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Full Length Research Paper

Cerebral Microbleeds in Egyptian Patients with Chronic Kidney Disease on Regular Haemodialysis

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Abstract

Background: Gradient-echo T2-weighted magnetic resonance imaging (T2*-weighted MRI) is highly sensitive for detecting cerebral microbleeds (CMBs). In haemodialysis patients, previous studies have delineate a high prevalence of cerebral microbleeds (CMBs), but no other reports have been achieved to describe the clinical impact of CMBs in these patients.In the present study, we analyzed the prevalence of CMBs and its existence was a prognostic factorfor subsequent cerebrovascular stroke (especially ICH) in CKD patients on haemodialysis patients. Methods: In this prospective study, T2*-weighted magnetic resonance imaging, was performed on 47 hemodialysis patients with no past history of cerebrovascular events. Subjects were divided into 2 groups with and without CMBs. Patients with cerebral microbleeds were classified according to the site of microbleeds into supratentorial and infratentorial cerebral microbleeds. Results: CMBs were found in 12 CKD patients on regular hemodialysis (25.5%), but not in control subjects. There were a significant higher proportion of CMB-related risk factors in haemodialysis patients such as hypertension, diabetes, atrial fibrillation, anticoagulation therapy and dyslipidemia in the form of elevated total cholesterol and triglycerides (all $p < 0.05$). There was statistically significant difference between haemodialysis patients with CMB and those without CBM as regard to supratentorial location of CMB with $p < 0.001$, but no statistically significant difference between haemodialysis patients with CMB and those without CBM as regard to infratentorial location of CMB with $p=0.06$. In the subgroup of haemodialysis patients with supratentorial CMB, there were statistically significant differences as regard to the presence of diabetes mellitus, hypertension, and elevated cholesterol level ($p < 0.05$), but no statistically significant differences as regard to age, sex, atrial fibrillation, triglyceride levels, presence of SLE, duration of dialysis, mean blood urea and serum creatinine and anticoagulant therapy when compared with haemodialysis patients without supratentorial CMBs.In the subgroup of haemodialysis patients with infratentorial CMB, there were statistically significant differences as regard to the presence of atrial fibrillation and anticoagulant therapy ($p < 0.05$), but no statistically significant difference as regard to age, sex, presence of DM, presence of HTN, dyslipidemia (total cholesterol and triglyceride levels), presence of SLE, duration of dialysis, mean blood urea and serum creatinine when compared with haemodialysis patients without infratentorial CMB. Conclusion: This study showed that altered renal function, presence of dyslipidemia, atrial fibrillation, anticoagulation therapy and hypertension were significantly and independently associated with the presence of CMBs in HD patients indicating that haemodialysis patients with CMBs should be carefully monitored for future occurrence of intracerebral hemorrhage. CMBs as assessed by T2*-weighted MRI, would be a useful and feasible clinical marker for the prediction of future intracerebral hemorrhages in stroke-free haemodialysis patients.*

Keywords: *Microbleeds, Kidney, Disease, Regular, Haemodialysis.*

Introduction

With the advent of MRI protocols, usage of sensitive techniques to paramagnetic blood products, such as T2- weighted gradient-recalled echo (GRE) resulted in recognition of cerebral microbleeds (CMBs) always in increasing numbers of patients. CMBs are defined as small, rounded, homogeneous, hypointense foci on T2*-weighed gradient-recalled echo (T2*-GRE) (1). They are not commonly seen on conventional magnetic resonance imaging (cMRI) or computed tomography (CT) imaging. CMBs diagnosed by Gradient MRI appear to correlate histologically to small focal mass areas of blood-disintegration products leaking out from injured delicate small cerebral blood vessels into adjacent brain tissues and are prognostic impact of bleeding in about cerebrovascular diseases, such as cerebral amyloid angiopathy (CAA) and hypertensive vasculopathy (2, 3). Among the risk factors for CMBs, advanced age (4, 5), high blood pressure (7, 8), hyperglycemia (6), hypocholesterolemia (7, 9), and APOE 4 carriership (10) have been established in some cohorts with cerebrovascular strokes or community-residence elderly subjects. In particular, older age and high blood pressure are most widely associated with CMBs. It has also been described that CMBs anticipate the future possibility of spontaneous intracerebral hemorrhage (ICH) and ischemic stroke (IS) in patients after development of ICH(11, 12), IS (13), and

transient ischemic attack (11, 12), as well as in strokefree individuals (14, 15).Recently, cerebral microbleeds (CMBs) have become detectable to a high degree of sensitivity with Gradient-echoT2*-weighted magnetic resonance imaging (T2*-weightedMRI), while they can barely be visualized with other conventional scans (16, 17). T2*-weighted MRI sensitively detects small areas of signal loss, which represent remnants of previous CMBs (16, 17). This T2* effect develops through local magnetic field variabilities caused by haemosiderin precipitates. It has been confirmed pathologically that the CMBs on T2*-MRI represent minor blood leakage through damaged blood vessels, in addition to minor hemorrhage (16, 17, 18). The existance of CMBs has been described to be linked with cerebrovascular events (17, 19, 20, and 23). It has been identified that with advanced stage of microangiopathy, the cerebral blood vessels are more liable to develop bleeding (17, 18, 19, 20, and 23). Kato et al (17) reported that 71.4% of patients with clinically evident cerebral hemorrhage had CMBs. Thus, CMBs have been accounted to demonstrate a higher probability of future intracerebralhemorrhage and to be an identifiable marker of cerebral small vessel disease in the general population (16, 17, 18, 20, 21, 22, and 23).

The widespread occurrence of CMBs in normal populations without cerebrovascular disease averages from 3.1 to 6.4% (20, 21, 22), 18% to 68%in patients with IS and 47% to 80% in patients with ICH (5, 22). In spite of the fact that haemodialysis (HD) not only an advantageous way to remove the uremic waste products such as high blood urea and serum creatinine for maintaining the life of patients with end-stage renal diseases(ESRD), but also can result in small cerebrovascular disorders, such as cerebral infarction, cerebral hemorrhage, and CMBs (24, 25,26). It has been reported that cerebrovascular disease is one of the leading causes of death in patients with haemodialysis (25). In these cerebrovascular diseases, intracerebral hemorrhage, which is more prevalent and fatal condition can be preceded by CMBs (27). To predict the existence of intracerebral hemorrhage in patients with haemodialysis, it might be convenient to recognize the small cerebrovascular disorders, especially microbleeds. Prior studies have explained a high prevalence of CMBs of 19.3% to 35% (25, 26, and 28). However, there have been no longitudinal studies to detect the clinical importance of CMBs in haemodialysis patients. In the present study, we evaluated the prevalence of CMBs and its existence was a predictor of future cerebrovascular stroke (particularly ICH) in haemodialysis patients.

Patients and methods

This prospective study consisted of 47 patients with chronic renal failure maintained on regular haemodialysis but no previous history of stroke who were referred to the Department of Radio-Diagnosis at Al-HuseinUniversity Hospital, Cairo, Egypt from January 2013 to October 2015. MRI imaging used a superconducting magnet at field strength of 1.5 T Philips Achiva machine. T1-, T2- weighted, fluid-attenuated inversion recovery (FLAIR) MRI, and 2-dimensional gradient-echo (repetition time, 606 ms; echo time, 23 ms; flip angle, 18°–20°; field of view, 200 mm; acquisition matrix, 256×175–224). T2*-weighted MRI in axial planes at 5-mm thick slices with an interslice gap of 1.5 mm.

Informed consent was obtained from all patients. The imaging features of the 47 patients were compared with age- and sex-matched control group of 43 patients without previous history of stroke or chronic renal failure who underwent brain screening during the same period.

Inclusion Criteria: All patients who were diagnosed to have stage 5 chronic kidney disease (estimated glomerular filtration rate [eGFR] <15 mL/min/1.73m2) on regular haemodialysis and presented with neurological symptoms were imaged. the age of patients was 18 years or above; all had haemodialysis 3 times weekly using the same device of Fresenius 4008S Haemodialysis System (Fresenius SE & Co. KGaA, Bad Homburg, Germany) in Haemodialysis Unit at Al-Husein University Hospital; all had the same types of dialysis concentrates and membranes and dialysis dose for haemdialysis; all had the same anticoagulants and antithrombotic agent therapeutic regimens to reduce the risk of bleeding during the haemodialysis according to the guiding principles for hemodialysis treatment; each haemodialysis time session took 4 hours to make sure about adequate dialysis; and all the informations about MRI from HD patients were attainable including: T1WI, T2WI, and SWI.

Exclusion Criteria: Traumaticbrain injury, AD, previous obvious ischemic stroke and hemorrhagic stroke, autosomal dominant polycystic kidney disease, chronic infection, chronic inflammatory disease, malignant disease, drug abuse, liver diseases, kidney transplantation, and neuropsychiatric diseases or epilepsy; the congenital abnormal structural findings were shown in the standard MRI, and the value of the images was not good enough to observe the brain abnormalities clearly.

MRI Parameters

All MRI data were obtained using a superconducting magnet at a field strength of 1.5 T on proton density, T1-, T2- weighted fluid-attenuated inversion recovery MRI, and 2-dimensional gradient-echo (repetition time, 606 ms; echo time, 23 ms; flip angle, 18°–20°; field of view, 200 mm; acquisition matrix, 256×175–224) T2*-weighted MRI in axial planes at 5-mm thick slices with an interslice gap of 1.5 mm. The number of CMBs was manually counted by 2 experienced and trained neuroradiologists, both of them were not known the clinical information of patients. The ultimate number of CMBs was detected after the discussion. The recognition of CMBs should fulfill the following inclusion criteria: small round or ovoid uniform hypointensity with a diameter of 2 to 10mm (blooming effect) on T* WI MRI, no hyperintensity on T1-weighted image or T2-weighted image to rule out cavernous hemangioma; at least half of the lesion was surrounded by brain parenchyma; the lesions should be distinguished from other microbleed mimics, such as

calcified lesions, vascular flow voids, or iron precipitating lesions; and the patients without history of traumatic scattered axonal injury.

When 47 patients with CKD on regular haemodialysis finished their brain follow-up MRI examinations, the number of CMBs was calculated and differentiated by an experienced and trained neuroradiologist, who did not know the clinical data and the number of CMBs of patients at the initial examination (Figures 1 and 2).

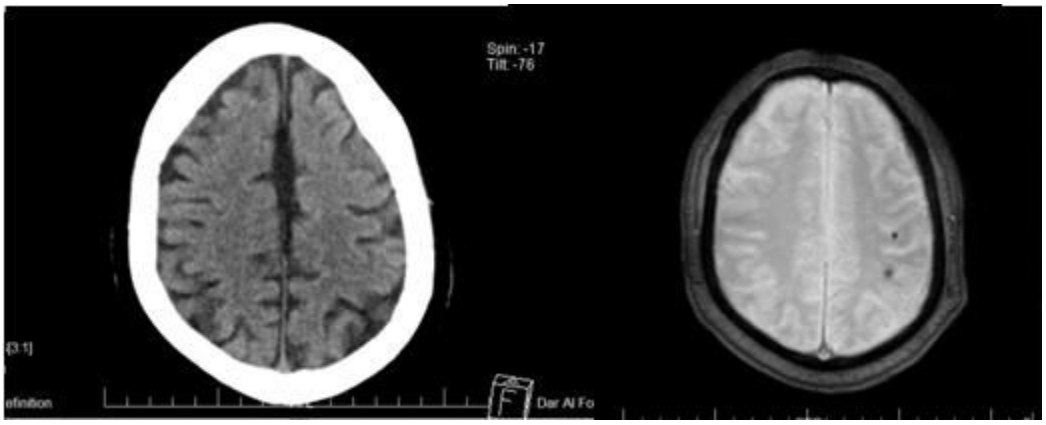

Fig 1: Right image, male patient 64 years old CT brain with no evidence of hemorrhagic changes or calcifications. Left image, T2* shows left high fronto-parietal hypointense foci related to blooming effect of microbleeds.

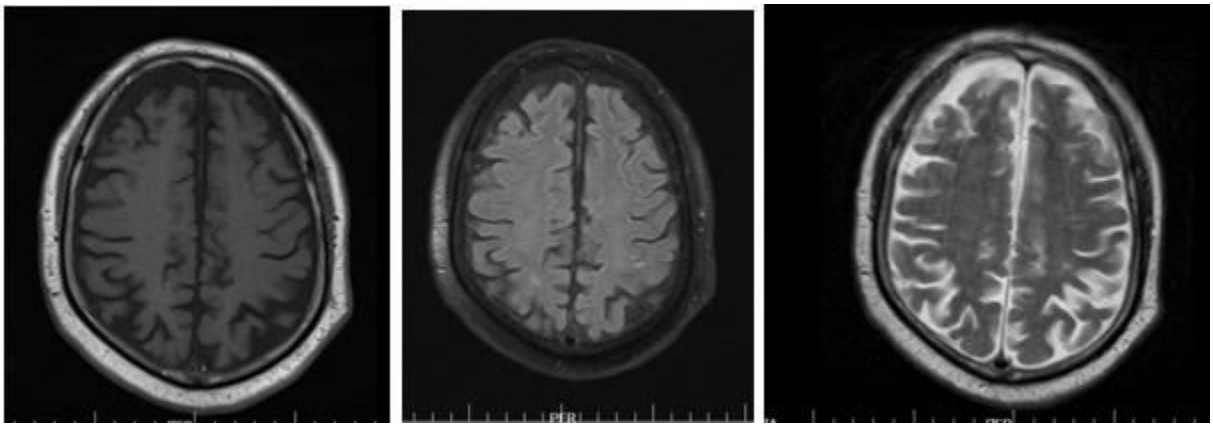

Fig 2: Left image; T1 WIs, Middle image; FLAIR image and left image; T2 WIs for the same patient in figure 1. There is no abnormal signal corresponding to the lesions seen on T2* WI in figure 1.

Laboratory Examination and Definition of Traditional Risk Factors

The age; dialysis duration; anticoagulation, systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse pressure (PP) before and after hemodialysis sessions; complete blood count; blood urea; serum creatinine; lipid profile; parathyroid hormone (PTH); and the presence or absence of diabetes mellitus (DM) were recorded. The above blood samples were collected from our patients with within seven days before MRI examination.

Hypertension was defined by (1) the administration of antihypertensive agents or a history of this disorder; (2) a systolic blood pressure >140 mm Hg; or (3) a diastolic blood pressure >90 mm Hg, and blood pressure was measured before the hemodialysis sessions. DM was defined by (1) the intake of insulin or oral antidiabetic agents or (2) defined according to the WHO criteria (The ExpertCommittee on the Diagnosis and Classification of Diabetes Mellitus, 2003). Hyperlipidemia was defined if the subject exhibited total cholesterol >200 mg/ dL, triglyceride >150 mg/dL, or a history of drug intake for lipid abnormalities. Blood samples were drawn from the arterial line before the haemodialysis sessions. Atrial fibrillation was diagnosed according to electrocardiographic findings or a prior history of atrial fibrillation.

Results

There was no significant difference between haemodialysis patients and controls as regard to age and sex. Hypertension was found in 23 of the 47 haemodialysis patients (48.9 %) and 11 of the 43 controls (25.6 %) with a significantly higher incidence in the haemodialysis patients ($p < 0.022$). Type 2 diabetes mellitus was found in 30 haemodialysis patients (63.8 %) and 10 of the 43

controls with a highly significant incidence in the haemodialysis patients ($p < 0.001$). Atrial fibrillation and anticoagulant therapy were found in 9 haemodialysis patients (19.9 %) and 1 of the 43 controls (2.3 %) in both with a significantly higher incidence in the haemodialysis patients ($p < 0.028$). The mean blood urea and serum creatinine were significantly higher in haemodialysis patients than the controls with the P value < 0.001 for both as shown in table 1.

Table 1: Comparison between patients and controls

	Case group (47)	Control group (43)	t- test	P value
Age				
Mean±SD	55.96 ± 3.25	55.72 ± 2.77	0.37#	0.71
Range	50 - 60	50 - 60		
Sex N (%)				
Male	27 (57.4)	33 (76.7)	3.76$	0.052
Female	20 (42.6)	10 (23.3)		
AF N (%)	9 (19.1)	1 (2.3)	4.84^	0.028*
DM N (%)	30 (63.8)	10 (23.3)	14.97$	0.001**
HTN N (%)	23 (48.9)	11 (25.6)	5.21$	0.022*
Urea				
Mean±SD	115.7 ± 50.82	30.47 ± 8.02	10.87#	0.001**
Range	55-200	20-51		
Creatinine				
Mean ± SD	7.06±1.89	0.81±0.26	21.46#	0.001**
Range	4-10	0.4-1		
MRI-MB N (%)	12 (25.5)	0 (0.0)	12.67$	0.001**
Anticoagulants N (%)	9 (19.1)	1 (2.3)	4.84^	0.028*

*#= Student t test $=Chi square ^=Fischer exact test *= Significant **=highly significant*

The prevalence of CMB in haemodialysis patients was 25.5% (n = 12), with 4.3% (n = 2) of CMBs located in the infratentorial regions and 21.3 (n=10) CMBs located in the supratentorialregions. Patients with CMB were not statistically significant from those without CMB as regard to both age and sex ($p = 0.65$ *and* 0.45) respectively. There was no statistically significant difference between patients with CMB and those without CMB as regard to both blood urea and serum creatinine ($p = 0.31, 0.12$) respectively. They also showed a higher proportion of CMB-related risk factors such as hypertension, diabetes, atrial fibrillation, anticoagulation therapy and dyslipidemia in the form of elevated total cholesterol and triglycerides (all $p < 0.05$). There was statistically significant difference between haemodialysis patients with CMB and those without CBM as regard to supratentorial location of CMB with $p < 0.001$, but no statistically significant difference between haemodialysis patients with CMB and those without CBM as regard to infratentorial location of CMB with p=0.06 as shown in table 2.

Table 2: Comparison between haemodialysis patients with and without cerebral microbleeds

MRI-MB	Cases with microbleeds (12)	Cases without microbleeds (35)	t- test	P value
Age				
Mean ± SD	56.33± 3.14	55.83 ± 3.32	0.46#	0.65
Range				
Sex N (%)				
Male	8 (66.7)	19 (54.3)	0.56$	0.45
Female	4 (33.4)	16 (45.7)		
AF N (%)	6(50)	3 (8.6)	9.9^	0.005**
DM N (%)	3(25)	27(77.1)	10.52^	0.004**
HTN N (%)	12(100)	11(31.4)	16.82$	0.001**
SLE N (%)	3(25)	4(11.4)	1.3^	0.35
Cholesterol N (%)	10(83.3)	16(45.7)	5.12$	0.024*
TG N (%)	10(83.3)	14(40)	6.72$	0.01*
Duration of dialysis				
Mean ± SD	5.5±0.90	5.57±1.01	0.22#	0.83
Range				
Urea				
Mean ± SD	128.75±55.85	111.23±49.03	1.03#	0.31
Range				
Creatinine				

Mean ± SD	6.33±1.83	7.31±1.88	1.57#	0.12
Range				
Site (Infratentorial) No. (%)	2(16.7)	0(0.0)	6.09^	0.06
Site (Supratentorial) No. (%)	10(83.3)	0(0.0)	37.05^	0.001**

*#= Student t test $=Chi square ^=Fischer exact test *= Significant **=highly significant*

In the subgroup of haemodialysis patients with supratentorial CMB, there were statistically significant differences as regard to the presence of diabetes mellitus, hypertension, and elevated cholesterol level ($p < 0.05$), but no statistically significant differences as regard to age, sex, atrial fibrillation, triglyceride levels, presence of SLE, duration of dialysis, mean blood urea and serum creatinine and anticoagulant therapy when compared with haemodialysis patients without supratentorial CMBs as shown in table 3.

Table 3: Comparison between haemodialysis patients with and without supratentorialmicrobleeds

Site (Supratentorial)	Positive I (10)	Negative 0 (37)	t-test	P value
Age				
Mean ± SD	55.9±3.28	55.97±3.29	0.06#	0.95
Range	51-60	50-60		
Sex N (%)				
Male	6(60)	21(56.8)	0.034^	1.0
Female	4(40)	16(43.2)		
AF N (%)	4(40)	5(13.5)	3.57^	0.08
DM N (%)	2(20)	28(75.7)	10.57$	0.001**
HTN N (%)	10(100)	13(35.1)	13.3^	0.001**
SLE N(5)	3(30)	4(10.8)	2.29^	0.16
Cholesterol N (%)	9(90)	17(45.9)	6.18^	0.015*
TG N (%)	8(80)	16(43.2)	4.26^	0.07
Duration of dialysis				
Mean ± SD	5.3±0.82	5.62±1.01	0.93#	0.36
Range	4-7	4-7		
Urea				
Mean ± SD	124.8±56.06	113.24±49.85	0.63#	0.53
Range	55-200	60-200		
Creatinine				
Mean ± SD	6.1±1.91	7.32±1.83	1.86#	0.07
Range	4-10	4-9		
MRI-MB N (%)	10(100)	2(5.4)	37.05^	0.001**
Anticoagulants N (%)	4(40)	5(13.5)	3.57^	0.08

*#= Student t test $=Chi square ^=Fischer exact test *= Significant **=highly significant*

In the subgroup of haemodialysis patients with infratentorial CMB, there were statistically significant differences as regard to the presence of atrial fibrillation and anticoagulant therapy ($p < 0.05$), but no statistically significant difference as regard to age, sex, presence of DM, presence of HTN, dyslipidemia (total cholesterol and triglyceride levels), presence of SLE, duration of dialysis, mean blood urea and serum creatinine when compared with hemodialysis patients without infratentorial CMB as shown in table 4.

Table 4: Comparison between haemodialysis patients with and without infratentorialmicrobleeds

Site (Infratentorial)	Positive I (2)	Negative 0 (45)	t-test	P value
Age				
Mean ± SD	58.9±0.71	55.84±3.27	1.13#	0.26
Range	50-60	58-59		
Sex N (%)				
Male	2(100)	25(55.6)	1.55^	0.50
Female	0(0.0)	20(44.4)		
AF N (%)	2(100)	7(15.6)	8.82^	0.033*
DM N (%)	1(50)	29(64.4)	0.17$	1.0
HTN N (%)	2(100)	21(46.7)	2.18^	0.14
SLE N(5)	0(0.0)	7(15.6)	0.37^	1.0
Cholesterol N (%)	1(50)	25(55.6)	0.024^	1.0

TG N (%)	2(100)	22(48.9)	2.0^	0.49
Duration of dialysis				
Mean ± SD	6.5±0.71	5.51±0.97	1.42#	0.16
Range	4-7	6-7		
Urea				
Mean ± SD	148.5±71.42	114.24±50.33	0.93#	0.36
Range	55-200	98-199		
Creatinine				
Mean ± SD	7.5±0.17	7.04±1.93	0.33#	0.74
Range	4-10	7-8		
MRI-MB N (%)	2(100)	10(22.2)	6.09^	0.06
Anticoagulants N (%)	2(100)	7(15.6)	8.82^	0.033*

*#= Student t test $=Chi square ^=Fischer exact test *= Significant **=highly significant*

Discussion

Recent studies show that individuals with progressive chronic kidney disease have a greater risk of cardiovascular events, hospitalization and death (32). Chronic kidney disease (CKD) is frequent in patients with acute cerebrovascular stroke with ratio ranging from 20–35% in ischemic stroke and from 20–46% in intracerebral hemorrhage (29, 33). Previously, a higher four to ten times prevalence of stroke in dialysis patients have been reported (33). It is well known that CKD is an expected and urgent possible risk factor generally for cardiovascular disease and especially for cerebrovascular disease. Chronic kidney disease is defined either by a decrease in the estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m2 or by the presence of albuminuria as a marker of an increased glomerular permeability (34). It denotes also a poor prognosis factor in patients with acute cerebrovascular stroke and its existence has been linked to stroke severity and poor impact on ischemic and hemorrhagic stroke. A study by Toyoda reported that patients with CKD had a 49% greater risk of neurological deterioration during hospital stay and in-hospital mortality, and higher degree of disability at discharge according to the modified Rankin scale score of 2 or more than patients without CKD. It has been reported that, there is a greater risk of recurrence of non-cardioembolic stroke in CKD patients (33). This unsatisfactory neurological prediction may be caused by the presence of proteinuria and albuminuria in these patients, and both conditions are importantly associated with high levels of inflammatory cytokines and oxidative stress, inflammation and conditions enhancing coagulation,potentially causing excessive vascular damage at stroke onset. These factors are also accompanied with hastened atherosclerosis and endothelial dysfunction. Albuminuria is also predictive of hemorrhagic transformation of stroke (29).

In this study, we found that haemodialysis patients had a significantly higher incidence of cerebral microbleeds compared to the control population and we revealed that significant factors associated with CMBs were higher blood pressure, presence of atrial fibrillation, presence of diabetes mellitus, elevated blood urea and serum creatinine, and the use of anticoagulants. Furthermore, these factors were significantly and independently associated with the presence of CMBs. In the general population, CMBs have been related to advanced age, high blood pressure, smoking, leukoaraiosis, paraventricular hyperintensity, lacuna infarcts and stroke (4, 16, 21, 22, and 31). In the present study, one of the most important factors associated with the CMBsexistence in CKD patients was elevated blood pressure; however presence of hypertension is a common risk factor in both normal subjects and CKD patients.

In CKD patients on regular haemodialysis, there was an importantly elevatedprevalence of CMBs compared to normal subjects, as high as 19.3 to 35.0% (20, 25). In the present study of CKD patients, 12 out of 47 CKD patients exhibited CMBs (25.5%), while none of the healthy control subjects exhibited CMBs. We found that the prevalence of CMBs in haemodialysis patients was associated with elevated BUN and serum creatinine.There was a significantly higher prevalence of CMBs in CKD patients. Considering both the prior study of haemodialysis patients and the present study, it is proposed that progressive renal failure could be accompanied with increased prevalence of CMBs. Kobayashi et al reported thatprogression of CKD was associated significantly with the increased prevalence of silent brain infarction. In their report, age, widespread presence of hypertension and systolic pressure were elevated in patients with silent brain infarction, whereas eGFR was significantly lower in patients with silent brain infarction (35). Our study, which investigated CMBs, was in accordance with the study by Kobayashi et al, in that CKD was associated with cerebrovascular disease. In multivariate logistic analysis in the study of Kobayashi et al., the most important factors associated with silent brain infarction were lower eGFR, older age and higher systolic pressure (35). Similarly, several studies have reported that CKD patients are associated with a high prevalence of overt clinical stroke (36, 37, and 38). In our study, as regard to location of cerebral microbleeds, two patients (4.3%) of CMBs located in the infratentorial regions and 21.3% (10 patients) CMBs located in the supratentorial regions. In the subgroup of haemodialysis patients with supratentorial CMB, there were statistically significant differences as regard to the presence of diabetes mellitus, hypertension, and elevated cholesterol level ($p < 0.05$), but no statistically significant differences as regard to age, sex, atrial fibrillation, triglyceride levels, presence of SLE, duration of dialysis, mean blood urea and serum creatinine and anticoagulant therapy when compared with haemodialysis patients without supratentorial CMBs. Moreover, an elevated blood urea and serum creatinine were correlated with strictly nonlobar CMBs but not with lobar CMBs, which suggests that the associations between CMBs and failed kidney function observed in prior studies may have pointed out to strictly nonlobar CMBs rather than CMBs in other sites. While CMBs have the same pathologies as presumptive markers of bleeding-prone angiopathy, they can develop

through two distinct mechanisms: small vessel disease related angiopathy due to traditional vascular risk factors, or cerebral amyloid angiopathy (CAA). Preferential sites for CMBs that appear due to traditional vascular risk factors and CAA are different because small-vessel pathologies originate in deep brain areas where the perforating arteries deliver the blood supply, whereas CAA originates mainly in the lobar area. Cerebral amyloid angiopathy (CAA) influences the arteries of the leptomeninges and cortex, and essentially does not affect the deep perforating arteries at the base of the brain and brain stem (39). On the contrary, hypertensive vasculopathy most vigorously affects the perforating arteries of the brain (40). In this regard, the preference site of CMBs may vary as regard to the pathophysiological mechanism of the angiopathy. The results of the present study support these prior findings.Furthermore, impaired kidney function is accompanied with cerebral small-vessel disease, independent of other traditional vascular risk factors (41, 42). The association between abnormal kidney function and small vessel pathologies in strictly nonlobar areas may be attributed to the anatomical similarities between the vessels and the mechanism underlying dysfunction of the endothelial and smooth-muscle cells (43). In the kidney, small juxtamedullary afferent arterioles are exposed to high pressure and maintain a strong vascular tone (44). Since the perforating arteries in the brain share similar vascular components to the kidney (44), the continuous delivery of high pressure (as in hypertension) to the deep perforating cerebral arteries may damage those arteries, resulting in the small vessel pathologies that give rise to CMBs. Impaired kidney function is also associated with endothelial dysfunctions such as reduced nitric oxide secretion(45), increased oxidative stress(46) and modulation of cellular adhesion molecules (45) which are also involved in cerebral small-vessel pathologies(47). Therefore, the anatomical and pathophysiological homogeneity of deep perforating vessel damage in the kidney and brain may describe the link between impaired kidney function and the strictly nonlobar location of CMBs.

In our study, type 2 diabetes mellitus was found in 30 haemodialysis patients (63.8 %) and 10 of the 43 controls (23.3%) with a highly significant incidence in the haemodialysis patients ($p < 0.001$). Type 2 diabetes mellitus was present in three (25%) of 12 patients with cerebral microbleeds and was normal in 27 (77.1%) of 35 patients without cerebral microbleeds. Also, type 2 DM was present in two (20%) of 10 patients with supratentorial cerebral microbleeds and was normal in 28 (75.7%) of 37 patients without supratentorial cerebral microbleeds, but there was no significant association of type 2 DM with infratentorial cerebral microbleeds. Thus in this study CMBs were not associated with diabetes. Howeverseveral studies have reported that small cerebral vessel diseases, such as CMBs, are not associated with diabetes (20, 21, 23, 31, 35, and 52).

In this study, there was a significantly elevated serum total cholesterol level in 9 (90%) of 10 patients with supratentorial cerebral microbleeds and was normal in 17 (45.9%) of 37 patients without supratentorial cerebral microbleeds with p value 0.015. Also, serum total cholesterol level was elevated in one (50%) of 2 patients with infratentorial cerebral microbleeds and was normal in 25 (55.6%) of 45 patients without infratentorial cerebral microbleeds with a P value 1.0. As regard to serum triglycerides, it was elevated in 10 (83.3%) of 12 patients with cerebral microbleeds and was normal in 14 (40%) of 35 patients without cerebral microbleeds with a P value of 0.024. Serum triglyceride level was significantly elevated in 8 (80%) of 10 patients with supratentorial cerebral microbleeds and was normal in 16 (43.2%) of 37 patients without supratentorialmicrobleeds, but there was no statistically significant association of serum triglyceride level in our patients with infratentorial cerebral microbleeds. Thus from our findings, there was a significant association between the prevalence of dyslipidaemia and the prevalence of CMBs. Our findings were consistent with the result of Tsumura et al (55) who observed hypercholesterolemia in their study of patients with CKD. Hypercholesterolemia in their cases was attributed to heavy proteinuria. The mechanism attributed to hypercholesterolemia due to heavy proteinuria in CKD involves altered gene expression of HMG-COA reductase, 7 alpha hydroxylase and hepatic LDL receptor (56). Other studies reveal that low serum total cholesterol levels are associated with increased mortality in HD patients, suggesting hypocholesterolemia as a surrogate for malnutrition or inflammation (57, 58). HD patients have moderately increased apoB and significantly increased apoC-III. Triglyceride-rich apoB containing lipoproteins (VLDL and IDL) are elevated because of decreased activities of lipoprotein lipase and hepatic lipase, resulting in hypertriglyceridemia. Besides this mechanism, some factors related to the process of HD itself may contribute to the increase of triglyceride levels in HD patients. It is possible that low molecular weight heparin used for anticoagulation in this patients group may potentate triglyceride elevation. It is believed that heparin releases lipoprotein lipase from the endothelia surface; hence, its prolonged use may cause depletion in lipoprotein lipase and thus reduce triglyceride-rich lipoproteins catabolism (57, 58). In general, diabetes mellitus and dyslipidaemia are independent risk factors for cardiovascular disease (48). In the recent Secondary Prevention of Small Subcortical Strokes (SPS3) trial, which included subjects with recent lacunar infarcts, those with a history of diabetes had discrete neuroimaging features on magnetic resonance imaging (MRI) as compared with those without diabetes, with an increased likelihood ratio of posterior circulation infarcts and a lower burden of microbleeds and enlarged perivascular spaces (49, 50, 51). Consistent with these reports, there was no significant association between the prevalence of diabetes mellitus and the prevalence of CMBs in the present study.

In our study, as regard to anticoagulant therapy, it was present in 9 (19.1%) of 47 patients with cerebral microbleeds when compared to 1 (2.3%) of 43 controls with a P value of 0.028. It was present in 4 (40%) of 10 patients with supratentorial cerebral microbleeds and in 5 (13.5%) of 37 patients without supratentorial cerebral microbleeds with a P value of 0.08. As regard to infratentorial cerebral microbleeds, anticoagulant therapy was present in almost all patients (100%) and present also in 7 (15.6%) of 45 patients without infratentorial cerebral microbleeds with a significant P value of 0.033. Anticoagulation or anti-platelet therapy in patients with small vessel cerebrovascular disease and a past history of ischemic stroke have a greater risk of intracerebralhaemorrhage (59). It is particularly important to identify and remove such patients who are more liable to bleeding complication after anticoagulation or anti-

platelet therapy (60). It is well established that the use of antithrombotic drugs (antiplatelet/anticoagulant drugs) is correlated to the increased incidence and recurrence of ICH (30). However, in almost all CKD patients on regular haemodialysis patients, anticoagulation therapy (systemic heparinization) is mandatory during the repeated haemodialysis sessions, and there are many other situations in which antithrombotic therapy can be used, such as coronary artery disease, arteriosclerosis obliterans, peripheral arterial disease, ischemic cerebrovascular disease, and vascular access burden. The use of these antithrombotic drugs may also increase the occurrence of hemorrhagic stroke in haemodialysis patients with CMBs (61).

Our findings reveal that atrial fibrillation was present in 9 (19.1%) of 47 patients with cerebral microbleeds and only in one control (2.3%) with a significant P value of 0.028. Also, it was present in 6 (50%) of 12 patients with cerebral microbleeds and in 3 (8.6%) of patients without cerebral microbleeds with a significant P value of 0.005. In patients with supratentorial cerebral microbleeds, there was no significant association between patients with and without supratentorial cerebral microbleeds but a significant association as regard to A.F between patients with and without infratentorial cerebral microbleeds with a P value of 0.033. Decreased glomerular filtration rate and chronic kidney disease are independently associated with cardiovascular events (32). Older patients with end-stage renal disease (ESRD) are a distinct group in which the incidence of CKD has tripled in the last decade (62). Cardiovascular prediction is even worse in patients with coexisting cardiovascular disease and ESRD requiring haemodialysis (HD) therapy (63) In addition, the specific pattern of intermittent haemodialysis may raise the risk ofdeveloping AF in that group of HD patients. Dissimilarity in the incidence of AF between HD and peritoneal dialysis patients (64) and the development of supraventricular arrhythmias in the last hours of HD (65) may suggest a link between HD practice patterns and the development of AF in HD patients. Our findings were collaborated with the results done by Song et al (66) who stated that coronary artery disease was associated with strictly nonlobar CMBs. This finding could be related to the risk factors of coronary artery disease being identical to those of deep or infratentorial CMBs, such as hypertension, which is the most common causative factor of nonlobar CMBs. Among the stroke subtypes, cardioembolism was significantly associated with strictly lobar CMBs, but negatively associated with strictly nonlobar CMBs. The negative relationship between strictly nonlobar CMBs and cardioembolism may be related to the lower frequency of hypertension in cardioembolism (71.1%) than in other stroke subtypes: large artery atherosclerosis, 76.5%; small artery infarction, 83.0%; undecided etiology due to negative evaluation, 73.2%; and undecided etiology due to two or more causes identified, 75.1%. However, the cause why atrial fibrillation was associated with strictly lobar CMBs in our study population remains to be elucidated.

Our results showed no significant correlation between the duration of HD and the presence of microbleeds, suggesting that HD was not responsible for the development of microbleeds. HD patients have many risk factors for hemorrhagic stroke, such as hypertension, systemic heparinization, ultrafiltration to treat fluid accumulation, poor platelet adhesion, and infection (67). Our findings are consistent with Yokoyama et al. who revealed the same results (28). Haemodialysis may increase the prevalence of the microangiopathy in patients with chronic renal failure, resulting in increased risk of lacunar stroke and ischemic white matter damage as well as microbleeds.

Previous studies have shown a positive correlation between microbleeds and hypertension (20, 21, and 31) but the possible causative factor for microbleeds in HD patients has not been identified. In our study, the incidence of hypertension was significantly higher in the HD patients than in the controls. This finding is consistent with the View that hypertension may be involved in the development of microbleeds. T2 and T1-weighted MR imaging demonstrated about 30% of microbleeds as hyperintensity or hypointensity. These patients are frequently treated with antiplatelet agents for presumed lacunar infarction. Microbleeds may be a risk factor for developing symptomatic intracerebral hemorrhage in patients receiving anticoagulation (6, 68, and 69). The mortality of anticoagulant-associated intracerebral hemorrhages is higher in HD patients than in non-HD patients (70), thus care should be taken in the use of anticoagulant and/or antiplatelet drugs in patients with ischemic stroke associated with microbleeds, especially in HD patients. We would recommend including T2* weighted MR imaging in the protocol for the study of cerebrovascular disease in haemodialysis patients.

In conclusion, we demonstrated that altered renal function, presence of dyslipidemia, atrial fibrillation, anticoagulation therapy and hypertension were significantly and independently correlated with the existence of CMBs in HD patients. Our findings suggest that haemodialysis patients with CMBs should be cautiously observed for future occurrence of intracerebral hemorrhage. Treatment of hypertension, adjustment of anticoagulant dose, correction of dyslipidemia and atrial fibrillation in hemodialysis patients are considered to be of significant value for prevention of CMBs and probably for clinically overt strokes. CMBs as assessed by T2*-weighted MRI, would be a useful and feasible clinical marker for the prediction of future intracerebral hemorrhages in stroke-free haemodialysis patients.

References

1. Nandigam RN, A. Viswanathan, P. Delgado, M.E, et al. MR Imaging Detection of Cerebral Microbleeds: Effect of Susceptibility-Weighted Imaging, Section Thickness, and Field Strength. AJNR Am J Neuroradiol February 2009; 30: 338-343
2. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. Cerebrovasc Dis. 2011; 32:528–534.

3. Colbert CA, Holshouser BA, Aaen GS, etal.Value of cerebral microhaemorrhages detected with susceptibility-weighted MR Imaging for prediction of long-term outcome in children with nonaccidental trauma. Radiology. 2010 Sep;256(3):898-905
4. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al; Microbleed Study Group. Cerebral microbleeds: a guide to detection and interpretation. *Lancet Neurol*. 2009; 8:165–174. doi: 10.1016/S1474-4422(09)70013-4.
5. Koennecke HC. Cerebral microbleeds on MRI: prevalence, associations, and potential clinical implications. *Neurology*. 2006; 66:165–171. doi: 10.1212/01.wnl.0000194266.55694.1e.
6. Nighoghossian N, Hermier M, Adeleine P, Blanc-Lasserre K, Derex L, Honnorat J, et al. Old microbleeds are a potential risk factor for cerebral bleeding after ischemic stroke: a gradient-echo T2*-weighted brain MRI study. *Stroke*. 2002; 33:735–742.
7. Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. *Neurology*. 2008; 70:1208–1214. doi:10.1212/01.wnl.0000307750.41970.d9.
8. Viswanathan A, Chabriat H. Cerebral microhaemorrhage. *Stroke*. 2006; 37:550–555. doi: 10.1161/01.STR.0000199847.96188.12.
9. Lee SH, Bae HJ, Yoon BW, Kim H, Kim DE, Roh JK. Low concentration of serum total cholesterol is associated with multifocal signal loss lesions on gradient-echo magnetic resonance imaging: analysis of risk factors for multifocal signal loss lesions. *Stroke*. 2002; 33:2845–2849.
10. Greenberg SM, Briggs ME, Hyman BT, Kokoris GJ, Takis C, Kanter DS, et al. Apolipoprotein E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. *Stroke*. 1996; 27:1333–1337.
11. Charidimou A, Werring DJ. Cerebral microbleeds as a predictor of macrobleeds: what is the evidence? *Int J Stroke*. 2014; 9:457–459. doi: 10.1111/ijs.12280.
12. Vernooij MW. Cerebral microbleeds: do they really predict macrobleeding? *Int J Stroke*. 2012; 7:565–566. doi: 10.1111/j.1747-4949.2012.00886.x.
13. Charidimou A, Kakar P, Fox Z, Werring DJ. Cerebral microbleeds and recurrent stroke risk: systematic review and meta-analysis of prospective ischemic stroke and transient ischemic attack cohorts. *Stroke*. 2013; 44:995–1001. doi: 10.1161/STROKEAHA.111.000038.
14. Bokura H, Saika R, Yamaguchi T, Nagai A, Oguro H, Kobayashi S, et al. Microbleeds are associated with subsequent hemorrhagic and stroke in healthy elderly individuals. *Stroke*. 2011; 42:1867–1871. doi: 10.1161/STROKEAHA.110.601922.
15. Nishikawa T, Ueba T, Kajiwara M, Fujisawa I, Miyamatsu N, Yamashita K. Cerebral microbleeds predict first-ever symptomatic cerebrovascular events. *ClinNeurolNeurosurg*. 2009; 111:825–828. doi: 10.1016/j. clineuro.2009.08.011.
16. Fazekas F, Kleinert R, Roob G et al. Histopathologic analysis of foci ofsignal loss on gradient-echo T2*-weighted MRimages in patientswithspontaneousintracerebral hemorrhage: evidence of microangiopathyrelatedmicrobleeds. AJNR Am J Neuroradiol 1999; 20: 637–64.
17. Kato H, Izumiyama M, Izumiyama K et al. Silent cerebral microbleedson T2*-weighted MRI: correlation with stroke subtype, strokerecurrence, and leukoaraiosis. Stroke 2002; 33: 1536–1540
18. Kinoshita T, Okudera T, Tamura H et al. Assessment of lacunar haemorrhageassociated with hypertensive stroke by echo-planar gradientechoT2*-weighted MRI. Stroke 2000; 31: 1646–1650
19. Offenbacher H, Fazekas F, Schmidt R et al. MR of cerebral abnormalitiesconcomitant with primary intracerebral hematomas. AJNRAm J Neuroradiol 1996; 17: 573–578
20. Roob G, Schmidt R, Kapeller P et al. MRI evidence of past cerebral microbleeds in a healthy elderly population. Neurology 1999; 52:991–994
21. Tsushima Y, Tanizaki Y, Aoki J et al. MR detection of microhaemorrhagesin neurologically healthy adults. Neuroradiology 2002; 44:31–36
22. Viswanathan A, Chabriat H. Cerebral microhaemorrhage. Stroke 2006;37: 550–555
23. JeerakathilT, Wolf PA, BeiserA et al. Cerebral microbleeds: prevalenceand associations with cardiovascular risk factors in the FraminghamStudy. Stroke 2004; 35: 1831–1835
24. Belmar L, de Francisco AL, Bueno L, et al. Strokes in patientsonhaemodialysis: incidence, onset time and associated factors. Nefrologia.2014; 34:347–352.
25. Watanabe A. Cerebral microbleeds and intracerebral hemorrhages inpatients on maintenance hemodialysis. J Stroke Cerebrovasc Dis.2007; 16:30–33.
26. Naganuma T, Takemoto Y, Yamasaki T, et al. Factors associated with silent cerebral microbleeds in hemodialysis patients. ClinNephrol. 2011; 75:346–355.
27. Kawamura M, Fijimoto S, Hisanaga S, et al. Incidence, outcome, and risk factors of cerebrovascular events in patients undergoingMaintenance hemodialysis. Am J Kidney Dis. 1998; 31:991–996.
28. Yokoyama S, Hirano H, Uomizu K, Kajiya Y, Tajitsu K, KusumotoK.High incidence of microbleeds in hemodialysis patients detected byT2*-weighted gradient-echo magnetic resonance imaging. *NeurolMedChir (Tokyo)*. 2005; 45:556–60; discussion 560.
29. Toyoda K, Ninomiya T. Stroke and cerebrovascular diseases in patients with chronic kidney disease. *Lancet Neurol*. 2014; 13:823–833. doi: 10.1016/S1474-4422(14)70026-2.
30. He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. *JAMA*. 1998; 280:1930–1935.
31. Roob G, Lechner A, Schmidt R et al. Frequency and location of microbleeds in patients with primary intracerebral hemorrhage. Stroke 2000; 31: 2665–2669.

32. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death,cardiovascular events, and hospitalization. N Engl J Med 2004 Sep 23; 351(13):1296–305.
33. Toyoda K. Cerebral small vessel disease and chronic kidney disease. J Stroke 2015 Jan; 17(1):31–7.
34. Levey AS, de Jong PE, CoreshJ, et al. The definition, classification, and prognosis of chronic kidneydisease: a KDIGO Controversies Conference report. Kidney Int 2011 Jul; 80(1):17–28.
35. Kobayashi M, Hirawa N, Yatsu K et al. Relationship between silent brain infarction and chronic kidney disease. Nephrol Dial Transplant 2009; 24: 201–207.
36. Ninomiya T, Kiyohara Y, Kubo M et al. Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama Study. Kidney Int 2005; 68: 228–236
37. Nakayama M, Metoki H, Terawaki H et al. Kidney dysfunction as a risk factor for first symptomatic stroke events in a general Japanese population–the Ohasama study. Nephrol Dial Transplant 2007; 22: 1910–1915
38. Weiner DE, Tabatabai S, Tighiouart H et al. Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. Am J Kidney Dis 2006; 48: 392–401
39. Biffi A, Greenberg SM. Cerebral amyloid angiopathy: a systematic review. J ClinNeurol 2011; 7:1-9.
40. Smith EE. Leukoaraiosis and stroke. Stroke 2010;41(10 Suppl):S139- S143
41. Khatri M, Wright CB, Nickolas TL, Yoshita M, Paik MC, Kranwinkel G, et al. Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS). Stroke 2007; 38:3121-3126.
42. Takahashi W, Tsukamoto Y, Takizawa S, Kawada S, Takagi S. Relationship between chronic kidney disease and white matter hyperintensities on magnetic resonance imaging. J Stroke Cerebrovasc Dis 2012; 21:18-23.
43. Iadecola C, Pelligrino DA, Moskowitz MA, Lassen NA. Nitric oxide synthase inhibition and cerebrovascular regulation. J Cereb Blood Flow Metab 1994; 14:175-192.
44. Ito S, Nagasawa T, Abe M, Mori T. Strain vessel hypothesis: a viewpoint for linkage of albuminuria and cerebro-cardiovascular risk. Hypertens Res 2009; 32:115-121.
45. Endemann DH, Schiffrin EL. Endothelial dysfunction. J Am SocNephrol 2004; 15:1983-1992.
46. Annuk M, Zilmer M, Lind L, Linde T, Fellström B. Oxidative stress and endothelial function in chronic renal failure. J Am SocNephrol 2001; 12:2747-2752.
47. Markus HS, Hunt B, Palmer K, Enzinger C, Schmidt H, Schmidt R. Markers of endothelial and hemostatic activation and progression of cerebral white matter hyperintensities: longitudinal results of the Austrian Stroke Prevention Study. Stroke 2005;36:1410-1414
48. Movahed MR, Hashemzadeh M, Jamal MM. Diabetes mellitus is a strong, independent risk for atrial fibrillation and flutter in addition to other cardiovascular disease. Int J Cardiol 2005; 105: 315–318
49. Shoamanesh A, Pearce LA, Bazan C, Catanese L, McClure LA, Marti-Fabregas J, Kase CS, Hart RG, Benavente OR. Cerebral microbleeds in 1278 lacunar stroke patients: the Secondary Prevention of Small Subcortical Strokes (SPS3) trial. Stroke. 2015; 46:A213.
50. Ohba H, Pearce L, Potter G, Benavente O. Abstract 151: enlarged perivascular spaces in lacunar stroke patients. The Secondary Prevention of Small Subcortical Stroked (SPS3) trial. Stroke. 2012; 43:A151.
51. Palacio S, McClure LA, Benavente OR, Bazan 3rd C, Pergola P, Hart RG. Lacunar strokes in patients with diabetes mellitus: risk factors, infarct location, and prognosis: the secondary prevention of small subcortical strokes study. Stroke. 2014; 45:2689–94.
52. Ikram MA, Vernooij MW, HofmanA et al. Kidney function is related to cerebral small vessel disease. Stroke 2008; 39: 55–61
53. Kontush A. HDL-mediated mechanisms of protection in cardiovascular disease. Cardiovasc Res. 2014; 103:341–349.
54. Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation. 1989; 79:08–15.
55. Tsumura M, Kinouchi T, Ono S, Nakajima T, Komoda T. Serum lipid metabolism abnormalities and change in lipoprotein contents in patients with advanced-stage renal disease. ClinChimAct20 01; 314: 27-37.
56. Liang K, Vaziri ND. Gene expression of LDL receptor, HMG-CoA reductase, and cholesterol-7 alpha-hydroxylase in chronic renal failure. Nephrol Dial Transplant 1997; 12: 1381-1386.
57. Weiner DE, Sarnak MJ. Managing dyslipidemia in chronic kidney disease. *J Gen Intern Med*. 2004; 19:1045–1052.
58. Shurraw S, Tonelli M. Statins for treatment of dyslipidemia in chronic kidney disease. *Perit Dial Int*. 2006; 26:523–539.
59. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: patterns and risk factors. Stroke Prevention in Reversible Ischemia Trial (SPIRIT). European Atrial Fibrillation Trial (EAFT) study groups. Neurology 1999; 53: 1319–1327
60. Kato H, Izumiyama M, Izumiyama K et al. Silent cerebral microbleeds on T2*-weighted MRI: correlation with stroke subtype, stroke recurrence, and leukoaraiosis. Stroke 2002; 33: 1536–1540
61. Soo YO, Yang SR, Lam WW, Wong A, Fan YH, Leung HH, et al. Risk vs benefit of anti-thrombotic therapy in ischemic stroke patients with cerebral microbleeds. *J Neurol*. 2008; 255:1679–1686. doi: 10.1007/ s00415-008-0967-7.
62. Hsu C, Vittinghoff E, Lin F et al. The incidence of end-stage renal disease is increasing faster than the prevalence of chronic renal insufficiency. Ann Intern Med 2004; 141: 95–101
63. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32(Suppl 3): S112–S119.

64. Abbott KC, Trespalacios F, Taylor AJ et al. Atrial fibrillation in chronic dialysis patients in the United States: risk factors for hospitalization and mortality. BMC Nephrol 2003; 4: 1.
65. Ansari N, Feinfeld D, Manis T. Symptomatic atrial arrhythmias in haemodialysis patients. ASN 1997; 8: 226A/227A.
66. Song TJ, Kim J, Lee HS, Nam CM, Nam HS, Kim YD, Heoa JH. Distribution of Cerebral Microbleeds Determines Their Association with Impaired Kidney Function. ClinNeurol 2014;10(3):222-228
67. Onoyama K, Kumagai H, Miishima T, Tsuruda H, Tomooka S, Motomura K, Fujishima M:Incidence of strokes and its prognosis in patients on maintenance hemodialysis. Jpn Heart J 1986; 27: 685–691.
68. Adams HP Jr, Adams RJ, Brott T, delZoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ: Guidelines for the early management of patients with ischemic stroke. Ascientific statement from the Stroke Council of American Stroke Association. Stroke 2003; 34:1056–1083.
69. Kwa VI, Franke CL, Verbeeten B Jr, Stam J: Silent intracerebral hemorrhages in patients with ischemic stroke. Ann Neurol 1998; 44: 372-377.
70. Onoyama K, Ibayashi S, Nanishi F, Okuda S, Oh Y, Hirakata H, Nishimura Y, Fujishima M: Cerebral hemorrhage in patients on maintenance hemodialysis. CT analysis of 25 cases.EurNeurol 1987; 26: 171–175.