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DISSERTATION

Association between White Matter Lesions, Renal Dysfunction and Functional Outcome in Ischemic Stroke Patients - A Berlin “Cream&Sugar” Substudy

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To my parents

Contents

I Abstract

Background and Purpose: White matter lesions (WMLs) are common in patients with renal dysfunction and associated with functional outcome after stroke. We sought to determine whether WMLs and decreased estimated glomerular filtration rate (eGFR) are indicative of stroke functional outcome at 1 year.

Methods: A retrospective analysis was performed in the Berlin "Cream&Sugar" cohort study (NCT 01378468) using data between Jan. 2009 to Mar. 2012. Patients over 18 years of age with first-ever acute ischemic stroke and with completed follow-up, eGFR and MRI data were included. Initial severity of stroke was assessed using National Institutes of Health Stroke Scale (NIHSS). Serum creatinine was obtained 3-7 days following stroke onset. eGFR was calculated based on the Modification of diet in renal disease (MDRD) formula. Severity of WMLs was assessed on FLAIR or T2-weighted sequences using the Fazekas visual rating scales. Functional outcome was assessed via telephone interview at 1 year using the modified Rankin Scale (mRS). Age, gender, NIHSS at admission, eGFR and WMLs were included in a binary logistic regression model.

Results: 160 first acute ischemic stroke patients (median age 66 years, IQR 52-73, male 63.1%, median NIHSS at admission 2, IQR 1-4) were included. A cross-table analysis showed that eGFR < 90 mL/min/1.73m^2 (OR 2.30, 95% CI 1.17-4.52, p = 0.014) was associated with the presence of WMLs (Fazekas score 1-3). A binary logistic regression analysis showed that eGFR 30-60 mL/min/1.73m^2 (OR 7.86, 95% CI 1.77-34.83, p = 0.007), moderate-to-severe WMLs (Fazekas 2-3) (OR 2.22, 95% CI 1.03-4.77, p = 0.042) and NIHSS ≥ 5 (OR 6.77, 95% CI 2.06-22.23, p = 0.002) were independently associated with unfavourable functional outcome (mRS score ≥ 2) after acute ischemic stroke at 1 year.

Conclusion: Our data suggested that renal dysfunction was associated with WMLs; both of them were independently associated with functional outcome after acute ischemic stroke at 1 year. Assessment of renal dysfunction and WMLs in acute stroke patients may be helpful to predict prognosis.

II Kurzzusammenfassung

Einleitung: Zerebrale Läsionen der weißen Substanz (LWS) finden sich häufig bei Patienten mit Nierendysfunktion. Diese Arbeit untersuchte Zusammenhänge zwischen LWS im Gehirn und der glomulären Filtrationsrate (eGFR) in der Niere sowie dem Ausmaß der Behinderung nach ischämischer Schlaganfall nach einem Jahr.

Methodik: Für diese retrospektive Analyse wurden Daten, die im Rahmen der Berliner „Cream&Sugar“ (C&S) Studie (NCT 01378468) zwischen Januar 2009 und März 2012 erhoben wurden, untersucht. Patientinnen und Patienten im Alter von mindestens 18 Jahren mit erstmaligem ischämischen Schlaganfall, deren Nachbefragungsergebnisse sowie eGFR- und MRT-Daten vorlagen, wurden in diese C&S Substudie eingeschlossen. Der Schweregrad des neurologischen Ausfallsmusters wurde mittels der „National Institutes of Health Stroke Scale“ (NIHSS) eingeschätzt. Das Serum Kreatinin wurde 3-7 Tage nach dem erstmaligen ischämischen Schlaganfall untersucht. Die eGFR-Werte wurden auf Basis der MDRD-Formel ermittelt. Der Schweregrad der LWS wurde unter Verwendung von FLAIR oder T2-gewichteten Sequenzen mit Hilfe der visuellen Fazekas-Skala bewertet. Ein Jahr später wurden die Patienten telefonisch befragt und es erfolgte eine Bewertung des klinischen Ergebnisses mittels des „modified Rankin Scale“ (mRS). Alter, Geschlecht, NIHSS der Patientinnen und Patienten bei Aufnahme sowie eGFR und LWS wurden in eine binäre logistische Regressionsanalyse aufgenommen.

Ergebnisse: Es wurden 160 Patientinnen und Patienten (medianes Alter: 66 Jahre, IQR: 52-73, männlich 63.1%, mediane NIHSS bei Aufnahme 2, IQR 1-4) in diese Substudie eingeschlossen. Im Chi-Quadrat-Test ergab sich ein signifikanter Zusammenhang zwischen Nierendysfunktion (eGFR < 90 mL/min/1.73m^2) und LWS (OR 2.30, 95% KI 1.17-4.52, p = 0.014). Einen signifikanten Zusammenhang mit einem schlechten klinischen Ergebnis nach einem Jahr zeigten die eGFR 30-60 mL/min/1.73m^2 (OR 7.86, 95% KI 1.77-34.83, p = 0.007), 2 - 3 Punkte auf der Fazekas-Skala (OR 2.22, 95% KI 1.03-4.77, p = 0.042), und ein NIHSS ≥ 5 (OR 6.77, 95% KI 2.06-22.23, p = 0.002).

Fazit: Die Ergebnisse dieser Arbeit deuten auf einen Zusammenhang zwischen Nierendysfunktion und LWS hin. Der unabhängige Zusammenhang zwischen klinischem Endergebnis nach einem Jahr und der Nierendysfunktion einerseits sowie LWS andererseits legen nahe, diese Faktoren im klinischen Alltag in die prognostische Einschätzung miteinzubeziehen.

III Abbreviations

ACR	Albumin-to-Creatinine Ratio
AF	Atrial Fibrillation
ALT	Alanine Aminotransferase
ARWMC	Age-related White Matter Changes
ARR	Absolute Risk Reduction
AST	Aspartate Aminotransferase
BBB	Blood-Brain Barrier
BI	Barthel Index Scale
BP	Blood Pressure
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Sub-Cortical Infarcts and Leukoencephalopathy
CARASIL	Cerebral Autosomal Recessive Arteriopathy with Sub-Cortical Infarcts and Leukoencephalopathy
CBF	Campus Benjamin Franklin
Ccr	Creatinine Clearances
95% CI	95% Confidence Interval
CKD	Chronic Kidney Disease
CNS	Central Nervous System
COL4A1	Collagen Type IV Alpha 1 Gene
CRP	C-Reactive Protein
C&S Study	Cream & Sugar Study
CSF	Cerebral Blood Flow
cSVD	Cerebral Small Vessel Disease
CT	X-ray Computed Tomography
CVD	Cardiovascular Disease
DALYs	Disability-Adjusted Life-Years
dL	Decilitre
DWI	Diffusion-Weighted Imaging
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease

EudraCT	European Union Drug Regulating Authorities Clinical Trials
FLAIR	Fluid-Attenuated Inversion Recovery
Hb	Haemoglobin
HbA1c	Glycosylated Haemoglobin
HDL-Cholesterol	High-Density Lipoprotein Cholesterol
HERNS	Hereditary Endotheliopathy with Retinopathy, Nephropathy and Stroke
HIFs	Hypoxia-Inducible Factors
ICF	International Classification of Functioning, Disability and Health
ICH	Intracranial Hemorrhage
IQR	Interquartile Range
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Dialysis Outcomes Quality Initiative
95% KI	95% Konfidenzintervall
LDL-Cholesterol	Low-Density Lipoprotein Cholesterol
LMW	Low Molecular Weight
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
MDRD	Modification of Diet in Renal Disease
MPV	Mean Platelet Volume
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MRT	Magnetresonanztomographie
NCT	ClinicalTrials.Gov Registry Number
NHANES	National Health and Nutrition Examination Survey
NIHSS	National Institutes of Health Stroke Scale
NNT	Numbers Needed to Treat
oGTT	Oral Glucose Tolerance Test
OR	Odds Ratio
oTTT	Oral Triglyceride Tolerance Test
PI	Perfusion Imaging

RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
Scr	Serum Creatinine
SU	Stroke Unit
SVD	Small Vessel Disease
TIA	Transient Ischemic Attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
TSH	Thyroid Stimulating Hormone
tPA	Tissue Plasminogen Activator
WBC	White Blood Cells
WHO	World Health Organization
WMH	White Matter Hyperintensity
WMLs	White Matter Lesions

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1 Introduction

Stroke, a major cause of death and disability, is a disease of the elderly[1]. Cerebral white mater lesions (WMLs) and impaired kidney function are also commonly observed in the elderly. The pathophysiology of these changes is not completely understood. Potentially WMLs and impaired kidney function with reduced glomerular filtration rates (GFR) may be regarded as different manifestations of an underlying systemic small vessel disease (SVD). Both conditions have hemodynamic similarities including the low resistance vascular beds exposed to high-volume blood flow throughout the cardiac cycle[2]. However, it was not well elucidated whether renal dysfunction was associated with WMLs. As we know, the effects of WMLs on functional outcome after stroke have previously been investigated[3,4]. However, the association between estimated GFR (eGFR) and functional outcome is still controversial[5,6]. In this thesis, it was sought to determine, whether decreased eGFR was related to WMLs, and furthermore to investigate the interplay of WMLs, eGFR and outcome after first ischemic stroke.

1.1 Ischemic Stroke

Stroke is the second most common cause of death and a major cause of disability worldwide[1,7]. Stroke is defined as "an episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥ 24 hours or until death"[8]. Stroke can be ischemic or hemorrhagic. The definition of ischemic stroke is" an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction"[8]. Central nervous system (CNS) infarction is "brain, spinal cord, or retinal cell death attributable to ischemia, based on 1) pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2) clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥ 24 hours or until death, and other etiologies excluded"[8]. Silent CNS infarction means "imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion"[8]. Cerebral hemorrhage is defined as "a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma"[8]. Subarachnoid hemorrhage is "rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between

the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma"[8]. About 80% of strokes are caused by ischemia[9].

1.1.1 Epidemiology of Ischemic Stroke

Stroke causes 6.5% of all deaths around the world and is the second most common cause of death[10]. The age-adjusted annual incidence rate worldwide in 2010 was 176.44 (95% CI 161.46-192.21) per million individuals per year. The mortality rate was 42.27 (95% CI 39.60-48.71) per million population per year, and disability-adjusted life-years (DALYs) lost due to ischemic stroke were 597.80 (95% CI 559.75-691.68) per million population per year[11].

According to the report of global burden of disease study 2010, from 1990 to 2010, in high income countries, incidence of ischemic stroke decreased significantly by 13% (95% CI 6-18), mortality by 37% (95% CI 19-39), DALYs lost by 34% (95% CI 16-36) and mortality-to-incidence ratios by 21% (95% CI 10-27). By contrast, in low-income and middle-income countries, incidence of ischemic stroke increased non-significantly by 6% (95% CI 7-18). Mortality rates fell by 14% (95% CI 9-19), DALYs lost by 17% (95% CI 11-21) and mortality-to-incidence ratios by 16% (95% CI 12-22)[11].

1.1.2 Etiology and Classification

Cerebral ischemia can be caused by thrombosis or embolism. Thrombotic stroke occurs when a thrombus, as a result of atherosclerosis, blocks the blood flow to parts of the brain[12]. The affected artery may be any of the brain supplying vessels including the internal carotid artery, the vertebral artery, the circle of Willis, or a small artery within the brain. Embolic stroke occurs when an embolus breaks loose. The clot travels through the blood vessel and lodges in an artery supplying the brain. Most emboli are cause by atrial fibrillation (AF)[12].

In order to improve uniformity in diagnosis, a classification of ischemic stroke based on etiology has been developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST), which includes five categories: 1) large-artery atherosclerosis (macroangiopathy), defined as > 50% stenosis or occlusion of a major brain artery or branch of a cortical artery; 2) cardioembolism; 3) cerebral small-vessel disease (microangiopathy, such as lacunar strokes), 4) stroke of other

determined etiology (dissection, cerebral vasculitis, coagulopathies, hematologic disorders and others) and 5) stroke of undetermined etiology (two or more causes identified, negative evaluation, incomplete evaluation). Neurologist diagnose the subtype of stroke based on clinical features, cranial CT or MRI, extracranial and transcranial Doppler or Duplex sonography, echocardiography and laboratory assessments[13]. The classification aims to facilitate prognosis and management of stroke patients[14,15].

1.1.3 Risk Factors for Ischemic Stroke

Stroke is a heterogeneous, multifactorial disease. A number of risk factors are associated with stroke. They are stratified into modifiable and non-modifiable risk factors[16]. Modifiable factors consist of treatable vascular risk factors and modifiable behavioral risk factors[17]. The treatable vascular risk factors include hypertension, diabetes and lipids[17,18]. The modifiable behavioral risk factors include cigarette smoking, alcohol consumption, lack of physical activity and the metabolic syndrome[17]. Non-modifiable factors include age, gender, race/ethnicity and family history[19]. Recent studies show that chronic kidney diseases (CKD) is also a risk factor for incidence of stoke[20].

1.1.4 Pathophysiology

In acute ischemic stroke, the reduction in cerebral blood flow and energy supply to the brain triggers several mechanisms leading to cell death, evolving from minutes to days over time and expanding from the infarct core to the surrounding “penumbra”.

The core is an infarction defined as a pan-necrosis of both glial and neuronal elements. The so called penumbra is defined as a region of constrained blood supply in which the energy metabolism is preserved[21-23]. Over time, the area of the core expands while the penumbra regresses[24]. The neurological deficits may be the result of both the core and the penumbra. While the tissue-at-risk in the ischemic penumbra is potentially salvageable, the core is lost.

The pathophysiological events include 1) excitotoxicity at a very early stage after the onset of the focal perfusion deficit, 2) peri-infarct depolarization from minutes to hours after stroke onset, 3)

more-delayed inflammation, from hours to days, and 4) programmed cell death (apoptosis) at late stage[25].

Apart from the neuron and glia injury, micro-vessels also undergo hypoxic damage of vascular endothelium and compression by swollen astrocyte cell end-feet. The blood brain-barrier is destroyed as consequence of astrocyte cell necrosis[26].

1.1.5 Magnetic Resonance Imaging

Multi-modal MRI plays an increasingly important role in diagnosis acute ischemic stroke[27,28]. In T2*-weighted images, hemorrhage appears dark due to the ferric iron deposition. It is often performed in priority of other scans to exclude patients with bleeds before thrombolytic therapy. T2*-weighted or other susceptibility-weighted sequences are also indispensable for the detection of microbleeds. Diffusion-weighted imaging (DWI) provides valuable information about restriction of proton mobility, such as cytotoxic edema in acute infarction[29]. Currently it is the most specific and sensitive method for identifying the core of the infarct at the early stages of ischemic stroke in clinical settings[30]. Perfusion imaging (PI) can be used to estimate blood volume, blood flow, mean transit time and time to peak in ischemic areas. In theory, PI provides information about the extent of the ischemic penumbra surrounding the infarct core visualized via DWI. Depending on its definition, at least 50% of patients have a DWI/PWI mismatch when imaged 3-6 h after stroke onset[31,32]. Magnetic resonance angiography (MRA) can detect major artery occlusion or stenosis in ischemic stroke. Fluid-attenuated inversion recovery (FLAIR) employs a very long inversion time to suppress CSF. The use of FLAIR is especially suited for WMLs detection. It can separate WMLs from Virchow-Robin spaces and cavitating lacunes, both of which can be bright on T2-weighted images.

1.1.6 Therapy

The treatments of acute ischemic stroke includes general supportive care, restoration or improvement of cerebral perfusion, antiplatelet agents for secondary prevention and management of neurological complications and rehabilitation[33,34,35].

Management of stroke patients ideally takes place in stroke care units (SCU), which can reduce mortality by about 20% and improve functional outcome by the same amount[36]. The most effective medical treatment for acute ischemic stroke is recombinant tissue plasminogen activator (tPA)

within 4.5 hours after stroke symptoms onset[37,38]. The major adverse effect of thrombolysis is symptomatic intracerebral hemorrhage, to be expected in about 6-7% of cases[39]. Administration of oral aspirin within 48 h after onset of ischemia can reduce 14-day morbidity and mortality[40]. For the prevention of stroke recurrence usually antiplatelet agents, anticoagulants, carotid endarterectomy, anti-hypertension and statins are used[34].

1.1.7 Ischemic Stroke Prognosis

1.1.7.1 Mortality and Survival

In hospital-mortality of ischemic stroke is about 7% within 7 days of onset[41]. About 14% of patients die within 3 months[42] and a third by 1 year[43,44]. The major causes of early mortality are cerebral herniation and pneumonia[45]. Later causes of death are cardiac disease and further complications of stroke[44]. Age, stroke severity, atrial fibrillation and dementia are associated with death within one year[43].

Using the TOAST classification, the highest mortality is found in cardioembolic strokes (22.6%) and the lowest in microangiopathy (3.3%)[15]. Patients with small-artery occlusion are three times more likely to survive than those with cardioembolism[46]. A recent study showed that CKD (eGFR < 60 mL/min/1.73m^2) and severe WMLs are associated with poor survival[47].

1.1.7.2 Functional Outcome after Stroke

Functional outcome in terms of activity of patients after stroke is based on the concept of functioning and disability reviewed as outcomes of interaction between health conditions and contextual factors by the WHO International Classification of Functioning, Disability and Health (ICF). Functioning of individual refers to body functions, body structures, activity and participation. Disability refers to impairment (organic structure), activity limitation (individual), and participation restrictions (social interaction)[48].

According to the German Stroke Data Bank with data of 4264 patients with acute ischemic stroke from 30 hospitals in Germany, 13.9% of stroke patient die, 53.7% of patients regain functional

independence (Barhtel Index, BI < 95) and 46.3% have no or mild residual symptoms (mRS score ≤ 1) after 100 days of stroke onset[42].

1.1.7.2.1 Spontaneous Functional Recovery

Stroke recovery is a non-linear pattern with time[49]. The most rapid improvements are observed within the first weeks after stroke onset, and it is also obvious within 3 months[50]. Severely affected patients have a slower functional recovery than mildly and moderately affected patients; some additional recovery can be demonstrated from 3 months to 6 months of stroke onset[51]. However, these changes level off after 6 months[50].

1.1.7.2.2 Measurement Scales for Functional Outcome

Several scales are developed to measure the outcomes of stroke patient. The most widely used and accepted score for functional outcome after stroke is the modified Rankin Scale (mRS). The mRS is a modified version[52] from the Rankin scale devised in 1957[53]. It reaches from 0-6 with 0 indicating no symptoms and 6 indicating death (Table 1). It is usually used for follow-up of patients after 3 months. However, longer follow-up up to 18 months to assess efficacy of treatment in stroke patients has recently gained attention[54]. The baseline National Institutes of Health Stroke Scale (NIHSS)[55,56], an 11-item scale of neurological deficits in the acute setting (Table 2) is strongly associated with functional outcome at 3 months[57].

Apart from the mRS, the BI (Table 3) shows good validity and reliability for measuring disability and is also commonly used to assess functional outcome after stroke[58].
The BI, a 10-item scale introduced in 1965[59], is used to measure stroke patients' activity related to self-care and mobility. The normal score is 100 and a lower score indicates a higher degree of dependency. The disability is usually dichotomized at a score of 60[58]. The BI scale has been criticized for a "ceiling effect"[60], hampering differentiation of disability levels among patients with relatively good functioning.
Both BI and mRS do not specifically measure the stroke patients´ recovery concerning cognition, language, visual function, emotional impairment, and pain[61]. However, the degree of overall functional recovery, which may be regarded as a result of a number of specific deficits, is well reflected by these scores.

Table 1: The Modified Rankin scales

Grade	Description
0	no symptoms at all
1	no significant disability despite symptoms
	able to carry out all usual duties and activities
2	slight disability
	unable to carry out all previous activities but able to look after own affairs without assistance
3	moderate disability
	requiring some help, but able to walk without assistance
4	moderate severe disability
	unable to walk without assistance, and unable to attend to own bodily needs without assistance
5	severe disability
	the patient is bedridden and incontinent and requires constant nursing care and attention
6	death

Original Rankin scale[53] did not contain Grade 0, defined Grade 1 as "No significant disability: able to carry out all usual duties," and defined Grade 2 as "Slight disability": unable to carry out some previous activities…"

*From J C van Swieten et al. *Stroke*. 1988; 19:604-607

Table 2: National Institutes of Health stroke scales

Current form of the NIHSS		
1a Level of consciousness	5a Left motor arm	8 Sensory
0=Alert	0=No drift	0=Normal
1=Not alert, arousable	1=Drift before 10s	1=Mild loss
2=Not alert, obtunded	2=Falls before 10s	2=Severe loss
3=Unresponsive	3=No effort against gravity	
	4=No movement	9 Language
1b Questions		0=Normal
0=Answers both correctly	5b Right motor arm	1=Mild aphasia
1=Answers one correctly	0=No drift	2=Severe aphasia
2=Answers neither correctly	1=Drift before 10s	3=Mute or global aphasia
	2=Falls before 10s	
1c Commands	3=No effort against gravity	10 Dysarthria
0=Performs both tasks correctly	4=No movement	0=Normal
1=Performs one task correctly		1=Mild
2=Performs neither task	6a Left motor leg	2=Severe
Table to be continued		

Current form of the NIHSS		
	0=No drift	
2 Gaze	1=Drift before 5s	11 Extinction/inattention
0=Normal	2=Falls before 5s	0=Normal
1=Partial gaze palsy	3=No effort against gravity	1=Mild
2=Total gaze palsy	4=No movement	2=Severe
3 Visual fields	6b Right motor leg	
0=No visual loss	0=No drift	
1=Partial hemianopsia	1=Drift before 5s	
2=Complete hemianopsia	2=Falls before 5s	
3=Bilateral hemianopsia	3=No effort against gravity	
	4=No movement	
4 Facial palsy		
0=Normal	7 Ataxia	
1=Minor paralysis	0=Absent	
2=Partial paralysis	1=One limb	
3=Complete paralysis	2=Two limbs	

*From Kasner SE. *Lancet Neurol* 2006; 5(7):603-12

Table 3: Barthel Index scales

Barthel Index
Bowels
0=Incontinent (or needs to be given enema)
5=Occasional accidents (once/week)
10=Continent
Bladder
0=Incontinent, or catherterised and unable to manage
5=Occasional accidents (max once per 24 h)
10=Continent (for more than 7 days)
Grooming
0=Needs help with personal care
5=Independent face/hair/teeth/shaving (implements provided)
Toilet use
0=Dependent
5=Needs some help, but can do something alone
10=Independent (on and off, dressing, wiping)
Feeding
0=Unable
5=Needs help cutting, spreading butter, etc
10=Independent (fod provided in reach)
Transfer
0=Unable, no sitting balance
5=Major help (one or two people, physical), can sit

Table to be continued

Barthel Index
10=Minor help (verbal or physical)
15=Independent
Mobility
0=Immobile
5=Wheelchair independent, including corners, etc.
10=Walks with help of one person (verbal or physical)
15=Independent (but may use any aid-eg, stick)
Dressing
0=Dependent
5=Needs help, but can do about half unaided
10=Independent (including buttons, zips,laces,etc)
Stairs
0=unable
5=Needs help (verbal, physical, carrying aid)
10=Independent up and down
Bathing
0=Dependent
5=Independent (or in shower)
Total (0-100)

*From Kasner SE. *Lancet Neurol* 2006; 5(7):603-12

1.1.7.2.3 Predictors of Functional Outcome after Stroke

Stroke recovery is heterogeneous and individual differences may be determined by factors such as location and size of the initial stroke lesion[62]. There is ongoing research conducted to detect the predictor of final stroke outcome. Strong evidence for prediction of stroke outcome is found for age[63], initial stroke severity measured with NIHSS[57], and previous stroke[53]. Other factors include pre-stroke physical ability (measured with mRS or BI)[42], diabetes mellitus[42,64], hypertension[65], heart failure[43], concurrent peripheral artery disease[66], CKD (measured with proteinuria[5,67,68] or decreased eGFR[6,69]), severe WMLs[3,65,70], cortical infarcts[71], left hemispheric infarcts[71] and infarct volume (CT[72] or DWI[73]).

Therapy improving functional outcome compromised therapy in stroke unit (SU)[74] (the numbers needed to treat (NNT*) for good outcome is 11)[75], early aspirin therapy (NNT* is 77.)[40], rt-PA[76] (NNT for mRS score < 2 is 4.5-14)[38], early decompressive surgery in malignant infarction (NNT for mRS score ≤ 3 is 4)[77], pre-stroke statin use[78], acute statin therapy within 72 hours of stroke onset[79], and early task-oriented rehabilitation[49]. (* indicates that the numbers of NNT came from the lecture of Prof. Dr. med. Heinrich Audebert on stroke. Based on each reference papers, they

are calculated by the equation that NNT = 100/ARR. Absolute risk reduction (ARR)). However, anticoagulant therapy, such as Low-molecular-weighted Heparins and Heparinoids, cannot improve the functional outcome after stroke[40,80].
Among ischemic stroke subtypes, cardioembolic stroke has the most severe disability at 6 months[81] and lacunar exhibits the best post-stroke functional outcome at 3 months and 1 year later[13,14].

1.1.7.3 Long-term Stroke Recurrence

Accounting for 25-30% of all strokes[34], stroke recurrence appears in 3.3% of first stroke survivors within 30 days[82], 9% 1 year[43], 14.1% 2 year[83], 26.4% 5 years and 39.2% 10 years[84]. Usually, the type of initial and stroke recurrence are the same[85], but mortality rate is about two fold higher with stroke recurrence[86]. Stroke recurrence may be predicted by a history of TIA[86], vascular risk factors (hypertension, diabetes)[83], embolic sources and causes (atrial fibrillation)[86], and possibly by severe WMLs[87]. For the subtype of stroke, large-artery atherosclerosis predicts higher rate of early stroke recurrence at 30 days, but for long-term (90 days, 6 months, 1 year, 2 year, and 5 year) estimated rates of stroke recurrence is not different among stroke subtype[14]. Antiplatelet therapy (aspirin, clopidogrel), anticoagulation (warfarin), lowering of blood pressure (calcium-channel blockers, ß blockers and diuretics), lowering of low-density lipoprotein (LDL) cholesterol concentration (statins) and early carotid revascularization are effective therapies to prevent stroke recurrence[34].

1.2 White Matter Lesions

White matter lesions (WMLs) are frequently observed in the aging brain, particularly in those with vascular risk factors, appearing as bilateral, patchy or diffuse areas of hypodensity on CT or hyperintensity on T2-weighted/FLAIR MRI scans. Theses lesions involve the periventricular white matter, the corona radiata, and the centrum semiovale with different severity, irregular margins and do not follow specific vascular territories[88]. To link the white matter and the radiologic phenomena, the term “Leuko-araiosis” was suggested by Hachinski in 1987. “The Greek root *leuko*- means ‘white’ and stands for “white matter of brain”. Araios is an adjective meaning ‘rarefied, with its units far apart’. And the suffix –osis creates a noun with the meaning ‘the action or process of’. Thus, araiosis was defined as ‘the action of rarefied or process of being rarefied; diminution of density’”[89]. Nowadays WMLs are recognized as one of the manifestations of cerebral small-vessel disease[90] and degeneration of myelinated fibers, due to chronic

hypoperfusion of the white matter[91], which is thought of as a form of incomplete infarct or selective necrosis[92].

Severity of WMLs is an independent predictor of occurrence of ischemic stroke[93], especially for lacunar infarcts[94]. The latter is likely to be caused by the same underlying small-vessel pathology. WMLs also represent a potential marker of poor prognosis for stroke patients in terms of increased infarct growth[95], increased bleeding on anticoagulation[96], or when undergoing cerebral thrombolysis[97], poor functional outcome[3], increased mortality[98] and increased risk for all types of stroke recurrence[99].

1.2.1 Prevalence of WMLs

Depending on the age of the studied population and the methodology used, prevalence of WMLs varies from study to study. The reported prevalence of WMLs ranges between 0.7-19% when CT scans are used and 8-92% with MRI in the healthy elderly population[100]. The prevalence and degree of WMLs increases with age. For stroke patients and normal volunteers around 55 years old, one study reported that the prevalence of WMLs was 47.5% and 44%, respectively. Beginning confluent and confluent foci were seen in 19.5% of patients and in 7.5% of normal subjects[101]. In the Rotterdam Scan Study, 1077 elderly people aged from 60-90 years were included, of those 92% with subcortical WMLs, 80% with periventricular WMLs, and 95% with WMLs in either of these locations. Lesions are found most prevalent in the frontal lobe compared with other lobes[102].

The mildest degree of WMLs is to be regarded as an almost normal finding in the brain of elderly, however moderate-to-severe WMLs is not a benign imaging appearance. It is associated with cognitive decline (particularly in terms of speed of mental processing, attention and executive functions)[103,104], dementia[105,106], gait disorder[107], bladder instability[108], and depression[109]. WMLs are present in almost half of the patients with stroke or TIA[101].

Longitudinal data on the natural course of WMLs showed that lesion progression is found in about 18% of individuals over 3 years, and regression of WMLs does not occur[110]. Significant predictors of progression are baseline WMLs severity (early confluent or confluent WMLs)[111] and diastolic blood pressure[110].

1.2.2 Pathophysiology

The pathophysiology of WMLS is not entirely understood. WMLs are recognized as one of the manifestations of cerebral SVD (cSVD)[90]. "cSVD encompasses all the pathological processes that affect the small vessels of the brain, including small arteries, arterioles, capillaries, and small veins"[90], which lead to the white and deep grey matter lesions in the brain[90,112].

The histopathology of WMLs shows concentric hyaline thickening, loss of smooth muscle cells, with luminal narrowing, enlarged perivascular space, gliosis surrounding white matter[113], axonal loss and demyelination[114].

There are two hypotheses on the mechanisms of WMLs pathophysiology.

1) Recently, the most likely mechanisms leading to WMLs are assumed to be impaired blood-brain barrier and the damage of endotheliaum with increased permeability and leakage of material into the vessel wall and perivascular tissue; damage to the vessel wall, inflammation, demyelination, glial scarring, thickening and stiffness of the vessel wall, impaired autoregulation, and at a late stage, luminal narrowing and occlusion, also precipitate discrete focal brain parenchymal ischemia and infarction resulting in WMLs[112].

2) The earlier main hypothesis on pathophysiology of WMLs is arteriolosclerosis, lipohyalinosis or fibrinoid necrosis leading to hypo-perfusion, and in turn, subclinical ischemia in white matter[92]. Cerebral blood flow (CBF) reductions of cerebral white matter was frequently observed in normal individuals with WMLs[115]. Persistent hypoxia-inducible factors (HIFs) are elevated in WMLs[91]. Arteriolosclerosis reduces perfusion in the centrum semiovale and chronic hypoperfusion of white matter leads to degeneration of myelinated fibers by the loss of oligodendrocytes[90]. This kind of damage may be a form of incomplete infarct or selective necrosis[116]. Aging[117], arterial hypertension[118] and diabetes mellitus[119] each can produce structural alterations in the wall of small blood vessels, narrowing or occluding the arteriolar lumen. The consequence may be a decrease or loss of auto-regulation, which in turn reduces perfusion and causes the chronic, diffuse, subclinical ischemia in white matter[92].

1.3 Chronic Kidney Disease

Chronic kidney disease (CKD) is a major public health problem, defined as either 1) "kidney damage for ≥ 3 months, structural or functional abnormalities of the kidney, with or without reduced GFR, manifest by pathological abnormalities or markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests" or 2) "GFR < 60 mL/min/1.73m^2 for ≥ 3 months, with or without kidney damage"[120,121]. This definition is regardless of the etiology of CKD. Kidney function is usually assessed by the estimated GFR. Kidney damage is defined as "structural or functional abnormalities of kidney, initially without decreased GFR, which over time can lead to decreased GFR"[120]. Proteinuria or more specially albuminuria is an early and sensitive marker of kidney damage. It needs to be noted that the elderly with GFR less than 90 mL/min/1.73m^2, but more than 60 mL/min/1.73m^2 without a marker of kidney damage should not be diagnosed as CKD[120].

1.3.1 Evaluation of Kidney Function

Glomerular filtration rate (GFR) is a measure of the filtering capacity of the kidneys to assess the level of kidney function and represents the product of the number of nephrons and the single nephron's filtrations rate[120].

The normal value varies according to age, gender, and body size. The level of GFR of a neonate of one week is 40.6 ± 14.8 mL/min/1.73m^2. The GFR of a two-year-old child reaches 133.0 ± 27.0 mL/min/1.73m^2 [122]. In young adults, it is approximately 130 mL/min/1.73m^2 in men and 120 mL/min/1.73m^2 in women[123]. At the age of 20-30 years, the GFR starts to decreases at the rate of approximately 0.75 mL/min/1.73m^2 per year with variation of individuals among the healthy population[124]. The mean value of a person at 70 years old is around 70 mL/min/1.73m^2. GFR in women is lower than in men. However, pregnancy increases GFR reaching values of 140% of normal. The level of GFR is also affected by CKD and by hemodynamic factors. In the natural history of CKD, GFR decreases at the rate of 4.0 mL/min/1.73m^2 per year among 85% patients with CKD during the two year follow-up[125]. Decreased blood flow to the kidneys will cause the decline of GFR without kidney damage if blood flow is restored within short time. Sustained reduction of blood flow will result in kidney damage[120].

1.3.2 Classification of Stages of CKD

The stages of CKD are based on the level of kidney function, irrespective of cause. Stage 1 is described as kidney damage with normal or increased GFR (> 90 mL/min/1.73m^2); stage 2: kidney damage with mild decrease in GFR (60-90 mL/min/1.73m^2); stage 3: moderate decrease in GFR (30-60 mL/min/1.73m^2); stage 4: severe decrease in GFR (15-30 mL/min/1.73m^2) and stage 5: kidney failure with GFR < 15 mL/min/1.73m^2, accompanied by signs and symptoms of uremia[120]. In principle, patients with GFR less than 30 mL/min/1.73m^2 have to be referred to a nephrologist[126].

1.3.3 Epidemiology of CKD

From a survey of the United States, the prevalence of CKD is 11% (19.2 million) in the general population aged from 20 years to older. Stage 1 is encountered in 3.3% (5.9 million), stage 2 in 3.0% (5.3 million), stage 3 (7.6 million) in 4.3%, stage 4 in 0.2% (0.4 million) and stage 5 in 0.2% (0.3 million) of all cases[127].

The prevalence of CKD increases with age. Among persons older than 65 years, 11% have an estimated GFR (eGFR) of less than 60 mL/min/1.73m^2 [127]. Similarly in another study, the prevalence of decreased GFR by age shows that among individuals aged 60-70 years old, 53.8% of them have a GFR 60-90 mL/min/1.73m^2, and 7.1% have a GFR 30-60 mL/min/1.73m^2; among individuals aged over 70 years old, 48.5% of them have a GFR 60-90 mL/min/1.73m^2, and 24.6% have a GFR 30-60 mL/min/1.73m^2 [120].

1.3.4 Estimated Glomerular Filtration Rate

GFR cannot be measured directly. It requires the calculation of the clearance of exogenous filtration markers (e.g. inulin) or endogenous filtration markers (serum creatinine). The gold standard for measurement of GFR is inulin clearance, which is costly and requires an intravenous infusion as well as timed urine collections. In clinical practice, eGFR based on the serum creatinine is accepted and wildly used.

Creatinine is an amino acid mainly derived from the metabolism of creatine in muscles. Creatinine is freely filtered by the glomerulus and also is secreted by proximal tubular cells. Thus the clearance of creatinine exceeds the GFR, which may be a limitation for eGFR.

The generation of creatinine is determined by the total muscle mass and dietary intake. The total muscle mass is associated with age, gender and race[128]. The clearance of creatinine can also be affected by medication, such as trimethoprim and cimetidine[129]. Due to the risk of overestimation of the GFR, the serum creatinine concentration alone should not be used to assess the kidney function[130].

Based on serum creatinine concentrations, there are two estimated equations applied to calculate the eGFR: The Cockcroft-Gault formula[131] developed in 1976 and the Modification of diet in renal disease (MDRD) study equation[132] developed in 1999.

The Cockcroft-Gault formula is Ccr = [(140−age) × weight × 0.85 (if female)] / (72×Scr). Creatinine clearance (Ccr) is expressed in mL/min, age in years, and weight in kg and serum creatinine (Scr) in mg/dL.

The MDRD study equation is eGFR = 186 × $(Scr)^{-1.154}$ × $(age)^{-0.203}$ × 0.742 (if female) or × 1.212 (if black).

eGFR is expressed in mL/min/1.73m^2, age in years, and serum creatinine (Scr) in mg/dL.

In contrast to the Cockcroft-Gault formula, the MDRD equation is adjusted for the body-surface area.

1.3.5 Proteinuria

Healthy people usually excrete little amounts of protein in the urine. In adults, the normal value is about 50 mg/day for total urine protein and 10 mg/day for albumin in urine. The clinically normal value for albumin in the urine is less than 30 mg/day, and for total protein is less than 300 mg/day. The total protein in urine consists of albumin, low molecular weight (LMW) globulins and protein derived from the urinary tract. Excretion of albumin is affected by upright posture, exercise, pregnancy and fever.

Proteinuria is an early and sensitive marker for kidney damage in CKD. The term proteinuria refers to “increased urinary excretion of albumin, other specific proteins, or total protein”[120]. A clinically relevant proteinuria is more than 300 mg/day. The term albuminuria refers to increased urinary albumin excretion of more than 300 mg/day. Micro-albuminuria refers to excretion of small but abnormal amounts of albumin, 30-300 mg/day. Albuminuria is a sensitive marker for CKD due to diabetes, hypertension and other glomerular diseases. Elevated LMW globulins in urine are a sensitive marker for some type of tubulointerstitial disease[120].

According to the National Health and Nutrition Examination Survey (NHANES III) in the United States, the prevalence of albuminuria in adults is 11.7%; the prevalence of albuminuria among

adults with GFR ≥ 90 mL/min/1.73m^2 is 3.3%, whereas it is 12.9% among persons with GFR 60-90 mL/min/1.73m^2.

1.3.6 Risk Factors for GFR Decline

The rate of GFR decline is related to non-modifiable risk factors and modifiable risk factors.
Non-modifiable risk factors include patients´ age, gender, race, and level of kidney function. Several studies suggest that older age[133,134], male sex[125,134], black persons[134,135] and lower baseline level of kidney function[125] are associated with faster GFR decline.
Modifiable risk factors include proteinuria, low serum albumin, blood pressure, diabetes and smoking. Higher level of proteinuria[125], lower serum albumin concentration[125], higher blood pressure level[134], poor glycemic control[136,137] and smoking[134] are associated with faster GFR decline.

1.3.7 Intervention to Slow GFR Decline

Effective interventions to slow down GFR decline include strict glucose control in diabetes[138], strict blood pressure control[139], and angiotensin-converting enzyme inhibition[140] or angiotensin-2 receptor blockade[139]. Interventions studied with negative or inconclusive results include dietary protein restriction[141], lipid-lowering therapy[125] and partial correction of anemia[142].

1.3.8 Complications of Decreased GFR

The complications of decreased GFR include high blood pressure, anemia, malnutrition, bone disease and disorders of calcium and phosphorus metabolism as well as neuropathy[120]. High blood pressure is a cause and also an effect of declined GFR. Symptoms of neuropathy may begin to present when GFR is less than 12-20 mL/min/1.73m^2, or uremia continues for at least 6 months[143]. The histopathology of neuropathy shows axonal degeneration and secondary demyelination of peripheral nerves[143]. Decreased GFR (eGFR < 60 mL/min/1.73m^2) is associated with the morbidity and mortality of cardiovascular disease (CVD) including coronary heart disease, cerebrovascular disease, peripheral vascular disease, and heart failure[144]. Moreover, decreased GFR (eGFR < 60 mL/min/1.73m^2) is also associated with the risk of the progression end point of end-stage renal disease (ESRD) and mortality, across by the length of period (1-3 year), age, diabetes status, or albuminuria[145].

1.4 Renal Function, WMLs and Stroke Outcome

Small vessel disease is thought to be a systemic disorder. WMLs, for instance, are more prevalent in patients with CKD[146] (eGFR < 60 mL/min/1.73m^2, or proteinuria/albuminuria). With similar anatomic and functional vascular beds, WMLs and CKD are considered as parallel damage to different target organs with similar risk factors[147], such as hypertension[148] and aging[2]. The "strain vessel injuries hypothesis"[149] was introduced as a possible explanation of the pathophysiological mechanisms linking cerebral and renal damage. Exposed to a high pressure, afferent arterioles of juxtamedullary nephrons of kidney resemble the perforating arteries branching from the middle cerebral arteries in the brain. Large arterial stiffness and high blood pressure add to the burden of these small vessels, followed by endothelial dysfunction and increased permeability of small vessels and arteriolosclerosis. Most cross-sectional studies investigated the association between CKD (defined as renal dysfunction, when eGFR < 60 mL/min/1.73m^2) and WMLs in community settings[150-152]. However, to date, there is no consistent conclusion that renal dysfunction (eGFR < 60 mL/min/1.73m^2) is associated with WMLs when adjusted for age, gender and vascular risk factors[153]. Few study examined the association between renal dysfunction and WMLs in stroke patients[47,154].

Renal dysfunction and WMLs are associated with traditional cardiovascular risk factor, such as older age, hypertension and diabetes mellitus; renal dysfunction is also associated with non-traditional risk factors including inflammation, oxidative stress, nitric oxide, homocysteine, and pro-coagulant factor, which will cause endothelial dysfunction and accelerate the progress of arteriosclerosis[112,155]. Several reports came to the conclusion that severe WMLs and renal dysfunction were predictors of the incidence of stroke[93,156,157], post-stroke mortality[47,158,159], and risk of hemorrhagic transformation after thrombolysis[97,160]. However, the effects of WMLs and renal dysfunction on functional outcome after stroke are still controversial. To date, not all[161] but most studies support the notion that WMLs are associated with unfavorable functional outcome after ischemic stroke at 3 month[162], 6 month[4] and 1 year[3]. Especially, severe WMLs are regarded as a risk factor for unfavorable outcome after stroke[3,4]. In the scope of CKD, compared to proteinuria or albuminuria, which is a stronger predictor of the unfavorable stroke functional outcome[5,67], the association between decreased renal function and functional outcome after stroke is still a controversial issue[5,69]. So far, no study, to the best of our knowledge, investigated simultaneously the association of renal dysfunction and WMLs with functional outcome after stroke.

1.5 Renal Function, WMLs and Stroke Recurrence

As renal dysfunction (eGFR < 60 mL/min/1.73m^2) was an established independent risk factor for the occurrence of CVD[163], previous research focused on the relation between renal dysfunction and the recurrence of CVD[159,164]. A few studies assessed the association between renal dysfunction and recurrence of ischemic stroke[165,166]. Patients with WMLs were older and had a higher incidence of hypertension and a higher frequency of lacunar infarction[167]; they had a higher cumulative incidence of stroke recurrence than patients without WMLs[168]. However, previous studies on the association between WMLs and stroke recurrence had conflicting results [87,169-172]. Therefore, it is interesting to investigate the relationship between both WMLs and renal dysfunction on stroke recurrence.

1.6 Aims of the Study

As mentioned above, previous studies showed that SVD affects both the kidney and the brain. However, the relationship between renal dysfunction and WMLs remains to be elucidated.

We hypothesized that renal dysfunction as determined by eGFR and cerebral small vessel disease (cSVD) as represented by WMLs are associated with each other and can be used to predict the functional outcome and stroke recurrence after first acute ischemic stroke.

The aims of the study are to investigate
(1) Whether, and if so to what extent, there is an association between renal dysfunction and WMLs,
(2) Whether, and if so to what extent, renal dysfunction and WMLs are risk factors for unfavorable functional outcome after stroke, and
(3) Whether renal dysfunction and WMLs are risk factors for stroke recurrence.

2. Methods

This was a retrospective sub-study of the Berlin "Cream&Sugar" (C&S) study (NCT 01378468). This sub-study focused on the association between white matter lesions, renal dysfunction, functional outcome and stroke recurrence one year after onset of first ischemic stroke.

2.1 The Berlin "Cream & Sugar" Study

The C&S study was a prospective cohort study to detect the role of fasting and post-challenge triglyceride levels for the risk of stroke recurrence within 12 months after the index event[173]. A standardized oral triglyceride tolerance test was used in the sub-acute setting, 3-7 days, after the first ischemic stroke.

The primary end-point of the study was recurrent fatal or nonfatal stroke within 12 months. The secondary outcomes were myocardial infarction, coronary revascularization, cardiovascular death, or a transient ischemic attack within 12 months after the qualifying event[173].
C&S study was initiated in January 2009, and conducted in three clinical centers, which are Campus Charité Mitte, Campus Benjamin Franklin, and Campus Virchow Klinikum.

2.2 Ethics

The C&S study had been approved by the ethics committee for all recruiting sites (EA4/100/08) and the conduction was in agreement with the Declaration of Helsinki[174]. It was registered under European Union Drug Regulating Authorities Clinical Trials (EudraCT). The corresponding EudraCT number was 2009-010356-97. It was also registered under ClinicalTrials.gov (NCT 01378468).

2.3 Patients

In this retrospective sub-study of the C&S study, C&S participants were included if they underwent MRI neuroimaging, had creatinine levels measured, and completed follow-up between January 2009 and March 2012.

2.3.1 Inclusion Criteria and Exclusion Criteria

In C&S, all suspected first ever acute ischemic stroke patients over 18 years of age admitted to the three university hospitals in Berlin were screened. According to the WHO definition, ischemic stroke was defined as a focal neurological deficit lasting for at least 24 hours with no signs of hemorrhage on cerebral imaging. Ischemic strokes were verified radiological for all patients included in this sub-study. The details of inclusion and exclusion criteria[173] are shown in Table 4.

Table 4: Inclusion/exclusion criteria for the Berlin "Cream&Sugar" Study

Inclusion criteria	Exclusion criteria
Age ≥ 18 years	Aphasia (cannot provide informed consent)
First ischaemic stroke ever	Inability to sign informed consent
Incidence within ≤ 7 days	Swallowing disorder (cannot drink cream)
Informed consent obtained	Renal or hepatic failure
	Pancreatitis
	Cholecystolithiasis
	Malabsorption
	Lactose intolerance
	Pregnancy
	Psychosis
	Drug and/or alcohol addiction
	Life expectancy ≤ 12 months
	Acute coronary syndrome
	Severe heart valve disorder
	Heart failure (NYHA III-IV)
	Severe infectious/rheumatic disease
	Severe metabolic disease
	(No oral glucose tolerance test in case of known diabetes)

*From *International J of Stroke* Vol 5, February 2010, 47-51

Additional inclusion criteria for this sub-study were MRI neuroimaging, Creatinine serum parameter, and completed follow-up between January 2009 and March 2012. The patients, who only had CT neuroimaging, were excluded.

2.4 Protocol of C&S Study

2.4.1 Oral Tolerance Tests

A combined oral triglyceride tolerance test (oTTT) and oral glucose tolerance test (oGTT) was performed after the patients gave informed consent to join the study. Tests were performed within 3-7 days after the first ischemic stroke incidence. Before the tolerance test, patients were fasting overnight (12 hour since last meal).

Fasting blood samples were drawn at 8 AM. Directly thereafter, patients drank 250 mL of 32% fat cream within 30 minutes in the presence of a Center for Stroke Research Berlin staff member to ensure that the cream was ingested. Three hours later (11 AM), a second blood draw was performed and was immediately followed by a standard 75 g oral glucose (glucose monohydrate) tolerance test. Subsequent blood draws were then performed at 12 PM and 1 PM. The serum parameters are shown in Table 5.

Table 5: Parameters determined during the combined oTTT and oGTT

	Before oTTT At 8AM	After oTTT Before oGTT At 11AM	After oGTT At 12AM	After oGTT At 1PM	
Parameters					Reference value
Triglyceride	x	x	x	x	<150 mg/dL
Glucose	x	x	x	x	55-110 mg/dL
Insulin	x	x	x	x	6-27 mU/L
Creatinine	x				<1,2 mg/dL
Cholesterol	x				<200 mg/dL
LDL	x				<100 mg/dL
HDL	x				>35 mg/dL
AST	x				<50 mg/dL
ALT	x				<45 mg/dL
CRP	x				<0,5 mg/dL
TSH	x				0.27-4.20 mU/L
Hb	x				14.0-17.5 g/dL
HbA1c	x				4.3-6.1%
WBC	x				4.5–11/nL
RBC	x				4.6–6.4/nL
Haematocrit	x				0.4–0.52 L/L
MCH	x				27–34 pg
MCHC	x				31–36 g/dL
Table to be continued					

	Before oTTT At 8AM	After oTTT Before oGTT At 11AM	After oGTT At 12AM	After oGTT At 1PM	
Parameters					Reference value
MCV	x				81–100 fL
RDW	x				11.9–14.5%
Platelets	x				150–400/nL
MPV	x				7–12 fL

HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, c-reactive protein; TSH, thyroid stimulating hormone; Hb, haemoglobin; HbA1c, glycosylated haemoglobin; WBC, white blood cells; RBC, red blood cells; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV,mean corpuscular volume; RDW, red blood cell distribution width;MPV,mean platelet volume; oTTT, oral triglyceride tolerance test; oGTT, oral glucose tolerance test.
*From *International J of Stroke* Vol 5, February 2010, 47-51

Physical examination was performed on heart rate, blood pressure, waist circumference, hip circumference, weight, and height measurement.

Stroke severity was assessed on hospital admission and at the day of testing using National Institute of Health Stroke Scale (NIHSS). Stroke etiology was categorized using a mechanism based classification scheme, according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST)[13].

2.4.2 One-Year Follow-up

Twelve months later, patients were contacted and interviewed with regard to primary stroke outcome and stroke recurrence via telephone. The primary stroke outcome was assessed by the modified Ranking Scale (mRS) and death of patients within one year was recorded. The phone interview was performed by personnel blinded to the results of the challenging tests. For the standardized follow-up phone interview a case report form was used. (Shown in Appendix)

2.5 Clinical Assessment

2.5.1 National Institutes of Health Stroke Scales

To quantify the neurological deficit of patients with acute cerebral infarction, we used the NIHSS[55,175], which consists of 11 items that measure the level of neurologic impairment including the level of consciousness, horizontal eye movements, visual field deficits, facial palsy, motor

deficits of arms and legs, limb ataxia, sensory deficits, language disorders, dysarthria, and extinction/inattention (formerly neglect). Total score on NIHSS range from 0 to 42, with higher values reflecting more severe cerebral infarcts (< 5, mild impairment; ≥ 25, very severe neurologic impairment). The NIHSS raters in C&S were all had an NIHSS certificate.

2.5.2 Modified Rankin Scales

The mRS[52] is a measure of disability of daily activities conventionally used for functional outcome of stroke patients at 90 days. In the "C&S" study, it was used to assess functional outcome of patients at one year (+/- 14 days) after ischemic stroke via telephone follow-up by certified raters. The assessment of mRS via telephone is reliable and has a good agreement with face-to-face assessment[176]. Scores on the mRS range from 0 to 6 (shown as table 1). Functional outcome was classified as either favorable outcome (mRS score 0-1) or unfavorable outcome (mRS score ≥ 2). "Favorable outcome" defined as that a patient did not require physical assistant or help to transfers, mobility, dressing, feeding or toileting. The patient failed any of these criteria meant "unfavorable outcome".

2.5.3 TOAST Classification

Stroke was categorized according to the mechanism-based classification scheme TOAST[13]. The TOAST classification denotes five subtypes of ischemic stroke: 1) large-artery atherosclerosis (LAA), 2) cardioembolism (CE), 3) small-vessel occlusion (SAO), 4) stroke of other determined etiology, other causes (OC), and 5) stroke of undetermined etiology (UND). The clinician diagnoses the TOAST classification of patients.

For LAA, the patient should have cerebral cortical, cerebellar or brain stem impairment syndrome with accordingly brain imaging findings of either significant stenosis (50%) or occlusion of a major cerebral artery or branch artery. If the imaging showed subcortical infarct, the diameter of infarct should be larger than 1.5 cm. For CE, the patient had brain artery occlusion due to an embolus of cardiac sources. The patient usually had atrial fibrillation, or sick sinus syndrome, or acute myocardial infarction, or left atrial/ atrial appendage thrombus et.al., as well. LAA should be excluded. For SAO, the patient should have a lacunar syndrome and no cortical syndrome. The diameter of brain stem infarct (thrombosis or embolism) is less than 1.5 cm. LAA and CE should

be excluded. For OC, it included patients with dissection of carotid artery, vasculitis, hypercoagulable states, or hematologic disorders et.al. LAA and CE should be excluded. For UND, the cause of stroke cannot be determined, nor had more than one causes of above[13].

2.6 Image Acquisition

MRI was performed in acute stroke patients, using both 3-T (Tim Trio; Siemens, Erlangen, Germany) scanners at Campus Benjamin Franklin (CBF) hospital and 1.5-T (Avanto; Siemens, Erlangen, Germany) scanners at Campus Charite Mitte and Campus Virchow Klinikum.
For this sub-study, T2*-weighted images, fluid attenuated inversion recovery imaging (FLAIR), T2 weighted images and diffusion weighted images (DWI) were used. K-PACS workstation program (version 1.6.0) was used to analysis the MRI images.
T2*-weighted images were used to identify the signs of hemorrhage and microbleeds[177]. FLAIR or T2 weighted images were used to assess previous silent lacunar infarctions and white matter hyperintensities (WMH). DWI was used to identify fresh ischemic regions.

2.7 Data Collection, Calculation and Rating

2.7.1 General Clinical Data

Data on demographics and clinical laboratory parameters were collected from case report forms, (Table 2). The ratio of LDL to HDL was calculated.
Data of the physical examinations (height, weight, blood pressure, waist circumference, hip circumference and heart rate) were collected from case report forms. Body mass index and hip-to-waist ratio were calculated. NIHSS scores at admission, diagnoses, TOAST classification and information on whether or not thrombolysis therapy had been applied were taken from hospital documentation.
Diabetes mellitus was defined as current use of antidiabetic medication and/or serum glycosylated hemoglobin (HbA1c) $\geq$ 6.5%[178]. Hypertension was defined as current antihypertensive medication use. Information on lacunar infarctions or microbleeds was taken from discharge summaries and verified on MRI.
Follow-up data after one year was recorded, which included mRS, stroke recurrence and "secondary event", which referred to any of the following: secondary cerebral infarction,

myocardial infarction, coronary revascularization, cardiovascular death, or TIA within 12 months after the first stroke event.

2.7.2 Infarct Volume

Lesion volume was determined on DWI. MRIcro medical image viewer program (version 1.40 build 1) was used to calculate infarct volume. The equation of infarct volume was: *Infarct Volume = region of interest (ROI) × each voxel volume (Dimension X × Dimension Y × Dimension Z).* The size (mm) of each dimension of each patient image was shown in MRIcro. The ROI was based on the bright area on each slice of DWI trace images.

2.7.3 WMLs Rating

FLAIR or T2 weighted images were used to assess WMLs severity according to both the Age-Related White Matter Changes (ARWMC) (Wahlund scores)[179] and the Fazekas[114] visual classification system.

In ARWMC scale, the degree of white matter changes is rated on a 4-point scale. The definitions of rating scores (0-3) are shown in Table 6.

Table 6: ARWMC Rating Scale for MRI

White matter lesions	
0	No lesions (including symmetrical, well-defined caps or bands)
1	Focal lesions
2	Beginning confluence of lesions
3	Diffuse involvement of the entire region, with or without involvement of U fibers
Basal ganglia lesions	
0	No lesions
1	1 focal lesion (≥5 mm)
2	>1 focal lesion
3	Confluent lesions

White matter changes on MRI were defined as bright lesions≥5mm on T2 or FLAIR images.
Left and right hemispheres were rated separately.The following brain areas were used for rating: frontal, parieto-occipital, temporal, infratentorial/cerebellum, and basal ganglia (striatum, globus pallidus, thalamus, internal/external capsule, and insula).
*From *Stroke*. 2001; 32:1318-1322

Five different regions were rated in the right and left hemispheres separately: 1) the frontal area, which was the frontal lobe anterior to the central sulcus; 2) the parieto-occipital area, which consisted of the parietal and occipital lobes together; 3) the temporal area, which was the temporal lobe (the border between the parieto-occipital and temporal lobe was approximated as a line drawn from the posterior part of the Sylvian fissure to the trigone areas of the lateral ventricles); 4) the infratentorial area, which included the brain stem and cerebellum; and 5) the basal ganglia, which included the striatum, globus pallidus, thalamus, internal and external capsules and insula[179]. The final score was reported as the sum of all regions and could range from 0 (no white matter hyperintensities (WMH)) to 30 (most severe WMH).

Fazekas scores range from 0 to 3 (0, no WMH; 1, punctate foci; 2, beginnings of confluent foci; 3 large confluent areas) and only the slice showing the most severe WMH was rated[114] (as Fig.1 in our study)

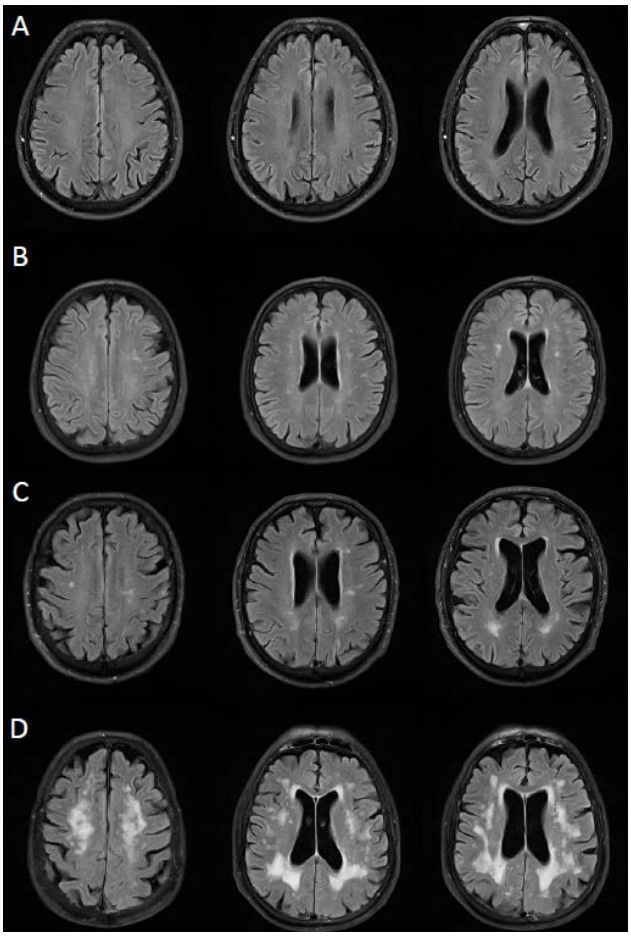

Figure 1: A fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) sequence of a 66-year-old male patient (A) with an overall Fazekas and Wahlund score of 0. A 70-year-old female patient (B) with a Fazekas score of 1 and Wahlund score of 4. An 82-year-old male patient (C) with a Fazekas score of 2 and Wahlund score of 9. A 65-year-old male patient (D) with a Fazekas score of 3 and Wahlund score of 20.

2.7.4 eGFR calculation and Classification

Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD)[120] study equation: $GFR\ (mL/min/1.73m^2) = 186 \times (Scr)^{-1.154} \times (age)^{-0.203} \times 0.742\ (if\ female) \times 1.210\ (if\ black)$. Scr is serum creatinine concentration in mg/dL and age is in years. All patients in our cohort were of white origin and therefore no correction had to be made for black race.

Based on guidelines of the National Kidney Foundation [Kidney Dialysis Outcomes Quality Initiative (KDOQI)], chronic kidney disease (CKD) severity was classified into five stages according to the level of estimated GFR[120]: stage 0, eGFR > 90 mL/min/1.73m^2 (with risk factors for CKD); stage 1, eGFR ≥ 90 mL/min/1.73m^2 (with demonstrated kidney damage, e.g., persistent proteinuria, abnormal urine sediment, abnormal blood and urine chemistry, abnormal imaging studies); stage 2, eGFR 60-90 mL/min/1.73m^2; stage 3, eGFR 30-60 mL/min/1.73m^2; stage 4, eGFR 15-30 mL/min/1.73m^2; stage 5, eGFR < 15 mL/min/1.73m^2. Due to C&S exclusion criteria, there was no patient with eGFR < 30 mL/min/1.73m^2 in the C&S study. In this sub-study, eGFR was measured and stratified into three groups: normal eGFR, eGFR ≥ 90 (mL/min/1.73m^2); mild declined eGFR, 60 ≤ eGFR < 90 (mL/min/1.73m^2); moderate declined eGFR, 30 ≤ eGFR < 60 (mL/min/1.73m^2). Impaired renal function was defined as eGFR < 90 mL/min/1.73m^2.

2.8 Statistical Analysis

Statistical analysis was performed with the SPSS software for windows (IBM® SPSS® Statistics, version 19).

2.8.1 Descriptive Statistics

Continuous dependent variables were tested for normality of distribution in each group of independent variable using the Shapiro-Wilk test (P ≥ 0.05, normally distribution; p < 0.05, not normally distributed) and Skewness value. If Skewness value was within ± 1, the variable was normally distributed. If Skewness was outside ± 1, the distribution of variable was skewed.

2.8.2 Test for Difference

Most of the measured parameters were not normally distributed. Therefore, Kruskall-Wallis tests were performed to examine the differences of baseline and serum parameters among WMLs groups and eGFR groups. If significant differences were found, post hoc analyses were performed (Level of significance set at 0.025).

Mann-Whitney U tests were performed to examine the differences of baseline and serum parameters between mRS functional outcome groups, stroke recurrence groups.

Categorical variables were assessed using Chi-Square tests and two-sided Fisher´s exact tests, when the expected frequency was smaller than five. For more than two groups, if a significant difference was found, post hoc analysis was performed (Level of significance set at 0.025).

2.8.3 Test for Association

For bivariate analysis, Spearman´s rank-order correlations were performed to calculate coefficients "rho" and p values. To identify the association between categorical variables, chi-square tests were performed to calculate the values X^2, OR, 95% CI, Phi (φ) and p value.

2.8.4 Test for Interaction

A hierarchical binary logistic regression analyses was performed to assess whether there was an interaction between WMLs (measured by Fazekas score) and decreased renal function (measured by eGFR) in their effect on stroke functional outcome. WMLs was stratified into two groups and was categorized (by Fazekas score: Fazekas 0-1 [reference] and Fazekas 2-3) and eGFR was stratified into three groups and was categorized (eGFR $\geq$ 90 mL/min/1.73m^2 [reference], eGFR (60, 90) mL/min/1.73m^2 and eGFR (30, 60) mL/min/1.73m^2). Two factors of WMLs and eGFR were added to the first regression model (the main effect model) and the additional interaction term (Fazekas score*eGFR) was added to the second regression model (the moderated multiple regression model). Dependent variable was unfavorable functional outcome (mRS score $\geq$ 2). The statistical significance of interaction term ($p < 0.05$) was used to indicate that there was an interaction effect between WMLs and renal dysfunction. The interaction effect, or named as moderator effect, was symmetrical.

2.8.5 Test for Prediction

For multivariate analysis on factors associated with WMLs, two dichotomizations of Fazekas scores were used. Firstly, WMLs Fazekas score (0-3) was stratified into patients without WMLs, Fazekas 0 and patients with WMLs, Fazekas 1-3. Secondly, WMLs Fazekas score was stratified into patients with no-to-mild WMLs, Fazekas 0-1 and moderate-to-severe WMLs, Fazekas 2-3. Diastolic blood pressure, systolic blood pressure and HbA1c of patients were transformed into quartiles. Forward stepwise binary logistic regression analyses were performed to assess if eGFR was associated with the presence of WMLs. Multivariate analysis included the factors of age, gender, eGFR, diastolic blood pressure, systolic blood pressure and HbA1c.

For multivariate analysis on factors associated with functional outcome after stroke, age was categorized by 10-year intervals. Age of included patients ranged from 22 to 94 years. Metric variables that were not normally distributed (e.g. NIHSS scores) were transformed into quartiles. Forward stepwise binary logistic regression analysis was performed to assess whether eGFR and WMLs independently associated with functional outcome. First model included factors of age, gender, NIHSS at admission, WMLs and eGFR. Second model included factors of age, gender, NIHSS at admission, WMLs, eGFR, HbA1c, CRP and Hypertension.

For multivariate analysis on factors associated with stroke recurrence and secondary event, Age, gender, LDL and LDL/HDL ratios were included as independent factors in two forward stepwise binary logistic regression models.

2.8.6 Confounders

Confounder meant that a variable was associated with the risk factor (e.g., eGFR or WMLs) and the outcome of interest (stroke functional outcome). The prediction of unfavorable functional outcome will be more accurate, when the predictor (e.g., eGFR or WMLs) were controlled and adjusted for confounders. In bivariate analysis, hypertension was associated with WMLs and mRS score. HbA1c was associated with WMLs, decreased eGFR (< 90 mL/min/1.73m^2) and mRS score. And CRP was associated with decreased eGFR (30-60 mL/min/1.73m^2) and mRS score. Therefore, confounders (e.g., hypertension, HbA1c and CRP) were taken into account in analyses of the association between eGFR, WMLs and functional outcome (binary logistic regression models).

3. Results

We enrolled 237 patients in the Berlin “Cream & Sugar” study from January 2009 to March 2011. By March 2012, the follow-up assessment of 203 patients was completed. 34 patients were lost to follow up, 161 patients had complete MRI examination and 42 patients were excluded as they only had CT scanning. MRI confirmed the clinical diagnosis of ischemic stroke in all 161 patients. Of 161 patients, serum parameter creatinine was not available in one patient.

In the remaining 160 patients (median age 66, IQR 52-73; 63.1% male; median NIHSS at admission 2, IQR 1-4) included in this sub-study FLAIR MRI data were available in 123 patients and 37 patients had T2-weighted MRI to rate Wahlund and Fazekas scores.

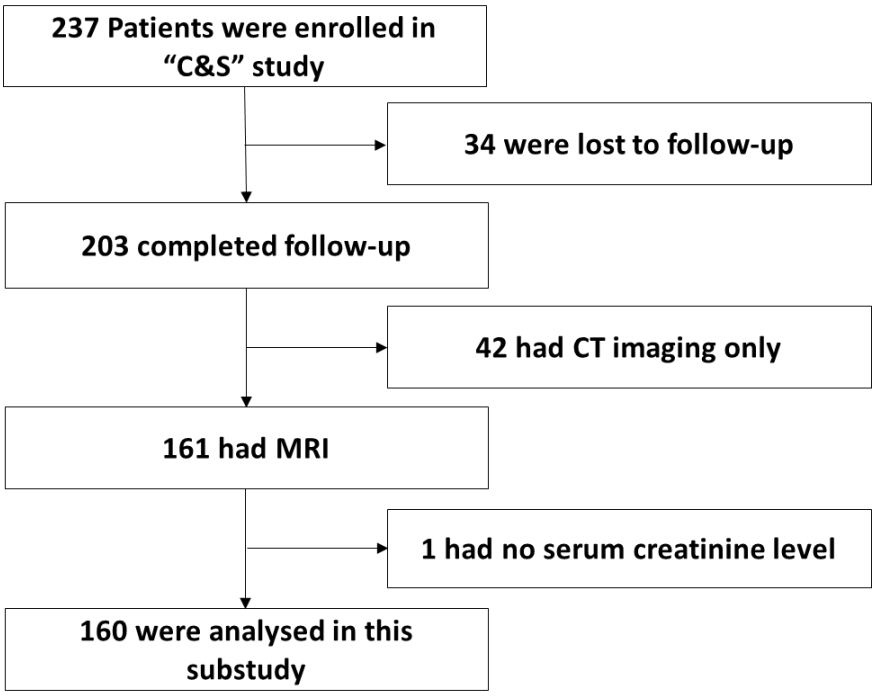

Figure 2: Flow diagram of patients included in the validation analysis

3.1 Demographic and Clinical Characteristics

Of the 160 patients, based on the TOAST classification, there were 66 patients (41.3% of total) with large artery atherosclerosis, 37 patients (23.1%) with cardioembolism, 27 patients (16.9%) with small artery occlusion, 15 patients (9.4%) with other determined etiology, and 15 patients (9.4%) with undetermined etiology. Thrombolysis therapy was applied in 19 patients. Regarding risk factors, 104 patients (65.4%) had a history of hypertension, 34 patients (21.3%) had a history of diabetes mellitus. Moderate-to-severe white matter lesions were observed in 59 patients (37%). Eleven patients (6.9%) had microbleeds. CKD was diagnosed in 15 patients (9.4%). In one year of follow-up, 106 patients (66.3%) had favorable functional outcome. Five patients (3.1%) had died. Stroke recurrence occurred in 14 patients (8.8%). A second event (i.e., second cerebral infarction, myocardial infarction, coronary revascularization, cardiovascular death, or TIA) occurred in 28 patients (17.5%).

In this retrospective analysis, 160 patients had a complete documentation on age, gender, serum creatinine, Hb, height, NIHSS at admission, TOAST classification, mRS at 1 year, and the documentation on whether having history of hypertension, history of diabetes, history of hyperlipidemia, stroke recurrence, second event or death. In all of these 160 patients the presence of WMLs and microbleeds was assessed. However, three of these patients did not have a value of CRP level, 7 had no value of TSH level, 2 had no record of systolic and diastolic BP, 1 did not have value of HbA1c level, 5 had no record of cholesterol level, LDL level and HDL level, and 4 had no record of AST level and ALT level. Four patients had no glucose level and triglyceride level measured at 8 am, 11 had no glucose level and triglyceride level at 11 am, 14 had no record of glucose level and triglyceride level at 12 am, and 11 had no glucose level and triglyceride level at 1 pm, 10 had no record of insulin level at 8 and 11 am, 18 had no record of insulin level at 12 am, and 15 had no record of insulin level at 1 pm. Eight patients had no data on heart rate, 1 had no record of weight, 3 did not have the record of waist circumference and 4 had no record of hip circumference.

3.1.1 Demographic and Clinical Characteristics of Participants according to WMLs

Baseline characteristics and serum parameters for patients grouped according to Fazekas scores (0-3) were compared in Table 7.

Five patients (3 male, median age 81 years; IQR 73 - 91 years, NIHSS score at admission 2, IQR 2-5.5) died before 1-year follow-up. Cause of death in all 5 was unknown. No significant association was observed between WMLs severity and death (Wahlund scores, p = 0.096; Fazekas scores, p = 0.115). There was no significant association between the level of renal function and death (eGFR, p = 0.418). Fischer´s exact test did not show a significant association between death and eGFR < 60 mL/min/1.73m^2. (p = 0.07)

Stroke lesion volumes were retrospectively analyzed in 160 patients. Stroke lesion volume was not normally distributed (skewness = 6.342), and median volume was 1.13 cm^3; IQR (0.4-4.27).

Percentage of patients with WMLs grouped by Fazekas (0-3) score was presented in Figure 3

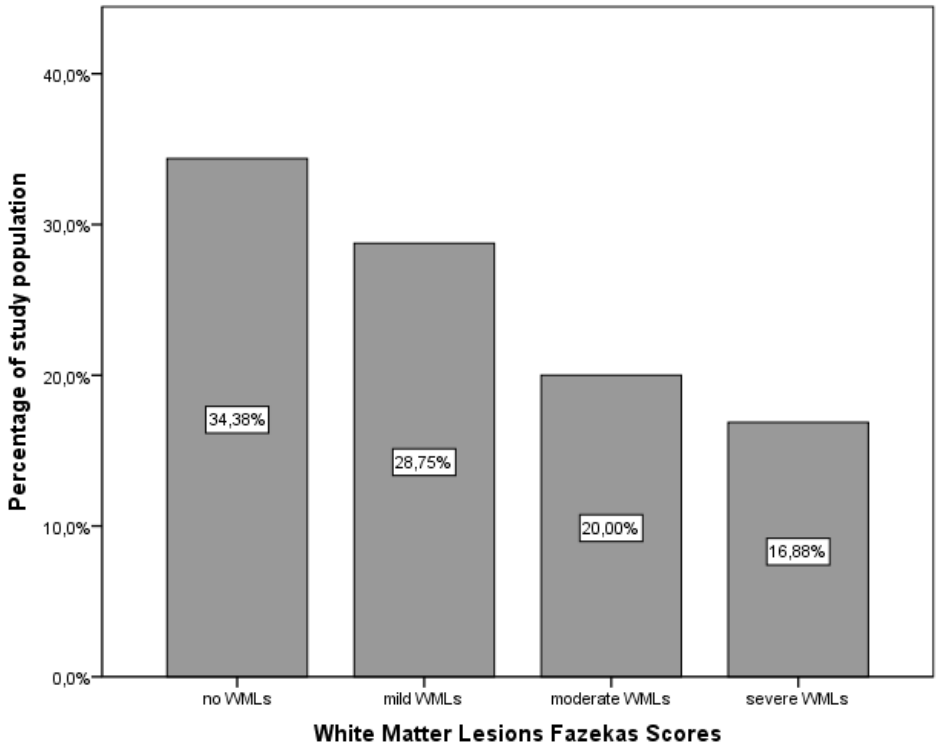

Figure 3: Bar chart showing the percentage of four WMLs grades in the retrospective study. There were 34.38 %of patients without WMLs (Fazekas 0), 28.75 %of patients with mild WMLs (Fazekas 1), 20 % of patients with moderate WMLs (Fazekas 2) and 16.88 % of patients with severe WMLs (Fazekas 3).

In bivariate analysis, WMLs were associated with ageing (Spearman´s rho = 0.557, $p < 0.0005$), hypertension (Chi-square test, for with or without WMLs: OR = 4.306, 95% CI 2.135-8.683, p = 0.0005; for moderate-to-severe WMLs: OR = 2.842, 95% CI 1.345-6.003, p = 0.005), lower eGFR (Spearman´s rho = − 0.305, $p < 0.0005$), higher HbA1c (Spearman´s rho = 0.286, $p < 0.0005$), higher fasting glucose (Spearman´s rho = 0.281, $p < 0.0005$), higher non-fasting glucose at 11 am (Spearman´s rho = 0.271, p = 0.001) higher diastolic blood pressure (Spearman´s rho = 0.208, p = 0.009), and higher mRS score after one year (Wahlund score, Spearman´s rho = 0.211, p = 0.008).

Table 7: Demographic and Clinical Characteristics of Participants According to WMLs Fazekas Score

variable	Fazekas 0	Fazekas 1	Fazekas 2	Fazekas 3	Total	P value	
No. Participant	55	46	32	27	160		
Age mean, years*	54.4 (42.6-64.3)	67.8 (52.1-73.1)	72.8 (61.3-79.5)	70.8 (68.49-75.32)	65.5 (52.1-72.5)	<0.001	a,b,c
Males, n (%)§	35 (63.6)	31 (67.4)	20 (62.5)	15 (55.6)	101 (63.1)	0.793	
Infarct Volume (cm3)*	2.24 (0.75-9.24)	0.91 (0.38-2.34)	1.05 (0.32-3.95)	0.63 (0.24-4.19)	1.13 (0.40-4.27)	0.041	a,c
Creatinine, (µmol/L)*	0.87 (0.78-1.01)	0.9 (0.74-1.01)	0.94 (0.74-1.09)	0.98 (0.85-1.1)	0.91 (0.77-1.04)	0.182	
eGFR, (mL/min/1.73m2)*	89.85 (75.90-103.42)	84.9 (72.5-102.2)	78.9 (66.1-90.8)	70.1 (60.9-82.7)	82.05 (69.57-96.67)	0.001	c,e
HbA1c, (%)*	5.5 (5.1-5.8)	5.4 (5.3-5.8)	5.8 (5.2-6.6)	5.9 (5.6-6.5)	5.6 (5.2-6.1)	0.002	c,e
CRP (mg/dL)*	0.25 (0.1-0.68)	0.22 (0.11-0.57)	0.35 (0.09-0.8)	0.24 (0.11-0.54)	0.25 (0.1-0.64)	0.689	
TSH (mU/L)*	2.1 (1.26-2.91)	1.37 (0.87-1.98)	1.57 (1-1.95)	1.96 (1.13-2.21)	1.72 (1.03-2.31)	0.023	a
Hb (g/dL)*	14.3 (13.6-15.3)	14.5 (13.6-15.2)	14.6 (13.9-15.4)	14.2 (13-15.4)	14.4 (13.6-15.4)	0.538	
TG 8 am (mg/dL)*	117 (91.5-156.25)	101 (80-128.5)	115.5 (82.25-155.25)	115 (90-190)	114.5 (85-146.5)	0.169	
TG 11 am (mg/dL)*	222 (158-274)	164 (126.25-211.25)	211 (135.25-274)	176 (141.75-276)	192 (142.5-257.5)	0.06	
TG 12 am (mg/dL)*	261 (190-335)	209.5 (127-280)	216 (135.75-281.25)	266 (190-335)	231.5 (150.5-309)	0.013	a
TG 1 pm (mg/dL)*	249 (182-329)	175 (128-244)	234 (114.5-339)	228 (160-330.25)	216 (153-305)	0.052	
Glc 8 am (mg/dL)*	92.5 (85.75-100.25)	96 (86-109.5)	103 (91.5-113)	105 (92-133)	95 (87-110)	0.005	b,c
Glc 11 am (mg/dL)*	89 (84-97)	92 (85-101.25)	98 (89-112.5)	100 (92.75-123.25)	93 (86-107)	0.009	c
Glc 12 am (mg/dL)*	141 (106-175)	148 (106.25-189)	145.5 (101.5-177.75)	175 (136-191)	150.5 (108.7-183.3)	0.219	
Glc 1 pm (mg/dL)*	126 (94.5-156.5)	134 (111-175)	130 (102-159.5)	182.5 (121-194.75)	135 (105.5-176)	0.057	
Insulin 8 am (mU/L)*	8 (4.25-13.75)	7 (5-12)	8 (5.5-13.5)	7 (5-13.5)	8 (5-13)	0.851	
Insulin 11 am (mU/L)*	10.5 (6-15)	11 (5-17)	12.5 (8-21.5)	13 (8-19.25)	12 (7-18)	0.343	
Insulin 12 am (mU/L)*	41 (21.25-59.75)	34.5 (18-48.75)	23 (11.5-67)	45 (26-56)	37 (18-56)	0.222	
Insulin 1 pm (mU/L)*	33 (20-74)	32.5 (17.75-66)	34 (11-70.75)	46 (28.25-72.75)	37 (18-72)	0.621	
Cholesterol (mg/dL)*	185.5 (155.5-214.25)	186.5 (162.5-205.5)	182.5 (156.3-211.8)	175 (162-210)	184 (158-210)	0.857	
LDL (mg/dL)*	113 (79.25-140.5)	115.5 (91.5-136.75)	107 (93.5-135.5)	100 (70-133)	110 (88-137)	0.522	
HDL (mg/dL)*	46 (41-55)	52 (43-62)	44 (36.75-51.25)	50 (41-58)	47 (41-58)	0.097	
LDL/HDL ratio*	2.51 (1.97-3.10)	2.15 (1.67-2.84)	2.44 (1.75-3.37)	2.2 (1.49-2.98)	2.34 (1.73-3.05)	0.247	

Table to be continued

variable	Fazekas 0	Fazekas 1	Fazekas 2	Fazekas 3	Total	P value	
AST (U/L)*	27.5 (20-38)	25 (22-32)	25 (21-29.5)	25 (23-33)	26 (21-34)	0.494	
ALT (U/L)*	30 (19.75-52.5)	24 (18-36.5)	22 (16.5-31)	25 (18-38)	25 (18-39.5)	0.107	
Height (m)*	1.77 (1.7-1.8)	1.76 (1.67-1.81)	1.73 (1.68-1.8)	1.7 (1.65-1.79)	1.76 (1.68-1.8)	0.377	
Weight (kg)*	83 (75-92)	80 (70-86.5)	80 (70-93)	75 (70-86)	80 (72-90)	0.153	
BMI (kg/m2)*	27.6 (25.1-29.6)	25.76 (24.15-28.14)	27.8 (23.1-30.9)	25.95 (23.12-29.38)	26.7 (24.4-29.4)	0.407	
Waist circumference (cm)*	101 (93.5- 105.5)	99 (86.5-105.5)	103.5 (95.88-109)	100.5 (94-110)	101 (93.25-108)	0.456	
Hip circumference (cm)*	105 (99-111.5)	103 (98-108.5)	104 (95.5-109.75)	103 (98-108)	104 (98-109.7)	0.694	
Waist-to-hip ratio*	0.96 (0.91-0.98)	0.96 (0.90-1)	0.99 (0.93-1.03)	0.97 (0.92-1.02)	0.969 (0.92-1)	0.079	
Heart Rate*	71 (64-79)	72 (64-80)	76 (69-80)	76 (64-80)	72 (65-80)	0.549	
Systolic BP (mmHg)*	130 (120-140)	140 (120-153,5)	140 (126-154)	140 (120-160)	136 (120-150.25)	0.143	
Diastolic BP (mmHg)*	75 (70-80)	80 (75-84.5)	80 (70-87)	80 (78-90)	80 (70-86.25)	0.041	c
Hypertension, n (%)§	24 (43.6)	34 (73.9)	24 (77.4)	22 (81.5)	104 (65.4)	0.0005	a,b,c
Diabetes, n (%)§	8 (14.5)	7 (15.2)	10 (31.3)	9 (33.3)	34 (21.3)	0.08	
Hyperlipidemia, n (%)§	15 (27.3)	14 (30.4)	14 (43.8)	9 (33.3)	52 (32.5)	0.452	
NIHSS at admission*	2 (1-3)	2 (1.75-4)	2 (1-4)	3 (2-4)	2 (1-4)	0.233	
Thrombolyse§	6 (10.9)	8 (17.4)	4 (12.5)	1 (3.7)	19 (11.9)	0.373	
mRS follow-up*	1 (0-2)	1 (0-2)	1 (0-3)	2 (1-3)	1 (0-2)	0.048	e
mRS favorable, n (%)	41 (74.5)	34 (73.9)	18 (56.3)	13 (48.1)	106 (66.3)	0.04	e
Lacunar Infarct, n (%)§	8 (14.5)	6 (13)	7 (21.9)	6 (22.2)	27 (16.9)	0.612	
Microbleeds, n (%)§	2 (3.6)	2 (4.3)	4 (12.5)	3 (11.1)	11 (6.9)	0.296	
Secondary Stroke, n (%)§	5 (3.1)	4 (8.7)	5 (15.6)	0 (0)	14 (8.8)	0.215	
Secondary Event, n (%)§	9 (16.7)	11 (23.9)	7 (21.9)	1 (3.7)	28 (17.6)	0.152	
patient death, n (%)§	1 (1.8)	0 (0)	2 (6.3)	2 (7.4)	5 (3.1)	0.216	
Stroke subtype, n (%)§						0.004	
LAA	16 (29.1)	24 (52.5)	11 (34.4)	15 (55.6)	66 (41.3)		
CE	10 (18.2)	10 (21.7)	12 (37.5)	5 (18.5)	37 (23.1)		
SAO	8 (14.5)	6 (13)	7 (21.9)	6 (22.2)	27 (16.9)		
OC	11 (20)	3 (6.5)	0 (0)	1 (3.7)	15 (9.4)		
UND	10 (18.2)	3 (6.5)	2 (6.3)	0 (0)	15 (9.4)		

eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; CRP, C-reactive protein; TSH, Thyroid-stimulating hormone; Hb, hemoglobin; TG, Triglyceride; Glc, Glucose; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; AST, Aspartate transaminase; ALT, Alanine transaminase; BMI, body mass index; BP, Blood pressure; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; mRS favorable, mRS score 0-1; Second Stroke, Cerebral infarction; Second Event, Myocardial infarction or Cerebral infarction or TIA; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-vessel occlusion; OC, stroke of other determined etiology; and UND, stroke of undetermined etiology.
Values are median (interquartile range) unless otherwise specified
* Kruskal-Wallis H test and post-hoc tests.
§ Chi-square test
a, Significant difference observed between Fazekas 0 and Fazekas 1
b, Significant difference between Fazekas 0 and Fazekas 2
c, Significant difference between Fazekas 0 and Fazekas 3
d, Significant difference between Fazekas 1 and Fazekas 2
e, Significant difference between Fazekas 1 and Fazekas 3
f, Significant difference between Fazekas 2 and Fazekas 3

3.1.2 Demographic and Clinical Characteristics of Participants according to eGFR

The eGFR was normally distributed (skewness = 0.488 < 1; mean = 84.7 mL/min/1.73m^2; standard deviation = 21; median = 82.1 mL/min/1.73m^2; IQR 69.6-96.7; minimum = 33 mL/min/1.73m^2; maximum = 164 mL/min/1.73m^2).

Demographic and clinical characteristics of participants grouped according to eGFR were presented in Table 8. Kruskal-Wallis H test and Fischer´s exact test were performed. If significant difference were found, *post hoc* analyses were used to detect the difference between each subgroup.

Figure 4 shows the proportion of patients with eGFR ≥ 90 mL/min/1.73m^2, 60-90 mL/min/1.73m^2, and 30-60 mL/min/1.73m^2. In this sub-study, there were no patients with eGFR below 30 mL/min/1.73m^2.

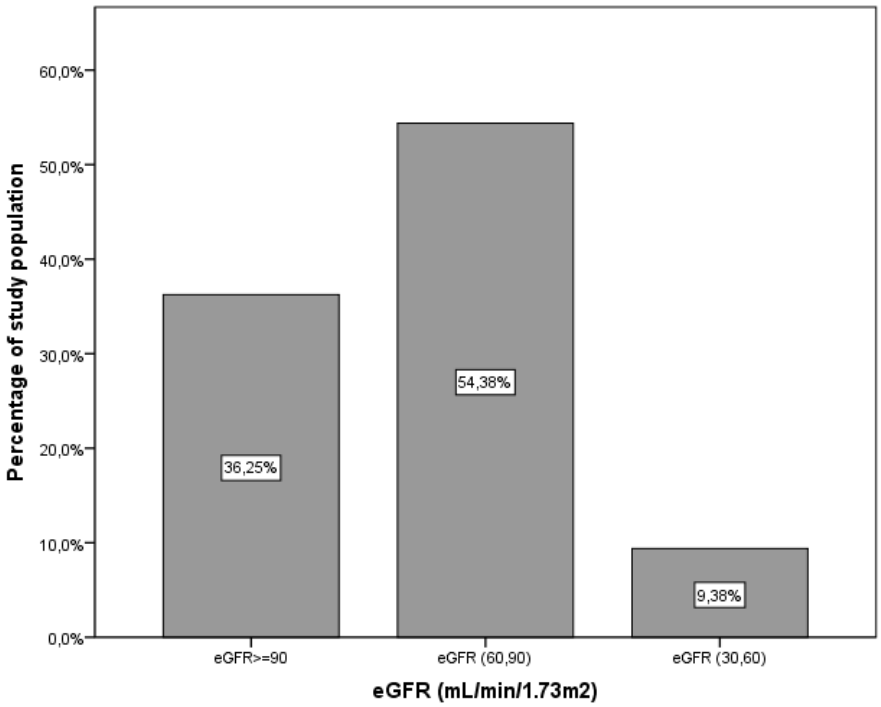

Figure 4: Bar Chart showing the percentages of three degrees of eGFR in the retrospective study. There were 36.25 % of patients with eGFR ≥ 90 mL/min/1.73m^2, 54.38 %of patients with eGFR [60, 90) mL/min/1.73m^2, and 9.38 %of patients with eGFR (30, 60) mL/min/1.73m^2. There was no patient with an eGFR below 30 mL/min/1.73m^2 in this study.

Patients with impaired renal function were older (Pearson r = 0.507, $p < 0.0005$), had a history of hypertension (OR = 2.271, 95% CI 1.156-4.461, p = 0.016), had higher HbA1c levels (Spearman´s rho = 0.285, $p < 0.005$), higher fasting glucose levels (Spearman´s rho = 0.183, p = 0.022), higher non-fasting glucose levels at 11 am (Spearman´s rho = 0.178, p = 0.029), higher Insulin levels at 11 am (Spearman´s rho = 0.23, p = 0.005), and a higher prevalence of WMLs by Fazekas score (Spearman´s rho = 0.305, $p < 0.0005$); by Wahlund score (Spearman´s rho = 0.375, $p < 0.0005$). Decreased eGFR was associated with CRP > 0.5 mg/dL (Chi-squared test, p = 0.001) and also associated with NIHSS ≥ 5 on admission (Chi-squared test, p = 0.022).

Table 8: Demographic and Clinical Characteristics of Participants According to eGFR

variable	eGFR≥90	eGFR [60,90)	eGFR (30-60)	Total	P value	
No. Participant	58	87	15	160		
Age mean, years*	54.2 (44.8-68.7)	67.5 (57.8-72.9)	79.3 (69.3-86.5)	65.5 (52.1-72.5)	<0.0005	a,b,c
Males, n (%)§	40 (69)	57 (65.5)	4 (26.7)	101 (63.1)	0.008	b,c
Infarct Volume (cm3)*	1.04 (0.51-4.66)	1.2 (0.33-4.63)	0.67 (0.25-1.37)	1.13 (0.40-4.27)	0.569	
Creatinine, (µmol/L)*	0.76 (0.67-0.85)	0.97 (0.89-1.06)	1.12 (1-1.35)	0.91 (0.77-1.04)	<0.0005	a,b,c
HbA1c, (%)*	5.3 (4.95-5.65)	5.7 (5.3-6.3)	6 (5.6-6.6)	5.6 (5.2-6.1)	<0.0005	a,b
CRP (mg/dL)*	0.23 (0.11-0.55)	0.23 (0.09-0.55)	0.84 (0.37-0.93)	0.25 (0.1-0.64)	0.004	b,c
TSH (mU/L)*	1.64 (1.14-2.32)	1.76 (1.11-2.27)	1.51 (0.81-3.27)	1.72 (1.03-2.31)	0.978	
Hb (g/dL)*	14.4 (13.8-15.2)	14.6 (13.7-15.5)	13 (12.1-14.2)	14.4 (13.6-15.4)	<0.0005	b,c
TG 8 am (mg/dL)*	107.5 (85.75-130.75)	115 (80-156)	119 (100-152)	114.5 (85-146.5)	0.567	
TG 11 am (mg/dL)*	187 (142-269)	202(141.5-257.75)	187 (151.75-232.75)	192 (142.5-257.5)	0.844	
TG 12 am (mg/dL)*	234 (155-317)	225 (145.5-299)	232 (167.25-303.5)	231.5 (150.5-309)	0.788	
TG 1 pm (mg/dL)*	210 (140.5-304.25)	218 (153-318.25)	217 (154-279)	216 (153-305)	0.99	
Glc 8 am (mg/dL)*	90.5 (84.75-101.75)	99 (90-112)	98 (94-112)	95 (87-110)	0.026	a
Glc 11 am (mg/dL)*	89 (82-101)	94.5 (88-114)	100 (94-113)	93 (86-107)	0.025	a,b,
Glc 12 am (mg/dL)*	155 (106-177)	151 (108-185.5)	145 (134-171.25)	150.5 (108.7-183.3)	0.937	
Glc 1 pm (mg/dL)*	135.5 (110.5-175.5)	129.5 (99-163.25)	186 (120-198)	135 (105.5-176)	0.056	
Insulin 8 am (mU/L)*	6 (4-10)	9 (6-13.25)	9 (5-12)	8 (5-13)	0.048	a
Insulin 11 am (mU/L)*	8 (4-14.25)	13 (9-18)	15 (9-26)	12 (7-18)	0.004	a,b
Insulin 12 am (mU/L)*	39 (16.25-50.5)	36 (17.5-59.5)	31 (22-49)	37 (18-56)	0.906	
Insulin 1 pm (mU/L)*	38 (20.5-73)	30.5 (15.75-65.75)	61 (30.5-73.25)	37 (18-72)	0.212	
Cholesterol (mg/dL)*	180 (155-212)	187 (161-210)	200 (164-218)	184 (158-210)	0.793	
LDL (mg/dL)*	110 (79.5-145.5)	110 (91-133)	126 (94-151)	110 (88-137)	0.656	
HDL (mg/dL)*	47 (42-60.5)	47 (40-58)	49 (42-53)	47 (41-58)	0.66	
LDL/HDL ratio*	2.2 (1.7-3.1)	2.41 (1.75-2.91)	2.57 (1.88-3.07)	2.34 (1.73-3.05)	0.811	
AST (U/L)*	26 (20-37.2)	26 (23-33)	24 (19-28)	26 (21-34)	0.471	
ALT (U/L)*	26 (17.75-46.75)	25 (18-40)	19 (15-28)	25 (18-39.5)	0.182	

Table to be continued

variable	eGFR≥90	eGFR [60,90)	eGFR (30,60)	Total	P value	
Height (m)*	1.77 (1.69-1.8)	1.75 (1.68-1.81)	1.68 (1.58-1.78)	1.76 (1.68-1.8)	0.112	
Weight (kg)*	80 (71.5-88.25)	82 (73-92)	80 (67.5-91.25)	80 (72-90)	0.485	
BMI (kg/m2)*	26 (22.5-28.3)	27.3 (24.6-29.6)	28.3 (25.3-30.3)	26.7 (24.4-29.4)	0.129	
Waist circumference (cm)*	97 (86-105)	101 (94-109.5)	104 (100-110)	101 (93.25-108)	0.089	
Hip circumference (cm)*	102.5 (97-109.5)	104 (99.5-110)	107 (102-109)	104 (98-109.7)	0.371	
Waist-to-hip ratio*	0.96 (0.90-0.99)	0.97 (0.92-1)	0.97 (0.93-1.01)	0.969 (0.92-1)	0.338	
Heart Rate*	72 (64-80)	72 (66.5-80)	74 (64-80)	72 (65-80)	0.992	
Systolic BP (mmHg)*	130 (120-150)	137 (120-153.25)	150 (120-158)	136 (120-150.25)	0.283	
Diastolic BP (mmHg)*	8 (70-84.5)	80 (70-88.5)	78 (70-80)	80 (70-86.25)	0.742	
Hypertension, n (%)§	31 (53.4)	61 (70.9)	12 (80)	104 (65.4)	0.044	a
Diabetes, n (%)§	8 (13.8)	22 (25.3)	4 (26.7)	34 (21.3)	0.219	
Hyperlipidemia, n (%)§	13 (22.4)	34 (39.1)	5 (33.3)	52 (32.5)	0.11	
NIHSS at admission*	2 (1-4)	2 (1-3)	4 (2-7)	2 (1-4)	0.007	c
Thrombolyse§	8 (13.8)	9 (10.3)	2 (13.3)	19 (11.9)	0.807	
mRS follow-up*	1 (0-2)	1 (0-2)	2 (2-3)	1 (0-2)	0.002	b,c
mRS favorable, n (%)§	43 (74.1)	60 (69)	3 (20)	106 (66.3)	<0.0005	b,c
Lacunar Infarct, n (%)§	11 (19)	14 (16.1)	2 (13.3)	27 (16.9)	0.838	
Microbleeds, n (%)§	0 (0)	11 (12.6)	0 (0)	11 (6.9)	0.007	a
Secondary Stroke, n (%)§	7 (12.3)	6 (6.9)	1 (6.7)	14 (8.8)	0.512	
Secondary Event, n (%)§	8 (14)	19 (21.8)	1 (6.7)	28 (17.6)	0.245	
patient death, n (%)§	2 (3.4)	1 (1.1)	2 (13.3)	5 (3.1)	0.043	c
WMLs. Yes, n (%)§	31 (53.4)	63 (72.4)	11 (73.3)	105 (65.5)	0.05	a
WMLs Severe, n (%)§	12 (20.7)	38 (43.7)	9 (60)	59 (36.9)	0.003	a,b
WMLs Fazekas scores*	1 (0-1)	1 (0-2)	2 (0-3)	1 (0-2)	0.003	a,b
WMLs Wahlund scores*	2 (0-3)	3 (1-6)	5 (2.75-10)	3 (1-6)	<0.0005	a,b

Table to be continued

variable	eGFR≥90	eGFR [60,90)	eGFR (30,60)	Total	P value
Stroke subtype, n (%)§					0.015
LAA	23 (39.7)	40 (46)	3 (20)	66 (41.3)	
CE	7 (12.1)	23 (26.4)	7 (46.7)	37 (23.1)	
SAO	11 (19)	14 (16.1)	2 (13.3)	27 (16.9)	
OC	11 (19)	3 (3.4)	1 (6.7)	15 (9.4)	
UND	6 (10.3)	7 (8)	2 (13.3)	15 (9.4)	

eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; CRP, C-reactive protein; TSH, Thyroid-stimulating hormone; Hb, hemoglobin; TG, Triglyceride; Glc, Glucose; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; AST, Aspartate transaminase; ALT, Alanine transaminase; BMI, Body mass index; BP, Blood pressure; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; mRS favorable, mRS score 0-1; Second Stroke, Cerebral infarction; Second Event, Myocardial infarction or Cerebral infarction or TIA.WMLs, white matter lesions; WMLs. Yes means WMLs with Fazekas score 1-3; WMLs Severe means WMLs with Fazekas score 2-3; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-vessel occlusion; OC, stroke of other determined etiology; and UND, stroke of undetermined etiology.
Values are median (interquartile range) unless otherwise specified
*Kruskal-Wallis H test and post-hoc tests; § Chi-square test
a, Significant difference observed between eGFR ≥ 90 and eGFR [60,90)
b, Significant difference between eGFR ≥ 90 and eGFR (30,60)
c, Significant difference between eGFR [60,90) and eGFR (30,60)

3.2 Association between eGFR and WMLs

3.2.1 Distribution and Difference of eGFR based on WMLs Degree

Figure 5 shows the relationship between eGFR and Fazekas score. With higher Fazekas score, the eGFR declines. There are significant differences between Fazekas 4 and Fazekas 1 (p = 0.001), and between Fazekas 3 and Fazekas 0 (p = 0.018).

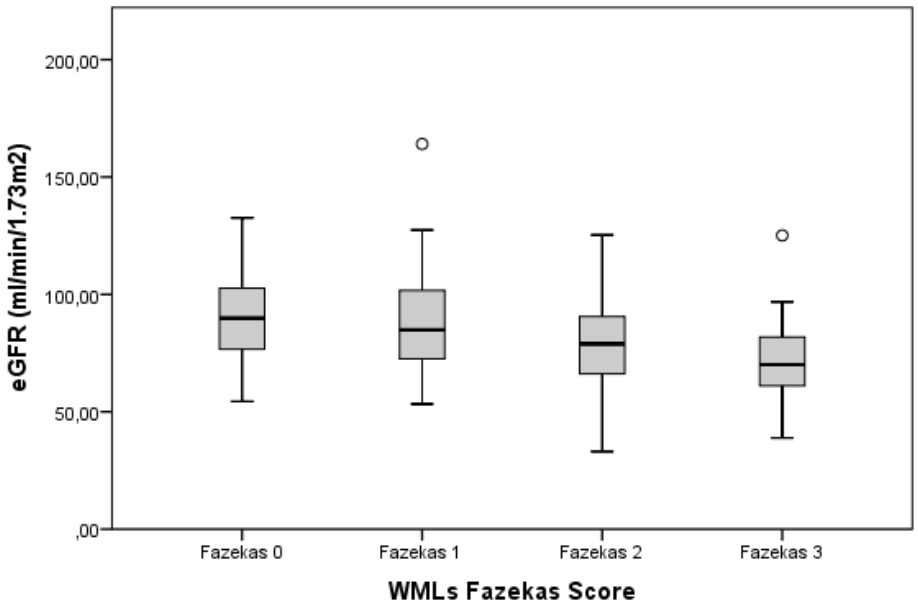

Figure 5: Boxplots of eGFR across different degrees of WMLs (Fazekas Score) with higher Fazekas score there was a decrease of eGFR, and there were significant differences of median eGFR between Fazekas 3 and Fazekas 1 (p = 0.001) as well as between Fazekas 3 and Fazekas 0 (p = 0.018). Outliers are denoted as circles (°).

Figure 6 shows the relationship between eGFR and Fazekas score across gender. With higher Fazekas scores, the eGFR level declined. Compared to men, the eGFR of women was lower in the group of Fazekas 2 and Fazekas 3.

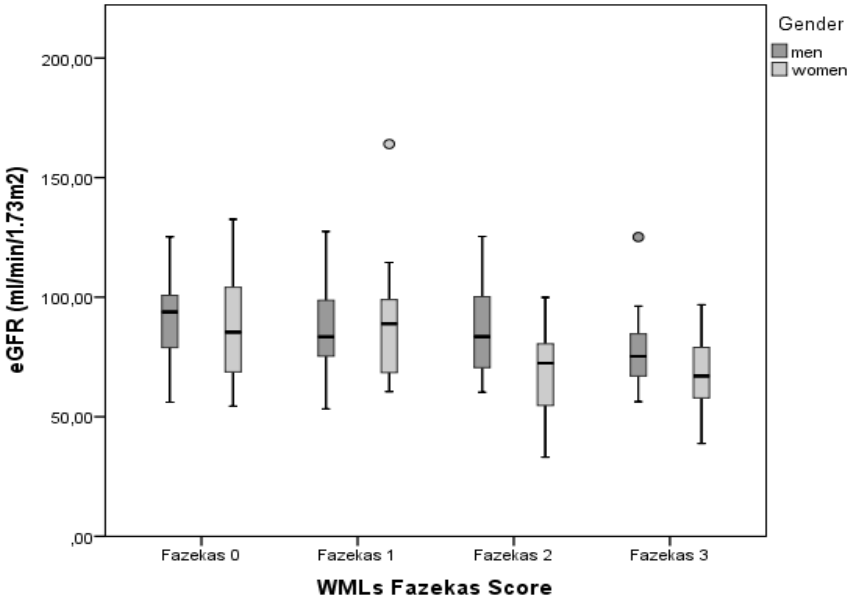

Figure 6: Boxplots of eGFR for each different degree of WMLs (Fazekas Score) divided by gender. The median eGFR of women in Fazekas 2 and Fazekas 3 were lower compared to men. Outliers are denoted as circules(°). Kruskal-Wallis H test and post-hoc tests showed a significant difference in eGFR level between severe WMLs (Fazekas score 3) and mild WMLs (Fazekas score 1) (p = 0.018), and a significant difference in eGFR level between severe WMLs (Fazekas score 3) and no WMLs (Fazekas score 0) (p = 0.001)

3.2.2 Distribution and Difference of WMLs Degree based on eGFR Level

Figure 7 shows the median Wahlund scores for each eGFR group.

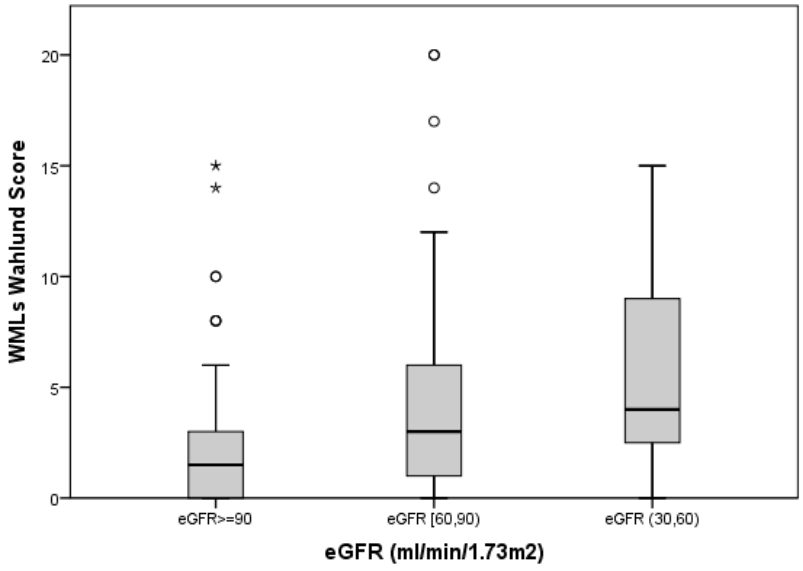

Figure 7: Boxplots of WMLs (Wahlund score) at different eGFR levels. There were significant differences of median Wahlund score between eGFR ≥ 90 mL/min/1.73m^2 and eGFR 60-90 mL/min/1.73m^2 (p = 0.001), between eGFR ≥ 90 mL/min/1.73m^2 and eGFR 30 - 60) mL/min/1.73m^2 (p = 0.004). (Kruskal-Wallis H test and post-hoc test). Outliers are denoted as circles (°), and extreme outliers are illustrated with an asterisk (*).

3.2.3 Association of eGFR and WMLs

eGFR was dichotomized (eGFR ≥ 90, eGFR < 90 mL/min/1.73m^2). Two different dichotomizations of WMLs Fazekas Score were used (Fazekas 0 vs. Fazekas 1-3 and Fazekas 0-1 vs. Fazekas 2-3). The results are shown in Figure 8, 9, and 10 separately.

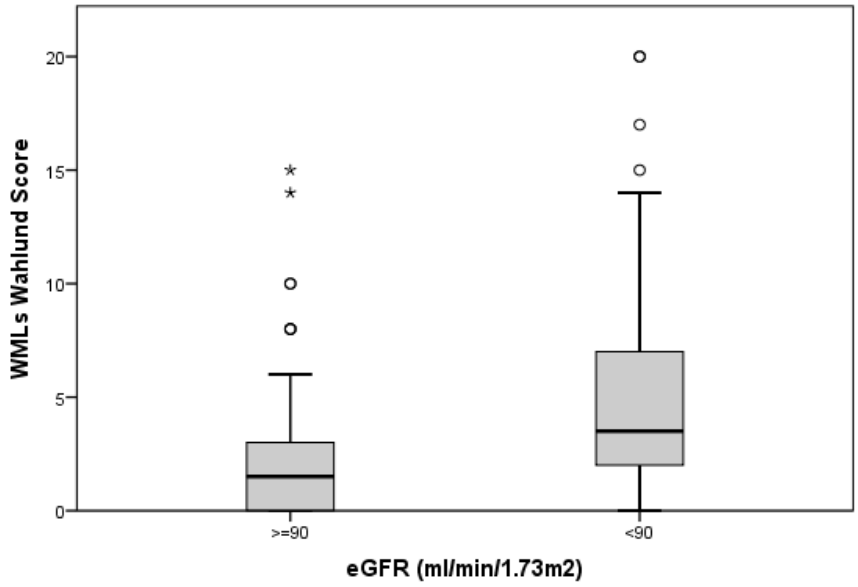

Figure 8: Difference of severity of WMLs between patients with eGFR ≥ 90 mL/min/1.73m^2 and patients with eGFR < 90 mL/min/1.73m^2, (p < 0.0005, Mann-Whitney-U Test). Median Wahlund score is higher in patients with eGFR < 90 mL/min/1.73m^2. The interquartile range was also larger. Outliers are denoted as circles (°), and extreme outliers are illustrated with an asterisk (*).

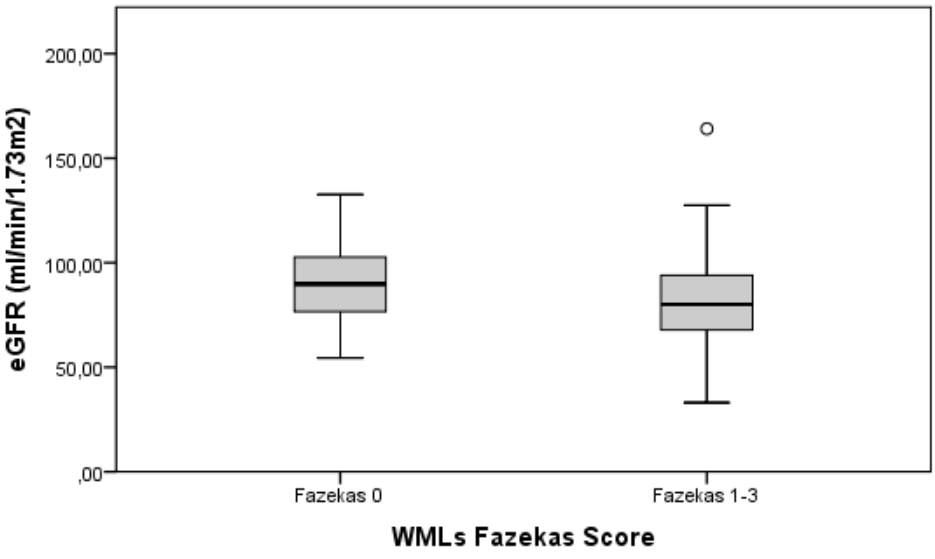

Figure 9: Difference of eGFR level between patients with Fazekas 0 and Fazekas 1-3 (p = 0.007, Mann-Whitney-U Test). Median eGFR in patients with Fazekas 0 was higher compared to patients with Fazekas 1-3. Outliers are denoted as circles (°).

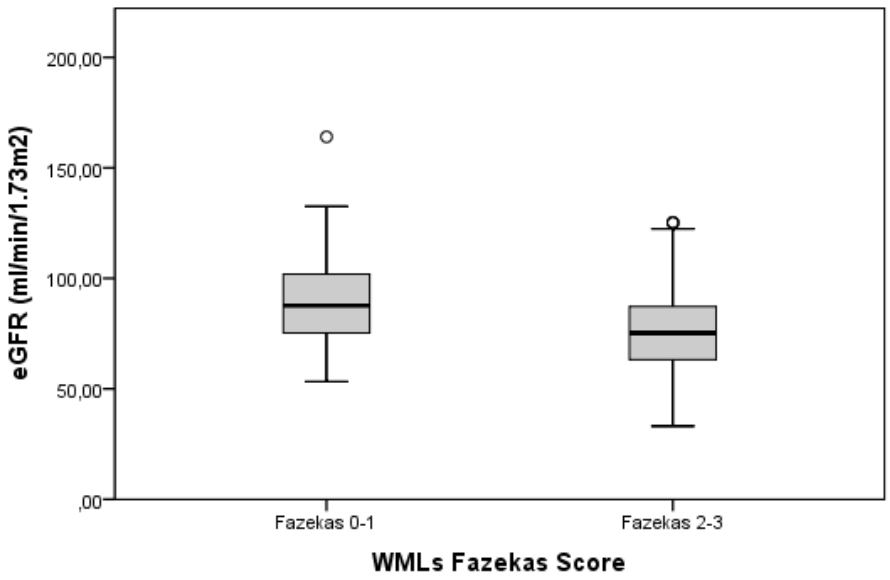

Figure 10: Difference of eGFR level between patients with Fazekas 0-1 and Fazekas 2-3 (P < 0.0005, Mann-Whitney-U Test). Median eGFR in patients with Fazekas 0-1 was higher compared patients with Fazekas 2-3. Outliers are denoted as circles (°).

Based on the dichotomization, two crosstables (2×2) of eGFR and Fazekas Score were created (Table 9).

Table 9: Cross-table of eGFR and Fazekas Score

	Fazekas 0			Fazekas 1-3		
	N.	Expected N.	%	N.	Expected N.	%
eGFR≥90	27	19.9	49.1	31	38.1	29.5
eGFR<90	28	35.1	50.9	74	66.9	70.5

	Fazekas 0-1			Fazekas 2-3		
	N.	Expected N.	%	N.	Expected N.	%
eGFR≥90	46	36.6	45.5	12	21.4	20.3
eGFR<90	55	64.4	54.5	47	37.6	79.7

"N" indicates the observed values and "Epected N"means the expected cell frequency in sample. "Fazekas" means WMLs Fazekas score and "eGFR" means estimated glomerular filtration rate.
All expected cell frequencies were greater than five.

Comparing the patients with and without WMLs, there was a statistically significant association between eGRF (eGFR ≥ 90 mL/min/1.73m^2 [Reference]; eGFR < 90 mL/min/1.73m^2) and WMLs, $X^2(1) = 5.98$, OR 2.302, 95% CI 1.172-4.52, p = 0.014. The strength of the association was weak, Phi (φ) = 0.193, p = 0.014. (Phi (φ) is a measure of the strength of association of a nominal by nominal relationship). Comparing patients with no to mild WMLs with patients with moderate to severe WMLs, there was a statistically significant association between eGFR (eGFR ≥ 90

mL/min/1.73m^2 [Reference]; eGFR < 90 mL/min/1.73m^2) and WMLs (X^2 (1) = 10.239, OR 3.279, 95% CI 1.555-6.901, p = 0.001.) The strength of the association was moderate, Phi (φ) = 0.253, p = 0.001.

3.2.4 Is Decreased eGFR a Risk Factor for WMLs or not

To determine if impaired eGFR was associated with WMLs, four forward stepwise binary logistic regression analyses were performed. First, a simple logistic regression model was used and secondly, it was adjusted by other variables in multiple logistic regression models.

3.2.4.1 Simple Logistic Regression Model

A forward stepwise binary logistic regression analysis was performed between the group of patients with WMLs (Fazekas score 1-3) and the group of patients without WMLs (Fazekas score 0). eGRF was stratified into two groups (eGFR ≥ 90 mL/min/1.73m^2 [Reference]; eGFR < 90 mL/min/1.73m^2). In the simple model, eGFR < 90 mL/min/1.73m^2 was a significant predictor of the presence of WMLs (OR 2.302, 95% CI 1.172-4.52, p = 0.015).

Another forward stepwise binary logistic regression was performed between the group of patients with no or mild WMLs (Fazekas score 0-1) and the group of patients with moderate or severe WMLs (Fazekas score 2-3). eGRF was stratified into three groups (eGFR ≥ 90 mL/min/1.73m^2 [Reference]; eGFR 60 to 90 mL/min/1.73m^2; eGFR 30 to 60 mL/min/1.73m^2). In the simple model, patients whose eGFR ranged from 60 to 90 mL/min/1.73m^2 had a significantly increased risk of having moderate or severe WMLs when compared with patients whose eGFR was above 90 mL/min/1.73m^2. (OR 2.973, 95% CI 1.385-6.38, p = 0.005). An eGFR of 30 to 60 mL/min/1.73m^2 was a significant predictor of having moderate or severe WMLs. (OR 5.75. 95% CI 1.71-19.335, p = 0.005). (Table 10)

Table 10: Results from a logistic regression analysis model assessing decreased eGFR as a risk factor for moderate-to-severe degree of WMLs

		95% CI		
	OR	Lower	Upper	p
eGFR≥90				Reference
60≤eGFR<90 §	2.97	1.38	6.38	0.005
30<eGFR<60 §	5.75	1.71	19.33	0.005

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate
§ Forward stepwise binary logistic regression

3.2.4.2 Multiple Logistic Regression Model

Two forward stepwise binary logistic regression analyses including age (10-year intervals), gender, systolic blood pressure quartiles (< 120 [reference], 120-136, 136-150, > 150 mm Hg), diastolic blood pressure quartiles (< 70 [reference], 70-80, 80-86, > 86 mm Hg), HbA1c quartiles (< 5.2 [reference], 5.2-5.6, 5.6-6.1, > 6.1%), and eGFR (three degrees: eGFR ≥ 90 mL/min/1.73m^2 [reference]; eGFR 60-90 mL/min/1.73m^2; eGFR 30-60 mL/min/1.73m^2) were performed. In the first binary logistic regression analysis, patients with WMLs (Fazekas score 1-3) were compared to patients without WMLs (Fazekas score 0). 157 patients were in the analysis. One patient had not HbA1c and two patients had not systolic BP and diastolic BP.

Age and diastolic blood pressure were significantly associated with the presence of WMLs. eGFR, gender; systolic blood pressure and HbA1c were not associated with WMLs. This model explained R^2 = 42.4% of the complete variation. (Table 11)

Table 11: Results from multiple logistic regression analysis assessing risk factors for the presence of WMLs (n = 157, R^2 = 0.424)

		95% CI		
	OR	Lower	Upper	p
Age §	2.96	2.02	4.34	0.0005
Diastolic BP §	1.57	1.09	2.27	0.015

OR, odds ratio; CI, confidence interval; BP, blood pressure
§ Forward stepwise binary logistic regression
Note: gender, systolic BP, eGFR and HbA1c were not significant in the analysis.

Another forward stepwise binary logistic regression was performed between the group of patients with no or mild WMLs (Fazekas score 0-1) and the group of patients with moderate-to-severe WMLs (Fazekas score 2-3). In the second binary logistic regression analysis (n = 157, R^2 = 0.291), only age (OR 2.36; 95% CI 1.69-3.29; p < 0.0005) was significantly associated with moderate-to-severe WMLs.

3.3 Functional Outcome at 1-year

3.3.1 Baseline Characteristics of Participants according to Follow-up mRS Score

Baseline demographic and clinical data for two groups were compared in Table 12. Mann-Whitney-U Test, Chi-square test and Fisher's Exact Test, if expected cell frequencies were smaller than five, were performed (Level of significance at 0.05).

Table 12: Baseline characteristics of participants according to functional outcome at 1-year

variable	favorable outcome	unfavorable outcome	Total	p value
No. Participant	106	54	160	
Age mean, years*	61.6 (50.9-69.5)	69.7 (57.7 -79.6)	65.5 (52.2-72.5)	<0.0005
Males, n (%) §	70 (66)	31 (57.4)	101 (63.1)	0.285
Infarct Volume (cm3)*	1.06 (0.34-3.91)	1.21 (0.44-4.59)	1.13 (0.39-4.27)	0.46
Creatinine, (µmol/L)*	0.88 (0.76-1.01)	0.94 (0.79-1.07)	0.91 (0.77-1.04)	0.06
eGFR, (mL/min/1.73m2)*	85.75 (74-99.7)	75.5(63.7-92.3)	82 (69.57-96.67)	0.003
HbA1c, (%)*	5.4 (5.1-6.1)	5.8 (5.4-6.4)	5.6 (5.2-6.1)	0.002
CRP (mg/dL)*	0.21 (0.09-0.48)	0.37 (0.12-0.92)	0.25 (0.1-0.64)	0.006
TSH (mU/L)*	1.88 (1.16-2.56)	1.42 (0.92-2.11)	1.72 (1.03-2.31)	0.017
Hb (g/dL)*	14.5 (13.6-15.4)	14.3 (13.6-15.4)	14.4 (13.6-15.4)	0.475
TG 8 am (mg/dL)*	114 (85-152)	115 (85-138)	114.5 (85-146.5)	0.741
TG 11 am (mg/dL)*	206 (142-270)	180 (141.7-238.2)	192 (142-257.5)	0.199
TG 12 am (mg/dL)*	241 (158-315)	212 (146.75-288.5)	231.5 (150.5-309)	0.298
TG 1 pm (mg/dL)*	236 (160-315.5)	185.5 (142.25-279)	216 (153-305)	0.267
Glc 8 am (mg/dL)*	95 (86-105)	99 (89.5-117.5)	95.5 (87-110)	0.025
Glc 11 am (mg/dL)*	91 (85-101)	99 (88-116.5)	93 (86-107)	0.018
Glc 12 am (mg/dL)*	155 (113.25-186)	146.5 (106.7-175.2)	150.5(108-183)	0.497
Glc 1 pm (mg/dL)*	136 (98-168)	134 (109.2 -186.7)	135 (105.5-176)	0.287
Insulin 8 am (mU/L)*	7 (4-12.25)	8.5 (6-14)	8 (5-13)	0.053
Insulin 11 am (mU/L)*	10 (5-15)	14.5 (9-19.75)	12 (7-18)	0.003
Insulin 12 am (mU/L)*	41 (20.75-57.25)	34 (17-51)	37 (18-56)	0.378
Insulin 1 pm (mU/L)*	34.5 (18.75-72)	38 (17-72)	37 (18-72)	0.975
Cholesterol (mg/dL)*	184.5 (160-213)	181 (154-206)	184 (158-210)	0.4
LDL (mg/dL)*	110 (90.75-137.25)	115 (76.5-135.5)	110 (88-137)	0.868
HDL (mg/dL)*	49 (42-57.25)	44 (38.5-58.5)	47 (41-58)	0.224
LDL/HDL ratio*	2.36 (1.76-2.91)	2.30 (1.58-3.15)	2.34 (1.73-3.05)	0.843
AST(U/l)*	26 (21-34)	25 (23-34.5)	26 (21-34)	0.821
ALT (U/l)*	26 (18-37)	25 (18-42.5)	25 (18-39.5)	0.976
Height (m)*	1.76 (1.68-1.80)	1.73 (1.64-1.8)	1.76 (1.68-1.8)	0.088
Weight (kg)*	80 (73-90)	80 (70-92)	80 (72-90)	0.764
BMI (kg/m2)*	25.95 (24.3-29.3)	27.7 (25.3-29.8)	26.73 (24.4-29.4)	0.108
Waist circumference (cm)*	99 (90-107)	103 (96.5-110)	101 (93.25-108)	0.012

Table to be continued

variable	favorable outcome	unfavorable outcome	Total	p value
Hip circumference (cm)*	103 (97-108)	106 (101.25-110)	104 (98-109.75)	0.07
Waist-to-hip ratio*	0.96 (0.92-1)	0.97 (0.91-1)	0.96 (0.91-1)	0.299
Systolic BP (mmHg)*	130 (120-149.5)	147 (130-154.25)	136 (120-150.25)	0.001
Diastolic BP (mmHg)*	80 (70-85.75)	80 (70-87.5)	80 (70-86.25)	0.891
Hypertension, n (%)§	60 (57.1)	44 (81.5)	104 (65.4)	0.002
Heart Rate*	72 (64-77)	76 (68-84)	72 (65-80)	0.003
Diabetes, n (%)§	19 (17.9)	15 (27.8)	34 (21.3)	0.15
Hyperlipidemia, n (%)§	36 (34)	16 (29.6)	52 (32.5)	0.58
NIHSS at admission*	2 (1-3)	3 (2-5)	2 (1-4)	0.0005
Thrombolyse§	12 (11.3)	7 (13)	19 (11.9)	0.761
Lacunar Infarct, n (%)‡	18 (17)	9 (16.7)	27 (16.9)	0.96
Microbleeds, n (%)‡	5 (4.7)	6 (11.1)	11 (6.9)	0.131
Secondary Stroke, n (%)‡	6 (5.7)	8 (15.1)	14 (8.8)	0.048
Secondary Event, n (%)§	14 (13.2)	14 (26.4)	28 (17.6)	0.039
patient death, n (%)‡	0 (0%)	5 (9.3)	5 (3.1)	0.001
WMLs. Yes, n (%)§	65 (61.3)	40 (74.1)	105 (65.5)	0.108
WMLs Severe, n (%)§	31 (29.2)	28 (51.9)	59 (36.9)	0.005
WMLs Fazekas scores*	1 (0-2)	2 (0-3)	1 (0-2)	0.01
WMLs Wahlund scores*	2 (0-4)	4 (2-9.5)	3 (1-6)	0.001
Stroke subtype, n (%)§				0.255
LAA	41 (38.7)	25 (46.3)	66 (41.3)	
CE	22 (20.8)	15 (27.8)	37 (23.1)	
SAO	18 (17)	9 (16.7)	27 (16.9)	
OC	12 (11.3)	3 (5.6)	15 (9.4)	
UND	13 (12.3)	2 (3.7)	15 (9.4)	

mRS, modified Rankin Scale; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; CRP, C-reactive protein; TSH, Thyroid-stimulating hormone; Hb, hemoglobin; TG, Triglyceride; Glc, Glucose; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; AST, Aspartate transaminase; ALT, Alanine transaminase; BMI, body mass index; BP, Blood pressure; NIHSS, national institute of health stroke scale; mRS, modified Rankin Scale; mRS favorable means mRS score 0-1; mRS poor means mRS score >1; Second Stroke, Cerebral infarction; Second Event, Myocardial infarction or Cerebral infarction or TIA.WMLs, white matter lesions; WMLs. Yes means WMLs with Fazekas score 1-3; WMLs Severe means WMLs with Fazekas score 2-3; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-vessel occlusion; OC, stroke of other determined etiology; and UND, stroke of undetermined etiology.
Values are median (interquartile range) unless otherwise specified.
*Mann-Whitney U test; §Chi-square test; ‡Fisher's Exact Test

In bivariate analysis, unfavorable functional outcome was associated with older age (Spearman´s rho = 0.193, p = 0.015), hypertension (Chi-square test, OR 3.3, 95% CI 1.501-7.256, p = 0.002), lower eGFR (Spearman´s rho = − 0.181, p = 0.022), higher HbA1c (Spearman´s rho = 0.23, p = 0.005), higher CRP (Spearman´s rho = 0.206, p = 0.01), higher NIHSS score (Spearman´s rho = 0.301, p < 0.0005), higher WMLs Wahlund score (Spearman´s rho = 0.211, p = 0.008), higher heart rate at (Spearman´s rho = 0.238, p = 0.003), higher systolic blood pressure (Spearman´s rho = 0.263, p = 0.001), lower TSH (Spearman´s rho = – 0.193, p = 0.017), higher CRP (Spearman´s

rho = 0.221,p = 0.005), higher fasting glucose (Spearman´s rho = 0.179, p = 0.025), higher insulin (Spearman´s rho = 0.242, p = 0.003) and bigger waist circumference (Spearman´s rho = 0.2, p = 0.012)

There was a significant difference in WMLs between patients with favorable and unfavorable outcome (Mann-Whitney U test, p = 0.001, Figure 11).

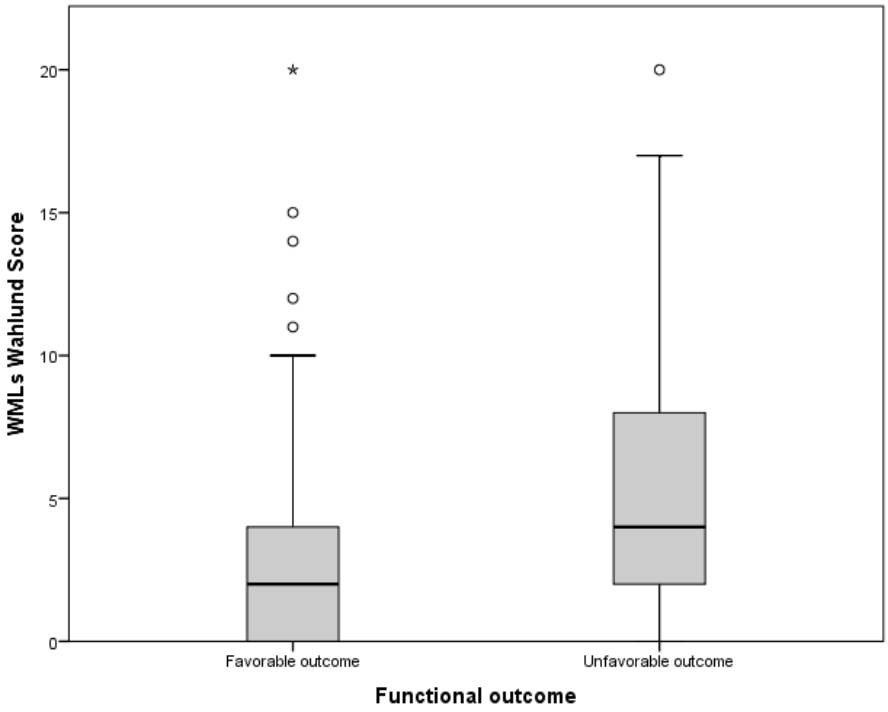

Figure 11: Boxplots of WMLs (Wahlund score) in patients with different functional outcomes. Median Wahlund score in patients with favorable outcome was lower compared to patients with unfavorable outcome. Outliers are denoted as circles (°), and extreme outliers are illustrated with an asterisk (*).

There was a significant difference in eGFR between patients with favorable and unfavorable outcome (Mann-Whitney U test, p = 0.003, Figure 12).

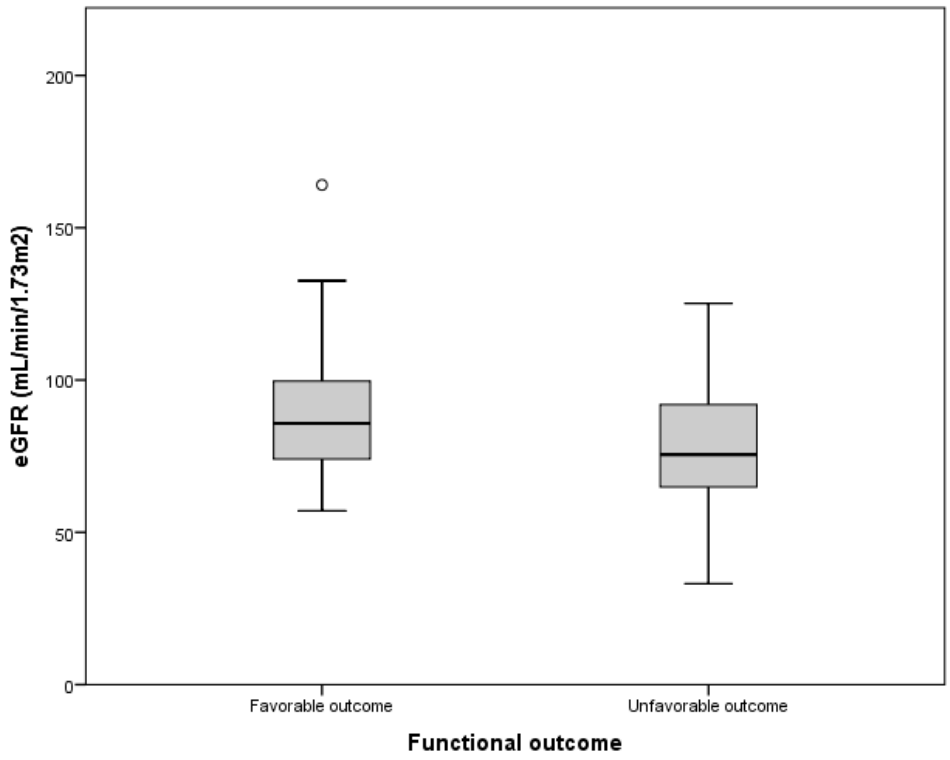

Figure 12: Boxplots of eGFR in patients with different functional outcomes. Median eGFR was lower in patients with unfavorable outcome compared to patients with favorable outcome. Outliers are denoted as circules (°).

3.3.2 Association of three Parameters: eGFR, WMLs and Functional Outcome

To assess the association between eGFR and functional outcome, a Chi-square test was performed (Table 13). All expected cell frequencies were greater than five. There was a statistically significant association between eGFR and mRS, $\chi 2$ (1) = 15.84, OR 9.81, 95% CI (2.633-36.54), $p < 0.0005$. The association was moderate, Phi (φ) = 0.315.

To assess the association between WMLs and mRS functional outcome, a Chi-square test was performed (Table 14). All expected cell frequencies were greater than five. There was a statistically significant association between WMLs and mRS functional outcome, χ^2 (1) = 7.854, OR 2.605, 95% CI 1.322-5.134, p = 0.005. The association was weak, Phi (φ) = 0.222.

Table 13: Cross-table of eGFR, WMLs Fazekas score and follow-up mRS

	favorable outcome			unfavorable outcome		
	N.	Expected N.	%	N.	Expected N.	%
Renal Function eGFR						
eGFR≥60	103	96.1	97.2	42	48.9	77.8
30<eGFR<60	3	9.9	2.8	12	5.1	22.2
WMLs Fazekas score						
Fazekas 0-1	75	66.9	70.8	26	34.1	48.1
Fazekas 2-3	31	39.1	29.2	28	19.9	51.9

N. indicates observed values; Expected N. is the expected cell frequency eGFR, estimated glomerular filtration rate

Table 14: Association between eGFR and functional outcome, and association between Fazekas score and functional outcome (mRS score ≥ 2)

	favorable outcome vs. unfavorable outcome					
			95% CI			
	X2 (1)	OR	Lower	Upper	Phi (ϕ)	p value
Renal Function eGFR						
eGFR≥60						Reference
30<eGFR<60 §	15.84	9.81	2.63	36.54	0.32	0.0005
WMLs Fazekas score						
Fazekas 0-1						Reference
Fazekas 2-3 §	7.85	2.61	1.32	5.13	0.22	0.005

X^2 indicates the value of chi-square; OR, odds ratio; CI, confidence interval, and Phi (ϕ) is a measure of the strength of association of a nominal by nominal relationship eGFR, estimated glomerular filtration rate. § Chi-square test

3.3.3 Interaction of WMLs and eGFR on Functional Outcome

To identify the interaction effect of WMLs and renal dysfunction on stroke functional outcome, a hierarchical binary logistic regression analyses was performed. In the analysis, the independent variables were WMLs (by Fazekas score: Fazekas 0-1 [reference] and Fazekas 2-3) and eGFR (eGFR ≥ 90 mL/min/1.73m^2 [reference], eGFR (60, 90) mL/min/1.73m^2 and eGFR (30, 60) mL/min/1.73m^2) in the first regression model (the main effect model). Then the additional interaction term, Fazekas score*eGFR, (Fazekas 0-1*eGFR ≥ 90 mL/min/1.73m^2 [reference], Fazekas 2-3*eGFR (60, 90) mL/min/1.73m^2, Fazekas 2-3* eGFR (30-60) mL/min/1.73m^2) was added to the second regression model (the moderated multiple regression model). Dependent variable was unfavorable functional outcome (mRS score ≥ 2).

The main effect regression model shown that independent variables of WMLs (by Fazekas score) eGFR were significantly associated with unfavorable functional outcome. (Table 15)

Table 15: Results from main effect regression model on the association between eGFR, WMLs and unfavorable functional outcome (mRS score ≥ 2) (n = 160, R^2 = 0.166)

		95% CI		
	OR	Lower	Upper	P value
eGFR≥90				Reference
60≤eGFR< 90	1.06	0.49	2.30	0.881
30<eGFR<60	8.93	2.15	37.05	0.003
Fazekas 0-1				Reference
Fazekas2-3	2.28	1.1	4.74	0.027

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; Fazekas, WMLs measured by Fazekas score.
*Hierarchical binary logistic regression analysis.

The moderated multiple regression model (n = 160, R^2 = 0.182) revealed that the interaction term of Fazekas (2-3)*eGFR (60, 90) mL/min/1.73m^2 was not significant (p = 0.174) and Fazekas (2-3)* eGFR (30, 60) mL/min/1.73m^2 was also not significant (p = 0.355). Thus, there was no significant interaction effect between WMLs and renal dysfunction on stroke functional outcome. Therefore, in the association analysis between eGFR, WMLs and functional outcome after stroke, the interaction term can be removed when there was no moderation effect[180].

3.3.4 Factors associated with Functional Outcome

First, to identify whether WMLs and lower eGFR were predictors of unfavorable functional outcome, a forward stepwise binary logistic regression analysis including age (10-year intervals), gender, NIHSS at admission quartiles (NIHSS 0-1 [reference], NIHSS 2, NIHSS 3-4, NIHSS 5), eGFR (three groups: normal eGFR ≥ 90 (mL/min/1.73m^2) [reference]; mild declined eGFR [60,90) (mL/min/1.73m^2); moderate declined eGFR (30,60) (mL/min/1.73m^2) and WMLs (no to mild WMLs, Fazekas score 0-1 vs. moderate to severe WMLs, Fazekas score 2-3) was performed.

This regression model revealed that patients with an eGFR of 30 to 60 mL/min/1.73m^2 were significantly more likely to exhibit functional disability after acute ischemic stroke than those patients with an eGFR above 90 mL/min/1.73m^2 (OR 7.859, 95% CI 1.774-34.825, p = 0,007). Moderate-to-severe WMLs (Fazekas 0-1 [reference], Fazekas 2-3: OR 2.216, 95% CI 1.031-4.765, p = 0.042) and NIHSS scores (NIHSS score 0-1 [reference], NIHSS score 3-4: OR 3.115, 95% CI 1.128-8.599, p = 0.028; NIHSS score ≥ 5, OR 6.772, 95% CI 2.063-22.229, p = 0.002) were both independently associated with unfavorable functional outcome after ischemic stroke. Patients whose eGFR ranged from 60 to 90 mL/min/1.73m^2 did not have an increased risk of functional disability following ischemic stroke when compared with patients whose eGFR was above 90 mL/min/1.73m^2. This model explained R^2 = 25% of the complete variation. (Table 16)

Table 16: Results from forward stepwise binary logistic regression analysis assessing the prediction of unfavorable functional outcome (mRS score ≥ 2) based on age, gender, NIHSS at admission, eGFR and WMLs (n = 160, R^2 = 0.25)

		95% CI		
	OR	Lower	Upper	P value
eGFR≥90				Reference
60≤eGFR< 90	1.32	0.58	3.01	0.505
30<eGFR<60	7.86	1.77	34.83	0.007
Fazekas 0-1				Reference
Fazekas 2-3	2.22	1.03	4.77	0.042
NIHSS 0-1				Reference
NIHSS 2	2.26	0.79	6.47	0.127
NIHSS 3-4	3.12	1.13	8.60	0.028
NIHSS ≥5	6.77	2.06	22.23	0.002

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; Fazekas, WMLs measured by Fazekas score; NIHSS, National Institutes of Health Stroke Scale. *Forward stepwise binary logistic regression analysis. Note: Age and gender were not significant in the analysis.

In the second regression model, three additional confounders, hypertension, HbA1c and CRP, were included. These additional confounders were included, because hypertension was associated with WMLs and functional outcome, HbA1c was associated with WMLs, eGFR and functional outcome, and CRP was associated with eGFR < 60 mL/min/1.73m^2 and functional outcome.

Two forward stepwise binary logistic regression analyses including age (10-year intervals), NIHSS quartiles (NIHSS 0-1 [reference], NIHSS 2, NIHSS 3-4, NIHSS 5), eGFR (normal, eGFR ≥ 90 (mL/min/1.73m^2) [reference]; mild declined, eGFR [60, 90) (mL/min/1.73m^2); moderate declined, eGFR (30,60) (mL/min/1.73m^2), WMLs (Fazekas score 0-1 [reference], Fazekas score 2-3), or (Wahlund score 0-4 [reference], Wahlund score 5-10, Wahlund score≥11), Hypertension (no[reference], yes), HbA1c quartiles (< 5.2 [reference], 5.2-5.6, 5.7-6.1, > 6.1%) and CRP quartiles (< 0.1 [reference], 0.1-0.25, 0.26-0.65, > 0.65 mg/dL) were performed. 156 patients were in the analysis. There was one patient without record of HbA1c level and three patients without records of CRP levels.

In the regression model for Fazekas scores, eGFR 30 to 60 mL/min/1.73m^2, WMLs Fazekas score 2-3 and Hypertension were significant predictors of disability after ischemic stroke. This model explained R^2 = 21.9% of the complete variation. (Table 17)

Table 17: Results from forward stepwise binary logistic regression analysis assessing the prediction of unfavorable functional outcome (mRS score ≥ 2) based on age, gender, NIHSS at admission, eGFR, WMLs (Fazekas score), Hypertension, HbA1c and CRP (n = 156, R^2 = 0.219)

		95% CI		
	OR	Lower	Upper	P value
eGFR≥90				Reference
60≤eGFR< 90	0.923	0.41	2.06	0.846
30<eGFR<60	7.64	1.81	32.59	0.006
Fazekas 0-1				Reference
Fazekas 2-3	2.20	1.03	4.69	0.041
Hypertension	2.68	1.14	6.28	0.023

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; Fazekas, white matter lesions´ Fazekas score.
*Forward stepwise binary logistic regression analysis.
Note: Age, gender, NIHSS at admission, HbA1c and CRP were not significant.

In the regression model for Wahlund scores, eGFR 30 to 60 (mL/min/1.73m^2), WMLs Wahlund score ≥ 11 and Hypertension were significant predictors for unfavorable functional outcome after ischemic stroke. This model explained R^2 = 23.7% of the complete variation. (Table 18)

Table 18: Results from forward stepwise binary logistic regression analysis assessing the prediction of unfavorable functional outcome (mRS score ≥ 2) based on age, gender, NIHSS at admission, eGFR, WMLs (Wahlund score), hypertension, HbA1c and CRP (n = 156, R^2 = 0.237)

		95% CI		
	OR	Lower	Upper	P value
eGFR≥90				Reference
60≤eGFR< 90	0.91	0.41	2.03	0.811
30<eGFR<60	8.07	1.91	34.08	0.004
Wahlund Score 0-4				Reference
Wahlund Score 5-10	1.70	0.71	4.05	0.232
Wahund Score ≥11	4.71	1.34	16.59	0.016
Hypertension	2.91	1.23	6.78	0.015

OR, odds ratio; CI, confidence interval
eGFR, estimated glomerular filtration rate ; Wahlund Score, white matter lesions´ Wahlund score
*Forward stepwise binary logistic regression analysis.
Note: age, gender, NIHSS at admission, HbA1c and CRP were not significant

3.4 Stroke Recurrence within 1 year

3.4.1 Baseline Characteristics of Participants according to Stroke Recurrence within 1 year

There were 14 patients (8 male, median age, 57 years; IQR, 44-73 years, NIHSS score at admission, 3; IQR, 1.75-3.5) with stroke recurrence within 1 year. Baseline demographic and clinical data for the two groups were compared in Table 19. Mann-Whitney-U Test, Chi-square test and Fisher's Exact Test, if expected cell frequencies were smaller than five, were performed (Level of significance at 0.05).

Table 19: Baseline characteristics of participants according to stroke recurrence within 1 year

variable	Recurrence (no)	Recurrence (yes)	Total	P value
N. Of Participant	146	14	160	
Age mean, years*	66.5 (54.2-72.7)	56.5 (43.8-72.5)	65.5 (52.3-72.5)	0.126
Males, n (%)	93 (63.7)	8 (57.1)	101 (63.1)	0.627
Infarct Volume (cm3)*	1.12 (0.38-4.49)	1.64 (0.53-4.56)	1.13 (0.39-4.34)	0.92
Creatinine, (µmol/L)*	0.92 (0.77-1.04)	0.81 (0.74-98)	0.91 (0.77-1.04)	0.395
eGFR, (mL/min/1.73m2)*	81 (70-95.7)	90.2 (66.2-110.8)	82 (69.5-96.3)	0.535
HbA1c, (%)*	5.6 (5.2-6.1)	5.7 (5.1-6.9)	5.6 (5.2-6.1)	0.534
CRP (mg/dL)*	0.24 (0.1-0.61)	0.32 (0.15-0.71)	0.25 (0.1-0.63)	0.344
TSH (mU/L)*	1.76 (1.02-2.32)	1.39 (0.97-2.26)	1.74 (1.02-2.31)	0.62
Hb (g/dL)*	14.4 (13.6-15.4)	14.5 (14.3-15)	14.4 (13.6-15.4)	0.616
TG 8 am (mg/dL)*	113.5 (84-144)	129 (88-163.5)	114 (85-145)	0.521
TG 11 am (mg/dL)*	192 (143-257)	210(139-284.5)	192 (142-257)	0.458
TG 12 am (mg/dL)*	230 (150-312.5)	227 (152.2-291.2)	230 (150-310)	0.906
TG 1 pm (mg/dL)*	216 (156-308)	190 (126-307)	216 (152-306)	0.609
Glc 8 am (mg/dL)*	95 (88-110)	96 (83.5-108)	95 (87-110)	0.592
Glc 11 am (mg/dL)*	93 (86-107)	95 (86.5-113.5)	93 (86-106.75)	0.535
Glc 12 am (mg/dL)*	150 (107.5-182.5)	158.5 (123-182)	150 (108-182)	0.518
Glc 1 pm (mg/dL)*	133 (105-177)	140 (113.5-167)	134.5 (105-173)	0.647
Insulin 8 am (mU/L)*	8 (5-13)	7.5 (4.25-14.25)	8 (5-13)	0.839
Insulin 11 am (mU/L)*	12 (7-17)	14 (6-23.5)	12 (7-18)	0.558
Insulin 12 am (mU/L)*	38 (18-56)	36 (15.5-67.75)	37 (18-56)	0.964
Insulin 1 pm (mU/L)*	37 (18-72)	47 (14.5-85)	37.5 (18-72)	0.775
Cholesterol (mg/dL)*	183 (157.5-210)	193 (161.5-228)	183.5 (157-210)	0.311
LDL (mg/dL)*	109 (87-134)	142 (101.5-167)	110 (88-137)	0.021
HDL (mg/dL)*	48 (41.5-58)	43 (37-60)	47 (41-58)	0.248
LDL/HDL ratio*	2.29 (1.71-2.92)	3.19 (2.23-3.87)	2.34(1.73-3.05)	0.022

Table to be continued

variable	Recurrence (no)	Recurrence (yes)	Total	P value
AST (U/L)*	26 (21-32)	26 (22-47.5)	26 (21-34)	0.444
ALT (U/L)*	25 (18-38.5)	29 (20-51.5)	25 (18-38)	0.192
Height (m)*	1.76 (1.68-1.8)	1.74 (1.67-1.78)	1.76 (1.68-1.8)	0.555
Weight (kg)*	80 (72.25-90)	80 (71.5-94.25)	80 (72-90)	0.648
BMI (kg/m2)*	26.5 (24.1-29.3)	27.9 (25.5-29.6)	26.7 (24.4-29.4)	0.426
Waist circumference (cm)*	100.5 (92.75-108)	104 (93.25-108.25)	101 (93-108)	0.673
Hip circumference (cm)*	103 (98-109.25)	106 (100-111)	104 (98-110)	0.41
Waist-to-hip ratio*	0.96 (0.91-1)	0.97 (0.91-1)	0.97 (0.91-1)	0.877
Heart Rate*	72 (64.5-80)	72 (64.75-82.25)	72 (65-80)	0.738
Systolic BP (mmHg)*	135 (120-150)	141.5 (120-153)	136 (120-150.5)	0.774
Diastolic BP (mmHg)*	80 (70-85)	80 (70-91)	80 (70-85.5)	0.699
Hypertension, n (%)‡	95 (66)	8 (57.1)	103 (65.2)	0.508
Diabetes, n (%)‡	30 (20.5)	4 (28.6)	34 (21.3)	0.499
Hyperlipidemia, n (%)‡	47 (32.2)	5 (35.7)	52 (32.5)	0.772
NIHSS at admission*	2 (1-4)	3 (1.75-3.5)	2 (1-4)	0.458
Thrombolyse‡	18 (12.4)	1 (7.1)	19 (11.9)	1
mRS follow-up*	1 (0-2)	2 (1-3)	1 (0-2)	0.032
mRS favorable, n (%)‡	100 (68.5)	6 (42.9)	106 (66.3)	0.074
Lacunar Infarct, n (%)‡	22 (15.2)	4 (28.6)	26 (16.4)	0.249
Microbleeds, n (%)‡	10 (6.8)	1 (7.1)	11 (6.9)	1
patient death, n (%)‡	5 (3.4)	0 (0)	5 (3.1)	1
WMLs. Yes, n (%)‡	96 (65.8)	9 (64.3)	105 (65.6)	1
WMLs Severe, n (%)§	54 (37)	5 (35.7)	59 (36.9)	0.92
WMLs Fazekas scores*	1 (0-2)	1 (0-2)	1 (0-2)	0.569
WMLs Wahlund scores*	3 (1-6)	3 (0-6)	3 (1-6)	0.761
Stroke subtype, n (%)§				0.64
LAA	61 (42.1)	5 (35.7)	66 (41.5)	
CE	35 (24.1)	2 (14.3)	37 (23.3)	
SAO	22 (15.2)	4 (28.6)	26 (16.4)	
OC	14 (9.7)	1 (7.1)	15 (9.4)	
UND	13 (9)	2 (14.3)	15 (9.4)	

eGFR, estimated glomerular filtration rate; HbA1c, glycosylated hemoglobin; CRP, C-reactive protein; TSH, Thyroid-stimulating hormone; Hb, hemoglobin; TG, Triglyceride; Glc, Glucose; LDL, Low-density lipoprotein; HDL, High-density lipoprotein; AST, Aspartate transaminase; ALT, Alanine transaminase; BMI, body mass index; BP, Blood pressure; NIHSS, national institute of health stroke scale; mRS, modified Rankin Scale; mRS favorable means mRS score 0-1; mRS poor means mRS score >1; Second Stroke, Cerebral infarction; Second Event, Myocardial infarction or Cerebral infarction or TIA.WMLs, white matter lesions; WMLs. Yes means WMLs with Fazekas score 1-3; WMLs Severe means WMLs with Fazekas score 2-3; LAA, large-artery atherosclerosis; CE, cardioembolism; SAO, small-vessel occlusion; OC, stroke of other determined etiology; and UND, stroke of undetermined etiology.
Values are median (interquartile range) unless otherwise specified.
*Mann-Whitney U test; §Chi-square test; ‡Fisher's Exact Test

In bivariate correlation analysis, patients with stroke recurrence had a higher LDL level (Spearman´s rho = 0.187, p = 0.02) and a higher LDL/HDL ratio (Spearman´s rho = − 0.189).

There was no significant association between stroke recurrence and eGFR (Spearman´s rho = 0.049, p = 0.537) or WMLs (Wahlund score, Spearman´s rho = − 0.022, p = 0.781).

3.4.2 Risk Factors for Stroke Recurrence

To identify if LDL level, LDL/HDL ratios were predictors of stroke recurrence, a forward stepwise binary logistic regression analysis including age (10-year intervals), gender, LDL, LDL/HDL ratio was performed. 155 patients were in the analysis because 5 patients had not the parameter of LDL level and LDL/HDL ratio.

This regression model revealed that higher LDL/HDL ratio (OR 2.031, 95% CI 1.127-3.661, p = 0.018) was a significant predictor of stroke recurrence. This model explained R^2 = 8.3% of the complete variation. (Table 20)

Table 20: Summary of results from Binary logistic regression analysis assessing the prediction of second stroke based on age, gender, LDL, and LDL/HDL ratio (n = 155, R^2 = 0.083)

		95% CI		
	OR	Lower	Upper	p value
LDL/HDL ratio	2.031	1.127	3.661	0.018

OR, odds ratio; CI, confidence interval
LDL, Low-density lipoprotein; HDL, High-density lipoprotein
*Forward stepwise binary logistic regression analysis
Note: age, gender and LDL cholesterol levels were not significant.

3.4.3 Risk Factors for Secondary Event

Secondary event referred to any of the following event: secondary cerebral infarction, myocardial infarction, coronary revascularization, cardiovascular death, or TIA within 12 months after primary stroke onset within 1 year. In analysis, there was no difference of WMLs Fazekas score (p = 0.430) and eGFR level (p = 0.602) between patients with and without incidence of secondary event. A forward stepwise binary logistic regression model revealed that higher LDL/HDL ratio (OR 1.754, 95% CI 1.122-2.741, p = 0.014) was significant associated with secondary event. Age, gender and LDL cholesterol level were not significant. This model explained R^2 = 6.7% of the complete variation (n = 155).

4. Discussion

This C&S sub-study sought to determine a link between kidney damage, cerebral small vessel disease and functional outcome in ischemic stroke patients. As renal dysfunction may reflect kidney damage and WMLs may present cerebral small vessel disease[181], the associations between eGFR, degree of WMLs, stroke functional outcome and stroke recurrence were investigated. The three main findings of this study were the following:

(1) Renal dysfunction eGFR 60-90 mL/min/1.73m^2 (OR 2.97, 95% CI 1.38-6.38, p = 0.005) and eGFR 30-60 mL/min/1.73m^2 (OR 5.75, 95% CI 1.71-19.33, p = 0.005) was significantly associated with WMLs (Fazekas ≥ 1) in bivariate analysis (Table 10). However, in multivariate analysis, renal dysfunction lost its association, and age (OR 2.95, 95% CI 2.02-4.34, p = 0.0005) and diastolic blood pressure (OR 1.57, 95% CI 1.09-2.27, p = 0.015) displayed a stronger association with WMLs (Table 11).

(2) Both moderate renal dysfunction eGFR 30-60 mL/min/1.73m^2 (OR 9.81, 95% CI 2.63-36.54, p = 0.0005, Phi (ϕ) 0.32) and moderate-to-severe WMLs (Fazekas ≥ 2) (OR 2.61, 95% CI 1.32-5.13, p = 0.005, Phi (ϕ) 0.22) were independently associated with 1-year unfavorable functional outcome after stroke (Table 14). Based on the higher value of Phi (ϕ) and the OR, renal dysfunction was stronger associated with unfavorable functional outcome than WMLs.
After adjusted age, gender and initial NIHSS score on admission, patients with moderate renal dysfunction eGFR 30-60 mL/min/1.73m^2 (OR 7.86, 95% CI 1.77-34.83, p = 0.007) were approximately 8 times more likely to have an unfavorable functional outcome than patients with an eGFR > 90 mL/min/1.73m^2; patients with moderate-to-severe WMLs (Fazekas ≥ 2) (OR 2.22, 95% CI 1.03-4.77, p = 0.042) were 2 times more likely to have unfavorable functional outcome compared to patients with no-to-mild WMLs (Fazekas ≤ 1) (Table 16).

(3) Neither eGFR nor WMLs were associated with stroke recurrence and secondary event within 1 year. Higher LDL/HDL ratio (OR 2.031, 95% CI 1.127-3.661, p = 0.018) was a significant predictor of stroke recurrence (Table 20). Higher LDL/HDL ratio (OR 1.754, 95% CI 1.122-2.741, p = 0.014) was significant associated with secondary event including secondary cerebral infarction,

myocardial infarction, coronary revascularization, cardiovascular death, or TIA within 12 months after primary stroke onset within 1 year as well.

The present study demonstrated that even mildly decreased renal function (eGFR < 90 mL/min/1.73m^2) was significantly associated with the presence of WMLs in stroke patients, regardless of age and gender. Renal dysfunction (eGFR 30-60 mL/min/1.73m^2) and WMLs were independently associate with stroke unfavorable functional outcome at 1 year. Neither renal dysfunction nor WMLs were associated with stroke recurrence within 1 year.

4.1 Association between eGFR and WMLs

To date, the most plausible theory on the cerebro-renal interaction is based on a common small vessel disease (SVD)[182]. SVD is a systematic disorder which mainly affects small arteries, arterioles, as well as capillaries and small veins in various organs in the body with the pathological features of arteriolosclerosis and cerebral amyloid angiopathy[90]. Strain vessels, i.e. juxtamedullary afferent arterioles in the kidney, are similar to perforating arterioles in the central nervous system; they both are small vessels exposed to high pressure with large flow and low vascular resistance[149]. Due to aging, hypertension and other vascular risk factors, increased large arterial stiffness leads to high pressure fluctuation with highly pulsatile pressure and flow in the microvasculature and subsequently small vessel damage[2]. In the kidney, this leads to glomerular sclerosis, endothelial dysfunction and increased capillary permeability. Diagnosis of renal damage is based on decreased renal function or albuminuria or proteinuria. In the brain, organ damage can be subdivided in lacunar infarcts, WMLs and microbleeds[148] due to different etiology and pathophysiology[112]. WMLs are the most prevalent sign in patients with cerebral SVD[181] and also are associated with lacunar infarcts[183,184] and microbleeds[185]. In a first step, this study investigated whether there was an association between renal dysfunction and WMLs.

It showed that patients with higher grade WMLs have lower renal function (P = 0.001) (Figure 5). The distribution of eGFR across the degree of WMLs was in line with a previous cross-sectional community-based study[151] and a hospital-based study on post ischemic stroke patients[154]. Patients with lower grade eGFR had higher prevalence of WMLs (Table 8) and higher WMLs score (Figure 7). This finding was in accordance with previous cross-sectional community-based studies[153,186], hospital-based studies on ischemic stroke patients[47,154], and a hospital-based study on CKD patients[146].

Impaired kidney function (eGFR < 90 mL/min/1.73m^2) was associated with the presence of WMLs (OR 2.30, 95% CI 1.17-4.52, p = 0.014) and with the degree of moderate-to-severe WMLs (OR 3.28, 95% CI 1.56-6.90, p = 0.001) in the Chi-square test. The data indicated that even mild renal dysfunction was associated with the presence of WMLs and the degree of WMLs.

Furthermore, impaired kidney function displayed a 'dose-effect' regarding the severity of moderate-to-severe WMLs in simple logistic regression analysis (Table 10); patients with eGFR 30 to 60 mL/min/1.73m^2 had a higher likelihood (OR 5.75, 95% CI 1.71-19.33, p = 0.005) to have moderate-to-severe WMLs than patients with an eGFR 60 to 90 mL/min/1.73m^2 (OR 2.97, 95% CI 1.38-6.38, p = 0.005).

The present results supported the finding by Steinicke et al. on kidney function and WMLs in young stroke patients (18-55 years). They observed that lower eGFR values (eGFR mL/min, in tenths, OR 0.93, 95% CI 0.88-0.98, p = 0.01) were associated with the presence of moderate-to-severe WMLs in stroke patients.[154]

However, in multiple logistic regression analysis, eGFR lost its association with WMLs after adjustment for age, gender, diastolic BP, systolic BP and HbA1c. Age and diastolic BP remained significantly associated with the presence of WMLs. The results indicated that age and diastolic BP at baseline were stronger risk factors for the presence of WMLs than renal dysfunction. The result was similar to the finding by Yao et al. that decreased eGFR (< 60 mL/min/1.73m^2) was not a significant risk factor for WMLs after adjustment for other stronger risk factors including age (OR 2.781/ 10 years, 95% CI 2.252-3.435), hypertension (OR 1.746, 95% CI 1.231-2.477) and diabetes mellitus (OR 1.854, 95% CI 1.070-3.213).[153]

To date, most previous cross-sectional studies suggested that renal dysfunction at the level of eGFR < 60 mL/min/1.73m^2 [47,150], or eGFR < 45 mL/min/1.73m^2 [152,187] was a risk factor for WMLs after adjustment for confounders, such as demographic characters and vascular risk factors. In 615 stroke-free community-based participants, the Northern Manhattan Study found that eGFR 15-60 mL/min was associated with increased white matter hyperintensity volume (β 0.322; 95% CI, 0.080 to 0.564)[150]. Similarly, a study by Takahashi et al., including 2106 subjects, found that eGFR (< 60 mL/min/1.73m^2) was associated with deep white matter hyperintensities (DWMH) (OR 2.26, 95% CI 1.53-3.34, p < 0.001) and periventricular hyperintensities (PVH) (OR 2.81 95% CI 1.67-4.72, p < 0.001)[151]. Likewise, a study by Wada et al. found that CKD, defined by urinary albumin-creatinine ratio of > 30 mg/g or an eGFR < 60 mL/min/1.73m^2, was associated with moderate-to-severe WMLs (OR 1.5) in 625 community-based Japanese elderly[151]. Similarly, a study by Ikram

et al. showed that persons with lower eGFR (< 45 mL/min/1.73m^2) had more WMLs (difference per SD decrease in GFR: 0.14, 95% CI 0.03-0.25) in a cohort of 484 individuals by cross-sectional analysis[151]. In acute stroke patients, eGFR (< 60 mL/min/1.73m^2) was associated with severe WMLs (relative risk 2.77, 95% CI 1.10-6.98, p 0.03) adjusted for age and gender[47]. Likewise in CKD patients, PVH was significantly associated with CKD stage[146].

Furthermore, a 5-year longitudinal study confirmed that renal dysfunction (eGFR < 45 mL/min/1.73m^2) was associated with deep white matter lesions (DWL) (OR 1.13, 95% CI 1.04-2.89, p = 0.04) and the progression of DWL (OR 1.43 95% CI 1.19-3.07, p = 0.04) after adjustment for vascular risk factors in 273 stroke-free participants[187].

Contrary to these previous studies, the association between eGFR and WMLs lost its significance in adjusted analyses in our study. This may be due to the following reasons.

Firstly, in our cohort, the proportion of patients with eGFR < 60 mL/min/1.73m^2 was low, approximately 10%, whereas in other previous studies, the proportions were 36.3%[151] and 40.2%[47]. Patients were not included in the C&S study when there was overt renal insufficiency (cp. Inclusion and exclusion criteria[173]). Furthermore, compared with other studies, patients in our study were relatively young and included fewer women (age 62.5 ± 15.1 years old, female 36.9%). Mean age of participants was 68.3 ± 4.2 years and there were 55.2% females in the study by Wada et al.[151]. In the study by Oksala et al., the participants had a mean age of 70.7 ± 7.6 years there were 52.1% females[47]. These differences matter, since eGFR is associated with age and gender[132]. Therefore, studies with older and more female patients tend to have higher proportions of patients with renal dysfunction (eGFR < 60 mL/min/1.73m^2).

Secondly, the sample size becomes even more important when the percentage of patients with renal dysfunction (eGFR < 60 mL/min/1.73m^2) is low. In the study by Takahashi et al.[186], the percentage of patients with renal dysfunction (eGFR < 60 mL/min/1.73m^2) was similar to our study (11.6%[186] vs. 9.38%). However the sample size was larger (2106[186] vs. 160). In the study by Khatri et al.[150], the percentage of patients with renal dysfunction (eGFR < 60 mL/min/1.73m^2) was 9.2% with a sample size of 615 patients. In the study by Steinicke et al.[154], the percentage of patients with renal dysfunction (eGFR < 60 mL/min/1.73m^2) was 4.4% and the sample size was 2500. Increasing the sample size is a method to increase the statistical power of a study and this C&S substudy may have simply lacked power in order to show a significant association after adjustment[188,189].

Thirdly, the grade of renal dysfunction was also an important factor when examining the relationship between renal impairment and WMLs. Some studies reported eGFR level below 45 mL/min/1.73m^2 associated with WMLs adjusted for age and gender[152,187]. This may suggest a stronger effect of an eGFR < 45 mL/min/1.73m^2 on the presence of WMLs compared to milder impairments of kidney function. Results from this C&S sub-study (Table 10) also support the notion that severer reductions of eGFR were associated with a higher likelihood of moderate-to-severe WMLs. However, patients with severe renal impairment were underrepresented in our study (only 15 patients with eGFR between 30 to 60 mL/min/1.73m^2)

In summary, compared to other established risk factors (age and hypertension) for WMLs, renal impairment may be of less importance based on our study findings and larger samples are required to detect an independent association.

4.2 Other risk factors for WMLs

In the present study, age and hypertension were stronger risk factors for WMLs. This finding was in agreement with previous studies[184,190,191]. Basile et al. found that age > 75 years (OR 1.95 95% CI 1.32-2.90) and arterial hypertension (OR 1.97 95% CI 1.27-3.07) were associated with severe WMLs in a cohort of 639 nondisabled subjects with different grade of WMLs on MRI[184].

Age, as an independent risk factor for WMLs, was confirmed in our study by multivariable analysis. In this C&S sub-study, the median age in patients was lowest in patients without WMLs and highest in patients with moderate to severe white matter disease (54.4 years in Fazekas 0, 67.8 years in Fazekas 1, 72.8 years in Fazekas 2, and 70.8 years in Fazekas 3, respectively). The distribution of age in patients with different degrees of WMLs can be explained as follows: 1) Prevalence of intracerebral arteriolosclerosis is higher among persons above 50 years old and aggravates over years[192]. 2) The permeability of the blood-brain barrier (BBB) increases per decade in healthy persons above 60 years old[193] and increases further in patients with vascular risk factors.[193] Both intracerebral arteriolosclerosis and BBB permeability are associated with WMLs and are deemed potential mechanisms underlying the presence of WMLs[112].

Hypertension is regarded as a key risk factor for WMLs[92,112]. The presence of WMLs mainly depends on the increase in blood pressure over years[190] and longitudinal cohort studies showed

that anti-hypertension treatment can reduce progression of WMLs[194,195]. However it has not yet been settled whether the effect of systolic or diastolic BP were more important[112]. The result of our study was in line with previous studies showing an association between diastolic BP and not systolic BP with WMLs[190,191]. A 32-year follow-up longitudinal study found that WMLs was related to diastolic BP (per 10 mm Hg increased, OR 1.3, 95% CI 1.0-1.6)[190]. Similarly, another 7-year follow-up longitudinal study with 1290 participants suggested that baseline diastolic BP and the increases in diastolic BP were independently associated with severe WMLs[191]. Others reported that systolic BP was a strong predictor of WMLs progression in 983 individuals[196]. From the finding of our study it cannot be deduced that diastolic BP was a cause of WMLs because of its cross-sectional design. Nonetheless, it seems reasonable that higher diastolic BP is associated with the presence of WMLs On the one hand, diastolic BP may be an indicator of peripheral resistance and increased diastolic BP might be a reflection of small vessel damage[197]. On the other hand, increased diastolic BP may lead to small vessel damage[191], and WMLs are thought to be the consequence of small vessel damage (lipohyalinosis, arteriolosclerosis and impaired BBB)[112].

Diabetes mellitus (DM) as a risk factor for WMLs was not confirmed in our study. This C&S sub-study included 34 patients with DM. The prevalence of DM was distributed similarly between the groups of patients with different grades of WMLs (Table 7). Although the higher grades of WMLs were associated with higher level of HbA1c in bivariate correlation analysis, the level of HbA1c was not an independent risk factor for the presence of WMLs in multivariate analysis (Table 16). The previous reports on the association between DM and WMLs were inconsistent[117,119,198,199]. A case-control and cross-sectional study by van Harten et al. found that type 2 DM was independently associated with deep WMLs in patients with DM and hypertension (n = 45), in patients with DM and without hypertension (n = 45), and in control subjects (n = 44)[119]. Similarly, a 3-year longitudinal study by Gouw et al. showed that diabetes and blood glucose were related to the WMLs progression in a cohort of 396 elderly subjects[199]. Other previous cohort studies showed DM was not related to WMLs, neither in stroke patients[198] nor in 3301 community-dwelling elderly people[117]. The mechanism supporting DM as a risk factor for WMLs has not yet been fully elucidated[92,112]. The potential pathogenesis of DM as a cause of WMLs studied by Umemura et al., found that the level of soluble intercellular adhesion molecule-1 (sICAM-1), a marker of inflammation reaction, was associated with WMLs in patients with type 2 DM[200]. The higher level of blood glucose may induce vascular endothelial cells to produce sICAM-1, which promotes the adhesion of neutrophils and causes cerebral small vessel disease[200]. The notion by Umemura et al. was supported by our findings that the higher level of blood glucose and HbA1c were correlated

with higher grades of WMLs. However, whether DM was an independent risk factor for WMLs requires further prospective studies.

Aside from the conventional vascular risk factors, genetics are of major importance in a variety of conditions associated with WMLs, such as 1) cerebral autosomal dominant arteriopathy with sub-cortical infarcts and leukoencephalopathy (CADASIL), 2) cerebral autosomal recessive arteriopathy with sub-cortical infarcts and leukoencephalopathy (CARASIL), 3) Fabry disease, 4) collagen type IV alpha 1 gene (COL4A1) mutations, 5) hereditary endotheliopathy with retinopathy, nephropathy and stroke (HERNS)[201,202]. However, these were not in the scope of our study and no genetic testing was performed in C&S sub-study.

Several limitations need to be acknowledged. Firstly, the study design for the association between renal dysfunction and WMLs was cross-sectional. In general, cross-sectional studies are not appropriate to investigate a cause-effect relationship. Secondly, the sample size was modest. This may explain that eGRF lost its statistical significance in multivariate analysis. Thirdly, there was no information on proteinuria or albuminuria in patients with decreased renal function. Therefore CKD could not be assessed comprehensively[121]. Finally, the diastolic BP at baseline does not present the day-to-day diastolic BP. Instead these BPs were measured in the hospital in the sub-acute setting of a first ischemic stroke. Approximately 80% of patients have an elevated BP in acute stroke[203]. This may be due to pre-existing hypertension[204], stress[205] as well as the cerebral infarct itself[206]. Despite above mentioned limitations, this C&S sub-study added information on the association between mild renal dysfunction and WMLs in stroke patients to the literature.

In the present study, the higher prevalence of WMLs and higher WMLs scores in patients with lower eGFR as well as the association between decreased renal function and WMLs supported the proposed “Strain vessel injuries hypothesis[149].” Our results suggested that decreased renal function and WMLs may be common signs of hypertensive damage in different organs and decreased eGFR may be an indicator of the state of cerebral small vessels. Early recognition of decreased eGFR and adapted antihypertensive treatment did not only slow down or prevent the progress of CKD[207] but also the progress of WMLs[194].

4.3 eGFR, WMLs and Functional Outcome after stroke at 1 year

The present study found that stroke patients with unfavorable outcome had higher WMLs scores (Figure 11) and lower eGFRs (Figure 12). These findings were in agreement with previous studies[4,69]. A study by Arsava et al. showed that patients with higher median normalized WML volume had higher mRS score at 6 months[4]. The study by Yahalom et al. found that stroke patients with unfavorable functional outcome at 1 year (BI ≤ 75 or death) had relatively lower eGFR[69].

Furthermore, renal dysfunction (eGFR 30-60 mL/min/1.73m^2) and WMLs were significantly associated with unfavorable functional outcome after stroke in two cross-table analysis, respectively. Renal dysfunction displayed higher values of OR and Phi (φ) indicating a stronger association with unfavorable functional outcome than moderate-to-severe WMLs (Table 14).

Prior to comparing our results with previous findings, some methodological issues of this C&S sub-study warrant to be addressed. In C&S, most of patients had mild strokes with a median NIHSS at admission of 2 (IQR 1-4). In order to avoid a ceiling effect encountered in BI, the mRS was used to assess functional outcome rather than BI; the BI is less sensitive for differentiating between patients with mild to moderated disability compared to the mRS[42]. A mRS score ≤ 1 indicates a complete independence and was interpreted as a favorable functional outcome in this sub-study. A mRS score ≥ 2 indicates that there is at least some degree of disability in daily living and this was interpreted as unfavorable functional outcome[208].

Age and initial severity of stroke are well established risk factors for functional outcome after stroke[209]. In the first logistic regression model, renal function, WMLs, age, gender, and NIHSS score at admission were included. The results showed that eGFR, WMLs and NIHSS score significantly predicted the unfavorable functional outcome. Of note, the OR of renal dysfunction for unfavorable outcome was higher compared to the ORs of WMLs and NIHSS score (Table 16).

In bivariate analyses we found that hypertension was associated with WMLs and mRS score, that HbA1c was associated with WMLs, eGFR and mRS score, and that CRP was associated with eGFR (when eGFR 30-60 mL/min/1.73m^2) and mRS score. In the second logistic regression model, these three factors (hypertension, HbA1c and CRP) were added to the second model as confounders to identify whether the effects of eGFR and WMLs on unfavorable functional

outcome would disappear. Confounder, a concept from statistics, means a variable is associated with the risk factors (eGFR and WMLs) and the outcome of the interest (stroke functional outcome mRS). The prediction of stroke functional outcome will be more accurate, when the risk factors (eGFR and WMLs) are controlled and adjusted for confounders. The second model revealed that eGFR, WMLs and hypertension were independently associated with unfavorable functional outcome (Table 16). The associations did not change when Wahlund scores instead of the Fazekas scale were used to assess WMLs (Table 17).

In regard to WMLs, the result of this C&S sub-study was in line with most previous studies showing that WMLs was related to unfavorable functional outcome after stroke[4,70,162]. In the study by Arsava et al., the volume of WMLs (OR 1.05, 95% CI 1.02-1.08, p 0.002) was independently associated with unfavorable functional outcome after ischemic stroke at 6 month (240 subjects, median age 67, IQR 55-77, female 44%)[4]. The study by Ntaios et al. also found that leukoaraiosis (OR 2.21, p 0.016) was independently associated with unfavorable functional outcome (defined mRS score > 2) after ischemic stroke at 3 months and at 1 year (1446 subjects, age 72 ± 21, female 43.7%)[162]. Henninger et al. reported that WMLs (severe WMLs: OR 13.86; 95% CI 1.94-∞, p 0.0056) and baseline NIHSS (OR 5.11, 95% CI 2.07-14.49, p 0.0001) may independently predict unfavorable functional outcome (defined mRS score > 2) at 90 days in patients with intracranial large artery occlusion (88 subjects, age 67 ± 16, male 55%)[70]. Patients included in the study by Henninger et al. had severe ischemic strokes (median NIHSS at baseline 15, IQR 9-21)[70]. While this study indicated that WMLs were associated with functional outcome in severe ischemic strokes, the present as well as a previous C&S sub-study showed that this association also existed after mild ischemic stroke[3].

However, our finding on WMLs was in contrast to the Copenhagen stroke study reporting no significant association between WMLs and functional outcome (p = 0.47) at discharge adjusted for age (mean age 70 years), gender and initial stroke severity[161]. The discrepancies between our study and Copenhagen stroke study may be due to different points in time to assess functional outcome (after one year vs. at discharge) as well as different neuroimaging methodology adopted for research (MRI vs. CT). CT is far less sensitive for identification of WMLs than MRI[179]. This may easily explain, a higher prevalence of patients with WMLs (65.6%) in our study compared to the 15% observed in the Copenhagen stroke study.

The baseline grade of WMLs was an important factor for unfavorable functional outcome after one year. Our study demonstrated that rather confluent WMLs (Fazekas 2-3) but not punctate foci of WMLs (Fazekas 1) associated with unfavorable functional outcome. This finding confirmed the notion that extensive WMLs, a surrogate marker for cerebral SVD, had adverse effects on clinical outcomes[181,210]. The different features of confluent WMLs and punctate foci of WMLs on clinical assessment may be due to different etiology[114] or simply be a matter of progression over time[110,111]. However, up to now, the final verdict on this issue is still out[112].

The mechanisms underlying the adverse effect of WMLs on stroke functional outcome are not well understood. Potentially, low vascular density[211] and hypoperfusion in the area of WMLs[212] affect the collateral circulation in the brain. Likewise, brain tissue with WMLs may have weak reserve capacity for injury of ischemia and this may have led to the association between infarct growth and volume of WMLs[95]. Increased BBB permeability in basal ganglia in patients with WMLs was also related to poor functional outcome after stoke[213]. Furthermore, patients with severe WMLs had higher risk for intracranial hemorrhage (ICH) after thrombolysis[97]. In general, however, this is unlikely to explain the observed association between WMLs and poor outcome after ischemic stroke since only a minority of stroke patients receive thrombolysis[214]. In this C&S sub-study, one of 19 patients receiving thrombolysis had a hemorrhagic transformation. This was asymptomatic and the patient had a favorable functional outcome (mRS score 1) at 1 year. Another potential reason for the association between WMLs and unfavorable functional outcome could be that the pre-existing network distribution in the brain is relevant to recovery after stroke. Namely, an impaired integrity of cerebral hemispheric connection and cerebellar-cerebral connection may limit the process of neuroplasticity and affect the recovery of motor deficit in stroke patients, subsequently associated with unfavorable functional outcome[215,216]. Finally, aside from the adverse effect of WMLs on stroke recovery, WMLs were independently associated with worse motor performances, falls and balance disturbances which might be due to the interruption of frontal-subcortical motor circuits[210]. Therefore, patients with WMLs had relatively higher mRS score than those without WMLs.

In regard to renal dysfunction, the previous studies on the association between renal dysfunction and functional outcome after stroke were inconsistent[5,6,67-69]. The findings of this C&S sub-study were in partial agreement with the report by Yahalom et al. who showed that decreased eGFR (eGFR < 45 mL/min/1.73m^2 by Mayo Clinic equation) was associated with functional outcome (BI ≤ 75) in stroke patients after 1 year (OR 3.9, 95% CI 1.5-11.0)[69]. However, in the study by

Yahalom et al., eGFR lost its association with functional outcome after stroke when it was calculated by the MDRD equation[69]. Similarly, our results were in line with the finding by Naganuma et al. that eGFR < 60 mL/min/1.73m^2 (OR 1.55, 95% CI 1.01-2.38) was associated with poor stroke functional outcome (mRS score 4-6) after intravenous rt-PA at 3 months[6], although the prevalence of eGFR < 60 mL/min/1.73m^2 in the study by Naganuma et al.[6] were higher than in this C&S sub-study (28.2%[6] vs. 9.38%), possibly due to the older age of the participants (mean age 71.4 ± 11.7 years[6] vs. 62.5 ± 15.1 years).

Our results were in contrast to other previous reports that did not find an association between decreased renal function (eGFR < 60 mL/min/1.73m^2) and unfavorable functional outcome (mRS score ≥ 2) at discharge after ischemic stroke[5,67,68]. All of these previous studies supported that proteinuria was independently associated with unfavorable functional outcome[5,67,68]. A possible explanation for this discrepancy between these studies and the C&S sub-study may be the assessment of mRS at different points in time (at discharge[5,68] vs. at 1 year), as mentioned above, and may be due to different cohort characteristics (ischemic stroke patients with diabetes[67] vs. ischemic stroke patients). The time course of recovery from stroke symptoms has to be considered for the selection of study endpoint[217]. The time point at discharge was not appropriate to measure the functional outcome of patients because the period in hospital was different among stroke patients as well as insufficient for the functional recovery which usually takes longer than the hospital stay[208]. Therefore, studies assessing functional outcome at discharge may fail to find an association between renal dysfunction and functional outcome. Stroke patients with diabetes usually had poorer functional outcome than patients without diabetes, especially in terms of motor function[218]. Compared to renal dysfunction, proteinuria was more prevalent in patients with diabetes and proteinuria (or albuminuria) may be an early and sensitive marker for kidney damage in CKD and may reflect widespread vascular endothelial damage[219].

Similar to the influence of WMLs on functional outcome, the mechanisms underlying the effects of renal dysfunction on functional outcome in stroke patients have not yet been fully elucidated. Decreased renal function (eGFR < 60 mL/min/1.73m^2) may reflect systemic vascular damage, endothelial dysfunction, hypoperfusion and may also be associated with systemic inflammation and thrombotic factors[220]. CKD was also associated with hemorrhagic transformation in ischemic stroke[160]. Out of the mentioned 19 patients in the C&S sub-study receiving thrombolysis, only 1 patient with CKD and mild WMLs had favorable functional outcome. Thus, again, hemorrhagic transformation did not explain the association observed in this C&S sub-study.

In regard to the interplay of renal dysfunction and WMLs to functional outcome after stroke, the present study showed that different grades of WMLs did not moderate the effect of renal dysfunction on functional outcome after stroke, or, vice versa, different degrees of renal dysfunction did not moderate the effect of WMLs on functional outcome. Therefore, decreased renal function (eGFR 30-60 mL/min/1.73m^2) and WMLs (Fazekas score ≥ 2) might be independent factors for prediction of functional outcome in clinical practice. However, Oksala et al. found that eGFR and WMLs were not independent from each other[47]. The discrepancy between our finding and the report by Oksala et al. might be due to different end-point (functional outcome vs. survival after stroke[47]), or due to different sample size (160 subjects vs. 378 subjects[47]). However, whether there is interaction effect between renal dysfunction and WMLs on functional outcome needs to be confirmed by larger longitudinal studies.

Stroke severity is an important factor for prognosis in stroke patients[208]. Our data was in line with the previous findings that baseline NIHSS at admission was a strong predictor of post stroke functional outcome[57,221,222]. We found that there was a graded and independent association between NIHSS score at admission and unfavorable functional outcome post stroke (Table 16). However, in our study, the cutoff score of NIHSS for the unfavorable outcome (NIHSS ≥ 3) was lower than in previous reports that found NIHSS scores < 6 were usually associated with favorable functional outcome in stroke patients[57,221]. The shifting of the NIHSS score to a lower level might be due to the fact that most of the C&S patients had mild ischemic strokes (NIHSS 2, IQR 1-4).

Generally, DWI lesion volume is perceived as a predictor of functional outcome after stroke[73,223]. However, others have noted that its predictive value does not exceed that of simple clinical variables such as age and stroke severity[224]. In the present study, we did not observe an association between DWI lesion volume and functional outcome. Whereas, Arsava et al.[4] and Liou et al.[65] showed that DWI lesion volume was independently associated with stroke functional outcome. Apparent discrepancies between the results of these studies and the results of the C&S sub-study may be due to the differences of median DWI infarct volume in stroke patients observed. The median DWI infarct volume in this C&S sub-study (1.13 IQR 0.39-4.27 mL) was small compared to the study by Arsava et al (4.6 IQR 1.1-21.5 mL)[4] and by Liou et al (7.2 ± 18.6 cm^3)[65]. In our C&S sub-study, infarct volumes were small in both functional outcome groups. Previous reports showed that the association between infarct volume on DWI and functional outcome was weak in mild acute stroke patients[225]. Similarly, Hand et al. speculated that DWI lesion volume may predict functional outcome only in severe cortical strokes[224]. In addition, patients of this C&S sub-study

had a variety of stroke types including small artery occlusions and infratentorial strokes. According to Engelter et al., DWI lesion volumes showed no correlation with NIHSS score at admission and functional outcome mRS at 3 months[226].

In line with previous studies, history of hypertension was independently associated with unfavorable functional outcome in this C&S sub-study[65,227]. Several other studies found no such association[42,162,228]. However, blood pressure (BP) is often elevated in acute stroke patients, most commonly among patients with premorbid hypertension[229]. Although elevated BP decreases spontaneously during the first week after stroke onset[230], high BP is associated with adverse clinical outcomes[203]. A U-shaped relation with unfavorable functional outcome has been proposed[231,232], which might be due to cerebral edema, early stroke recurrence, or hemorrhagic transformation[231].

In our study, diabetes mellitus was not identified as a predictor of unfavorable functional outcome after stroke, which was in line with previous reports[65,227,233]. However, this finding was in contrast to the reports showing an association between diabetes mellitus and disability after stroke[42,218]. In this C&S sub-study, we found relatively low median plasma glucose level both functional outcome group (favorable: 95 mg/dL, IQR 86-105 mg/dL versus unfavorable: 99 mg/dL IQR 89.5-117.5 mg/dL) in the sub-acute setting. It was reported that serum glucose at admission, between 67 mg/dL and 144 mg/dL, exhibit a J-shaped association with functional outcome with lower[162]. Other findings showed that persistent hyperglycaemia in the acute stage within 24 hours of stroke onset was more frequent among patients with a history of diabetes[229], was related to infarct growth[234], symptomatic ICH transformation after thrombolytic treatment[235] and worse functional outcome after stroke[229]. In this present study, fasting blood glucose was measured in sub-acute stage after stroke, 3-7 days, and eighteen patients had fasting glucose level above 126 mg/dL. Of the eighteen hyperglycaemia patients, 16 had previous DM and 2 did not have DM. Twenty-eight patients had HbA1c level equal or above 6.5%. Both hyperglycaemia and HbA1c level were not associated with unfavorable functional outcome after stroke in multivariable analysis, which might be due to low frequency.

In our study, it was not found that plasma CRP concentration related to functional outcome after stroke in multivariable analysis, possibly due to relatively low CRP levels in our patients (median plasma CRP level 0.25mg/dL, IQR 0.1-0.64). Previous studies found that elevated CRP levels were associated with functional outcome after storke[236-238]. Di Napoli reported that patients with

CRP levels above 1.5 mg/dL at discharge had a worse prognosis[236], and Hamidon et al. showed that elevated CRP levels was related to worse functional outcome (BI < 5) at one month among stroke patients with CRP levels (median 1.64 ± 3.07 mg/dL, range 0.06 to 16.21 mg/dL)[237]. There were two drawbacks about the present investigation on CRP levels and functional outcome. Firstly, the plasma CRP concentration may reflect not only the extent of cerebral infarct but also underlying conditions, such as systemic infection, inflammation, surgery or cancer[239]. In C&S study, we excluded the patients with severe infectious/rheumatic disease[173]. However, we did not exclude the patients with other underlying conditions. Secondly, in the present study, the timing for measurement of CRP levels was distributed between 3 to 7 days after stroke onset. The CRP levels might increase in patients with large brain infarct and peak around 48 hours[239]. Therefore, a previous study suggested samples should be taken within 24 to 48 hours after stroke onset to assess the association between CRP levels and unfavorable functional outcome[238].

Using the TOAST classification, large-artery atherosclerosis was the most frequent etiology of stroke (41.3%) in this C&S sub-study. Hypertension, diabetes and hypercholesterolemia were more common in large-artery atherosclerosis and least frequent in stroke of other determined or undetermined cause. WMLs was more frequent in large-artery atherosclerosis, cardioembolic stroke and small vessel occlusion than in stroke of other determined or undetermined cause ($p = 0.004$). similarly, Lee et al. reported that WMLs was most common in large-artery atherosclerosis[240]. Renal dysfunction (eGFR 30 to 60 mL/min/1.73m^2) was more common in cardioembolic stroke than in other etiological subtypes ($p = 0.015$), which was in line with the theory that eGFR below 60 mL/min/1.73m^2 was a risk factor for cardiac disease[121]. Our study found no significant differences in terms of NIHSS score at admission or functional outcome among stroke subtypes, possibly because most of our patients had mild neurological deficits on admission. Previous studies reported that patients with cardioembolic stroke had more severe neurological deficits on admission as well as a higher likelihood of unfavorable functional outcome, and patients with small vessel occlusion had the least neurological deficits as well as a higher likelihood of favorable functional outcome compared with patients with other etiological subtypes[57,81].

4.4 eGFR, WMLs and Stroke Recurrence within 1 year

Renal dysfunction was not only associated with traditional vascular risk factors, but also had a relationship with risk factors, such as inflammation, oxidative stress, nitric oxide, homocysteine, and pro-coagulant factor, which cause endothelial dysfunction and accelerate the progress of arteriosclerosis[155]. Renal dysfunction (eGFR < 60 mL/min/1.73m^2) is an established independent risk factor for the occurrence of CVD, including ischemic stroke[163]. As renal dysfunction (eGFR < 60 mL/min/1.73m^2) was associated with first ischemic stroke, it might be associated with stroke recurrence as well. In this C&S sub-study, no association between renal dysfunction and stroke recurrence could be detected. Patients with stroke recurrence had a relatively higher median eGFR level than patients without stroke recurrence (90.2 mL/min/1.73m^2, IQR 66.2-110.8 vs. 81 mL/min/1.73m^2, IQR 70-95. P = 0.535), although the difference was not statistically significant.

To date, most of the previous studies demonstrated that renal dysfunction (eGFR < 60 mL/min/1.73m^2) was associated with stroke recurrence[159,164-166,241]. A cross-sectional study by Micozkadioglu et al. reported that CKD (eGFR < 60 mL/min/1.73m^2) adjusted by age, gender and other vascular risk factors was associated with stroke recurrence (OR 2.395, 95% CI 1.039-5.518) in 160 patients with acute ischemic stroke (mean age 67.9 ± 12.63 years, female 43.8%)[165]. Similarly, Kuwashiro et al. found that eGFR < 60 mL/min/1.73m^2 (HR 1.7, 95% CI 1.05-2.77), age (HR 1.03, 95% CI 1.01-1.05) and HDL cholesterol (HR 1.74, 95% CI 1.04-2.92) were all associated with stroke recurrence within 1 year in 876 patients with non-cardioembolic stroke onset (age 70 ± 12 years, females 38.7%)[166]. Likewise, a study by Ovbiagele et al. showed that low eGFR (eGFR < 60 mL/min/1.73m^2) was associated with a higher risk of stroke recurrence (HR 1.16, 95% CI 1.04-1.31) in 18666 patients with ischemic stroke onset over 2.5 years[241]. Similarly, Weiner et al. found that CKD (defined as eGFR < 60 mL/min/1.73m^2) was related to increased risk for CVD recurrence including stroke (HR 1.3, 95% CI 1.04-1.63) in patients with preexisting CVD over around 7 years[164]. Finally, Tsagalis et al. found that renal dysfunction on admission (eGFR 30-60 mL/min/1.73m^2, HR 1.29, 95% CI 1.01-1.64; eGFR < 30 mL/min/1.73m^2, HR 1.86, 95% CI 1.05-3.29) was related with new cardiovascular morbidity including stroke recurrence over 10 years in 1350 patients with first-ever stroke[159]. The results of the present C&S sub-study were not in line with these previous studies. Potential explanations for the discrepancies might be due to lower frequency of renal dysfunction in C&S patients (9.38% in this C&S sub-study vs. 28.8%[159], 17.7%[164], 26.9%[165], 34.7%[166] and 20.1%,[241] respectively) the shorter follow-

up period (1 year vs. 2.5 years[241], 7 years[164] and 10 years[159]), and smaller sample size (160 patients vs. 876 patients[166], 1193 patients[159], 3630 patients[241] and 4278 subjects[164]).

WMLs are a marker of the extent of SVD in the brain[90], which associate with lacunar infracts and are frequent in patients with large-artery atherosclerosis[214]. WMLs maybe the result of traditional vascular risk factors[92], such as hypertension and diabetes mellitus, which are associated with first-ever stroke and stroke recurrence[34]. Furthermore, independent of other risk factors, WMLs has been reported as a predictor of stroke[93]. However, our study found no difference of the grades of WMLs ($p = 0.569$) between the patients with stroke recurrence (median WMLs Fazekas scores 1, IQR 0-2) and the patients without stroke recurrence (median WMLs Fazekas scores 1, IQR 0-2) within one year.

The findings of previous studies on the association between WMLs and stroke recurrence were not consistent. Putaala et al.[169] and Podgorska et al.[170] found no association between WMLs and stroke recurrence. Putaala et al. found that WMLs did not increase the risk for stroke recurrence in young patients (mean age 40.0 ± 8.0 year) with first-ever ischemic stroke over around 8 years follow-up[169]. Likewise, the study by Podgorska et al. demonstrated that WMLs were not related to stroke recurrence within 1 year in stroke patients[170]. However, other studies reported that WMLs were related with stroke recurrence over 2 years[171], 3 years[172] and 5 years[87]. Fu et al. showed that WMLs (HR: 4.177, 95% CI: 2.033-8.564, $p < 0.0005$) predicted stroke recurrence in 228 stroke patients over 23 months follow-up[171]. Similarly, the study by Henon et al. found that WMLs (RR: 1.70, 95% CI: 1.23-2.36, $p = 0.0013$) were related to stroke recurrence within 3 years in 202 stroke patients (mean age 75 years, range 42-101 years, male 48%)[172]. The study by Melkas et al. demonstrated that the presence of severe WMLs (HR 1.8, 95% CI 1.11-2.95, $p = 0.018$ adjusted for age, gender and vascular risk factors) predicted stroke recurrence up to 5 years in 320 patients with first-ever ischemic stroke (mean age 70.8 years, range 55-85, female 50.3%)[87]. Of note, there was no distinction between ischemic or hemorrhagic recurrent stroke in these studies. Likewise, in the C&S study that included ischemic strokes only, there was no differentiation between hemorrhagic and ischemic strokes for stroke recurrence. During the follow-up telephone interview patients or their relatives were simply asked whether or not they had symptoms attributable to a stroke (cp. Appendix [in German]). Stroke recurrence rate in this C&S sub-study was relatively low (8.75% vs. 13.4%[171], 15%[172] and 23.8%[87], respectively) and follow-up was relatively short (1 year vs. 2 years[171], 3 years[172] and 5 years[87], respectively). The studies by Henon et al., Fu et al.,

and Melkas et al. may suggest that WMLs increases the risk of stroke recurrence in a long-term follow-up beyond one year[87,171,172].

The present study found that higher LDL/HDL ratio (OR 2.031, 95% CI 1.127-3.661, p = 0.018) was significantly associated with stroke recurrence after adjusting for age and gender, and that higher LDL/HDL ratio (OR 1.754, 95% CI 1.122-2.741, p = 0.014) was significantly associated with secondary event including secondary cerebral infarction, myocardial infarction, coronary revascularization, cardiovascular death, or TIA within 12 months after primary stroke onset within 1 year. These results demonstrated that elevated LDL/HDL ratio levels increased the risk for the development of stroke recurrence and CVD events. Our finding was in agreement with the previous report by Anarenco et al. that LDL/HDL ratio (HR 1.31, 95% CI 1.06-1.62, p = 0.012) was associated with ischemic stroke recurrence[242]. However, our study did not confirm the notion by Anarenco et al. that lower baseline HDL cholesterol levels (HR 0.87, 95% CI 0.79-0.97, p = 0.012) were associated with ischemic stroke recurrence[242]. This may be due to our smaller sample size (160 patients vs. 4731 patients[242]) and the shorter period of follow-up (1 year vs. 4.9 years[242]) leading to a lack of statistical power. In regard to the effect of LDL cholesterol level on stroke recurrence, our finding was in line with result by Micozkadioglu et al. that there was no relationship between LDL cholesterol level (OR 1.02, 95% CI 0.958-1.089) and stroke recurrence[165]. Our finding implied that incidence of stroke recurrence was the result of a balance of LDL cholesterol levels and HDL cholesterol levels. On one hand, high LDL cholesterol levels caused atherosclerosis in large vessels including intracranial and extracranial leading to atherothrombotic infarctions in the brain[243], and on the other hand high HDL cholesterol levels have protective effect on large vessels[242,244]. The association between dyslipidemia and incidence of stroke was different among stroke sub-types. The effects of higher LDL cholesterol levels and lower HDL cholesterol levels were most prominent in atherothrombotic infarctions[242-244]. In general, stroke due to large artery atherosclerosis associates with early stroke recurrence within 7 days[15] and 30 days[14], or over the first few months[245]. However, in regard to long-term stroke recurrence over 5 years, some studies showed no difference among stroke subtype[14,46]. Others reported large artery atherosclerosis posed the highest risk for long-term stroke recurrence[246]. In our study, about 40% of strokes were due to large artery atherosclerosis. This relatively high proportion might have had an influence on the assessment of association between LDL/HDL ratio and stroke recurrence.

In summary, our findings supported the notion that LDL/HDL ratio seem to be a good predictor of stroke recurrence and CVD events[247]. Intensive lipid lowering by Statin therapy was recommended to prevent stroke recurrence and CVD events among patients with primary stroke and TIA in a guideline for healthcare professionals from the American Heart Association/American Stroke Association[248].

Lowering blood pressure reduces recurrent strokes in most stroke sub-types[34]. Although, diabetes mellitus might be a risk factor for stroke recurrence, there is limited evidence to support that controlling of glycaemia level reduces the risk of secondary strokes[246,249]. In our study, we did not find that hypertension and diabetes mellitus on hospital admission were associated with stroke recurrence. In contrast, several reports described hypertension or diabetes mellitus, or both as risk factors for early[82] as well as long-term stroke recurrence[86,245,246,250,251]. A potential explanation for this discrepancy may be different sample sizes (160 patients vs. 337 patients[245], 1273 patients[82], 1138 patients[86], 2744 patients[251] and 8311 patients[250]) and different periods of follow-up (1 year vs. 4 years[86], 5 years[245,250,251] and 10 years[250]). The cumulative risk of first recurrent stroke increases over the years (12.5%, 95% CI, 8.5-16.6 % for the first year; 22.5%, 95% CI, 16.8-28.1 % after 5 years)[245]. Therefore, the small sample size and a shorter follow-up time may be the reasons for a lack of statistical power to detect an association between hypertension, diabetes mellitus and stroke recurrence in this C&S sub-study.

4.5 Strengths of the Study

The study had several strengths. Firstly, eGFR was used to assess renal function. Compared with serum creatinine, eGFR is the more accurate parameter in this context[120]. There was no significant difference of serum creatinine levels among the different degrees of WMLs (p = 0.182). However, when eGFR was calculated, the difference of renal function among the different degrees of WMLs (p = 0.001) became evident. (Table 7)

Secondly, the MDRD equation was used to calculate eGFR. Compared with the Cockcroft-Gault formula, the MDRD equation was more accurate since it adjusted for body-surface area[120].

Thirdly, in this C&S sub-study, a broad range of clinical characteristics, such as traditional vascular risk factors and TOAST classification et al., was compared between the different subgroups of WMLs, eGFR, stroke functional outcome and stroke recurrence. This allowed for a comprehensive assessment on the clinical profile of the presence of WMLs, renal dysfunction in patients with ischemic stroke as well as their stroke functional outcome. For the first time, the factors of renal function, WMLs, initial severity of stroke, traditional vascular risk factors (hypertension and diabetes), age and gender were put in one model to assess functional outcome after ischemic stroke.

Finally, instead of the usual 3 months follow-up in stroke patients, a one year follow-up was chosen. Although the stroke functional recovery tends to level of after three months[50], the patient's condition may still change over longer periods of time[51]. Some recovery takes place even after three months and the frequency of stroke recurrence increases with time[51].

4.6 Limitations of the Study

The study had several limitations. Firstly, the sample was not representative of the general stroke population because of the C&S in- and exclusion criteria (selection bias). 1) Most of the stroke patients included had relatively mild ischemic strokes with low NIHSS scores at hospital admission (median 2, IQR 1-4). This was because only patients willing and able to give informed consent to ingest 250 mL of cream could be included. 2) Men were overrepresented in the study (63.1%). This requires cautious interpretations of any observed gender differences across eGFR groups. 3) Renal failure was an exclusion criterion of the Berlin C&S study. Therefore, in this study, there were no patients with eGFR < 15 mL/min/1.73m^2. Thus the association of renal failure, WMLs and functional outcome after stroke could not be investigated in this C&S sub-study.

Secondly, sample size was relatively modest in this study. Therefore, the number of predictor variables in binary logistic regression was limited. Only five predictor variables were included in the first model and 8 in the second model analyzing the association of WMLs, eGFR and functional outcome after stroke. The accuracy of the prediction model and the certainty of estimated ORs were also limited which was reflected by wider 95% confidence intervals[208]. (Table 16)

Thirdly, although a routine method, assessment of renal function by a formula based on serum creatinine levels ideally requires knowledge of the total muscle mass and dietary intake. The total muscle mass is associated with age, gender and race[128]. Other factors also may influence creatinine levels. Extra-renal creatinine excretion occurs via the degradation by intestinal bacteria, which is increased in patients with CKD[252]. Furthermore, the clearance of creatinine can be affected by medication, such as trimethoprim and cimetidine[129]. We did not control for these influences on creatinine levels. In addition, the serum creatinine level for a given patient in this sub-study was based on a single rather than multiple blood samples of patients.

Fourthly, since patients included in the Berlin C&S study were from three clinical hospitals, the MRI scans at different sites had different field strengths (1.5- and 3-T). In this sub-study, T2 weighted or FLAIR images could be used for the assessment of WMLs. When FLAIR was not available, T2 weighted imaging was used as an alternative. There was a risk that for patients only with T2 weighted MRI or with 1.5-T field strength, the severity of WMLs would be underreported

compared to FLAIR or 3-T. Inclusion of patients with CT scans only would have increased this risk even further[179].

Fifthly, 34 patients who were lost to follow-up were excluded. We cannot be sure about the further course of these patients although some reports suggest unfavorable outcomes in patients lost-to-follow-up[253]. This relatively high drop-out rate may have decreased the frequency of outcome events, which might have reduced the statistical power, increased a potential for bias[253] and influenced the precision of our investigation[208].

Sixthly, since the cumulative risk of first recurrent stroke increases over the years[245], the period of follow-up of one year was not enough to assess whether renal dysfunction and WMLs were risk factors for stroke recurrence. Most of previous studies were over five years as the periods of follow-up[87,159,164].

Finally, this study was a retrospective observational sub-study from the Berlin C&S study. Therefore, some important covariates associated with stroke functional outcome, such as premorbid mRS score[42] and post-stroke rehabilitation[254], were not available. Similarly, there was no information on proteinuria/albuminuria of patients which was important to diagnose and classify the stages of CKD as previously suggested[121]. The association between eGFR and adverse outcomes was increased with higher stages of urine albumin-to-creatinine ratio (ACR) in general population[121]. The absence of these parameters may have had an impact on the precision of our assessment of the association between renal function, WMLs and functional outcome after stroke.

4.7 Conclusions and Perspectives

In summary, renal impairment and WMLs may be different features of a common disorder, namely small vessel disease. They both seem to have adverse effects on functional outcome after stroke and physicians should use the information gained from both in conjunction with other established predictors of functional outcome, such as age and NIHSS. However, neither eGFR nor WMLs can be recommended for the prediction of stroke recurrence based on this C&S sub-study.

Further studies are needed to determine the effect of renal dysfunction as a cause for WMLs as well as for unfavorable outcome after stroke. Larger prospective observational cohort studies should be conducted. In these studies the incidence, prevalence, clinical feature and functional outcome of stroke patients with renal dysfunction and WMLs should be well recorded and documented. Apart from the traditional vascular risk factors, such as hypertension, diabetes, dyslipidemia and smoking, both proteinuria and eGFR should be used to assess cause and effect for the presence of WMLs, occurrence of stroke and post-stroke functional outcome in a population with and without renal dysfunction in a longitudinal cohort study. MRI should be acquired using a uniform protocol, ideally with 3-T and FLAIR images.

Only randomized controlled trails (RCT) would be able to test whether treatments, such as active blood pressure lowing therapy, would slow down the progress of WMLs and the decline of renal function in stroke patients, and whether this would be associated with improved functional outcome after stroke. These studies emphasize the importance of identification and management of unrecognized renal dysfunction and WMLs in stroke patients to improve functional outcome after stroke.

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7. Affidavit

“I, [Li, Wang] certify under penalty of perjury by my own signature that I have submitted the thesis on the topic [Association between White Matter Lesions, Renal Dysfunction and Functional Outcome in Ischemic Stroke Patients - A Berlin “Cream&Sugar” Substudy] I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

8. Curriculum Vitae

My curriculum vitae will not be published in the electronic version of my work for privacy reasons.

9. Publications

1. Wang, L., Leonards, C.O., Sterzer, P. & Ebinger, M. White matter lesions and depression: a systematic review and meta-analysis. *J Psychiatr Res* **56**, 56-64 (2014).

2. Leonards, C.O., Wang, L., Fiebach, J.B., Endres, M. & Ebinger, M. Fasting versus post-challenge triglycerides and pre-existing cavitating lacunes: a berlin "cream & sugar" substudy. *Front Neurol* **4**, 92 (2013).

10. Appendix

CHARITÉ UNIVERSITÄTSMEDIZIN BERLIN

CSB Center for Stroke Research Berlin

CREAM & SUGAR ERGÄNZUNGSBOGEN

Interviewer: *Diesen Fragebogen verwenden, wenn die Nachbefragung nach 12 Monaten über die PROSPEKTIVE CSB SCHLAGANFALLKOHORTE erfolgt!*

C&S PatID:

Kohorte PatID:

Name Interviewer

(in Blockbuchstaben)

Datum Interview

Interviewer: Die folgenden Fragen bitte nach Frage 20 des TICS - Fragebogen stellen!

1. Wurden von Ihrem Arzt oder von Ihnen Cholesterinsenkende Medikamente, sogenannte Statine, in den letzten 12 Monaten abgesetzt?

wenn ja, **Name des Medikamentes**

Dosis

wann

2. Hat Ihr Arzt eine Zuckerkrankheit, also einen Diabetes mellitus bei Ihnen innerhalb des letzten Jahres neu festgestellt?

Ja **Nein**

wenn ja, **wann**

Modul Telefonische Nachbefragung nach 12 Monaten

PatID	☐☐☐☐☐☐
Name Interviewer (in Blockbuchstaben)	_____ **Name** _____ **Vorname**
Datum Interview	☐☐☐☐☐☐☐☐ **Tag Monat Jahr**
Beginn Interview	☐☐☐☐ **Stunde Minute**

Mit wem wird das Interview geführt?

! Interviewer: nur eine Antwort möglich

mit dem Patienten selbst.....[ ]
mit Verwandten oder Freunden.....[ ]
mit einer Pflegeperson.....[ ]
mit einer anderen Person.....[ ]

! Interviewer: wenn das Interview nicht mit dem Patienten selbst geführt wird, ist im gesamten Interview die direkte Anrede durch „den Patienten/ die Patientin" zu ersetzen

- Sie wurden vor circa 12 Monaten aufgrund eines Schlaganfalls bzw. einer vorübergehenden Durchblutungsstörung des Gehirns stationär in unserer Klinik behandelt.
- Wir würden gerne wissen, wie es Ihnen **zum jetzigen Zeitpunkt**, etwa 12 Monate nach dem Schlaganfall, geht.
- Aus diesem Grund stelle ich Ihnen im Folgenden einige kurze Fragen. Im Anschluss an die jeweilige Frage lese ich Ihnen eine Reihe von möglichen Antworten vor.
- Wir sind uns bewusst, dass nicht alle Fragen auf Ihre persönliche Situation zutreffen. Bitte nennen Sie mir diejenige Antwort, die nach Ihrer Meinung die Frage **am zutreffendsten** beantwortet.
- Falls Sie eine Frage oder eine Antwort nicht genau verstanden haben, wiederhole ich selbstverständlich die jeweilige Frage oder Antwort noch einmal.

- Die folgenden Fragen beschäftigen sich mit Ihren Fähigkeiten, sich selbst zu versorgen. Einige der Fragen treffen vielleicht nicht auf Sie persönlich zu; wir möchten Sie dennoch darum bitten, **alle** Fragen zu beantworten.
- Bitte achten Sie bei der Beantwortung der Fragen darauf, dass Sie nur die Tätigkeiten angeben, die Sie zum jetzigen Zeitpunkt auch **ausführen** und nicht solche Tätigkeiten, die Sie vielleicht durchführen könnten!

1. Wie bewegen Sie sich zur Zeit innerhalb Ihrer Wohnung fort?

! Interviewer: nur eine Antwort möglich

a. Ich kann innerhalb meiner Wohnung ohne Unterstützung gehen
….....**[ ]weiter mit Frage 3**
b. Ich kann mich innerhalb meiner Wohnung nur mit Unterstützung fortbewegen
….....**[ ] weiter mit Frage 2**

2. Welche Unterstützung benötigen Sie bei der Fortbewegung innerhalb Ihrer Wohnung?

! Interviewer: nur eine Antwort möglich a. Ich kann innerhalb meiner Wohnung unter Zuhilfenahme von Hilfsmitteln
wie z.B. einem Gehstock selbstständig gehen….....**[ ]**
b. Ich kann innerhalb meiner Wohnung nur mit körperlicher Unterstützung
oder Ermunterung durch eine andere Person gehen….....**[ ]**
c. Ich kann mich innerhalb meiner Wohnung nur mit Hilfe eines Rollstuhles
fortbewegen, kann den Rollstuhl aber selbstständig bedienen….....**[ ]**
d. Ich kann weder selbstständig innerhalb meiner Wohnung gehen
noch kann ich einen Rollstuhl selbstständig benutzen….....**[ ]**

3. Wie viel Hilfe benötigen Sie, wenn Sie von Ihrem Bett aufstehen und sich auf einen Stuhl oder in einen Sessel setzen?

! Interviewer: nur eine Antwort möglich a. Ich benötige keinerlei Hilfe beim Aufstehen vom Bett und dem Hinsetzen
in einen Stuhl oder einen Sessel.....**[ ] weiter mit Frage 5**
b. Ich kann vom Bett in einen Stuhl oder Sessel nur mit Unterstützung
durch eine oder mehrere andere Personen wechseln.....**[ ] weiter mit Frage 4**
c. Ich kann nicht alleine im Stuhl oder Sessel sitzen oder
ich bin vollständig bettlägerig.....**[ ] weiter mit Frage 5**

4. Wie viel Unterstützung durch eine oder mehrere andere Personen benötigen Sie, wenn Sie von Ihrem Bett aufstehen und sich auf einen Stuhl oder in einen Sessel setzen?

! Interviewer: nur eine Antwort möglich a. Ich kann vom Bett in einen Stuhl oder Sessel nur mit geringer körperlicher
Unterstützung oder Ermunterung durch eine andere Person wechseln.....**[ ]**
b. Ich benötige beim Wechsel vom Bett in einen Stuhl oder Sessel
große körperliche Unterstützung durch ein oder zwei andere Personen,
ich kann jedoch alleine sitzen.....**[ ]**
c. Ich benötige beim Wechsel vom Bett in einen Stuhl oder
Sessel große körperliche Unterstützung durch zwei andere Personen,
ich kann nicht alleine sitzen.....**[ ]**

5. Benötigen Sie Hilfe beim Treppensteigen?

! Interviewer: nur eine Antwort möglich
a. Ich benötige keine Hilfe beim Treppensteigen.....**[ ]**
b. Ich benötige entweder körperliche Hilfe oder Ermunterung beim Treppensteigen
oder Unterstützung durch Hilfsmittel wie z.B. einen Gehstock.....**[ ]**
c. Ich kann keine Treppen steigen.....**[ ]**

6. Benötigen Sie Hilfe beim Essen?

! Interviewer: nur eine Antwort möglich
a. Ich benötige keine Hilfe beim Essen,
das Essen kann durch andere Personen gekocht oder bereitgestellt werden.....**[ ]**
b. Ich benötige Hilfe beim Essen,
z.B. beim Schneiden oder beim Aufstreichen von Butter.....**[ ]**
c. Ich kann nicht alleine essen oder bin auf speziell zubereitete Nahrung

angewiesen wie z.B. Sondenkost, pürierte Kost oder Brei.....**[ ]**

7. Benötigen Sie Hilfe beim An- und Ausziehen Ihrer Kleidung (einschließlich Knöpfen und Zuziehen von Reißverschlüssen)?

! Interviewer: nur eine Antwort möglich

a. Ich benötige keine Hilfe beim An- und Ausziehen.....**[ ] weiter mit Frage 9**
b. Ich benötige Hilfe beim An- und Ausziehen.....**[ ] weiter mit Frage 8**

8. Wie viel Hilfe benötigen Sie beim An- und Ausziehen Ihrer Kleidung?

! Interviewer: nur eine Antwort möglich

a. Ich benötige Hilfe beim An- und Ausziehen,
kann mich jedoch mindestens zur Hälfte selbst an- und ausziehen.....**[ ]**
b. Ich kann mich nicht selbst an- und ausziehen.....**[ ]**

9. Benötigen Sie Hilfe beim Baden oder Duschen?

! Interviewer: nur eine Antwort möglich

a. Ich benötige keine Hilfe beim Baden oder Duschen, ich komme ohne Hilfe
in die Badewanne hinein und wieder heraus und kann mich alleine waschen.....**[ ]**
b. Ich benötige Hilfe beim Baden oder Duschen.....**[ ]**

10. Benötigen Sie Hilfe bei der Körperpflege (z.B. beim Zähne putzen, Gebiss einsetzen, Haare kämmen, Rasieren oder Gesicht waschen)?

! Interviewer: nur eine Antwort möglich

a. Ich benötige keine Hilfe bei der Körperpflege,
Hilfsmittel wie z.B. Kamm oder Rasierer können bereitgestellt werden….....**[ ]**
b. Ich benötige Hilfe bei der Körperpflege….....**[ ]**

11. Benötigen Sie Hilfe bei der Benutzung der Toilette (z.B. beim Hinsetzen und Aufstehen, beim An- und Ausziehen sowie beim Abwischen)? ***! Interviewer: nur eine Antwort möglich***

a. Ich benötige keine Hilfe bei der Benutzung der Toilette...**[ ] weiter mit Frage 13**
b. Ich benötige Hilfe bei der Benutzung der Toilette.....**[ ] weiter mit Frage 12**

12. Wie viel Hilfe benötigen Sie bei der Benutzung der Toilette?

! Interviewer: nur eine Antwort möglich

a. Ich benötige einige Hilfe bei der Benutzung der Toilette, kann aber einzelne
Tätigkeiten alleine ausführen, wie z.B. Hinsetzen oder An- und Ausziehen.....**[ ]**
b. Ich benötige große Hilfe bei der Benutzung der Toilette.....**[ ]**

13. Hatten Sie in der vergangenen Woche Probleme beim Wasserlassen? ***! Interviewer: nur eine Antwort möglich***

a. Ich hatte in der vergangenen Woche keinerlei Probleme beim Wasserlassen
.....**[ ] weiter mit Frage 16**
b. Ich hatte in der vergangenen Woche Probleme beim Wasserlassen
.....**[ ] weiter mit Frage 14**
c. Ich habe einen Blasenkatheter
.....**[ ] weiter mit Frage 15**

14. Welcher Art waren die Probleme beim Wasserlassen in der vergangenen Woche? ***! Interviewer: nur eine Antwort möglich***

a. Ich verliere gelegentlich die Kontrolle über meine Blase, höchstens jedoch einmal am Tag.....**[ ] weiter mit Frage 16**

b. Ich verliere mehr als einmal am Tag die Kontrolle über meine Blase .....**[ ] weiter mit Frage 16**

15. Wie versorgen Sie Ihren Blasenkatheter?
! Interviewer: nur eine Antwort möglich

a. Ich versorge meinen Blasenkatheter selbst.....**[ ]**

b. Ich kann meinen Blasenkatheter nicht selbst versorgen.....**[ ]**

16. Hatten Sie in der vergangenen Woche Probleme beim Stuhlgang?
! Interviewer: nur eine Antwort möglich

a. Ich hatte in der vergangenen Woche keinerlei Probleme beim Stuhlgang .....**[ ] weiter mit Frage 18**

b. Ich hatte in der vergangenen Woche Probleme beim Stuhlgang .....**[ ] weiter mit Frage 17**

17. Welche Probleme beim Stuhlgang hatten Sie in der vergangenen Woche? ***! Interviewer: nur eine Antwort möglich***

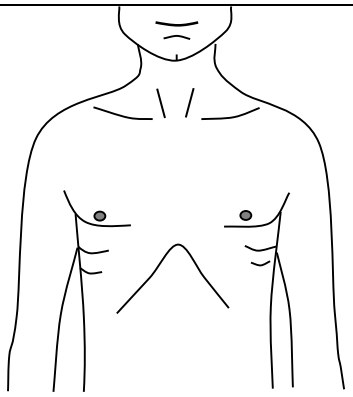
a. Ich verliere gelegentlich die Kontrolle über meinen Stuhlgang, höchstens jedoch einmal in der Woche.....**[ ]**

b. Ich verliere mehr als einmal pro Woche die Kontrolle über meinen Stuhlgang ..... **[ ]**

c. Ich bin auf die Gabe von Einläufen angewiesen.....**[ ]**

18. Sie wurden vor circa 12 Monaten aufgrund eines Schlaganfalles in einem Krankenhaus behandelt.

A. Haben Sie seitdem je Schmerzen oder ein Druckgefühl in der Brust gehabt?	[ ] ja [ ] nein → ***Weiter mit Frage 19***
B. Bekommen Sie diese Schmerzen oder Druckgefühle, wenn Sie bergauf oder schnell gehen?	[ ] ja [ ] nein → ***Weiter mit Frage H***
C. Treten diese Schmerzen oder Druckgefühle auch auf wenn Sie in gewöhnlichem Schritttempo auf ebener Strecke gehen?	[ ] ja [ ] nein
D. Was tun Sie jeweils wenn diese Schmerzen oder Druckgefühle in der Brust auftreten? (Mehrfachantworten möglich)	[ ] ich stehe still [ ] ich gehe langsamer [ ] ich gehe im gleichen Tempo weiter
E. Hören diese Schmerzen oder Druckgefühle auf, wenn Sie stillstehen?	[ ] ja [ ] nein → ***Weiter mit Frage G***
F. Wie schnell gehen diese Schmerzen oder Druckgefühle vorbei?	[ ] in 10 Minuten oder weniger [ ] nach mehr als 10 Minuten
G. Wo haben Sie diese Schmerzen oder Druckgefühle genau? ***Interviewer! Bitte den genannten Ort oder die Orte mit einem X auf der nebenstehenden Zeichnung markieren)***	

	
H. Hatten Sie je einen starken Schmerz in der Brustmitte der eine halbe Stunde oder länger dauerte?	[ ] ja [ ] nein
I. Waren Sie aufgrund dieser Symptome bei einem Arzt in Behandlung?	[ ] ja [ ] nein [ ] weiß nicht
J. Wenn ja, wann?	Monat Jahr ☐☐ ☐☐☐☐
K. Waren Sie seit Ihrem Schlaganfall aufgrund eines Herzinfarktes, einer Angina Pectoris oder einer peripheren arteriellen Verschlusskrankheit (pAVK) bei einem Arzt in Behandlung?	[ ] ja → ***Weiter mit Frage L.*** [ ] nein [ ] weiß nicht
L. Wenn ja, bitte geben Sie den Grund der Behandlung, den Zeitpunkt und den behandelnden Arzt an.	[ ] Herzinfarkt [ ] Angina Pectoris [ ] periphere arterielle Verschlusskrankheit (pAVK**)**
I. Wenn ja, wann?	Monat Jahr ☐☐ ☐☐☐☐
19. Wir würden gerne wissen, ob es bei Ihnen zu einem Auftreten der im folgenden beschriebenen Symptome oder eines erneuten Schlaganfalls gekommen ist.	
A. Wurde bei Ihnen seit dem Schlaganfall vor 1 Jahren ein weiterer Schlaganfall oder eine transitorische ischämische Attacke (TIA) von einem Arzt diagnostiziert?	[ ] ja [ ] nein → **weiter mit E** [ ] weiß nicht
B. Wenn ja, bitte beschreiben Sie an dieser Stelle kurz die Art der Symptome und Ihre Dauer.	_____ _____
C. Waren Sie aufgrund dieser Symptome bei einem Arzt in Behandlung?	[ ] ja [ ] nein

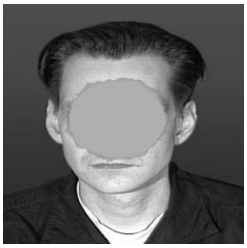
	[ ] weiß nicht
D. Wenn ja, wann?	Monat Jahr ☐☐ ☐☐☐☐
E. Hatten Sie jemals eine oder mehrere der Sehstörungen auf einem oder beiden Augen?	[ ] ja [ ] nein → **weiter mit I** [ ] weiß nicht

F. Wenn ja, beschreiben Sie bitte kurz die Art und Dauer der Sehstörung(en).

☐

Doppelbilder

☐



Zentraler Gesichtsfeldverlust

☐

Dreifachbilder

☐

Gesichtsfeldausfälle oben

☐

Gesichtsfeldausfälle seitlich

Dauer:

G. Waren Sie aufgrund dieser Symptome bei einem Arzt in Behandlung	[ ] ja [ ] nein [ ] weiß nicht
H. Wenn ja, wann und wo? Name und Adresse des behandelnden Arztes oder der Klinik	Monat Jahr ☐☐ ☐☐☐☐

I. Hatten Sie jemals eine verwaschene Sprache oder Probleme mit jemandem zu sprechen, weil Sie unfähig waren die Worte oder Sätze auszusprechen?	[ ] ja [ ] nein [ ] weiß nicht
J. Wenn ja, bitte beschreiben Sie an dieser Stelle kurz die Art der Symptome und Ihre Dauer.	_____ _____
K. Waren Sie aufgrund dieser Symptome bei einem Arzt in Behandlung?	[ ] ja [ ] nein [ ] weiß nicht
D. Wenn ja, wann?	Monat Jahr ☐☐ ☐☐☐☐

20. Mussten Sie seit der Entlassung aus dem Krankenhaus oder aus der Rehabilitationsklinik erneut in ein Krankenhaus aufgenommen werden? **! !*Interviewer: nur eine Antwort möglich***

a. Nein..... **[ ] weiter mit Frage 22**
b. Ja..... **[ ] weiter mit Frage 21**

21. Aus welchem Grund mussten Sie erneut in ein Krankenhaus aufgenommen werden?

a. Ich wurde aufgrund eines **erneuten Schlaganfalles** in einem Krankenhaus behandelt..... **[ ]**
b. Ich wurde aufgrund einer **anderen Erkrankung** (**kein** Schlaganfall) in einem Krankenhaus behandelt..... **[ ]**

22. Wurden von Ihrem Arzt oder von Ihnen Cholesterinsenkende Medikamente, sogenannte Statine, in den letzten 12 Monaten abgesetzt?

I. Wenn ja welche und wann? **Medikament:_____** **Dosis:_____**	Monat Jahr ☐☐ ☐☐☐☐

23. Hat Ihr Arzt eine Zuckerkrankheit, also einen Diabetes mellitus bei Ihnen innerhalb des letzten Jahres neu festgestellt?

J. Wenn ja, wann?	Monat Jahr ☐☐ ☐☐☐☐

25. Wie sehr sind Sie derzeit in Ihrem Alltag durch den Schlaganfall beeinträchtigt? Bitte geben Sie die Aussage an, die am ehesten auf Sie zutrifft. ***! Interviewer: nur eine Antwort möglich***

a. Die Ausfälle durch den Schlaganfall sind vollständig zurückgegangen, ich habe keinerlei Einschränkungen in meinem Alltag ……**[ ]**

b. Ich habe durch den Schlaganfall keine wesentlichen Einschränkungen in meinem Alltag, obwohl seit dem Schlaganfall einige Ausfälle zurückgeblieben sind. Ich kann jedoch alle von früher gewohnten Aufgaben und Aktivitäten verrichten.....**[ ]**

c. Ich leide durch den Schlaganfall an geringen Einschränkungen in meinem Alltag und bin nicht fähig, wieder alle früheren Aktivitäten zu verrichten. Ich kann aber meine eigenen Angelegenheiten ohne Hilfe erledigen……**[ ]**

d. Ich leide an mäßigen Einschränkungen in meinem Alltag und benötige einige Unterstützung durch andere Personen. Ich bin aber in der Lage, ohne Hilfe zu gehen……...**[ ]**

e. Ich leide an mittelschweren Einschränkungen in meinem Alltag und bin nicht fähig, ohne Hilfe zu gehen und nicht in der Lage, ohne Hilfe für meine körperlichen Bedürfnisse zu sorgen……..**[ ]**

f. Ich leide an schweren Einschränkungen in meinem Alltag. Ich bin bettlägerig und ständig auf die Pflege und Aufmerksamkeit anderer Personen angewiesen…….**[ ]**

Ende Interview

Stunde **Minute**

Zum Schluss möchten wir uns ganz herzlich bei Ihnen
für Ihre Mühen bei dem Interview bedanken!

Dokumentation auftretender Probleme/ Verständnisschwierigkeiten

Frage Nr.	Probleme /Queries