

Raffaella Valenti, MD,<sup>1,2</sup> Andreas Charidimou, MD PhD,<sup>1</sup> Gregoire Boulouis, MD MSc,<sup>1</sup> Yael D. Reijmer, PhD,<sup>1</sup> Martinez Sergi Ramirez, MD,<sup>1</sup> Li Xiong, MD PhD,<sup>1</sup> Panagiotis Fotiadis, BS,<sup>1</sup> Sigurros Davidsdottir, PhD,<sup>3</sup> Michael Jessel, BSc,<sup>1</sup> Alison Ayres, BA,<sup>1</sup> Grace Riley, BA,<sup>1</sup> Leonardo Pantoni, MD PhD,<sup>2</sup> Edip M. Gurol, MD MSc,<sup>1</sup> Steven M. Greenberg, MD PhD,<sup>1</sup> Anand Viswanathan, MD PhD.<sup>1</sup>

<sup>1</sup> Hemorrhagic Stroke Research Program, Department of Neurology, Massachusetts General Hospital Stroke Research Center, Harvard Medical School, Boston, MA, USA

<sup>2</sup> NEUROFARBA Department, Neuroscience Section, University of Florence, Florence, Italy

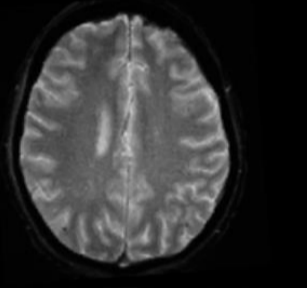
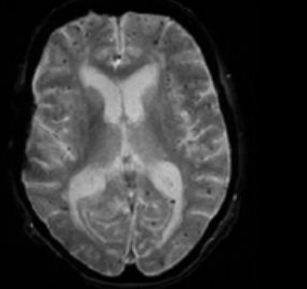
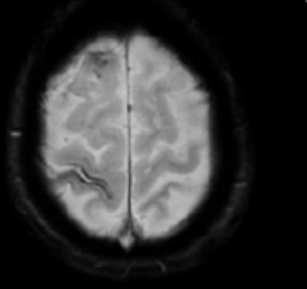
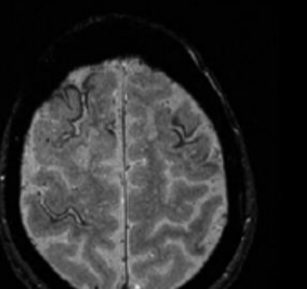
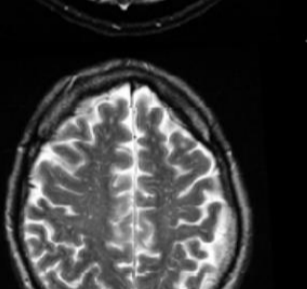
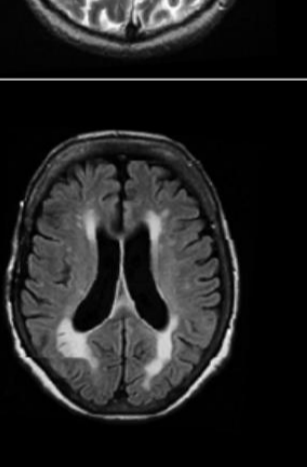
<sup>3</sup> Psychiatry Department, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

## BACKGROUND AND OBJECTIVES

Cerebral amyloid angiopathy (CAA) is a major cause of lobar intracerebral hemorrhage and cognitive impairment in the elderly. Different neuroimaging markers of CAA are related to distinct biological or clinical aspects of the disease. We investigated the biological significance of a specific composite score to capture the total brain MRI burden in the CAA, by evaluating its correlation with white matter connectivity, and overall disability measures.

## METHODS

CAA total small vessel disease score: MRI signatures, categories and points

MRI marker	Visual assessment	Definition	Score	MRI example
Lobar CMBs	International consensus definition <sup>16, 21</sup>	2-4 CMBs	1 point	
		≥ 5 CMBs	2 points	
cSS	Visual rating scale <sup>7, 23</sup>	Focal cSS (≤3 sulci)	1 point	
		Disseminated cSS (≥4 sulci)	2 points	
CSO-PVS	International consensus definition <sup>21</sup>	Moderate-to-severe, i.e. ≥20 CSO-PVS	1 point	
WMH	Fazekas scale <sup>25</sup>	Confluent deep WMH (Fazekas score 2 or 3) and/or irregular periventricular WMH extending into the deep white matter (Fazekas score 3)	1 point	

We applied the total MRI small vessel disease (SVD) score in a prospective cohort of 96 patients with probable or possible CAA (according to Boston criteria).

The score, ranging from 0 to 6, considered 4 MRI features:

- lobar microbleeds
- focal or disseminated cortical superficial siderosis
- moderate-to-severe enlarged perivascular spaces in the centrum semiovale
- moderate-severe white matter hyperintensities

*Statistical analysis:* We explored the association of the score with white matter connectivity in adjusted ordinal and linear regression analyses.

## RESULTS

Figure. Total MRI small vessel disease score

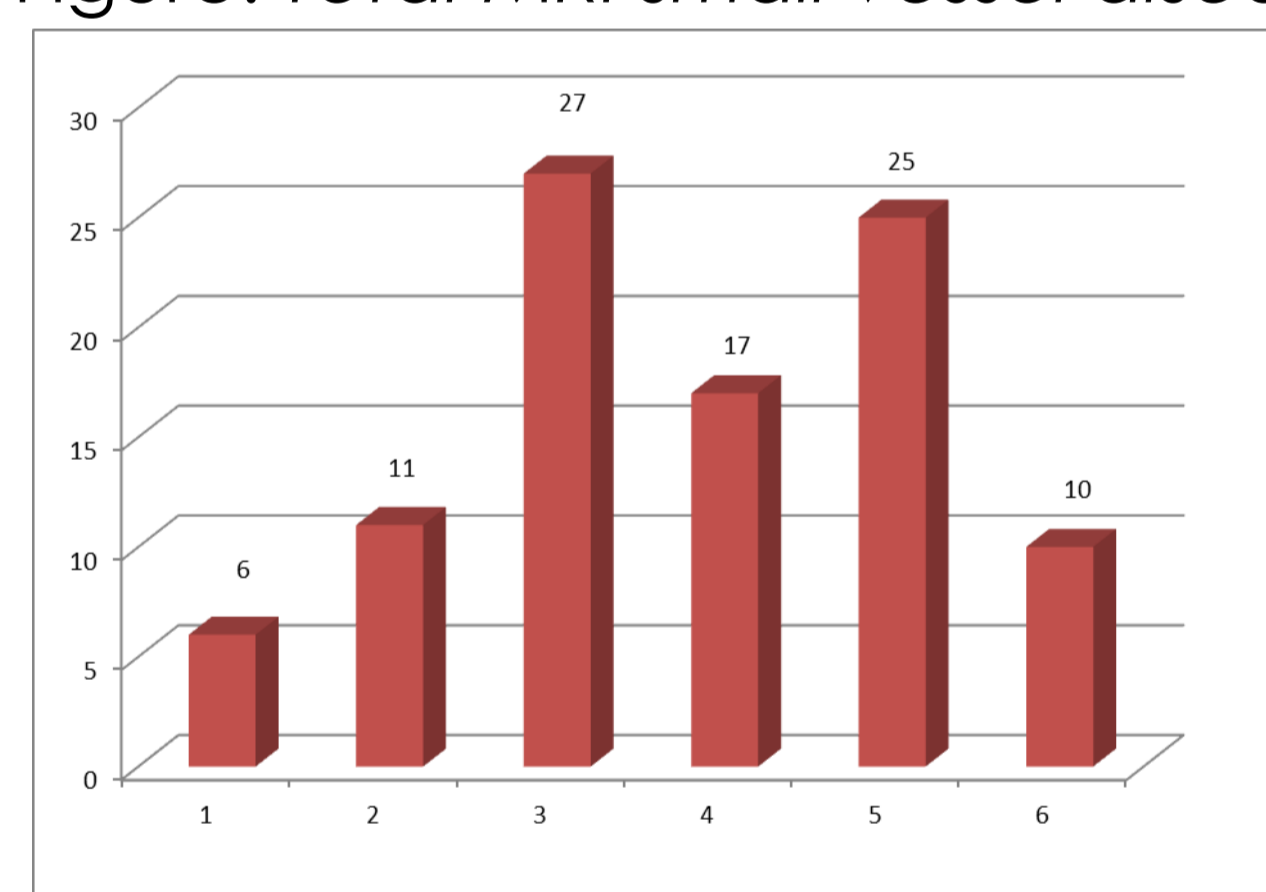


Table 2. Associations between total MRI SVD score and clinical outcome measures

	N	Coefficient (95% CI)	p-value		
<b>Measures of impairment</b>					
GDS	87	1.17 (0.30 - 2.04)	<b>0.009</b>		
apathy	80	0.57 (-0.33 - 1.48)	0.212		
gait velocity	62	-0.04 (-0.012 - 0.02)*	0.202		
	N	OR (95% CI)	p-value		
LADIS score	53	-0.20 (-0.69 - 0.40)	0.520		
	N	Coefficient (95% CI)**	p-value	Coefficient (95% CI)**	p-value
<b>Cognitive domains</b>					
memory	92	-0.14 (-0.28 to -0.01)	<b>0.042</b>	-0.08 (-0.22 to 0.06)	0.252
speed	92	0.01 (-0.08 to 0.10)	0.795	0.01 (-0.02 to 0.02)	0.774
executive functions	92	-0.05 (-0.14 to 0.05)	0.319	-0.10 (-0.11 to 0.09)	0.813
language	92	-0.10 (-0.25 to 0.05)	0.184	-0.06 (-0.21 to 0.10)	0.471

Derived from linear regression model adjusted for age and sex and ICH  
OR derived ordinal logistic regression model adjusted for age and sex  
\*Derived from linear regression model adjusted for age and sex and education level  
\*\*Derived from linear regression model adjusted for age and sex, education level, ICH and atrophy  
Abbreviations: GDS=Geriatric Depression Scale

Table 1. Characteristics of the study sample

Clinical variables	CAA cohort (N=96)
Age (years), mean (SD)	69.82 (8.26)
Male, N (%)	74 (77.1)
Years of education, mean (SD)	16.74 (3.02)
Hypertension, n (%)	55 (57.3)
Diabetes, n (%)	9 (9.4)
Hypercholesterolemia, n (%)	45 (46.9)
Smoking, n (%)	3 (3.3)
Dementia, n (%)	5 (5.2)
<b>Brain MRI markers</b>	
CMBs, N (%)	89 (92.7)
CMBs > 5, N (%)	76 (79.2)
cSS, N (%)	51 (53.1)
Focal cSS, N (%)	20 (20.8)
Disseminated cSS, N (%)	31 (32.3)
CSO-EPVS >20, N (%)	55 (57.3)
WMH (Fazekas score), mean (SD)	1.81 (0.80)
moderate-severe, N (%)	60 (62.5)
Occipital gradient, N (%)	57 (59.4)
Moderate-severe global cortical atrophy (Pasquier scale), N (%)	61 (63.5)
<b>Global disability, cognitive and gait measures</b>	
IQCODE at baseline (79) <sup>†</sup> , mean (SD)	3.13 (0.24)
mRS (88) <sup>‡</sup> , mean (SD)	0.66 (0.86)
GDS (87) <sup>‡</sup> , median (IQR)	5.00 (2.00, 9.00)
Apathy Scale (80) <sup>‡</sup> , median (IQR)	10.00 (5.25-13.00)
MMSE (91) <sup>‡</sup> , mean (SD)	27.64 (2.37)
SPPB total (53) <sup>‡</sup> , median (IQR)	4.00 (3.00-4.00)
Gait velocity (62) <sup>‡</sup> , m/sec	1.19 (0.35)

Abbreviations: CMBs=cerebral microbleeds, cSS=cortical superficial siderosis, WMH=white matter hyperintensities, IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly, mRS=modified Rankin Scale, GDS=geriatric depression scale, MMSE=mini mental state examination, SPPB=Short Physical Performance Battery.

<sup>†</sup>Number of patients with available data

Table 3. Association between total MRI SVD score and APOE genotype and other neuroimaging markers

	N	OR (95% CI)	p-value
ApoE e2	73	2.95 (1.26 - 1.87)	<b>0.012</b>
ApoE e3	73	0.85 (0.51 - 1.44)	0.556
ApoE e4	73	0.73 (0.42 - 1.27)	0.269
Cerebral global cortical atrophy	96	1.57 (1.16 - 2.12)	<b>0.003</b>
ICH presence	96	0.72 (0.35 - 1.48)	0.374
Occipital predominance WMH	96	1.65 (1.11 - 2.46)	<b>0.014</b>
	N	coefficient (95% CI)	p-value
Global network efficiency	74	-0.004 (-0.008 to -0.002)*	<b>0.039</b>

Derived from ordinal regression model adjusted for age and sex  
\* Derived from linear regression model adjusted for age and sex  
Abbreviations: ICH=intracerebral hemorrhage  
Global network efficiency measure is for ICH-free hemisphere

## DISCUSSION

The total MRI SVD score reflects the global network efficiency, and might be helpful to capture the cumulative effects of microangiopathy burden in patients affected by sporadic CAA. Larger studies are needed to validate our findings.

### References:

- Greenberg SM, Al-Shahi Salman R, Biessels GJ, van Buchem M, Cordonnier C, Lee JM, Montaner J, Schneider JA, Smith EE, Vernooij M, Werring DJ. Outcome markers for clinical trials in cerebral amyloid angiopathy. *Lancet Neurol*. 2014 Apr;13(4):419-28. doi: 10.1016/S1474-4422(14)70003-1.
- Charidimou A, Martinez-Ramirez S, Reijmer YD, Oliveira-Filho J, Lauer A, Roongpiboonsopit D, Frosch M, Vashkevich A, Ayres A, Rosand J, Gurol ME, Greenberg SM, Viswanathan A. Total MRI small vessel disease burden in cerebral amyloid angiopathy: a concept validation study [submitted].