Impact of Chronic Kidney Disease on Stroke Risk, Mechanisms, and Outcomes

Thesis submitted for the degree of D.Phil.

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Gabhaim buíochas le m’athair Phil, mo mháthair Aileen, Yvelynne, Eimear agus Eoin, as ucht an grá, an tacaíocht agus an spreagadh seasmhach a fuaireas uathu le fada agus an mhuinín a bhi acu asam ná dearúdfad go deo

ABSTRACT

The Impact of Chronic Kidney Disease on Stroke Risk, Mechanisms, and Outcomes

Dearbhla Kelly, St. Hilda's College, University of Oxford
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Chronic kidney disease (CKD) has a rapidly rising global prevalence, affecting as many as one third of the population over the age of 75 years. CKD is a well-known risk factor for cardiovascular disease and in particular, there is a strong association with stroke. Cohort studies and trials indicate that reduced glomerular filtration rate increases the risk of stroke by about 40% and that proteinuria increases the risk by about 70%. In addition, CKD is also strongly associated with subclinical cerebrovascular abnormalities, vascular cognitive impairment, and dementia. There are however a number of outstanding questions regarding the relationship between CKD and stroke.

Firstly, the mechanisms underpinning this relationship are currently unclear. CKD is associated with traditional risk factors such as hypertension, diabetes mellitus, and atrial fibrillation, but non-traditional risk factors such as uraemia, oxidative stress, mineral and bone abnormalities, and dialysis-related factors such as changes in cerebral blood flow or cardiac structure are also purported mechanisms. Hypertension is the leading modifiable risk factor for stroke in the general population and is highly prevalent in CKD, but its role has not been systematically examined. Secondly, it is not known which stroke subtypes are most closely associated with CKD. Thirdly, although CKD is associated with greater short- and long-term mortality post-stroke, its impact on initial stroke severity, recovery, and recurrence risk are less clear. Fourthly, it has been hypothesized that cerebral small vessel disease (SVD) and CKD may be part of a multisystem small-vessel disorder, but

their association may simply be confounded as a result of shared risk factors (e.g. hypertension) rather than represent a systemic susceptibility to premature SVD. Finally, CKD has also been associated with cognitive dysfunction but it is not known whether this association is independent of cerebrovascular disease.

The aim of my thesis therefore was to determine the role of hypertension in the relationship between CKD and stroke risk. Using the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, I also aimed to describe which transient ischaemic attack (TIA) and ischaemic stroke subtypes occur most frequently in patients with CKD. I sought to determine whether CKD is associated with worse initial stroke severity and recovery, and whether CKD is independently predictive of recurrent stroke. I aimed to study the age-specific associations of CKD and the overall burden of SVD (total SVD score), as well as individual SVD markers. Lastly, I investigated the association between CKD and dementia before and after TIA and stroke.

The work of this thesis forms two parts. For the first part, I undertook two large and complex systematic reviews and meta-analyses to better describe what data were already available on the relationship between renal function, proteinuria, and stroke. For these reviews, I developed a search strategy, identified >10,000 studies for title and abstract review, and then >400 studies for full text review. I selected studies and extracted study, patient, stroke characteristics, and outcome data according to a pre-defined protocol. I assessed the quality of included studies, and performed all statistical analysis including meta-analysis, sub-analysis, meta-regression and funnel plots for publication bias. I categorized all studies according to a hierarchy of hypertension adjustment.

For the second part of my thesis, I have collected, collated and analysed data from the Oxford Vascular Study (OXVASC), a population-based prospective cohort study. In

particular I worked as one of the Clinical Research Fellows at OXVASC and was involved in regular recruitment, assessment and follow up of study patients. I studied a panel of 16 blood biomarkers related to inflammation, thrombosis, atherogenesis, and cardiac or neuronal cell damage in 1297 patients with TIA or ischaemic stroke. Biomarker levels were log-transformed and correlated with eGFR, adjusted for age. All ischaemic events were classified by TOAST subtypes (cardioembolism, large artery disease, small vessel disease, undetermined, multiple, other aetiology, or incompletely investigated). I used logistic regression analysis to determine the relationship between CKD and TIA/stroke subtypes in 2969 patients who presented between April 1, 2002 to March 31, 2017. I also studied initial stroke severity and early recovery measured using the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS), respectively, in ordinal regression analyses in the same cohort of patients. I used Cox proportional hazard models to determine if CKD was an independent predictor of stroke and other vascular event recurrences.

For the third part of my thesis, I focused on the relationship between CKD, subclinical cerebrovascular disease, and dementia in phenotyped cohorts within OXVASC. I investigated the age-specific associations of CKD and total SVD burden (total SVD score) adjusting for age, sex, and vascular risk factors in 1939 consecutive patients with TIA or ischaemic stroke who underwent cerebral magnetic resonance imaging (MRI) from 2004 to 2018. Finally, I examined associations between pre-event dementia and CKD using logistic regression, and between post-event dementia and CKD using both Cox and competing risk regression models (to account for the competing risk of death), adjusted for age, sex, education, cerebrovascular burden (stroke severity, prior stroke, white matter disease), diabetes mellitus, and dysphasia.

There are several clinically relevant findings in this thesis. Firstly, I have shown that the association between CKD and stroke appears to be highly dependent on the method of

adjustment for hypertension. The apparently independent relationship between CKD and stroke may be confounded by their shared association with long-term blood pressure burden. Secondly, I have demonstrated that proteinuria is strongly and independently associated with incident stroke risk even after robust adjustment for hypertension, possibly indicating a shared renal and cerebral susceptibility to vascular injury in this subset of patients of kidney disease that is not fully explained by traditional vascular risk factors. Thirdly, I found that correlations between biomarkers related to inflammation and thrombosis with renal dysfunction in the setting of cerebrovascular events were generally modest after adjustment for age, suggesting that putative risk factors such as chronic inflammation or coagulopathy are unlikely to be important stroke mechanisms in patients with CKD. Fourthly, I have shown that there were no independent positive associations between CKD and specific TOAST subtypes which suggests that renal-specific risk factors are unlikely to play an important role in the aetiology of particular subtypes. Fifthly, I have highlighted that CKD is associated with severity of cerebrovascular events (stroke vs TIA; initial NIHSS; 1-month mRS) and that it is independently predictive of stroke recurrence, particularly early recurrence. Sixthly, I have shown how the association of CKD and cerebral SVD is attenuated with adjustment for shared risk factors at older ages, but remains at younger ages, consistent with a shared susceptibility to premature vascular disease. Finally, in patients with TIA and stroke, CKD was not independently associated with either pre- or post-event dementia, suggesting that age, sex, education, and cerebrovascular burden may play a more important role in the aetiology of dementia in CKD than renal-specific neurodegenerative mechanisms.

DECLARATION

I certify that this thesis entitled “The impact of chronic kidney disease on stroke risk, mechanisms, and outcomes” was performed whilst I was a full-time postgraduate student at the University of Oxford.

I declare that this thesis is of my own composition, and the research contained herein is my own original work under the supervision of Professor Peter Rothwell. No portion of this work has been submitted in support of an application for any other degree.

ACKNOWLEDGEMENTS

As a medical student, I was enthralled by Neurology; fascinated by the basal ganglia pathways, the contents of the cavernous sinus, the anatomy of our consciousness. I loved the intricate inter-workings of the nervous system whose fragile nature was manifest in the many neurodegenerative, demyelinating and cognitive disorders that my clinical years opened my eyes to. Although ultimately destined to be a Nephrology fellow in my later life, I was then intrigued and compelled by the interface between neurological and renal diseases. In particular, I was struck by the frequent and severe presentations of cerebrovascular disease in patients with kidney disease, particularly those that are dialysis-dependent, and then frustrated by the seemingly low-level of evidence that informed their subsequent management. There was clearly a need for greater research in this vulnerable, high-risk population and hence, the idea of my DPhil was born. Vincent Van Gogh once said that “Great things are done by a series of small things brought together” and I hope that the work presented in this DPhil will be one ‘small thing’ that will ultimately contribute to something greater than itself.

I would like to thank Professor Peter Rothwell, my DPhil supervisor. I think it’s not an overstatement to say that he has changed stroke care throughout the world. He’s a truly inspirational figure who provides exceptional evidence-based care for his patients, having created much of this evidence himself, and who mentors research fellows to ask and answer the most pertinent research questions. One such fellow is the irreplaceable Dr. Linxin Li, who must be destined for world domination, if not stroke medicine domination! Her intelligence is surpassed only by her kindness and grace that were unwavering in the face of my seemingly endless statistical questions!

I must thank all my colleagues at the Wolfson Centre for Prevention of Stroke and Dementia, University of Oxford including all the other clinical fellows, research nurses and therapists, administrators, and database managers, not only for their help in patient ascertainment and data collection, but also for their good humour and friendship. I particularly owe a debt of gratitude to Dr. Cyrus Daruwalla for taking on much of our clinical load in the final year to allow us time to finish and write up our theses.

This research would not have been possible or meaningful without the many Oxford Vascular Study volunteers who selflessly gave much of their information, blood samples, imaging sequences, and above all else, time, to the pursuit of prevention and treatment of stroke in others. I dedicate this thesis to them and their endless generosity of spirit.

I am also grateful to the Irish Nephrology Society that have generously funded this project, and continue to support interdisciplinary research such as mine that is increasingly relevant in this era of multi-morbidity and increasing cardiovascular disease burden.

I have to acknowledge the pandemic-sized interruption that was the Covid-19 virus in my final term. However, playing a very small part in the collective clinical and research efforts to battle the virus reminded me that I have been privileged to stand on the shoulders of some giants during my time here in Oxford.

Finally, I would like to thank my family and my partner Eoin for their support, encouragement, and love, without which none of this would be possible, and with which, everything is.

PUBLICATIONS, PRESENTATIONS AND PRIZES

The work in this thesis has led to the following publications, presentations, and awards:

Publications:

Kelly DM, Rothwell PM. *Disentangling the multiple links between renal dysfunction and cerebrovascular disease.* J Neurol Neurosurg Psychiatry. 2019 Sep 11.

Kelly DM, Rothwell PM. *Blood pressure and the brain: the neurology of hypertension.* Pract Neurol. 2019 Sep 26.

Kelly DM, Rothwell PM. *Does chronic kidney disease predict stroke risk independent of blood pressure? A systematic review and meta-regression.* Stroke. 2019 Oct 9.

Kelly DM, Rothwell PM. *Proteinuria as an Independent Predictor of Stroke: Systematic Review and Meta-analysis.* Int J Stroke. 2020 Jan 14.

Kelly DM, Rothwell PM. *Prevention and treatment of stroke in patients with chronic kidney disease: an overview of evidence and current guidelines.* Kidney Int. 2020 Feb;97(2):266-278.

Kelly DM, Li L, Burgess AI, Poole DL, Duerden DM, Rothwell PM. *Associations of blood biomarkers with glomerular filtration rate in patients with TIA and stroke: population-based study.* Stroke Vasc Neurol. 2020 Sep 3:svn-2020-000422.

Kelly DM, Li L, Rothwell PM. *Etiological subtypes of transient ischaemic attack and ischaemic stroke in chronic kidney disease: population-based study.* Stroke. 2020 Sep;51(9):2786-2794.

Kelly DM, Rothwell PM. *Impact of Multimorbidity on Risk and Outcome of Stroke: Lessons from Chronic Kidney Disease.* Int J Stroke. 2020 (under review)

Presentations:

Kelly DM, Rothwell PM. *Albuminuria and stroke risk: a systematic review and meta-analysis.* Presented at the European Stroke Organisation Conference in Milan in May 2019 and at the American Society of Nephrology Kidney Week in Washington in November 2019.

Kelly DM, Rothwell PM. *Is the association between chronic kidney disease and stroke risk truly independent?* Presented at the European Stroke Organisation Conference in Milan in May 2019 and at the American Society of Nephrology Kidney Week in Washington in November 2019.

Kelly DM, Li L, Burgess AI, Poole DL, Duerden JM, Rothwell PM. *Associations of Blood Biomarkers with Glomerular Filtration Rate in Patients with TIA and Stroke: Population-Based Study.* Due to be presented at the European Stroke Organisation -World Stroke Organisation joint conference in Vienna in November 2020.

Kelly DM, Li L, Rothwell PM. *Aetiological classification of TIA and ischaemic stroke in chronic kidney disease: population-based Study.* Due to be presented at the European Stroke Organisation-World Stroke Organisation joint conference in Vienna in November 2020.

Kelly DM, Li L, Rothwell PM. *Stroke severity, recovery and recurrence in chronic kidney disease: population-based study.* Due to be presented at the European Stroke Organisation -World Stroke Organisation joint conference in Vienna in November 2020.

Work from this thesis also led to participation in the *KDIGO Controversies Conference on Central & Peripheral Arterial Diseases in CKD* in Dublin in February 2020, during which time I co-chaired the breakout group on cerebrovascular disease in CKD. Consensus papers from this conference will be shortly submitted to the *Kidney International* and to *Stroke*, and I will be first author of the latter paper.

Prizes:

Best Poster Award for "*Albuminuria and stroke risk: a systematic review and meta-analysis"*, European Stroke Organisation Conference, Milan 2019.

William Stokes Poster Presentation Award for "*Albuminuria and stroke risk: a systematic review and meta-analysis"*, Royal College of Physicians of Ireland, Dublin 2019.

Shortlisted for the Royal Society of Medicine Stewart Cameron Science Award for "*Proteinuria as an Independent Predictor of Stroke: Systematic Review and Meta-analysis*", London 2019.

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ABBREVIATIONS

AAA	Abdominal aortic aneurysm
AASK	African American Study of Kidney Disease and Hypertension
ABPM	Ambulatory blood pressure monitor
A- β	Amyloid-beta
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes trial
ACE-I	Angiotensin-converting-enzyme inhibitor
ACR	Albumin:creatinine ratio
AD	Alzheimer's disease
A&E	Accident & Emergency
AHA	American Heart Association
AKI	Acute kidney injury
AMTS	Abbreviated mental test score
Anti-PC	Anti-phosphorylcholine antibodies
APS	Antiphospholipid antibody syndrome
AR	Aortic regurgitation
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial
ARRIVE	Aspirin to Reduce Risk of Initial Vascular Events
ASA/AHA	American Stroke Association/American Heart Association
ASCEND	A Study of Cardiovascular Events iN Diabetes
ASPREE	ASPirin in Reducing Events in the Elderly study
ATTACK	Aspirin To Target Arterial events in Chronic Kidney Disease trial

AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
A2RB	Angiotensin 2 receptor blocker
BBB	Blood brain barrier
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BMS	Bare metal stent
BP	Blood pressure
CAA	Cerebral amyloid angiopathy
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CANVAS	CANagliflozin cardioVascular Assessment Study
CBF	Cerebral blood flow
CCF	Congestive cardiac failure
CE	Cardioembolic
CEA	Carotid endarterectomy
CHANCE	Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events
CI	Confidence interval
CKD	Chronic kidney disease
CLD	Chronic liver disease
CMB	Cerebral microbleed
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
CSA	Central sleep apnoea
CSPPT	China Stroke Primary Prevention Trial
CPAP	Continuous positive airway pressure

CVD	Cardiovascular disease
DAPT	Dual anti-platelet therapy
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMPA-Reg	[Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients
ENCHANTED	Enhanced Control of Hypertension and Thrombolysis Stroke Study
ESC	European Society of Cardiology
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times Trial
ESKD	End stage kidney disease
ETOH	Alcohol
FGF	Fibroblast growth factor
HARP	Heart and Renal Protection trial
Hb	Haemoglobin
HDL	High density lipoprotein
hFABP	Heart-type fatty acid binding protein
HIV	Human immunodeficiency virus
HOT	Hypertension optimal treatment trial
HR	Hazard ratio
HRS	Heart Rhythm Society
HRT	Hormone replacement therapy
HTN	Hypertension
ICD	International Classification of Diseases
ICH	Intracerebral haemorrhage

IHD	Ischaemic heart disease
IL-6	Interleukin-6
IMD	Index of multiple deprivation
INTERACT	Intensive blood pressure reduction in acute cerebral haemorrhage trial
IVT	Intravenous thrombolysis
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes trial
KDIGO	Kidney Disease Improving Global Outcomes
LAD	Large artery disease
LDL	Low density lipoprotein
LIFE	Losartan Intervention For Endpoint reduction in hypertension study
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MCA-PI	Middle cerebral artery pulsatility index
MDRD	Modification of diet in renal disease
MI	Myocardial infarction
MUL	Multiple causes
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NGAL	Neutrophil gelatinase-associated lipocalin
NIHSS	National institute of health stroke scale
NOAC	Novel oral anticoagulant
NSAID	Non-steroidal anti-inflammatory drug
NSE	Neuron specific enolase
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OCSP	Oxfordshire Community Stroke Project

OSA	Obstructive sleep apnoea
OTH	Other defined aetiology
OXVASC	The Oxford Vascular Study
PCI	Percutaneous coronary intervention
PCR	Protein:creatinine ratio
PCSK9	Proprotein convertase subtilisin/kexin type 9
PP	Pulse pressure
PRES	Posterior Reversible Encephalopathy Syndrome
PROGRESS	Perindopril Protection against Recurrent Stroke Study
PTH	Parathyroid hormone
PVH	Periventricular hyperintensities
PWV	Pulse wave velocity
PZ	Protein Z
RAS	Renin-angiotensin system
RCT	Randomized controlled trial
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy trial
RENAL-AF	RENal hemodialysis patients ALlocated apixaban versus warfarin in Atrial Fibrillation trial
REVASCAT	RandomizEd Trial of reVascularizAtion With Solitaire FR® Device Versus Best mediCal Therapy in the Treatment of Acute Stroke Due to anTerior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset
ROCKET-AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
ROS	Reactive oxygen species
RR	Relative risk
SBP	Systolic blood pressure

SCREAM	Stockholm creatinine measurements project
SDB	Sleep-disordered breathing
SES	Socio-economic status
SGLT-2	Sodium-glucose co-transporter-2
SHARP	Study of Heart and Renal Protection
SHR	Spontaneously-hypertensive rats
SLE	Systemic lupus erythematosus
SPRINT	Systolic blood pressure intervention trial
sTNF- α	Soluble tumour necrosis factor-alpha
STS	Society of Thoracic Society score
SVD	Small vessel disease
SWIFT-PRIME	Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment
TAVI	Transcatheter aortic valve implantation
TC	Total cholesterol
TCD	Transcranial doppler
TE	Thromboembolic
TG	Triglyceride
TIA	Transient ischaemic attack
TM	Thrombomodulin
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
TREAT	Trial to Reduce Cardiovascular Events with Aranesp Therapy
UACR	Urine albumin:creatinine ratio
UAER	Urine albumin excretion rate
UDE	Undetermined aetiology
UNK	Unknown aetiology
UPCR	Urine protein:creatinine ratio
USRDS	United States Renal Data System

VISP	Vitamin Intervention for Stroke Prevention (VISP) trial,
VLDL	Very low-density lipoprotein
vWF	Von Willebrand factor
WMH	White matter hyperintensities
WML	White matter lesion

PREFACE

From a global perspective, the burden of chronic kidney disease (CKD) is on the rise with a prevalence estimate of 9.1% (8.5-9.8) for all CKD stages.[1] It is well established that impaired kidney function is an independent risk factor, above and beyond traditional risk factors, for cardiovascular disease. Kidney function, as determined by the estimated glomerular filtration rate (eGFR), demonstrates an inverse step-wise relationship with incident stroke risk increasing by 3-, 4.1-, 5.4- and 7.1-fold for CKD stage 3-5 and dialysis compared to the general population.[2] Proteinuria itself is an under-recognized risk factor for stroke, independent of blood pressure and diabetes mellitus, and coupled with declines in kidney function, substantively elevates stroke risk.[3] Further, there is a dose-response with higher levels of proteinuria conferring an elevated risk (macro- vs microalbuminuria: adjusted relative risk [RR] 2.65, 95% confidence interval [CI] 2.25 to 3.14 vs RR 1.58, 95% CI 1.39 to 1.80).[4]

Both traditional and non-traditional mechanisms contribute to the pathophysiology of stroke risk in CKD.[5] Shared traditional risk factors or mechanisms include hypertension, diabetes, AF, carotid artery disease, heart failure,[6] obesity, and dyslipidaemia – all of which are frequently co-morbid with CKD and accentuated in its presence. Hypertension, in particular, is present in 67-92% of patients with CKD,[7] and is well-known to be the leading modifiable risk factor for stroke in the general population, regardless of age, gender or stroke subtype.[8] The impact of hypertension on brain health is examined in detail in Chapter 1 of this thesis including the role of the brain in blood pressure control, the impact of hypertension on cerebral physiology, and some of the clinical consequences including cerebrovascular disease, dementia, and sleep disorders.

Non-traditional CKD-related risk factors such as chronic inflammation, uremic toxins, reactive oxygen radicals, anaemia, and mineral-bone disorder (MBD) are proposed to contribute to stroke risk in CKD by triggering vascular injury and endothelial dysfunction.[5] Uraemia can cause protein carbamylation which has pro-atherosclerotic effects via enhanced dyslpidemia.[9] It can also impair platelet adhesiveness and platelet endothelial interaction, increasing the risk of haemorrhagic stroke.[10] Hyperphosphatemia, arising from CKD-related MBD, causes arterial medial calcification by inducing an osteogenic phenotype change of vascular smooth muscle cells.[11] The role and relative contribution of non-traditional risk factors above and beyond traditional risk factors for cerebrovascular disease in CKD is discussed in Chapter 2.

CKD has a substantial impact on stroke severity and functional outcomes.[12, 13] In an analysis of the Get With The Guidelines (GWTG)-Stroke cohort, advanced CKD was associated with greater risk of institutionalization.[13] The combination of CKD and stroke have considerable socioeconomic costs[14] and CKD portends both short- and long-term mortality post-stroke.[15, 16] A recent post hoc analysis of the SPS3 (Secondary Prevention of Small Subcortical Strokes) Trial reported a 50% increased risk of recurrent stroke in patients with CKD.[17] Prior stroke in patients with CKD appears to have long-term consequences with higher risks for death, reaching ESKD and suffering another non-fatal cardiovascular event.[18]

The downstream effects of this cerebrovascular disease burden are high rates of cognitive impairment and dementia that worsen with declining renal function.[19] In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, each 10mL/min/1.73 m^2 decrease in eGFR <60 mL/min/ 1.73m^2 was associated with an 11% increase in prevalence of cognitive dysfunction.[20] Both subclinical and symptomatic cerebrovascular disease is thought to play a key role in the aetiology of cognitive impairment in CKD as the cognitive phenotyping is typically consistent with vascular

cognitive impairment[21] and imaging studies in these cognitively impaired patients with renal disease tend to have a greater burden of white matter lesions and lacunar infarcts.[22]

A recent systematic review of major cardiovascular trials highlighted that CKD patients have been excluded from over one-third of clinical trials of stroke interventions and of these trials, only 3% subsequently reported baseline kidney function and none prespecified or reported subgroup analyses by baseline kidney function.[23] Therefore, the safety and efficacy of many acute treatments have not been demonstrated in the CKD population and similarly, much of the evidence that supports current preventative therapies in this group is observational or based on post hoc analyses. The available evidence for current stroke treatments in CKD is outlined in detail in Chapter 3.

Patients with CKD are therefore clearly a high-risk group with a high burden of both symptomatic and asymptomatic cerebrovascular disease. In Chapters 4-11 of this thesis, using a combination of systematic reviews and cohort study analyses, I will endeavour to contribute to the current understanding of the impact of CKD on stroke risk, mechanisms, and outcomes.

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Chapter 1 Blood pressure and the brain: the neurology of hypertension

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1.1 Introduction

The global prevalence of hypertension is estimated to be 1.13 billion. Hypertension is responsible for at least 45% of deaths due to heart disease and 51% of deaths due to stroke.[1] Given that stroke accounts for the largest share of the neurological burden of disease, hypertension is increasingly recognized as a global neurological problem. In this chapter, I will explore the role of the brain in blood pressure (BP) control, the impact of hypertension on cerebral physiology, and some of the clinical consequences including cerebrovascular disease, dementia, and sleep disorders.

1.2 Is hypertension a neurological disease?

The brain plays an important role in BP homeostasis (see Figure 1-1). The cardiovascular centre in the medulla oblongata is responsible for the regulation of cardiac output.[2] By mediating changes in heart rate, stroke volume or vascular tone via sympathetic or parasympathetic stimulation, it facilitates the short-term control of BP whereas renal regulation is more important for long-term control. The cardiovascular centre responds to signals from baroreceptors that detect stretch and from chemoreceptors that detect changes in oxygen/carbon dioxide concentrations.

The rostral ventrolateral medulla and upper cervical spinal cord regions play a key role in central BP control. For example, high cervical spinal cord injury is associated with very erratic BP and dysregulated neural network dynamics in caudal pressor regions have been implicated in the development of hypertension.[3]

The brainstem control centres may also receive modulation from higher brain regions, such as the cerebral cortex, hypothalamus, and limbic system. Lesion studies of epilepsy surgery patients have given us greater insight into cortical cardiovascular control. In a

study of five patients undergoing intraoperative insular stimulation prior to temporal lobectomy for seizure control, stimulation of the left insular cortex tended to produce bradycardia and depressor responses while stimulation of the right insular cortex resulted in tachycardia and pressor effects, suggesting a right-sided dominance for sympathetic cardiovascular effects.[4] Because the insular cortex is located in the region of the middle cerebral arteries (MCA), it tends to be particularly susceptible to cerebrovascular disease, and right MCA infarction may disinhibit insular function, resulting in increased sympathetic cardiovascular tone and the cardiac consequences of stroke, including sudden death.[5]

Further supporting evidence of the role that the brain may play in the genesis and maintenance of hypertension is that BP starts to decrease three years before overt development of dementia and continues to decline afterwards.[6] Subtle neurodegenerative lesions in these strategic locations of the brain that regulate BP may initiate this premorbid decline.

1.3 Pathophysiology of hypertension-induced brain injury

Between the ages 40–69 years, each difference of 20 mm Hg usual systolic BP (SBP) (or, approximately equivalently, 10 mm Hg usual diastolic BP [DBP]) is associated with more than a twofold difference in stroke mortality.[7] Hypertension also worsens stroke outcomes as patients with pre-existing hypertension tend to have smaller penumbras and larger infarctions compared to normotensive patients.[8]

Regulation of cerebral blood flow (CBF) in a normal brain is determined by a variety of intrinsic control mechanisms including myogenic/stretch, chemical, metabolic, and neurogenic control.[9] Autoregulation ensures that CBF remains relatively constant over a wide range of BP changes (Figure 1-2). Autoregulation is impaired when extremes of BP exceed the compensatory vasoconstrictive or vasodilatatory capacity. This usually occurs

if the mean arterial BP (MAP) falls below 50 mmHg or rises above 150 mmHg in a normotensive person. However, this plateau phase may be shifted to higher BP values during chronic hypertension to maintain the same level of CBF. The exact mechanisms by which hypertension affects cerebral autoregulation are not completely understood but they likely include a combination of myogenic tone alterations and inward vessel remodelling with an increase in wall-to-lumen ratio in response to tangential stress on the artery wall.[10]

A role for angiotensin II in cerebral artery remodelling is supported by studies using angiotensinogen knockout mice[11] with a reduction in wall thickness and wall-to-lumen ratio in aged spontaneously-hypertensive rats (SHR) treated with angiotensin-converting enzyme inhibitors (ACE-Is).[12] Angiotensin II and aldosterone have also been linked to the production of reactive oxygen species (ROS).[13] ROS are key mediators of cerebrovascular dysfunction in hypertension, as they contribute to vessel rarefaction (loss of arterioles and capillaries) and structural remodelling of cerebral blood vessels with resultant chronic hypoperfusion of the brain. Hypertension also enhances blood-brain-barrier (BBB) permeability via ROS and impairs its ability to regulate central nervous system homeostasis.[14] The increased BBB permeability associated with hypertension may also be attenuated by ACE inhibition.[15]

1.3.1 Arterial stiffness and hypertension

Arterial stiffness is related to age, heart rate, and MAP, and in hypertensive diabetic subjects, to diabetes mellitus duration and insulin treatment.[16] It is not fully understood whether stiffness is a cause or consequence of hypertension. Carotid artery stiffening has only been shown to be elevated independently of BP in young hypertensive patients and not in older ones.[17] Based on data from the Framingham Heart Study, higher aortic stiffness was associated with higher risk of incident hypertension and initial BP was not

independently associated with risk of progressive aortic stiffening.[18] However, hypertension may contribute to or worsen arterial stiffness as a result of increases in distension pressure, vascular thickness, and structural stiffening.[19]

1.3.2 Pulsatility

Trans Cranial Doppler (TCD) has been used to evaluate the haemodynamics of cerebral blood vessels including the MCA. The Pulsatility Index (PI) is calculated by subtracting the end diastolic velocity from the peak systolic velocity and then dividing by the time averaged (mean) velocity. In a study of patients with recent transient ischaemic attack (TIA) or minor stroke, MCA-PI was the strongest physiological correlate of leukoaraiosis, independent of age and other parameters.[20] MCA-PI also strongly associated with aortic pulsatility, DBP, and aortic stiffness, indicating that cerebral pulsatility is mainly dependent on aortic pulsatility and large artery stiffness rather than on distal small vessel resistance.

The Reykjavik study, a large community-based study of older adults, also found that higher pressure, flow pulsatility, and carotid-femoral pulse wave velocity parameters were associated with diffuse microvascular brain lesions, including subcortical infarcts and greater white matter hyperintensity volume, and reduced scores in multiple cognitive domains.[21] It would appear that significant proximal aortic stiffening in older people facilitates transmission of excessive pressure and flow pulsatility into the carotid circulation and that these abnormal pulsatile forces can cause flow-limiting small vessel damage and remodelling, cerebral ischaemia, and reduced cognitive reserve.

1.3.3 Prognostic value of blood pressure variability

BP is characterized by short-term fluctuations occurring within a 24-hour period (beat-to-beat, minute-to-minute, hour-to-hour, and day-to-night changes) and also by long-term fluctuations occurring over more-prolonged periods of time (days, weeks, months, seasons, and even years).[22] These variations may result from the interaction of environmental and behavioural factors as well as innate changes in cardiovascular regulatory mechanisms.

Based on analysis of data from multiple cohorts of patients with previous TIA or stroke and patients with hypertension, visit-to-visit clinic BP variability and 'episodic hypertension' was predictive of an increased risk of vascular events, including stroke, myocardial infarction, heart failure, independent of mean BP.[23] BP variability increases with age and is higher in females, diabetics, smokers, and those with peripheral vascular disease, atrial fibrillation, or previous TIA or stroke.[22]

In analyses of randomised trials of BP-lowering drugs, different drug-classes had similar effects on mean BP, but very different effects on visit-to-visit variability.[24] Calcium channel blockers and thiazide diuretics reduce variability whereas beta-blockers and ACE/ARB-based drugs increase variability. In an analysis of the Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm (ASCOT-BPLA), compared to the atenolol group, the amlodipine group had lower variability of BP from visit-to-visit, on 24-hour ambulatory BP monitor (ABPM) and on three measurements within a 10 minute clinic visit.[23] Treatment with amlodopine was associated with a lower risk of stroke and this association was almost completely attenuated after adjusting for within-individual BP variability. Similar drug class effects and correlations with outcome were found in the Medical Research Council (MRC) trial of BP-lowering in older hypertensive patients.[23]

Anti-hypertensive drugs should therefore be chosen to reduce variability as well as the mean level, particularly in the setting of stroke prevention. The deleterious impact of BP variability may potentially have implications for neurological conditions associated with dysautonomia such as Parkinson's disease, multiple system atrophy and spinal cord trauma. Spinal cord injury at or above T6 may be complicated by a phenomenon known as autonomic dysreflexia, whereby acute hypertension is generated by unmodulated sympathetic reflexes below the injury level that is often accompanied by baroreceptor-mediated bradycardia.[25] Typically, autonomic dysreflexia is precipitated by noxious visceral or somatic stimulation below the level of injury that activates a massive sympathetic reflex causing widespread vasoconstriction and hypertension. The most common triggers include bladder distension, constipation, pressure sores, fractures, or occult visceral disturbances. Hypertensive episodes should be managed by sitting the patient up, removing tight-fitting garments, searching for potential noxious stimuli, and of use of rapid-onset, short-duration antihypertensive agents such as labetalol or nitrates.

1.4 Small vessel disease

The term small vessel disease (SVD) encompasses all the pathological processes that affect the small vessels of the brain, including small arteries, arterioles, capillaries, and small veins.[26] There are several types but type 1 (arteriolosclerosis) is particularly related to hypertension and also affects the kidney and retina. Pathological type 1 SVDs are characterized by loss of smooth muscle cells from the tunica media, deposits of fibro-hyaline material, narrowing of the lumen, and thickening of the vessel wall. Postulated mechanisms of cerebral damage include chronic hypoperfusion, acute vessel occlusion, BBB damage, local subclinical inflammation, and oligodendrocyte apoptosis. The neuroimaging correlates of SVD are small deep infarcts, cerebral haemorrhages, microbleeds, white matter lesions (WML), dilated perivascular spaces, and cerebral atrophy (An example of SVD changes is shown in Figure 1-3). Clinical manifestations of

hypertension-related SVD include stroke, depression, gait disturbance, cognitive decline, and dementia. An acute small vessel occlusion is the cause of about a quarter of all acute ischaemic strokes.[27]

Hypertension is one of the most important risk factors for WML progression. Long-term hypertension results in medial lipohyalinosis, thickening of the vessel walls, and narrowing of the lumen of the arterioles and small perforating arteries that supply the deep white matter.[28] From the Rotterdam scan study[29], subcortical WML were associated with a 1.4 times greater risk of ischaemic stroke while periventricular WML were associated with two-to-three fold excess risk of ischaemic stroke. Deficiencies in gait and balance performance, and urinary urgency also correlate with the severity of these white matter changes.[30]

Frequently associated with WML, lacunar infarcts are defined as hypointense foci (<15 mm) on magnetic resonance imaging (MRI) T1-weighted sequences, typically seen in locations such as the basal ganglia, internal capsule, thalamus, and pons. The overall prevalence of silent brain infarcts (most of which are lacunar infarcts) is about 28% in the general population.[31] Apart from age, hypertension is the most widely accepted risk factor for silent brain infarcts.[32] Silent brain infarcts also increase the risk of future ischaemic and haemorrhagic stroke.[33]

Cerebral microbleeds (CMBs) are seen as small, homogeneous, round foci of low signal intensity on MRI gradient echo T2 sequences. The prevalence of CMBs is 5% in healthy adults, 34% in people with ischaemic stroke, and 60% in people with intracerebral haemorrhage (ICH).[34] Hypertension-associated cerebral microbleeds are typically located in basal ganglia, thalamus, brain stem, and cerebellum, while a lobar distribution is frequently linked to cerebral amyloid angiopathy (CAA).[35] The Modified Boston Criteria are helpful to distinguish CAA from SVD that is more likely to be related to hypertension.[36]

The presence of CAA should be suspected clinically in patients over the age of 55 who have multiple lobar hemorrhages in the absence of an obvious alternative cause. Lobar lacunes are also more likely to be associated with CAA, whereas deep lacunes are more frequent in hypertensive SVD.[37] It can be challenging to manage anti-platelet therapy in patients with CMBs as the relative risk of ICH increases as the CMB burden increases. However, a recent pooled analysis of individual patient-level data has shown that in those with recent TIA or ischaemic stroke, regardless of the CMB number, distribution, and presence of anti-coagulant/antiplatelet treatment, the absolute risk of ischaemic stroke is consistently substantially higher than that of ICH.[38] Similarly, in the REstart or STop Antithrombotics Randomised Trial (RESTART), restarting antiplatelet therapy in patients with prior ICH did not seem to increase recurrence, even in the presence of microbleeds.[39]

1.5 Cognitive impairment and dementia

Higher BP is associated with smaller total brain volume and reduced regional brain volumes in Alzheimer's disease (AD) brain regions.[40] While the mechanisms underlying these associations are unclear, some evidence suggests that cortical neuronal apoptosis related to subcortical vascular pathology and abnormalities in CBF underlie brain atrophy.[41]

In addition to its casual role, the presence of hypertension appears to augment the clinical significance of SVD. The progression of periventricular WML in hypertensive patients is related to cognitive impairment (especially executive function), whereas there is no association between baseline periventricular WML and cognitive dysfunction.[42] High home BP and multiple lacunar infarcts have been shown to be significantly independent predictors for the progression of both cognitive impairment and stroke recurrence.[43]

Hypertensive vasculopathy and CAA may also combine to cause cognitive decline with variable phenotype depending on the location and number of CMB.[44]

Cerebrovascular disease appears to interact with and augment neurodegenerative pathologies. At autopsy, hypertensive older adults have evidence of greater AD pathology in the brain, including neurofibrillary tangles and neuritic amyloid-beta (Aβ) plaques.[45] Positron emission tomography (PET) studies have shown that the extent of Aβ deposition in the brain is positively associated with higher BP.[46]

The duration of hypertension may be a stronger risk factor for cognitive dysfunction than age. Multiple studies have indicated that midlife hypertension and persistence of elevated blood pressure into late life are leading risk factors for late-life dementia.[47] In contrast, studies of late-life BP suggest that only the extremes of BP (SBP>180mmHg, DBP <70mmHg) increase the risk for dementia.[48]

1.6 Large artery disease

Hypertension is an important risk factor for atherosclerosis with a significant dose-response relationship. A 10 mmHg increase in BP increases the risk of complex aortic atherosclerosis (protruding atheroma, ulcerated plaques, mobiles debris) by about 40% and is highly predictive of ischaemic strokes.[49] Atherosclerotic lesions are observed at sites of turbulent flow, such as the carotid bifurcation and cause stroke by releasing fragments with artery-to-artery embolism, or by rupture and/or haemorrhage resulting in acute cerebrovascular occlusions (see an example in Figure 1-4*)*. Carotid atherosclerosis can progress silently with increasing SBP and hypertension is also a risk factor for large artery intracranial stenosis.[50]

Hypertensive patients are therefore high-risk for the development of large vessel atherothrombotic stroke which may make them candidates for thrombolytic therapy. However, special considerations apply to BP control in this setting. According to the 2018 American Stroke Association/American Heart Association (ASA/AHA) guidelines,[51] patients with elevated BP who are otherwise eligible for thrombolysis should have their BP carefully lowered to < 185/110 mmHg and kept <180/105 mmHg for the first 24 hours after treatment. This recommendation is based on observational studies that higher BPs are associated with greater risk of haemorrhage but the exact BP at which the risk of haemorrhage after thrombolysis increases is unknown. Treatment options include intravenous (IV) labetalol, nicardipine or clevidipine. In patients with BP ≥ 220/120 mmHg who do not receive thrombolysis or endovascular therapy, the benefit for initiating or reinitiating treatment of hypertension within the first 48-72 hours is uncertain. The guidelines suggest that it may be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.

Importantly, patients with extracranial or intracranial large artery stenoses may require a slower reduction in BP and to a less aggressive BP target, as some degree of BP elevation may be necessary to maintain cerebral perfusion to ischaemic brain regions.

1.7 Cerebral hypertensive emergencies

Patients with hypertensive emergencies present with significantly elevated BP (usually SBP ≥ 180 and/or DBP ≥120 mmHg) and signs or symptoms of acute target-organ damage. They can develop in patients with or without known pre-existing hypertension. Neurological emergencies account for approximately 30% of patients presenting with severe acute hypertension, and the majority of those who die.[52] Most are due to cerebral infarction with hypertensive encephalopathy and ICH also accounting for many. 20–40%

of cases may be attributable to secondary causes and most often consist of renal parenchymal disease and renal artery stenosis.[53]

Hypertensive encephalopathy is defined as an acute organic brain syndrome occurring as a result of failure of the upper limit of cerebral vascular autoregulation.[54] The degree of hypertension necessary to trigger encephalopathy can vary and the rate of BP increase appears to be more important than the absolute BP value with rapidly developing, fluctuating, or intermittent hypertension in younger patients being particularly high risk. It is also associated with poorly controlled hypertension and secondary causes such as immunosuppressive therapy, erythropoietin use, and thrombotic thrombocytopenic purpura.

Proposed mechanisms for hypertensive encephalopathy include brain endothelial dysfunction, BBB disruption with increased permeability, cerebral oedema, and microhaemorrhage formation.[52]

The diagnosis is a clinical one, relying on the presence of neurological symptoms in a patient who is severely hypertensive, supported by additional imaging.[55] Symptoms may include headache, visual disturbance, somnolence, lethargy, partial or generalised seizures. Focal neurological lesions are rare and should raise the suspicion of an acute stroke. If not adequately treated, hypertensive encephalopathy can progress to cerebral haemorrhage, coma, and death. Physical examination should focus on cardiovascular as well as neurological assessment. A proposed pathway of evaluation is outlined in Table 1-1. BP should be measured in both arms and in the lower limbs to detect pressure differences caused by aortic dissection.

Apart from acute BP lowering in stroke patients, there are no randomized controlled trials that have examined different treatment strategies for most hypertensive emergencies with

recommendations instead based on consensus opinion. Large reductions in BP (exceeding a >50% decrease in mean arterial pressure) have been associated with increased risk of ischaemic stroke and death.[56] The most recent recommendations of the European Society of Cardiology (ESC)[55] are summarized in Table 1-2. Because patients are often volume depleted as a result of pressure natriuresis, IV saline infusion can be used to correct precipitous BP falls if necessary. In patients with hypertensive encephalopathy, IV labetalol may be preferable as it leaves CBF relatively intact for a given BP reduction compared with nitroprusside.[57]

1.7.1 Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is a clinico-radiological disorder of heterogenous aetiologies characterised by the sudden onset of neurological symptoms associated with potentially reversible lesions on brain imaging.[58] There is substantial overlap between the clinical syndrome of hypertensive encephalopathy and PRES, and it is unclear whether they represent distinct entities. The pathogenesis of PRES appears to be related to cerebral autoregulatory dysfunction with subsequent dilation of cerebral arterioles and extravasation of plasma and red blood cells leading to vasogenic oedema. MRI typically shows symmetrical oedema primarily in the cortex and subcortical white matter of the parieto-occipital regions. The lower level of sympathetic innervation in the posterior cerebral arterial circulation may lead to less effective damping of BP oscillations, contributing to the susceptibility to hyperperfusion and vasogenic oedema during acute BP elevation.[59]

Hypertension from renal disease has been reported to be a significant cause of PRES accounting for over 25% of cases in one study of both paediatric and adult patients, implicating a role for volume expansion or uraemia.[58] There is also a clustering of other

well-known risk factors in this population including autoimmune disease, solid-organ transplantation, and immunosuppression.

The clinical syndrome, characterized by headache, altered consciousness, visual disturbances, and seizures, is identical to that of hypertensive encephalopathy. Unfortunately, there are no established and validated diagnostic criteria for PRES, and it is important to rule out other important differential diagnoses such as posterior circulation stroke and viral or autoimmune encephalitis. A diagnostic algorithm for PRES has been proposed that requires at least one acute neurological symptom (seizure, altered mental state, headache, visual disturbances), one or more risk factors (severe hypertension, renal failure, immunosuppressant drugs or chemotherapy, eclampsia, autoimmune disorder), and neuroimaging with bilateral vasogenic oedema, cytotoxic oedema with patterns of PRES or normal brain imaging; and no other alternative diagnosis.[60]

The four most common patterns of brain involvement are the parieto-occipital pattern with vasogenic oedema predominantly in the parieto-occipital lobes, the superior frontal sulcus pattern with oedema mainly along the anterior and media watershed region located in the deep superior frontal sulcus, the holohemispheric watershed pattern, with oedema located in both anterior and posterior, medial and lateral watershed zones, and the central pattern with vasogenic oedema located predominantly in the deep white matter, basal ganglia, thalami, brainstem, and pons.[61]

The mainstay of therapy is treatment of hypertension with gradual BP lowering as per the hypertensive emergency guidelines. The offending immunosuppressant or cytotoxic agent should also be stopped if possible. This may require co-ordinated discussion with other subspecialists (e.g. nephrologist, oncologist or rheumatologist) involved in the patient's care. With removal of the inciting factor and BP control, resolution of findings on neuroimaging within days to weeks is expected. However, occasionally in severe cases,

death may result from progressive cerebral oedema, from ICH, or as a complication of the underlying condition.[62] If another immunosuppressive agent is substituted or later started, patients must be monitored closely for recurrence. Avoidance of severe hypertension, fluid overload, or progressive injury in this setting will help mitigate risk.

1.7.2 Haemorrhagic stroke

ICH accounts for 10-15% of all strokes in high-income Western countries, but between 20-50% of those in low- to middle-income developing countries.[63] Hypertensive vasculopathy is the most common aetiology of spontaneous ICH.[64] Hypertensive haemorrhages typically occur in the territory of the small penetrating arteries that branch off major intracerebral arteries as they are directly exposed to the pressure of the much larger parent vessel.

The anatomical distribution of microbleeds varies with their aetiology, with hypertensive microbleeds arising in the deep subcortical (Figure 1-5) and infratentorial regions, and CAA-related microbleeds in more superficial lobar regions of the cerebral hemispheres. In a meta-analysis of 28 studies, hypertension was twice as common in patients with deep ICH as in those with lobar ICH.[65] Hypertension has also been shown to be a risk factor for ICH in the setting of other underlying aetiologies (e.g. CAA, antithrombotic-associated ICH).[66]

Patients with acute ICH should be managed in an intensive care unit or dedicated stroke unit. In the acute phase of ICH, patients may require intubation and mechanical ventilation, anticoagulation reversal, aggressive BP control, interventions for elevated intracranial pressure (ICP) and mass effect, treatment for seizures, ventriculostomy, or surgical haematoma evacuation.

Severe BP elevation may worsen ICH by representing a continued force for bleeding, causing haematoma expansion and potentially worse outcomes. A systematic review of observational studies showed that a SBP greater than 140–150 mmHg within 12 hours of ICH was associated with a more than doubling in the risk of subsequent death or dependency.[67] Treatment is a delicate balance as increased BP may be necessary to maintain cerebral perfusion in some patients with ICH, and lowering it might cause ischaemia and worsen neurological injury.

For patients with acute ICH who present with SBP between 150 and 220 mmHg, the European guidelines suggest, based on RCTs, that acute lowering of SBP to 140 mmHg is safe and may improve functional outcome.[68] For patients with acute ICH who present with SBP >220 mmHg, aggressive reduction of BP with IV antihypertensive therapy and frequent BP monitoring is required.

1.7.3 Eclampsia and pre-eclampsia

Pre-eclampsia refers to the new onset of hypertension and proteinuria, or hypertension and significant end-organ dysfunction with or without proteinuria after 20 weeks of gestation (or in the postpartum period) in a previously normotensive woman (Table 1-3*)*.[69] It occurs in 3-8% of all pregnancies.[70] The pathophysiology involves abnormal trophoblast invasion of spiral arteries during placentation leading to placental ischemia and release of pro-inflammatory and anti-angiogenic placental-derived soluble factors into the maternal circulation.[71]

Eclampsia refers to the development of generalised tonic-clonic seizures in a woman with preeclampsia in the absence of other neurologic conditions that could account for the seizure. In the United Kingdom (UK), recent figures show that 15.5% of direct maternal

deaths were due to the hypertensive disorders of pregnancy, and more than half of these women had eclampsia.[72]

Risk factors for pre-eclampisa include prior history, pre-gestational diabetes, chronic hypertension, systemic lupus erythematosus (SLE), antiphospholipid syndrome, body mass index (BMI) >30, chronic kidney disease (CKD), multi-foetal pregnancy, first pregnancy, family history, prior pregnancy complications associated with placental insufficiency, advanced maternal age, and use of assisted reproductive technology.

Patients may present with persistent and/or severe headache, visual abnormalities (scotomata, photophobia, diplopia, amaurosis fugax, or rarely transient blindness), upper abdominal or epigastric pain, altered mental status, dyspnoea, retrosternal chest pain. Headache, when present, is a feature of the severe end of the disease spectrum. The pain usually has a throbbing or pounding quality. It can be quite incapacitating and refractory to treatment.

Pre-eclampsia/eclampsia may also cause stroke due to disruption of cerebral autoregulation and alterations in BBB. It is responsible for 36% of pregnancy-associated stroke.[73] Most strokes in this setting are haemorrhagic and preceded by severe and fluctuating BP levels.

Eclamptic seizures develop in 1 in 400 women with pre-eclampsia without severe features and 1 in 50 women with pre-eclampsia with severe features. It has variously been proposed that eclamptic convulsions result from intracerebral haemorrhage, hypertensive encephalopathy, cerebral oedema, or vasospasm. Different mechanisms may be operating in different patients, with the compounding effects of cerebral hypoxia, IV fluid and drug administration, and varying degrees of hypertension.

For women with pre-eclampsia at ≥37 weeks of gestation, even in the absence of features of severe disease, delivery is recommended.[69] If features of severe disease are present, then delivery at ≥34 weeks of gestation after maternal stabilization is indicated. When there is no evidence of serious end-organ dysfunction, an expectant approach with close monitoring is reasonable to achieve further foetal maturity. However, at any gestational age, evidence of severe hypertension, serious maternal end-organ dysfunction, or non-reassuring foetal monitoring tests are generally an indication for urgent delivery.

BP should be measured daily at home in patients being managed expectantly with pre-eclampsia without severe features and at least twice weekly in the office. Antihypertensive therapy should be initiated if persistent SBP ≥150 mmHg or DBP ≥100 mmHg. IV labetalol or hydralazine are the recommended first-line agents for acute therapy of severe hypertension. Magnesium sulfate is the drug of choice for the prevention of eclampsia.[69]

Women with a history of pre-eclampsia have a two- to four-fold increased risk of cerebrovascular disease and stroke later in life[74] and thus preeclampsia has being identified as an important sex-specific risk factor for stroke by the ASA/AHA guidelines.[51] In the California Teachers Study, this excess stroke risk appeared to be reduced by long-term aspirin use.[75] The increased risk of cerebrovascular disease in women with prior pre-eclampsia is also associated with subjective cognitive complaints and increased white matter lesion burden on MRI, suggestive of a continued susceptibility to brain injury that persists after prgenancy.[76]

1.8 Sleep-disordered breathing and hypertension

Sleep-disordered breathing (SDB) is an umbrella term for a constellation of sleep-related breathing disorders including obstructive sleep apnoea (OSA), central sleep apnoea

(CSA), both with and without Cheyne-Stokes respiration, and sleep-related hypoventilation.

Typical symptoms of OSA including excessive daytime sleepiness, frequent awakening during sleep, snoring, reduced concentration and impaired memory. Risk factors include increasing age, male gender, obesity, craniofacial and upper airway soft tissue abnormalities, and certain medical conditions (pregnancy, heart or renal failure, prior Stroke/TIA, hypothyroidism).[77]

Approximately 50% of OSA patients in turn have hypertension.[78] OSA was associated with a 2.2 fold increased risk of incident ischaemic stroke in a meta-analysis of five studies (8435 participants).[79] In addition to hypertension, proposed mechanisms for cardiovascular risk include sympathetic activation, metabolic dysregulation, left atrial enlargement, endothelial dysfunction, systemic inflammation, and hypercoagulability. Treatment with continuous positive airway pressure (CPAP) therapy in OSA patients is associated with a lower risk of hypertension, stroke and cardiac events.[80]

SDB can also occur in patients post-stroke irrespective of type and is typically obstructive in nature. In a meta-analysis of studies inclusive of 2,343 ischaemic or haemorrhagic stroke and TIA patients, the frequency of SDB with an apnoea–hypopnoea index (AHI) > 5 was 72% and with an AHI > 20 was 38%.[81] Only 7% of the SDB was primarily central apnoea. Patients with unknown aetiology of stroke had a higher percentage of SDB than other aetiologies. According to the ASA/AHA guidelines, a sleep study should therefore be considered for patients with an ischaemic stroke or TIA on the basis of the very high prevalence of sleep apnoea in this population.[82] Although it is likely that patients are still under-investigated for SDH post-stroke, there is at least an increasing awareness that it is associated with worse outcomes including increase risk of recurrence, [83] and worse functional and cognitive function at 90 days poststroke.[84]

1.9 Conclusions

Neurologists frequently bear witness to the consequences of untreated and uncontrolled hypertension, not only in the form of acute stroke but also in memory or sleep clinics, and more rarely, in the emergency department with the encephalopathic patient. Early diagnosis of hypertension with regular monitoring and treatment is essential to promote and sustain brain health.

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TABLES

Table 1-1 Proposed diagnostic studies in patients with suspected hypertensive emergency

Proposed evaluation in patients with suspected hypertensive emergency
History-taking • Symptoms (headache, confusion, somnolence, visual disturbance, seizures, focal neurological deficits) • Pre-existing hypertension, current treatment, withdrawal, compliance, previous control • Over-the-counter medication use (e.g. NSAIDS, sympathomimetics) • Recent steroid exposure • Recreational drug use (e.g. cocaine) • Co-morbidities (e.g. kidney disease, renal artery stenosis) Diagnostic examination • BP both arms • Radio-femoral delay • Signs of heart failure (gallop rhythm, raised JVP, bibasal crepitations, peripheral oedema) • Detailed neurological exam • Fundoscopy (papilloedema, haemorrhages) • ECG (ischaemia, arrhythmias, left ventricular hypertrophy) • Urinalysis (proteinuria, haematuria) Further investigations as indicated • Troponin-T, CK, CK-MB • Peripheral blood smear (for assessment of schistocytes) • Chest X-ray (volume overload) • Transthoracic echocardiography (cardiac structure and function) • CT/MRI-brain (ICH) • CT-angiography of thorax and abdomen (acute aortic disease) • Renal ultrasound (postrenal obstruction, kidney size, asymmetry suggestive of renal artery stenosis) • Secondary hypertension work-up (Renal profile, 24-hour urine metanephrines/catecholamines or spot plasma metanephrines, plasma renin and aldosterone, 24-h urinary cortisol, TSH)

BP indicates blood pressure; CK, creatine kinase; CK-MB, creatine kinase myocardial band; CT, computed tomography; ECG, electrocardiogram; ICH, intracerebral haemorrhage; JVP, jugular venous pressure; MRI, magnetic resonance imaging; NSAIDs, non-steroid anti-inflammatory drugs; TSH, thyroid stimulating hormone.

Table 1-2 European Society of Cardiology (ESC)-recommended treatment strategies for hypertensive emergencies.[55]

Hypertensive Emergency	Timeline and Target BP	First-line Treatment	Alternative
Hypertensive encephalopathy	Immediate, MAP −20% to −25%	• Labetalol • Nicardipine	Nitroprusside
Acute ischaemic stroke and BP >220 mmHg systolic or >120 mmHg diastolic	1 h, MAP −15%	• Labetalol • Nicardipine	Nitroprusside
Acute ischaemic stroke with indication for thrombolytic therapy and BP >185 mmHg systolic or >110 mmHg diastolic	1 h, MAP −15%	• Labetalol • Nicardipine	Nitroprusside
Acute haemorrhagic stroke and systolic BP >180 mmHg	Immediate, systolic 130<BP <180 mmHg	• Labetalol • Nicardipine	Urapidil
Eclampsia and severe pre-eclampsia/HELLP	Immediate, systolic BP < 160 mmHg and diastolic BP <105 mmHg	• Labetalol or Nicardipine and Magnesium sulphate	

BP indicates blood pressure; HELLP, haemolysis, elevated liver enzymes, and low platelets; MAP, mean arterial pressure.

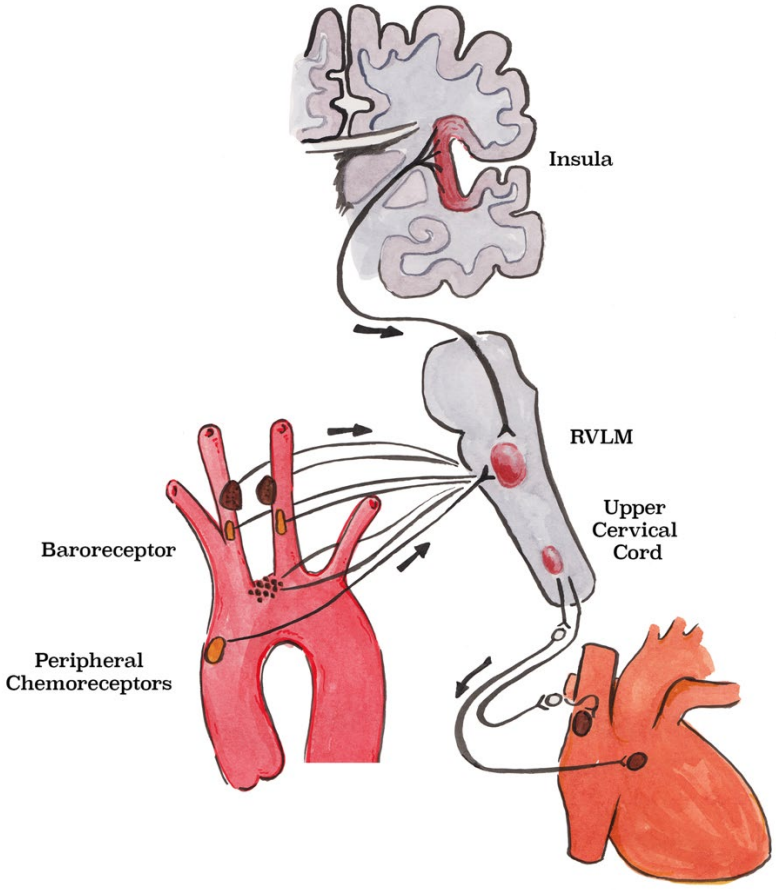
Table 1-3 American College of Obstetricians and Gynecologists (ACOG) Criteria for the diagnosis of pre-eclampsia.[69]

Systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on at least two occasions at least four hours apart after 20 weeks of gestation in a previously normotensive patient AND the new onset of one or more of the following:

- Proteinuria ≥0.3 g in a 24-hour urine specimen or protein/creatinine ratio ≥0.3 (mg/mg) (30 mg/mmol) in a random urine specimen or dipstick ≥2+ if a quantitative measurement is unavailable
- Platelet count <100,000/μL.
- Serum creatinine 97.2 μmol/L or doubling of the creatinine concentration in the absence of other renal disease
- Liver transaminases at least twice the upper limit of the normal concentrations for the local laboratory
- Pulmonary oedema
- Cerebral or visual symptoms (e.g., new-onset and persistent headaches not accounted for by alternative diagnoses and not responding to usual doses of analgesics; blurred vision, flashing lights or sparks, scotomata)

FIGURES

Figure 1-1 Short-term neural regulation of blood pressure: the rostral ventrolateral medulla and upper cervical spinal cord regions play a key role in central BP control



BP indicates blood pressure; RVLM, rostral ventrolateral medulla.

Figure 1-2 Cerebral autoregulation curve: in patients with chronic systemic hypertension, this range is "right-shifted", or in other words, the normal range of mean arterial pressure in which cerebral blood flow remains constant due to cerebral autoregulation is higher.

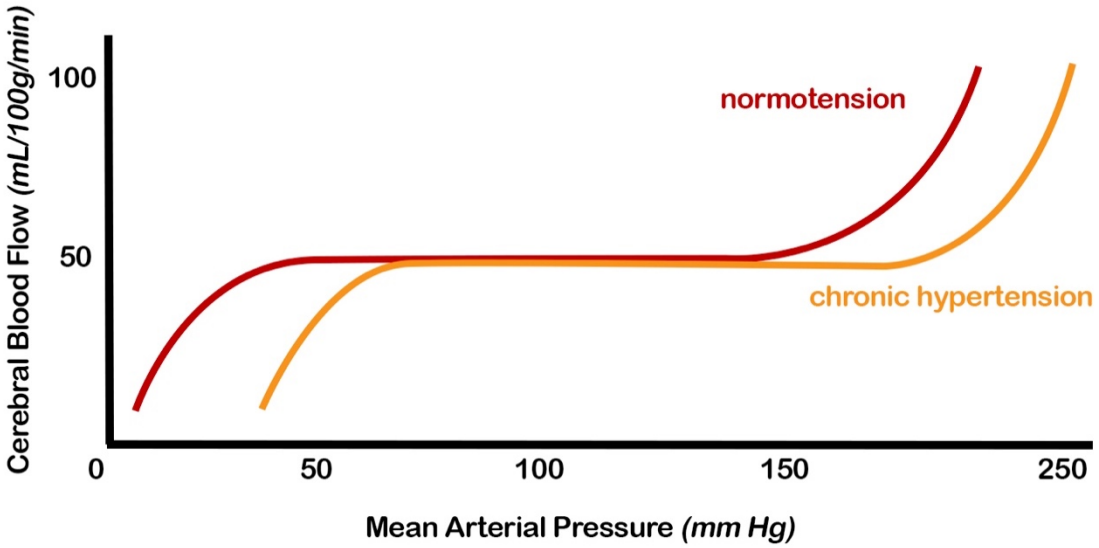


Figure 1-3 MRI brain of patient with severe small vessel disease showing (A) Area of restricted diffusion in the right parietal lobe, (B) Periventricular and deep subcortical white matter lesions, and (C) Multiple basal ganglia microbleeds.

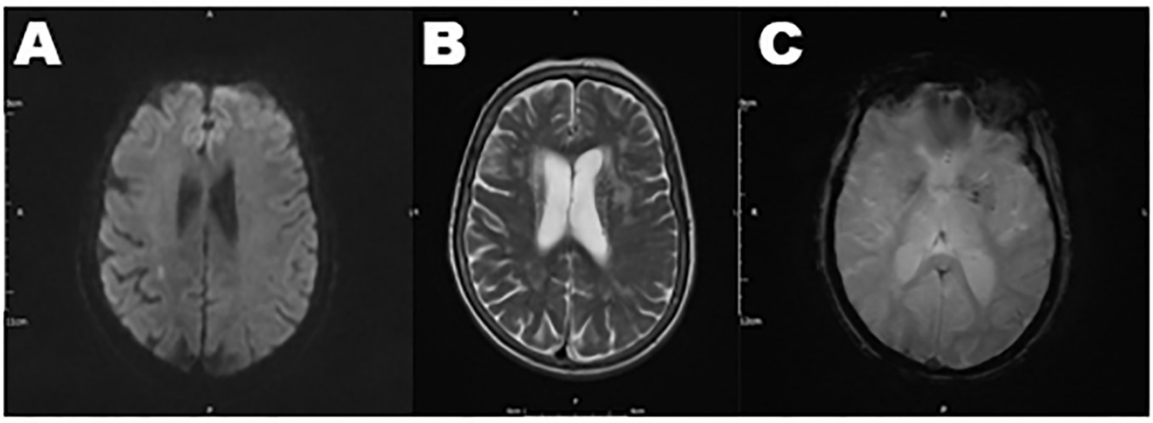


Figure 1-4 An MRI brain of a poorly controlled hypertensive patient showing (A) Area of restricted diffusion in the left parietal and temporal lobes, (B) Hyperintense T2 signal change, and (C) Severe left internal carotid artery stenosis.

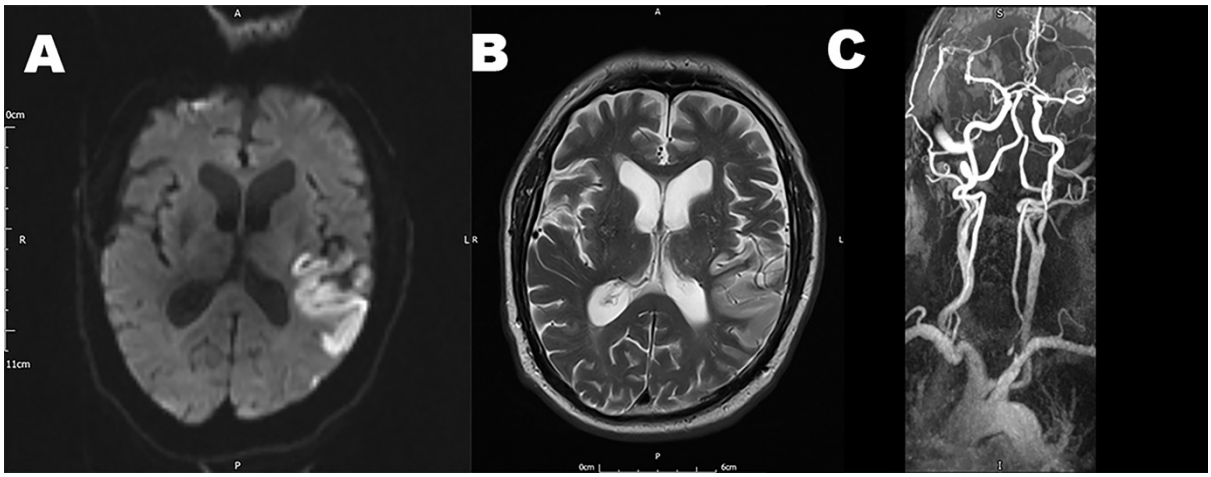
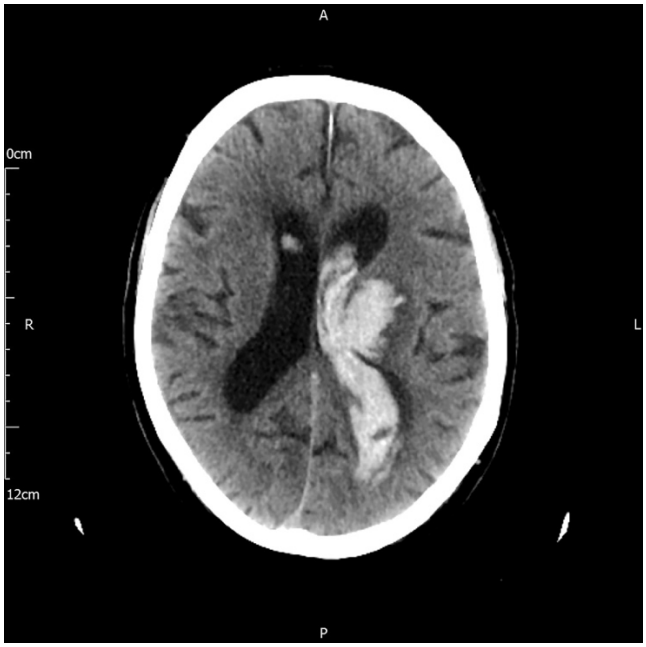


Figure 1-5 A classic example of a hypertensive haemorrhage centred on the left basal ganglia, extending into the left lateral ventricle, with modest dilatation of the ventricles in keeping with early hydrocephalus.



Chapter 2 Disentangling the multiple links between renal dysfunction and cerebrovascular disease

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2.1 Introduction

Chronic Kidney Disease (CKD) has a high global prevalence of between 8-16% of populations.[1] It is an increasingly important global health burden, mainly because it is an established risk factor for cardiovascular disease. Compared with the general population, cardiovascular diseases such as stroke are more frequent and severe, and often undertreated in people with CKD. Even in less advanced stages of CKD, cardiovascular mortality is still much higher than the incidence of kidney failure.[2] Despite improvements in cardiovascular disease survival in the general population, the rate of progress in patients with CKD, especially those who are dialysis-dependent, has lagged behind.[3] In particular, CKD contributes to the risk and severity of stroke, subclinical cerebrovascular abnormalities, and vascular dementia.[4]

In this chapter, I will explore the risk, severity, and mechanisms for stroke in CKD. Firstly, I will discuss the clinical associations between renal and cerebrovascular diseases including ischaemic stroke, small vessel disease (SVD), haemorrhagic stroke, vascular cognitive impairment and dementia. Secondly, I will highlight the mechanisms of susceptibility and injury, including shared pathophysiology and risk factors, secondary consequences of renal dysfunction, and diseases that can cause both CKD and stroke.

2.2 Associations between CKD and cerebrovascular disease

2.2.1 Stroke risk

There is conflicting evidence about whether CKD, specifically low estimated glomerular filtration rate (eGFR), is a risk factor for stroke independent of traditional cardiovascular risk factors. In a meta-analysis of 22634 people from four population-based longitudinal studies, individuals with an eGFR <60 mL/min/1·73 m^2 had an incidence rate of 10.3

stroke events per 1000 person years compared to 3.4 events per 1000 person years in those without; however, this apparent excess risk of stroke was no longer statistically significant after adjusting for conventional vascular risk factors (hazard ratio [HR] = 1·17, 95% confidence interval [CI]: 0·95–1·44; p=0.13).[5]

However, this attenuation of risk association may simply have been the result of inadequate statistical power as a larger meta-analysis of 33 prospective studies with 284,672 participants experiencing 7863 stroke events reported that patients with an eGFR <60 mL/min/1·73 m^2 had a 43% increased risk of stroke in a pooled multivariate-adjusted analysis that adjusted for conventional vascular risk factors[6], with increase in both ischaemic and haemorrhagic stroke.

Similarly in the most recent meta-analysis of 83 studies (over two million participants), there was an inverse linear relationship between eGFR and the risk of stroke, with risk of stroke increasing 7% for every 10ml/min/1.73m^2 decrease in GFR.[7] A 25 mg/mmol increase in albumin-creatinine ratio (ACR) was associated with a 10% increased risk of stroke. As in the previous meta-analysis, the results were consistent across stroke subtypes, by sex or in subgroup strata with higher prevalence of vascular risk factors (hypertension, diabetes, smoking), suggesting an independent relationship between CKD and stroke risk. Stroke risk increased linearly and additively with declining GFR and increasing albuminuria.

There is a particularly strong and independent association between proteinuria and stroke. In a meta-analysis of 10 cohort studies (140, 231 participants; 3,266 strokes), participants with proteinuria had a 71% greater risk of stroke compared with those without (95% CI: 1.39-2.10).[8] The risk of stroke remained high after adjustment for other cardiovascular risk factors but there may be residual confounders. There is a dose-response relationship with higher levels of albuminuria conferring greater stroke risk. In

another meta-analysis, patients with macroalbuminuria had a higher risk of incident stroke (Relative Risk [RR] = 2.65, 95% CI: 2.25-3.14) compared to those with microalbuminuria (RR=1.58, 95% CI: 1.39-1.80).[9]

2.2.2 Stroke outcomes

Patients with CKD tend to suffer more severe strokes with worse functional outcomes, morbidity and mortality. This was demonstrated by the Fukuoka Stroke Registry multi-center study of 3778 patients with first-ever ischaemic stroke.[10] On admission, the National Institutes of Health Stroke Scale score (NIHSS) of CKD patients was significantly higher than that of those without CKD. After adjustment for possible confounding factors, including age, baseline NIHSS, cardioembolic aetiology, blood pressure on admission, history of hypertension or diabetes, thrombolytic therapy, and infectious complications, patients with CKD had a 49% (95% CI: 17–89) greater risk of neurological deterioration during their hospitalization (defined as a ≥2-point increase in the NIHSS), 138% (95% CI: 61–257) greater risk of in-hospital mortality, and a 25% (95% CI: 5–48) greater risk of a Modified Rankin Scale (mRS) score of ≥2 at discharge.

Functional outcomes and stroke mortality are worse in advanced CKD. In a cohort study of 232,236 patients, patients with an eGFR < 15 ml/min/1.73m^2 (not on dialysis) had a 2.5 times greater risk of in-hospital mortality after acute ischaemic stroke when compared to those with normal renal function, even after adjusting for comorbidities and initial NIHSS.[11] This subgroup of patients also had much lower rates of functional independence and discharge to home.

2.2.3 Cerebral SVD and CKD

CKD is also highly prevalent in patients with SVD. In a single-centre study of acute ischaemic stroke survivors, patients with silent lacunar infarction, white matter lesions, or cerebral microbleeds had significantly lower eGFR than those without such lesions (60.4 ± 34.8 versus 87.5 ± 28.4 mL/min/1.73 m^2, 60.5 ± 37.1 versus 73.9 ± 33.3 mL/min/1.73 m^2, and 57.6 ± 33.3 versus 73.9 ± 32.9 mL/min/1.73 m^2, respectively).[12] Even with adjustment for age and vascular risk factors, the odds ratio for the presence of SVD and each subtype increased inversely with eGFR, with the highest prevalence in more advanced CKD. CKD patients with each SVD subtype had lower survival than those without such lesions and in particular, the presence of white matter lesions was an independent risk factor for cardiovascular death. Stratified meta-analyses consistently show significant associations with low eGFR across different SVD subtypes, with a nearly three-fold increased risk of silent cerebral infarctions and microbleeds.[13] From the Cilostazol versus Aspirin for Secondary Ischemic Stroke Prevention (CASISP) study,[14] decreased baseline eGFR, CKD progression and history of hypertension were independently associated with the presence of deep or infratentorial CMB at follow-up, but not lobar CMB.

There appears to be a particular pattern of white matter disease in CKD. In a Chinese group of 1632 patients, CKD was independently associated with the severity of periventricular hyperintensities (PVH) but not deep subcortical white matter in patients with acute ischaemic stroke.[15] The severity of white matter hyperintensities was evaluated using Fazekas scale. Each 30 ml/min/1.73 m^2 increase in eGFR was associated with 75 % of risk of the presence of degree 3 of PVH compared with degree 0. These findings highlight potentially differential pathological mechanisms underlying white matter changes in CKD.

The Oxford Vascular Study previously highlighted an age-specific association between SVD and CKD in 1080 patients with TIA and ischaemic stroke.[16] CKD was associated with total SVD score but only in a younger population (<60 years) (OR=3.97; 95% CI: 1.69-9.32; P=0.002). This association was diminished but remained after adjustment for age, sex, history of hypertension or diabetes, and premorbid average systolic blood pressure (OR=3.11; 95% CI: 1.21-7.98; P=0.018). The strong association between CKD and SVD at younger ages could indicate a shared genetic vulnerability to premature cardiovascular disease, accentuated by acquired risk factors such as hypertension.

Subclinical SVD has also been proposed to underlie the association between CKD and cognitive impairment, as patients with CKD have a tendency to develop a pattern of cognitive dysfunction with prominent deficits in executive function, attention, planning, and information processing speed which is typical for a vascular cognitive impairment profile.[17, 18]

While intensive glycemic control is known to reduce the incidence and progression of nephropathy in diabetic patients[19], it does not however appear to have any impact on cerebral SVD.[20]

2.2.4 Intracerebral haemorrhage in CKD

CKD is prevalent in nearly one third of patients presenting with intracerebral haemorrhage (ICH) and it is associated with much worse mortality when compared to those with normal renal function.[21] The high CKD prevalence rates in those with ICH may be attributable to their disproportionate burden of resistant hypertension, which affects one third of the patients with an eGFR <45 mL/min/1.73m^2 and nearly half of patients with a urinary ACR >300 mg/g.[22] In addition, people with CKD (particularly black patients) appear to have a greater presence and number of cerebral microbleeds, further increasing their

vulnerability.[23] Mineral and bone abnormalities may also play a role since higher serum phosphate levels in these patients have been associated with an increased ICH risk, whereas low levels have been associated with increased risk of cerebral infarction in haemodialysis patients.[24]

Compounding the problem, CKD was predictive of poorer outcomes in acute ICH in a secondary analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial 2 (INTERACT-2) although intensive blood pressure reduction appears to be equally effective in those with reduced eGFR compared to those with normal renal function.[25] Patients with more advanced kidney failure had the highest risk for death or major disability at 90 days (adjusted OR = 1.82; 95% CI: 1.28-2.61).

2.2.5 Vascular cognitive impairment and dementia

CKD is associated with a significant burden of cognitive impairment and dementia that increases with worsening renal function.[26] In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, each 10mL/min/1.73 m^2 decrease in eGFR <60 mL/min/ 1.73m^2 was associated with an 11% increase in prevalence of cognitive dysfunction.[27] In the haemodialysis population, the prevalence of cognitive impairment may be as high as 37% with lower rates described in patients on peritoneal dialysis.[18, 28]

Both vascular and neurodegenerative hypotheses for cognitive impairment in CKD have been proposed (Table 2-1).[29] Transcranial Doppler studies reveal a positive correlation between haemodynamic compromise and cognitive impairment—indicating that microvascular damage contributes to the cognitive changes observed in dementia.[30] The pattern of cognitive change with prominent impairment of executive function is also consistent with vascular cognitive impairment.[31]

Neurodegenerative mechanisms may also be augmented in CKD and this may be partly attributable to hypertension, often co-morbid in CKD patients, and thought to potentiate Alzheimer's pathology, lowering the threshold at which signs and symptoms manifest.[32] In addition, high uraemic toxin concentrations of guanidine compounds present in patients with CKD are suggested to be causal as they have been found in strategic brain regions for cognition, such as the thalamus, mammillary bodies, and cerebral cortex.[33]

The Sefuri study was a population-based cohort study of 560 non-demented elderly patients that explored the relationships between CKD, subclinical cerebrovascular abnormalities, and cognition, using structural equation modeling, and tests of global cognitive function (Mini-Mental State Examination) and executive function (modified Stroop test).[34] The results of this study indicate that CKD confers a risk of vascular cognitive impairment or executive dysfunction through mechanisms both dependent and independent of subclinical cerebral infarctions. This may be a consequence of longstanding untreated hypertension in early CKD as blood pressure is positively associated with risk of vascular dementia, independent of preceding TIA or stroke.[35]

Cognitive impairment is also associated with abnormal neuroimaging in dialysis patients.[36] In a study comparing 90 dialysis patients to 30 non-dialysis-dependent CKD patients, cognitive impairment was found to be significantly more severe in the dialysis group. Haemodialysis patients also had more severe white matter hyperintensities, sulcal and ventricular atrophy, and lacunar infarcts than other patients. In all groups, higher white matter grade, ventricular grade, and hippocampal atrophy were significantly associated with global cognitive impairment, with HRs of 1.80 (95% CI: 1.22-2.64), 1.67 (1.09-2.57), and 2.49 (1.07-5.77), respectively. Although haemodialysis patients had more severe neuroimaging features, dialysis modality showed no association with cognitive impairment,

Proteinuria shares similar associations with cognitive abnormalities. In the SPRINT-Memory and Cognition in Decreased Hypertension (SPRINT-MIND) substudy, patients with higher urine ACR had worse global cognitive function, executive function, memory, attention and abnormal white matter volume, such that each doubling of urine ACR had the same association with cognitive performance as being 7, 10, 6, and 14 months older, respectively.[37]

2.3 Stroke pathophysiology in renal disease: mechanisms of susceptibility and injury

There is a complex relationship between CKD and cerebrovascular disease with many potential contributing mechanisms (Figure 2-1). Some of their association may be attributable to their shared unique pathophysiology resulting in a shared susceptibility to 'traditional' vascular risk factors. Putative 'non-traditional' causal factors directly resulting from the sequelae of renal disease may also play a role. However, there is obviously overlap in this classification as many vascular risk factors are over-represented and accentuated in patients with renal disease. In addition, there are also some genetic or acquired conditions that may cause both CKD and stroke.

2.3.1 Key shared pathophysiology and risk factors

The kidney and brain share unique anatomical and physiological features that render them vulnerable to conventional cardiovascular risk factors such as hypertension, diabetes, and smoking. They are both characterized by high blood flow rates and are dependent on local autoregulation. However, the kidney consumes twice as much oxygen as the brain and requires 20% of cardiac output to deliver a high GFR of 100–125 ml/min.[38] I will now outline some of the proposed hypotheses that take into account the relationship between CKD and some of the major traditional vascular risk factors below.

Hypertension and the strain vessel hypothesis

As outlined in Chapter 1, Cardiovascular mortality doubles with every 20/10 mmHg increment in systolic/diastolic blood pressure in the general population.[39] It follows then that since hypertension occurs in 67-92% of patients with CKD,[40] that the adverse cardiovascular consequences, particularly stroke, should be expected in this group.

The ‘strain vessel hypothesis’, based on hypertensive vascular damage, has been suggested as a possible mechanism for the association between CKD and stroke (Figure 2-2) since both organs share similar, vulnerable microvascular vasoregulation.[41] Both the kidney and the brain are characterized by low vascular resistance systems, allowing continuous high-volume perfusion with autoregulation ensuring constant blood flow to maintain cerebral perfusion pressure in the brain and GFR in the kidney, irrespective of fluctuations in blood pressure.[42]

In the kidney, the juxtamedullary afferent arterioles are small, short vessels that have to maintain a strong vascular tone in order to provide a large pressure gradient in a short distance.[43] These types of vessels are therefore referred to as ‘strain vessels’ as they are most susceptible to hypertensive renal injury. Myogenic reflexes of the smooth muscle arterioles (along with tubuloglomerular feedback) mediate the kidney’s autoregulatory response. However, with the development of hypertension, hyaline arteriolosclerosis, replaces the arteriolar smooth muscle, impairing autoregulation with resultant transmission of increased systemic pressure into the glomerulus.[44] When these afferent arterioles are damaged by hypertension, they lose their autoregulatory ability, leading to glomerular hypertension and sclerosis, progressive loss of renal function, and worsening systemic hypertension.[45] Thus, microalbuminuria, the classic manifestation of glomerular injury, may be an early marker of vascular damage of renal strain vessels.

Strain vessels also exist in the central nervous system in the form of deep perforating arteries that arise directly from large high-pressure arteries, such as anterior, middle or posterior cerebral arteries, and then penetrate into the brain tissues.[46] Similar to the juxtamedullary afferent arterioles, these perforating arteries are also exposed to high pressures and therefore have to transmit large pressure gradients from their parent arteries to brain tissue capillaries. Analogous to renal arteriolosclerosis, lipohyalinosis may form in these strain vessels as a result of chronic hypertension and this is also a characteristic finding in lacunar stroke. Lipohyalinosis can impair cerebral autoregulation and decrease regional cerebral blood flow, resulting in higher rates of ischaemic or haemorrhagic stroke in the areas supplied by these subcortical perforating arteries.[47, 48]

Thus, there are ‘strain vessels’ common to the kidney and brain which seem to be preferentially damaged by hypertension, exacerbated by the haemodynamics of large arteries, particularly arterial stiffness.[42] Although blood flow and pressure are usually fairly constant in small vessels in the peripheral circulation, the strain vessels are exposed to pulsatile pressure and flow, and therefore more vulnerable to the deleterious effects of large artery stiffness. However, this proposed mechanism based on shared hypertensive injury would appear to be discordant with reported epidemiological observations that stroke risk in renal disease remains after adjustment for hypertension.[6, 7]

Injury of the juxtamedullary afferent arterioles (the ‘strain’ vessels) and glomeruli, of which microalbuminuria is a marker, may impair downstream medullary circulation through the vasa recta. As the medullary circulation has an important role in the mechanisms of pressure natriuresis to accomplish complete sodium balance (in response to salt ingestion),[49] microalbuminuria may also indicate a reduction in pressure natriuresis, and therefore, salt-sensitive hypertension. This was exemplified in stroke-prone spontaneously hypertensive rats fed a high-salt diet, where the subsequent development

of significant albuminuria was closely associated with vascular injuries in both the juxtamedullary nephrons and the cerebral perforating arteries.[50] In addition to hypertensive injury, salt itself may be directly toxic to the cerebral endothelium via the production of reactive oxygen species and inflammatory cytokines from the kidney cortex.[51, 52]

Albuminuria and generalized endothelial dysfunction (Steno hypothesis)

It has been suggested that albuminuria reflects not only localized renal damage, but that it is also a surrogate biomarker of more generalized endothelial dysfunction associated with increased risk of vascular events such as stroke. This is the basis of the Steno hypothesis.[53] This theory was originally derived from type 1 diabetic patients with albuminuria and proposes that albuminuria is a marker of widespread vascular damage, linking impaired vascular endothelial function with vascular leakage of albumin via glomerular barrier changes. The authors acknowledge that there is variation in the presence and level of albuminuria between diabetic patients with corresponding differences in their cardiovascular risk, and they hypothesize that variable genetic polymorphisms of enzymes involved in the metabolism of heparin sulphate proteoglycan may be responsible for these differences. In the Framingham Heart Study, low-grade urinary albumin excretion was also associated with increased cardiovascular risk and mortality in non-hypertensive, non-diabetic middle-aged individuals.[54] This increased risk was present even at levels well below the current diagnostic threshold for microalbuminuria. It would seem that individuals, regardless of diabetic status, are born with varying degrees of vascular function (within a physiological range) and thus excrete variable amount of albumin.[55] In keeping with this theory, high levels of albuminuria may already be found in young children[56] and may reflect a normal physiological variation in endothelial function that could be associated with differential cardiovascular and renal risk at later age.

Breakdown of blood brain and glomerular barriers

Blood brain barrier (BBB) dysfunction with altered permability plays an important role in both acute and chronic cerebrovascular disease.[57] It may contribute to SVD via the toxic leakage of fluid, proteins, and other plasma constituents into the perivascular tissues with consequent oedema, arteriolar stiffening, impaired cerebral vasodilatation and oxygenation.[58]

As the BBB and glomerular barrier in the kidney share similar structural features with tight junction complexes, they may also share similar susceptibility to mechanisms of disruption such as hypoperfusion, ischaemic and inflammatory stimuli.[57] The vascular endothelium, a specialized basement membrane, astrocyte foot processes, and pericytes form the BBB and this serves to restrict blood-borne substances from entering the brain.[59] In the kidney, the glomerular filtration barrier is comprised of the endothelial cell, glomerular basement membrane, and the podocyte. It determines the composition of the plasma ultrafiltrate by restricting the filtration of molecules primarily on the basis of size.[60]

Animal models of acute kidney injury (AKI) and CKD have demonstrated loss of BBB integrity in the setting of uraemia[61, 62] and clinical studies have shown CSF leakage of gadolinium in patients with CKD after contrast-enhanced brain MRI, consistent with impaired BBB function in these patients.[63] Although underlying mechanisms for this disruption are unclear, it may explain some of the association between CKD, particularly proteinuric disease, and SVD.

Atrial fibrillation

Patients with CKD are at high-risk of atrial fibrillation (AF). From the recently published Stockholm CREAtinine Measurements (SCREAM) project, 13,412 (12%) of adult CKD

patients followed for a mean of 3.9 years developed AF with increasing incidence rates with advancing kidney disease stages: from 29.4 to 46.3 per 1000 person-years in patients with eGFR=45–60 and <30 ml/min/1.73 m^2, respectively.[64] Even after adjustment for age, hypertension and cardiac disease, CKD patients with AF were still at much higher risk of stroke and death (HR=2.00; 95% CI: 1.88-2.14 and HR=1.76; 95% CI: 1.71-1.82, respectively).

To compound matters, rates of prescription of anti-coagulant drugs have been found to be suboptimal in people with CKD.[65] In addition, CKD has been associated with a left atrial (LA) thrombogenic milieu (defined as the presence of LA thrombus, dense spontaneous echo contrast, or LA appendage velocity ≤25cm/s) among patients with non-valvular AF undergoing transesophageal echocardiography.[66] The prevalence of thrombogenic milieu increased with declining eGFR (4%, 18%, 36%, and 86% for each group, p <0.001).

Therefore, it has been suggested to incorporate a measure of renal function in thromboembolic risk prediction scores including the CHA_2DS_2-VASc-R and CHA_2DS_2-VAK scores.[67, 68] Increasing CHA_2DS_2-VASc-R score correlated significantly with mortality, thromboembolism, and incident AF. In the CHA_2DS_2-VAK score, CKD was substituted for female sex, and there was enhanced discrimination of low to intermediate thromboembolic risk AF patients in a Korean population. However, the study was methodologically flawed there was no data on oral anticoagulant use at follow-up which would impact on event rates, no censoring of patients initiated on anticoagulation, and no time-in-therapeutic range monitoring. In general, use of risk prediction scores in this group has been problematic as CKD is associated with many co-morbidities (i.e. heart failure, diabetes mellitus and hypertension) which are already accounted for by the current CHA_2DS_2-VASc score, and model discrimination appears to worsen with increasing CKD severity.

Carotid artery disease

Although carotid artery disease is a common cause of large artery atherosclerotic stroke in the general population, it appears to have a particularly strong association with kidney disease. In a community-based cohort study of 3364 participants, kidney function was a strong predictor of greater carotid intima-media thickness, progression of subclinical atherosclerosis, and increased fatal and nonfatal vascular events independent of traditional and non-traditional cardiovascular risk factors in multivariable analysis (HR= 1.04; 95% CI: 1.02 to 1.23; P = 0.03 per 1-mL/min/1.73 m^2 decrease).[69] This suggests that the association between CKD and carotid disease cannot be entirely explained by their common risk factors (e.g. hypertension, dyslipidaemia).

It may be the case that the uraemic or pro-inflammatory milieu causes CKD to impact plaque composition, lesion stability and risk of rupture in patients with advanced carotid stenosis.[70] Comparison of plaque morphology was performed retrospectively on 41 CKD patients and 56 patients with normal renal function who were undergoing carotid endarterectomy (CEA). Patients with CKD had significantly higher percentage of total calcification (17% vs. 7%, $p<0.001$), unstable and ruptured plaques (83% vs. 52%, $p=0.001$ and 59% vs. 36%, $p=0.039$, respectively) compared with patients with normal renal function. The content of collagenous fibres was also significantly reduced in CKD patients. It would seem therefore that patients with CKD have a greater susceptibility to carotid disease and its cerebrovascular complications via enhanced calcification and lower collagenous content of their carotid plaques leading to plaque instability and rupture.

A similar German study analysed metabolic and chemical parameters along with plaque composition in relation to stroke events and renal function in patients with advanced

carotid disease.[71] Patients with CKD again had more end-stage calcification, unstable and ruptured lesions, and lower collagenous content of their plaques. Relevant serum markers of inflammation, vascular calcification, and vessel wall degradation were significantly elevated in CKD patients compared to those with normal renal function including enhanced levels of fibrinogen, parathyroid hormone, fetuin-A, and matrix metalloproteinase-7. In accordance with this, CKD patients experienced a higher prevalence of prior cerebrovascular events before carotid surgery (84.0% vs 26.2% $P < .001$).

Thus, CKD appears to not only be associated with progression of carotid atherosclerosis but also possibly an inflammatory milieu that creates a greater propensity for unstable plaques more likely to rupture and result in cerebrovascular embolic events.

Dyslipidaemia

CKD patients can develop a secondary form of dyslipidemia that is similar to the atherogenic dyslipidemia of insulin-resistant patients. In addition, progressive proteinuric kidney disease can interfere with lipoprotein transport causing an increase in serum triglycerides with elevated very-low-density lipoprotein (VLDL), small dense low-dense lipoprotein (LDL) particles, and reduced high-density lipoprotein (HDL) cholesterol which have significant atherogenic potential.[72] This is particularly prominent in patients with type 1 diabetes where serum total cholesterol, VLDL, LDL cholesterol, and triglycerides all rise with increasing albuminuria.[73]

One of the mechanisms of this ‘renal dyslipidaemia’ may be the increase in hepatic LDL synthesis that results from urinary protein loss causing upregulation of 3-hydroxy-3-methylglutaryl CoA reductase with consequent hypercholesterolemia.[74] Urinary losses of

the enzyme lecithin-cholesterol acyltransferase also lead to low HDL with a poor maturation of HDL-3 to cholesterol-rich HDL-2.[75]

Diabetes mellitus

The CKD prevalence in the diabetic population is much higher than that of the general population at 36%.[76] Approximately 20-30% of both type 1 and type diabetics will have moderately increased albuminuria.[77, 78]

In addition to the associated dyslipidaemia that may result from urinary protein loss, albuminuria also appears to correlate with certain inflammatory biomarkers indicative of endothelial dysfunction such as intercellular adhesion molecule-1. Increased levels of intercellular adhesion molecule-1 have in turn being associated with greater burden of WMH[79] and progression of urinary protein loss in diabetic nephropathy.[80]

In the Finnish Diabetic Nephropathy Study, 4,083 patients with type 1 diabetes were studied.[81] In an adjusted analysis, the presence of microalbuminuria was associated with an increased risk of stroke with a HR of 3.2 (95% CI: 1.9-5.6). The HRs for diabetic nephropathy patients with macroalbuminuria and end-stage kidney disease (ESKD) were 4.9 (2.9-8.2) and 7.5 (4.2-13.3) respectively, with similar risks for cerebral infarction, haemorrhage, and lacunar stroke. Progression of diabetic kidney disease was associated with worse stroke outcomes.[82]

2.3.2 Secondary consequences of renal dysfunction

Non-traditional CKD-related risk factors can promote cerebrovascular injury by triggering vascular injury and endothelial dysfunction. These factors include chronic inflammation, endothelial dysfunction, uremic toxins, anaemia, and mineral-bone disorder (Figure 2-1).[4] A recent meta-analysis of studies of risk factors in 27,465 CKD patients identified left

ventricular hypertrophy, serum albumin, phosphate, urate and haemoglobin as associated with cardiovascular events independent of traditional risk factors.[83]

Uraemia

High levels of urea may contribute directly to stroke risk in CKD patients via a reaction known as carbamylation whereby urea dissociates to form cyanate which in turn reacts irreversibly with proteins and free amino acids.[84] There is evidence that protein carbamylation may cause endothelial dysfunction as impaired acetylcholine-induced vasorelaxation has been described in mice with elevated urea levels. Carbamylated-oxidized LDL has also been shown to have pro-atherosclerotic effects on endothelial cells and macrophages, and to impair myocardial function.[85]

The gut microbiome is also emerging as a potential source of uraemic toxins.[86] Disruption of the intestinal epithelial barrier due to substantial reductions in the tight junction proteins claudin-1, occludin and ZO-1 in the colonic mucosa has been observed in animal models of CKD[87, 88] and this may cause gut bacterial toxins to translocate into the systemic circulation.[89] It is proposed that this translocation of gut toxins may promote systemic inflammation and adverse cardiovascular outcomes. In keeping with this theory, CKD patients have different gut microbiome patterns, and uraemic toxins such as p-cresol sulfate, indoxyl sulfate, and trimethylamine-N-oxide are derived from this colonic microbiome. Increased circulating levels of these uraemic solutes have been associated with a higher risk of cardiovascular morbidity and mortality in patients with ESKD.[90]

Platelet dysfunction in the setting of uraemia may also increase the risk of haemorrhagic stroke in patients with advanced CKD.[91] The mechanisms of impaired platelet function in CKD include impaired platelet adhesiveness and abnormal platelet endothelial interaction.

There is an imbalance between platelet agonists, ADP and serotonin, and its inhibitor, cAMP can result in an activation defect. There is also a deficiency in platelet cytoskeletal proteins that can impair motility and secretory function. Binding of both von Willebrand factor and fibrinogen to the platelet receptor glycoprotein, GPIIb/IIIa is reduced in uraemia, leading to impaired platelet adhesion to the subendothelium.

Oxidative stress and chronic inflammation

The kidney is one of the most important sources of antioxidant enzymes such as glutathione peroxidases and thus levels of pro-oxidants increase with in CKD. There was a significant elevation in malondialdehyde levels (a biomarker of oxidative stress) in CKD patients with cardiovascular disease compared to CKD patients without cardiovascular disease, suggesting that oxidative stress potentiates atherosclerosis in CKD.[92]

Iron therapy, frequently required to treat anaemia in advanced CKD, may also contribute to oxidative stress. Supersaturation of iron sequestration proteins such as transferrin and ferritin following the administration of intravenous iron may result in elevated levels of free iron with damaging oxidative properties.[93]

CKD accelerates atherosclerosis by enhancing inflammation and dyslipidaemia.[94] Inflammation is initiated by innate immune reactions to modified lipoproteins and is perpetuated by TH1 cells that react to autoantigens from the apolipoprotein B100 protein of LDL. In addition, patients with CKD have higher levels of haemostatic factors, particularly Factor VIII and von Willebrand factor, which may also augment their risk of thrombotic events.[95]

Dialysis-dependent patients are particularly prone to chronic inflammation resulting from exogenous factors such as dialysis membranes and central venous catheters, cellular factors such as oxidative stress, tissue factors such as hypoxia, salt and fluid overload, microbial factors such as immune dysfunction, and from the retention of uraemic toxins.[96]

Mineral and bone abnormalities

Hyperphosphataemia complicates advanced CKD as a result of reduced urinary phosphate excretion, ongoing intestinal phosphate absorption and the development of secondary hyperparathyroidism.[97] 'Adynamic' bone disease may also occur with low bone turnover, decreased bone buffering capacity, higher serum calcium and higher risk of extra-skeletal, particularly vascular, calcification. Arterial calcification and stiffness can lead to left ventricular hypertrophy and increase cardiovascular morbidity and mortality.[98]

Hyperphosphatemia contributes to arterial medial calcification by inducing an osteogenic phenotype change of vascular smooth muscle cells.[99] Phosphate balance is regulated by Fibroblast growth factor (FGF)-23, a protein secreted primarily by bone tissue. FGF-23 signaling requires the presence of the coreceptor Klotho.[100] CKD is characterized by Klotho deficiency and increased FGF23 levels which are independently associated with cardiovascular mortality.[101] In mouse models of Klotho deficiency, an accelerated ageing syndrome results with vascular calcification that resembles features of uraemia.[102]

From a systematic review of the risk of all-cause mortality, cardiovascular mortality and cardiovascular events associated with bone-mineral abnormalities in CKD, the findings suggest a higher mortality risk with phosphate, followed by calcium and parathyroid hormone (PTH).[103] There was however substantial discrepancy and heterogeneity in

results with better evidence to support this association in dialysis patients than in pre-dialysis.

Hyperuricemia

Under normal conditions, two thirds of the uric acid that is produced in the body is excreted in the urine and one third is removed by the biliary tree.[104] CKD impairs uric acid excretion and the problem is compounded by often co-existent diuretic use, insulin resistance, and increased renal vascular resistance.[105]

Results from a meta-analysis of 15 studies with 22,571 cases of stroke and 1,042,358 participants indicate that hyperuricemia may modestly increase the risks of both stroke incidence and mortality.[106] In an analysis of the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, baseline serum uric acid was significantly associated with cardiovascular complications. Losartan's reduction of uric acid accounted for 29% of its treatment effect on the primary composite end point (cardiovascular death, myocardial infarction, or stroke) compared with atenolol.[107]

However, some propose that hyperuricemia is simply a marker for other risk factors such as hypertension or diabetes, rather than a causal factor itself.[108] A discrepancy in line with this suggestion is that in acute ischaemic stroke patients, there is a 12% increase in the odds of good clinical outcome for each milligram per decilitre increase of serum uric acid[109] and the administration of uric acid therapy to patients post-thrombolysis has been associated with lower rates of early ischaemic worsening.[110] It has been postulated that uric acid may act as a neuroprotectant in the acute phase of stroke due to its efficient antioxidant capacity.

Genetic susceptibility

There is a large natural variation in nephron numbers between typical two-kidney individuals and there is an association between nephron number and blood pressure.[111] The hypothesis follows that any decrease in nephron number would be accompanied by glomerular hyperfiltration, glomerular enlargement, and culminate in systemic hypertension. An individual's total nephron composition combined with a susceptibility to confounding disease factors ("second hit") may lead to increased risk of cardiovascular and renal diseases later in life.[112]

Polygenic models derived using genome-wide association studies meta-analysis results for three kidney traits suggest that some of the risk association between CKD and cerebrovascular disease may be related to shared genetic factors. This association may vary depending on the ischaemic stroke subtypes, being particularly strong for large vessel stroke.[113] Polygenic scores correlating with higher eGFR using serum creatinine were associated with lower risk of large artery atherosclerosis. Their results also indicate possible polygenic overlap between microalbuminuria and SVD.

COL4A1 mutations have been identified as a monogenic cause of cerebral SVD and are associated with stroke (Table 2-2).[114, 115] Missense mutations of COL4A1 are also implicated in kidney disease such as HANAC syndrome (hereditary angiopathy, nephropathy, aneurysms and cramps).[116] COL4A1 mutations have also been recently reported as a potential novel cause of autosomal-dominant congenital anomalies of the kidney and urinary tract (CAKUT) in humans (the most common cause of kidney disease under the age of 30).[117]

APOE allelles ε2 and ε4 are independent risk factors for lobar ICH, consistent with their known associations with amyloid biology.[118] APOE allelic variation is also a risk factor for CKD progression that is independent of established CKD risk factors such as diabetes and hypertension.[119]

Dialysis-associated factors

Haemodialysis patients appear to have abnormal autonomic function as evident from their lower baroreflex sensitivity values compared with the general population[120] and thus are less able to tolerate acute blood pressure dips during ultrafiltration on dialysis.[121] Myocardial stunning can develop during haemodialysis resulting in or worsening any pre-existing cerebral hypoperfusion.[122] It has been hypothesized that such circulatory stress could produce cumulative ischaemic brain insults ("haemodialysis-induced brain injury").[123] In this UK study of a small group of haemodialysis patients (N=73), brain MRI and blood pressure variability were examined to assess the impact of haemodialysis on brain white matter microstructure. Increased intradialytic haemodynamic instability was associated with ischaemic white matter changes but patients who were treated with cooled dialysate (0.5 °C below core body temperature) showed improved haemodynamic tolerability and demonstrated complete protection against white matter changes at 1 year.

Blood pressure control is more complex in dialysis patients and several studies have linked lower blood pressure to adverse outcomes including increased mortality, especially in older or diabetic patients, or in those with pre-existing cardiac disease.[124] In a study of 58 haemodialysis patients, every 10 mmHg decrease in MAP was associated with a 3% increase in ischaemic events and the incidence of ischaemic events was particularly marked below an absolute MAP of 60 mmHg.[125] In 23.5% of haemodialysis sessions, patients developed some evidence of transient cerebral ischaemia (measured using near-

infrared spectroscopy with cerebral oxygen desaturation as a surrogate marker of ischaemia) and this intradialytic cerebral ischaemia correlated with decreased executive dysfunction one year later.

In a prospective observational cohort study of 97 maintenance haemodialysis patients, cerebral arterial mean flow velocity (MFV) was shown to decline significantly during dialysis and this decline correlated with intradialytic decline in cognitive function.[126] Decline in MFV also correlated significantly with progression of white matter burden and cerebrovascular disease at 12 months follow-up. Haemodialysis is thus capable of inducing transient 'cerebral stunning', analogous to myocardial stunning, and may be a major mechanism of cerebral injury and accelerated cognitive decline in ESKD.

CKD is associated with increased blood pressure variability partly due to arterial stiffness.[127] Greater blood pressure variability has been shown to increase the risk of ICH in CKD patients.[128] Arterial stiffness is a particularly prominent cardiovascular risk factor in haemodialysis patients. In a study examining the prognostic significance of ambulatory brachial BP, central BP, pulse wave velocity (PWV), and heart rate-adjusted augmentation index in this population, 48-hour PWV was the only vascular parameter independently associated with the primary composite cardiovascular outcome in a multivariate analysis (HR=1.579; 95% CI: 1.187-2.102).[129]

2.3.3 Diseases that cause both CKD and stroke

There are certain genetic and acquired conditions that can be complicated by both renal and cerebrovascular sequelae. These are outlined in Table 2-2. Anti-phospholipid syndrome (APS) is an important example, occurring either as a primary condition or in the setting of an underlying autoimmune condition such as systemic lupus erythematosus

(SLE), is an important example. It is defined as an autoimmune multisystem disorder characterized by arterial, venous, or small vessel thromboembolic events and/or pregnancy morbidity in the presence of persistent antiphospholipid antibodies.[130] Renal involvement, in the form of a thrombotic microangiopathy, may occur in as many as 25% of those with primary APS.[131] In patients with APS associated with SLE, renal disease may result from microthrombi and/or deposits of immune complexes.[132] An ischaemic stroke occurring in a young patient with renal dysfunction and no obvious risk factors for cerebrovascular disease is an important setting in which to suspect APS.

2.4 Conclusions and future research

Patients with CKD clearly represent a high-risk group for stroke that warrant clinical prioritization and further research focus. CKD has already been incorporated into risk prediction models such as QRISK3.[133] There is a need to better understand the epidemiology of cerebrovascular risk in renal disease and particularly to what extent prior hypertension may confound this relationship. There may be different mechanisms underlying the association between low GFR versus proteinuria with stroke. Better aetiological classification of stroke outcomes in future studies may help provide mechanistic insights. Preventing stroke in patients with CKD may also be a potential strategy to protect against important downstream consequences such as vascular cognitive impairment or dementia.

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TABLES

Table 2-1 Supporting evidence for the central role of cerebrovascular disease in cognitive impairment in CKD

Vascular Hypothesis	Neurodegenerative Hypothesis
• Frequently occurring traditional risk factors including hypertension, smoking, diabetes mellitus, and ageing. • Positive correlation between haemodynamic and cognitive impairment from TCD studies. • Transient 'cerebral stunning' in haemodialysis patients associated with accelerated cognitive decline. • High burden of subclinical SVD including silent lacunar infarcts, WMH, and CMBs. • Typical pattern of cognitive impairment with greater deficits in executive function and speed of information processing.	• Chronic hypertension, highly prevalent in CKD, is known to lower the pathologic threshold at which Alzheimer's disease features manifest. • Chronic cerebral inflammation due to CKD and associated vascular risk factor exposure can increase beta-amyloid production. • Higher beta-amyloid levels and impaired clearance in CKD, compounded by SVD and vascular inflammation.

CKD indicates chronic kidney disease; CMB, cerebral microbleeds; SVD, small vessel disease; TCD, transcranial doppler; WMH, white matter hyperintensities.

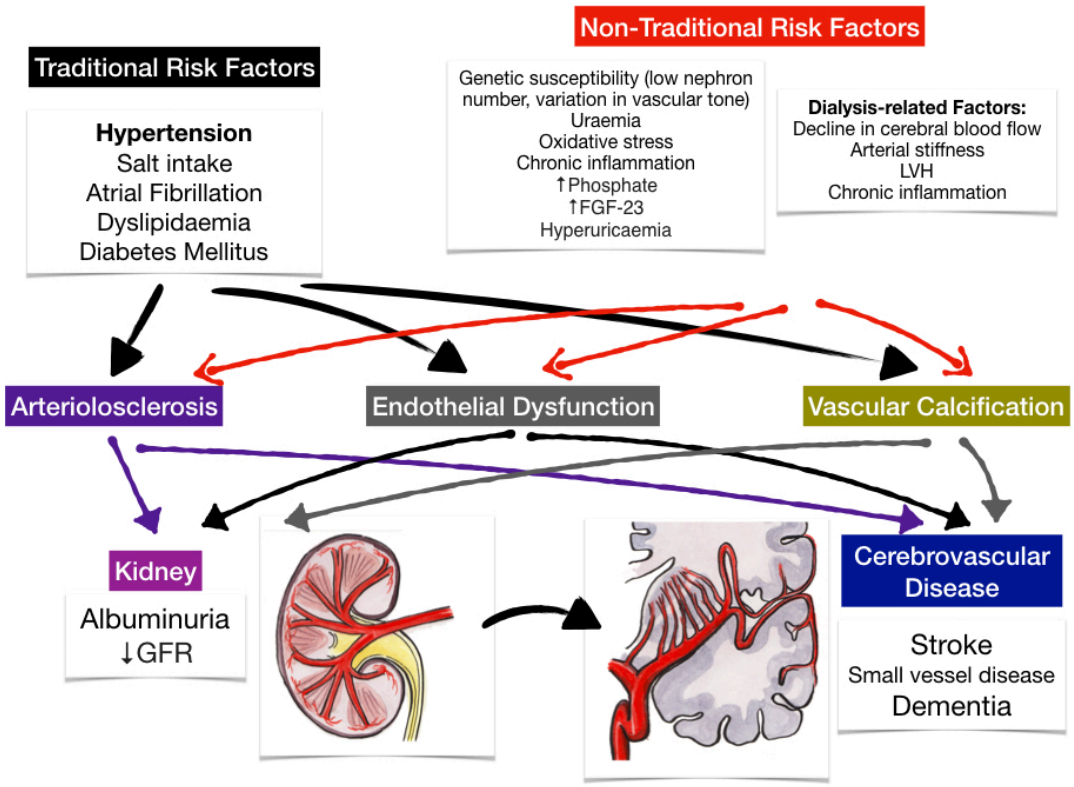
Table 2-2 Genetic or acquired conditions causing both kidney disease and stroke

Genetically determined diseases	Features
Polycystic kidney disease	Affects 1 in 400-1000 live births. Caused by mutations in PKD1 (Chr16) or PKD2 (Chr4). Renal manifestations include haematuria, hypertension, renal stones, urinary tract infections, and progressive renal failure. Subarachnoid haemorrhage may be a complication of ruptured cerebral aneurysms.
COL4A1/A2-related disorders	Autosomal dominant type 4 collagen disorders causing a broad spectrum of cerebrovascular disease including SVD, ischaemic or haemorrhagic stroke. Can also be associated with hereditary nephropathy manifest as proteinuria, haematuria, cysts, or CKD.
Fabry's disease	X-linked metabolic disorder caused by a deficiency of the enzyme α-galactosidase A. Renal manifestations such as proteinuria, isosthenuria, polyuria, and polydipsia or otherwise unexplained renal insufficiency are common. TIAs and strokes occur in 25% of patients with a mean age of onset of 40 years.
Sickle cell anaemia	Autosomal recessive haemoglobinopathy. Renal complications include hyposthenuria, proteinuria, papillary/renal infarcts, hypertension, and focal segmental glomerulosclerosis. Vaso-occlusive and haematological crises may result in ischaemic and haemorrhagic stroke respectively.
Mitochondrial disorders	Renal involvement (including CKD, nephrolithiasis, nephrotic syndrome, cysts, renal tubular acidosis, Bartter-like syndrome, Fanconi syndrome, focal segmental glomerulosclerosis, tubulointerstitial nephritis, and nephrocalcinosis) has been most frequently reported in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome (MELAS) and Kearns-Sayre syndrome.
Acquired conditions	
Connective tissue disorders	
Fibromuscular dysplasia	Noninflammatory, nonatherosclerotic disorder that leads to arterial stenosis, occlusion, aneurysm, dissection, and arterial tortuosity. The renal and internal carotid arteries are frequently involved.
Systemic lupus erythematosus	Up to 75% of patients may develop lupus nephritis which can present with proteinuria, haematuria, or progressive CKD. Stroke may result from secondary APS or vasculitis.
Vasculitides	
Polyarteritis nodosa	The kidneys are the most commonly affected organs, resulting in hypertension, CKD and renal infarctions. Rupture of renal arterial aneurysms can lead to perirenal hematomas. 5-10% can have CNS involvement with subarachnoid haemorrhage or focal infarction.
ANCA-associated	Characterized by focal necrotizing, crescentic, pauci-immune glomerulonephritis. Ischaemic infarction and intracranial hemorrhage, though rare, can be the initial presentation of ANCA-associated vasculitis and are always associated with significant morbidity
Haematological disorders	
Anti-phospholipid syndrome	Renal disease occurs in a minority of patients with primary disease. Antiphospholipid antibodies also frequently occur in patients with lupus in whom renal disease is more frequently caused by immune deposits. Can cause ischaemic stroke in young patients along with white matter abnormalities and cognitive defects.
Plasma cell dyscrasias	Waldenström's macroglobulinaemia is caused by a lymphoplasmacytic lymphoma in the bone marrow with an IgM monoclonal gammopathy in the blood. It can cause proteinuria, nephrotic syndrome and CKD, along with stroke due to a hyperviscosity syndrome.
Cryoglobulinemia	A type of vasculitis caused by the deposition of circulating cryoglobulins. Can be primary or associated with autoimmune diseases, malignancy, or infection (particularly hepatitis C). 20% may have glomerulonephritis at presentation. TIAs and stroke can rarely occur.
Infections	
Infective endocarditis	Renal complications include bacterial infection-related immune complex-mediated glomerulonephritis, renal infarction from septic emboli, and cortical necrosis. Symptomatic cerebrovascular complications occur in up to 35% of patients including embolic stroke or rupture of mycotic aneurysms.
HIV	CKD secondary to medication nephrotoxicity, HIV-associated nephropathy, and immune complex kidney diseases are well-described. Potential causes of ischaemic stroke in this setting include HIV-associated vasculopathy, opportunistic infections or neoplasia, cardio-embolism, and coagulopathy.
TB	Globally, tuberculosis is a common disease, with 8 to 10 million new cases annually and a rising incidence, particularly in regions with a high incidence of HIV infection. Classical renal tuberculous can present with symptoms suggestive of cystitis with a sterile pyuria. Other features include calyceal distortion, ureteric strictures, bladder fibrosis, and interstitial nephritis. It can also cause an intracranial vasculitis resulting in stroke.
Miscellaneous	
Cocaine use	Cocaine abuse can lead to kidney injury by rhabdomyolysis, vasculitis, infarction, thrombotic microangiopathy and accelerated-phase hypertension. It may also cause stroke through a number of mechanisms including vasospasm, cerebral vasculitis, enhanced platelet aggregation, cardioembolism, and hypertensive surges associated with altered cerebral autoregulation

ANCA indicates antineutrophil cytoplasmic antibodies; APS, antiphospholipid antibody syndrome; CKD, chronic kidney disease; CNS, central nervous system; HIV, human immunodeficiency virus; SVD, small vessel disease; TB, tuberculosis; TIA, transient ischaemic attack.

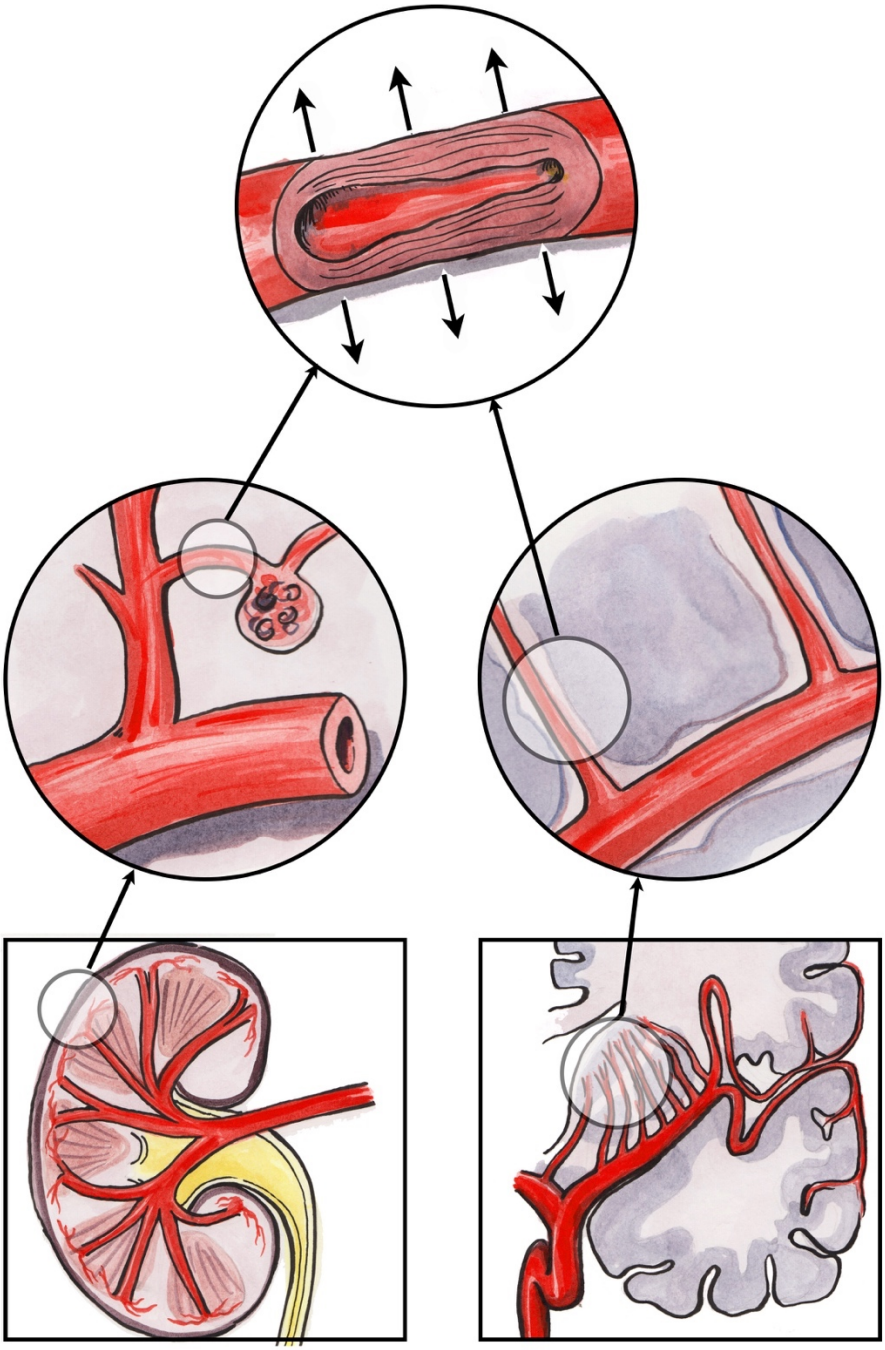
FIGURES

Figure 2-1 Mechanisms of susceptibility and injury in the shared pathway of renal and cerebrovascular diseases.



FGF-23 indicates fibroblast growth factor-23; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy.

Figure 2-2 The strain vessel hypothesis: juxtamedullary afferent arterioles and cerebral perforating arteries are both exposed to high pressure and have to maintain large pressure gradients, rendering them susceptible to hypertensive injury.



Chapter 3 Prevention and treatment of stroke in patients with chronic kidney disease: an overview of evidence and current guidelines

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3.1 Introduction

As outlined in Chapter 2, chronic kidney disease (CKD) is an increasing global health burden[1] and it is associated with an eight- to ten-fold increase in cardiovascular mortality, equivalent to that in patients with diabetes or prior myocardial infarction.[2, 3] Even mild reductions in glomerular filtration rate (GFR) are associated with substantial increases in cardiovascular risk.[4] There is a particularly strong association between CKD and cerebrovascular disease. Meta-analyses of cohort studies and trials indicate that reduced GFR increases the risk of stroke by about 40%[5] and that proteinuria increases the risk up to 70%[6] even after adjusting for traditional cardiovascular risk factors. These associations may be attributable to a clustering of shared vascular risk factors including hypertension, diabetes mellitus, and atrial fibrillation but 'non-traditional' risk factors such as anaemia, hyperuricemia, and mineral-bone disorders may also play a role (Figure 3-1).[7] CKD is a strong independent predictor of mortality and poor functional outcomes in patients with acute stroke[8] but there is a lack of clinical trials of prevention and treatment of stroke in the renal population with most of evidence to support use of existing treatments derived from post hoc subgroup analyses.[9, 10] In this chapter, I will explore this evidence for the primary and secondary prevention of stroke and acute treatment. Current recommendations for the primary and secondary prevention of stroke in CKD are outlined in Table 3-1.

3.2 Primary prevention of stroke in CKD

3.2.1 Antiplatelets

Among high-risk patients with prior vascular disease or some other predisposing condition, anti-platelet therapy has been associated with a 25% relative risk reduction in nonfatal stroke compared with placebo.[11] Despite their proven benefit in the general

population, major gaps exist in our understanding of the effects of antiplatelet drugs on thrombosis and bleeding in CKD, particularly in the setting of primary prevention.[12] Clinical practice guidelines are ambiguous about their use in CKD patients, because those with moderate-to-severe CKD were systematically excluded from most clinical trials evaluating efficacy and safety.[13]

In a large Cochrane review of 50 randomised controlled trials (RCTs) (27,139 participants) of antiplatelet treatment for the prevention of cardiovascular outcomes in CKD, antiplatelet agents reduced the risk of myocardial infarction (relative risk [RR]=0.87, 95% confidence interval [CI]: 0.76-0.99), but not all-cause mortality (RR=0.93, 0.8-1.06), cardiovascular mortality (RR=0.89, 0.70-1.12) or stroke (RR=1.00, 0.58-1.72).[14] Antiplatelet agents increased the risk of major (RR=1.33, 1.10- 1.65) and minor bleeding (RR=1.49, 1.12-1.97). Though few studies were available for direct comparison, meta-regression analysis indicated no differences in the relative benefit or harms of treatment by type of antiplatelet agent. They concluded that there is currently insufficient evidence to support the role of antiplatelets in primary prevention, particularly in those with early stages of CKD who do not have clinically-evident occlusive cardiovascular disease. However, data on the effects of antiplatelet agents in primary prevention in CKD were available only from a post-hoc subgroup analysis of a single study, the Hypertension Optimal Treatment (HOT) Trial.[15] In this trial, the relative risk of major cardiovascular events were reduced by 9% (95% CI: -9% to 24%), 15% (-17% to 39%), and 66% (33% to 83%) for patients with baseline eGFR of ≥60, 45 to 59, and <45mL/min/1.73m2 respectively (p for trend = 0.03) but there was no significant benefit for stroke as an individual endpoint and a near doubling in the risk of major bleeding (RR=2.04, 1.05 to 3.96).

In a more recent meta-analysis that focused only on primary prevention studies in CKD, three trials (HOT, Heart and Renal Protection [HARP], Japanese Primary Prevention of

Atherosclerosis with Aspirin for Diabetes [JPAD] trial) were identified providing data for 4468 participants.[16] Overall, there was no statistically significant reduction in major cardiovascular events including stroke (RR=0.92, 0.49-1.73, p = 0.79) but there was a high level of heterogeneity between studies (I^2 = 71% p = 0.06) and only one trial (HARP) was CKD-specific.

The Aspirin To Target Arterial events in Chronic Kidney Disease (ATTACK) trial (NCT03796156) is an open-label, multi-centre primary prevention trial currently underway that is investigating whether the addition of daily aspirin to usual care will reduce the risk of major vascular events in patients with CKD (excluding those who are stage 5 or dialysis-dependent). The investigators intend on recruiting 25, 210 patients and anticipate finishing in 2025.

In addition to the bleeding concerns, there are reports of high rates of antiplatelet hyporesponsiveness in patients with CKD that may partially explain poorer outcomes.[17] CKD and end-stage kidney disease (ESKD) are independent risk factors for clopidogrel resistance; 50-80% of patients with ESKD have high on-treatment residual platelet reactivity (resistance) when treated with clopidogrel[18]. However, it has been suggested that the high burden of co-morbidities in CKD patients may account for this observation rather than CKD itself.[19]

Overall, the current guideline recommendations to generally avoid primary prevention with aspirin in CKD patients are reasonable in the context of recent randomized trials (ASPirin in Reducing Events in the Elderly study [ASPREE], Aspirin to Reduce Risk of Initial Vascular Events [ARRIVE], A Study of Cardiovascular Events iN Diabetes [ASCEND])[20-22] that did not find aspirin to be beneficial for stroke prevention in other at-risk groups (Elderly, moderate cardiovascular risk, and diabetes, respectively) (Table 3-1).

3.2.2 Anticoagulants

Warfarin

Anti-coagulation has been shown to reduce the risk of stroke by approximately two thirds in the general population, and it is also associated with reduced stroke severity and lower mortality rates.[23, 24] However, there has been recognition of the underuse of oral anticoagulation for stroke prevention in atrial fibrillation (AF) in renal disease, and their use is often complicated by high bleeding rates and uncertain benefit.[25] In particular, there are concerns regarding warfarin use given the association with vascular calcification due to inhibition of the enzyme matrix gamma-carboxyglutamate Gla protein that scavenges calcium phosphate in tissues.[26]

Outcomes reported with warfarin use in both non-end stage CKD and dialysis-dependent patients with nonvalvular AF have been conflicting. In a Danish cohort study, warfarin treatment was associated with a significantly decreased risk of stroke or systemic thromboembolism overall (hazard ratio [HR]=0.76, 0.64 to 0.91; P=0.003) and among patients requiring renal-replacement therapy (HR=0.44, 0.26-0.74; p=0.002), but with a non-significantly decreased risk among patients with non–end-stage CKD (HR=0.84, 0.69-1.01).[27] There was an increasing risk of bleeding among all warfarin users with renal disease (HR=1.33, 1.16 to 1.53; P<0.001). This contrasts with the results of Swedish registry data (SWEDEHEART) that showed a lower risk of stroke in both groups without a higher risk of bleeding.[28] However, the latter cohort were a higher risk group post recent myocardial infarction and included fewer dialysis patients, limiting the generalizability of their results.

A systematic review and meta-analysis of 13 observational studies (>48,500 patients) evaluated the use of warfarin in patients with AF and CKD to assess the risks of ischaemic stroke/thromboembolism, major bleeding, and mortality.[29] In patients with AF and non-end-stage CKD, warfarin use was associated with a lower risk of ischaemic stroke/thromboembolism (HR=0.70, 0.54-0.89; P = 0.004) and mortality (HR=0.65, 0.59-0.72; P < 0.00001), but had no effect on major bleeding (HR=1.15; 0.88-1.49; P =0.31). Most of the patients included in this analysis had stage 3 or 4 CKD, and this group appears to derive benefit from warfarin with a reasonable safety profile.

However, in patients with AF and ESKD, warfarin had no apparent effect on the risks of stroke (HR=1.12, 0.69-1.82; P =0.65) and mortality (HR=0.96, 0.81-1.13; P = 0.60), but increased the risks of major bleeding (HR=1.30, 1.08-1.56; P = 0.005). A major limitation of this meta-analysis is that it is based solely on observational cohort studies as there are no RCTs that have addressed this question. However, the majority of studies do not support a protective effect for warfarin in ESKD patients with AF. Similarly in a 2017 meta-analysis of only dialysis patients, warfarin was not associated with a significant reduction in ischaemic stroke (HR=0.77, 0.55-1.07), but possibly increased intracranial haemorrhage (ICH) (HR=1.93, 0.93-4.00), although without effect on gastrointestinal bleeding (HR=1.19, 0.8-1.76), or all-cause mortality (HR=0.89, 0.72-1.11).[30]

These analyses suggest that warfarin is not associated with a clear benefit but likely increased harm among dialysis patients with AF. The risk estimates may be confounded though by variable time in the therapeutic range and by the inclusion of low-risk patients not expected to benefit from anticoagulation. However, in the absence of any definitive trial data to support its efficacy or safety, it is difficult to recommend routine use of warfarin in dialysis patients with AF. It should possibly be reserved for the highest-risk

patients in this group such as those with a history of prior stroke or a documented cardiac thrombus. The results of the ongoing trial (AVKDIAL [NCT02886962]) that will compare vitamin K antagonists with no anticoagulation in dialysis-dependent patients with AF are eagerly awaited.

Non-Vitamin K Anticoagulants

Novel oral anticoagulant agents (NOACs) appear to have at least an equivalent, if not more favourable, safety and efficacy profile when compared to vitamin K antagonists in CKD. Most of the randomized trials of NOACs (Randomized Evaluation of Long-Term Anticoagulation Therapy [RE-LY], Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation [ARISTOTLE], Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation [ROCKET-AF]) have included non-valvular AF patients with an eGFR ≥ 30 mL/min/1.73 m^2 and therefore, the best evidence for their use is in CKD patients with an eGFR of 30-59 ml/min/1.73m^2.[31-33] In a systematic review and meta-analysis of eight RCTs (9693 participants) that compared NOACs to vitamin K antagonists for stroke prevention in patients with CKD (defined as creatinine clearance of 30-50 ml/min), there was no significant difference in the risk of stroke and systemic thromboembolism (RR=0.64, 0.39 to 1.04), recurrent thromboembolism or thromboembolism-related death (RR=0.97, 0.43 to 2.15), or bleeding events (RR=0.89, 0.68 to 1.16) between NOACs versus vitamin K antagonists.[34] However, although not statistically significant, there was clearly a trend towards better thromboembolic and bleeding outcomes with NOAC use.

A recent, larger systematic review and meta-analysis of 11 trials (16, 787 participants) confirmed superiority of high-dose NOACs compared with vitamin K antagonists for stroke or systemic embolism (RR=0.79, 0.66 to 0.93), haemorrhagic stroke (RR=0.48, 0.30 to 0.76), and all-cause death (RR=0.88, 0.78 to 0.99).[35] However, the reduction in major bleeding (RR=0.80, 0.61 to 1.04) was non-significant when compared to warfarin. This meta-analysis was again limited only to patients with a creatinine clearance >25 mL/min as there was no data available for patients with more advanced CKD including dialysis-dependent ESKD.

However, NOAC use in dialysis patients appears promising from observational data so far. A comparison of warfarin versus apixaban in dialysis patients was performed using a retrospective cohort study of 25, 523 patients included in the United States Renal Data System (USRDS).[36] In matched cohorts, there was no difference in the risks of stroke/systemic embolism between apixaban and warfarin (HR=0.88, 0.69-1.12; P=0.29), but apixaban was associated with a significantly lower risk of major bleeding (HR=0.72, 0.59-0.87; P<0.001). In sensitivity analyses, standard-dose apixaban was superior to both reduced-dose apixaban and warfarin with lower risks of stroke/systemic embolism and death.

In the recently presented Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients With Atrial Fibrillation (RENAL-AF) (NCT02942407), patients were randomized to standard dose apixaban versus warfarin with a lower apixaban dose used in select patients.[37] Unfortunately, the trial was stopped early owing to lack of funding and therefore, only 154 out of a planned 760 patients were enrolled and the results were inconclusive. Ongoing trials include AXADIA (Compare Apixaban and Vitamin-K Antagonists in Patients With Atrial Fibrillation and End-Stage Kidney Disease; NCT02933697), in which chronic haemodialysis patients are randomized to receive either

apixaban 2.5 mg twice daily or the Vitamin-K antagonist, phenprocoumon,[38] and the Strategies for the Management of Atrial Fibrillation in Patients Receiving Dialysis (SAFE-D; NCT03987711) trial, comparing warfarin, apixaban, and no anticoagulation (with a planned enrolment of 150 patients). These trials are anticipated to be completed in July 2022 and December 2021, respectively. Their results may confirm those of the earlier observational USRDS data,[36] that standard dose apixaban is associated with a lower risk of stroke, major bleeding and mortality when compared with warfarin in haemodialysis patients. However, with low enrolment numbers planned (79 and 150 patients for AXADIA and SAFE-D, respectively), there are concerns that the trials will be under-powered to evaluate the important intracerebral haemorrhage risk and to demonstrate significant superiority over vitamin K antagonists for stroke outcomes.

NOACs are preferentially recommended as first-line therapy for those with a GFR 15-50 ml/min in the latest American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines and they have also recommended consideration of either warfarin or apixaban use in ESKD (Grade IIb; moderate quality evidence) (Table 3-1*)*.[39] NOAC use in those with a GFR of 30-50 ml/min is clearly appropriate in the context of the pooled trial data that indicate superiority to vitamin K antagonists. However, there is less evidence to support their use in those with a GFR < 30 ml/min, a group who are at higher risk of abrupt and unpredictable deterioration in their renal function, resulting in reduced NOAC clearance and increased risk of bleeding. Warfarin should potentially still be the drug of choice in these patients pending trial data confirming their safety in this vulnerable group. Low-dose apixaban is an alternative in patients who wish to avoid or who are intolerant of warfarin, provided that they are aware of the added risk. In the absence of wider clinical experience with NOAC use in dialysis patients and again trial evidence to support its safety, one would be reluctant to advocate for its unselect use at this time in this group, but would instead recommend careful

consideration in individual situations with involvement of a stroke physician and discussion of the potential benefits and risks with the patient.

3.2.3 Statins

Guidelines generally recommend lipid-lowering therapy for primary prevention in the general population if the patient has a 10% or greater 10-year risk of developing cardiovascular disease, or the patient is over 40 years old in the setting of diabetes mellitus.[40, 41] In patients with prior unstable angina or myocardial infarction, statin use appears to reduce the risk of subsequent stroke by 50%.[42] As a coronary artery disease equivalent in terms of vascular risk,[43] patients with CKD appear to derive similar benefits. A Cochrane review and meta-analysis of RCTs of statins in people with non-dialysis dependent CKD included a sensitivity analysis for major cardiovascular events, death, and myocardial infarction, limited to studies in which pre-existing cardiovascular disease was an exclusion criterion at baseline. They found significant treatment effects on major cardiovascular events (five studies, 13,766 participants: RR=0.60, 0.46 to 0.79; I^2 = 59%), death (three studies, 7215 participants: RR=0.63, 0.44 to 0.90; I^2 = 38%), and myocardial infarction (four studies, 7519 participants: RR=0.54, 0.38 to 0.76; I^2 = 0%) but uncertain effects on cardiovascular mortality (one study study, 304 participants: RR 0.37, 0.01 to 8.90).[44] Although data for treatment effects on cardiovascular events were predominantly derived from post hoc subgroup analyses, there wasn't substantial heterogeneity. The best evidence to support the role of statin therapy in primary prevention for CKD patients comes from the Study of Heart and Renal Protection (SHARP) trial, in which 9270 patients with CKD (including 6247 non-dialysis patients) and without pre-existing vascular disease were randomly assigned to placebo or to the combination of simvastatin 20 mg daily plus ezetimibe 10 mg daily. This confirmed benefit for CKD patients with a 25% reduction in non-haemorrhagic stroke in the treatment arm.[45]

The potential role of statins in the primary prevention of death and major cardiovascular events in CKD has been recognized in both US and international guidelines though there are some differences in terms of need for additional risk stratification (Table 3-1).[13, 40, 46] According to Kidney Disease Improving Global Outcomes (KDIGO),[46] CKD patients over 50 years of age are considered at sufficiently high risk of a cardiovascular event (≥10% risk of manifest coronary heart disease over 10 years) to justify statin therapy without the need to apply any formal risk calculation in individual patients.

However, the use of lipid-lowering therapy in patients on chronic dialysis is contentious. The relative decrease in cardiovascular risk by statins diminishes as renal function declines, even after allowing for the smaller reductions in low-density lipoprotein (LDL) cholesterol obtained in more advanced CKD.[47] The dialysis subgroup analysis of the SHARP (Study of Heart and Renal Protection) trial[45] and other randomized trials investigating statins for primary prevention of cardiovascular events in ESKD, such as the 4D study (Die Deutsche Diabetes Dialyse Studie)[48] and AURORA study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events),[49] found no benefit of statin therapy in the dialysis population. Suggested reasons for this “statin resistance” include the poor association of LDL cholesterol with cardiovascular risk in the this population, owing to the predomination of non-traditional risk factors (e.g., mineral and bone abnormalities, uraemia),[50] lipid abnormalities (e.g., lipoproteins rendered highly atherogenic by oxidation or carbamylation), intracellular cholesterol synthesis activated by inflammatory stress,[51] and its pro-calcifying effects.[52] Both the 2014 KDIGO Lipid Work Group and 2018 AHA/ACC guidelines suggest that statins should not be initiated in patients on dialysis, but that statins could be continued in patients already receiving them at the time of dialysis initiation (Table 3-1).[40, 53]

In practice, given the excess baseline cardiovascular risk in this group, it is recommended to have a low threshold for starting statin therapy for the purpose of primary prevention for patients with non-dialysis CKD over the age of 40, particularly in the presence of an unfavourable lipid profile or an additional risk factor (e.g. hypertension, smoking).

3.2.4 Anti-hypertensive agents

A collaborative prospective meta-analysis of randomised trials of blood pressure (BP) lowering versus control and major cardiovascular events in people with and without CKD (26 trials -152, 290 participants), included 30, 295 individuals with an eGFR <60 mL/min/1.73 m^2.[54] Compared with placebo, BP lowering regimens reduced the risk of major cardiovascular events by about 16% per 5 mm Hg reduction in systolic blood pressure (SBP) in individuals with (HR=0.83, 0.76-0.90) and without reduced eGFR (0.83, 0.79-0.88). Nor was there any evidence that the effects of different drug classes on major cardiovascular events varied between patients with different eGFR (all P>0.60 for homogeneity). The major limitation of this meta-analysis is that most participants with CKD were in stage 3a (45-60 mL/min/m^2), and few participants (0.4%) had eGFR ≤30 mL/min/1.73 m^2, limiting the generalizability of these results to people with more advanced CKD.

The ideal BP target for cardiovascular protection in the CKD population remains elusive. There has never been a dedicated BP RCT in the renal population for the prevention of stroke and most of the existing evidence has been derived from post hoc or subgroup analysis (see Table 3-2*)*. Earlier studies (Modification of diet in renal disease [MDRD], African American Study of Kidney Disease and Hypertension [AASK])[55, 56] failed to demonstrate benefits of intensive BP lowering (Target mean arterial pressure [MAP] ≤ 92 vs ≤ 107 mmHg) in this group for reducing cardiovascular morbidity and mortality but were

inadequately powered for these outcomes and had short follow-up in their trial phases. From a recent prespecified Systolic Blood Pressure Intervention Trial (SPRINT) subgroup analysis, among patients with CKD and hypertension without diabetes, targeting an SBP<120 mm Hg compared with <140 mm Hg reduced rates of major cardiovascular events and all-cause death without evidence of effect modifications by CKD or deleterious effect on the main kidney outcome.[57] However, the trial excluded people with diabetes, proteinuria >1000 mg/g and prior stroke, and the risk of stroke was similar in both treatment groups (HR=0.99, 0.57–1.70; P = 0.96) though the trial was stopped early (median follow-up was 3.3 years). The results of SPRINT are weighted heavily in the recent US blood pressure guidelines[58] while international guidelines have traditionally been more conservative with their BP targets, risk stratifying on the basis of proteinuria or diabetes (Table 3-1).[13, 46]

A post hoc analysis of the China Stroke Primary Prevention Trial (CSPPT),[59] evaluated the impact of actual achieved blood pressure on first stroke among hypertensive patients with mild-to-moderate CKD. 3230 hypertensive patients with eGFR 30–60 mL/min/1.73 m^2 and/or proteinuria were included. Compared with participants with a time-averaged on-treatment SBP of 135 to ≤140 mmHg, the incidence of total first stroke (1.7% vs 3.3%; HR=0.51, 0.26–0.99) and ischaemic stroke (1.3% versus 2.8%; HR=0.46, 0.22–0.98) diminished significantly in patients with a time-averaged SBP of ≤135 mmHg. A time-averaged diastolic blood pressure (DBP) of ≤80 mmHg, compared with a time-averaged DBP level of 80 to ≤90 mmHg, was significantly associated with a lower risk of haemorrhagic stroke (0.2% versus 0.9%; HR=0.18, 0.04–0.80). Therefore, their findings are supportive of more intensive BP control for cerebrovascular protection in CKD patients as per the SPRINT trial.

However, intensive blood pressure control may be deleterious for dialysis patients. A retrospective cohort study of 113, 255 haemodialysis patients over a 5-year period found U-shaped associations between change in systolic blood pressure, all-cause mortality and cardiovascular mortality.[60] Post-dialytic drops in SBP of up to 30 were associated with greater survival, but larger decreases of SBP and any increase in SBP (over 0 mm Hg) were related to increased mortality. Approximately 7% of participants had pre-existing cerebrovascular disease.

The method of measurement of BP may also be important in prognostication. Most clinical management of hypertension is based on office BP readings in patients with CKD and pre- and post-dialysis BP readings obtained in the dialysis clinic in patients with ESKD. Compared with ambulatory BP readings, home BP monitoring in patients with CKD has been shown to be superior to office BP monitoring in diagnosing hypertension and reducing incidences of white-coat hypertension and masked hypertension.[61] Home BP readings, when compared to pre- or post-dialysis BP readings, have been shown to correlate more closely with ambulatory BP readings in dialysis patients. Out-of-office BP readings in patients with CKD are associated strongly with target-organ damage.

3.2.5 Dialysis and related interventions

There is a higher incidence of stroke in ESKD than in earlier stages of CKD and the rate is particularly high during the period of dialysis initiation.[62] There may be mechanisms intrinsic to dialysis (such as haemodynamic instability or circulatory stress) that independently increase stroke risk and in keeping with this hypothesis, the long interdialytic gap has been associated with greater stroke event rates.[63] The addition of convection therapy to dialysis in haemodiafiltration was associated with a significant 61% risk reduction in stroke in a multicentre, open-label, RCT of 906 chronic haemodialysis

patients.[64] This may be linked to higher removal of inflammatory mediators or middle-sized molecules that may influence endothelial function, or improved haemodynamic stability. More frequent haemodialysis also appears to be associated with improved surrogate markers or mediators of stroke risk such as hypertension control and left ventricular mass.[65]

Dialysate cooling may be novel approach to prevent ischaemic brain injury, mediated through its positive effects on haemodynamic stability and its reduction of circulatory stress. Higher mean arterial pressure (MAP) extrema points frequencies (indicative of greater haemodynamic instability) have been shown to correlate with brain white matter damage and worse neurocognitive test scores in haemodialysis patients.[66] In a study of dialysate cooling, 73 haemodialysis patients were randomized to dialyze with a dialysate temperature of either 37°C or 0.5°C below the core body temperature.[67] In the group randomized to a lower dialysate temperature, the MAP extrema points frequencies and brain white matter microstructure parameters including fractional anisotropy, axial diffusivity, and radial diffusivity did not vary significantly at 12 months, indicating that dialysate cooling may be protective against chronic haemodialysis-induced brain injury. However, no studies to date have examined incident stroke as an outcome for patients treated with cooled dialysate.

While anaemia (defined as haemoglobin levels of <130 g/L for men or <120 g/L for women) has been associated with increased stroke risk in CKD patients,[68] higher haemoglobin targets achieved with erythropoietin-stimulating agents (ESA) have been linked to increased stroke risk in more advanced stages. In the TREAT study (4048 patients with diabetes, CKD and moderate anaemia) using Aranesp (darbapoetin alpha), a doubling of stroke (both ischaemic and haemorrhagic) risk was observed in the higher (130 g/L) compared with the lower (90 g/L) targeted group.[69] It is for this reason that most guidelines recommend using ESA therapy to generally target haemoglobin values ranging

between 100 and 120 g/L in CKD patients, individualizing the value in this target range according to the possible comorbidities of the patients.[70]

3.3 Acute stroke treatments in CKD

3.3.1 Thrombolysis

Intravenous thrombolysis (IVT) has become the standard of care for many patients admitted with acute ischaemic stroke with better functional outcomes and survival.[71] However, its use may be more problematic in CKD patients given their greater bleeding diasthesis[72] and pre-existing cerebrovascular disease burden.[73] Some studies have reported an increased bleeding risk in IVT-treated patients with advanced CKD compared with patients with normal renal function. In a pooled analysis of seven observational studies (7168 patients), IVT-treated patients with CKD had a higher risk of symptomatic ICH and mortality [pooled odds ratio [OR]=1.56, 1.05-2.33 and 1.70, 1.03-2.81, respectively].[74] Patients with CKD also had increased risk of poor functional outcomes at three months. The interpretation of this meta-analysis is limited however by heterogeneity, lack of detail on the effect of IVT dose or time window, and lack of comparative data on outcomes in patients not given IVT.

Post-hoc analysis of the Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) trial confirmed an association between CKD and increased mortality but not disability or symptomatic ICH.[75] Compared with patients with normal renal function (>90 mL/min/1.73 m^2), those with an eGFR <30 mL/min/1.73 m^2 had increased mortality (adjusted OR=2.07, 0.89-4.82; P=0.04 for trend); every 10 mL/min/1.73 m^2 lower eGFR was associated with an adjusted 9% increased odds of death in IVT-treated patients; a risk which did not seem to vary between low-dose and

standard-dose alteplase. However, the excess mortality in patients with advanced CKD did not seemed to be explained by a greater number of ICH but was mostly attributable to higher rates of pneumonia, sepsis, or other non-vascular aetiologies, consistent with earlier reports of important confounders in the relationship between IVT-treated CKD patients and stroke outcomes.[76]

Stroke guidelines continue to recommend IVT use in otherwise-eligible CKD patients without restriction including in patients with ESKD on haemodialysis in the presence of a normal activated partial thromboplastin time (aPTT).[77] This seems reasonable in the context of the considerable benefits derived from treatment in the general population (2.5 fold increased odds of a good outcome if treated within three hours[78]) and the absence of a trial directly comparing IVT versus no IVT in CKD patients, where outcomes may conceivably be expected to be worse in the latter case.

3.3.2 Intra-arterial interventions

Since several thrombectomy trials (Solitaire™ FR With the Intention For Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke [SWIFT-PRIME], Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptom Onset [REVASCAT]) excluded patients with advanced CKD[79, 80] and only one trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times [ESCAPE]) reported baseline renal function of participants,[81] there are no trial data to support or caution against intra-arterial treatments in patients with CKD. However, it is clearly a very efficacious treatment in the general population as the

number needed to treat to reduce disability with mechanical thrombectomy was 2.6 in pooled data of these trials.[82] 90-day mortality and symptomatic ICH rates did not differ between intervention and control groups.

There is only limited observational evidence as to whether CKD influences the procedural risk, clinical outcomes or mortality associated with thrombectomy. In a prospective study of 505 consecutive patients with anterior-circulation stroke treated with mechanical thrombectomy, CKD (present in 20.2% of included patients) did not associate with poor functional outcome (defined as a modified Rankin score [mRS] of 3-6; OR=1.13, 0.99-1.28; p=0.072) or ICH.[83] However, it was associated with a higher risk of 90-day mortality (OR=1.15, 1.01-1.31; p = 0.038). In contrast to these findings, in a smaller study (106 patients; 20.6% CKD prevalence) of vertebrobasilar stroke treated with thrombectomy, CKD was associated with a higher risk of any ICH but did not predict mortality.[84] It is difficult to interpret these conflicting results given the observational nature of these studies and their small size but the benefits of unselected posterior circulation thrombectomies in the general population have also been less clear. It must be acknowledged though that CKD would also be expected to be associated with worse outcomes in the absence of thrombectomy. In a Japanese multi-centre study of nearly 4000 patients, those with CKD had a 49% (95% CI 17–89) greater risk of neurological deterioration during their hospitalization, a 138% (95% CI 61–257) greater risk of in-hospital mortality, and a 25% (95% CI 5–48) greater risk of significant disability at discharge, even after adjusting for confounding variables such as age, initial stroke severity, cardio-embolic stroke subtype, and infectious complications.[85]

3.3.3 Stroke units

Stroke units have very clear benefits in the general population with a 28% reduction in death or dependency and a number needed to benefit of only 6.[86] This may be

attributable to better access to specialist stroke nursing care as well as the specialised multi-disciplinary team of physiotherapists, occupational therapists, speech and language therapists, and other rehabilitation experts. These benefits appear to be maintained in the CKD population where admission to a stroke unit has been associated with lower risk of death (HR= 0.68, 0.55−0.84; p<0.001).[87] However, in a Scottish cohort study, dialysis patients were less frequently admitted to an acute stroke unit (64.6 vs 79.6%; p<0.001), less likely to receive aspirin acutely (75.3 vs 83.2%; p=0.01), and more likely to die (22.9 vs 14.4%; p=0.002) than their non-ESKD counterparts.[87]

3.4 Secondary prevention of stroke in CKD

In patients with ischemic stroke, CKD has consistently been shown to be an independent risk factor for stroke recurrence.[88-90] In a post-hoc analysis of the Vitamin Intervention for Stroke Prevention (VISP) trial, patients with recent ischaemic stroke with a baseline eGFR <45 mL/min/1.73m^2 had a risk of recurrent stroke events that was 53% greater than those with eGFR of 60-74 mL/min/1.73 m^2 even after adjustment for traditional vascular risk factors.[90] The magnitude of this risk emphasizes the importance of a comprehensive secondary prevention regime for these patients.

3.4.1 Antiplatelets

There is strong evidence from pooled trial data that aspirin is effective at reducing recurrent stroke risk in the general population.[91] In 15,778 participants, aspirin reduced the six week risk of recurrent ischaemic stroke by about 60% and disabling or fatal ischaemic stroke by about 70%. As I have already discussed, there are some bleeding concerns and potential anti-platelet hypo-responsiveness that have rendered uncertain the role of aspirin in primary prevention in CKD. Furthermore, the Cochrane review, based largely on secondary prevention studies, did not reveal any significant benefits in terms of

long-term stroke prevention for this population.[92] However, it is unlikely that the large benefits of acute treatment would be completely nullified in patients with CKD and the guidelines consistently recommend its use for secondary prevention in this setting (Table 3-1).[13, 46, 93]

Patients with CKD may not derive the same benefits from the use of dual antiplatelet therapy (DAPT) in mild stroke/TIA as those with normal renal function. In a post-hoc analysis of the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) in which these patients were randomized to clopidogrel-aspirin or aspirin-alone treatment, patients with moderate CKD (defined as eGFR <60 ml/min/1.73m^2; majority stage 3) treated with combination therapy did not experience a reduction in early recurrent stroke (HR=1.00, 0.43-2.35; P=0.99).[94] The CHANCE investigators later demonstrated though that carriage of the CYP2C19 loss of function allele (a genetic polymorphism for clopidogrel resistance) was associated with significantly increased risk of stroke, ischaemic stroke and combined vascular events in patients on DAPT with an eGFR < 75 ml/min/1.73 m^2.[95]

The choice of anti-platelet agent or combination may be important. In a recent systematic review and meta-analysis of 11 secondary prevention RCTs (13, 628 participants) of DAPT (variable combinations) in CKD, compared to the control group, there was a reduction in the risk of major adverse cardiovascular events (RR=0.87, 0.78-0.97), myocardial infarction (RR=0.76, 0.61-0.92), and stroke (RR=0.81, 0.68-0.94).[96] Compared to aspirin/clopidogrel, aspirin plus ticagrelor or prasugrel reduced the risk of all-cause death (RR=0.74, 0.6-0.88) in CKD; and with no differences for major adverse cardiovascular events (RR=0.88, 0.61-1.14), or major bleeding (RR=0.93, 0.37-1.48). However, dialysis patients and those with advanced CKD (stages 4-5) were not well-represented in the included trials so although DAPT appeared to improve outcomes in

early stages of CKD, it is unclear whether those with more advanced disease would derive the same benefits.

3.4.2 Statins

In a meta-analyses of trials of statins in patients with established cardiovascular disease, the subgroups of patients with CKD derived the same relative benefit from statins on major outcomes as the subgroups without CKD (40% reduction in the risk of stroke).[44, 97] Their impact may be greater when given as high-intensity therapy (either atorvastatin 80mg or rosuvastatin 20mg once daily). In another meta-analysis of six RCTs (10, 993 participants), a significant decrease in stroke was observed in the high-intensity statin therapy group (RR=0.69, 0.56 to 0.85) without a clear difference in adverse events between those with CKD and those without.[98]

However, it remains uncertain whether statins reduce specifically recurrent stroke risk in dialysis-dependent patients as the dedicated trials in this group included people with and without previous cerebrovascular events and there was no overall statistically significant benefit for all-comers.[48, 49] Certain high-risk subgroups did appear to benefit in post-hoc analyses including those with a baseline LDL-cholesterol concentration >145 mg/dL (3.76 mmol/L)[99] and diabetic patients.[100]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may also have a role in secondary stroke prevention. The American College of Cardiology (ACC) recommends their addition (or ezetimibe) to maximally tolerated statin therapy in high-risk patients with atherosclerotic cardiovascular disease and CKD where less than 50% LDL-C reduction has been achieved with statins, including high-intensity statins.[101] In a pooled analysis of eight ODYSSEY phase three trials (4629 participants; 10% of which had impaired renal

function) that compared alirocumab with either placebo or ezetimibe (with most participants also taking statins), the mean reduction in LDL-C observed with alirocumab was approximately 60% in both those with and without impaired renal function.[102]

3.4.3 Antihypertensive agents

There is clear evidence to support the use of anti-hypertensive therapy, particularly with renin-angiotensin (RAS) inhibitors, in the secondary prevention of stroke in CKD patients from the Perindopril Protection against Recurrent Stroke Study (PROGRESS). The PROGRESS study enrolled 6105 participants with recently symptomatic cerebrovascular disease and randomly allocated them to perindopril-based blood pressure–lowering therapy or placebo.[103] In a post-hoc analysis of the PROGRESS study, compared with those with normal renal function, CKD patients (N = 1757) had approximately 1.5-fold greater risk of major vascular events, stroke, and coronary heart disease, and were more than twice as likely to die (all P≤0.002). The use of perindopril produced a 30% reduction in the risk of major cardiovascular events and a 35% reduction in the risk of stroke among CKD patients. The absolute benefits of treatment were 1.7-fold greater for those with CKD than for those without. Perindopril prevented one stroke or other cardiovascular event among every 11 patients with CKD treated over five years, although it was unclear what the achieved blood pressure or level of urine albumin were in either arm of the trial. However, intensive anti-hypertensive therapy (to target SBP <120 mmHg) in high-risk diabetic patients with CKD in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial (ACCORD BP) was associated with a significant reduction in stroke risk (albeit with an NNT of 89 to prevent one stroke over five years).[104]

The European and US guidelines are somewhat conflicting in their recommendations for CKD patients and do not stratify their blood pressure target goals according to primary or

secondary prevention in CKD (Table 3-1).[58, 105] The US guidelines are driven largely by the results of the SPRINT-CKD substudy[57]and assume that the vast majority of patients with CKD have a 10-year atherosclerotic cardiovascular disease risk greater than 10%, placing them in the high risk category that requires initiation of antihypertensive drug therapy at BP ≥130/80 mmHg. Although these guidelines are less individualized and more prescriptive than the European[105] or KDIGO[46] ones, there is a general consensus that the current body of evidence supports this target for both primary and secondary cardiovascular disease prevention in CKD patients, regardless of proteinuria or diabetic status.[106]

3.4.4 Carotid interventions

The North American Symptomatic Carotid Endarterectomy Trial (NASCET) was the only large randomized trial of carotid endarterectomy in which renal function was assessed in trial participants.[107] For medically treated patients with symptomatic high-grade stenosis, risk for ipsilateral stroke at two years was significantly higher in patients with CKD than in those with preserved renal function (31.6 versus 19.3%; P = 0.042).[108] With surgery, there was a statistically significant RR reduction of 82.3% (95% CI: 54.5-93.1%) in stroke risk for patients with CKD and 50.8% (95% CI: 12.6-72.3%) for patients without CKD. The number needed to treat by surgery to prevent one ipsilateral stroke within two years was four for patients with CKD and 10 for patients without CKD. The risk for perioperative death was similar between groups; however, rates of perioperative cardiac complications (myocardial infarction, congestive heart failure, and arrhythmias) were higher in the CKD group. However, among the 524 patients with CKD analysed in this study, the mean eGFR was 49 ml/min/1.73 m^2 (with a minimum of 19 ml/min/1.73 m^2) which limits the generalizability of these results to those with stage 4/5 CKD.

Based on observational data from the Vascular Study Group of New England database, the 30-day mortality post carotid intervention appeared to increase with worsening renal function (0.4% mild vs 0.9% moderate [eGFR 30-59ml/min/1.73m^2] and 0.9% severe [eGFR <30 ml/min/1.73m^2]; P = 0.01).[109] However, in a multi-variate regression model, CKD status did not predict 30-day stroke or death. Although the one-, five-, and 10-year survival rates also decreased with worsening renal function, patients with severe CKD maintained a 71% survival at five years. In contrast to patients with peripheral arterial occlusive disease, for whom severe CKD reduces the five-year survival rate to 21% irrespective of revascularization procedures,[110] patients with CKD and carotid interventions appear to do much better. Carotid revascularization may therefore have utility in carefully selected patients with moderate and severe CKD, particularly in symptomatic disease.

However, do the risks outweigh the benefits in dialysis patients? Based on USRDS data, the perioperative and long-term outcomes after carotid endarterectomy (CEA) of 5142 dialysis patients with both symptomatic and asymptomatic diseases were studied.[111] 83% of patients were asymptomatic. The 30-day stroke rate, myocardial infarction, and mortality for the asymptomatic and symptomatic groups were 2.7% vs 5.2% (P = 0.001), 4.6% vs 5.0% (P =0 .69), and 2.6% vs 2.9% (P = 0.61), respectively. The perioperative risks of CEA are therefore clearly high, even for asymptomatic patients. The overall long-term (three-year) survival was also poor at 46% and 42% in the asymptomatic and symptomatic cohorts respectively. The authors therefore concluded that surgery should only be considered in judiciously selected very-high risk symptomatic patients.

The only official guidance on the management of carotid disease in CKD patients comes from the Society for Vascular Surgery who recommend carotid endarterectomy rather than stenting for symptomatic patients with moderate-severe stenosis (Table 3-1).[112] These patients evidently require careful perioperative assessment and management

given their higher rate of short-term complications, but the long-term outcomes appear promising in non-dialysis CKD.

3.4.5 SGLT-2 Inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors were originally developed to treat hyperglycaemia in people with diabetes but now appear to have promising protective cardio-metabolic effects in CKD patients with (and potentially without) diabetes.[113] They restore tubuloglomerular feedback and reduce intraglomerular pressure by increasing afferent arteriolar tone even in the presence of ambient normoglycaemia. Recent large placebo-controlled outcome trials have shown that empagliflozin and canagliflozin reduce the risk of cardiovascular disease in high-risk people with type 2 diabetes mellitus.[114-116] In the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), empagliflozin 10–25 mg was shown to reduce the primary cardiovascular composite outcome (death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke) by 14% compared with placebo (HR=0.86, 0.74–0.99).[115] This effect was driven by a 38% (HR=0.62, 0.49–0.77) reduction in cardiovascular death. These cardiovascular effects appear to be largely independent of effects on glycaemic control, BP and body weight.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program randomized 10, 142 participants with type 2 diabetes and eGFR >30 mL/min/1.73 m2 to canagliflozin or placebo with the same primary outcome as EMPA-REG OUTCOME. The effect of canagliflozin on the primary outcome was similar in CKD patients (HR= 0.70, 0.55-0.90) and those with preserved kidney function (HR= 0.92, 0.79-1.07; P heterogeneity = 0.08).[117] Heterogeneity was observed for the effect on fatal/nonfatal stroke, with possibly greater benefits with declining kidney function (P heterogeneity = 0.01).

3.5 Conclusions

Stroke prevention and treatment are evidently more complex in the CKD population. Current controversies within existing guidelines are whether there should be stratification in treatment strategies depending on age, frailty, CKD stage, diabetes status, presence of proteinuria, transplant status, or dialysis requirement.[46, 58, 105] Based often only on observational studies or on post hoc subgroup analysis of trial data, there are clearly still gaps in the evidence for efficacy and safety for primary and secondary preventative treatments that are used routinely in the general population. There is a need for dedicated stroke prevention trials in the CKD population, particularly in those with more advanced disease or who are dialysis-dependent.

3.6 References

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TABLES

Table 3-1 Current available guidelines for the primary or secondary prevention of cerebrovascular disease in CKD

Guidelines	NICE[13]	KDIGO[46, 118]	ACC/AHA/ASA[39, 40, 58, 93, 119]	Society for Vascular Surgery[112]
Anti-platelet therapy	• Offer only for secondary prevention but caution as to the increased risk of bleeding	• Aspirin is indicated for secondary prevention but not for primary prevention	• Aspirin may be considered for primary prevention for GFR 30-45 ml/min and should be given for secondary prevention	
BP control	• Target BP <140/90 mmHg in general, but <130/80 mmHg if ACR≥70 mg/mmol or diabetic. • Use preferably RAS antagonist	• Individualize targets according to age, CVD, co-morbidities. • <140/90 mmHg if not diabetic and UAE<30mg/24hr	• Target <130/80 mmHg • Use RAS antagonist	
Anticoagulation	• Consider apixaban in preference to warfarin if GFR 30-50 ml/min in at-risk non-vavlular AF.		• Consider reduced dose NOACs if GFR 15-50 ml/min. • Consider warfarin or apixaban in ESKD.	
Statins	• Give atorvastatin 20 mmHg for primary or secondary prevention. • Discuss higher doses with renal specialist if GFR<30 ml/min	• Check a lipid profile in all new CKD patients. • If >50 years and stage 3-5, treat with statin or statin/ezetimibe. • >50yo CKD stage 1-2, treat with statin • In dialysis-dependent CKD, don't start statins but continue if already taking	• Initiate a moderate-intensity statin +/- ezetimibe in non-dialysis CKD if 40-75 years of age with LDL-C 70-189mg/dL and if 10-year ASCVD risk ≥ 7.5%. • In dialysis-dependent CKD, don't start statins but continue if already taking	
Carotid interventions				• Consider if symptomatic with moderate-severe stenosis. • CEA > CAS • CAS may have a role in selected patients.

ACC indicates American College of Cardiology; ACR, albumin:creatinine ratio; AF, atrial fibrillation; AHA, American Heart Association; ASA, American Stroke Association; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CAS, carotid artery stenting; CEA, carotid endarterectomy; CKD, chronic kidney disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; NOAC, novel oral anti-coagulant; RAS, renin-angiotensin system, UAE, urine albumin excretion.

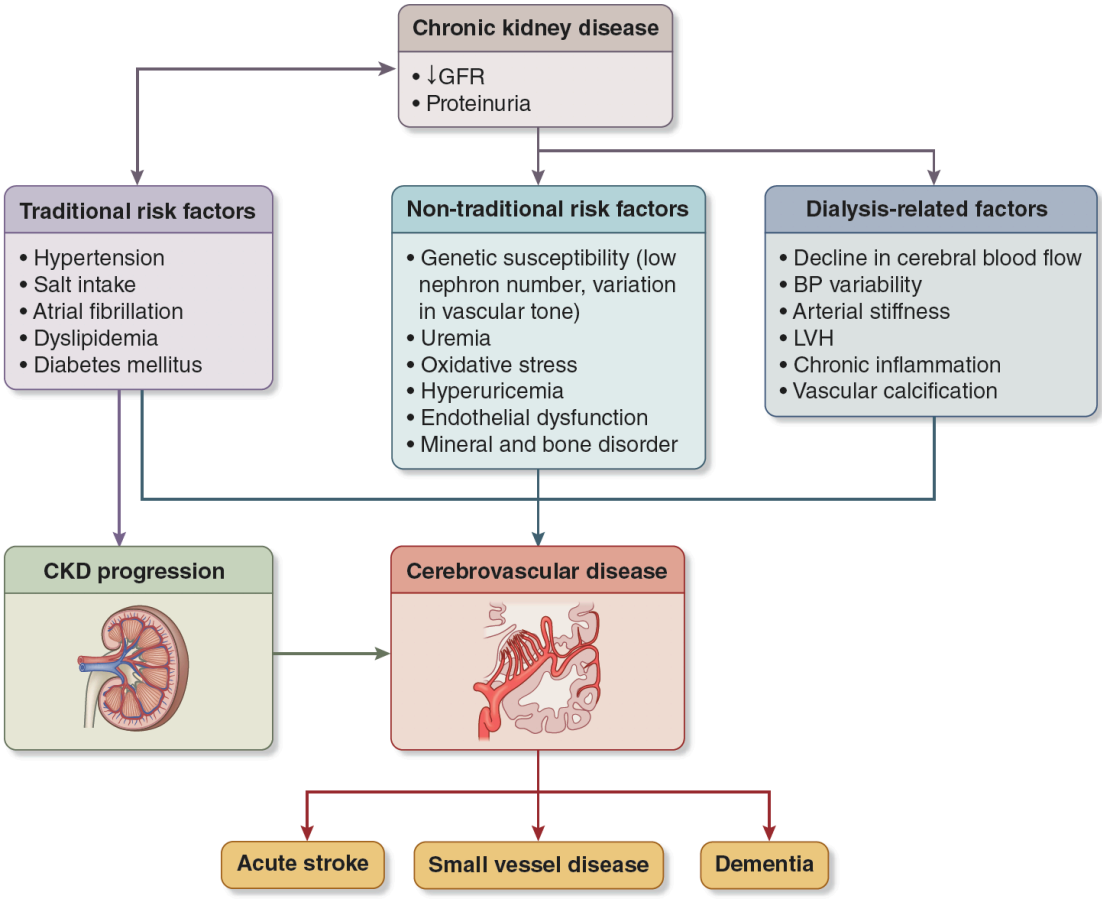
Table 3-2 Trials of blood pressure lowering in the CKD population

Trial Name	Year	Patients	Intervention	Follow-up	Results	Comments
MDRD[120, 121]	1993; follow-up 2005	• N=840 • All CKD	Target MAP ≤92 vs ≤ 107 mmHg	2.2 years (initial study); 6.2 years follow-up	23% reduction in composite kidney failure/mortality outcome	BP not recorded during the follow-up study
HOPE[122]	2001	• Post hoc analysis • N= 980 with mild renal insufficiency + prior vascular disease or other risk factor (124-200 µmol/L)	Ramipril vs Placebo	4.5 years	31% reduction in stroke risk with ramipril	
RENAAL[123]	2003	• N=1513 • Type 2 diabetes with nephropathy	Losartan vs Placebo; target <140/90mmHg	3.4 years	16% reduction in renal outcomes/mortality and 10% non-significant reduction in CV events.	Patients with non-diabetic nephropathies excluded
PROGRESS[103]	2007	• Post hoc analysis • 1757 CKD patients with history of TIA/stroke	Perindopril vs Placebo	4 years	Reduced risk of major vascular events by 30% and stroke by 35% in CKD.	No data on patients with proteinuria
AASK[56, 124]	2002 trial phase; 2010 cohort phase	• N=1094 black hypertensive CKD	Target MAP ≤92 vs ≤ 107 mmHg	4 years trial follow-up; 5 years additional cohort	No significant differences in ESKD/mortality except in those with proteinuria	All patients had same BP target in cohort phase
SPRINT[57]	2017	• N=2646 • GFR 20-59 ml/min (mean 48)	SBP<120 vs <140	3.3 years	19% reduction in primary CV outcome but no significant difference on stroke events	Patients with proteinuria were excluded
CSPPT[59]	2018	• N= 3230 hypertensive patients with GFR 30-60 +/or proteinuria	Enalapril/Folic acid vs Enalapril alone	4.7 years	49% reduced first stroke with time-averaged SBP of ≤135 (compared to SBP 135 - ≤140)	

AASK indicates African American Study of Kidney Disease and Hypertension MDRD; BP, blood pressure; CKD, chronic kidney disease; CSPPT, China Stroke Primary Prevention Trial; CV, cardiovascular; ESKD, ends-stage kidney disease; GFR, glomerular filtration rate; HOPE, Heart Outcomes Prevention Evaluation; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; PROGRESS, The Perindopril Protection against Recurrent Stroke Study; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; SBP, systolic blood pressure; SPRINT, Systolic Blood Pressure Intervention Trial.

FIGURES

Figure 3-1 Traditional and non-traditional risk factors for cerebrovascular diseases in patients with CKD



BP indicates blood pressure; CKD, chronic kidney disease; GFR, glomerular filtration rate; LVH, left ventricular hypertrophy.

Chapter 4 Aims and Methods

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4.1 Aims of thesis

The aims of my thesis are the following:

1) To determine if there is an independent relationship between chronic kidney disease (CKD) and stroke risk after adjusting for traditional risk factors, particularly with more complete adjustment for confounding by blood pressure
2) To assess the impact of proteinuria on stroke risk and whether any association present remains after more complete adjustment for blood pressure
3) To investigate in a large prospective population-based study of patients with transient ischaemic attack (TIA) or stroke, the correlations of a panel of biomarkers related to inflammation, thrombosis, and cardiac or neuronal function or injury with renal function
4) To determine which TIA and stroke subtypes occur most frequently in patients with CKD, and whether any associations present remain after adjustment for potential confounders
5) To determine whether CKD is associated with worse initial stroke severity and disability, and whether CKD is independently predictive of recurrent stroke
6) To determine the age-specific associations of CKD and the overall burden of small vessel disease (SVD), as well as individual SVD markers
7) To investigate the association between CKD and dementia before and after TIA and stroke.

4.2 Systematic reviews and meta-analyses

For the first part of my thesis, I performed two systematic reviews and meta-analyses of randomized controlled trials and cohort studies that estimated firstly the association between low estimated glomerular filtration rate (eGFR) and the risk of stroke, and then secondly, the association between proteinuria and the risk of stroke. These reviews were an update of earlier review[1] and used a similar study protocol. The study protocol was registered prospectively on PROSPERO (CRD42019127301) and conformed with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[2] I searched MEDLINE (2013-February 2018) and EMBASE (2013-February 2018) databases using a search strategy developed by a specialized librarian in the John Radcliffe Hospital in Oxford that combined text word and medical subject headings without language restrictions (Table 4-1). Study and participant characteristics and relative risks were extracted. Estimates were combined using a random effects model. Heterogeneity was assessed by x^2 statistics and I^2, and by subgroup strata and meta-regression, with a particular focus on the impact of more complete adjustment for blood pressure on the association. The quality of cohort studies and post hoc analyses was assessed using the Newcastle–Ottawa Scale.[3] Specific details of the methodology will be outlined further in the individual chapters.

4.3 The Oxford Vascular Study

The data used in the second part of this thesis have been obtained from the Oxford Vascular Study. The Oxford Vascular Study (OXVASC) is a prospective, population-based cohort study of all acute vascular events (including TIA, stroke, acute coronary syndromes, and peripheral vascular events) in Oxfordshire, UK. The study population is defined by registration with nine general practices (Figure 4-1) and comprises approximately 92,728 individuals of all ages. The methodology of OXVASC is based on the Oxfordshire Community Stroke Project (OCSP),[4] a similarly designed population based incidence study of stroke and TIA performed in the 1980s in the same population.

4.3.1 Study population

The OXVASC study population comprises all individuals, irrespective of age, registered with about 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK. In Oxfordshire, an estimated 97% of the true residential population is registered with a general practice, with most non-registered individuals being young students. All participating practices provide accurate age-sex patient registers and hold individual lifelong records of all medical consultations, and details of medications, blood pressure measurements, and investigations. All practices refer patients with acute vascular events to one main secondary care centre (John Radcliffe Hospital, Oxford). The practices had all collaborated on a previous population-based study (the OCSP), for which they were originally selected to be representative of the urban and rural mix and the deprivation range of Oxfordshire as a whole.[4] Based on the index of multiple deprivation (IMD), the population was less deprived than the rest of England, but had a broad range of deprivation. The OXVASC population is 94% white, 3% Asian, 2% Chinese, and 1% Afro-Caribbean.[4] The proportion of Caucasians is similar to that of the UK as a whole (86%

Caucasian) and to many other western countries (Australia - 90%; France - 85%; Germany - 93.9%).[5]

3178 patients presenting with TIA and stroke recruited from April 2002 to March 2017 were included in the main OXVASC analyses in this thesis (Chapter 8 and Chapter 9). Smaller, more specifically phenotyped cohorts were included in the other chapters – 1297 patients underwent biomarker assessment between 2002 and 2011 in Chapter 7, 1939 patients had detailed MRI neuroimaging between 2004 and 2008 in Chapter 10, and 2305 patients had comprehensive cognitive phenotyping with 5 years follow-up between 2002 and 2012 in Chapter 11.

4.3.2 Case ascertainment

After a 3-month pilot study, the study started on April 1, 2002, and is ongoing.[6] Multiple overlapping methods of “hot” and “cold” pursuit are used to achieve near complete case ascertainment.

Hot pursuit includes:

1) A daily (weekdays only), urgent open-access “TIA clinic” to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital, with alternative on-call review provision at weekends. Patients too frail to attend are assessed at their residence by a study nurse or doctor.

2) Daily searches and case note review of admissions to the Emergency Assessment Unit, Medical Short Stay Unit, Coronary Care Unit and Cardiothoracic Critical Care Unit, Cardiology, Cardiothoracic, and Vascular Surgery wards, Acute Stroke Unit, Neurology ward and all other general wards when indicated.

3) Daily searches of the local A&E and eye hospital attendance registers.

4) Daily identification via the Bereavement Office of patients dead on arrival at hospital or who died soon after.

5) Daily searches of lists of all patients from the study population in whom a troponin-I level had been requested.

6) Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify both total burden of vascular invention and any potential missed prior acute events.

Cold pursuit procedures includes:

1) Frequent visits to the study practices and monthly searches of practice diagnostic codes.
2) Monthly practice-specific list of all patients admitted to all acute and community NHS hospitals.
3) Monthly listings of all referrals for brain or carotid imaging studies performed in local hospitals.
4) Monthly reviews of all death certificates and coroners reports to review out-of-hospital deaths.

5) Practice-specific listings of all ICD-10 death codes from the local Department of Public Health.

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who were not registered with one of the study practices are excluded. A study clinician assessed patients as soon as possible after the event in the hospital or at home. Data are collected using event-specific forms, for TIA and stroke, acute coronary syndrome or acute peripheral vascular events. Standardised clinical history and cardiovascular examination are recorded. Information recorded from the patient, their hospital records and their general practice records includes details of the clinical event, medication, past medical history, education and occupational history, marital status, living arrangements, family history, functional status, abbreviated mental test score (AMTS), all investigations relevant to their admission (including blood results, electrocardiography, brain imaging and vascular imaging-duplex ultrasonography, computed tomography angiography [CTA], magnetic resonance angiography [MRA] or digital subtraction angiography [DSA]) and all interventions occurring subsequent to the event.

If a patient died before assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant records. If death occurred outside the hospital or before investigation, the autopsy result was reviewed. Clinical details are sought from primary care physicians or other clinicians on all deaths of possible vascular aetiology. In a previous study, only 3/823 interviewed patients reported previous vascular events that had not been ascertained using these multiple methods, thus the ascertainment rate is >99% of events presenting to medical attention.[7]

All surviving patients are followed-up face-to-face at 1, 6, 12, 60 and 120 months after the initial event by a research nurse or physician and all recurrent vascular events are

recorded together with the relevant clinical details and investigations. If face-to-face follow up is not possible, telephone follow-up is performed or enabled via the general practitioner. All recurrent vascular events that presented to medical attention would also be identified acutely by ongoing daily case ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient is re-assessed and investigated by a study physician.

4.3.3 Definition of TIA/stroke events

Although new definitions for stroke and TIA have been suggested,[8, 9] in order to enable comparison with previous studies, the classic definitions of TIA and stroke are used throughout.[9] A stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at time global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[10] A TIA is an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease. All cases were reviewed as soon as possible after presentation by the same senior neurologist (PMR) throughout the study.

4.3.4 Definition of CKD

CKD was defined as eGFR less than 60 mL/min/1.73 m^2 for three or more months as per 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[11] eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI). eGFR was then categorized into 5 groups based on modified CKD classification by

the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative: eGFR ≥ 90 (reference), 60-89, 30-59, 15-30 and <15 ml/min/1.73m^2. For the purpose of statistical analysis, the latter two groups were frequently combined as the individual numbers within each group were small.

4.3.5 Patient consent and ethical approval

All patients eligible for the study are given an information sheet. If the patient is willing to decide about participation in the study immediately, then written consent is obtained. If the patient requests a period of time to consider the decision then this is respected. Study assent is obtained from next of kin if the patient is unable to consent. OXVASC is approved by Oxfordshire Clinical Research Ethics committee (South Central-Oxford A: 05/Q1604/70).

4.4 References

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11. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis*. 2002;39:S1-266

TABLES

Table 4-1 Search strategies

MEDLINE	**Embase**
1. Kidney Diseases/ 2. exp Renal Replacement Therapy/ 3. Renal Insufficiency/ 4. exp Renal Insufficiency, Chronic/ 5. dialysis.tw. 6. (hemodialysis or haemodialysis).tw. 7. (hemofiltration or haemofiltration).tw. 8. (hemodiafiltration or haemodiafiltration).tw. 9. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw. 10. (ESRF or ESKF or ESRD or ESKD).tw. 11. (chronic kidney or chronic renal).tw. 12. (CKF or CKD or CRF or CRD).tw. 13. (CAPD or CCPD or APD).tw. 14. (predialysis or pre-dialysis).tw. 15. or/1-14 16. exp Stroke/ 17. Brain ischemia/ 18. Cerebral Small Vessel Diseases/ 19. Intracranial Hemorrhages/ 20. stroke.tw. 21. (CVA or TIA).tw. 22. or/16-21 23. and/15,22 24. albuminuria/ 25. proteinuria/ 26. (proteinuria or albuminuria).tw. 27. or/24-26 28. or/15,27 29. and/22,28	1. kidney disease/ 2. exp renal replacement therapy/ 3. dialysis.tw. 4. (CKF or CKD or CRF or CRD).tw. 5. (end?stage kidney or end?stage renal).tw. 6. (chronic kidney or chronic renal).tw. 7. exp cerebrovascular accident/ 8. brain hemorrhage/ 9. brain infarction/ 10. stroke.tw. 11. exp proteinuria/ 12. albuminuria/ 13. (proteinuria or ?albuminuria).tw. 14. or/1-6 15. or/7-10 16. or/11-13 17. or/14, 16 18. and/15, 17

FIGURES

Figure 4-1 The nine OXVASC GP practices

● **OXVASC GP practice**

1. Exeter, Kidlington, OX5 1AP
2. Kidlington & Yarnton, Kidlington, OX5 1AP
3. 19, Beaumont Street, Oxford, OX1 2NA
4. Bartlemas surgery, Oxford, OX4 1XD
5. Stert Street, Abingdon, OX14 3LB
6. Malthouse, Abingdon, OX14 3JY
7. Marcham Road, Abingdon, OX14 1BT
8. Berinsfield, OX10 7NE
9. Church Street, Wantage, OX12 9BN

Chapter 5 Does chronic kidney disease predict stroke risk independent of blood pressure? A systematic review and meta-regression.

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5.1 Chapter outline

Chronic kidney disease (CKD) is strongly associated with stroke with various purported mechanisms proposed. Low glomerular filtration rate (eGFR) appears to be a risk factor for stroke independent of cardiovascular risk factors in epidemiological studies, but there has been no systematic assessment of the impact of more complete adjustment for blood pressure (BP) on the association.

I did a systematic review to February 2018 (MEDLINE/EMBASE) for cohort studies or randomized controlled trials that reported stroke incidence in adults according to baseline eGFR. Study and participant characteristics and relative risks (RR) were extracted. Estimates were combined using a random effects model. Heterogeneity was assessed by x^2 statistics and I^2, and by subgroup strata and meta-regression.

I identified 168 studies reporting data on 5,611,939 participants with 115,770 stroke outcomes. 85 studies (3,417,098 participants; 72,996 strokes) provided adequate data for meta-analysis of eGFR and stroke risk. Incident stroke risk was increased among participants with eGFR <60 ml/min/1.73m^2 (RR=1.73, 95% CI: 1.57-1.90; p<0.001), but there was substantial heterogeneity between studies (p<0.0001; I^2 - 78.5%). Moreover, the association was reduced after adjustment for cardiovascular risk factors, with progressive attenuation on more thorough adjustment for hypertension: single baseline BP measure (RR=1.63, 1.34-1.99; p<0.001); history or treated hypertension (RR=1.35, 1.24-1.46, p<0.001); multiple BP measurements over months to years (RR=1.10, 1.02-1.18; p=0.01).

The association between CKD and stroke appears to be highly dependent on the method of adjustment for hypertension. The apparently independent relationship between CKD and stroke may be confounded by their shared association with long-term prior BP.

5.2 Introduction

Chronic kidney disease (CKD) is a global health burden with an estimated prevalence of 11 to 13%.[1] In patients with CKD, compared with the general population, cardiovascular disease such as stroke is more frequent and severe.[2] CKD prevalence varies from 20% to 35% in patients with acute ischaemic stroke[3, 4] and from 20% to 46% in patients with acute intracerebral haemorrhage (ICH).[5, 6] Even in patients with mild to moderate CKD, the incidence of cardiovascular death is much higher than the incidence of kidney failure.[7]

The mechanisms of increased stroke risk in CKD remain unclear with possible contributions from traditional risk factors such as diabetes mellitus and atrial fibrillation, and 'non-traditional' risk factors such as uraemia, chronic inflammation, abnormal calcium metabolism.[8] There is conflicting epidemiological evidence about whether low eGFR is a risk factor for stroke independent of traditional cardiovascular risk factors. In a pooled analysis of 22, 634 participants from community-based longitudinal studies including the Atherosclerosis Risk in Communities study, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study, an excess risk of stroke with a lower eGFR was not statistically significant after adjusting for traditional cardiovascular risk factors.[9] However in larger meta-analyses, in which multivariate-adjusted relative risks were pooled, the risk of incident stroke increased by 43% in patients with an eGFR below 60 mL/min/1·73 m^2 with risk of stroke increasing 7% for every 10ml/min/1.73m^2 decrease in GFR.[10, 11] These associations were not different across subtypes of stroke, sex and varying prevalence of cardiovascular risk factors.

Increased vascular risk in individuals with CKD may, however, be mostly attributable to co-existent or prior hypertension, the most prevalent comorbidity in individuals with CKD, occurring in 67-92% of patients.[12] It is the leading modifiable risk factor for stroke in the general population, regardless of age, gender or stroke subtype.[13] However, the extent of

its contribution to increased stroke risk in CKD patients in the context of other potential mechanisms is not clear.

I aimed to determine if there is still an independent relationship between CKD and stroke risk after adjusting for traditional risk factors, particularly with more complete adjustment for confounding by blood pressure. I hypothesized that the association between CKD and stroke is not independent of long-term blood pressure burden.

5.3 Methods

5.3.1 Data sources and searches

As outlined in Chapter 4 (4.2 Systematic reviews and meta-analyses), I updated an earlier systematic review and meta-analysis of randomized controlled trials (RCTs) and cohort studies that had estimated the association between GFR and the risk of stroke.[11] The study protocol was registered prospectively on PROSPERO (CRD42019126862) and conformed with PRISMA guidelines. I searched MEDLINE (2013-February 2018) and EMBASE (2013-February 2018) databases using a search strategy developed by a specialized librarian that combined text word and medical subject headings without language restrictions (Table 4-1).

5.3.2 Study selection

I included all RCTs and cohort studies that measured GFR at baseline and reported quantitative estimates with a measure of precision (or original data which allowed their calculation) of the risk of incident or recurrent stroke in relation to GFR. GFR had to be either estimated using a validated formula [Cockcroft-Gault, modification of diet in renal disease (MDRD), CKD epidemiology collaboration (CKD-EPI)], measured directly,

approximated from urinary creatinine clearance or estimable from serum creatinine. The outcome of interest was symptomatic stroke confirmed by physician examination, hospital record review or identified from data-linkage of administrative records. Eligible articles were evaluated for overlap based on geographical setting, study period, sample size, and outcome. I excluded cross-sectional and case–control studies due to the greater risk of bias than in prospective cohort studies, studies where GFR was measured using non-validated methods, studies that had mostly participants with end stage renal disease (by history of dialysis or an eGFR <15 ml/min/1.73 m^2), studies where outcomes were measured by self-reports or proxy reports and studies that reported radiological but clinically silent stroke disease. Studies that used slightly varying eGFR intervals were included if they were otherwise comparable.

5.3.3 Data abstraction and quality assessment

Key descriptive and quantitative data were recorded for study characteristics, participants, exposures and outcomes. I collected details of the year of study publication, location, size and duration. Abstracted participant characteristics included age, gender, race and the prevalence of diabetes, known vascular diseases, smoking and hypertension. I also noted if participants were recruited at a time of high stroke risk including around an acute coronary event, coronary revascularization procedure or carotid arterial intervention. I recorded the GFR, the method of measurement, and the units of quantification used. I then extracted data for the relative risk (RR), odds risk or hazard ratio of stroke associated with each specified GFR and noted whether reported strokes were fatal or non-fatal, incident or recurrent, as well as the subtype of stroke (haemorrhagic, ischaemic or unspecified). I obtained effect estimates from both the unadjusted (or minimally adjusted) and the most fully adjusted model reported, noting which variables the model had adjusted for. The standard error of the estimate was also extracted or estimated from

the reported 95% confidence interval (CI). I assessed the quality of cohort studies and post hoc analyses using the Newcastle–Ottawa Scale.[14]

5.3.4 Statistical analysis

The leading outcome of interest was the risk of stroke in patients with an eGFR <60ml/min/1.73m^2. When articles provided estimates based on both the MDRD and CKD-EPI equations, we used estimates from the CKD-EPI equation as these result in more accurate risk prediction for adverse outcomes compared with the MDRD study equation.[15] I converted RRs associated with averaged GFR to their natural logarithms and combined log RRs and standard errors using the DerSimonian and Laird method in a random effects model. A fixed effect model was also used for comparison with the random effects model on the overall risk estimate. Reported P values were two sided, with significance set at less than 0.05. Heterogeneity among included studies was assessed by x^2 statistics and the I^2 test. I regarded heterogeneity as possibly unimportant when the I^2 value was less than 40% and considerable when more than 75%.[16] I used subgroup analyses and meta-regression to explore sources of inconsistency and heterogeneity. Subgroups were pre-specified and included study characteristics (study design, size, location, duration of follow-up), participant characteristics (age, gender, race, prevalence of diabetes, hypertension, smoking, atrial fibrillation, undergoing cardiac or carotid intervention, GFR defined by CKD stage) and characteristics of stroke recorded (subtype, severity, and whether incident or recurrent).

To evaluate the impact of the type of hypertension adjustment on effect estimates, I derived and reported results according to a hierarchy of adjustment from worst to best: no adjustment; adjustment for single (or few) blood pressure readings at one sitting at study entry alone; composite adjustment for a single blood pressure measurement or historical

or treated hypertension; adjustment for historical or treated hypertension; and adjustment for multiple blood pressure readings generally over months or years.

Publication bias was assessed by visual examination of funnel plots. For all analyses, I used Stata software version 13 (Stat Corp., College Station, TX).

5.4 Results

Combining with the earlier review of 83 studies,[11] I identified a further 120 studies that assessed stroke risk in CKD, resulting in 203 studies reporting 118, 851 strokes in 5,567,768 participants. 85 studies (3,417,098 participants) provided appropriate quantitative data to be included in the meta-analysis of GFR and stroke risk (Figure 5-1 and Appendix Table 5-4). The data were derived from 67 cohort studies and 18 RCTs. Characteristics of the included studies and randomized trials are described in Table 5-1 and Appendix Table 5-4. GFR was most commonly estimated using the MDRD formula (42 studies; 49.4%) followed by the CKI-EPI formula (18 studies; 21.2%) and then the Cockcroft-Gault equation (17 studies; 20%). 53 of the included studies (62.4%) were published from 2010 onwards. The majority of studies were based in Asia (31 studies; 36.5%) followed by North America (24 studies; 28.2%).

In total, there were 72,996 stroke outcome events including 36,085 which were not classified by pathological subtype (unspecified), 35,143 ischaemic, and 1758 haemorrhagic strokes. Sixty-three studies (74.1%) reported unspecified stroke types, 29 studies (34.1%) reported ischaemic strokes and 17 studies (20%) reported haemorrhagic strokes (Table 5-1). Pooling unadjusted results from the random effects model showed that incident stroke risk was increased among patients with an eGFR <60 ml/min/1.72m^2 (RR=1.73, 95% CI: 1.57-1.90; p<0.001) (Figure 5-2). In pooled multivariate adjusted

analysis, usually after adjustment for age, sex and cardiovascular risk factors, this risk association attenuated to an RR of 1.36 (1.29-1.43; p<0.001) (Figure 5-3).

Significant heterogeneity existed between multivariate-adjusted estimates among patients with an eGFR <60 ml/min/1.73m^2 (p<0.001, I^2=78.5%). The size of the estimate was reduced in a fixed effects model but similar when the analysis was confined to studies that provided both unadjusted and adjusted risk estimates (Figure 5-4 and Figure 5-5). There was a similar association with ischaemic (Adjusted RR=1.25, 1.06-1.44) and haemorrhagic (Adjusted RR=1.33, 0.97-1.82) stroke risk (Figure 5-6 and Figure 5-7).

An eGFR < 60 ml/min/1.73m^2 was associated with an increased risk of subsequent stroke in all subgroups when estimates were stratified by study design, location, size, quality, duration of follow-up, GFR formula used, mean age groups, gender, race, percentage of diabetics/hypertensives/atrial fibrillation/smokers, setting of high-risk procedure, and stroke type (Table 5-2). These subgroups were investigated for heterogeneity, and although not statistically significant, there was a stronger association between CKD and stroke risk reported in smaller studies (<2500 participants) (RR=1.73, 1.46 to 2.01), those with longer follow-up (≥96 months) (RR=1.49, 1.31-1.70), when the Cockcroft and Gault GFR estimating equation was used (RR=1.55, 1.34-1.79), when the study quality was poor (RR=5.29, 2.25-12.40), when patients were younger (<60 years) (RR=1.57, 1.38-1.77), when studies included a larger proportion (≥30%) of smokers (RR=1.52, 1.32-1.76), or when the event type reported were all recurrent (RR=1.65, 1.18-2.32). In addition, in studies where the participants were undergoing cardiac or carotid procedures, the excess risk of stroke was much greater (RR = 1.73 [1.41-2.12] vs 1.33 [1.26-1.40] and 2.2 [0.92-5.26] vs 1.36 [1.29-1.43], respectively) The funnel plot also showed some asymmetry consistent with publication bias with smaller studies showing an exaggerated stroke risk in CKD (Figure 5-8). Egger's test confirms the presence of small-study effects in adjusted analysis (P=0.001).

However, two meta-regressions did reveal statistically significant heterogeneity. Firstly, reported CKD severity (as defined by eGFR category) appeared to account for some of the heterogeneity. There was a non-significant 5% increased risk of stroke in participants with a GFR 60-89 ml/min/1.73m^2 (Adjusted RR=1.05, 0.99-1.11). The risk of stroke was increased by 20% in participants with a GFR of 30-59 ml/min/1.73m^2 (Adjusted RR=1.20, 1.11-1.29), rising to 54% in those with a GFR of <30 ml/min/1.73m^2 (Adjusted RR=1.54, 1.36-1.74) (P trend <0.001) (See Figure 5-9A).

Secondly, based on my proposed hierarchy of how hypertension was adjusted for in the included studies (Table 5-3*)*, Figure 5-9B demonstrates how the risk association between CKD and stroke varied depending on the method of hypertension adjustment employed in the studies, with progressive attenuation of risk with more complete adjustment (P for heterogeneity = 0.004; adjusted R^2 =13.7%). The risk estimate when only studies adjusting for multiple prior blood pressure readings were included was only 1.10 (1.02-1.18; I^2=31.6%, p=0.2). Adjusting for only historical or treated hypertension appeared to have a similar effect to a more composite definition with minimal impact on the risk estimate when adjusting for single (or few) blood pressure readings at study or trial entry.

5.5 Discussion

In this meta-analysis of 85 studies, which included 3,417,098 participants experiencing nearly 73,000 stroke events, I showed that patients with CKD (eGFR <60 ml/min/1.73m^2) had a risk of stroke that was 36% greater than those without in multivariate-adjusted analysis. There was a dose-response relationship with the excess risk rising to 54% in those with advanced CKD (eGFR<30 ml/min/1.73m^2). These findings are consistent with stroke risk estimates from earlier, smaller meta-analyses.[10, 11] The risk association was similar for ischaemic and haemorrhagic stroke subtypes (albeit insignificant in the latter)

though this analysis was limited by lack of data reported on specific stroke subtypes in the majority of studies.

I used subgroup analyses to assess the influence of several factors on the association between CKD and stroke risk. The magnitude of risk was larger in smaller or poor quality studies, in those with longer follow-up, in younger populations, in cardiac procedure-based studies, and in those that reported recurrent event types. The association of CKD and cerebrovascular disease (in the form of small vessel disease) has been previously shown to attenuate with adjustment for shared risk factors at older ages, but remained at younger ages, suggestive of a shared susceptibility to premature vascular disease.[17] Similar to the earlier meta-analyses,[10, 11] I also found a higher stroke risk in Asian populations compared to Caucasian ones. This may be due to their higher prevalence of uncontrolled hypertension that tends to develop at an earlier age than other races.[18]

I report a hierarchy of adjustment for hypertension. The differential risk association between CKD and stroke depending on the method of hypertension adjustment used, particularly the effect of adjusting for multiple prior blood pressure readings, may have broader epidemiological implications for how we interpret allegedly independent relationships when the exact method of adjustment for confounding variables may be important. Based on these results, long-term blood pressure burden or control does appear to be a potentially important confounder of the CKD and stroke risk association. The degree of risk attenuation would tend to refute the hypothesis that low eGFR is a significant independent risk factor for incident stroke, outside of traditional vascular risk factors, particularly hypertension.

Adjusting for actual achieved blood pressure over time better reflects blood pressure control and duration, and may be a more meaningful method of considering this important confounder in the relationship between CKD and stroke than a single measurement or

diagnostic label. A recently published post-hoc analysis of the China Stroke Primary Prevention Trial aimed to test the impact of achieved blood pressure on first stroke and renal function decline among hypertensive patients with mild-to-moderate CKD.[19] In patients with a time-averaged systolic BP (SBP) of ≤135 mmHg compared with participants with a time-averaged on-treatment SBP of 135 to 140 mmHg, the incidence of total first stroke (1.7% vs 3.3%; HR 0.51, 0.26–0.99) and ischaemic stroke (1.3% versus 2.8%; HR 0.46, 0.22–0.98) diminished significantly.

Understanding the long-term sequelae of middle life hypertension beyond the typical duration of BP trials is important as clinical practice shifts toward more intensive blood pressure control.[20] This is particularly true for patients with CKD where the optimal blood pressure target is controversial and for whom most of the evidence comes from short trials insufficiently powered to assess cardiovascular outcomes.[21, 22] There have been concerns from the Systolic Blood Pressure Intervention Trial (SPRINT)[20] and other trials[21, 23] that treating to lower BP targets results in higher risk for acute kidney injury (AKI) and more rapid loss of eGFR. However, in a SPRINT subgroup analysis of CKD patients, those assigned to the intensive SBP arm did not experience an increase in urinary biomarkers of tubule cell damage despite loss of eGFR.[24] It is likely that eGFR declines in this setting reflect haemodynamic changes rather than intrinsic kidney cell damage in patients with CKD.

To the best of my knowledge, this study is the largest systematic review of CKD and stroke risk and the first to attempt to address confounding by hypertension in detail. However, this meta-analysis had several limitations. Firstly, there was only one reviewer and thus the results may be biased if the selection criteria for including a study were applied in a subjective manner. To mitigate this risk, any questionable studies for inclusion were discussed with the senior author (P.M.R). Secondly, a significant amount of heterogeneity was observed in the analysis and sub-analyses did not fully explain the

variance, although differential risk association depending on the type of hypertension adjustment did appear to account for a large part with very little heterogeneity in the subgroup with the most robust BP adjustment (I^2 =31.6%; p=0.2). In addition, there was less statistical heterogeneity in studies of older (≥70 years) patients (RR=1.19, 1.07-1.32; I^2=40.7%, p=0.062) where the association between CKD and stroke is more likely to be confounded by traditional cardiovascular risk factors such as BP. There may be residual confounding in our results as I was unable to adjust for other known renal vascular risk factors, which may play a more important role in stroke aetiology in younger patients with CKD, accounting for the greater heterogeneity observed in this subgroup (I^2=70.2%, p<0.001). In a recent systematic review and meta-analysis of cardiovascular risk factors in CKD, serum albumin, phosphate, urate and haemoglobin were all found to be statistically significant in their association with future cardiovascular events in addition to traditional risk factors.[25] Thirdly, since included studies employed a variety of GFR estimating equations, there was a risk of misclassification bias since the MDRD and the Cockcroft-Gault equations under- and over-estimate GFR respectively. The adjusted stroke risk was lowest in the CKD-EPI studies (RR=1.20) which is known to correlate better with worse cardiovascular outcomes.[15] Although albuminuria has been independently associated with a higher risk of stroke,[26] I did not examine the interaction between eGFR and albuminuria. Finally, very few studies categorized stroke subtypes according to established stroke classification systems such as the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[27] Stroke is a heterogeneous disease with different subtypes often reflecting different aetiologies or mechanisms[28, 29] which may limit our ability to interpret a summary risk estimate for all-cause stroke in the CKD population.

In summary, I found a significant association between CKD and increased stroke risk across various populations in this meta-analysis,. However, the degree of attenuation of this risk with adjustment for traditional cardiovascular risk factor and then multiple prior

blood pressure readings would question previous assertions of an independent relationship. To better understand the epidemiology of stroke risk in CKD, further studies should explore the impact of adjustment for long-term blood pressure burden.

5.6 References

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TABLES

Table 5-1 Characteristics of studies included in the meta-analysis

Characteristics	Number of studies, total = 85 N	 %
Study		
Design		
Randomized controlled trial	18	21.2
Cohort study	67	78.8
Location		
North America	24	28.2
Europe	16	18.8
Asia	31	36.5
Multinational	14	16.5
Number of participants		
0 to <2500	29	34.1
≥2500 to <5000	18	21.2
≥5000 to <20000	19	22.4
≥20000	19	22.4
Duration of follow-up (months)		
0 to <24	18	21.2
≥24 to <60	35	41.2
≥60 to <96	14	16.5
≥96	16	18.8
Decade of publication		
1970s	1	1.2
1980s	0	0
1990s	0	0
2000s	31	36.5
2010s	53	62.4
Participant		
Mean age (years)		
<60	22	25.9
≥60 to <65	17	20
≥65 to <70	25	29.4
≥70	20	23.5
Hypertensives (%)		
<25	5	5.9
≥25 to <50	19	22.4
≥50 to <75	27	31.8
≥75	25	29.4
Diabetics (%)		
<15	23	27.1
≥15 to <30	29	34.1
≥30	27	31.8
Time of high stroke risk		
Undergoing cardiac procedure	17	20
Undergoing carotid intervention	4	4.7
Stroke		
Subtype		
Unspecified	63	74.1
Ischaemic	29	34.1
Haemorrhagic	17	20

Table 5-2 Subgroup analysis and meta-regression: the effect of study, participant and stroke characteristics on the association between CKD and adjusted risk of stroke.

Subgroups	Number of studies	RR (95% CI)	P value for subgroup interaction
Study characteristics			
Design: Cohort	54	1.35 (1.23-1.54)	0.81
Randomized controlled trial	15	1.37 (1.23-1.54)	
Location: North America	19	1.35 (1.23-1.48)	0.50
Europe	13	1.36 (1.20-1.53)	
Asia	25	1.46 (1.31-1.64)	
Multinational	12	1.28 (1.15-1.42)	
Size: 0 to <2500	21	1.73 (1.46-2.01)	0.08
≥2500 to <5000	15	1.35 (1.19-1.52)	
≥5000 to <20000	16	1.50 (1.33-1.69)	
≥20000	17	1.20 (1.13-1.28)	
Duration of follow-up (months): 0 to <24	11	1.38 (1.17-1.63)	0.47
≥24 to <60	30	1.30 (1.21-1.40)	
≥60 to <96	12	1.31 (1.20-1.43)	
≥96	14	1.49 (1.31-1.70)	
GFR estimation: MDRD	31	1.34 (1.25-1.44)	0.90
CKD-EPI	16	1.20 (1.12-1.29)	
Cockcroft & Gault	16	1.55 (1.34-1.79)	
Study Quality: Good	65	1.33 (1.27-1.40)	0.93
Fair	2	2.49 (1.65-3.77)	
Poor	2	5.29 (2.25-12.40)	
Patient characteristics			
Mean age (years): <60	20	1.57 (1.38-1.77)	0.39
≥60 to <65	15	1.42 (1.25-1.61)	
≥65 to <70	21	1.29 (1.21-1.39)	
≥70	13	1.19 (1.07-1.32)	
Gender: Mainly male	41	1.39 (1.30-1.48)	0.45
Mainly female	26	1.34 (1.21-1.50)	
Race: Mainly Caucasian	27	1.29 (1.20-1.39)	0.50
Mainly Asian	25	1.46 (1.31-1.64)	
Diabetics (%): <15	20	1.39 (1.22-1.57)	0.94
≥15 to <30	23	1.43 (1.28-1.59)	
≥30	20	1.33 (1.23-1.44)	
Hypertensives (%): <25	5	1.34 (1.09-1.65)	0.87
≥25 to <50	15	1.34 (1.18-1.53)	
≥50 to <75	25	1.41 (1.29-1.55)	
≥75	18	1.26 (1.16-1.37)	
Smokers (%): <15	15	1.33 (1.20-1.47)	0.39
≥15 to <20	10	1.36 (1.17-1.59)	
≥20 to <30	9	1.36 (1.15-1.62)	
≥30	20	1.52 (1.32-1.76)	
Atrial fibrillation (%): <10	5	1.18 (1.02-1.38)	0.85
≥10	6	1.17 (1.05-1.31)	
Undergoing cardiac procedure: No	59	1.33 (1.26-1.40)	0.06
Yes	10	1.73 (1.41-2.12)	
Undergoing carotid procedure: No	66	1.36 (1.29-1.43)	0.66
Yes	3	2.20 (0.92-5.26)	
Stroke characteristics			
Stroke type: Incident	43	1.32 (1.24-1.40)	0.23
Recurrent	6	1.65 (1.18-2.32)	
Incident or recurrent	19	1.46 (1.29-1.65)	

CI indicates confidence interval; GFR, glomerular filtration rate; RR, relative risk.

Table 5-3 Studies categorized according to a hierarchy of hypertension adjustment, from least (1) to best (4) adjustment

1 = Adjusting for baseline blood pressure at study entry	2= Adjusting for a history of hypertension and/or anti-hypertensive treatment and/or baseline blood pressure at study entry	3= Adjusting for either a history of hypertension and/or anti-hypertensive treatment	4 = Adjusting for multiple blood pressure readings over time
De Mattos 2006 Devbhandari 2006 Garcia-Gill 2016 Irie 2006 Kobuko 2009 Ohsawa 2013 Perticone 2009 Sandsmark 2015 Synhaeve 2016 Tonelli 2005	Bansal 2016 Bax 2008 Bos 2007 Cheng 2008 Deo 2008 Ford 2009 Guo 2013 Ix 2005 Konishi 2011 Koren-Morag 2006 Kurth 2009 Kuwashiro 2012 Lee 2016 Li 2015 Luo 2014 Mann 2001 Mann 2008 Matsue 2013 Muntner 2012 Nagai 2014 Nakayama 2007 Papademetriou 2016 Papademetriou 2017 Shimizu 2011 Weiner 2004 Zheng 2012	Banerjee 2013 Bedimo 2011 Cea Soriano 2015 Dukkipati 2004 Go 2009 Hwang 2014 John 2000 Kooiman 2014 Marui 2013 McAlister 2017 Micelli 2011 Nakamura 2009 Nickolas 2008 Shih 2017 Shlipak 2001 Wang 2017 Yano 2011	Anguilar 2010 De Leeuw 2002 Kovesedy 2016 Lee 2013 McMullan 2014 Zhang 2015

FIGURES

Figure 5-1 Identification and inclusion of study reports of CKD and stroke risk.

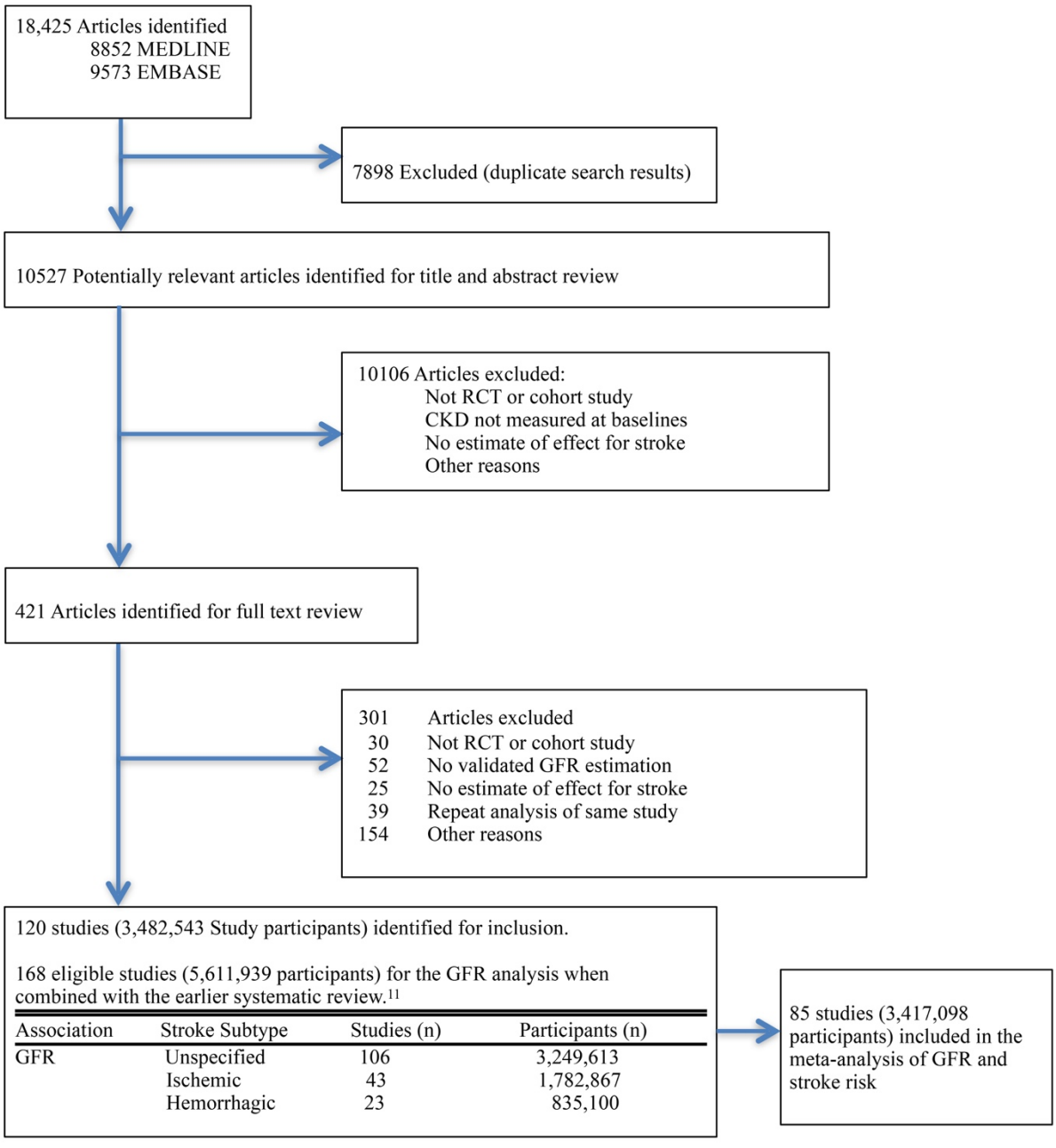


Figure 5-2 Unadjusted risk ratio (RR) for the association of CKD (defined as eGFR < 60 ml/min/1.73m2) and stroke risk

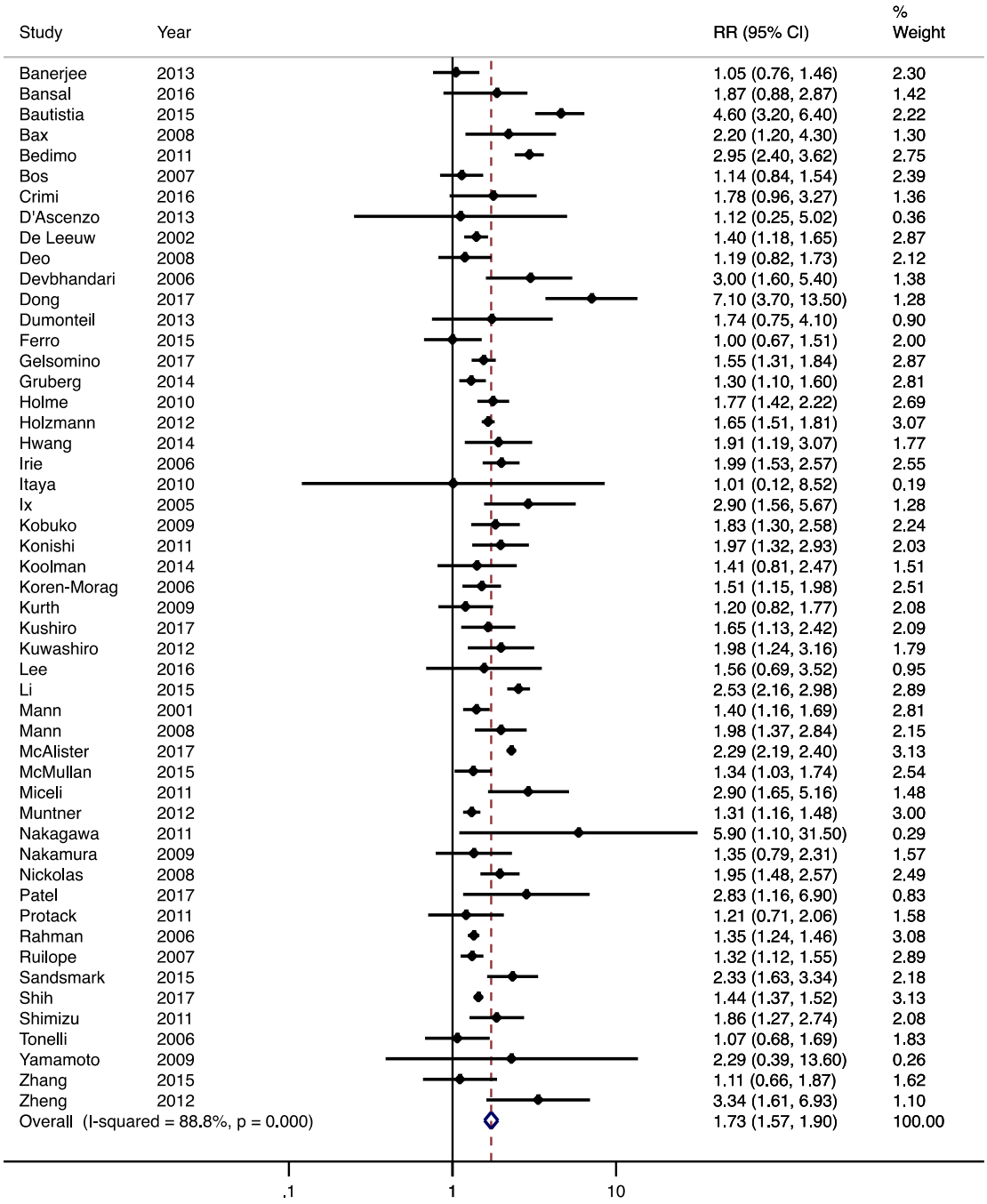


Figure 5-3 Risk ratio (RR) for the association of CKD (defined as eGFR < 60 ml/min/1.73m^2) and stroke risk adjusted for traditional cardiovascular risk factors

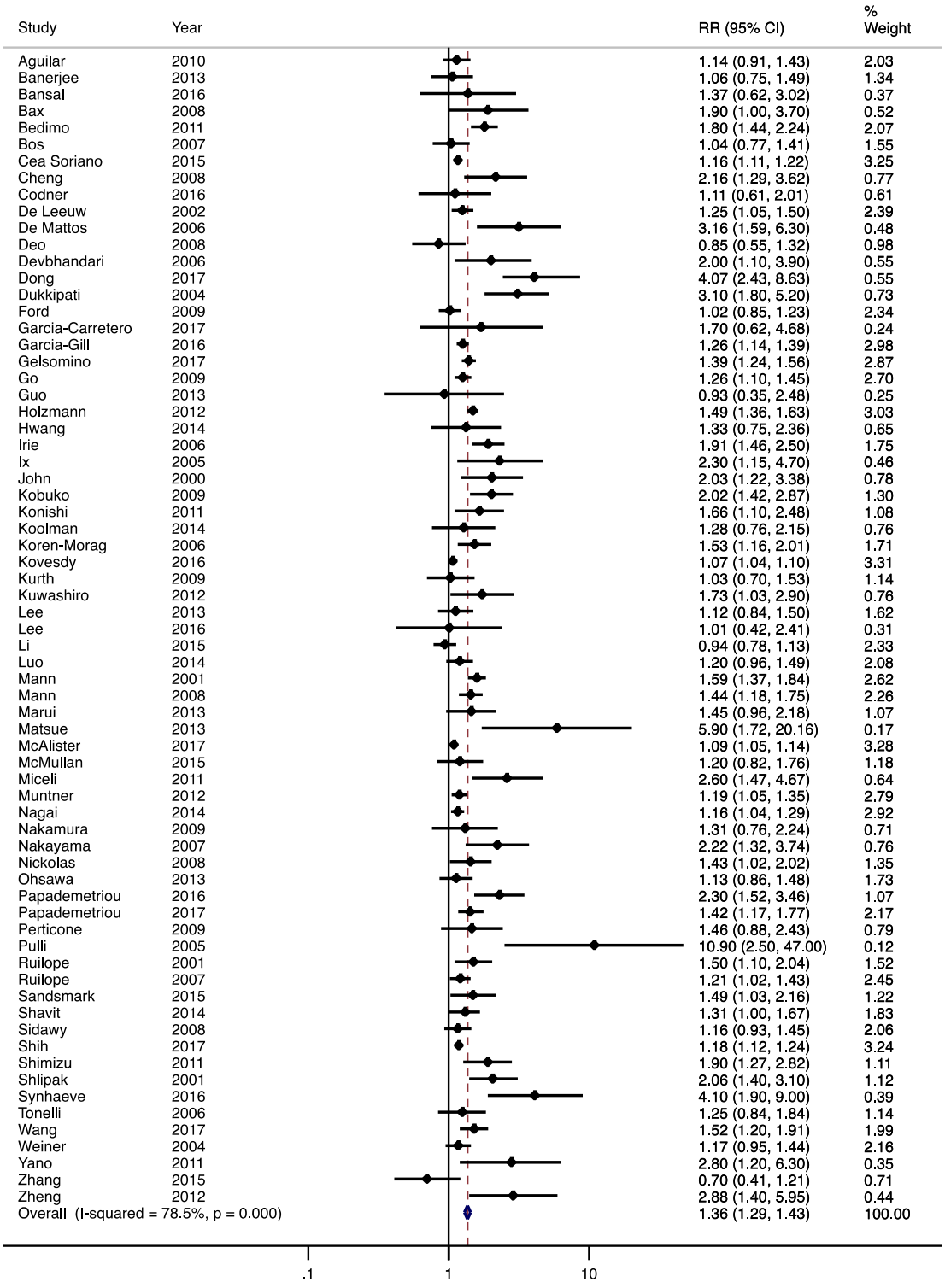


Figure 5-4 Risk ratio (RR) for the association of CKD (defined as eGFR < 60 ml/min/1.73m^2) and stroke risk adjusted for traditional cardiovascular risk factors, using a fixed-effects model.

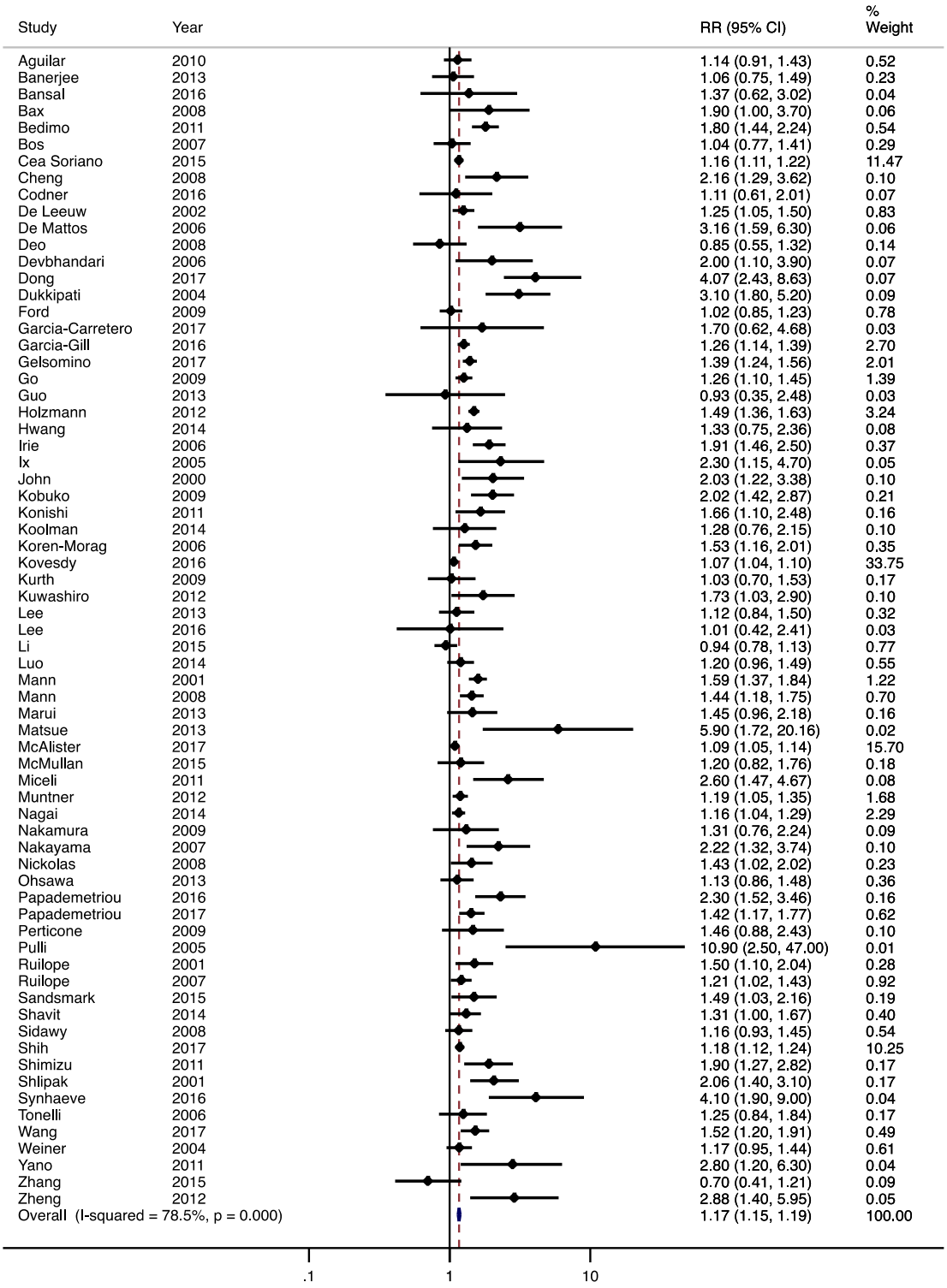


Figure 5-5 Unadjusted and adjusted risk ratios (RR) reported for the association of CKD (as defined by eGFR < 60ml/min/1.73m^2) and stroke risk using paired study estimates only. Risk ratios were adjusted for traditional cardiovascular risk factors (exact methods varied between studies).

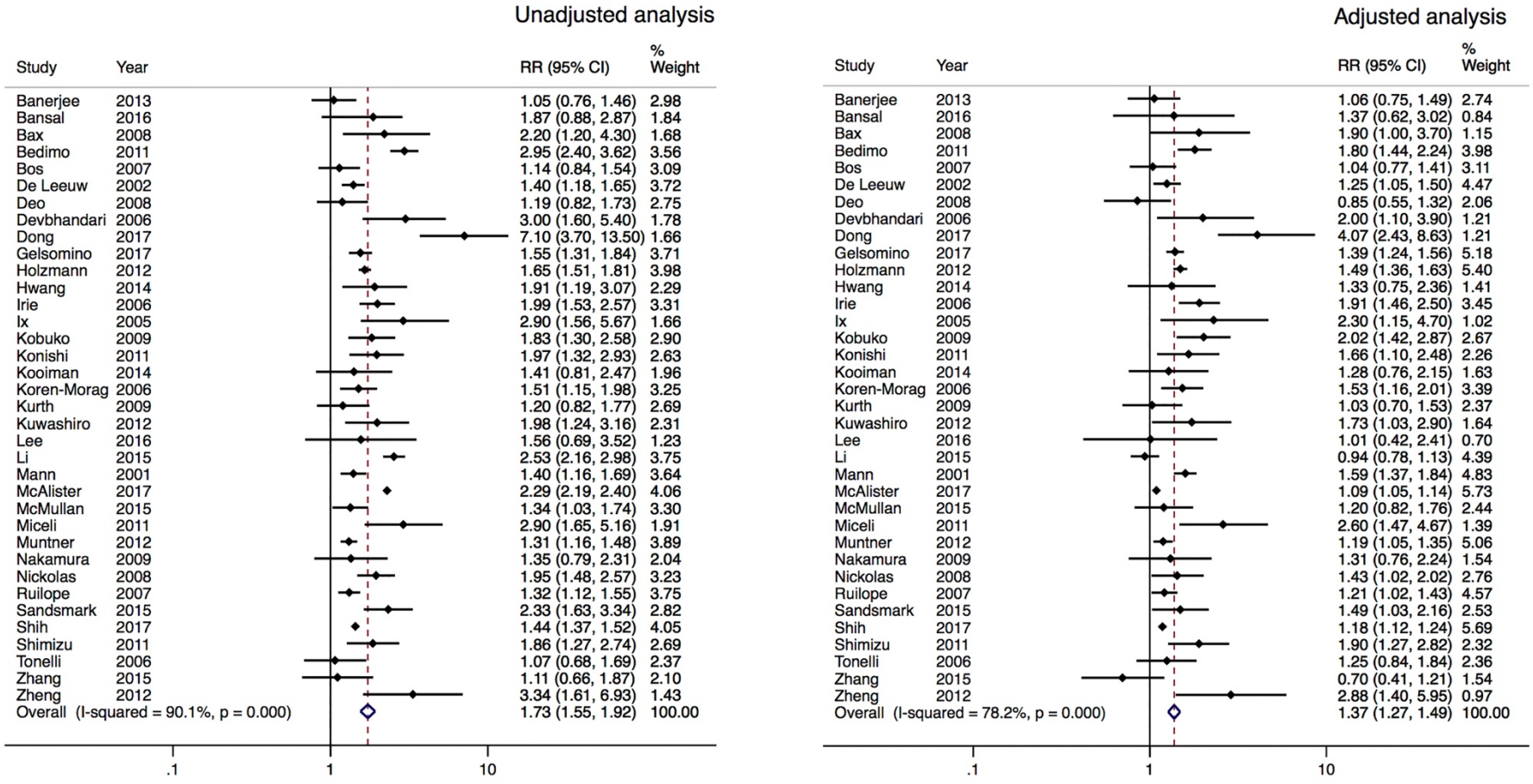


Figure 5-6 Risk ratio (RR) for the association of CKD and ischaemic stroke risk adjusted for traditional cardiovascular risk factors.

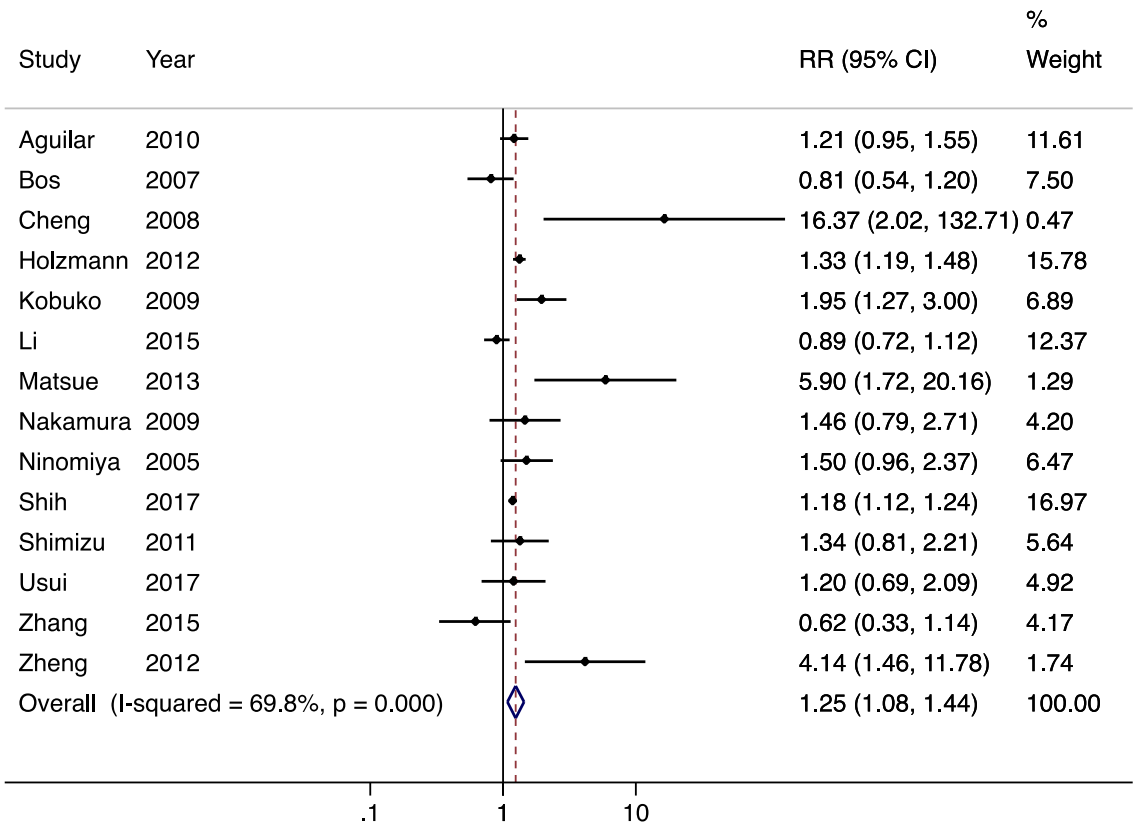


Figure 5-7 Risk ratio (RR) for the association of CKD and haemorrhagic stroke risk adjusted for traditional cardiovascular risk factors

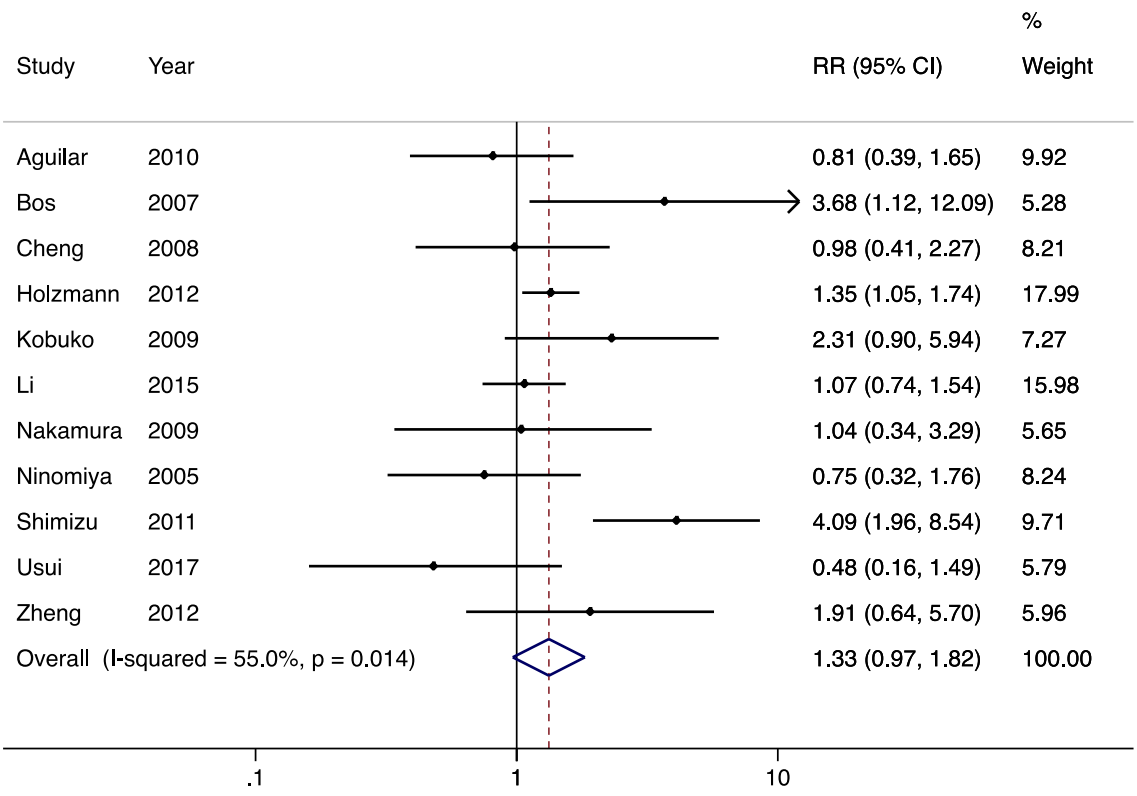


Figure 5-8 Funnel plot to assess for publication bias

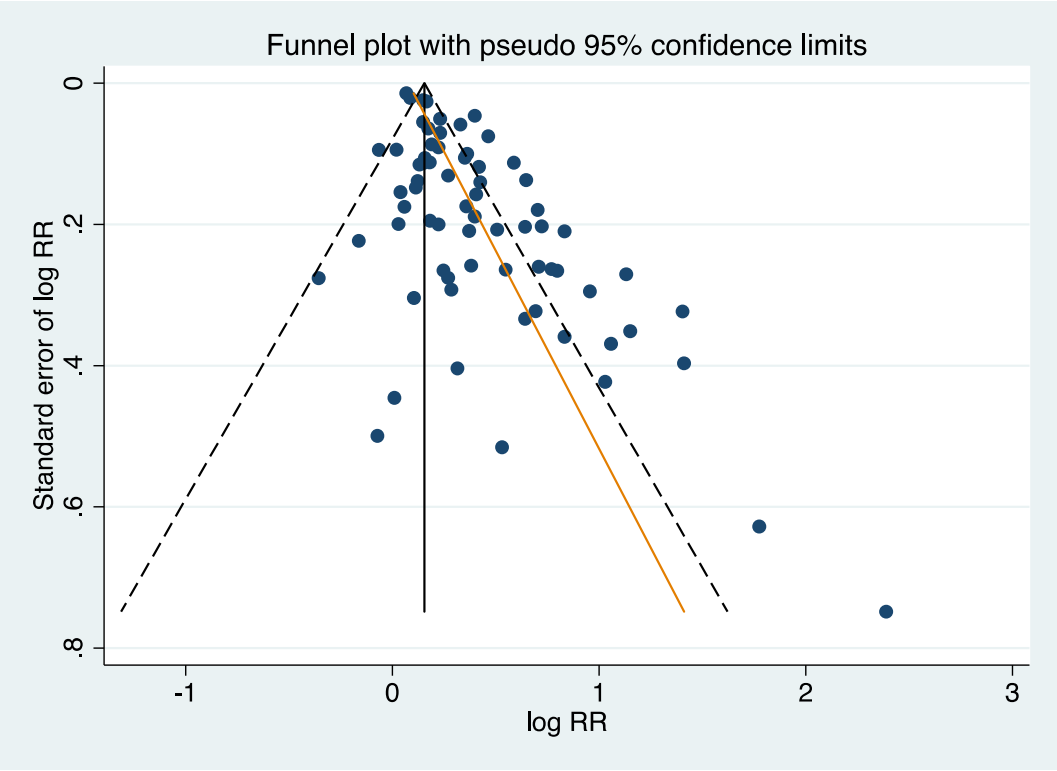
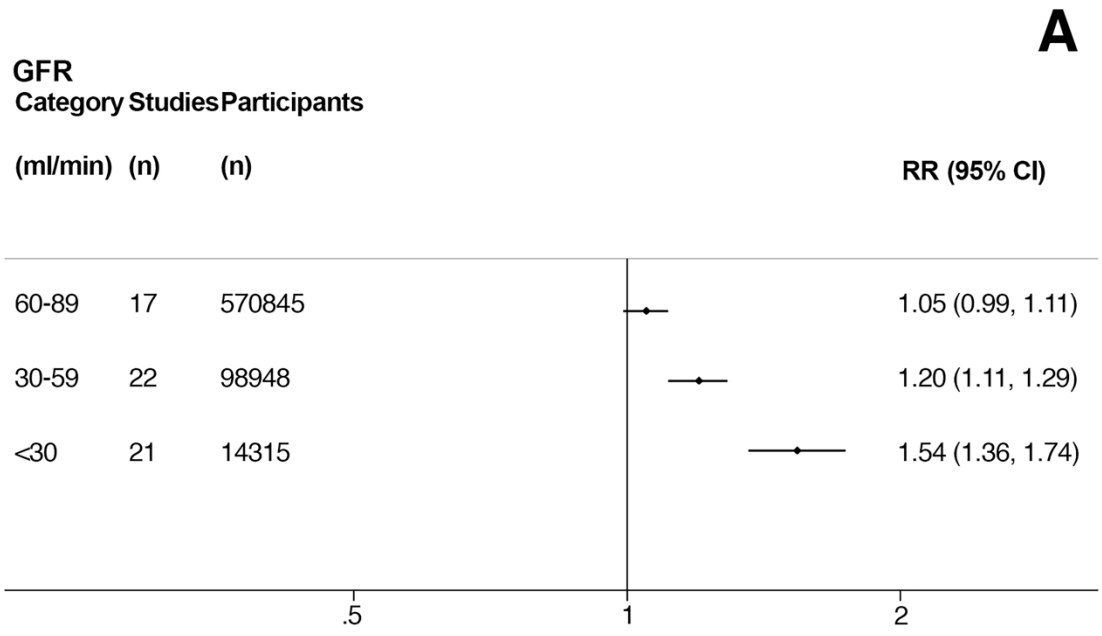
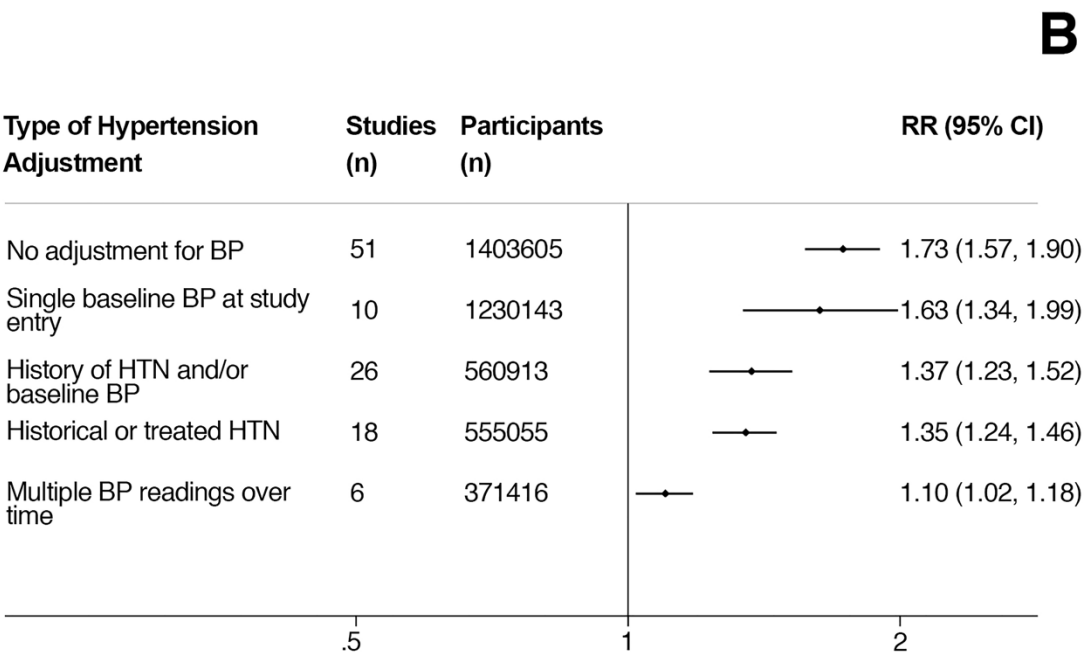


Figure 5-9 A: Adjusted relative risk (RR) of stroke by GFR categories. B: Variation in the RR for the association of CKD and stroke risk depending on the method of hypertension adjustment used in the studies. All studies were also adjusted for other traditional risk factors.





5.7 Appendix

Table 5-4 Characteristics of included studies.

Study reference, Country, Name, (Reference)	Design, population, ethnicity	Size, (% men)	Mean or median age (SD or range)	GFR (ml/min/1.73m^2)	Albuminuria (category)	Stroke type(n) (Classification)	Follow-up (months)	Other stroke characteristics	Adjustment (Hypertension)
				Formula ***Reference*****: range(n)** ***Comparison*****: range (n)**	**Measurement** ***Reference*****: range (n)** ***Comparison*****: range (n)**				
Aguilar 2010, USA, Cardio-vascular Health Study, [1]	Cohort, No cerebrovascular disease, 14.4% DM, 61.8% HTN, 52.4% ever smoker, 3.9% AF. 17% African-American	3,205, (39)	78.5 (4.8)	MDRD *Reference*: ≥60 (unknown) *Comparison*: <60 (unknown)	ACR *Reference*: None (2,630) *Comparison*: Micro (560) Macro (15) Any (575)	Unspecified (26) Ischaemic (316) Haemorrhagic (48)	104.4	Incident Fatal or non-fatal	Age, sex, race, BMI, smoking, hypertension, diabetes, LVH, AF, internal carotid artery stenosis ≥75%, SBP, DBP (Categorical/Continuous variables - ≥140/90 or physician's diagnosis + use of Rx, SBP, DBP – average over 4-7 years)
Banerjee 2013, France, The Loire Valley Atrial Fibrillation Project [2]	Cohort 100% AF, 34.4% vascular disease, 16.4% DM, 12.6% smoking, 42.9% HTN. Unknown ethnicity	5912 (62.9)	70.1 (13.3)	MDRD *Reference:* ≥60 (2930) *Comparison:* 30-59 (2640) <30 (341)		Ischaemic (171)	29.4	Incident	Age, gender, type of AF, hypertension, DM, vascular disease, heart failure (Categorical variable - hypertension)
Bansal 2016, USA, CRIC study, [3]	Cohort 95% HTN, 61.4% DM, 14.8% smoking, 46.3% atherosclerotic disease. 46% Black, 33.8%, White, 16.7% Hispanic, 3.4% other	1794 (54)	59.9 (11.3)	MDRD *Reference:* None *Comparison:* <30 (1794)		Ischaemic (67)	56.9	Incident	Age, sex, race, site, smoking, BMI, DM, proteinuria, statins, BP components & no. of BP medication classes (Ordinal/categorical - variable –SBP [>140/120-140/<120], DBP [>90/80-90/<80],

									PP [69-153/51-69/15-51] & no. of med classes)
Bautistia 2015, USA, [4]	Cohort 100% AF, 78.1% HTN, 34.9% DM, 25.4% vascular disease, 15.8% prior stroke. 50% Hispanic, 32.2% Black, 17.7% Other	524 (55.1)	71	MDRD *Reference:* >90 (79) *Comparison:* 60-90 (212) 45-59 (92) 30-44 (43) 15-29 (32) <15 (33)		Ischaemic (145)	12	Incident	Age, gender, CCF, DM, HTN, previous stroke, vascular disease (Categorical variable – HTN = multiple SBP>160 mmHg)
Bax 2008, Netherlands, [5]	Cohort, 22% diabetics, 30% cerebrovascular disease, 54% other atherosclerotic disease, 50.6% HTN, 81.2% ever smoker, Unknown ethnicity	3,216, (76)	60 (10.4)	MDRD *Reference*: ≥90 (602) *Comparison*: 60-90 (2,097) <60 (517)	ACR, not used to estimate association with stroke *Reference*: None (2,646) *Comparison*: Micro (570)	Unspecified (112)	39	Incident or recurrent Fatal or non-fatal	Age, sex, BMI, hypertension, IHD, previous CVA, PVD, AAA, diabetes, smoking, ACE/Angiotensin II Receptor Blocker use (Categorical variable SBP≥160 mmHg or a DBP ≥95 mmHg) or on Rx – single reading)
Bedimo 2011, USA, [6]	Cohort, 100% HIV positive on retro-viral medication, 13% diabetics, 38% HTN, 29% smokers Unknown ethnicity	19,424, (98)	46	MDRD *Reference*: ≥90 (unknown) *Comparison*: 60-90 (unknown) <60 (1,554)		Unspecified (868)	47.2	Incident Fatal or non-fatal	Age, hypercholesterolemia, HTN, T2DM, smoking (Categorical variable - history of hypertension)

Bos 2007, Netherlands, [7]	Cohort, 10% diabetics, no cerebrovascular disease, 12% IHD, 13% HTN, 5% AF. 99% White	4,937, (39)	68.9 (57.3-78.8)	Cockroft-Gault *Reference:* ≥60 (2,652) *Comparison:* <60 (2,285)	Unspecified (204) Ischaemic (338) Haemorrhagic (44)	122.4	Incident or recurrent Fatal or non-fatal	Age, sex, systolic/diastolic blood pressure, antihypertensive drug use, LVH, diuretic use, smoking, DM, cholesterol, HDL, uric acid, CRP, IHD, antithrombotic and lipid lowering drug use (Continuous/categorical variables – SBP, DBP, Rx – 2 readings at same visit)
Cea Soriano 2015, UK, [8]	Cohort 100% T2DM, 56.5% HTN, 17.5% smoking, 9.8% previous stroke. Unknown ethnicity	57946 (55.4)	65.7	MDRD *Reference:* ≥60 (40034) *Comparison:* 45-59 (12614) 30 –44 (4326) 15-29 (972)	Ischaemic (3785)	81.1	Incident	Age, sex, BMI, smoking, HTN, hyperlipidaemia, history of MI/IS/TIA, IHD, duration of DM, HbA1c, polypharmacy (Categorical variable - HTN)
Cheng 2008, Taiwan, [9]	Cohort, 9% diabetics, no vascular disease, 38.5% HTN, 23.1% current smokers, Unknown ethnicity	17,026, (76)	57.2 (5.2)	MDRD *Reference:* ≥90 (4190) *Comparison:* 60-90 (11,583) <60 (1,253)	Unspecified (67) Ischaemic (28) Haemorrhagic (57)	180	Incident or recurrent Fatal	Age, sex, BMI, smoking, total cholesterol, haemoglobin, diabetes, systolic blood pressure, hypertension, cardiovascular disease (Continuous/categorical variables – Hx of, >140/90, on Rx)

Codner 2016, Multinational, [10]	Cohort 100% TAVI patients, 95.1% HTN, 31.7% DM, 16.7% smoking, 14.4% previous MI. Unknown ethnicity	1204 (44.5)	81.5 (5.7)	MDRD *Reference:* >60 (288) *Comparison:* 31-60 (458) ≤30 (452) 15D (66)		Unspecified	12	Incident	Gender, device, NYHA class, STS score, peak gradient across the valve, LVEF (Not adjusted for HTN)
Crimi 2016, Italy, PRODIGY trial, [11]	RCT *Inclusion criteria:* CAD requiring PCI *Intervention:* BMS, paclitaxel, zotarolimus-, or everolimus eluting stent. 6 vs 24mth DAPT 71.8% HTN, 24.4% DM, 24.2% smoking. Unknown ethnicity	1981 (76.5)	75 [70-81]	MDRD *Reference:* ≥ 60 (1608) *Comparison:* <60 (373)		Unspecified (48)	24	Incident	Age, LVEF, DM, ACS at presentation, total stent length, DAPT duration, stent type. (Not adjusted for HTN)
D'Ascenzo 2013, Italy, [12]	Cohort 100% TAVI patients 72.8% HTN, 28% DM, 23% cerebrovascular disease, 14.6% previous MI. Unknown ethnicity	364 (34.5)	82.4 (5)	Cockcroft & Gault *Reference:* ≥60 (72) *Comparison:* 30-59 (219) 15-29 (73)		Unspecified (20)	18	Incident	Age, EF, pulmonary HTN, previous MI, PCI/CABG, PVD, previous stroke. (Not adjusted for HTN)
De Leeuw 2002, Multinational, Syst-Eur trial, [13]	RCT, *Inclusion criteria*: isolated systolic hypertension, age≥60. *Intervention*: Ca-channel blocker +/- ACE *Control:* Placebo 11% diabetics, 30% previous cardiovascular disease, 7.3% smoking Unknown ethnicity	4,658, (33)	70 (6.6)	Cockcroft & Gault Serum Creatinine Per 20 µmol/l increase	Dipstick *Reference*: None (4,225) *Comparison*: Micro (324) Macro (109)	Unspecified (129)	24	Incident Fatal or non-fatal	Active treatment, sex, age, systolic blood pressure smoking, previous cardiovascular disease, diabetes (Continuous/categorical variables – on Rx, SBP – 6 readings in 1-month run-in)

De Mattos 2006, USA, [14]	Cohort, 100% renal transplant recipients, 28% diabetics, 35% smokers, 56.2% HTN, 85% white, 4% black, 6% Asians, 4% Hispanic	922 (56)	44.2 (12.1)	Serum Creatinine; Reference: ≤140 µmol/l, eGFR >45 (593) Comparison: >140 µmol/l, eGFR <45 (264)	Unspecified (48)	85	Incident or recurrent Fatal or non-fatal	Diabetes, age, prior CVA, peritoneal dialysis, BMI, era of transplant, pulse pressure. (Continuous variable – PP)
Devbhandari 2006, UK, [15]	Cohort, 17% diabetics, 8% cerebrovascular disease, 76% known IHD, 53% hypertensive, 12.2% current smokers. Unknown ethnicity	19,558, (79)	63.4 (57-73)	Serum Creatinine *Reference*: <200 µmol/l, eGFR>60 (19,172) *Comparison*: >200 µmmol/l, eGFR <60 (386)	Unspecified (238)	36	Unknown	Propensity score: (Logistic EUROSCORE), hypertension, emergent procedure, cerebrovascular disease, diabetes, prior cardiac surgery, sex, EF<30%, BMI, respiratory disease, off-pump surgery, left main stenosis, hypercholesterolemia. (Categorical variable - HTN = A history of blood pressure > 140/90 mm Hg or lower if treated)
Deo 2008, USA , Health ABC study, [16]	Cohort, 15% diabetics, 2% cerebrovascular disease, 9% IHD, 63.3% HTN. 10.3% smokers. 42% black	3,044, (49)	73.6 (2.8)	MDRD *Reference*: ≥60 (2389) *Comparison*: <60 (654)	Unspecified (163)	72	Incident Non-fatal	Race, age, sex, BMI, ETOH, smoking, diabetes, hypertension, aspirin, diuretic, ACE, beta-blocker, statin, LDL/HDL cholesterol, CRP, albumin, IL-6 (Categorical variable - HTN =self-report plus use of antihypertensive medications, or measured systolic blood pressure ≥140 mm Hg or diastolic

								blood pressure ≥ 90 mm Hg)
Dong 2017, China, [17]	Cohort 100% acute ischemic stroke. 67% HTN, 52.2% smoking, 40.2% DM, 10% CAD	972 (53.2)	68 (10.1)	MDRD *Reference:* ≥90 (556) *Comparison:* 60-90 (286) 30-59 (90)	Ischaemic (79)	3	Recurrent	Unknown
Dukkipati 2004, USA, [18]	Cohort, 27% diabetics, 9% cerebrovascular disease, 100% undergoing percutaneous coronary intervention, 65% HTN. Unknown ethnicity	20,679, (68)	65 (12)	Cockroft Gault *Reference*: ≥40 (unknown) *Comparison*: <40 (unknown)	Unspecified (92)	Unknown	Incident and recurrent Fatal and non-fatal	Age, sex, body surface area, diabetes, hypertension, hypercholesterolemia, CCF, previous PCI, PVD, emergent PCI, heparin prior to PCI, year, fluoroscopy time. (Categorical variable - History of hypertension)
Dumonteil 2013, Multinational, PRAGMATIC-Plus Initiative study, [19]	Cohort 100% TAVI patients, 69.5% HTN, 45.2% CAD, 28.5% DM, 15.7% previous stroke	942 (53.8)	81 (7)	MDRD *Reference:* ≥90 (109) *Comparison:* 60-89 (329) 30-59 (399) <30 (72) 15D (33)	Major (22) Minor (3)	1	Incident	Age, sex, DM, COPD, CAD, PVD, LVEF≤35, baseline anaemia category, learning effect, sheath size, access type, paravalvular AR grade ≥2. (Not adjusted for HTN)
Ferro 2015, UK, [20]	Cohort 100% TAVI patients 22.5% previous MI, 22.4% DM, 17.9% previous stroke, 2.5% smoking. Unknown ethnicity	3696 (53.5)		MDRD *Reference:* ≥60 (1390) *Comparison:* 45-59 (1046) 30-44 (846) 15-29 (315)	Unspecified (96)	17.5	Incident	Sex, DM, COPD, extra cardiac arteriopathy, AF, previous cardiac surgery, BMI, LVEF<30%, no coronary vessel with >50% stenosis,

				<15 or D (99)				procedure urgency, aortic valve gradient, non-transfemoral approach, successful valve deployment. (Not adjusted for HTN)
Ford 2009, Multinational, PROSPER study, [21]	RCT, *Inclusion criteria*: Pre-existing or increased risk of vascular disease. *Intervention*: Pravastatin *Control*: Placebo, 12.8% DM, 61.9% HTN, 26.9% current smokers. Unknown ethnicity	5,796, (48)	75.3 (3.3)	MDRD *Reference:* ≥60 (2,702) *Comparison*: 50-60 (1,641) 40-50 (1,104) 20-40 (349)	Unspecified (415)	38	Incident or recurrent Fatal or non-fatal	Randomized treatment, country, sex, smoking, age, hypertension, diabetes, previous vascular disease, systolic/diastolic blood pressure, LDL, HDL, glucose, BMI, CRP. (Continuous/categorical variables – HTN, SBP/DBP)
Garcia—Carretero 2017, Spain, [22]	Cohort 100% HTN, 30.6% DM, Unknown ethnicity	2016 (49.3)	57 (17)	CKD-Epi *Reference:* >90 (1198) *Comparison:* 60-90 (630) ≤ 60 (188)	Unspecified (52)	55.2	Incident	Age, gender, DM, HDL-C, LDL-C. (Not adjusted for HTN)
Garcia-Gill 2016, Spain, [23]	Cohort 21% HTN, 34.3% smoking. Unknown ethnicity	1,081,865 (49.1)	49.5 (11.6)	CKD-Epi *Reference:* ≥90 (703242) *Comparison:* 60-89 (354041) 45-59 (20465) 30-44 (3447) 15-29 (475) <15 (195)	Unspecified (8900)	60	Incident	Age, sex, smoking, DM, SBP, DBP, TC, HDL-C. (Continuous variable)

Gelsomino 2017, Italy, [24]	Cohort 100% CABG patients, 64.3% HTN, 18.3% DM, 0.6% CVD. Unknown ethnicity	1186 (84.9)	69.1 (8.7)	CKD-Epi *Reference:* ≥60 (791) *Comparison:* 45-59 (224) 30-44 (93) ≤29 (78)		Unspecified 30d -early (124) late (72)	66	Incident	Age, LVEF. (Not adjusted for HTN)
Go 2009, USA, [25]	Cohort, 17% diabetics, 9% cerebrovascular disease, 59% other vascular disease.,50.9% HTN, 100% AF. 86% White, 4% black, 5% Asian	13,535, (57)	71.6 (unknown)	MDRD *Reference*: ≥60 (13,535) *Comparison:* 45-60 (7,746) <45 (5,789)	Dipstick *Reference*: None (unknown) *Comparison*: Macro (unknown)	Ischaemic (637)	96	Incident or recurrent Fatal or non-fatal	Age, sex, race, SES, educational attainment, prior ischemic stroke, CCF, diabetes, hypertension, IHD (Categorical variable - Hypertension identified from outpatient sources.)
Gruberg 2014, USA, CARE Registry, [26]	Cohort 100% CAS or CEA, 89.1% HTN, 73.8% smoker, 53.8% IHD, 35.9% DM, 45% prior stroke. 93.5% White	11832 (60.3)	70.8 (10.5)	MDRD *Reference:* ≥90 (2042) *Comparison:* 60-89 (5359) 30-59 (4116) ≤29 (315)		Unspecified In-hospital (353) 30-day (461)	1	Incident	Age, HTN, future major surgery, prior stroke, symptomatic lesions, CCF. (Categorical variable)
Guo 2013, China, [27]	Cohort, 100% AF. 78% HTN, 46% diabetics, 68% IHD, 19% PVD, 25% known cerebrovascular disease	617 (unknown)	78 (11)	MDRD *Reference*: ≥60 (541) *Comparison:* <60 (76)		Ischaemic (40)	12	Incident or recurrent Fatal or non-fatal	Age, sex, HTN, diabetes, CCF, vascular disease, prior stroke, warfarin/statin/diuretic use. (Categorical variable - HTN: resting blood pressure ≥ 140 mm Hg systolic and/or ≥ 90 mm Hg diastolic on at least 2 occasions or current antihypertensive drug treatment.)

Holme 2010, Multinational, IDEAL trial, [28]	RCT, *Inclusion criteria*: ≥80 years, or younger and previous myocardial infarction. *Intervention*: Simvastatin 20mg *Control*: Atorvastatin 80mg 12% diabetics, 7% known cerebrovascular disease, 40% previous coronary revascularization, 32.9% HTN, 79.1% ever smokers, 7.5% AF. Unknown ethnicity	8,863, (unknown)	61.8 (9.5)	MDRD *Reference*: ≥60 (6,542) *Comparison*: <60 (2,321)	Unspecified (323)	57.6	Incident or recurrent Fatal or non-fatal	CCF at baseline. (Not adjusted for hypertension)
Holzmann 2012, Sweden, AMORIS study, [29]	Cohort, 3% DM	539,287, (53.3)	47.7 (14.2)	MDRD *Reference:* >90 (477,046) *Comparison*: 60-90 (59,016) 30-60 (3,006) 15-30 (350)	Unspecified (467) Ischaemic (2,284) Haemorrhagic (605)	141.6	Incident Fatal or non-fatal	Age, sex, diabetes, total cholesterol, triglycerides. (Not adjusted for hypertension)
Hwang 2014, South Korea, [30]	Cohort 100% AMI, 50% HTN, 42.7% smoking, 31.5% DM, 4.2% AF	4738 (71.5)	62.6 (12)	CKD-Epi *Reference:* ≥60 (3556) *Comparison:* <60 (1182)	Unspecified (84)	42	Incident	Age, gender, HTN, DM, smoking, stroke history, Kilip class, LVEF, Hb, hsCRP, medical treatment at discharge. (Categorical variable)

Irie 2006, Japan, [31]	Cohort, 7% diabetics, Mainly Asian	91,432, (34)	58.8 (unknown)	MDRD *Reference*: ≥100 (17,636) *Comparison*: 90-100(21,846) 80-90 (20,402) 70-80 (20,461) 60-70 (8,190) <60 (2,897)	Dipstick *Reference*: None (88,438) *Comparison*: Macro (1,929)	Unspecified (985)	120	Incident Fatal	Age, hypertension, smoking, ETOH, diabetes, total cholesterol, HDL cholesterol, BMI, urinary protein (for eGFR analyses) (Categorical variable – adjusted for hypertensive category).
Itaya 2010, Japan, [32]	Cohort, 51% diabetics, 100% undergoing percutaneous coronary intervention for evaluation of chest pain, 29.6% HTN, 45.3% smoking, Unknown ethnicity	715, (74)	66.8 (11.6)	MDRD *Reference*: ≥60 (563) *Comparison*: <60 (152)		Unspecified (12) Haemorrhagic (1)	20.9	Incident Fatal or non-fatal	Unadjusted
Ix 2005, Multinational, ARTS study, [33]	RCT, *Inclusion criteria*: Ischemic cardiac symptoms *Intervention*: PCI *Control*: CABG, 18.1% DM, 50.4% HTN, 13.2% current smokers. Unknown ethnicity	1,205, (77)	60.5 (9.4)	Cockcroft Gault *Reference*: ≥60 (886) *Comparison*: <60 (290)		Unspecified (37)	36	Incident Fatal or non-fatal	Diabetes, hypertension, ejection fraction, ACE, aspirin, PVD, haemoglobin, COPD, silent ischemia, hyperlipidemia. (Categorical variable – HTN = blood pressure >160/95 on repeat measurements or on antihypertensive medications)
John 2000, USA, [34]	Cohort, 28% diabetics, 68.6% HTN, 7.5% smokers, 13% cerebrovascular disease, 31% IHD. 100% undergoing coronary revascularization, Unknown ethnicity	19,224, (72)	65 (10)	Serum Creatinine *Reference*: ≥2.5mg/dl, eGFR >30 (583) *Comparison*: <2.5mg/dl, eGFR<30 (18,641)		Unspecified (270)	0.03	Incident and recurrent Fatal or non-fatal	Previous CVA, smoking, carotid vascular disease, age, PVD, diabetes, previous CABG. (Categorical variable)

Kokubo 2009, Japan, [35]	Cohort, 5% diabetics, no previous vascular disease, 30.3% HTN, 29.9% current smokers. Mainly Asian	5,494, (47)	54.7 (13.2)	MDRD *Reference*: ≥90 (2,415) *Comparison*: 60-90 (2,452) 50-60 (387) <50 (124)	Unspecified (18) Ischaemic (141) Haemorrhagic (54)	140.4	Incident Fatal or non-fatal	Age, sex, BMI, smoking, ETOH, hypertension, diabetes, hypercholesterolemia. (Ordinal variables - At the time of the baseline examination, subjects were classified into 1 of the 5 BP categories based on the European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 criteria: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg), high-normal BP (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg), and hypertensive (SBP ≥140 mm Hg or DBP ≥90 mm Hg).
Konishi 2011, Japan, [36]	Cohort, 100% undergoing CABG, 38% diabetics, 67% HTN, 69% smokers, 48% IHD, 4% known cerebrovascular disease, 12% AF	1,809 (85)	54.5 (12.0)	Japan-specific *Reference*: >60 (1,488) *Comparison:* <60 (321)	All-cause (127) Unspecified.	136.8	Incident or recurrent Fatal or non-fatal	Age, sex, HTN, SBP/DBP, diabetes, previous IHD or CVA, re-vascularization, aspirin. (Categorical/continuous variables - Hypertension was defined as a systolic blood pressure ≥140mmHg, a diastolic blood pressure ≥90 mmHg, or treatment

								with antihypertensive medications.) .
Koolman 2014, Netherlands, [37]	Cohort 100% AF, 55.1% HTN, 17.5% prior stroke, 17% DM. Unknown ethnicity	724 (56.5)	74.8 (9.7)	MDRD *Reference:* >60 (300) *Comparison:* 30-60 (294) <30 (130)	Unspecified (45)	25.2	Incident	Age, gender, antiplatelets, NSAIDs, HTN, DM, CCF. (Categorical variable)
Koren-Morag 2006, Israel, BIP study, [38]	RCT, *Inclusion criteria*: IHD *Intervention*: Bezafibrate *Control*: Placebo 16% diabetics, no cerebrovascular disease, 100% other vascular disease, 31.8% HTN, 10.7% smokers. Unknown ethnicity	6,685, (89)	59.4 (7.1)	Cockcroft Gault *Reference*: ≥60 (5,345) *Comparison*: <60 (1,340)	Ischaemic (287)	57.6 to 97.3	Incident or recurrent Fatal or non-fatal	Age, sex, inclusion in clinical trial, systolic blood pressure, HTN, diabetes, TGs, %HDL, NYHA functional class, BMI, PVD, smoking, anti-platelets, anti-hypertensives, lipid-lowering agents. (Categorical/continuous variables – HTN, SBP)
Kovesdy 2016, USA, RCAV Study, [39]	Cohort 87% HTN, 49% DM, 40% CAD. 79% White, 17% Black, 2% Hispanic, 2% Other	339887 (97)	69 (10)	CKD-Epi *Reference:* None *Comparison:* <60 (339887)	Ischaemic (14557)	57.6	Incident	Age, sex, race, marital status, income, HTN, DM, CAD, CCF, previous stroke, PVD, malignancy, liver disease, rheumatologic disease, chronic lung disease, dementia, HIV/ AIDS, depression, weight loss, number of antihypertensive, SBP or DBP. (Categorical/continuous variables - baseline BP = average of all measurements during the first 90 days following cohort entry)

Kurth, 2009, USA, Women's health study, [40]	Cohort, 2% diabetics, no known vascular disease, 25.1% HTN. 11.7% current smokers. 94% White.	27,939, (0)	54.7 (1.1)	MDRD *Reference*: ≥90 (14,979); *Comparison*: 75-90 (8,073) 60-75 (3,572) <60 (1,315)	Unspecified (389)	144	Incident Fatal or non-fatal	Age, SBP, HTN, antihypertensive treatment, smoking, body mass index, alcohol consumption exercise, total cholesterol concentration, C reactive protein concentration, postmenopausal hormone use, history of diabetes, as well as randomised treatment assignments. (Categorical/continuous variables - History of hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive drugs), SBP)
Kushiro 2017, Japan, HONEST Study, [41]	Cohort 100% HTN, 20.5% DM, 12.3% smoking, 10.5% CVD.	21591 (49.4)	64.9 (11.9)	MDRD *Reference:* ≥60 (17082) *Comparison:* <60 (4346)	Atherothrombotic infarction (42) Cardioembolic (3) Lacunar (40) Unclassified (16) ICH (17) SAH (8)	24	Incident	Age, sex, DM, FHx of CVD, past CVD, smoking, dyslipidaemia, HTN type. (Categorical variable in stratified analysis

									according to HTN – well controlled, white coat, masked, poorly controlled)
Kuwashiro 2012, Japan, Fukuoka stroke registry, [42]	Cohort, 35% diabetics, 52% smokers, 100% ischemic stroke, 76.5% HTN, 8.6% AF. Unknown ethnicity	876 (61)	69.8 (11.5)	Japan-specific *Reference:* ≥60 (641); *Comparison:* <60 (235)		Ischaemic (876) (TOAST)	12	Incident Non-fatal	Age, systolic blood pressure, anti-hypertensive treatment, smoking, BMI, ETOH, exercise, total cholesterol, CRP, HRT, diabetes, assigned treatments. (Categorical/continuous variables – on Rx, SBP)
Lee 2013, Multinational, VISP trial, [43]	RCT, *Inclusion criteria*: Prior ischemic stroke *Intervention*: High dose vitamin B *Control*: Low dose vitamin B 79% white, 15% black, 6% other. 74% HTN, 29% diabetics, 16% IHD, 17% smokers.	3,673 (63)	66.3 (10.8)	CKD-EPI *Reference*: 60-74 (881) *Comparison*: >105 (220) 90-104 (663) 75-89 (942) 45-59 (631) <45 (336)		Ischaemic (300)	20	Recurrent Fatal or non-fatal	Age, sex, previous CEA, diabetes, IHD, SBP, CCF, smoking, ETOH, BMI, anti-thrombotic use, homocysteine level. (Continuous variable - average seated systolic blood pressure during the trial (follow up at 6/12/24 mths))
Lee 2016, South Korea, [44]	Cohort 74.9% HTN, 28.1% DM, 25.4% smoking, 19.7% IHD	295 (53.2)	67.6 (14-94)	CKD-Epi *Reference:* ≥60 (239) *Comparison:* <60 (56)	UACR *Reference:* <30 (165) *Comparison:* ≥30 (130)	Ischaemic (26) SAH (1)	22	Recurrent Fatal or non-fatal	Age, sex, DM, HTN, smoking, AF, previous stroke, alcohol Hx, NIHSS score. (Categorical variable – on treatment or SBP≥140 or DBP≥90 on repeated exam)

Li 2015, China, [45]	Cohort 43.6% HTN, 32.8% smoking, 9% DM	92013 (70.6)	51.8	CKD-Epi *Reference:* ≥90 (30609) *Comparison:* 60-89 (49089) 30-60 (11801) <30 (514)	Urine dipstick *Reference:* None (88164) *Comparison:* ≥1+ (3849)	Ischaemic (1128) Haemorrhagic (406)	48	Incident	Age, sex, smoking, drinking, BMI, LDL-C, HDL-C, TG, TC, DM, HTN, hyperlipidaemia, AF. (Categorical variable - SBP≥140 or DBP≥90 or on Rx or self-reported Hx)
Luo 2014, China, China National Stroke Registry, [46]	Cohort 100% T2DM, 71.3% HTN, 36.2% smoking, 15.7% CAD	4836 (60.5)	64.9 (11.4)	CKD-Epi *Reference:* ≥120 (387) *Comparison:* 90-119 (2209) 60-89 (1591) 45-59 (381) <45 (268)		Unspecified (1012)	12	Recurrent Fatal or non-fatal	Age, sex, history of stroke, HTN, hyperlipidaemia, AF, CAD, DM, smoking, alcohol, BMI, baseline NIHSS, lipid-lowering drug at discharge, antihypertensive drug at discharge, pneumonia, urethral infection. (Categorical variable - SBP≥140 or DBP≥90 or on Rx or self-reported Hx)
Mann 2001, USA, HOPE trial, [47]	RCT, *Inclusion criteria*: Vascular disease or diabetes and another risk factor *Intervention:* Ramipril, Vitamin E *Control:* Placebo 42% diabetics, 7% known cerebrovascular disease, 80% IHD, 49.7% HTN, 71.1% ever smoker. Unknown ethnicity	9,287, (73)	65.9 (6.7)	Cockcroft Gault *Reference*: ≥65 (5,888) *Comparison*: <65 (3,394)	ACR, but not used to estimate association with stroke. All participants had < macro	Unspecified (381)	54	Incident Fatal or non-fatal	Age; sex; waist-to-hip ratio; body mass index; and history of hypertension, diabetes, coronary artery disease, peripheral vascular disease, smoking, ramipril use, renal insufficiency, SBP/DBP (Both continuous and categorical variables – SBP, DBP, History of HTN)

Mann 2008, Multinational, HOPE-2 trial, [48]	RCT, *Inclusion criteria:* >55 years, high cardiovascular risk. *Intervention:* Folic acid, vitamins B6, B12. *Control:* Placebo 38% diabetics, 9% cerebrovascular disease, 85% other vascular disease, 53.5% HTN. 12% smokers. Unknown ethnicity	3,296, (75)	69 (6.7)	MDRD *Reference:* ≥60 (2,691) *Comparison*: <60 (619)	Unspecified (41)	60	Incident and recurrent Fatal or non-fatal	Gender, systolic and diastolic blood pressure, body mass index, waist-to-hip ratio, history of hypertension, history of stroke and active treatment. (Both continuous and categorical variables – SBP, DBP, hx of)
Marui 2013, Japan, CREDO-Kyoto, [49]	Cohort, 100% PCI/CABG, 71.3% HTN, 43.2% DM, 25.4% smoking	1842 (75.1)	66.7 (8.4)	Cockcroft & Gault *Reference:* ≥60 (1339) *Comparison:* <60 (503)	Unspecified (144)	44.4	Incident	Age, sex, BMI, emergency procedure, prior MI, CCF, stroke, PVD, AF, COPD, malignancy, HTN, DM, hyperlipidaemia, anaemia, proximal LAD & use of certain vessels. (Categorical variable)
Matsue 2013, Japan, [50]	Cohort 100% AMI with PCI, 60.9% smoking, 60.6% HTN	312 (77.6)	66.9 (11.2)	MDRD *Reference:* ≥60 (146) *Comparison:* <60 (166)	Ischaemic	46.1	Incident	Age, sex, smoking, HTN, DM, Hyperlipidaemia, cerebral infarction, medications, culprit lesion, EF, max CK, TC, LDL-C. (Categorical variable = SBP ≥140 +/or DBP≥90 or on Rx)

McAlister 2017, Canada, [51]	Cohort 100% AF, 64.1% HTN, 21.6% DM, 11.3% CAD. Unknown ethnicity	58451 (53.2)	66	CKD-Epi *Reference:* ≥60 (44217) *Comparison:* 45-59 (8046) 30-44 (4264) <30 (1924)	Urine dip/ACR/PCR *Reference:* Neg/<3/<15 (52132) *Comparison:* Trace or 1+/ 3-30/15-50 (3354) 2+/>30/>50 (2965)	Unspecified (5620)	31	Incident	Age, sex, aboriginal status, social assistance, postal code income quintile, rural/urban status, previous TE or bleeding event, CCF, HTN, DM, PVD. (Categorical variable)
McMullan 2014, Multinational, Jichi Medical School ABPM Study, Miyazaki ABPM study, AASK cohort study, [52]	Pooled cohort 100% HTN, 17% CVD, 16% smoking. 50% Japanese, 50% African American	394 (46)	67.5 (6.7)	CKD-Epi *Reference:* ≥65 (None) *Comparison:* <65 (394)		Unspecified (22)		Incident	Age, gender, smoking, BMI, mean 24h SBP, LDL-C, glucose. HR for sleep trough morning blood pressure surge, (10 mmHg), nocturnal dipping (10% increments) & events. (Continuous variables)
Micelli 2011, Multinational, [53]	Cohort, 15% diabetics, 100% undergoing coronary artery bypass grafting, 65.2% HTN. Unknown ethnicity	9,159, (80)	64.1 (9.2)	Cockcroft Gault *Reference*: ≥60 (5,484) *Comparison*: <60 (3,675)		Unspecified (53)	1	Incident or recurrent Fatal or non-fatal	Age, sex, functional capacity, diabetes, hypertension, COPD, neurologic disease, ejection fraction, recent MI, number of previous grafts, off-pump surgery, propensity score (Categorical variable - History of hypertension)

Muntner 2012, USA , REGARDS study, [54]	Cohort, 13% smokers, 48% hypertensive, 17.9% diabetic. 37% black	20,386, (46)	64.4 (9.2)	CKD-EPI *Reference*: >90 (9,431) *Comparison*: 60-90 (9,053) 45-60 (1,321) <45 (581)	ACR *Reference*: None (13,310) *Comparison*: Micro (6,844) Macro (440)	Unspecified (2,548)	25.2	Incident Fatal or non-fatal	Age, race, sex, geographic region, education, household income, smoking, ETOH, BMI, systolic blood pressure, antihypertensive medication use, dyslipidemia, diabetes and CRP (Continuous & Categorical variables – SBP, on Rx)
Nagai 2014, Japan, [55]	Cohort 26.3% HTN, 13.7% smoking	298148 (39.7)	63.2 (8.1)	MDRD *Reference:* ≥60 (98987) *Comparison:* <60 (19391)	Urine dipstick *Reference:* Negative/trace (284567) *Comparison:* ≥1+ (13581)	Unspecified (4426)	36	Incident	Age, sex, BMI, HTN category, smoking, anti-dyslipidaemia drugs, hyperglycemia, hypoglycemic drugs. (Categorical variable – HTN categories = normotensive, untreated, treated, drug-resistant. SBP≥140 or DBP≥90 mmHg)
Nakagawa 2011, Japan, [56]	Cohort, 100% chronic or paroxysmal atrial fibrillation, 17% DM, 41% HTN Unknown ethnicity	387, (75)	66 (11)	Japan-specific *Reference*: >60 (258) *Comparison*: <60 (129)		Ischaemic (5) Haemorrhagic (2)	67.2	Incident or recurrent Fatal or non-fatal	Not adjusted for hypertension.
Nakamura 2009, Japan, MEGA study, [57]	RCT, *Inclusion criteria*: Hypercholesterolemia, no previous cardiovascular events. *Intervention:* Pravastatin + dietary intervention *Control:* Dietary intervention alone. 20.9% DM, 43.1% HTN, 15% smokers.	7,196, (unknown)	58.2	MDRD *Reference*: >60 (2,156) *Comparison*: 30-60 (1,516)		Ischemic (43) Haemorrhagic (13)	63.6	Incident or recurrent Fatal or non-fatal	Age, sex, baseline HDL-cholesterol, hypertension, diabetes, smoking status (Categorical variable)

	Unknown ethnicity								
Nakayama 2007, Japan, Okashama study, [58]	Cohort, 18.6% DM, 22.5% HTN, 15.6% ever smokers Mainly Asian	1,977, (37)	62.9	Cockcroft Gault *Reference*: >70 (555) *Comparison*: 40-70 (1,246) <40 (176)	Dipstick Reference: Micro (unknown) Comparison: Macro (unknown)	Unspecified (112)	96	Incident Fatal or non-fatal	Age, sex, systolic blood pressure, BMI, smoking, use of antihypertensive medication, history of cardiovascular disease, hypercholesterolemia and diabetes (Categorical and continuous variables – SBP, use of antihypertensive medications)
Nickolas 2008, USA, NOMAS study, [59]	Cohort, 19.6% DM, 47.3% ever smoker, 57% White, 22% black	3,298, (33)	69.2 (10.1)	Cockcroft Gault *Reference*: > 60 (945) *Comparison*: 15-60 (2,353)		Ischaemic (177) Haemorrhagic (24)	78	Incident Fatal or non-fatal	Age, sex, education, hypertension, LDL cholesterol, DM, IHD, smoking, ETOH (Categorical variable)
Ninomiya 2005, Japan, Hisayama study, [60]	Cohort, 10.9% DM, 37.9% HTN, 25.2% smokers. 100% Asian	2,634, (42)	59.4 (11.7)	MDRD *Reference*: >60 (2,364) *Comparison*: 15-60 (270)		Ischaemic (137) Haemorrhagic (60)	144	Incident Fatal or non-fatal	Age, systolic blood pressure, antihypertensive medication, ECG abnormalities, diabetes, total cholesterol, HDL, TGs, BMI, smoking, ETOH, homocysteine, CRP The mean of three measurements was used for the analysis.

									Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. (Continuous and categorical variables - systolic blood pressure, antihypertensive medication, hypertension)
Ohsawa 2013, Japan, Iwate-KENCO study, [61]	Cohort 40.2% HTN, 24.1% smoking, 5.1% DM	24560 (34.1)	62.3 (11.4)	CKD-Epi * *Reference:* ≥90 (2508) *Comparison:* 60-90 (20612) 45-60 (1259) <45 (190) *MDRD also reported	UACR *Reference:* None (18620) *Comparison:* 30-299 (5453) ≥300 (487)	Unspecified (605)	67.2	Incident	Age, sex, SBP, BMI, TC, HDL-C, HbA1c, smoking habit, regular drinking habit, exercise habit. (Continuous variable – SBP)
Papademetriou 2016, USA/Canada, ACCORD, [62]	RCT *Inclusion criteria* T2DM with HbA1c ≥ 7.5%, age 40-79 with CVD or 55-79 significant atherosclerosis, albuminuria, LVH, or other RFs> *Intervention:* Target SBP < 120 mmHg *Control:* Target SBP < 140 mmHg 54.2% smoking, 33.7% CVD, 58.9% White, 23.7% Black, 6.8% Hispanic	4678 (52.3)	62.2 (6.9)	MDRD *Reference:* ≥90 (3645) *Comparison:* 60-89 (693) 30-59 (632)		Unspecified (95)	42	Incident Fatal or non-fatal	Study group assignment, center, age, gender, previous CVD/CV event, BMI, HbA1c, SBP, smoking, insulin, anti-hypertensive use. (Continuous & categorical variables - SBP, study group, on treatment)

Papademetriou 2017, Multinational, ORIGIN Trial, [63]	RCT *Inclusion criteria:* ≥50 years with pre- or early T2DM with prior CV event or additional RFs. *Intervention:* Basal insulin *Control:* Standard care without insulin. 88% T2DM, 12% Pre-diabetes, 79.4% HTN, 12.3% smoking. 59% White, 25.3% Latin, 3.3% Black	12174 (65)	63.5 (7.81)	MDRD *Reference:* ≥90 (2940) *Comparison:* 60-89 (6855) 30-59 (2379)	UACR *Reference:* <30 (9786) *Comparison:* 30-300 (1838) >300 (550)	Unspecified (634)	74.4	Incident Fatal or non-fatal	Age, gender, BMI, factorial allocation, glycemic status, CVD Hx, smoking, SBP, PP, HR, history of HTN, use of ACE/ARB or statins, fasting glucose, HbA1c, K+ & lipid levels. (Continuous & categorical variables - SBP at entry & Hx of HTN)
Patel 2017, USA, [64].	Cohort 100% PCI, 83.3% HTN, 37.7% DM, 28.6% smoking. 49.2% White, 14.9% Black, 11.2% Asian, 20.4% Hispanic	6478 (71.3)	67.1 (12.2)	CKD-Epi *Reference:* >90 (1351) *Comparison:* 60-89 (2882) 30-59 (1742) 15-29 (191) <15 or D (312)		Unspecified (20)	42	Incident	Age, CCF NYHA class, previous stroke, HTN, EF <40%, history of PCI, statin, beta blocker, ACE/ARB use, post-procedure transfusion. (Categorical variable)
Perticone 2009, Italy, [65]	Cohort, 100% post-menopausal women, 56.6% HTN, 32.1% current smokers. Southern Italians	1,500, (unknown)	52.7 (5.7)	MDRD *Reference*: >60 (1,071) *Comparison*: <60 (429)		Unspecified (65)	72.6	Incident Fatal or non-fatal	Age, smoking, cholesterol, systolic blood pressure, fasting glucose, BMI, menopause, MS (Continuous variable – SBP)
Protack 2011, USA, [66]	Cohort, 100% undergoing carotid revascularization, 32% DM, 87% HTN, 73% ever smokers. Unknown ethnicity	921, (64)	71 (10)	MDRD *Reference*: >60 (604) *Comparison*: 30-60 (262) <30 (55)		Unspecified (28)	1	Incident	Unadjusted
Pulli 2005, Italy, [67]	Cohort, 100% undergoing carotid revascularization	1,883, (2)	70 (7.3)	Serum Creatinine *Reference*: >30 (1,870) *Comparison*: <30 (13)		Unspecified (48)	36	Incident	Age, sex, respiratory insufficiency, cardiac disease, re-intervention.

									Not adjusted for hypertension.
Rahman 2006, USA, ALLHAT trial, [68]	RCT, *Inclusion criteria*: >55 years, HTN with ≥1 risk factor for coronary heart disease. *Intervention:* Chlorthalidone *Control:* Amlodipine/Lisinopril 36.1% DM, 21.9% smoking, 48% white/31% black	31,897, (54)	67.9 (7.8)	MDRD *Reference*: >90 (8,126) *Comparison*: 60-90 (18,109) 15-60 (5662)		Unspecified (1,435)	72	Incident or recurrent Fatal or non-fatal	(Continuous variable – SBP, DBP)
Ruilope 2001, Multinational, HOT study, [69]	RCT, *Inclusion criteria:* Hypertensive *Intervention:* Aspirin, DBP target ≤80/85/90mmHg *Control:* Placebo, DBP target ≤80/85/90mmHg, 8% DM, 15.9% smokers. Unknown ethnicity	18,790, (53)	61.5 (7.5)	Cockcroft Gault *Reference*: >60 (15,770) *Comparison*: <60 (2,821)		Unspecified (288)	45.6	Incident or recurrent Fatal or non-fatal	Blood pressure, age, sex, smoking, previous cardiovascular disease, diabetes, total serum cholesterol (Categorical variable – target DBP groups)
Ruilope 2007, Multinational, VALUE trial, [70]	RCT, *Inclusion criteria*: Hypertensive, high cardiovascular risk. *Intervention:* Valsartan *Control:* Amlodipine, 89% white/4% black/4% Asian. 31.7% DM, 24% smokers	15,245, (58)	67.2 (8.1)	Cockcroft Gault *Reference*: >60 (9,214); *Comparison*: <60 (5,999)	Dipstick *Reference*: None (11,788) *Comparison*: Any (3,435)	Unspecified (603)	45.6	Incident or recurrent Fatal or non-fatal	Age, sex, IHD, LVH, all-cause death. Not adjusted for hypertension.
Sandsmark 2015, USA, CRIC study, [71]	Cohort 55.2% DM, 33.9% CVD, 13.4% smoking. 42.4% White	3939 (55.2)	58.1 (10.9)	MDRD *Reference:* >60 (702) *Comparison:* 45-60 (1091) 30-44 (1339) <30 (807)	24h urine protein *Reference:* <0.1g/24h (1375) *Comparison:* 0.1-0.5 (1094) 0.5-1.5 (582)	Unspecified (143)	76.8	Incident	Age, sex, race, DM, SBP, hyperlipidaemia, smoking, alcohol use. (Continuous variable – baseline SBP, single reading)

				>1.5 (690)				
Shavit 2014, Israel, [72]	Cohort 100% cardiac surgery, 81% HTN, 42% DM, 12% previous stroke	788 (60)	70 (10)	MDRD *Reference:* ≥60 (none) *Comparison:* <60 (788)	Unspecified (20)	0.5	Incident	Preoperative Hb, sex, severity of preop HF, DM, incidence of blood transfusion, type of surgery, use of diuretics, intraoperative inotrope use. (Not adjusted for HTN)
Shih 2017, Taiwan, [73]	Cohort 100% sepsis survivors, 87.5% HTN, 59.9% CAD, 58.7% DM	304902 (56.5)	67.4 (14.4)	MDRD *Reference:* ≥60 (none) *Comparison:* <60 (304902)	Ischemic (8352)	30	Incident	Subgroup analysis of HR: sex, age, Charlson comorbidity index, HTN, DM, CCF, CAD, stroke, number of organ failure, site of infection, ICU, shock, use of mechanical ventilator. (Categorical variable)
Shimizu 2011, Japan, CIRCS study, [74]	Cohort, 3.7% DM, 14.1% HTN, 26.3% current smokers. 100% Asian	12,222, (37)	53.5 (unknown)	Japan-specific *Reference*: >90 (4,131) *Comparison*: 60-90 (6,340) <60 (1,309)	Unspecified (53) Ischaemic (327) Haemorrhagic (186)	204	Incident Fatal or non-fatal	Family history of stroke, BMI, SBP, anti-hypertensives, smoking, ETOH, total cholesterol, diabetes, menopausal status. (Continuous (SBP) and categorical (HTN) variables)

Shlipak 2001, USA, HERS study, [75]	RCT, *Inclusion criteria:* Post menopause, aged <80, known IHD, no hysterectomy. *Intervention:* HRT *Control:* Placebo 25% DM, 58.7% HTN, 13.4% current smokers. 89.2% White	2,763, (0)	66.5 (6.8)	Cockcroft Gault *Reference*: >60 (1,306) *Comparison*: 40-60 (1,135) <40 (322)		Unspecified (214)	49.2	Incident or recurrent Non-fatal	Age, race, hypertension, diabetes, smoking, previous CABG, BMI, waist: hip ratio, LDL/HDL cholesterol, TGs, lipoprotein(a) level, physical activity, lipid lowering medication and diuretic use, AF (categorical variable)
Sidawy 2008, USA, [76]	Cohort, 100% undergoing carotid artery intervention. 18% diabetics, 40% smokers, 9% previous CVA, 82% white	22,080 (98)	68.3 (8.6)	MDRD *Reference*: >60 (13,965) *Comparison*: 30-60 (6,423) <30 (511)		Unspecified (374)	1	Incident or recurrent Non-fatal	Age, sex, history of CVA, CCF, COPD, diabetes, smoking, ETOH, functional status, hemoglobin, albumin. Not adjusted for hypertension.
Synhaeve 2016, Netherland, FUTURE study, [77]	Cohort 100% stroke, 52.4% smoking, 35.2% HTN, 8.3% DM. Unknown ethnicity	460 (47.4)	41.2 (7.6)	CKD-Epi *Reference:* >120 (39) *Comparison:* 60-120 (392) <60 (29)		Unspecified (52)	138	Recurrent	Age, gender, HTN, DM, CVD. (Categorical variable – HTN = SBP≥135 or DBP≥85 or both – single reading)
Tonelli 2005, USA, CARE trial, [78]	RCT, *Inclusion criteria:* Hyperlipidemia and previous MI *Intervention:* Pravastatin *Control:* Placebo, 14.1% DM, 42.5% HTN, 16.1% current smokers. Unknown ethnicity	4,098, (86)	59.7 (50-70)	MDRD *Reference*: >60 (3,218) *Comparison*: <60 (880)	Dipstick *Reference*: None (3,546) *Comparison*: Macro (552)	Unspecified (130)	58.9	Incident Non-fatal	Age, sex, ethnic origin, smoking, BMI, waist: hip ratio, fasting glucose, hemoglobin, albumin, LDL/HDL cholesterol, TGs, systolic/diastolic blood pressure, location, LVEF, use of drugs (ACEi, aspirin, or pravastatin). (Continuous variables – SBP/DBP)

Usui 2017, Japan, Hisayama Study, [79]	Cohort 21.3% smoking, 12% DM	2630 (42.1)	58.9 (11.4)	CKD-Epi *Reference:* ≥60 (2273) *Comparison:* <60 (357)	Ischaemic (212) Haemorrhagic (65)	228	Incident	Age, sex, SBP, antihypertensive Rx, DM, BMI, serum albumin, serum hs-CRP, ECG abnormalities, smoking habit, alcohol intake, regular exercise. (Cateogrical & continuous variables – on Rx, SBP)
Wang 2017, China, [80]	Cohort 100% stroke, 75.9% HTN, 43.1% smoking, 18.8% DM, 12.9% IHD	21075 (62.7)	64.3 (12)	CKD-Epi *Reference:* ≥90 (11847) *Comparison:* 60-89 (5292) <60 (1596)	Unspecified (916)	12	Recurrent	Age, sex, history of stroke, DM, dyslipidaemia, baseline NIHSS, current/previous smoking, alcohol, AF, CAD, BMI on admission & pneumonia. Stratified by HTN status. (Categorical variable – self-reported history, on Rx before index event or new diagnosis at DC)
Weiner 2004, Multinational, ARIC, [81] Framingham, Framingham offspring and Cardiovascular health studies,	Cohort, 25% smokers, 9.5% DM, 39.7% HTN, 18% black	22,634, (44)	57.1 (11.6)	MDRD *Reference*: >60 (20,970) *Comparison*: 15-60 (1,664)	Unspecified (712)	99	Incident or recurrent Fatal or non-fatal	Age, sex, hypertension, diabetes, blood pressure, BMI, total /HDL cholesterol, smoking, ETOH, LVH, education, race Hypertension was defined as systolic BP ≥140 mmHg, diastolic ≥90 mmHg, or use of an antihypertensive medication.

									(Categorical [history of] and continuous [sbp] variables)
Yamamoto 2009, Japan, [82]	Cohort, 100% T2DM, Unknown ethnicity	653, (65)		Japan-specific *Reference*: >60 (506) *Comparison*: <60 (147)	ACR *Reference*: None (312) *Comparison*: Micro (341)	Unspecified (5)	36	Incident or recurrent Fatal or non-fatal	Unadjusted
Yano 2011, Japan, [83]	Cohort, 100% hypertensive, 14.6% DM, 16.8% current smokers. Unknown ethnicity	514, (37)	72.2 (8.6)	Cockcroft Gault *Reference*: >60 (289) *Comparison*: <60 (225)		Unspecified (8) – Ischaemic (30) Haemorrhagic (5)	41	Incident Fatal or non-fatal	HTN = clinic BP ≥ 140/90 mmHg or on medication with anti-hypertensive drugs. (Categorical variable – all patients were hypertensive but analysis was adjusted for antihypertensive med use)
Zhang 2015, China, CSPPT, [84]	RCT *Inclusion criteria:* 45-75 yrs with HTN *Intervention:* Enalapril & folic acid *Control:* 31% smoking, 11.1% DM	19599 (40.8)	60 (7.5)	CKD-Epi *Reference:* ≥90 (13418) *Comparison:* 60-89 (5768) <60 (413)	Urine dipstick *Reference:* None (16663) *Comparison:* Trace (1812) ≥1+ (1154)	Ischaemic (472) Haemorrhagic (111) Undefined (2)	54	Incident	Age, study centre, gender, treatment group, smoking, alcohol, BMI, baseline SBP/DBP, mean SBP/DBP over treatment period, TC, HDL, FPG, homocysteine, folate. (Continuous variables – baseline & mean)
Zheng 2012, China, [85]	Cohort, 100% HTN, 11% diabetics, 39% smokers. Mainly Chinese	3,711 (43)	56.3 (10.7)	CKD-EPI *Reference*: >90 (1625) *Comparison*: 60-90 (1967) <60 (119)		Ischaemic (98) Haemorrhagic (75)	55.4	Incident Fatal or non-fatal	Age, sex, ethnicity, BP, BMI, antihypertensive drug use, smoking, ETOH, DM, lipids, duration of HTN, lipid lower medications. The mean of three BP measures was

	calculated and used for all analysis. Participants with hypertension at baseline were defined as they had an average systolic BP at least 140 mmHg, and/or an average diastolic BP at least 90 mmHg, and/or use of antihypertensive medications within the previous 2 weeks. (Both continuous [SBP & DBP] and categorical variables [antihypertensive medication & duration > 10 years])

Abbreviations: AAA indicates abdominal aortic aneurysm; ACE, Angiotensin Converting Enzyme inhibitor; ACR, albumin:creatinine ratio; AF, atrial fibrillation; AR, aortic regurgitation; A2RB, Angiotensin 2 Receptor Blocker; BMI, body mass index; BMS, bare metal stent; Ca, calcium; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCF, congestive cardiac failure; CEA, carotid endarterectomy; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CRP, C Reactive Protein; CVA, cerebrovascular accident; CVD, cardiovascular disease; DAPT, dual anti-platelet therapy; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiograph; ETOH, alcohol; GFR, glomerular filtration rate; Hb, haemoglobin; HDL, high density lipoprotein; HIV, Human Immunodeficiency Virus; HRT, hormone replacement therapy; HTN, hypertension; IHD, ischemic heart disease; IS, ischemic stroke; LAD, left anterior descending artery; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale; NSAIDs, Nonsteroidal anti-inflammatory drugs; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PCR, protein:creatinine ratio; PP, pulse pressure; PVD, peripheral vascular disease; Rx, treatment; SBP, systolic blood pressure; SD, standard deviation; SES, socio-economic status; STS score, Society of Thoracic Surgery score; TAVI, transcatheter aortic valve implantation; TC, total cholesterol; TE, thromboembolic; TG, triglyceride; TIA, transient ischemic attack

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Chapter 6 Proteinuria as an independent predictor of stroke: systematic review and meta-analysis

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6.1 Chapter outline

Proteinuria has emerged as an important vascular risk factor for adverse cardiovascular events including stroke. Hypertension has been proposed as the principal confounder of this relationship but its role has not been systematically examined. In this chapter, I aimed to determine if proteinuria remains an independent predictor of stroke after more complete adjustment for blood pressure (BP).

I performed a systematic review, searching MEDLINE and EMBASE (to February 2018) for cohort studies or randomized controlled trials that reported stroke incidence in adults according to baseline proteinuria +/- glomerular filtration rate (GFR). Study and participant characteristics and relative risks (RR) were extracted. Estimates were combined using a random effects model. Heterogeneity was assessed by x^2 statistics and I^2, and by subgroup strata and meta-regression, with a particular focus on the impact of more complete adjustment for BP on the association. I identified 38 studies comprising 1,735,390 participants with 26,405 stroke events. Overall, the presence of any level of proteinuria was associated with greater stroke risk (18 studies; Pooled crude RR 2.00, 95%CI: 1.63-2.46; p<0.001) even after adjustment for established cardiovascular risk factors (33 studies; Pooled adjusted RR 1.72, 1.51-1.95; p<0.001), albeit with considerable heterogeneity between studies (p< 0.001; I^2=77.3%). Moreover, the association did not substantially attenuate with more thorough adjustment for hypertension: single baseline BP measure (10 studies; Pooled adjusted RR=1.92, 1.39-2.66; p<0.001); history or treated hypertension (4 studies; Pooled adjusted RR=1.76, 1.13-2.75, p=0.013); multiple BP measurements over months to years (4 studies; RR=1.68, 1.33-2.14; p<0.001).

Even after extensive adjustment for hypertension, proteinuria is strongly and independently associated with incident stroke risk, possibly indicating a shared renal and

cerebral susceptibility to vascular injury that is not fully explained by traditional vascular risk factors.

6.2 Introduction

Proteinuria has emerged as an important vascular risk factor for adverse cardiovascular events across a range of populations.[1-3] It has been suggested that proteinuria not only reflects glomerular damage, but also is a sensitive indicator of generalized endothelial dysfunction and capillary vasculopathy that allows penetration of atherosclerotic lipoproteins into vessel walls.[4]

There appears to be a particularly strong association between proteinuria and stroke. In a previous meta-analysis of 10 cohort studies (140, 231 participants; 3,266 strokes), participants with proteinuria had a 71% greater risk of stroke compared with those without proteinuria.[5] The excess risk of stroke also remained significant after adjustment for other vascular risk factors (relative risk [RR]=1.63). In a larger meta-analysis of 83 studies (over 2 million participants), a 25 mg/mmol increase in albumin-creatinine ratio (ACR) was associated with a 10% increased risk of stroke.[6] Stroke risk increased linearly and additively with declining glomerular filtration rate (GFR) and increasing albuminuria. However in Chapter 5, in my systematic review and meta-analysis of low glomerular filtration rate (GFR) and stroke risk, I showed that this risk association was greatly attenuated by adjustment for long-term blood pressure burden, suggesting that hypertension might confound the association.[7]

As described in Chapter 2, the ‘strain vessel hypothesis’ has been proposed as a possible mechanism for the relationship between renal and cerebrovascular diseases.[8] In the kidney, the juxtamedullary afferent arterioles are small and short vessels that have to maintain a strong vascular tone in order to provide a large pressure gradient in a short distance.[9] These types of vessels are therefore referred to as ‘strain vessels’ as they are most susceptible to hypertensive renal injury with loss of their autoregulatory ability, resulting in glomerular hypertension, sclerosis, and subsequently microalbuminuria.[10]

Cerebral ‘strain vessels’ refer to the deep perforating arteries that arise directly from large high-pressure arteries, such as anterior, middle or posterior cerebral arteries that also have to maintain large pressure gradients from their parent arteries to brain tissue capillaries.[11] The areas of blood supply governed by these perforating arteries are frequently the sites of ischaemic or haemorrhagic stroke when cerebral autoregulation is impaired by chronic hypertension.[12] Thus, ‘strain vessel injuries’ mediated by hypertension may explain the link between vascular damage and microalbuminuria in the kidney and cerebrovascular diseases in the brain.

I hypothesized then that any association between proteinuria and stroke risk may therefore be greatly diminished with adequate adjustment for longer-term blood pressure or prior hypertension. Using a systematic review and meta-analysis, I aimed to assess the impact of proteinuria on stroke risk and whether any association present remained after more complete adjustment for blood pressure.

6.3 Methods

6.3.1 Data sources and searches

As outlined in Chapter 4 (4.2 Systematic reviews and meta-analyses), I updated an earlier systematic review and meta-analysis of randomized controlled trials and cohort studies that had estimated the association between proteinuria and the risk of stroke.[6] The study protocol was registered prospectively on PROSPERO (CRD42019127301) and conformed with PRISMA guidelines.[13] I searched MEDLINE (2013-February 2018) and EMBASE (2013-February 2018) databases using a search strategy developed by a specialized librarian that combined text word and medical subject headings without language restrictions (Table 4-1).

6.3.2 Study selection

I included all randomised controlled trials (RCTs) and cohort studies that measured proteinuria at baseline and reported quantitative estimates with a measure of precision (or original data which allowed their calculation) of the risk of incident or recurrent stroke. Proteinuria must have been quantified by 24-hour urine collection, urine aliquot albumin:creatinine (UACR) or protein:creatinine ratio (UPCR), urine dipstick or agglutination assay. The pre-specified definitions of proteinuria are listed in Table 6-1. However, studies using equivalent or sex-specific cut-off points were also included. Where data on baseline estimated glomerular filtration rate (eGFR) were available, GFR had to be either estimated using a validated formula [Cockcroft-Gault, modification of diet in renal disease (MDRD), CKD epidemiology collaboration (CKD-EPI)], measured directly, approximated from urinary creatinine clearance or estimable from serum creatinine. The outcome of interest was symptomatic stroke confirmed by physician examination, hospital record review or identified from data-linkage of administrative records. Eligible articles were evaluated for overlap based on geographical setting, study period, sample size, and outcome. I excluded cross-sectional and case–control studies, studies where albuminuria or GFR was measured using non-validated methods, studies that had mostly participants with end stage renal disease (by history of dialysis or an eGFR <15 ml/min/1.73 m^2), studies where outcomes were measured by self-reports or proxy reports and studies that reported radiological but clinically silent stroke disease. Studies that used slightly varying eGFR intervals were included if they were otherwise comparable. Disagreement over eligibility was resolved by discussion with the senior author (P.M.R).

6.3.3 Data abstraction and quality assessment.

Key descriptive and quantitative data were recorded for study characteristics, participants, exposures and outcomes. I collected details of the year of study publication, location, size

and duration. Abstracted participant characteristics included age, gender, race and the prevalence of diabetes, known vascular diseases, smoking and hypertension. I also noted if participants were recruited at a time of high stroke risk including around an acute coronary event, coronary revascularization procedure or carotid arterial intervention. I recorded the quantity of albuminuria, the method of measurement, and the units of quantification used. I then extracted data for the relative risk (RR), odds, rate or hazard ratio of stroke associated with each quantity of albuminuria (and with each specified eGFR category if available) and noted whether reported strokes were fatal or non-fatal, incident or recurrent, as well as the subtype of stroke (haemorrhagic, ischaemic or unspecified). I obtained effect estimates from both the unadjusted (or minimally adjusted) and the most fully adjusted model presented noting which variables the model had adjusted for. The standard error of the estimate was also extracted or estimated from the reported 95% confidence interval (CI). I assessed the quality of cohort studies and post hoc analyses of trials using the Newcastle–Ottawa Scale.[14]

6.3.4 Statistical analysis

The leading outcome of interest was the risk of stroke in patients with any level of proteinuria and according to categories (microalbuminuria, macroalbuminuria). I also performed an analysis of studies that reported risk in patients with varying levels of both albuminuria and low eGFR (defined as < 60 ml/min/1.72m^2). When articles provided estimates based on both the MDRD and CKD-EPI equations, I used estimates from the CKD-EPI equation as these result in more accurate risk prediction for adverse outcomes compared with the MDRD study equation.[15] I converted RRs associated with the presence or categories of albuminuria to their natural logarithms and synthesized log RRs and standard errors using the DerSimonian and Laird method in a random effects model. A fixed effect model was also used for comparison with the random effects model on the

overall risk estimate. Reported P values were two sided, with significance set at less than 0.05. When studies published more than one estimate of the association between proteinuria and risk of stroke according to subtypes (e.g. by gender or type of diabetes), a within-study summary estimate was obtained. Heterogeneity among included studies was assessed by x^2 statistics and the I^2 test. Based on the suggestion of the Cochrane Collaboration we regarded heterogeneity as possibly unimportant when the I^2 value was less than 40% and considerable when more than 75%.[16] I used subgroup analyses and meta-regression to explore sources of inconsistency and heterogeneity. Subgroups were pre-specified and included study characteristics (study design, size, location, duration of follow-up), participant characteristics (age, gender, race, prevalence of diabetes, hypertension, smoking, atrial fibrillation, undergoing cardiac or carotid intervention, quantity of albuminuria, eGFR defined by CKD stage) and characteristics of stroke recorded (subtype, severity and whether incident or recurrent). To evaluate the impact of the type of hypertension adjustment on effect estimates, I derived and reported results according to a hierarchy of adjustment. I proposed the following hierarchy from least adjustment to best: no adjustment, adjustment for single (or few) blood pressure readings at study entry alone, composite adjustment for either historical or treated hypertension or single blood pressure measurement, adjustment for only historical or treated hypertension, and adjustment for multiple blood pressure readings over time. I did not specify a single numeric definition of hypertension as the definition of hypertension has clearly changed over time and can differ between guidelines.[17] I also conducted a sensitivity analysis including only studies that specifically adjusted for angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use to determine if this treatment mitigated stroke risk. Publication bias was assessed by visual examination of funnel plots. For all analyses, I used Stata software version 13 (Stat Corp., College Station, TX).

6.4 Results

Combining with the earlier review of 83 studies,[6] I identified a further 120 studies that assessed stroke risk in CKD, resulting in 203 studies reporting 118, 851 strokes in 5,567,768 participants. 38 studies (1,735,390 participants) provided appropriate quantitative data to be included in the meta-analysis of proteinuria and stroke risk (Figure 6-1 and Appendix Table 6-6). The data were derived from 6 RCTs and 32 cohort studies. In total, there were 26,405 stroke events including 21,853 which were not classified by pathological subtype (unspecified), 3730 ischaemic, and 822 haemorrhagic strokes. Characteristics of the included studies and trials are described in Table 6-2 and Appendix Table 6-6. The participant number ranged from 295 to 1,023,686. The follow-up duration ranged from 1 to 324 months. Thirty studies (78.9%) reported unspecified stroke types, 14 (36.8%) reported ischaemic strokes and 10 (26.3%) reported haemorrhagic strokes (Table 6-2). Proteinuria was most commonly quantified using either urine dipstick (14 studies; 36.8%) or UACR (14 studies; 36.8%) followed by multiple methods (4 studies; 10.5%), urine albumin excretion rate (2 studies; 5.3%), 24-hour urine collection (2 studies: 5.3%) and UPCR ratio (1 study; 2.6%). The majority of studies were based in North America (12 studies; 31.6%) followed by Asia (10 studies; 26.3%). 36.8% of included studies reported a high prevalence of diabetes (≥30%). Most studies (35/38) were of good quality and provided multivariate adjusted risk estimates.

Pooling unadjusted results from the random effects model showed that incident stroke increased among patients with any level of proteinuria (RR 2.00, 95%CI 1.63-2.46; $p<0.001$) (Figure 6-2 and Figure 6-4). In pooled multivariate adjusted analysis, this risk association attenuated to an RR of 1.72 (1.51-1.95; $p<0.001$) (Figure 6-3).

Significant heterogeneity existed between studies ($p<0.001$, $I^2=77.3\%$). The size of the estimate was reduced in a fixed effects model but similar when the analysis was confined

to paired studies only (Figure 6-5 and Figure 6-6). From the studies that reported specific stroke subtypes, there was a similar association with ischaemic (Adjusted RR=1.99, 1.48-1.66; p<0.001) and haemorrhagic (Adjusted RR=2.08, 1.65-2.63; p<0.001) stroke risk (Figure 6-7).

Eighteen studies (1,181,884 participants) and 24 studies (1,709,402 participants) reported estimates of the association between microalbuminuria and macroalbuminuria respectively with stroke risk. In adjusted analysis, stroke risk was similar for both macroalbuminuria (Adjusted RR=1.78, 1.53-2.08) and microalbuminuria (Adjusted RR=1.66, 1.28-2.16) (Figure 6-4 and Figure 6-8).

The presence of proteinuria was associated with an increased risk of subsequent stroke in all subgroups when estimates were stratified by study design, location, size, quality, duration of follow-up, GFR formula used, mean age groups, gender, race, percentage of diabetics/hypertensives/atrial fibrillation/smokers, setting of high-risk procedure, and stroke type (Table 6-3). Significant heterogeneity between pooled analyses in univariate meta-regression was noted for smaller studies (< 5000 participants) compared with larger studies (> 5000 participants) (Adjusted RR=2.05, 1.78-2.37 vs RR=1.40, 1.22-1.60, P for heterogeneity among subgroups = 0.002) and for studies with younger populations (<60 years) compared with those with larger ones (≥60 years) (Adjusted RR=2.12, 1.65-2.70 vs RR=1.50, 1.32-1.70, P for heterogeneity = 0.02). In addition, there was a 53% lower risk of stroke reported in randomized trials compared to cohort studies (P for heterogeneity = 0.12) and a 51% greater risk in studies that quantified albuminuria using laboratory methods when compared to those that used only urine dipstick (P for heterogeneity = 0.06). I also observed a stronger association with stroke risk in studies with higher prevalence rates of diabetes (≥30%) (Adjusted RR=2.18, 1.60-2.99, P value for heterogeneity = 0.08). Risk of stroke did not vary substantially or consistently by any other

study, participant, or stroke characteristic. No variable contributed significantly to heterogeneity in a multivariate meta-regression model. In a sensitivity analysis of three studies that specifically adjusted for ACEi/ARB use (along with other covariates), the presence of proteinuria was still associated with a significantly increased stroke risk (RR=1.50, 1.05-2.13; p=0.02).

Seven studies (1,072,129 participants) provided data on the interaction between proteinuria and eGFR. In the presence of a low eGFR, the addition of any level of proteinuria substantially increased the risk of stroke in adjusted analysis (RR=2.23, 1.48-3.37; p<0.01) (Figure 6-9*).*

The funnel plot showed some asymmetry consistent with publication bias with smaller studies showing an exaggerated stroke risk association with proteinuria (Figure 6-10). Egger's test confirms the presence of small-study effects in adjusted analysis (P=0.003).

As I have previously reported in the meta-analysis of low eGFR and stroke risk (Chapter 5), our proposed hierarchy of methods for hypertension adjustment in the included studies is outlined in Table 6-4*.* There was a downward attenuation of the risk association of proteinuria and stroke after crude analysis with adjustment for a single or few blood pressure readings at study entry resulting in an RR of 1.92 (1.39-2.66) followed by adjustment on the basis of a history of or treated hypertension or a baseline blood pressure reading (a composite definition) (RR=1.77, 1.44-2.17). Adjusting for only historical or treated hypertension had a similar impact on the relationship as a more composite definition (RR=1.76, 1.13-2.75). The risk association did not substantially attenuate when only studies adjusting for multiple prior blood pressure readings were included (RR=1.68, 1.33-2.14) (Figure 6-11).

6.5 Discussion

In this meta-analysis of nearly two million participants with over 26,000 stroke events, I found that the presence of proteinuria confers about a 70% greater risk of stroke compared to that in those without it. This association was consistent across various subgroups and stroke subtypes in the presence of adjustment for cardiovascular risk factors. Although residual confounding may remain, it would appear that albuminuria is an important and likely independent risk factor for stroke. The magnitude of this stroke risk estimate with proteinuria is very consistent with that of an earlier, smaller meta-analysis of 10 studies (140, 231 participants; RR=1.71).[5]

However, the exact mechanism mediating the relationship between proteinuria and stroke is not clear. Linked to ischaemic electrocardiographic changes,[18] carotid artery intima media thickness,[19] and left ventricular hypertrophy,[20] albuminuria is thought to be a surrogate marker of subclinical vascular disease and atherosclerosis.[21] The Steno hypothesis suggests that urinary protein excretion not only reflects localized subclinical renal disease but also a more generalized vascular endothelial dysfunction.[22] Although albuminuria may reflect generalized endothelial dysfunction, there may also be more specific haemodynamic mechanisms underlying these associations. In the strain vessel hypothesis,[8] blood pressure has been proposed as the underlying link and I attempted to examine its impact in a sensitivity analysis where we categorized studies according to the extent of their adjustment for hypertension and determined the differential risk associations. Although there were few studies, even in those that extensively adjusted for prior blood pressure, the effect of proteinuria on stroke risk remained suggesting an independent relationship. This contrasts with my previous meta-analysis of low eGFR and stroke risk where the risk association was greatly attenuated when the analysis was confined to studies that adjusted for multiple prior blood pressures.[7] These results do align with those of previous cohort studies and meta-analyses that have suggested that

proteinuria is better predictive of cardiovascular and cerebrovascular events than eGFR.[23, 24]

Albuminuria is clearly a marker of stroke risk and post hoc analysis of large-scale clinical trials suggest that it is also a potential target for risk reduction with anti-proteinuric agents. In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study, of 8,200 patients with hypertension and left ventricular hypertrophy, losartan therapy reduced occurrence of the primary composite endpoint including death, myocardial infarction, and stroke in both diabetic and non-diabetic participants concomitant with reduction in albuminuria.[25] In this study, a major part of the risk predicted by values of albuminuria during treatment was also not explained by the level of systolic blood pressure.

Mechanistically it is unclear whether the associations of albuminuria pathways with stroke reflect a causal relationship or mere correlation due to parallel changes in blood pressure or some other similar pathophysiologic process (e.g. generalized endothelial dysfunction). It is likely that the potentially plausible explanations are not mutually exclusive but could act concurrently. From a genome-wide association study of albuminuria in UK Biobank, using Mendelian Randomization, a genetic risk score of up to 46 albuminuria variants was strongly associated with increased risk of hypertension and stroke.[26] There are clearly bidirectional effects between albuminuria and blood pressure that may contribute to stroke risk but our analysis would suggest that there are other important aetiological factors outside of this complex interplay.

A shared genetic susceptibility for premature vascular disease may explain the higher stroke risk that was observed in studies of younger populations. There is an extension of the Steno hypothesis[27] proposing that the level and the inter-individual variation of

albuminuria in early life reflect differential vascular states and that one may be endowed at birth with a level of albuminuria that may represent a high-risk vascular state associated with increased susceptibility to organ damage in later life.

There are several potential limitations of this meta-analysis. Firstly, there was only one reviewer and thus the results may be biased if the selection criteria for including a study were applied in a subjective manner. To reduce this risk, any questionable studies for inclusion were discussed with the senior author (P.M.R). Secondly, there was considerable heterogeneity in the magnitude of the association between albuminuria and stroke risk across studies. However, although there was significant quantitative heterogeneity, there was remarkably little qualitative heterogeneity. The associations may vary in strength but are almost always in the same direction. Meta-regression analysis did also identify certain characteristics of the studies and study populations that may explain the level of heterogeneity. Some of it may be attributable to study size with greater associations between proteinuria and stroke risk described in smaller studies. Small-study effects could reflect poor methodological quality and lead to an over-estimation of the risk estimate, although generally the quality of included studies in this meta-analysis was good when rated using the previously described tools. The mean age of study participants also contributed significantly to heterogeneity, indicating that there may be residual confounding in younger populations such as other renal vascular or genetic risk factors that have not been adjusted for, which is consistent with findings from the meta-analysis of low eGFR and stroke risk.[7] The method of urinary protein quantification may also have been a source of heterogeneity. Sensitivity analysis according to method of albuminuria was undertaken to avoid potential misinterpretation of findings due to assessment bias since urine dipstick measurements have a lower diagnostic accuracy than the other described methods.[28] In keeping with earlier reviews,[5] the risk estimate was attenuated in studies that used dipstick testing as the method of measurement, and given that this is an imprecise method of measurement, there may have been regression dilution bias and

these studies have likely underestimated the strength of the association between albuminuria and stroke. Indeed, two of the studies[29, 30] contributing most to heterogeneity based their risk estimates on dipstick or mixed method urinary protein quantification. Thirdly, it is challenging to disentangle the potential confounding effects of comorbidities and since this meta-analysis was performed using study-level data as opposed to using individual patient-level data, I was unable to apply a uniform adjustment for confounding variables to all studies which may have led to an overestimation of the true association.

This meta-analysis supports the hypothesis that proteinuria is an independent risk factor for stroke. The association remained even after adjustment for established cardiovascular risk factors including long-term prior blood pressure. My findings would therefore tend to refute the 'strain vessel hypothesis',[8] that hypertensive vascular damage completely underpins the relationship between proteinuria and cerebrovascular disease. There may be a causal relationship between pathways leading to albuminuria, likely at a genetic level, and subsequent stroke risk. Proteinuria could be routinely screened for when cardiovascular risk profiling and may need to be incorporated in risk prediction scores.

6.6 References

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TABLES

Table 6-1 Prespecified Definitions of Albuminuria Categories

Measurement Method	Microalbuminuria	Macroalbuminuria
24-hour urine collection (mg/d)	30-300	>300
Urine albumin excretion rate	30-300 mg/day or 20-200 µg/min	>300 mg/day or >200 µg/min
Spot urine albumin:creatinine ratio (mg/g, mg/mmol)	30-300, 3.4-34	>300, >34
Spot urine protein:creatinine ratio (mg/g, mg/mmol)	N/A	>300, >45
Spot Urine dipstick	N/A	≥ 1+

N/A=Not applicable

Table 6-2 Characteristics of studies included in the meta-analysis.

Characteristics	Number of studies, total = 38	
	N	%
Study Design		
Randomized controlled trial	6	15.8
Cohort study	32	84.2
Location		
North America	12	31.6
South America	1	2.6
Europe	8	21.1
Asia	10	26.3
Multinational	7	18.4
Number of participants		
0 to <2500	14	36.8
≥2500 to <5000	11	28.9
≥5000 to <20000	5	13.2
≥20000	8	21.1
Duration of follow-up (months)		
0 to <24	5	13.2
≥24 to <60	16	42.1
≥60 to <96	5	13.2
≥96	12	31.6
Decade of publication		
1980s	1	2.6
1990s	3	7.9
2000s	19	50.0
2010s	15	39.5
Participant Mean age (years)		
<60	13	34.2
≥60 to <65	10	26.3
≥65 to <70	7	18.4
≥70	5	13.2
Hypertensives (%)		
<25	4	10.5
≥25 to <50	5	13.2
≥50 to <75	7	18.4
≥75	12	31.6
Diabetics (%)		
<15	11	28.9
≥15 to <30	10	26.3
≥30	14	36.8
Stroke Subtype		
Unspecified	30	78.9
Ischaemic	14	36.8
Haemorrhagic	10	26.3

Table 6-3 Subgroup analysis and meta-regression: the effect of study, participant and stroke characteristics on the association between proteinuria and adjusted risk of stroke.

Subgroups	Number of studies	RR (95% CI)	P value for heterogeneity
Study characteristics			
Design			
Cohort	28	1.80 (1.56-2.08)	0.12
Randomized controlled trial	5	1.27 (1.09-1.48)	
Location			
North America	11	1.78 (1.42-2.22)	0.4
Europe	6	1.88 (1.18-3.00)	
Asia	9	1.45 (1.31-1.62)	
Multinational	6	1.75 (1.25-2.47)	
South America	1	2.18 (1.16-4.09)	
Size			
0 to <5000	20	2.05 (1.78 to 2.37)	0.002
≥20000	13	1.40 (1.22 to 1.60)	
Duration of follow-up (months)			
0 to <24	4	1.63 (1.08-2.46)	0.39
≥24 to <60	13	1.39 (1.21-1.60)	
≥60 to <96	5	2.23 (1.66-2.99)	
≥96	11	1.98 (1.61-2.44)	
Albuminuria quantification			
Urine dipstick	13	1.43 (1.28-1.60)	0.06
Laboratory methods	20	1.94 (1.57-2.39)	
Patient characteristics			
Mean age (years)			
<60	11	2.12 (1.65-2.70)	0.02
≥60	22	1.50 (1.32-1.70)	

Gender			
Mainly male	14	1.80 (1.42-2.28)	0.7
Mainly female	19	1.66 (1.44-1.92)	
Race			
Mainly Caucasian	10	1.60 (1.31-1.94)	0.71
Mainly Asian	10	1.49 (1.31-1.70)	
Diabetics (%)			
<15	10	1.59 (1.40-1.82)	0.08
≥15 to <30	9	1.38 (1.13-1.69)	
≥30	12	2.18 (1.60-2.99)	
Hypertensives (%)			
<25	4	1.80 (1.25-2.58)	0.74
≥25 to <50	5	1.41 (1.18-1.67)	
≥50 to <75	6	1.63 (1.17-2.26)	
≥75	10	1.49 (1.26-1.76)	
Smokers (%)			
<15	6	1.64 (1.18-1.26)	0.38
≥15 to <20	5	1.46 (1.09-1.95)	
≥20 to <30	3	1.44 (0.86-2.40)	
≥30	10	1.88 (1.54-2.29)	
Atrial fibrillation (%)			
<10	5	1.83 (1.48-2.26)	0.16
≥10	4	1.29 (0.92-1.82)	
Stroke type			
Incident	20	1.67 (1.42-1.96)	0.23
Recurrent	2	2.16 (1.28-3.64)	
Incident or recurrent	10	1.77 (1.40-2.23)	

CI indicates confidence interval; CKD-EPI, chronic kidney disease epidemiology collaboration; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; RR, relative risk, UACR, urine albumin-creatinine ratio; UAER, urine albumin excretion rate; UPCR, urine protein-creatinine ratio.

Table 6-4 Studies categorized according to a hierarchy of hypertension adjustment, from least (1) to best (4) adjustment

1 = Adjusting for baseline blood pressure at study entry	2= Adjusting for either history of hypertension and/or on antihypertensive treatment and/or baseline blood pressure at study entry	3= Adjusting for either history of hypertension and/or on antihypertensive treatment	4 = Adjusting for multiple blood pressure readings over time*
Hagg 2013 Hitman 2007 Irie 2006 Menne 2014 Nakayama 1997 Sander 2012 Sandsmark 2015 Tonelli 2006 Wagener 1994 Yang 2008	Fuller 2001 Lee 2016 Li 2015 Madison 2006 Miettinen 1996 Muntner 2012 Nagai 2014 Nakayama 2007 Yuyun 2004 Zang 2008	Bello 2011 Go 2009 McAlister 2017 Valmadrid 2000	Aguilar 2010 Da Costa 2017 De Leeuw 2002 Zhang 2015

** Including 24-hour ambulatory blood pressure monitor*

FIGURES

Figure 6-1 Identification and inclusion of study reports of proteinuria and stroke risk.

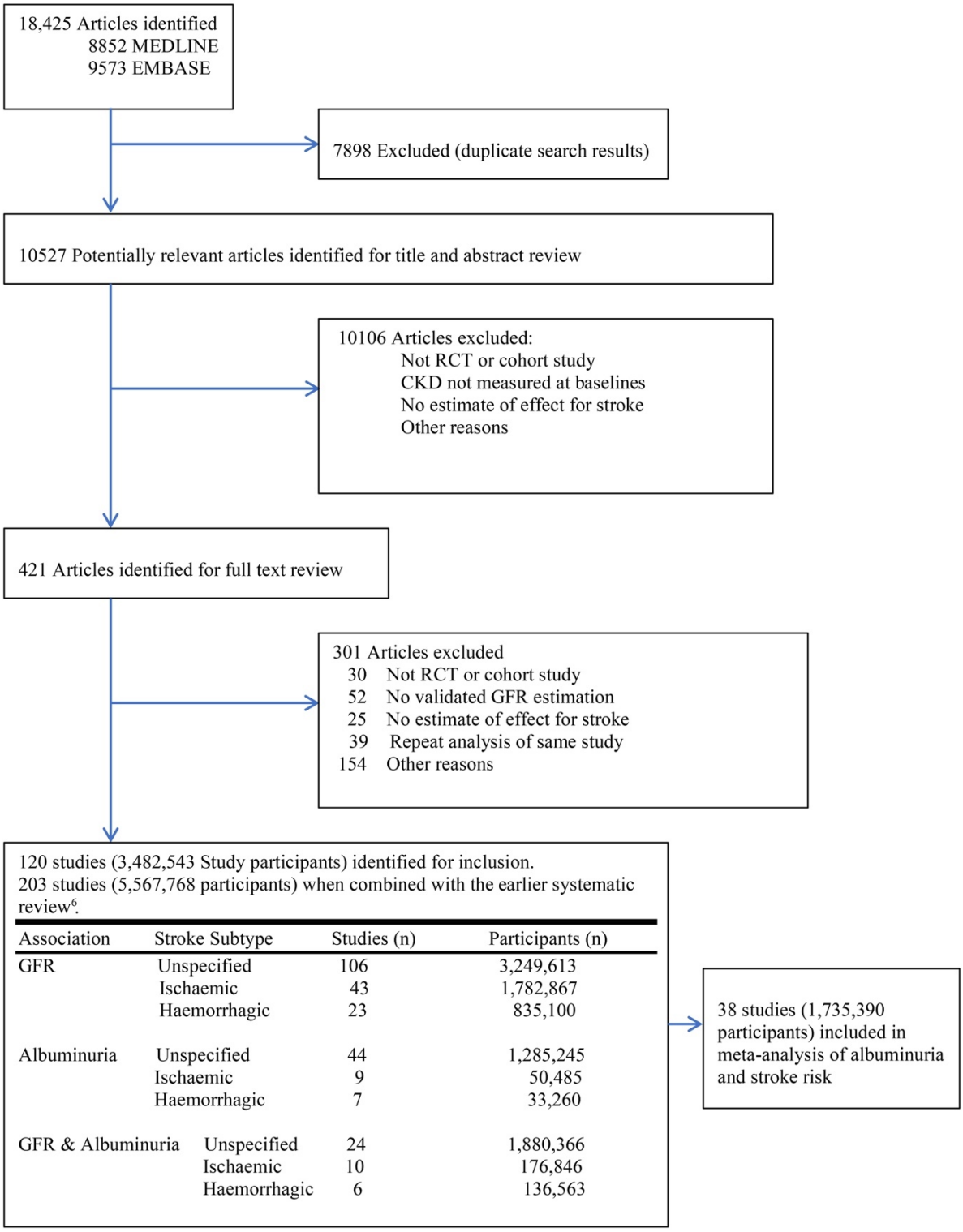


Figure 6-2 Unadjusted risk ratio (RR) for the association of proteinuria and stroke risk.

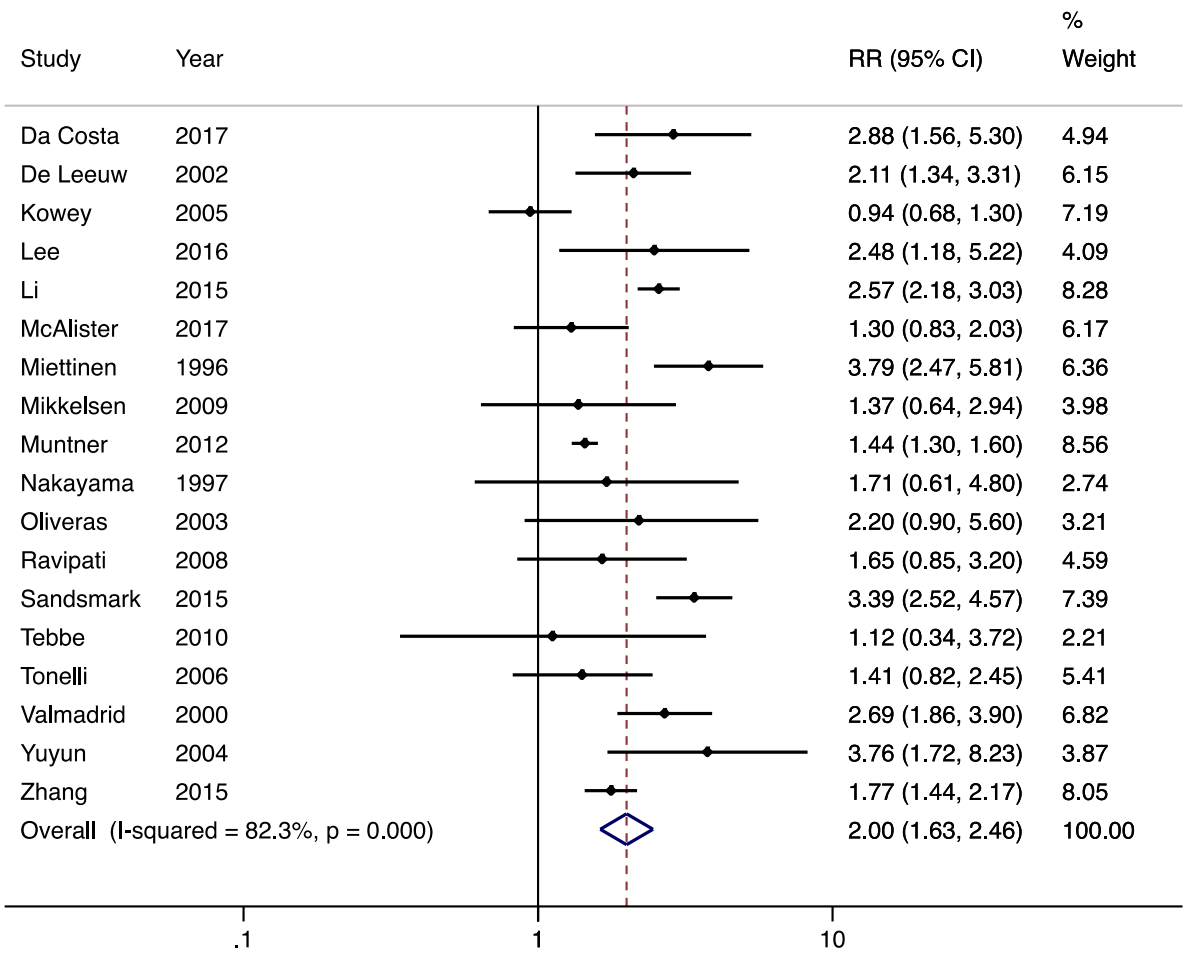


Figure 6-3 Risk ratio (RR) for the association of proteinuria and stroke adjusted for traditional cardiovascular risk factors (exact methods varied between studies).

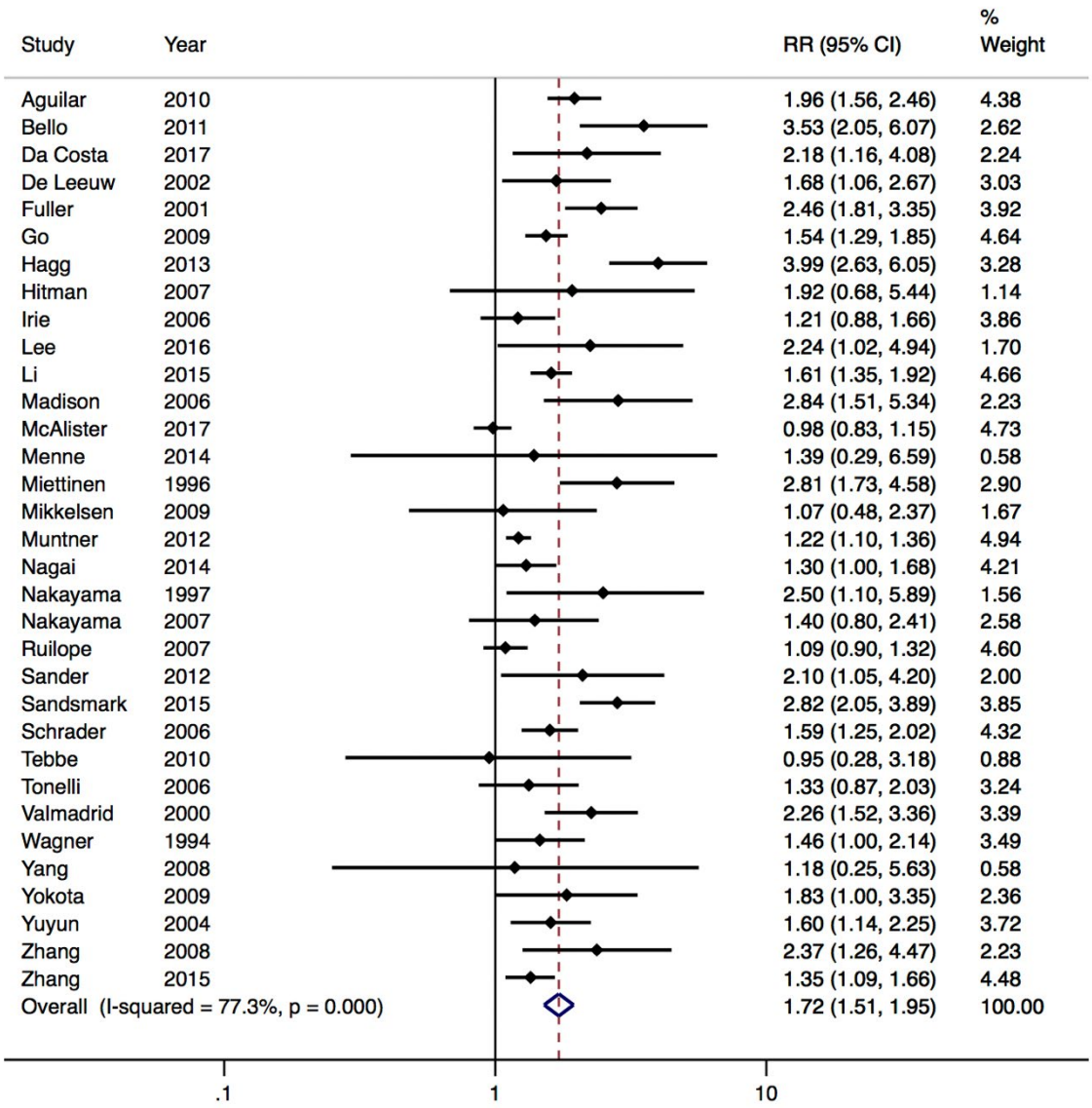


Figure 6-4 Risk ratios (RR) for the association of proteinuria and stroke in unadjusted analysis, in multivariate adjusted analysis that adjusted for conventional vascular risk factors, and in adjusted analysis according to the level of albuminuria. Study and participant numbers along with the level of heterogeneity (I^2 and P value) also described.

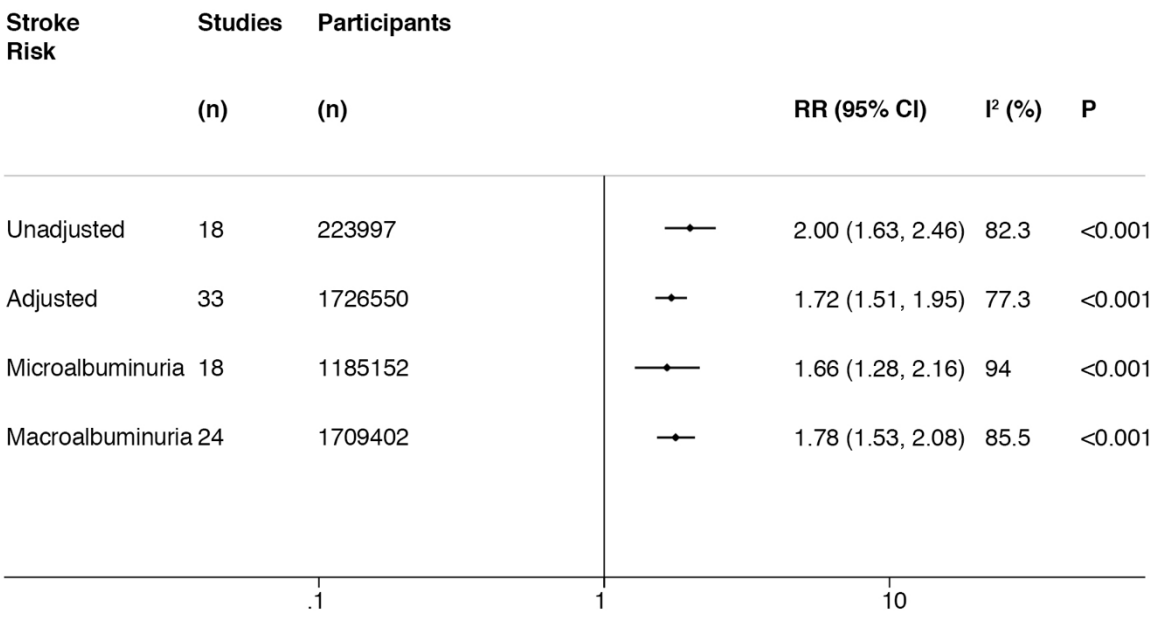


Figure 6-5 Risk ratio (RR) for the association of proteinuria and stroke risk using a fixed effects model adjusted for traditional cardiovascular risk factors (exact methods varied between studies).

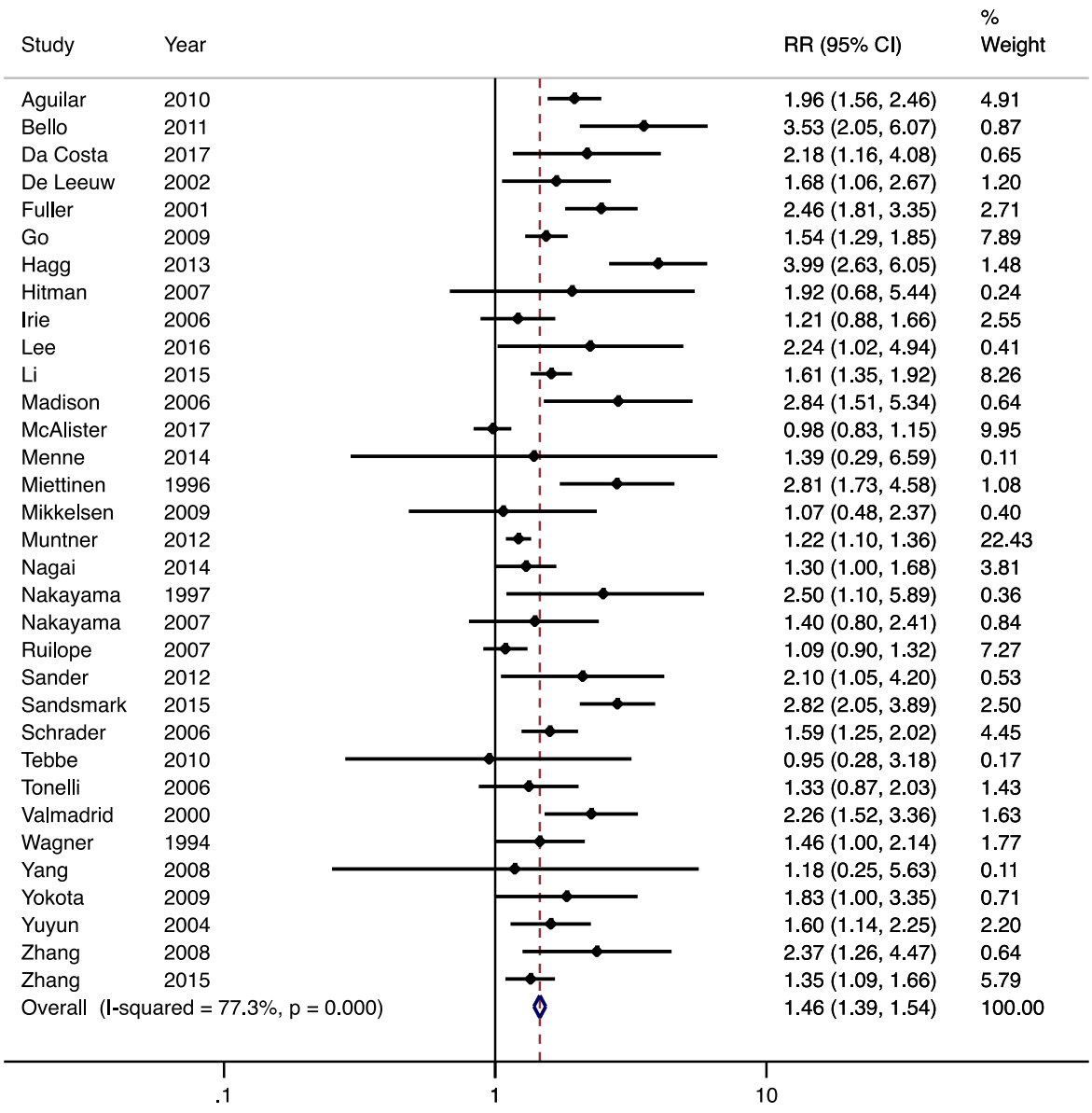


Figure 6-6 Unadjusted (A) and adjusted (B) risk ratios (RR) for the association of proteinuria and stroke risk using paired study estimates only.

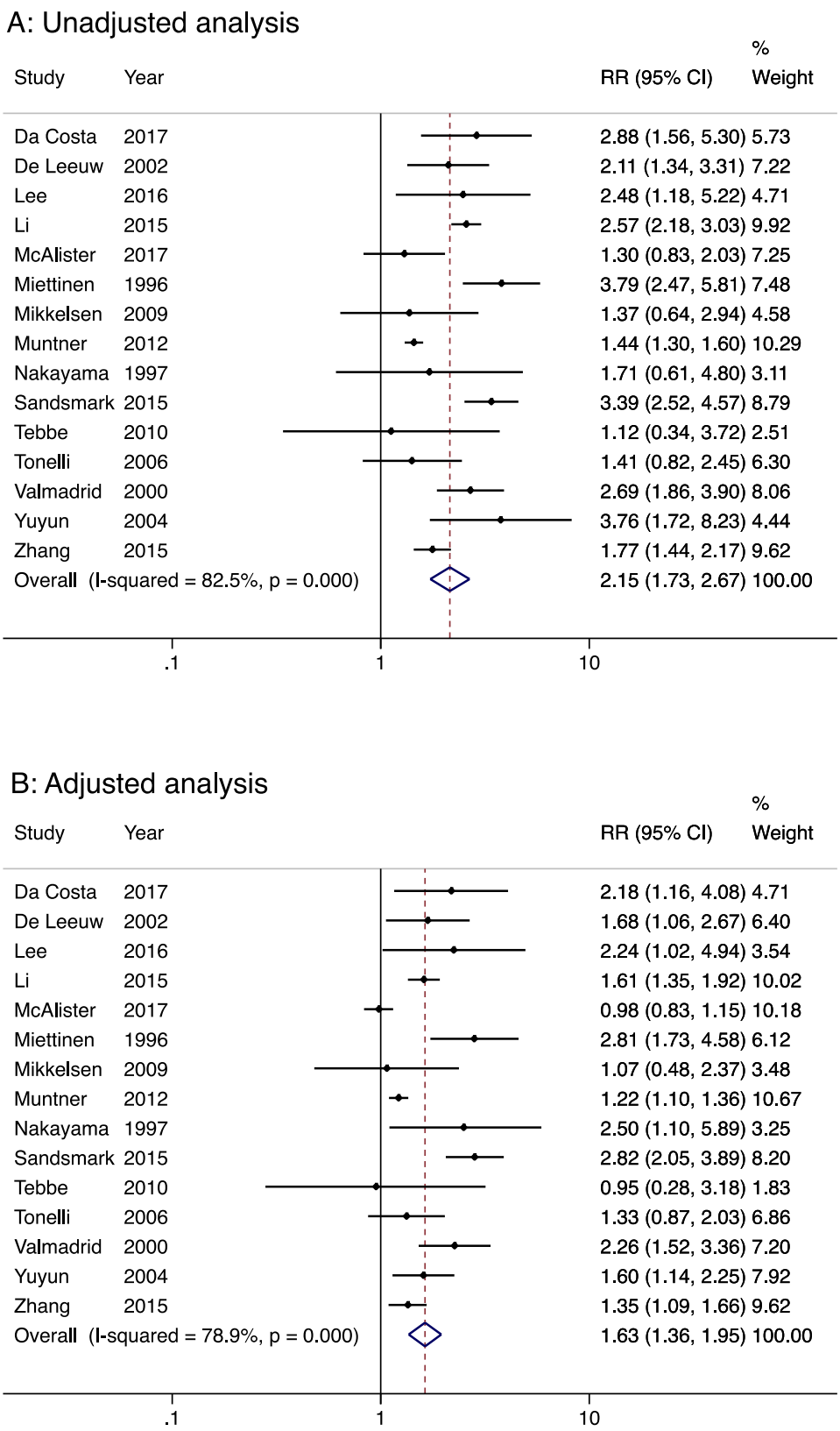
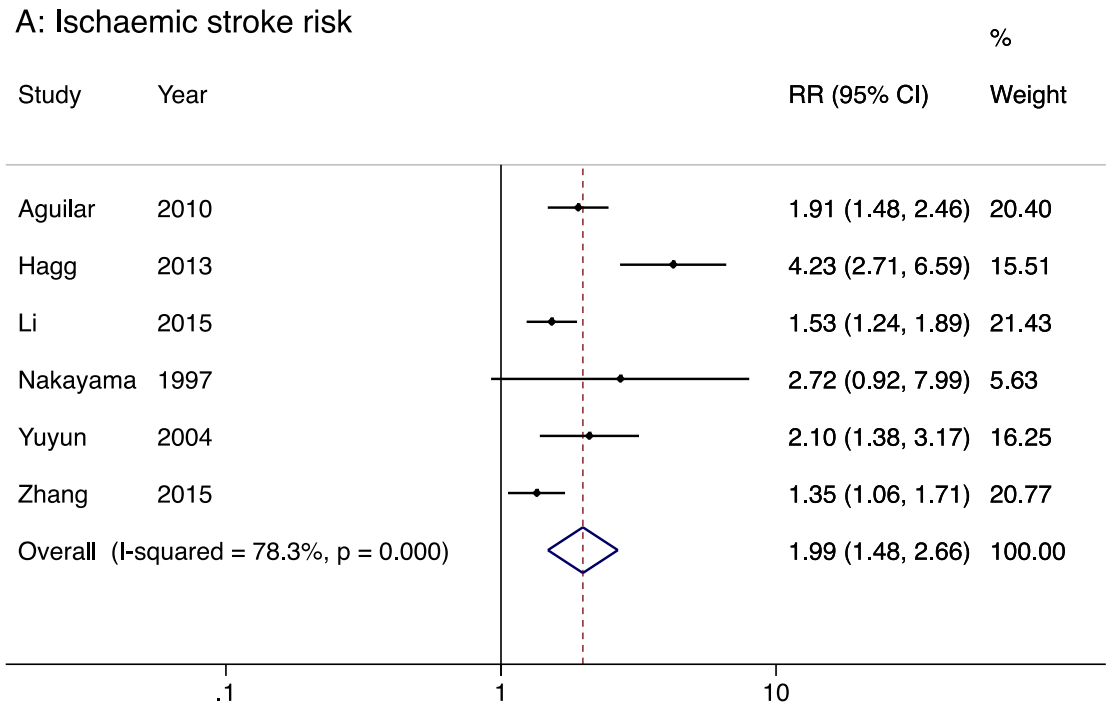


Figure 6-7 Risk ratio (RR) for the association of proteinuria and (A) ischaemic stroke and (B) haemorrhagic stroke risk. RRs were adjusted for traditional cardiovascular risk factors (exact methods varied between studies).



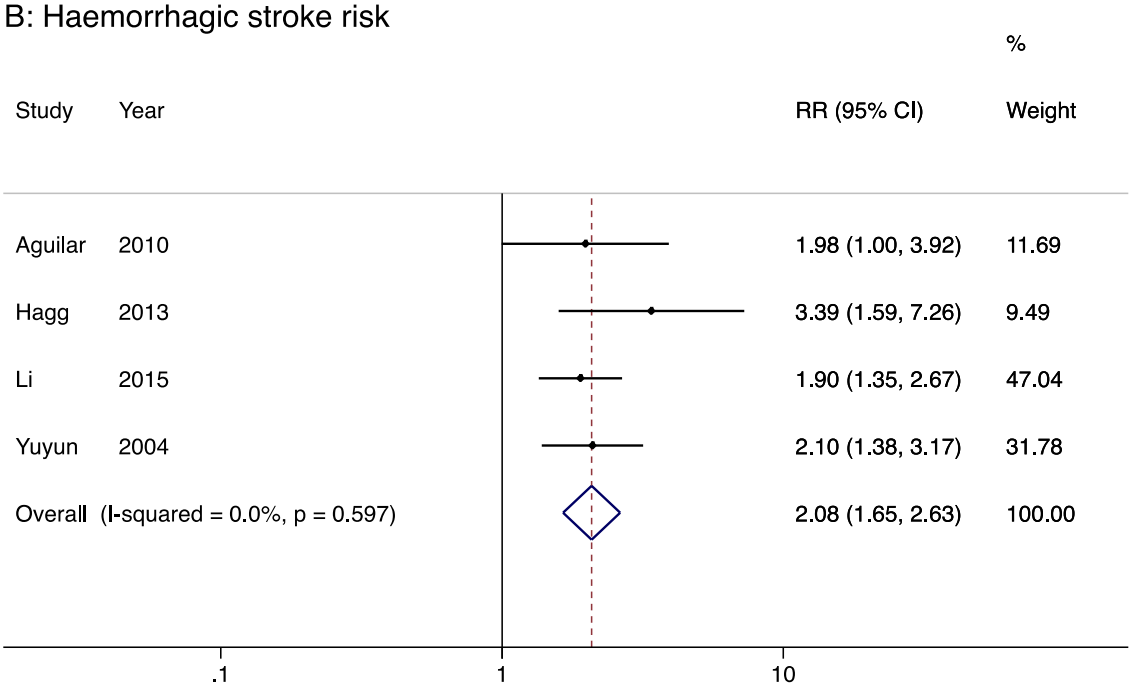
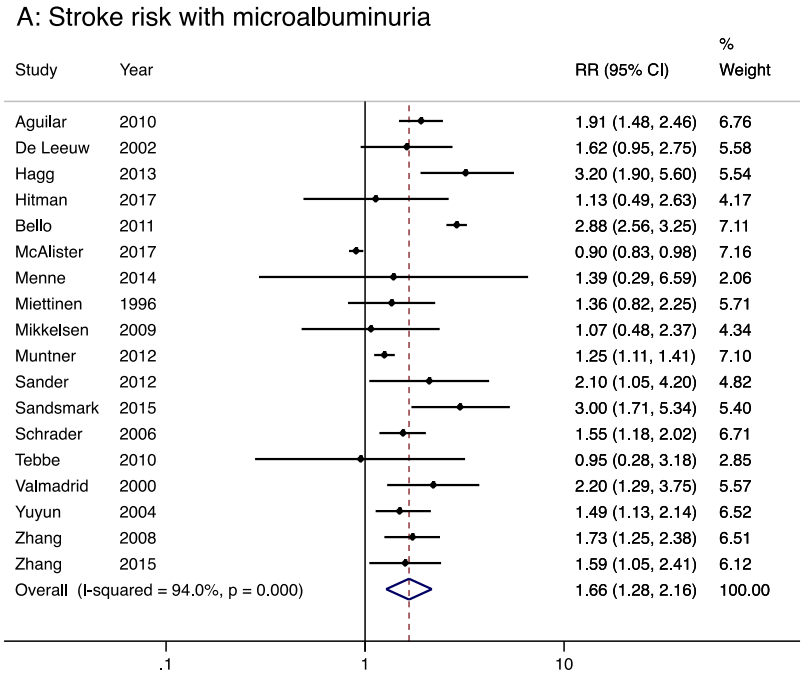


Figure 6-8 Impact of albuminuria level on stroke risk. (A) Studies reporting Microalbuminuria and (B) Macroalbuminuria.



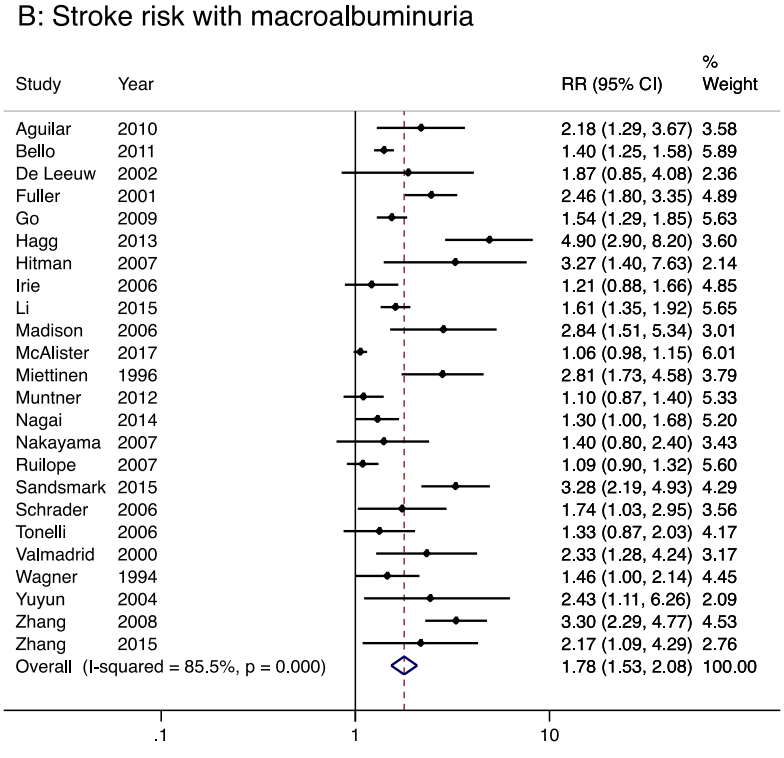


Figure 6-9 Overall risk ratio (RR) for the association of combined albuminuria and low eGFR with stroke risk adjusted for traditional cardiovascular risk factors (exact methods varied between studies).

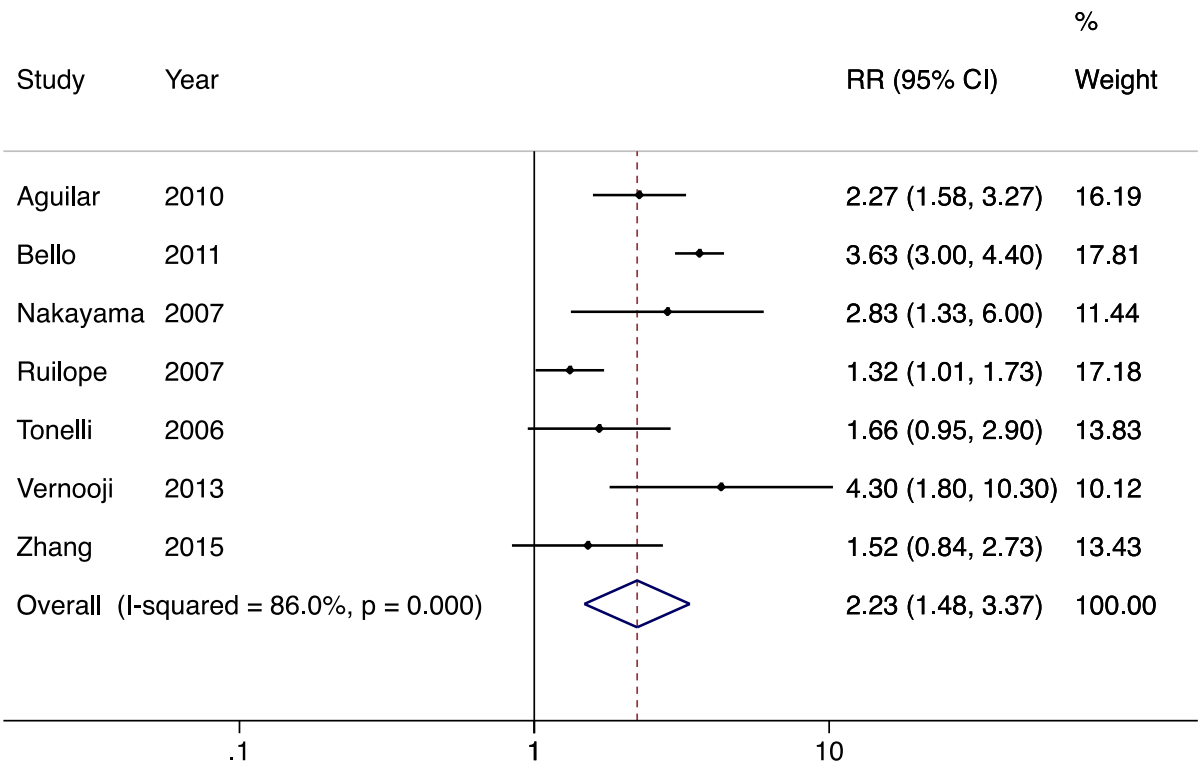


Figure 6-10 Funnel plot evaluating potential systematic bias in studies included in the meta-analysis.

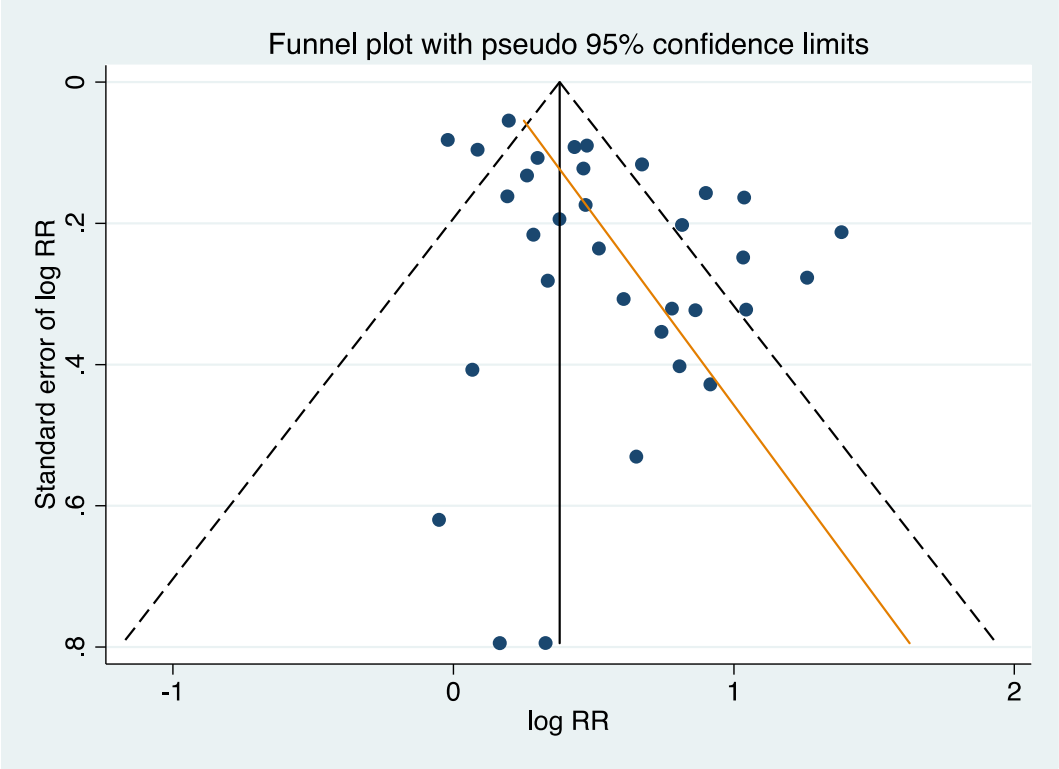
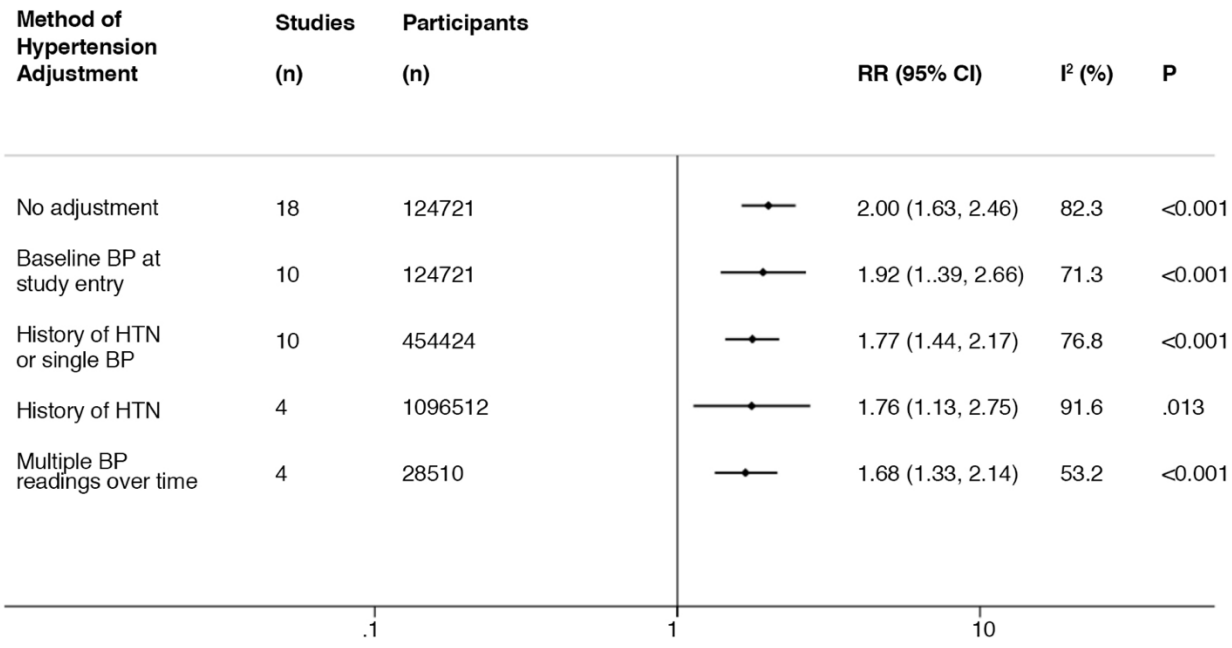


Figure 6-11 Variation in the risk ratio (RR) for the association of proteinuria and stroke risk depending on the method of hypertension adjustment used in the studies. All studies were also adjusted for other traditional risk factors. Study and participant numbers along with the level of heterogeneity (I^2 and P value) also described.



BP indicates blood pressure; HTN, hypertension

6.7 Appendix

Table 6-5 Characteristics of included studies

Study reference, Country, Name, (Reference)	Design, population, ethnicity	Size, (% men)	Mean or median age (SD or range)	GFR (ml/min/1.73m^2)	Albuminuria (category)	Stroke type(n) (Classification)	Follow-up (months)	Other stroke characteristics	Adjustment (Hypertension)
				Formula ***Reference*****: range(n)** ***Comparison*****: range (n)**	**Measurement** ***Reference*****: range (n)** ***Comparison*****: range (n)**				
Aguilar 2010, USA, Cardio-vascular Health Study,[1]	Cohort, No cerebrovascular disease, 17% Black.	3,205, (39)	78.5 (4.8)	MDRD *Reference*: ≥60 (unknown) *Comparison*: <60 (unknown)	ACR *Reference*: None (2,630) *Comparison*: Micro (560) Macro (15) Any (575)	Unspecified (26) Ischaemic (316) Haemorrhagic (48)	104.4	Incident Fatal or non-fatal	Age, sex, race, BMI, smoking, hypertension, diabetes, LVH, AF, internal carotid artery stenosis ≥75%, SBP, DBP (Categorical/Continuous variables - ≥140/90 or physician's diagnosis + use of Rx, SBP, DBP – average over 4-7 years)
Bello 2011, Canada,[2]	Cohort, 7% diabetics, 3% cerebrovascular disease, 22.3% HTN. Unknown ethnicity.	1,023,686, (45)	48.7 (16.6)	MDRD *Reference:* ≥60 (820,571) *Comparison*: 45-60 (79, 845) 30-45 (16,713) 15-30 (3,856)	Dipstick, ACR *Reference*: None (913,830) *Comparison*: Micro (91,774) Macro (18,082)	Unspecified (4,692)	35	Incident or recurrent Fatal or non-fatal	Age, sex, diabetes, SES, previous malignancy, CVA, CCF, COPD, dementia, HIV, IHD, chronic liver disease, PVD, HTN. (Categorical variable – history of HTN)

Da Costa 2017, Brazil,[3]	Cohort 100% resistant HTN. 47.5% DM, 24.2% CAD, 15.7% previous stroke, 9.7% smoking.	1048 (27.7)	70.6 (11.3)	CKD-Epi *Reference:* ≥60 (637) *Comparison:* 30-59 (363) <30 (48)	UAER *Reference:* <30 (701) *Comparison:* ≥30 (347)	Unspecified (90)	90	Incident Fatal or non-fatal	Age, sex, DM, smoking, HDL-C, TG, LVMI, HF, PVD, uncontrolled ambulatory BP & non-dipping pattern. (Categorical variables: Uncontrolled ABPM = mean 24h >130/80, & non-dipping pattern)
De Leeuw 2002, Multinational, Syst-Eur trial,[4]	RCT, *Inclusion criteria*: isolated systolic hypertension, age≥60. *Intervention*: Ca-channel blocker +/- ACE *Control:* Placebo 11% diabetics, 30% previous cardiovascular disease, Unknown ethnicity.	4,658, (33)	70 (6.6)	Serum Creatinine Per 20 µmol/l increase	Dipstick *Reference*: None (4,225) *Comparison*: Micro (324) Macro (109)	Unspecified (129)	24	Incident Fatal or non-fatal	Active treatment, sex, age, systolic blood pressure smoking, previous cardiovascular disease, diabetes (Continuous/categorical variables – on Rx, SBP – 6 readings in 1-month run-in)
Fuller 2001, Multinational, WHO multinational study of vascular disease in diabetes,[5]	Cohort, 100% diabetics, Unknown ethnicity	4,743, (49)	46.4 (5.8)		ACR *Reference*: None (unknown) *Comparison*: Micro (unknown); Macro (unknown)	Unspecified (293)	144	Incident or recurrent Fatal or non-fatal	Age, duration of DM, SBP, serum cholesterol, smoking status, proteinuria, retinopathy, & ECG abnormalities. (Categorical/continuous variables - Hypertension = SBP >140 or DBP>90 or on treatment)

Go 2009, USA,[6]	Cohort, 17% diabetics, 9% cerebrovascular disease, 59% other vascular disease. 100% AF, 86% White, 4% black, 5% Asian.	13,535, (57)	71.6 (unknown)	MDRD *Reference*: ≥60 (13,535) *Comparison:* 45-60 (7,746) <45 (5,789)	Dipstick *Reference*: None (unknown) *Comparison*: Macro (unknown)	Ischaemic (637)	96	Incident or recurrent Fatal or non-fatal	Age, sex, race, SES, educational attainment, prior ischaemic stroke, CCF, diabetes, hypertension, IHD (Categorical variable - Hypertension identified from outpatient sources.)
Hagg 2013, Finland, FinnDianne study,[7]	Cohort, 100% type 1 diabetics, 47% previous/current smokers, 7% dialysis-requiring ESKD. Mainly white.	4,083, (52)	37.4 (11.8)		UAER *Reference*: None (2482) *Comparison*: Micro (510) Macro (549)	Ischaemic (286) Haemorrhagic (120).	108	Incident Fatal or non-fatal	Age, sex, blood pressure, BMI, LDL/HDL cholesterol, TGs, smoking (Continuous variable - Blood pressure was measured twice in the sitting position with a 10-min rest before the first measurement, and the mean values of these two measurements were calculated for both systolic blood pressure (SBP) and diastolic blood pressure (DBP).)
Hitman 2007, UK, CARDS trial,[8]	RCT, *Inclusion criteria*: Type 2 diabetes and no previous cardiovascular disease *Intervention*: Atorvastatin *Control*: Placebo 0.4% AF, 22% smokers, 37% BMI>30, 79.4% HTN.	2838, (68)	62.1 (8.0)		Dipstick or ACR or AER Reference: None (2144) Comparison: Micro (694)	Unspecified (13) Ischaemic (47)	46.8	Incident Fatal or non-fatal	Age, sex, HbA1c>10%, treatment arm, SBP. (Continuous variable)

Irie 2006, Japan,[9]	Cohort, 7% diabetics, Mainly Asian.	91,432, (34)	58.8 (unknown)	MDRD *Reference*: ≥100 (17,636) *Comparison*: 90-100(21,846) 80-90 (20,402) 70-80 (20,461) 60-70 (8,190) <60 (2,897)	Dipstick *Reference*: None (88,438) *Comparison*: Macro (1,929)	Unspecified (985)	120	Incident Fatal	Age, hypertension, smoking, ETOH, diabetes, total cholesterol, HDL cholesterol, BMI, urinary protein (for eGFR analyses) (Categorical variable – adjusted for hypertensive category).
Kowey 2005, Multinational, RENAAL study,[10]	RCT, *Inclusion criteria*: Type 2 diabetes with nephropathy *Intervention*: Losartan *Control*: Placebo 100% diabetics, 18% smoking. Unknown ethnicity.	1,513, (63)	60 (7.4)		ACR or 24 hour collection *Reference*: Micro (378) *Comparison*: Macro (1,135)	Unspecified (97)	40.8	Incident Fatal or non-fatal	Unadjusted
Lee 2016, South Korea,[11]	Cohort 74.9% HTN, 28.1% DM, 25.4% smoking, 19.7% IHD.	295 (53.2)	67.6 (14-94)	CKD-Epi *Reference:* ≥60 (239) *Comparison:* <60 (56)	UACR *Reference:* <30 (165) *Comparison:* ≥30 (130)	Ischaemic (26) SAH (1)	22	Recurrent Fatal or non-fatal	Age, sex, DM, HTN, smoking, AF, previous stroke, alcohol Hx, NIHSS score. (Categorical variable – on treatment or SBP≥140 or DBP≥90 on repeated exam)
Li 2015, China,[12]	Cohort 43.6% HTN, 32.8% smoking, 9% DM.	92013 (70.6)	51.8	CKD-Epi *Reference:* ≥90 (30609) *Comparison:* 60-89 (49089) 30-60 (11801) <30 (514)	Urine dipstick *Reference:* None (88164) *Comparison:* ≥1+ (3849)	Ischaemic (1128) Haemorrhagic (406)	48	Incident	Age, sex, smoking, drinking, BMI, LDL-C, HDL-C, TG, TC, DM, HTN, hyperlipidaemia, AF. (Categorical variable - SBP≥140 or DBP≥90 or on Rx or self-reported Hx)

Madison 2006, USA, Honolulu heart study,[13]	Cohort, 15% diabetics, no known vascular disease, 51.6% HTN, 35.3% smokers. 100% Asian.	6,252, (100)	60.0 (0.4)		Dipstick *Reference*: None (5802) *Comparison*: Macro (69)	Unspecified (457)	324	Incident Fatal or non-fatal	Age, BMI, physical activity index, cholesterol, hypertension, diabetes, smoking, ETOH. (Categorical variable - Hypertension was defined as systolic pressure of 140 mm Hg or higher or diastolic pressure of 90 mm Hg or higher, or there was documented use of antihypertensive agents.)
McAlister 2017, Canada,[14]	Cohort 100% AF, 64.1% HTN, 21.6% DM, 11.3% CAD. Unknown ethnicity.	58451 (53.2)	66	CKD-Epi *Reference:* ≥60 (44217) *Comparison:* 45-59 (8046) 30-44 (4264) <30 (1924)	Urine dip/ACR/PCR *Reference:* Neg/<3/<15 (52132) *Comparison:* Trace or 1+/ 3-30/15-50 (3354) 2+/>30/>50 (2965)	Unspecified (5620)	31	Incident	Age, sex, aboriginal status, social assistance, postal code income quintile, rural/urban status, previous TE or bleeding event, CHF, HTN, DM, PVD. (Categorical variable)

Menne 2014, Multinational, ROADMAP-OFU study,[15]	Cohort 100% T2DM, 21.7% CAD, 15.8% smoking. Unknown ethnicity.	1758 (48.9)	61.2 (8.4)	UACR *Reference:* None (1626) *Comparison:* 30-300 (132)	Unspecified (26)	39.6	Incident Fatal or non-fatal	Treatment strategy (olmesartan/placebo), SBP, DBP, HbA1c at baseline. (Continuous variables)
Miettinen 1996, Multinational,[16]	Cohort, 43% diabetics, Unknown ethnicity.	2,431, (50)	58.1 (0.2)	PCR *Reference*: None (unknown) *Comparison*: Micro (unknown) Overt proteinuria (unknown)	Unspecified (155)	84	Incident or recurrent Fatal or non-fatal	Sex, age, location, previous stroke, TC, HDL-C, smoking, TG, HTN. (Categorical variable – HTN = receiving drug treatment for hypertension or if systolic blood pressure was ≥160 mm Hg or diastolic blood pressure was ≥95 mm Hg measured in the sitting position after a 5-minute rest.)
Mikkelsen 2009, Denmark,[17]	Cohort, 100% undergoing elective cardio-thoracic surgery, 15% DM, 57.1% HTN, 64.6% ever smoker, 15.1% previous AF. Unknown ethnicity	962, (73)	65.6 (18-93)	ACR *Reference*: None (782) *Comparison*: Micro (180)	Unspecified (38)	1	Incident or recurrent Fatal or non-fatal	Unadjusted

Muntner 2012, USA , REGARDS study,[18]	Cohort, 13% smokers, 48% hypertensive, 37% black	20,386, (46)	64.4 (9.2)	CKD-EPI *Reference*: >90 (9,431) *Comparison*: 60-90 (9,053) 45-60 (1,321) <45 (581)	ACR *Reference*: None (13,310) *Comparison*: Micro (6,844) Macro (440)	Unspecified (2,548)	25.2	Incident Fatal or non-fatal	Age, race, sex, geographic region, education, household income, smoking, ETOH, BMI, systolic blood pressure, antihypertensive medication use, dyslipidemia, diabetes and CRP (Continuous & Categorical variables – SBP, on Rx)
Nagai 2014, Japan,[19]	Cohort 26.3% HTN, 13.7% smoking.	298148 (39.7)	63.2 (8.1)	MDRD *Reference:* ≥60 (98987) *Comparison:* <60 (19391)	Urine dipstick *Reference:* Negative/trace (284567) *Comparison:* ≥1+ (13581)	Unspecified (4426)	36	Incident	Age, sex, BMI, HTN category, smoking, anti-dyslipidaemia drugs, hyperglycemia, hypoglycemic drugs. (Categorical variable – HTN categories = normotensive, untreated, treated, drug-resistant. SBP≥140 or DBP≥90 mmHg)
Nakayama 1997, Japan, Shibata study,[20]	Cohort, 100% Asian.	2,302, (42)	Unknown		Dipstick *Reference*: Micro (unknown) *Comparison*: Macro (unknown)	Unspecified (28) Ischaemic (76) Haemorrhagic (38)	186	Incident Fatal or non-fatal	Age, blood pressure, Physical activity, Fundus abnormality, AF, Smoking, IHD (Continuous variables - SBP, DBP, MBP)
Nakayama 2007, Japan, Okashama study,[21]	Cohort, Mainly Asian.	1,977, (37)	62.9	Cockcroft Gault *Reference*: >70 (555) *Comparison*: 40-70 (1,246) <40 (176)	Dipstick Reference: Micro (unknown) Comparison: Macro (unknown)	Unspecified (112)	96	Incident Fatal or non-fatal	Age, sex, systolic blood pressure, BMI, smoking, use of antihypertensive medication, history of cardiovascular disease,

									hypercholesterolemia and diabetes (Categorical and continuous variables – SBP, use of antihypertensive medications)
Oliveras 2003, Spain,[22]	Cohort, 100% renal transplant recipients. 6% diabetic, 13% IHD, 64.8% HTN, 17.1% smokers. Unknown ethnicity.	403, (37)	49.8 (23 to 63)		24 hour collection *Reference*: <1g/24 hours (327) *Comparison*: >1g/24 hours (76)	Ischaemic (12) Haemorrhagic (7)	120	Incident or recurrent Fatal or non-fatal	(Categorical variable - Hypertension was defined either as a systolic blood pressure of 140 mmHg or higher and/or diastolic blood pressure of 90 mmHg or higher or cases in which treatment for HT had been implemented.)
Ravipati 2008, USA,[23]	Cohort, 100% diabetics or hypertensive. 54% White.	306, (53)	57 (10)		ACR *Reference*: None (195) *Comparison*: Micro (111)	Unspecified (31)	39	Incident Fatal or non-fatal	Unadjusted
Ruilope 2007, Multinational, VALUE trial,[24]	RCT, *Inclusion criteria*: Hypertensive, high cardiovascular risk. *Intervention:* Valsartan *Control:* Amlodipine, 89% white/4% black/4% Asian	15,245, (58)	67.2 (8.1)	Cockcroft Gault *Reference*: >60 (9,214); *Comparison*: <60 (5,999)	Dipstick *Reference*: None (11,788) *Comparison*: Any (3,435)	Unspecified (603)	45.6	Incident or recurrent Fatal or non-fatal	Age, sex, IHD, LVH, all-cause death. Not adjusted for hypertension.
Sander 2012, Germany, INSIGHT registry,[25]	Cohort, 35% diabetics, 79% HTN, 18% current smokers.	1,167 (58.1)	66 (11.9)		Dipstick *Reference*: None (781) *Comparison*: Micro (386)	Unspecified (35)	12	Recurrent Fatal or non-fatal	Age, BMI, diabetes, SBP, total:HDL cholesterol, use of ACE/ARB, Ca-blockers, insulin, oral hypoglycemic, IHD, PAD, stroke subtype.

									(Continuous variable – SBP)
Sandsmark 2015, USA, CRIC study,[26]	Cohort 55.2% DM, 33.9% CVD, 13.4% smoking. 42.4% White.	3939 (55.2)	58.1 (10.9)	MDRD *Reference:* >60 (702) *Comparison:* 45-60 (1091) 30-44 (1339) <30 (807)	24h urine protein *Reference:* <0.1g/24h (1375) *Comparison:* 0.1-0.5 (1094) 0.5-1.5 (582) >1.5 (690)	Unspecified (143)	76.8	Incident	Age, sex, race, DM, SBP, hyperlipidaemia, smoking, alcohol use. (Continuous variable – baseline SBP, single reading)
Schrader 2006, Multinational, MARPLE study,[27]	Cohort study, 100% hypertensive, Unknown ethnicity.	3,529, (43)	63 (8.3)		ACR *Reference*: None (1,750) *Comparison*: Micro (832) Overt proteinuria (118)	Unspecified (24)	42.5	Incident or recurrent Non-fatal	Unadjusted
Tanaka 1985, Japan,[28]	Cohort, Unknown ethnicity.	2,299, (42)	All ≥ 40		Dipstick *Reference*: <Macro (2,143) *Comparison*: Macro (156)	Ischaemic (34)	20	Incident	Age (Continuous variables – SBP, DBP, MBP)
Tebbe 2010, Germany,[29]	Cohort 22.6% DM, 12.1% current smoker, 6.8% AF, Unknown ethnicity.	2,173, (48)	61.4 (11.3)		ACR *Reference*: None (1,382) *Comparison*: Micro (791)	Unspecified (5)	12	Incident or recurrent Non-fatal	Age Not adjusted for hypertension.

Tonelli 2005, USA, CARE trial,[30]	RCT, *Inclusion criteria:* Hyperlipidemia and previous MI *Intervention:* Pravastatin *Control:* Placebo, Unknown ethnicity.	4,098, (86)	59.7 (50-70)	MDRD *Reference*: >60 (3,218) *Comparison*: <60 (880)	Dipstick *Reference*: None (3,546) *Comparison*: Macro (552)	Unspecified (130)	58.9	Non-fatal	Age, sex, ethnic origin, smoking, BMI, waist: hip ratio, fasting glucose, hemoglobin, albumin, LDL/HDL cholesterol, TGs, systolic/diastolic blood pressure, location, LVEF, use of drugs (ACEi, aspirin, or pravastatin). (Continuous variables – SBP/DBP)
Valmadrid 2000, USA,[31]	Cohort, 100% diabetics, 65.9% HTN, 47.2% ever smoker. Unknown ethnicity.	840, (45)	67.9 (11.0)		Agglutination assay *Reference*: None (460) *Comparison*: Micro (208) Overt proteinuria (172)	Unspecified (85)	144	Incident or recurrent Fatal or non-fatal	Age, sex, glycemic control, insulin use, ETOH use, physical activity, history of cardiovascular disease, use of antihypertensive medication, severity of diabetic retinopathy. history of hypertension (defined as systolic blood pressure of ≥160 mm Hg or a diastolic of ≥95 mm Hg or taking antihypertensive medications). (Categorical variable – hypertension history or on meds)

Vernooij 2013, Netherlands, SMART study,[32]	Cohort 94.3% HTN, 65.3% IHD, 36% smoking, 18.3% T2DM. Unknown ethnicity.	4319 (79.6)	65.5 (10.8)	MDRD *Reference:* ≥60 (3672) *Comparison:* <60 (647)	UACR *Reference:* ≤3.0 mg/mmol (3558) *Comparison:* >3.0 (761)	Unspecified (156)	52.8	Incident	Age, sex, BMI, SBP, antihypertensive Rx, T2DM, CAD. (Categorical & continuous variables – on Rx, SBP)
Wagener 1994, USA, NHANES (1/2/3),[33]	Cohort, 13% IHD, 30% smokers, 23% HTN, 7.1% DM. 100% White.	6,135, (47)	45-74		Dipstick *Reference*: None (5,952) *Comparison*: Any (183)	Unspecified (771)	192	Incident or recurrent Fatal or non-fatal	Age, systolic blood pressure, diabetes, IHD, education, smoking (Continuous variable – SBP)
Yang 2008, Hong Kong,[34]	Cohort, 100% T2DM, 19.4% current smokers. Mainly Asian.	6,969, (46)	57 (46-67)	MDRD *Reference:* >115 (2,622) *Comparison*: 60-115 (3,704) <60 (643)	ACR *Reference*: None (4,008) *Comparison*: Any (2961)	Ischaemic (314)	64.3	Incident Fatal or non-fatal	Age, sex, BMI, smoking, hyperlipidemia, antihypertensive medication, SBP/DBP (Continuous variables – SBP/DBP)
Yokota 2008, Japan,[35]	Cohort, 100% admitted with stroke, 84% HTN, 31% diabetics, 26% AF, 15% IHD. Unknown ethnicity	474, (66)	70 (11)		ACR *Reference:* None (309) *Comparison:* Micro (133) Macro (32)	Ischaemic (49) Haemorrhagic (5)	12.8	Recurrent Fatal or non-fatal	Sex, diabetes (Not adjusted for HTN)
Yuyun 2004, UK, EPIC-Norfolk study,[36]	Cohort, 2% diabetics, 41% smokers, 13% HTN, no previous cerebrovascular disease.	23,630, (46)	59.0 (9.3)		ACR *Reference*: None (20,684) *Comparison*: Micro (2,749) Macro (197)	Unspecified (85) Ischaemic (112) Haemorrhagic (49)	86.4	Incident Fatal or non-fatal	Age, sex, smoking, use of antihypertensive medication, systolic blood pressure, total cholesterol, diabetes, BMI, family history of stroke, and baseline coronary heart disease (Categorical variable [hypertension] and

								continuous variable [sbp – per SD])
Zhang 2008, USA,[37]	Cohort, 48.8% DM, 39.2% HTN. 33.9% current smokers. 100% American-Indian.	4,549, (40)	56.3 (8.0)	ACR *Reference*: None (3,084) *Comparison*: Micro (831) Macro (464)	Unspecified (48) Ischaemic (221) Haemorrhagic (37)	160.8	Incident Fatal or non-fatal	Age, sex, blood pressure, BMI, waist circumference, LDL/HDL cholesterol, TGs, physical activity, fasting glucose, smoking, ETOH Hypertension was defined by the criteria of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (JNC-7; systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication). Prehypertension was defined as systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg. Normal blood pressure was defined as <120/80 mm Hg.

									(Categorical [preHTN & HTN] and continuous variables [SBP & DBP})
Zhang 2015, China, CSPPT,[38]	RCT *Inclusion criteria:* 45-75 yrs with HTN *Intervention:* Enalapril & folic acid *Control:* 31% smoking, 11.1% DM.	19599 (40.8)	60 (7.5)	CKD-Epi *Reference:* ≥90 (13418) *Comparison:* 60-89 (5768) <60 (413)	Urine dipstick *Reference:* None (16663) *Comparison:* Trace (1812) ≥1+ (1154)	Ischaemic (472) Haemorrhagic (111) Undefined (2)	54	Incident	Age, study centre, gender, treatment group, smoking, alcohol, BMI, baseline SBP/DBP, mean SBP/DBP over treatment period, TC, HDL, FPG, homocysteine, folate. (Continuous variables – baseline & mean)

Abbreviations:
AAA indicates abdominal aortic aneurysm; ACE, Angiotensin Converting Enzyme inhibitor; ACR, albumin:creatinine ratio; AF, atrial fibrillation; AR, aortic regurgitation; A2RB, Angiotensin 2 Receptor Blocker; BMI, body mass index; BMS, bare metal stent; Ca, calcium; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCF, congestive cardiac failure; CEA, carotid endarterectomy; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; CRP, C Reactive Protein; CVA, cerebrovascular accident; CVD, cardiovascular disease; DAPT, dual anti-platelet therapy; DBP, diastolic blood pressure; DM, diabetes mellitus; ECG, electrocardiograph; ETOH, alcohol; GFR, glomerular filtration rate; Hb, haemoglobin; HDL, high density lipoprotein; HIV, Human Immunodeficiency Virus; HRT, hormone replacement therapy; HTN, hypertension; IHD, ischaemic heart disease; IS, ischaemic stroke; LAD, left anterior descending artery; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MDRD, Modification of Diet in Renal Disease; MI, myocardial infarction; NIHSS, National Institute of Health Stroke Scale; NSAIDs, Nonsteroidal anti-inflammatory drugs; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PCR, protein:creatinine ratio; PP, pulse pressure; PVD, peripheral vascular disease; Rx, treatment; SBP, systolic blood pressure; SD, standard deviation; SES, socio-economic status; STS score, Society of Thoracic Surgery score; TAVI, transcatheter aortic valve implantation; TC, total cholesterol; TE, thromboembolic; TG, triglyceride; TIA, transient ischaemic attack.

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Chapter 7 Associations of blood biomarkers with glomerular filtration rate in patients with transient ischaemic attack and stroke: population-based study

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7.1 Chapter outline

Non-traditional risk factors such as chronic inflammation, oxidative stress, and thrombogenic factors are believed to contribute to the excess stroke risk in chronic kidney disease (CKD) by triggering vascular injury and endothelial dysfunction. I aimed to determine how well a panel of biomarkers representative of these factors would correlate with estimated glomerular filtration rate (eGFR) in patients with recent transient ischaemic attack (TIA) or stroke. I also investigated whether eGFR would confound previously reported associations between biomarkers and mortality.

I studied a panel of 16 blood biomarkers related to inflammation, thrombosis, atherogenesis, and cardiac or neuronal cell damage in TIA or ischaemic stroke in a population-based study (Oxford Vascular Study). Biomarker levels were log-transformed and correlated with eGFR, adjusted for age. Cox proportional hazard models were used for survival analysis.

Among 1297 patients with TIA or stroke, 52.7% (n=684) of patients had CKD (eGFR <60 ml/min/1.73m2). There was a moderate correlation between log-eGFR and the log-transformed soluble tumour necrosis factor receptor-1 (R^2=0.21), attenuating with adjustment for age (R^2= 0.12). There were moderate-to-strong correlations with markers of cardiac injury, N-terminal pro-brain natriuretic peptide and heart-type fatty acid binding protein (hFABP) (R^2=0.14 and 0.34, respectively). The strongest correlation after adjustment for age was between hFABP and eGFR (R^2=0.20). Adjusting for eGFR did not impact any biomarker associations with mortality.

Correlations between biomarkers related to inflammation and thrombosis with renal dysfunction in the setting of cerebrovascular events were generally modest after

adjustment for age, suggesting that putative risk factors such as chronic inflammation or coagulopathy are unlikely to be important stroke mechanisms in patients with CKD.

7.2 Introduction

Chronic kidney disease (CKD) affects as many as 10-15% of the population worldwide.[1] It is a rapidly growing global health burden, mainly because it is an established risk factor for cardiovascular disease and stroke.[2] Meta-analyses of cohort studies and trials indicate that reduced glomerular filtration rate (GFR) increases the risk of stroke by about 40%[3] and that proteinuria increases the risk up to 70%[4] even after adjusting for traditional cardiovascular risk factors.

As described in Chapter 2, traditional cardiovascular risk factors including hypertension,[5] diabetes mellitus,[6] and atrial fibrillation,[7] are all highly prevalent in the CKD population, likely confounding much of the association between CKD and stroke. However, unconventional risk factors directly resulting from renal disease, such as chronic inflammation, oxidative stress, and thrombogenic factors, are also proposed to contribute to the excess cerebrovascular risk observed in CKD patients by triggering vascular injury and endothelial dysfunction.[8, 9]

Use of blood biomarkers related to these potential disease pathways of inflammation,[10] coagulation,[11] atherogenesis,[12] cardiac or neuronal injury[13, 14] have been studied in the general population to aid stroke diagnosis, determine subtype or mechanism, and to predict outcome or response to therapy.[13, 15-17] In CKD patients, inflammatory biomarkers (including interleukin 6 [IL-6], tumour necrosis factor α [TNF-α], high-sensitivity C-reactive protein [CRP], fibrinogen, and serum albumin) have been shown to be independently associated with incident atherosclerotic events and death, even after adjustment for GFR and traditional risk factors, suggesting a possible causative role for inflammation in cardiovascular events such as stroke in CKD.[18] However, previous studies have not had a large population-based cohort design, have not focused specifically on stroke, and have included only a narrow range of biomarkers.

Similar biomarker associations with mortality have been shown in patients with TIA and stroke in the general population however, they have not previously been adjusted for renal function, and thus CKD or its associated renal vascular risk factors may be a confounder in this relationship.[19]

I therefore aimed to investigate in a large prospective population-based study of patients with TIA or stroke, the correlations of a broad panel of biomarkers related to inflammation, thrombosis, and cardiac or neuronal function or injury with renal function. I hypothesized that if non-traditional risk factors such as CKD-related coagulopathy or inflammation are aetiologically important in stroke pathogenesis, then representative biomarkers should independently correlate with GFR in this setting. Furthermore, I also aimed to determine if previously reported biomarker-mortality associations[19] are confounded by renal dysfunction.

7.3 Materials and methods

7.3.1 Patients

Patients were recruited from the Oxford Vascular Study (OXVASC), a population-based study of all acute vascular events (including TIA, stroke, acute coronary syndromes, and peripheral vascular events), described in detail in section 4.3. The multiple methods of ascertainment used to ascertain patients with TIA or stroke, are also detailed here.[20]

All patients provided written informed consent or assent was obtained from relatives, and they were seen by study physicians as soon as possible after their initial presentation. A detailed clinical history was recorded in all patients using a standardized questionnaire. Assessments were made for severity of event using the National Institute of Health Stroke

Scale (NIHSS)[21] and clinical features. All cases were reviewed by the study senior neurologist (P.M.R) and classified as stroke or other condition using standard definitions.[22] Events were classified as minor stroke if there was a focal neurological deficit lasting >24 hours and an NIHSS score ≤ 3 at time of assessment by a study physician.

Non-fasting blood samples were taken as soon as possible after the event, usually within a couple of days. These included serum, 3.2% buffered tri-sodium citrate plasma and lithium heparin plasma (Vacutainer tubes; Becton Dickinson, United Kingdom). Samples were centrifuged at 3000 g for 10 minutes, and aliquots of serum and plasma were stored at -80°C before analysis when they were thawed for use at 37°C. All times from sampling to freezing were documented, typically within 4 hours of taking.

CKD was defined as eGFR less than 60 mL/min/1.73 m^2 for three or more months as per 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (see section 4.3.4).[23] eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI). However, I also performed a sensitivity analysis of eGFR-biomarker correlations using the Full Age Spectrum equation (eGFR-FAS) to estimate GFR as this has been proposed to provide better continuity of prediction at extremes of ages.[24] I reviewed all available premorbid creatinine values for each patient to ensure that they fulfilled the duration criteria for a definition of a CKD.

Classification of deaths was blind to biomarker results and was done by review of clinical records and death certificates in the study practices. Practice-specific listings of all *ICD-10 (International Classification of Diseases, Tenth Revision)* death codes were also obtained from central registers.

7.3.2 Assay methods

Our assay methods, which have been previously described, included a mixture of chip systems and separate ELISA assays.[17, 19] Briefly, a Biochip multiple immunoassay system (Randox Laboratories Ltd, Co. Antrim, Northern Ireland) using lithium-heparin simultaneously measured biomarkers via two panels: Cerebral Array I for brain-derived neurotrophic factor (BDNF), IL-6, and heart type fatty acid-binding protein (hFABP), and Cerebral Array II for CRP, neurone-specific enolase (NSE), neutrophil gelatinase-associated lipocalin (NGAL), soluble tumor necrosis factor receptor-1 (sTNF-R1) and thrombomodulin (TM). All assays underwent reproducibility studies using an internal control of pooled normal lithium-heparin plasma in addition to control materials supplied by the manufacturers.

Citrate plasma was used for measuring the thrombotic markers fibrinogen, D-dimer and von Willebrand Factor (vWF) antigen by immunoturbidometric assays (Sta-Liatest D-Dimer, DiagnosticaStago, Asniers, France) using a diagnostic automated coagulation analyser STA (Diagnostica Stago, Asniers, France). These assays have well defined internal quality control and external control through participation in national quality assurance schemes. Commercial ELISA kits were used to assay human P-selectin (R&D Systems, UK), Protein Z (PZ) (DiagnosticaStago, France) and NT-proBNP (Biomedica, Austria). Serum samples were used for anti-phosphorylcholine (anti-PC) antibodies (CVDefine; Athera Biotechnologies AB, Stockholm, Sweden), adhering to manufacturers recommendations. Percentage of intra- and inter-coefficients of variation of each assay are shown in Table 7-1. All assays were performed blind to study status.

7.3.3 Statistical analysis

Continuous data were given as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate, categorical data were given as n (%). Independent-samples T-tests and Chi-squared tests were used to test the significance of differences between two groups for continuous and categorical variables respectively. One-way analysis of variance (ANOVA) was used to compare differences between more than two groups. A Mann-Whitney U test and a Kruskall-Wallis test were used as non-parametric alternatives for T-tests and one-way ANOVA respectively. Age-adjusted P values for difference were calculated using logistic and linear regression where appropriate. Correlations of biomarkers and GFR were calculated by Spearman rank correlations. To further evaluate potentially linear relationships, biomarkers and GFR were then both log-transformed and correlated using Pearson correlations. Partial correlations were used to adjust for age. Subgroup analysis was performed according to age category, sex, and hypertension status. Correlation coefficients were compared using Fisher's Z transformations and the Chi-square test of heterogeneity. For survival analysis, Cox proportional hazard models were used after testing that the proportional hazards assumption was met. Associations of biomarkers with all-cause death were calculated unadjusted, adjusted for age and sex (model 1); adjusted for variables included in model 1 plus eGFR (model 2); and adjusted for variables included in model 2 plus hypertension, diabetes, atrial fibrillation, previous myocardial infarction, previous ischaemic stroke, previous peripheral artery disease, hyperlipidemia, smoking, previous therapy with antiplatelet agents, previous therapy with antihypertensive agents and previous therapy with statins (model 3). Results were considered significant at $p < 0.05$. All statistical analyses were performed using SPSS version 25.0.

7.4 Results

A total of 1297 consecutive eligible patients with TIA (n=427), minor stroke (n=549) or major stroke (n=321) were recruited from 2002 to 2011, and followed-up until 2013. Table 7-2 shows the baseline characteristics at the time of the event for all patients and according to CKD status. The median age was 75.2 (65.2-83.2) years, 47.8% (n=620) were men, and hypertension was the most prevalent risk factor being found in 59.1% (n=766). The median (interquartile range) days from event to sampling were 5 (3-12) days. A maximum of 1210 samples were analysed by the Randox panels with numbers limited in certain cases by inadequate sample volumes and assay failure. Thrombotic markers were measured in a maximum of 1213 patients after exclusion of cases with inadequate sample volumes and anticoagulant therapy. The median eGFR was 58.7 (46.7-70.6) ml/min/1.73m^2. 684 patients (52.7%) had CKD, 637 (93.1%) of whom had stage 3 (eGFR = 30-59 ml/min/1.73m^2), 64 (6.4%) had stage 4 (eGFR = 15-29 ml/min/1.73m^2), and 3 (0.4%) had stage 5 (eGFR < 15 ml/min/1.73m^2).

Correlations between biomarker levels are shown in Table 7-3. There was good cross-correlation within the subset of inflammatory markers, the greatest was between IL-6 and sTNF-R1 (R=0.47). Within the thrombotic subset, fibrinogen correlated well with VWF (R=0.42) and D-dimer (R=0.41) but none of these factors correlated with P-selectin, thrombomodulin, PZ, or anti-PC antibodies. NSE, a marker of neuronal cell damage, correlated with BDNF (R=0.47). Moderate correlations existed between biomarker subsets, the greatest was between IL-6 and D-dimer (R=0.50), and between sTNF-R1 and D-dimer (R=0.54).

The median (IQR) levels of biomarkers according to eGFR categories are described in Table 7-4. There were significant differences in levels in the inflammatory, thrombotic, and

cardiac biomarker subsets. IL-6, NGAL, sTNFR-1, TM, Fibrinogen, VWF, D-dimer, NT-proBNP, and hFABP levels all increased with declining eGFR (all p<0.001).

The relationship between biomarker levels and eGFR was examined using scatter-plot graphs. Log transformation of both biomarker levels and eGFR highlighted some linear relationships, examples of which are shown in Figure 7-1. Correlations between biomarker levels and eGFR were first assessed using Spearmann rank correlation analysis (Table 7-5*)*. There were moderate correlations between the inflammatory markers NGAL and eGFR (R= -0.26), and sTNFR-1 and eGFR (R= -0.41). Within the thrombotic biomarker subset, TM and D-dimer also moderately correlated with eGFR (R= -0.35 and -0.34, respectively). There were also moderate-to-large correlations between markers of cardiac injury, NT-proBNP and hFABP, and eGFR (R= -0.38 and -0.56, respectively). In subgroup analysis of the strongest correlations with eGFR, hFABP and sTNF-R1, there were no significant differences according to sex or hypertension status. However, the associations were stronger in older age categories (> 65 years) (R= -0.50 vs -0.27 and R= -0.37 vs -0.14, for hFABP and sTNFR-1 respectively; p<0.001).

Correlation coefficients were also compared between TIA, minor and major stroke subgroups in Table 7-6. There were no significant differences apart from CRP, fibrinogen and D-dimer, but the strength of these correlations did not increase in the major stroke subgroup. Unadjusted and age-adjusted correlations of log-biomarker levels and log-eGFR were then performed using Pearson correlation analysis (Table 7-5*)*. After adjustment for age, log-eGFR similarly correlated mostly strongly and significantly with log-sTNFR-1 (R^2=0.12), log-TM (R^2=0.10), log-NT-proBNP (R^2=0.05), and log-hFABP (R^2=0.20) (all p <0.001). There were little or no correlations between the other log-biomarkers and log-eGFR after adjustment. When the correlations were repeated using eGFR-FAS, the results were similar in all analyses (Table 7-7).

During 9628 patient-years of follow-up (median 7.7 years; IQR=5.8-9.4), there were 567 deaths (43.7% of the population). CKD was associated with all-cause death (unadjusted HR=1.97, 95% CI: 1.68-2.32; p<0.001), however, this association became non-significant after adjustment for age and sex (adjusted HR=1.04, 0.87-1.23; p=0.69). The associations of biomarkers with all-cause death are shown in Table 7-8. After fully adjusting for demographics (age, sex), previous therapy (antiplatelet agents, antihypertensive agents, statin therapy) and risk factors (hypertension, diabetes mellitus, atrial fibrillation, smoking, previous stroke, previous myocardial infarction, previous peripheral artery disease, hyperlipidaemia), IL-6, sTNFR-1, fibrinogen, vWF, P-Selectin, D-dimer, NT-proBNP, hFABP, NSE, and BDNF all remained predictive of death of any cause. However, adjustment for GFR specifically did not attenuate any of the associations with all-cause death.

7.5 Discussion

In this population-based cohort study, I showed that certain biomarkers related to inflammation (NGAL, sTNFR-1), thrombosis (TM), and cardiac injury (NT-proBNP, hFABP) correlated with renal function in patients with TIA or stroke independently of age. However, the strength of these associations, apart from hFABP, were generally weak, suggesting that putative renal vascular factors such as chronic inflammation, oxidative stress, or coagulopathy are unlikely to explain the association between CKD and stroke risk. These findings are consistent with the hypothesis that traditional risk factors, particularly blood pressure, remain mechanistically more meaningful. In a systematic review and meta-analysis of low GFR and stroke risk,[25] this risk association was greatly attenuated by adjustment for long-term blood pressure burden, suggesting that hypertension is the an important confounder.

In keeping with earlier studies,[26] many circulating biomarkers (IL-6, NGAL, sTNFR-1, TM, Fibrinogen, VWF, D-dimer, NT-proBNP, and hFABP) were elevated in patients with CKD, increasing with worsening renal function. There was a small correlation between sTNFR-1 and eGFR. sTNFR-1 interacts with its membranous counterpart (mTNFR) leading to a pro-inflammatory stimulus via activation of nuclear factor kappa B (NF-κB) or activator protein 1 (AP-1).[27] It has previously been associated with renal progression, cardiovascular events, and all-cause mortality in patients with CKD regardless of the underlying cause.[28, 29]

Even after adjustment for age, there was still a moderate correlation between TM and eGFR. TM is a vasculo-protective transmembrane glycoprotein that has both anticoagulant and anti-inflammatory activity.[30] It can also be released/shed from the endothelium as an extracellular soluble form, indicative of inflammatory cellular damage. In an unadjusted analysis of 59 children with CKD, TM has been previously shown to be strongly correlated with eGFR as well as other markers of endothelial dysfunction and oxidative stress such as asymmetric dimethylarginine and serum oxidized LDL.[31] In the studied children with higher TM concentrations, significantly higher albuminuria was also found. Although albuminuria was not measured in this study, it is postulated to be surrogate biomarker of generalized endothelial dysfunction associated with increased risk of cardiovascular events such as stroke.[32]

Some of the stronger biomarker-eGFR correlations in this study, after adjustment, were those of the cardiac injury markers, NT-proBNP and hFABP, particularly in the case of the latter. NT-proBNP is a peptide secreted from the cardiac ventricles in response to increasing tension in the ventricular wall.[33] It is also a diagnostic and prognostic tool in congestive heart failure. Since NT-proBNP clearance occurs only in the kidney, elevated levels may result from decreasing renal function because of increased intravascular

volume, in addition to impaired cardiac function.[34] Extravascular volume expansion is known to be an important mechanism in the pathophysiology of hypertension in CKD[35], which may explain the correlation in the setting of TIA or stroke in this study. Similarly, hFABP is a marker of myocardial injury and heart failure.[36] Although it is mostly expressed in the heart and skeletal muscle, hFABP has also been described in human glomeruli,[37] localized largely along the capillary wall and appears to be associated with proteinuria in obese patients in a process that might be related to podocytes and lipid dysmetabolism.[38]

The reported correlations were not confounded by stroke severity as the strength of correlation between these biomarkers and eGFR did not generally differ between TIA, minor or major stroke group. However, given the strong cross-correlation within biomarker subsets, if renal function was truly associated with inflammatory or thrombotic processes at the time of a vascular event, then eGFR should correlate similarly with all biomarkers within a subset instead of with individual ones without a clear pattern of association. Furthermore, many of these circulating biomarkers including NGAL, TM, and NT-proBNP are elevated in CKD patients and appear to rise contemporaneously with a drop in GFR.[39-41] Thus, their interpretation in this setting may be unclear as elevated levels may not necessarily reflect increased production but rather a prolonged half-life caused by impaired clearance.

Similar to previous systematic review and meta-analysis,[42] I found that the association of CKD and all-cause mortality was greatly attenuated with adjustment for age and sex. I did not find that eGFR confounded the previously reported associations between certain biomarkers and all-cause mortality, namely sTNFR-1, vWF, hFABP, and NT-proBNP.[19] These findings are in keeping with earlier work demonstrating that inflammatory

biomarkers such as IL-6, TNF-alpha, fibrinogen, and albumin are associated with mortality independently of eGFR, even within the CKD population.[18, 43]

Our study had a number of limitations. Firstly, we were unable to measure all biomarkers in the entire patient cohort. Secondly, we may have overestimated the prevalence of CKD in this study since GFR was estimated from baseline creatinine at the time of the vascular event, and acute kidney injury (AKI) is a common complication following stroke.[44] However, most of the included patients had either a TIA or minor stroke which are not frequently associated with as many systemic sequelae such as AKI. Thirdly, with only one-time measurement of each parameter, some dilution of correlations is possible. Fourthly, urine albumin was not measured in this study and we have previously shown that the relationship between albuminuria and stroke may be mechanistically different to that of low eGFR and stroke.[45]

As the global burden of CKD rises,[46] so too will its potential contribution to stroke mechanisms and its prevalence in stroke survivors. However, disentangling the pathophysiology of stroke in CKD and the importance of non-traditional or renal-specific risk factors has been challenging.[47] Large studies such as this one with a population-based design help provide further insights into potential causal pathways and the importance of adjustment for confounders such as age. Most older adults develop ‘inflammageing’, a condition characterized by elevated levels of blood inflammatory markers that carries high susceptibility to cardiovascular disease, which is not specific to CKD.[48]

In conclusion, there were some correlations between biomarkers related to inflammation, thrombosis, and cardiac injury with renal function in the setting of TIA or stroke. The correlations with cardiac biomarkers may represent volume expansion and higher blood

pressure at the time of the vascular event. Endothelial dysfunction in CKD may also play a role since TM and hFABP did correlate with eGFR, and have both previously been associated with albuminuria, a sensitive biomarker of endotheliopathy. However, the strength of the correlations were generally weak or attenuated with adjustment for age, and any putative causal relationships may be confounded by impaired biomarker excretion in advanced kidney disease. Further studies should investigate the association between these biomarkers and albuminuria in the setting of cerebrovascular events.

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TABLES

Table 7-1 Biomarker Measurement Methods and Intra- and inter-assay coefficients of variation.

Biomarker	N	Measurement System	Intra-assay CV%	Inter-assay CV%
Inflammatory markers				
IL-6, pg/ml	1158	Randox microchip	21	13.4
CRP, mg/l	914	Randox microchip	5.7	11.1
NGAL, ng/ml	977	Randox microchip	4.7	9.0
sTNFR-1, ng/ml	1210	Randox microchip	7.8	14.1
Thrombotic or anti-atherogenic Markers				
TM, ng/ml	1213	Randox microchip	10.1	14.1
Fibrinogen, g/L	1036	Stago analyzer	2.3	5.7
vWF, iu/ml	1047	Stago analyzer	4.6	4.6
P-selectin, ng/ml	1059	ELISA	4.9	9.0
PZ, ng/ml	1021	ELISA	4.9	14.8
D-dimer, ng/ml	1189	Stago analyzer	4.3	4.3
Anti-PC, U/ml	901	ELISA	6.7	8.2
ADAMTS-13, U/ml	865	ELISA	8.9	8.2
Markers of cardiac or neuronal function/injury				
Nt-proBNP, pmol/l	1049	ELISA	8.6	10.1
hFABP, ng/ml	1213	Randox microchip	14.6	10.8
NSE, ng/ml	1211	Randox microchip	7.5	20.0
BDNF, pg/ml	1208	Randox microchip	9.6	11.1

Total samples analysed differ because of constraints on sample size, where warfarin may have affected protein synthesis, and according to the materials available. Anti-PC indicates anti- phosphorylcholine antibodies; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; CV, coefficient of variation; hFABP, heart type fatty acid binding protein; IL-6, interleukin-6; NGAL, neutrophil gelatinase-associated lipocalin; NSE, neurone specific enolase; Nt-proBNP, N-terminal pro-B-type natriuretic peptide; PZ, protein Z; sTNFR-1, soluble tumor necrosis factor receptor type 1; TM, thrombomodulin; vWF, von Willebrand Factor.

Table 7-2 Baseline characteristics of all patients with TIA and stroke, and stratified according to the presence of CKD.

Characteristics*	All patients n=1297	No CKD n=607	CKD n=684	P value†	Age-adjusted P value
Age years, median (IQR)	75.2 (65.2-83.2)	67.3 (58.5-77.5)	80.3 (72.7-85.2)	<0.001	N/A
Male sex	620 (47.8)	343 (56.5)	276 (40.4)	<0.001	<0.001
Days to sample, median (IQR)	5 (3-12)	5 (3-11)	5 (2-12)	0.69	0.44
Hypertension	766 (59.1)	307 (50.9)	456 (67)	<0.001	0.007
Diabetes mellitus	157 (12.1)	62 (10.3)	94 (13.8)	0.07	0.002
Previous history of stroke	168 (13.1)	66 (10.9)	102 (15)	0.04	0.64
Previous history of MI	128 (10)	31 (5.1)	97 (14.2)	<0.001	<0.001
Previous history of PAD	104 (8.1)	24 (4)	80 (11.7)	<0.001	<0.001
Atrial fibrillation	226 (17.6)	70 (11.6)	156 (22.9)	<0.001	0.03
Current smoker	206 (16)	137 (22.7)	69 (10.1)	<0.001	0.16
Hyperlipidaemia	412 (32.1)	175 (13.6)	237 (18.5)	0.03	0.001
Previous antiplatelet therapy	513 (40)	185 (30.6)	328 (48.3)	<0.001	0.01
Previous antihypertensive therapy	750 (58.5)	278 (46)	472 (69.5)	<0.001	<0.001
Previous statin therapy	312 (24.3)	108 (17.9)	204 (30)	<0.001	<0.001
NIHSS index event, median (IQR)	1 (0-4)	1 (0-3)	1 (0-4)	0.35	<0.001
Cause of stroke				<0.001	0.20
Cardioembolism	258 (20.1)	88 (14.6)	170 (25)		
Large artery	143 (11.1)	57 (9.5)	86 (12.6)		
Small artery	194 (15.1)	107 (17.7)	87 (12.8)		
Undetermined cause	477 (37.1)	243 (40.3)	234 (34.4)		
Unknown	86 (6.7)	35 (5.8)	51 (7.5)		
Multiple	25 (1.9)	8 (1.3)	17 (2.5)		
Other	32 (2.5)	23 (3.8)	9 (1.3)		
PICH	47 (3.7)	27 (4.5)	20 (2.9)		
SAH	22 (1.7)	15 (2.5)	7 (1)		

*Numbers are n (%) unless otherwise stated.
†P-values are from Chi-squared tests or Mann-Whitney U tests, as appropriate. Logistic/linear regression was used to adjust for age.
CKD indicates chronic kidney disease; IQR, interquartile range; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; PICH, primary intracranial haemorrhage; SAH, subarachnoid haemorrhage.

Table 7-3 Correlations of biomarkers (Spearman rank correlation, p-value).

	CRP	NGAL	sTNFR-1	TM	Fibrinogen	vWF	P-selectin	PZ	D-dimer	Anti-PC	ADAMTS-13	NT-proBNP	hFABP	NSE	BDNF
Il-6	0.46	0.35	0.47	0.13	0.45	0.46	0.18	-0.18	0.50	-0.08	-0.30	0.29	0.39	0.24	0.23
	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.06	<0.001	<0.001	<0.001	<0.001	<0.001
CRP		0.25	0.33	0.08	0.47	0.29	0.11	-0.02	0.33	0.001	-0.09	0.13	0.21	0.11	0.12
		<0.001	<0.004	0.01	<0.001	<0.001	0.01	0.74	<0.001	0.98	0.06	<0.001	<0.001	0.001	<0.001
NGAL			0.45	0.25	0.21	0.23	0.19	-0.14	0.36	0.01	-0.14	0.18	0.31	0.30	0.38
			<0.001	<0.001	<0.001	<0.001	<0.001	0.001	<0.001	0.90	0.003	<0.001	<0.001	<0.001	<0.001
sTNFR-1				0.42	0.32	0.42	0.19	-0.14	0.54	-0.10	-0.20	0.32	0.53	0.21	0.17
				<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.01	<0.001	<0.001	<0.001	<0.001	<0.001
TM					0.01	0.15	0.06	-0.02	0.24	-0.08	-0.02	0.10	0.33	0.09	0.02
					0.89	<0.001	0.13	0.61	<0.001	0.05	0.64	0.001	<0.001	0.002	0.56
Fibrinogen						0.42	0.09	-0.06	0.41	-0.03	0.002	0.17	0.24	0.11	0.15
						<0.001	0.004	0.07	<0.001	0.33	0.95	<0.001	<0.001	0.003	<0.001
vWF							0.12	-0.09	0.47	-0.06	-0.19	0.30	0.43	0.15	0.12
							<0.001	0.01	<0.001	0.07	<0.001	<0.001	<0.001	<0.001	0.001
P-selectin								-0.01	0.22	-0.01	-0.01	0.09	0.13	0.14	0.14
								0.73	<0.001	0.73	0.84	0.01	<0.001	<0.001	<0.001
Protein Z									-0.11	0.03	0.07	-0.07	-0.09	-0.03	-0.06
									0.004	0.40	0.03	0.40	0.02	0.41	0.14
D-dimer										-0.10	-0.30	0.35	0.44	0.20	0.16
										0.02	<0.001	<0.001	<0.001	<0.001	<0.001
Anti-PC											0.16	0.03	-0.09	0.07	-0.003
											<0.001	0.36	0.32	0.11	0.94
ADAMTS-13												-0.04	-0.23	-0.09	-0.14
												0.24	<0.001	0.03	0.001
NT-proBNP													0.31	0.08	-0.04
													<0.001	0.007	0.17
hFABP														0.17	0.14
														<0.001	<0.001
NSE															0.47
															<0.001

Anti-PC indicates anti- phosphorylcholine antibodies; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; hFABP, heart type fatty acid binding protein; IL-6, interleukin-6; NGAL, neutrophil gelatinase-associated lipocalin; NSE, neurone specific enolase; Nt-proBNP, N-terminal pro-B-type natriuretic peptide; PZ, protein Z; sTNFR-1, soluble tumor necrosis factor receptor type 1; TM, thrombomodulin; vWF, von Willebrand Factor.

Table 7-4 Median (IQR) levels of biomarkers according to eGFR category (ml/min/1.73m^2).

	GFR ≥90	GFR 60-89	GFR 30-59	GFR <30	
Biomarker	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**P Value***
Inflammatory markers					
Il-6, pg/ml	1.8 (0.6-3.6)	1.7 (0.9-4.7)	2.2 (1.1-6.3)	4.9 (2.6-12.6)	<0.001
CRP, mg/l	2.8 (1.3-6.1)	2.1 (1.1-4.1)	2.4 (1.2-4.9)	3.3 (1.3-8.4)	0.04
NGAL, ng/ml	646.7 (389.4-887.3)	631.9 (462.8-837.3)	768.1 (580.4-954.0)	978.6 (856.1-1151.0)	<0.001
sTNFR-1, ng/ml	0.7 (0.6-1.0)	0.8 (0.6-1.0)	1.0 (0.7-1.4)	2.1 (1.9-3.1)	<0.001
Thrombotic or anti-atherogenic markers					
TM, ng/ml	1.4 (1.1-1.7)	1.5 (1.3-1.8)	1.8 (1.4-2.2)	2.7 (2.3-4.0)	<0.001
Fibrinogen, g/L	366.0 (323.0-481.3)	384.5 (319.8-468.0)	395.5 (331.0-482.0)	481.5 (394.5-569.8)	<0.001
vWF, iu/ml	145.0 (114.0-217.0)	149.0 (119.0-191.5)	174.5 (137.0-217.3)	233.0 (203.0-268.0)	<0.001
P-selectin, ng/ml	41.0 (25.0-58.5)	32.0 (16.0-46.0)	36.0 (22.0-52.0)	32.0 (17.0-48.0)	0.002
Protein Z, ng/ml	1.7 (1.4-2.2)	1.6 (1.3-2.1)	1.7 (1.2-2.1)	1.6 (1.1-2.1)	0.64
D-dimer, ng/ml	157.3 (84.6-303.4)	184.5 (111.1-333.2)	272.1 (183.8-446.1)	412.5 (303.3-627.1)	<0.001
Anti-PC, U/ml	42.2 (20.6-61.1)	43.6 (27.4-71.4)	39.4 (24.4-71.4)	38.0 (28.4-61.5)	0.67
ADAMTS-13, U/ml	84.4 (65.6-103.7)	87.2 (68.7-103.4)	85.4 (66.6-98.9)	76.4 (50.1-98.6)	0.13
Markers of cardiac or neuronal function/injury					
NT-proBNP, pmol/l	332.5 (147.0-597.3)	411.0 (196.8-939.0)	820.0 (399.0-1574.5)	2350.0 (1342.0-4354.0)	<0.001
hFABP, ng/ml	1.9 (1.4-2.9)	2.4 (1.8-3.3)	4.2 (2.6-5.4)	8.8 (6.1-12.7)	<0.001
NSE, ng/ml	7.1 (3.7-11.1)	7.2 (4.6-11.4)	6.9 (4.7-11.1)	9.1 (5.4-12.4)	0.20
BDNF, pg/ml	662.9 (359.8-1543.1)	972.2 (547.4-1597.1)	890.8 (512.7-1446.0)	841.9 (565.7-1758.3)	0.18

Anti-PC indicates antiphosphorylcholin; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; hFABP, heart-type fatty-acid-binding protein; IL6, interleukin-6; NGAL, neutrophil-gelatinase-associated lipocalin; NSE, neuron-specific enolase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTNFR-1, soluble tumor necrosis factor α receptor-1; TM, thrombomodulin; and vWF, von Willebrand factor.
*Mann–Whitney U test.

Table 7-5 Correlations of biomarker levels with eGFR on both linear and log-log scales using Spearman rank and Pearson correlations.

	eGFR		Log eGFR		Log eGFR	
Biomarker	**R (unadjusted)**	**p-value**	**R^2 (unadjusted)**	**p-value**	**R^2 (age-adjusted)**	**p-value**
Inflammatory markers						
Il-6	-0.18	<0.001	0.03	<0.001	0.002	0.18
CRP	-0.07	0.049	0.01	0.02	0.001	0.29
NGAL	-0.26	<0.001	0.06	<0.001	0.03	<0.001
sTNFR-1	-0.41	<0.001	0.21	<0.001	0.12	<0.001
Thrombotic or anti-atherogenic markers						
TM	-0.35	<0.001	0.13	<0.001	0.10	<0.001
Fibrinogen	-0.15	<0.001	0.02	<0.001	0.01	0.02
vWF	-0.27	<0.001	0.08	<0.001	0.02	<0.001
P-selectin	-0.08	0.008	0.003	0.05	0.001	0.33
Protein Z	0.03	0.298	0.001	0.48	0.001	0.35
D-dimer	-0.34	<0.001	0.11	<0.001	0.01	0.01
Anti-PC	0.05	0.125	0.002	0.21	0.003	0.13
ADAMTS-13	0.09	0.008	0.007	0.02	0.0008	0.40
Markers of cardiac or neuronal function/injury						
NT-proBNP	-0.38	<0.001	0.14	<0.001	0.05	<0.001
hFABP	-0.56	<0.001	0.34	<0.001	0.20	<0.001
NSE	-0.08	0.009	0.01	0.003	0.005	0.02
BDNF	0.01	0.852	0	0.99	0.0002	0.6

Anti-PC indicates antiphosphorylcholin; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; hFABP, heart-type fatty-acid-binding protein; IL6, interleukin-6; NGAL, neutrophil-gelatinase-associated lipocalin; NSE, neuron-specific enolase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTNFR-1, soluble tumor necrosis factor α receptor-1; TM, thrombomodulin; and vWF, von Willebrand factor.

Table 7-6 Correlations of biomarker levels with eGFR in TIA, minor and major stroke subgroups (Spearman rank correlation, p-value).

	TIA		Minor Stroke (NIHSS≤ 3)		Major Stroke (NIHSS>3)		
	eGFR		eGFR		eGFR		
Biomarker	**R**	**p-value**	**R**	**p-value**	**R**	**p-value**	**P value for difference**
Inflammatory markers							
Il-6	-0.18	0.001	-0.25	<0.001	-0.13	0.395	0.23
CRP	-0.09	0.086	-0.12	0.016	0.13	0.129	0.04
NGAL	-0.28	<0.001	-0.31	<0.001	-0.20	0.005	0.41
sTNFR-1	-0.36	<0.001	-0.46	<0.001	-0.46	<0.001	0.15
Thrombotic or anti-atherogenic markers							
TM	-0.29	<0.001	-0.34	<0.001	-0.43	<0.001	0.11
Fibrinogen	-0.20	<0.001	-0.22	<0.001	-0.03	0.666	0.03
vWF	-0.35	<0.001	-0.26	<0.001	-0.25	<0.001	0.29
P-selectin	-0.10	0.078	-0.08	0.128	-0.09	0.103	0.96
Protein Z	0.11	0.056	-0.04	0.409	0.05	0.352	0.13
D-dimer	-0.43	<0.001	-0.42	<0.001	-0.18	0.003	<0.001
Anti-PC	0.08	0.173	0.09	0.087	-0.06	0.412	0.20
ADAMTS-13	0.17	0.002	0.06	0.301	0.01	0.856	0.16
Markers of cardiac or neuronal function/injury							
NT-proBNP	-0.32	<0.001	-0.42	<0.001	-0.39	<0.001	0.29
hFABP	-0.56	<0.001	-0.60	<0.001	-0.61	<0.001	0.55
NSE	0.01	0.845	-0.14	0.001	-0.05	0.391	0.08
BDNF	0.04	0.459	-0.02	0.726	0.09	0.141	0.54

Anti-PC indicates antiphosphorylcholin; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; hFABP, heart-type fatty-acid-binding protein; IL6, interleukin-6; NGAL, neutrophil-gelatinase-associated lipocalin; NIHSS, National Institutes of Health Stroke Scale; NSE, neuron-specific enolase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTNFR-1, soluble tumor necrosis factor α receptor-1; TM, thrombomodulin; vWF, von Willebrand factor.

Table 7-7 Correlations of biomarker levels with eGFR-FAS (eGFR estimated using the Full Age Spectrum) on both linear and log-log scales using Spearman rank and Pearson correlations

	eGFR		Log eGFR		Log eGFR	
Biomarker	**R (unadjusted)**	**p-value**	**R^2 (unadjusted)**	**p-value**	**R^2 (age-adjusted)**	**p-value**
Inflammatory markers						
Il-6	-0.23	<0.001	0.05	<0.001	0.001	0.23
CRP	-0.08	0.02	0.008	0.009	0.001	0.29
NGAL	-0.27	<0.001	0.07	<0.001	0.03	<0.001
sTNFR-1	-0.45	<0.001	0.23	<0.001	0.11	<0.001
Thrombotic or anti-atherogenic markers						
TM	-0.35	<0.001	0.11	<0.001	0.09	<0.001
Fibrinogen	-0.18	<0.001	0.02	<0.001	0.01	0.02
vWF	-0.32	<0.001	0.10	<0.001	0.02	<0.001
P-selectin	-0.09	0.005	0.004	0.04	0.001	0.46
Protein Z	0.05	0.08	0.002	0.16	0.001	0.35
D-dimer	-0.43	<0.001	0.17	<0.001	0.006	0.01
Anti-PC	0.09	0.009	0.006	0.02	0.003	0.10
ADAMTS-13	0.14	<0.001	0.01	0.001	0.002	0.25
Markers of cardiac or neuronal function/injury						
NT-proBNP	-0.43	<0.001	0.16	<0.001	0.03	<0.001
hFABP	-0.60	<0.001	0.37	<0.001	0.19	<0.001
NSE	-0.07	0.01	0.007	0.004	0.004	0.03
BDNF	-0.006	0.84	0.00005	0.80	0.0002	0.66

Anti-PC indicates antiphosphorylcholin; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; hFABP, heart-type fatty-acid-binding protein; IL6, interleukin-6; NGAL, neutrophil-gelatinase-associated lipocalin; NSE, neuron-specific enolase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTNFR-1, soluble tumor necrosis factor α receptor-1; TM, thrombomodulin; and vWF, von Willebrand factor.

Table 7-8 Univariate and Multivariate Associations (According to 3 Models*) of Each Log-Biomarker with Risk of All-Cause Death.

	Unadjusted		Model 1	Model 2	Model 3	
Biomarker†	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**P Value**
Inflammatory markers						
Il-6	1.34 (1.24-1.45)	<0.001	1.33 (1.24-1.45)	1.33 (1.23-1.44)	1.31 (1.20-1.42)	<0.001
CRP	1.09 (0.98-1.22)	0.12	1.11 (0.99-1.25)	1.11 (0.99-1.24)	1.12 (0.99-1.25)	0.07
NGAL	1.15 (1.03-1.29)	0.01	1.11 (0.99-1.24)	1.14 (1.02-1.28)	1.10 (0.98-1.24)	0.09
sTNFR-1	1.43 (1.29-1.57)	<0.001	1.34 (1.21-1.48)	1.42 (1.27-1.58)	1.38 (1.24-1.54)	<0.001
Thrombotic or anti-atherogenic markers						
TM	1.07 (0.97-1.18)	0.20	1.01 (0.91-1.12)	1.03 (0.93-1.15)	1.04 (0.93-1.16)	0.50
Fibrinogen	1.26 (1.13-1.41)	<0.001	1.24 (1.11-1.39)	1.24 (1.11-1.39)	1.23 (1.10-1.37)	<0.001
vWF	1.43 (1.28-1.60)	<0.001	1.38 (1.24-1.55)	1.40 (1.25-1.57)	1.40 (1.25-1.57)	<0.001
P-selectin	1.17 (1.06-1.28)	0.001	1.18 (1.07-1.30)	1.18 (1.07-1.30)	1.17 (1.07-1.29)	0.001
Protein Z	0.96 (0.88-1.05)	0.34	0.98 (0.89-1.07)	0.98 (0.90-1.07)	0.98 (0.89-1.07)	0.59
D-dimer	1.41 (1.27-1.56)	<0.001	1.30 (1.17-1.45)	1.31 (1.18-1.47)	1.34 (1.20-1.50)	<0.001
Anti-PC	0.96 (0.87-1.05)	0.35	0.99 (0.90-1.09)	1.00 (0.91-1.10)	0.98 (0.89-1.08)	0.72
ADAMTS-13	0.88 (0.80-0.98)	0.02	0.93 (0.84-1.03)	0.93 (0.84-1.03)	0.93 (0.83-1.03)	0.17
Markers of cardiac or neuronal function/injury						
NT-proBNP	1.45 (1.29-1.62)	<0.001	1.34 (1.20-1.50)	1.37 (1.22-1.54)	1.34 (1.18-1.52)	<0.001
hFABP	1.49 (1.36-1.64)	<0.001	1.40 (1.27-1.55)	1.59 (1.42-1.79)	1.59 (1.42-1.79)	<0.001
NSE	1.17 (1.08-1.27)	<0.001	1.19 (1.09-1.29)	1.19 (1.10-1.30)	1.19 (1.10-1.30)	<0.001
BDNF	1.09 (1.01-1.17)	0.04	1.12 (1.04-1.21)	1.12 (1.03-1.21)	1.10 (1.02-1.19)	0.02

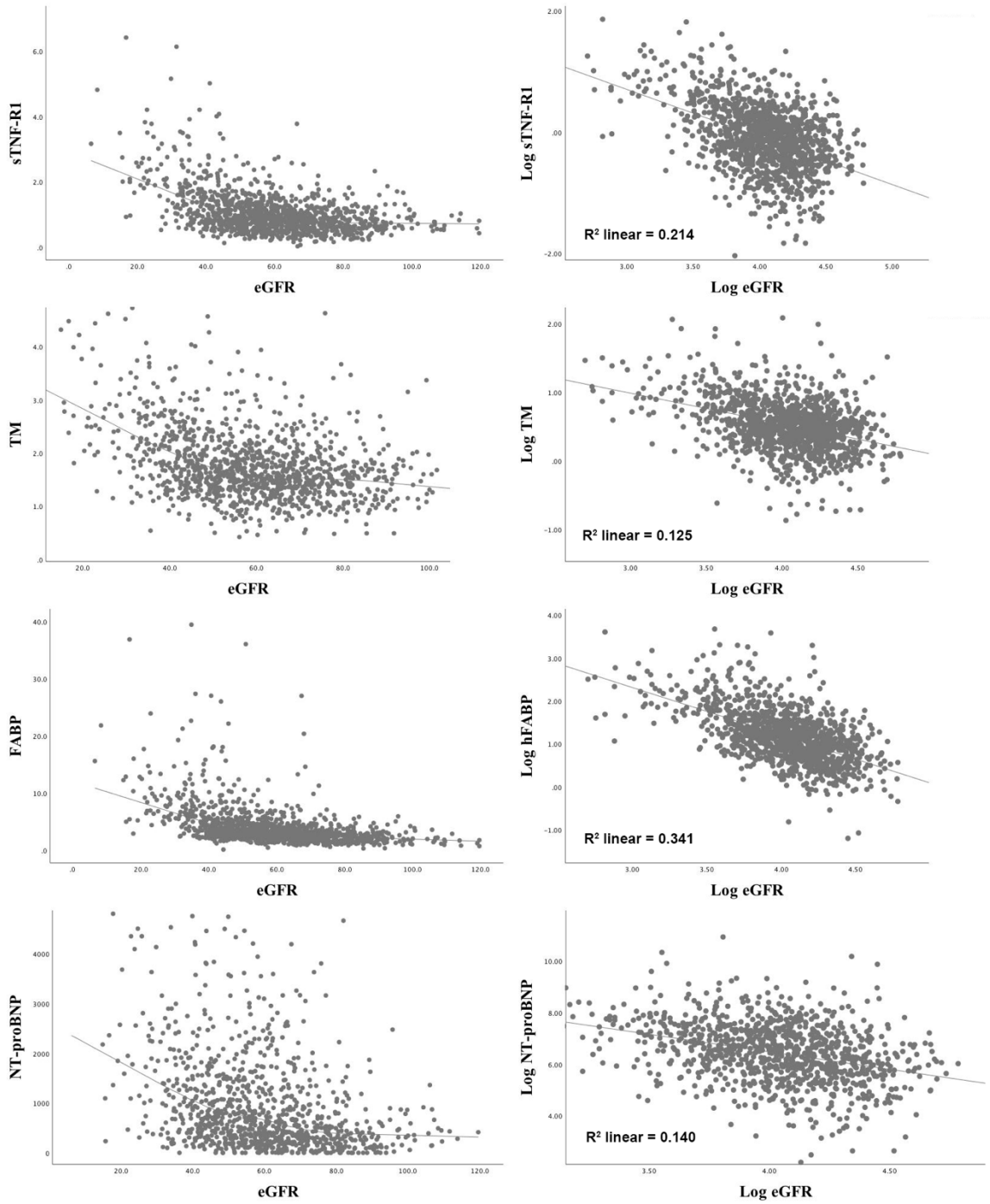
Anti-PC indicates antiphosphorylcholin; BDNF, brain-derived neurotrophic factor; CRP, C-reactive protein; hFABP, heart-type fatty-acid-binding protein; HR, hazard ratio; IL6, interleukin-6; NGAL, neutrophil-gelatinase-associated lipocalin; NSE, neuron-specific enolase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTNFR-1, soluble tumor necrosis factor α receptor-1; TM, thrombomodulin; and vWF, von Willebrand factor.

*Model 1: adjusted for age and sex; model 2 adjusted for variables in model 1 plus eGFR; model 3 adjusted for variables in model 2 plus hypertension, diabetes mellitus, previous myocardial infarction, previous peripheral vascular disease, previous ischaemic stroke, atrial fibrillation, current smoker, hyperlipidaemia, previous therapy with antiplatelet agents, statins, or antihypertensive agents.

† Given per SD(Ln).

FIGURES

Figure 7-1 Non-linear and log-linear correlations between sTNFR-1, TM, hFABP, NT-proBNP and eGFR.



eGFR indicates estimated glomerular filtration rate; hFABP, heart-type fatty-acid-binding protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sTNFR-1, soluble tumor necrosis factor α receptor-1; TM, thrombomodulin.

Chapter 8 Aetiological subtypes of transient ischaemic attack and ischaemic stroke in chronic kidney disease: population-based study

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8.1 Chapter outline

Chronic kidney disease (CKD) is strongly associated with stroke risk but the mechanisms underlying this association are not unclear, and might be informed by subtype-specific analyses. However, few studies have reported stroke subtypes in CKD according to established classification systems such as the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria. I therefore aimed to determine which transient ischaemic attack (TIA) and ischaemic stroke subtypes using the TOAST classification occur most frequently in patients with CKD.

In a population-based study of all TIA and stroke (Oxford Vascular Study; 2002-2017), all ischaemic events were classified by TOAST subtypes (cardioembolism, large artery disease, small vessel disease, undetermined, multiple, other aetiology, or incompletely investigated). Logistic regression was used to determine the relationship between CKD (defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2) and TIA/stroke subtypes adjusted for age, sex, and hypertension, and then stratified by age and eGFR category.

Among 3178 patients with TIA (n=1167), ischaemic stroke (n=1802), and intracerebral haemorrhage (n=209), 1267 (40%) had CKD. Although there was a greater prevalence of cardioembolic events (31.8 vs 21.2%; p<0.001) in patients with CKD, this association was lost after adjustment for age, sex, and hypertension (Adjusted OR=1.20, 95% CI: 0.99-1.45; p=0.07). Similarly, although patients with CKD had a lower prevalence of small vessel disease (8.8 vs 13.6%; p<0.001), undetermined (26.1 vs 39.4%; p<0.001), and other aetiology (1.0 vs 3.6%; p<0.001) subtypes, these associations were also lost after adjustment (Adjusted OR=0.86, 0.65-1.13; p=0.27 and 0.73, 0.36-1.43; p=0.37 for small

vessel disease and other defined aetiology, respectively) for all but undetermined events (Adjusted OR=0.81, 0.67-0.98; p=0.03).

There were no independent positive associations between CKD and specific TOAST subtypes which suggests that renal-specific risk factors are unlikely to play an important role in the aetiology of particular subtypes. Future studies of stroke and CKD should report subtype-specific analyses to gain further insights into potential mechanisms.

8.2 Introduction

As an established cardiovascular risk factor, chronic kidney disease (CKD) is a rising global health burden with prevalence rates of between 11 to 13%.[1, 2] It has been associated with a 43% increased risk of incident stroke,[3] greater disability and likelihood of institutionalization,[4] and higher short- and long-term mortality post-stroke.[5, 6]

Although CKD appears to be a risk factor for stroke analogous to diabetes mellitus,[7] the mechanisms underpinning this relationship are unclear. Previous meta-analyses have suggested that the relationship between CKD and stroke risk is independent of conventional cardiovascular risk factors frequently co-morbid with CKD, such as hypertension, diabetes, and atrial fibrillation.[3, 8] Proposed causal mechanisms include chronic inflammation, oxidative stress, or thrombogenic factors induced by the uraemic milieu, that subsequently contribute to vascular injury and endotheliopathy.[9] In particular, CKD has been associated with increased left atrial thrombogenic milieu in patients with atrial fibrillation (AF),[10] heavily calcified and unstable carotid plaque morphology in large artery disease,[11] and uraemic disruption of blood-brain barrier integrity[12] which may have implications for small vessel disease and lacunar stroke risk.[13]

Aetiological classification of stroke into different causative subtypes, like the widely used TOAST (Trial of ORG 10172 in Acute Stroke Treatment) system[14] can provide mechanistic insights as studies have shown that different stroke subtypes may represent different risk factor profiles.[15, 16] The heterogenous pathophysiology of stroke is further highlighted by recent genome-wide association studies that have identified different genetic loci associated with specific stroke subtypes, reflecting differing causal pathways.[17, 18]

However, very few studies to date have reported the frequency of the various aetiological stroke subtypes that occur in CKD, reporting only the risk of all-type events or ischaemic versus haemorrhagic strokes. Those that have subtyped in more detail variably suggest a preponderance of cardioembolic, large vessel or lacunar events.[19-21] However these studies have been small and did not report adjusted risk estimates. CKD is strongly related to age and other risk factors. My meta-analysis in Chapter 5 has demonstrated that the association between CKD and stroke appears to be highly dependent on the method of adjustment for hypertension, implicating long-term blood pressure burden as the primary confounder of this relationship.[22]

In a large prospective population-based study, I aimed to determine which TIA and stroke subtypes occur most frequently in patients with CKD, and whether any associations present remained after adjustment for potential confounders.

8.3 Methods

8.3.1 Patients

Patients were recruited from the Oxford Vascular Study (OXVASC), a population-based study of all acute vascular events (including TIA, stroke, acute coronary syndromes, and peripheral vascular events), described in detail in section 4.3. The study population comprises all 92,728 individuals, irrespective of age, registered with about 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK. The OXVASC population is 94% Caucasian, 3% Asian, 2% Chinese, and 1% Afro-Caribbean.[23] The multiple methods of ascertainment used to ascertain patients with TIA or stroke, have been detailed in section 4.3.2.[24]

Patients with incident TIA and stroke recruited from April 2002 to March 2017 were included in this analysis. All patients provided written informed consent or assent was obtained from relatives, and they were seen by study physicians as soon as possible after their initial presentation. A detailed clinical history was recorded in all patients using a standardized questionnaire. Neurological impairment, medical history and risk factors were recorded in all patients. Hypertension was defined on the basis of a historical diagnosis (either patient-reported or GP-coded) and/or the presence of anti-hypertensive treatment. Patients routinely had brain imaging, vascular imaging, 12-lead electrocardiogram (ECG), and standard blood tests. However, during the 15-year study period of OXVASC, different imaging protocols were used in two different time periods. From April 1, 2002, to March 31, 2010 (phase 1), computerized tomography (CT) brain and carotid doppler were the first-line imaging methods, with magnetic resonance imaging (MRI) or magnetic resonance angiography (MRA) done in selected patients when clinically indicated. Echocardiography, 24-h ECG (Holter monitor), and 5-day ambulatory home ECG monitoring (R test) were also done when clinically indicated (e.g., potential cryptogenic TIA/stroke; multi-territory infarct; patients at high risk of endocarditis, with known valve problems, or with other cardiologic complaints). From April 1, 2010, to March 31, 2017 (phase 2), brain MRI and MRA of extracranial and intracranial vessels became the first-line imaging methods, and all clinic patients had R tests and transthoracic echocardiography.

As described in section 4.3.4, CKD was defined as eGFR less than 60 mL/min/1.73 m^2 for three or more months as per 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[26] eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) and then categorized into 5 groups based on modified CKD classification by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative: eGFR $\geq$ 90 (reference), 60-89, 30-59, 15-30 and <15 ml/min/1.73m^2. For the

purpose of statistical analysis, the latter two groups were combined as the individual numbers within each group were small.

All clinical history and investigation results were reviewed in detail by a study physician using a standardized form (*Appendix*) as soon as completion of all investigations, and cases were then reviewed with a senior neurologist (PMR) and TIA/ischaemic stroke aetiology was classified (blind to CKD status) according to the modified TOAST criteria into seven subtypes: cardioembolic stroke, large artery disease, small vessel disease, undetermined aetiology, unknown aetiology, multiple causes or other defined etiology.[14] The specific criteria used to diagnose each TOAST subtype have previously been described in detail.[26] The patients were classified as undetermined stroke only if the diagnostic work-up included at least brain imaging, ECG and carotid imaging, and no clear aetiology was found. Patients with more incomplete investigations were classified as unknown stroke while stroke of multiple causes was classified separately. Although TOAST criteria have not been specifically validated for TIA events, its practical application in a TIA cohort has been previously demonstrated with comparable results to other classification systems.[27]

8.3.2 Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the cohort stratified by CKD status. Continuous data were given as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate, categorical data were given as n (%). Mann-Whitney U tests and Chi-squared tests were used to test the significance of differences between two groups for continuous and categorical variables respectively. The relative frequency of TOAST subtypes was reported according to CKD status. Associations between CKD and TOAST subtypes were determined by binary logistic regression whereby specific subtypes were treated as dichotomous dependent variables

and compared to all other subtypes, adjusted for age, sex, and hypertension, and stratified by age (<65 years versus ≥65 years) and eGFR category. Statistical heterogeneity in CKD prevalence among TOAST subtypes was investigated using metaregression to determine if age was a significant predictor of between-subtype variance. Logistic regression analysis was also used to determine the association between intracerebral haemorrhage (ICH) and CKD using ischaemic stroke as the reference category. Events of unknown aetiology (i.e. incompletely investigated) were excluded from all regression analyses to avoid the risk of reverse causation (i.e. under-investigation of elderly, frail patients with CKD due to contraindications or frailty). The analyses were also repeated using multinomial logistic regression. Results were considered significant at $p < 0.05$. All statistical analyses were performed using SPSS version 25.0.

8.4 Results

A total of 3178 consecutive eligible patients with TIA (n=1167), ischaemic stroke (n=1802), and ICH (n=209), were recruited from 2002 to 2017. Table 8-1 shows the baseline characteristics at the time of the event for all TIA/ischaemic stroke patients and according to CKD status. The median age was 75.8 (66.0-83.7) years, 49.1% (n=1458) were men, and hypertension was the most prevalent risk factor being found in 58.5% (n=1738). The median eGFR was 65.9 ml/min/1.73m^2 and 1197 patients had CKD (40.3% of the study population). 422 patients (14.2%) had an eGFR≥90, 1346 (45.3%) had an eGFR 60-89, 1064 (35.8%) had an eGFR 30-59, 133 (4.5%) had an eGFR <30 ml/min/1.73m^2. Only 11 patients (0.3%) were dialysis-dependent. Notably, compared to those with normal renal function, the CKD group were older and had a significantly higher burden of vascular risk factors and co-morbidities including hypertension, diabetes mellitus, ischaemic heart disease, peripheral arterial disease, congestive cardiac failure, and atrial fibrillation (all p<0.05).

Table 8-1 and Figure 8-1 demonstrate the relative frequency of TIA/ischaemic stroke TOAST subtypes occurring with the entire population and according to the presence or absence of CKD. There was a greater prevalence of cardioembolic subtype (31.8 vs 21.2%; p<0.001), unknown (16.6 vs 8.8%; p<0.001) and multiple aetiology (4.3 vs 2.8%; p=0.03) events in patients with CKD while small vessel disease (8.8 vs 13.6%; p<0.001), undetermined (26.1 vs 39.4%; p<0.001), and other aetiologies (1.0 vs 3.6%; p<0.001) were more common in patients without CKD. There was no significant difference in large artery disease subtype prevalence between groups (11.3 vs 10.6%; p=0.59).

Although there appeared to be major differences in CKD prevalence between TIA/stroke subtypes (p<0.001; Figure 8-1), CKD prevalence was also strongly associated with age. When the median age of each TIA/stroke subtype was plotted against the odds ratio (OR) of individual subtypes, there was a linear association suggesting potential confounding by age (p value of weighted regression=0.001; Figure 8-2). Consistent with this hypothesis, the prevalence of CKD showed a similar pattern of variation according to age within TIA/stroke subtypes (Figure 8-3).

The association between CKD and TOAST subtypes was further examined using univariate and multivariate regression analysis (Table 8-2*).* In unadjusted analysis, CKD appeared to be associated with a significantly increased risk of cardioembolic TIA/stroke (Crude OR=2.04, 95% CI: 1.72-2.42; p<0.001) and events of multiple aetiologies (Crude OR=1.75, 1.18-2.61; p=0.006). However, these risk associations attenuated and became non-significant after adjustment for age, sex, and hypertension (Adjusted OR=1.20, 0.99-1.45; p=0.07 for cardioembolic events and adjusted OR=1.13, 0.73-1.74; p=0.59 for events of multiple aetiologies). CKD initially appeared to be associated with lower risk of small vessel disease (Crude OR=0.67, 0.52-0.86; p=0.001), events of undetermined aetiology (Crude OR=0.60, 0.51-0.71; p<0.001), and events of other defined aetiology

(Crude OR=0.30, 0.16-0.56; p<0.001), but again these associations were lost after adjustment for age, sex, and hypertension (Adjusted OR=0.86, 0.65-1.13; p=0.27 for small vessel disease events and adjusted OR=0.73, 0.37-1.45; p=0.36 for events of other defined aetiology), apart from events of undetermined aetiology which remained significantly negatively associated with CKD (Adjusted OR=0.81, 0.67-0.98; p=0.03). There was no overall association between CKD and large artery disease in either unadjusted or adjusted analysis. Additional adjustment for any temporal trend in CKD prevalence over time did not alter the findings. Results were also similar when analyses were repeated using multinomial logistic regression.

Table 8-3 shows the crude and adjusted ORs of TOAST subtypes according to eGFR categories. Similar to the overall analysis, there was no association between cardioembolic, large artery disease, small vessel disease, undetermined, multiple, and other aetiologies with individual eGFR categories after adjustment for age and hypertension (all p>0.05).

The age-specific associations of CKD and TOAST subtypes are shown in Table 8-4 CKD was associated with a significantly increased risk of cardioembolic events in patients < 65 years even after adjustment for age, sex, and hypertension (Adjusted OR=1.99, 1.02-3.82; p=0.04) but not at older ages (Adjusted OR=1.10, 0.90-1.35; p=0.35). There was a non-significant association between CKD and large artery disease events in those aged less than 65 years (Adjusted OR=1.32, 0.62-2.82; p=0.47). With further analysis though, there was an independent association between CKD and large artery disease in those aged less than 55 years (Adjusted OR=6.20, 1.18-32.51; p=0.03) (Figure 8-3). There was also a significant inverse association between CKD and other aetiologies in older patients (Adjusted OR=0.40, 0.17-0.96; p=0.04).

The baseline characteristics of all patients with ICH are summarized in Table 8-5. Of the 208 patients, 70 (33.7%) had CKD. Patients with CKD were older (median age 81 vs 71 years; p<0.001), more hypertensive (71.4 vs 43.5%; p<0.001), and more likely to have AF (21.4 vs 9.4%; p=0.03). Compared to ischaemic stroke, there initially appeared to be a lower prevalence of ICH in CKD (Unadjusted OR=0.64, 0.48-0.87; p=0.004) but after adjustment for age and hypertension, there was no association between CKD and ICH (Adjusted OR=0.76, 0.35-1.06; p=0.11).

8.5 Discussion

Using a population-based cohort study, I report for the first time the relative frequency of TIA and stroke subtypes in CKD using the TOAST classification.[14] Although there was a greater prevalence of cardioembolic, large artery disease, and multiple aetiology subtypes in the CKD population, attenuation of any associations present with adjustment for mainly age but also hypertension is consistent with the stroke risk meta-analysis in Chapter 5,[22] suggesting that there are no important renal-specific vascular risk factors beyond these covariates.

Similar to previous studies,[19, 21] cardioembolic events were the most frequent subtype within the CKD group, accounting for 32% of TIA/ischaemic stroke events. Patients with CKD are known to be at high-risk of AF with prevalence rates of 12% reported and increasing incidence rates with advancing kidney disease stages.[28] However, as the association between CKD and cardioembolic events was greatly diminished with adjustment for age, sex, and hypertension, this would suggest that despite being linked to a greater left atrial thrombogenic milieu,[10] CKD itself is not an overall independent risk factor for these events. The notable exception appears to be for younger patients whom the association remained significant even with adjustment, suggesting possible synergy with other underlying risk factors such as female sex and hypertension in this subgroup.

However, the addition of renal function to existing stroke risk prediction tools in AF (e.g. $CHADS_2$ or CHA_2DS_2-VASc) has not been shown to independently add to the predictive value of these scores,[29] though this may also be a reflection of the accuracy of such scores in a group where their use has not been validated.

Although low eGFR has been consistently associated with subclinical small vessel disease, particularly silent cerebral infarction,[30, 31] I report a lower frequency of symptomatic lacunar TIA/stroke events in the CKD population in this study. There was in fact no association between CKD and small vessel disease events after adjustment for age and sex. However, these findings are in keeping with an earlier systematic review and meta-analysis that also did not find any specific association between CKD and symptomatic lacunar stroke, but that in those without stroke, greater small vessel disease burden on imaging was associated with worse renal function.[32] The authors postulated that small vessel disease events may be underestimated in this group due to imprecise subtyping with an overreliance on clinical and CT diagnosis. Similarly, in this study, not all patients would have had DWI-MRI in the acute phase, particularly those with more advanced CKD, which may limit the sensitivity of our lacunar stroke subtyping. Previous studies have also suggested that there may be age-specific associations between small vessel disease (either markers or strokes) and CKD,[32, 33] however, I did not find any differential risk association between those aged greater or less than 65 years old.

Although there was no overall association between CKD and large artery disease events, there did appear to be an age-specific association present for those aged less than 55 years. There are a number of potential mechanisms that may underlie this relationship. Renal function has been shown to be a strong predictor of greater carotid intima-media thickness and progression of subclinical atherosclerosis independent of traditional and non-traditional cardiovascular risk factors.[34] Dialysis appears to accelerate medial vascular calcification in children and young people,[35] and blood vessels from children with

CKD show features of premature aging including oxidative DNA damage and elevated senescence markers.[36] There is also evidence of polygenic correlation between CKD and large artery disease stroke.[37] However, the total number of stroke events among younger people in this category was quite low so further research in this area is required.

CKD was associated with a significantly lower risk of TIA/stroke events of undetermined aetiology. Since cryptogenic TIA/strokes have been associated with few traditional atherosclerotic or cardioembolic markers,[26] this finding is in keeping with our hypothesis that most of the stroke risk in kidney disease may be accounted for by age and hypertension.[22] If non-traditional risk factors such as inflammation, oxidative stress, or coagulopathy related to the uraemic milieu were aetiologically important, one might have expected a higher burden of events of undetermined aetiology in CKD patients, as these factors are not measured in conventional TIA/stroke work-up and may be better represented by this subtype.

Similar to previous studies,[38] CKD was present in one-third of patients with ICH. However, there was no specific association between ICH and CKD as compared to ischaemic stroke risk. This is consistent with earlier work that suggests that proteinuria associates more strongly with haemorrhagic stroke risk than low eGFR.[39, 40] It may also be a reflection of the underlying predominantly Caucasian population as the relationship between CKD and ICH appears to be stronger in Asian[41] and black populations, possibly attributable to a higher presence and number of cerebral microbleeds in the latter.[42]

This study had a number of limitations. Firstly, there are shortcomings with all aetiological classifications of TIA/ischemic stroke. Although the TOAST classification is the most widely used system, there may be multiple different pathologies within each of the TOAST subcategories, particularly strokes of undetermined aetiology. Secondly, cryptogenic events (undetermined and unknown subtypes) accounted for a large proportion of cases,

limiting mechanistic insights. However, this is consistent with other large epidemiological studies where cryptogenic strokes accounted for 26-40% of cases.[43, 44] Thirdly, since a minority of patients did not have intracranial vessel imaging or brain MRI, it is possible that there was misclassification bias whereby large artery disease and small vessel disease events were misclassified as undetermined. The changes to diagnostic evaluation over time could have resulted in differences in subtype designation through the study period. Fourthly, lack of association between CKD and specific TOAST subtypes after adjustment for age and hypertension does not necessarily indicate that renal-specific risk factors do not play a role in the aetiology of all stroke. One can only conclude that any such role does not differ in importance between the different aetiological subtypes. Fifthly, direct comparison of individual subtype-CKD associations in a case only setting can be challenging given that each subtype group is then included in the referent group of the other. Finally, as previously stated, the Oxford Vascular Study population study is 94% Caucasian which may limit the generalizability of these results to other settings.

However, this study has broader implications for stroke research. It highlights how any study of risk association and stroke should be carefully stratified by and adjusted for age. Previous studies that reported CKD prevalence according to stroke subtype did not adjust for age,[19-21] and as evidenced by this paper, subtype-specific associations are particularly prone to confounding by age.

In conclusion, to the best of my knowledge, this was the first study to subtype in detail TIA/stroke events in CKD patients according to the TOAST classification. I found few associations between CKD and specific event subtypes after adjustment for age, sex, and hypertension, suggesting that addressing traditional risk factors may be most important in terms of prevention and treatment.

8.6 References

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TABLES

Table 8-1 Baseline characteristics of all patients with TIA and ischaemic stroke, and stratified according to the presence of CKD.

Characteristics*	All patients n= 2969	No CKD n= 1772	CKD present n= 1197	P value
Age years, median (IQR)	75.8 (66.0-83.7)	70.6 (59.8)	81.7 (74.7-87.4)	<0.001
Male sex	1458 (49.1)	984 (55.7)	474 (39.6)	<0.001
Black race	34 (1.1)	22 (1.2)	12 (1.0)	0.18
eGFR (ml/min/1.73m^2), median (IQR)	65.9 (50.5-82.0)	78.6 (69.4-89.3)	46.9 (38.3-54.1)	<0.001
Hypertension	1738 (58.5)	897 (50.7)	841 (70.3)	<0.001
Diabetes mellitus	425 (14.3)	222 (12.6)	203 (17)	0.001
Previous history of hyperlipidaemia	909 (30.6)	499 (28.2)	410 (34.3)	0.001
Previous history of MI	318 (10.7)	137 (7.7)	18.1 (15.1)	<0.001
Previous history of PAD	206 (6.9)	79 (4.5)	127 (10.6)	<0.001
Previous history of VHD	280 (9.4)	127 (7.2)	153 (12.8)	<0.001
Previous history of CCF	268 (9.0)	88 (5)	180 (15)	<0.001
Previous history of atrial fibrillation	554 (18.7)	247 (14.0)	306 (25.6)	<0.001
Current or history of smoking	1628 (54.8)	1020 (57.8)	608 (51.2)	<0.001
Event Type				<0.001
TIA	1167 (39.3)	763 (43.2)	403 (33.7)	
Ischaemic stroke	1802 (60.7)	1005 (56.8)	794 (66.3)	
TOAST classification				<0.001
Cardioembolism	757 (25.5)	375 (21.2)	381 (31.8)	
Large artery	322 (10.8)	187 (10.6)	135 (11.3)	
Small artery	347 (11/7)	241 (13.6)	105 (8.8)	
Undetermined cause	1011 (34.1)	697 (39.4)	313 (26.1)	
Unknown	355 (12)	155 (8.8)	199 (16.6)	
Multiple	101 (3.4)	49 (2.8)	52 (4.3)	
Other	75 (2.5)	63 (3.6)	12 (1.0)	

*Numbers are n (%) unless otherwise stated.

CCF indicates congestive cardiac failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR indicates interquartile range; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; TIA, transient ischaemic attack; VHD, valvular heart disease.

Table 8-2 Associations of CKD and TOAST subtypes, adjusted for age, sex, and hypertension.

TIA/Stroke TOAST Subtype†	Crude OR (95% CI)	P value	Model 1 OR* (95% CI)	P value	Model 2 OR** (95% CI)	P value
Cardioembolic	2.04 (1.72-2.42)	<0.001	1.22 (1.01-1.48)	0.04	1.20 (0.99-1.45)	0.07
Large artery disease	1.19 (0.94-1.51)	0.15	1.17 (0.90-1.52)	0.25	1.11 (0.85-1.45)	0.45
Small vessel disease	0.67 (0.52-0.86)	0.001	0.86 (0.66-1.13)	0.28	0.86 (0.65-1.13)	0.27
Undetermined	0.60 (0.51-0.71)	<0.001	0.78 (0.65-0.94)	0.01	0.81 (0.67-0.98)	0.03
Multiple	1.75 (1.18-2.61)	0.006	1.14 (0.74-1.75)	0.56	1.13 (0.73-1.74)	0.59
Other	0.30 (0.16-0.56)	<0.001	0.73 (0.37-1.46)	0.38	0.73 (0.36-1.43)	0.37

CKD indicates chronic kidney disease (defined as eGFR<60 mL/min per 1.73 m^2); CI, confidence interval; OR, odds ratio; TIA, transient ischaemic attack.

† Events of unknown aetiology were excluded.

*Model 1 adjusted for age and sex.

**Model 2 adjusted for variables in model 1 and hypertension.

Table 8-3 Associations of GFR categories and TOAST subtypes, adjusted for age, sex, and hypertension.

	GFR Categories (ml/min/1.73m^2)						
Stroke Subtype*	**≥90**	**60-89**		**30-59**		**<30**	
Cardioembolic			**P value**		**P value**		**P value**
Crude OR	1.00 (ref)	1.82 (1.35-2.45)	<0.001	3.08 (2.28-4.15)	<0.001	5.50 (3.38-8.96)	<0.001
Age-adjusted OR	1.00 (ref)	0.85 (0.61-1.19)	0.34	1.02 (0.71-1.45)	0.93	1.71 (1.00-2.92)	0.05
Age and hypertension-adjusted OR	1.00 (ref)	0.85 (0.61-1.18)	0.34	1.00 (0.70-1.42)	0.98	1.65 (0.96-2.82)	0.07
Large artery disease							
Crude OR	1.00 (ref)	1.20 (0.83-1.74)	0.32	1.39 (0.96-2.03)	0.08	1.19 (0.59-2.42)	0.63
Age-adjusted OR	1.00 (ref)	1.11 (0.74-1.66)	0.62	1.23 (0.79-1.93)	0.37	1.04 (0.49-2.22)	0.91
Age and hypertension-adjusted OR	1.00 (ref)	1.10 (0.73-1.64)	0.65	1.16 (0.74-1.81)	0.53	0.94 (0.44-2.01)	0.88
Small vessel disease							
Crude OR	1.00 (ref)	0.76 (0.56-1.03)	0.07	0.57 (0.41-0.79)	0.001	0.32 (0.14-0.77)	0.01
Age-adjusted OR	1.00 (ref)	1.01 (0.72-1.41)	0.97	0.88 (0.59-1.32)	0.54	0.52 (0.21-1.27)	0.15
Age and hypertension-adjusted OR	1.00 (ref)	1.01 (0.72-1.41)	0.97	0.88 (0.59-1.32)	0.53	0.51 (0.21-1.26)	0.15
Undetermined							
Crude OR	1.00 (ref)	0.77 (0.61-0.96)	0.02	0.51 (0.40-0.65)	<0.001	0.32 (0.19-0.54)	<0.001
Age-adjusted OR	1.00 (ref)	1.14 (0.88-1.47)	0.32	0.93 (0.70-1.25)	0.64	0.60 (0.35-1.05)	0.07
Age and hypertension-adjusted OR	1.00 (ref)	1.15 (0.89-1.48)	0.30	0.98 (0.73-1.31)	0.87	0.65 (0.37-1.14)	0.13
Multiple							
Crude OR	1.00 (ref)	1.49 (0.72-3.09)	0.29	2.33 (1.13-4.81)	0.02	3.04 (1.05-8.76)	0.04
Age-adjusted OR	1.00 (ref)	0.68 (0.31-1.51)	0.35	0.76 (0.33-1.77)	0.52	0.90 (0.28-2.88)	0.85
Age and hypertension-adjusted OR	1.00 (ref)	0.68 (0.31-1.51)	0.34	0.75 (0.32-1.75)	0.51	0.88 (0.27-2.84)	0.83
Other							
Crude OR	1.00 (ref)	0.60 (0.36-1.03)	0.06	0.21 (0.10-0.44)	<0.001	0.19 (0.03-1.42)	0.11
Age-adjusted OR	1.00 (ref)	1.66 (0.91-3.03)	0.10	1.13 (0.47-2.70)	0.79	1.09 (0.14-8.78)	0.93
Age and hypertension-adjusted OR	1.00 (ref)	1.66 (0.91-3.02)	0.10	1.11 (0.46-2.68)	0.81	1.08 (0.13-8.67)	0.94

eGFR indicated estimated glomerular filtration rate; OR, odds ratio.

*Events of unknown aetiology were excluded.

Table 8-4 The age-specific associations of CKD and TOAST subtypes, adjusted for age, sex, and hypertension.

TIA/Stroke TOAST Subtype†	<65 years	P value	≥65 years	P value
Cardioembolic				
Crude OR	1.87 (0.98-3.54)	0.06	1.58 (1.31-1.91)	<0.001
Model 1 OR*	1.98 (1.02-3.82)	0.04	1.14 (0.93-1.40)	0.21
Model 2 OR**	1.99 (1.02-3.86)	0.04	1.10 (0.90-1.35)	0.35
Large artery disease				
Crude OR	1.87 (0.90-3.87)	0.10	1.04 (0.80-1.35)	0.78
Model 1 OR	1.43 (0.67-3.02)	0.35	1.20 (0.91-1.58)	0.20
Model 2 OR	1.32 (0.62-2.82)	0.47	1.14 (0.86-1.51)	0.35
Small vessel disease				
Crude OR	0.82 (0.40-1.66)	0.58	0.79 (0.60-1.05)	0.10
Model 1 OR	0.78 (0.38-1.60)	0.50	0.92 (0.69-1.24)	0.60
Model 2 OR	0.73 (0.35-1.51)	0.40	0.95 (0.70-1.28)	0.71
Undetermined				
Crude OR	0.57 (0.33-0.98)	0.04	0.71 (0.59-0.86)	<0.001
Model 1 OR	0.54 (0.31-0.93)	0.03	0.86 (0.70-1.05)	0.13
Model 2 OR	0.57 (0.33-1.00)	0.05	0.90 (0.73-1.10)	0.29
Multiple				
Crude OR	N/A†	N/A†	1.24 (0.82-1.86)	0.30
Model 1 OR			1.15 (0.75-1.76)	0.54
Model 2 OR			1.15 (0.75-1.76)	0.54
Other				
Crude OR	1.26 (0.48-3.32)	0.64	0.31 (0.13-0.73)	0.007
Model 1 OR	2.33 (0.83-6.53)	0.11	0.41 (0.17-0.98)	0.04
Model 2 OR	2.33 (0.83-6.58)	0.11	0.40 (0.17-0.96)	0.04

CKD indicates chronic kidney disease (defined as eGFR<60 mL/min per 1.73 m^2); OR, odds ratio; TIA, transient ischaemic attack.

†Events of unknown aetiology were excluded and no cases of multiple aetiology observed in CKD patients < 65 years.

*Model 1 adjusted for age and sex.

**Model 2 adjusted for variables in model 1 and hypertension.

Table 8-5 Baseline characteristics of all patients with ICH, and stratified according to the presence of CKD.

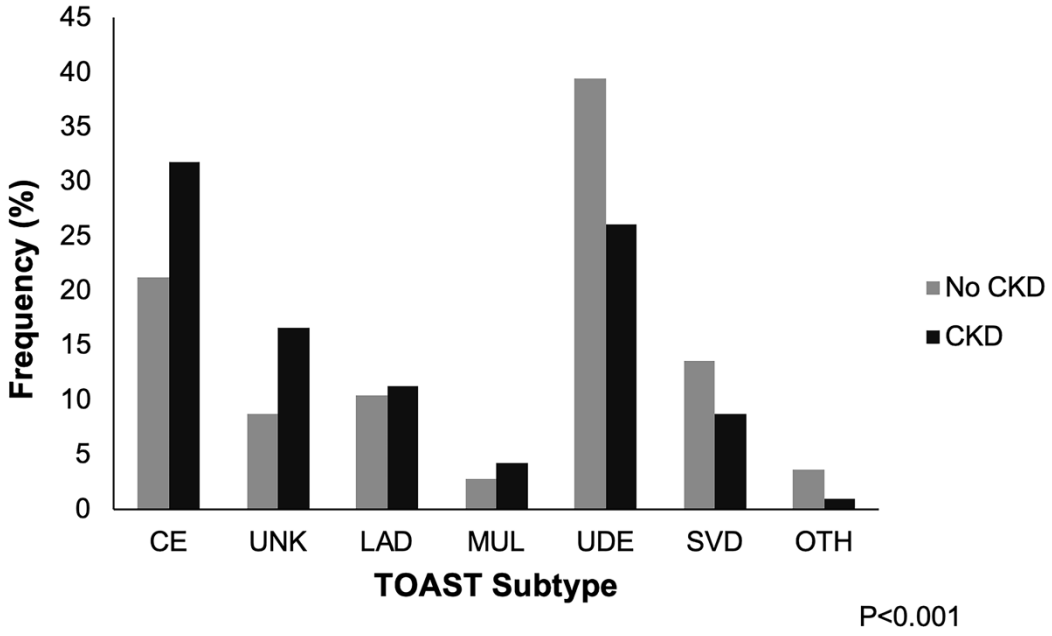
Characteristics*	All patients n= 209	No CKD n= 138	CKD present n= 70	P value
Age years, median (IQR)	76 (61.5-83.0)	71 (56.8-80.3)	81 (75.0-88.0)	<0.001
Male sex	103 (49.3)	71 (51.4)	32 (45.7)	0.53
Black race	3 (1.4)	3 (2.2)	0 (0)	0.53
eGFR (ml/min/1.73m^2), median (IQR)	72.3 (53.1-87.4)	83.4 (72.2-93.1)	47.5 (39.7-53.3)	<0.001
Hypertension	110 (52.6)	60 (43.5)	50 (71.4)	<0.001
Diabetes mellitus	24 (11.5)	12 (8.7)	12 (17.1)	0.12
Previous history of hyperlipidaemia	43 (20.6)	26 (18.8)	17 (24.3)	0.46
Previous history of MI	5 (2.4)	4 (2.9)	1 (1.4)	0.86
Previous history of PAD	9 (4.3)	5 (3.6)	4 (5.7)	0.73
Previous history of atrial fibrillation	28 (13.4)	13 (9.4)	15 (21.4)	0.03
Current or history of smoking	99 (49)	70 (52.2)	29 (43.3)	0.30

*Numbers are n (%) unless otherwise stated.

CCF indicates congestive cardiac failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate ICH indicates intracerebral haemorrhage, IQR indicates interquartile range; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; TIA, transient ischaemic attack; VHD, valvular heart disease;

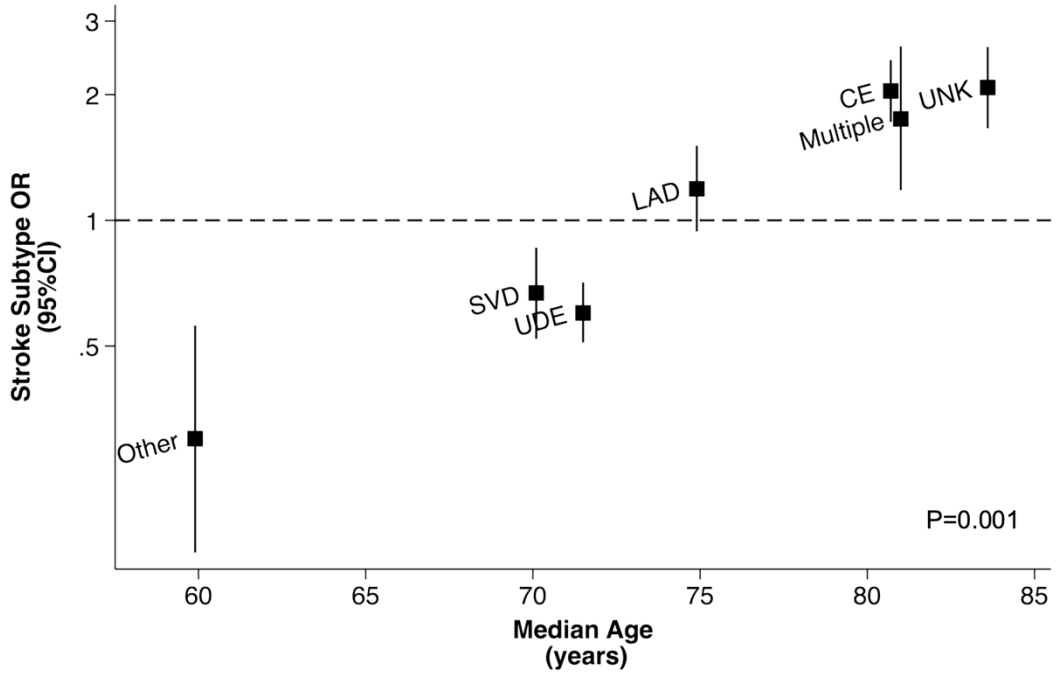
FIGURES

Figure 8-1 Relative frequencies of TOAST TIA/stroke subtypes according to CKD status.



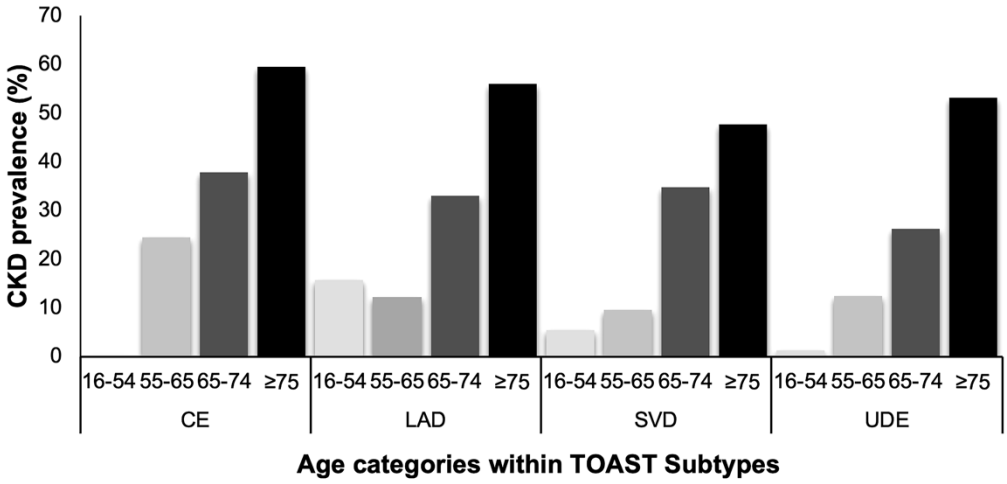
CE indicates cardioembolism; CKD, chronic kidney disease; LAD, large artery disease; MUL, multiple causes, OTH, other causes; SVD, small vessel disease; UDE, undetermined; UNK, unknown.

Figure 8-2 The odds ratio (OR) of specific TOAST subtypes in CKD versus the median age within individual subtypes.



CE indicates cardioembolism; CKD, chronic kidney disease; LAD, large artery disease; Multiple, multiple causes, Other, other causes; SVD, small vessel disease; UDE, undetermined; UNK, unknown.

Figure 8-3 CKD prevalence within TOAST subtypes according to age category.



CE indicates cardioembolism; CKD, chronic kidney disease; LAD, large artery disease; SVD, small vessel disease; UDE, undetermined.

8.7 Appendix

TOAST for OXVASC

Patient Name: **Event Date :**

OXVASC ID: **Event Type :**

Age at event:

Risk factor profile (for **all patients**; please circle)

Cardioembolic-related:

Diagnosed AF (including atrial flutter) prior to the index event: Yes / No
Mechanical prosthetic /Bioprosthetic cardiac valve prior to the index event: Yes / No

If yes to either→Treatment: anticoagulation / antiplatelet / none INR (if on warfarin) _____

Recent MI (<4 weeks): Yes / No

Atherosclerotic risk factors:

Hypertension / DM / hyperlipidaemia / myocardial infarction / PVD / stroke / TIA / smoking (ex/current).

Other risk factors:

None / Migraine with aura / Migraine without aura / Autoimmune disease/ Active cancer

Clinical syndrome (for **all patients;** please circle)

NINDS criteria (PMR): Positive / Negative

Clinical syndrome according to the OXVASC classification (PMR):

OCSP: PACI / LACI / TACI / POCI

Vascular territory: LACA / LMCA / LPCA / RACA / RMCA / RPCA / VB/uncertain

Investigations (**ONLY** for **prob/def patients**; please circle)

Brain imaging **CT / MRI / Both**

Acute lesion Yes / No If Yes, please circle the appropriate description below:
Single: L / R, Size _____ mm, Carotid / VB, Cortical / Subcortical
lacunar infarct Yes / No
Multiple: L / R / Both; Anterior / Posterior / Both

Old lesion Yes / No If Yes, please describe _____

Vascular imaging **Carotid Doppler only**

Normal Yes / No

Dissection Yes / No, if Yes, please describe _____

Stenosis Yes / No If Yes, please circle the appropriate description below:
Symptomatic / asymptomatic / Both
If symptomatic, please choose the location below:
Extracranial / Intracranial I / Both, Carotid / VB / Both

Severity (≥ 50%) Yes / No

Known stenosis from previous scans (Doppler/CTA/MRA/DSA)? No / Yes, please specify_____

Bubble TCD R-L shunt Yes / No

Cardiac investigation

ECG: SR / AF (including atrial flutter) / sick-sinus syndrome / other: _____

Echo: EF _____ %

Left ventricular or Left atrial / atrial appendage thrombus	Yes / No
Akinetic / hypokinetic left ventricular segment	Yes / No
Mitral stenosis	Yes / No
Mitral valve prolapse	Yes / No
Infective / non-bacterial thrombotic endocarditis	Yes / No
PFO / Atrial septum aneurysm	Yes / No
Myxoma	Yes / No

R-test/HOLTER: AF>30s Yes / No

Other investigation results _____

(*e.g.* thrombophilia screen, CADASIL genetics)

TOAST (**ONLY** for **prob/def patients;** please circle)

LAD / CE / SVD / UDE / UNK / MULT_____**/ Other**_____

OXCODE (for **all patients**)

Chapter 9 Chronic kidney disease predicts stroke severity, disability, and recurrence: a systematic review, meta-analysis, and population-based cohort study

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9.1 Chapter outline

Chronic kidney disease (CKD) is associated with cerebrovascular disease and related mortality, and with under-utilisation of acute and preventive treatments, but any impact on initial event severity and recurrence risk is unclear. I aimed to determine whether CKD is associated with worse initial stroke severity and disability, and whether CKD is independently predictive of recurrent stroke and other vascular events.

I did a systematic review to May 2020 (MEDLINE/EMBASE) for cohort studies or randomized controlled trials that reported stroke severity, disability, and recurrence risk in adults according to baseline renal function. Study and participant characteristics and risk estimates were extracted. Estimates were combined using a random effects model. The study protocol was registered with PROSPERO (CRD42020199983). Then, in a population-based study of all transient ischaemic attack (TIA)/stroke (Oxford Vascular Study), I studied initial stroke severity and disability using the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS), respectively, in relation to CKD (defined as an eGFR < 60ml/min/1.73m^2) in all patients presenting with TIA and stroke from April 1, 2002 to March 31, 2017. Associations between CKD and event severity, and between CKD and risk of recurrent vascular events (stroke, myocardial infarction, and sudden cardiac death) were examined using ordinal and Cox regression models, respectively, adjusted for age, sex, and known vascular risk factors, and stratified by TOAST subtype.

Among 3178 patients with TIA (n=1167), ischaemic stroke (n=1802), and intracerebral haemorrhage (ICH) (n=209), 1267 (40%) had CKD. CKD was independently associated with greater risk of ischaemic stroke compared to TIA (adjusted OR=1.31, 95%CI=1.11-1.56; p=0.002) and with greater initial NIHSS (adjusted OR=1.28, 1.04-1.46; p=0.018), driven mostly by those with an estimated glomerular filtration rate (eGFR) < 30

ml/min/1.73m^2 (adjusted OR=2.59, 1.44-4.66; p=0.001 for ischaemic stroke; adjusted OR=4.06, 2.04-8.06; p<0.001 for initial NIHSS). Among patients with ischaemic stroke, CKD was also associated with higher one-month mRS scores (adjusted OR=1.40, 1.13-1.74; p=0.002), driven by those with an eGFR < 30 ml/min/1.73m^2 (Adjusted OR=6.51, 3.04-13.97, p<0.001). Risk of early (< 90 days) recurrent stroke was increased with CKD (adjusted HR=1.60, 1.15-2.21; p=0.005) as was the risk of longer-term (1-15 years) composite vascular outcomes (adjusted HR=1.24, 1.05-1.46; p=0.01).

The consistent independent impact of CKD on initial event severity, early disability and recurrence risk suggests that there may be processes intrinsic to CKD leading to uniformly worse outcomes. Further research should determine whether there are CKD-specific treatments that may improve stroke outcomes.

9.2 Introduction

Chronic kidney disease (CKD) is consistently associated with a significantly increased risk of stroke.[1,2] For every 10 mL/min/1.73 m^2 decline in estimated glomerular filtration risk (eGFR) and for every 25 mg/mmol increase in albuminuria, stroke risk increases by 7% and by 10% respectively.[2] Although the relationship appears to be dependent on age and hypertension,[3] CKD is highly prevalent in patients with both ischaemic and haemorrhagic stroke subtypes.[4,5]

Stroke is the second most common cause of death and the main cause of neurological disability worldwide.[6,7] It is also a leading contributor to the global burden of disease, as measured in disability-adjusted life-years (DALYs).[8] There is some evidence that CKD is associated with worse stroke outcomes with greater likelihood of institutionalization,[9] and both short- and long-term mortality.[10,11] These poorer outcomes are variably attributed to the presence of triggers for larger infarcts (e.g. high prevalence of atrial fibrillation [AF][12]) and lower rates of prescription of standard guideline-based therapies such as lipid-lowering or anti-thrombotic agents.[13] However, less is known about the impact of CKD on initial stroke severity and risk of recurrence, and whether its impact varies depending on the underlying event subtype. A recent study of only lacunar stroke events indicated that CKD may increase the risk of recurrent stroke by 50%.[14] Stratification by stroke subtype may provide insights into potential mediating or confounding factors that may underlie stroke severity, disability or recurrence risk.

Therefore, I firstly performed a systematic review and meta-analysis of published studies of CKD, stroke severity and outcomes to ascertain what was previously known about these associations. Then, using the Oxford Vascular Study (OXVASC), a large prospective population-based study with detailed event subtyping,[15] I aimed to determine whether CKD is associated with higher likelihood of stroke rather than TIA, worse initial

stroke severity, and whether CKD is independently predictive of recurrent stroke and other vascular events.

9.3 Methods

9.3.1 Search strategy and selection criteria of the systematic review, and data extraction

Using the same protocol, with a renewed focus on stroke severity, disability, and recurrence, I updated our earlier systematic reviews and meta-analyses of randomized controlled trials and cohort studies that had estimated the associations between low GFR, proteinuria and the risk of stroke (Chapter 5 and Chapter 6).[3,16] The study protocol was registered prospectively on PROSPERO (CRD42020199983) and conformed with PRISMA guidelines. I searched MEDLINE (2018-May 2020) and EMBASE (2018-May 2020) databases using a search strategy developed by a specialized librarian that combined text word and medical subject headings without language restrictions (Table 4-1).

I included all RCTs and cohort studies that reported quantitative estimates with a measure of precision (or original data which allowed their calculation) of the association between CKD and stroke severity, disability, or recurrence risk. GFR had to be either estimated using a validated formula [Cockcroft-Gault, modification of diet in renal disease (MDRD), CKD epidemiology collaboration (CKD-EPI)], measured directly, approximated from urinary creatinine clearance or estimable from serum creatinine. The outcomes of interest were stroke severity (measured using the National Institutes of Health Stroke Scale [NIHSS]), disability (measured using the modified Rankin Scale (mRS) or equivalent measure such as risk of institutionalization), and recurrence risk. As per the previous reviews, I excluded cross-sectional and case–control studies due to the greater risk of bias than in prospective cohort studies, studies where GFR was measured using non-

validated methods, and studies where outcomes were measured by self-reports or proxy reports and studies that reported radiological but clinically silent stroke disease.[3,16]

Key descriptive and quantitative data were recorded for study characteristics, participants, exposures and outcomes. I collected details of the year of study publication, location, size and duration. Abstracted participant characteristics included age, gender, race and the prevalence of diabetes, known vascular diseases, smoking and hypertension. I recorded the GFR or level of albuminuria, the method of measurement, and the units of quantification used. I then extracted data for the relative risk (RR), odds risk (OR) or hazard ratio (HR) of stroke outcome (severity, disability, or recurrence) associated with CKD, each specified GFR category, or level of albuminuria. I obtained effect estimates from the most fully adjusted model reported, noting which variables the model had adjusted for. The standard error of the estimate was also extracted or estimated from the reported 95% confidence interval (CI). I assessed the quality of cohort studies and post hoc analyses using the Newcastle–Ottawa Scale.[17]

9.3.2 Study design, participants and procedures

OXVASC is an ongoing population-based study of the incidence and outcome of cerebrovascular, cardiovascular and peripheral vascular events since 2002, and is described in detail in section 4.3. Multiple methods of ascertainment are used for patients with TIA or stroke, as detailed here.[18]

Patients with TIA and stroke recruited from April 2002 to March 2017 were included. Patients were assessed urgently by study clinicians and considered for inclusion. Stroke was diagnosed per the WHO definition.[19] Neurological impairment, medical history and risk factors were recorded in all patients. Hypertension was defined on the basis of a

historical diagnosis (either patient-reported or GP-coded) and/or the presence of anti-hypertensive treatment. Stroke severity was measured using the National Institutes of Health Stroke Scale (NIHSS). Patients routinely had brain imaging, vascular imaging, 12-lead ECG, and standard blood tests, as described in section 8.3.1.

All cases were reviewed by a senior neurologist (PMR) daily and imaging was reviewed by the study neuroradiologist. TIA/ischaemic stroke aetiology was classified (blind to CKD status) according to the TOAST criteria into seven subtypes: cardioembolic stroke, large artery disease, small vessel disease, undetermined aetiology, unknown aetiology, multiple causes or other defined etiology.[20] The patients were classified as undetermined stroke only if the diagnostic work-up included at least brain imaging, electrocardiogram (ECG) and carotid imaging, and no clear aetiology was found. Patients with more incomplete investigations were classified as unknown stroke while stroke of multiple potential causes was classified separately.

All patients in OXVASC had face-to-face follow-up with a research nurse or physician at 1, 3, 6, 12, 24, 60, and 120 months after the index event. Functional status was assessed using the modified Rankin Scale (mRS) which was recorded at each follow-up visit as well as recurrent ischaemic or bleeding events. The mRS is a 7-point disability scale ranging from 0 (no symptoms) to 6 (death).[21] Raters were trained in mRS assessment using an instructional DVD with written materials produced by the University of Glasgow, previously used in large-scale trials.[21] Pre-stroke mRS was determined at enrolment. Patients who moved out of the study are were followed up by telephone. Additional information was obtained from carers in patients with significant speech or cognitive impairment. Recurrent vascular events were identified by daily OXVASC ascertainment, follow-up interviews and review of GP/hospital diagnostic codes. All deaths were also recorded from death certificates, coroners' reports and the National Health Service Central Register.

As outlined in section 4.3.4, CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 for three or more months as per 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[22] eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI). CKD was staged according to KDIGO guidelines (stage 1: eGFR ≥ 90, stage 2: eGFR 60-89, stage 3a: eGFR 45-59, stage 3b: eGFR 30-44, stage 4: eGFR 15-29, stage 5: eGFR < 15 ml/min/1.73m^2). Where numbers were small, stages 3a and b, and stages 4 and 5 were combined, respectively.

9.3.3 Statistical analysis

For the meta-analysis, I converted ORs and HRs associated with CKD to their natural logarithms and combined log ORs/HRs and standard errors using the DerSimonian and Laird method in a random effects model. Reported P values were two sided, with significance set at less than 0.05. Heterogeneity among included studies was assessed by x^2 statistics and the I^2 test. I regarded heterogeneity as possibly unimportant when the I^2 value was less than 40% and considerable when more than 75%.[23] I used Stata software version 13 (Stat Corp., College Station, TX) to perform the meta-analysis.

For the OXVASC analysis, descriptive statistics were used to summarize the baseline characteristics of the cohort stratified by CKD status. Continuous data were given as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate, categorical data were given as n (%). Mann-Whitney U tests and Chi-squared tests were used to test the significance of differences between two groups for continuous and categorical variables respectively. Linear, logistic and ordinal regressions were used to calculate age-adjusted P values for baseline characteristics. Logistic regression analysis was used to determine the risk of ischaemic stroke compared to TIA in the presence of

CKD and according to eGFR categories, adjusting for age, sex and vascular risk factors. Similarly, multinomial regression was used to calculate the unadjusted and adjusted odds of minor (defined as an NIHSS ≤ 3 at presentation) and major (NIHSS>3) stroke using TIA as the reference category. Ordinal regression analysis was used to explore associations of CKD and initial event severity measured using the NIHSS Score, stratified by history of atrial fibrillation, event subtype and eGFR category, and adjusted for age, sex and for known vascular risk factors. The ordinal categories for the NIHSS Score were as follows: 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, ≥30. I also used ordinal regression to compare early functional outcomes in ischaemic stroke patients, measured using 1-month mRS scores (0-6), between those with and without CKD, stratified by eGFR category and event subtype, and adjusting for the same co-variates. To account for pre-morbid disability in the assessment of poststroke mRS, patients with premorbid mRS>2 were excluded from the analysis. I then assessed change in mRS score from premorbid score to 1 month after ischaemic stroke using ordinal regression analysis with the same stratification and modelling. Severity analyses were repeated separately for primary intracerebral haemorrhage (ICH) events. Cox proportional hazard models were used to estimate the hazard ratio (HR) of recurrent stroke (All/Early [< 90 days]/Late [> 90 days]) and vascular events (1-15 year risk) in CKD patients compared with those with normal renal function, stratified by eGFR category and index event subtype, and adjusted for age, sex, and vascular risk factors. The proportional hazards assumption was met. All statistical procedures were performed using SPSS version 25. Statistical significance was set at $p<0.05$.

9.4 Results

I identified 17 relevant studies that fit the inclusion criteria from my earlier systematic reviews (from database inception to 2018).[1,2] I then updated these reviews until May 2020

resulting in the identification of a further 22 studies. In total, 39 relevant studies with 2,247,047 participants were included in the systematic review of CKD and stroke severity, disability, and recurrence risk (Figure 9-1 and Appendix Table 9-12). Although 17 studies compared differences in the median baseline NIHSS score between those with and without CKD, no study determined if CKD was independently associated with initial NIHSS score after adjustment for the usual confounders (e.g. age, sex, vascular risk factors). 13 studies provided appropriate quantitative data to be included in a meta-analysis of the risk of disability post-stroke with CKD (Figure 9-2). Pooling adjusted results from the random effects model showed that the risk of post-stroke disability, although variably defined, was increased among patients with an eGFR <60 ml/min/1.72m^2 (OR=1.44, 95% CI: 1.26-1.64; p<0.001). Moderate heterogeneity existed between multivariate-adjusted estimates among patients with an eGFR <60 ml/min/1.73m^2 (p=0.008, I^2=55.7%). 11 studies were included in the meta-analysis of CKD and recurrent stroke risk (Figure 9-3). In pooled multivariate-adjusted analysis, usually after adjustment for age, sex and cardiovascular risk factors, CKD was independently associated with stroke recurrence (HR=1.52, 1.28-1.81; p<0.001). Similarly, there was moderate heterogeneity among included studies (p=0.002, I^2=64.8%).

For the OXVASC analysis, a total of 3178 consecutive eligible patients with TIA (n=1167), ischaemic stroke (n=1802), and ICH (n=209), were recruited from 2002 to 2017. Of those with an ischaemic stroke, 1055 and 721 patients had minor and major strokes, respectively. Table 9-1 shows the baseline characteristics at the time of the event for all TIA/ischaemic stroke patients and according to CKD status. The median age was 75.8 (66.0-83.7) years, 1458 (49.1%) were men, and hypertension was the most prevalent risk factor being found in 1738 individuals (58.5%).

The median eGFR was 65.9 ml/min/1.73m^2. 1197 patients had CKD (40.3% of the study population). 422 patients (14.2%) had an eGFR≥90 ml/min/1.73m^2, 1346 (45.3%) 60-89

ml/min/1.73m^2, 1064 (35.8%) 30-59 ml/min/1.73m^2, 133 (4.5%) <30 ml/min/1.73m^2. Only 10 patients (0.3%) were dialysis-dependent. Notably, compared to those with normal renal function, the CKD group were older and had a significantly higher burden of vascular risk factors and co-morbidities including hypertension, diabetes mellitus, ischaemic heart disease, peripheral arterial disease, congestive cardiac failure, and atrial fibrillation (all p<0.05). There was no significant difference in terms of prior anticoagulation use but those with CKD were consistently more likely to have prior use of antiplatelet, antihypertensive, and lipid-lowering therapy (all p<0.01). In terms of TOAST classification, cardioembolic, large artery, unknown, and multiple subtypes were more common in patients with CKD but not significantly so after adjustment for age (all p>0.05).

The unadjusted odds ratio (OR) for ischaemic stroke compared to TIA in patients with CKD was 1.50 (95% CI: 1.28-1.74; p<0.001), attenuating to 1.36 (1.15-1.61; p<0.001) after adjustment for age and sex, and to 1.31 (1.11-1.56; p=0.002) after adjustment for age, sex, and vascular risk factors (Table 9-2*)*. There was an inverse association between eGFR and ischaemic stroke versus TIA risk with declining eGFR associated with greater stroke risk with a multivariate-adjusted OR of 5.60, 1.52-20.60; p=0.01 for an eGFR <15 ml/min/1.73m^2. Similarly, CKD was associated with greater odds of minor (adjusted OR 1.31, 1.09-1.60; p=0.004) and major (adjusted OR 1.48, 1.21-1.83; p<0.001) stroke compared to TIA events (Table 9-3).

The median initial NIHSS score was higher for patients with CKD compared to those without (NIHSS=3 [IQR=1-9] versus 2 [IQR=1-5]; p<0.001) (Table 9-1). The associations of CKD and initial NIHSS score in an ordinal analysis, stratified by prior history of AF and according to event subtype, are shown in Table 9-4. In the unadjusted model that included both patients with TIA and ischaemic stroke, CKD was associated with the initial NIHSS score (OR=2.01, 1.69-2.41; p<0.001) attenuating (adjusted OR=1.28, 1.04-1.46; p=0.018) with adjustment for age, sex, and known vascular risk factors. The association

was driven by those with an eGFR < 30 ml/min/1.73m^2 (adjusted OR=2.74, 1.30-5.79; p=0.008 and 7.64, 2.78-21.01; p<0.001 for eGFR 15-29 and < 15 ml/min.1.73m^2, respectively). There was greater initial event severity in CKD patients with a prior history of AF (adjusted OR=1.49, 1.02-2.19; p=0.04). When the analysis was confined to ischaemic stroke patients only, there was no association between CKD and NIHSS score after adjustment (adjusted OR=1.17, 0.94-1.45; p=0.15). When stratified according to index event TOAST subtype, only events of undetermined aetiology were associated with initial NIHSS after adjustment for age, sex, and vascular risk factors (adjusted OR=1.81, 1.01-3.24; p=0.04) (Table 9-4).

The distribution of mRS according to baseline eGFR category in all patients prior to ischaemic stroke, at 1 month after ischaemic stroke, excluding those with premorbid disability (defined as premorbid mRS>2), and the change in mRS score from premorbid to 1 month after ischaemic stroke is shown in Figure 9-4. Patients with CKD had greater pre-stroke disability compared to those with normal renal function (30.2% with premorbid mRS>2 versus 16.2% in those with normal renal function; p<0.001) (Table 9-1). When those with premorbid disability were excluded, CKD was associated with greater disability at one month in an ordinal regression (OR=2.21, 1.81-2.69; p<0.001) – an association that remained significant after adjustment for age, sex, and known vascular risk factors (Adjusted OR=1.40, 1.13-1.74; p=0.002) (Table 9-5). The association was again driven by those with an eGFR <30 ml/min/1.73m^2 (adjusted OR=5.22, 2.23-12.22; p<0.001 and 12.59, 4.06-39.02; p<0.001 for eGFR 15-29 and < 15 ml/min/1.73m^2, respectively), largely due to high case-fatality rates (Figure 9-4). The impact of age on post-stroke disability is highlighted in Figure 9-5 where the distribution of mRS scores 1 month after ischaemic stroke according to baseline eGFR category is stratified into patients < 75 years and ≥ 75 years. Similar to the NIHSS analysis, only events of undetermined aetiology appeared to be associated with 1-month mRS score in the ordinal analysis after adjustment for age, sex, and vascular risk factors (adjusted OR=1.90, 1.28-2.83; p=0.002). However, Figure

9-6 demonstrates that the worse outcomes were evident for cardioembolic events and events of unknown aetiology in those with an eGFR<30 ml/min/1.73m^2. The association between CKD and change in mRS score from premorbid mRS to 1-month after ischaemic stroke was also examined in an ordinal regression in Table 9-6. There was no overall or subtype-specific association between CKD and change in mRS score after adjustment (adjusted OR=1.12, 0.92-1.36; p=0.25). However, the association did remain for those with those with an eGFR <30ml/min/1.73m^2 (adjusted OR=3.50, 1.81-6.77; p<0.001).

The baseline characteristics and associations of CKD with stroke severity in ICH patients are presented separately in Table 9-7, Table 9-8 and Table 9-9. 70 ICH patients (33.5%) had CKD. Those with CKD were older (median age = 81 vs 75 years; p<0.001), more hypertensive (71.4 vs 43.5%, p<0.001) and had greater premorbid disability (median mRS= 2 vs 0; p<0.001) (Table 9-7). However, in multivariate-adjusted analysis, CKD was not associated with either initial NIHSS score (Adjusted OR=0.66, 0.37-1.18; p=0.16) or 1-month mRS score (Adjusted OR=1.72, 0.81-3.68; p=0.16) (Table 9-8 and Table 9-9).

During 15,506 patient years of follow-up, 517 patients developed a recurrent stroke. 478 patients (16.1%) and 40 patients (1.3%) had recurrent ischaemic and haemorrhagic events, respectively. There was a significantly greater risk of recurrent events, particularly early stroke recurrence, in patients with CKD compared to those with normal renal function (Log-rank p <0.001) (Figure 9-7*A*). The unadjusted HR of recurrent stroke with CKD was 1.72, 1.45-2.05 (p<0.001), attenuating to 1.36, 1.13-1.64 (p=0.001) with adjustment for age and sex, and to 1.29, 1.07-1.57 (p=0.008) with additional adjustment for vascular risk factors (Table 9-10*)*. CKD was independently predictive of early (< 90 days) stroke recurrence (Adjusted HR= 1.60, 1.15-2.21; p=0.005) but not late (≥ 90 days) recurrence (Adjusted HR= 1.15, 0.91-1.46; p=0.24). No individual eGFR category was significantly predictive of stroke recurrence. In subtype analysis, after multivariate adjustment, CKD was only significantly predictive of recurrent events in those whose

index event was of unknown aetiology (Adjusted OR=2.03, 1.13-3.65; p=0.02) (Table 9-10*)*.

CKD was also associated with a greater risk of long-term recurrent vascular events over the 15-year study period compared to those with normal renal function (Log-rank p <0.001) (Figure 9-7B). The unadjusted HR for recurrent vascular events (the composite outcome of recurrent stroke, MI, or sudden cardiac death) with CKD was 1.76, 1.52-2.05 (p<0.001), attenuating to 1.24, 1.05-1.46 (p=0.01) with complete adjustment (Table 9-11). The risk was highest for those with large artery disease events and events of unknown aetiology at baseline (Adjusted HR=1.68, 1.05-2.69; p=0.03 and HR=1.65, 1.02-2.67; p=0.04, respectively).

9.5 Discussion

Using a systematic review, meta-analysis, and population-based study, I describe the natural history of cerebrovascular disease in CKD from index event to recurrence. I found a higher likelihood of stroke events than TIA events in CKD, that stroke events were associated with worse initial severity and later disability, particularly in those with an eGFR < 30ml/min/1.73m^2, and that CKD was independently predictive of stroke and further vascular event recurrence.

Firstly, I used a systematic review and meta-analysis to establish whether there was any existing evidence of association between CKD and stroke severity, disability or recurrence risk, and to contextualize my findings from the OXVASC analysis. No study had previously examined if CKD was independently associated with initial event severity (TIA vs stroke; baseline NIHSS score) after adjustment for important confounders such as age, premorbid disability, or comorbidities such as diabetes. Pooling results from 13 relevant studies suggested that regardless of its definition or measurement, CKD is independently

associated with post-stroke disability. However, few studies had previously examined early disability in detail,[4, 24-26] or according to the degree of renal dysfunction[9, 27, 28] and no study stratified the analysis according to stroke subtype. CKD was also independently predictive of stroke recurrence in pooled analysis, although similarly, few studies explored how this association varied depending on eGFR category[29] or event subtype,[14, 30, 31] and no study compared the risk of early versus late recurrent events. There was considerable heterogeneity amongst the pooled study estimates.

Subsequently in the OXVASC analysis, I included patients with TIA in order to chart the full spectrum of cerebrovascular disease severity in CKD and showed that there is a greater risk of ischaemic stroke than TIA in CKD and that stroke is initially more severe with higher NIHSS scores even after adjustment for age, premorbid disability, and vascular risk factors. There are several possible mechanisms for this association between CKD and cerebrovascular event severity. It has been shown that lower eGFR is independently associated with lower cerebral blood flow.[32] As such, patients with CKD may have reduced cerebrovascular reserve and may be less likely to collateralize and compensate for vascular insults. Furthermore, AF is highly prevalent in CKD[12] and is a known predictive factor for more severe and disabling strokes.[33] In keeping with this observation, when results were stratified by known history of prior AF, CKD was only associated with initial NIHSS in those with a history of prior AF. It has also been proposed that there may be higher levels of inflammatory cytokines and oxidative stress resulting in excessive vascular damage at stroke onset in CKD[34] but we previously found poor correlation between eGFR and such markers in this setting (Chapter 7).[35]

Consistent with the meta-analysis results, I have shown that CKD is associated with worse functional outcome at one month, However, the OXVASC analysis highlights that this association is largely driven those with an eGFR <30 ml/min/1.73m^2. This is in keeping with the poor short-term outcomes also evident from the Get With The

Guidelines-Stroke cohort where this group had lower odds of being discharged home and increased in-hospital mortality.[9] Poor stroke outcomes in CKD appear to be consistent across different stroke subtypes,[5, 36] race,[28] in populations of varying prevalence of vascular risk factors,[37, 38] and even in renal transplant recipients.[39] These worse outcomes may be attributable to reduced efficacy of acute stroke treatments in this group. Some studies have suggested that CKD patients have a higher risk of symptomatic ICH and mortality with thrombolysis and mechanical thrombectomy.[40, 41] However, this higher mortality appears to be related to peri-stroke pneumonia, sepsis, and other non-vascular aetiologies rather than ICH.[42] Since CKD patients are also more susceptible to acute kidney injury (AKI), it's possible that peri-stroke AKI may contribute to worse short-term outcomes.[43] Patients with advanced CKD are also less likely to be admitted to acute stroke units, undergo swallow tests within 24 hours, receive aspirin on arrival, and thrombolysis is frequently delayed.[44]

It is not clear why CKD was particularly associated with severity and worse initial functional outcomes in those who had events of undetermined aetiology. Cryptogenic ischaemic strokes typically result in less severe presenting neurologic deficits, less final disability, and lower mortality in the general population,[45] contrasting with the findings here in the CKD population, suggesting that there may be CKD-specific mechanisms underlying the greater stroke severity observed. In mouse models of transient middle cerebral artery occlusion, CKD aggravated ischaemic brain damage by increasing apoptosis and neuronal loss both in the ischaemic core and the ischaemic penumbra leading to impaired post-stroke recovery.[46] The acute phase of stroke recovery in CKD mice was associated with an early increase in local inflammation due to increased activation of pro-inflammatory microglia/macrophages and decreased activation of reparatory ones. It is also likely that a significant proportion of the cryptogenic events (both undetermined and unknown) in this group may have been due to unidentified

paroxysmal AF since its prevalence is known to increase with advancing CKD[47] and it is independently predictive of stroke or death in those with eGFR <30 ml/min/1.73m^2.[48]

There was no association between CKD and stroke severity demonstrated in the ICH group. Previous studies have shown that CKD overall is associated with both higher mortality and disability in ICH,[49, 50] but that the outcomes for those with mild-to-moderate disease, as mainly represented in this cohort, are generally similar to those with normal renal function.[49] The lack of association in this group may also be a reflection of the predominantly Caucasian population as there appear to be stronger links between CKD and ICH in black patients.[51]

In keeping with the meta-analysis results, I have demonstrated that CKD is independently associated with increased risk of stroke recurrence, particularly early recurrence, even after adjustment for age, hypertension, and other vascular risk factors. These findings are consistent with a post-hoc analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial of 18 666 patients with recent ischaemic stroke, in which CKD patients had a 16% greater risk of recurrent stroke after multivariate adjustment for possible confounders.[52] A recent post hoc analysis of 3020 patients with recent MRI–defined symptomatic lacunar infarction in the SPS3 (Secondary Prevention of Small Subcortical Strokes) Trial reported a 50% increased risk of recurrent stroke in patients with CKD.[14] I did not find such an excess risk of recurrent stroke in the lacunar stroke subgroup in our study; however, this discrepancy may relate to subtype sensitivity as not all patients in our study would necessarily have had an MRI-defined index event and as such, there may be heterogeneity within this subtype or under-diagnosis of lacunar events.

There are several possible explanations for the increased risk of stroke recurrence in CKD. There is a tendency to undertreat these patients with guideline-recommended

therapies such as antiplatelet agents, anticoagulants, or smoking cessation counselling[13, 44] though we did not find these treatment discrepancies at baseline. There is also some evidence that these preventative treatments may not be as effective in CKD, for example, with high rates of antiplatelet hyporesponsiveness reported.[53] 50-80% of patients with end-stage kidney disease have high on-treatment residual platelet reactivity (resistance) when treated with clopidogrel.[54] Since CKD was only independently predictive of recurrence in subtype analysis in those whose index event was of unknown aetiology, this suggests that there may be an important subgroup of patients within this group that are potentially under-investigated and under-treated.

On the other hand, the sequential and consistent impact of CKD on initial event severity, early disability and early recurrence risk, suggests that there may be associated inflammatory or other processes intrinsic to CKD leading to uniformly worse outcomes in the early or acute stroke phase. One such unifying mechanism may be nitric oxide deficiency which is known to occur in CKD.[55] Nitric oxide has a crucial role in angiogenesis after ischaemic stroke[56] and the associated collateralization is predictive of post-stroke neurological outcomes.[57] It is also a cerebral and systemic vasodilator, modulator of vascular and neuronal function, and inhibitor of apoptosis.[58] Nitric oxide donors are candidate treatments for acute stroke. Although they showed some promise in preclinical studies,[59] any efficacy in clinical trials has not been demonstrated.[60] However, it is not known if such novel drugs may be specifically beneficial in an already nitric-oxide-deficient group such as CKD patients.

This study has several strengths including a population-based design, high rates of ascertainment of all incident TIAs and strokes, and completeness of follow-up. I also did a prior systematic review and meta-analysis to put our research in context. However, there are also a number of limitations that must be acknowledged. Firstly, urine protein quantification is not performed routinely as part of OXVASC and therefore, I cannot

comment from this data on whether the risk of stroke severity or recurrence varies depending on the presence or degree of proteinuria in kidney disease. Some studies have previously suggested that it is proteinuria rather than low eGFR that is best predictive of worse stroke severity and outcomes.[61, 62] Secondly, since assessors were not blinded to premorbid mRS scores, 1-month disability assessments could have been unfavourably biased in patients with higher premorbid scores. Thirdly, the Oxford Vascular Study population study is 95% white which may limit the generalizability of our results to other settings.

In conclusion, advanced CKD is strongly associated with cerebrovascular disease severity. Though this association may be confounded to an extent by age, premorbid disability and AF, advanced CKD is clearly an important multimorbidity marker and adverse prognostic factor in stroke, including stroke recurrence. Further research is needed to determine to what extent this reflects under-treatment/prevention or whether there are limitations to the available evidence to guide the prevention and treatment of stroke in this group, particularly whether there are CKD-specific processes driving worse stroke severity and outcomes that could be therapeutically targeted.[63] Closer collaboration between nephrologists and stroke physicians may help bridge this therapeutic gap.

9.6 References

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TABLES

Table 9-1 Baseline characteristics of all patients with TIA and ischaemic stroke, and stratified according to the presence of CKD

Characteristics*	All patients n= 2969	No CKD n= 1772	CKD present n= 1197	P value†	Age-adjusted P value†
Age years, median (IQR)	75.8 (66.0-83.7)	70.6 (59.8)	81.7 (74.7-87.4)	<0.001	N/A
Male sex	1458 (49.1)	984 (55.7)	474 (39.6)	<0.001	<0.001
Black race	34 (1.1)	22 (1.2)	12 (1.0)	0.18	0.55
eGFR (ml/min/1.73m^2), median (IQR)	65.9 (50.5-82.0)	78.6 (69.4-89.3)	46.9 (38.3-54.1)	<0.001	<0.001
PREVIOUS RISK FACTORS					
Hypertension	1738 (58.5)	897 (50.7)	841 (70.3)	<0.001	<0.001
Diabetes mellitus	425 (14.3)	222 (12.6)	203 (17)	0.001	<0.001
Hyperlipidaemia	909 (30.6)	499 (28.2)	410 (34.3)	0.001	<0.001
Myocardial infarction	318 (10.7)	137 (7.7)	18.1 (15.1)	<0.001	<0.001
Peripheral artery disease	206 (6.9)	79 (4.5)	127 (10.6)	<0.001	<0.001
Valvular heart disease	280 (9.4)	127 (7.2)	153 (12.8)	<0.001	0.01
Congestive cardiac failure	268 (9.0)	88 (5)	180 (15)	<0.001	<0.001
Atrial fibrillation	554 (18.7)	247 (14.0)	306 (25.6)	<0.001	0.01
Current or history of smoking	1628 (54.8)	1020 (57.8)	608 (51.2)	<0.001	0.21
PRIOR MEDICATIONS					
Anticoagulant	178 (6)	97 (5.5)	81 (6.8)	0.17	0.60
Antiplatelet	926 (31.2)	427 (24.2)	499 (41.7)	<0.001	<0.001
Antihypertensive	1682 (56.7)	841 (47.6)	841 (70.3)	<0.001	<0.001
Statin	800 (26.9)	431 (24.4)	369 (30.9)	<0.001	0.01
EVENT TYPE				<0.001	<0.001
TIA	1183 (39.8)	778 (44.1)	404 (33.9)		
Minor stroke (NIHSS≤3)	1055 (35.3)	645 (36.6)	410 (34.4)		
Major stroke (NIHSS>3)	721 (24.3)	340 (19.3)	378 (31.7)		
TOAST CLASSIFICATION				<0.001	
Cardioembolism	757 (25.5)	375 (21.2)	381 (31.8)	<0.001	0.05
Large artery	322 (10.8)	187 (10.6)	135 (11.3)	0.59	0.58
Small artery	347 (11/7)	241 (13.6)	105 (8.8)	<0.001	0.13
Undetermined cause	1011 (34.1)	697 (39.4)	313 (26.1)	<0.001	0.01
Unknown	355 (12)	155 (8.8)	199 (16.6)	<0.001	0.19
Multiple	101 (3.4)	49 (2.8)	52 (4.3)	0.03	0.69
Other	75 (2.5)	63 (3.6)	12 (1.0)	<0.001	0.27
ISCHAEMIC STROKE PATIENTS					
NIHSS index event, median (IQR)	2 (1-7)	2 (1-5)	3 (1-9)	<0.001	<0.001
NIHSS categories				<0.001	0.02
0-4	1255 (65.1)	754 (71.8)	499 (58.4)		
5-9	297 (15.4)	143 (13.6)	152 (17.8)		
10-14	153 (7.9)	68 (6.5)	84 (9.8)		
15-19	92 (4.8)	44 (4.2)	48 (5.6)		
20-24	70 (3.6)	33 (3.1)	37 (4.3)		
25-29	31 (1.6)	7 (0.7)	24 (2.8)		
≥ 30	11 (0.6)	1 (0.1)	10 (1.2)		
Premorbid mRS score, median (IQR)	1 (0-2)	1 (0-1)	1 (0-3)	<0.001	0.11
Premorbid mRS score categories				<0.001	0.61
0-2	1489 (77.2)	885 (83.8)	602 (69.8)		
3-6	436 (22.6)	171 (16.2)	261 (30.2)		

*Numbers are n (%) unless otherwise stated.

†P-values are from Chi-squared tests or Mann-Whitney U tests, as appropriate. Logistic/ordinal/linear regression was used to adjust for age.

CCF indicates, congestive cardiac failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; mRS, Modified Rankin Score; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; TIA, transient ischaemic attack; VHD, valvular heart disease.

Table 9-2 The odds of presentation with ischaemic stroke versus TIA according to CKD status and eGFR categories

	Crude OR (95% CI)	P value	Model 1 OR* (95% CI)	P value	Model 2 OR** (95% CI)	P value	Model 3 OR*** (95% CI)	P value
CKD status								
No CKD	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
CKD present	1.50 (1.28-1.74)	<0.001	1.36 (1.15-1.61)	<0.001	1.35 (1.14-1.60)	<0.001	1.31 (1.11-1.56)	0.002
eGFR categories								
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	1.19 (0.96-1.48)	0.12	1.03 (0.81-1.31)	0.80	1.03 (0.81-1.31)	0.81	1.05 (0.83-1.34)	0.68
45-59	1.59 (1.24-2.04)	<0.001	1.60 (1.13-2.27)	0.008	1.59 (1.12-2.25)	0.01	1.58 (1.11-2.25)	0.01
30-44	1.70 (1.28-2.25)	<0.001	1.99 (1.28-3.10)	0.002	1.99 (1.27-3.11)	0.003	1.87 (1.18-2.95)	0.008
15-29	2.31 (1.46-3.67)	<0.001	2.45 (1.35-4.43)	0.003	2.40 (1.32-4.35)	0.004	2.28 (1.22-4.23)	0.009
<15	5.78 (1.69-19.75)	0.005	6.27 (1.77-22.16)	0.004	6.00 (1.70-21.21)	0.005	5.60 (1.52-20.60)	0.01

CKD is defined as eGFR<60 mL/min per 1.73 m^2. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; OR, odds ratio.

*Model 1 adjusted for age and sex.

**Model 2 adjusted for variables in model 1 and hypertension.

***Model 3 adjusted for variables in model 2 and history of ischaemic heart disease, diabetes, hyperlipidaemia, smoking or atrial fibrillation.

Table 9-3 The odds ratio for minor or major stroke according to CKD status and eGFR categories (using TIA as a reference category)

	Minor Stroke (NIHSS ≤ 3)						Major stroke (NIHSS>3)					
	Crude OR (95% CI)	**P value**	**Model 1 OR* (95% CI)**	**P value**	**Model 2 OR** (95% CI)**	**P value**	**Crude OR (95% CI)**	**P value**	**Model 1 OR* (95% CI)**	**P value**	**Model 2 OR** (95% CI)**	**P value**
CKD status												
No CKD	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
CKD present	1.22 (1.03-1.40)	0.02	1.32 (1.09-1.60)	0.004	1.31 (1.08-1.59)	0.006	2.14 (1.77-2.59)	<0.001	1.49 (1.21-1.83)	<0.001	1.48 (1.21-1.83)	<0.001
eGFR categories												
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	1.00 (0.79-1.27)	0.98	1.03 (0.78-1.35)	0.98	1.02 (0.78-1.34)	0.86	1.98 (1.42-2.79)	<0.001	1.16 (0.79-1.69)	0.45	1.16 (0.79-1.69)	0.45
30-59	1.23 (0.95-1.57)	0.11	1.79 (1.24-2.58)	0.002	1.76 (1.22-2.53)	0.002	3.33 (2.36-4.69)	<0.001	1.68 (1.07-2.65)	0.03	1.71 (1.08-2.71)	0.02
<30	1.25 (0.74-2.10)	0.41	1.39 (0.74-2.61)	0.30	1.45 (0.77-2.76)	0.25	7.94 (4.72-13.33)	<0.001	5.08 (2.54-10.0)	<0.001	5.52 (2.72-11.1)	<0.001

CKD is defined as eGFR<60 mL/min per 1.73 m2. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio

*Model 1 adjusted for age and sex.

**Model 2 adjusted for variables in model 1 and hypertension.

Table 9-4 Associations of CKD and initial NIHSS Score in an ordinal analysis, adjusted for age/sex and for known vascular risk factors, and stratified by history of atrial fibrillation, eGFR category and event TOAST subtype.

	Crude		Model 1*		Model 2**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
All TIA/ischaemic stroke patients (N=2969)						
Overall	2.01 (1.69-2.41)	<0.001	1.35 (1.11-1.64)	0.003	1.28 (1.04-1.46)	0.018
All TIA/ischaemic stroke patients according to eGFR category (m/min/1.73m^2) (N=2969)						
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	1.95 (1.38-2.77)	<0.001	1.11 (0.76-1.64)	0.59	1.20 (0.81-1.79)	0.36
45-59	2.73 (1.89-3.93)	<0.001	1.07 (0.66-1.74)	0.77	1.04 (0.63-1.73)	0.88
30-44	3.56 (2.42-5.24)	<0.001	1.58 (0.87-2.85)	0.13	1.72 (0.90-3.28)	0.10
15-29	7.89 (4.87-12.79)	<0.001	3.21 (1.61-6.40)	0.001	2.74 (1.30-5.79)	0.008
<15	9.88 (4.31-22.65)	<0.001	7.57 (3.02-18.95)	<0.001	7.64 (2.78-21.01)	<0.001
Stratified by history of AF (N=2969)						
No history of AF	1.71 (1.38-2.12)	<0.001	1.23 (0.97-1.56)	0.08	1.20 (0.95-1.53)	0.13
History of AF	2.01 (1.41-2.86)	<0.001	1.47 (1.01-2.12)	0.04	1.49 (1.02-2.19)	0.04
Ischaemic stroke patients only (N=1802)						
Overall	1.83 (1.51-2.22)	<0.001	1.25 (1.01-1.54)	0.04	1.17 (0.94-1.45)	0.15
All TIA/ischaemic stroke patients stratified by event TOAST subtype (N=2969)						
Cardioembolic	1.81 (1.35-2.42)		1.29 (0.58-1.77)		1.28 (0.93-1.77)	
Large artery disease	0.57 (0.26-1.25)		0.59 (0.26-1.37)		0.70 (0.29-1.70)	
Small vessel disease	1.85 (0.84-4.05)		1.55 (0.66-3.65)		1.59 (0.66-3.84)	
Undetermined	1.79 (1.09-2.93)		1.71 (0.98-3.01)		1.81 (1.01-3.24)	
Unknown	1.13 (0.76-1.67)		1.14 (0.76-1.71)		1.12 (0.74-1.69)	
Multiple	1.21 (0.46-3.16)		1.25 (0.44-3.59)		1.31 (0.41-4.21)	
Other	1.48 (0.33-6.67)		2.68 (0.48-14.94)		4.09 (0.44-37.68)	

CKD is defined as eGFR<60 mL/min per 1.73 m^2. The ordinal categories for the NIHSS Score were as follows: 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, ≥30. AF indicates atrial fibrillation; CI, confidence interval; eGFR, estimated glomerular filtration rate; mRS, modified rankin scale; OR, odds ratio.

*Model 1: adjusted for age and sex.
**Model 2: adjusted for age, sex, premorbid mRS, history of hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia, AF, and smoking.

Table 9-5 Associations of CKD and 1-month mRS Score in all ischaemic stroke patients in an ordinal analysis, adjusted for age/sex and for known vascular risk factors, and stratified according eGFR category and event TOAST subtype.

	Crude		Model 1*		Model 2**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
All ischaemic stroke patients (N=1802)						
Overall	2.46 (2.07-2.93)	<0.001	1.38 (1.15-1.66)	0.001	1.31 (1.08-1.57)	0.005
All ischaemic stroke patients excluding those with premorbid mRS>2 (N=1398)						
Overall	2.21 (1.81-2.69)	<0.001	1.48 (1.20-1.83)	<0.001	1.40 (1.13-1.74)	0.002
According to eGFR category (m/min/1.73m^2) (N=1398)						
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	1.46 (1.09-1.96)	0.01	0.82 (0.59-1.15)	0.26	0.83 (0.59-1.17)	0.30
45-59	2.57 (1.84-3.57)	<0.001	0.98 (0.63-1.53)	0.93	0.90 (0.57-1.41)	0.65
30-44	3.49 (2.36-5.16)	<0.001	1.64 (0.93-2.90)	0.09	1.58 (0.88-2.84)	0.13
15-29	11.94 (6.10-23.34)	<0.001	6.30 (2.75-14.44)	<0.001	5.22 (2.23-12.22)	<0.001
<15	14.48 (5.42-38.71)	<0.001	12.01 (4.24-34.02)	<0.001	12.59 (4.06-39.02)	<0.001
According to index event TOAST subtype† (N=1398)						
Cardioembolic	2.14 (1.56-2.92)		1.23 (0.88-1.71)		1.14 (0.81-1.60)	
Large artery disease	1.10 (0.65-1.87)		0.74 (0.40-1.36)		0.73 (0.38-1.39)	
Small vessel disease	1.02 (1.02-2.79)		1.09 (0.64-1.87)		1.06 (0.61-1.86)	
Undetermined	2.73 (1.89-3.94)		1.95 (1.31-2.89)		1.90 (1.28-2.83)	
Unknown	1.23 (0.69-2.21)		1.24 (0.68-2.25)		1.16 (0.63-2.15)	
Multiple	3.74 (1.55-8.99)		2.73 (1.06-7.00)		2.60 (0.94-7.21)	
Other	4.35 (0.96-19.79)		4.35 (0.84-22.22)		5.05 (0.92-27.80)	

CKD is defined as eGFR<60 mL/min per 1.73 m^2. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; mRS, modified rankin scale; OR, odds ratio. The mRS is an ordinal scale that ranges from 0 (no symptoms at all) to 6 (death).

*Model I: adjusted for age and sex.
**Model II: adjusted for age, sex, history of hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia, atrial fibrillation, and smoking.

Table 9-6 Associations of CKD and change in mRS Score (Premorbid to 1 month post-stroke) in all ischaemic stroke patients in an ordinal analysis, adjusted for age/aex and for known vascular risk factors, and stratified according eGFR category and event TOAST subtype.

	Crude		Model 1*		Model 2**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
All ischaemic stroke patients (N=1802)						
Overall	1.38 (1.16-1.64)	<0.001	1.17 (0.97-1.42)	0.10	1.12 (0.92-1.36)	0.25
According to eGFR category (m/min/1.73m^2) (N=1802)						
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	1.18 (0.90-1.56)	0.24	0.92 (0.67-1.26)	0.60	0.92 (0.67-1.26)	0.60
30-59	1.39 (1.05-1.84)	0.02	1.04 (0.71-1.54)	0.83	1.04 (0.70-1.54)	0.85
<30	4.15 (2.61-6.61)	<0.001	3.96 (2.11-7.44)	<0.001	3.50 (1.81-6.77)	<0.001
According to index event TOAST subtype (N=1802)						
Cardioembolic	1.35 (0.98-1.85)	0.06	1.06 (0.76-1.49)	0.72	1.05 (0.75-1.48)	0.77
Large artery disease	0.54 (0.31-0.94)	0.03	0.60 (0.32-1.11)	0.11	0.57 (0.30-1.08)	0.09
Small vessel disease	1.06 (0.64-1.76)	0.82	1.09 (0.63-1.88)	0.75	1.05 (0.61-1.83)	0.858
Undetermined	0.93 (0.65-1.34)	0.69	1.04 (0.70-1.54)	0.86	1.08 (0.72-1.61)	0.72
Unknown	1.25 (0.79-1.99)	0.34	1.39 (0.86-2.23)	0.18	1.30 (0.81-2.11)	0.28
Multiple	1.38 (0.59-5.75)	0.45	1.11 (0.44-2.82)	0.82	1.40 (0.50-3.90)	0.52
Other	1.52 (0.35-6.63)	0.58	1.45 (0.29-7.16)	0.65	2.49 (0.45-13.82)	0.30

CKD is defined as eGFR<60 mL/min per 1.73 m^2. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; mRS, modified Rankin scale; OR, odds ratio.

*Model I: adjusted for age and sex.
**Model II: adjusted for age, sex, history of hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia, atrial fibrillation, and smoking.

Table 9-7 Baseline characteristics of all patients with ICH, and stratified according to the presence of CKD

Characteristics*	All patients n= 209	No CKD n= 138	CKD present n= 70	P value
Age years, median (IQR)	76 (61.5-83.0)	71 (56.8-80.3)	81 (75.0-88.0)	<0.001
Male sex	103 (49.3)	71 (51.4)	32 (45.7)	0.53
Black race	3 (1.4)	3 (2.2)	0 (0)	0.53
eGFR (ml/min/1.73m^2), median (IQR)	72.3 (53.1-87.4)	83.4 (72.2-93.1)	47.5 (39.7-53.3)	<0.001
PREVIOUS RISK FACTORS				
Hypertension	110 (52.6)	60 (43.5)	50 (71.4)	<0.001
Diabetes mellitus	24 (11.5)	12 (8.7)	12 (17.1)	0.12
Previous history of hyperlipidaemia	43 (20.6)	26 (18.8)	17 (24.3)	0.46
Previous history of MI	5 (2.4)	4 (2.9)	1 (1.4)	0.86
Previous history of PAD	9 (4.3)	5 (3.6)	4 (5.7)	0.73
Previous history of atrial fibrillation	28 (13.4)	13 (9.4)	15 (21.4)	0.03
Current or history of smoking	99 (49)	70 (52.2)	29 (43.3)	0.30
NIHSS index event, median (IQR)	7 (3-15)	7 (2-16)	7 (3-15)	0.91
EVENT SEVERITY & DISABILITY				
NIHSS categories				0.49
0-4	67 (32.1)	45 (32.8)	22 (31.9)	
5-9	53 (25.4)	31 (22.6)	21 (30.4)	
10-14	30 (14.4)	22 (16.1)	8 (11.6)	
15-19	28 (13.4)	20 (14.6)	8 (11.6)	
20-24	13 (6.2)	8 (5.8)	5 (7.2)	
25-29	5 (2.4)	5 (3.6)	0 (0)	
≥ 30	11 (5.3)	6 (4.4)	5 (7.2)	
Premorbid mRS score, median (IQR)	1 (0-2)	0 (0-2)	2 (0-3)	<0.001
Premorbid mRS score categories				<0.001
0-2	165 (80.9)	119 (88.1)	45 (66.2)	
3-6	39 (19.1)	16 (11.9)	23 (33.8)	

*Numbers are n (%) unless otherwise stated.
CCF indicates congestive cardiac failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate ICH indicates intracerebral haemorrhage, IQR indicates interquartile range; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral artery disease; TIA, transient ischaemic attack; VHD, valvular heart disease;

Table 9-8 Associations of CKD and initial NIHSS Score in ICH patients, adjusted for age/sex and for known vascular risk factors, and stratified according to eGFR category

	Crude		Model 1*		Model 2†	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
CKD status						
No CKD	1.00 (reference)		1.00 (reference)		1.00 (reference)	
CKD present	0.92 (0.55-1.54)	0.76	0.80 (0.46-0.72)	0.42	0.66 (0.37-1.18)	0.16
eGFR categories						
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	0.75 (0.40-1.43)	0.39	0.44 (0.20-0.95)	0.04	0.31 (0.14-0.71)	0.006
30-59	0.73 (0.36-1.45)	0.36	0.30 (0.11-0.81)	0.02	0.25 (0.09-0.74)	0.01
<30	1.02 (0.22-4.66)	0.98	0.49 (0.09-2.56)	0.40	0.12 (0.01-1.10)	0.06

CKD is defined as eGFR<60 mL/min per 1.73 m2. CI indicates confidence interval; eGFR, estimated glomerular filtration rate; ICH, intracerebral haemorrhage; NIHSS, National Institute of Health Stroke Scale; and OR, odds ratio.

*Model I: adjusted for age and sex.

‡Model II: adjusted for age, sex, history of hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia, and smoking.

Table 9-9 Associations of CKD and 1-month mRS Score in ICH patients in an ordinal analysis, adjusted for age/sex and for known vascular risk factors, and stratified according to event TOAST subtype

	Crude		Model 1*		Model 2**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
CKD	2.20 (1.22-3.97)	0.009	1.75 (0.94-3.23)	0.08	1.52 (0.80-2.86)	0.20
Excluding those with premorbid mRS>2						
CKD	2.43 (1.18-5.00)	0.02	1.96 (0.93-4.10)	0.08	1.72 (0.81-3.68)	0.16
According to eGFR category						
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	1.23 (0.56-2.69)	0.61	0.63 (0.24-1.64)	0.34	0.42 (0.15-1.18)	0.10
30-59	2.85 (1.10-7.41)	0.03	1.39 (0.43-4.52)	0.58	1.62 (0.41-6.44)	0.50
<30	N/A		N/A		N/A	

CKD is defined as eGFR<60 mL/min per 1.73 m2. CI indicates confidence interval; ICH, intracerebral haemorrhage; mRS, modified Rankin scale; and OR, odds ratio.
† Events of unknown aetiology were excluded from the analyses.
*Model I: adjusted for age and sex.
**Model II: adjusted for age, sex, history of hypertension, diabetes mellitus, ischaemic heart disease, hyperlipidaemia, and smoking.
N/A= Not applicable. Numbers too small to generate an OR.

Table 9-10 Univariate and multivariate associations (according to 3 models*) of CKD with risk of recurrent stroke, stratified according to eGFR category and index event TOAST subtype

	CKD							
	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	P Value	HR (95% CI)	P value	HR (95% CI)	P Value	HR (95% CI)	P Value
Recurrent stroke	1.72 (1.45-2.05)	<0.001	1.36 (1.13-1.64)	0.001	1.33 (1.10-1.61)	0.003	1.29 (1.07-1.57)	0.008
Early (<90 days)	1.80 (1.34-2.40)	<0.001	1.67 (1.21-2.31)	0.002	1.61 (1.17-2.22)	0.004	1.60 (1.15-2.21)	0.005
Late (≥90 days)	1.69 (1.36-2.10)	<0.001	1.22 (0.97-1.54)	0.10	1.20 (0.95-1.52)	0.13	1.15 (0.91-1.46)	0.24
According to eGFR category (m/min/1.73m^2)								
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	1.45 (1.05-1.98)	0.02	1.04 (0.74-1.46)	0.83	1.03 (0.73-1.45)	0.87	1.03 (0.73-1.45)	0.87
30-59	2.31 (1.69-3.17)	<0.001	1.41 (0.98-2.03)	0.06	1.37 (0.95-1.97)	0.09	1.33 (0.93-1.92)	0.12
<30	2.30 (1.36-3.89)	0.002	1.38 (0.79-2.41)	0.26	1.31 (0.75-2.30)	0.34	1.27 (0.72-2.22)	0.41
According to index event TOAST Classification†								
Cardioembolic	1.74 (1.26-2.40)		1.31 (0.93-1.83)		1.30 (0.92-1.82)		1.28 (0.91-1.80)	0.16
Large artery	1.84 (1.12-3.03)		1.84 (1.07-3.17)		1.64 (0.94-2.84)		1.75 (1.00-3.08)	0.05
Small vessel disease	0.83 (0.50-1.37)		0.78 (0.45-1.34)		0.77 (0.45-1.34)		0.78 (0.45-1.34)	0.37
Undetermined	1.92 (1.37-2.70)		1.41 (0.97-2.06)		1.39 (0.95-2.04)		1.28 (0.87-1.88)	0.21
Unknown	2.11 (1.20-3.71)		2.06 (1.16-3.66)		2.04 (1.15-3.64)		2.03 (1.13-3.65)	0.02
Multiple	1.67 (0.69-4.05)		1.84 (0.68-5.00)		1.92 (0.69-5.31)		1.76 (0.58-5.32)	0.32

CI indicates confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
† Events of other definted aetiology were not included in the table as there were no recurrent events for CKD patients whose index event was of other defined aetiology.
*Model 1: adjusted for age and sex; model 2 adjusted for variables in model 1 plus hypertension; model 3 adjusted for variables in model 2 plus diabetes mellitus, ischaemic heart disease, atrial fibrillation, smoking, hyperlipidaemia.

Table 9-11 Univariate and multivariate associations (according to 3 models*) of CKD with the risk of long-term recurrent vascular events (the composite outcome of recurrent stroke, myocardial infarction, and sudden cardiac death), stratified according to eGFR category and index event TOAST subtype

	CKD							
	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	P Value	HR (95% CI)	P value	HR (95% CI)	P Value	HR (95% CI)	P Value
Recurrent vascular events	1.76 (1.52-2.05)	<0.001	1.36 (1.15-1.60)	<0.001	1.31 (1.11-1.55)	0.001	1.24 (1.05-1.46)	0.01
According to eGFR category (m/min/1.73m^2)								
≥ 90	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
60-89	1.60 (1.20-2.14)	0.001	1.10 (0.81-1.50)	0.54	1.09 (0.80-1.48)	0.58	1.08 (0.79-1.46)	0.65
30-59	2.53 (1.90-3.37)	<0.001	1.47 (1.06-2.04)	0.02	1.41 (1.01-1.95)	0.04	1.32 (0.95-1.83)	0.10
<30	2.90 (1.86-4.52)	<0.001	1.63 (1.01-2.62)	0.04	1.52 (0.94-2.44)	0.09	1.37 (0.85-2.20)	0.20
According to index event TOAST Classification†								
Cardioembolic	1.68 (1.28-2.25)	<0.001	1.29 (0.95-1.75)	0.10	1.27 (0.93-1.72)	0.13	1.24 (0.91-1.70)	0.17
Large artery	1.96 (1.29-2.99)	0.002	1.83 (1.16-2.88)	0.01	1.62 (1.02-2.58)	0.04	1.68 (1.05-2.69)	0.03
Small vessel disease	0.86 (0.55-1.35)	0.51	0.74 (0.45-1.22)	0.24	0.74 (0.45-1.22)	0.24	0.75 (0.46-1.22)	0.25
Undetermined	2.01 (1.50-2.71)	<0.001	1.50 (1.08-2.09)	0.02	1.45 (1.04-2.03)	0.03	1.30 (0.93-1.82)	0.13
Unknown	1.76 (1.11-2.80)	0.02	1.72 (1.07-2.76)	0.03	1.65 (1.03-2.67)	0.04	1.65 (1.02-2.67)	0.04
Multiple	1.31 (0.66-2.57)	0.44	1.18 (0.55-2.52)	0.67	1.26 (0.58-2.74)	0.56	1.22 (0.54-2.77)	0.64

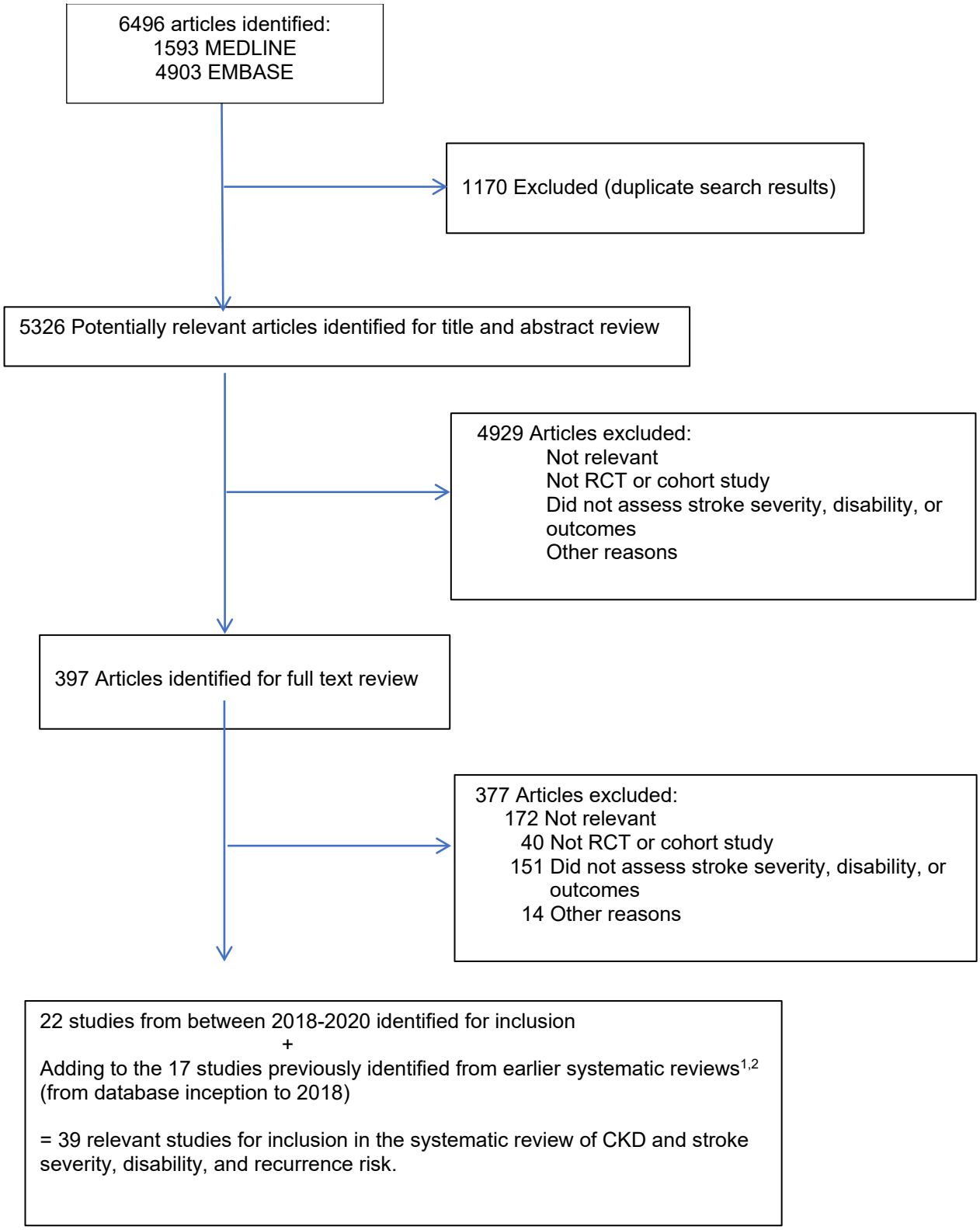
CI indicates confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

† Events of other defined aetiology were not included in the table as there were no recurrent events for CKD patients whose index event was of other defined aetiology.

*Model 1: adjusted for age and sex; model 2 adjusted for variables in model 1 plus hypertension; model 3 adjusted for variables in model 2 plus diabetes mellitus, ischaemic heart disease, atrial fibrillation, smoking, hyperlipidaemia.

FIGURES

Figure 9-1 Identification and inclusion of study reports of CKD and stroke severity, disability, and recurrence risk.



[1]Kelly DM, Rothwell PM. Does Chronic Kidney Disease Predict Stroke Risk Independent of Blood Pressure?: A Systematic Review and Meta-Regression. Stroke 2019 Nov;50(11):3085-3092.
[2]Kelly DM, Rothwell PM. Proteinuria as an independent predictor of stroke: Systematic review and meta-analysis. Int J Stroke. 2020 Jan;15(1):29-38.

Figure 9-2 Meta-analysis of the risk of disability post-stroke with CKD. Odds ratios (OR) were adjusted for traditional cardiovascular risk factors (exact methods varied between studies).

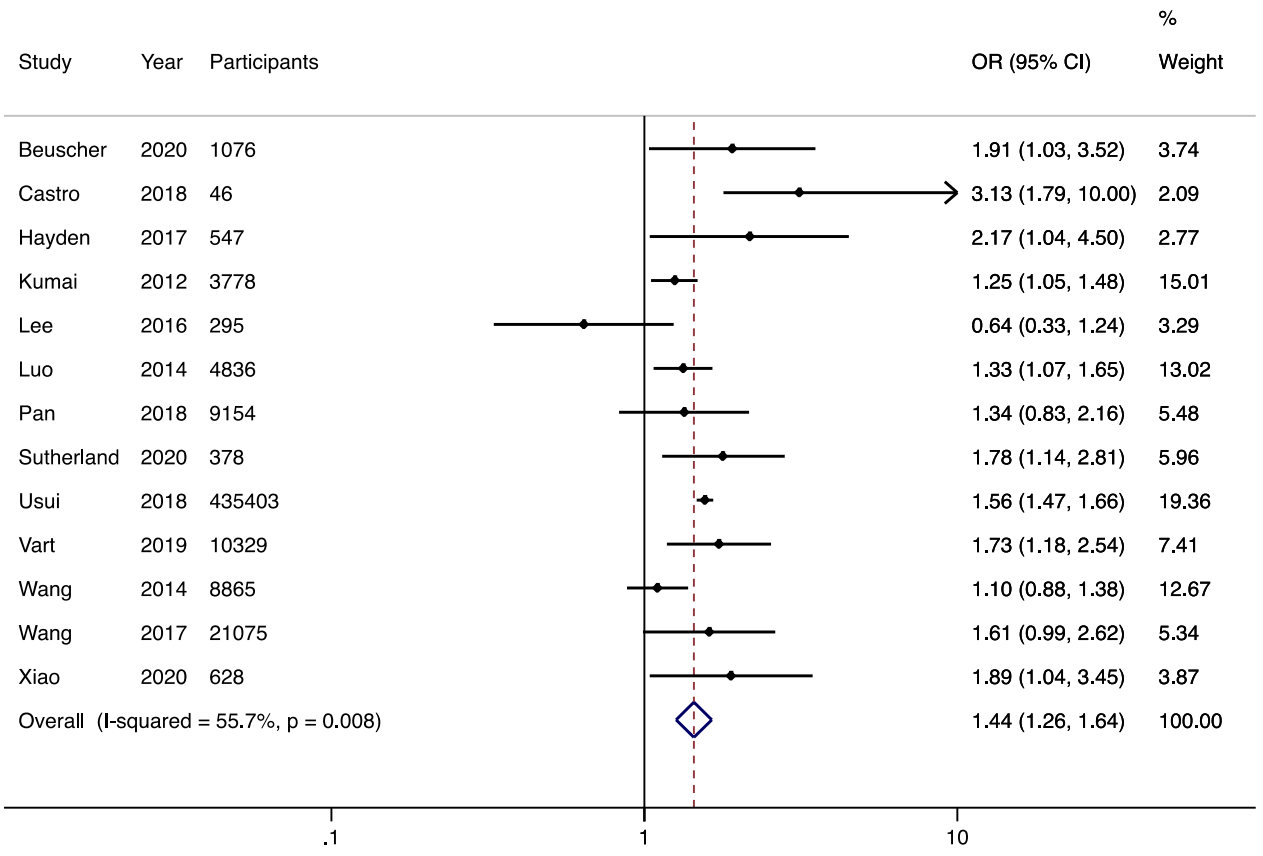


Figure 9-3 Meta-analysis of the risk of stroke recurrence with CKD. Hazard ratios (HR) were adjusted for traditional cardiovascular risk factors (exact methods varied between studies).

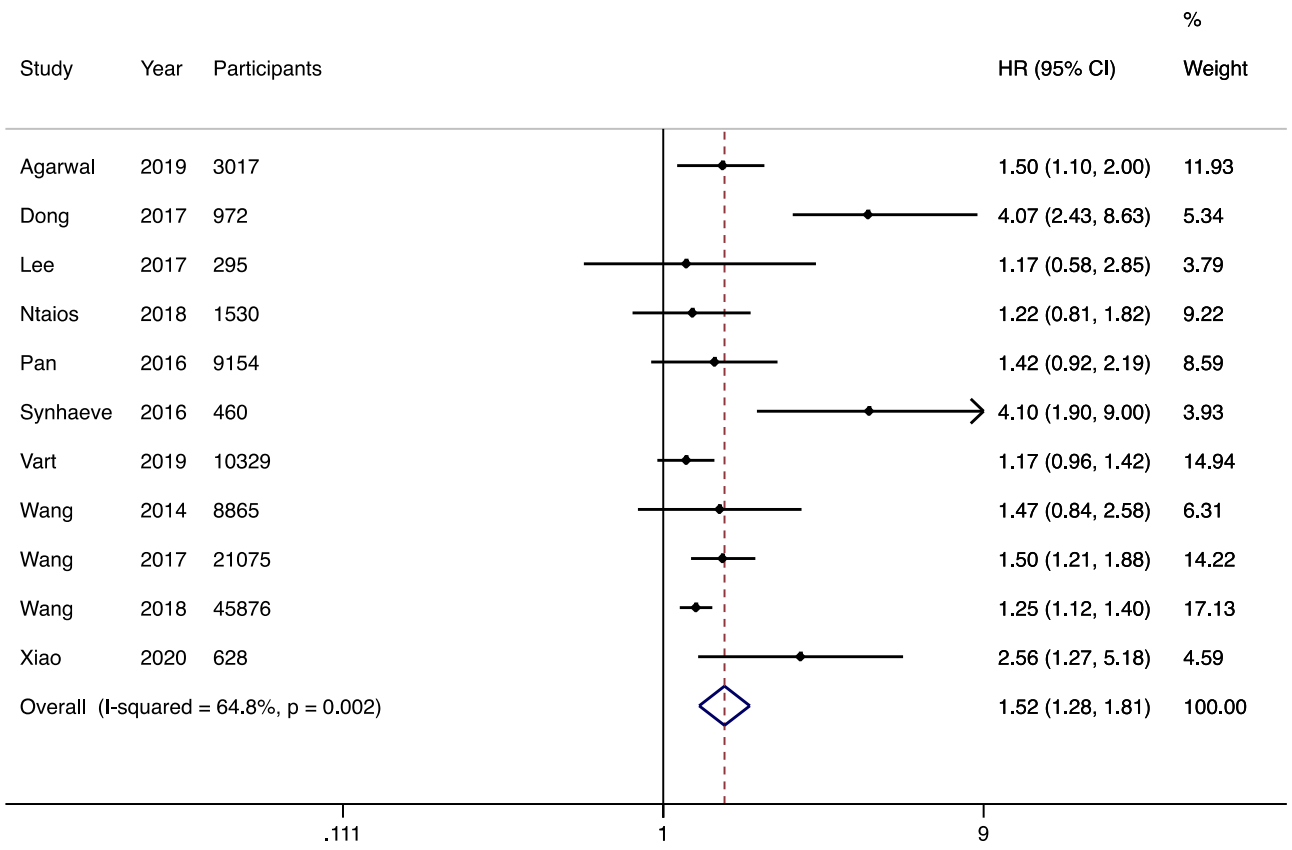


Figure 9-4 Distribution of modified Rankin Scale (mRS) according to baseline eGFR category (A) in all patients prior to ischaemic stroke (B) at 1 month after ischaemic stroke (C) excluding those with premorbid mRS>2, (D) and the change from premorbid to 1 month mRS post-event score in all ischaemic stroke patients.

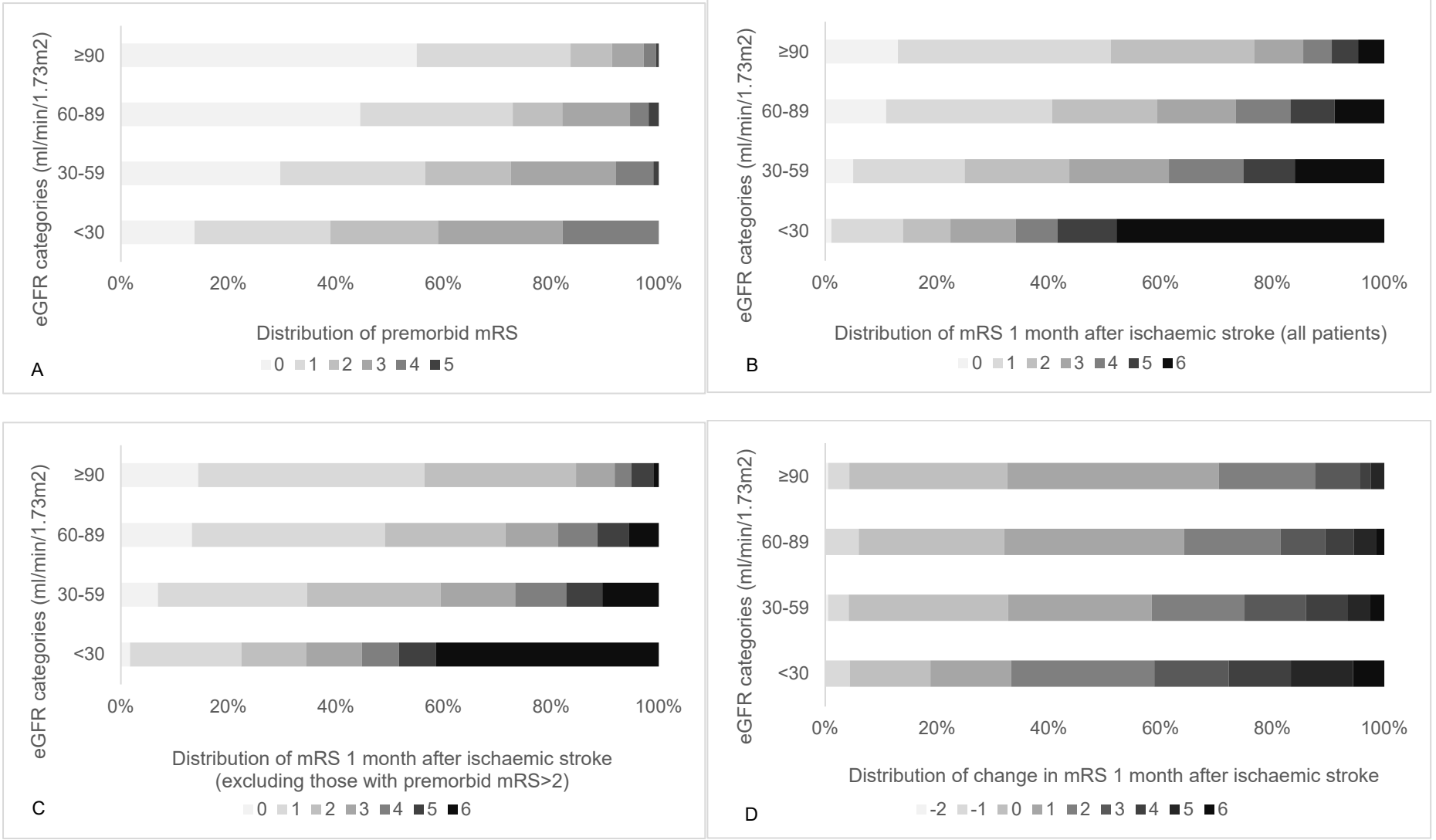


Figure 9-5 Distribution of modified Rankin Scale (mRS) 1 month after ischaemic stroke according to baseline eGFR category (A) in patients < 75 years and (B) ≥ 75 years

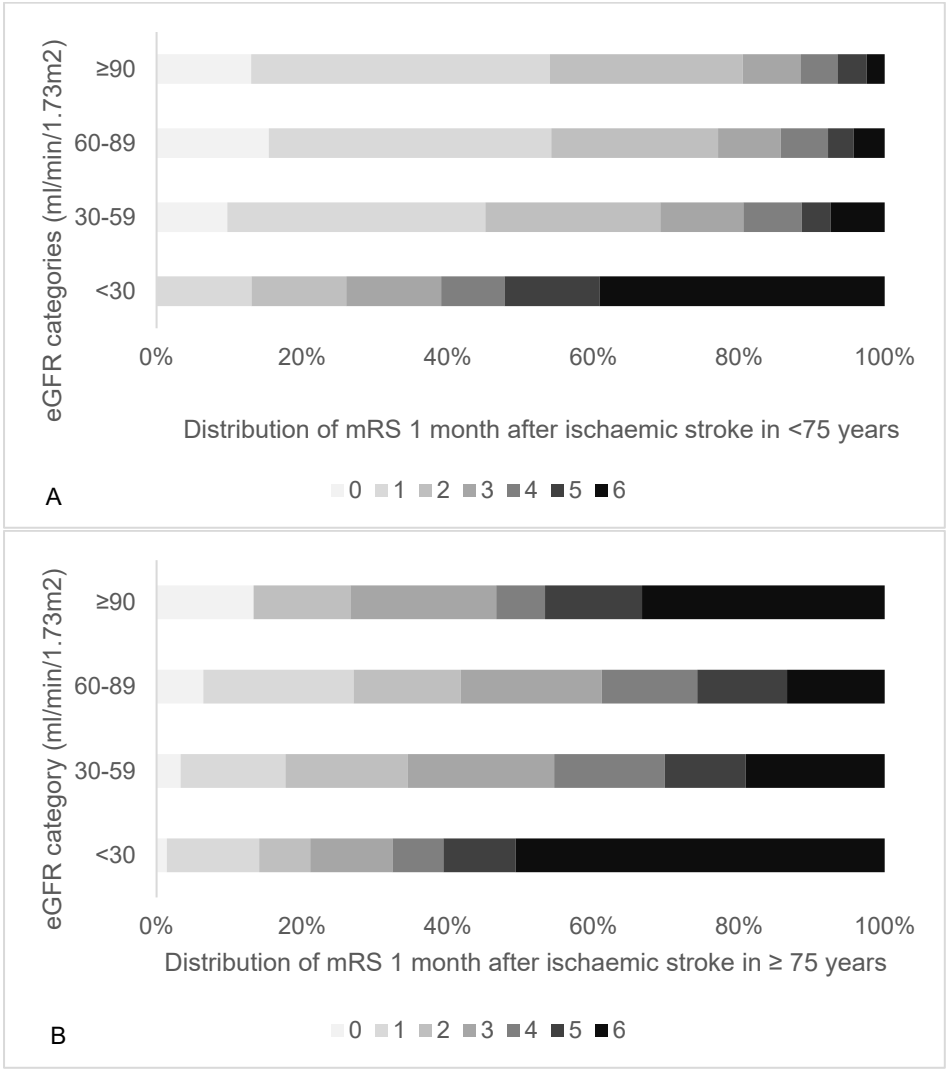
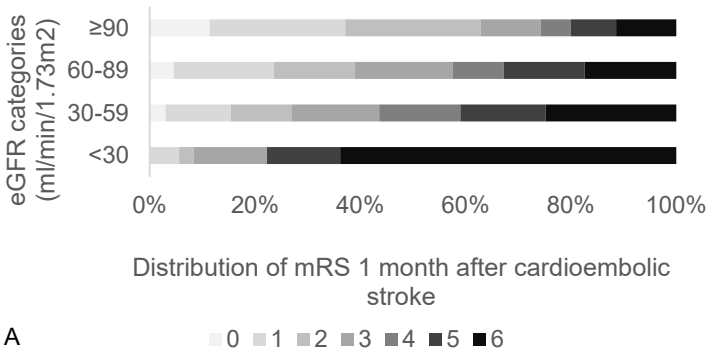
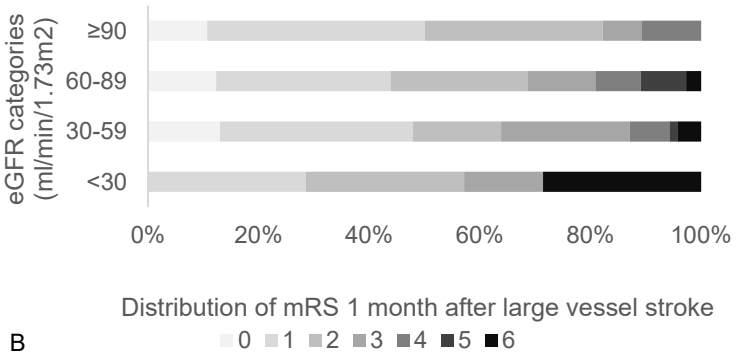


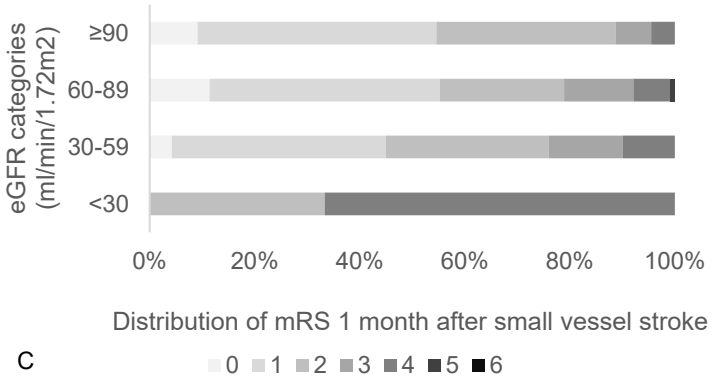
Figure 9-6 Distribution of modified Rankin Scale (mRS) at 1 month according to eGFR categories and stratified by TOAST ischaemic stroke subtype



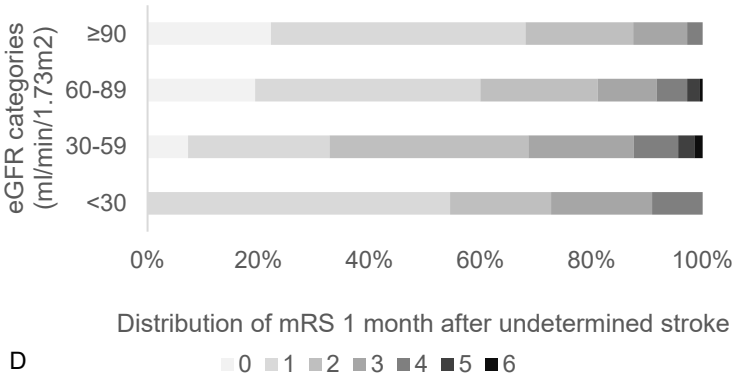
A



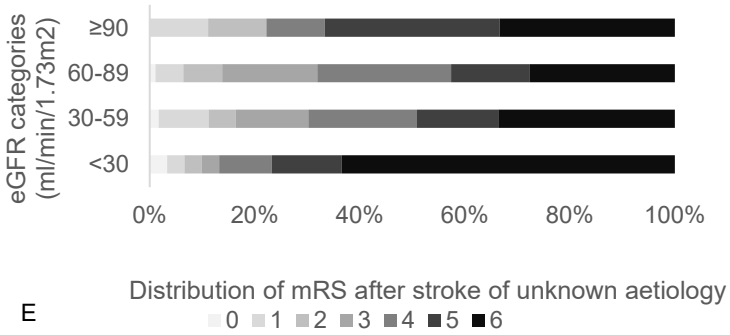
B



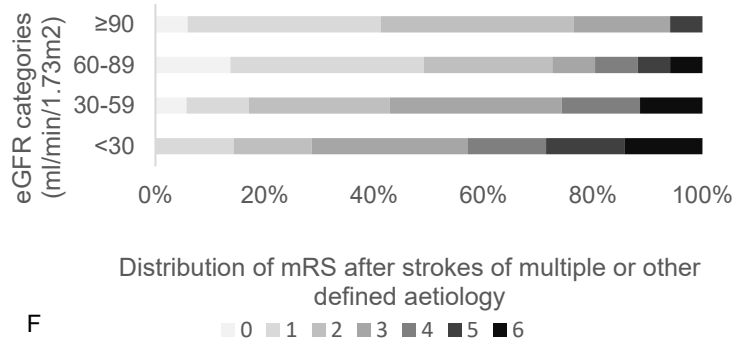
C



D

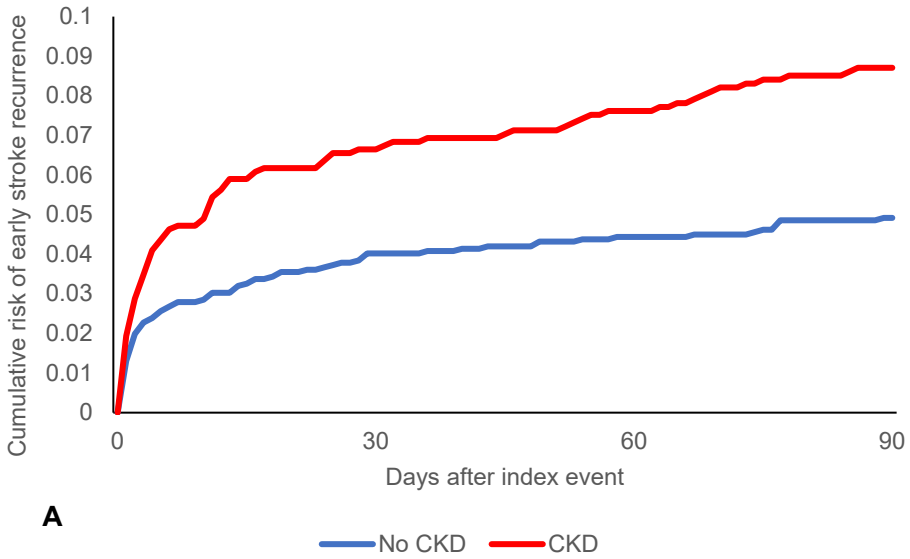


E

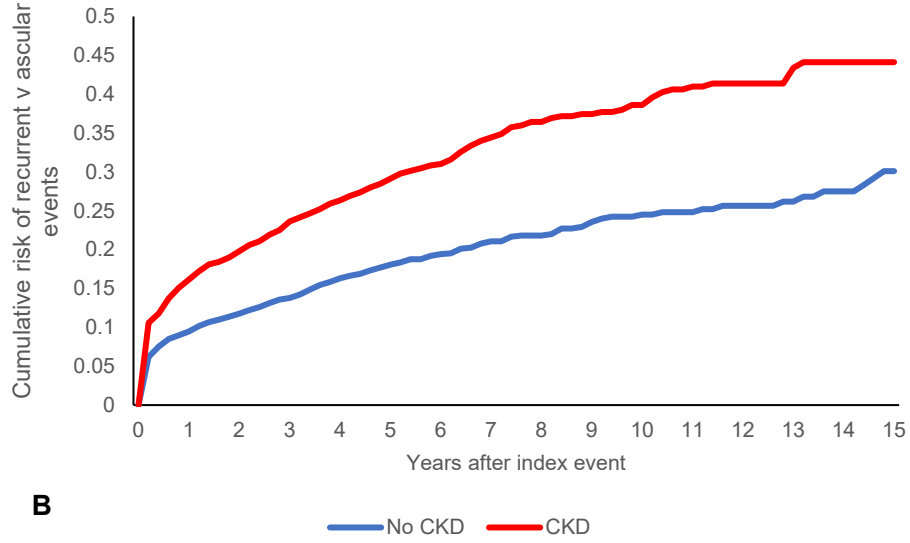


F

Figure 9-7 Cumulative risk of (A) early (<90 days) recurrent stroke and (B) long-term (0-15 years) recurrent vascular events in those with and without CKD



A



B

9.7 Appendix

Table 9-12 Characteristics of included studies

Study reference, Country, Name, (Reference)	Design, population, ethnicity	Size, (% men)	Mean or median age (SD or range)	GFR (ml/min/1.73m^2)		Albuminuria (category)		Follow-up (months)	Stroke severity	Disability post-stroke	Risk of stroke recurrence
				Formula ***Reference***: range(n) ***Comparison***: range (n)		Measurement ***Reference***: range (n) ***Comparison***: range (n)					
Agarwal 2019, Multinational, SPS3 Trial,[1]	RCT *Inclusion criteria*: ≥30 years, recent symptomatic lacunar stroke confirmed by MRI. *Intervention*: SBP <130 *Control:* SBP 130-149 mmHg. 75% HTN, 60.4% smoker, 33.2% DM, 8.4% CAD. 50.7% Non-Hispanic white, 30.5% Hispanic, 16.3% Black.	3,017 (62.9)	62.8 (10.8)	CKD-Epi *Reference:* ≥60 (2543) *Comparison:* <60 (474)				44.4	Not assessed	Not assessed	CKD was associated with an increased risk of recurrent stroke.
Alqahtani 2018, US,[2]	Cohort 100% acute ischaemic stroke patients. 79.6% HTN, 34% DM, 18.2% AF, 14.9% smoker, 14.8% CAD. 69.8% White, 17% Black, 7.7% Hispanic.	930, 010 (46.9)	70.9 (14)	Non-Dialysis patients vs maintenance haemodialysis patients				In-hospital outcomes	In-hospital mortality was significantly higher in the dialysis group	Surrogates of severe disability (mechanical ventilation, tracheostomy and non-home discharges) were more frequent in the dialysis group	Not assessed
Bax 2008, Netherlands, [3]	Cohort, 22% DM, 30% cerebrovascular disease, 54% other atherosclerotic disease, Unknown ethnicity	3,216, (76)	60 (10.4)	MDRD *Reference*: ≥90 (602) *Comparison*: 60-90 (2,097) <60 (517)		ACR, not used to estimate association with stroke *Reference*: None (2,646) *Comparison*:		39	Not assessed	Not assessed	Recurrent stroke risk assessed as a component of a composite outcome

				Micro (570)				
Beuscher 2020, Germany,[4]	Cohort, 100% ICH patients 83.1% HTN, 28.5% prior stroke, 25.7% DM.	1,076 (53.5)	74	MDRD *Reference:* ≥60 (945) *Comparison:* <60 (131)	12	No difference in baseline NIHSS	CKD was independently associated with unfavourable outcome (mRS=3-6) and mortality at 12 months	Not assessed
Castro 2018, Portugal,[5]	Cohort 100% MCA territory ischaemic strokes. 61% HTN, 43% AF, 30% DM, 9% smoker, 4% previous MI.	46 (41%)	73 (12)	CKD-Epi *Reference:* ≥60 (33) *Comparison:* <60 (13)	3	Not assessed	CKD reduced the likelihood of a good functional outcome at 3 months (mRS=0-2)	Not assessed
Cheng 2008, Taiwan, [6]	Cohort, 9% DM, no vascular disease, Unknown ethnicity.	17,026, (76)	57.2 (5.2)	MDRD *Reference:* ≥90 (4190) *Comparison:* 60-90 (11,583) <60 (1,253)	180	CKD was associated with increased stroke mortality	Not assessed	Not assessed
Cherng 2018, Taiwan,[7]	Cohort 42.5% HTN, 24.6% CAD, 20.6% DM, 3.9% AF.	17,914 (47.7)		CKD-Epi *Reference:* ≥60 (11024) *Comparison:* <60 (5512) ESKD (1378)	1	Increased 30-day post-stroke mortality for CKD and ESKD	Not assessed	Not assessed
Cohen-Hagai, Israel,[8]	Cohort 100% stroke patients. 91.3% HTN, 64.4% DM, 39.4% prior stroke, 31.7% smokers, 20.2% AF.	104 (59.6%)	67.7 (11.3)	CKD-Epi: *Reference:* Creatinine < 1.2 mg/dL *Comparison:* Maintenance HD for > 3 months	12	Not assessed	Mean hospital length of stay was longer and the mean Rankin scale score was greater in the HD group	Not assessed

De Leeuw 2002, Multinational, Syst-Eur trial, [9]	RCT, *Inclusion criteria*: isolated systolic HTN, age≥60. *Intervention*: Ca-channel blocker +/- ACE *Control:* Placebo 11% diabetics, 30% previous cardiovascular disease, Unknown ethnicity.	4,658, (33)	70 (6.6)	Serum Creatinine Per 20 µmol/l increase	Dipstick *Reference*: None (4,225) *Comparison*: Micro (324) Macro (109)	24	Worsening renal function was associated with higher stroke mortality	Not assessed	Not assessed
Dong 2017, China, [10]	Cohort 100% acute ischaemic stroke. 67% HTN, 52.2% smoking, 40.2% DM, 10% CAD.	972 (53.2)	68 (10.1)	MDRD *Reference:* ≥90 (556) *Comparison:* 60-90 (286) 30-59 (90)		3	Higher baseline NIHSS in the CKD group.	Not assessed	CKD was associated with increased risk of recurrent stroke.
El Husseini 2017, USA, Get With The Guidelines-Stroke cohort,[11]	Cohort 100% ischaemic stroke. 79.9% HTN, 30.8% CAD, 30.3% DM, 27.9% previous stroke, 24.8% AF. 80,3% White, 10.7% Black, 4.3% Hispanic, 2.6% Other, 1.8% Asian.	232,236 (41.4)	81.0 (74.0-87.0)	MDRD *Reference:* ≥60 (109913) *Comparison:* 45-59 (61719) 30-44 (39201) 15-29 (13118) <15 (1700) <15D (6585)		In-hospital outcomes	Higher baseline NIHSS in the CKD group along with increased risk of in-hospital mortality.	An eGFR 15-29 eGFR <15 and dialysis were associated with lower odds of discharge home.	Not assessed
El Husseini 2018, USA, Get With The Guidelines-Stroke cohort,[12]	Cohort 100% ischaemic stroke. 80% HTN, 30.7% DM, 30.4% prior CAD, 27.7% previous stroke, 22.7% AF, 9.4% smoker. 79.8% White, 11.2% Black, 4.3% Hispanic, 2.6% Other, 1.9% Asian.	204,652 (42.4%)	80.0 (73.0-86.0)	CKD-Epi *Reference:* ≥60 (99789) *Comparison:* 45-59 (54158) 30-44 (33369) 15-29 (10433) <15 (1201) <15D (5702)		12	Median NIHSS higher on admission for eGFR < 60.	Not assessed	eGFR <45 was associated with increased 30-day mortality with the risk highest among those with eGFR<15 without dialysis.

Findlay 2016, Scotland,[13]	Cohort 100% renal transplant recipients. 17.2% DM, 9.2% AF, 7% prior CVD, 4.4% prior stroke.	956 (59.9)	40.1			64.8	Higher stroke mortality in the CKD group		
Findlay 2018, Scotland,[14]	Cohort 100% stroke patients 42.2% HTN, 19.8% IHD, 14.1% DM, 5.8% prior cerebrovascular disease.	61,367 (48.7)	70	*Reference:* Non-ESKD (61087) *Comparison:* ESKD (dialysis & transplant) (280)		47.3	Higher in-hospital mortality in ESKD patients.	ESKD patients were more likely to remain in an National Health Service inpatient bed and were less likely to be discharged to home.	Not assessed
Hayden 2017, Ireland,[15]	Cohort 60.8% HTN, 23.7% IHD, 14.8% previous stroke, 13.1% DM. Unknown ethnicity.	547 (50.8)	71.1 (13.2)	CKD-Epi *Reference:* ≥60 (408) *Comparison:* <60 (139)		48	eGFR <45 predicts death at 28 days post-stroke	eGFR < 60 predicts poor functional outcome at 2 years.	Increased stroke recurrence with CKD but no dose-response relationship observed.
Jhund 2015, Multinational, ALTITUDE trial,[16]	RCT *Inclusion criteria:* ≥35yo with Type 2 DM, CKD &/or CVD. *Intervention:* Aliskerin *Control:* Placebo 94.5% HTN, 48.3% prior CVD, 14.5% smoking, 62.8% White, 34.2% Asian, 9.1% Other, 3.5% Black.	8561 (35)	64.5 (9.7)	MDRD *Reference:* ≥60 (2783) *Comparison:* 45-60 (3028) 30-45 (2538) <30 (210)	UACR *Reference:* None (1813) *Comparison:* 20-200 mg/g (1879) ≥200 mg/g (4869)	30	Albuminuria associated with increased risk of stroke death.	Not assessed	Not assessed
Kumai 2012, Japan, Fukoka Stroke Registry,[17]	Cohort 100% first-ever ischaemic stroke. 73.4% HTN, 31.1% DM, 25.9% AF.	3778 (61.1)	70.0 (11.9)	3-variable Japanese equation *Reference:* ≥60 (2458) *Comparison:* <60 (1320)	Urine dipstick *Reference:* Negative (2844) Trace (332) Mild (338) Severe (264)	1	CKD patients had a higher median NIHSS on admission. CKD was associated with in-hospital mortality as were all levels of proteinuria.	CKD was associated with poor functional outcome at discharge (mRS≥2) as was mild and severe proteinuria	Not assessed

Lee 2016, South Korea,[18]	Cohort 74.9% HTN, 28.1% DM, 25.4% smoking, 19.7% CAD.	295 (53.2)	67.6 (14-94)	CKD-Epi *Reference:* ≥60 (239) *Comparison:* <60 (56)	UACR *Reference:* <30 (165) *Comparison:* ≥30 (130)	22	Higher baseline median NIHSS in the CKD group.	CKD associated with good functional outcome at 6 months (mRS =0-2). Albuminuria associated with poor functional outcomes.	CKD associated with increased risk of recurrent stroke.
Luo 2014, China, China National Stroke Registry,[19]	Cohort 100% Type 2 DM, 71.3% HTN, 36.2% smoking, 15.7% CAD	4836 (60.5)	64.9 (11.4)	CKD-Epi *Reference:* ≥120 (387) *Comparison:* 90-119 (2209) 60-89 (1591) 45-59 (381) <45 (268)		12	Higher baseline median NIHSS in the CKD group.	CKD associated with increased risk of stroke disability at 1-year	CKD associated with increased risk of stroke recurrence at 1-year
Ninomiya 2008, Multinational, PROGRESS trial,[20]	RCT, *Inclusion criteria:* History of cerebrovascular disease *Intervention:* Perindopril *Control:* Placebo Southern Italians.	6,071, (70)	64 (10)	Cockcroft Gault *Reference*: >60 (4,314) *Comparison*: <60 (1,757)		78	Not assessed	Not assessed	Perindopril-based BP lowering effectively prevented recurrent stroke in people with CKD, across a wide range of BP levels.
Ntaios 2018, Multinational,[21]	Cohort (12 hospital-based stroke registries) 100% embolic stroke of undetermined source	1530 (56.3)	68.8 (57.0–78.0)	MDRD *Reference:* ≥90 (549) *Comparison:* 60-89 (689) 45-59 (192) 30-44 (74) <30 (26)		25.6	Baseline median NIHSS was similar across eGFR categories	Not assessed	CKD was not independently associated with risk of stroke recurrence in multivariate analysis
Nugroho 2018, Japan, Shiga Stroke Registry,[22]	Cohort 100% acute stroke patients. 72.2% HTN, 31.2% ever smoker, 26.9% DM, 26.2% prior stroke, 20.4% AF, 6% prior MI.	2,813 (53.7)	74.0 (13.3)	3-variable Japanese equation *Reference:* 60-89 (1306) *Comparison:* ≥90 (435) 45-59 (1306) <45 (431) RRT (70)			eGFR < 45 was associated with in-hospital death.	eGFR<45 was associated with in-hospital death/disability (mRS=2-6).	Not assessed

Pan 2018, China, China National Stroke Registry,[23]	Cohort. 62.5% HTN, 39.9% ever smoker, 33.8% previous stroke, 21.5% DM, 14.8% CAD.	9,154 (61.8)	65.4 (12.4)	CKD-Epi *Reference:* ≥90 (4509) *Comparison:* 60-89 (3502) <60 (1143)		12	Higher baseline median NIHSS in the CKD group.	CKD was associated with poor functional outcomes (mRS 3-6) at 1 year with (but not without AF) and with ordinal mRS for both.	In patients with AF, CKD was associated with risk of recurrent stroke at 1 year.
Sander 2012, Germany, INSIGHT registry,[24]	Cohort, 35% diabetics, 79% HTN, 18% current smokers.	1,167 (58.1)	66 (11.9)		Dipstick *Reference*: None (781) *Comparison*: Micro (386)	12	MAU patients had a similar baseline median NIHSS score	Not assessed	MAU was predictive for recurrent stroke during the following year
Schutte 2014, South Africa,[25]	Cohort 100% Africans, 52.4% smoking, 49.8% HTN.	1061 (38)	51.5 (10.2)		UACR *Reference:* Normoalbumin ura (954) *Comparison:* Micro (97) Macro (10)	54.2	Increased risk of stroke mortality with albuminuria.	Not assessed	Not assessed
Sutherland 2020, New Zealand,[26]	Cohort 100% ischaemic stroke patients treated with EVT. 67% HTN, 47% AF, 44% smoking, 20% DM, 17% CAD.	378 (59)	65 (15)	CKD-Epi *Reference:* ≥60 (261) *Comparison:* <60 (117)		3	No difference in initial NIHSS scores.	CKD was associated with worse 3-month mRS and lower likelihood of functional independence at 3 months.	Not assessed
Synhaeve 2016, Netherland, FUTURE study,[27]	Cohort 100% stroke, 52.4% smoking, 35.2% HTN, 8.3% DM. Unknown ethnicity.	460 (47.4)	41.2 (7.6)	CKD-Epi *Reference:* >120 (39) *Comparison:* 60-120 (392) <60 (29)		138	Higher baseline median NIHSS in the CKD group.	Not assessed	CKD associated with increased risk of recurrent stroke

Tollitt 2019, UK, Salford Kidney Study,[28]	Cohort 100% non-dialysis CKD. 90.1% HTN, 65.4% ever smoker, 16.1% prior MI, 6.9% AF. 96% Caucasian, 4% Non-Caucasian.	3060 (62.5)	67	CKD-Epi: *Reference:* eGFR <60 + no prior stroke (2833) *Comparison:* eGFR <60 + prior stroke (227)	38	Not assessed	Not assessed	Not assessed.
Usui 2018, Japan,[29]	Cohort 100% community-onset stroke. 56% HTN, 26.1% smokers, 21.7% DM, 12.4% AF, 6.1% CAD.	435 403 (56.4)	72.6 (13)	*Reference:* No dialysis (427841) *Comparison:* Dialysis (7562)	1	Dialysis was associated with an increased risk of in-hospital mortality	Dialysis was associated with an increased risk of in-hospital disability progression	Not assessed
Vart 2019, UK,[30]	Cohort 100% stroke patients. 51.8% HTN, 26.9% AF, 24.6% prior stroke, 23.4% CAD, 14.6% DM.	10,329 (47.5)	77.8 (11.9)	CKD-Epi *Reference:* ≥90 (1106) *Comparison:* 60-89 (4866) 45-59 (2177) 30-44 (1427) 15-29 (496) <15 (157)	34.8	Not assessed	CKD was associated with prolonged hospitalisation and disability.	CKD was not associated with recurrent stroke risk.
Wang 2014, China, China National Stroke Registry,[31]	Cohort 100% ischaemic stroke & AF, 34.1% HTN, 17.9% smoking, 14.8% CAD, 7% DM.	229 (40.2)	66.4 (13.5)	MDRD *Reference:* ≥60 (124) *Comparison:* <60 (105)	12	Higher baseline median NIHSS in the CKD group.	Groups did not differ significantly in disability (mRS 3-5) rates at 3, 6 or 12 months	Similar 1-year cumulative stroke recurrence for those with and without CKD
Wang 2014, China National Stroke Registry, China,[32]	Cohort 100% acute ischaemic stroke, 63.6% HTN, 40.2% ever smokers, 33.8% prior stroke, 21.4% DM, 14.8% CAD, 7.5% AF.	8865 (62.4)	65.5 (10.5)	CKD-Epi *Reference:* ≥90 (4263) *Comparison:* 60-89 (3533) 45-59 (675) <45 (394)	12	Baseline NIHSS increased with declining eGFR categories	eGFR <45 was not associated with 1-year stroke disability (mRS 2-6)	eGFR < 45 was associated with 1-year recurrent stroke risk
Wang 2017, China, China National Stroke Registry,[33]	Cohort 100% stroke, 75.9% HTN, 43.1% smoking, 18.8% DM, 12.9% CAD.	21075 (62.7)	64.3 (12)	CKD-Epi *Reference:* ≥90 (11847) *Comparison:* 60-89 (5292) <60 (1596)	12	Not assessed	In patients without hypertension, CKD was associated with poor functional outcome (mRS	In patients with hypertension, low eGFR was associated with recurrent stroke at 1 year.

								3-6) and with ordinal mRS.	
Wang 2018, Taiwan, Taiwan Stroke Registry,[34]	Cohort 100% ischaemic stroke, 38.9% DM, 31.6% ever smoker, 12.2% CAD, 7.8% AF, 2.4% past stroke.	52, 732 (61.4)	57.5-75.4	CKD-Epi *Reference:* ≥90 (10197) *Comparison:* 60-89 (22437) 30-59 (15706) 15-29 (2390) <15 (2022)		12	Baseline NIHSS increased with declining eGFR categories	Not assessed.	Not assessed
Wang 2018, Taiwan, Taiwan Stroke Registry,[35]	Cohort 100% acute ischaemic stroke. 38.8% DM, 36.1% ever smoker, 24.9% previous stroke, 12.5% CAD.	45876 (61.2)	69.6 (59.3-77.9)	CKD-Epi *Reference:* ≥90 (8703) *Comparison:* 60-89 (19517) 30-59 (13813) <30 (3843)		12	Baseline NIHSS increased with declining eGFR categories	Not assessed	CKD associated with increased risk of 1-month and 1-year stroke recurrence
Wetmore 2020, USA,[36]	Cohort 100% patients with CKD4-5 in Medicare. 94.3% HTN, 53.3% DM, 24.7% AF, 1.7% prior stroke.	145, 305 (47,5)	80.7 (8.2)	CKD-Epi *Reference:* None *Comparison:* 15-29 (123251) <15 (22045)		24	Not assessed	Not assessed	Not assessed
Xiao 2020, China, ACTUAL registry,[37]	Cohort 100% ischaemic stroke treated with EVT. 65.4% HTN, 42% AF, 19.3% DM, 14.6% prior stroke.	628 (60.2)	64.7 (12.5)	CKD-Epi *Reference:* >60 (529) *Comparison:* ≤60 (99)		23.7	CKD patients had a higher baseline NIHSS	CKD was associated with lower rates of functional independence at 3 months	CKD was associated with increased risk of recurrent stroke
Yokota 2008, Japan,[38]	Cohort, 100% admitted with stroke, 84% HTN, 31% diabetics, 26% AF, 15% IHD. Unknown ethnicity	474, (66)	70 (11)		ACR *Reference:* None (309) *Comparison:* Micro (133) Macro (32)	12.8	Not assessed	Not assessed	Albuminuria was a significant predictor of stroke recurrence
Zhou 2016, China, CHANCE Trial,[39]	RCT *Inclusion criteria:*	5170 (66.3)		CKD-Epi *Reference:* ≥90 (2732) *Comparison:*		1.5	No significant difference in initial NIHSS scores.	Not assessed	Dual antiplatelets did not reduce the risk of recurrent stroke in CKD

	≥40yrs with minor ischaemic stroke or High-risk TIA. *Intervention:* ASA + Clopidogrel *Control:* ASA + Placebo 65.5% HTN, 21% DM, 1.9% MI.	60-89 (2064) <60 (354)	compared to aspirin alone.

Abbreviations:
ACE indicates angiotensin Converting Enzyme inhibitor; ACR, albumin:creatinine ratio; AF, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CKD, chronic kidney disease; CKD-Epi, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DM, diabetes mellitus; ESKD, end-stage kidney disease; EVT, endovascular thrombectomy; GFR, glomerular filtration rate; HD, haemodialysis; HTN, hypertension; ICH, intracerebral haemorrhage; MAU, microalbuminuria; MCA, middle cerebral artery; MDRD, modification of diet in renal disease; MI, myocardial infarction; Micro, micro albuminuria; Macro, macro albuminuria; MRI, magnetic resonance imaging; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; RCT, randomized controlled trial; RRT, renal replacement therapy; SBP, systolic blood pressure; SD, standard deviation.; UACR, urinary albumin:creatinine ratio.

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Chapter 10 Age-specific associations of chronic kidney disease with imaging markers of cerebral small vessel disease in transient ischaemic attack and minor stroke

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10.1 Chapter outline

Cerebral small vessel disease (SVD) is highly prevalent in chronic kidney disease (CKD) but the mechanisms underpinning this relationship are unclear. I aimed to explore whether their association was independent of shared vascular risk factors (e.g. hypertension), and whether any association present varied depending on age.

In a population-based study of TIA and ischaemic stroke (Oxford Vascular Study), I evaluated the MRI markers of cerebral SVD including lacunes, white matter hyperintensities (WMH), cerebral microbleeds and enlarged perivascular space. I studied the age-specific associations of CKD and total SVD burden (total SVD score), as well as individual SVD markers, adjusting for age, sex, and usual vascular risk factors.

1939 consecutive patients had complete MRI protocol and creatinine measured at baseline. CKD was associated with total SVD score (OR=3.01, 95%CI: 2.46-3.69, p<0.001), largely driven by those aged <60-years (<60y 6.45, 2.41-17.27, p<0.001; 60-79y 1.43, 1.07-1.91, p=0.01; ≥80y 1.10, 0.78-1.55, p=0.59). The overall association of CKD and total SVD score also disappeared after adjustment for age, sex, and usual vascular risk factors (adjusted OR=0.99, 0.79-1.24, p=0.93), but the independent association of CKD and total SVD score at age <60-years was maintained (adjusted OR=4.51, 1.65-12.4, p=0.003). Associations of CKD and SVD were consistent for each SVD marker at age <60-years, but were strongest for cerebral microbleeds (adjusted OR=7.44, 2.41-22.93, p<0.001) and moderate-to-severe periventricular WMH (adjusted OR=8.41, 2.50-28.28, p=0.001).

The association of CKD and cerebral SVD was attenuated with adjustment for shared risk factors at older ages, but remained at younger ages, suggesting a possible shared genetic susceptibility to SVD of the brain and kidney.

10.2 Introduction

There is a strong association between cerebral small vessel disease (SVD) and chronic kidney disease (CKD),[1] and this is consistent for each SVD subtype including white matter hyperintensities (WMH),[2] silent lacunes,[3] perivascular spaces (PVS),[4] and cerebral microbleeds (CMB).[5] It has been shown that over half of asymptomatic patients with CKD have silent brain infarctions.[6, 7] Their presence in CKD appears to portend a greater risk of symptomatic cerebrovascular events,[6] vascular cognitive impairment,[8] and kidney disease progression.[9]

It has been hypothesized that cerebral SVD may be part of a multisystem disorder affecting other vascular beds, such as the kidney.[10, 11] However, other mechanisms for the association of SVD and CKD have also been proposed including their shared anatomical and physiological susceptibility to hypertensive vascular injury,[12] their shared vascular risk factors such as hypertension and diabetes,[3] or shared genetic susceptibility.[13]

In a preliminary, exploratory analysis of the Oxford Vascular Study (OXVASC) cohort, there appeared to stronger, more independent associations of CKD and SVD at younger ages, suggesting that shared genetic factors leading to premature vascular disease may play a role.[14] However, this initial analysis was small and used the creatinine-based Modification of Diet in Renal Disease (MDRD) formula for the calculation for estimated glomerular filtration rate (eGFR) which is not as accurate as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, particularly in older adults, and may have resulted in over-estimation of the true prevalence of CKD in the population.[15]

Therefore, I repeated this analysis in a larger cohort of patients with transient ischaemic attack (TIA) and minor ischaemic stroke from OXVASC to validate these earlier findings and confirm if there were age-specific associations of CKD with the overall burden of SVD

(total SVD score),[16] as well as individual SVD markers, with detailed adjustment for shared vascular risk factors.

10.3 Methods

10.3.1 Patient population

I studied consecutive patients with TIA or ischaemic stroke who underwent cerebral magnetic resonance imaging (MRI) in OXVASC from 2004-2018. The detailed methodology of OXVASC has been previously outlined in section 4.3 including the multiple overlapping methods used to achieve near complete ascertainment of all individuals with TIA and ischaemic stroke.[17] All cases were reviewed by the senior study neurologist (PMR) and TIA/stroke aetiology was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. For the current analyses, patients with cerebral or systemic vasculitis, Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy (CADASIL), or Fabry disease were excluded. CKD was defined as eGFR less than 60 mL/min/1.73 m^2 for three or more months as per 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[18] eGFR was estimated using the CKD-EPI formula.

One neuroradiologist (WK) provided ongoing supervision of interpretation of the MRI images throughout the study period and the independently derived and proposed total SVD score was used to assess the overall burden of SVD.[16] One point was allocated to each of the following: 1) presence of lacunes; 2) presence of CMB; 3) moderate-severe (>10) basal ganglia perivascular spaces (BG-PVS) and 4) severe periventricular and/or moderate-severe deep WMH. Lacunes were defined as rounded or ovoid lesions, >3 and <20mm in diameter, in the basal ganglia (BG), internal capsule, centrum semiovale (CS) or brainstem, of cerebrospinal fluid signal density on T2 and fluid-attenuated inversion recovery (FLAIR) and no increased signal on diffusion weighted imaging (DWI).[19] CMBs

were defined as rounded, hypodense foci up to 10mm in size and were differentiated from microbleed mimics based on current guidelines.[20] Perivascular spaces (PVSs) were defined as small (<3mm) punctate (if perpendicular to the plane of scan) or linear (if longitudinal to the plane of scan) hyperintensities on T2 images in BG or CS based on a previously validated scale[21] and only BG-PVS were used in the total SVD score. The severity of white matter disease was determined for periventricular vs. deep WMH respectively according to the Fazekas scale.[22]

10.3.2 Statistical analysis

Categorical variables are reported as absolute numbers with percentages and continuous variables are reported as means with SD. χ^2 and ANOVA tests were performed to compare categorical and continuous variables between groups. I first used ordinal regression to determine the age-specific (overall/<60years, 60-79 years and ≥80 years) associations of CKD and the total SVD score. I then used logistic regression to study the age-specific associations of CKD and individual SVD markers including presence of lacunes, presence of CMBs, BG-PVS, moderate-to-severe periventricular WMH, and moderate-to-severe deep WMH. All analyses were adjusted for age, sex, history of hypertension, diabetes, atrial fibrillation (AF), ischaemic heart disease (IHD), and smoking. All analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL).

10.3.3 Brain imaging protocol

From April 1, 2002, to March 31, 2010 (phase 1), MRI and magnetic resonance angiography (MRA) was performed in selected patients when clinically indicated.[17] From April 1, 2010 onwards (phase 2), brain MRI and MRA became the first-line imaging methods. Patients were scanned predominantly with 2 scanners: Achieva (Philips Healthcare, Best, the Netherlands) and Magnetom Verio (Siemens health care, Munich,

Germany).[23] The detailed sequence parameters are listed in the Table 10-1. One neuroradiologists (W.K.) provided ongoing supervision of interpretation of the MRI throughout the study period. The intra-rater κ for 50 randomly selected scans was as follows: lacunes 0.85; microbleed burden (0, 1, 2–4, ≥5) 0.88; periventricular WMH burden (Fazekas grade 0, 1, 2, 3) 0.66; subcortical WMH burden (Fazekas grade 0, 1, 2, 3) 0.75; PVS burden (<11, 11–20, >20) 0.86 (BG), 0.84 (CS).[24]

10.4 Results

1939 consecutive patients with a TIA or ischaemic stroke presentation who underwent MR brain imaging were included in the analyses. The median (interquartile range [IQR]) age was 70 (57.5-78.5) years and 553 (28.5%) were <60 years. The baseline characteristics of patients stratified by the total SVD score are shown in Table 10-2. As expected, patients with higher total SVD score were older, more likely to have history of hypertension, AF, history of stroke/TIA or IHD, and were more likely to present with an ischaemic stroke (all p<0.001).

The median eGFR and the prevalence of CKD decreased and increased, respectively, with increasing total SVD score (both p_{trend}<0.001; Table 10-2). In total, 434 (22.4%) of the study population had CKD. In an ordinal regression, CKD was associated with total SVD score (OR=3.01, 95%CI: 2.46-3.69, p<0.001; Table 10-3), but this association was only apparent at age <80 years and was mostly driven by those aged <60 years (<60y – 6.45, 2.41-17.27, p<0.001; 60-79y 1.43, 1.07-1.91, p=0.01; ≥80y 1.10, 0.78-1.55, p=0.59). The overall association of CKD and total SVD score also disappeared after adjustment for age and sex (1.10, 0.88-1.38, p=0.39; Table 10-3), and was attenuated with additional adjustment for history of hypertension (1.00, 0.80-1.25, p=0.99; Table 10-3), with even further attenuation when adjusted for other vascular risk factors (0.99, 0.79-1.24, p=0.93; Table 10-3). However, although similar attenuation was observed for all age groups, the

independent association of CKD and total SVD score was maintained in the multivariate analyses at age <60 years (adjusted OR=4.51, 1.65-12.40, p=0.003; Table 10-3).

When the associations of CKD and individual SVD markers were studied, the results were also consistent, with attenuation of apparent associations after adjustment for known risk factors but with independent associations of CKD and SVD remaining at younger ages (Table 10-4), particularly for the presence of CMB (7.44, 2.41-22.93, p<0.001; Table 10-4) and for moderate-to-severe periventricular WMH (8.41, 2.50-28.28, p=0.001; Table 10-4).

10.5 Discussion

In this population-based study of patients presenting with TIA and ischaemic stroke, I found that the associations of CKD and SVD were attenuated after adjustment for age, sex, and known vascular risk factors, and disappeared at older ages. However, the association was maintained at younger ages, both for the overall SVD burden and for individual SVD markers.

These findings of age-specific associations of CKD and cerebral SVD in TIA and minor stroke are in line with an earlier, preliminary analysis of OXVASC,[14] and with a previous systematic review and meta-analysis that showed that the four-fold increased risk of CKD in lacunar vs. non-lacunar stroke was only observed at younger ages.[3] Similarly, in the non-stroke population, compared with studies of a mean age of 70 years, there was a stronger relationship between CKD and WMH in studies with an average age of 50-60 years.[3] The same pattern was also seen for CKD and CMB or enlarged perivascular spaces, where studies including younger patients tended to report a strong association[4, 25] and studies of older cohorts tended to find no association.[26] My prior meta-analyses of CKD and stroke risk also indicated that there were stronger associations present at younger ages (Chapter 5 and Chapter 6).[27, 28]

The independent associations of CKD and SVD at younger ages could represent a shared genetic susceptibility. Two genome-wide association studies have indicated genetic pleiotropy between kidney and cerebrovascular disease, particularly with large artery atherosclerotic and small vessel stroke.[13, 29] In the most recent of these studies that leveraged large-scale data from international consortia, a locus at 2q33 showed pairwise associations between urinary albumin:creatinine ratio and both small vessel stroke and WMH, indicating that 2q33 may play a role across small vessel pathologies in both the kidney and brain through microalbuminuria, small vessel stroke, and WMH, and that there may be a shared common pathway among cerebral and renal manifestations of SVD.[29] However, our recent subtype analysis of OXVASC did not demonstrate any independent association between CKD and symptomatic small vessel stroke either in the overall cohort or at younger ages (Chapter 8).[30]

Notably, we did not observe any apparent associations of CKD and SVD at older ages. Moreover, after adjustment for age, sex, and usual vascular risk factors, the association of CKD and SVD even showed a trend of reversed relationship at older ages. Given that both CKD and SVD are associated with premature death,[31] the non-association of CKD and SVD could be explained by a survival bias at older ages, where patients with stronger associations of CKD and SVD might have died early. Similarly, patients with multiple comorbidities might also die prematurely, leaving those with fewer risk factors or less susceptibility to risk factors in the cohort, leading to a reverse association after adjustment for these risk factors.

There are several potential limitations that should be considered. Firstly, a number of different MRI scanners with different field strengths, echo times and haemosiderin-sensitive sequences were used for detection of microbleeds which may have affected the

sensitivity of microbleed detection. Secondly, there may have been an inadvertent selection bias whereby older, frailer patients may have been less likely to have undergone MRI scanning if they were unable to tolerate lying flat for a prolonged period, and as such, the older population may not be as well represented. Thirdly, I used the total SVD score to assess the burden of cerebral SVD. However, quantitative measurements of SVD markers might be more accurate in measuring the overall burden particularly for the more severe end. Finally, this study is based in a predominantly Caucasian population and might not be generalizable to the Asian population, where there seems to be a stronger association of CKD and SVD.

In conclusion, an analysis of a larger cohort of patients presenting with TIA or ischaemic stroke in a prospective, population-based study confirmed that there are age-specific associations between CKD and stroke, and that the relationship is only independent of age, sex, and vascular risk factors at younger ages. Further studies of younger patients with CKD and SVD are required to delineate any potential shared genetic mechanisms underlying this relationship

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TABLES

Table 10-1 Imaging sequence parameters used in the Oxford Vascular Study

MR parameters	OXVASC scanner 1 Magnetom Verio, Siemens Healthcare	OXVASC scanner 2 Discovery MR750, GE Healthcare	OXVASC scanner 3 Achieva, Philips Healthcare	OXVASC scanner 4 Signa HDxt, GE Healthcare
Patients scanned	388	62	493	137
Field strength (T)	3	3	1.5	1.5
T1W TR/TE/TI (ms)	2000/1.94/880	-	701/16	-
T2W TR/TE (ms)	6000/96	5800/94	5061/100	3760/100
FLAIR TR/TE/TI (ms) (3D)	9000/88/2500	9600/130/2350	11000/140/2800	8080/112/2200
Diffusion TR/TE (ms)	5300/91	6000/84	2891/73	6100/71
GRE / SWI TR/TE (ms) (3D)	GRE 504/15	GRE 500/20	GRE 694/23	GRE 560/25
Pixel bandwidth (Hz)	240 (T1W) 220 (T2W) 202 (FLAIR) 1374 (Diffusion) 200 (GRE)	- 50 (T2W) 41.7 (FLAIR) 250 (Diffusion) 31.3 (GRE)	87.4 (T1W) 88.5 (T2W) 375 (FLAIR) 25.3 (Diffusion) 109.3 (GRE)	- 47.6 (T2W) 31.3 (FLAIR) - 75 (GRE)
Matrix	256x256 (T1W) 320x320 (T2W) 192x192 (FLAIR) 130x130 (Diffusion) 320x256 (GRE)	- 512 (T2W) 384x224 (FLAIR) 128x128 (Diffusion) 288x224 (GRE)	118x214 (T1W) 356x193 (T2W) 236x159 (FLAIR) 97x84 (Diffusion) 256x163 (GRE)	416x256 (T2W) 256x224 (FLAIR) 128x128 (Diffusion) 288x192 (GRE)
No. of slices	208 (T1W) 25 (T2W) 50 (FLAIR) 25 (Diffusion) 25 (GRE)	25	25 (T1W) 25 (T2W) 28 (FLAIR) 25 (Diffusion) 22 (GRE)	25
Slice thickness (mm)	1 (T1W) 5 (T2W) 3 (FLAIR) 5 (Diffusion) 5 (GRE)	5	5	5
Inter-slice gap (mm)	0 (T1W) 1 (T2W) 0 (FLAIR coronal) 1 (Diffusion) 1 (GRE)	1	1	1
Voxel size (mm^3)	1.0x1.0x1.0 (T1W) 0.8x0.8x5.0 (T2W) 1.0x1.0x3.0 (FLAIR) 1.8x1.8x5.0 (Diffusion) 0.9x0.8x5.0 (GRE)	-	0.53x0.53x5.0 (T1W) 0.65x0.65x5.0 (T2W) 0.82x0.81x5.0 (FLAIR) 1.74x1.73x5.0 (Diffusion) 0.90x0.90x5.0 (GRE)	-

FLAIR indicates fluid-attenuated inversion recovery; GRE, gradient echo; MR, magnetic resonance; SWI, susceptibility weighted imaging; T1W, T1-weighted; TE, echo time; TR, repetition time.

Table 10-2 Baseline characteristics of patients included in analyses stratified by the total small vessel disease score

	All (n=1939)	SVD score 0 (n=812)	SVD score 1 (n=494)	SVD score 2 (n=336)	SVD score ≥ 3 (n=223)	P value	P_{trend}
Age (median/IQR)	70.0 (57.5-78.5)	59.0 (49.0-70.0)	72.0 (64.0-79.3)	77.0 (70.0-82.2)	79.9 (71.3-85.2)	<0.001	<0.001
Female	954 (49.2)	393 (48.4)	244 (49.4)	162 (48.2)	120 (53.8)	0.52	0.35
Hypertension	1011 (52.2)	300 (36.9)	282 (57.2)	231 (69.0)	160 (71.7)	<0.001	<0.001
Hyperlipidaemia	662 (34.2)	231 (28.4)	174 (35.4)	144 (43.0)	86 (38.6)	<0.001	<0.001
Diabetes mellitus	254 (13.1)	85 (10.5)	77 (15.7)	47 (14.0)	34 (15.2)	0.03	0.02
Ever smoker	968 (50.0)	402 (49.6)	244 (49.5)	179 (53.4)	111 (49.8)	0.65	0.50
Atrial fibrillation	281 (14.5)	61 (7.5)	79 (16.1)	75 (22.4)	55 (24.7)	<0.001	<0.001
TIA/stroke prior to the index event	302 (15.6)	79 (9.7)	73 (4.8)	72 (21.5)	58 (26.0)	<0.001	<0.001
History of IHD	236 (12.2)	64 (7.9)	59 (12.0)	62 (18.5)	42 (18.8)	<0.001	<0.001
Type of index event: ischaemic stroke	767 (39.6)	272 (33.5)	205 (41.5)	146 (43.5)	110 (49.3)	<0.001	<0.001
BASELINE RENAL FUNCTION							
eGFR (median/IQR)	77.9 (62.1-91.8)	72.5 (59.4-87.3)	60.2 (46.6-77.3)	55.3 (41.0-69.4)	50.3 (36.0-66.5)	<0.001	<0.001
eGFR ≥90	534 (27.6)	354 (43.6)	111 (22.5)	40 (11.9)	21 (9.4)	<0.001	<0.001
eGFR 60-89	969 (50.0)	370 (45.6)	262 (53.0)	185 (55.1)	117 (52.5)		
eGFR 30-59	390 (20.1)	84 (10.3)	109 (22.1)	100 (29.8)	71 (31.8)		
eGFR <30	44 (2.3)	4 (0.5)	12 (2.4)	11 (3.3)	14 (6.3)		
CKD (eGFR <60)	434 (22.4)	88 (10.8)	121 (24.5)	111 (33.0)	85 (38.1)	<0.001	<0.001

Data are presented as numbers (%) unless otherwise stated.
CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; IHD, ischaemic heart disease; SVD, small vessel disease

Table 10-3 Associations of CKD and total small vessel disease score stratified by age and adjusted for age/sex and for known vascular risk factors

	Crude		Model 1*		Model 2†		Model 3‡	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Overall	3.01 (2.46-3.69)	<0.001	1.10 (0.88-1.38)	0.39	1.00 (0.80-1.25)	0.99	0.99 (0.79-1.24)	0.93
STRATIFIED BY AGE								
<60 y	6.45 (2.41-17.27)	<0.001	4.63 (1.70-12.59)	0.003	4.56 (1.68-12.4)	0.003	4.51 (1.65-12.4)	0.003
60-79 y	1.43 (1/07-1.91)	0.01	1.13 (0.83-1.52)	0.44	0.99 (0.72-1.34)	0.93	0.98 (0.72-1.33)	0.88
≥ 80 y	1.10 (0.78-1.55)	0.59	1.02 (0.71-1.45)	0.93	0.97 (0.68-1.38)	0.85	0.94 (0.65-1.34)	0.72

CKD (defined as eGFR<60 mL/min per 1.73 m^2) indicates chronic kidney disease; CI, confidence interval; and OR, odds ratio.
*Model I: adjusted for age and sex.
†Model II: adjusted for age, sex, and history of hypertension.
‡Model III: adjusted for age, sex, history of hypertension, diabetes mellitus, atrial fibrillation, ischaemic heart disease, smoking.

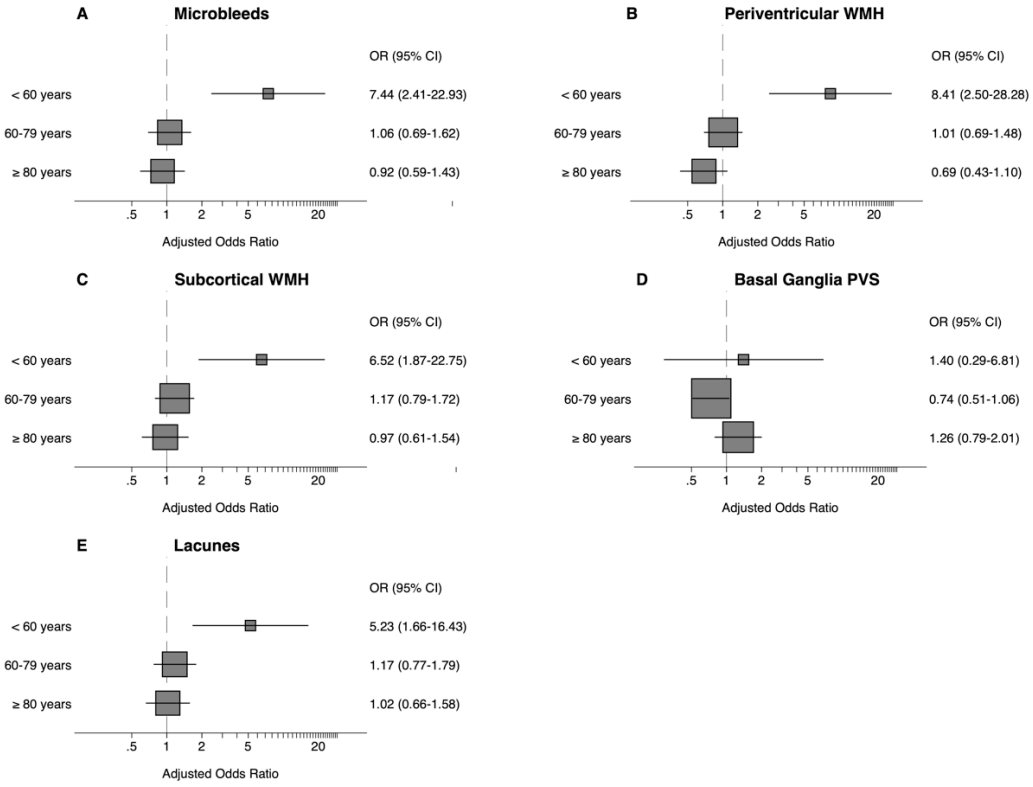
Table 10-4 Associations of CKD and the presence of individual small vessel disease markers stratified by age and adjusted for age/sex and for known vascular risk factors

	Crude		Model 1*		Model 2**	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
CEREBRAL MICROBLEEDS						
<60 y	7.96 (2.77-22.82)	<0.001	7.12 (2.44-20.81)	<0.001	7.44 (2.41-22.93)	<0.001
60-79 y	1.20 (0.80-1.79)	0.38	1.09 (0.72-1.65)	0.69	1.06 (0.69-1.62)	0.80
≥ 80 y	1.01 (0.67-1.54)	0.96	0.93 (0.60-1.42)	0.73	0.92 (0.59-1.43)	0.70
MODERATE TO SEVERE PERIVENTRICULAR WMH						
<60 y	10.17 (3.37-30.68	<0.001	8.98 (2.85-28.36)	<0.001	8.41 (2.50-28.28)	0.001
60-79 y	1.48 (1.04-2.10)	0.03	1.16 (0.80-1.67)	0.45	1.01 (0.69-1.48)	0.96
≥ 80 y	0.75 (0.49-1.17)	0.20	0.69 (0.44-1.09)	0.11	0.69 (0.43-1.10)	0.12
MODERATE TO SEVERE SUBCORTICAL WMH						
<60 y	9.02 (2.85-28.57)	<0.001	7.04 (2.16-22.96)	0.001	6.52 (1.87-22.75)	0.003
60-79 y	1.63 (1.14-2.32)	0.01	1.30 (0.90-1.89)	0.17	1.17 (0.79-1.72)	0.44
≥ 80 y	0.98 (0.63-1.52)	0.93	0.94 (0.60-1.48)	0.79	0.97 (0.61-1.54)	0.89
MODERATE TO SEVERE BASAL GANGLIA PVS (>10)						
<60 y	1.73 (0.38-7.89)	0.48	1.23 (0.26-5.72)	0.80	1.40 (0.29-6.81)	0.68
60-79 y	1.05 (0.75-1.47)	0.77	0.84 (0.59-1.19)	0.32	0.74 (0.51-1.06)	0.10
≥ 80 y	1.42 (0.91-2.20)	0.12	1.34 (0.85-2.11)	0.21	1.26 (0.79-2.01)	0.34
LACUNES						
<60 y	7.67 (2.60-22.58)	<0.001	5.80 (1.90-17.69)	0.002	5.23 (1.66-16.43)	0.01
60-79 y	1.42 (0.96-2.11)	0.08	1.33 (0.88-2.00)	0.18	1.17 (0.77-1.79)	0.46
≥ 80 y	1.09 (0.71-1.67)	0.69	1.09 (0.71-1.68)	0.69	1.02 (0.66-1.58)	0.93

CKD (defined as eGFR<60 mL/min/1.73m^2) indicates chronic kidney disease; CI, confidence interval; OR, odds ratio; PVS, perivascular spaces; WMH, white matter hyperintensity.
*Model I: adjusted for age, and sex;
**Model II: adjusted for age, sex, history of hypertension, diabetes mellitus, atrial fibrillation, ischaemic heart disease, smoking.

FIGURES

Figure 10-1 Associations of CKD (adjusted odds ratio and 95% CI) and the presence of individual small vessel disease markers stratified by age. Analyses were adjusted for age, sex, history of hypertension, diabetes mellitus, atrial fibrillation, ischaemic heart dis



CI indicates confidence interval; CKD, chronic kidney disease; CMB, cerebral microbleeds; eGFR, estimated glomerular filtration rate; PVS, perivascular spaces; and WMH, white matter hyperintensity.

Chapter 11 Associations of chronic kidney disease with dementia before and after transient ischaemic attack and stroke in a population-based cohort study

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11.1 Chapter outline

Individuals with chronic kidney disease (CKD) appear to have a greater risk of developing cognitive disorders than the general population. Both vascular and neurodegenerative hypotheses have been proposed to underlie this cognitive burden. To explore the vascular hypothesis further, I investigated the association between CKD and dementia before and after transient ischaemic attack (TIA) and stroke.

In a prospective, population-based cohort study of TIA and stroke (Oxford Vascular Study; 2002-2012), pre-event and new post-event dementia were ascertained through direct patient assessment and follow-up for 5 years, supplemented by review of hospital/primary care records. Associations between pre-dementia and CKD (defined as an estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73m^2) were examined using logistic regression, and between post-event dementia and CKD using both Cox and competing risk regression models, adjusted for age, sex, education, cerebrovascular burden (stroke severity, prior stroke, white matter disease), diabetes mellitus, and dysphasia.

Among 2305 TIA/stroke patients (median [IQR] age, 77 [67-84] years, 1174 [51%] male, 688 [30%] TIA), 1174 (50.9%) had CKD. CKD initially appeared to be associated with both pre-event (odds ratio [OR], 2.04 [95% CI: 1.52–2.72]; P<0.001) and post-event dementia (hazard ratio [HR], 2.01 [95% CI: 1.65–2.44]; P<0.001); however, these associations attenuated and became non-significant after adjustment for the above covariates (OR=0.92 [0.65-1.31]; p=0.65 and HR=1.09 [0.85-1.39]; p=0.50). The results were similar when a competing risk model was used (subdistribution HR [SHR] =1.74 [1.43-2.12]; p<0.001, attenuating to 1.01 [0.78-1.33]; p=0.92 with complete adjustment). CKD was more strongly associated with late (>1 year) post-event dementia (SHR=2.32, 1.70-3.17; p<0.001), particularly in the minor events subgroup (SHR=3.08, 2.05-4.64;

p<0.001), but not significantly so after complete adjustment (SHR=1.53, 0.90-2.60; p=0.12).

In patients with TIA and stroke, CKD was not independently associated with either pre- or post-event dementia, suggesting that age, sex, education, and cerebrovascular burden may play a more important role in the relationship than renal-specific neurodegenerative mechanisms.

11.2 Introduction

Chronic kidney disease (CKD) is associated with a significant burden of cognitive impairment that worsens with declining renal function.[1] In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study, each 10mL/min/1.73 m^2 decrease in eGFR <60 mL/min/ 1.73m^2 was associated with an 11% increase in prevalence of cognitive dysfunction.[2] Haemodialysis patients are three times more likely to have severe cognitive impairment than age-matched non-dialysis patients with reported prevalence rates of 37%.[3]

Both vascular and neurodegenerative hypotheses have been proposed to underlie CKD-related cognitive impairment.[4, 5] In support of the vascular hypothesis, there is a high prevalence of cardiovascular risk factors[6] and a strong, blood-pressure dependent association with stroke in CKD.[7] Furthermore, the pattern of cognitive change observed in these patients is prominent impairment of executive function and processing speed[8, 9] which is consistent with cognitive deficits associated with cerebrovascular disease.[10] However, CKD is also thought to augment potential neurodegenerative mechanisms through the interplay of hypertension and Alzheimer's pathology.[11] High concentrations of uraemic toxins such as neuroexcitatory guanidine compounds have also been implicated in CKD-related cognitive impairment as they have been found in strategic brain locations for cognition, such as the thalamus, mammillary bodies, and cerebral cortex.[12]

Therefore, it is currently unclear whether CKD is a risk factor for dementia independent of cerebrovascular disease. Silent cerebral infarctions may be prevalent in as many as 56% of patients with CKD[13, 14] and have been associated with vascular cognitive impairment.[15] However, CKD has previously been shown to be predictive of all-cause dementia independent of both previous symptomatic cerebrovascular disease and asymptomatic small vessel disease.[16]

Given these conflicting reports, using a large, longitudinal population-based study of all transient ischemic attack (TIA) and stroke with standardized assessment of confounders and follow-up for dementia to 5-years, I aimed to determine the associations between CKD and dementia before and after TIA and stroke, and how these associations vary depending on the severity of the initial event and the timing of dementia onset.

11.3 Methods

11.3.1 Patient cohort and eligibility

Consecutive patients with TIA or stroke were prospectively recruited from April 1, 2002 to March 31, 2012 from the Oxford Vascular Study (OXVASC), an ongoing population-based study of all acute vascular events (including TIA, stroke, acute coronary syndromes, and peripheral vascular events). The methodology of OXVASC is described in detail in section 4.3. along with the multiple methods of ascertainment used to ascertain patients with TIA or stroke.[17] Briefly, multiple overlapping methods of hot and cold pursuit were used to achieve near-complete ascertainment of all individuals with TIA or stroke and to minimize selection biases in determining dementia risk.[18] These included a daily, rapid access TIA clinic to which participating GPs and the local emergency department (ED) refer all individuals with unhospitalized TIA or stroke; daily searches of ward admissions (medical, cardiology, stroke unit, neurology), ED attendance register and in-hospital bereavement office death records; and monthly searches of death certificates, coroner's reports (for out-of-hospital deaths), GP and hospital diagnostic/discharge codes, and brain/vascular imaging referrals. Informed consent (or assent from relatives) was obtained for study interview and follow-up, including ongoing review of all primary care/hospital records and death certificates.

11.3.2 Baseline data collection

Patients were assessed by a study physician as soon as possible after their TIA/stroke. TIA and stroke were defined using the World Health Organization criteria[19] (i.e. patients with relevant infarction on brain imaging but focal neurological symptoms lasting <24 hours were classed as TIA) with review of all cases by the same senior (vascular) neurologist (P.M. Rothwell) throughout the study. A detailed clinical history was recorded in all patients by interview using a standardized questionnaire including education, medical history and vascular risk factors were recorded in all patients, supplemented by primary care records. Premorbid functional status was assessed using modified Rankin and Barthel scores, and stroke severity assessed with the National Institutes of Health Stroke Scale (NIHSS) score. Baseline brain and vascular imaging and other investigations were performed as reported previously.[17, 20]

As outlined in section 4.3.4, CKD was defined as eGFR less than 60 mL/min/1.73 m^2 for three or more months as per 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.[21] eGFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI). eGFR was then categorized into 5 groups based on modified CKD classification by the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative: eGFR ≥ 90, 60-89, 30-59, 15-30 and <15 ml/min/1.73m^2. For the purpose of statistical analysis, eGFR ≥ 60 ml/min/1.73m^2 was used as the reference, as there were no post-stroke dementia events for eGFR ≥ 90 ml/min/1.73m^2 in some of the subgroup analyses. Similarly, the eGFR 15-30 and <15 ml/min/1.73m^2 groups were combined as the individual numbers within each group were small.

11.3.3 Brain imaging and white matter disease severity grading

In the early years of the OXVASC study, computed tomography (CT) was the default baseline brain imaging modality. In later periods, magnetic resonance imaging (MRI) was used. Therefore, methodology was developed to define the severity of leukoaraiosis in a reproducible manner whether the patient had received CT or MR brain imaging.[22] Leukoaraiosis was prospectively and independently coded by a neuroradiologist and by an experienced neurologist. Assessments were made blind to clinical data.

Leukoaraiosis was graded according a qualitative scale ("Oxford scale") based on the severity score (absent, mild, moderate, or severe) of the Blennow scale for CT scans, and a modified version of the Fazekas scale, considering periventricular and deep white matter lesions altogether, for MRI scans. Within the OXVASC cohort, the inter-rater agreement on presence and severity of leukoaraiosis on CT was assessed by κ statistics in a subset of 996 consecutive cases and for MRI on 100 cases. An agreement study between CT and MRI was also performed in the 416 patients who had had both modalities of imaging, using the SAS software to calculate both simple and weighted κ.

The inter-rater agreement on presence of leukoaraiosis in 996 consecutive cases imaged by CT and rated by the Oxford scale was moderate to good (κ = 0.64, 0.59–0.69, for presence of any leukoaraiosis, and 0.58, 0.55–0.62 for severity). The inter-rater agreement on presence of leukoaraiosis in 100 consecutive cases imaged by MRI and rated by the Oxford scale was also good (κ = 0.78, 0.65–0.90 for presence and 0.66, 0.56–0.76 for severity of leukoaraiosis). In the 416 patients who had both CT and MRI, agreement between independent assessments made on the different modalities was not significantly less than the interobserver reproducibilities of either modality alone. Therefore, intra- and inter-rater reproducibility for both CT and MRI evaluations of leukoaraiosis was good as well as the concordance between the MRI and CT data.

11.3.4 Follow-up methodology and dementia diagnosis

Multiple methods of follow-up were used to reduce attritional biases in identification of dementia.[23] Follow-up interviews were done by trained nurses or study physicians at 1 month, 6 months, 1 year, and 5 years. If follow-up at a clinic was not possible, patients were assessed at home or via telephone. Cognitive function was tested with the mini-mental-state-examination (MMSE)[24] and Montreal Cognitive Assessment[25] at face-to-face interviews and with the telephone version of the Montreal Cognitive Assessment and the Telephone Interview for Cognitive Status-modified during telephone follow-up.[26, 27]

Dementia was defined as pre- or post-event according to whether the diagnosis was made before or after the index event, as described previously.[18, 23, 28, 29] Briefly, pre-event dementia diagnosis was made using the following information: (1) baseline clinical assessment by study physician and discussion with relatives or other informant; (2) the presence of any dementia diagnosis, and related consultations and investigations, where available, in the primary care record, with hand-searching of the entire record including individual consultations, clinic letters, and hospitalization documentation. The diagnosis of pre-event dementia was made by an experienced consultant physician/geriatrician with subspecialty interest in dementia (S.T. Pendlebury) using the Diagnostic and Statistical Manual-IV criteria after review of the baseline clinical assessment and the medical records.

In patients without pre-event dementia, post-event dementia was diagnosed by S.T. Pendlebury using the same methodology (i.e. with baseline and follow-up clinical and cognitive assessment data, supplemented by hand-searching of primary care records to death or 5-years' follow-up).[18, 23, 28, 29] MMSE was done at each follow-up interview, and

dementia was diagnosed if MMSE was <24 and remained <24 for all subsequent follow-ups.[18, 23, 28, 29] In patients who had problems that interfered with testing (e.g. dysphasia), incomplete testing (e.g. because of blindness), were followed up by telephone, could not be tested at the study interview (e.g. because of severe deafness) follow-up, or who did not have a follow-up assessment, dementia was diagnosed on the basis of study records where available and hand-searching of primary care, hospital and death records, based on Diagnostic and Statistical Manual-IV criteria.[18, 23, 28, 29]

11.3.5 Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the cohort stratified by CKD status. Continuous data were given as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate, categorical data were given as n (%). Mann-Whitney U tests and Chi-squared tests were used to test the significance of differences between two groups for continuous and categorical variables respectively.

Associations between CKD and pre-event dementia were determined by binary logistic regression to generate ORs adjusted for (1) age, sex, and education (model 1) and (2) age, sex, education, and other factors previously reported as associated with pre-event dementia,[29] including white matter disease, prior stroke, diabetes mellitus, and also index stroke event severity (NIHSS) and dysphasia occurring after the index stroke (model 2).

All analyses involving post-event dementia were done after exclusion of cases of pre-event dementia. Cumulative incidence of dementia post-event was calculated by Kaplan-Meier methods censoring at death as described previously.[29] After testing that the proportional hazards assumption was met, Cox regression was used to determine hazard ratios (HRs) for associations between overall 5-year risk of post-event dementia, and separately for early (≤1 year) and late (>1 year) post-event dementia (patients with late

dementia were excluded from analyses of early dementia and vice versa). Regression analyses were adjusted (1) for age, sex, and education (model 1), (2) age, sex, education, and other factors reported as associated with dementia after TIA/stroke,[29] including stroke severity (NIHSS), white matter disease, dysphasia, prior stroke, and diabetes mellitus, and (3) with further adjustment for baseline cognitive test score (model 3). Similar analyses were done restricted to TIA and minor stroke (defined as NIHSS <3 as per OxVASC protocol) and major stroke (NIHSS ≥3).[29]

I did not examine primary intracerebral hemorrhage (PICH) separately owing to small numbers with this stroke subtype, but we undertook sensitivity analyses for pre- and post-event dementia in which PICH was excluded. I performed further sensitivity analyses excluding recurrent stroke on follow-up in analyses of post-event dementia.

Given that death is a competing risk for dementia (i.e. it precludes its occurrence), I performed exploratory analyses using competing risks regressions using cumulative incidence function (CIF) covariate analysis, similarly adjusted for the above covariates, to study the overall associations of CKD with post-event dementia and according to onset, early versus late post-event dementia.[33] From these regressions, I generated subdistribution hazard ratios (SHRs) for comparison as these are thought to be more informative of risk or prognosis whereas standard (cause-specific) HRs are thought to be better indicators of aetiology.[34]

Results were considered significant at $p < 0.05$. Statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL) and Stata version 13 (Stat Corp., College Station, TX).

11.4 Results

Of 2305 patients recruited from 2002-2012, 1133 (49%) were male, 688 (30%) had TIA, and 1617 (70%) had stroke of which 1482 were ischaemic stroke, and 135 were primary intracerebral haemorrhage (PICH). Table 11-1 shows the baseline characteristics at the time of the event for all patients and according to CKD status. The median age was 76.9 years (IQR=66.9-83.9) and hypertension was the most prevalent risk factor being found in 1405 individuals (61%).

The median eGFR was 59.5 ml/min/1.73m^2. 1174 patients had CKD (50.9% of the study population). 169 patients (7.4%) had an eGFR≥90 ml/min/1.73m^2, 956 (41.6%) 60-89 ml/min/1.73m^2, 1040 (45.2%) 30-59 ml/min/1.73m^2, 134 (5.8%) <30 ml/min/1.73m^2. Only 12 patients (0.5%) were dialysis-dependent. Compared to those with normal renal function, the CKD group were older and had a significantly higher burden of vascular risk factors and co-morbidities including hypertension, diabetes mellitus, hyperlipidaemia, ischaemic heart disease, peripheral vascular disease, atrial fibrillation, and prior stroke. Individuals with CKD were also more likely to have moderate-to-severe white matter disease, to be less well-educated, and to have a low baseline cognitive score.

Pre-event dementia was present in 225/2305 (9.8%) of patients. Compared with those with normal renal function, CKD was strongly associated with pre-event dementia in the unadjusted analysis (OR=2.04, 95% CI=1.52-2.72; p<0.001) (Table 11-2). This association increased with declining renal function (unadjusted OR=3.21, 1.96-5.26; p<0.001 for eGFR < 30 ml/min/1.73m^2). However, all associations between renal function and pre-event dementia completely attenuated and became non-significant after adjustment for age, sex and education (model 1). After additional adjustment for other factors associated with pre-event dementia (model 2), there was further diminution of any

previous association with CKD (adjusted OR= 0.92, 0-65-1.31; p=0.65; Table 11-2). Exclusion of PICH did not impact the results (Table 11-2). Stratifying by event severity, showed broadly similar associations (Table 11-2).

Excluding those with pre-event dementia, during 7,721 patient-years of follow-up (median/IQR=4.2/1.5-5.5), 432 patients developed dementia (mean/sd age 82.1/8.7 years at diagnosis). There was a significantly greater risk of post-event dementia in patients with CKD compared to those with normal renal function (Log-rank p <0.001; Figure 11-1). However, although in unadjusted Cox regression analysis, CKD was strongly associated with post-event dementia to 5-years follow-up (HR=2.01, 1.65-2.44; p<0.001 for all CKD), this association also diminished and became non-significant after adjustment for age, sex and education, and other factors associated with post-event dementia (model 3 OR=1.09, 0.85-1.39; p=0.50) (Table 11-3). Results were similar when PICH was excluded and when the 194 patients with recurrent stroke on follow-up, were excluded (Table 11-3). Looking separately at early (≤1 year) versus late (>1 year) post-event dementia, CKD was overall more strongly associated with late vs early post-event dementia (HR=2.63, 1.96-3.53, p<0.001 vs 1.60, 1.23-2.09, p=0.001) (Table 11-4). Associations were lost after adjustment for age, sex and education (model 1) and after additional adjustment for other factors associated with post-event dementia (model 3, HR=1.40, 0.98-2.00, p=0.06 for late dementia vs 0.90, 0.64-1.28, p=0.57 for early dementia).

The results were qualitatively and quantitatively similar when analyses were then repeated using competing risk regressions (Table 11-5 and Table 11-6). CKD was again associated with post-event stroke in the unadjusted model (SHR=1.74, 1.43-2.12; p<0.001) but not in the multivariate-adjusted models (SHR=0.97, 0.79-1.20; p=0.77, 0.94, 0.76-1.17; p=0.60; and 1.01, 0.78-1.33; p=0.92, for models 1, 2 and 3, respectively) (Table 11-5). The crude associations between eGFR categories and post-event dementia were lower than those from the cause-specific hazards model, particularly for eGFR < 30

ml/min (SHR=1.51, 0.98-2.30 vs HR=2.48, 1.62-3.78). However, as per the cause-specific models, there were no independent associations between specific eGFR categories and post-event dementia after multivariate adjustment (Table 11-5). Restricting analysis to only ischaemic or major stroke events produced similar results. Competing risk analysis for early (≤1 year) versus late (>1 year) post event dementia is shown in Table 11-6 where CKD is again more strongly associated with later events (SHR=2.32, 1.70-3.17; p<0.001 vs 1.42, 1.10-1.83; p=0.01) but the association did not quite reach significance after complete adjustment (SHR=1.47, 0.99-2.18; p=0.06). CKD was particularly associated with late post-event dementia in the TIA and minor stroke subgroup (SHR=3.08, 2.05-4.64; p<0.001), attenuating with adjustment for age, sex, education, stroke severity, prior stroke, white matter disease, diabetes, and dysphasia (SHR=1.70, 1.05-2.76; p=0.03), and with additional adjustment for baseline cognitive score (SHR=1.53, 0.90-2.60; p=0.12).

11.5 Discussion

In a large, prospective, population-based cohort study, CKD was not independently associated with either pre- or post-event dementia in patients with TIA and stroke. Associations were greatly attenuated after adjustment for age, sex, education, and other factors previously shown to be associated with dementia including stroke severity and white matter disease,[29] suggesting that renal-specific neurodegenerative mechanisms are unlikely to play an important role in the relationship between CKD and dementia. However, the consistently higher prevalence rates of pre- and post-event dementia in CKD patients does identify them as a vulnerable group.

Although CKD has been consistently associated with an increased risk of cognitive decline,[2, 30, 31] I did not find a strong independent association with dementia in this study, even at greater levels of renal dysfunction or when restricted to major stroke events.

There a number of potential explanations for this discordance. Firstly, most of the cognitive studies to date have focused on the relationship between CKD and mild cognitive impairment (MCI) rather than dementia.[32-34] Secondly, in contrast to our study, where most patients had pre-dialysis CKD and the majority had stage 3 (mild) CKD, the dementia studies that have been published to date have been mainly dialysis-based.[35-37] Dialysis patients have unique additional risk factors intrinsic to the dialysis procedure including cerebral hypoperfusion[38] and this intradialytic hemodynamic instability causes transient 'cerebral stunning', leading to cumulative ischemic white matter changes and cognitive changes over time.[38 39] Thirdly, although I did not find an association between those with more advanced CKD and dementia, this is in keeping with the literature that suggests that it is the duration of kidney disease or the rate of eGFR decline that better correlates with cognitive dysfunction rather than the severity.[40, 41]

To date, the mechanisms underlying the pathogenesis of MCI and dementia in CKD have been poorly understood. It has been proposed that uraemic neurotoxins interacting with neural progenitor cells, the brain vasculature, the glymphatic system and monoaminergic neurons may play a role.[42] High concentrations of uraemic toxins such as tumour necrosis factor (TNF) can impair synapse function and memory.[43] The glymphatic clearance of waste products occurs primarily during sleep[44] and CKD is associated with sleep disorders.[45] In addition, high levels of the circulating phosphaturic hormone fibroblast growth factor 23 (FGF-23), often found in CKD, have been associated with incident dementia.[46] However, the absence of an independent association between CKD and dementia in this cohort of TIA/stroke patients implicates vascular disease as the main mediator of this relationship. Consistent with this hypothesis, any associations present were greater for late (>1 year) post-event dementia rather than early (<1 year) post-event dementia, particularly in the TIA and minor stroke subgroup. Up to half of new vascular dementia cases occur more than one year after stroke related to new, recurrent strokes, or progressive cerebral small vessel disease (SVD).[47] Severe SVD has been implicated

as the most important mechanism in late post-stroke dementia[48] and is strongly associated with CKD, especially at younger ages.[49]

In addition to the large study size, population-based design, and comprehensive adjustment for potential confounders, a further strength of this study is the inclusion of a competing risk analysis to account for the risk of death - the importance of which is being increasingly recognized in survival analyses of CKD given the high baseline mortality rate.[37, 50, 51] The results from the competing risk analysis were qualitatively and quantitatively similar to those from the Cox (cause-specific) proportional hazards model with the exception of the associations between advanced CKD (eGFR < 30 ml/min/1.73m^2) and post-event dementia which decreased. This likely reflects the stronger association between advanced CKD and the competing event (i.e. death) resulting in lower SHRs than expected.[52] A previous study similarly found that dialysis was associated with a lower cumulative risk for developing dementia from the subdistribution hazard models compared to the Cox models, suggesting a lower risk for the occurrence of dementia over time because of premature mortality.[37]

This study has a number of limitations. Firstly, TIA/stroke and dementia diagnoses were adjudicated by P.M. Rothwell and S.T. Pendlebury, respectively, rather than by a consensus panel but this ensured consistency diagnostic methodology over the 15-year time period of this study. Secondly, pre-event dementia was retrospectively diagnosed but the use of multiple sources should have minimised misclassification bias. Thirdly, I did not study the relationship between CKD and specific subtypes of dementia because clinical classification is challenging in older patients and mixed pathology is the most common finding in neuropathological studies.[53] Moreover, most dementia occurring after stroke is coded as being of “unspecified” cause in routine practice.[35] Fourthly, I was unable to measure urine albumin excretion which is potentially an important omission in terms of understanding the mechanisms of cognitive dysfunction in CKD since some studies

suggest that albuminuria is more strongly and independently associated with cognitive dysfunction than eGFR.[54, 55] Fifthly, as GFR was estimated from serum creatinine, this can lead to an overestimation of GFR in those with low muscle mass.[56] Since muscle mass loss is also associated with cognitive decline,[57] this may have underestimated the effect size of any association between CKD and cognitive decline. This study should be replicated using GFR estimated from cystatin-C molecule independent of muscle mass,[58] which may increase precision of eGFR equations and it has also been shown to colocalize with beta-amyloid in the brain.[59]

In conclusion, dementia is more common in patients with CKD than in the general population but CKD itself appears not to be independently associated with either pre- or post-stroke dementia, except possibly with late-onset dementia in those with minor stroke events. Patients with CKD appear to have a clustering of risk factors associated with dementia including pre-stroke factors (advanced age, diabetes, and atrial fibrillation), stroke factors (greater event severity, dysphasia, and disability), and lower brain reserve (low education, pre-morbid dependency, and leukoareosis) that likely mediate much of the relationship between CKD and dementia. Further studies are needed to determine if there are additional unique mechanisms or pathways leading to late-onset dementia in those with CKD and minor stroke events.

11.6 References

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TABLES

Table 11-1 Baseline characteristics of all patients with TIA and stroke, and stratified according to the presence of CKD

Characteristics*	All patients n= 2305	No CKD n= 1125	CKD present n= 1174	P value
Age years, median (IQR)	76.9 (66.9-83.9)	69.9 (59.6-79.3)	81.4 (74.4-86.2)	<0.001
Age ≥ 75 years	1281 (55.6)	418 (37.2)	859 (73.2)	<0.001
Male sex	1133 (49.2)	659 (58.6)	474 (40.4)	<0.001
eGFR (ml/min/1.73m^2), median (IQR)	59.5 (46.3-73.5)	74.0 (66.7-84.1)	46.6 (38.2-53.6)	<0.001
Previous history of hypertension	1405 (61)	589 (52.4)	814 (69.3)	<0.001
Previous history of diabetes mellitus	328 (14.2)	142 (12.6)	186 (15.8)	0.03
Previous history of hyperlipidaemia	683 (29.6)	299 (26.6)	384 (32.7)	0.002
Previous history of angina	371 (16.1)	128 (11.4)	243 (20.7)	<0.001
Previous history of MI	256 (11.1)	82 (7.3)	174 (14.8)	<0.001
Previous history of PVD	178 (7.7)	61 (5.4)	117 (10)	<0.001
Previous history of atrial fibrillation	469 (20.3)	150 (13.3)	319 (27.2)	<0.001
Current smoking	323 (14.1)	232 (20.7)	91 (7.8)	<0.001
Prior stroke	274 (11.9)	95 (8.4)	177 (15.1)	<0.001
Moderate/severe WMD	699 (32.7)	287 (26.8)	411 (38.6)	<0.001
Event Type				0.02
TIA	688 (29.8)	357 (31.7)	330 (28.1)	
Ischaemic stroke	1482 (64.3)	693 (61.6)	786 (67)	
Primary ICH	135 (5.9)	75 (6.7)	58 (4.9)	
NIHSS, median (IQR)	1 (0-5)	1 (0-4)	1 (0-5.1)	<0.001
Dysphasia	402 (17.5)	166 (14.8)	234 (20.1)	0.001
Education ≤ 12 years	1543 (67)	715 (63.6)	826 (70.4)	0.001
Rankin ≥ 3	473 (20.5)	151 (13.4)	321 (27.4)	<0.001
Barthel < 20	481 (20.9)	163 (15.5)	317 (30.8)	<0.001
Low baseline cognitive score	354 (20.7)	136 (15.5)	217 (26.1)	<0.001
Pre-event dementia	225 (9.8)	75 (6.7)	149 (12.7)	<0.001
Post-event dementia	432 (20.8)	158 (15)	273 (26.6)	<0.001
Post-event dementia, early	450 (19.5)	169 (15)	279 (23.8)	<0.001
Post-event dementia, late	657 (28.5)	233 (20.7)	422 (35.9)	<0.001
Time to death, y, median (IQR)	2.8 (0.9-5.5)	3.7 (1.5-5.5)	2.4 (0.4-5.5)	<0.001
Death < 31 days	255 (11.1)	71 (6.3)	180 (15.3)	<0.001

*Numbers are n (%) unless otherwise stated. CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; PVD, peripheral vascular disease; TIA, transient ischaemic attack; WMD, white matter disease

Table 11-2 Odds ratio for pre-event dementia according to CKD status and eGFR category

OR (95% CI)						
	Unadjusted	**P Value**	**Model 1***	**P Value**	**Model 2****	**P Value**
All patients, N=2305						
No CKD (eGFR≥60)	1.00		1.00		1.00	
CKD (eGFR < 60)	2.04 (1.52-2.72)	<0.001	1.02 (0.74-1.40)	0.91	0.92 (0.65-1.31)	0.65
eGFR≥60	1.00		1.00		1.00	
eGFR 30-59	1.90 (1.40-2.56)	<0.001	0.96 (0.70-1.33)	0.81	0.88 (0.61-1.26)	0.48
eGFR < 30	3.21 (1.96-5.26)	<0.001	1.49 (0.88-2.52)	0.14	1.24 (0.88-2.52)	0.14
Excluding PICH, N=2170						
No CKD (eGFR≥60)	1.00		1.00		1.00	
CKD (eGFR < 60)	2.00 (1.48-2.69)	<0.001	1.00 (0.72-1.38)	1.00	0.89 (0.62-1.28)	0.54
eGFR≥60	1.00		1.00		1.00	
eGFR 30-59	1.85 (1.36-2.51)	<0.001	0.94 (0.67-1.31)	0.71	0.85 (0.58-1.24)	0.40
eGFR < 30	3.20 (1.95-5.27)	<0.001	1.49 (0.88-2.53)	0.14	1.17 (0.65-2.12)	0.60
TIA and minor stroke only, N=1436						
No CKD (eGFR≥60)	1.00		1.00		1.00	
CKD (eGFR < 60)	2.47 (1.53-3.98)	<0.001	1.06 (0.64-1.77)	0.82	0.97 (0.55-1.71)	0.91
eGFR≥60	1.00		1.00		1.00	
eGFR 30-59	2.46 (1.51-3.99)	<0.001	1.06 (0.63-1.78)	0.82	0.96 (0.54-1.71)	0.89
eGFR < 30	2.62 (0.97-7.11)	0.06	1.07 (0.38-3.03)	0.91	1.07 (0.33-3.43)	0.91
Major stroke (NIHSS ≥3) only, N=869						
No CKD (eGFR≥60)	1.00		1.00		1.00	
CKD (eGFR < 60)	1.57 (1.08-2.29)	0.02	0.99 (0.66-1.50)	0.98	0.88 (0.56-1.38)	0.57
eGFR≥60	1.00		1.00		1.00	
eGFR 30-59	1.44 (0.97-2.13)	0.07	0.92 (0.60-1.40)	0.68	0.80 (0.50-1.29)	0.36
eGFR < 30	2.38 (1.31-4.31)	0.004	1.49 (0.79-2.79)	0.22	1.29 (0.65-2.56)	0.47

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; OR, odds ratio; NIHSS, National Institutes of Health Stroke Scale; PICH, primary intracerebral haemorrhage.

*Model 1: adjusted for age, sex, education

**Model 2: adjusted for the variables in model 1 + stroke severity, prior stroke, white matter disease, diabetes mellitus, dysphasia

Table 11-3 Hazard ratios for 5-year incidence of post-event dementia according to CKD status and eGFR category

HR (95% CI)								
	Unadjusted	**P Value**	**Model 1 ***	**P Value**	**Model 2****	**P Value**	**Model 3*****	**P Value**
All patients, N=2080								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.01 (1.65-2.44)	<0.001	0.97 (0.79-1.19)	0.78	1.03 (0.83-1.28)	0.78	1.09 (0.85-1.39)	0.50
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.97 (1.61-2.41)	<0.001	0.96 (0.78-1.18)	0.70	1.02 (0.82-1.26)	0.88	1.08 (0.85-1.39)	0.53
eGFR < 30	2.48 (1.62-3.78)	<0.001	1.11 (0.72-1.70)	0.63	1.20 (0.77-1.86)	0.43	1.15 (0.69-1.92)	0.58
Excluding PICH, N=1954								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.08 (1.70-2.55)	<0.001	1.01 (0.81-1.24)	0.96	1.08 (0.87-1.35)	0.48	1.13 (0.88-1.45)	0.34
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.04 (1.66-2.51)	<0.001	0.99 (0.80-1.23)	0.94	1.07 (0.85-1.34)	0.57	1.12 (0.87-1.45)	0.37
eGFR < 30	2.59 (1.69-3.96)	<0.001	1.17 (0.76-1.79)	0.49	1.26 (0.81-1.96)	0.31	1.19 (0.71-1.98)	0.51
Excluding recurrent stroke on follow-up, N= 1607								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.26 (1.77-2.89)	<0.001	1.05 (0.81-1.35)	0.74	1.12 (0.86-1.47)	0.40	1.11 (0.81-1.51)	0.52
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.23 (1.74-2.86)	<0.001	1.04 (0.80-1.35)	0.77	1.12 (0.85-1.47)	0.42	1.13 (0.83-1.54)	0.45
eGFR < 30	2.68 (1.56-4.60)	<0.001	1.10 (0.64-1.91)	0.73	1.15 (0.65-2.04)	0.63	0.83 (0.40-1.75)	0.63
TIA and minor stroke only, N=1354								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.92 (2.16-3.95)	<0.001	1.26 (0.92-1.72)	0.15	1.32 (0.95-1.84)	0.10	1.20 (0.84-1.72)	0.31
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.89 (2.12-3.92)	<0.001	1.25 (0.91-1.72)	0.17	1.32 (0.95-1.84)	0.10	1.22 (0.86-1.75)	0.27
eGFR < 30	3.36 (1.81-6.25)	<0.001	1.32 (0.71-2.48)	0.38	1.32 (0.68-2.56)	0.41	0.98 (0.47-2.05)	0.96
Major stroke (NIHSS ≥3) only, N=726								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.38 (1.06-1.79)	0.02	0.79 (0.60-1.05)	0.10	0.86 (0.65-1.14)	0.30	0.97 (0.69-1.36)	0.85
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.34 (1.03-1.76)	0.03	0.78 (0.59-1.04)	0.09	0.82 (0.61-1.09)	0.17	0.94 (0.67-1.33)	0.73
eGFR < 30	1.74 (0.98-3.11)	0.06	0.95 (0.53-1.71)	0.86	1.07 (0.59-1.93)	0.84	1.29 (0.63-2.64)	0.49

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazards ratio; NIHSS, National Institutes of Health Stroke Scale; PICH, primary intracerebral haemorrhage.

*Model 1: adjusted for age, sex, education **Model 2: adjusted for the variables in model 1 + stroke severity, prior stroke, white matter disease, diabetes mellitus, dysphasia

***Model 3: adjusted for the variables in model 2 + baseline cognitive score

Table 11-4 Hazard ratio for early (≤1 year) and late (>1 year) post-event dementia in patients with CKD

HR (95% CI)								
	Unadjusted	**P Value**	**Model 1 ***	**P Value**	**Model 2****	**P Value**	**Model 3*****	**P Value**
All patients, N=2080								
Early Postevent Dementia (≤1 Year)								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.60 (1.23-2.09)	0.001	0.79 (0.60-1.04)	0.09	0.88 (0.66-1.17)	0.37	0.90 (0.64-1.28)	0.57
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.55 (1.18-2.03)	0.002	0.76 (0.58-1.01)	0.06	0.86 (0.64-1.15)	0.31	0.89 (0.63-1.27)	0.52
eGFR < 30	2.24 (1.30-3.88)	0.004	1.06 (0.61-1.84)	0.84	1.06 (0.60-1.88)	0.85	1.05 (0.51-2.16)	0.89
Late Postevent Dementia (>1 Year)								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.63 (1.96-3.53)	<0.001	1.33 (0.98-1.82)	0.07	1.34 (0.96-1.86)	0.08	1.40 (0.98-2.00)	0.06
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.62 (1.94-3.53)	<0.001	1.34 (0.98-1.84)	0.07	1.33 (0.95-1.86)	0.09	1.40 (0.98-2.01)	0.07
eGFR < 30	2.72 (1.40-5.29)	0.003	1.25 (0.64-2.47)	0.51	1.42 (0.72-2.82)	0.32	1.41 (0.68-2.92)	0.36

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio

*Model 1: adjusted for age, sex, education

**Model 2: adjusted for the variables in model 1 + stroke severity, prior stroke, white matter disease, diabetes mellitus, dysphasia

***Model 3: adjusted for the variables in model 2 + baseline cognitive score

Table 11-5 Subdistribution hazard ratios (HR) for 5-year incidence of post-event dementia accounting for the competing risk of death, according to CKD status and eGFR category

Subdistribution HR (95% CI)								
	Unadjusted	**P Value**	**Model 1***	**P Value**	**Model 2****	**P Value**	**Model 3*****	**P Value**
All patients, N=2080								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.74 (1.43-2.12)	<0.001	0.97 (0.79-1.20)	0.77	0.94 (0.76-1.17)	0.60	1.01 (0.78-1.33)	0.92
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.77 (1.45-2.16)	<0.001	0.99 (0.80-1.23)	0.96	0.97 (0.78-1.21)	0.80	1.03 (0.79-1.35)	0.82
eGFR < 30	1.51 (0.98-2.30)	0.06	0.76 (0.48-1.20)	0.24	0.70 (0.43-1.13)	0.14	0.85 (0.48-1.51)	0.57
Excluding PICH, N=1954								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.79 (1.46-2.19)	<0.001	0.97 (0.78-1.21)	0.81	0.96 (0.76-1.20)	0.71	1.03 (0.78-1.36)	0.83
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.82 (1.48-2.23)	<0.001	0.99 (0.80-1.25)	1.00	0.99 (0.79-1.25)	0.95	1.05 (0.79-1.39)	0.34
eGFR < 30	1.57 (1.02-2.41)	0.04	0.76 (0.48-1.21)	0.25	0.68 (0.41-1.11)	0.12	0.85 (0.47-1.52)	0.58
TIA and minor stroke only, N=1354								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.74 (2.04-3.69)	<0.001	1.28 (0.93-1.76)	0.13	1.32 (0.94-1.84)	0.11	1.20 (0.83-1.73)	0.34
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.75 (2.03-3.71)	<0.001	1.29 (0.93-1.78)	0.12	1.32 (0.94-1.86)	0.10	1.22 (0.84-1.76)	0.29
eGFR < 30	2.72 (1.45-5.08)	0.002	1.16 (0.60-2.25)	0.66	1.21 (0.60-2.44)	0.59	0.94 (0.41-2.12)	0.88
Major stroke (NIHSS ≥3) only, N=726								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.01 (0.77-1.31)	0.95	0.73 (0.55-0.96)	0.03	0.71 (0.53-0.94)	0.02	0.86 (0.59-1.24)	0.41
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	1.06 (0.81-1.39)	0.67	0.77 (0.58-1.02)	0.07	0.75 (0.56-1.00)	0.05	0.86 (0.59-1.26)	0.44
eGFR < 30	0.70 (0.39-1.26)	0.24	0.50 (0.27-0.92)	0.03	0.48 (0.26-0.89)	0.02	0.79 (0.37-1.71)	0.55

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale; PICH, primary intracerebral haemorrhage.

*Model 1: adjusted for age, sex, education

**Model 2: adjusted for the variables in model 1 + stroke severity, prior stroke, white matter disease, diabetes mellitus, dysphasia

***Model 3: adjusted for the variables in model 2 + baseline cognitive score

Table 11-6 Subdistribution hazard ratio (HR) for early (≤1 year) and late (>1 year) post-event dementia in patients with CKD accounting for the competing risk of death

Subdistribution HR (95% CI)								
	Unadjusted	**P Value**	**Model 1***	**P Value**	**Model 2****	**P Value**	**Model 3*****	**P Value**
All patients, N=2080								
Early Postevent Dementia (≤1 Year)								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	1.42 (1.10-1.83)	0.01	0.74 (0.57-0.97)	0.03	0.70 (0.53-0.92)	0.01	0.75 (0.53-1.06)	0.10
eGFR≥60	1.41 (1.09-1.84)	0.01	0.75 (0.57-0.98)	0.03	0.72 (0.54-0.95)	0.02	0.75 (0.53-1.07)	0.11
eGFR 30-59	1.46 (0.85-2.52)	0.17	0.70 (0.39-1.23)	0.21	0.55 (0.30-1.04)	0.06	0.71 (0.33-1.53)	0.38
eGFR < 30	1.42 (1.10-1.83)	0.01	0.74 (0.57-0.97)	0.03	0.70 (0.53-0.92)	0.01	0.75 (0.53-1.06)	0.10
TIA and minor stroke only								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.38 (1.54-3.69)	<0.001	1.05 (0.67-1.66)	0.82	0.99 (0.63-1.55)	0.96	0.92 (0.56-1.51)	0.73
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.29 (1.47-3.59)	<0.001	1.02 (0.64-1.62)	0.93	0.97 (0.61-1.54)	0.90	0.90 (0.54-1.50)	0.69
eGFR < 30	3.38 (1.49-7.68)	0.004	1.42 (0.61-3.33)	0.42	1.20 (0.48-3.00)	0.70	1.11 (0.40-3.09)	0.84
Late Postevent Dementia (>1 Year)								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	2.32 (1.70-3.17)	<0.001	1.47 (1.04-2.07)	0.03	1.46 (1.02-2.09)	0.04	1.47 (0.99-2.18)	0.06
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	2.41 (1.76-3.30)	<0.001	1.53 (1.08-2.15)	0.02	1.50 (1.05-2.15)	0.03	1.49 (1.00-2.23)	0.05
eGFR < 30	1.61 (0.82-3.14)	0.16	0.94 (0.46-1.91)	0.86	1.05 (0.51-2.15)	0.90	1.17 (0.54-2.56)	0.69
TIA and minor stroke only								
No CKD (eGFR≥60)	1.00		1.00		1.00		1.00	
CKD (eGFR < 60)	3.08 (2.05-4.64)	<0.001	1.57 (1.00-2.46)	0.05	1.70 (1.05-2.76)	0.03	1.53 (0.90-2.60)	0.12
eGFR≥60	1.00		1.00		1.00		1.00	
eGFR 30-59	3.17 (2.10-4.78)	<0.001	1.61 (1.03-2.53)	0.04	1.74 (1.07-2.82)	0.02	1.59 (0.93-2.71)	0.09
eGFR < 30	2.15 (0.84-5.45)	0.11	1.04 (0.39-2.80)	0.93	1.26 (0.46-3.39)	0.65	0.86 (0.26-2.80)	0.80

CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

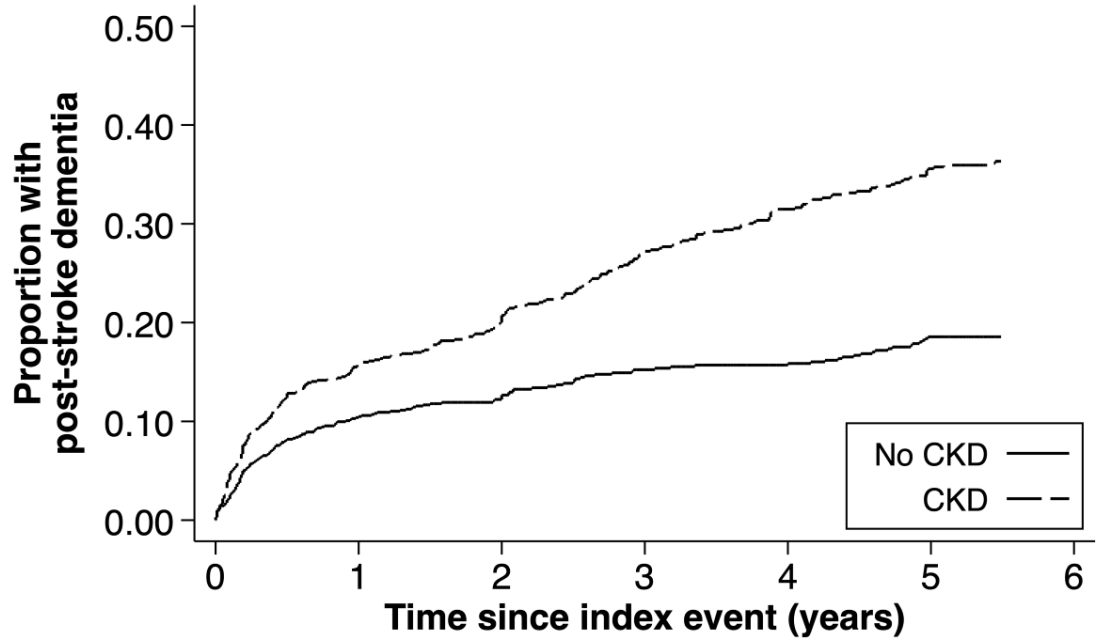
*Model 1: adjusted for age, sex, education

**Model 2: adjusted for the variables in model 1 + stroke severity, prior stroke, white matter disease, diabetes mellitus, dysphasia

***Model 3: adjusted for the variables in model 2 + baseline cognitive score

FIGURES

Figure 11-1 Kaplan-Meier (1-survival) curve showing the cumulative incidence of new post-event dementia (excluding pre-event dementia) for all patients (with and without CKD) to 5-years follow-up.



Number at risk

CKD	1050	847	597	546	518	468	0
No CKD	1025	688	554	472	419	363	0

Chapter 12 Conclusions and future research

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12.1 Key findings

Several interesting and original observations as a result of this thesis warrant further study.

First, I have endeavoured to disentangle the pathophysiology of stroke in chronic kidney disease (CKD). Although it has been postulated that stroke risk in CKD may be attributable to a combination of both traditional and non-traditional cardiovascular mechanisms,[1] I aimed to investigate whether this relationship was truly independent of hypertension, the most prevalent comorbidity in individuals with CKD[2] and the leading modifiable risk factor for stroke in the general population.[3] I performed a systematic review and meta-analysis of stroke risk with low eGFR (<60 ml/min/1.73m^2) with a particular focus on how robustly studies adjusted for hypertension,[4] including 85 studies in which 3,417,098 participants experienced nearly 73,000 stroke events. Although patients with CKD appeared to have a 36% greater risk of stroke than in those with normal renal function in multivariate-adjusted analysis, this risk association varied considerably depending on the way in which hypertension was adjusted for. When multiple prior blood pressure (BP) readings over time were adjusted for, a better marker of long-term burden or control, there was near-complete attenuation of the risk association between CKD and stroke. The degree of risk attenuation would tend to suggest that this relationship is strongly confounded by hypertension and that CKD, as determined by low eGFR, is unlikely to be a significant independent risk factor for stroke outside of such traditional risk factors.

Second, I investigated whether mechanisms of stroke risk may be similarly confounded for patients with proteinuria. The ‘strain vessel hypothesis’ has been proposed whereby juxtamedullary afferent arterioles in the kidney and cerebral perforating arteries in the brain are both small, short vessels exposed to the large pressure gradients and therefore

most vulnerable to hypertensive vascular injury, manifest as albuminuria and cerebrovascular disease, respectively.[5] I performed another systematic review and meta-analysis of nearly two million participants to study the impact of hypertension on the relationship between proteinuria and stroke risk and found that the presence of proteinuria conferred about a 70% greater risk of stroke compared to that in those without it.[6] However, in contrast to low eGFR and stroke, the risk association between proteinuria and stroke did not substantially vary or attenuate even with the extensive adjustment for blood pressure. The association was also stronger in younger populations suggesting that shared genetic susceptibility for premature vascular disease may underpin the relationship between proteinuria and stroke risk.

Third, in an analysis of nearly 1300 transient ischaemic attack (TIA)/stroke patients within a population-based cohort study, the Oxford Vascular Study (OXVASC), correlations between biomarkers related to inflammation and thrombosis with renal dysfunction in the setting of cerebrovascular events were generally modest after adjustment for age, providing further evidence for my hypothesis that putative risk factors such as chronic inflammation or coagulopathy are unlikely to be important stroke mechanisms in patients with CKD.[7] Most older adults develop ‘inflammageing’, a condition characterized by elevated levels of blood inflammatory markers that carries high susceptibility to cardiovascular disease, but this is not specific to CKD.[8]

Fourth, using OXVASC, I have subtyped in detail TIA/stroke events occurring in over 3000 CKD patients according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) aetiological classification.[9] Although there was a greater prevalence of cardioembolic, large artery disease, and multiple aetiology subtypes in the CKD population, most subtype-CKD associations attenuated with adjustment for age and with additional adjustment for hypertension, again suggesting that there are no important renal-specific vascular risk factors beyond these covariates. This chapter highlights how

any study of risk association and stroke should be carefully stratified by and adjusted for age. Previous studies that reported CKD prevalence according to stroke subtype did not adjust for age,[10-12] and as evidenced by this analysis, subtype-specific associations are particularly prone to confounding by age.

Fifth, I have described the natural history of cerebrovascular disease in CKD from index event to recurrence, examining in detail its impact on stroke severity, disability and vascular recurrence in an analysis of OXVASC. I found that CKD was independently associated with greater risk of ischaemic stroke compared to TIA and with greater initial National Institutes of Health Stroke Scale (NIHSS) score, driven mostly by those with advanced CKD. Among patients with ischaemic stroke, CKD was also associated with higher one-month modified Rankin scale (mRS) scores, similarly driven by those with an eGFR < 30 ml/min/1.73m^2. It was also independently associated with an increased risk of recurrent stroke, which was particularly pronounced for early (<90 days) stroke recurrence. The consistent impact of CKD on early event severity and outcomes suggests that there may be associated inflammatory or other processes intrinsic to CKD leading to uniformly worse outcomes. One possible mechanism may be nitric oxide deficiency which is known to occur in CKD.[13] Although the efficacy of nitric oxide donors in the setting of acute stroke in the general population has not yet been demonstrated in the trials to date,[14] it would seem that CKD patients have often not been included or been the focus of such trials and may represent a group that could potentially derive unique benefit.

Sixth, I investigated whether the association between CKD and small vessel disease (SVD) may be confounded by their shared vascular risk factors such as hypertension and diabetes[15] or whether there was any evidence to support the hypothesis that SVD and CKD may be part of a multi-system small vessel disorder.[16] In an OXVASC analysis of nearly 2000 consecutive patients with TIA/stroke who underwent MRI imaging, CKD was found to be associated with total SVD burden (as measured by the total SVD score), but

only at age <60 years. The overall association of CKD and total SVD score was also attenuated after adjustment for age, sex, and vascular risk factors, but the independent association of CKD and total SVD score at age <60 years was maintained. These findings indicate that there is an age-specific association between CKD and SVD that is predominantly seen at younger ages and that may be explained by a shared genetic susceptibility. At older (> 60 years) ages, much of the association appears to be confounded by age and other vascular risk factors.

Seventh, although CKD has been associated with increased risk of cognitive decline,[17-19] I did not find a strong independent association with dementia either pre- or post-stroke in a final OXVASC analysis. This may be because previous studies have focused on mild cognitive impairment rather than dementia diagnosis,[20-22] or because they have been more dialysis-based rather than pre-dialysis like this study.[23-25] However, there was a signal to suggest a possible independent association between CKD and late-onset dementia post-stroke in those who initially had minor events. This may be consistent with a vascular pattern of dementia related to new, possibly subclinical recurrent strokes, or progressive cerebral SVD.[26]

12.2 Impact of multimorbidity on risk and outcome of stroke: lessons from chronic kidney disease

CKD is often underrecognized as an important and frequent co-morbidity that affects stroke survivors. This is partly because patients with kidney disease have been excluded from over one-third of clinical trials of cerebrovascular disease interventions and only 3% of trials have subsequently reported baseline renal function.[27] In addition, many of the existing multimorbidity scores or measurements tools do not take CKD into account or acknowledge only severe disease as in the case of the Charlson Comorbidity Index,[28] the most commonly used tool in studies of stroke and multimorbidity.[29] However, this is an

important omission since even early stages of CKD are associated with cardiovascular mortality[30] and CKD itself frequently portends or is a marker of multimorbidity.[31]

Using CKD as an example, I have endeavoured to highlight the impact of multimorbidity on stroke risk, mechanisms, severity, functional recovery and risk of recurrence or death post-stroke (Figure 12-1). It's clear that multimorbidity will have increasingly important implications for further research, practice, and policy, as recently recognized by the Academy of Medical Sciences.[32]

As the global burden of CKD rises,[33] so too will its prevalence in stroke survivors and potential contribution to stroke mechanisms. Newer multimorbidity measurement tools may need to be developed to take account of even mild stages of CKD and to reflect the increasing risk and morbidity of incremental loss of renal function, as represented by eGFR categories. Patients with proteinuric kidney disease and those who are dialysis-dependent should be recognized as being particularly high-risk for cerebrovascular events and should be given appropriate clinical and research prioritization.

Through our various systematic reviews[4] and OXVASC analyses,[7, 9] I have highlighted the central role that age, hypertension, and other traditional vascular risk factors play in the aetiology of stroke in CKD. Although it is likely that there is synergy between comorbidities within multimorbidity, our analyses would suggest that proposed 'inflammageing' and other non-traditional pathways are likely less relevant than the usual confounders. Analysis of stroke subtypes with careful adjustment for and stratification for age can provide useful mechanistic insights.[34] However, the prevalence of multimorbidity in stroke in younger populations is clearly increasing[35] and CKD may be a more important risk factor in such groups,[6, 36] possibly related to common causal genetic pathways.[37]

The multi-fold consequences of multimorbidity on stroke severity and outcomes have been highlighted by examining the impact of CKD. Though CKD may not be an independent risk factor for stroke, it is independently associated with much worse initial severity, early disability, greater institutionalisation and socioeconomic costs, recurrent stroke and other vascular events, and both short- and long-term mortality.[34, 38-40] This excess morbidity and mortality may partly relate to under-prescription of standard preventative treatments and the withholding of or delay to acute interventions, but it's possible that mechanisms intrinsic to CKD such nitric oxide deficiency may also play a role.[13]

While CKD may share risk factors or certain treatment strategies with stroke, it should still merit special consideration in the design or implementation of stroke prevention and recovery programs. Currently, one must cross-reference multiple disparate CKD or stroke guidelines in order to be appropriately guided in the prevention and management of stroke in CKD.[41] Given the increasing prevalence of overlapping disease comorbid conditions such as CKD, there is a need to standardize or integrate clinical practice guidelines to guide real-world decision-making in frequently multimorbid patients.[42]

12.3 Future research directions

Further research is required to better understand the pathophysiology of stroke in such patients which may be aided by more consistent reporting of aetiological stroke subtypes in CKD. There is also clearly a need for dedicated CKD trials or enriched trials to expand the evidence base for integrated guidelines. As stated, few cerebrovascular trials to date have reported baseline renal function and many have excluded CKD patients entirely.[27] Pragmatic trial design may offer advantages over traditional trial design for CKD or other multimorbid patient groups. I have outlined recommendations for selected key research priorities in CKD and multimorbidity in Table 12-1, several on which aim to establish the

safety and efficacy of many standard treatments in the CKD population that have not previously been demonstrated.

However, research is needed to explore multimorbidity in stroke more broadly. Detailed examination of individual comorbidities, as well as comorbidity clusters and overall multimorbidity, on long-term stroke recurrence by stroke subtype is warranted. Few studies to date, for example, have examined the long-term impact of multimorbidity in stroke with its implications for stroke rehabilitation, secondary prevention, and outcomes, as well as non-stroke-related care and outcomes. Interdisciplinary collaboration will be central to the redesign of stroke healthcare to adapt to the increasing complexity of multimorbid patients including those with CKD.

12.4 References

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TABLES

Table 12-1 Selected research priorities for CKD and multimorbidity in stroke

Research agenda for CKD
Determine the role of genetic factors in the aetiology of stroke in CKD.
Determine if there are novel risk factors that contribute to stroke risk in patients with proteinuria.
Regular audit and monitoring of times to acute treatment and rates of treatment in patients with CKD versus those with normal renal function.
Evaluate the efficacy and safety of intravenous thrombolysis and thrombectomy in CKD.
Investigate potential novel mechanisms by which CKD may increase the severity of stroke event and the risk of early recurrence, such as the nitric oxide deficiency hypothesis.
Determine the role for antiplatelet treatment in primary stroke prevention in CKD.
Determine when anticoagulation should be used in dialysis patients and which agent has the greatest safety and efficacy.
Clarify whether carotid stenting or endarterectomy are superior in CKD.
Investigate the mechanisms of cognitive decline in CKD and chart its natural history.
Research agenda for multimorbidity
Develop a consensus definition for multimorbidity in stroke and determine the best tool to measure it in this setting.
Design and implement care pathways and programs that accommodate patient preferences and priorities.
Explore the short-term impact of multimorbidity on acute stroke care.
Explore the longer-term impact of multimorbidity on stroke rehabilitation services, recurrence risk, and mortality, as well as potential predictors of worse outcomes.
Creation of integrated, collaborative stroke guidelines to reduce fragmented care.
Investigate the impact of treatment burden and polypharmacy on multimorbid stroke survivors.

Figure 12-1 The interplay of CKD, stroke, and multimorbidity.