



VALIDATION OF THE BIRMINGHAM VASCULITIS ACTIVITY SCORE  
(VERSION 3)

by

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*For Bina, my wife*

*This would not be possible without her unquestioning patience!*

*For Aanya and Sasha*

*Who missed daddy on many many evenings and weekends but did not complain  
(much)*

## **DECLARATION OF CONTRIBUTION**

I declare that this thesis is my work, made possible with the assistance of several people, all of whom have been acknowledged on the following page. My work in this project is as under

- Recruitment of cases and controls in Oxford (with assistance from Denise Brown and Raashid Luqmani)
- Acquiring data from other centres (with assistance from Denise Brown)
- Creating the databases for data-entry, including an electronic version of both BVAS versions used in this study
- Data entry
- Creating a BVAS calculator for both versions of BVAS used in this study
- Finalising the scoring system, and the glossary for the score (with the help of my supervisor, Dr Raashid Luqmani)
- Analysing the data with advise from Robert Lee
- Writing the manuscripts which have been published as a result of this work

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**ABSTRACT**

**Background:** The Birmingham Vasculitis Activity Score is a clinical tool to quantify disease activity in systemic vasculitis. Following its extensive use, a previous version of BVAS has been revised to improve the face validity and the feasibility. Changes were made and approved by an expert committee.

**Objective:** To validate the third version of the Birmingham Vasculitis Activity Score (BVAS version 3)

**Methods:** In a series of prospective, multi-centre studies, different aspects of the BVAS (version 3) were validated in patients with systemic vasculitis. The data collection was done using standardized data entry forms. The studies were approved by local ethics committees. The recruitment of controls was approved by the local clinical audit and effectiveness department.

**Results:** The convergent validity was established by correlating the BVAS (version 3) to the physician's treatment decision (Spearman's  $\rho$  0.66, 95% CI 0.59-0.72), BVAS1 of version 2 ( $\rho$  0.94, 95% CI 0.92-0.96), BVAS2 of version 2 in patients with persistent disease ( $\rho$  0.60, 95% CI 0.21-0.83), C-reactive protein levels ( $\rho$  0.43, 95% CI 0.31-0.54), physician's global assessment ( $\rho$  0.91, 95% CI 0.89-0.93), and vasculitis activity index ( $\rho$  0.88, 95%CI 0.86-0.91). The BVAS (version 3) was reproducible and repeatable (intra-class correlation coefficients were 0.96 (95%CI 0.95-0.97) and 0.96 (95%CI 0.92-0.97) respectively). The BVAS (version 3) was sensitive to changing disease status with a fall of 16.9 (95% CI 14.8-18.9) units ( $P < 0.001$ , paired t test) after 3 months of treatment. The BVAS (version 3) demonstrated an ability to differentiate systemic vasculitis from some non-vasculitis conditions.

**Conclusion:** BVAS (version 3) is validated for use in clinical trials of systemic vasculitis. It is repeatable, reproducible, sensitive to change and can differentiate between systemic vasculitis and some non-vasculitic rheumatological conditions.

## TABLE OF CONTENTS

<b>Chapter 1 INTRODUCTION .....</b>	<b>1</b>
WHAT IS SYSTEMIC VASCULITIS? .....	2
CLASSIFICATION .....	2
ASSESSMENT OF VASCULITIS .....	5
THE NEED FOR CHANGE IN BVAS (VERSION 2) .....	23
THE CHANGE .....	24
SUMMARY .....	26
THE AIMS OF THIS PROJECT .....	26
<b>Chapter 2 CONVERGENT VALIDITY OF BVAS (VERSION 3).....</b>	<b>28</b>
AIM .....	30
METHODS .....	30
RESULTS.....	33
DISCUSSION.....	42
CONCLUSIONS.....	47
<b>Chapter 3 RELIABILITY OF BVAS (VERSION 3).....</b>	<b>48</b>
AIM .....	49

METHODS.....	49
RESULTS.....	51
DISCUSSION.....	53
CONCLUSION.....	55
<b>Chapter 4 SENSITIVITY TO CHANGE.....</b>	<b>56</b>
AIM.....	57
METHODS.....	57
RESULTS.....	60
DISCUSSION.....	62
CONCLUSION.....	64
<b>Chapter 5 USING BVAS (VERSION 3) TO DIFFERENTIATE VASCULITIS FROM OTHER MUSCULOSKELETAL DISEASES.....</b>	<b>65</b>
AIM.....	66
METHODS.....	67
RESULTS.....	68
DISCUSSION.....	74
CONCLUSION.....	76

<b>Chapter 6 CONCLUSIONS .....</b>	<b>77</b>
CONVERGENT VALIDITY .....	78
RELIABILITY .....	80
DISCRIMINATION .....	81
<b>Chapter 7 FUTURE WORK.....</b>	<b>85</b>
DISEASE SPECIFIC INDEX.....	86
PROGNOSTIC INDEX.....	87
DAMAGE INDEX .....	88
<b>BIBLIOGRAPHY .....</b>	<b>89</b>
<b>FULL LIST OF PUBLICATIONS DURING THE MASTERS PROGRAMME .....</b>	<b>103</b>
PAPERS.....	104
ABSTRACTS .....	107
BOOK CHAPTERS.....	109
<b>APPENDIX 1 .....</b>	<b>110</b>
<b>APPENDIX 2 .....</b>	<b>114</b>
<b>APPENDIX 3 .....</b>	<b>121</b>

## LIST OF FIGURES

Figure 1-1: Birmingham Vasculitis Activity Score (version 2) .....	18
Figure 1-2: Vasculitis Damage Index .....	21
Figure 2-1: Microsoft Access database used to record patient information.....	31
Figure 2-2: Histogram of BVAS (version 3) values in 313 patients with systemic vasculitis .....	35
Figure 2-3: Correlation of BVAS (version 3) with BVAS 1 sub-score of BVAS (version 2) in 138 patients. ....	36
Figure 2-4: Correlation between BVAS (version 3) and BVAS 2 of BVAS (version 2) in 19 patients with persistent disease .....	37
Figure 2-5: Correlation between BVAS (version 3) and C-reactive protein levels in 185 patients.....	38
Figure 2-6: Correlation between BVAS (version 3) and 100 mm VAS PGA in 307 patients. ....	39
Figure 2-7: Correlation between BVAS (version 3) and VAI in 304 patients .....	40
Figure 2-8: Correlation of BVAS (version 3) with treatment decision in 302 patients with systemic vasculitis.....	41
Figure 2-9: Correlation between BVAS (version 3) and treatment decision in 158 patients with Wegener's granulomatosis.....	42

Figure 4-1: Microsoft Access database used for recording patient information.....	59
Figure 4-2: Box-plot of BVAS (version 3) scores at 0 and 3 months in 39 patients.....	61
Figure 5-1 BVAS (version 3) scores in cases and controls.....	70
Figure 5-2 Receiver operating characteristics curve for BVAS (version 3) to diagnose vasculitis (when comparing with rheumatoid arthritis controls).....	71
Figure 5-3 Receiver operating characteristics curve for BVAS (version 3) to diagnose vasculitis (when comparing with other non-systemic rheumatic controls).....	73

## LIST OF TABLES

Table 1-1 Chapel Hill Consensus conference definitions .....	4
Table 2-1: Definitions of treatment categories .....	32
Table 2-2: Demographics of the cohort.....	34
Table 2-3: A comparison of patient numbers split by vasculitis syndromes in two studies.....	43
Table 3-1: Repeatability of BVAS (version 3). Linear weighted kappa values for the organ-system subscores in 39 patients.....	52
Table 3-2: Reproducibility of BVAS (version 3). Linear weighted kappa values for the organ-system subscores in 99 patients.....	53
Table 3-3: Number of patients recruited in reliability analysis of previous versions of BVAS.....	53
Table 5-1 Co-ordinates for the ROC curve distinguishing vasculitis from controls with rheumatoid arthritis.....	72
Table 5-2 Co-ordinates for the ROC curve distinguishing vasculitis from other non-systemic rheumatic conditions.....	74
Table 6-1 Common disease activity indices in rheumatology and the variables against which their construct was established.....	80

## LIST OF ABBREVIATIONS

<b>AAV</b>	ANCA associated vasculitis
<b>ANCA</b>	Antineutrophil cytoplasmic antibody
<b>BVAS</b>	Birmingham Vasculitis Activity Score
<b>BVAS/WG</b>	Birmingham Vasculitis Activity Score for Wegener's granulomatosis
<b>C ANCA</b>	cytoplasmic ANCA
<b>CRP</b>	C-Reactive protein
<b>CT</b>	Computed tomography
<b>ELISA</b>	Enzyme Linked Immunosorbent Assay
<b>ICC</b>	Intra-class correlation
<b>MPO</b>	myeloperoxidase
<b>P ANCA</b>	perinuclear ANCA
<b>PGA</b>	Physician's global assessment
<b>PR3</b>	proteinase 3
<b>ROC</b>	Receiver operating characteristics
<b>SD</b>	Standard deviation
<b>SF-36</b>	36 item Short form general health survey
<b>VAI</b>	Vasculitis Activity Index
<b>VAS</b>	Visual analogue scale
<b>VDI</b>	Vasculitis Damage Index

## **Chapter 1 INTRODUCTION**

## **WHAT IS SYSTEMIC VASCULITIS?**

The systemic vasculitides are a group of uncommon life-threatening conditions which cause inflammation of the blood vessels leading to their occlusion and subsequent tissue necrosis. They give rise to distinct clinical syndromes depending on the calibre of the blood vessels and the organ involvement. Vasculitis may be secondary to other autoimmune disease like systemic lupus erythematosus and rheumatoid arthritis.

## **CLASSIFICATION**

Classification of vasculitis has been driven by the need to identify homogenous groups of patients to assist treatment decisions, facilitate research and define specific outcomes. Classification criteria for 7 vasculitic syndromes (polyarteritis nodosa, Churg-Strauss syndrome, Wegener's granulomatosis, hypersensitivity vasculitis, Henoch-Schönlein purpura, giant cell arteritis, and Takayasu arteritis) defined by the American College of Rheumatology in 1990 are still used for recruitment of patients into clinical trials (Fries et al. 1990). The main drawback of this classification was the omission of microscopic polyangiitis as a distinct diagnosis. The Chapel Hill Consensus conference in 1994 defined 10 vasculitis syndromes as in Table 1 (Jennette et al. 1994). The systemic vasculitides are now commonly classified into large, medium and small vessel vasculitides

depending on the smallest calibre of blood vessel affected. Within the small vessel vasculitides, Wegener's granulomatosis, microscopic polyangiitis and Churg-Strauss syndrome are associated with the presence of antineutrophil cytoplasm antibody (ANCA). There are two principal immunofluorescence patterns of ANCA, cytoplasmic (C ANCA) and perinuclear (P ANCA). The C ANCA pattern is associated with an antibody targeted against proteinase 3 (PR3). P ANCA is associated with antibodies targeted against several antigens, of which myeloperoxidase (MPO) is of specific interest in systemic vasculitis. Classification criteria should be restricted for research and they perform poorly when used for diagnostic purposes in clinical practice. (Rao et al. 1998; Sorensen et al. 2000).

Name	Definition
Large vessel vasculitis	
Giant-cell (temporal) arteritis	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients more than 50 years old and is often associated with polymyalgia rheumatica
Takayasu arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50
Medium-sized-vessel vasculitis	
Polyarteritis nodosa	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules
Kawasaki disease	Arteritis involving large, medium-sized, and small arteries and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children
Small vessel vasculitis	
Wegener granulomatosis	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small-to medium-sized vessels (e.g., capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common
Churg–Strauss syndrome	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels and associated with asthma and eosinophilia
Microscopic polyangiitis	Necrotizing vasculitis with few or no immune deposits affecting small vessels (capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs
Henoch-Schönlein purpura	Vasculitis with iga-dominant immune deposits affecting small vessels (capillaries, venules, or arterioles).  Typically involves skin, gut, and glomeruli and is associated with arthralgias or arthritis
Essential cryoglobulinemic vasculitis	Vasculitis with cryoglobulin immune deposits affecting small vessels (capillaries, venules, or arterioles) and associated with cryoglobulins in serum. Skin and glomeruli are often involved
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis

Table 1-1 Chapel Hill Consensus conference definitions

## **ASSESSMENT OF VASCULITIS**

### *The importance of assessment*

Disease assessment in systemic vasculitis is complicated by the multi-system nature of vasculitis and the variation in activity in different organ systems at any given time. Accurate assessment of disease activity informs treatment decisions. The toxicity of the immunosuppressive drugs demands accurate differentiation of manifestations due to active vasculitis, from those due to inactive scars of disease or other co-morbidities. For example, haematuria may be due to active glomerulonephritis, haemorrhagic cystitis induced by cyclophosphamide, or bacterial infection of the urinary tract. A treatment decision cannot be made without accurate differentiation. The assessment of disease activity relies on the information provided by a structured interview and clinical examination, aided by laboratory and radiological investigations. The absence of validated biomarkers for disease monitoring makes this information even more valuable. The development and use of structured clinical tools provides a qualitative and quantitative assessment of systemic vasculitis providing surrogate markers of disease activity. Disease assessment includes the determination of disease activity, damage due to irreversible scarring; and health related quality of life.

### *Biological assessment*

The gold standard for assessing disease activity is the presence of active vasculitis on biopsy. Repeated biopsies are impractical for the regular evaluation of patients and the sensitivity of biopsies from different organ sites can vary considerably. For example a nasal biopsy has 60% sensitivity in WG, whereas a renal biopsy is almost always positive in active renal disease (Aasarod et al. 2001; Del Buono and Flint 1991; Devaney et al. 1990). Serological markers lack sufficient sensitivity and specificity to provide reliable assessment of disease activity in most forms of vasculitis. Treatment decisions should not be based solely on the basis of changes in serological markers (Boomsma et al. 2000; Hoffman and Ahmed 1998). A major advance in the diagnosis and understanding of the immunopathogenesis of small vessel vasculitis has been the discovery of ANCA in the 1980's (Davies et al. 1982; van der Woude et al. 1985). ANCA are identified using an indirect immunofluorescence technique. There are two typical labelling patterns, diffuse cytoplasmic uptake is termed C ANCA, and perinuclear uptake is termed P ANCA. These antibodies are specifically targeted against antigens in the primary granules of neutrophils. There are two relevant antigens in vasculitis, identified as proteinase 3 (PR3) and myeloperoxidase (MPO) (Falk and Jennette 1988; Niles et al. 1989). The specificity of the ANCA to those antigens can be measured using an Enzyme

Linked Immunosorbent Assay (ELISA) technique. The combination of indirect immunofluorescence to determine the pattern of labelling, and ELISA to determine the specificity of the antibodies, is 85% sensitive and 99% specific for the diagnosis of small vessel vasculitis in patients with a clinical suspicion of vasculitis (H. K. Choi et al. 2001). It is recommended that these two tests are combined for the detection of ANCA in regular clinical practice (Savige et al. 1999). The presence of ANCA at diagnosis, persistent ANCA positivity, a four-fold rise in ANCA titres or a reappearance of ANCA are all associated with a clinical relapse (Boomsma et al. 2000; Hogan et al. 2005; Slot et al. 2004; Stegeman et al. 1996). The absence of ANCA in patients with features of vasculitis does not exclude the diagnosis. 20% of patients with Wegener's granulomatosis do not demonstrate ANCA; this figure is higher in patients with localized disease (confined to the upper respiratory tract) (Finkielman et al. 2007; Luqmani et al. 1994b; Stone and Wegener's Granulomatosis Etanercept Trial (WGET) Research Group 2003). The monitoring of the complement factors 3 and 4, the total haemolytic serum complement, rheumatoid factor and cryoglobulins can be helpful in determining disease activity in immune-complex mediated vasculitis such as cryoglobulinaemia (Agnello and Romain 1996). Inflammatory markers, especially C-reactive protein (CRP) and erythrocyte sedimentation rate, are non-specific markers of systemic inflammation. They are not helpful in distinguishing between infection and disease activity. When

vasculitis is established as the cause of the high inflammatory markers, serial measurements can be helpful in monitoring response to therapy. Normal inflammatory markers do not exclude a diagnosis of active vasculitis (Daum et al. 1995; D. Jayne et al. 2003). Endothelial involvement has long been recognised in vasculitis (Donald et al. 1976). Antiendothelial cell antibodies, a family of different antibodies binding to a variety of endothelial antigens, have been detected in many forms of vasculitis (Belizna et al. 2006), but their exact mechanism of action, if any, is unclear. Von Willebrand Factor is released from damaged endothelium and platelets and has been proposed as a marker of disease activity in vasculitis (D'Cruz et al. 1999). Activated endothelium as well as damaged endothelium produces large amounts of circulating von Willebrand factor (Kloczko et al. 1994), but this is not specific to vasculitis (Hoffman and Ahmed 1998). Active endothelium expresses adhesion molecules and the release of these into the circulation provides another marker to measure disease activity (Stegeman et al. 1994). It is possible to measure circulating levels of endothelial debris (so-called endothelial dust or dots), but it is important to note that elevated levels have been reported in patients with atherosclerosis and other conditions (K. W. Lee et al. 2005; Woywodt et al. 2003; Zhang et al. 2005). Atherosclerosis may be highly prevalent in patients with vasculitis, because both diseases are more common with advancing age, and patients with chronic inflammatory conditions are known to be susceptible to accelerated

atherosclerosis (de Leeuw et al. 2005). It remains unclear whether the endothelial activity is primary or a response to other immunological events. The clearest evidence for the atherogenic potential of vasculitis comes from longitudinal studies of patients with Kawasaki disease. Flow-mediated dilatation, an endothelial-dependent response, was markedly reduced in the brachial artery of patients with Kawasaki disease many years after the illness (Dhillon et al. 1996).

#### *Radiological assessment*

Radiological assessment plays a particularly important role in the diagnosis and assessment of the medium and large vessel vasculitides as these vessels can be imaged directly. Conventional arteriography has been used to demonstrate aneurysms, occlusions and stenoses. This method has associated problems of invasiveness, a substantial radiation dose, administration of large quantities of iodinated contrast and technical difficulties in patients with lengthy stenotic segments. It also lacks the ability to image the vessel wall. Chest X-rays have been used to assist diagnosis and monitoring of ANCA associated vasculitis (AAV) (Y. H. Choi et al. 2000).

#### - Magnetic resonance imaging

Magnetic Resonance Imaging and angiography provide good quality images without the problems of conventional radiography. In addition, it provides qualitative information regarding the state of the vessel wall, for example vessel wall oedema and progressive vessel wall thickening (Andrews et al. 2004; Kerr et al. 1994). Magnetic resonance angiography can over estimate the degree of stenoses (Marcos and Choyke 2000). The level of gadolinium enhancement of the vessel wall does not reliably reflect disease activity (Andrews et al. 2004). High resolution magnetic resonance techniques producing sub millimetre sections can demonstrate the distribution of vessel involvement in giant cell arteritis (Bley et al. 2005). Magnetic resonance imaging has also allowed greater visualization of the arterial tree enabling a greater understanding of the involvement of vessels beyond the temporal arteries.

#### - Ultrasonography

Ultrasonography is useful for imaging of medium and large superficial vessels such as the temporal artery and the subclavian artery. This technique has proven useful in the diagnosis of temporal arteritis. It demonstrates a 'halo' around the temporal artery which is responsive to glucocorticoid therapy (Schmidt et al. 1997). Colour Doppler demonstrates flow abnormalities, which

provide surrogate information regarding luminal narrowing. The sensitivity and specificity of ultrasonography for the diagnosis of giant cell arteritis is 95% and 93% respectively when compared to histology, and 88% and 97% when compared to clinical diagnosis (Schmidt and Blockmans 2005). These figures are comparable to the diagnostic yield of temporal artery biopsy as compared with clinical diagnosis (Schmidt and Gromnica-Ihle 2002). Temporal arteritis may be patchy. This contributes to the lowering of the sensitivity of temporal artery biopsy. Ultrasonography can help to overcome the problem of skip lesions by allowing wider access. Ultrasonography is operator dependant. It cannot provide a differential diagnosis in the rare scenario when temporal arteritis is a manifestation of a systemic vasculitis other than giant cell arteritis (Hamidou et al. 2003).

#### - Positron Emission Tomography

Positron Emission Tomography with radiolabelled 18-fluorodeoxyglucose assesses the metabolic activity of an organ. Vascular inflammation leads to increased metabolic activity and thus lends itself to imaging. It can be used to assess vessels with a calibre of greater than 4 mm. Temporal arteries are therefore not suitable for imaging by this modality. The superficial anatomy and the superimposed intense fluorodeoxyglucose signal from the brain are other reasons for not accurately visualising the temporal arteries (Schmidt and

Blockmans 2005). The use of fluorodeoxyglucose positron emission tomography has revealed that giant cell arteritis is widespread, often involving clinically silent areas, for example subclavian arteries and the aorta. (Blockmans et al. 2000). Since inflammatory atherosclerotic plaques may exhibit isotope uptake it is important not to rely solely on positron emission findings in making a diagnosis of large vessel vasculitis particularly in the abdominal aorta and the leg vessels which are more prone to atherosclerosis (Tawakol et al. 2005). Low level isotope uptake may persist even with normalisation of inflammatory markers (Andrews et al. 2004). This would be in keeping with the finding of active inflammation in over 40% of biopsies from patients in apparent remission (Kerr et al. 1994). The sensitivity (60% to 89%) and specificity (90.9% to 99.8%) of this technique for diagnosing large vessel vasculitis (giant cell arteritis and Takayasu arteritis) has been reported in two studies (Kobayashi et al. 2005; Walter et al. 2005).

#### - Computed tomography

Computed tomography (CT) is very useful in assessing structural lesions and monitoring the response to therapy. This is particularly important in granulomatous conditions such as Wegener's granulomatosis where most patients will have paranasal sinus or lung involvement. CT findings that suggest the possibility of paranasal Wegener's granulomatosis include: nodular thickening of the nasal mucosa, punctate bony destruction mainly in the midline,

sparing of the ethmoid labyrinth, periantral soft tissue infiltration associated with bone demineralization, orbital extension and sclerosing osteitis of the mastoid air cells and maxillary sinuses (Lohrmann et al. 2006). CT scanning is of value in the delineation of the nature, extent and position of thoracic lesions in Wegener's granulomatosis. Nodules or masses are seen in about 90% of patients. Characteristically, these are multiple, bilateral and subpleural, but can sometimes be peribronchovascular (Lohrmann et al. 2005). They are typically about 30 mm in diameter (range 4–65 mm) and occasionally (6%) spiculated (Lohrmann et al. 2005). Other findings of note are thickening of the bronchial wall, large airways abnormality, patchy consolidation and ground-glass shadowing (K. S. Lee et al. 2003; Lohrmann et al. 2005). Among the AAV, nodulosis is common in Wegener's granulomatosis and infiltrative lesions are more common in microscopic polyangiitis and Churg-Strauss syndrome (Pesci et al. 2005). The presence of severely abnormal chest CT scans (covering > 80% of the lungs) is an independent predictor of mortality (Stangou et al. 2005). CT scanning of the chest is of value in the monitoring of disease in Wegener's granulomatosis. Typically, infiltrates respond best to treatment and often resolve completely. Atelectasis, fibrotic bands and areas of bronchiectasis represent damage and will not respond to treatment (Pesci et al. 2005). Images obtained with spiral CT scanners can be reconstructed to produce three-dimensional virtual bronchoscopy (Summers et al. 2002). This technique can be tried in

patients who cannot undergo bronchoscopy. CT angiography is aided by the use of radioiodine contrast and is superior to standard angiography in its ability to view the mural as well as luminal changes. It has been used for diagnosis and monitoring of Takayasu arteritis. The spectrum of changes on CT angiography includes: stenosis, occlusions, aneurysms, concentric arterial wall thickening and heavy calcification in chronic disease. The calcification is usually transmural and thus can be differentiated from atherosclerosis (Gotway et al. 2005). Multislice spiral CT scanning in Kawasaki disease was 100% sensitive in detecting coronary artery aneurysms and 87.5% sensitive and 92.5% specific for significant stenoses or occlusions (in comparison with coronary angiography) (Kanamaru et al. 2005).

All the imaging technologies discussed here are of value for the monitoring and/or diagnosis of the systemic vasculitides. However, most of them are expensive and operator dependent. They will need validation in multi-centred clinical trials.

#### *Clinical assessment*

The failure of serological tests to provide reliable disease assessment has driven the development of clinical assessment tools. These tools also offer the opportunity to evaluate complex dimensions such as disease damage and

quality of life which cannot be measured by laboratory tests. There are three main aspects to the clinical assessment of vasculitis: disease activity, disease damage and the functional and social consequences of having vasculitis and its treatment. These three aspects of disease are common to other inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus. A structured and standardised method of assessment will allow comparison of the findings over time and between different physicians.

#### Disease activity

Clinical assessment tools which quantify disease activity to produce a tangible outcome measure in clinical trials of vasculitis have been developed using standardised clinical examination ± laboratory assessments (de Groot et al. 2001; Kallenberg et al. 1990; Luqmani et al. 1994a; Whiting-O'Keefe et al. 1999). The Birmingham Vasculitis Activity Score (BVAS) is the current standard tool for assessment of disease activity in systemic vasculitis and has been used in large randomised trials of vasculitis (de Groot et al. 2005; D. Jayne et al. 2003; D. R. Jayne et al. 2007). It was validated for assessing disease activity in patients with systemic vasculitis in 1994 (Luqmani et al. 1994a). The present form (version 2) [Figure 1-1] was designed in 1997 for use in European collaborative clinical trials (Luqmani et al. 1997). BVAS (version 2) is a list of 66 manifestations of systemic vasculitis, divided into 9 organ based systems. Each

item can either be 'new or worse' if it has presented, recurred or worsened within the previous 4 weeks, or 'persistent' if it is present but not worse in the previous 4 weeks. The manifestations have to be attributable to active vasculitis because they may be due to sequelae of previous activity, drug induced, or due to comorbidities. Lack of attribution may cause spurious elevation of BVAS. Each item has a pre-determined numerical score, which may be different depending on whether an item is new/worse or persistent. Each organ system has a predetermined ceiling score. The sum of the scores of all the organ systems reflects disease activity. The BVAS (version 2) generates two scores; BVAS 1 reflects new or worse disease, and BVAS 2 reflects persistent disease. The Wegener's granulomatosis Etanercept Trial Group adapted BVAS for use specifically in Wegener's granulomatosis and introduced a different, again arbitrary, scoring by attaching a value of 1 to disease manifestations which are usually treated with less aggressive immunosuppression and a value of 3 to items which usually would require the introduction of cyclophosphamide (Stone et al. 2001). The use of the BVAS requires training to reduce the inter-observer variation. BVAS (version 2) has been used in clinical trials as an outcome, an outcome measure, to define entry criteria, and to define remission and relapse. (C. B. Mukhtyar et al. 2006) The BVAS (version 2) has been shown to have prognostic value. In patients with microscopic polyangiitis, Churg-Strauss

syndrome, and polyarteritis nodosa, it correlates with the validated five factor prognostic score (Gayraud et al. 2001)

VASCULITIS ACTIVITY SCORE			
<input type="checkbox"/> Tick box <b>only</b> if abnormality is <b>newly present</b> since last assessment or <b>worse</b> in the last <b>few weeks</b> (use the Vasculitis Damage Index, VDI to score items of damage) <input type="checkbox"/> Tick box <b>only</b> if abnormality is due to <b>active</b> (but not new or worse) vasculitis <input type="checkbox"/> Tick box if more information (specialist opinion/tests) is requested <input type="checkbox"/> oral/axillary temperatures; rectal temperatures are 0.5°C higher		<b>DEMOGRAPHY</b> <b>Trial Number</b> <b>Visit Date</b> / / <b>Investigator</b>	
PERSISTENT		NEW/WORSE	
<b>1. GENERAL</b> <input type="checkbox"/> (none)			
malaise	<input type="checkbox"/>		<input type="checkbox"/>
myalgia	<input type="checkbox"/>		<input type="checkbox"/>
arthralgia/arthritis	<input type="checkbox"/>		<input type="checkbox"/>
headache	<input type="checkbox"/>		<input type="checkbox"/>
fever (< 38.5°C) <sup>Ⓢ</sup>	<input type="checkbox"/>		<input type="checkbox"/>
fever (≥ 38.5°C) <sup>Ⓢ</sup>	<input type="checkbox"/>		<input type="checkbox"/>
wt loss (≥ 2kg)	<input type="checkbox"/>		<input type="checkbox"/>
<b>2. CUTANEOUS</b> <input type="checkbox"/> (none)			
Infarct	<input type="checkbox"/>		<input type="checkbox"/>
purpura	<input type="checkbox"/>		<input type="checkbox"/>
other skin vasculitis	<input type="checkbox"/>		<input type="checkbox"/>
ulcer	<input type="checkbox"/>		<input type="checkbox"/>
gangrene	<input type="checkbox"/>		<input type="checkbox"/>
multiple digit gangrene	<input type="checkbox"/>		<input type="checkbox"/>
<b>3. MUCOUS MEMBRANES/EYES</b> <input type="checkbox"/> (none)			
mouth ulcers	<input type="checkbox"/>		<input type="checkbox"/>
genital ulcers	<input type="checkbox"/>		<input type="checkbox"/>
significant proptosis	<input type="checkbox"/>		<input type="checkbox"/>
red eye- conjunctivitis	<input type="checkbox"/>		<input type="checkbox"/>
red eye- epi/scleritis	<input type="checkbox"/>		<input type="checkbox"/>
blurred vision	<input type="checkbox"/>		<input type="checkbox"/>
sudden visual loss	<input type="checkbox"/>		<input type="checkbox"/>
ophthalmic opinion		<input type="checkbox"/>	
no active vasculitis		<input type="checkbox"/>	
uveitis		<input type="checkbox"/>	
retinal exudates		<input type="checkbox"/>	
retinal haemorrhage		<input type="checkbox"/>	
<b>4. ENT</b> <input type="checkbox"/> (none)			
Nasal obstruction	<input type="checkbox"/>		<input type="checkbox"/>
Bloody nasal discharge	<input type="checkbox"/>		<input type="checkbox"/>
Nasal crusting	<input type="checkbox"/>		<input type="checkbox"/>
Sinus involvement	<input type="checkbox"/>		<input type="checkbox"/>
Hearing loss	<input type="checkbox"/>		<input type="checkbox"/>
Hoarseness/stridor	<input type="checkbox"/>		<input type="checkbox"/>
ENT opinion		<input type="checkbox"/>	
no active vasculitis		<input type="checkbox"/>	
Granulomatous sinusitis		<input type="checkbox"/>	
Conductive hearing loss		<input type="checkbox"/>	
Sensorineural hearing loss		<input type="checkbox"/>	
Significant Subglottic inflammation		<input type="checkbox"/>	
<b>5. CHEST</b> <input type="checkbox"/> (none)			
persistent cough	<input type="checkbox"/>		<input type="checkbox"/>
dyspnoea or wheeze	<input type="checkbox"/>		<input type="checkbox"/>
Haemoptysis/haemorrhage	<input type="checkbox"/>		<input type="checkbox"/>
chest radiology performed		<input type="checkbox"/>	
no active vasculitis		<input type="checkbox"/>	
nodules or cavities		<input type="checkbox"/>	
pleural effusion/pleurisy		<input type="checkbox"/>	
Infiltrate		<input type="checkbox"/>	
massive haemoptysis or alveolar haemorrhage	<input type="checkbox"/>		<input type="checkbox"/>
respiratory failure	<input type="checkbox"/>		<input type="checkbox"/>
<b>6. CARDIOVASCULAR</b> <input type="checkbox"/> (none)			
aortic incompetence	<input type="checkbox"/>		<input type="checkbox"/>
pericardial pain/rub	<input type="checkbox"/>		<input type="checkbox"/>
ischaemic cardiac pain	<input type="checkbox"/>		<input type="checkbox"/>
congestive cardiac failure	<input type="checkbox"/>		<input type="checkbox"/>
cardiology opinion/tests		<input type="checkbox"/>	
no active vasculitis		<input type="checkbox"/>	
pericarditis		<input type="checkbox"/>	
myocardial infarct/angina		<input type="checkbox"/>	
cardiomyopathy		<input type="checkbox"/>	
<b>7. ABDOMINAL</b> <input type="checkbox"/> (none)			
severe abdominal pain	<input type="checkbox"/>		<input type="checkbox"/>
bloody diarrhoea	<input type="checkbox"/>		<input type="checkbox"/>
surgical opinion/tests		<input type="checkbox"/>	
no active vasculitis		<input type="checkbox"/>	
gut perforation/infarct		<input type="checkbox"/>	
acute pancreatitis		<input type="checkbox"/>	
<b>8. RENAL</b> <input type="checkbox"/> (none)			
hypertension (diastol>95)	<input type="checkbox"/>		<input type="checkbox"/>
proteinuria >1+>0.2g/24h	<input type="checkbox"/>		<input type="checkbox"/>
haematuria>1+>10rbc/ml	<input type="checkbox"/>		<input type="checkbox"/>
creatinine 125-249 umol/l		<input type="checkbox"/>	
creatinine 250-499 umol/l		<input type="checkbox"/>	
creatinine >500 umol/l		<input type="checkbox"/>	
rise in creatinine >30% or fall in creatinine clearance>25%		<input type="checkbox"/>	
<b>9. NERVOUS SYSTEM</b> <input type="checkbox"/> (none)			
organic confusion/dementia	<input type="checkbox"/>		<input type="checkbox"/>
seizures(not hypertensive)	<input type="checkbox"/>		<input type="checkbox"/>
stroke	<input type="checkbox"/>		<input type="checkbox"/>
cord lesion	<input type="checkbox"/>		<input type="checkbox"/>
sensory peripheral neuropathy	<input type="checkbox"/>		<input type="checkbox"/>
cranial nerve palsy	<input type="checkbox"/>		<input type="checkbox"/>
motor mononeuritis multiplex	<input type="checkbox"/>		<input type="checkbox"/>
<b>10. OTHER</b>			
	<input type="checkbox"/>		<input type="checkbox"/>

BVAS for EUVAS studies 04/02/05  
 Modified from Luqmani R. A., Bacon P. A., Moots R. J. et al (1994) BVAS in systemic necrotizing vasculitis. Quart J Med 87: 671-678

Figure 1-1: Birmingham Vasculitis Activity Score (version 2)

## Damage

Damage is defined as the irreversible scar of disease which will not respond to immunosuppressive treatment. Damage can result from (recurring) disease activity, treatment toxicity and seemingly unrelated causes. The Vasculitis Damage Index (VDI) [Figure 1-2] is the only tool which has been widely accepted for measuring damage due to the systemic vasculitides (Exley et al. 1997). It represents a list of 64 damage items grouped into 11 organ systems. The items are not weighed; damage has to be present for at least 3 months before it is scored to avoid scoring disease activity and items are by definition irreversible so that the score can only increase or remain static over time. The VDI has been widely used in trials of vasculitis (de Groot et al. 2005; D. Jayne et al. 2003; D. R. Jayne et al. 2007; Seo et al. 2005). It provides a description of damage occurring in vasculitis, and it has prognostic value (Luqmani et al. 1997). Accumulation of even a single VDI item is associated with reduced response to treatment (Koldingsnes and Nossent 2003), and reduced survival (Koldingsnes and Nossent 2002). Early accrual of damage is linked to a poor prognosis. A 6-month VDI score  $\geq 4$  has been shown to be associated with increased mortality rates (Exley et al. 1997). In longitudinal studies, a damage index may have an even more important role. Damage accrual is bimodal in distribution (Exley et al. 1997). The early phase is related to disease activity, and

the late phase is due to ongoing therapy and disease flares. Comparing the results of various therapies on damage control over the long term would be of value, particularly for low-activity disease states. For example, a clinician may be tempted to increase the level of immunosuppression to combat a low-activity disease state, unless evidence indicated that treatment conferred greater damage and an adverse prognosis.

<b>VASCULITIS DAMAGE INDEX (VDI)</b>											
This is for recording organ damage that has occurred in patients <u>since the onset of vasculitis</u>											
Patients often have co-morbidity before they develop vasculitis, <b>which must not be scored</b>											
Record features of active disease using the Birmingham Vasculitis Activity Score (BVAS)											
A new patient should <u>usually have a VDI score of zero</u> , unless:											
(a) they have had vasculitis for more than three months of onset of disease, and											
(b) the damage has developed or become worse since the onset of vasculitis											
<b>1. Musculoskeletal</b>	No	Yes	<table border="1"> <tr> <td>Name</td> <td></td> </tr> <tr> <td>Trial Number</td> <td></td> </tr> <tr> <td>Date</td> <td></td> </tr> <tr> <td>Centre</td> <td></td> </tr> </table>	Name		Trial Number		Date		Centre	
Name											
Trial Number											
Date											
Centre											
None	<input type="checkbox"/>										
Significant muscle atrophy or weakness		<input type="radio"/>									
Deforming/erosive arthritis		<input type="radio"/>									
Osteoporosis/vertebral collapse		<input type="radio"/>									
Avascular necrosis		<input type="radio"/>	<b>7. Peripheral vascular disease</b>	No	Yes						
Osteomyelitis		<input type="radio"/>	None	<input type="checkbox"/>							
<b>2. Skin/Mucous membranes</b>			Absent pulses in one limb		<input type="radio"/>						
None	<input type="checkbox"/>		2 <sup>nd</sup> episode of absent pulses in one limb		<input type="radio"/>						
Alopecia		<input type="radio"/>	Major vessel stenosis		<input type="radio"/>						
Cutaneous ulcers		<input type="radio"/>	Claudication >3 mths		<input type="radio"/>						
Mouth ulcers		<input type="radio"/>	Minor tissue loss		<input type="radio"/>						
<b>3. Ocular</b>			Major tissue loss		<input type="radio"/>						
None	<input type="checkbox"/>		Subsequent major tissue loss		<input type="radio"/>						
Cataract		<input type="radio"/>	Complicated venous thrombosis		<input type="radio"/>						
Retinal change		<input type="radio"/>	<b>8. Gastrointestinal</b>								
Optic atrophy		<input type="radio"/>	None	<input type="checkbox"/>							
Visual impairment/diplopia		<input type="radio"/>	Gut infarction/resection		<input type="radio"/>						
Blindness in one eye		<input type="radio"/>	Mesenteric insufficiency/pancreatitis		<input type="radio"/>						
Blindness in second eye		<input type="radio"/>	Chronic peritonitis		<input type="radio"/>						
Orbital wall destruction		<input type="radio"/>	Oesophageal stricture/surgery		<input type="radio"/>						
<b>4. ENT</b>			<b>9. Renal</b>								
None	<input type="checkbox"/>		None	<input type="checkbox"/>							
Hearing loss		<input type="radio"/>	Estimated/measured GFR $\leq$ 50%		<input type="radio"/>						
Nasal blockage/chronic discharge/crusting		<input type="radio"/>	Proteinuria $\geq$ 0.5g/24hr		<input type="radio"/>						
Nasal bridge collapse/septal perforation		<input type="radio"/>	End stage renal disease		<input type="radio"/>						
Chronic sinusitis/radiological damage		<input type="radio"/>	<b>10. Neuropsychiatric</b>								
Subglottic stenosis (no surgery)		<input type="radio"/>	None	<input type="checkbox"/>							
Subglottic stenosis (with surgery)		<input type="radio"/>	Cognitive impairment		<input type="radio"/>						
<b>5. Pulmonary</b>			Major psychosis		<input type="radio"/>						
None	<input type="checkbox"/>		Seizures		<input type="radio"/>						
Pulmonary hypertension		<input type="radio"/>	Cerebrovascular accident		<input type="radio"/>						
Pulmonary fibrosis		<input type="radio"/>	2 <sup>nd</sup> cerebrovascular accident		<input type="radio"/>						
Pulmonary infarction		<input type="radio"/>	Cranial nerve lesion		<input type="radio"/>						
Pleural fibrosis		<input type="radio"/>	Peripheral neuropathy		<input type="radio"/>						
Chronic asthma		<input type="radio"/>	Transverse myelitis		<input type="radio"/>						
Chronic breathlessness		<input type="radio"/>	<b>11. Other</b>								
Impaired lung function		<input type="radio"/>	None	<input type="checkbox"/>							
<b>6. Cardiovascular</b>			Gonadal failure		<input type="radio"/>						
None	<input type="checkbox"/>		Marrow failure		<input type="radio"/>						
Angina angioplasty		<input type="radio"/>	Diabetes		<input type="radio"/>						
Myocardial infarction		<input type="radio"/>	Chemical cystitis		<input type="radio"/>						
Subsequent myocardial infarction		<input type="radio"/>	Malignancy		<input type="radio"/>						
Cardiomyopathy		<input type="radio"/>	Other		<input type="radio"/>						
Valvular disease		<input type="radio"/>	<table border="1"> <tr> <td>Total VDI Score. Record the number of positive items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage.</td> <td><input type="text"/></td> </tr> </table>			Total VDI Score. Record the number of positive items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage.	<input type="text"/>				
Total VDI Score. Record the number of positive items (1 point for each). The VDI score can either increase or remain the same over time. Remember to carry forward any previous items of damage.	<input type="text"/>										
Pericarditis $\geq$ 3 mths or pericardectomy		<input type="radio"/>									
Diastolic BP $\geq$ 95 or requiring antihypertensives		<input type="radio"/>									
VDI Modified from: Exley AR, Bacon PA, Lughmani et al (1997) Development and initial validation of the VDI ... <i>Arthritis Rheum</i> 40: 371-380											

Figure 1-2: Vasculitis Damage Index

## Quality of life assessment

The survival of untreated connective tissue disease and systemic vasculitis is poor. (Merrell and Shulman 1955; Walton 1958) Current therapies have improved survival and transformed these conditions into chronic disease states, creating morbidity related to relapses and immunosuppressive treatment. (Cervera et al. 2006; Hoffman et al. 1992) Patients with these chronic conditions continue suffering the ill effects of disease in spite of being considered to be in remission due to a significant impairment in the quality of life (Boomsma et al. 2002; Koutantji et al. 2003). Improved survival without improvement in functional status is no longer a satisfactory outcome. There is no disease specific tool to assess quality of life in vasculitis. In the limited literature pertaining to health related quality of life in systemic vasculitis, a common clinical instrument used is the Medical Outcomes Study 36 item Short-form General Health Survey (SF-36). The SF-36 was designed to evaluate the physical and mental well-being of a patient. It was created for use in clinical practice and research, health policy evaluations, and population surveys; and consists of 36 individual questions. Answers to 35 questions are used to score 8 sub-scales from 0 – 100, higher values indicative of better health related quality of life. The eight sub-scales are physical function, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. These eight domains represent

the most frequently tested measures in health surveys and were selected from forty health concepts (Ware and Sherbourne 1992). These domains form two higher order summary measures of 'physical health' and 'mental health'. The 36th item is a self reported health transition over the previous 1 year. The SF-36 is a generic assessment tool. It has been used in clinical trials without the need for modification across age groups, diseases and treatments. It has been translated and validated in other languages. It is also suitable for the assessment of the individual patient. However, because of its generic nature it might fail to capture items more specific for patients with systemic vasculitis. There is no data regarding the overall socio-economic impact of the newer medical therapies of vasculitis. Although most of the newer treatments are much more expensive than the current standard therapies there is the potential of substantial savings if they prove to be more effective and safer in the long term control of systemic vasculitis. There is no significant correlation between the VDI and any of the SF36 domains suggesting that self-reported measures like the SF36 provide unique information on quality of life experienced by patients with vasculitis (Koutantji et al. 2003).

## **THE NEED FOR CHANGE IN BVAS (VERSION 2)**

BVAS (version 2) was adopted as the clinical instrument for assessment of disease activity by the European vasculitis study group for clinical trials

conducted under their auspices. There were two main concerns flagged up from the feedback received from the extensive use of BVAS (version 2)

1. Persistent disease: BVAS (version 2) produces two sub-scores. BVAS 1 reflects active disease and BVAS 2 reflects persistent disease. BVAS 1 was used as the outcome measure in the clinical trials, and was also used to define remission. A BVAS 1 of 0 has been commonly accepted as defining remission. In these circumstances, the BVAS 2 was ignored and patients with continuing disease activity, albeit not new or worse in the prior 4 weeks were accepted to have attained remission.
2. Redundancy and uncommon items: Some items were felt to be redundant and others to be too common / uncommon (and thus non-discriminatory) to feature on the BVAS list.

## **THE CHANGE**

Considering the above feedback, a committee of vasculitis experts made the following changes to the items in the BVAS (version 2) form–

1. Change in the item list
  - a. Omission of items:

- i. malaise, fever  $<38.5^{\circ}\text{C}$ , nasal obstruction, persistent cough, pancreatitis were removed from the list because they were non-discriminatory.
  - ii. multi digit gangrene, sinus involvement, hearing loss, hoarseness/stridor, haemoptysis/haemorrhage, myocardial infarct/angina, pericardial pain/rub were removed because they were redundant.
- b. Amended items: 'fever  $\geq 38.5^{\circ}\text{C}$ ' to 'fever  $\geq 38^{\circ}\text{C}$ ', 'aortic incompetence' to 'valvular heart disease', 'severe abdominal pain' to 'peritonitis', 'gut perforation/infarction' to 'ischaemic abdominal pain'
  - c. New items: 'Adnexal inflammation' to include lacrimal and salivary gland involvement; 'meningitis' to include aseptic meningeal involvement.
2. Change in the scoring: The BVAS (version 2) required the investigators to decide whether each item was 'new/worse' or 'persistent'. In version 3, this decision has to be made for the disease as a whole. In the presence of any new or worsening manifestation of vasculitis, the disease is scored as 'new/worse'. If however, every single item that is present (and attributable to active vasculitis) is 'persistent', a single box at the bottom of the form can be ticked. Thus, patients with purely persistent disease will generate a BVAS value on the same scale as those with 'new/worse' disease.

## **SUMMARY**

The primary systemic vasculitides are a group of rare conditions with severe consequences to health and life if left untreated. There are no validated biomarkers to assist diagnosis and treatment decisions. The clinical decisions must be taken on the basis of structured interview and clinical examination and supported by laboratory and imaging investigations. Damage accrual has prognostic implications and along with the measurement of health-related quality of life, it forms an important facet in the assessment of vasculitis. BVAS (version 2) is clinical tool of choice for assessment of disease activity. It has been adopted by the European vasculitis study group for collaborative clinical trials. Feedback from the use of this clinical instrument has led to changes in the structure of the item list and methodology of scoring. This revision of the BVAS needs to be validated prior to use in clinical trials.

## **THE AIMS OF THIS PROJECT**

To validate the third version of the Birmingham Vasculitis Activity Score (BVAS version 3)

To validate a clinical tool, convergence with established modalities of assessing disease need to be demonstrated; the tool should be reliable, demonstrating comparable results with repeated use, and in the hands of multiple observers;

the tool should be sensitive to change so that changes in the score are clinically meaningful. Each one of these aspects of validation is examined separately over Chapters 2-4. Chapter 5 assesses the ability of BVAS (version 3) to discriminate between vasculitis and non-vasculitic conditions, testing the sensitivity and specificity of BVAS (version 3) scores for a diagnosis of vasculitis.

**Chapter 2 CONVERGENT VALIDITY OF BVAS  
(VERSION 3)**

Convergent validity is the degree to which a clinical tool is similar to another modality of assessment which aims to assess a similar facet of the disease. Ideally, convergent validity of a clinical instrument should be assessed against a gold standard. In the absence of a gold standard for the assessment of vasculitis, a number of parameters commonly used to assess disease activity of systemic vasculitis were selected. The items selected for assessing the convergent validity of the BVAS (version 3) are as follows-

1. BVAS (version 2) has been the clinical assessment tool of choice for the assessment of disease activity in clinical trials of systemic vasculitis (Hellmich et al. 2007).
2. CRP is an inflammatory marker which is commonly used in clinical practice for assessing disease activity of systemic vasculitis.
3. Physician's global assessment (PGA) is a 100 mm visual analogue scale (VAS) with 0 correlating with remission and 100 correlating with very severe disease. The PGA correlates well with the BVAS version specific for Wegener's granulomatosis (BVASWG) (Stone et al. 2001), but not with BVAS (version 1) (Luqmani et al. 1994a).
4. Vasculitis Activity Index (VAI) is a 5 point Likert scale from 0 to 4. 0 correlates with clinical remission and 4 signifies severe disease.

5. Treatment decision: The decision of the physician on the intensity of treatment will depend on the perceived level of disease activity. The treatment decision classified into ordered categories would therefore be an indirect representation of disease activity.

## **AIM**

To establish the convergent validity of BVAS (version 3) with BVAS (version 2), CRP, PGA, VAI, treatment decision categories.

## **METHODS**

Setting: Multi-centre cross-sectional study

Centres: Birmingham (Birmingham City Hospital), Cambridge (Addenbrooke's Hospital), Edinburgh (Western General Hospital), Norwich (Norfolk and Norwich University Hospital), Nottingham (Nottingham University Hospital), Oxford (Oxford Radcliffe Hospitals and Nuffield Orthopaedic Centre), Reading (Royal Berkshire Hospital) and Westcliff-on-sea (Southend General Hospital).

Inclusion criteria: Patients seen in out-patient clinics and hospital wards with a probable or definite diagnosis of systemic vasculitis, of any duration, at any stage of their disease.

Exclusion criteria: Patients with a probable or definite diagnosis of giant cell arteritis were excluded.

Ethical approval: The study was approved by local ethics committees and all patients gave written informed consent.

Data was recorded on a standardized case record form and transferred to an electronic database, created on Microsoft Access (Figure 2-1). The information recorded included patient demographics, diagnosis, disease duration, medication in previous 5 years, laboratory results in the previous 4 weeks, treatment decisions for specific drugs, physician's global assessment and the vasculitis activity index. All patients were assessed using the BVAS (version 3). All patients recruited at Oxford and Edinburgh were also assessed using BVAS (version 2) at the same visit.

The screenshot shows a Microsoft Access form with the following fields and sections:

- Patient Demographics:** ID (text), Date of birth (date), Diagnosis (dropdown), Gender (text).
- Visit Information:** ID (text), Date of assessment (date), Disease duration (months) (text), Assessor (text).
- Medication in the last 5 years:** A grid of checkboxes for Cyclophosphamide oral, Cyclophosphamide IV, Methylprednisolone, Plasmapheresis, Prednisolone, Azathioprine, Methotrexate, Mycophenolate, Lefunomide, Cyclosporin, Etanercept, Infliximab, Rituximab, Immunoglobulin, and Other (text).
- Laboratory results:** Date (date), CRP (text), Serum Creatinine (text), Date (ANCA) (date), ANCA IIF (checkbox), Titre (dropdown), Anti PR3 (text), Anti MPO (text), Physicians global (text), Vasculitis Activity Index (text).
- Treatment decision:** A series of dropdown menus for selecting specific treatments, followed by a final Treatment decision dropdown.
- Buttons:** BVAS and BVAS 2003.

Figure 2-1: Microsoft Access database used to record patient information

The treatment decisions were classified into six ordered categories – no therapy, reduction of therapy, continue at minor level, minor escalation, continue at major level, major escalation. (Table 2-1)

Category	Definition
Major escalation	<ul style="list-style-type: none"> <li>• Commencing any immunosuppressive agent, glucocorticoid or plasmapheresis, without stopping or reducing the dose of any other treatment OR</li> <li>• Increasing the dose of glucocorticoid and immunosuppressive agent</li> </ul>
Continue at major level	<ul style="list-style-type: none"> <li>• No change to a therapeutic regimen which includes cyclophosphamide or biologic therapy</li> </ul>
Minor escalation	<ul style="list-style-type: none"> <li>• Increasing the dose of immunosuppressive agent or glucocorticoid</li> </ul>
Continue at minor level	<ul style="list-style-type: none"> <li>• No change to a therapeutic regimen which excludes cyclophosphamide and biologic therapy</li> </ul>
Reduction of therapy	<ul style="list-style-type: none"> <li>• Reduction or stopping of one or more drugs without increasing or commencing any other drug</li> </ul>
No therapy	<ul style="list-style-type: none"> <li>• No therapy</li> </ul>

Table 2-1: Definitions of treatment categories

The BVAS values for both versions were calculated on a Microsoft Excel based programme, created for this study.

Convergent validity was assessed by examining the association of BVAS (version 3) with

1. BVAS 1 sub-score of BVAS (version 2) in patients who were assessed using both clinical instruments at the same hospital visit.

2. Nearest serum CRP level within 1 month of the consultation (when values were reported to be less than the lowest measurable value for that laboratory, the value was recorded as 0 mg/L for the purpose of statistical analysis)
3. PGA
4. VAI
5. Treatment decision categories (Table 2-1)

The ability of the BVAS (version 3) to record persistent disease was assessed in a sub-group of patients recruited at Oxford and Edinburgh. Patients were included in this assessment if they had persistent disease on assessment with the BVAS (version 2). Persistent disease was defined as a BVAS 2 sub-score higher than the BVAS 1 sub-score at the same visit.

Statistical analysis: Spearman's rank correlation test was used to assess the association of BVAS (version 3) with sub-scores of BVAS (version 2), treatment decision, serum CRP levels, PGA and VAI. The statistical analysis was performed using SPSS 15.0 (SPSS Inc, Chicago, USA).

## **RESULTS**

313 patients with systemic vasculitis were recruited from 9 centres. The mean age of the cohort was 55.0 (SD 15.9; range 18-87). There were 162 females

(52%), and 149 males (48%). The median disease duration was 3.8 years (lower and upper quartiles 1.0, 8.7 years). The range of vasculitis syndromes and the specific demographics for a particular disease group are tabulated in Table 2-2. The median BVAS (version 3) was 2. The histogram for the range of the BVAS (version 3) is in Figure 2-2.

Diagnosis	N	Gender M/F	Median age (Lower quartile, Upper quartile)	Median duration in months (lower quartile, upper quartile)
Takayasu arteritis	9	0/9	37 (32, 58.5)	49 (30, 150)
Polyarteritis nodosa	10	5/4*	62 (30.5, 67)	60.5 (45, 85.5)
Wegener's granulomatosis	155	82/72*	58 (45, 68)	55.5 (12, 113)
Churg-Strauss syndrome	28	17/11	59 (48, 61)	60 (12, 120)
Microscopic polyangiitis	15	8/7	68 (58, 76)	12 (3, 36)
Henoch-Schonlein purpura	10	7/3	45 (34, 61)	39 (19, 66)
Cryoglobulinemic vasculitis	6	1/5	69.5 (65, 82)	9 (0, 132)
Cutaneous vasculitis	11	3/8	45 (22, 67)	48 (36, 78)
Behcet's disease	25	10/15	42 (35.5, 48)	102 (40, 165)
Cerebral vasculitis	9	3/6	56 (52.5, 62)	1 (0, 27)
Rheumatoid vasculitis	8	3/5	69.5 (65.5, 76)	16.5 (4, 39)

Table 2-2: Demographics of the cohort

\* Gender was not recorded for 1 patient

N = Number of patients; M = Male; F = Female

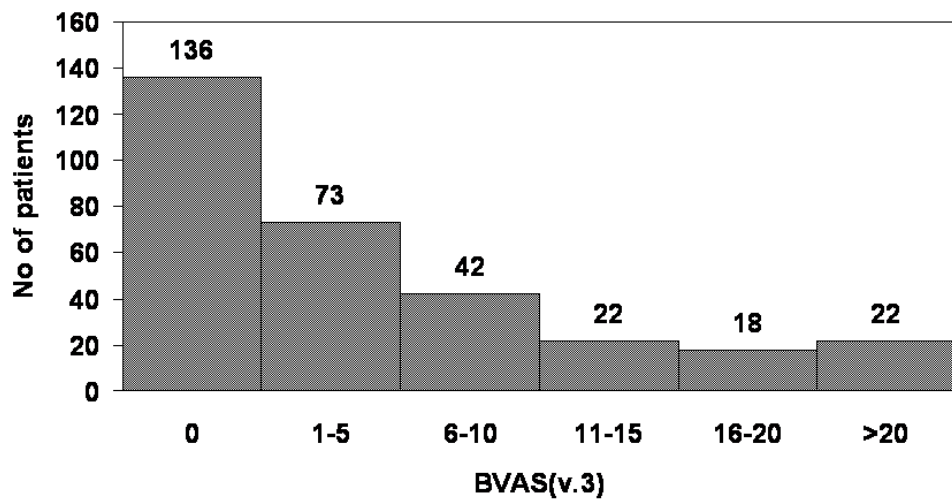


Figure 2-2: Histogram of BVAS (version 3) values in 313 patients with systemic vasculitis

*Correlation with BVAS 1 sub-score of BVAS (version 2)*

138 patients were assessed using the BVAS (version 2) and the BVAS (version 3). The correlation between the BVAS (version 3) and the BVAS 1 sub-score was strong (Spearman's correlation coefficient 0.94, 95% CI 0.92, 0.96) [Figure 2-3]

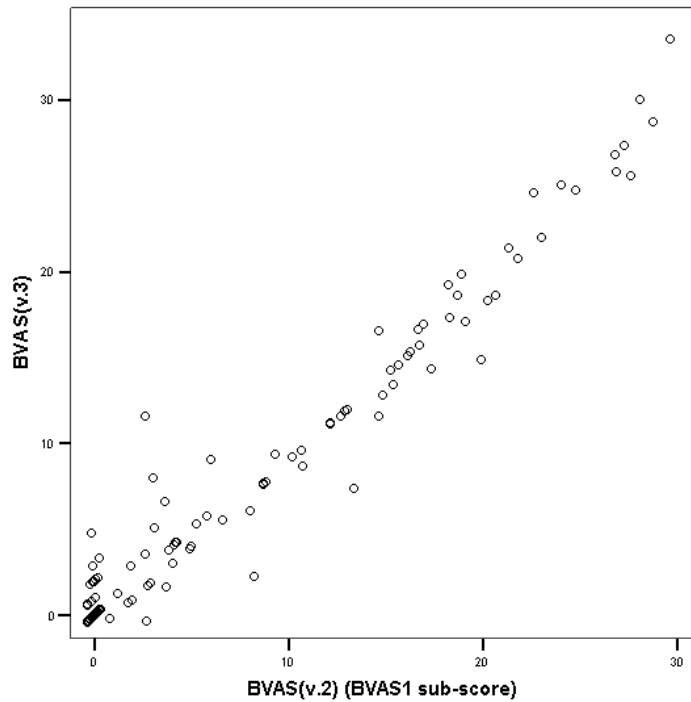


Figure 2-3: Correlation of BVAS (version 3) with BVAS 1 sub-score of BVAS (version 2) in 138 patients.

Spearman's correlation coefficient 0.94 (95% CI 0.92, 0.96)

*Correlation with BVAS 2 sub-score of BVAS (version 2)*

On follow-up, 19 patients were found to have persistent disease. Assessment with BVAS (version 2) and BVAS (version 3) at the same consultation demonstrated a correlation between BVAS (version 3) and the BVAS 2 sub-score of BVAS (version 2) (Spearman's correlation coefficient 0.60, 95% CI 0.21, 0.83) (Figure 2-4).

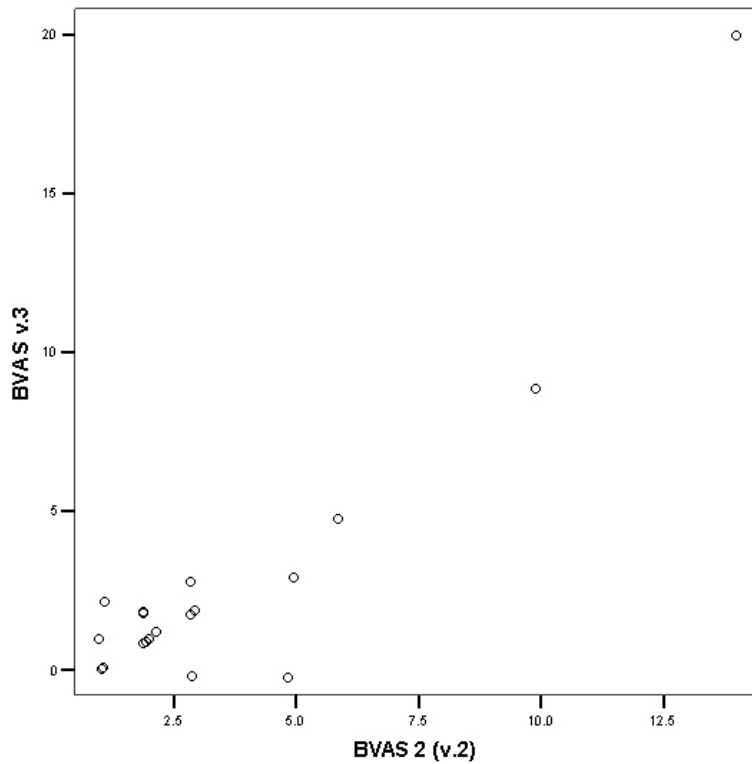


Figure 2-4: Correlation between BVAS (version 3) and BVAS 2 of BVAS (version 2) in 19 patients with persistent disease

Spearman's correlation coefficient 0.60 (95% CI 0.21, 0.83)

*Correlation with serum CRP levels*

185 patients had CRP levels checked within 4 weeks of their BVAS assessment. There was a moderate correlation between BVAS (version 3) and CRP levels (Spearman's correlation coefficient 0.43, 95% CI 0.31, 0.54) [Figure 2-5]

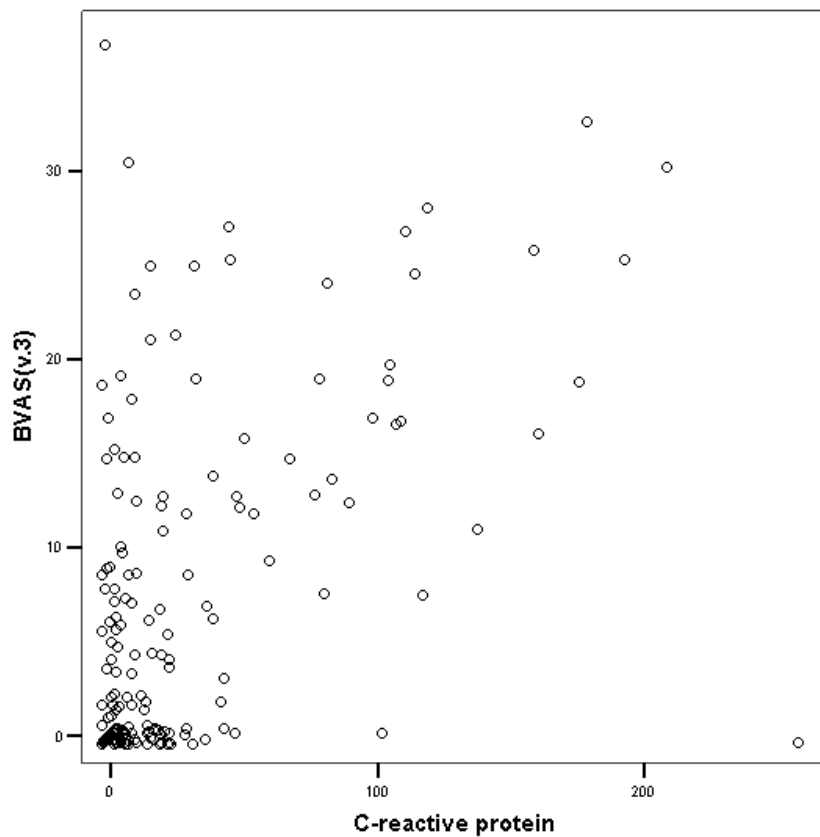


Figure 2-5: Correlation between BVAS (version 3) and C-reactive protein levels in 185 patients

Spearman's correlation coefficient 0.43 (95% CI 0.31, 0.54)

### Correlation with PGA

A strong correlation of BVAS (version 3) was demonstrated with a PGA in 307 patients (Spearman's correlation coefficient 0.91, 95% CI 0.89, 0.93) [Figure 2-6].

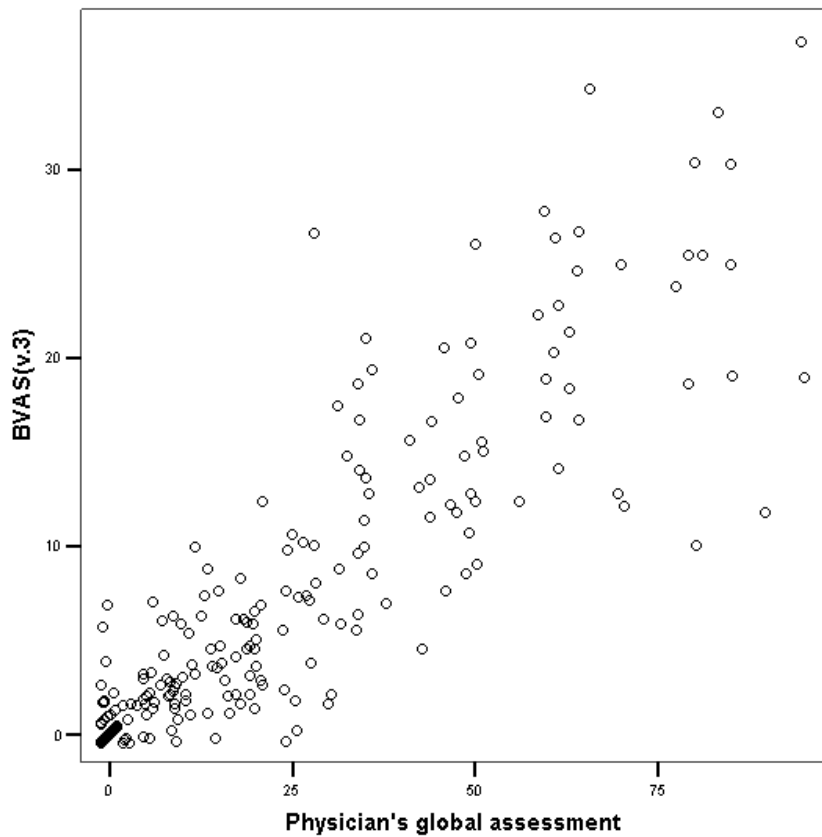


Figure 2-6: Correlation between BVAS (version 3) and 100 mm VAS PGA in 307 patients.

Spearman's correlation coefficient 0.91 (95% CI 0.89, 0.93)

### Correlation with VAI

A strong correlation was observed between BVAS (version 3) and a 5 point Likert scale VAI in 304 patients (Spearman's correlation coefficient 0.88, 95% CI 0.86, 0.91) (Figure 2-7).

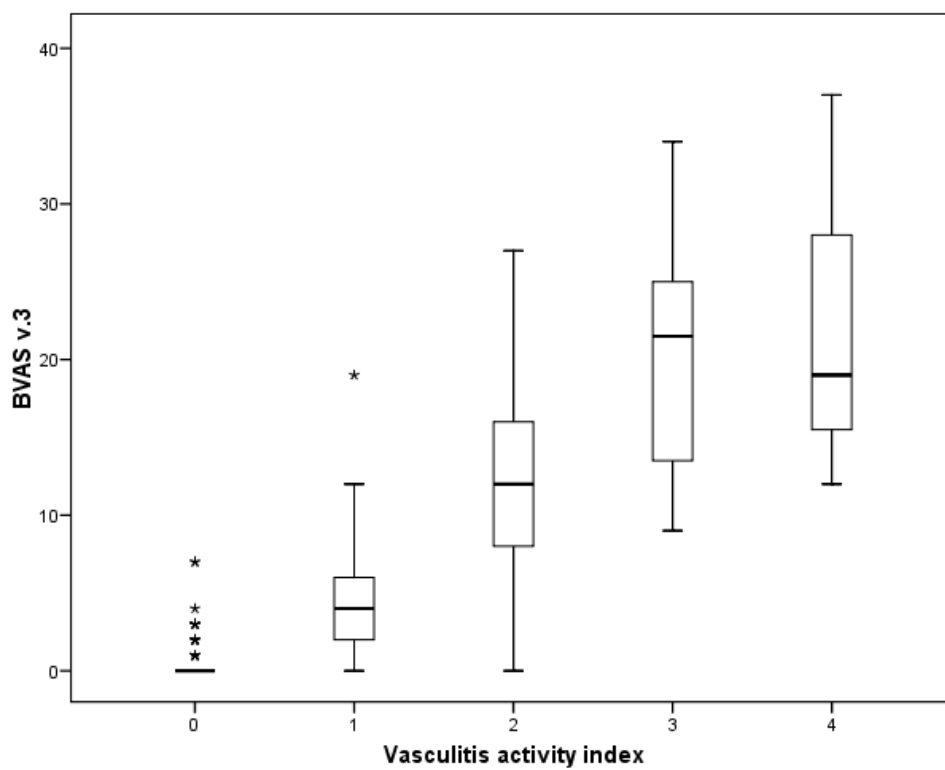


Figure 2-7: Correlation between BVAS (version 3) and VAI in 304 patients

Spearman's correlation coefficient 0.88 (95% CI 0.86, 0.91)

*Correlation with treatment decision*

302/313 patients had a recorded treatment decision. There was a correlation between the treatment decision and the BVAS (version 3) (Spearman's correlation coefficient 0.66, 95% CI 0.59, 0.72) [Figure 2-8]. Sub-group analysis in 153 patients with Wegener's granulomatosis revealed a similar correlation (Spearman's correlation coefficient 0.72, 95% CI 0.64, 0.79) [Figure 2-9].

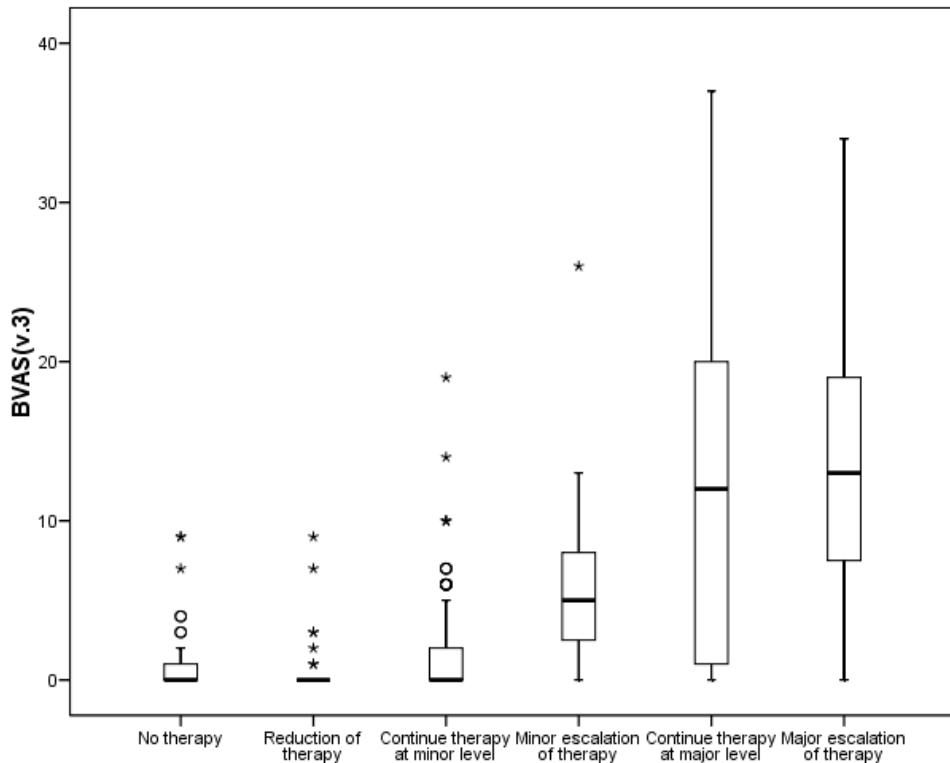


Figure 2-8: Correlation of BVAS (version 3) with treatment decision in 302 patients with systemic vasculitis

Spearman's correlation coefficient 0.66 (95% CI 0.59, 0.72)

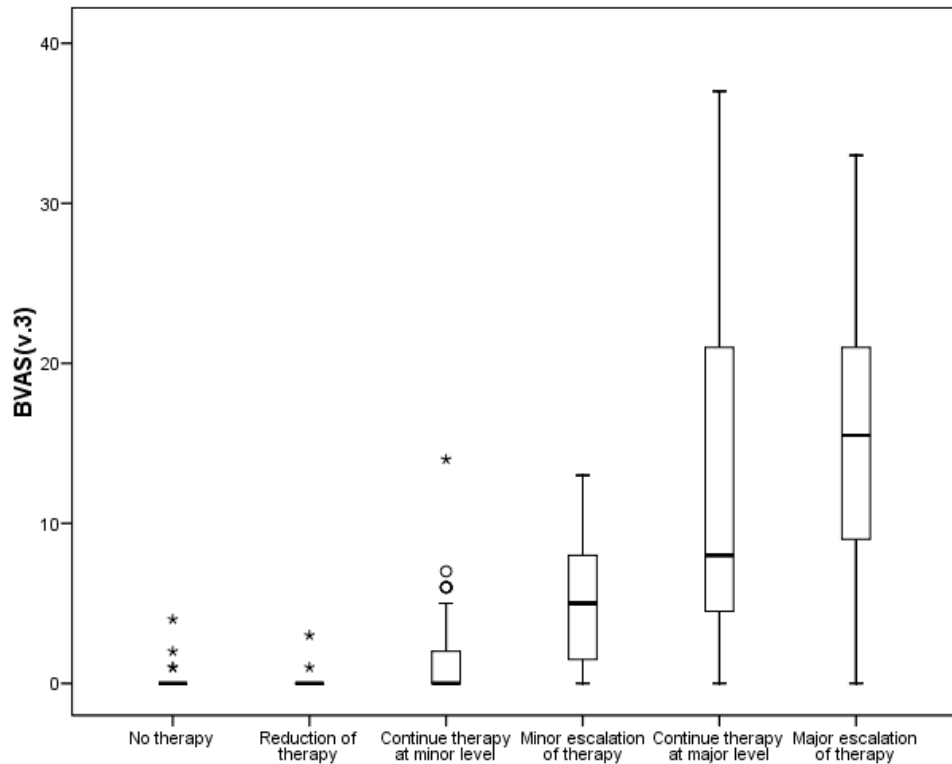


Figure 2-9: Correlation between BVAS (version 3) and treatment decision in 158 patients with Wegener's granulomatosis

Spearman's correlation coefficient 0.72 (95% CI 0.64, 0.79)

## DISCUSSION

This is the third validation study of a version of the BVAS. The other two were validation of BVAS (version 1) (Luqmani et al. 1994a), and validation of BVAS/WG (Stone et al. 2001). This study was larger than the other two studies. Luqmani et al 1994 recruited 213 patients with systemic vasculitis and Stone et al 2001 recruited 117 patients. The breadth of vasculitis syndromes included in

this study is higher than Luqmani et al 1994. This study includes patients with Henoch-Schonlein purpura, cryoglobulinemic vasculitis, and cerebral vasculitis, which were not represented in the validation of BVAS (version 1) (Table 2-3).

Syndrome	TAK	PAN	WG	CSS	MPA	HSP	Cryo	Cut	Beh	CNS	Rheum
This study	9	10	155	28	15	10	6	11	25	9	8
Luqmani et al 1994	11	14	28	*	6	0	0	*	11	0	51

Table 2-3: A comparison of patient numbers split by vasculitis syndromes in two studies

\* In Luqmani et al 1994, CSS, Cutaneous vasculitis and unclassified vasculitis were reported as a combined group of 60 patients.

TAK Takayasu arteritis; PAN polyarteritis nodosa; WG Wegener's granulomatosis; CSS Churg-Strauss syndrome; MPA microscopic polyangiitis; HSP Henoch-Schonlein purpura; Cryo Cryoglobulinemic vasculitis; Cut Cutaneous vasculitis; Beh Behcet's disease; CNS Cerebral vasculitis; Rheum Rheumatoid vasculitis

The BVAS (version 3) has a strong correlation with BVAS (version 2) with respect to recording 'new/worse' disease and 'persistent' disease. This will allow persistent disease to be considered when assessing disease activity and defining remission in clinical trials and studies of vasculitis. However, there were only 19 patients with persistent disease on follow up and this relationship will need further assessment in a larger cohort.

The BVAS (version 3) correlates moderately with the CRP. The patient with the highest BVAS (version 3) in this study (BVAS=37) had active disease in 5 organ systems but had a CRP <10 mg/L. Similarly, the patient with the highest CRP

(260 mg/L) had a BVAS (version 3) = 0. There are two potential causes for this less than expected correlation –

1. CRP generated by causes other than vasculitis would not reflect vasculitic activity
2. Treatment effect: BVAS (version 3), like previous versions of BVAS, considers all vasculitic manifestations in the previous 4 weeks. However, if patients had been treated prior to recruitment, but within the previous 4 weeks, the CRP would be spuriously low at the time of recruitment.

The relationship between CRP and BVAS was not tested in the two previous BVAS validation studies. In a further study by Jayne et al, there was no relationship between CRP and BVAS (D. R. Jayne et al. 1995).

This study demonstrates an excellent correlation between the PGA and the BVAS (version 3) score. This correlation is consistent with BVAS/WG (Stone et al. 2001), but not with BVAS (version 1) (Luqmani et al. 1994a). This discrepancy can be explained by a fundamental difference in the way in which the exercise was carried out in the three studies. For BVAS (version 1), the PGA and the BVAS assessment were independently done by two investigators. For this study, as for BVAS/WG, the PGA was performed by the same investigator after the BVAS assessment. Combining the results of all three studies, it would

be reasonable to conclude that a PGA in itself may not correlate significantly with BVAS value, but a PGA informed by the completion of a structured clinical interview and examination would have a good correlation with the BVAS value.

The correlation of BVAS (version 3) with a 5 point Likert scale informed by a structured clinical interview and examination, was strong. This exercise was not carried out in the other BVAS validation studies. The graph (Figure 2-7) suggests that the median value for point 4 is lower than point 3. This may be artefactual as suggested by the higher values for the 1<sup>st</sup> and 3<sup>rd</sup> quartiles. The reason for this artefact is the low numbers of patients at point 4 (n=4).

The BVAS (version 3) correlates with the treatment decision. However, there seem to be some patients who have high BVAS (version 3) values and have not had any treatment, and similarly, some patients who have had major escalation of treatment in spite of having low BVAS (version 3) values. 40 patients had 'No therapy'; 26 of them had BVAS (version 3) = 0. 2/40 had BVAS (version 3) = 9; 1/40 had BVAS (version 3) = 7; the rest had BVAS (version 3) ≤4. For the 3 patients who had mild to moderate activity, the decision to not commence treatment may have been dictated by the patient but the justification for the treatment decision has not been recorded. 67 patients had a 'major escalation' of their treatment, 12 had a BVAS (version 3) <5. The potential reasons for this discrepancy may be two-fold-

1. If the patient was recruited >4 weeks after onset of symptoms, BVAS (version 3) values would be low because the presenting features would no longer be scored. The initial manifestations may have been treated with prednisolone resulting in lowered disease activity (correctly reflected by a low BVAS (version 3) value). However, at the time of their BVAS assessment they may have been commenced on a maintenance immunosuppressive regimen, which would be classified as 'major escalation' resulting in the discrepancy. This scenario is an artefact of the definitions of treatment decisions used for this study, and although this may have happened only in a minority of cases (N=12/67), the inclusion of such cases will not have added information when analysing the data for correlation with treatment decision. During recruitment, patients were recruited without regard to the state of disease and the events in the recent past (>4 weeks ago). In retrospect, this artefact of the study methodology would have been assisted by making allowances for such special situations when recording treatment decisions. However, these cases would still be of value when analysing the relationship of BVAS (version 3) with other variables like CRP, PGA, BVAS (version 2) and VAI.
2. The range of BVAS (version 3) values is different for different vasculitis syndromes. The rise of a few units may be a major flare in patients with certain vasculitis syndromes needing major escalation of therapy. For

example, loss of pulses along with magnetic resonance imaging evidence of active aortitis in a patient with Takayasu arteritis would give a BVAS (version 3) value of 4, but would be an indication for 'major escalation of therapy'.

## **CONCLUSIONS**

The BVAS (version 3) demonstrates convergent validity with other common modalities of assessment of systemic vasculitis.

## **Chapter 3 RELIABILITY OF BVAS (VERSION 3)**

Reliability can be defined as the extent to which the measurements from a clinical assessment tool remain consistent under identical conditions. Reliability can be further sub-divided into 'repeatability' and 'reproducibility'. 'Repeatability' can be defined as the extent to which the measurements from a clinical tool remain consistent when repeated by the same person under identical conditions (intra-observer reliability). 'Reproducibility' can be defined as the extent to which measurements from a clinical tool remain consistent when reproduced by another person under identical conditions. (inter-observer reliability)

The rarity of systemic vasculitis requires clinical trials to have a multi-centre design. A clinical assessment tool needs to demonstrate reliability to be valid. All versions of the BVAS have also required training to prior use, which is achieved by the completion of paper-case exercises. These exercises serve the dual purpose of training and testing the reproducibility of the BVAS.

## **AIM**

To demonstrate the reliability of the BVAS (version 3)

## **METHODS**

Setting: Multi-centre cross-sectional study

Centres: Birmingham (Birmingham City Hospital), Cambridge (Addenbrooke's Hospital), Edinburgh (Western General Hospital), Oxford (Oxford Radcliffe Hospitals and Nuffield Orthopaedic Centre), and Reading (Royal Berkshire Hospital).

A comprehensive manual of operations, glossary, and beginner and advanced level paper case exercises were made available to all investigators. All investigators completed 20 beginner level and 40 advanced level paper cases prior to recruiting real patients. Physicians with an interest in vasculitis, not recruiting patients for the study were also requested to complete the paper-case exercises to provide data for reproducibility.

Inclusion criteria: Patients seen in out-patient clinics and hospital wards with a probable or definite diagnosis of systemic vasculitis, of any duration, at any stage of their disease.

Exclusion criteria: Patients with a probable or definite diagnosis of giant cell arteritis were excluded.

Ethical approval: The study was approved by local ethics committees and all patients gave written informed consent.

Data was recorded on a standardized case record form (same form as in Figure 2-1). To assess repeatability, patients were re-assessed within 10 days by the same investigator. To assess reproducibility, patients were assessed by two investigators at the same visit.

The BVAS values were calculated on a Microsoft Excel based programme created for this study.

Statistical analysis: Single measures intra-class correlation (ICC) was used to assess the consistency of the BVAS (version 3) scores. Weighted linear kappa analysis was used to assess the consistency of the organ-system sub-scores. ICC was calculated using SPSS 15.0 for Windows (SPSS Inc, Chicago, USA). Kappa analysis was done using an online software package hosted by Vassar college (<http://faculty.vassar.edu>).

## **RESULTS**

### *Paper-case exercise*

19 individuals completed 20 beginner level training paper cases. The reproducibility of BVAS (version 3) for this exercise was high with an ICC of 0.89 (95% CI 0.81, 0.94). 14 individuals completed a further 40 advanced level paper cases; the reproducibility was high with an ICC of 0.95 (95% CI 0.93, 0.97).

*Repeatability analysis (Intra-observer reliability)*

39 patients were recruited for this analysis. The ICC comparing the two sets of BVAS (version 3) was 0.96 (95% CI 0.92, 0.97). The mean (SD) difference between the two sets of BVAS (version 3) scores was 0.17 (2.5). A linear weighted kappa statistic for each organ-system sub-score was high with a minimum kappa of 0.75. (Table 3-1)

Organ-system	Intra-observer reliability (Repeatability)
	(N=39)
General	0.75 (0.58, 0.91)
Cutaneous	0.97 (0.91, 1.00)
Mucous membranes / Eyes	0.67 (0.40, 0.93)
Ear, Nose and Throat	0.94 (0.83, 1.00)
Chest	0.93 (0.79, 1.00)
Cardiovascular	0.79 (0.78, 0.80)
Abdominal	1.00 (0.88, 1.00)
Renal	0.89 (0.78, 1.00)
Nervous	0.99 (0.97, 1.00)

Table 3-1: Repeatability of BVAS (version 3). Linear weighted kappa values for the organ-system subscores in 39 patients

*Reproducibility analysis (Inter-observer reliability)*

99 patients were recruited for this analysis. The reproducibility of BVAS (version3) was high with an ICC of 0.96 (95% CI 0.95, 0.97). The mean (SD) difference between the two scores was 0.14 (1.8). A linear weighted kappa statistic for each of the nine organ-system sub-scores was high with a minimum kappa of 0.78.

Organ-system	Inter-observer reliability (Reproducibility) (N=99)
General	0.79 (0.67 to 0.90)
Cutaneous	0.89 (0.79 to 0.98)
Mucous membranes / Eyes	0.84 (0.71 to 0.96)
Ear, Nose and Throat	0.89 (0.78 to 1.00)
Chest	0.90 (0.81 to 0.98)
Cardiovascular	1.00
Abdominal	Not defined †
Renal	0.94 (0.86 to 1.00)
Nervous	0.78 (0.52 to 1.00)

Table 3-2: Reproducibility of BVAS (version 3). Linear weighted kappa values for the organ-system subscores in 99 patients

† Kappa was not defined because all the items in the abdomen system were recorded as being absent by both sets of observers for all 99 patients.

## DISCUSSION

A clinical assessment tool should be repeatable and reproducible. This study demonstrates the high reliability of the BVAS (version 3). Table 3-3 shows that this reliability analysis was more stringent when compared to previous BVAS validation studies.

	This study (N)	BVAS (version 1) (N)	BVAS/WG (N)
Repeatability	39	NA	NA
Reproducibility	99	14	17

Table 3-3: Number of patients recruited in reliability analysis of previous versions of BVAS

NA – Not assessed; Repeatability was assessed in 3 paper cases in BVAS/WG validation

Paper case exercises serve the dual purpose of training and providing data for inter-observer reliability. The first set of 20 beginner level cases were completed by observers who were relatively untrained. However, the ICC of 0.89 in this

group is still high, suggesting that the BVAS (version 3) is easy to use. The manual and the paper case exercise still seem to have a training value as the ICC for the advanced level cases rises to 0.95. However, it was possible that the five worst performers may have dropped out of the advanced paper case exercises, resulting in a spurious difference. The data for the first 20 paper cases was re-analysed for the 14 observers who completed all 60 paper cases. The ICC of 0.92 (95% CI 0.87, 0.97) for the first 20 cases for those 14 observers is not much different from the ICC of 0.95 (95% CI 0.93, 0.97). This may suggest that the advanced paper cases may have more training value for those observers who do not perform well in the first 20 cases.

This study demonstrates an excellent intra-observer reliability for BVAS (version 3). The mean difference between the two assessments was <1 unit. The intra-observer reliability of BVAS/WG was assessed in a paper-case exercise of 3 cases re-evaluated 6 months apart by 12 observers; the ICC was 0.62 (Stone et al. 2001). This is much lower than the ICC of 0.96 demonstrated in this study on real patients.

Inter-observer reliability is of great importance to establish the validity of BVAS (version 3) in multi-centre clinical trials of systemic vasculitis. Patients recruited at different centres must be assessed in a uniform way and the high ICC for reproducibility in this study will serve as a quality control assurance for use of

BVAS (version 3) in a clinical study with the proviso that all observers should be trained in the use of BVAS (version 3). The mean difference between the two assessments is <1 unit, which is at least comparable with the reproducibility data of BVAS (version 1), which had a mean (SD) difference between the two assessments of 1.14 (1.99) (Luqmani et al. 1994a). The ICC for reproducibility of BVAS/WG was reported to be 0.97 (Stone et al. 2001).

## **CONCLUSION**

The BVAS (version 3) has excellent repeatability and reproducibility.

## **Chapter 4 SENSITIVITY TO CHANGE**

An ideal clinical tool should be able to differentiate between different conditions and disease states. The sensitivity of the BVAS (version 3) for vasculitis should be three-fold. It should be have the ability to --

1. discriminate between vasculitis and other conditions
2. discriminate between active disease and damage
3. discriminate between active vasculitis, persistent disease and remission

In this chapter, the sensitivity of the BVAS (version 3) to changing disease status will be examined. In the absence of any valid external comparator, it is difficult to truly assess the ability of BVAS (version 3) to recognize a change in disease state.

## **AIM**

To test the ability of BVAS (version 3) to change with a change in disease state.

## **METHODS**

Setting: Multi-centre, 3 month longitudinal study.

Centres: Adelaide (Royal Adelaide Hospital), Birmingham (University Hospital), Cambridge (Addenbrooke's Hospital), Lund (University Hospital), Maastricht

(University hospital), Oxford (Nuffield Orthopaedic Centre), Prague (Charles University Hospital), and Zurich (University Hospital)

Inclusion criteria: Patients with a new diagnosis of ANCA associated vasculitis (Wegener's granulomatosis or microscopic polyangiitis) with active renal involvement (defined as presence of red cell casts and/or haematuria 2+ on urine analysis, and/or renal biopsy demonstrating focal segmental glomerulonephritis)

Exclusion criteria: Previous use of daily oral or pulsed intravenous cyclophosphamide (>2 weeks).

Ethical approval: The study was approved by local ethics committees and all patients gave written informed consent.

All patients were assessed with BVAS (version 3) at recruitment, and at 3 months following treatment classified as 'major escalation of treatment' (Table 2-1). All patients were treated with cyclophosphamide and glucocorticoid therapy. In addition, some patients also received rituximab. Data was recorded on a Microsoft Access database (Figure 4-1). Data recorded included demographics, C-reactive protein level, and treatment decisions regarding individual drugs. The treatment was classified into categories as in table 2-1.

The image shows a Microsoft Access database form with the following fields and sections:

- ID Section:**
  - ID: [Text Box]
  - Date of birth: [Text Box]
  - Diagnosis: [Dropdown Menu]
  - Gender: [Text Box]
- Visits Section:**
  - ID: [Text Box]
  - Date of assessment: [Text Box]
  - Disease duration (months): [Text Box]
  - Assessor: [Text Box]
  - CRP: [Text Box] [Text Box]
  - Treatment decision: [Dropdown Menu] [Dropdown Menu] (repeated 6 times)
  - Treatment decision: [Dropdown Menu]
- Other:**
  - BVAS 2003: [Button]

Figure 4-1: Microsoft Access database used for recording patient information

The BVAS values were calculated on a Microsoft Excel based programme created for this study.

Statistical analysis: The BVAS (version 3) and the CRP values at 0 and 3 months were compared using the paired T test. The fall in CRP was correlated to the fall in BVAS (version 3) using Spearman's correlation coefficient. The statistics package use for analysis was SPSS 15.0 for Windows (SPSS Inc, Chicago, USA).

## RESULTS

44 patients were recruited into the study. 22 of them had Wegener's granulomatosis, 13 patients had microscopic polyangiitis and 9 patients had renal limited vasculitis. 4 patients had died prior to the 3 month follow up. 1 patient was lost to follow up. Paired data was available for 39 patients.

### *BVAS (version 3) score*

The mean (SD) BVAS (version 3) at recruitment was 18.92 (6.06). At 3 months the mean (SD) BVAS (version 3) fell to 2.03 (2.48). The mean fall of BVAS (version 3) was 16.9 (95% CI 14.8, 18.9) ( $P < 0.001$  by paired samples t test).

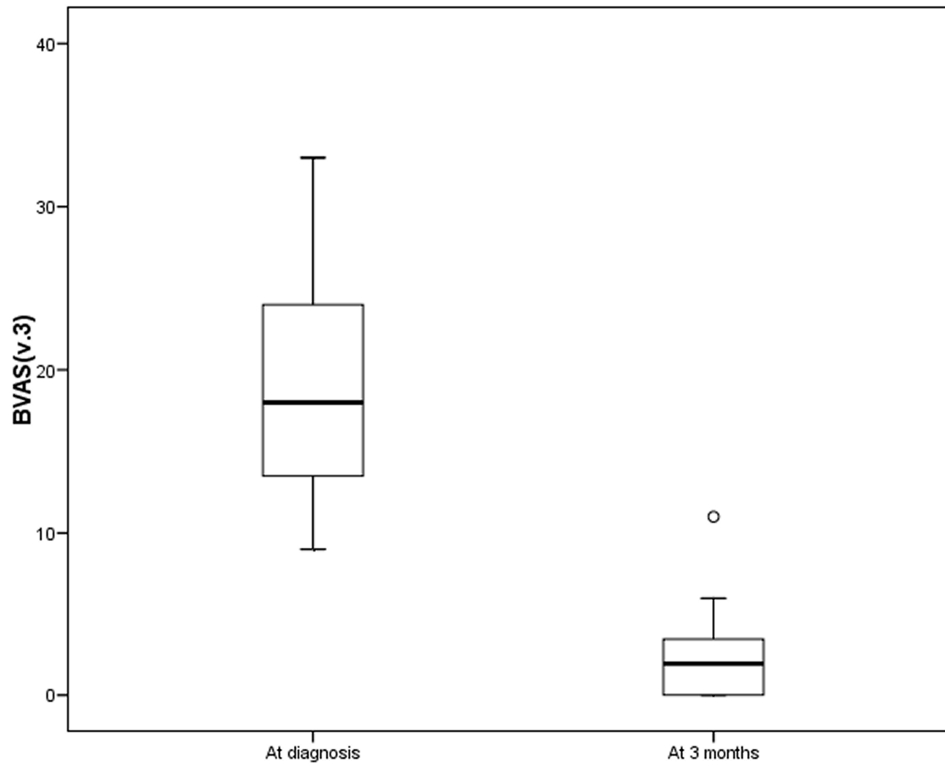


Figure 4-2: Box-plot of BVAS (version 3) scores at 0 and 3 months in 39 patients

### *CRP levels*

The mean (SD) CRP at recruitment was 55.7 (60.5). At 3 months the mean (SD) CRP fell to 15.6 (52.5) mg/L. The mean fall of CRP was 40.1 (95% CI 15.4, 64.7) mg/L (P = 0.02 by paired samples t test).

### *Correlation between fall in CRP with fall in BVAS (version 3) at 3 months*

The Spearman's correlation coefficient for correlating the fall in CRP compared to fall in BVAS was 0.16 (P=0.33)

### *Treatment decision*

All 39 patients had 'major escalation of treatment' according to our treatment category definitions (Table 2-1). At 3 months, 1/39 patients had treatment categorised as 'continue at major level', and 38/39 had reduction of therapy.

## **DISCUSSION**

Quantifying the sensitivity of the BVAS (version 3) to change with changing disease is difficult due to the lack of a valid external comparator. The patients in this study were all treated with cyclophosphamide and glucocorticoid therapy with or without rituximab. The combination of cyclophosphamide and glucocorticoid is recommended as first line therapy for the treatment of AAV, and rituximab is recommended in patients with refractory AAV (C. Mukhtyar et al. 2008c). At 3 months, the CRP levels fell significantly by over 40 mg/L. 38 patients had a reduction in the intensity of their treatment. It would be reasonable to conclude that patients had lower disease activity at 3 months than at recruitment. In the absence of a gold standard for quantifying 'true disease

activity', the fall of over 16 units in BVAS (version 3) is clinically meaningful. The maximum achievable score for an organ system is 12 units. Thus, a score of 16 units would be associated with complete disappearance of vasculitis related manifestations in at least one organ system, with an improvement in at least one more organ system. The fall in BVAS (version 3) does not correlate to the magnitude of fall in CRP levels. CRP does not have a strong correlation with BVAS (version 3) as shown in Chapter 2. The correlation of ANCA with disease activity is contentious and was therefore avoided (Birck et al. 2006).

For the validation of BVAS/WG, the sensitivity to changing disease status was assessed in 36 patients, reassessed at a mean of 117 days (range of 10 – 224 days) (Stone et al. 2001). Physician's global assessment was used as the external comparator. They measured the strength of rank correlation of the difference between the PGA values and BVAS/WG values between the two assessments. The Spearman's correlation coefficient was 0.73 (95% CI 0.53, 0.85). In Chapter 2, we have discussed the possibility that the correlation of BVAS and PGA may be a function of completing the score sheet prior to marking the PGA, and therefore influencing the value of the PGA. On that basis, we postulated that testing the correlation between the change in BVAS (version 3) and the change in PGA at 3 months might produce a spurious correlation. Correlating a change in BVAS (version 3) and the categorised treatment

decision (Table 2-1) at 3 months would be a more valid test of assessing the sensitivity of BVAS (version 3) to changing disease status. However, this is not possible because 38/39 patients had a reduction of therapy. Although, statistical testing is difficult with such a polar distribution of data, it strongly suggests that a reduction in BVAS is associated with a reduction of therapy as a surrogate disease activity marker.

## **CONCLUSION**

The BVAS (version 3) score changes with a change in disease status.

**Chapter 5 USING BVAS (VERSION 3) TO  
DIFFERENTIATE VASCULITIS FROM OTHER  
MUSCULOSKELETAL DISEASES**

The previous chapters have established the convergent validity, and demonstrated the reliability and sensitivity of BVAS (version 3) to changing disease status. As discussed in chapter 4, an ideal clinical tool should be able to differentiate between the disease of interest and other similar diseases. This would validate a further facet of BVAS (version 3). However, according to the rules laid out in the original BVAS (version 1) validation, items should only be scored if they can be attributed to active vasculitis (Luqmani et al. 1994a). The subsequent versions of the BVAS, including this one have remained true to that rule. This rule has meant that testing the ability of BVAS (version 3) to discriminate between vasculitis and other similar conditions is impossible. Strict application of this rule, when assessing other diseases, would produce a spuriously high ability of BVAS to distinguish vasculitis from non-vasculitic conditions. In this chapter, this ability of BVAS (version 3) to differentiate between vasculitis and other rheumatological conditions is tested by ignoring the rule of attribution. This would also allow us to examine the performance of BVAS (version 3) in clinical practice where it is often not possible to attribute a manifestation to systemic vasculitis at first assessment.

## **AIM**

To validate the ability of BVAS (version 3) to differentiate between vasculitis and other musculoskeletal conditions.

## **METHODS**

Setting: Prospective case-control study in two centres (Nuffield Orthopaedic Centre, Oxford, UK and the Western General Hospital, Edinburgh, UK)

### Inclusion criteria

Cases: Patients with a definite diagnosis of systemic vasculitis who had untreated or uncontrolled disease. Each patient required escalation or commencement of an immunomodulatory agent and/or glucocorticoid. Patients were recruited from both centres.

Controls: Patients with an untreated or uncontrolled musculoskeletal illness not associated with systemic vasculitis. Each patient required active intervention (escalation of immunomodulatory treatment or a diagnostic/therapeutic procedure). Patients were recruited from Oxford only.

### Exclusion criteria

Cases: Patients with a probable or definite diagnosis of giant cell arteritis.

Controls: Patients known to have secondary vasculitis.

Ethical approval: Recruitment of cases was approved by local ethics committees. Recruitment of controls was approved by the audit and clinical

effectiveness department at the Nuffield Orthopaedic Centre. For each case, we obtained written informed consent. For the controls, verbal consent was obtained and the BVAS (version 3) assessment was completed following examination for their routine clinical care.

For each patient, BVAS (version 3) was completed following thorough clinical examination. For the cases, the BVAS assessment followed the standard rules of attributing the presence of clinical manifestations to active vasculitis. For the controls, all clinical manifestations present were recorded without regard to aetiology. The diagnosis of each patient was recorded.

### Statistics

The difference in the BVAS scores between cases and controls was measured using the independent T test. A receiver-operating characteristics (ROC) analysis was performed to determine the sensitivity and specificity of BVAS (version 3) to diagnose systemic vasculitis. The statistical analysis was performed on SPSS 15.0 for Windows (SPSS Inc, Chicago, USA).

## **RESULTS**

50 cases were recruited. The diagnoses of the 50 cases were Wegener's granulomatosis (n=20), cerebral vasculitis (n=5), Behcet's disease (n=4),

microscopic polyangiitis (n=4), Churg-Strauss syndrome (n=2), cryoglobulinemic vasculitis (n=2), rheumatoid vasculitis (n=2), Henoch-Schonlein purpura (n=1), polyarteritis nodosa (n=1), Takayasu arteritis (n=1), urticarial vasculitis (n=1). Seven cases had an unclassified vasculitis. 49 patients with other rheumatological conditions were recruited. The 49 controls were divided into three diagnostic groups - rheumatoid arthritis (n=26), connective tissue disease (N=5), and other rheumatic diseases (N=18).

*Ability to discriminate between vasculitis and non-vasculitis*

The mean (SD) BVAS (version 3) score for the cases was 12.96 (8.70), and for the controls was 4.88 (6.30) for rheumatoid arthritis, 11.80 (8.22) for connective tissue disease, and 4.28 (4.07) for other rheumatological conditions (Figure 5-1). The difference between the BVAS (version 3) means for cases and rheumatoid arthritis controls was 8.07 (95% CI 4.59, 11.55;  $P < 0.001$ ). The difference between the BVAS (version 3) means for cases and connective tissue disease controls was 1.16 (95% CI -8.85, 11.17;  $P = 0.77$ ). The difference between the BVAS (version 3) means for cases and other rheumatic disease controls was 8.68 (95% CI 5.56, 11.80;  $P < 0.001$ ).

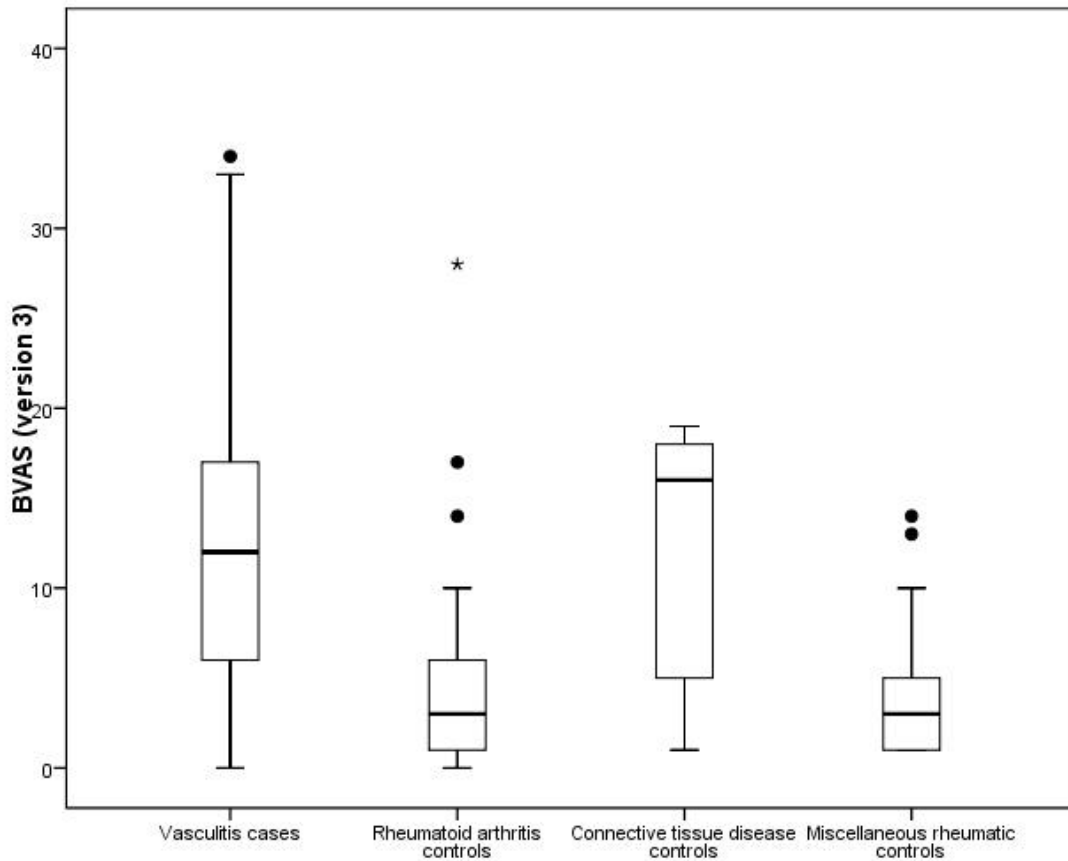


Figure 5-1 BVAS (version 3) scores in cases and controls

In figure 5-1, 3 rheumatoid arthritis controls, and 2 controls included in the miscellaneous rheumatic diseases had BVAS (version 3) scores which were statistical outliers. On reviewing these cases, 1 control in each arm was reclassified as having systemic vasculitis (1 Wegener's granulomatosis, 1 rheumatoid vasculitis). For the rest of the analysis, these 2 controls were treated as cases.

*The sensitivity and specificity of BVAS (version 3) for diagnosis of systemic vasculitis (when comparing with rheumatoid arthritis controls)*

In a ROC analysis including 76 patients, (51 cases and 25 controls), the area under curve was 0.82 (95% CI 0.72, 0.92; P <0.001) (Figure 5-2). The coordinates of the curve are as in Table 5-1.

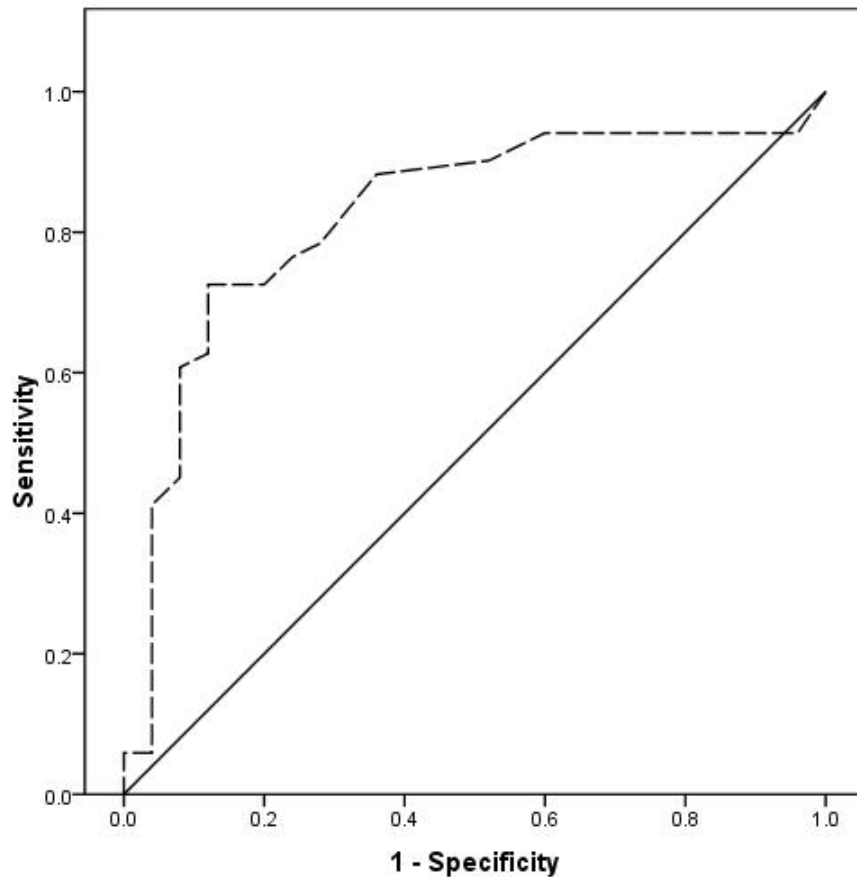


Figure 5-2 Receiver operating characteristics curve for BVAS (version 3) to diagnose vasculitis (when comparing with rheumatoid arthritis controls)

Positive if Greater Than or Equal To <sup>a</sup>	Sensitivity	1 - Specificity	Positive if Greater Than or Equal To <sup>a</sup>	Sensitivity	1 - Specificity
-1.00	1.000	1.000	14.50	.412	.040
.50	.941	.960	15.50	.333	.040
1.50	.941	.600	16.50	.314	.040
2.50	.902	.520	17.50	.216	.040
3.50	.882	.360	18.50	.196	.040
4.50	.784	.280	20.00	.176	.040
5.50	.765	.240	23.00	.157	.040
6.50	.725	.200	25.50	.118	.040
7.50	.725	.120	26.50	.078	.040
8.50	.667	.120	27.50	.059	.040
9.50	.627	.120	29.00	.059	.000
10.50	.608	.080	31.50	.039	.000
11.50	.569	.080	33.50	.020	.000
12.50	.490	.080	35.00	.000	.000
13.50	.451	.080			

Table 5-1 Co-ordinates for the ROC curve distinguishing vasculitis from controls with rheumatoid arthritis

\*The smallest cut-off value is the minimum observed test value minus 1, and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.

*The sensitivity and specificity of BVAS (version 3) for diagnosis of systemic vasculitis (when comparing with miscellaneous rheumatic controls)*

In a ROC analysis including 68 patients, (51 cases and 17 controls), the area under curve was 0.84 (95% CI 0.74, 0.94; P <0.001) (Figure 5-3). The co-ordinates of the curve are as in Table 5-2.

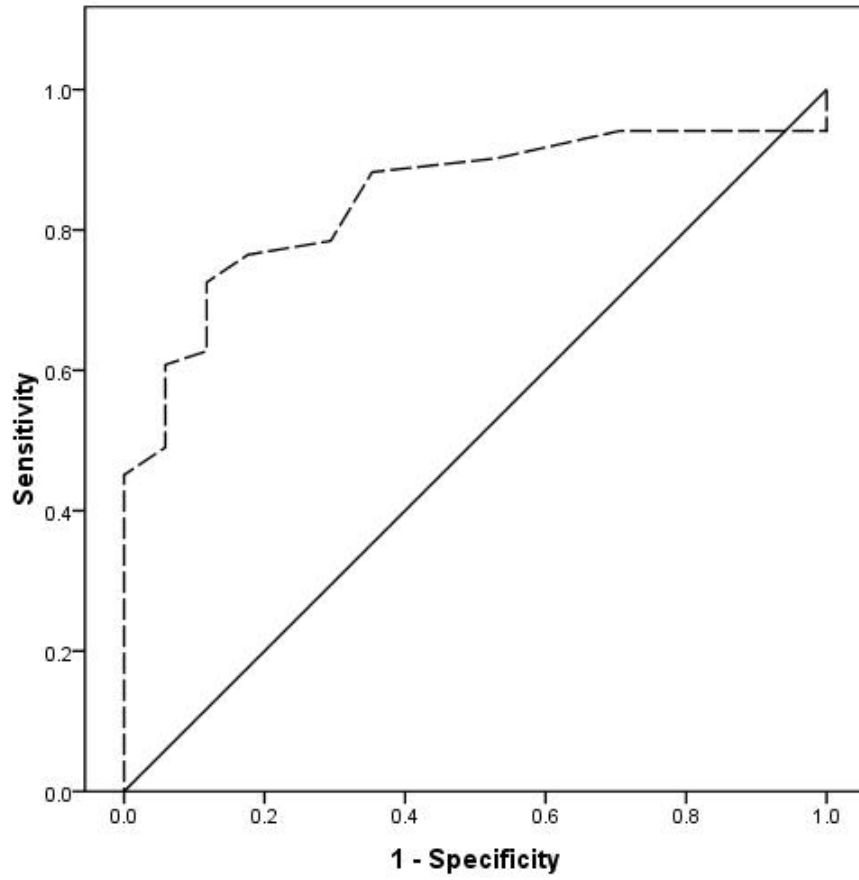


Figure 5-3 Receiver operating characteristics curve for BVAS (version 3) to diagnose vasculitis (when comparing with other non-systemic rheumatic controls)

Positive if Greater Than or Equal To <sup>a</sup>	Sensitivity	1 - Specificity	Positive if Greater Than or Equal To <sup>a</sup>	Sensitivity	1 - Specificity
-1.00	1.000	1.000	14.50	.392	.000
.50	.941	1.000	15.50	.314	.000
1.50	.941	.706	16.50	.294	.000
2.50	.902	.529	17.50	.216	.000
3.50	.882	.353	18.50	.196	.000
4.50	.784	.294	20.00	.176	.000
5.50	.765	.176	23.00	.157	.000
7.00	.725	.118	25.50	.118	.000
8.50	.667	.118	26.50	.078	.000
9.50	.627	.118	28.50	.059	.000
10.50	.608	.059	31.50	.039	.000
11.50	.569	.059	33.50	.020	.000
12.50	.490	.059	35.00	.000	.000
13.50	.451	.000			

Table 5-2 Co-ordinates for the ROC curve distinguishing vasculitis from other non-systemic rheumatic conditions

\*The smallest cut-off value is the minimum observed test value minus 1, and the largest cut-off value is the maximum observed test value plus 1. All the other cut-off values are the averages of two consecutive ordered observed test values.

## DISCUSSION

The control population in this study constitutes patients with rheumatological diseases who needed a diagnostic / therapeutic procedure or escalation of their disease specific treatment. These patients had active / uncontrolled rheumatological illness. The 50 cases with systemic vasculitis also had active / uncontrolled vasculitis. The mean scores in controls with rheumatoid arthritis,

and other non-systemic rheumatic diseases were significantly different from the BVAS (version 3) scores of the cases. The difference of over 8 units in each instance is clinically meaningful as well. There were only 5 patients recruited in controls with connective tissue disease, but these controls had BVAS (version 3) scores which were as high as the scores in the vasculitis cases.

This study demonstrates that the BVAS (version 3) check list may have a role in the formulation of diagnostic criteria. From Figure 5-2 and Table 5-1, BVAS (version 3) score of 8 has a sensitivity of 0.72 and a specificity of 0.78 for a diagnosis of vasculitis when compared with rheumatoid arthritis controls. When comparing vasculitis and non-systemic rheumatic conditions, a BVAS (version 3) score of 7 has sensitivity of 0.72 and a specificity of 0.79. However, the real value of BVAS (version 3) for diagnosing vasculitis is probably best tested in a control group of patients with connective tissue diseases, which closely mimic the manifestations of systemic vasculitis. In this study, BVAS (version 3) could not differentiate between cases and connective tissue disease controls. This will need testing in a larger series in a formal diagnostic criteria project.

In patients with an unclear diagnosis, completing a BVAS (version 3) assessment may assist differentiating between vasculitis and some other rheumatological conditions. For patients with pyrexia of unknown origin, it has been suggested that magnetic resonance imaging should become part of the

diagnostic process on a regular basis.(Wagner et al. 2005) In comparison, completing a BVAS form will be much quicker and more economical, and lead to a high diagnostic yield.

In this study, cases and controls had differing methods of assessment. The rule of attribution was obeyed for the cases, but not for the controls. If the rule of attribution had been ignored for the cases as well, the mean score for the cases might have been higher. This would have enhanced the difference between the cases and the controls.

## **CONCLUSION**

BVAS (version 3) can differentiate between vasculitis and some other musculoskeletal conditions. This is an initial step towards the formulation of diagnostic criteria for the various systemic vasculitides.

## **Chapter 6 CONCLUSIONS**

In a series of prospective studies, the BVAS (version 3) has been validated for quantifying disease activity in patients with systemic vasculitis [Appendix 1: The new version of the BVAS with the glossary of items]. The salient findings of this study are discussed as under.

### **CONVERGENT VALIDITY**

The absence of valid biomarkers that accurately reflect disease activity in rheumatological conditions has led to the development of clinical assessment tools and outcome measures. However, this lack of a 'gold standard' disease activity outcome measure posed a problem in validating the disease activity indices. Commonly, the convergent validity of the common disease activity indices has been established against one or several subjective measures, or biomarkers of interest, or other disease activity indices. [Table 6-2] Similarly, in this study the BVAS (version 3) has been compared to several subjective and objective measures of assessing disease activity in systemic vasculitis, and a previous version of BVAS. By demonstrating a correlation of BVAS (version 3) to a 100 mm PGA VAS (Spearman's correlation coefficient 0.91 (95% CI 0.89, 0.93)), 5 point Likert scale VAI (Spearman's correlation coefficient 0.88 (95% CI 0.86, 0.91)), categorised treatment decisions (Spearman's correlation coefficient 0.66 (95% CI 0.59, 0.72)), and CRP levels (Spearman's correlation coefficient 0.43 (95% CI 0.31, 0.54)), the convergent validity has been established. One of

the needs of this project was unification of the two scores produced by BVAS (version 2), to make the BVAS more reflective of true disease activity. In this project the unified BVAS (version 3) score demonstrates satisfactory correlation with BVAS 1 sub-score of BVAS (version 2) (Spearman's correlation coefficient 0.94 (95% CI 0.92, 0.96)) in patients with active disease, and BVAS 2 sub-score of BVAS (version 2) in patients with persistent disease (Spearman's correlation coefficient 0.60 (95% CI 0.21, 0.83)). Correlation of BVAS (version 3) with both sub-scores of BVAS (version 2) is a testimony to the validity of the construct of the new version.

<b>Disease activity index</b>	<b>Condition</b>	<b>Variables against which the convergent validity was established</b>	<b>Reference</b>
BVAS	Systemic vasculitis	Physicians global assessment, 5 point Likert score, CRP, ESR, haemoglobin, von Willebrand factor, VAI, Kallenberg Index	(Luqmani et al. 1994a)
BVAS/WG	Wegener's granulomatosis	Physicians global assessment,	(Stone et al. 2001)
SLEDAI	Systemic lupus erythematosus	None	(Bombardier et al. 1992)
BILAG index	Systemic lupus erythematosus	Treatment decision	(Hay et al. 1993)

DAS 28	Rheumatoid arthritis	HAQ, grip strength, radiographic progression	(Prevo et al. 1995)
BASDAI	Ankylosing spondylitis	Bath disease activity index, Newcastle enthesitis index	(Garrett et al. 1994)

Table 6-1 Common disease activity indices in rheumatology and the variables against which their construct was established

BVAS – Birmingham Vasculitis Activity Score, CRP – C reactive protein, ESR – Erythrocyte sedimentation rate, VAI – Vasculitis activity index, BVAS/WG – Birmingham vasculitis activity score of Wegener’s granulomatosis, SLEDAI – Systemic lupus erythematosus disease activity index, BILAG – British Isles lupus activity group, DAS 28 – Disease activity score with 28 joint count, BASDAI – Bath ankylosing spondylitis index

## RELIABILITY

A reliable clinical instrument should give the same results, or at least comparable results when used in similar scenarios. In this project, the BVAS (version 3) has been shown to give comparable results on repeated assessments of the same patient by the same observer at different times within a reasonable time-frame (ICC 0.96 (95% CI 0.92, 0.97)); and to give comparable results on repeated assessments of the same patient by different observers at the same time (ICC 0.96 (95% CI 0.95, 0.97)). In both instances the health-care professionals completing the assessments were experienced in managing systemic vasculitis, and were trained in the use of the BVAS (version 3). A

detailed manual of operations (available from [www.vasculitis.org/scoring/BVAS%202003%20manual.pdf](http://www.vasculitis.org/scoring/BVAS%202003%20manual.pdf)) was available to the investigators to instruct them in the use of the clinical tool. However, data from paper cases suggests that the BVAS (version 3) may have a high reproducibility even in the hands of healthcare professionals untrained in the use of the clinical instrument. The ICC of 0.89 (95% CI 0.81, 0.94) for the entry level cases completed by 19 observers suggests a high degree of reproducibility. The ICC for the advanced level cases is higher (0.95 (95% CI 0.93, 0.97)) suggesting that the investigators improved with training. However, as discussed in chapter 3, this may be artefactual and be due to the worst performers dropping out of the advanced cases.

## **DISCRIMINATION**

Any clinical tool for assessment of disease activity needs to be able to discriminate in three different ways –

1. Discriminate between differing disease states
2. Discriminate between active disease and sequelae of disease
3. Discriminate between the disease of interest and other similar conditions.

In the validation of BVAS (version 1) and BVAS/WG, the sensitivity of the clinical tool to change was assessed in a longitudinal analysis involving two visits at

variable time intervals. The treatment received by the patients in this time frame was not specified and it is likely that the patients may have received different treatments. In BVAS (version 1), the scores were higher in the active state than during remission, but remission was not defined and may have been physician opinion or related to treatment decision. In BVAS/WG, the sensitivity to change was assessed by correlating the change in BVAS/WG score with the change in physician's global assessment score. As discussed in chapter 4, this correlation may be spurious as completion of BVAS/WG may have influenced the physician's global assessment. In this study, time and treatment were relative constants. All patients were seen exactly 3 months after recruitment, and all patients received the same glucocorticoid regimen. Patients also received one of two immunosuppressive regimens, both of which are well documented to induce remission in systemic vasculitis (Adu et al. 1997; C. Mukhtyar et al. 2007). They received -

1. intravenous cyclophosphamide 15mg/kg, two weekly for three infusions, followed by the same dose at three weekly intervals for a further 3 – 6 infusions OR
2. two sets of intravenous cyclophosphamide 15 mg/kg two weeks apart, plus rituximab 375 mg/m<sup>2</sup> body surface area every week for four weeks.

The fall of over 16 units in this study, is clinically meaningful. According to the rules of scoring BVAS (version 3), each organ-system carries a ceiling score. The maximum score for any organ-system is 12 units for the renal system. The fall of over 16 units would therefore be consistent with complete disappearance of disease activity in at least one organ-system along with at least a partial amelioration of activity in other organ-systems. This is consistent with physician expectations in the majority of patients with AAV treated with the above drugs. The fall in CRP is also significant, but there is no correlation between the fall of BVAS (version 3) scores and CRP levels. It is probably of greater significance, that 38/39 patients had a reduction in the intensity of their treatment suggesting that the physicians were convinced of reduction of disease activity.

To demonstrate that BVAS (version 3) can discriminate between disease activity and damage, patients would require simultaneous assessment with BVAS (version 3) and VDI. A correlation analysis demonstrating lack of a significant correlation would establish that the construct of BVAS (version 3) measures activity and not damage. However, this experiment like the analysis to establish the ability of BVAS (version 3) to distinguish between systemic vasculitis and other similar conditions, would be flawed if the assessments were carried out with strict adherence to the principles governing BVAS (version 3) scoring. No item can be scored in BVAS (version 3) unless it can be attributed to active

systemic vasculitis. Discrimination between activity and damage has not been carried out in this study, and it forms part of future research agenda.

The discrimination between systemic vasculitis and other musculoskeletal conditions was carried out with a slight twist in the rules of assessment. All the vasculitis cases continued to be assessed with the rule of attributing items to active vasculitis, but controls were assessed without attribution of manifestations to aetiology. This study suggested that BVAS (version 3) could discriminate between systemic vasculitis and other predominantly non-systemic rheumatological conditions. This information may be of value when formulating diagnostic criteria for the systemic vasculitides.

In conclusion, the BVAS (version 3) has undergone a robust validation in comparison to its predecessors and other commonly used disease activity indices in rheumatological conditions. Future research agenda, as outlined in the next chapter can further exploit the potential of the BVAS (version 3)

## **Chapter 7 FUTURE WORK**

The BVAS (version 3) is now validated for the assessment of disease activity in systemic vasculitis (C. Mukhtyar et al. 2008a) [Appendix 2: The published manuscript of the validation]. It is an improvement over the previous versions, and there is further potential for expanding the scope of the BVAS.

### **DISEASE SPECIFIC INDEX**

The BVAS (version 3) is an excellent generic tool for assessing disease activity in systemic vasculitis. However, different vasculitis syndromes produce a varying range of scores, for example the range of possible scores in Takayasu arteritis is much smaller than the range of possible scores in Wegener's granulomatosis. The scores are therefore not comparable across the vasculitic syndromes. Disease specific activity scores have been developed for Wegener's granulomatosis (Stone et al. 2001) and Takayasu arteritis (Misra et al. 2008). In patients with suspected systemic vasculitis, it may not always be possible to diagnose the exact vasculitic syndrome early in disease and the BVAS (version 3) would be the appropriate tool for quantifying disease activity. Following exact diagnosis, it may be useful to use a more appropriate disease specific tool. The development of disease specific modules for different vasculitis syndromes which can complement the BVAS (version 3) (which would act as a core set of vasculitis features) would greatly assist such a process of accurately quantifying

disease. The disease specific modules could also take into account any future validated disease specific biomarker.

## **PROGNOSTIC INDEX**

The five factor score is a prognostic score for patients with polyarteritis nodosa, Churg-Strauss syndrome and microscopic polyangiitis (Guillevin et al. 1996). A previous version of the BVAS has been shown to correlate with the five factor score (Gayraud et al. 2001) and have prognostic value in predicting death (Luqmani et al. 1994a). A longitudinal study to assess the prognostic significance of BVAS (version 3) would have an additional benefit. In all versions of the BVAS, the weighting of the manifestations has been based on expert consensus. Such a study would allow re-weighting of the items according to their role in producing a hard end-point, for example death, cerebrovascular accident, myocardial infarction etc. This in turn would lead the way to future versions of BVAS. In a systematic review of literature, the role of age, lung involvement and renal involvement have quantified, and these can be also be considered when deciding weights to the chest and renal organ-systems in future versions of BVAS (C. Mukhtyar et al. 2008b) [Appendix 3: The published manuscript]

## **DAMAGE INDEX**

Activity and damage are two sides of a coin. Damage is defined as the irreversible sequelae of disease which is not responsive to treatment. When assessing the activity of systemic vasculitis, it is important to differentiate activity from damage. Damage can be quantified by the VDI (Exley et al. 1997). Similar to the BVAS, the VDI is a list of common sequelae of vasculitis, each being weighted equally. The VDI has prognostic value. Accumulation of damage is linked with resistance to treatment (Koldingsnes and Nossent 2003) and impaired survival (Koldingsnes and Nossent 2002). The VDI is being revised under the auspices of the OMERACT group in a joint European-American effort (Seo et al. 2007)

In summary, the future may see more than one version of the BVAS. Depending on the outcome to be analyzed, the outcome measure may vary significantly. A prognostic BVAS index may be much different than the BVAS with disease specific modules to allow its use in clinical practice as well as clinical trials. The damage index may similarly change. Increasingly, as remission becomes the norm in systemic vasculitis, limitation of damage may become the primary outcome, or we may see the advent of a composite outcome measure for clinical trials in vasculitis – one incorporating, disease activity, damage and quality of life.

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**FULL LIST OF PUBLICATIONS DURING THE MASTERS  
PROGRAMME**

(Hilary 2007 to Hilary 2009)

## **PAPERS**

### *Original Work*

Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossmann O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani R. Modification and validation of the Birmingham Vasculitis Activity Score (Version 3). *Ann Rheum Dis*. 2008 Dec 3. [Epub ahead of print]

### *Practice guidelines*

Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, Hauser T, Hellmich B, Jayne D, Kallenberg CG, Merkel PA, Raspe H, Salvarani C, Scott DG, Stegeman C, Watts R, Westman K, Witter J, Yazici H, Luqmani R. EULAR Recommendations for the management of primary small and medium vessel vasculitis. *Ann Rheum Dis*. 2009 Mar;68(3):318-23.

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### *Systematic review of literature*

Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, Gross WL, Guillevin L, Jayne D, Mahr A, Merkel PA, Raspe H, Scott D, Witter J, Yazici H, Luqmani RA; European Vasculitis Study Group (EUVAS). Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis*. 2008 Jul;67(7):1004-10.

### *Research agenda*

Seo P, Luqmani RA, Flossmann O, Hellmich B, Herlyn K, Hoffman GS, Jayne D, Kallenberg CG, Langford CA, Mahr A, Matteson EL, Mukhtyar CB, Neogi T, Rutgers A, Specks U, Stone JH, Ytterberg SR, Merkel PA. The future of damage assessment in vasculitis. *J Rheumatol*. 2007 Jun;34(6):1357-71.

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#### *Editorial*

Mukhtyar C, Boumpas D, Gordon C, Gross W, Jayne D, Luqmani R. Why we need guidelines for clinical trials in vasculitis and systemic lupus erythematosus. *Ann Rheum Dis*. 2007 May;66(5):569-70.

#### *Case reports*

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## **APPENDIX 1**

Birmingham Vasculitis Activity Score (version 3) and glossary

## **APPENDIX 2**

Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossmann O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani R. Modification and validation of the Birmingham Vasculitis Activity Score (Version 3). *Ann Rheum Dis*. 2008 Dec 3. [Epub ahead of print]

### **APPENDIX 3**

Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, Gross WL, Guillevin L, Jayne D, Mahr A, Merkel PA, Raspe H, Scott D, Witter J, Yazici H, Luqmani RA; European Vasculitis Study Group (EUVAS). Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis*. 2008 Jul;67(7):1004-10.



## **APPENDIX 1**

Birmingham Vasculitis Activity Score (version 3) and glossary



## GLOSSARY AND SCORING FOR BVAS version 3

### Rules for scoring BVAS

1. Disease manifestations are scored **only when they are attributable to active vasculitis**. The manifestation should not be scored if there is reasonable evidence of another aetiology for the symptoms e.g. infection, drug reaction, other co-morbidity.
2. Tick "Persistent Disease" box if **all** the abnormalities are due to active (but not new or worse) vasculitis.
3. Specialist opinion, or the results of laboratory or imaging investigations will be required for some items. Excepting those circumstances, the whole form should be completed at the time of the consultation.
4. The bands of serum creatinine should be scored **only** on the first visit.
5. Items marked with an asterisk (\*) are not compatible with 'persistent' disease. These manifestations always suggest new or worse disease when due to active vasculitis.

Manifestation	Definition	Persistent	New / Worse
<b>1. General</b>	<b>Maximum scores</b>	<b>2</b>	<b>3</b>
Myalgia	Pain in the muscles	1	1
Arthralgia or arthritis	Pain in the joints or joint inflammation	1	1
Fever ≥38° C	Documented oral / axillary temperature. If rectal temperature is measured, raise threshold to 38.5° C	2	2
Weight Loss ≥2 kg	Loss of dry body weight without dieting	2	2

<b>2. Cutaneous</b>	<b>Maximum scores</b>	<b>3</b>	<b>6</b>
Infarct	Area of tissue necrosis or splinter haemorrhages	1	2
Purpura	Subcutaneous or submucosal haemorrhage in the absence of trauma	1	2
Ulcer	A disruption in the continuity of the skin	1	4
Gangrene	Extensive tissue necrosis	2	6
Other skin vasculitis	Livedo reticularis, subcutaneous nodules, erythema nodosum, etc	1	2

<b>3. Mucous Membranes / eyes</b>	<b>Maximum scores</b>	<b>3</b>	<b>6</b>
Mouth ulcers / granulomata	Aphthous stomatitis, deep ulcers, strawberry gingival hyperplasia	1	2
Genital ulcers	Ulcers on the genitalia or perineum	1	1
Adnexal inflammation	Salivary or lacrimal gland inflammation.	2	4
Significant proptosis	>2 mm protrusion of the eyeball	2	4
Scleritis / Episcleritis	Inflammation of the sclera	1	2
Conjunctivitis / Blepharitis / Keratitis	Inflammation of the conjunctiva, eyelids or cornea - but not due to sicca syndrome	1	1
Blurred vision	Deterioration of visual acuity from previous or baseline	2	3
Sudden visual loss*	Acute loss of vision	*	6
Uveitis	Inflammation of the uvea (iris, ciliary body, choroid)	2	6
Retinal changes (vasculitis, thrombosis / exudate / haemorrhage)	Sheathing of retinal vessels or evidence of retinal vasculitis on fluorescein angiography; thrombotic retinal arterial or venous occlusion; soft retinal exudate (exclude hard exudates) / retinal haemorrhage	2	6

<b>4. ENT</b>	<b>Maximum scores</b>	<b>3</b>	<b>6</b>
Bloody nasal discharge / crusts / ulcers / granulomata	Bloody, mucopurulent, nasal secretion, light or dark brown crusts frequently obstructing the nose, nasal ulcers or granulomatous lesions observed on rhinoscopy	2	4
Paranasal sinus involvement	Tenderness or pain over paranasal sinuses (usually confirmed by imaging)	1	2
Subglottic stenosis	Stridor or hoarseness due to inflammation and narrowing of the subglottic area observed by laryngoscopy	3	6
Conductive hearing loss	Hearing loss due to middle ear involvement (usually confirmed by audiometry)	1	3
Sensorineural hearing loss	Hearing loss due to auditory nerve or cochlear damage (usually confirmed by audiometry)	2	6

<b>5. Chest</b>	<b>Maximum scores</b>	<b>3</b>	<b>6</b>
Wheeze	Wheeze on clinical examination	1	2
Nodules or cavities*	New lesions detected on imaging	*	3
Pleural effusion / pleurisy	Pleural pain and/or friction rub on clinical assessment; radiologically confirmed pleural effusion.	2	4
Infiltrate	Detected on chest X-ray or CT scan	2	4
Endobronchial involvement	Endobronchial pseudotumor or ulcerative lesions. NB: smooth stenotic lesions to be included in VDI; subglottic lesions to be recorded in the ENT section.	2	4
Massive haemoptysis / alveolar haemorrhage	Major pulmonary bleeding, with shifting pulmonary infiltrates	4	6
Respiratory failure	The need for artificial ventilation	4	6

<b>6. Cardiovascular</b>	<b>Maximum scores</b>	<b>3</b>	<b>6</b>
Loss of pulses	Clinical absence of peripheral arterial pulsation in any limb	1	4
Valvular heart disease	Clinical or echo detection of aortic / mitral / pulmonary valve involvement	2	4
Pericarditis	Pericardial pain / friction rub on clinical assessment	1	3
Ischaemic cardiac pain	Typical clinical history of cardiac pain leading to myocardial infarction or angina.	2	4
Cardiomyopathy	Significant impairment of cardiac function due to poor ventricular wall motion confirmed on echocardiography	3	6
Congestive cardiac failure	Heart failure by history or clinical examination	3	6

<b>7. Abdominal</b>	<b>Maximum scores</b>	<b>4</b>	<b>9</b>
Peritonitis	Typical abdominal pain suggestive of peritoneal involvement	3	9
Bloody diarrhoea	Of recent onset	3	9
Ischaemic abdominal pain	Typical abdominal pain suggestive of bowel ischaemia, confirmed by imaging or surgery	2	6

<b>8. Renal</b>	<b>Maximum scores</b>	<b>6</b>	<b>12</b>
Hypertension	Diastolic >95 mm Hg	1	4
Proteinuria	>1+ on urinalysis or >0.2g/24 hours	2	4
Haematuria	'Moderate' on urinalysis or ≥10 RBC per high power field, usually accompanied by red cell casts	3	6
Serum creatinine 125-249 µmol/L	At first assessment only	2	4
Serum creatinine 250-499 µmol/L		3	6
Serum creatinine ≥500 µmol/L		4	8
>30% rise in creatinine or >25% fall in creatinine clearance *	Progressive worsening of renal function. Can be used at each assessment if the renal function has deteriorated from prior value	*	6

<b>9. Nervous system</b>	<b>Maximum scores</b>	<b>6</b>	<b>9</b>
Headache	Unaccustomed & persistent headache	1	1
Meningitis	Clinical evidence of meningism	1	3
Organic confusion	Impaired orientation, memory or other intellectual function in the absence of metabolic, psychiatric, pharmacological or toxic causes.	1	3
Seizures (not hypertensive)	Clinical or EEG evidence of aberrant electrical activity in the brain	3	9
Stroke	Focal neurological signs lasting >24 hours due to a CNS vascular event	3	9
Spinal cord lesion	Clinical or imaging evidence of spinal cord involvement	3	9
Cranial nerve palsy	Clinical evidence of cranial nerve palsy – score VIII nerve palsy as sensorineural hearing loss, do not score ocular palsies if they secondary to pressure effects	3	6
Sensory peripheral neuropathy	Objective sensory deficit in a non-dermatomal distribution	3	6
Mononeuritis multiplex	Single or multiple specific motor nerve palsies	3	9

## **APPENDIX 2**

Mukhtyar C, Lee R, Brown D, Carruthers D, Dasgupta B, Dubey S, Flossmann O, Hall C, Hollywood J, Jayne D, Jones R, Lanyon P, Muir A, Scott D, Young L, Luqmani R. Modification and validation of the Birmingham Vasculitis Activity Score (Version 3). *Ann Rheum Dis.* 2008 Dec 3. [Epub ahead of print]

# Modification and validation of the Birmingham Vasculitis Activity Score (version 3)

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► Additional data are published online only at <http://ard.bmj.com/content/volXX/issueX>

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## ABSTRACT

**Background:** Comprehensive multisystem clinical assessment using the Birmingham Vasculitis Activity score (BVAS) is widely used in therapeutic studies of systemic vasculitis. Extensive use suggested a need to revise the instrument. The previous version of BVAS has been revised, according to usage and reviewed by an expert committee.

**Objective:** To modify and validate version 3 of the BVAS in patients with systemic vasculitis.

**Methods:** The new version of BVAS was tested in a prospective cross-sectional study of patients with vasculitis.

**Results:** The number of items was reduced from 66 to 56. The subscores for new/worse disease and persistent disease were unified. In 313 patients with systemic vasculitis, BVAS(v.3) correlated with treatment decision (Spearman's  $r_s = 0.66$ , 95% CI 0.59 to 0.72), BVAS1 of version 2 ( $r_s = 0.94$ , 95% CI 0.92 to 0.96), BVAS2 of version 2 in patients with persistent disease ( $r_s = 0.60$ , 95% CI 0.21 to 0.83), C-reactive protein levels ( $r_s = 0.43$ , 95% CI 0.31 to 0.54), physician's global assessment ( $r_s = 0.91$ , 95% CI 0.89 to 0.93) and vasculitis activity index ( $r_s = 0.88$ , 95% CI 0.86 to 0.91). The intraclass correlation coefficients for reproducibility and repeatability were 0.96 (95% CI 0.95 to 0.97) and 0.96 (95% CI 0.92 to 0.97), respectively. In 39 patients assessed at diagnosis and again at 3 months, the BVAS(v.3) fell by 17 (95% CI 15 to 19) units ( $p < 0.001$ , paired t test).

**Conclusion:** BVAS(v.3) demonstrates convergence with BVAS(v.2), treatment decision, physician global assessment of disease activity, vasculitis activity index and C-reactive protein. It is repeatable, reproducible and sensitive to change. The new version of BVAS is validated for assessment of systemic vasculitis.

The systemic vasculitides are heterogeneous conditions resulting in inflammation of blood vessels. They can be primary, or secondary to other autoimmune conditions, drugs or infections.<sup>1-3</sup> Depending on the size of the blood vessels involved and the organ distribution of the vasculitis, the primary systemic vasculitides are classified into discrete clinical syndromes.<sup>4</sup> Systemic vasculitis commonly involves multiple organ systems and can present to any specialty. There are no absolute tests or clinical criteria for diagnosing vasculitis. The biopsy yield depends on the sampled organ and varies considerably.<sup>5-7</sup> Pattern recognition and a standardised assessment technique assists diagnosis and monitoring of these conditions (reviewed by Nataraja *et al*).<sup>8</sup>

The Birmingham Vasculitis Activity Score (BVAS) was validated for assessment of disease activity in systemic vasculitis in 1994.<sup>9</sup> It was modified in 1997—BVAS(v.2)—for use in collaborative European trials; and again in 2001 to produce a disease-specific instrument for Wegener's granulomatosis (BVAS/WG).<sup>10-11</sup> BVAS(v.2) has been used in clinical trials for assessment of disease activity, defining entry criteria, defining remission and relapse and as an outcome measure.<sup>12-16</sup> The European League Against Rheumatism (EULAR) recommendations for the conduct of clinical trials in systemic vasculitis advocate the use of the BVAS to standardise disease assessment in clinical trials.<sup>17</sup> BVAS(v.2) may have prognostic value; patients with a high BVAS(v.2) at diagnosis may have a greater risk of mortality.<sup>9</sup> BVAS(v.2) has been shown to have a strong correlation with the five factor score (Spearman correlation coefficient ( $r_s$ ) 0.69).<sup>18</sup>

BVAS(v.2) is a list of 66 manifestations of systemic vasculitis, divided into nine organ-based systems. Each item can either be "new or worse" if it has presented, recurred or worsened within the previous 4 weeks, or "persistent" if it is present but not worse than in the previous 4 weeks. The manifestations have to be attributable to active vasculitis because they may be due to sequelae of previous activity, drug induced, or due to comorbidities. Lack of attribution may cause spurious elevation of the BVAS. Each item has a predetermined numerical score, which may be different depending on whether an item is new/worse or persistent. Each organ system has a predetermined ceiling score. The sum of the scores of all the organ systems reflects disease activity. The BVAS(v.2) generates two scores; BVAS1 reflects new or worse disease, and BVAS2 reflects persistent disease.

## The need for revision

Most recent clinical trials in vasculitis have used a BVAS1 of zero as a definition of remission. (reviewed by Mukhtyar *et al*).<sup>19</sup> Ignoring BVAS2 (persistent disease) underestimates true disease activity. This has therapeutic implications because persistent disease needs a different approach.<sup>16</sup> Redundant and/or uncommon items have been identified in BVAS(v.2).<sup>20</sup> Removal of those items would increase the feasibility of the modified clinical tool.

## Aim

To validate a new version of BVAS for use in studies of systemic vasculitis.

## Extended report

## METHODS

The new clinical tool (see supplementary online appendix) was designed by consensus (face validity).<sup>20</sup> The number of items was reduced from 66 in BVAS(v.2) to 56 in BVAS(v.3) either by omission or by merging with other items. The “persistent” boxes for each item were replaced by a single “persistent” box for the whole form. This box was marked, only if every disease manifestation was attributable to “persistent” disease. All items were treated as “new/worse” if any of them were “new/worse”. Disease manifestations were recorded if they had been active in the previous 4 weeks, and were directly attributable to vasculitis.

Weighting was largely unchanged, but new items were given weights by consensus. An extensive glossary and manual of operations was constructed. The BVAS(v.3) forms, training manual and glossary sheet are available online at the EUVAS website (<http://www.vasculitis.org/disease.htm>, accessed 13 July 2009).

Nineteen subjects completed 20 beginner-level training paper cases, and 14 of them, including all investigators recruiting patients for this study, completed 40 advanced-level paper cases. This paper-case exercise had two benefits; it trained each investigator in the use of BVAS(v.3) and provided information on interobserver reliability.

**Inclusion criteria:** Patients seen in outpatient clinics and hospital wards with a probable or definite diagnosis of systemic vasculitis, of any duration, at any stage of their disease, were recruited from nine UK centres: Birmingham (Birmingham City Hospital), Cambridge (Addenbrooke’s Hospital), Edinburgh (Western General Hospital), Norfolk (Norfolk and Norwich University Hospital), Nottingham (Nottingham University Hospital), Oxford (Oxford Radcliffe Hospitals and Nuffield Orthopaedic Centre), Reading (Royal Berkshire Hospital) and Westcliff-on-sea (Southend General Hospital). The investigators were rheumatologists (CM, DC, SD, PL, LY, RAL), nephrologists (OF, DJ, RJ), or allied health professionals with an interest in vasculitis (DB, CH, JH, AM).

**Exclusion criteria:** Patients with a probable or definite diagnosis of giant cell arteritis were excluded.

The study was approved by local ethics committees and all patients gave written informed consent. The data recorded on a standardised case record form included demographics, diagnosis, treatment in the previous 5 years, serum C-reactive protein (CRP), serum creatinine, antineutrophil cytoplasmic antibody (ANCA) status with titres and antibody levels, BVAS(v.3), treatment decision, physician’s global assessment (100 mm visual analogue scale), vasculitis activity index (five-point Likert scale, with 0 signifying remission and 4 suggesting maximum activity). Patients in Oxford and Edinburgh were also assessed using BVAS(v.2) at the same visit. Table 1 shows the treatment decisions classified into six ordered categories. When treatment decisions did not match the definitions, the category was jointly assigned by RAL and CM. The BVAS values for both versions were calculated on a Microsoft Excel based program developed by CM.

Convergent validity was assessed by examining the association of BVAS(v.3) with

- ▶ BVAS1 subscore of BVAS(v.2) in patients who were assessed using both clinical instruments at the same hospital visit;
- ▶ treatment decision (table 1);
- ▶ nearest serum CRP level within 1 month of the consultation (when values were reported to be less than the lowest measurable value for that laboratory, the value was recorded as 0 mg/l for the purpose of statistical analysis);

**Table 1** Definitions of treatment decision categories

Category	Definition
Major escalation	<ul style="list-style-type: none"> <li>▶ Starting any immunosuppressive agent, glucocorticoid or plasmapheresis, without stopping or reducing the dose of any other treatment</li> <li>OR</li> <li>▶ Increasing the dose of glucocorticoid and immunosuppressive agent</li> </ul>
Continue at major level	▶ No change to a therapeutic regimen which includes treatment with cyclophosphamide or biological agents
Minor escalation	▶ Increasing the dose of immunosuppressive agent or glucocorticoid
Continue at minor level	▶ No change to a therapeutic regimen which excludes treatment with cyclophosphamide and biological agents
Reduction of treatment	▶ Reduction or stopping of one or more drugs without increasing or starting any other drug
No treatment	▶ No treatment

- ▶ physician’s global assessment;
- ▶ vasculitis activity index.

The ability of the BVAS(v.3) to record persistent disease was assessed in patients with persistent disease on a follow-up assessment with BVAS(v.2). They were defined as having persistent disease if the BVAS2 subscore was higher than the BVAS 1 subscore.

Interobserver reliability (reproducibility) of BVAS(v.3) was examined in patients independently assessed by two observers on the same day. This was also assessed in the paper-case exercise.

Intraobserver reliability (repeatability) of BVAS(v.3) was examined in the subgroup of patients with a second assessment by the same observer within 9 days of the first assessment.

Sensitivity of BVAS to a change in disease state was assessed in a separate cohort of patients with a new diagnosis of ANCA-associated vasculitis. Thirty-nine patients were assessed at diagnosis and at 3 months using the BVAS(v.3), following treatment which was categorised as “major escalation” (table 1). It was expected that the patients would improve with the treatment and the change in BVAS was assessed as a marker of sensitivity to change in disease status.

## Statistical analysis

The Spearman rank correlation coefficient was used to assess the association of BVAS(v.3) with subscores of BVAS(v.2), treatment decision, serum CRP levels, physician’s global assessment and vasculitis activity index. Reliability of the BVAS(v.3) was assessed using the intraclass correlation coefficient (ICC), and the linear weighted  $\kappa$  statistic for the organ-system subscores. Sensitivity to change was assessed by paired t test comparing BVAS(v.3) scores at 0 and 3 months. The statistical analysis was performed using SPSS 15.0 except for the linear weighted  $\kappa$  analysis which was performed using an online statistics package (<http://faculty.vassar.edu/lowry/VassarStats.html>, accessed 13 July 2009).

## RESULTS

Three hundred and thirteen patients with systemic vasculitis were recruited between 28 July 2004 and 11 December 2007. The mean (SD) age of the cohort was 55.0 (15.9); range 18–87

**Table 2** Demographics of the cohort

Diagnosis	No	Gender M/F	Median age (lower quartile, upper quartile)	Median duration in months (lower quartile, upper quartile)	ANCA by indirect immunofluorescence†	
					cANCA	pANCA
Takayasu arteritis	9	0/9	37 (32, 58.5)	49 (30, 150)		
Polyarteritis nodosa	10	5/4*	62 (30.5, 67)	60.5 (45, 85.5)		
Wegener's granulomatosis	155	82/72*	58 (45, 68)	55.5 (12, 113)	45	4
Churg–Strauss syndrome	28	17/11	59 (48, 61)	60 (12, 120)	3	3
Microscopic polyangiitis	15	8/7	68 (58, 76)	12 (3, 36)	0	7
Henoch–Schönlein purpura	10	7/3	45 (34, 61)	39 (19, 66)		
Cryoglobulinaemic vasculitis	6	1/5	69.5 (65, 82)	9 (0, 132)		
Cutaneous vasculitis	11	3/8	45 (22, 67)	48 (36, 78)		
Behçet disease	25	10/15	42 (35.5, 48)	102 (40, 165)		
Cerebral vasculitis	9	3/6	56 (52.5, 62)	1 (0, 27)		
Rheumatoid vasculitis	8	3/5	69.5 (65.5, 76)	16.5 (4, 39)		

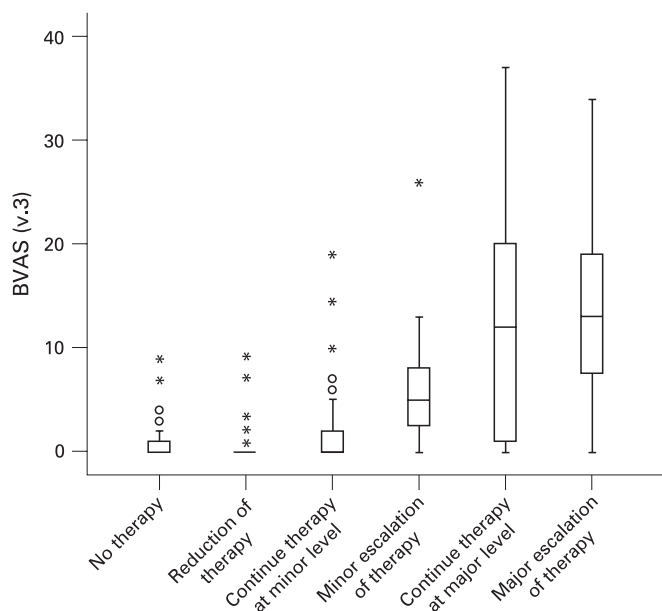
\*Gender was not recorded for one patient; †of the 198 patients with ANCA-associated vasculitis (Wegener's granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome), 102 were tested for ANCA within 30 days of the Birmingham Vasculitis Activity Score assessment, 67 were positive; the ANCA pattern in five patients was not recorded. ANCA, antineutrophil cytoplasmic antibody; cANCA, cytoplasmic pattern; pANCA, perinuclear pattern.

years. There were 162 women (52%), and 149 men (48%). Table 2 shows the demographics of the cohort. The median disease duration was 3.8 years (lower and upper quartiles 1.0, 8.7 years). The median BVAS(v.3) was 2 (for histogram see supplementary online figure 1).

### Convergent validity

Of 313 patients, 302 had a recorded treatment decision. There was a correlation between the treatment decision and the BVAS(v.3) (Spearman's correlation coefficient ( $r_s$ ) = 0.66, 95% CI 0.59 to 0.72) (fig 1). Subgroup analysis in 153 patients with Wegener's granulomatosis revealed a similar correlation ( $r_s$  = 0.72, 95% CI 0.64 to 0.79) (see supplementary online fig 2).

One hundred and thirty-eight patients were assessed using the BVAS(v.2) and the BVAS(v.3). The correlation between the

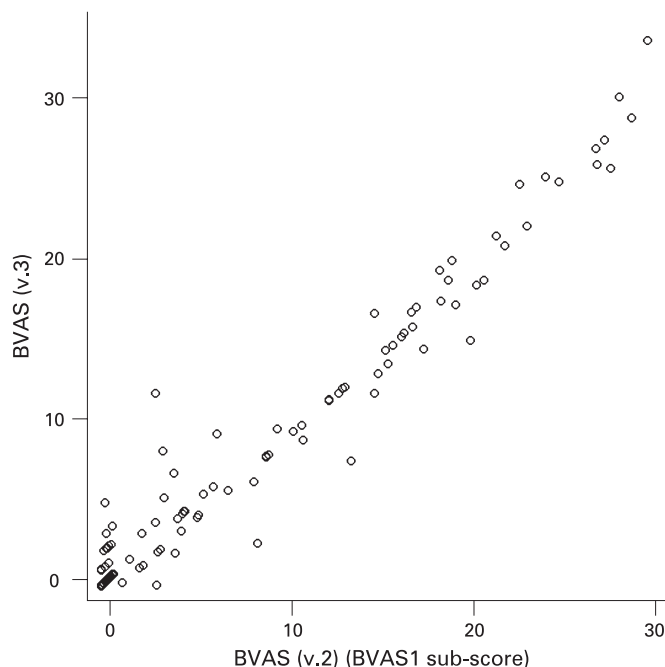


**Figure 1** Correlation between treatment decision and the Birmingham Vasculitis Activity Score (version 3) (BVAS(v.3)).

BVAS(v.3) and the BVAS1 subscore was strong ( $r_s$  = 0.94, 95% CI 0.92 to 0.96) (fig 2). On follow-up, 19 patients were found to have persistent disease. Assessment with BVAS(v.2) and BVAS(v.3) at the same consultation demonstrated a strong correlation between BVAS(v.3) and the BVAS2 subscore of BVAS(v.2) ( $r_s$  = 0.60, 95% CI 0.21 to 0.83).

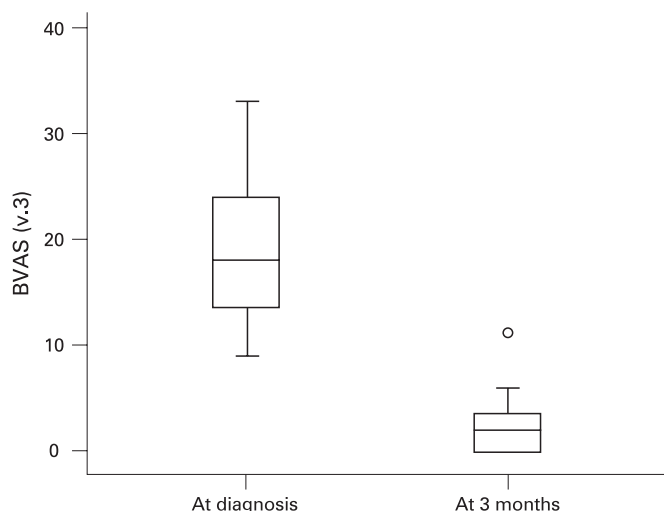
One hundred and eighty-five patients had CRP levels available within 4 weeks of their BVAS assessment. There was a moderate correlation between BVAS(v.3) and CRP levels ( $r_s$  = 0.43, 95% CI 0.31 to 0.54) (see supplementary online fig 3).

A strong correlation of BVAS(v.3) was demonstrated with a physician's global assessment available for 307 patients ( $r_s$  = 0.91, 95% CI 0.89 to 0.93) (see supplementary online figure 4), and a five-point Likert scale vasculitis activity index



**Figure 2** Correlation between the Birmingham Vasculitis Activity Score (version 3) (BVAS(v.3)) and the BVAS1 subscore.

## Extended report



**Figure 3** Birmingham Vasculitis Activity Score (version 3) (BVAS(v.3)) at diagnosis and at 3 months.

available for 304 patients ( $r_s = 0.88$ , 95% CI 0.86 to 0.91) (see supplementary online fig 5).

### Reliability

Reproducibility of BVAS(v.3) for the 20 basic-level paper cases completed by 19 observers was high with an ICC of 0.89 (95% CI 0.81 to 0.94). In the 40 advanced level paper cases completed by 14 observers the reproducibility was high with an ICC of 0.95 (95% CI 0.93 to 0.97).

In the 99 patients independently assessed by two observers on the same day the reproducibility of BVAS(v.3) was high with an ICC of 0.96 (95% CI 0.95 to 0.97). The reproducibility as measured by the linear weighted  $\kappa$  statistic was high for each of the nine organ-system subscores with the lowest weighted kappa being 0.78 ( $\kappa$  scores available as online supplementary table 1).

Repeatability of BVAS(v.3) in 39 patients assessed twice within 9 days, by the same investigator was high with an ICC of 0.96 (95% CI 0.92 to 0.97). A linear weighted  $\kappa$  statistic for the organ-system subscores showed good repeatability, minimum linear weighted  $\kappa$  was 0.75 ( $\kappa$  scores available as online supplementary table 1).

### Sensitivity to change in disease status

Thirty-nine patients with a new diagnosis of ANCA-associated vasculitis (11 microscopic polyangiitis, 8 renal limited vasculitis, 20 Wegener's granulomatosis) were assessed at diagnosis and 3 months using the BVAS(v.3). Each patient received treatment classified as "major escalation" (table 1). At diagnosis the mean (SD) BVAS(v.3) was 18.92 (6.06). Three months after treatment, the mean (SD) BVAS(v.3) fell to 2.03 (2.48) (fig 3). The mean fall in BVAS(v.3) of 16.9 (95% CI 14.8 to 18.9) was statistically significant ( $p < 0.001$  using paired t test). During this period the mean fall in the CRP levels was 40.0 (95% CI 15.4 to 64.7) mg/l.

### DISCUSSION

We have shown in this study that BVAS(v.3) has face validity, convergent validity with a number of parameters, and it is repeatable, reproducible and sensitive to changing disease states. In comparison with the previous validation studies of BVAS, this study is more robust, having larger patient numbers, wider breadth of vasculitis syndromes and a comparison with a higher number of parameters (table 3). Like previous validation exercises, we have not included assessment of giant cell arteritis. Giant cell arteritis is a distinct clinical syndrome with a limited range of abnormalities as measured using BVAS items. This homogeneity of clinical manifestations would produce a limited range of scores and is not conducive to activity assessment using BVAS.

The BVAS(v.3) was designed by consensus of a multispecialty group of vasculitis experts. It is a list of 56 items considered to be vasculitis manifestations with a numerical weight attached to each item, and each organ system has a ceiling score. These scores reflect the proportional importance of each manifestation and each organ system. This design of the BVAS(v.3) satisfies the conditions to meet "face validity".

An ideal clinical tool should possess the ability to differentiate between diseases and/or disease states of interest. This ability of BVAS(v.3) can potentially be assessed in three different ways: first, the ability to differentiate between vasculitis and other conditions; second, the ability to differentiate active disease from damage; and lastly, the ability to differentiate between active disease, persistent disease and remission. The first two abilities are difficult to test owing to the rules governing the scoring of the BVAS(v.3). The marking of any manifestation on the BVAS sheet requires the doctor to be able to attribute its

**Table 3** Comparison of this study with other validation studies of different versions of the Birmingham Vasculitis Activity Score (BVAS)

Characteristics	This study	Luqmani, 1994 <sup>8</sup>	Stone, 2001 <sup>11</sup>
No of patients in the study	313	213	117
Face validity	✓	✓	✓
Convergent validity			
Treatment decision	$r_s = 0.66$	–	–
Other validated score	$r_s = 0.92$ with BVAS(v.2)	T = 0.29 with Kallenberg index	–
C-reactive protein level	$r_s = 0.43$	–	–
Physician's global assessment	$r_s = 0.91$	T = 0.35*	$r_s = 0.92$
Vasculitis activity index	$r_s = 0.88$	T = 0.56	–
Repeatability in real patients	ICC = 0.96	–	–
Reproducibility in real patients	ICC = 0.96	✓ (No statistic done)	ICC = 0.97
Sensitive to change in disease states	✓	✓	✓

The assessments for each form of validation were conducted on a subset of the whole cohort in each of the three studies. Absent values denote that the test was not performed.

\*Not statistically significant.

✓, correlation was looked for and concluded to be positive; ICC, intraclass correlation coefficient;  $r_s$ , Spearman rank correlation coefficient; T, Kendall rank correlation coefficient.

presence to active vasculitis. Strict application of this rule would automatically give all patients without vasculitis a score of zero, creating a spurious difference. In 39 patients we assessed the sensitivity of BVAS(v.3) to a change in disease status. In the absence of a valid external comparator, it is difficult to interpret a change in BVAS, but a fall of over 16 units is clinically meaningful. This improvement in clinical assessment was associated with a fall in CRP levels. There is no relationship between the magnitudes of change for the BVAS(v.3) and the CRP levels.

The BVAS(v.3) correlates only moderately with the CRP. This suggests that the inflammatory response is of value in making treatment decisions, but only in the correct clinical context. For example, the subject with the highest BVAS in our study (BVAS = 37) had active disease in five organ systems but had a CRP of <10 mg/l. Potential causes for this moderate correlation include—generation of CRP due to causes other than vasculitis, and treatment in the preceding 4 weeks producing a spuriously low CRP at the time of recruitment. A previous study did not find any correlation between CRP and disease activity.<sup>21</sup> This study demonstrates an excellent correlation between the physician's global assessment and the BVAS(v.3) score. This result is consistent with the results of Stone 2001,<sup>11</sup> but not with those of Luqmani 1994 (table 3).<sup>9</sup> This discrepancy can be explained by a fundamental difference in the way in which the exercise was carried out in the three studies. In Luqmani 1994, the physician's global assessment and the BVAS assessment were independently done by two investigators. In this study, as in Stone 2001, the physician's global assessment was performed by the same investigator after the BVAS assessment. It can be concluded that a physician's global assessment in itself may not correlate significantly with disease activity, but a physician's global assessment informed by the completion of a structured clinical interview and examination would have a good correlation with disease activity.

The BVAS(v.3) correlates with the treatment decision, but this correlation is not absolute. Of 67 patients who had a "major escalation" of their treatment, 12 had a BVAS(v.3) <5. This may be due to two reasons. First, initial treatment with prednisolone may have reduced disease activity. If the patient was recruited more than 4 weeks after the onset of symptoms, disease activity would be low but the start of an immunosuppressive maintenance regimen would be classified as "major escalation", resulting in a discrepancy. Second, a rise of a few units may be a major flare in patients with certain vasculitis syndromes needing major escalation of treatment.

The BVAS(v.2) has been the "gold standard" for assessment of disease activity in clinical trials of systemic vasculitis. The excellent correlation between the two clinical tools makes the BVAS(v.3) a better tool owing to its ability to record persistent disease activity without the need for a separate subscore and its relative ease of use. It does not take any more time to complete than a structured clinical assessment. We have designed a Microsoft Excel based BVAS calculator which offers free online scoring of the BVAS at our website <http://www.ndos.ox.ac.uk/research/rluqmani> (accessed 13 July 2009). The calculator is a modification of the Microsoft excel programme developed for this study.

The BVAS(v.3), in common with all structured clinical assessments in vasculitis requires initial training, for which we have made the training manual freely available online at <http://www.vasculitis.org/disease.htm>. Training ensures that clinical observers, irrespective of their specialty, agree on what to score as directly attributable to active vasculitis.

The BVAS(v.3) is validated and ready for use in clinical trials. The focus of the BVAS has always been on clinical trials, but it may be of value in daily clinical practice. There is evidence that relapse of disease activity can occur in a previously unaffected organ system, so routine clinical examination and interview should be comprehensive and structured.<sup>22</sup> The BVAS(v.3) serves as a checklist of items to screen for in daily practice. In the past, the complex scoring system has deterred routine clinical use of the BVAS, but the online BVAS calculator resolves that problem. With adequate prior training in the use of BVAS(v.3), the specialist and the general doctor can use the online calculator to convert disease activity into a tangible score giving them an accurate idea of the disease activity of their patient.

Disease-specific clinical assessment tools for vasculitis have been developed for Wegener's granulomatosis (BVAS/WG) and Takayasu arteritis (Indian Takayasu Arteritis Score).<sup>11 23</sup> These clinical tools may be more specific than BVAS when used for assessing disease activity in those conditions, although this has not been formally tested. However, early disease may not be accurately classifiable or the vasculitis syndrome may have overlap features.<sup>24 25</sup> In these situations, the BVAS(v.3) may be used in preference to the disease-specific clinical assessment tools. The magnitude of activity as suggested by the BVAS(v.3) is not comparable across well-differentiated vasculitis syndromes, especially when they do not involve blood vessels of similar calibre, consistent with previously reported data.<sup>9</sup> However, disease-specific modules could be developed to supplement BVAS, especially for diseases with a limited number of systems involved such as Takayasu arteritis. By retaining a generic set of items, it will be possible to compare core data between different vasculitis syndromes in order to provide more information on the long-term status of patients with systemic vasculitis, who now have a much improved life expectancy as a result of modern treatment. There may be a relationship between BVAS(v.3) and mortality but this could not be examined in our cross-sectional study.

Inevitably, with more extensive use, this version of BVAS may require editing and revision, as would be expected in any biological measurement. However, BVAS (v3) currently represents a robust and useful tool for standard assessment of systemic vasculitis.

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**Ethics approval:** Approval from the multicentre research ethics committee.

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### **APPENDIX 3**

Mukhtyar C, Flossmann O, Hellmich B, Bacon P, Cid M, Cohen-Tervaert JW, Gross WL, Guillevin L, Jayne D, Mahr A, Merkel PA, Raspe H, Scott D, Witter J, Yazici H, Luqmani RA; European Vasculitis Study Group (EUVAS). Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force. *Ann Rheum Dis*. 2008 Jul;67(7):1004-10.



# Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force

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## ABSTRACT

**Objectives:** We undertook a systematic literature review as a background to the European League Against Rheumatism (EULAR) recommendations for conducting clinical trials in anti-neutrophil cytoplasm antibody associated vasculitis (AAV), and to assess the quality of evidence for outcome measures in AAV.

**Methods:** Using a systematic Medline search, we categorised the identified studies according to diagnoses. Factors affecting remission, relapse, renal function and overall survival were identified.

**Results:** A total of 44 papers were reviewed from 502 identified by our search criteria. There was considerable inconsistency in definitions of end points. Remission rates varied from 30% to 93% in Wegener granulomatosis (WG), 75% to 89% in microscopic polyangiitis (MPA) and 81% to 91% in Churg–Strauss syndrome (CSS). The 5-year survival for WG, MPA and CSS was 74–91%, 45–76% and 60–97%. Relapse (variably defined) was common in the first 2 years but the frequency varied: 18% to 60% in WG, 8% in MPA, and 35% in CSS. The rate of renal survival in WG varied from 23% at 15 months to 23% at 120 months. Methods used to assess morbidity varied between studies. Ignoring the variations in definitions of the stage of disease, factors influencing remission, relapse, renal and overall survival included immunosuppressive therapy used, type of organ involvement, presence of ANCA, older age and male gender.

**Conclusions:** Factors influencing remission, relapse, renal and overall survival include the type of immunosuppressive therapy used, pattern of organ involvement, presence of ANCA, older age and male gender. Methodological variations between studies highlight the need for a consensus on terminology and definitions for future conduct of clinical studies in AAV.

Outcome measures in primary small vessel vasculitis help to describe the natural history of treated disease. Cyclophosphamide and glucocorticoids have reduced mortality in antineutrophil cytoplasm antibody (ANCA) associated vasculitides (AAV), although cure remains uncommon.<sup>1</sup> The 5-year survival of treated AAV is over 70%,<sup>2–5</sup> but relapse and low grade persistent disease result in poor quality survival.<sup>4 6–8</sup> There is an increased focus on preserving target organ function.<sup>3 9 10</sup>

Terms used to describe and quantify different disease states have been inconsistent. Methodological agreement is important to enable inter-study comparison, and enable uniform management in future studies.

We undertook a systematic literature review to define disease specific outcomes in primary systemic vasculitis, and the factors affecting them. We concentrated on remission, relapse, renal survival and mortality. This systematic review forms the basis of recently published recommendations for conducting clinical studies in vasculitis.<sup>11</sup>

## METHODS

### Search methods

We identified the following medical subject headings (MeSH) in the indexing database of Medline through PubMed to construct our search: “Antibodies, Antineutrophil cytoplasmic”, “Vasculitis”, “Wegener Granulomatosis” (WG), “Churg–Strauss Syndrome” (CSS), “Epidemiologic Study Characteristics”, “Evaluation Studies” and “Study characteristics”. “Microscopic polyangiitis” (MPA) is not a MeSH term, therefore it was used as a free text phrase to be used in “all fields”. The search identified 832 citations, excluding case reports. These were limited by the terms “Adult” and “Abstracts” to 502 results, but there were no limits by time or language. A search of the Cochrane library did not produce any additional papers. No manual searching of papers was performed.

### Selection criteria

From 502 papers identified, 44 were selected using the following criteria:

- ▶ >20 patients per cohort/arm of a study.
- ▶ Disease specific subanalysis in heterogeneous cohorts (one paper did not meet this criterion, but was included because the cohort had 94% homogeneity).<sup>12</sup> Papers were ignored if the patient population was defined by their serological status only, without a specific diagnosis.
- ▶ Relevant outcome data.
- ▶ Multivariate analysis for risk factors affecting the outcomes.
- ▶ Elimination of duplicate data.

## Data analysis

Patients were classified as WG, MPA and CSS as described in the articles. The identified risk factors for outcomes have been awarded a level of evidence according to European League Against Rheumatism (EULAR) standardised operating procedures.<sup>13</sup> We discussed the variability in terminology, outcomes and risk factors affecting the outcomes.

## RESULTS

### Methodological quality of the studies

A total of 44 papers met the selection criteria; 25 were retrospective studies. Of the 19 prospective studies, 6 were randomised controlled trials.<sup>12 14–18</sup> Three of these trials had heterogeneous cohorts,<sup>12 14 18</sup> and only one had disease specific analysis.<sup>18</sup>

### Wegener granulomatosis

#### Remission

The remission rate for WG (table 1) ranges from 30% to 93% depending on the definition of remission and remission induction therapy.<sup>1 3 12 15 19–23</sup> The definition of remission varied from “commencement of clinical improvement”, to “complete absence of disease manifestations for at least 6 months”. In most studies, the time to achieve remission (where stated) is less than 6 months. The heterogeneity of remission induction therapy and the definition of remission make this data difficult to interpret.

#### Factors affecting remission

Two main factors affected remission. Firstly, in a retrospective study, severe disease as defined by a Birmingham Vasculitis Activity Score (BVAS) of >23, was associated with an increased likelihood of achieving remission independent of treatment intensity; relative hazard (RH) 2.94, 95% CI 1.48 to 5.85, level of evidence = 3.<sup>23</sup> This finding may reflect increased responsiveness of severe disease to immunosuppression. Patients with higher activity have poorer survival.<sup>24 25</sup> It is possible to have life threatening disease, responsive to treatment. Subsequent studies have not re-examined this relationship.

Secondly, in a retrospective cohort, each 1-point increase in the Vasculitis Damage Index (VDI) score increased treatment resistance; odds ratio (OR) 1.53 (95% CI 1.03 to 2.27), level of evidence = 3.<sup>25</sup> Damage occurred early in disease,<sup>26</sup> and its presence may have influenced the definition of remission in this study, but it is likely that damage makes disease less responsive to therapy.

#### Relapse

Relapse was common in WG (table 2). The rate (18–40% at 24 months) and time to first relapse (15 to 29 months) varied.<sup>1 14–17 20 23 27–32</sup> This variability may be spurious (due to differing definitions of relapse) or genuinely due to differing remission maintenance therapies or the presence or absence of risk factors for relapse (table 3).

#### Factors associated with relapse

Three factors were associated with relapse. The first was treatment; receiving <10 g (compared to ≥10 g) of cyclophosphamide in the first 6 months was associated with an increased relapse rate (relative risk (RR) 2.83, 95% CI 1.33 to 6.02) despite maintenance of immunosuppression.<sup>23</sup> Patients who tolerated oral cyclophosphamide 2 mg/kg/day received >10 g in 6 months (10 g in 6 months = 55 mg/day). For intravenous therapy, three regimens have been used in trials: (a) 15 mg/kg/pulse, first three pulses twice weekly, then every 3 weeks;<sup>34</sup> (b) 0.7 g/m<sup>2</sup> thrice weekly;<sup>15</sup> and (c) 0.75 g/m<sup>2</sup>/month.<sup>35</sup>

At a maximum of 1 g/pulse, only regimen (a) can deliver 10 g of cyclophosphamide in 6 months. This regimen is being validated in a prospective study.<sup>36</sup>

Maintaining a high dose of prednisolone (>20 mg/day) for less than 2.75 months increases risk of relapse (RH 2.41, 95% CI 1.12 to 5.21). This supports the current use of intensive initial therapy.

The use of adjunctive trimethoprim/sulfamethoxazole 160/800 mg twice daily, maintained remission for longer (RR 0.32, 95% CI 0.13 to 0.79),<sup>16</sup> but resulted in a withdrawal rate of 20%.<sup>16</sup> However, trimethoprim/sulfamethoxazole as monotherapy for remission maintenance had a higher relapse rate in

**Table 1** Rates of remission from studies of Wegener granulomatosis (WG) with definitions of remission and the remission induction therapy

Author	Study	Size (n)	Remission rate (%)	Time to remission	Remission induction therapy	Definition of remission
Hoffman <i>et al</i> 1992 <sup>1</sup>	P	133	75	NA	Oral daily CYC (2 mg/kg/day) + Pred (1 mg/kg/day, tapered after 2–4 weeks)	Complete absence of disease
Reinhold-Keller <i>et al</i> 1994 <sup>19</sup>	P	43	30	NA	CYC iv (mean 667 mg/m <sup>2</sup> /month) + iv Pred 100 mg +/- oral Pred	Complete absence of disease for 6 months
Sneller <i>et al</i> 1995 <sup>20</sup>	P	42	71	4.2 months (median)	MTX (20–25 mg/week) + Pred 1 mg/kg/day	Complete absence of disease
Guillevin <i>et al</i> 1997 <sup>15</sup>	P	27	89	6 months	CYC iv (0.7 g/m <sup>2</sup> thrice weekly) + Pred 1 mg/kg/day	Clinical improvement
		23	78	6 months	Oral daily CYC (2 mg/kg) + Pred 1 mg/kg/day	
Aasarod <i>et al</i> 2000 <sup>3</sup>	R	108	81	4 months (median)	Heterogeneous regimens	Complete absence of disease
Reinhold-Keller <i>et al</i> 2000 <sup>21</sup>	P	155	54	NA	Heterogeneous regimens	Complete absence of disease for 3 months
Bolley <i>et al</i> 2000 <sup>22</sup>	R	38	68	NA	Heterogeneous regimens	Undefined
Koldingsnes and Nossent 2003 <sup>23</sup>	R	52	85	NA	Heterogeneous regimens	Complete absence of disease
De Groot <i>et al</i> 2005* <sup>12</sup>	P	49	90	3 months (median)	MTX (20–25 mg/week) + Pred 1 mg/kg/day	BVAS 1 = 0 and BVAS 2 < 2
		46	93	2 months (median)	Oral CYC 2 mg/kg/day + Pred 1 mg/kg/day	

\*There were six patients with MPA in this cohort, divided between the two arms.

BVAS, Birmingham Vasculitis Activity Score (score 1 is for active disease and score 2 is for persistent disease); CYC, cyclophosphamide; iv, intravenous; MPA, microscopic polyangiitis; MTX, methotrexate; P, prospective; Pred, prednisolone; R, retrospective.

**Table 2** Incidence of relapse from studies of Wegener granulomatosis (WG) with definition of relapse and the remission maintenance regimen

Author	Study	Size (n)	Relapse rate	Time to relapse	Maintenance regimen	Definition of relapse
Hoffman <i>et al</i> 1992 <sup>1</sup>	P	98	56% at 60 months	NA	Heterogeneous regimen	Undefined
Sneller <i>et al</i> 1995 <sup>20</sup>	P	30	36% at 29 months	29 months	MTX 20–25 mg/week + tapering Pred	Reappearance of disease
Reinhold-Keller <i>et al</i> 1996 <sup>27</sup>	P	24	42% at 13 months	NA	TMP + SMX (2×960 mg/day)	Undefined
		21	29% at 23 months	NA	None	
Stegeman <i>et al</i> 1996*	P	41	18% at 24 months	NA	TMP/SMX (2×960 mg/day) + standard therapy	Reappearance of disease
		40	40% at 24 months	NA	Placebo + standard therapy	
Guillevin <i>et al</i> 1997 <sup>15</sup>	P	24	59% at 54 months	NA	CYC iv (0.7 g/m <sup>2</sup> thrice weekly) + tapering Pred	Reappearance of major disease manifestation
Haubitz <i>et al</i> 1998 <sup>28</sup>	R	35 (with ESRD)	49% at 41 months	NA	Heterogeneous regimens	Reappearance of disease
Boomsma <i>et al</i> 2000 <sup>29</sup>	P	100	37% at 35 months	NA	Heterogeneous regimens	Undefined
Fauchais <i>et al</i> 2001 <sup>30</sup>	R	35	60% at 39 months	NA	Heterogeneous regimens	Undefined
Koldingsnes and Nossent 2003 <sup>23</sup>	R	52	60% at 42.5 months	18 months	Heterogeneous regimens	Reappearance of disease after complete or partial remission
Langford <i>et al</i> 2003 <sup>31</sup>	P	42	52% at 32 months	15 months	MTX 20–25 mg/week	Reappearance of disease
Jayne <i>et al</i> 2003 <sup>14</sup>	P	92	18% at 18 months	NA	AZA 2 mg/kg OR CYC 1.5 mg/kg + Pred 10 mg/day	Reappearance of one major or three minor BVAS items
WGEM 2005 <sup>†17</sup>	P	89	30% at 25 months	NA	Eta 25 mg s/c twice weekly + standard therapy	Reappearance of an item on the BVAS/WG
		85	25% at 19 months	NA	Placebo + standard therapy	
Pavone <i>et al</i> 2006 <sup>32</sup>	R	36	16% at 12 months	NA	Heterogeneous regimens	Reappearance of disease requiring immunosuppressive therapy
		36	26% at 24 months			

Where defined, relapse was considered only after achievement of remission.

\*Standard therapy was cyclophosphamide and/or prednisolone. It was not offered to all patients, there were no differences in the number of patients on standard therapy in each arm. †Standard therapy was methotrexate or azathioprine depending on renal function, for 12 months following remission.

AZA, azathioprine; BVAS, Birmingham Vasculitis Activity Score (Score 1 is for active disease and score 2 is for persistent disease); BVAS/WG, BVAS for Wegener granulomatosis; CYC, cyclophosphamide; ESRD, end-stage renal disease; Eta, etanercept; iv, intravenous; MTX, methotrexate; NA, not available; P, prospective; Pred, prednisolone; R, retrospective; s/c, subcutaneous; TMP + SMX, trimethoprim + sulphamethoxazole.

comparison to conventional remission maintenance therapy (18% at 18 months with CYC 1.5 mg/kg/day or AZA 2 mg/kg/day in combination with prednisolone 10 mg/kg/day; 42% at 23 months with trimethoprim/sulphamethoxazole monotherapy).<sup>14 27</sup>

The second factor was ANCA; presence of ANCA at diagnosis conferred an increased risk of relapse (RR 2.89, 95% CI 1.12 to 7.45).<sup>16</sup> ANCA are likely to be important in the pathogenesis of disease,<sup>37 38</sup> absence may represent a milder disease less prone to relapse.

In patients who had been positive for ANCA, a fourfold rise in cytoplasmic (C)/proteinase 3 (PR3) ANCA predicted subsequent relapse (RR 42.5, 95% CI 9.48 to 180.8).<sup>29</sup> However, about a third of patients did not suffer a relapse.<sup>29</sup> Aggressive treatment solely on the basis of a rise in ANCA titres would expose patients to unnecessary cytotoxic therapy. Persistence of ANCA at the onset of remission has been associated with a high

risk of relapse in mixed cohorts.<sup>39</sup> Serial ANCA testing for guiding therapy remains controversial; a meta-analysis of 22 studies could not reach a conclusion about the value of serial ANCA testing due to the heterogeneity in the assay methodologies.<sup>40</sup>

The final factor was target organ involvement. Cardiac involvement increased risk of relapse (RH 2.87, 95% CI 1.09 to 7.58;  $p = 0.03$ ).<sup>23</sup> A creatinine clearance >60 ml/min was associated with an increased risk of relapse (RR 2.94, 95% CI 1.27 to 6.67;  $p = 0.01$ );<sup>33</sup> perhaps due to non-renal, granulomatous disease (for example otolaryngological involvement), which is more prone to relapse.<sup>41</sup> Chronic nasal carriage of *Staphylococcus aureus* was an independent risk factor for relapse (RR 7.16; 95% CI 1.63 to 31.50;  $p = 0.009$ ).<sup>33</sup> The presence of *S aureus* may provide a nidus of inflammation required by ANCA to produce an inflammatory response.<sup>38</sup>

**Table 3** Factors associated with Wegener granulomatosis (WG) relapse with level of evidence

Risk factor	Risk of relapse	Level of evidence	Reference
A fourfold rise in C ANCA/PR3 ANCA titre	RR 42.5 (95% CI 9.48 to 180.8)	3	Boomsma <i>et al</i> 2000 <sup>29</sup>
Chronic nasal carriage of <i>Staphylococcus aureus</i> *	RR 7.16 (95% CI 1.63 to 31.50); $p = 0.009$	2B	Stegeman <i>et al</i> 1994 <sup>33</sup>
Creatinine clearance >60 ml/min	RR 2.94 (95% CI 1.27 to 6.67); $p = 0.01$	3	Stegeman <i>et al</i> 1994 <sup>33</sup>
The presence of ANCA at diagnosis	RR 2.89 (95% CI 1.12 to 7.45)	1B	Stegeman <i>et al</i> 1996 <sup>16</sup>
Cardiac involvement at diagnosis	RH 2.87 (95% CI 1.09 to 7.58); $p = 0.03$	3	Koldingsnes and Nossent 2003 <sup>23</sup>
Cumulative cyclophosphamide dose <10 g in the first 6 months	RH 2.83 (95% CI 1.33 to 6.02); $p = 0.007$	3	Koldingsnes and Nossent 2003 <sup>23</sup>
Prednisolone ≥20 mg/day for <2.75 months	RH 2.41 (95% CI 1.12 to 5.21); $p = 0.03$	3	Koldingsnes and Nossent 2003 <sup>23</sup>
Co-trimoxazole as adjuvant to remission maintenance therapy	RR 0.32 (95% CI 0.13 to 0.79)	1B	Stegeman <i>et al</i> 1996 <sup>16</sup>

\*Nasal carriage of *Staphylococcus aureus* tended to decrease the relapse rate in Pavone *et al*;<sup>32</sup> this was not statistically significant. ANCA, antineutrophil cytoplasm antibody; C, cytoplasmic; PR3, proteinase 3; RH, relative hazard; RR, relative risk.

The presence of these risk factors cannot be used to justify treatment decisions.

Relapses have been classified according to severity in some clinical trials, but there have been methodological differences.<sup>14–17</sup> In one study,<sup>14</sup> a major relapse was defined as the appearance of at least one major (eg, haematuria) item; minor relapse required the presence of three minor (eg, myalgia, arthritis, nasal crusting) BVAS items. By contrast, in the Wegener's Granulomatosis Etanercept Trial (WGET), relapses were classified as limited or severe depending on the need for cyclophosphamide and/or reappearance of specific organ involvement.<sup>17</sup> The qualification of relapses is useful in comparing interventions since it may make an intervention with a higher overall relapse rate superior, if it lowers the incidence of severe, life-threatening relapse.

### Renal survival in WG

There is a progressive rise in renal mortality over time in patients with WG. In a retrospective cohort, 7% of patients developed end stage renal disease at 12 months; increasing to 14% at 5 years and 23% at 10 years.<sup>9</sup> In two other studies, end stage renal disease occurred in 19% at 38 months, and 23% at 15 months.<sup>3, 10</sup> Factors predicting progression to end stage renal disease were as follows. Renal factors: dialysis dependence at diagnosis (RR 3.3 (95% CI 1.3 to 8.8),  $p = 0.001$ ,<sup>3</sup> HR 4.78 (95% CI 1.27 to 17.86),  $p = 0.02$ ,<sup>9</sup> level of evidence = 3). A rise in serum creatinine of 100  $\mu\text{mol/litre}$  (HR 1.35 (95% CI 1.11 to 1.49),  $p = 0.001$ ,<sup>9</sup> level of evidence = 3). A rise in the 24 h urinary protein of 1 g (HR 1.50 (95% CI 1.08 to 2.07),  $p = 0.02$ ,<sup>9</sup> level of evidence = 3).

Other factors: a fall in haemoglobin of 1 g/dl (HR 1.64 (95% CI 1.05 to 2.57),  $p = 0.03$ ,<sup>9</sup> level of evidence = 3). An increase in age of 10 years (HR 1.47 (95% CI 0.95 to 2.24),  $p = 0.08$ ,<sup>9</sup> level of evidence = 3).

### Survival

WG is associated with higher mortality compared to the general population (mortality risk ratio (MRR) 3.8 (95% CI 2.6 to 5.6), MRR 4.0 for men (95% CI 2.5 to 6.3), MRR 3.4 for women (95% CI 1.6 to 7.2)).<sup>3</sup> The mean survival for untreated WG is 5 months and the 2-year mortality is 93%.<sup>42</sup> Immunosuppressive therapy has changed the outlook. In a historical cohort of 265 patients, the median survival of 27 patients not receiving any initial immunosuppression was 4.2 years;<sup>43</sup> however, 57 patients treated with azathioprine +/- prednisolone and 74 patients treated with oral cyclophosphamide +/- prednisolone had a median survival of 7.3 years

**Table 4** Survival in antineutrophil cytoplasm antibody associated vasculitides (AAV)

Time	WG	MPA	CSS
12 months	85–97% (data from six studies including 398 patients) <sup>9, 21, 22, 44–46</sup>	82–92% (data from four studies including 252 patients) <sup>45–48</sup>	93–94% (data from two studies including 155 patients) <sup>48, 49</sup>
24 months	86–97% (data from two studies including 263 patients) <sup>21, 50</sup>	NA	NA
60 months	69–91% (data from seven studies including 427 patients) <sup>5, 9, 44–46, 50, 51</sup>	45–76% (data from five studies including 217 patients) <sup>1, 45–47, 51</sup>	60–97% (data from five studies including 187 patients) <sup>2, 49, 52–54</sup>
120 months	75–88% (data from two studies including 211 patients) <sup>9, 21</sup>	NA	NA

CSS, Churg–Strauss syndrome; MPA, microscopic polyangiitis; NA, not available; WG, Wegener granulomatosis.

and 8.5 years, respectively.<sup>45</sup> A median survival of 21.7 years was recorded in a series of 155 treated patients.<sup>21</sup>

### Factors affecting survival

There are three main factors that affect survival (table 5). They are as follows. Age: a rise of each decade in age increases the risk of death in patients with WG (HR 2.18, 95% CI 1.38 to 3.42,  $p < 0.001$ ).<sup>9</sup> Over the age of 52 years, the older population has a poorer survival (HR 3.4, 95% CI 1.03 to 11.21,  $p = 0.04$ ).<sup>5</sup> Two other studies, which stratified patients at 50 and 60 years, respectively, found similar results.<sup>21, 55</sup> Patients aged >50 had a HR of 5.73 (95% CI 2.07 to 15.85) for death in a calendar year when compared to younger patients.<sup>21</sup> There was no control group to prove that the increasing risk of death was not simply a function of increasing mortality in an older sub-group.

The second factor is target organ damage. WG has vasculitic and granulomatous components, each of which may respond to different treatment.<sup>56</sup> Upper respiratory tract involvement is the granulomatous end of the spectrum and renal involvement is the pure vasculitis manifestation. Upper respiratory tract involvement is associated with better survival (HR 0.31, 95% CI 0.11 to 0.84,  $p = 0.02$ ) and renal involvement with poorer survival (HR 4.45, 95% CI 1.48 to 13.65).<sup>5, 21</sup> This would fit with the clinical observation that vasculitic manifestations are more acute and life-threatening than granulomatous manifestations, which are more likely to be indolent. The presence of lung involvement may be a risk factor for mortality (HR 3.74, 95% CI 1.26 to 11.13),<sup>21</sup> but this is disputed<sup>5</sup> and can only be resolved by larger prospective studies.

The third factor is damage. The presence of even minimal damage is associated with a higher risk of mortality.<sup>9</sup> This observation would correlate with data from the original VDI validation exercise, where a comparison of 12 non-survivors vs 47 survivors revealed that the median VDI score

**Table 5** Factors affecting survival

Risk factor	Risk of death (95% CI)	Level of evidence	Reference
Dialysis dependence at diagnosis	HR 8.2 (2.03 to 33.11) $p = 0.003$	3	Koldingsnes and Nossent 2002 <sup>9</sup>
VDI $\geq 1$ at diagnosis	HR 5.54 (1.28 to 24.05) $p = 0.022$	3	Koldingsnes and Nossent 2002 <sup>9</sup>
Impaired renal function at diagnosis	HR 5.10 (1.59–10.16)	3	Reinhold-Keller <i>et al</i> 2000 <sup>21</sup>
A serum albumin level of $\leq 30$ g/litre at diagnosis	RR 4.5 (1.3 to 16)	3	Aasarod <i>et al</i> 2000 <sup>3</sup>
Renal involvement at diagnosis*	HR 4.45 (1.48 to 13.65)	3	Reinhold-Keller <i>et al</i> 2000 <sup>21</sup>
Lung involvement at diagnosis†	HR 3.74 (1.26 to 11.13)	3	Reinhold-Keller <i>et al</i> 2000 <sup>21</sup>
Age >52	HR 3.4 (1.03 to 11.21), $p = 0.04$	3	Bligny <i>et al</i> 2004 <sup>5</sup>
Age (rise of 10 years)	HR 2.18 (1.38 to 3.42), $p < 0.001$	3	Koldingsnes and Nossent 2002 <sup>9</sup>
Upper respiratory tract involvement at diagnosis‡	HR 0.31 (0.11 to 0.84), $p = 0.02$	3	Bligny <i>et al</i> 2004 <sup>5</sup>

\*Affected only univariate analysis, not multivariate analysis.<sup>5</sup> †Did not affect survival.<sup>9</sup>

‡Affected only univariate analysis, not multivariate analysis.<sup>9</sup> HR, hazard ratio; RR, relative risk; VDI, Vasculitis Damage Index.

for non-survivors was significantly higher than that for survivors (7 vs 4).<sup>57</sup>

### Microscopic polyangiitis

There are very few studies of MPA due to the absence of a definition until the Chapel Hill consensus conference.<sup>58</sup> It is possible that previously published studies of WG may have inadvertently included patients with MPA. These are limitations of classification and we have excluded those papers that do not describe MPA as a separate entity. We have also excluded cohorts with renal limited vasculitis because they have the potential to differentiate into either WG or MPA.

### Remission

In two studies, remission rates for MPA were 75% and 89%.<sup>18–41</sup> Objective inter-study comparison and with WG (table 1) cannot be made due to differences in defining remission and variable remission induction regimens.

### Relapse

The relapse rates in MPA from three studies are 34% at 70 months (mean time to relapse 43 months),<sup>4</sup> 41% at 32 months (mean time to relapse 22.5 months)<sup>47</sup> and 8% at 18 months.<sup>14</sup> The latter was directly compared to the relapse rate in WG (18% at 18 months), demonstrating that WG has a higher rate of relapse than MPA (level of evidence = 2B).<sup>14</sup> Variations in trial methodology (treatment, baseline characteristics for the cohort and definition of outcomes) hamper inter-trial comparison.

### Survival

The 1-year survival in MPA is 82–92%,<sup>45–48</sup> and the 5-year survival estimates are between 45% and 76%,<sup>4–45–47–51</sup> which is worse than in WG (RR 1.917, 1.075–3.419,  $p = 0.025$ ) (table 4).<sup>59</sup> In two separate studies, the 1-year (83% vs 85%,  $p =$  not significant and 87% vs 97%,  $p < 0.01$ ) and 5-year (45% vs 76%,  $p = 0.02$  and 63% vs 91.5%,  $p < 0.01$ ) survival of MPA was lower than WG.<sup>45–46</sup> The survival advantage of WG may be lost following the onset of end stage renal disease.<sup>60</sup>

The presence of significant renal insufficiency at diagnosis is an adverse survival marker in MPA (HR 3.69, 95% CI 1.006 to 13.4) (level of evidence = 3).<sup>48</sup>

### Churg–Strauss syndrome

#### Remission

The search yielded only two papers where Churg–Strauss syndrome (CSS) was studied as a distinct diagnosis.<sup>2–49</sup> Disease specific sub-analysis for CSS was not available in other studies. The remission rate for CSS is 81–91%.<sup>2–49</sup>

#### Relapse

Relapse rates in CSS increase with time; 10%, 15% and 21% at 1, 2 and 4 years in one study,<sup>2</sup> and 27% and 35% at 1 and 2 years in another.<sup>32</sup> The relapse rate of CSS maybe lower than MPA (20% vs 34%), as seen in a prospective cohort (which also included polyarteritis nodosa (PAN)).<sup>25</sup> Intravenous methotrexate (0.3 mg/kg/week) and low dose prednisolone as remission maintenance therapy resulted in a relapse rate of 48% after 4 years.<sup>6</sup> The median time to relapse was 9 months.<sup>6</sup> The variable definition of relapse has an affect on the relapse rate. For example, when defined as “reappearance of disease except asthma and eosinophilia”, the relapse rate was lower than in comparison with a definition of relapse “...requiring

immunosuppression”.<sup>2–32</sup> Gastrointestinal involvement is a risk factor for relapse in CSS (HR 6.75, 95% CI 1.55 to 29.52;  $p = 0.011$ ) (level of evidence = 3).<sup>32</sup>

### Survival

Patient survival in CSS is 93–94% at 1 year<sup>48–49</sup> and 60–97% at 5 years (table 4).<sup>2–49–52–54</sup> The five factor score (proteinuria >1 g/day, creatinine >1.58 mg/dl, gastrointestinal involvement, cardiomyopathy, neurological involvement) was validated in a heterogeneous cohort of CSS and PAN (which may have included MPA),<sup>61</sup> but did not include a CSS specific sub-analysis. The score was indirectly validated in a later study.<sup>2</sup> The absence of any of the five factors carries a good prognosis (RR 0.52, 95% CI 0.42 to 0.62;  $p < 0.03$ ) and the presence of two or more of the factors increases the risk of mortality (RR 1.36, 95% CI 1.10 to 1.62;  $p < 0.001$ ) (level of evidence = 3).<sup>2</sup> Of the five factors, cardiomyopathy is an independent risk factor in CSS (HR 3.39, 95% CI 1.6 to 7.3) (level of evidence = 3)<sup>48</sup> Proteinuria >1 g/day was not associated with adverse survival in a prospective cohort.<sup>2</sup>

### CONCLUSIONS

This literature review summarises the clinical outcomes and the factors influencing them in studies of AAV. A small number of manuscripts met our selection criteria, indicating a lack of good quality research for outcome measures in AAV. There have only been six randomised controlled trials in AAV, and only one had disease-specific analysis. There is limited data available from structured clinical studies for specific diseases. From the identified papers, it is difficult to compare outcomes due to the variation in trial regimen and differing definitions of clinical states. The identification of risk factors was restricted to multivariate analysis. However, most risk factors are derived from descriptive cohorts and there have been no controlled studies to validate them. Definitions used for inclusion of patients varied considerably. In some instances, the data was published prior to any international classification scheme. The use of the Chapel Hill Consensus Conference definition<sup>58</sup> has helped identify a homogeneous group of patients with MPA. The variation in methodology of the studies reviewed in this paper formed the basis of the recommendations by EULAR/EUVAS for conduct of studies in AAV.<sup>11</sup> The differences between outcomes in the studies we have discussed may be genuine (dependent on stage of disease, organ involvement, therapy and so on) or perceived (due to a variation in the definition of the outcome). Future trial design should address this variation when calculating sample sizes by stratifying patients according to identified risk factors. The outcome measures and results in this paper may require updating in future when data emerges from new studies. Currently, the recommendations and the literature search are restricted to AAV, primarily because the majority of controlled trials and long-term observational studies have focussed on these forms of vasculitis. A similar approach would apply to other forms of primary small vessel vasculitis and may lead to the development and implementation of recommendations in these diseases in future. Disease related damage and the quality of life of patients with these chronic debilitating diseases are measures of prognostic and economic importance.<sup>8–62–63</sup> We have not concentrated on those outcomes, but they are discussed elsewhere.<sup>64</sup>

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