Associations of renal function with cerebral small vessel disease and functional outcome in acute intracerebral haemorrhage: a hospital-based prospective cohort study

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Data availability
The datasets generated and analysed during this study are available from the corresponding author on reasonable request.

ABSTRACT

Background: Intracerebral haemorrhage (ICH) is a severe clinical consequence of cerebral small vessel disease (SVD), but associations between renal impairment and SVD in patients with ICH have not been fully characterised.

Methods: Using data from the CROMIS-2 ICH observational study, we compared SVD neuroimaging markers and total burden (score 0-3) identified using CT brain imaging in patients with and without renal impairment (estimated glomerular filtration rate, eGFR<60). We assessed functional outcome at 6-month follow-up using the modified Rankin scale.

Results: 1027 participants were included (mean age 72.8, 57.1% male); 274 with and 753 without renal impairment. 18.7% of the eGFR<60 group had moderate-to-severe SVD burden (score 2-3), compared with 14.0% of those with eGFR>60 (p=0.039). SVD burden was associated with renal impairment after adjusting for hypertension (OR 1.36, 95% CI 1.04-1.77, p=0.023), but not after adjusting for age. Cerebral atrophy was more prevalent in patients with eGFR<60 (81.2% vs. 72.0%, p=0.002), as were WMH (45.6% vs. 36.6%, p=0.026). Neither was associated with renal function after adjusting for age and vascular risk factors. Renal impairment was associated with functional outcome (OR 0.65, 95% CI 0.47-0.89, p=0.007), but not after adjusting for age, pre-morbid function and comorbidities (OR 0.95, 95% CI 0.65-1.38, p=0.774).

Conclusion: In acute ICH, renal impairment is associated with a higher cerebral SVD burden independent of hypertension, but not age. Reduced eGFR is associated with worse functional outcome, but not independent of age and comorbidities. Since CT has limited sensitivity to detect SVD severity and distribution, further studies including MRI are needed.

1. Introduction

Chronic kidney disease (CKD) is an established independent risk factor for cerebrovascular diseases, including stroke due to cerebral ischaemia or intracerebral haemorrhage (ICH) [1, 2]. Cerebral small vessel disease (SVD), a key cause of stroke and dementia, is hypothesized to be part of a multisystem disorder which may share mechanisms with CKD. Indeed, a recent population-based study reported a significant association of total SVD score with presence of

CKD in those aged under 60, after adjusting for shared risk factors such as hypertension or diabetes [3]. However, this study was limited to patients presenting with minor ischaemic stroke or transient ischaemic attack (TIA). ICH, a stroke type which is often severe and has a high mortality, is most frequently caused by SVD, but associations with renal function have not been fully characterised.

CROMIS-2 (Clinical Relevance of Microbleeds in Stroke) ICH [4] was a large multicentre UK-wide prospective observational study of patients presenting with acute symptomatic ICH. Imaging and clinical outcome data were collected, including acute CT and serum creatinine. Our aims were to investigate associations of eGFR with CT-defined neuroimaging features of SVD, total SVD burden score, and functional outcome at 6 – 12 months. We hypothesised that the presence of white matter hypoattenuation (WMH), brain atrophy and combined SVD burden score are associated with CKD, and that CKD would be associated with worse functional outcome.

2. Materials and methods

We included all eligible participants from the CROMIS-2 (ICH) observational study (clinictrials.gov; NCT02513316); the study protocol has been described [4]. (CROMIS-2 (Clinical Relevance of Microbleeds in Stroke) ICH. Patients with capacity gave informed written consent; in those without capacity, written consent was obtained from a proxy, as defined by relevant local legislation. The study was approved by the National Research Ethics Service (IRAS reference 10/H0716/61).

2.1. Data collection

We collected clinical and outcome variables using pre-specified data collection sheets, and imaging data including location of haematoma, haematoma volume, Van Swieten scores, atrophy scores, lacunes and combined SVD burden score (full details below).

We used the serum creatinine on admission to calculate the estimated glomerular filtration rate (eGFR) using the Modified Diet in Renal Disease (MDRD) equation [5]. We assumed that the patient's creatinine reflected their baseline renal function. Patients without a creatinine value or age were excluded. Renal impairment was defined as an eGFR<60, which

is the accepted worldwide definition of decreased GFR, according to the International Society of Nephrology [6].

2.2. Follow up data

For 6-12 months after the index ICH, we collected outcomes using multiple methods as previously published in the study protocol [4]. Briefly, these included postal questionnaires sent to patients and their general practitioners, and notifications from NHS Digital, which included hospital episode statistics and information on registered deaths from the Office of National Statistics. The outcome of interest for this study was modified Rankin Score (mRS) at 6-12 months.

2.3. Imaging data

Brain CT imaging was acquired acutely on hospital admission at the time of the index event as part of patients' routine clinical care. Neuroimaging analysis was carried out by two experienced trained raters (D.S. and D.W.) who were blinded to the clinical details. To assess inter-rater reliability, both raters independently rated a random sample of 50 CT scans. Any disagreements were resolved by review by a professor of vascular neuroradiology (R.J.). Haematoma location was classified using the Cerebral Haemorrhage Anatomical Rating Instrument [7]. Images were rated for the presence of lacunes which were defined in accordance with STRIVE criteria [8], and WMH were rated using the Van Swieten score [9]; the highest scores for anterior and posterior regions were combined to generate a total score (range 0-4). We evaluated deep and superficial cerebral atrophy using a template based 3-point scale (absent/mild, moderate and severe) [10]. A composite SVD burden score was calculated as used in analysis of the Third International Stroke Trial [10]: 1 point was assigned for (1) severe WMH, (2) severe (≥2) lacunes, and (3) presence of severe deep or cortical atrophy, giving a 4-point ordinal score (0-3), as illustrated in **figure 1**.

We considered assessing SVD markers using MRI, but only 245 (24%) of the population, just 57 in the eGFR<60 group, had this data available. As the statistical power to detect a difference would have been much smaller, and there would have been additional selection bias, we decided to base the primary analysis on CT neuroimaging markers.

One point each for:

1. Severe anterior or posterior WMH (score 2 on Van Swieten scale
2. >1 lacunes (arrows)
3. Severe deep (a) or cortical (b) atrophy

This gives a 4 point ordinal scale from 0, indicating no significant SVD, to 3 indicating severe buden of SVD.

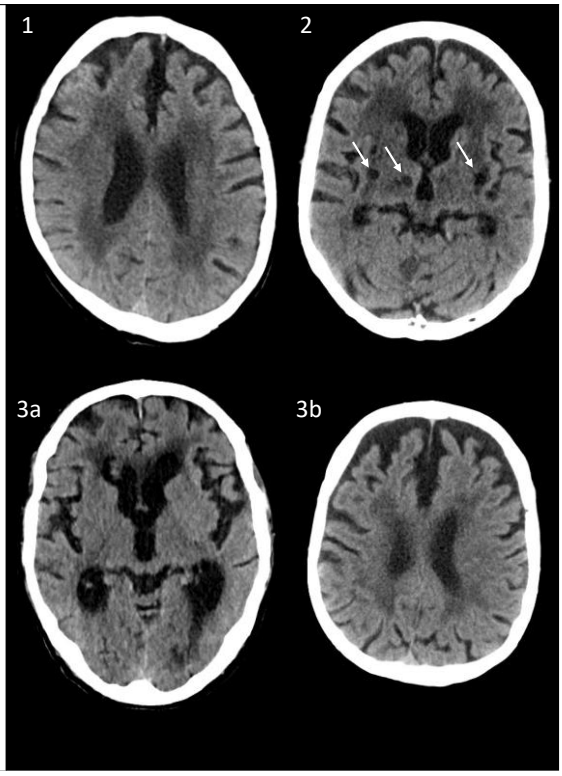


Fig. 1. The CT SVD burden score

2.4. Statistical analyses

We described numerical variables using mean and median values where appropriate, with corresponding standard deviations (SD) and inter-quartile ranges. We described compared categorical variables using number (%) and compared them using the Chi-squared or Fisher's exact test. Mean values were compared using a 2-sample t-test and medians with the Mann-Whitney U Test. We used univariable and multivariable logistic regression analysis to identify variables associated with functional outcome and mortality. To investigate the impact of missing data, we compared the characteristics of the group with missing follow up mRS to the group with complete follow up data. Since a proportion of the sample had a pre-morbid mRS higher than our outcome of interest (mRS≤2), we ran a sensitivity analysis excluding these participants.

For the neuroimaging data, we used median and inter-quartile range to describe measures of SVD, atrophy and combined SVD burden score. We tested for univariable associations with demographic and clinical variables using with the Mann-Whitney U and Chi-squared tests. We then used ordinal logistic regression analysis to adjust for other covariates in the analysis. We adjusted for age, sex and the presence of hypertension, diabetes, previous

ischaemic stroke, congestive heart failure and peripheral vascular disease. This was based on biological plausibility and a univariable association with 10% significance. In model 1 of the multivariable analysis, we adjusted for hypertension alone, as this is the modifiable risk factor most commonly associated with SVD. In model 2 we additionally adjusted for age and sex, and in model 3 we included all the variables mentioned above. Since there were only 7 participants with a SVD burden score of 3, these were combined with those with a score of 2. We used Brant's test to test whether the proportional odds assumption held for the model. As a sensitivity analysis, we also performed linear regression analyses of SVD burden score against eGFR and age as numerical variables. We carried out a subgroup analysis using the following subgroups: eGFR>60 (normal renal function); eGFR 45-60 (mild renal impairment); eGFR<45 (moderate-to-severe renal impairment). We combined the moderate and severe groups because there were only 25 participants with eGFR<30 so there was insufficient statistical power to detect an effect for this subgroup.

Statistical analyses were performed using Stata version 16.1 (StataCorp LLC, College Station, TX, USA).

3. Results

Out of 1094 patients recruited to CROMIS-2 (ICH), 1027 were included in the neuroimaging analysis and 900 in the follow up outcome analysis. 67 participants were excluded owing to missing baseline variables needed to calculate the MDRD eGFR, and 127 had missing follow up mRS values. Exclusions are shown in **figure 2**. The baseline characteristics are described in **table 1**. The eGFR<60 group was significantly older, with a higher proportion of female participants, and significantly higher rates of hypertension, diabetes, previous myocardial infarction (MI) and atrial fibrillation (AF), and a lower rate of current alcohol use.

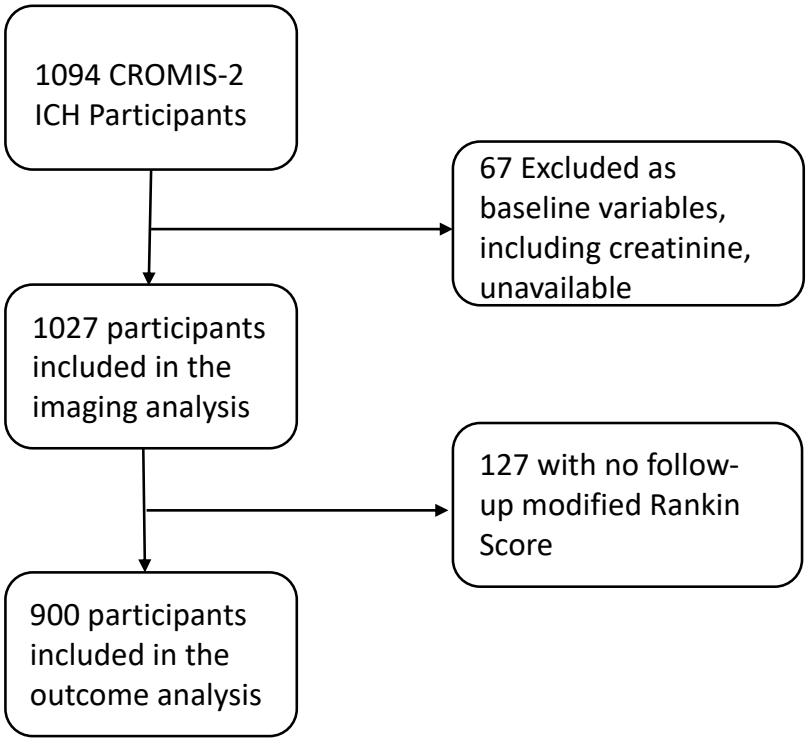


Fig. 2. Flow chart of study participants

Table 1: Baseline characteristics

	eGFR>60	eGFR<60	Total	p
n	753	274	1027	
Age, years, mean (SD)	71.4 (12.6)	76.7 (11.5)	72.8 (12.5)	**<0.001**
Sex				
Male, n (%)	450 (59.8)	136 (49.6)	586 (57.1)	**0.004**
Ethnicity, n (%)				
White	657 (87.3)	240 (87.6)	897 (87.3)	0.549
Black	43 (5.7)	12 (4.4)	55 (5.4)	
Asian	40 (5.3)	15 (5.5)	55 (5.4)	
Other	13 (1.7)	7 (2.6)	20 (2.0)	
Comorbidities				
Hypertension, n (%)	477 (64.5)	205 (75.4)	682 (67.4)	**0.001**
Diabetes, n (%)	122 (16.3)	68 (25.1)	190 (18.6)	**0.001**
Previous ischaemic stroke, n (%)	92 (12.4)	40 (15.1)	132 (13.1)	0.268
Previous TIA, n (%)	79 (11.0)	39 (15.1)	118 (12.1)	0.080
Previous ICH, n (%)	32 (4.3)	16 (5.8)	48 (4.7%)	0.296
Previous MI, n (%)	52 (7.0)	32 (11.9)	84 (8.3)	**0.012**
Previous PCI, n (%)	48 (6.4)	21 (7.8)	69 (6.8)	0.455
Angina, n (%)	48 (6.5)	26 (9.7)	74 (7.3)	0.088
AF, n (%)	226 (32.7)	129 (51.0)	355 (37.6)	**<0.001**
PAD, n (%)	22 (3.0)	12 (4.5)	34 (3.4)	0.222
Previous smoking, n (%)	369 (50.6)	129 (49.8)	498 (50.4)	0.838
Current alcohol use, n (%)	439 (61.5)	133 (52.6)	572 (59.2)	**0.013**
Median pre-event mRS	0 (0 – 1)	1 (0 – 2)	0 (0 – 1)	**<0.001**
Mean eGFR, ml/min (SD)	87.4 (22.3)	46.6 (11.0)	76.5 (26.9)	**<0.001**
Admission medications				
Anticoagulants, n (%)	269 (35.8)	147 (53.7)	416 (40.6)	**<0.001**
Warfarin, n (%)	252 (33.6)	130 (47.5)	382 (37.3)	**<0.001**
DOAC, n (%)	15 (2.0)	12 (4.5)	27 (2.7)	**0.032**
Heparin, n (%)	7 (0.9)	6 (2.2)	13 (1.3)	0.109
Antiplatelets, n (%)	172 (23.1)	75 (27.6)	247 (24.3)	0.137
Median follow up, days	228 (193 – 658)	249 (194 – 441)	233.5 (193 – 610)	0.626

eGFR estimated glomerular filtration rate, *TIA* transient ischaemic attack, *ICH* intracerebral haemorrhage, *AF* atrial fibrillation, *PAD* peripheral arterial disease, *DOAC* directly-acting oral anticoagulant

A comparison of the data excluded owing to missing follow up mRS scores (n=127) with the data included in the analysis (n=900) demonstrated no statistically significant differences, except for a higher proportion of black and Asian ethnicities in the excluded group (13.4% vs.

4.2%, p<0.001), and a higher rate of previous ICH (8.7% vs. 4.1%, p=0.024); please refer to **table A.1** in the supplementary materials for full details.

3.1. ICH location and volume

There was no significant difference in ICH location or volume between those with renal impairment and those with normal kidney function. In the eGFR<60 group there were 158 deep haemorrhages (57.9%) and 112 lobar haemorrhages (41.0%). In the group with normal renal function there were 440 deep haemorrhages (58.7%) and 301 lobar haemorrhages (40.2%, p=0.803 for the comparison of deep ICH). The median ICH volume in the eGFR<60 group was 6.1 ml (2.2 – 17.3), compared to 7.2 ml (2.2 – 18.3) in the group with normal kidney function (p=0.211)

3.2. Small vessel disease markers

The eGFR<60 group had significantly higher rates of cortical and deep brain atrophy and anterior WMH, as shown in **table 2**. There was a univariable statistically significant association between kidney disease with both cortical and deep cerebral atrophy, but not with cerebellar atrophy. There were no significant differences between the groups in the number of lacunes.

3.3. Combined SVD burden score

18.7% of those in the eGFR<60 group had a moderate to severe SVD burden, compared with 14.0% of those with normal kidney function (p=0.039). SVD burden score was higher in patients with renal impairment (median 1 vs 0, IQR for both 0-1, p=0.012). There was no significant difference in the scores for hypertension (p=0.117) or diabetes (p=0.823). The median scores for groups with and without hypertension or diabetes were all 0 (0-1). Groups with previous ischaemic stroke (median score 1, p<0.001) and previous ICH (median score 1, p<0.001) had significantly higher median SVD burden scores than those without. **Table 2** summarizes the data according to eGFR.

Table 2: Small vessel disease markers according to eGFR

	Score/n	eGFR>60 n (%)		eGFR<60 n (%)		Total n (%)		p
Atrophy								
Cortical Atrophy	0	132	(18.0)	30	(11.1)	162	(16.1)	**0.003**
	1	480	(65.3)	175	(64.6)	655	(65.1)	
	2	123	(16.7)	66	(24.4)	189	(18.8)	
Deep Atrophy	0	206	(28.0)	51	(18.8)	257	(25.6)	**0.002**
	1	377	(51.3)	142	(52.4)	519	(51.6)	
	2	152	(20.7)	78	(28.8)	230	(22.9)	
Cerebellar Atrophy	0	427	(58.1)	137	(50.6)	564	(56.1)	0.085
	1	242	(32.9)	102	(37.6)	344	(34.2)	
	2	66	(9.0)	32	(11.8)	98	(9.7)	
Van Swieten Score								
Anterior Choroid	0	466	(63.4)	148	(54.4)	614	(61.0)	**0.026**
	1	194	(26.4)	85	(31.3)	279	(27.7)	
	2	75	(10.2)	39	(14.3)	114	(11.3)	
Anterior Cella	0	516	(70.2)	171	(62.9)	687	(68.2)	**0.033**
	1	132	(18.0)	53	(19.5)	185	(18.4)	
	2	87	(11.8)	48	(17.7)	135	(13.4)	
Posterior Cella	0	462	(62.9)	162	(59.6)	624	(62.0)	0.524
	1	110	(15.0)	48	(17.7)	158	(15.7)	
	2	163	(22.2)	62	(22.8)	225	(22.3)	
Posterior Cingulate	0	518	(70.5)	194	(71.3)	712	(70.7)	0.929
Cortex	1	110	15.0)	41	(15.1)	151	(15.0)	
	2	107	(14.6)	37	(13.6)	144	(14.3)	
Lacunes								
Deep	0	676	(92.0)	248	(91.2)	924	(91.8)	0.631
	1	46	(6.3)	17	(6.3)	63	(6.3)	
	2-5	13	(1.9)	5	(2.6)	20	(2.0)	
Lobar	0	725	(98.6)	270	(99.3)	995	(98.8)	0.666
	1	9	(1.2)	2	(0.7)	11	(1.1)	
	9	1	(0.1)			1	(0.1)	
Total	0	684	(90.8)	247	(90.2)	931	(90.7)	0.729
	1	55	(7.3)	19	(6.9)	74	(7.2)	
	2-11	14	(1.9)	8	(2.9)	22	(2.2)	
Combined SVD	0	413	(54.9)	128	(46.7)	541	(52.7)	**0.039**
burden score	1	235	(31.2)	95	(34.7)	330	(32.1)	
	2	102	(13.6)	47	(17.2)	149	(14.5)	
	3	3	(0.4)	4	(1.5)	7	(0.7)	
Combined SVD burden score, median (IQR)		0	(0-1)	1	(0-1)	0	(0-1)	**0.012**

eGFR estimated glomerular filtration rate, *SVD* small vessel disease

Univariable ordinal logistic regression analysis demonstrated a significant association of total SVD burden score with eGFR<60, age, sex, Black and Asian ethnicities, and a history of previous ischaemic stroke, TIA, ICH, congestive heart failure, AF, dementia or cognitive impairment, current alcohol use, anticoagulant use and pre-stroke mRS score, as shown in **table A.2** in the supplementary materials. Of note hypertension did not have a significant effect, and eGFR<60 retained its statistical significance after adjusting for hypertension alone (Model 1 of the multivariable analysis, shown in **table 3**). Model 2 of the multivariable analysis demonstrated a significant effect of age, previous ischaemic stroke and previous ICH on combined SVD burden score. The Brant test showed that the proportional odds assumption held for all variables with the exception of diabetes, which was subsequently excluded from the analysis.

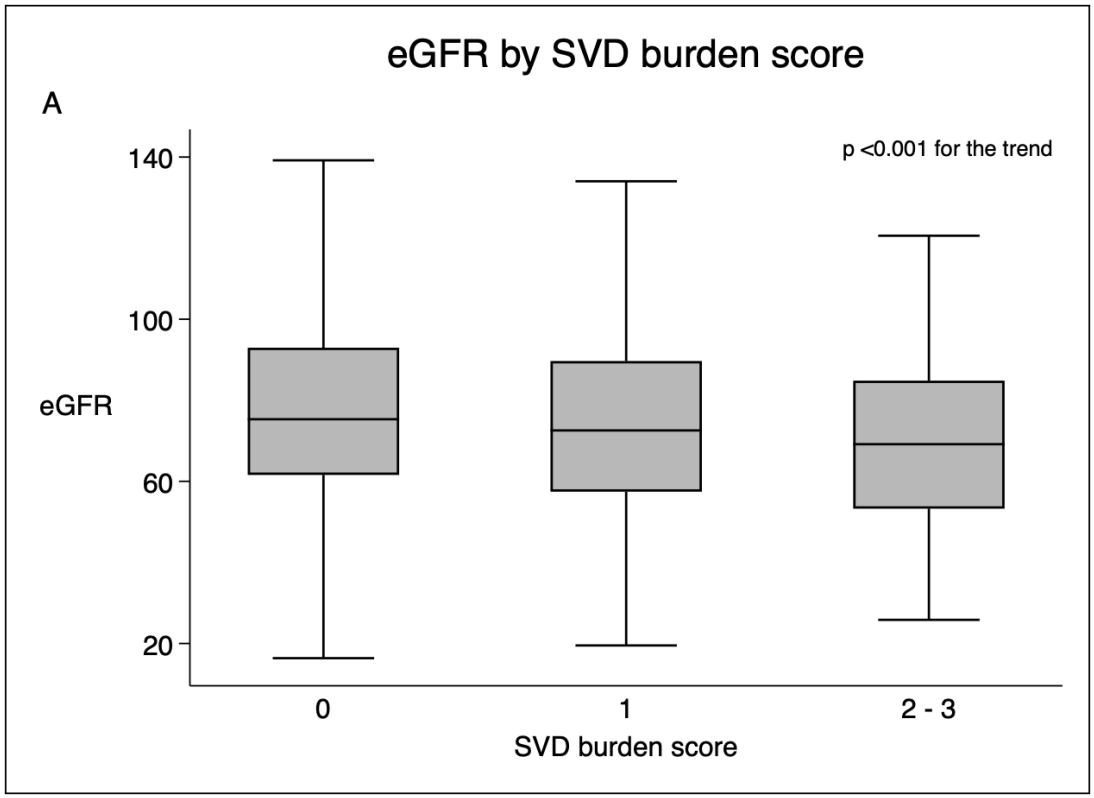
Table 3: Multivariable ordinal logistic regression analysis for odds of increased SVD burden score

	Variable	**OR**	**95% CI**	**p**
Model 1	eGFR<60	1.36	1.04 - 1.77	**0.023**
	Hypertension	1.18	0.92 - 1.53	0.196
Model 2	eGFR<60	0.99	0.75 - 1.31	0.934
	Age	1.07	1.06 - 1.09	**<0.001**
	Sex, female	1.17	0.91 - 1.51	0.222
	Hypertension	1.09	0.84 - 1.43	0.508
Model 3	eGFR<60	0.91	0.68 - 1.22	0.516
	Age	1.07	1.06 - 1.09	**<0.001**
	Sex, female	1.10	0.85 - 1.44	0.459
	Ethnicity			
	White			Ref.
	Asian	0.64	0.34 - 1.22	0.286
	Black	1.51	0.80 - 2.85	
	Other	1.14	0.46 - 2.82	
	Previous IS	1.87	1.30 - 2.70	**0.001**
	Hypertension	1.00	0.76 - 1.32	0.979
	Congestive HF	1.72	0.97 - 3.06	0.064
	PAD	1.22	0.64 - 2.33	0.536

eGFR estimated glomerular filtration rate, *IS* ischaemic stroke, *HF* heart failure, *PAD* peripheral arterial disease
Model 1 – adjusts for hypertension; model 2 – adjusts for age, sex and hypertension; model 3 – adjusts for age, sex, ethnicity, previous stroke, hypertension, congestive heart failure, peripheral arterial disease

An unadjusted linear regression analysis of combined SVD burden score against eGFR as a continuous variable against showed a statistically significant association as shown in figure 2

(coefficient -3.95, 95% CI -6.13 to -1.77, r^2=0.012, p<0.001). A similar analysis of SVD burden against age showed a similar association (coefficient 6.15, 95% CI 5.19 to 7.10, r^2=0.136, p<0.001) with a closer fit of the data to the model and a greater magnitude of effect.



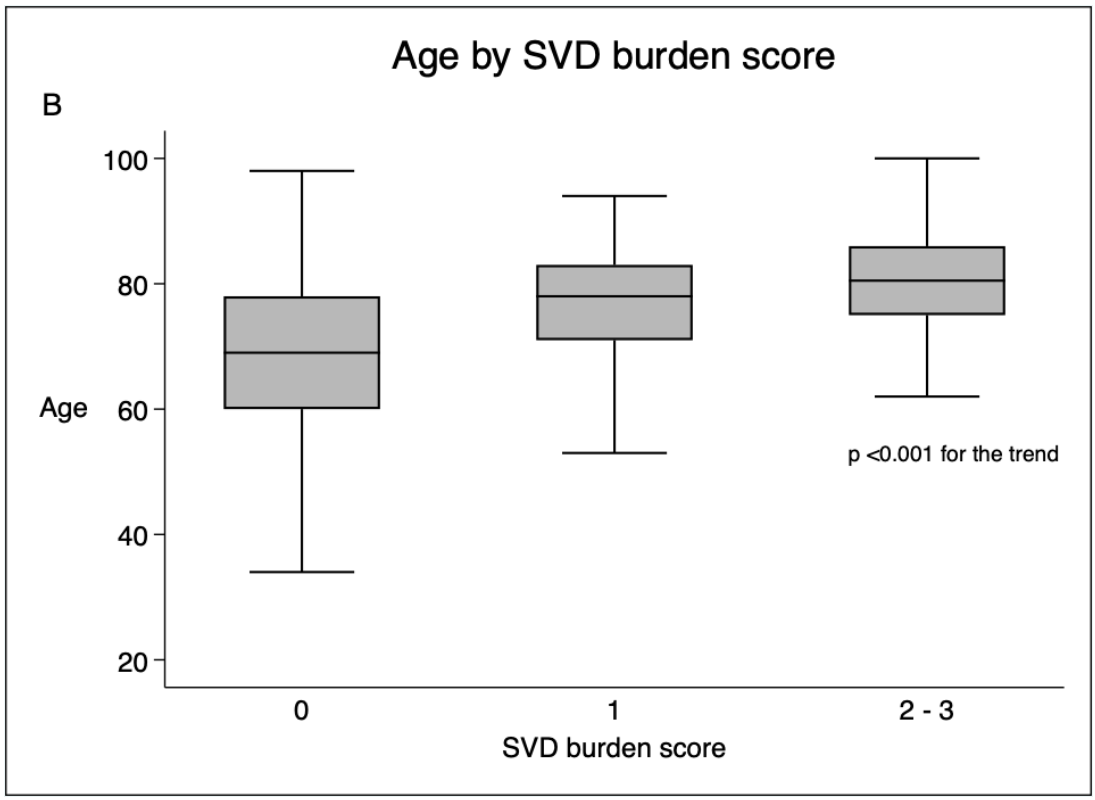


Fig. 3: Box plots displaying unadjusted linear regression of: A) eGFR against SVD burden and B) Age against SVD burden

In the subgroup analysis we found increasing SVD burden score with increasing severity of renal impairment, median (IQR) 1 (0-1) for eGFR<45 compared to 0 (0-1) for both the eGFR 45-60 and eGFR>60 groups, as shown in **figure 4** (p=0.003 using the Kruskal-Wallis test). However, when including the severity of renal impairment in the same ordinal logistic regression models as above, we did not find a significant adjusted association with SVD burden (using model 3, adjusted OR 1.03, 95% CI 0.85-1.26, p=0.756).

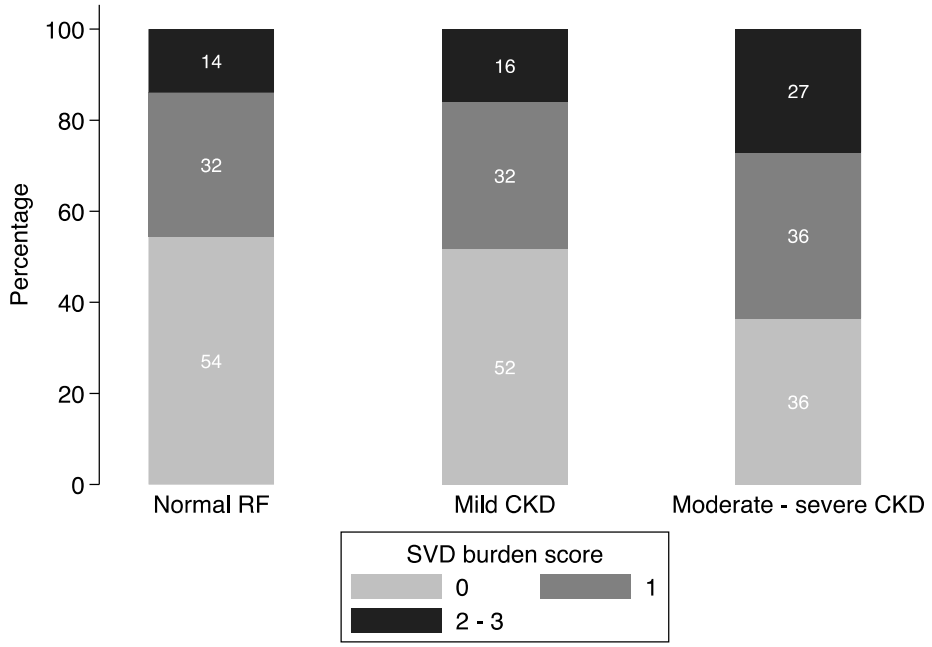


Fig 4: SVD burden score according to severity of renal impairment

3.4. Functional outcome

30.7% of participants in the eGFR<60 group had a favourable functional outcome (mRS 0-2) at 6-12 months, compared to 40.5% of those with normal kidney function (OR 0.65, 95% CI 0.47-0.89, p=0.007). In univariable logistic regression analysis, favourable functional outcome was associated with eGFR<60, previous ischaemic stroke, history of hypertension, AF, age, anticoagulant use, pre-event mRS. In multivariable logistic regression, only age, female sex and pre-event mRS were associated with outcome.

Table 4: Logistic regression analysis for odds of favourable outcome (mRS≤2)

	Univariable			Multivariable		
Variable	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
eGFR<60	0.65	0.47 - 0.89	**0.007**	0.95	0.65 - 1.38	0.774
Age	0.95	0.94 - 0.96	**<0.001**	0.97	0.95 - 0.98	**<0.001**
Sex, female	0.49	0.37 - 0.65	**<0.001**	0.66	0.47 - 0.92	**0.013**
Previous stroke	0.46	0.29 - 0.73	**0.001**	0.89	0.52 - 1.53	0.675
Previous TIA	0.69	0.45 - 1.07	0.099	0.89	0.53 - 1.49	0.662
Previous ICH	0.59	0.28 - 1.24	0.162	0.82	0.35 - 1.91	0.639
Hypertension	0.62	0.47 - 0.83	**0.001**	0.74	0.52 - 1.04	0.085
Diabetes	0.69	0.48 - 0.99	**0.044**	0.76	0.50 - 1.17	0.220
AF	0.60	0.44 - 0.80	**0.001**	0.75	0.45 - 1.27	0.286
Anticoagulant use	0.68	0.52 - 0.90	**0.007**	1.26	0.76 - 2.08	0.365
Pre-event mRS	0.55	0.48 - 0.65	**<0.001**	0.67	0.57 - 0.80	**<0.001**

eGFR estimated glomerular filtration rate, *TIA* transient ischaemic attack, *ICH* intracerebral haemorrhage, *AF* atrial fibrillation, *mRS* modified Rankin score

The sensitivity analysis, with those participants with pre-event mRS>2 excluded, gave similar results, with the only difference being statistical significance for hypertension as a covariate (p=0.048) in the multivariable analysis.

4. Discussion

Our major finding was that impaired renal function was associated with cortical and deep atrophy, anterior WMH, and the total burden of SVD in univariable analyses. This association with SVD burden remained statistically significant after adjusting for hypertension alone, but not after more comprehensive multivariable analysis. We also found that the SVD burden score showed a graded increase according to the severity of renal impairment. We found that SVD was most strongly associated with age. We also found that reduced eGFR was associated with worse functional outcome, but this was not independent of other vascular risk factors such as age and AF. Finally, we found that the group with renal impairment was significantly older, had a higher proportion of female patients, and had higher rates of hypertension, previous ischaemic stroke, AF and anticoagulant use, and worse pre-morbid functional status.

The vascular beds of the brain and the kidneys are very similar structurally and functionally [11]. Both are low resistance, high flow circuits with maintained perfusion pressures during systole and diastole. This is achieved through tight vascular autoregulation. Both vascular beds are particularly vulnerable to damage from raised blood pressure or fluctuations in blood pressure. This is referred to as the "strain vessel hypothesis" [11]. Because of these similarities, and the high rates of stroke and dementia [12] in patients with kidney disease, investigation of renal disease in populations with SVD is an important area of research.

To date there have been very few studies examining populations of CKD patients presenting with ICH. A small prospective Chinese cohort study examined the presence and severity of MRI markers of SVD and their associations with renal impairment [13]. Like our analysis they did not find a significant association between the presence of lacunes and CKD. In the multivariate analysis they did find a significant association of CKD with deep WMH, and both deep and peri-ventricular cerebral micro-bleeds (CMB). However, there was no association of CKD with overall or periventricular WMH. These findings are in keeping with the strain vessel hypothesis mentioned above, since the small vessels in the deep perforator territories are exposed to the highest pressures and are most vulnerable to damage from hypertension and other factors, such as endothelial dysfunction related to CKD.

The only study to date examining the relationship between total SVD burden and kidney disease is the Oxford Vascular Study [3], a population presenting with TIA or minor ischaemic

stroke. Although there was an unadjusted association, like us they found that the significance was attenuated when adjusting for age and other vascular risk factors. Unlike us they found that the adjusted association remained for a subgroup under the age of 60. Our study was not powered to investigate this. Another difference is that the Oxford group used an MRI-derived SVD burden score. Our findings add to this work, with similar results in a different study population.

We found an association of renal impairment with SVD burden independent of hypertension, suggesting that the observed associations are not caused by this shared risk factor. Alternative possible mechanisms for associations between renal function and cerebral SVD include endothelial dysfunction caused by uraemic toxins [14], impaired bone mineral metabolism causing vascular calcification and stiffness, or chronic inflammation [15]. The increased SVD burden at lower eGFR levels supports this hypothesis. Our logistic regression models showed a stronger association of SVD burden with age than any other risk factor as shown in many previous observational studies. We hypothesize that the longer that an individual is exposed to renal-related mechanisms of microvascular damage, the more SVD that person would accrue. This could partially explain the strong influence of age on SVD, particularly in patients without hypertension. An alternative hypothesis is that impaired renal function reflects increased severity and duration of hypertension, but we found no difference in the severity of WMH, brain atrophy, lacune count or SVD burden scores of the eGFR<60 group in those with and without hypertension (**table A.3** in the supplementary materials); this suggests that other pathogenic mechanisms are at least as important as the effects of hypertension on perforating vessels. We propose longitudinal studies of MRI SVD biomarkers, involving populations with CKD, to better investigate this possible explanation. This research could open up new therapeutic strategies to prevent SVD and its clinical consequences in patients with renal impairment.

The associations of CKD with anterior WMH (but not posterior WMH) might indicate a selective influence of renal function on anterior white matter; a posterior WMH emphasis has been reported in cerebral amyloid angiopathy (CAA) [16], a cerebral SVD less likely to be related to hypertension and renal function.

We found that renal function was associated with deep and cortical atrophy, but not cerebellar atrophy. This suggests that the cerebellum may be less vulnerable to the effects of renal impairment and associated SVD.

We did not find a higher proportion of deep ICH in the group with renal impairment compared to the reference group. Although this is contrary to what one might expect, there are few published reports of studies investigating this, and the available evidence is conflicting [17-19]. We explored the possibility that high rate of anticoagulation (54%) in the renal impairment group could have led to a higher rate of lobar ICH than expected. When anticoagulated patients were excluded, there was a lower rate of lobar ICH overall, but the reduced frequency was similar in both groups, 36.2% in the eGFR<60 group and 39.5% in the group with normal renal function (p=0.500). The similar proportions of lobar ICH in both study groups could be related to the older mean age of the eGFR<60 group (76.7 years) compared to the eGFR>60 group (71.4 years), as lobar ICH is usually more common in older populations [20]. This was the case for our study (mean age of the lobar 74.9 compared to 71.1 for the deep group, p<0.001 for the comparison of all locations).

After adjusting for age, sex and comorbidities, we did not find a statistically significant difference in functional outcome between those with eGFR<60 and those with normal kidney function. The group with renal impairment was significantly older, which is not surprising since chronic kidney disease is a condition associated with advancing age. The higher relative proportion of female participants in the eGFR<60 group may seem surprising, but this is probably because on average women live longer than men and have more time to develop CKD. This hypothesis is supported by our data since the mean age of female participants was 76.0 (SD 11.5) compared to 70.4 (SD 12.6) for male participants (p<0.001). This is reflected by the similar prevalence of chronic kidney disease for both sexes [21], despite men dying younger owing their higher rates of cardiovascular diseases and stroke.

As expected, we found higher rates of several comorbidities in patients with renal impairment, probably owing to an increased overall vascular risk factor burden. Our finding that the group with reduced eGFR had much higher rates of AF is previously well documented. Population based studies have shown that the prevalence of AF is approximately 1 in 5 for the non-dialysis CKD population, and as high as 1 in 3 for those on dialysis [22, 23] compared to a background worldwide prevalence of 2.5 to 3.2% [24]. This difference is probably caused by the high rates of hypertension and ischaemic heart disease in those with kidney disease. The higher median pre-stroke modified Rankin Score (mRS) in the eGFR<60 group also likely reflects increased comorbidity, age and frailty in this group.

Unlike a large USA registry study [25], we did not find a significant difference in mortality between the two study groups, after adjusting for age and baseline functional status. The probable reason for this is that CROMIS-2 was a survivor study, so some early deaths from ICH will not have been included.

The main strengths of this study are its relatively large sample size, and the completeness of the CT imaging and outcome data available. Its multi-centre UK-wide design give a representative sample of the UK population, and the blinding of the imaging analysis to the outcomes and clinical data provides robust results. We are not aware of previous studies investigating associations of CT markers with CKD; whilst acknowledging that MRI is a more sensitive imaging modality to detect SVD, our findings could have increased clinical relevance given the widespread access to CT in clinical practice. This is particularly true in places with limited or no access to MRI, such as the developing world.

A significant limitation of this study was the inability to detect acute kidney injury (AKI) as the cause of the renal impairment. Any undetected AKI would bias the results in favour worse functional outcome since any AKI is well known to be associated with mortality and poor outcome. However, we did not find worse functional outcome for the eGFR<60 group in the adjusted analysis, so the impact of this limitation can be estimated to be small. The impact on the imaging analysis is more difficult to predict. The majority of published reports on the relationship between renal impairment and SVD do not account for AKI, and we propose future studies specifically designed to investigate this. Another limitation of this study is the potential selection bias introduced by the survivor cohort design, which meant that on average patients had less severe ICH with smaller volumes than would be expected from an unselected cohort. A final limitation is the low rate of MRI SVD markers.

5. Conclusions

This study has demonstrated that cerebral small vessel disease is very common in a population with renal impairment presenting with intracerebral haemorrhage. The association of renal function with SVD burden even after adjustment for hypertension suggests that other factors may contribute to SVD in renal patients; this may have implications for prevention and treatment of renal and cerebral small vessel diseases. Our study shows that renal impairment on presentation identifies patients with acute ICH who are more likely

to have severe SVD and poor functional outcome. It is likely that CT is an insufficiently sensitive imaging modality to detect associations of renal impairment and SVD independent of age. Future prospective and longitudinal studies, including MRI, should help to better characterise the associations of CKD with cerebral SVD and stroke outcomes. If independent associations are found, this would suggest that further research is needed to identify suitable SVD treatments in those with CKD.

Supplementary materials

Table A.1: Demographics of participants excluded from functional outcome analysis

	Included		Excluded		p
n	900		127		
Mean age, yr (SD)	73.0	(12.1)	71.2	(15.2)	0.136
Sex, male n (%)	509	(56.6)	77	(60.6)	0.385
Ethnicity					
White	788	88.3	103	81.1	**<0.001**
Black	37	4.2	17	13.4	
Asian	50	5.6	5	3.9	
Other	17	1.9	2	1.6	
Comorbidities					
eGFR<60	241	(26.8)	33	(26.0)	0.850
Hypertension	604	(67.9)	78	(63.1)	0.315
Diabetes	164	(18.3)	26	(20.8)	0.498
Previous ischaemic stroke	110	(12.4)	22	(18.3)	0.072
Previous TIA	105	(12.2)	13	(11.3)	0.790
Previous ICH	37	(4.1)	11	(8.7)	**0.024**
Previous MI	75	(8.4)	9	(7.3)	0.661
Previous PCI	60	(6.7)	9	(7.1)	0.859
Angina	62	(7.0)	12	(9.7)	0.287
AF	315	(38.0)	40	(34.5)	0.464
Mean eGFR, ml/min (SD)	76.5	(27.1)	76.4	(25.6)	0.972
Medications					
Anticoagulants	370	(41.1)	46	(36.5)	0.324
Warfarin	341	(38.0)	41	(32.5)	0.234
DOAC	23	(2.6)	4	(3.2)	0.673
Antiplatelets	210	(23.5)	37	(30.1)	0.108
Median follow up, days	234	(193 - 610)	197.5	(182.5 - 893.5)	0.410

eGFR estimated glomerular filtration rate, *TIA* transient ischaemic attack, *ICH* intracerebral haemorrhage, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *AF* atrial fibrillation, *mRS* modified Rankin score, *DOAC* directly-acting oral anticoagulant

Table A.2: Univariable ordinal logistic regression analysis for odds of increased SVD burden score

Variable	OR	95% CI	p
eGFR<60	1.39	1.07 - 1.81	**0.013**
Age	1.07	1.06 - 1.09	**<0.001**
Sex, female	1.59	1.26 - 2.02	**<0.001**
Ethnicity			
White			Ref.
Asian	0.38	0.21 - 0.68	**0.002**
Black	0.54	0.31 - 0.94	
Other	0.78	0.34 - 1.83	
Previous ischaemic stroke	2.02	1.44 - 2.85	**<0.001**
Previous TIA	1.40	0.97 - 2.01	**0.071**
Previous ICH	2.78	1.63 - 4.76	**<0.001**
Hypertension	1.22	0.95 - 1.57	0.122
Hypercholesterolaemia	1.26	0.99 - 1.60	0.056
Diabetes	1.03	0.76 - 1.40	0.832
Previous smoking	0.98	0.77 - 1.24	0.854
Current alcohol use	0.85	0.58 - 1.24	0.393
Previous MI	0.71	0.55 - 0.90	0.006
Previous PCI	1.31	0.86 - 1.98	0.207
Congestive HF	1.30	0.82 - 2.04	0.260
Angina	2.07	1.22 - 3.50	**0.007**
Peripheral arterial disease	1.28	0.82 - 1.99	0.272
Dementia or Cog Impairment	1.68	0.92 - 3.05	0.088
AF	3.83	2.51 - 5.86	**<0.001**
Anticoagulant use	1.95	1.52 - 2.51	**<0.001**
Pre-stroke mRS			
1	2.34	1.68 - 3.27	**<0.001**
2	2.91	1.98 - 4.28	**<0.001**
3	4.78	3.18 - 7.17	**<0.001**
4	4.23	2.06 - 8.68	**<0.001**
5	17.71	3.18 - 98.62	**0.001**

eGFR estimated glomerular filtration rate, *TIA* transient ischaemic attack, *ICH* intracerebral haemorrhage, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *AF* atrial fibrillation, *mRS* modified Rankin score

Table A.3: Cerebral small vessel disease markers according to blood pressure in the eGFR<60 group

	Score/n	Hypertensive, n (%)		Normotensive, n (%)		p
Atrophy						
Cortical Atrophy	0	24	(11.7)	6	(9.1)	0.579
	1	134	(65.4)	41	(62.1)	
	2	47	(22.9)	19	(28.8)	
Deep Atrophy	0	41	(20.0)	10	(15.2)	0.680
	1	106	(51.7)	36	(54.6)	
	2	58	(28.3)	20	(30.3)	
Cerebellar Atrophy	0	108	(52.7)	29	(43.9)	0.431
	1	73	(35.6)	29	(43.9)	
	2	24	(11.7)	8	(12.1)	
Van Swieten Score						
Anterior Choroid	0	113	(54.6)	35	(53.0)	0.913
	1	63	(30.6)	22	(33.3)	
	2	30	(14.6)	9	(13.6)	
Anterior Cella	0	132	(64.1)	39	(59.1)	0.711
	1	38	(18.5)	15	(22.7)	
	2	36	(17.5)	12	(18.2)	
Posterior Cella	0	122	(59.2)	40	(60.6)	0.318
	1	40	(19.4)	8	(12.1)	
	2	44	(21.4)	18	(27.3)	
Posterior Cingulate Cortex	0	148	(71.8)	46	69.7	0.694
	1	29	(14.1)	12	18.2	
	2	29	(14.1)	8	12.1	
Lacunes						
Total	0	187	90.3	60	89.6	0.409
	1	15	7.3	4	6.0	
	≥2	5	2.5	3	4.5	
Combined SVD burden score	0	98	47.3	30	44.8	0.953
	1	72	34.8	23	34.3	
	2	34	16.4	14	20.9	
	3	3	1.5	1	1.5	
Combined SVD burden score, median (IQR)		1 (0-1)		1 (0-1)		0.622

eGFR estimated glomerular filtration rate, *IS* ischaemic stroke, *TIA* transient ischaemic attack, *AF* atrial fibrillation, *SVD* small vessel disease

References

1. Lee M, Saver JL, Chang KH, Liao HW, Chang SC, Ovbiagele B (2010) Low glomerular filtration rate and risk of stroke: meta-analysis. BMJ 341:c4249. DOI: 10.1136/bmj.c4249
2. Kelly DM, Rothwell PM (2019) Does Chronic Kidney Disease Predict Stroke Risk Independent of Blood Pressure?: A Systematic Review and Meta-Regression. Stroke 50:3085-3092. DOI: 10.1161/STROKEAHA.119.025442
3. Liu B, Lau KK, Li L, Lovelock C, Liu M, Kuker W, Rothwell PM (2018) Age-Specific Associations of Renal Impairment With Magnetic Resonance Imaging Markers of Cerebral Small Vessel Disease in Transient Ischemic Attack and Stroke. Stroke 49:899-904. DOI: 10.1161/STROKEAHA.117.019650
4. Charidimou A, Wilson D, Shakeshaft C, Ambler G, White M, Cohen H, Yousry T, Al-Shahi Salman R, Lip G, Houlden H, Jager HR, Brown MM, Werring DJ (2015) The Clinical Relevance of Microbleeds in Stroke study (CROMIS-2): rationale, design, and methods. Int J Stroke 10 Suppl A100:155-161. DOI: 10.1111/ijs.12569
5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461-470. DOI: 10.7326/0003-4819-130-6-199903160-00002
6. Group KDIGOKCW (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. In:International Society of Nephrology
7. Charidimou A, Schmitt A, Wilson D, Yakushiji Y, Gregoire SM, Fox Z, Jager HR, Werring DJ (2017) The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): Development and assessment of reliability. J Neurol Sci 372:178-183. DOI: 10.1016/j.jns.2016.11.021
8. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR, Black SE, Brayne C, Breteler M, Chabriat H, Decarli C, de Leeuw FE, Doubal F, Duering M, Fox NC, Greenberg S, Hachinski V, Kilimann I, Mok V, Oostenbrugge R, Pantoni L, Speck O, Stephan BC, Teipel S, Viswanathan A, Werring D, Chen C, Smith C, van Buchem M, Norrving B, Gorelick PB, Dichgans M, nEuroimaging STfRVco (2013) Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 12:822-838. DOI: 10.1016/S1474-4422(13)70124-8
9. van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J (1990) Grading white matter lesions on CT and MRI: a simple scale. J Neurol Neurosurg Psychiatry 53:1080-1083. DOI: 10.1136/jnnp.53.12.1080
10. Arba F, Mair G, Carpenter T, Sakka E, Sandercock PAG, Lindley RI, Inzitari D, Wardlaw JM, Collaborators ISTT (2017) Cerebral White Matter Hypoperfusion Increases with Small-Vessel Disease Burden. Data From the Third International Stroke Trial. J Stroke Cerebrovasc Dis 26:1506-1513. DOI: 10.1016/j.jstrokecerebrovasdis.2017.03.002

11. Ito S, Nagasawa T, Abe M, Mori T (2009) Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens Res 32:115-121. DOI: 10.1038/hr.2008.27
12. Seliger SL, Siscovick DS, Stehman-Breen CO, Gillen DL, Fitzpatrick A, Bleyer A, Kuller LH (2004) Moderate renal impairment and risk of dementia among older adults: the Cardiovascular Health Cognition Study. J Am Soc Nephrol 15:1904-1911. DOI: 10.1097/01.asn.0000131529.60019.fa
13. Tsai YH, Lee M, Lin LC, Chang SW, Weng HH, Yang JT, Huang YC, Lee MH (2018) Association of Chronic Kidney Disease With Small Vessel Disease in Patients With Hypertensive Intracerebral Hemorrhage. Front Neurol 9:284. DOI: 10.3389/fneur.2018.00284
14. Lano G, Burtey S, Sallee M (2020) Indoxyl Sulfate, a Uremic Endotheliotoxin. Toxins (Basel) 12DOI: 10.3390/toxins12040229
15. Marini S, Georgakis MK, Anderson CD (2021) Interactions Between Kidney Function and Cerebrovascular Disease: Vessel Pathology That Fires Together Wires Together. Front Neurol 12:785273. DOI: 10.3389/fneur.2021.785273
16. Hostettler IC, Schwarz G, Ambler G, Wilson D, Banerjee G, Seiffge DJ, Shakeshaft C, Lunawat S, Cohen H, Yousry TA, Al-Shahi Salman R, Lip GYH, Brown MM, Muir KW, Houlden H, Jager HR, Werring DJ, Collaborators C- (2021) Cerebral Small Vessel Disease and Functional Outcome Prediction After Intracerebral Hemorrhage. Neurology 96:e1954-e1965. DOI: 10.1212/WNL.0000000000011746
17. Ovbiagele B, Wing JJ, Menon RS, Burgess RE, Gibbons MC, Sobotka I, German L, Shara NM, Fernandez S, Jayam-Trouth A, Edwards DF, Kidwell CS (2013) Association of chronic kidney disease with cerebral microbleeds in patients with primary intracerebral hemorrhage. Stroke 44:2409-2413. DOI: 10.1161/STROKEAHA.113.001958
18. Zheng D, Sato S, Arima H, Heeley E, Delcourt C, Cao Y, Chalmers J, Anderson CS, Investigators I (2016) Estimated GFR and the Effect of Intensive Blood Pressure Lowering After Acute Intracerebral Hemorrhage. Am J Kidney Dis 68:94-102. DOI: 10.1053/j.ajkd.2016.01.020
19. Fukuda-Doi M, Yamamoto H, Koga M, Doi Y, Qureshi AI, Yoshimura S, Miwa K, Ishigami A, Shiozawa M, Omae K, Ihara M, Toyoda K (2021) Impact of Renal Impairment on Intensive Blood-Pressure-Lowering Therapy and Outcomes in Intracerebral Hemorrhage: Results From ATACH-2. Neurology 97:e913-e921. DOI: 10.1212/WNL.0000000000012442
20. Roh D, Boehme A, Young C, Roth W, Gutierrez J, Flaherty M, Rosand J, Testai F, Woo D, Elkind MSV (2020) Hematoma expansion is more frequent in deep than lobar intracerebral hemorrhage. Neurology 95:e3386-e3393. DOI: 10.1212/WNL.0000000000010990
21. Wetzels JF, Kiemeney LA, Swinkels DW, Willems HL, den Heijer M (2007) Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. Kidney Int 72:632-637. DOI: 10.1038/sj.ki.5002374
22. Ananthapanyasut W, Napan S, Rudolph EH, Harindhanavudhi T, Ayash H, Guglielmi KE, Lerma EV (2010) Prevalence of atrial fibrillation and its predictors in nondialysis patients with chronic kidney disease. Clin J Am Soc Nephrol 5:173-181. DOI: 10.2215/CJN.03170509

23. Wetmore JB, Mahnken JD, Rigler SK, Ellerbeck EF, Mukhopadhyay P, Spertus JA, Hou Q, Shireman TI (2012) The prevalence of and factors associated with chronic atrial fibrillation in Medicare/Medicaid-eligible dialysis patients. Kidney Int 81:469-476. DOI: 10.1038/ki.2011.416
24. Alonso A, Bengtson LG (2014) A rising tide: the global epidemic of atrial fibrillation. Circulation 129:829-830. DOI: 10.1161/CIRCULATIONAHA.113.007482
25. Ovbiagele B, Schwamm LH, Smith EE, Grau-Sepulveda MV, Saver JL, Bhatt DL, Hernandez AF, Peterson ED, Fonarow GC (2014) Hospitalized hemorrhagic stroke patients with renal insufficiency: clinical characteristics, care patterns, and outcomes. J Stroke Cerebrovasc Dis 23:2265-2273. DOI: 10.1016/j.jstrokecerebrovasdis.2014.04.016