.12 (0.62–2.02)	0.71
BMI			1.03 (0.93–1.14)	0.57
Ever smoked				
No	160	15 (9.4)	0.61 (0.32–1.18)	0.14
Yes	132	20 (15.2)	1.00	
Diabetes mellitus				
No	339	40 (11.8)	1.00	
Yes	14	3 (21.4)	2.06 (0.57–7.40)	0.27
New hypertension				
No	350	33 (9.4)	1.00	
Yes	72	16 (22.2)	2.74 (1.41–5.30)	0.003
Hemoglobin	426		0.86 (0.75–1.00)	0.051
Log WBC†	427		1.20 (0.56–2.59)	0.63
Platelets‡	427		0.97 (0.95–0.99)	0.011
Estimated GFR (MDRD)	426		0.83 (0.74–0.93)	0.001
BVAS score	422		1.02 (0.99–1.05)	0.23
VDI 6-month score	238		1.38 (1.09–1.74)	0.007

* CV = cardiovascular; OR = odds ratio; 95% CI = 95% confidence interval; CYCAZAREM = maintenance therapy with azathioprine vs. cyclophosphamide in patients with a renal manifestation or with generalized life-threatening disease; CYCLOPS = induction therapy comparing daily oral cyclophosphamide with pulsed intravenous cyclophosphamide in patients with generalized disease; MEPEX = comparison of plasma exchange to methyl prednisone in patients with severe renal disease; NORAM = comparison of methotrexate to cyclophosphamide for induction treatment in patients with creatinine <150 mmoles/liter and without critical organ-threatening disease; MPA = microscopic polyangiitis; WG = Wegener's granulomatosis; PR3 = proteinase 3; ANCA = antineutrophil cytoplasmic antibody; MPO = myeloperoxidase; BMI = body mass index; WBC = white blood cell; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease study equation; BVAS = Birmingham Vasculitis Activity Score (new/worse); VDI = Vasculitis Damage Index.
† A log transformation was performed on the WBC count to achieve a normal distribution.
‡ For a 10-unit increase in platelet count.

sures how closely predicted risk agrees with the observed risk. This was assessed for each tenth of predicted risk ensuring 10 equally sized groups, and a Hosmer-Lemeshow goodness-of-fit test was performed (27). Discrimination is the ability of the model to differentiate between patients who experienced a CV event during the 5 years of followup in this study and those who did not. We tested discrimination by calculating the area under the receiver operating characteristic (AUROC) curve 1) in the original data set, 2) by bootstrapping, and 3) by testing in the WGET cohort (18). To assess the goodness of fit of a logistic model, we used McKelvey-Zavoina pseudo R^2 (28,29).

In addition, classification and regression tree (CART) analysis, a binary recursive partitioning method, was performed in the R statistical software package (R Foundation) using the "party" package. In each node of the tree, a significance test was made between any of the covariates and the response, and a split was established when the *P* value was <0.05.

RESULTS

A total of 535 patients (281 with WG, 254 with MPA), including patients who died, had 5 years of followup; 74

Table 3. Predictor variables included in developing the final regression model*

	Complete case, univariable OR (95% CI)	Multiple imputation (n = 427)			
		Univariable OR (95% CI)	Pseudo R^2, %	Multivariable OR (95% CI) (R^2 = 22.1%)	Reduced model OR (95% CI) (R^2 = 18.5%)
Age (n = 427)†	1.58 (1.22–2.06)	1.58 (1.22–2.06)	11.7	1.35 (1.02–1.79)	1.45 (1.11–1.90)
Sex (n = 427)					
Female	1.00	1.00		1.00	–
Male	1.12 (0.62–2.02)	1.12 (0.62–2.02)	0.1	1.10 (0.56–2.15)	–
BMI (n = 196)	1.03 (0.93–1.14)	1.03 (0.93–1.14)	1.3	–	–
BVAS1 (n = 422)	1.02 (0.99–1.05)	1.02 (0.99–1.05)	1.0	–	–
Estimated GFR (n = 426)†	0.83 (0.74–0.93)	0.83 (0.74–0.93)	11.3	0.93 (0.82–1.06)	–
ANCA MPO (n = 425)					
No	1.00	1.00		–	–
Yes	2.77 (1.52–5.05)	2.78 (1.52–5.06)	6.7	–	–
ANCA PR3 (n = 425)					
No	1.00	1.00		1.00	1.00
Yes	0.29 (0.16–0.54)	0.29 (0.16–0.54)	10.0	0.41 (0.21–0.80)	0.39 (0.20–0.74)
Ever smoked (n = 427)					
Yes	1.00	1.00		1.00	–
No	0.58 (0.28–1.18)	0.61 (0.32–1.18)	2.3	0.62 (0.29–1.31)	–
New hypertension (n = 422)					
No	1.00	1.00		1.00	1.00
Yes	2.74 (1.42–5.32)	2.74 (1.41–5.30)	4.0	1.92 (0.93–3.95)	1.97 (0.98–3.95)
Previous diabetes mellitus (n = 353)					
No	1.00	1.00		–	–
Yes	2.04 (0.55–7.62)	2.06 (0.57–7.40)	0.9	–	–

* OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index; BVAS1 = Birmingham Vasculitis Activity Score, version 1; GFR = glomerular filtration rate; ANCA = antineutrophil cytoplasmic antibody; MPO = myeloperoxidase; PR3 = proteinase 3.
† For a 10-unit increase.

(13.8%) of 535 patients had at least 1 CV event: 33 (11.7%) of 281 WG versus 41 (16.1%) of 254 MPA. There were 32 (6.0%) CV deaths, 25 (4.7%) nonfatal strokes, and 42 (7.9%) had a nonfatal MI, coronary artery bypass graft, or percutaneous coronary intervention. The observed age-standardized CV death rate for the EUVAS cohort was 699 compared to the predicted rate of 190 per 100,000 population per year.

When developing the predictive model, 31 patients were excluded due to missing baseline values, 32 due to missing outcome records, and 45 due to CV disease prior to trial entry. The remaining 427 patients, 50 with a CV event (19 of 237 WG versus 31 of 190 MPA; $P < 0.01$), were used to develop the model. A summary of the baseline variables analyzed for the 427 patients is provided in Table 2. Smoking status was available in 292 of 427 patients in the study: 7.3% were current smokers, 23.7% were ex-smokers, and 37.5% had never smoked. For analysis, we combined the current and ex-smokers as an ever smoked group. Comparing those that had never smoked to ever smoked gave an

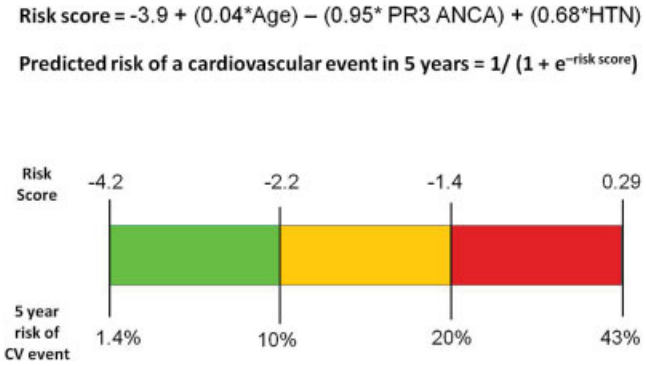

Figure 1. Final model to predict the risk of a cardiovascular (CV) event in the first 5 years from diagnosis with microscopic polyangiitis or Wegener's granulomatosis. The 5-year CV risk is shown as: green = low risk (<10%), orange = moderate risk (10–20%), and red = high risk (>20%). HTN = hypertension, defined as diastolic blood pressure >95 mm Hg at the time of diagnosis (score 1 if present, 0 if absent); PR3 = proteinase 3; ANCA = antineutrophil cytoplasmic antibody; PR3 ANCA = 1 if present, 0 if absent.

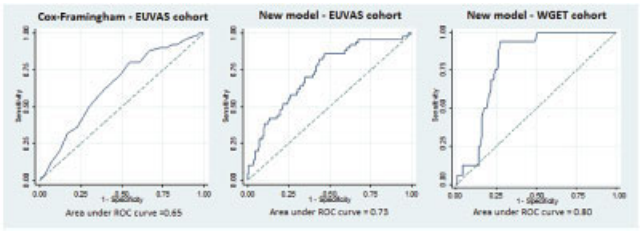

Figure 2. Receiver operating characteristic (ROC) curves comparing our new disease-specific model with the traditional points-based Cox Framingham model. EUVAS = European Vasculitis Study Group; WGET = Wegener's Granulomatosis Etanercept Trial.

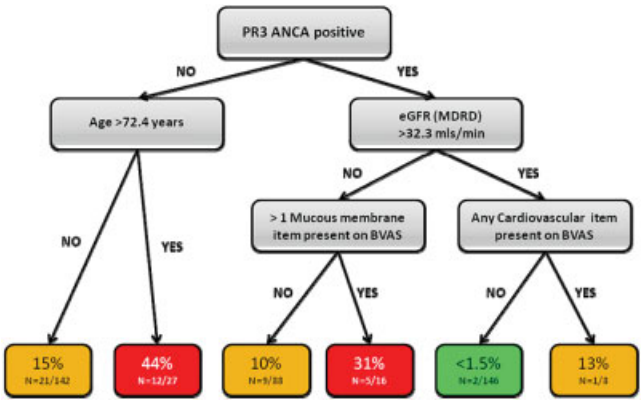

Figure 3. Conditional inference tree showing an approximate risk of a cardiovascular event within 5 years based on baseline clinical features. The percentage shown is the risk of a cardiovascular event within 5 years of diagnosis of Wegener's granulomatosis or microscopic polyangiitis. N = cardiovascular events/number of individuals in group; PR3 = proteinase 3; ANCA = antineutrophil cytoplasmic antibody; eGFR = estimated glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; BVAS = Birmingham Vasculitis Activity Score.

odds ratio (OR) of 0.61 (95% confidence interval [95% CI] 0.32–1.18, $P = 0.14$) for any CV event within 5 years. Reanalyzing the data comparing never smoked to current smokers gave an OR of 0.90 (95% CI 0.24–3.36, $P = 0.87$).

All of the traditional and disease-specific risk factors were considered for inclusion in the final model (Table 3). To avoid overfitting, we considered the effect of each predictor independently and assessed the effect of confounding for that predictor with each risk factor. Variables that were significantly associated with CV events in univariate analysis or were important confounders were included in the full multivariable regression model. Older age was associated with an increased risk of a CV event; however, the effect was slightly attenuated due to confounding by the estimated GFR. Crude analyses suggested that an increasing estimated GFR was associated with a reduced CV risk, but this was attenuated after adjustment for age and PR3 ANCA. Because MPO ANCA and PR3 ANCA were strongly inversely associated with each other, only PR3 ANCA was considered for inclusion in the full model because it was a statistically stronger predictor. PR3 ANCA was associated with a reduced CV risk and MPO ANCA with an increased CV risk. In both cases this was attenuated slightly after adjusting for age, estimated GFR, and diastolic hypertension. Patients with diastolic hypertension were at an increased risk of CV events. This effect was attenuated after adjusting for age, estimated GFR, and PR3 ANCA, but strengthened if adjusting for sex and smoking status. Sex, BMI, smoking status, baseline BVAS score, and diabetes mellitus were not associated with CV events.

Age, sex, estimated GFR, PR3 ANCA status, smoking status, and diastolic hypertension at baseline were included in creating the full multivariable regression model. After backward selection, age, PR3 ANCA status, and diastolic hypertension remained in the final model. The final model is shown in Figure 1. Cutoffs of <10% as low risk, 10–20% as moderate risk, and >20% as high risk were chosen to provide memorable categories. In the EUVAS cohort, 245 patients (57.4%) fell into the low-risk group, 106 (24.8%) fell into the moderate-risk group, and 76 (17.8%) fell into the high-risk group using our new 5-year risk prediction model. Observed CV events consisted of 15 (6.1%) of 245 for the low-risk group, 14 (13.2%) of 106 for the medium-risk group, and 21 (27.6%) of 76 for the high-risk group.

The Hosmer-Lemeshow goodness-of-fit test suggested that the model was well calibrated ($P = 0.55$). The model demonstrated good discrimination, with an AUROC of 0.73 for the original data set, bootstrapped analysis gave a bias-corrected AUROC of 0.72, and validation with the WGET cohort demonstrated very good discrimination, with an AUROC of 0.80 (Figure 2). The pseudo R^2 (McKelvey-Zavoina) for the final model was 18.5%. The model was better at predicting coronary events than strokes: an AUROC of 0.85 (95% CI 0.77–0.92) with a pseudo R^2 of 49.7% versus an AUROC of 0.70 (95% CI 0.60–0.80) and a pseudo R^2 of 19.6% for the EUVAS cohort. In comparison, the AUROC for any cardiac event using the points-based Cox Framingham model was 0.65 (95% CI 0.57–0.72) (Figure 2).

Figure 3 shows the conditional inference trees we created using CART analysis to predict CV events. In this tree, PR3 ANCA status was the most discriminative starting point. Thereafter, age, estimated GFR, and BVAS items were important predictors of the risk of a CV event. Using this inference tree, a patient that was PR3 ANCA positive, had an estimated GFR of >32.3 ml/minute, and no items present on the CV section of the BVAS had the lowest risk (1.4%) of a CV event in the following 5 years. In the EUVAS cohort, 146 individuals fit these criteria and 2 (1.4%) of them had a CV event. Conversely, 12 (44%) of 27 patients that were PR3 ANCA negative and age >72.4 years had a CV event.

DISCUSSION

Within 5 years of diagnosis of WG or MPA, approximately 14% of patients will have a major CV event. The age-standardized annual CV mortality rate of 699 per 100,000 in this cohort is 3.7 (95% CI 3.2–4.3) times higher than we would expect in the background population. The result of our study adds further weight to the growing body of evidence that individuals with a diagnosis of WG or MPA are at a significantly increased risk of CV morbidity and mortality (10,11).

There are many potential reasons for the increased CV risk. Endothelial dysfunction, which is a recognized risk factor for CV disease (16,30–32), has been shown to be present in ANCA-associated vasculitis and is independent of disease activity or renal involvement (33). Renal dysfunction, which occurs frequently in patients with MPA and WG, is an established contributor to CV disease by affecting metabolic, inflammatory, and hemodynamic pathways (34). In addition, vasculitis represents a chronic inflammatory state, and other inflammatory diseases, such as rheumatoid arthritis and systemic lupus erythematosus, have strong associations with CV disease (35,36). Animal

models suggest that vessels following arteritis are more prone to atherosclerotic change (37). Furthermore, corticosteroids, which are a routine part of treatment for vasculitis, present an interesting conflict: they increase CV risk by accelerating the development of diabetes mellitus (38), dyslipidemia (39), and hypertension (40), but may also have a protective role in vasculitis by reducing systemic inflammation and improving endothelial dysfunction (13,15,41).

We have developed 2 complementary models (logistic regression and CART) to predict the 5-year CV risk at the time of the first presentation with WG and MPA. The regression model was validated in the WGET cohort and performed better than existing generic risk tools available for the general population. Both models identified a positive PR3 ANCA status as an important determinant of lower risk among those with vasculitis. However, almost all of the patients in the EUVAS trials were either MPO or PR3 ANCA positive, implying that those with a positive MPO ANCA are associated with an increased risk of CV disease. Interestingly, neither model identified sex as a predictor of risk, suggesting that vasculitis may remove the CV risk benefit usually observed in women. A potential explanation for this is that a large proportion of the women enrolled in the EUVAS trials were in the peri- or postmenopausal age group (mean ± SD age 58 ± 14 years, i.e., 84% were age >46 years at baseline), and others may have been pushed into premature menopause by the use of cyclophosphamide. In the regression model, a positive PR3 ANCA status decreased the risk of a CV event, and older age and the presence of diastolic hypertension at the time of enrollment into the study increased the risk. The discrimination of this model compares very favorably with the QRISK score (AUROC curve of 0.76 for men and 0.79 for women) and the 1991 Framingham equation (AUROC curve of 0.74 for men and 0.76 for women) (42–44). Our second model used CART analysis to create an inference tree to determine the CV risk, which provides insight into possible interactions between variables. For example, the inference tree shows that patients who are PR3 ANCA positive and have good renal function are generally at low risk for CV events; however, if these patients have any CV system involvement at baseline then their risk of a major CV event is 9-fold higher.

The main reason for developing risk algorithms is not just prognostication, but prognostication that allows clinicians to develop and test preventative strategies. For vasculitis, we do not yet know whether treating traditional risk factors such as smoking and dyslipidemia would change the CV outcome or whether it is more important to treat the inflammation and renal disease. Our model could be used to do the power calculation to determine how many patients would be needed in an interventional study to detect a 20% reduction in CV events. For example, you would need X, high-risk patients versus Y, low-risk patients or Z, all patients.

There are limitations to our study. Lipid results, glycosylated hemoglobin levels, and specific CV medications associated with the prevention of CV disease (e.g., aspirin, statins, angiotensin-converting enzyme inhibitors) were absent from the baseline data set, which may have omitted important predictor variables. The original EUVAS trials were not designed to evaluate CV risk and therefore, a study designed to look specifically at this issue may have resulted in an even stronger model. This is something to aspire to for future studies. However, ours is the only disease-specific model currently available for vasculitis. When interpreting our statistical model, it is important to remember that we are trying to predict a specific outcome and the key objective is to predict the risk accurately. There are potentially a large number of variables that have overlapping contributions to the CV risk, but if a few variables are able to predict the risk with the same accuracy, then whether or not we include the other variables in the equation should not matter. For example, "hypertension" in our model would very likely have an overlapping contribution to CV risk with renal impairment. The patients included in our development data set comprised a larger proportion of patients with mild WG (NORAM trial) and more patients with severe MPA (MEPEX trial); therefore, patient selection bias may have unduly influenced the CV outcomes despite our best efforts to correct for renal function and disease severity in our statistical modeling. In addition, there are some major differences between the development and validation groups; all of the patients had newly diagnosed WG or MPA in the EUVAS trials, whereas the WGET cohort only included WG but comprised patients with new and existing disease. We acknowledge that a large mixed cohort with both WG and MPA patients would have been the best cohort for testing and validation. However, there are currently no other suitable cohorts available (i.e., with sufficient number of patients, a long enough duration of followup, and accurate recording of CV events). Therefore, we have used the best alternative possible. There was only 1 stroke in the WGET cohort, so validation of this outcome needs to be interpreted with caution. Despite these potential biases and cohort differences, our model still works very well in both groups, confirming the strength of our model and reinforcing that age, diastolic hypertension, and PR3 ANCA status are strong predictors of CV outcomes in patients with ANCA-associated vasculitis. A further consideration is that renal function may change dramatically from baseline to later in the disease; therefore, its use as a predictive variable may depend on when it is measured. The effect of disease flares, cumulative dose of steroids, and changes in renal function will need to be taken into account when evaluating CV risk at different time points in the disease course.

In conclusion, we have shown that the risk of a CV event in the first 5 years after the diagnosis of WG or MPA is raised. To quantify this risk for an individual patient, we have created and validated a statistical model using baseline clinical features. Identifying those at highest risk may help target those who require closer monitoring and further intervention.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Suppiah had full

access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Suppiah, Harper, Jayne, Mukhtyar, Westman, Davis, McCune, Stone, Luqmani.
Acquisition of data. Flossmann, Jayne, Mukhtyar, Westman, Davis, Hoffman, McCune, Merkel, St.Clair, Seo, Spiera, Stone, Luqmani.
Analysis and interpretation of data. Suppiah, Judge, Batra, Höglund, Javaid, Jayne, Luqmani.

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