A RETROSPECTIVE STUDY OF RENAL DYSFUNCTION IN ACUTE STROKE: INCIDENCE, IMPACT AND OUTCOMES

by

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Abstract

Stroke is a leading cause of death and neurological disability worldwide. Chronic kidney disease (CKD) is associated with an increased risk of stroke. Conversely, CKD confers worse outcomes following a stroke, with the highest mortality seen in end-stage renal disease. In comparison, the relationship between AKI and stroke is not well described, with a lack of UK data. In this single-centre, retrospective observational study of hospitalisations with acute stroke, I sought to determine the incidence of renal dysfunction and its impact on outcomes. AKI incidence was determined using preadmission serum creatinine (SCr) as 'baseline' renal function, compared with 4 surrogate methods. AKI was common, with an overall incidence of 20%, and was associated with increased 30-day and 1-year mortality using all AKI methods. Admission SCr most closely agreed with preadmission SCr but all surrogate methods exhibited bi-directional misclassification of AKI. CKD prevalence was high (over 30%) and was associated with increased mortality in univariable analyses. CKD patients underwent fewer imaging modalities and thrombectomy, possibly suggesting the presence of 'renalism'. Contrast exposure was not found to be a risk factor for AKI. Vascular calcification and carotid artery disease were univariably associated with CKD. Multi-centre studies are needed to confirm the findings.

Dedication

To my parents, who are much loved

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List of Abbreviations

ACEi	angiotensin-converting enzyme inhibitor
ACQUATIK	Acute Care QUAliTy In chronic Kidney Disease
ACR	albumin-to-creatinine ratio
ACS	acute coronary syndrome
ADC	apparent diffusion coefficient
ADQI	Acute Dialysis Quality Initiative
AF	atrial fibrillation
AHA/ASA	American Heart Association and American Stroke Association
AIS	acute ischaemic stroke
AKI	acute kidney injury
AKI^{adm}	acute kidney injury ascertained using first serum creatinine on admission as baseline renal function
AKI-D	acute kidney injury requiring dialysis treatment
AKI^{EPI}	acute kidney injury ascertained by assigning an eGFR of 75 mL/min/1.73m^2 and back-calculating serum creatinine using the CKD-EPI equation

AKI^{low}	acute kidney injury ascertained using lowest serum creatinine during admission as baseline renal function
AKI^{MDRD}	acute kidney injury ascertained by assigning an eGFR of 75 mL/min/1.73m^2 and back-calculating serum creatinine using the MDRD equation
AKIN	Acute Kidney Injury Network
AKI^{pre}	acute kidney injury ascertained using preadmission serum creatinine as baseline renal function
ARB	angiotensin II receptor blocker
ARIC	Atherosclerosis in Communities
ASPECTS	Alberta Stroke Programme Early CT Score
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events
AVM	arteriovenous malformation
BCE	Before the Common Era
BEST Kidney	Beginning and Ending Support Therapy for the Kidney
BP	blood pressure
c.	circa
CARDS	Collaborative Atorvastatin Diabetes Study

CBF	cerebral blood flow
CBV	cerebral blood volume
CCA	common carotid artery
CHD	coronary heart disease
CHF	congestive heart failure
CHOICE	Choices for Healthy Outcomes in Caring for ESRD
CI	confidence intervals
CIN	contrast induced nephropathy
CK	creatine kinase
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease- mineral and bone disorder
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
CRIC	Chronic Renal Insufficiency Cohort
CRP	c-reactive protein
CT	computerised tomography

CTA	computerised tomography angiography
CTP	computerised tomography perfusion
CTT	Cholesterol Treatment Trialists
CVD	cardiovascular disease
4D	Die Deutsche Diabetes Dialyze Studie
DALY	disability-adjusted life year
DOPPS	Dialysis Outcomes and Practice Patterns Study
DSA	digital subtraction angiogram
DWI	diffusion weighted imaging
ECA	external carotid artery
eGFR/ GFR	estimated glomerular filtration rate/ glomerular filtration rate
EHR	electronic health record
ERBP	European Renal Best Practice
ESCAPE	Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times
ESR	erythrocyte sedimentation rate
ESRD	end-stage renal disease
EVT	endovascular therapy

EXTEND-IA	Extending the Time for Thrombolysis in Emergency Neurological Deficits- Intra-Arterial
HbA1c	glycated haemoglobin
HD	haemodialysis
HDL	high-density lipoprotein
HES	Hospital Episode Statistics
HR	hazard ratio
HT	haemorrhagic transformation
IA	intra-arterial
IAT	intra-arterial thrombectomy
ICA	internal carotid artery
ICD-9	International Classification of Diseases- 9th Edition
ICD-10	International Classification of Diseases- 10th Edition
ICH	intracerebral/ intracranial haemorrhage
IDMS	isotope dilution mass spectrometry
i.e.	id est = Latin for “that is”
IGFBP7	insulin-like growth factor-binding protein 7
IHD	ischaemic heart disease

IMD	Index of Multiple Deprivation
INR	international normalised ratio
IL-18	interleukin-18
IQR	interquartile range
ITU	intensive care unit
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
KIM-1	kidney injury molecule-1
LDL	low-density lipoprotein
LOS	length of stay
LVH	left ventricular hypertrophy
LVO	large vessel occlusion
M1	most proximal (sphenoidal) segment of middle cerebral artery
MCA	middle cerebral artery
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction

MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
MRSA	meticillin resistant Staphylococcus aureus
MSU	mid-stream urine
MTT	mean transit time
NASCET	North American Symptomatic Carotid Endarterectomy Trial
NCCT	Non-contrast computerised tomography
NGAL	neutrophil gelatinase-associated lipocalin
NHS	National Health Service
NIHSS	National Institutes of Health Stroke Scale
NICE	National Institute for Health and Care Excellence
NINDS	National Institute of Neurological Disorders and Stroke
NIS	Nationwide Inpatient Sample
NOAC	non-vitamin K antagonist oral anticoagulant
NOS	Newcastle-Ottawa Scale
NSSA	National Sentinel Stroke Audit

OAC	oral anticoagulants
ONS	Office of National Statistics
OPCS-4	Classification of Interventions and Procedures, version 4
OR	odds ratio
PACS	picture archiving and communications system
PAS	Patient Administration System
PCOM	posterior communicating artery
PD	peritoneal dialysis
PICS	Prescribing Information and Communications System
PTH	parathyroid hormone
PTT	partial thromboplastin time
QEHB	Queen Elizabeth Hospital Birmingham
QOF	Quality Outcomes Framework
RAAS	renin-angiotensin-aldosterone system
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 Eight Hours of Symptom Onset
RIFLE	Risk, Injury, Failure, Loss of function and End-stage renal disease

RCP	Royal College of Physicians
RCT	randomised controlled trial
RR/ RRR	relative risk/ relative risk reduction
RRT	renal replacement therapy
RSNA	Radiological Society of North America
rt-PA	recombinant tissue plasminogen activator
SAH	subarachnoid haemorrhage
SCr	serum creatinine
SD	standard deviation
SES	socioeconomic status
SHARP	Study of Heart and Renal Protection
SINAP	Stroke Improvement National Audit Programme
SQL	Structured Query Language
SPRINT	Systolic Blood Pressure Intervention Trial
SSNAP	Sentinel Stroke National Audit Programme
SWIFT PRIME	Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment
TIA	transient ischaemic attack

TIMP-2	tissue inhibitor of metalloproteinases-2
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UK	United Kingdom
US	United States
USD	United States Dollars
USS	ultrasound scan
UHBFT	University Hospitals' Birmingham NHS Foundation Trust
USRDS	United States Renal Data System
UTI	urinary tract infection
vs.	versus
WBC	white blood cell count
WHO	World Health Organisation
WW1/ 2	World War 1/ 2
YLLs	years of life lost

List of Publications

Publications arising from this thesis

Arnold J, Sims D, Ferro CJ. Modulation of Stroke Risk in Chronic Kidney Disease. *Clin Kidney J*. 2016 Feb;9(1)29-38. Epub 2015 Dec 23.

Arnold J, Ng KP, Sims D, Gill P, Cockwell P, Ferro C. Incidence and Impact on Outcomes of Acute Kidney Injury after a Stroke: A Systematic Review and Meta-Analysis. *BMC Nephrol*. 2018 Oct 22;19(1):283.

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Other publications

Ng KP, **Arnold J**, Sharif A, Gill P, Townend JN, Ferro CJ. Cardiovascular actions of mineralocorticoid receptor antagonists in patients with chronic kidney disease: A systematic review and meta-analysis of randomized trials. *J Renin Angiotensin Aldosterone Syst*. 2015 Sep;16(3):599-613. doi: 10.1177/1470320315575849. Epub 2015 Mar 17.

Arnold JJ, Hayer M, Sharif A, Begaj I, Tabriez M, Bagnall D, Ray D, Hoye C, Nazir M, Dutton M, Fifer L, Kirkham K, Sims D, Townend JN, Gill PS, Dasgupta I, Cockwell P, Ferro CJ. Acute Care QUAliTy in chronic Kidney disease (ACQUATIK): a prospective cohort study exploring

outcomes of patients with chronic kidney disease. *BMJ Open*. 2015 May 3;5(4):e006987. doi: 10.1136/bmjopen-2014-006987.

Ferro CJ, **Arnold J**, Bagnall D, Ray D, Sharif A. Fracture risk and mortality post-kidney transplantation. *Clin Transplant*. 2015 Nov;29(11):1004-12. doi: 10.1111/ctr.12621. Epub 2015 Oct 9.

Arnold J, Mytton J, Evison F, Gill PS, Cockwell P, Sharif A, Ferro CJ. Fractures in Kidney Transplant Recipients: A comparative study between England and New York State. *Exp Clin Transplant*. 2018 Aug;16(4):410-418. doi: 10.6002/ect.2017.0016. Epub 2017 Nov 15.

CHAPTER 1 RISK OF STROKE IN KIDNEY DISEASE

1.1 Clinical Importance of Stroke and Chronic Kidney Disease- the 'Cerebro-Renal' Link

Stroke represents a major public health burden. Globally, it is the second most common cause of death, after ischaemic heart disease (IHD), and has remained one of the leading causes of death for the last 15 years [1]. In 2017, there were 6.17 million deaths caused by stroke [2]. It is the third leading cause of disability, accounting for 5.3% of all disability-adjusted life years (DALYs) worldwide [3, 4]. The DALY, a measure of health status, integrates both mortality and disability [5] and incorporates a factor developed by the World Health Organisation (WHO)-Global Burden of Disease (GBD) study called disability weight (DW), which indicates disease severity on a scale of 0 (perfect health) to 1 (death) [6]. In contemporary stroke research, the modified Rankin Scale (mRS) score is a widely reported outcome measure of overall disability and is used to assess recovery after stroke and as a primary endpoint in clinical trials [7, 8]. A higher mRS score post-stroke is associated with increased stroke severity and worse outcomes [8-11]. Previously, the WHO-GBD study assigned only 2 DWs for stroke, 0.920 for acute stroke and 0.266 for chronic states after a stroke [12]. However, a handful of studies have since investigated the application of DWs for different mRS scores [12-14]. Subsequently, mRS is now routinely incorporated into the DALY calculation, with higher weighting assigned to greater degree of disability (ranging from mRS 0, no symptoms: DW 0 to mRS 5, severe disability: DW 0.998 and mRS 6, death: DW 1), allowing the application of DALYs to enhance granularity in stroke research [14, 15]. The National Institutes of Health Stroke Scale (NIHSS),

a tool used to assess stroke severity at presentation, is not incorporated into the DALY since it does not represent an outcome measure. In the United States (US) alone, approximately new 610,000 strokes happen every year, costing an estimated $45.5 billion [16]. In the United Kingdom (UK), there were 107,600 new strokes in 2017, with annual aggregate care costs of £5.3 billion (of which £1.6 billion is National Health Service (NHS) care) [17, 18]. Patients with more severe stroke stay longer in hospital and at increased cost [19-21], with one study of 1341 acute ischaemic stroke (AIS) patients reporting a median institutional length of stay (LOS) of 19 days for very mild stroke compared with 84 days for severe stroke, with corresponding mean total costs of 10,560 US Dollars (USD) (interquartile range (IQR) 3685-15,385 USD) and 16,173 USD (IQR 9460-21,287 USD) respectively [20]. Furthermore, the suffering and negative consequences to patients, carers and society as a whole cannot be measured. Stroke is predominantly a disease of older age with the very elderly (over 85 years of age) making up 17% of all stroke patients in the US [16].

The association between chronic kidney disease (CKD) and cardiovascular disease (CVD) has been well researched, but up until now studies have mainly focussed on the association between cardiac disease and CKD. Both myocardial infarction (MI) and stroke are more common in the CKD population [22, 23]. Using an economic model, Kerr *et al*. estimated that approximately 7000 excess strokes and 12000 excess MIs occurred in the CKD population between 2009 and 2010 when compared with a non-CKD matched population [24]. The estimated additional cost of these events to the NHS was estimated at £178 million. CKD, end-stage renal disease (ESRD) and stroke are associated with premature death, falls, cognitive

impairment and decreased quality of life [3, 25-28]. Despite these data, the cerebro-renal link has attracted considerably less interest and research than the widely recognised cardio-renal connection.

In this Chapter I will begin by defining stroke, before examining the relationship between CKD and stroke, emphasising areas in need of further research. I will briefly outline the relationship between AKI and stroke, which I will discuss in more detail in Chapter 2. I will then go on to highlight the evolving field of acute stroke treatments, incorporating trials on acute reperfusion treatments and the potential implications for clinical practitioners.

1.2 Definitions of Stroke

Stroke has not been consistently defined in clinical practice or research. It is thought that the term “stroke” was introduced to medicine in 1689 by the English physician, William Cole (1635-1716) [29]. The WHO definition, introduced in 1970, defined a stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin” [30]. However, this definition, based solely on clinical criteria, is decades old and does not incorporate the significant developments in basic science, neuropathology and imaging since that time.

Taking these advances into account, the American Heart Association and American Stroke Association (AHA/ASA) have redefined the term “stroke”, encompassing 10 categories [31], including the three main stroke subtypes, cerebral infarction or AIS, intracerebral haemorrhage (ICH) and subarachnoid haemorrhage (SAH). The AHA/ASA define central nervous system (CNS) infarction as, “brain, spinal cord or retinal cell death attributable to ischaemia, based on 1) pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischaemic injury in a defined vascular distribution; or 2) clinical evidence of cerebral, spinal cord, or retinal focal ischaemic injury based on symptoms persisting ≥24 hours or until death, and other aetiologies excluded” [31]. AIS is caused by vascular occlusion within the cerebral circulation, usually by thrombosis or embolism, causing infarction of CNS tissue.

AIS is responsible for approximately 87% of strokes in the general population [32] and is the main topic of consideration in this Chapter. Since the aetiology of AIS determines treatment strategies and prognosis, further subclassification is recommended by AHA/ASA [33]. One such recognised classification is the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, which subdivides AIS into the following: 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined aetiology (for example dissection, hypercoagulable state or sickle cell crisis), and 5) stroke of undetermined aetiology [34].

Strokes caused by ICH occur in around 10% of the population [32] and are defined by the AHA/ASA as, “Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma” [31]. This definition also includes “haemorrhagic infarction” and “parenchymal haemorrhages” after CNS infarction. “Haemorrhagic infarction” is more commonly but confusingly known as haemorrhagic transformation (HT) of an infarct. Haemorrhage may occur spontaneously following brain infarction, or as a complication of antiplatelet or thrombolytic treatments [35, 36] and may range from petechial bleeding to massive haemorrhage resulting in space-occupying effect and secondary brain injury.

SAH is responsible for approximately 3% of all strokes [32] and carries a high mortality rate of up to 45% [37-39]. Stroke caused by SAH is defined as, “rapidly developing signs of neurological dysfunction and/ or headache because of bleeding into the subarachnoid space, which is not caused by trauma” [31]. The aetiology of SAH is vascular, for example, 85% of cases occur as consequence of saccular aneurysmal rupture at the base of the brain [40]. As a result of this very different pathophysiology, SAH is not considered further as part of this thesis.

1.3 Chronic Kidney Disease and the Risk of Stroke

1.3.1 Definition of CKD

CKD is defined as a reduction in estimated glomerular filtration rate (eGFR) for a duration of 3 months or more, accompanied by one or more markers of kidney damage, including the presence of albuminuria or urinary sediment, electrolyte abnormalities due to tubular disorders, histological or structural abnormalities detected by imaging, or a history of kidney transplantation [41]. A CKD staging system based on level of eGFR and albuminuria denotes severity and is used for risk stratification and to guide clinical management (Figure 1-1) [41, 42].

1.3.2 Prevalence and Aetiology of CKD

CKD is common, affecting 11-13% of the population worldwide with a predominance of CKD stage 3 (approximately 7.6%) [43]. In the Global Burden of Disease Study 2017, CKD was the 16th leading cause of years of life lost (YLL) worldwide, with 1.2 million deaths worldwide [2]. Overall, CKD mortality has increased by 33.7% from 2007 to 2017, making it one of the fastest rising major causes of death, together with type 2 diabetes and dementia [2]. Epidemiological data has shown up to a 15% higher estimated prevalence of CKD in low income and middle-income countries, where growth in obesity and diabetes is highest, compared with high income countries [2, 44]. In the UK, prevalence estimates of CKD stages 3 to 5 (eGFR <60 mL/min/1.73m^2) vary by study, ranging from 4.3 to 8.5% [45-48]. The prevalence of ESRD on

renal replacement therapy (RRT) as per UK Renal Registry 2016 data was 962 per million population [49].

Figure 1-1. CKD staging and prognosis by GFR and albuminuria category.

Adapted from Levey AS *et al*. [42]. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. *Kidney Int* 2011; 80: 17-28. Accessed https://www.kidney-international.org/article/S0085-2538(15)54924-7/fulltext.

				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73m^2) Description and range	**G1**	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red: very high risk.

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.

The world population is aging and carries with it an increase in comorbidities [50, 51]. The continued rise in the incidence of diabetic kidney disease, fuelled by overnutrition, inadequate physical activity and obesity, is thought to be the key driver of CKD burden globally [2]. Age itself is associated with a decline in renal function which cannot be attributed to other known risk factors [52]. The adjusted CKD prevalence in adults over the age of 75 is 35.6% in the UK [53] with similar data reported from the United States Renal Data System (USRDS) [54]. Both US and European studies from the previous decade have shown a rise in CKD prevalence over time [27, 55]. However, more recent studies indicate that the CKD population is stabilising out [56]. Explanations for this observed 'plateau' may be a result of in advances in medical therapy in the last few decades [56], including improvements in blood pressure (BP) and glycaemic control [54]. The burden of CKD will unfortunately have greatest impact on lower and middle income countries, due to lesser availability of treatments to manage risk factors, as well as access to life-saving RRT [2, 57].

1.3.3 Cost of CKD

CKD is a huge public health problem, with an estimated annual cost of £1.45 billion in the UK (approximately 1.3% of the NHS budget), of which over half is spent on RRT [24]. Costs are summarized in Table 1-1. CKD is associated with major morbidity and mortality including increased risk of infection [58], bone fractures [59] and importantly, cardiovascular disease [41]. As such, the indirect costs associated with CKD are significant, including excess stroke, MI and meticillin-resistant Staphylococcus aureus (MRSA) infection (Table 1-1).

Table 1-1. NHS expenditure on CKD for the year 2009-2010.

Adapted from Kerr, M [60]. Chronic Kidney Disease in England: The Human and Financial Cost. Retrieved from: https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/Chronic-Kidney-Disease-in-England-The-Human-and-Financial-Cost.pdf

Care category		Expenditure
Direct costs		
Primary	Tests and consultations	£ 142,620,986
	Anti-hypertensive medications	£ 152,204,595
	Osteoporosis prevention and vitamin D supplements	£ 26,557,185
Total		£ 321,382,767
Acute	Outpatient attendance	£ 53,132,543
	Inpatient care	£ 74,891,121
Total		£ 128,023,664
ESRD	Transplantation	£ 225,404, 520
	Dialysis	£ 504,680,228
	Transport for dialysis	£ 49,521,157
Total		£ 779,605,905
Indirect costs		
	Excess LOS	£ 45,815,625
	Excess strokes	£ 79,703,607-£ 82,155,382
	Excess MIs	£ 94,269,590- £ 95,391,156
	Excess MRSA	£ 1,416,108
Total		£ 221,204,929- £ 224,778,271
Sum total		£ 1,450,217,265- £ 1,453,790, 607

Abbreviations: ESRD, end stage renal disease; LOS, length of stay; MI, myocardial infarction; MRSA, meticillin-resistant Staphylococcus aureus.

1.3.4 Outcomes in CKD

CKD is widely and consistently associated with adverse outcomes, including increased morbidity and mortality [41]. Over a decade ago Tonelli *et al*. showed that both all-cause mortality (adjusted Hazard Ratio (HR) 2.73, 95% confidence intervals (CI) 1.64-4.54) and cardiovascular mortality (adjusted HR 2.47, 95% CI 1.42-4.30) are increased in CKD (defined as an eGFR <60 mL/min/1.73m^2). Odds of death increased with declining eGFR (Odds Ratio (OR) 1.9, 2.6 and 4.4 for eGFR of 80, 60 and 40 mL/min/1.73m^2 respectively, compared with an eGFR of 100 mL/min/1.73m^2) [61]. Since then, 4 large meta-analyses have produced similar results [62-65]. These studies also analysed outcomes according to albuminuria and found that even low levels independently predict mortality and progression to ESRD. In mild to moderate kidney disease, the incidence of cardiovascular mortality is much greater than the incidence of ESRD [62, 64, 65], suggesting that the principal burden of disease in CKD patients is related to increased cardiovascular risk, rather than progression to ESRD [22]. Many other acute and chronic diseases have a worse prognosis in the context of CKD, including stroke, diabetes, chronic obstructive pulmonary disease (COPD) and acute infections [66, 67]. The influence of CKD on outcomes is only partly understood and likely due to a complex interplay of pathophysiological factors in a very heterogeneous patient population with different aetiologies of renal disease, degrees of renal impairment and albuminuria and other comorbidities. Uraemia in CKD causes upregulation of inflammatory cascades that may exacerbate the response to tissue injury. Left ventricular hypertrophy (LVH) caused by cardiac fibrosis, heightened activity of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, as well as enhanced vascular calcification all contribute to increased cardiovascular risk in CKD patients [22].

1.3.5 CKD and the Risk of Stroke

CKD and ESRD are associated with an increased risk of stroke [68, 69]. A recent systematic review and meta-analysis by Masson *et al.* comprising 83 studies, over 2 million patients and 30,392 strokes, has confirmed the strong inverse relationship between renal function and stroke risk. The authors demonstrated that for every 10 mL/min/1.73m^2 decline in GFR the risk of stroke increases by 7% [68].

Albuminuria is an important non-traditional risk factor that has been shown to correlate with both CKD progression and increased cardiovascular risk and mortality in a number of large landmark studies [70-74]. Even very low levels of albuminuria (undetectable on urine dipstick) are associated with increased all-cause mortality and cardiovascular mortality [62]. In keeping with these findings, Masson *et al*. also demonstrated a strong direct relationship between albuminuria and stroke risk. Any degree of albuminuria increases stroke risk by 68%, and for every 25 mg/mmol increase in albuminuria, stroke risk increases by 10% [68]. The effect of GFR and albuminuria appear to be additive with no evidence of interaction [68]. These findings were consistent through categories of CKD and albuminuria, gender and patient risk groups (including diabetes, hypertension and smoking) and stroke type.

Two large cohort studies have demonstrated that dialysis patients are at the greatest risk of stroke. The Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study, which examined traditional cardiovascular risk factors in 1041 dialysis patients, showed a stroke prevalence of

11% [75], compared with approximately 2.9% in the general US adult population [16]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) looked at outcomes of 16,720 haemodialysis (HD) patients in the US, Europe and Japan and showed a stroke prevalence of 18.4%, 13.7% and 12.5% in these respective geographical regions [76]. Overall, stroke risk in patients with ESRD on HD is 5-10 times higher than in those with normal renal function [77].

Increasing age, male sex, positive family history and non-White ethnicity are all well-established non-modifiable risk factors for stroke [78]. In the general population, the major modifiable risk factors for AIS are diabetes mellitus, hypertension, smoking, hypercholesterolaemia and atrial fibrillation (AF) [33]. The risk of ICH increases with higher BP, alcohol intake, bleeding diatheses and blood vessel wall fragility, as often seen in the elderly. All these risk factors are over-represented in patients with CKD and ESRD. As in the cardio-renal syndrome, it is often very difficult to disentangle cause and effect [79]. In addition, there are a number of risk factors that are unique to patients with CKD and ESRD, including the mineral bone disorder associated with CKD (CKD-MBD) and the dialysis process itself.

Stroke had been for many centuries considered a natural and inevitable consequence of aging [80]. However, with increasing understanding of the natural history and pathophysiology of the condition, the last few years have seen very rapid advances, not only in preventative strategies [33], but also in acute treatments aimed at improving outcomes and reducing disability [81]. These are discussed forthwith with an emphasis on CKD and ESRD patients.

1.4 Primary and Secondary Prevention of Stroke

1.4.1 Hypertension

In the general population there is a well-established relationship between BP and stroke, with a meta-analysis demonstrating a two-fold increase in stroke mortality for every 20 mmHg rise in systolic BP in subjects aged 40 to 69 [82]. In the recent Systolic Blood Pressure Intervention Trial (SPRINT) trial, targeting patients to a lower systolic BP (<120 mmHg, compared with <140 mmHg) in CKD patients (defined as an eGFR <60 mL/min/1.73m^2) demonstrated a reduction in both cardiovascular events and mortality [83]. The relationship between BP and stroke in ESRD patients is less clear, with some studies reporting no relationship and others only a weak association [78]. BP measurement in HD patients is challenging, since patients may have 'burnt out' hypertensive heart disease (leading to reduced myocardial contractility and low BP) [84] and dialysis patients exhibit significant diurnal variation in BP, especially on dialysis days [85]. Two meta-analyses of randomised controlled trials (RCTs) in dialysis patients confirmed that BP reduction is associated with a reduction in cardiovascular events [86, 87]. However, the optimum blood pressure range in HD patients is yet to be determined, with a suggestion that home and ambulatory blood pressure monitoring may add value [88]. The benefits of treating BP to tight targets in dialysis patients, who are older and frailer than the general population and more prone to side effects of medication, must be weighed up against the complications, such as intra-dialytic hypotension [89].

1.4.2 Hypercholesterolaemia

In patients with CKD and ESRD, dysregulation of lipid metabolism leads to particular lipid profile characterised by increased levels of triglycerides, reduced levels of high-density lipoprotein (HDL) cholesterol and typically normal levels of low-density lipoprotein (LDL) cholesterol [90-92]. Several meta-analyses conducted by the Cholesterol Treatment Trialists' (CTT) Collaboration have shown overwhelmingly that lowering LDL cholesterol with statin therapy reduces the risk of cardiovascular disease, including stroke, in both high and low-risk populations [93-95]. However, in ESRD, the relationship between LDL cholesterol and cardiovascular risk may not be so straightforward. In ESRD patients on dialysis, low levels of LDL cholesterol are negatively associated with overall mortality, and higher levels appear to have only a neutral or weakly positive relationship [92, 96]. This 'reverse epidemiology' may potentially be explained by the higher rates of sudden cardiac death and heart failure in dialysis patients, compared with fewer deaths attributable to atherosclerotic heart disease in this population [97, 98]. This observation nevertheless complicates the focus on LDL cholesterol as a treatment target for reducing cardiovascular risk in patients with CKD and ESRD.

All of the published RCTs to date, that have investigated the effect of lipid-lowering therapy on cardiovascular risk in patients with CKD, have used statins [99-101]. All demonstrated that statin therapy was associated with a reduction in cardiovascular events in patients with renal impairment (eGFR <60 mL/min/1.73m^2) [99-101]. However, two large RCTS of dialysis patients, the Die Deutsche Diabetes Dialyze Studie (4D) [102] and A study to evaluate the Use

of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events (AURORA) [103] demonstrated no reduction in major cardiovascular events, despite a significant reduction in LDL cholesterol levels. A third, larger trial, the Study of Heart and Renal Protection (SHARP), comprising 9270 patients with both CKD and ESRD on dialysis, demonstrated a significant reduction in major atherosclerotic events (HR 0.83, 95% CI 0.74–0.94; P=0.002) and AIS (HR 0.75, 95% CI 0.60-0.94; P=0.01) in the treatment group randomised to receive simvastatin and ezetimibe compared to placebo [104]. In keeping with the results of 4D and AURORA, a subgroup analysis of dialysis patients at enrolment into SHARP demonstrated no significant reduction in major atherosclerotic events in the treatment group compared with placebo, although the trial was not powered to estimate the effect of ESRD on the primary outcome.

The SHARP study showed clearly that lowering LDL cholesterol reduces the risk of primary major atherosclerotic events in CKD patients not on dialysis [104]. However, the data from all three of the RCTS outlined above showed no benefit in dialysis patients. A recent systematic review and meta-analysis by the CTT collaboration summarised individual participant data from 28 trials investigating the effect of statin therapy in patients with varying CKD severity [105]. Overall, statin therapy reduced the risk of first major cardiovascular event (defined as major coronary event, stroke or coronary revascularisation) by 21% and stroke by 16% per mmol/L reduction in LDL cholesterol. However, smaller relative effects on major cardiovascular events were observed with declining eGFR. Notably, there was no evidence that statin therapy reduced the risk of major cardiovascular events in patients on dialysis

(Relative Risk (RR) 0.94, 95% CI 0.79-1.11). Similar effects were also observed for non-fatal MI and death due to coronary heart disease (CHD).

Based on the current evidence, the Kidney Disease: Improving Global Outcomes (KDIGO) Working Group currently recommend a statin in patients ≥ 50 years with CKD stages 3 to 5 or in patients aged 18-49 with established CHD, diabetes, previous AIS or an estimated 10-year risk of coronary death or non-fatal MI of greater than 10% [106]. However, they stop short of recommending treatment for patients on dialysis due to a lack of evidence. Notwithstanding the lack of trial data on the benefit of statins in dialysis patients, such treatment has been shown to be safe [102-104], and should therefore not be omitted without good reason in the non-dialysis CKD population. A number of novel treatments for dyslipidaemia are currently being developed, including biologics which target mediators of generation and clearance of atherogenic factors [92]. However, as is the challenge with all other therapies applied to patients with CKD, proven efficacy, as well as an acceptable safety profile, must be demonstrated in clinical trials in order to benefit this high-risk population.

1.4.3 Atrial Fibrillation

AF is the most common sustained cardiac arrhythmia with an estimated global prevalence of 3 million [107]. Patients with AF have a five-fold increased risk of stroke, which is not homogeneous and depends on the presence or absence of other risk factors [108]. In the US, AF is thought to be responsible for 10-12% (>70,000) of all AIS each year [109, 110]. In patients with CKD, the prevalence of AF is two to three times greater and increases with severity of

CKD [111]. The Chronic Renal Insufficiency Cohort (CRIC) study reported a prevalence of 18% in a population of non-dialysis CKD patients (defined as an eGFR 20-50, 20-60 and 20-70 mL/min/1.73m^2 for age ranges 21-44, 45-64 and 65-75 years respectively) [112], compared with a prevalence of 7-8% in the general population over the age of 65 [113]. Patients with ESRD on dialysis have the highest rates of AF, with estimated prevalence rates up to 27% [114].

CKD and AF share common cardiovascular risk factors, such as older age, diabetes, hypertension, obesity and obstructive sleep apnoea [115]. Not surprisingly therefore, they are not independent conditions and the high prevalence of AF in CKD patients can be partly explained by the high rates of such risk factors, as well as the high prevalence of cardiovascular disease observed in this patient group. However, CKD has also been shown to be an independent risk factor for AF, with the risk of incident AF increasing with both declining eGFR and increasing levels of albuminuria in the Atherosclerosis in Communities (ARIC) study [116]. Moreover, there appears to be a bi-directional relationship between CKD and AF, with several studies showing that incident AF is associated with both an increased risk of developing CKD and progression to ESRD [117-119].

CKD and AF produce a thrombogenic state through a complex interplay of mechanisms which cause disruption of the three components of Virchow's triad – 1) blood flow abnormalities as a result of left atrial dilatation and loss of atrial systole [120], activation of the RAAS [121-123] and systemic inflammation [124-126]; 2) abnormalities of blood constituents including coagulation cascade modulators (increased circulation of prothrombin 1 and 2, plasminogen

activator inhibitor [127], von Willebrand factor and tissue factor [128]), increased platelet aggregation and reactivity; and 3) blood vessel and cardiac structural abnormalities including myocardial fibrosis, which is common even in mild CKD [129, 130], LVH [131], accelerated atherosclerosis, arterial wall calcification [132], increased arterial stiffness [133, 134] and endothelial dysfunction [111]. These factors are the main drivers behind the high prevalence of AF observed in CKD patients. Mechanisms linked to an accelerated decline in renal function and progression to ESRD in the presence of AF are haemodynamic changes in the context of impaired systolic and diastolic function [135] and possibly renal microinfarction due to the formation of emboli [132].

Patients with coexisting AF and CKD are at increased risk of stroke, thromboembolism and mortality than those with either condition alone [111, 136-140]. In dialysis patients, having AF is associated with an approximately 25% increased risk of AIS [141], and has been shown to be a stronger risk factor for AIS than age [142].

The risk of stroke associated with AF is significantly reduced with anticoagulation, but this is at the expense of an increased risk of bleeding [108]. In advanced CKD, the paradox of both a prothrombotic state, which starts earlier in CKD, and a bleeding diathesis occur. Prohaemorrhagic mechanisms include intrinsic factors such as decreased platelet activity and vessel wall interactions, increased fibrinolysis and disruption of the coagulation cascade [111, 143], as well as extrinsic factors, such as undergoing dialysis catheter insertion or cannulation of arteriovenous fistulas in the context of antiplatelet or anticoagulant use (including

heparinisation of HD circuits) [111]. Antiplatelet agents, namely aspirin, are not as efficacious as oral anticoagulants (OACs) [144-146]. Several risk stratification scores, such as the $CHADS_2$ and CHA_2DS_2-VASc scores, have been developed to identify patients at high risk of stroke who would derive most net benefit from OACs [108]. Interestingly, the inclusion of CKD as a risk factor in CHA_2DS_2-VASc does not appear to increase the predictive value [147-149]. This may be because CKD is strongly associated with other score parameters including age >65 years and the presence of hypertension, diabetes and congestive heart failure (CHF) [115]. There is limited data on the use of CHA_2DS_2-VASc in dialysis patients [150, 151], however the predictive performance appears to be similar to that reported in studies of general AF populations [152].

The potential benefits of OACs need to be weighed against the increased bleeding risk associated with such therapy, using scores such as HAS-BLED [153, 154]. This score adds one point for 'renal disease', defined as being on dialysis or a transplant recipient or having a serum creatinine >200 µmol/L (>2.26 mg/dL) [153]. Other available scoring systems, such as HEMORR2HAGES [155] and ATRIA [156], also allocate points for the presence of renal disease. As for the CHA_2DS_2-VASc stroke risk stratification score, there is limited data on the use of the HAS-BLED scoring system to predict bleeding in ESRD. Previous studies have shown that HAS-BLED predicts both minor [151] and major bleeding events [157] and ICH [158] in dialysis populations. However, most recently, Ocak *et al*. demonstrated that HAS-BLED, ATRIA and HEMORR2HAGES had poor discriminative performance in dialysis patients (C-statistic for HASBLED 0.58, 95% CI 0.54-0.62), with a higher incidence of bleeding than predicted in the

calibration analyses [159]. As such, they should probably not be used in populations with ESRD.

Patients with advanced CKD with AF have generally been excluded from anticoagulation trials. A meta-analysis of 13 observational studies and nearly 50,000 patients demonstrated that warfarin therapy is associated with a reduced risk of AIS or systemic embolism and mortality and has no effect on the risk of major bleeding compared with no warfarin treatment in CKD patients [160]. More recently, a propensity-matched retrospective cohort study of 14,892 subjects with AF favoured warfarin use at all stages of CKD for the composite primary outcome of all-cause mortality, AIS and TIA [161]. These findings should give confidence to clinicians regarding the use of warfarin in non-dialysis CKD patients.

To date, there is no RCT data on warfarin use in patients with ESRD on dialysis, and the results from observational studies are conflicting [115], with some showing a reduction in the risk of stroke or systemic thromboembolism [136] and mortality [162-164], some showing no benefit [165-168] and others an increased risk of bleeding [160, 169] or an increased risk of AIS [170], particularly in patients over the age of 75 [171]. In addition to these contradictory findings, further unease about the use of warfarin in ESRD populations arises from the association with vascular calcification [172, 173], which may accelerate CVD or induce potentially fatal calciphylaxis [174].

Our attention is now increasingly being drawn away from warfarin, towards the performance and safety profiles of the newer non-vitamin K antagonist oral anticoagulants (NOACs) in CKD populations. NOACs have had a huge impact on the field of stroke prevention in AF, with a number of landmark trials demonstrating that the direct thrombin inhibitor dabigatran [175] and the direct factor X inhibitors rivaroxaban [176], apixaban [177] and edoxaban [178] all had superior efficacy and safety profiles than warfarin. However, the trial of apixaban [177] excluded patients with a creatinine clearance (CrCl) <25 mL/min and the other three trials [175, 176, 178] excluded patients with a CrCl <30 mL/min. As such, the efficacy of these agents in patients with ESRD was not tested. A systematic review and meta-regression analysis of 5 studies and 72,845 patients showed similar efficacy and safety of all four NOACS compared with warfarin across all levels of renal function [179]. The authors also reported apixaban had an improved safety profile over warfarin in patients with a CrCl of 25-49 mL/min. As such, NOACs offer a feasible alternative to warfarin in patients with AF and mild to moderate CKD and no dose reductions are required with a CrCl of ≥30 mL/min, with the exception of dabigatran, which requires a small dose reduction [108, 180].

All NOACS have a degree of renal excretion, with dabigatran exhibiting the most renal excretion (80%) and apixaban the least (27%) [108, 180]. The European Society of Cardiology and the European Heart Rhythm Association have approved the use of rivaroxaban, apixaban and edoxaban with dose reductions in patients with advanced CKD (CrCl 15-29 mL/min), but not in those with ESRD on dialysis [108, 180]. Since all RCTs of NOACs determined renal

function using CrCl calculated by the Cockcroft-Gault formula, it is recommended that this is used in clinical practice to guide anticoagulation with NOACs in patients with CKD [180].

In summary, despite the conflicting evidence for warfarin, it remains the anticoagulant of choice over NOACs in patients with CKD stage 5 or ESRD on dialysis in Europe. In the near future, left atrial appendage closure devices, which negate the requirement for long-term anticoagulation, may be an appealing option in ESRD patients with AF [115]. However, more data are needed to define the role of these devices in CKD populations compared with NOAC therapy before specific recommendations can be incorporated into national guidance [108, 181].

1.4.4 Antiplatelet agents

Antiplatelet agents are recommended for secondary prevention after AIS, based on robust evidence [33]. However, there have been no appropriately sized clinical trials to determine the efficacy of aspirin or other antiplatelet agents for stroke or other cardiovascular end points in patients with CKD or ESRD. A meta-analysis by Palmer *et al*. found that the evidence for antiplatelet agents for patients with CKD was of low quality and frequently derived from post-hoc analyses of trials of broader populations [182]. The review concluded that antiplatelet therapy (with aspirin, thienopyridines such as clopidogrel or glycoprotein IIb/IIIa inhibitors) reduced the risk of MI but did not appear to lower cardiovascular mortality or risk of stroke and importantly, increased major bleeding risk by 33% [182]. In a meta-analysis by the

Antithrombotic Trialists' Collaboration of high risk patients, aspirin was found to reduce serious vascular events including stroke, in HD patients by 41% [183]. However, the number of subjects was low, with just over 1000 patients in each group and less than 40 events in the antiplatelet group. Interestingly, patients with CKD and ESRD have higher rates of aspirin resistance than the general population [184], which is associated with an increased risk of cardiovascular events [184].

Taking all studies to date into account, there is currently insufficient evidence to define the role of antiplatelet therapy in both primary and secondary prevention of cardiovascular events in CKD. The potential bleeding hazards and lack of clear efficacy of antiplatelet agents for the prevention of AIS need to be acknowledged in patients with CKD and ESRD and discussed in that context. As for anticoagulation, the decision to treat with antiplatelet agents should probably be individualised to patients [185].

1.4.5 Chronic Kidney Disease – Mineral and Bone Disorder

CKD-MBD is a term used to describe mineral, bone and calcific cardiovascular abnormalities that develop as a complication of CKD. The definition by KDIGO encompasses the following criteria: 1) abnormalities of calcium, phosphorus, parathyroid hormone (PTH) or vitamin D metabolism; 2) abnormalities of bone turnover, mineralisation, volume, linear growth and strength; 3) vascular or other soft tissue calcification [186]. The term 'renal osteodystrophy', which was traditionally used to describe renal bone disease did not incorporate the more

diverse clinical spectrum (including serum biomarkers and imaging) of CKD-MBD and is now restricted to describing bone pathology on bone biopsy, which is infrequently performed in clinical practice [186].

It is known that arterial medial calcification of the aorta [187, 188] and intracranial arteries [189] increases in prevalence with age and worsening renal function. This leads to increased arterial stiffness and systolic BP, both of which are associated with an increased risk of stroke and subsequent mortality [187, 188, 190]. The biochemical markers of CKD-MBD, especially raised serum phosphate, PTH and fibroblast growth factor 23 have all been associated with increased mortality [191-194]. Although these observations are compelling, to date, a causal role for these abnormalities is yet to be proven [195]. Lowering of these parameters to target has failed to demonstrate any improvement in hard trial endpoints [196-199].

1.4.6 The Process of Haemodialysis

Although having ESRD in itself remains the greatest risk factor for stroke, several lines of evidence have suggested that the process of HD itself further increases the risk of stroke. Firstly, the risk of stroke is much higher in the first few weeks after starting dialysis [200, 201]. Secondly, strokes appear to be more common during or immediately after an HD session [202, 203]. Thirdly, strokes also appear to be more common after the weekend break from dialysis, when fluid overload and electrolyte abnormalities are at their peak [204]. The increased risk of stroke related to HD could potentially be explained by episodes of cardiovascular instability

causing hypotension or cerebral hypoperfusion during fluid removal, the induction of thrombogenic arrhythmias due to electrolyte shifts [205], or in the case of ICH, as a result of the temporary anticoagulation required during dialysis (despite dialysis correcting uraemic bleeding diathesis) [206].

The problem of haemodynamic changes during HD led to a trial where the addition of convection therapy to dialysis, termed haemodiafiltration, which promoted improved cardiovascular stability, was shown to significantly reduce all-cause and cardiovascular mortality as well as stroke deaths [207]. Other methods of increasing haemodynamic stability and thus reducing circulatory stress and cerebral dysfunction have been investigated, including daily dialysis and long nocturnal dialysis. Although the trials have been small, they have consistently been associated with improved surrogate markers of cardiovascular and cerebrovascular risk, including improved BP control, less LVH and improved serum biomarkers, particularly those related to CKD-MBD [208, 209]. Cooling of dialysate fluid has previously been shown to attenuate myocardial stunning during the dialysis process, with the effect of reducing intra-dialytic hypotension [210, 211]. More recently, a small RCT of 73 HD patients investigated the effect of using standard dialysate at body temperature versus cooled dialysate (0.5^{o}C below core body temperature) on white matter ultrastructural damage in the brain [212]. The cooled dialysate group exhibited greater haemodynamic stability and there were no statistically significant white matter changes on brain magnetic resonance imaging (MRI) at 1 year, compared with the standard dialysate group. These are promising findings,

but whether they can be reproduced in larger studies or translate into improved patient outcomes remains to be answered.

1.5 Acute Kidney Injury and the Risk of Stroke

Acute kidney injury (AKI) is defined and discussed in detail in Chapter 2. AKI and CKD are closely connected and it is recognised that pre-existing CKD is a risk factor for AKI [64, 213, 214] and conversely, that AKI is a risk factor for both the development of *de novo* CKD and accelerated progression of existing CKD [215-217]. A systematic review published in 2012 showed that the risk of CKD and ESRD increases with AKI severity [218]. The same study reported a pooled mortality HR of 1.98 (95% CI 1.26-3.11) for the AKI group compared with the non-AKI group [218].

To date, the risk of stroke after an episode of AKI has not been well studied. Odutayo *et al*. conducted a systematic review and meta-analysis of AKI and the long-term risk of cardiovascular events and found that AKI was associated with a 15% increased risk of stroke (RR 1.15; 95% CI, 1.03 to 1.28; I^2: 0%) [219]. AKI causes a cascade of inflammatory mediator release and uraemic sequelae, which have been proposed as pathophysiological mechanisms for endothelial dysfunction, inflammation and subsequent vascular events in the brain [220, 221]. These pathways have also been implicated in the development of acute cardiac dysfunction, including decompensated heart failure and arrhythmias in patients with AKI [222, 223], as well as an increased risk of CHF over time, which is thought to be secondary to the

effects of left ventricular remodelling in response to cytokines [224]. Indeed, Odutayo *et al*. reported an 86% higher risk of cardiovascular mortality and 38% higher risk of a cardiovascular event in patients who developed AKI [219]. An additional factor which may increase the risk of acute stroke in severe AKI is the HD process itself. This has been shown to inhibit chemotaxis, oxidation and apoptosis of polymorphonuclear leucocytes through exposure to dialysate fluid [225] and can cause haemodynamic instability and hypotension [226, 227], which can lead to cerebral ischaemia. Furthermore, heparinisation of the HD circuit may predispose patients to *de novo* ICH or HT of an acute infarct [228, 229].

The relationship between acute stroke and the subsequent development of AKI will form the basis of Chapters 2, 4 and 5 of this thesis, starting with a systematic review of the current literature in Chapter 2.

1.6 Management of Acute Stroke

1.6.1 Specialised Stroke Units

Specialised stroke units have been shown to decrease morbidity and mortality after a stroke in multiple studies over the last two decades [230-232]. A comprehensive systematic review by the Stroke Unit Trialists' Collaboration in 2013 found that patients who received care on a dedicated stroke unit were more likely to be alive, independent and living at home 1 year after a stroke event and there was no evidence that stroke unit care resulted in a longer inpatient

stay [231-234]. Regular communication, coordinated multidisciplinary care, strict adherence to protocols and best practice are all key features of stroke units [81].

Patients with advanced CKD or ESRD may preferentially be admitted to renal units for specialised renal care, including dialysis. Inadvertently, in doing this we may be denying these patients 'best care' for an acute stroke. Ideally, measures should be placed to ensure that patients who may potentially derive benefit have access to stroke units and that regular dialysis sessions have minimal impact on stroke treatment and rehabilitation. However, the demands placed on HD patients, both in terms of duration of actual treatment and the recovery period after an HD session, may make some interventions difficult (for example daily physiotherapy) and thus, negate the potential benefits offered by a dedicated stroke unit. Despite the multitude of evidence that patients with CKD or ESRD have worse mortality after stroke, there is a lack of studies investigating functional status and quality of life in these groups in comparison to the non-CKD population [206]. Studies aimed at investigating functional outcomes in CKD patients after a stroke, including decisions about renal (or indeed other medical) preferential care and the effect of dialysis treatment are needed.

1.6.2 Acute Reperfusion Therapy

The primary goal of reperfusion therapy in AIS is to quickly restore blood flow to salvageable ischaemic brain tissue (termed 'ischaemic penumbra') that has not irreversibly infarcted [235]. Recanalisation of an occluded artery produces tissue reperfusion, limiting the degree of tissue

injury and death, that unequivocally improves outcome and function in patients with AIS [236]. The therapeutic window for treatment is crucial- as more ischaemic tissue infarcts and the unsalvageable ischaemic core enlarges, the potential benefit of reperfusion diminishes [81, 236]. Figure 1-2 demonstrates evidence of 'ischaemic penumbra' in the right middle cerebral artery (MCA) territory on computerised tomography perfusion (CTP) brain parametric maps, which would be amenable to acute reperfusion therapy. Reperfusion treatments broadly fall into two categories: 1) thrombolysis with intravenous (IV) recombinant tissue plasminogen activator (rt-PA) and intra-arterial (IA) therapy approaches to directly remove the clot with mechanical thrombectomy alone or in conjunction with IA thrombolysis, which are discussed in sections 1.6.3 and 1.6.4 respectively.

Figure 1-2. CTP brain parametric maps.

Clockwise from left:

A) CBF map demonstrating a large area of reduced perfusion in the right MCA territory (*arrows*);

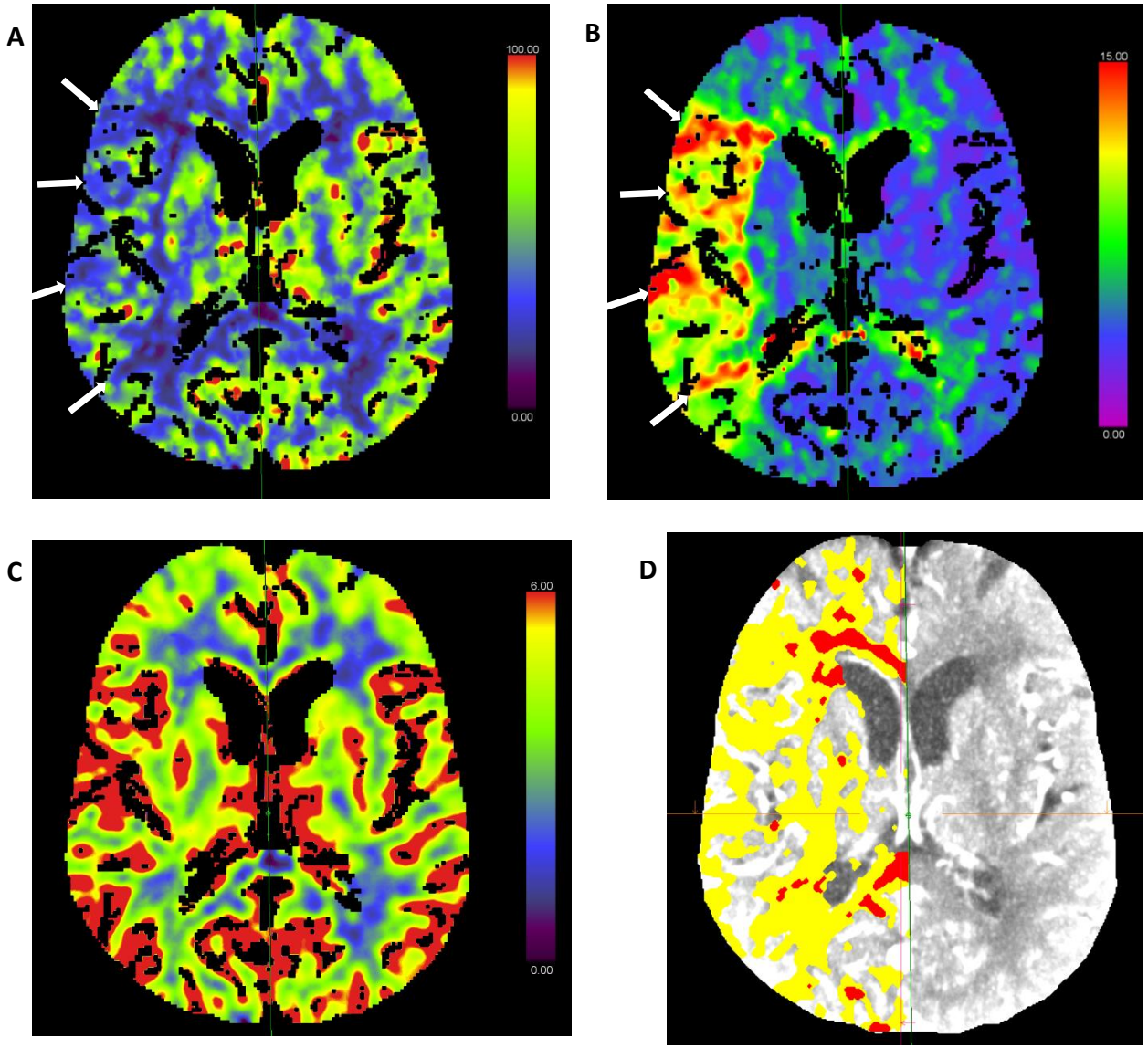
B) MTT map shows prolongation within the right MCA territory (*arrows*), corresponding with reduced CBF in the same region;

C) CBV map demonstrating no abnormality. This represents a CBV/ MTT mismatch or 'ischaemic penumbra' (salvageable brain tissue);

D) Map demonstrating region of 'ischaemic penumbra' (seen in *yellow*).

Abbreviations:

CTP = Computerised tomography perfusion; CBF = cerebral blood flow; MCA = middle cerebral artery; MTT = mean transit time; CBV = cerebral blood volume.



1.6.3 Intravenous thrombolysis

A systematic review and meta-analysis of 12 RCTs and 7012 patients investigating the effect of administration of IV rt-PA given within 6 hours of AIS found increased rates of symptomatic ICH (5.9%), fatal ICH (3.0%) and death (2.5%) in the first 7 days [237]. However, by the end of follow up (1-6 months), patients in the thrombolysis group had increased survival free of dependency (OR 1.17, 95% CI 1.06–1.29; P=0.001), and there was no significant difference in mortality compared with control (OR 1.06, 95% CI 0.94–1.20; P=0.33) [237]. These findings have been replicated in large observational studies [238, 239], confirming the trial findings and cost-effectiveness of IV rt-PA in clinical practice [240]. As such, thrombolysis with IV rt-PA has become the standard of care in many countries for patients with AIS. There is a paucity of data on outcomes of patients with CKD and ESRD who received thrombolysis treatment. A few studies have reported an increased bleeding risk in stroke patients with advanced CKD compared to patients with normal renal function after thrombolysis [241-244]. However, these were observational in design and included only small numbers of patients with CKD. To date, there is no good quality data on the use of IV rt-PA in dialysis patients.

Interestingly, a recent multi-centre RCT published in May this year showed that in patients with hypoperfused but salvageable areas of ischaemic brain tissue detected on perfusion imaging, thrombolysis treatment administered within 4.5 to 9 hours of symptom onset resulted in a higher proportion of patients with minor or no neurological deficit compared with placebo [245]. This may soon result in an extension of the current recommendation of the 4.5 hour time window and holds promise for improving stroke outcomes where time of

symptom onset is not exact or there are delays in presentation to hospital [246]. However, despite clear evidence of efficacy of IV rt-PA in the general population, strokes caused by large proximal arterial occlusions are more resistant to thrombolysis treatment. These account for about one third of all AIS and typically result in more severe neurological disability [236]. After IV rt-PA alone only 10-15% of internal carotid artery (ICA) occlusions and 25-50% of proximal MCA occlusions recanalise, and only 35-40% of patients achieve functional independence [247-249]. This has led to the development and study of techniques to improve recanalisation rates with more direct IA therapies, which are discussed in the following section.

1.6.4 Endovascular Treatments

Early studies established that endovascular treatments were effective in rapidly re-establishing blood flow after AIS. However, the first three RCTs of endovascular recanalisation published in 2013 failed to demonstrate any improvement in patient outcomes [248, 250, 251]. Several factors have been postulated to be responsible for these failures, including the fact that these trials were performed using IA thrombolysis or mechanical thrombectomy using first-generation devices, and the inclusion of patients who may have been less likely to benefit from endovascular reperfusion, for example, those who had mild to moderate stroke severity or absence of intracranial vessel occlusions confirmed on imaging (partly due to the limited availability of CT angiography (CTA) at that time) [252].

On the basis of these trial findings, five RCTs with stricter inclusion criteria and using second-generation stent-retriever devices published in 2015 showed overwhelming evidence of benefit in patients with AIS [253-257] (see Table 1-2). Interestingly, two of these trials excluded patients with significant renal impairment (exclusion criteria creatinine ≥3.0 mg/dL (265.2 µmol/L) in the 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 Eight Hours of Symptom Onset (REVASCAT) trial [257] and creatinine >2.0 mg/dL (176.8 µmol/L) or GFR <30 mL/min/1.73m^2 in the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial [256]) and only one published baseline renal function in the supplementary material [255] (Table 1-2). Furthermore, the average age of patients included in 4 of the 5 studies was less than 70. In more recent RCTs, who included patients up to the age of 85 years [258, 259], one made no mention of renal function at all [258]. The other did not report baseline renal function but explored renal failure as an adverse outcome and found no difference between the thrombolysis versus thrombolysis and thrombectomy group (6% (n=13) vs. 10% (n=21), P=0.12) [259]. It is unclear whether patients with advanced age and CKD and ESRD were not recruited into these studies by the investigators because of concerns regarding general frailty or potential renal toxicity from radiological contrast. As it stands, the risk-benefit ratio of endovascular treatment in patients with CKD and ESRD remains to be determined in a clinical trial and concerns about potential differences in efficacy, as well as adverse effects such as bleeding rates and the risk of AKI associated with the use of contrast media, remain unanswered.

Table 1-2. Summary of published intra-arterial thrombectomy trials in 2015.

Trial Acronym *n*	Baseline NIHSS (range)		mRS 0-2 at 90 days		Mortality		Mean age	Upper age limit	Baseline renal function	Renal exclusion criteria
	Control	Treated	Control	Treated	Control	Treated				
MR CLEAN[253] 500	18 (14-21)	17 (14-22)	19%	33%	19%	18%	65	None	Not reported	None specified
EXTEND IA[254] 70 (stopped early)	13 (9-19)	17 (13-20)	40%	71%	20%	9%	69	None	Not reported	None specified
ESCAPE[255] 315 (stopped early)	17 (12-20)	16 (13-20)	29%	53%	19%	10%	71	None	Control: 84 (SD 27) Treated: 84 (SD 28)	None specified
SWIFT PRIME[256] 196 (stopped early)	17 (13-19)	17 (13-20)	36%	60%	12%	9%	66	85	Not reported	Creatinine >176.8 µmol/L or GFR <30 mL/min/1.73m^2 or on dialysis
REVASCAT[257] 206	17 (12-19)	17 (14-20)	28%	44%	16%	18%	66	85	Not reported	Creatinine > 265.2 µmol/L

Abbreviations: NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale; SD, standard deviation; GFR, glomerular filtration rate.

Figure 1-3 shows successful recanalisation of the right MCA following mechanical thrombectomy using a stent-retriever device. Endovascular therapy (EVT) provides an alternative to thrombolysis for patients who are not eligible for rt-PA, either due to unknown time of symptom onset ("wake up" stroke), presentation outside the therapeutic window or other contraindications, or those who fail to recanalise after treatment. Yet only 5 to 10% of AIS are currently treated with EVT [260]. The AHA/ASA recommends the use of mechanical thrombectomy with a stent-retriever in combination with standard therapy (IV rt-PA) in AIS patients meeting the following criteria: aged ≥18 years, either ICA or proximal (M1) MCA occlusion on imaging, absence of a large infarct on CT (Alberta Stroke Programme Early CT Score (ASPECTS) ≥ 6), NIHSS score ≥ 6, premorbid functional independence (mRS score 0-1), angiographically confirmed large vessel occlusion (LVO) and presentation within 6 hours of symptom onset [81, 261]. Limitations to treatment include the rapid availability of specialist imaging, such as CTA to identify LVOs and CTP or magnetic resonance perfusion scans to identify ischaemic penumbra, as well as the appropriately skilled clinical staff required to perform these highly specialised interventions [262]. Further questions around widening the time window for patient selection using advanced imaging-based approaches, the use of local compared with general anaesthetic, treatment of posterior circulation strokes and multimodal reperfusion (or bridge) therapy (combining IV and endovascular treatment approaches) are yet to be addressed and the results of ongoing trials are eagerly awaited [263].

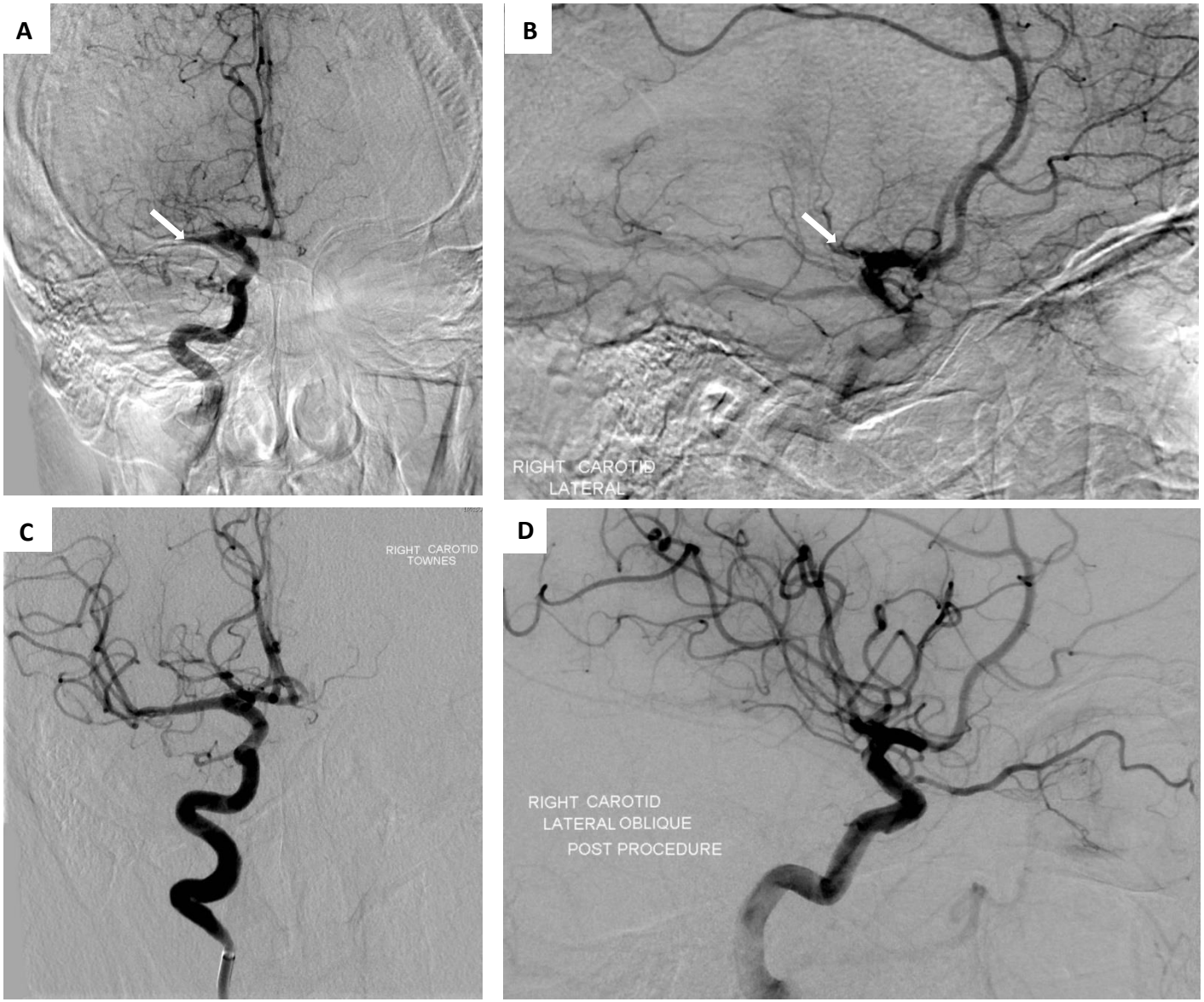


Figure 1-3. Mechanical thrombectomy for acute right MCA thromboembolic stroke.

Pre-treatment DSA: anterior (A) and lateral (B) views demonstrate proximal M1 occlusion of the right MCA. Defects are shown by *arrows*.

Post treatment DSA: anterior (C) and lateral (D) views demonstrate recanalisation of the proximal MCA and restoration of flow in its distal branches.

Abbreviations: MCA, middle cerebral artery; M1, most proximal (sphenoidal) segment of MCA; DSA, digital subtraction angiogram.

1.7 Conclusions

Stroke remains a major cause of disability and mortality worldwide. The increased risk found in CKD and ESRD patients is being more widely recognised but current thought processes about risk are insufficient to explain the pathophysiology, which remains poorly understood. In keeping with most conditions associated with CKD and ESRD, there is a distinct lack of good quality large RCTs with which to guide treatment. Proven effective therapies for reversing such a sizeable stroke risk in patients with CKD, and especially ESRD, do not exist. History has shown that blindly extrapolating the results of trials in the general population to patients with CKD and ESRD, who have an increased level of comorbidity and unique pathophysiological factors which influence cardiovascular disease processes, is unwise. This situation needs to be urgently addressed, especially in light of the rapid development of interventions to reduce stroke risk and improve functional outcomes after stroke in the general population.

1.8 What's next?

In the following chapters of this thesis, I will now attempt to address some of the gaps in the literature on stroke and outcomes in the setting of renal dysfunction, namely AKI and CKD. In Chapter 2, I will discuss the history, definitions and clinical importance of AKI, before going on to present the results of a systematic review and meta-analysis of the current literature on AKI incidence in patients hospitalised with acute stroke and its influence on outcomes. In Chapter 3, I describe how I set up a retrospective observational study investigating the influence of renal dysfunction on outcomes and stroke treatments using a multi-source

dataset of hospitalised stroke patients at a large tertiary centre, the Queen Elizabeth Hospital Birmingham (QEHB). In Chapter 4 I describe the incidence of AKI in the study cohort and explore the methodology of ascertaining a diagnosis of AKI, comparing the performance of five different methods. In Chapter 5, I describe the influence of AKI on mortality using the five different methods outlined in Chapter 4. In Chapter 6, I explore the prevalence of CKD in the study cohort and the relationship between CKD and mortality. I also investigate whether the presence of CKD influences whether stroke treatments are received. In Chapter 7, I present the radiological imaging results of the study cohort and how the findings relate to the presence of CKD. I also explore complications of therapy including AKI following exposure to radiological contrast and risk of HT or bleeding post-thrombolysis or thrombectomy. Finally, in Chapter 8, I conclude by discussing to what extent my study has addressed deficiencies in the available data and future directions of study.

CHAPTER 2 INCIDENCE AND IMPACT ON OUTCOMES OF ACUTE KIDNEY INJURY AFTER STROKE: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 Introduction

2.1.1 History of Acute Kidney Injury

The term AKI, formerly known as acute renal failure (ARF), is only a few years old, yet the condition has afflicted humans long before medicine was invented. Early medicine describes reduced or increased urine output and the discomfort associated with the passage of renal calculi [264]. Interestingly, polyuria was termed diabetes in the 2nd century Before the Common Era (BCE) [265] and in the centuries that followed oliguria came to be recognised as a poor prognostic sign in other diseases [266]. Galen (circa 129 – c. 216/217 CE), a Greek physician and philosopher in the Roman Empire, gives the clearest historical description of causes of anuria due to 'kidney infection', bloody urine caused by renal calculi, malignancy or glomerulonephritis and 'tissue fragments' caused by papillary necrosis or malignancy [267].

Emergence of a true concept of ARF came about during the period of the notable military conflicts, World War 1 (WW1) and World War 2 (WW2), where cases of severe traumatic injuries and shock were frequently observed to lead to renal failure. Alfred Newton Richards (1876-1966), an American Pharmacologist, first determined the functions of the nephron [268, 269]. Building on studies from WW2 (1939-1945) and the description of the 'crush

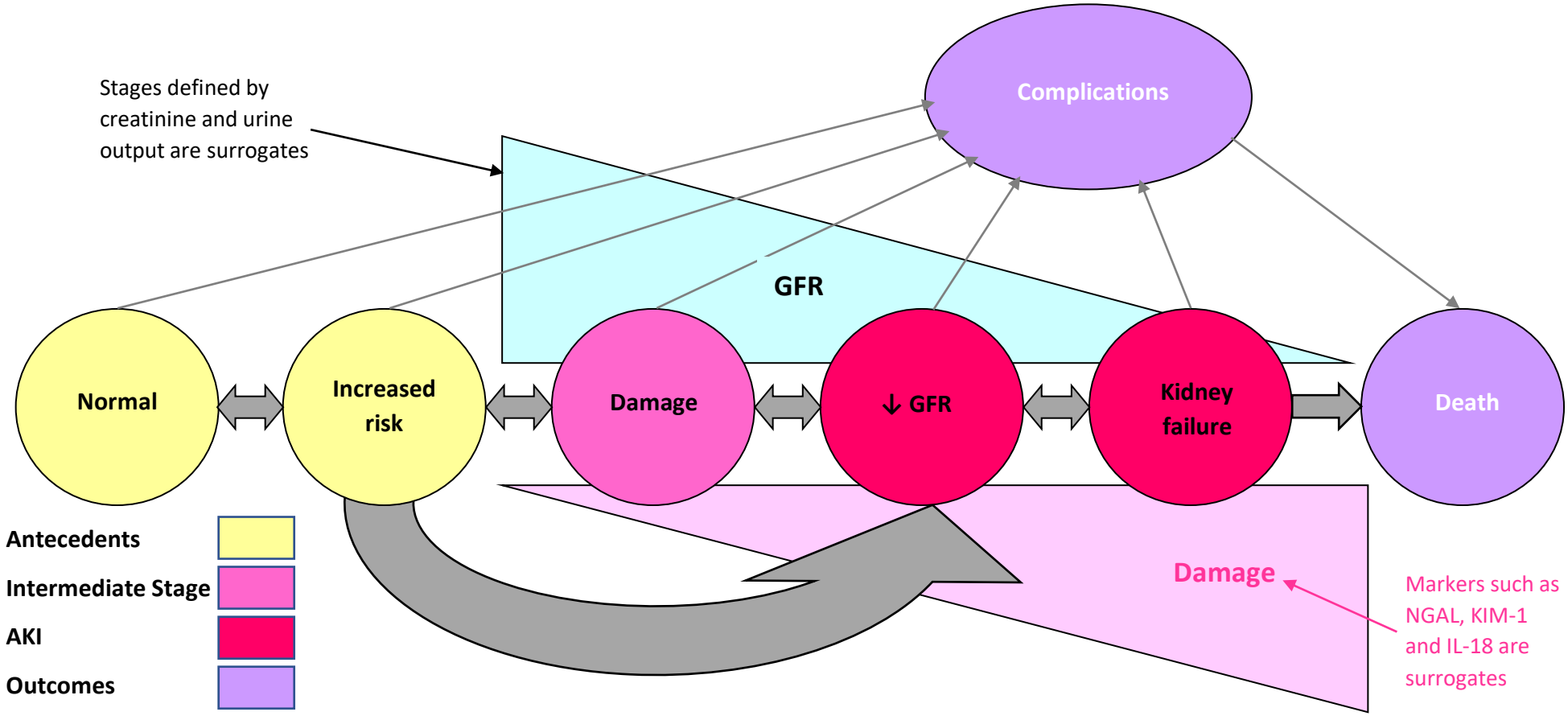
kidney' [270], Jean Redman Oliver (1889-1976), an American pathologist, described a number of models of both toxic and ischaemic renal injury in humans and animals which greatly contributed to the understanding of the underlying pathophysiology of ARF [271]. Notably, Homer William Smith (1895-1962), an American renal physiologist, worked extensively on mechanisms of renal clearance of solutes and water and developed non-invasive methods for the measurement of GFR, ultimately introducing the term 'acute renal failure' [272, 273].

In the post-war period, ARF was now a reversible and treatable condition. Willem Johan Kolff (1911-2009), who developed the first 'artificial kidney' in a rural hospital during WW2, was a pioneer of HD treatment and went onto develop cardiopulmonary bypass machines [274, 275]. John Putnam Merrill (1917-1984), an American physician, described the clinical course, treatment and potential reversibility of ARF [276]. He fully appreciated that HD was not a cure for ESRD and went on to the lead the team who performed the world's first successful kidney transplant between identical twins in 1954 [277]. George Schreiner (1922-2012), another prominent American Nephrologist, also contributed to the understanding of ARF and dialysis treatment in that era [278].

The concept of AKI as we know it has been largely influenced by the development of a definition of CKD within a public health model [41]. In this model, CKD is defined as evidence of kidney damage lasting 3 months or more. This implies that a reduction in kidney function of less than 3 months duration may potentially be reversible and may therefore be considered

a separate entity to CKD. Based on this, a conceptual model of AKI was developed (Figure 2-1) [279, 280]. This model is analogous to that of CKD, in that both AKI and CKD can progress to ESRD but may initially present in less severe forms. The evolution of ARF into AKI can therefore be explained by the concept that AKI is a preventable or treatable illness at earlier stages and therefore an important public health problem on which to focus further research efforts. ARF, seen as a finite condition, such as ESRD, was therefore replaced by the term AKI.

Figure 2-1. A conceptual model for AKI. Adapted from Murray *et al*. Clin J Am Soc Nephrol 2008; 3 (3): 864–868 [279]. AKI, acute kidney injury; GFR glomerular filtration rate; IL-8, interleukin-18; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin.



In this model, the red circles represent stages of AKI, the yellow circles potential antecedents of AKI, and the pink circle represents an intermediate stage, not yet defined. The thick grey arrows between the circles represent risk factors associated with the initiation and progression of disease that can be influenced or detected by interventions. The purple circles represent outcomes following AKI. "Complications" refers to all complications of AKI, including efforts at prevention and treatment, and complications in other organ systems.

2.1.2 Definition of Acute Kidney Injury

AKI is broadly defined as a rapid reduction in kidney function resulting in a failure to maintain fluid, electrolyte and acid-base homeostasis. AKI is considered to be a spectrum, extending from mild, asymptomatic injury to severe injury requiring acute RRT. Until recently, the renal community lacked a unanimous definition of AKI. In order to address this, several classifications were devised by the Acute Dialysis Quality Initiative (ADQI), namely the Risk, Injury, Failure, Loss of function and End-stage renal disease (RIFLE) [281] and Acute Kidney Injury Network (AKIN) [282] staging criteria, shown in Table 2-1. Most recently, the RIFLE and AKIN criteria have been assimilated to form the most current staging system, KDIGO [280], which has now been adopted globally (Table 2-1).

The kidney is a robust organ that can withstand a variety of insults without sustaining any structural or functional damage [280]. Therefore, any acute change in renal function is likely to reflect severe systemic illness and often confers a poor prognosis. As such, it is recognised that even small rises in serum creatinine (SCr) are associated with worse outcomes [283, 284]. The risk of AKI is determined by both exposure to factors that cause AKI and the presence of factors that increase susceptibility to AKI [280]. Risk factors for AKI are shown in Table 2-2.

Table 2-1. Classification Systems for AKI: 1) RIFLE, 2) AKIN and 3) KDIGO. Adapted from Bellomo et al. Crit Care 2004;8:R204 [281], Mehta et al. Crit Care 2007;11:R31 [282], KDIGO 2012 Clinical Practice Guideline for Acute Kidney Injury [280].

RIFLE Classification				**AKIN Classification**			**KDIGO Classification**		
Class		**GFR**	**UO**	**Stage**	**Serum Cr**	**UO**	**Stage**	**Serum Cr**	**UO**
Severity	**1 Risk**	↑ SCr × 1.5 or ↓ GFR >25%	<0.5 mL/kg/h for 6 h	**1**	↑ SCr ≥26.5 µmol/L (≥0.3 mg/dL) or ↑SCr ≥150 - 199% (1.5–1.9 fold increase from baseline)	<0.5 mL/kg/h (>6 h)	**1**	1.5–1.9 times baseline OR ≥0.3 mg/dL (≥26.5 mmol/L) increase	≤0.5 mL/kg/h for 6–12 h
	2 Injury	↑ SCr × 2 or ↓ GFR >50%	<0.5 mL/kg/h for 12 h	**2**	↑ SCr >200 -299% (2–2.9 fold increase from baseline)	<0.5 mL/kg/h (>12 h)	**2**	2.0–2.9 times baseline	≤0.5 mL/kg/h for ≥12 h
	3 Failure	↑ SCr × 3 or ↓ GFR >75% or if baseline SCr ≥353.6 µmol/L(≥4 mg/dL) ↑ SCr >44.2 µmol/L (>0.5 mg/dL)	<0.3 mL/kg/h for 24 h or anuria for 12 h	**3***	↑ SCr >300% (>3 fold increase from baseline) **OR** if baseline SCr ≥353.6 µmol/L (≥4 mg/dL) ↑SCr ≥44.2 µmol/L (≥0.5 mg/dL) **OR** initiation of RRT independent of SCr	<0.3 mL/kg/h (24 h) or anuria (>12 h)	**3**	3.0 times baseline **OR** increase in SCr to ≥4.0 mg/dL (≥353.6 mmol/L) **OR** initiation of renal replacement therapy **OR** in patients of 18 years, decrease in GFR to <35 mL/min per 1.73 m^2	≤0.3 mL/kg/h for ≥24 h **OR** anuria for ≥12 h
Outcome	**Loss of function**	Complete loss of kidney function for >4 weeks		*Stage 3 also includes patients requiring RRT independent of the stage (defined by SCr and/or UO) they are in at the moment they initiate RRT.					
	End stage renal disease	Complete loss of kidney function for >3 months							

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; SCr, serum creatinine; RIFLE, Risk, Injury, Failure, Loss of function and End-stage renal disease; RRT, renal replacement therapy; UO, urine output.

Table 2-2. Risk factors for Acute Kidney Injury. Adapted from Kellum *et al*. Kidney Int Suppl 2012;2(1):1-138 [280].

Exposures	**Susceptibilities**
Sepsis	Dehydration or volume depletion
Critical illness	Advanced age
Circulatory shock	Female gender
Burns	Black race
Trauma	Chronic kidney disease
Cardiac surgery (especially cardiopulmonary bypass)	Chronic diseases of the heart, lung and liver
Major non-cardiac surgery	Diabetes mellitus
Nephrotoxic drugs	Cancer
Radiocontrast agents	Anaemia
Poisonous plants and animals	

2.1.3 AKI and Outcomes

The incidence of AKI has increased over time [285, 286]. Multiple factors are considered to be responsible for this rise, including population factors such as an increase in CVD, diabetes and CKD, as well as increased identification through wider recognition amongst clinicians and advances in diagnostic testing and classification systems [287, 288]. AKI is common in

hospitalised patients, with an estimated world incidence of 20% using KDIGO derived definitions [289]. Numerous studies over the last decade have shown AKI to be associated with poor outcomes, including increased LOS and mortality [290-295]. For example, Chertow *et al*. found a 6.5-fold increase in the odds of death and a 3.5 day increase in LOS for a SCr rise of ≥0.5mg/dl (stage 2 and 3 AKI) in a study of 19,982 patients in a San Francisco hospital [292]. The mortality rate in patients with AKI in a critical care setting and where RRT is required is estimated to be over 50% [296, 297]. Not surprisingly, the cost of AKI to the NHS is great, with an estimated £1.02 billion pounds, just over 1% of the NHS budget, being spent on inpatient care alone [298]. In a recent US study, adjusted hospitalisation costs of patients with AKI were $1795 greater than for patients without AKI, with costs rising to $11,016 for patients requiring RRT [295].

2.1.4 Use of Electronic Health Records for Acute Kidney Injury Research

Over the last decade, with the development and wide adoption of an international classification system [280-282], there has been an increasing amount of research into the incidence of AKI and its potential role as a contributor to adverse outcomes in a number of conditions in both high and low income countries [283, 292, 299, 300]. Within this timeframe, research using 'big data' has risen exponentially. Big data research refers to the use of large, complex datasets for predictive and risk stratification modelling [301]. Massive advances in computational technology and a drive for increased collaboration have led to the adoption of eResearch [302]. eResearch has been widely utilised in health informatics and is particularly suited to use in AKI research, since AKI can be defined using a range of numerical values that

are easily programmed [303]. In addition, SCr values may be readily available in the electronic health record (EHR) of a patient, along with significant comorbidities, medications and basic demographic information, all of which can be harnessed for research purposes. However, programming criteria in order to extract this data is challenging for a number of reasons, including consideration of a definition of a reference SCr to use as a baseline for comparison and subsequent ascertainment of AKI.

To date, most AKI and EHR studies have used retrospective 'data mining' of administrative coding data, which is recognised to have numerous confounders. These include bias from the individual coder, who may be a physician or another member of staff, institution bias and inaccurate documentation on, for example, 'renal dysfunction' without further specifying whether this is acute or chronic [304]. Information such as urine output is also lacking in such studies [305]. Studies using coding data are known to underestimate the burden of AKI and are more likely to detect higher stages of AKI, which equates to higher mortality [306]. Administrative data, even with its limitations, may still be a useful tool in AKI research, particularly in conjunction with the vast amount of laboratory data held in EHR [303].

2.1.5 Ascertainment of Acute Kidney Injury

As discussed above, EHR is a powerful tool for eResearch in AKI. However, there are a number of limitations which require attention. An appreciation of which data is available, as well as

that which is not, is essential for validity. Most important amongst data for AKI research is the availability of a preadmission SCr value. Diagnosing AKI relies on determining a change in SCr from a reference or 'baseline' value, that is, preadmission SCr [280]. Several studies to date have suggested a suitable timeframe for obtaining a baseline is 7 to 365 days prior to admission [307-313]. However, preadmission SCr values can be missing in approximately 50% of patients [314]. Although preadmission SCr is the preferred reference, it has its own limitations. These include the fact that blood tests in the outpatient setting may be prompted because of an acute illness or for monitoring of chronic conditions. Such patients may not be representative of the normal population. Both such factors may introduce bias. In addition, different laboratory assays for measuring SCr may be used in the outpatient versus inpatient setting, although the risk of error is likely to have reduced significantly since the introduction of the isotope dilution mass spectrometry (IDMS) standard [315-317].

In circumstances where preadmission SCr is missing, first SCr on admission, lowest SCr during admission or back-calculated SCr can be used as a reference or 'baseline'. AKIN [308, 309] and the European Renal Best Practice (ERBP) working group [318] recommend first SCr on admission to diagnose AKI, where preadmission SCr is unavailable. However, this method has low sensitivity and may therefore fail to detect AKI, particularly milder stages [308, 319]. It may also miss community-acquired AKI or AKI which is evolving around the time of hospital admission [320, 321]. Use of lowest or nadir SCr has been investigated in several studies and found to overestimate the incidence of AKI by up to 50% [308, 319, 322]. Depending on the

method used, worsening CKD on hospital admission may be incorrectly diagnosed as AKI, with one study reporting a misclassification rate of 14% [323].

Another strategy to deal with missing preadmission SCr is to assume a low normal eGFR of 75 mL/min/1.73m^2 and back-calculate SCr using the Modification of Diet in Renal Disease (MDRD) equation (outlined in Chapter 3, section 3.14). This is the recommended method by ADQI [281, 324] and KDIGO [280]. This may be a suitable method where preadmission SCr is unavailable and patients have suspected community-acquired AKI [321]. However, AKI incidence can be overestimated in cases where a patient has CKD but this has been missed or is unknown [308, 320]. Consequently, this method is unsuitable for diagnosing AKI in a population with CKD [320, 321]. In addition, if the assigned low normal eGFR of 75 mL/min/1.73m^2 is too low, for example in young adults or children, then AKI may be underestimated [325].

Urine output criteria are incorporated into both the definition and staging of AKI, and oliguric AKI is recognised as a more severe phenotype than azotaemia alone [280, 326]. However, the accuracy of urine measurements can be challenging in the clinical setting and this is further compounded by the need for large amounts of electronic data to be adjudicated for accuracy and missingness before reaching a suitable state for analysis.

2.1.6 Acute Kidney Injury after a Stroke

AKI is common in hospitalised patients and associated with worse outcomes, including increased mortality [289, 292]. After a stroke, neurological deficit leading to dysphagia and physical disability, physiological effects including changes in BP and cerebral salt wasting, as well as subsequent investigations and treatments, can all potentially contribute to the development of AKI. Furthermore, older, comorbid patients at increased risk of stroke are also most susceptible to AKI [292]. Strategies to prevent AKI in stroke patients, thus leading to improved outcomes could therefore be of great importance. Although the association between CKD and stroke outcomes has been the subject of several systematic reviews and meta-analyses [68, 169], the relationship between AKI and stroke is much less clear.

2.2 Aims

I therefore aimed to define the pooled incidence of AKI after a stroke and the associations between AKI and outcomes.

2.3 Methods

This systematic review was registered with PROSPERO (CRD42017064588) and adhered to the PRISMA reporting statement [327]. A literature search of MEDLINE was performed from 1946 through to 30 June 2017 using relevant text words and medical subject headings *acute kidney*

injury, acute kidney failure, acute renal failure, acute renal insufficiency, combined with *stroke, cerebrovascular disorders and CVA* or *TIA*. Embase was searched from 1974 to 30 June 2017, using the same medical subject headings for AKI as for MEDLINE, combined with *cerebrovascular accident, cerebrovascular disease, cerebrovascular disorder, brain haemorrhage; brain infarction* and *stroke*. A detailed search strategy is outlined in Table 2-3. All searches were limited to human studies with no language restrictions. The reference lists of all retrieved articles were also manually reviewed for additional relevant studies.

2.3.1 Study Selection

Study eligibility was determined using a standardised proforma (Appendix 1). Titles and abstracts of all studies were individually screened for relevance before obtaining full text versions of studies deemed to be eligible for inclusion. To improve generalisability, studies were included if they were a case control or cohort (prospective or retrospective) study and had a sample size greater than 500 adult subjects hospitalised with either AIS or ICH [289]. Included studies had a clear statement regarding the definition of AKI- SCr values alone were not sufficient. SAH was not included in this systematic review in view of the different underlying pathophysiology.

2.3.2 Data collection and analysis

Data was collected using a standardised proforma (Appendix 1). The following study details were recorded: authors, year of publication, country of publication, type of study, clinical setting, sample size, patient characteristics (age, sex, ethnicity, and comorbidities), definition, type and severity of stroke and definition of AKI. Clinical parameters on admission, including SCr and/or eGFR, exposure to radiocontrast media (where specified) and number of patients who developed AKI were recorded. Outcomes including mortality, disability, LOS, re-stroke or cardiac events were also recorded.

Study quality assessment was performed using the Newcastle-Ottawa Scale [328]. A maximum of 9 points can be allocated to a particular study based on quality of selection, comparability and study outcome, including follow up. Scores were defined as poor (0-3), fair (4-6) and good (7-9) [289].

Data synthesis, meta-analysis and statistical analysis were performed using Review Manager v5.3.5 software (The Cochrane Collaboration, UK) and StatsDirect v3.0 (StatsDirect Limited, UK). Meta-analysis of proportions was carried out using the Stuart-Ord (inverse double arcsine square root) method in a DerSimonian-Laird (random effects) model [329]. The OR with accompanying 95% CI were used to report individual and summary effect measures for dichotomous data. Chi squared tests for heterogeneity were performed to examine if the degrees of freedom were greater than the Cochran Q statistic, with α of below 0.05 considered

to be statistically significant. In addition, the I^2 statistic was calculated to provide the estimated percentage of heterogeneity observed. I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity. Any heterogeneity was further explored. A two-sided P value of <0.05 was considered significant for all analyses.

Table 2-3. Search strategies in MEDLINE and Embase.

MEDLINE	EMBASE
1. acute kidney injury.mp. or exp Acute Kidney Injury/ 2. acute kidney failure.mp. 3. acute renal failure.mp. 4. acute renal insufficiency.mp. 5. 1 or 2 or 3 or 4 6. exp Stroke/ 7. cerebrovascular disorders.mp. 8. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or brain ischemia/ or cerebral small vessel diseases/ or "intracranial embolism and thrombosis"/ or intracranial hemorrhages/ or stroke/ 9. stroke.mp. 10. (CVA or TIA).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] 11. 6 or 7 or 8 or 9 or 10 12. 5 and 11 13. Limit 12 to humans	1. acute kidney failure.mp. or exp acute kidney failure/ 2. acute kidney injury.mp. 3. acute renal failure.mp. 4. acute renal insufficiency.mp. 5. 1 or 2 or 3 or 4 6. exp cerebrovascular accident/ or exp cerebrovascular disease/ 7. cerebrovascular disorder.mp. 8. cerebrovascular accident.mp. 9. cerebrovascular disease.mp. 10. brain hemorrhage.mp. or exp brain haemorrhage/ 11. brain infarction.mp. or exp brain infarction/ 12. stroke.mp. 13. 6 or 7 or 8 or 9 or 10 or 11 or 12 14. 5 and 13 15. Limit 14 to humans

2.4 Results

2.4.1 Study characteristics

A total of 6173 potentially relevant citations were identified (Figure 2-2), of which 816 were duplicates. A further 5309 articles were excluded after review of title and abstract and an additional 40 excluded after full text review. The characteristics of the eight included studies are displayed in Table 2-4 [330-337] and the study outcomes summarised in Table 2-5. All eight studies were published in the English language between 2007 and 2015. Seven studies were considered to be of good quality and one of fair quality. The eight studies provided data on 12,325,652 patients (range 897 to 7,068,334) from four countries (five from US [331, 333-335, 337], and one each from China [332], Greece [336] and Romania [330]).

The US studies overwhelmingly had the largest sample sizes, with a total of 12,319,724 patients representing 99.9% of all included patients. Three of the US studies used Nationwide Inpatient Sample (NIS) data [334, 335, 337]. Although the same database was used, one study included only patients with AIS [334], one study included only patients with ICH [335] and a third included only patients who sustained AKI-D [337]. Therefore, it was considered appropriate to include only the first two in the meta-analysis [334, 335].

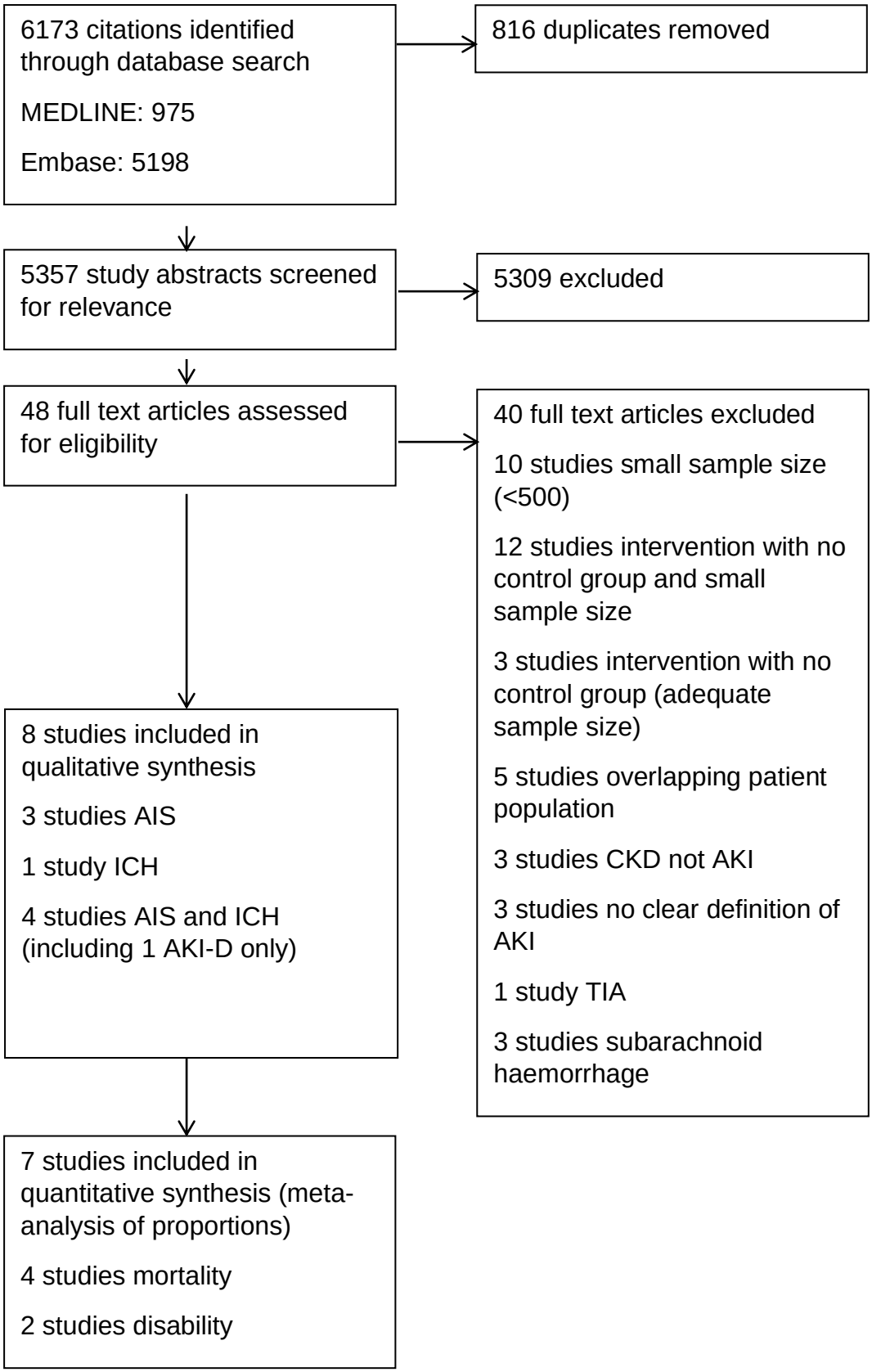
Five out of eight studies used the International Classification of Diseases-9th or 10th Edition (ICD-9/ 1CD-10) coding to define AKI [332-335, 337] and AKI-D [337]. Only one of the studies reported data on AKI-D in addition to overall AKI incidence [335]. Of the three studies that used SCr values, two used the AKIN classification [331, 336] and one the RIFLE classification

[330]. Although there are some differences in the grading of AKI severity between these classifications, both define the absolute incidence of AKI as an increase in serum creatinine >150%. None of the studies used urine output criteria.

Stroke was determined using ICD-coding in four studies [333-335, 337]. Three studies utilised the WHO definition of stroke [30] and extracted clinical data from medical records prospectively [332, 336] or retrospectively [330]. Two studies [332, 336] further subclassified the aetiology of ischaemic stroke using TOAST criteria (see Chapter 1, section 1.2) [34]. One study utilised stroke registry data as well as clinical records and ICD-coding [331]. AIS and ICH patients were included in four of the studies [330, 331, 336, 337], AIS alone in three [332-334] and ICH alone in one study [335].

Two studies excluded patients with known CKD [334, 335] and two studies excluded patients with ESRD [331, 337] (Table 2-4). Five studies followed patients until discharge from hospital [331, 333-335, 337], one for 30 days [330], one from hospitalisation up to one year [332] and one from 30 days up to 10 years [336] (Table 2-5).

Figure 2-2. PRISMA flow diagram for literature search and study selection.



Abbreviations: AIS, acute ischaemic stroke; AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis treatment; CKD, chronic kidney disease; ICH, intracranial haemorrhage; TIA, transient ischaemic attack.

Table 2-4. Characteristics of the 8 studies included in the systematic review.

Author	Type of study/ country	No. of subjects	Age (years) (SD)	Men (%)	AIS cases (%)	AKI definition	CKD excluded?	NOS score
Covic et al., 2008[330]	Observational, retrospective, Romania	1090	66.1 ± 11.5	49.3	932 (85.5%)	Creatinine values; RIFLE	No	7 (3, 2, 2)
Khatri et al., 2014[331]	Observational, retrospective, United States	1357	64 ± 16	56.0	528 (38.9%)	Creatinine values; AKIN	GFR <15 mL/min excluded	6 (2, 2, 2)
Lin et al., 2011[332]	Observational, prospective, China	2683	66.1 ± 13.59 (AF) 63.58 ± 13.64 (no AF)	58.4	2683 (100%)	ICD-10 coding	No	7 (3, 2, 2)
Mohamed et al., 2015[333]	Observational, retrospective, United States	897	64.4 ± 14.7	44.0	897 (100%)	ICD-9 coding	No	7 (3, 2, 2)
Saeed et al., 2014[334]	Observational, retrospective, United States (Nationwide Inpatient Sample data)	7,068,334	No AKI: 71 ± 31 AKI: 74 ± 28	46.1	7,068,334 (100%)	ICD-9 coding	Yes	7 (3, 2, 2)

Author	Type of study/ country	No. of subjects	Age (years) (SD)	Men (%)	AIS cases (%)	AKI definition	CKD excluded?	NOS score
Saeed et al., 2015[335]	Observational, retrospective, United States (Nationwide Inpatient Sample data)	614,454	No AKI: 69 ± 37 AKI: 68 ± 34	52.2	All cases were haemorrhagic stroke (0%)	ICD-9 coding	Yes	7 (3, 2, 2)
Tsagalis et al., 2008[336]	Observational, prospective, Greece	2155	70.3 ± 11.9	61.2	1832 (85%)	Creatinine values; AKIN	No	8 (4, 2, 2)
Nadkarni et al., 2015[337] AKI-D only	Observational, retrospective, United States (Nationwide Inpatient Sample data)	4,634,682	AIS No AKI: 73 ± 0.2 AKI: 66 ± 0.3 ICH No AKI: 69.7 ± 0.13 AKI: 65.4 ± 0.21	AIS 50.0 ICH 60.0	3,937,928 (85%)	ICD-9 coding AKI-D only	No	7 (3, 2, 2)

Abbreviations: AIS, acute ischaemic stroke; AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis treatment; AKIN, Acute Kidney Injury Network; CKD, chronic kidney disease; GFR, glomerular filtration rate; ICD-9/ ICD-10, International Classification of Diseases- 9th/ 10th Edition; ICH, intracranial haemorrhage; NOS, Newcastle-Ottawa Scale; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease.

Table 2-5. AKI risk factors, measured outcomes and adjustments in the 8 included studies.

Study	Follow up	Factors associated with AKI	Crude Mortality in AKI	AKI an independent risk factor for mortality	Disability and AKI	LOS (days) and AKI	Cost and AKI
Covic et al., 2008[330]	30 days	Age, renal function on admission, IHD, CHF, haemorrhagic stroke	43.1% vs 12.8% (P=0.001)	No	Not reported	Not reported	Not reported
Khatri et al., 2014[331]	Hospital discharge	Admission creatinine, NIHSS score	AIS: 33% vs 10% (P≤0.001) ICH: 40% vs 30% (P=0.020)	For AIS only OR 3.08 (95% CI 1.49-6.35, P=0.002) Adjusted for age, sex, ethnicity, comorbidities, smoking, CTA, creatinine, NIHSS score	Not reported	Unadjusted AIS: 17.6 vs. 8.4 days (P≤0.001) ICH: 13.0 vs 8.0 days (P≤0.001)	Not reported
Lin et al., 2011[332]	1 year	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Study	Follow up	Factors associated with AKI	Crude Mortality in AKI	AKI an independent risk factor for mortality	Disability and AKI	LOS (days) and AKI	Cost and AKI
Mohamed et al., 2015[333]	Hospital discharge	Not reported	Not reported	Not reported	Not after adjustment	OR 2.63, 95% CI 1.51-4.58 Adjusted for comorbidities, complications, NIHSS score	Not reported
Saeed et al., 2014[334]	Hospital discharge	Not reported	8.4% vs 2.9% (P≤0.001)	OR 2.2 (95% CI 2.0-2.2, P≤0.001) Adjusted for age, sex, ethnicity, comorbidities, GI bleeding, sepsis, nicotine dependence	OR for moderate/ severe disability 1.3 (95% CI 1.3-1.4, P≤0.001) Adjusted as for mortality	Unadjusted 6 vs. 4 days (P <0.0001)	Unadjusted USD 38,613 vs. 24,474 (P<0.0001)

Study	Follow up	Factors associated with AKI	Crude Mortality in AKI	AKI an independent risk factor for mortality	Disability and AKI	LOS (days) and AKI	Cost and AKI
Saeed et al., 2015[335]	Hospital discharge	Not performed	AKI: 28.7% vs 22.4% (P≤0.001) AKI-D vs AKI: 50.2% vs 28.4% (P≤0.001)	OR 1.5 (95% CI 1.4-1.6, P≤0.001) Adjusted for age, sex, ethnicity, comorbidities, nicotine dependence, alcohol abuse, hospital bed size, hospital teaching status	OR for moderate/ severe disability 1.2 (95% CI 1.1-1.3, P≤0.001) Adjusted as for mortality	Unadjusted 12 vs. 7 days (P <0.0001)	Unadjusted USD 104,142 vs. 54,315 (P<0.0001)
Tsagalis et al., 2008[336]	10 years	NIHSS score, CHF, ICH, GFR	30-day mortality 21.8% vs. 12.5% (P=0.001) 10-year mortality 75.9% vs. 57.7% (P=0.001)	10-year HR 1.24 (95% CI 1.07-1.44, P≤0.01), Adjusted for sex, SBP, haematocrit, comorbidities, brain oedema, antihypertensives, statin use	Not reported	Not reported	Not reported

Study	Follow up	Factors associated with AKI	Crude Mortality in AKI	AKI an independent risk factor for mortality	Disability and AKI	LOS (days) and AKI	Cost and AKI
Nadkarni et al., 2015[337] AKI-D only	Hospital discharge	Not performed	AIS: 31.8% vs. 5.6% (P≤0.01) ICH: 40.4% vs. 28.5% (P≤0.01)	AIS: OR 1.30 (95% CI 1.02-1.48, P≤0.001) ICH: OR 1.95 (95% CI 1.61-2.36, P≤0.01) Adjusted for demographics, hospital characteristics, Charlson comorbidity index and other diagnoses	OR for adverse discharge category AIS: 1.18, 95% CI 1.02-1.37, P≤0.01 ICH: 1.74; 95% CI 1.34-2.24, P≤0.01 Adjusted as for mortality	Unadjusted AIS: 14.1 vs. 3.6 days (P≤0.01) ICH: 23.5 vs. 5.3 days (P≤0.01)	Unadjusted AIS: USD 32,596 vs. 8039 (P≤0.01) ICH: USD 58,111 vs. 11,255 (P≤0.01)

Abbreviations: AF, atrial fibrillation; AIS, acute ischaemic stroke; AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis treatment; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence intervals; CT, computerised tomography; CTA, computerised tomography angiography; GFR, glomerular filtration rate; GI, gastrointestinal; ICH, intracranial haemorrhage; IHD, ischaemic heart disease; LOS, length of stay; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; OR, Odds Ratio; RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease; SBP, systolic blood pressure; TIA, transient ischaemic attack; USD, United States Dollars.

2.4.2 Pooled Incidence of AKI after stroke

Nadkarni *et al*. reported the incidence of AKI-D only [337]. This was 0.15% in hospitalisations with AIS and 0.35% in ICH, with an overall incidence of 0.5%. Saeed *et al*. reported an overall incidence of AKI-D of 1.7% [335]. Using the remaining seven studies, the pooled proportion of AKI as a percentage was 9.61% (95% CI 8.33-10.98) (Figure 2-3) with an I^2 statistic of 99.8% indicating high heterogeneity. Excluding Lin *et al*. [332], which reported a much lower incidence of AKI than any other study (0.82%), made no difference to the heterogeneity (I^2 99.9%).

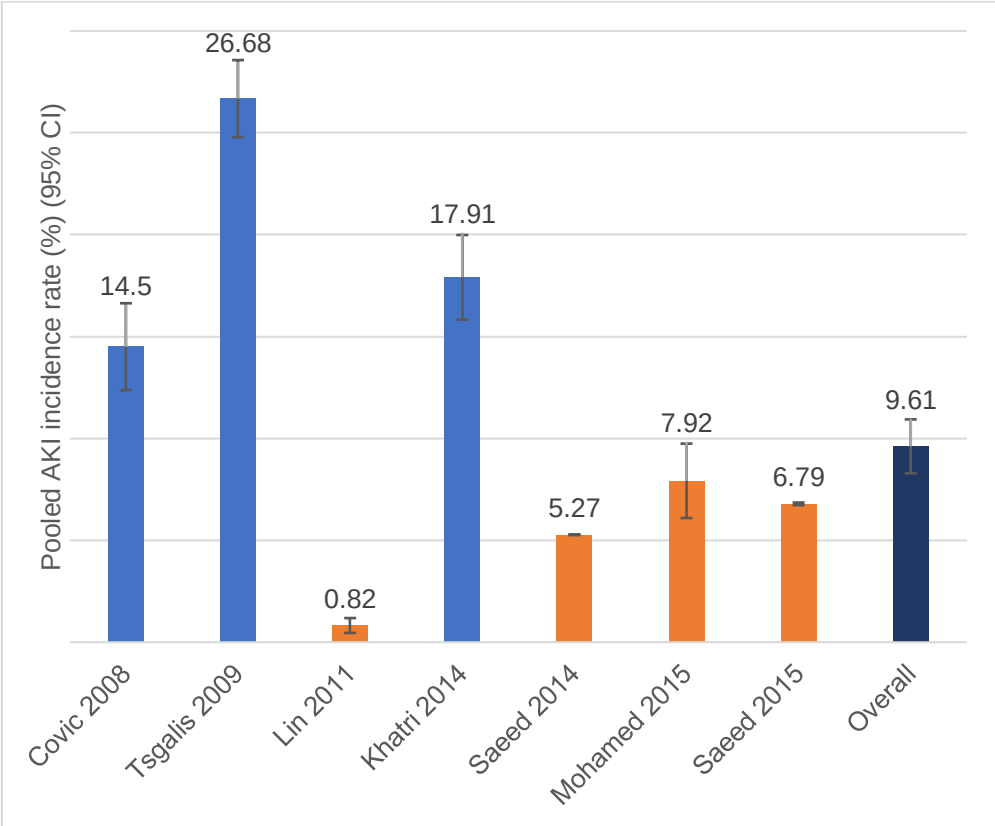
2.4.2.1 Studies using administrative coding versus SCr to define AKI

The pooled incidence of AKI in the studies that utilised ICD-coding to define AKI [332-335] was 4.63% (95% CI 3.65-5.72%). Heterogeneity was high (I^2 99.9%). Excluding Lin *et al*. [332], which appeared to be an outlier, the pooled incidence of AKI increased to 6.46% (95% CI 5.18-7.86%) and heterogeneity remained high (I^2 99.9%). Further excluding the study of ICH hospitalisations [335], the pooled incidence of AKI remained similar (6.42%, 95% CI 4.07-9.27%) with high heterogeneity (I^2 90.6%).

In comparison, the pooled incidence in studies using creatinine-based AKI definitions [330, 331, 336] was 19.51% (95% CI 12.75-27.32%), again with high heterogeneity (I^2 97.4%).

Figure 2-3. Pooled incidence rates of AKI in all studies listed by year.

Data labels are percentages with 95% CI. AKI, acute kidney injury; CI, confidence intervals.



2.4.2.2 Acute ischaemic stroke

The pooled incidence of AKI in AIS [330-334, 336] was 9.62% (95% CI 4.20-16.96%; I^2 statistic 99.5%). Excluding Lin *et al*. [332], AKI incidence increased to 12.45% (95% CI 4.96-22.70%) and

heterogeneity remained high (I^2 99.5%). Using studies with a coding definition for AKI, the pooled incidence was 4.05% (95% CI 1.06-8.86%; I^2 statistic 99.1%). Pooled incidence of AKI in studies utilising creatinine-based definitions was 17.33% (95% CI 9.42-27.05%) with high heterogeneity (I^2 97.6%).

2.4.2.3 Intracranial haemorrhage

The pooled incidence of AKI in ICH [330, 331, 335, 336] was 19.17% (95% CI 7.75-34.15%). Heterogeneity was high (I^2 99.0%). Excluding Saeed *et al*. 2015 [335], the only study in this group to use a coding definition for AKI, the pooled incidence increased to 24.50% (95% CI 18.03-31.61%). Heterogeneity decreased but remained high (I^2 84.9%).

2.4.3 Risk factors for AKI after stroke

Factors associated with the development of AKI after multivariate analyses are shown in Table 2-5. A total of three studies explored risk factors for the development of AKI after stroke [330, 331, 336]. Older age [330], worse renal function on admission [330, 331, 336], IHD [330], CHF [330, 336] and higher NIHSS score on admission [331, 336] were all found to be associated the development of AKI in stroke patients. Use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) were only marginally associated with AKI (OR 1.004, 95% CI 0.99-1.06; P=0.057) in one study [330]. One study also tested the association

between contrast-enhanced computerised tomography (CT) and AKI and found no relationship [331].

None of the studies presented data on the adjusted rates of AKI associated with cerebral angiography, thrombolysis or any vascular intervention (mechanical thrombectomy, carotid stenting or endarterectomy).

Two studies [330, 336] examined the relationship between stroke type and risk of developing AKI after adjustment for confounders. Covic *et al*. [330] reported an OR of 2.50 (95% CI 1.42-4.41; P=0.001) in ICH and Tsagalis *et al*. [336] an OR of 2.02 (95% CI 1.34-3.04; P=0.001) with lacunar stroke used as the reference.

2.4.4 AKI and severity of stroke

Two studies found an association between increased stroke severity (as determined by NIHSS score) and the development of AKI [331, 336]. In Khatri *et al*. [331] the adjusted OR per 5-point increase in NIHSS score was 1.13 (95% CI 1.07-1.19; P<0.001). Tsagalis *et al*. [336] reported an OR of 1.02 (95% CI 1.01-1.03; P=0.02) after adjustment for age, sex, presence of AF, serum glucose, haematocrit level and antihypertensive agent use in the first 48 hours.

2.4.5 AKI and degree of disability

Five studies reported disability post stroke with varying definitions. Two studies [332, 333] recorded degree of disability post stroke, as measured by the mRS. However, data from Lin *et al*. [332] was grouped according to the presence of AF and could not be analysed with respect to AKI and disability, as the individual patient data could not be obtained. Mohamed *et al*. [333] found no association between AKI and degree of disability after adjustment for age, NIHSS score, previous stroke and insurance status.

Two studies [334, 335] used coded discharge destination from NIS data as a surrogate marker for disability. Discharge was categorised as none to minimal disability and any other discharge status (home health care, short-term hospital or other facility including intermediate care and skilled nursing home or death) as moderate to severe disability. Both studies found a higher incidence of moderate to severe disability in patients with AKI after adjustment for multiple confounders (Saeed *et al*. 2014, OR 1.3, 95% CI 1.3-1.4, P<0.0001 and Saeed *et al*. 2015, OR 1.2, 95% CI 1.1-1.3; P<0.0001)). A further study utilised an 'adverse discharge' category to classify patients as being discharged to a nursing care facility, hospice or long-term care hospital [337]. Here AKI-D was associated with increased odds of adverse discharge (adjusted OR 1.18, 95% CI 1.02-1.37; P<0.01 for AIS and adjusted OR 1.74, 95% CI, 1.34-2.24; P<0.01 for ICH) after adjustment for baseline demographics, hospital-level characteristics, Charlson comorbidity index and concurrent diagnoses.

2.4.6 AKI and Length of Hospital Stay and Hospitalisation Costs

Five studies collected data on LOS [331, 333-335, 337]. All studies reported that AKI was associated with an increased LOS ranging from 2 to 18 extra days spent in hospital (Table 2-5). In Mohamed *et al*. [333], this finding persisted after adjustment for age, NIHSS score, previous stroke and insurance status (no OR given, adjusted P<0.0001).

Three studies analysed crude inpatient costs using NIS data [334, 335, 337] and all showed AKI was associated with increased costs ranging from 14,139 to 49,827 USD (Table 2-5).

2.4.7 AKI and Cardiovascular Events

Only one study [336] examined the relationship between AKI after a stroke and long-term cardiovascular events. The probability of having a composite cardiovascular event during the 10-year period after a stroke was higher in the AKI group than the non-AKI group (cumulative probability 66.8, 95% CI 56.6-76.9 vs 52.7, 95% CI 48.5-56.1; P=0.001). In a Cox multivariable regression, AKI was an independent predictor of new composite cardiovascular events at 10 years (HR 1.22, 95% CI 1.01-1.48; P<0.05) after adjustment for hypertension, diabetes, stroke subtypes, presence of brain oedema on imaging and haematocrit level.

2.4.8 AKI and post-thrombolysis ICH

One study, Saeed *et al*. 2014 [334] found that patients with AKI were more likely to suffer a post-thrombolytic ICH (OR 1.4, 95% CI 1.3-1.6; P<0.001) after multiple adjustments including age, sex, race/ ethnicity, hypertension, diabetes, AF, dyslipidaemia, CHF, chronic lung disease, MI, gastrointestinal bleeding, sepsis and nicotine dependence.

2.4.9 AKI and Mortality

Six studies [330, 331, 334-337] compared mortality in AKI versus non-AKI groups with all reporting increased mortality in patients who developed AKI (Table 2-5). Two studies also reported higher crude mortality rates associated with severity of AKI [330, 331].

Figure 2-4 shows a Forest plot of in-hospital mortality and 30-day mortality. Four studies reported in-hospital mortality [331, 334, 335, 337] and two reported 30-day mortality [330, 336]. The OR for all-cause in-hospital mortality in patients with AKI was 2.11 (95% CI 1.09-4.07) with high heterogeneity (I^2 100%; Figure 2-4). Excluding Saeed *et al*. 2015, a study of ICH only, the OR increased to 2.67 (95% CI 1.86-3.83) and heterogeneity decreased but remained high (I^2 84%). The OR for all-cause 30-day mortality in patients with AKI was 3.13 (95% CI 1.20-8.19), again with high heterogeneity (I^2 95%; Figure 2-4).

Figure 2-5 shows a Forest plot of in-hospital mortality grouped into AIS and ICH. Two studies [331, 334] provided data on in-hospital mortality after AIS with a pooled OR of 3.30 (95% CI 2.56-4.26) and low heterogeneity (I^2 31%; Figure 2-5). Two studies [331, 335] provided data on in-hospital mortality after ICH with a pooled OR of 1.40 (95% CI 1.37-1.43) and low heterogeneity (I^2 0%; Figure 2-5).

Figure 2-6 shows a Forest plot of in-hospital mortality grouped into studies using administrative coding versus SCr. Two coding studies [334, 335] provided data on in-hospital mortality with a pooled OR of 2.09 (0.94-4.65) and high heterogeneity (I^2 100%; Figure 2-6). Three studies that used SCr values to diagnose AKI provided in-hospital mortality data with a pooled OR of 3.31 (1.40-7.82) with high heterogeneity (I^2 92%; Figure 2-6).

Nadkarni *et al*. reported an adjusted OR for in-hospital mortality in AKI-D of 1.30 (95% CI 1.12-1.48; P<0.001) in AIS and 1.95 (95% CI 1.61-2.36; P<0.01) in ICH [337]. Since this study included AKI-D only it was excluded from the meta-analysis. Saeed *et al*. 2015 reported a higher crude mortality rate in patients with AKI-D than AKI without dialysis (50.2% vs. 28.4%, P<0.001) [335].

Only one study provided long-term mortality data up to 10 years [336], demonstrating higher cumulative mortality in the AKI group at 1 year (34.6 vs. 22.1 in non-AKI group) and 10 years (75.9 vs. 57.7; P=0.001). In a Cox proportional hazards model, AKI was an independent

predictor of 10-year mortality (HR 1.24, 95% CI 1.07-1.44; P<0.01) after adjustment for confounders including sex, hypertension, hypercholesterolemia, smoking, systolic BP, brain oedema, haematocrit, antihypertensive agent use after the event and ACEi/ARB and statin use on follow-up. The probability of 10-year mortality also increased with severity of AKI.

Figure 2-4. AKI and In-Hospital and 30-Day Mortality for all Stroke.

AKI, acute kidney injury; CI, confidence intervals.

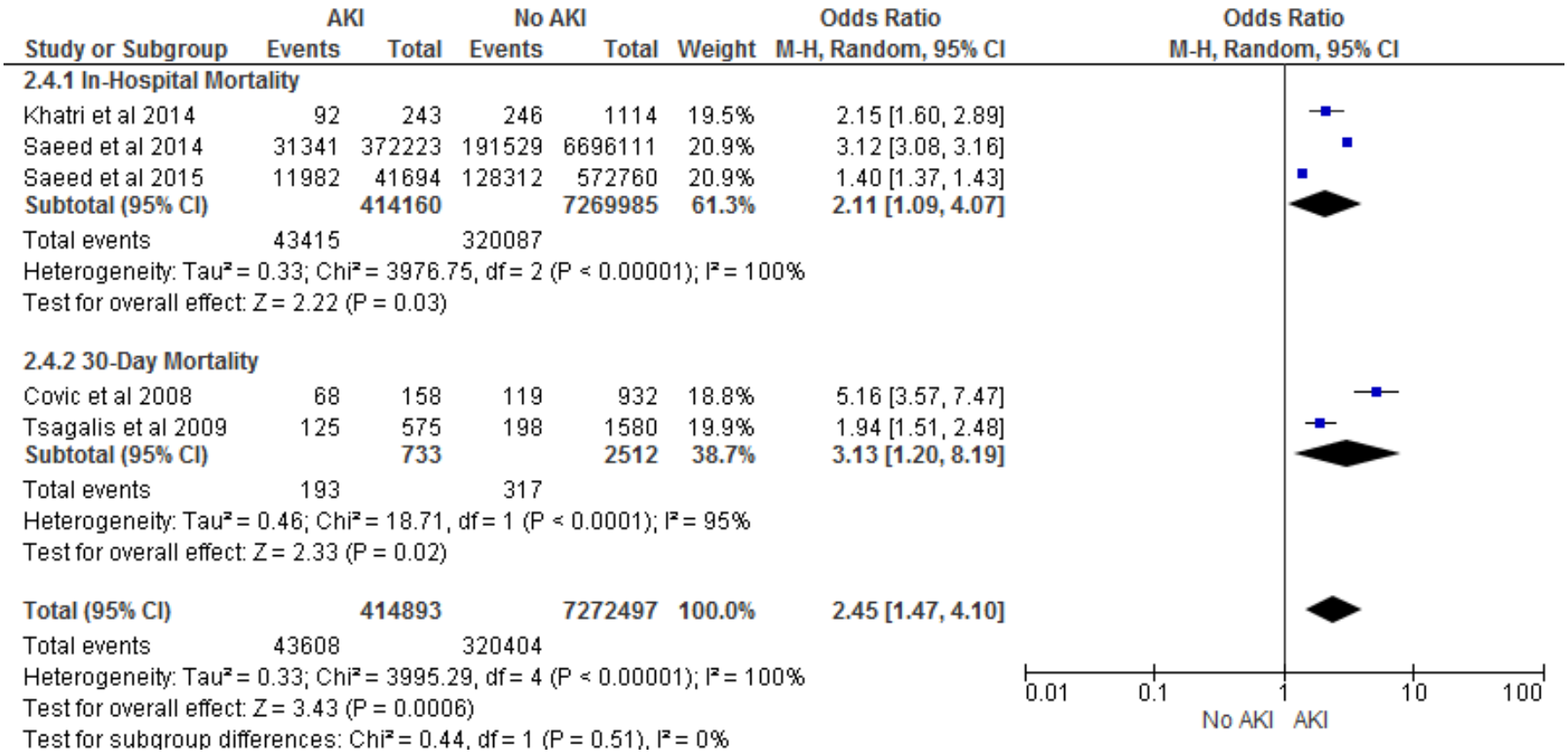


Figure 2-5. AKI and In-Hospital Mortality for Ischaemic Stroke and Haemorrhagic Stroke.

AKI, acute kidney injury; CI, confidence intervals.

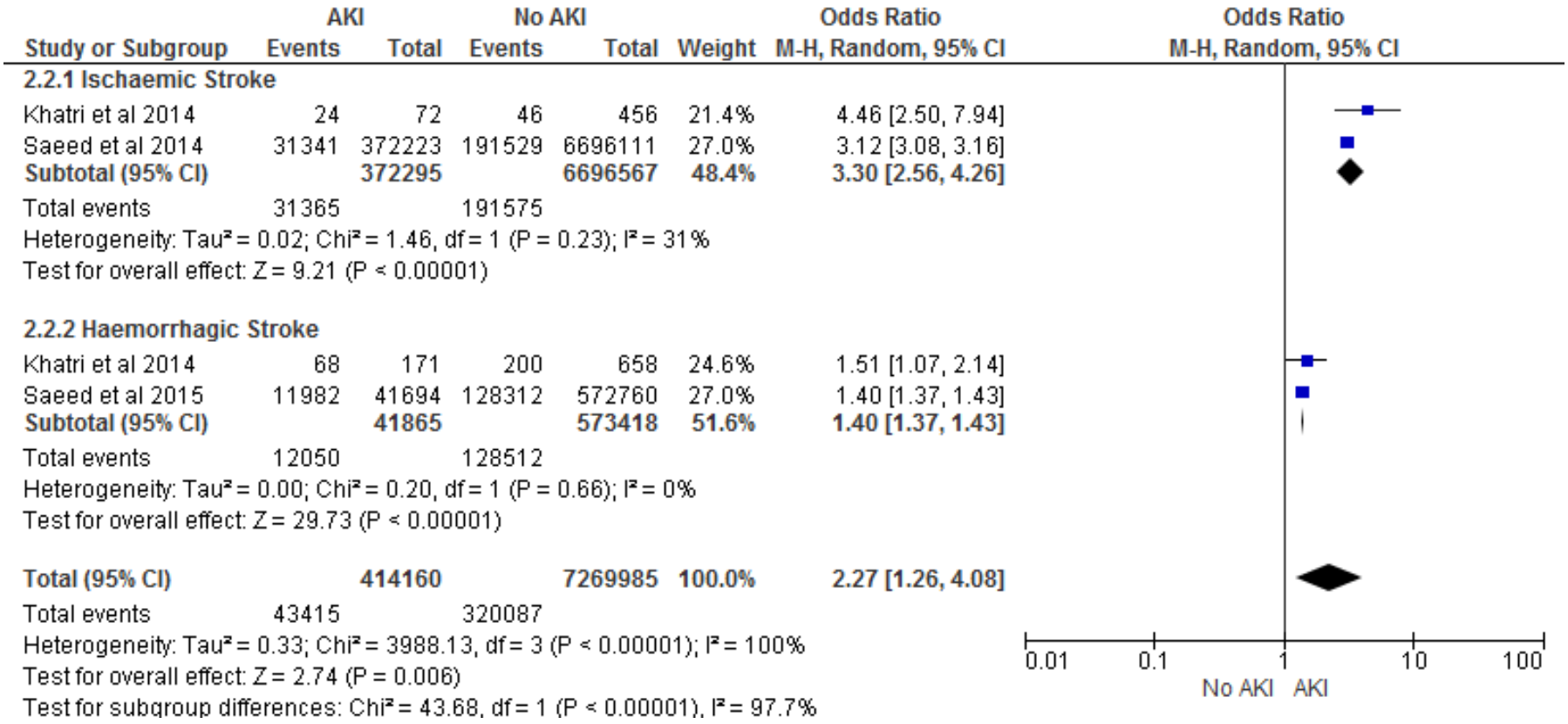
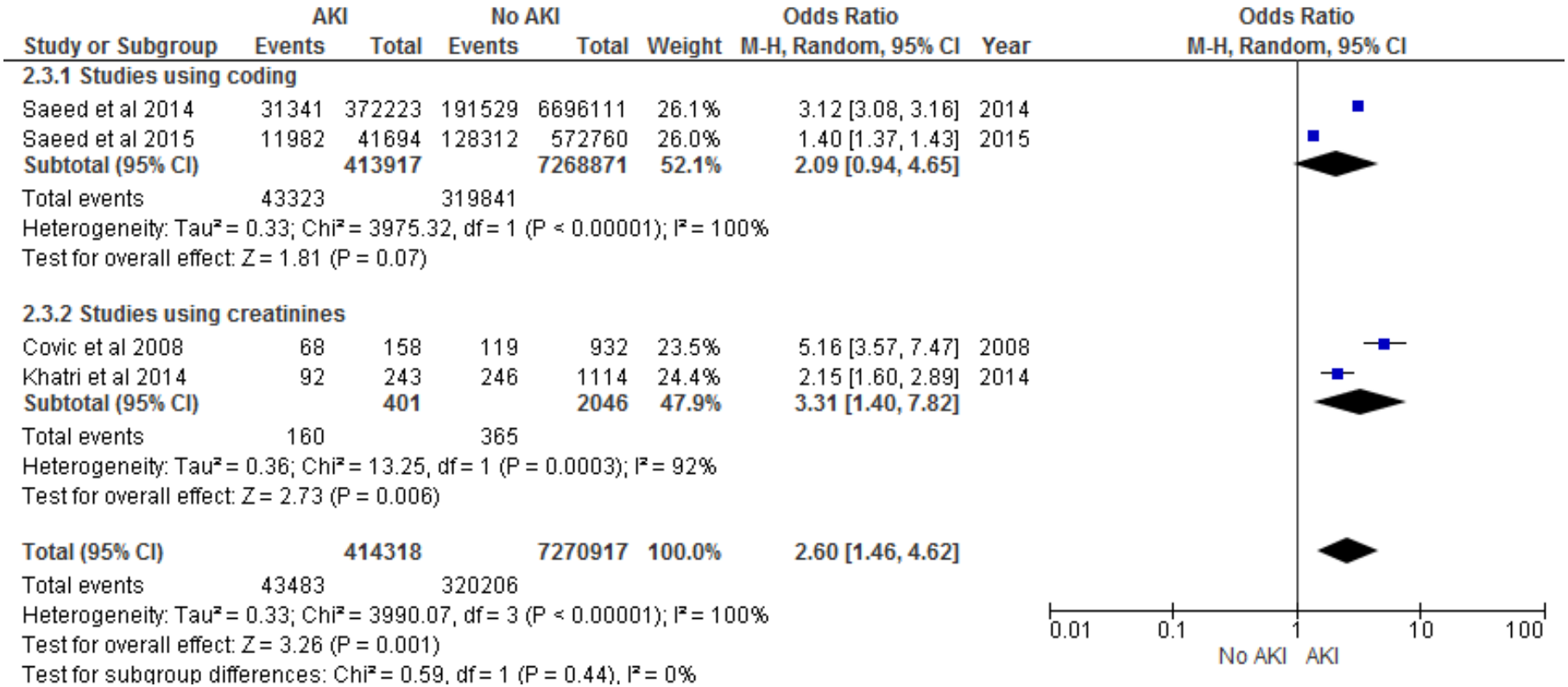


Figure 2-6. AKI and In-Hospital Mortality in Coding versus Creatinine Studies.

AKI, acute kidney injury; CI, confidence intervals.



2.5 Discussion

In this systematic review and meta-analysis, I have shown that AKI appears to be common after a stroke, with an overall pooled incidence of 9.61%. However, the reported incidence of AKI varies widely (0.82% to 26.68%) and studies exhibit high heterogeneity. The incidence of AKI appears to be higher in ICH than AIS. Risk factors for AKI after stroke are similar to those for AKI in other conditions including older age, worse renal function on admission and diagnoses of IHD and CHF [280]. In addition, the stroke severity at presentation was also found to be directly related to the risk of AKI. Sustaining an episode of AKI after a stroke was associated with worse disability, increased inpatient mortality, LOS and costs, increased risk of future cardiovascular events, and longer-term mortality.

There are stark differences in the reported incidence rates depending on the methodology used to identify patients with AKI. Using coding definitions, the pooled incidence of AKI was 4.63%, compared with 19.51% for definitions based on SCr (overall combined incidence 9.61%). ICD-coding is known to underestimate the incidence of AKI [338, 339]. Validation of ICD-9 codes for ARF (which predates present use of the term AKI), used in Saeed *et al*. 2014 and Saeed *et al*. 2015 are reported to have a sensitivity of 35.4% and a specificity of 97.7%, with a corresponding positive predictive value of 47.9% and negative predictive value of 96.1% [338]. ICD-9 codes for ARF requiring dialysis have a higher positive predictive value of 94% and a negative predictive value of 90% and this was used to justify the study of AKI-D patients by Nadkarni *et al*. [337]. Thus, the low sensitivity for ARF codes may fail to identify patients with

mild AKI that is more likely to go unrecognised and uncoded [339]. We know that severe AKI influences a number of outcomes, at high cost to individual patients, the health service and society as a whole [292, 340, 341]. Given that milder categories of AKI are much more common, they may potentially be even more important to detect and prevent [283, 292, 342]. Apart from Nadkarni *et al*. [337], only one other study reported data on the incidence of AKI-D and outcomes [335]. Since more severe AKI is related to worse outcomes, this is a significant limitation of our meta-analysis.

In this systematic review, only three studies reported risk factors associated with AKI after stroke [330, 331, 336]. They generally confined themselves to reporting traditional risk factors known to be associated with AKI, including older age, lower renal function on admission, presence of IHD and CHF and increased stroke severity, after adjustment for confounders. Two studies reported that stroke severity at presentation was associated with an increased risk of AKI [331, 336]. In addition, haemorrhagic stroke type was associated with the development of AKI in two studies [331, 336]. Patients with ICH were generally younger and had fewer comorbidities but had higher NIHSS scores [331], longer LOS [337], increased hospital costs [337], higher disability and mortality [330, 331, 337]. It therefore follows that this was a more unwell and unstable group of patients who were potentially at higher risk of developing AKI. Use of ACEi and ARBs was not associated with AKI in the single study that explored this association [330].

Interestingly, only one study [331] investigated the relationship between radiological contrast exposure and risk of AKI and found no association. None of the studies presented data on the association between thrombolysis, angiographic procedures or vascular intervention (in AIS) and AKI. There have been rapid advances in diagnostic scans and interventional treatments for stroke in recent years, including the use of intra-arterial thrombectomy (IAT) [23]. These radiological procedures all utilise radiological contrast, a well-established risk factor for AKI [343-345]. It ensues therefore that the incidence of AKI in stroke patients may well increase as these interventions become more widespread.

Lower baseline renal function (defined by SCr on admission) was associated with an increased rate of AKI in three of the studies in this systematic review [330, 331, 336] after adjustment for confounding factors. Pre-existing CKD therefore appears to be an important risk factor for the development of AKI in stroke patients, consistent with the current literature [218, 346]. We know that patients with advanced CKD are both at increased risk of stroke [68] and have poorer outcomes after a cerebrovascular insult [25, 27, 28]. This leads to the question of whether AKI adds further clinical relevance to what is already known about CKD and stroke. Of the studies that excluded patients with CKD [334, 335], AKI was still a clinically significant determinant of both disability on discharge and in-hospital mortality, after multiple adjustments. Khatri *et al*. excluded patients with an eGFR less than 15 mL/min/1.73m^2 and demonstrated that AKI was independently associated with in-hospital mortality after adjustment for multiple variables including admission SCr [331]. Tsagalis *et al*. found that AKI was an independent predictor of new composite cardiovascular events and long-term

mortality after adjustment for baseline eGFR and other confounders [336]. Nadkarni *et al*. found that AKI-D was associated with increased odds of adverse discharge, increased LOS and hospital costs and higher mortality after adjustment for concurrent diagnoses including CKD [337]. Mohamed *et al*. also adjusted for the presence of CKD and found that AKI was independently associated with increased LOS [333]. These findings support the theory that AKI is not merely an extension of the CKD spectrum and represents an important standalone factor that predicts worse outcomes in patients with acute stroke.

Severity of stroke was independently associated with the development of AKI in two studies [331, 336]. It is biologically plausible that a more severe stroke would increase the risk of AKI for a number of reasons, including neurological deficits such as dysphagia, hemiparesis and impaired communication, leading to malnutrition and dehydration, susceptibility to infection, haemodynamic instability causing labile blood pressure, increased risk of MI [347, 348], exposure to radiological contrast, urinary retention and possibly renal microemboli as a result of thrombolysis treatment. Conversely, it is also plausible that the physiological derangement that occurs in AKI, such as inflammation [349], uraemia [221, 350], oxidative stress [351] and insulin resistance [352] might also precipitate a stroke event. There is also evidence in animal models that inflammation in AKI may worsen neurological injury [220]. It is already well established that CKD is associated with increased risk of stroke [68] and CKD patients have higher mortality and cardiovascular event rates following a stroke [353]. There is increasing evidence that AKI is associated with increased short and long-term risk of stroke and other cardiovascular events [336, 354, 355]. The ‘chicken or egg’ phenomenon cannot be addressed

in this systematic review and developing AKI after a stroke may simply reflect a greater burden of illness rather than stroke as a causal factor or vice versa.

Interestingly, Saeed *et al*. 2014 found an increased risk of post thrombolysis ICH in patients with AKI after adjustment. There is a known association between CKD and increased bleeding risk in the context of anticoagulant use [136, 356, 357], acute coronary syndrome (ACS) [358] and cardiac surgery [359]; conversely patients with CKD also have increased thrombotic risk [136, 360]. Uraemic bleeding diathesis is a recognised phenomenon in severe renal impairment (both acute and chronic) and was described decades ago [361, 362]. Several studies have demonstrated an increased bleeding risk in AKI after ACS and cardiac surgery [363, 364] but to date no such studies have investigated bleeding risk in AKI after stroke.

This systematic review demonstrates a clear association between AKI and short-term mortality after stroke. The effect of AKI on mortality persisted after adjustment for CKD in three studies [330, 333, 337]. A further study [336] also found a relationship between AKI and long-term mortality, up to 10 years post stroke, after adjustment for CKD and post-stroke treatments. This is consistent with the effect of AKI on short and long-term mortality in the context of other acute illnesses including sepsis, MI and major surgery [292, 365-367] [368, 369], with the effect persisting after adjustment for CKD [292, 369]. It therefore follows that interventions to prevent AKI may improve outcomes after stroke. Methods to risk stratify patients, for example on the basis of age, comorbidities, baseline renal function, as well as

simple interventions such as close monitoring on a specialised stroke unit (including regular blood tests), avoidance of nephrotoxic exposure, ensuring adequate hydration and nutrition, maintaining steady state BP, prompt treatment of infection and electrolyte and metabolic disturbance may reduce the risk of developing AKI after stroke. Patients who do develop AKI in this setting would be detected quickly and tailored management and intervention would ensue.

In this systematic review, AKI was associated with a two-fold increase in in-hospital mortality (OR 2.11, 95% CI 1.09-4.07) [370]. In comparison, a multi-centre study of 1753 patients admitted to the Intensive Care Unit (ITU) with septic AKI reported a 1.5-fold increase in mortality (OR 1.48 (95% CI 1.17-1.89; P=0.001) [365]. This may potentially be important given that AKI-associated mortality in stroke is likely to be underestimated due to the predominance of studies using ICD-coding to diagnose AKI. As such, the impact of AKI on patients with acute stroke may be much greater than patients with sepsis. However, in a single-centre study of 19,249 unselected hospitalisations, all AKI was associated with a four-fold increase in all-cause in-hospital mortality (adjusted OR 4.43, 95% CI 3.68-5.35), a four-fold increase where circulatory diseases was recorded as the primary discharge diagnosis (OR 3.76, 95% CI 2.49-5.69) and a five-fold increase where infection was the discharge diagnosis (OR 5.06, 95% CI 3.45-7.43) [369]. These data highlight the need for further large epidemiological studies using SCr values to ascertain the real risk of AKI in different susceptible patient groups, including those with acute stroke.

Interestingly, I observed that AKI appeared to have a greater effect on mortality after AIS than ICH, although there were only 2 studies in each group. I also found that AKI-associated in-hospital mortality in studies using SCr values was higher than in those using coding, however again there were only 2 studies in each group.

This systematic review has implications for the public health community as well as practising physicians in general internal medicine, stroke medicine and nephrology. Estimates of AKI after a stroke and its associated increased in mortality, disability and LOS should be acknowledged by the medical community and incorporated into planning for public health policies on risk stratification in AKI, as well as future interventional trials, including stroke treatments. The paucity of clinical trials in AKI should act as a catalyst to enhance collaboration between research communities to address potential interventions that can improve outcomes in this common condition. Furthermore, there is a requirement for more studies from countries outside the US and use of creatinine-based methods to enable increased generalisability and validity of data. This systematic review brings to light not only the paucity of studies reporting on the incidence of AKI but also the lack of standardised definitions of stroke and AKI, which are likely to cause significant distortion of true effects.

2.5.1 Strengths and limitations

This review encompassed several studies, all within the last decade, with a large cumulative sample size and a large number of statistical adjustments. However, there are several significant limitations. Firstly, there was disproportionate representation of US data, accounting for 99.9% of the patient sample, which clearly affects generalisability of the estimates. There may also be significant ascertainment bias in view of the US being a high-income country with increased availability of blood test monitoring and other diagnostic tests. Secondly, the number of studies included in the systematic review was small and those included in the meta-analysis smaller still. Despite sensitivity analyses, heterogeneity between studies remained extremely high, potentially suggesting that these studies should not be combined in a meta-analysis. However, I opted to present the data, 'warts and all', as this both highlights the need for further research into this area but also gives potential future researchers some idea of the numbers needed to be recruited into studies as well as the rate and range of AKI to be expected using different definitions. Thirdly, all the studies with large sample sizes used coding definitions of AKI (based on NIS data). As discussed, this methodology is dependent upon the accuracy of diagnostic and procedure codes and has been shown to underestimate rates of AKI. Such studies also lack granularity and it may therefore be difficult to explore findings in detail utilising this type of data. Fourthly, all but one of the studies analysed short-term outcomes following AKI and although evidence suggests that AKI contributes to poor long-term outcomes post stroke, including increased cardiovascular events, further work is needed to strengthen the evidence in this area. In addition, the studies that determined AKI diagnosis based on creatinine levels, none used the current KDIGO

staging criteria to define AKI and none of the studies used urine output criteria. Furthermore, of the eight studies included in the review, only two assessed the impact of stroke treatments (Khatri *et al*. investigated the association between AKI and radiological contrast and Saeed *et al*. 2014 the association between AKI and post-thrombolysis ICH). Importantly, none of the studies were conducted in the era of IAT or clot retrieval therapy for stroke and AKI may potentially become more common in stroke patients as advances continue in the field of interventional radiology and potential complications of such therapies emerge.

2.6 Conclusions

AKI appears to be a very common complication in hospitalised stroke patients and is associated with increased mortality, disability and healthcare costs. As a potentially preventable condition, further studies are needed in this area to attenuate the effects of AKI, including longer-term morbidity and mortality and the development of CKD. However, in the first instance, additional representative studies, ideally using creatinine-based definitions of AKI are required to accurately define point estimates of AKI after a stroke and determine clinical outcomes in the short and long term.

CHAPTER 3 ACUTE STROKE AND RENAL DYSFUNCTION STUDY- RATIONALE, STUDY DESIGN AND METHODS

In this chapter I will describe in detail the background and rationale of this study, study design, methods, including data sources and data collection processes and statistical approaches to data analysis.

3.1. Study Rationale

A report published by the Health Economics Research Centre revealed that stroke, along with dementia, remains an underfunded area in research when compared with the burden of disease, estimated at 5.5 million DALYs [371]. Stroke research is challenging for a number of reasons, including patients' ability to provide consent in the acute phase when strict therapeutic windows may apply [372]. There have however, been dramatic advances in stroke medicine over the last two decades, not only in medical treatments but also around rehabilitation and holistic stroke care [373]. In recent years, there has been a movement towards capturing data on care quality, and the former National Sentinel Stroke Audit (NSSA) and the Stroke Improvement National Audit Programme (SINAP), run by the Royal College of Physicians (RCP), have combined to form the Sentinel Stroke National Audit Programme (SSNAP). Since December 2012, SSNAP has collected data on every single stroke patient and is now the "single source of data for stroke" in the UK [374]. It captures the quality of care

received by patients in the stroke care pathway focussing on acute care, rehabilitation and outcomes at 6 months.

Research in CKD has historically been fraught with challenges, with RCTs for cardiovascular treatments generally omitting patients with multiple comorbidities, including moderate to severe CKD and older age [375]. In those trials where such patients were included, there were problems with early withdrawal and cessation of therapy [376, 377]. Applying treatment strategies tested in a younger population with normal renal function to an older, frailer population with CKD is problematic, for example, in the context of an increased bleeding risk with the use of antiplatelet therapy in ACS [378, 379] and anticoagulation for AF [380] .

RCTs are considered to yield the highest grade of evidence in research. However, they are notoriously expensive, with an estimated cost of $12 million per trial in the US [381]. By design, they specifically determine the efficacy of an intervention or treatment but are not necessarily best poised for answering certain research questions, for example, ascertaining the risk of AKI in acute stroke. Observational studies, which include a wider variety of recruits more representative of a typical patient population than RCTs may be superior in this context, and in many cases have produced comparable results to RCTs [382-384], although findings from observational studies should still, where possible, be confirmed in RCTs before being integrated into medical care.

There is a rapidly emerging wealth of information stored in EHRs. The richness and completeness of such data has increased over time and more information is now shared across healthcare organisations and paper-based records replaced. Since patients can be preidentified and followed up using routinely collected clinical data, the huge potential to harness EHR data for research purposes is now well recognised. The use of EHR in research trials was acknowledged over 10 years ago, although at this time there were significant shortcomings in the data [385]. Since then, several clinical trials have been conducted using EHR data [386]. Recently, Acute Care QUAliTy In chronic Kidney Disease (ACQUATIK), an observational pilot study of novel design set up at University Hospitals Birmingham NHS Foundation Trust (UHBFT), has used routinely collected electronic data from both primary and secondary care, Hospital Episode Statistics (HES) and the Office of National Statistics (ONS) to track long-term outcomes of patients with and without CKD [387]. UHBFT is one of 17 NHS Acute Hospital Trusts designated as a Global Digital Exemplar by NHS England [388].

Data from hospitalised stroke patients in the UK is needed to contribute to the limited data on stroke and renal dysfunction generated by studies in North America, Europe and Asia thus far. Investigating AKI as a potential complication of acute stroke will increase our awareness of the scale of risk and influence on outcomes, leading to better risk stratification and timely recognition and treatment in this vulnerable group of patients. Since CKD bears a close relationship with AKI, a greater understanding of the influence on pre-existing renal impairment on outcomes in stroke is important to drive developments in clinical care with the ultimate goal of improving short and long-term outcomes.

3.2 Aims and Research Questions

In this study, I aimed to determine the incidence of renal dysfunction, in both AKI and CKD, and their influence on outcomes in a cohort of hospitalised stroke patients.

To fulfil the aims of the study, the following research questions were generated:

1. What is the incidence of AKI in patients admitted to hospital with acute stroke?
2. What are the risk factors/ determinants of AKI?
3. Does AKI influence mortality in patients admitted with acute stroke?
4. Are patients who develop AKI during admission with stroke more disabled at baseline, as determined by mRS score?
5. What is the prevalence of CKD in patients admitted to hospital with acute stroke?
6. What are the risk factors or determinants of CKD?
7. Does CKD influence mortality in patients admitted with acute stroke?
8. Are patients with CKD who are admitted with stroke more disabled at baseline, as determined by mRS score?
9. Does a diagnosis of CKD influence which stroke treatments are received?
10. Do patients who undergo contrast-enhanced imaging have an increased risk of developing AKI?
11. Do patients with CKD have an increased risk of HT after cerebral infarction?
12. Do patients with CKD have an increased risk of bleeding post-thrombolysis or thrombectomy?

13. Do patients with CKD exhibit higher rates of vascular calcification compared with non-CKD patients?
14. Do patients with CKD exhibit higher rates of carotid artery disease compared with non-CKD patients?

3.3 Study Outcomes

The main outcomes of interest in each study arm are shown in Table 3-1.

Table 3-1. Summary of Outcomes of Interest according to each Arm of Stroke Study.

Study Arm	**Outcomes**
AKI arm	Incidence of AKI in patients admitted with an acute stroke Risk factors/ determinants of AKI- age, gender, ethnicity, concurrent comorbidities including CHF, hypertension, AF, diabetes, previous stroke/ TIA, admission mRS Relationship between AKI and stroke severity Influence of AKI on 30-day and 1-year mortality

Study Arm	Outcomes
CKD arm	Prevalence of CKD in patients admitted with an acute stroke Risk factors/ determinants of CKD- age, gender, ethnicity, concurrent comorbidities including CHF, hypertension, AF, diabetes, previous stroke/ TIA, admission mRS Relationship between CKD and stroke severity Influence of CKD on treatments received for stroke including thrombolysis and IAT Influence of CKD on 30-day and 1-year mortality
Imaging arm	**Contrast induced nephropathy** Incidence of AKI and relationship to radiological contrast exposure **Bleeding risk** Risk of HT haemorrhagic transformation in patients with AIS and a diagnosis of CKD Risk of bleeding post thrombolysis or IAT in patients with AIS and a diagnosis of CKD **Atheroma/ calcification** Degree of carotid artery disease in patients with CKD Degree of vascular calcification in patients with CKD

Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; CHF, congestive heart failure; CKD, chronic kidney disease; IAT, intra-arterial thrombectomy; mRS, modified Rankin Scale; SES, socioeconomic status; TIA, transient ischaemic attack.

3.4 Ethical Approval and Authorisations

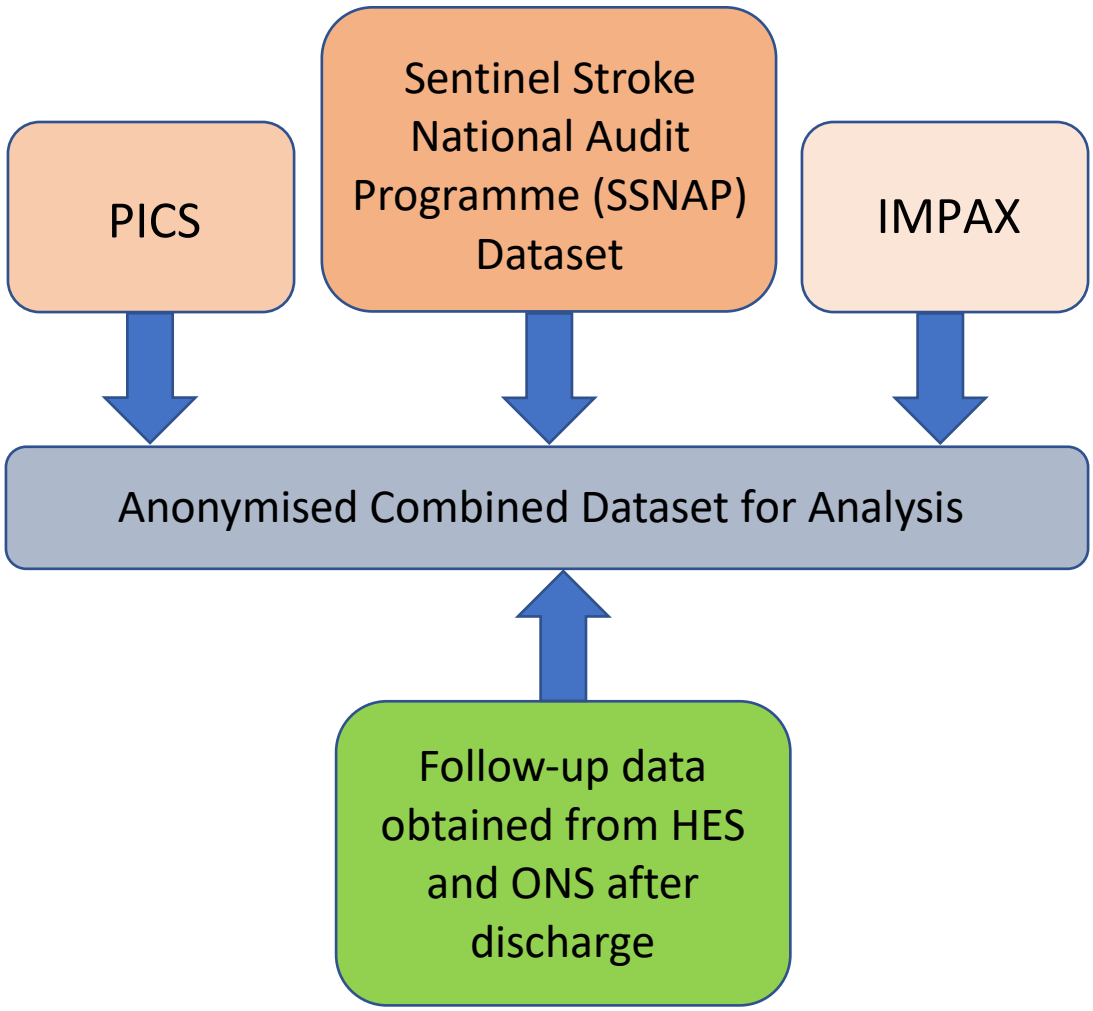
Professor Charles Ferro was the Principal Investigator for this study. Since the project utilised anonymised patient data through data linkage, criteria were met for proportionate ethical review. Approval was granted by the East of England - Essex Research Ethics Committee (REC Reference 16/EE/0166). The study was also given local approval by UHBFT's Research and Development Governance Office and registered as an audit (audit code number/ CARMS-11934). UHBFT acted as a sponsor for this study (Ref. RRK5793). No specific funding was apportioned to the project. The conduct and reporting of this study adhered to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement [389].

3.5 Study Design

This was a single-centre, retrospective observational study of patients in the UK admitted to hospital with acute stroke to determine the incidence of renal dysfunction, both acute and chronic, and its influence on outcomes. The study centre is a large tertiary hospital in the West Midlands, QEHB, part of UHBFT. UHBFT merged with the Heart of England NHS Foundation Trust on 1st April 2018, making UHBFT one of the largest Trusts in the country. QEHB is the leading university teaching hospital in the West Midlands. On 16 June 2010, the new QEHB opened as a new £545 million acute hospital with 1200 beds. The hospital receives 42,000 emergency admissions annually and offers an acute stroke service, including thrombolysis and IAT and operates a Neurosurgical unit, receiving transfers from peripheral hospitals.

A diagrammatic description of the study is shown in Figure 3-1. A number of data sources were used to collect demographics and outcome variables, as well as routinely collected clinical data leading up to and during the admission period. These are described in more detail in the study process outlined in the following section.

Figure 3-1. Stroke and Renal Dysfunction Study Design.



Abbreviations: HES, Hospital Episode Statistics; IMPAX, picture archiving and communications system programme by AGFA HealthCare; PICS, Prescribing Information and Communications System; ONS, Office of National Statistics.

3.6 Study Process

1. All patients admitted to QEHB with an acute stroke are captured prospectively by the stroke medical or nursing team using the SSNAP audit data collection tool. The data collection period for this study was 12 December 2012 to 30 September 2015 inclusive. Data on stroke admissions were extracted by QEHB's SSNAP data manager and imported into an anonymised Excel spreadsheet for cleaning and analysis. A summary of the data captured by the SSNAP audit tool is displayed in Appendix 2.

2. Imaging data was collected retrospectively using two clinical data systems: Prescribing Information and Communications System (PICS) (see section 3.7.2.1), which displays all radiology reports, and IMPAX (see section 3.7.2.3), which stores all images as well as prose reports. IMPAX was used predominantly to obtain all ultrasound (USS) carotid Doppler reports, which are not available in PICS. Since all radiology reports are dictated in prose, a rule-based data collection proforma was developed using Microsoft Access (see Appendix 3). Data from Access was then imported into Microsoft Excel for further handling and quality control checks, before being imported into SPSS for statistical analysis. The degree of atherosclerosis demonstrated on USS carotid Dopplers was reported as per the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria [390, 391].

3. Routinely collected clinical data, namely blood and urine tests and basic observation results were extracted retrospectively through PICS. All test results extracted are

shown in Table 3-2. For all parameters, 3 values- baseline, peak and low- were extracted for each admission. For SCr only, all available results in the 7 to 365 days leading up to admission were also extracted.

4. Socioeconomic status (SES) was obtained retrospectively from HES. This is calculated using the Index of Multiple Deprivation (IMD) model 2010, consisting of seven domains, each weighted to give an overall composite score ranging from 1, representing the most deprived area, to 10, representing the least deprived area [392]. The domains include the following, with their respective weightings: income, 22.5%; employment, 22.5%; health deprivation and disability, 13.5%; education, skills and training, 13.5%; barriers to housing and services, 9.3%; crime, 9.3% and living environment, 9.3%.

5. Data on interventions for acute stroke, including thrombolysis or IAT were collected prospectively through SSNAP. All cases recorded as undergoing thrombolysis or IAT were individually checked retrospectively using PICS and discharge letter summaries uploaded to Clinical Portal.

6. Short-term outcomes from SSNAP were collected retrospectively, including development of a urinary tract infection (UTI) or pneumonia during admission, inpatient mortality, mRS score on discharge and presence of AF on discharge. Large amounts of this data were missing and could therefore not be used for the purposes of this study. Data completeness for SSNAP and all clinical parameters is shown in Table

3-3, excluding imaging data. For the imaging arm of the study, all data collection was undertaken by manually reviewing each individual patient record and was 100% complete.

7. Data on outcomes at 6 months including mRS score, presence of AF, pharmacological treatments including antiplatelets, anticoagulants, lipid lowering therapy or antihypertensives and further cardiovascular events (MI or re-stroke) or other hospitalisations were captured through SSNAP retrospectively. Again, large amounts of data were missing and could not be used.

8. Data on mortality up to 1 year from the index admission were extracted retrospectively through HES and ONS databases. Ethnicity data and SES were also obtained through HES.

Table 3-2. Clinical parameters extracted through PICS.

Test	Parameters
Routine laboratory blood tests	Haemoglobin, MCV, platelets, INR, PTT ratio, WBC, urea, creatinine, sodium, potassium, albumin, calcium, phosphate, magnesium, CRP, D-dimer, troponin T, ferritin, HbA1c, serum glucose, CK, total cholesterol, triglycerides
Urine	Dipstick, MSU, albumin-to-creatinine ratio
Observations	Blood pressure, heart rate, respiratory rate, oxygen saturation level, temperature, capillary blood glucose

Abbreviations: CK, creatine kinase; CRP, c-reactive protein; HbA1c, glycated haemoglobin; INR, international normalised ratio; MCV, mean corpuscular volume; MSU, mid-stream urine; PTT, partial thromboplastin time; WBC, white blood cell count.

Table 3-3. Data completeness for stroke study cohort (n=1375).

SSNAP data		
Section 1- Demographics/ onset/ arrival		
Variable	**N**	**Data completeness**
Age	1375	100%
Gender	1375	100%
Ethnicity	1375	100%
Date of birth	1375	100%
Hospital number	1375	100%
Onset date and time	1375	100%
Arrival date and time	1375	100%
Arrival to stroke unit date and time	1375	100%
Section 2- Casemix/ first 24 hours		
CHF	54/1375	100%
Hypertension	663/1375	100%
AF	257/1375	100%
Diabetes	289/1375	100%
Previous stroke/ TIA	344/1375	100%
AF on antiplatelet	257/257	100% of AF cases
AF on anticoagulant	257/257	100% of AF cases

SSNAP data		
Section 2- Casemix/ first 24 hours		
mRS before stroke	1375	100%
NIHSS score on arrival	1375	100%
NIHSS level of consciousness	1375	100%
NIHSS level of consciousness questions	1375	100%
NIHSS level of consciousness commands	1375	100%
NIHSS best gaze	1375	100%
NIHSS visual fields	1375	100%
NIHSS facial paresis	1375	100%
NIHSS motor arm left	1375	100%
NIHSS motor arm right	1375	100%
NIHSS motor leg left	1375	100%
NIHSS motor arm right	1375	100%
NIHSS limb ataxia	1375	100%
NIHSS sensory	1375	100%
NIHSS best language	1375	100%
NIHSS dysarthria	1375	100%
NIHSS extinction and inattention	1375	100%
Brain imaging date and time	1375	100%

SSNAP data		
Section 2- Casemix/ first 24 hours		
Stroke type	1375	100%
Thrombolysis	164	100%
Thrombolysis date and time	164	100% of thrombolysis cases
Thrombolysis complications	164	100% of thrombolysis cases
NIHSS 24 hours after arrival	140	10.18%
TIA in last month	138	10.04%
Brain imaging modality	895	65.09%
Section 3- Assessments- first 72 hours		
Palliative care decision in first 72 hours	1375	100%
End of life pathway	0	0%
Stroke Nurse assessment date and time	1223	88.95%
Stroke Consultant assessment date and time	1293	94.04%
Section 4- This admission		
First ward	1009	73.38%
Stroke unit arrival date and time	976	70.98%
Section 5- Patient condition in first 7 days		
Worst level of consciousness in first 7 days	1024	74.47%
UTI in first 7 days	1024	74.47%
Antibiotics for pneumonia in first 7 days	1024	74.47%

SSNAP data		
Section 6- Assessments- by discharge		
Palliative care by discharge	988	71.85%
Section 7- Discharge/ transfer		
Hospital death date recorded	101	7.35%
Death on stroke unit	88	6.40%
Discharge destination	856	62.25%
Discharge date	755/1274	59.26% of survivors to discharge
mRS on discharge	856	62.25%
Diagnosis of AF on discharge	752	54.69%
If diagnosis of AF on discharge, anticoagulation status	79	5.75%
Section 8- Six month (post admission) follow up		
Follow up at 6 months	718/1274	56.36%
Follow up date/ type	181/1248	14.50%
Living arrangements	181/1248	14.50%
mRS at 6 months	205/1248	16.43%
Persistent AF	181/1248	14.50%
On antiplatelet agent	181/1248	14.50%
On anticoagulant	181/1248	14.50%
On lipid lowering agent	181/1248	14.50%

SSNAP data			
Section 8- Six month (post admission) follow up			
On antihypertensive agent		181/1248	14.50%
Readmission with stroke within 6 months		181/1248	14.50%
Readmission with MI within 6 months		181/1248	14.50%
Readmission with other illness within 6 months		181/1248	14.50%
PICS data			
Available preadmission SCr value		743	54.04%
Inpatient blood results			
Urea	Baseline	1294	94.11%
	Peak	1308	95.13%
	Low	1287	93.6%
Creatinine	Baseline	1357	98.69%
	Peak	1309	95.20%
	Low	1302	94.69%
Sodium	Baseline	1294	94.11%
	Peak	1308	95.13%
	Low	1287	93.6%
Potassium	Baseline	1357	98.69%
	Peak	1259	91.56%
	Low	1032	75.05%
Haemoglobin	Baseline	1259	91.56%
	Peak	1259	91.56%
	Low	1259	91.56%
WBC	Baseline	1250	90.91%
	Peak	1309	95.20%
	Low	1239	90.11%
MCV	Baseline	1297	94.33%
	Peak	1309	95.20%
	Low	1292	93.96%

PICS data			
Inpatient blood results			
Platelets	Baseline	1247	90.69%
	Peak	1309	95.20%
	Low	1236	89.89%
INR	Baseline	1069	77.75%
	Peak	1137	82.69%
	Low	1038	75.49%
PTT ratio	Baseline	327	23.78%
	Peak	346	25.16%
	Low	322	23.42%
Albumin	Baseline	1252	91.05%
	Peak	1264	91.93%
	Low	1245	90.55%
Calcium	Baseline	1067	77.60%
	Peak	1077	78.33%
	Low	1061	77.16%
Phosphate	Baseline	198	14.40%
	Peak	206	14.98%
	Low	195	14.18%
Magnesium	Baseline	255	18.55%
	Peak	258	18.76%
	Low	254	18.47%
CRP	Baseline	835	60.73%
	Peak	843	61.31%
	Low	685	49.82%
Serum glucose	Baseline	205	14.91%
	Peak	205	14.91%
	Low	205	14.91%
HbA1c	Baseline	420	30.55%
	Peak	422	30.69%
	Low	418	30.40%
Total cholesterol	Baseline	653	47.49%
	Peak	653	47.49%
	Low	652	47.42%

PICS data			
Inpatient blood results			
Triglycerides	Baseline	366	26.62%
	Peak	366	26.62%
	Low	366	26.62%
D-dimer	Baseline	37	2.69%
	Peak	37	2.69%
	Low	36	2.62%
Troponin T	Baseline	140	10.18%
	Peak	144	10.47%
	Low	134	9.75%
CK	Baseline	86	6.25%
	Peak	91	6.62%
	Low	83	6.04%
Ferritin	Baseline	93	6.76%
	Peak	93	6.76%
	Low	93	6.76%
Urine results			
Urinary ACR		19	1.38%
Dipstick		421	30.62%
MSU		164	11.93%
Observations			
Systolic BP	Baseline	1366	99.35%
	Peak	1366	99.35%
	Low	1366	99.35%
Diastolic BP	Baseline	1366	99.35%
	Peak	1366	99.35%
	Low	1366	99.35%
Heart rate	Baseline	1366	99.35%
	Peak	1366	99.35%
	Low	1366	99.35%
Respiratory rate	Baseline	1366	99.35%
	Peak	1366	99.35%
	Low	1366	99.35%
Oxygen saturations	Baseline	1366	99.35%
	Peak	1366	99.35%
	Low	1366	99.35%

PICS data			
Observations			
Oxygen flow	Baseline	1353	98.40%
	Peak	1353	98.40%
	Low	1353	98.40%
Temperature	Baseline	1366	99.35%
	Peak	1366	99.35%
	Low	1366	99.35%
HES data			
Ethnicity		1375	100%
IMD score		1358	98.76%
Reason for admission		1342	97.60%
HES data			
Discharge date		1375	100%
Death at discharge		1375	100%
ONS data			
Month/ year of death		367/367	100%

Abbreviations: ACR, albumin-to-creatinine ratio; AF, atrial fibrillation; CHF, congestive heart failure; CK, creatine kinase; CRP, c-reactive protein; HbA1c, glycated haemoglobin; HES, Hospital Episode Statistics; IMD, Index of Multiple Deprivation; INR, international normalised ratio; MCV, mean corpuscular volume; MI, myocardial infarction; mRS, modified Rankin Scale; MSU, mid-stream urine; NIHSS, National Institutes of Health Stroke Scale score; ONS, Office of National Statistics; PTT, partial thromboplastin time; SCr, serum creatinine; SSNAP, Sentinel Stroke National Audit Programme; TIA, transient ischaemic attack; UTI, urinary tract infection; WBC, white blood cell count.

3.7 Data Sources

3.7.1 Sentinel Stroke National Audit Programme (SSNAP)

The former NSSA and SINAP have now combined to form the SSNAP audit programme (see also section 3.1). Since December 2012, SSNAP has collected data on every stroke patient [374]. This audit captures data on the quality of care received by patients in the stroke care pathway from the index admission up to 6-months post discharge, focussing on immediate medical care, rehabilitation and outcomes at discharge and 6 months. Data from SSNAP forms the backbone of this study and a summary of the information captured is outlined in Appendix 2.

3.7.2 Hospital Clinical Data Systems

3.7.2.1 Prescribing Information and Communication Systems (PICS)

PICS is a commercially available EHR. It displays clinical data such as blood, urine and histology results, clinical imaging reports, basic observations, past and present prescribed medications, details of ceiling of care and resuscitation status as well as demographic information. All clinical parameters extracted for this study are previously shown in Table 3-2. Data extraction from the system is robust and supports all national clinical reports. UHBFT's informatics team also build international reporting tools for HES [393]. Imaging data collection was performed separately as described previously, by manual interpretation of each individual report displayed in PICS and transcription onto a separate rule-based proforma in Microsoft Access (see Appendix 3).

3.7.2.2 Clinical Portal

Clinical Portal is a digital interface containing a variety of clinical documents including primary care communications, secondary care outpatient letters, discharge letters, death certificates and certain clinical investigations such as endoscopy, cardiac and respiratory physiology tests. For the purposes of this study, Clinical Portal was used to cross check whether patients received thrombolysis or IAT during admission. This was done retrospectively.

3.7.2.3 IMPAX

IMPAX (AGFA HealthCare) is a picture archiving and communications (PACS) system programme which displays all radiographic images as well as radiology reports. In this study, IMPAX was used to access all USS carotid Doppler reports which were not available in PICS.

3.7.3 Hospital Episode Statistics (HES)

HES is an administrative dataset that collects information on all NHS hospital admissions in England. Every admission includes a primary diagnosis and up to 19 secondary diagnoses, derived from the ICD-10 standard system and up to 24 procedural codes, derived from the Classification of Interventions and Procedures, version 4 (OPCS-4) [394]. Each patient record in HES also contains demographic data (including age, gender, ethnicity, postcode and SES using IMD) and details of the episode of care (including the name of the hospital, whether the admission was an emergency and date of admission and discharge). In this study, HES was used to track outcomes up to 1 year after the index admission. It is a requirement for all

hospitals in England to submit data to HES. Our group has already had success in using these data sources with a string of recent publications, including a study on fracture risk in UK patients post renal transplantation [395].

3.7.4 Office of National Statistics (ONS)

All deaths in England must be notified by law and recorded by the ONS. Deaths during the study period, including date of death, were derived through linkage between HES records and death registry information via the ONS. This improves mortality capture by including deaths outside of hospitals.

3.8 Data Extraction

Data were extracted by way of Structured Query Language (SQL) using SQL Server Management Studio 16.5.1 (Microsoft, Redmond WA, USA). SQL is the standard programming language used to communicate with relational database management systems. A unique patient identifier was used to link UHBFT's Patient Administration System (PAS) and PICS to HES and ONS to obtain data on readmissions and mortality respectively. SQL scripts were constructed for each database separately and coded to link all servers together.

3.9 Eligibility

Inclusion criteria

The patient has a diagnosis of acute stroke as captured by the SSNAP audit tool and is hospitalised at QEHB.

Exclusion criteria

Any patient entered into the SSNAP database subsequently found not to have had a stroke, for example, neurological symptoms arising from a brain tumour.

3.10 Recruitment and Follow-up Data

Any patient admitted 'through the front door' with an acute stroke or any existing inpatient referred with a new stroke was automatically captured on the SSNAP database once assessed by UHBFT's stroke team. SSNAP data was combined with EHR data from PICS, Clinical Portal, IMPAX and separately collected imaging data, as outlined in section 3.7.2.

HES outcomes were linked at 1 year and included date of admission and discharge, ICD-10 codes for diagnoses and OPCS-4 codes for procedures and SES using IMD 2010. ONS was used to ascertain which patients died within the 1-year follow up period.

3.11 Timescale, End of Follow-up and Study End

The data collection period was from December 2012 to September 2015, a total of 33 months. Patients were followed up until death, or for a maximum of 1 year from the date of the index admission. The end of the study was marked by the expiry of 1 year, applicable to the last patient admitted to QEHB in September 2015 on the SSNAP database. The study therefore ended in September 2016.

3.12 Data Management

All identifiable data was stored on NHS computers. As necessary, data from the study was sent securely to the informatics department through secure NHS email accounts and stored in a separate, password-encrypted database in compliance with the Data Protection Act 1998. Access was granted only to delegated persons involved in the study, all of whom complied with UHBFT's policy on the collection, storage, processing and disclosure of personal information.

3.13 Statistics and Data Analysis

All data were analysed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Data distribution was determined using the Kolmogorov-Smirnov test and normality plots. Normally distributed continuous variables were presented as mean ± standard deviation (SD) and non-normally distributed variables were presented as median and IQR. Comparisons between 2 groups were performed using the independent samples *t*-test for normally distributed variables or the

Mann-Whitney U test for non-normally distributed variables. Categorical variables are expressed as proportions (percentage) and compared using the Chi-squared test or McNemar test for dichotomous variables [396]. A two-tailed P value of <0.05 was considered statistically significant.

Logistic regression was used to determine the relationship between outcomes and parameters under investigation [397], expressed as an OR with 95% CI [398]. Variables found to be associated with the outcome under investigation in the univariable analysis were included in the multivariable models [397, 398]. A P value threshold of <0.15 was selected in order to retain all potential risk factors and minimize the chance of type II errors. Kaplan-Meier survival curves were drawn to compare group differences for time-to-event data and compared using the Log rank test [399]. A Cox proportional hazards model was used to determine the relationship between parameters under investigation and 1-year mortality, expressed as a HR with 95% CI [400, 401]. For inclusion in the multivariable model, a P value threshold of <0.15 was used in order to retain all potential associations and reduce the chance of type II errors.

3.14 Definitions of AKI

Diagnosis of AKI requires ascertainment of change in SCr from a known 'baseline' value, as per KDIGO [280]. In all AKI analyses (see Chapters 4 and 5), AKI was defined according to the KDIGO staging system [280]. Where one or more preadmission SCr values were available, the mean

of these was calculated and used as the 'baseline' to ascertain a change in SCr and calculate AKI. Preadmission SCr used to ascertain a diagnosis of AKI was termed AKI^{pre}. This was set as the standard for comparison against 4 'surrogate' methods recognised in the literature:

1) Use of first SCr measured on admission, termed AKI^{adm};
2) Use of lowest (nadir) SCr measured on admission, termed AKI^{low};
3) Back-calculation of SCr, assigning all patients an eGFR of 75 mL/min/1.73m^2 using the MDRD formula, termed AKI^{MDRD};
4) Back-calculation of SCr, assigning all patients an eGFR of 75 mL/min/1.73m^2 using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, termed AKI^{EPI}.

The MDRD equation is as follows [324]:

$$eGFR = 175 \times (SCr/\ 88.4)^{-1.154} \times (age)^{-0.203} \times 0.742\ [\text{if female}] \times 1.212\ [\text{if Black ethnicity}]$$

where eGFR is measured in mL/min/1.73m^2, SCr is standardised serum creatinine in µmol/L and age is in years; a conversion factor of 88.4 is applied to convert from mg/dL to µmol/L.

The CKD-EPI equation incorporates log serum creatinine, modelled as a two-slope linear spline with sex specific cut-offs, sex, race and age on the natural scale, as shown in Table 3-4 [317].

This is in comparison to log serum creatinine without a spline, sex, race and age on the log scale in the MDRD equation (shown above) [324].

Table 3-4. The CKD-EPI equation for estimating GFR on the natural scale. Adapted from Levey *et al*. Ann Intern Med 2009; 150(9): 604-612 [317].

Ethnicity	**Sex**	**SCr µmol/L (mg/dL)**	**Equation**
Black	Female	≤62 (≤0.7)	$GFR = 166 \times ((SCr/88.4)/ 0.7)^{-0.329} \times (0.993)^{Age}$
		>62 (>0.7)	$GFR = 166 \times ((SCr/88.4) 0.7)^{-1.209} \times (0.993)^{Age}$
	Male	≤80 (≤0.9)	$GFR = 163 \times ((SCr/88.4) 0.9)^{-0.411} \times (0.993)^{Age}$
		>80 (>0.9)	$GFR = 163 \times ((SCr/88.4) 0.9)^{-1.209} \times (0.993)^{Age}$
White or other	Female	≤62 (≤0.7)	$GFR = 144 \times ((SCr/88.4) 0.7)^{-0.329} \times (0.993)^{Age}$
		>62 (>0.7)	$GFR = 144 \times ((SCr/88.4) 0.7)^{-1.209} \times (0.993)^{Age}$
	Male	≤80 (≤0.9)	$GFR = 141 \times ((SCr/88.4) 0.9)^{-0.411} \times (0.993)^{Age}$
		>80 (>0.9)	$GFR = 141 \times ((SCr/88.4) 0.9)^{-1.209} \times (0.993)^{Age}$

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; SCr, standardised serum creatinine.

A conversion factor of 88.4 is applied to convert mg/dL to µmol/L.

The CKD-EPI equation expressed as a single equation is as follows:

$GFR = 141 \times \min (SCr/\kappa, 1)^{\alpha} \times \max (SCr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female]_1.159 [if Black ethnicity]

where SCr is standardised serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of SCr/κ or 1 and max indicates the maximum of SCr/κ or 1.

In the table, multiplication factors for ethnicity and race are incorporated into the intercept, which results in different intercepts for age and sex combinations.

The surrogate methods for ascertaining AKI diagnosis by assigning an eGFR of 75 mL/min/1.73m^2 and subsequently back-calculating the SCr value (AKI^{MDRD} and AKI^{EPI}, referred to in points 3) and 4) above) were performed by solving the MDRD and CKD-EPI equations for SCr.

To back-calculate SCr using MDRD, the equation was rearranged as follows:

$$SCr = (75/\ 186 \times (age^{-0.203}) \times [0.742 \text{ if female}] \times [1.21 \text{ if Black ethnicity}])^{-0.887} \times 88.4$$

where an eGFR of 75 mL/min/1.73m^2 is assigned.

To back-calculate SCr using CKD-EPI, the equation was rearranged as follows:

$SCr = 0.7 \times 88.4\ (75/\ (144 \times 0.993^{age})\ )^{(1/-0.329)}$ for a White female with a SCr ≤ 62 µmol/L

$SCr = 0.7 \times 88.4\ (75/\ (144 \times 0.993^{age})\ )^{(1/-1.209)}$ for a White female with a SCr > 62 µmol/L

$SCr = 0.9 \times 88.4\ (75/\ (141 \times 0.993^{age})\ )^{(1/-0.411)}$ for a White male with a SCr ≤ 80 µmol/L

$SCr = 0.9 \times 88.4\ (75/\ (141 \times 0.993^{age})\ )^{(1/-1.209)}$ for a White male with a SCr > 80 µmol/L

$SCr = 0.7 \times 88.4\ (75/\ (166 \times 0.993^{age})\ )^{(1/-0.329)}$ for a Black female with a SCr ≤ 62 µmol/L

$SCr = 0.7 \times 88.4\ (75/\ (166 \times 0.993^{age})\ )^{(1/-1.209)}$ for a Black female with a SCr > 62 µmol/L

$SCr = 0.9 \times 88.4\ (75/\ (163 \times 0.993^{age})\ )^{(1/-0.411)}$ for a Black male with a SCr ≤ 80 µmol/L

$SCr = 0.9 \times 88.4\ (75/\ (163 \times 0.993^{age})\ )^{(1/-1.209)}$ for a Black male with a SCr > 80 µmol/L

where an eGFR of 75 mL/min/1.73m^2 is assigned.

AKI^{pre} and all surrogate methods were compared using the Bland-Altman method [402, 403]. Linear regression modelling was used to assess for degree of proportional bias between surrogate methods and preadmission SCr [397]. Sensitivity and specificity were reported for each method with the Kappa value and 95% CI used to denote the level of agreement between different methods. Misclassification rates were calculated as the proportion of patients incorrectly assigned as having AKI, as compared with AKI^{pre}. I compared correctly classified and misclassified AKI using the McNemar test [396, 404].

Differences between AKI methods in determining outcomes were investigated by dividing patients into 3 groups depending on the availability of SCr data. Group A included all patients with at least 1 preadmission SCr available in the 7 to 365 days preceding admission. Group B included all patients with a SCr measured on admission and at least 1 further SCr measured before discharge and Group C, all patients that that fulfilled criteria for Groups A and B. Patients could therefore be assigned to more than 1 group.

3.15 Definitions of CKD

CKD was defined as per KDIGO guidelines (see Chapter 1, section 1.3.1) [41]. Where available, the mean of all SCr values in the preceding 7 to 365 days leading up the index admission was used to define 'baseline' renal function. This approach has been shown to most closely approximate clinical adjudication of 'baseline' renal function [311]. From this, eGFR was calculated using both CKD-EPI and MDRD formulae (outlined in section 3.14) and CKD stage subsequently derived.

Of the total cohort, 54.0% (n=743) had one or more preadmission SCr and of these, 30.8% (n=229) had only one SCr value available. Where only one preadmission SCr was available, this was used to denote 'baseline' renal function and classify CKD. Whilst it is acknowledged that a single preadmission SCr does not meet the diagnostic criteria for CKD as per KIDGO, multiple preadmission measurements are not always available and single SCr values have been used to denote 'baseline' function and classify CKD in several published studies investigating the incidence of AKI to date [307, 308, 310, 314]. Where preadmission SCr data was missing, 'baseline' renal function and CKD stage were derived from the first SCr value on admission. This is in keeping with the methodology of the few published studies investigating the incidence of AKI in stroke populations using SCr values [370].

3.16 Data Completeness and Quality

Data completeness is shown in Table 3-3. SSNAP data was largely 100% complete for sections 1 to 2, including demographics, comorbidities and thrombolysis treatment. Data from sections 3 and 4 was not utilised for the purposes of this study. In sections 5 and 6, approximately 25% of data was missing. Unfortunately, over 50% of data was missing for each parameter in sections 7 to 8, including discharge arrangements, medications and 6-month outcomes and therefore could not be used. The data extracted from PICS, HES and ONS was largely complete with less than 5% of values missing, except for less routine blood parameters, such as D-dimer.

Ethnicity data from HES was utilised since after cross checking data held in SSNAP with data extracted from UHBFT's EHR for a random selection of cases, SSNAP was found to be inaccurate. Ethnicity recorded in HES is approximately 95% concordant with self-reported ethnicity, with the highest concordance rates seen for patients who identify themselves as White British [405].

For the imaging arm of the study, individual data on all thrombolysis and thrombectomy cases was collected using UHBFT's clinical data systems. During this process, 167 thrombolysis cases were identified, compared with 164 cases recorded in the SSNAP dataset. This discrepancy of 3 cases can be explained by the fact that some patients were thrombolysed in peripheral hospitals before being transferred to UHBFT for ongoing treatment, for example thrombectomy or decompressive craniectomy. Such cases will not have been recorded as

receiving thrombolysis on SSNAP since this treatment happened preceding transfer in another hospital.

All the studies to be performed were critically dependent on accuracy of the SCr values extracted. Therefore, to ensure accuracy of SCr data, quality control checks on a random selection of cases was performed. This revealed some discrepancies in admission (baseline), low and peak SCr values. This may have been due to differences in the date of the index admission and discharge coded by HES and UHBFT's PAS, resulting in the incorrect values being extracted. This was mostly related to patients arriving to hospital just before or after midnight, marking the cut off of the next day. For example, a patient who presented to the Emergency department at 23:30 on 1st January may have had a blood test taken immediately on arrival but may not have been formally admitted by administrative staff until after midnight on 2nd January. Conversely, a patient may be admitted at 23:30 on 1st January but may not have had a blood test until after midnight on 2nd January. In both cases, the SCr result will not have been extracted as the admission value since the patient's admission date is a day later or earlier respectively. These discrepancies between timing of admission and blood tests may have also impacted upon the low and peak values extracted through PICS. Other reasons that may have caused incorrect admission, low and peak values to be extracted are outlined in Table 3-5 below.

As a result, **all** SCr values included in the dataset were manually crosschecked against those in PICS corresponding to the date of admission. Less than 10% of values in the database were changed during this process.

Table 3-5. Mechanisms for incorrect extraction of admission, minimum and peak SCr values.

Mechanism	**Possible scenario**
Discrepancy between admission date and first blood test	Arrival before midnight but not 'admitted' formally until after midnight Blood test taken before midnight
	Admission before midnight Blood test taken after midnight
Discrepancy between time of first blood test and booking into laboratory	Blood test taken on admission before midnight but not labelled with date and time Sample received in laboratory after midnight with no time or date, labelled as being received the day after admission
	Blood test taken on admission before midnight and labelled with date and time Sample misplaced/ delay in processing e.g. 24 hours/ lost, leading to repeat blood sampling and misclassification of the 'admission' sample

Mechanism	Possible scenario
Discrepancy between time of first blood test and booking into laboratory	Blood test taken on admission before midnight and labelled with date and time Sample time/ date not correctly documented by lab, leading to misclassification of the 'admission' sample

Abbreviations: SCr, serum creatinine.

CHAPTER 4 INCIDENCE OF ACUTE KIDNEY INJURY AFTER AN ACUTE STROKE- A COMPARISON OF 5 DIFFERENT METHODS FOR DETERMINING 'BASELINE' RENAL FUNCTION TO CALCULATE AKI

4. 1 Introduction

Like CKD, AKI is a global public health concern that is associated with increased morbidity, mortality and healthcare costs [280]. In order to improve outcomes, an accurate understanding of the epidemiology of AKI is crucial; yet it remains a diagnostic challenge. SCr is an imperfect measurement of dynamic GFR [406] and is modified by age, sex and ethnicity, as well as nutritional state, muscle mass and fluid status [407]. Consequently, a number of novel biomarkers for earlier and more accurate detection of AKI are under investigation [408]. Potential promise has been demonstrated in rodent models for neutrophil gelatinase-associated lipocalin (NGAL) [409, 410], kidney injury molecule-1 (KIM-1) [411] and Interleukin-18 (IL-18) [412]. However, to date these have not progressed to use in routine medical practice [408, 413, 414]. The search for a kidney 'troponin' has been hampered by the heterogeneous pathophysiology of AKI (in contrast to the simpler mechanism of injury of an acute MI), as well as the challenges of translating successful animal models into human trials where the aetiology of AKI may be multifactorial and influenced by patient comorbidities [415]. The Sapphire study holds promise for 2 novel biomarkers, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), which predicted the onset of AKI stage 2 to 3 (as defined by KIDGO) with better accuracy than NGAL, KIM-1 and IL-18 [416]. However, substantial work is required to fully determine the diagnostic ability and

subsequent clinical application of these biomarkers. To date therefore, SCr remains the only routinely used laboratory test for the diagnosis of AKI [417-419].

As outlined in Chapter 2, section 2.1.5, determining whether a patient has AKI relies on assessing a change in SCr from a known 'baseline' or preadmission value [280] between 7 and 365 days up to admission [307-313]. Patients with CKD are more likely to have a pre-recorded SCr but these values are missing in approximately 50% of patients [314].

In cases where preadmission SCr is unavailable as a baseline, several other surrogate methods have been used. The ADQI Working Group recommends back-calculation of SCr by assuming a GFR of 75 mL/min/1.73m^2 using the MDRD equation [281, 324]. This method has also since been recommended by KIDGO [376]. Use of first SCr on admission is recommended by AKIN and ERBP and has been shown to correlate with patient outcomes including the requirement for acute dialysis and mortality [308, 309, 318]. A third method of estimating 'baseline' renal function is the use of the lowest or nadir SCr value during admission, which has also been associated with increased mortality [322]. Each of these surrogate methods has its own limitations, which are discussed in more detail in Chapter 2, section 2.1.5. In summary, the AKI community currently lacks a universally agreed definition of 'baseline SCr', and when it can be obtained, preadmission SCr is regarded as the best available modality.

4.1.1 Rationale of AKI Study Arm

Stroke is the second most common cause of death and the leading cause of neurological disability worldwide [236, 420]. CKD is associated with an increased risk of stroke, due to shared traditional causes, as well as a number of other risk factors unique to CKD [23, 68]. The risk of stroke in CKD has been discussed extensively in Chapter 1, sections 1.3 and 1.4. Furthermore, patients who suffer a stroke are typically older and have significant comorbidities, including CKD [23, 68]. All of these factors are recognised to be associated with AKI [407]. The history and emergence of the concept of AKI, definitions and clinical importance are previously discussed in Chapter 2, sections 2.1.1 to 2.1.3. However, in comparison to CKD, the relationship between AKI and stroke has not been well described.

My systematic review and meta-analysis, outlined in Chapter 2, drew attention to the small number of studies investigating AKI and its influence on outcomes after an acute stroke. Six out of the eight included studies reported short-term mortality [330, 331, 334-337], and one study reported long-term mortality (up to 10 years) [336]. Five studies provided data on degree of disability after stroke [332-335, 337], however due to different definitions of disability used (mRS [332, 333], coded discharge destination from NIS data [334, 335] and 'adverse discharge' category [337]), the results could not be pooled. Five studies reported LOS [331, 333-335, 337] and three compared inpatient costs [334, 335, 337]. Only one study examined the association between AKI and long-term risk of cardiovascular events [336]. A further study investigated the risk of post-thrombolysis ICH [334].

The review also highlighted that that risk factors for AKI after a stroke have not been extensively examined, with most studies confining themselves to known generic risk factors for AKI [370]. Importantly, only two of the included studies investigated the association between stroke severity and AKI [331, 336], and only one study explored the relationship between radiological contrast exposure and the development of AKI [331]. Furthermore, none of the studies explored the association between thrombolysis, angiographic procedures or vascular interventions, including IAT and the development of AKI after AIS.

In the context of an aging population and increasing prevalence of CKD, together with wider use of interventional procedures in stroke medicine, it is crucial to establish risk factors for, as well as the true incidence of AKI after an acute stroke so that we can design interventional studies to potentially improve outcomes in this group of patients. To date, all studies investigating AKI in acute stroke have used first SCr on admission [330, 331, 336], or more commonly, ICD-9/ ICD-10 coding diagnoses [332-335, 337], which are known to underestimate the incidence of AKI [338, 339]. The use of different surrogate methods to diagnose AKI has important implications for epidemiologists, clinical trialists and those responsible for the allocation of healthcare resources. Variation in the use of different surrogate methods between studies causes problems with comparison of AKI rates and makes it difficult to power AKI trials with accuracy. Crucially, it also has an impact on the ability to develop valid risk-prediction models that might help improve clinical outcomes, including mortality. These challenges are compounded by a lack of data in selected patient populations, such as those

hospitalised with acute stroke. To date, no study has investigated the use of different methods to classify AKI and their relationship to outcomes in acute stroke.

4.2 Aims of AKI Study Arm 1- Incidence and Risk Factors

The AKI arm of the study is subdivided further into two arms. In the first, I sought to determine the following:

1) incidence of AKI in a population of stroke patients admitted to a large tertiary centre in the UK using preadmission SCr as the 'gold standard' and comparing this with 4 surrogate methods, outlined in section 4.3.4;
2) risk factors for AKI in stroke patients.

4.3 Methods

4.3.1 Study design and population

This was a retrospective cohort study of all patients with acute stroke admitted to a large tertiary centre, QEHB in the UK. All consecutive admissions between December 2012 and September 2015 with a clinical diagnosis of stroke were included. A total of 1375 patients were eligible for the study.

4.3.2 Data collection and follow-up period

The methods for this study are outlined in full in Chapter 3, including study design and process, data sources and extraction, outcomes of interest, statistical analysis, definitions and data completeness and quality.

4.3.3 Inclusion criteria

All patients that presented to QEHB with first ever stroke, either AIS or ICH were included. Readmissions and patients with ESRD were excluded. Ascertainment of each stroke case was based on clinical assessment by the attending stroke physician, including history, neurological examination and relevant brain imaging.

4.3.4 Definition of Acute Kidney Injury

Risk factors associated for AKI were determined *a priori* from the available literature (see Chapter 2, Table 2-2) [280].

Baseline SCr was considered to be the mean of all preadmission SCr values collected in the 7 to 365 days leading up to hospital admission [309], which were available in 53.5% (n=725) of patients. All SCr values for each admission episode were extracted from PICS and first SCr measured on admission, peak SCr and lowest SCr during the admission subsequently obtained.

The rate of AKI using preadmission SCr, termed **AKI^{pre}**, was compared with 4 surrogate methods:

1) first SCr measured on hospital admission, termed **AKI^{adm}**;
2) lowest SCr measured during admission, termed **AKI^{low}**;
3) back-calculated SCr using the MDRD equation, assuming an eGFR of 75 mL/min/1.73m^2, termed **AKI^{MDRD}**; and
4) back-calculated SCr using the CKD-EPI equation, assuming an eGFR of 75 mL/min/1.73m^2, termed **AKI^{EPI}**.

AKI was defined as per the KDIGO classification [280] and all patients with a rise in SCr were accordingly categorised as stages 1, 2 and 3 (see Chapter 2, Table 2-1). Urine output criteria were not used since records of urine output were poorly recorded in PICS.

4.3.5 Other definitions

CKD was defined as an eGFR of <60 mL/min/1.73m^2, calculated using the MDRD [324] and CKD-EPI [317] equations (outlined in Chapter 3, section 3.14). Anaemia was defined as a haemoglobin level less than 135 g/L for males and less than 115 g/L for females, as per QEHB's laboratory reference ranges.

4.3.6 Statistical analysis

Analyses were performed using SPSS 25.0 (SPSS Inc., Chicago IL, USA). Continuous variables are expressed as mean ± SD for normally distributed variables or median and IQR for non-normally distributed variables and compared using the *t*-test or Mann-Whitney U test as appropriate. Categorical variables are expressed as proportions and compared using the Chi-squared test or McNemar test for dichotomous variables [396]. All variables used in the analysis had <5% of the values missing and were therefore treated as missing completely at random with case-wise deletion. A two-tailed P value of <0.05 was considered to be statistically significant.

Differences between preadmission SCr and all four surrogate methods for diagnosis of AKI were compared using the Bland-Altman method [402, 403]. Linear regression modelling was used to assess for degree of proportional bias between surrogate methods and preadmission SCr [397]. Sensitivity and specificity was reported for each method with the Kappa value and 95% CI used to denote the level of inter-rater agreement between different methods used [421]. Misclassification rates were calculated as the proportion of patients incorrectly assigned as having AKI as compared with preadmission SCr and I compared correctly classified and misclassified AKI using the McNemar test [396, 404].

Logistic regression was used to assess the relationship between outcomes and categorical variables under investigation [397], expressed as an OR with 95% CI [398]. Variables found to

be associated with the outcome under investigation in the univariable analysis were included in the multivariable models [397, 398]. A P value threshold of <0.15 was selected in order to retain all potential risk factors and minimize the chance of type II errors. For all regression analyses, where variables were closely related, separate models were created and only one variable was entered at a time.

4.4 Results

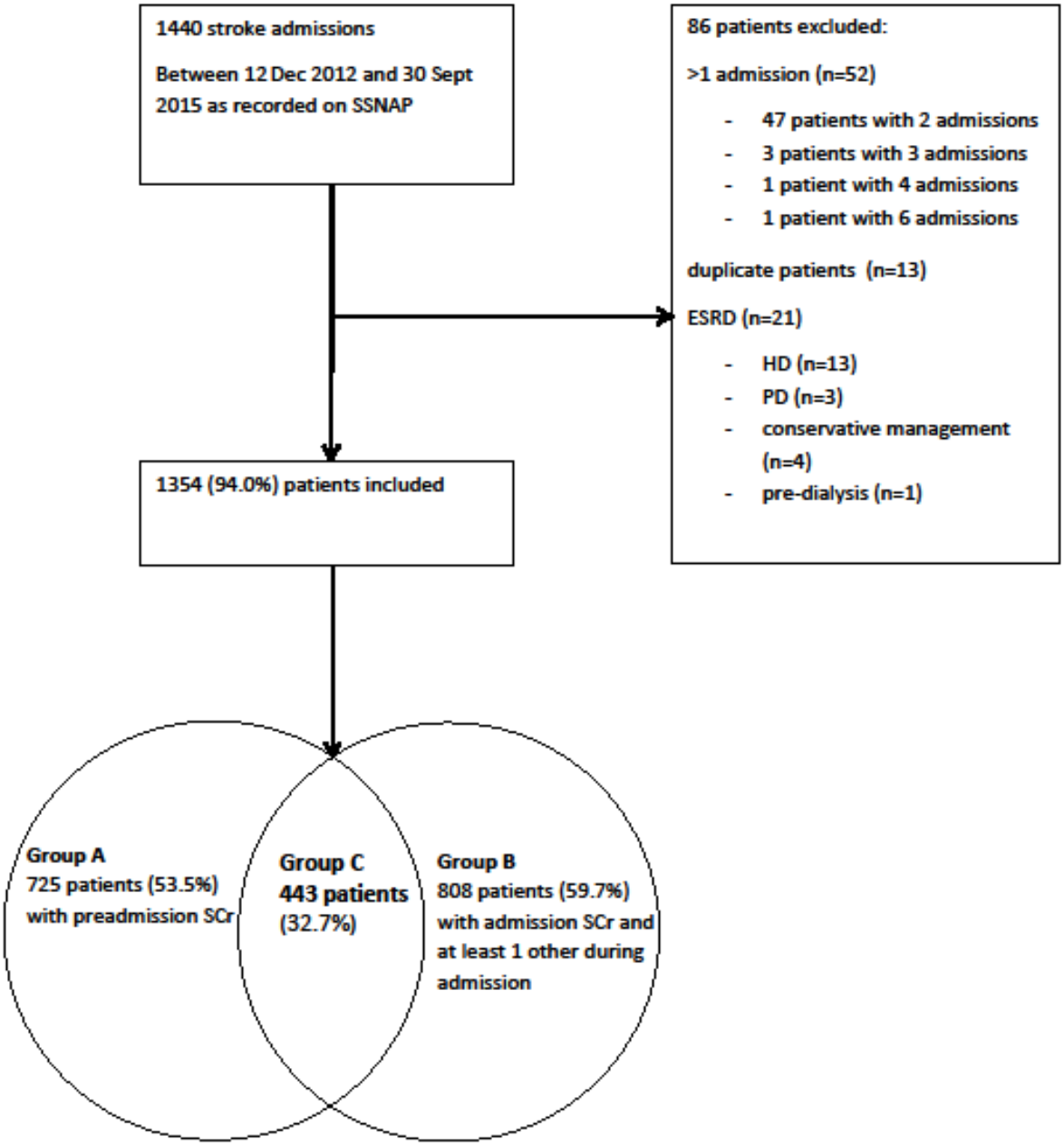
In total, 1440 hospital admissions with acute stroke occurred within the study period (Figure 4-1). From these, 52 patients who were readmitted over the same period were excluded, as well as 13 duplicate patients and 21 patients who had ESRD (13 HD, 3 peritoneal dialysis (PD), 4 conservative management and 1 pre-dialysis). The remaining 1354 patients were included for analysis.

Among these patients, 725 (53.5%), had preadmission SCr data available, measured in the preceding 12 months leading up to the admission and were assigned to **Group A** (median number of SCr tests 2, IQR 5).

A total of 808 (59.7%) had a SCr measured on admission and at least 1 further SCr measured before discharge and were assigned to **Group B** (median number of SCrs 4, IQR 5).

A total of 443 (32.7%) patients had both a preadmission SCr and at least 2 SCrs measured during admission (i.e. fulfilling the criteria for both Groups A and B), and comprised **Group C**, the core cohort of patients for analysis (median number of SCrs 4, IQR 5).

Figure 4-1. Study flow diagram.



Abbreviations: ESRD, end-stage renal disease; HD, haemodialysis; SCr, serum creatinine; PD, peritoneal dialysis; SSNAP, Sentinel Stroke National Audit Programme.

4.4.1 Characteristics of Patients with and without Preadmission Serum Creatinine

The baseline characteristics of the study population with and without a preadmission SCr are shown in Table 4-1. Of the total cohort (n=1354), 53.5% (n=725) had at least one preadmission SCr result. The majority of patients presented with AIS (88.3%, n=1196). The median age of the total cohort was 76 years (IQR 21), 53.8% (n=728) were male and 83.5% (n=1130) were of White ethnicity. CKD (as defined by an eGFR <60 mL/min/1.73m^2) comprised 32.1% (n=434) of the cohort calculated using the CKD-EPI formula and 25.6% (n=347) calculated using the MDRD formula.

Patients with a preadmission SCr were older (74.8 vs. 69.0, P<0.001), more were female (49.5% vs. 42.4%, P<0.001) and of White ethnicity (86.2% vs. 80.3%, P<0.001), and a larger proportion had a concurrent diagnosis of CKD ascertained using admission SCr (37.9% vs. 25.3%, P<0.001 for CKD-EPI and 31.2% vs. 19.2%, P<0.001 for MDRD), diabetes (24.1% vs. 16.7%, P<0.001), hypertension (52.1% vs. 43.4%, P=0.003), AF (24.7% vs. 11.9%, p<0.001), CHF (4.8% vs. 2.7%, P<0.001) or previous stroke/ TIA (30.1% vs. 19.4%, P<0.001). There was no significant difference in stroke severity between groups (NIHSS score 3.0 vs. 4.0, P=0.64).

Table 4-1. Baseline characteristics of the study group according to the presence or absence of preadmission SCr (n=1354).

	With preadmission SCr (n=725)	**Without preadmission SCr (n=629)**	**P value**
Age- Mean (SD)	74.83 (14.09)	69.04 (16.33)	<0.001
Female (%)	359 (49.5)	267 (42.4)	<0.001
Acute ischaemic stroke (%)	643 (88.7)	553 (87.9)	0.38
NIHSS score on admission- Median (IQR)	3.0 (8)	4.0 (8)	0.64
mRS score on admission- Median (IQR)	0 (1)	0 (1)	<0.001
IMD score- Mean (SD)	30.51 (15.37)	30.60 (17.82)	<0.001
Ethnic group (%) White Asian/ Asian British Black/ Black British Mixed/ Other/ Unknown	 625 (86.2) 68 (9.4) 18 (2.5) 14 (1.9)	 505 (80.3) 61 (9.7) 32 (5.1) 31 (4.9)	 <0.001
Preadmission SCr (µmol/L)- Mean (SD)	91.32 (31.40)	-	-

	With preadmission SCr (n=725)	Without preadmission SCr (n=629)	P value
Preadmission eGFR calculated using CKD-EPI (mL/min/1.73m^2)- Mean (SD)	68.45 (22.72)	-	-
Preadmission eGFR calculated using MDRD (mL/min/1.73m^2)- Mean (SD)	73.24 (25.20)	-	-
Admission SCr (µmol/L)- Mean (SD)	91.15 (41.55)	84.14 (24.78)	<0.001
Admission eGFR calculated using CKD-EPI (mL/min/1.73m^2)- Mean (SD)	67.90 (22.71)	75.84 (22.35)	0.17
Admission eGFR calculated using MDRD (mL/min/1.73m^2)- Mean (SD)	74.82 (28.21)	81.89 (28.47)	0.20
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI) (%)	278 (38.3)	-	-
CKD (eGFR <60 mL/min/1.73m2 using preadmission SCr and MDRD) (%)	230 (31.7)	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI) (%)	275 (37.9)	159 (25.3)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD) (%)	226 (31.2)	121 (19.2)	<0.001

	With preadmission SCr (n=725)	Without preadmission SCr (n=629)	P value
CKD by stage CKD-EPI (%)			
3a	156 (21.5)	105 (16.7)	
3b	82 (11.3)	43 (6.8)	
4	37 (5.1)	11 (1.7)	<0.001
CKD by stage MDRD (%)			
3a	137 (18.9)	83 (13.2)	
3b	62 (8.6)	32 (5.1)	
4	27 (3.7)	6 (1.0)	<0.001
Diabetes mellitus (%)	175 (24.1)	105 (16.7)	<0.001
Hypertension (%)	378 (52.1)	273 (43.4)	0.003
AF (%)	179 (24.7)	75 (11.9)	<0.001
Previous stroke/ TIA (%)	218 (30.1)	122 (19.4)	<0.001
CHF (%)	35 (4.8)	17 (2.7)	<0.001

Data are presented as mean (SD), median (IQR) or n (%).

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SCr, serum creatinine; SD, standard deviation; TIA, transient ischaemic attack.

A logistic regression analysis of factors associated with having a preadmission SCr is shown in Table 4-2. For closely related variables, namely CKD ascertained using CKD-EPI and MDRD formulae, separate models were created and only one variable was entered into the model at a time.

In the univariable analysis, patients with a preadmission SCr were more likely to be older, female, have a concurrent diagnosis of CKD, diabetes, hypertension, AF, previous stroke/ TIA or CHF, higher disability score on admission and more severe stroke as determined by NIHSS score. Black ethnicity was inversely associated with having a preadmission SCr in the univariable model.

In the multivariable analysis, the strongest associations with having a preadmission SCr were the presence of diabetes (OR 1.47, 95% CI 1.11-1.96; P=0.008), AF (OR 1.85, 95% CI 1.36-2.53; P<0.001) and previous stroke/ TIA (OR 1.53, 95% CI 1.17-1.99, P=0.002). In addition, older age (OR 1.02, 95% CI 1.01-1.02; P<0.001) and higher disability score on admission (OR 1.18, 95% CI 1.06-1.30; P=0.002) were associated with having a preadmission SCr. Black ethnicity was inversely associated with having a preadmission SCr in the multivariable model (OR 0.49, 95% CI 0.26-0.91, P=0.02).

Table 4-2. Regression analysis of factors associated with having a preadmission serum creatinine (n=725).

	Univariable Analysis		**Multivariable Analysis***	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.025 (1.018-1.033)	<0.001	1.015 (1.007-1.023)	<0.001
Female sex	1.330 (1.073-1.649)	0.009	-	-
Black ethnicity	0.475 (0.264-0.855)	0.013	0.490 (0.263-0.912)	0.024
IMD score	1.000 (0.993-1.006)	0.923		
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)**	1.784 (1.411-2.256)	<0.001	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)**	1.879 (1.458-2.421)	<0.001	-	-
Diabetes	1.588 (1.212-2.080)	0.001	1.472 (1.108-1.956)	0.008
Hypertension	1.421 (1.146-1.761)	0.001	-	-
AF	2.422 (1.804-3.250)	<0.001	1.851 (1.358-2.525)	<0.001
Previous stroke/ TIA	1.787 (1.387-2.302)	<0.001	1.528 (1.172-1.993)	0.002
CHF	1.826 (1.013-3.293)	0.045	-	-
Stroke type	0.928 (0.666-1.293)	0.659	-	-
mRS on admission (as continuous variable)	1.324 (1.203-1.457)	<0.001	1.176 (1.061-1.303)	0.002
NIHSS score on admission (as continuous variable)	0.995 (0.981-1.010)	0.529	-	-

*Adjusted for age, gender, black ethnicity, presence of CKD, diabetes, hypertension, AF, previous stroke/ TIA, CHF and disability on discharge in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

4.4.2 Comparison of preadmission SCr and admission SCr

Since first SCr on admission most closely agreed with preadmission SCr in diagnosing AKI, the distribution of change between preadmission SCr and first SCr were compared to investigate the effect on ascertainment of AKI.

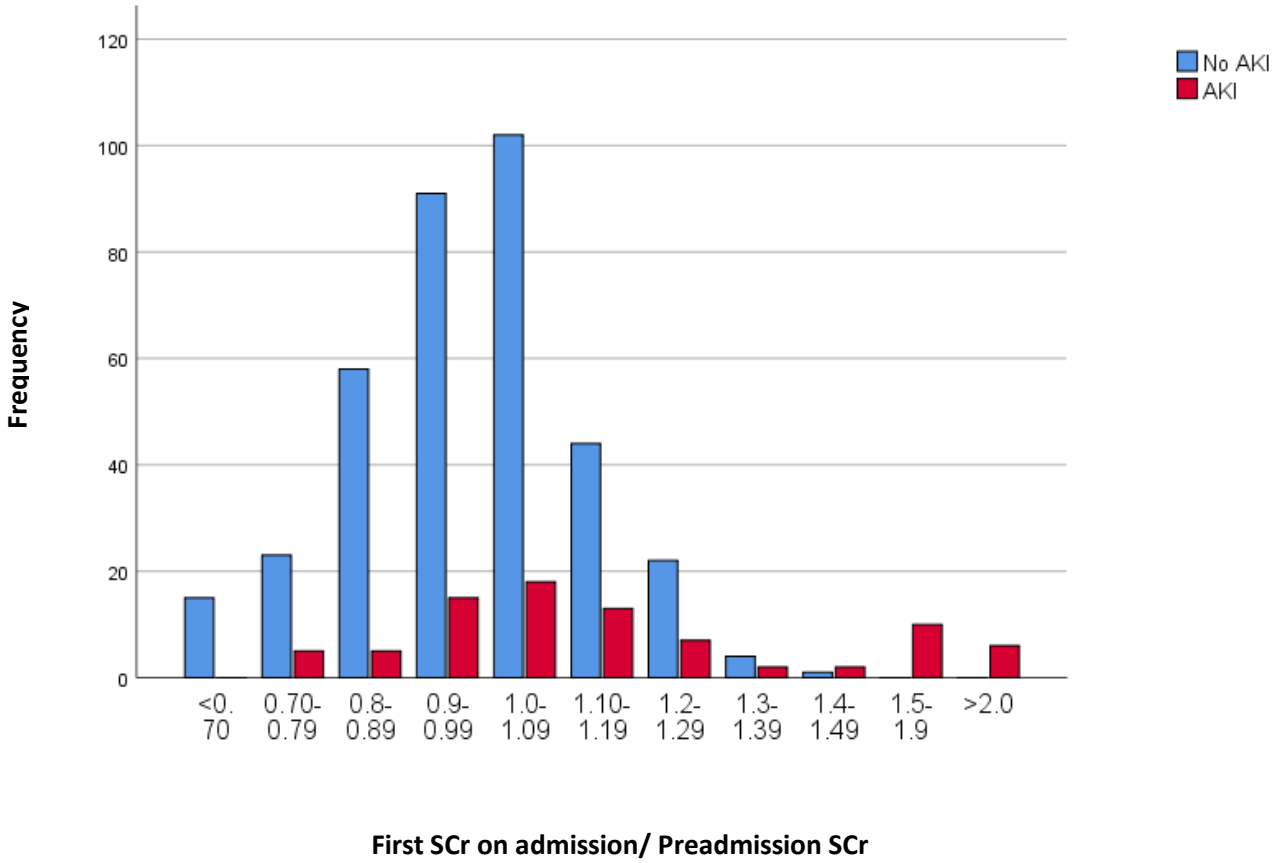
For Group C (n=443), Figures 4-2 and 4-3 show the distribution of change between preadmission SCr and first SCr on admission.

In Group C, 25.1% had a first admission SCr that was ≥110% above the preadmission SCr. A greater proportion of patients classified as having AKI^{pre} experienced this pattern compared with patients classified as having AKI^{adm} (48.2% and 20.5% respectively). That is to say that, patients with an admission SCr higher than preadmission SCr were more likely to be diagnosed with AKI^{pre}.

Conversely, 23.9% had a first admission SCr that was ≤90% of the preadmission SCr. A greater proportion of patients with AKI^{adm} compared with AKI^{pre} experienced this pattern (33.0% and 12.0% respectively). That is, patients with an admission SCr lower than preadmission SCr were more likely to be diagnosed with AKI^{adm}.

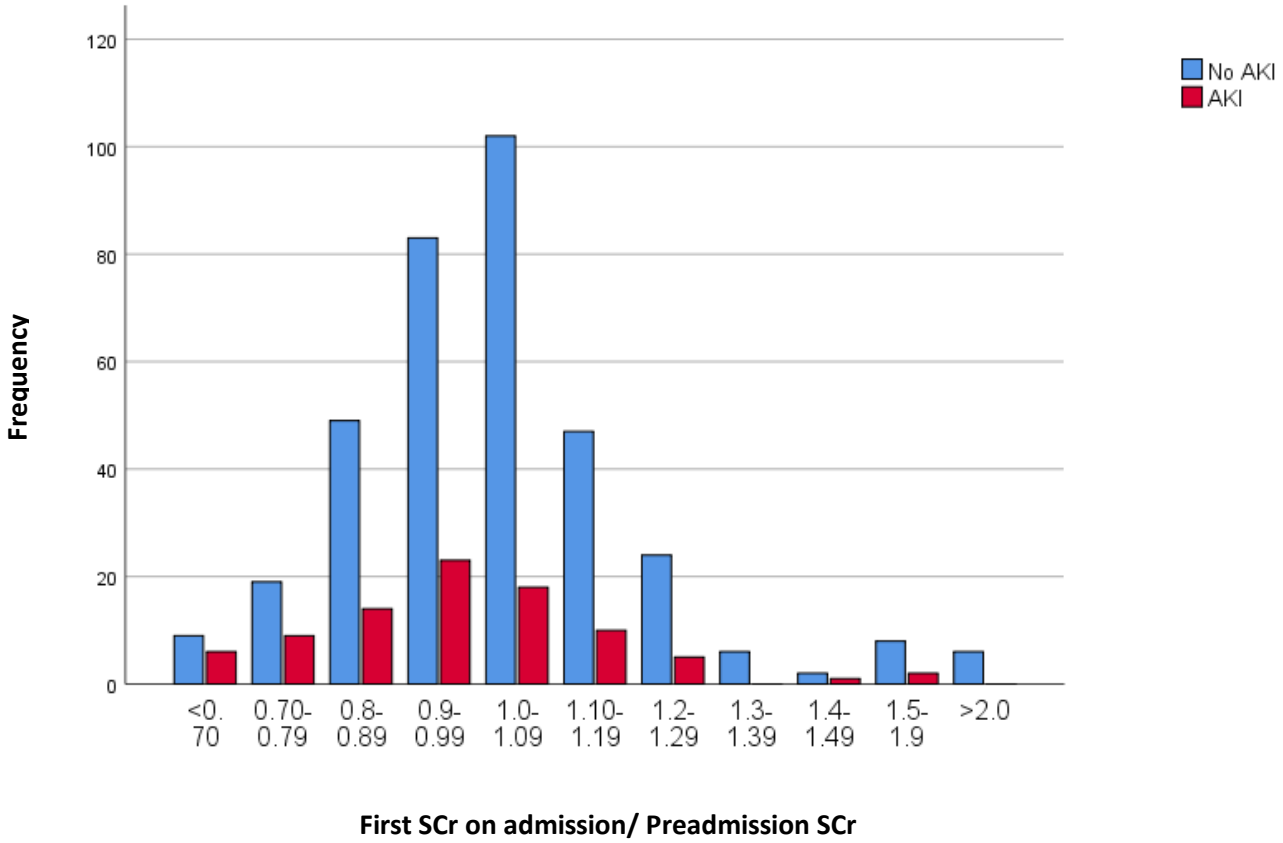
These findings demonstrate how cases of community-acquired AKI can be misclassified using the AKI^{adm} method, since admission SCr may be higher (in the case of community-acquired AKI) or lower (in the case of acute illness [313, 422, 423]) than the true 'baseline', thereby leading to under or over-detection of AKI cases where admission SCr is used to determine baseline renal function.

Figure 4-2. Change between preadmission serum creatinine and first serum creatinine on admission in Group C (n=443) stratified by acute kidney injury status, as determined by AKI[pre].



Abbreviations: AKI[pre], acute kidney injury diagnosed using preadmission serum creatinine; SCr, serum creatinine.

Figure 4-3. Change between preadmission serum creatinine and first serum creatinine on admission in Group C (n=443) stratified by acute kidney injury status, as determined by AKI^{adm}.



Abbreviations: AKI^{adm}, acute kidney injury diagnosed using first serum creatinine on admission; SCr, serum creatinine.

4.4.3 Acute Kidney Injury Diagnosis

In order to compare the rate of AKI ascertained using preadmission SCr against the 4 surrogate methods, I used Group C (n=443), which comprised all patients who had a preadmission SCr, a SCr on admission and at least one other SCr measured during the admission period.

Using preadmission SCr, the overall incidence of AKI^{pre} was 18.7%, shown in Table 4-3. In the AKI^{pre} group, 83.1% (n=69) had AKI stage 1 and 16.9% (n= 14) had AKI stage 2. There were no cases of AKI stage 3. The incidence of AKI using first SCr on admission (AKI^{adm}) was similar to AKI^{pre}, (18.7% vs. 19.9%, P=0.63). AKI rates were significantly higher using lowest SCr on admission (AKI^{low}, 41.1%, P<0.001) and back-calculation methods assuming an eGFR of 75 mL/min/1.73m^2 using both MDRD (AKI^{MDRD}, 37.0%, P<0.001) and CKD-EPI formulae (AKI^{EPI}, 40.2%, P<0.001).

AKI^{adm} exhibited moderate inter-rater agreement with AKI^{pre} (Kappa value 0.52). The other 3 surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI} exhibited weaker but still moderate inter-rater agreement with AKI^{pre} (Kappa values 0.44, 0.43 and 0.40 respectively). Of the surrogate methods, AKI^{low} was the most sensitive (92.8%) and AKI^{adm} the most specific (90.0%).

Table 4-3. AKI agreement between use of AKI^{pre} and 4 surrogate methods for ascertaining AKI: AKI^{adm}, AKI^{low}, AKI^{MDRD} and AKI^{EPI} in Group C (n=443).

Method of ascertaining AKI	**AKI (%, 95% CI)**	**Sensitivity**	**Specificity**	**Kappa (95% CI)**	**McNemar**
Preadmission SCr **AKI^{pre}**	83 (18.7, 95% CI 15.2-22.7)	-	-	-	-
First SCr on admission **AKI^{adm}**	88 (19.9, 95% CI 16.2-23.9)	62.7	90.0	0.515 (0.413-0.617)	0.625
Lowest SCr on admission **AKI^{low}**	182 (41.1, 95% CI 36.5-45.8)	92.8	70.8	0.436 (0.358-0.514)	<0.001
MDRD back-calculated SCr **AKI^{MDRD}**	164 (37.0, 95% CI 32.5-41.7)	85.5	74.2	0.434 (0.350-0.518)	<0.001
CKD-EPI back-calculated SCr **AKI^{EPI}**	178 (40.2, 95% CI 35.6-44.9)	86.7	70.6	0.398 (0.318-0.478)	<0.001

Abbreviations: AKI, acute kidney injury; AKI^{adm}, acute kidney injury diagnosed using first serum creatinine on admission; AKI^{EPI}, acute kidney injury diagnosed using back-calculated serum creatinine and CKD-EPI formula; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; AKI^{MDRD}, acute kidney injury diagnosed using back-calculated serum creatinine and MDRD formula; AKI^{pre}, acute kidney injury diagnosed using preadmission serum creatinine; CI, confidence intervals; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

Tables 4-4 to 4-7 show the number of cases per stage of AKI according to AKI^{pre} compared with each of the 4 surrogate methods.

Table 4-4 shows the number of cases per stage of AKI comparing AKI^{adm} against AKI^{pre}. The overall rate of AKI^{adm} was similar to AKI^{pre} with no significant difference between the groups, as shown in Table 4-3 (19.9% vs. 18.7%, P=0.63). However, the overall misclassification rate for AKI stages was 17.4% and there was weak inter-rater agreement between AKI^{pre} and AKI^{adm} (Kappa 0.46).

Table 4-4. Misclassification rates of AKI comparing AKI^{adm} with AKI^{pre}.

		Preadmission SCr **AKI^{pre}**			
		No AKI	**1**	**2**	**Total**
First SCr on admission **AKI^{adm}**	**No AKI**	324	25	6	355
	1	36	38	3	77
	2	0	6	4	10
	3	0	0	1	1
	Total	360	69	14	443

Kappa 0.459 (95% CI 0.363-0.555).
Misclassification rate 17.38% (overestimation 9.71% and underestimation 7.68%).

AKI^{adm}, acute kidney injury diagnosed using first serum creatinine on admission; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CI, confidence intervals; SCr, serum creatinine.

Table 4-5 shows the number of cases per stage of AKI comparing AKI^{low} against AKI^{pre}. The overall rate of AKI^{low} was higher than AKI^{pre} with a significant difference between the groups, as shown in Table 4-3 (41.1% vs. 18.7%, P<0.001). In keeping with this, the overall misclassification rate for AKI stages was 31.8%, with a predominance of overestimation (30.0% vs. 1.8% underestimation) and there was minimal inter-rater agreement between AKI^{pre} and AKI^{low} (Kappa 0.33).

Table 4-5. Misclassification rates of AKI comparing AKI^{low} with AKI^{pre}.

		Preadmission SCr **AKI^{pre}**			
		No AKI	**1**	**2**	**Total**
Lowest SCr during admission **AKI^{low}**	**No AKI**	255	6	0	261
	1	86	43	2	131
	2	16	15	4	35
	3	3	5	8	16
	Total	360	69	14	443

Kappa 0.327 (95% CI 0.258-0.396).
Misclassification rate 31.83% (overestimation 30.02% and underestimation 1.81%).

AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CI, confidence intervals; SCr, serum creatinine.

Table 4-6 shows the number of cases per stage of AKI comparing AKI^{MDRD} against AKI^{pre}. The overall rate of AKI^{MDRD} was higher than AKI^{pre} with a significant difference between the groups, as shown in Table 4-3 (37.0% vs. 18.7%, P<0.001). In keeping with this, the overall misclassification rate for AKI stages was 31.6%, with a predominance of overestimation (28.9% vs. 2.7% underestimation) and there was minimal inter-rater agreement between AKI^{pre} and AKI^{MDRD} (Kappa 0.30).

Table 4-6. Misclassification rates of AKI comparing AKI^{MDRD} with AKI^{pre}.

		Preadmission SCr **AKI^{pre}**			
		No AKI	**1**	**2**	**Total**
MDRD back-calculated SCr **AKI^{MDRD}**	**No AKI**	267	12	0	279
	1	79	25	0	104
	2	11	24	11	46
	3	3	8	3	14
	Total	360	69	14	443

Kappa 0.295 (95% CI 0.222-0.368).
Misclassification rate 31.60% (overestimation 28.89% and underestimation 2.71%).

AKI^{MDRD}, acute kidney injury diagnosed using back-calculated serum creatinine and MDRD formula; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CI, confidence intervals; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

Table 4-7 shows the number of cases per stage of AKI comparing AKI^{MEPI} against AKI^{pre}. The overall rate of AKI^{EPI} was higher than AKI^{pre} with a significant difference between the groups, as shown in Table 4-3 (40.2% vs. 18.7%, P<0.001). In keeping with this, the overall misclassification rate for AKI stages was 34.8%, with a predominance of overestimation (32.1% vs. 2.7% underestimation) and there was minimal inter-rater agreement between AKI^{pre} and AKI^{EPI} (Kappa 0.26).

Table 4-7. Misclassification rates of AKI comparing AKI^{EPI} with AKI^{pre}.

		Preadmission SCr **AKI^{pre}**			
		No AKI	**1**	**2**	**Total**
CKD-EPI back-calculated SCr **AKI^{EPI}**	**No AKI**	254	11	0	265
	1	89	27	1	117
	2	14	22	8	44
	3	3	9	5	17
	Total	360	69	14	443

Kappa 0.260 (95% CI 0.191-0.329).
Misclassification rate 34.76% (overestimation 32.05% and underestimation 2.71%).

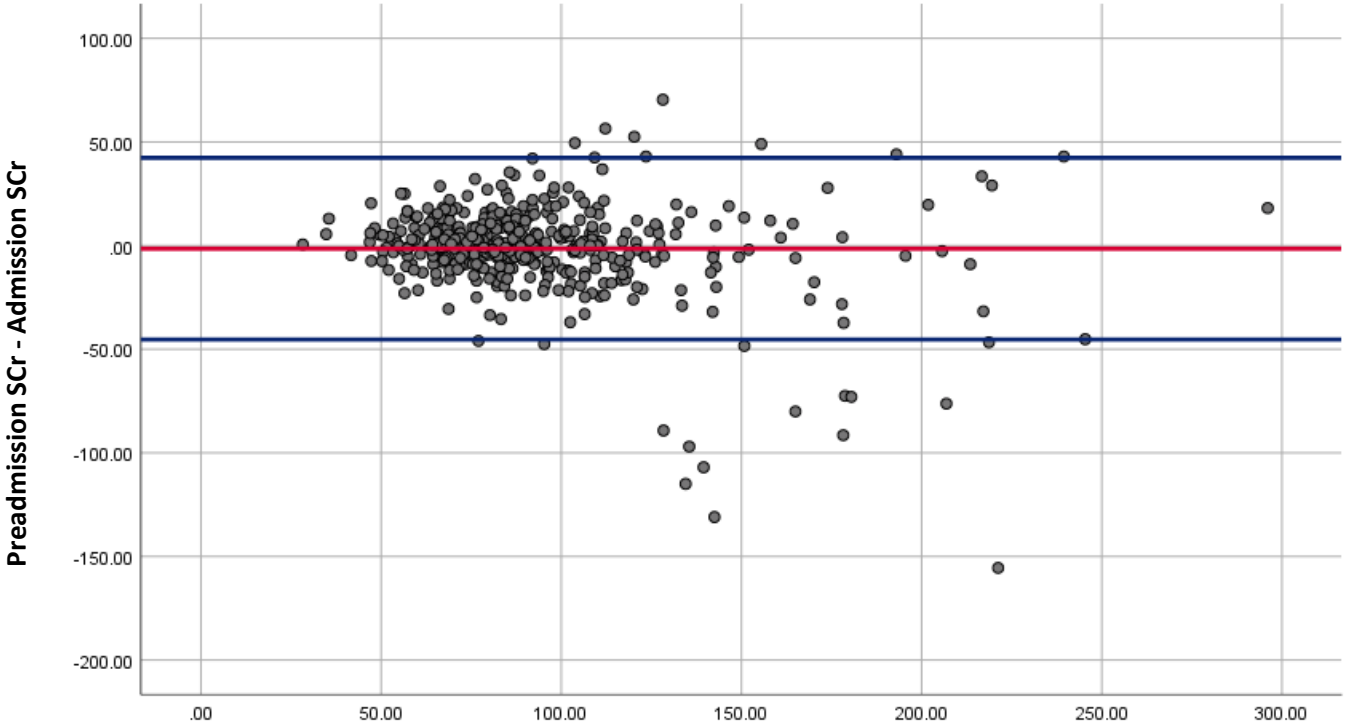
AKI^{EPI}, acute kidney injury diagnosed using back-calculated serum creatinine and CKD-EPI formula; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CI, confidence intervals; SCr, serum creatinine.

Figures 4-4 to 4-7 show the estimated limits of agreement between AKI^{pre} and each of the 4 surrogate methods using Bland-Altman plots and linear regression analyses.

Of the 4 surrogate methods for AKI diagnosis, AKI^{adm}, AKI^{low} and AKI^{MDRD} exhibited the closest agreement intervals with AKI^{pre} (B unstandardized coefficient for the mean -0.15, 95% CI -0.21- -0.09, P<0.001 for AKI^{adm}). AKI^{EPI} exhibited the least agreement (B unstandardized coefficient 0.87, 95% CI 0.68-1.07; P<0.001). The coefficient for the mean was statistically significant for all 4 surrogate methods, indicating proportional bias for all methods compared to AKI^{pre}.

Figure 4-4. Bland Altman plot showing agreement of acute kidney injury status between AKI^{pre} and AKI^{adm}.

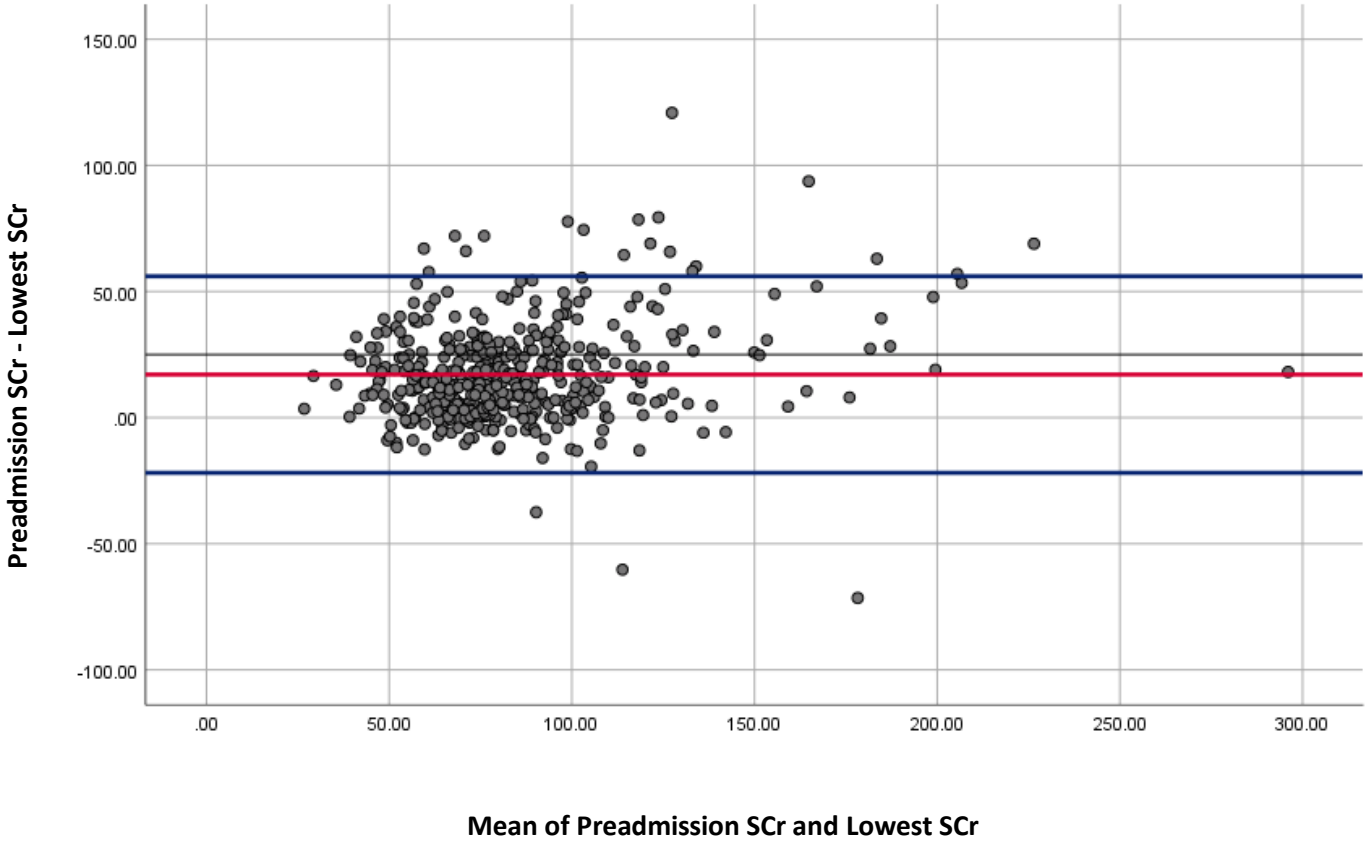
B unstandardized coefficient -0.149, 95% CI -0.206- -0.092; P<0.001.



Abbreviations: AKI^{adm}, acute kidney injury diagnosed using first serum creatinine on admission; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CI, confidence intervals; SCr, serum creatinine.

Figure 4-5. Bland Altman plot showing agreement of acute kidney injury status between AKI^{pre} and AKI^{low}.

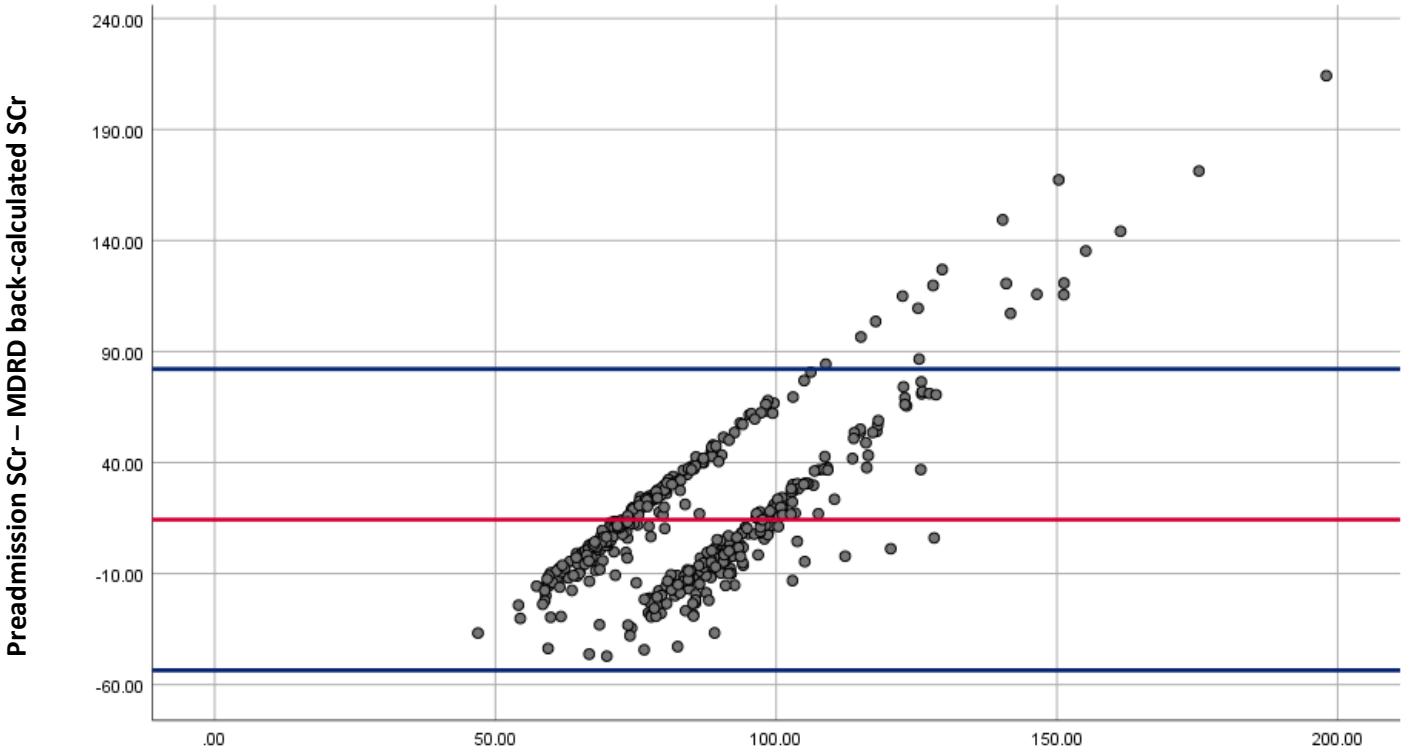
B unstandardized coefficient 0.144, 95% CI 0.086-0.203; P<0.001.



Abbreviations: AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CI, confidence intervals; SCr, serum creatinine.

Figure 4-6. Bland Altman plot showing agreement of acute kidney injury status between AKI^{pre} and AKI^{MDRD}.

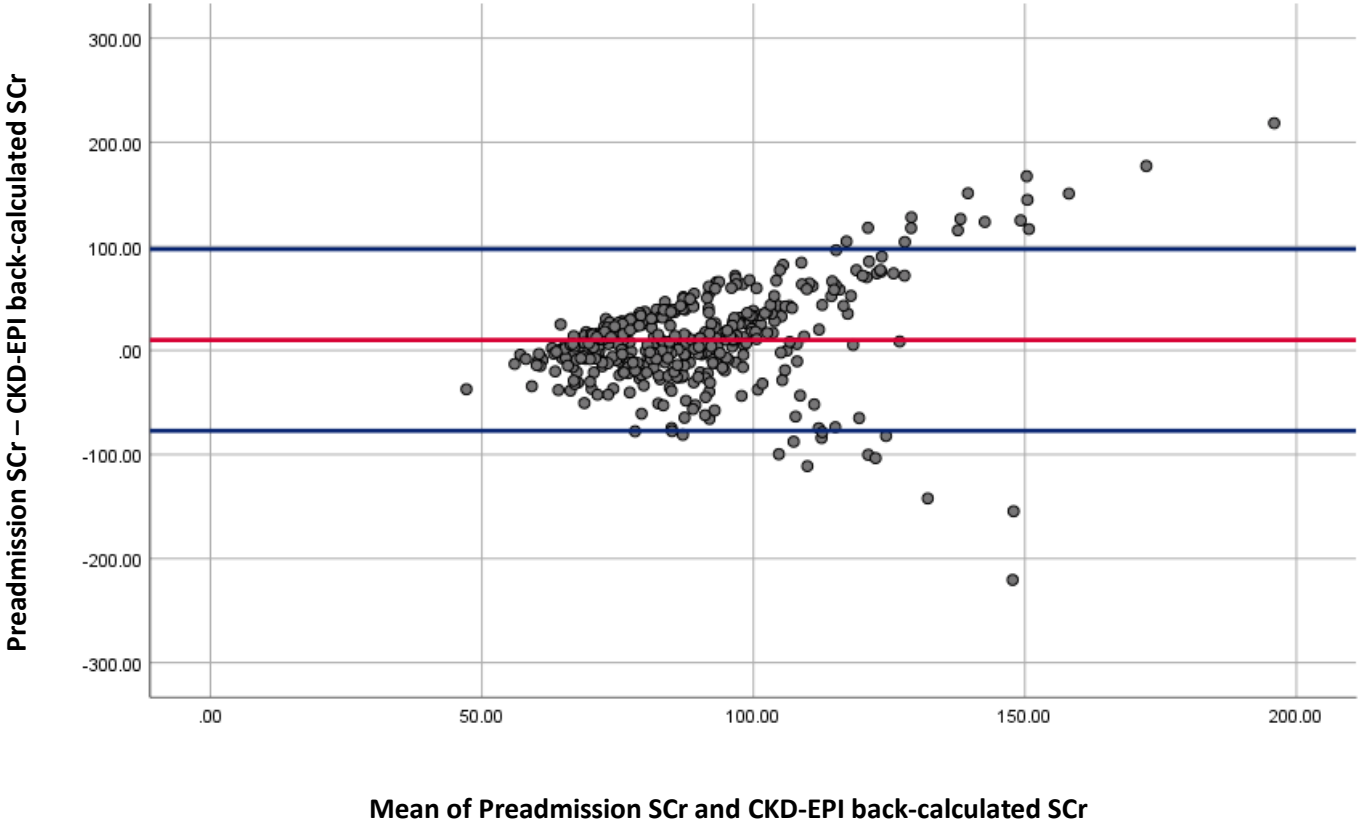
B unstandardized coefficient 0.133, 95% CI 1.226-1.440; P<0.001.



Abbreviations: AKI^{MDRD}, acute kidney injury diagnosed using back-calculated serum creatinine and MDRD formula; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CI, confidence intervals; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

Figure 4-7. Bland Altman plot showing agreement of acute kidney injury status between AKI^{pre} and AKI^{EPI}.

B unstandardized coefficient 0.873, 95% CI 0.675-1.071; P<0.001.



Abbreviations: AKI^{EPI}, acute kidney injury diagnosed using back-calculated serum creatinine and CKD-EPI formula; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CI, confidence intervals; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SCr, serum creatinine.

4.4.4 Factors Associated with Acute Kidney Injury

Univariable and multivariable logistic regression models to explore risk factors for AKI were constructed for all 5 methods of ascertaining AKI in Group C (n=443), since this Group represents a 'core cohort' including patients with both a preadmission SCr, a SCr on admission and at least 1 other SCr measured during admission. In all analyses, for closely related variables, namely CKD ascertained using both CKD-EPI and MDRD formulae, separate models were created and only one variable was entered into the model at a time.

In Group A (n=725), factors associated with AKI^{pre} were explored. The results are displayed in Appendix 4. Other methods were not investigated in this Group since for the surrogate methods, more than 1 SCr on admission was required to diagnose AKI, excluding some patients from the Group.

In Group B (n=808), factors associated with AKI^{adm}, AKI^{low}, AKI^{MDRD} and AKI^{EPI} were explored. The results are displayed in Appendices 5-8 respectively. AKI^{pre} was not investigated in this Group since having a preadmission SCr was not part of the inclusion criteria for Group B and all cases of AKI^{pre} included in Group B (n=83) are already included in Group C.

4.4.4.1 Group C

4.4.4.1.1 AKI^{pre}

Factors associated with AKI^{pre} in Group C are shown in Table 4-8. In the univariable analysis, older age, Black ethnicity, presence of CKD (ascertained using preadmission SCr and both CKD-EPI and MDRD formulae), CHF and anaemia were all associated with AKI^{pre}.

In the multivariable analysis, factors associated with AKI^{pre} were CKD (OR 2.78, 95% CI 1.69-4.57; P<0.001 for preadmission SCr and CKD-EPI used to calculate eGFR) and anaemia (OR 1.78, 95% CI 1.06-2.97; P=0.03). The results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Table 4-8. Binomial logistic regression analysis of factors associated with AKI^{pre} in Group C (n=443).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.013 (0.995-1.031)	0.149	-	-
Female sex	1.379 (0.850-2.236)	0.193	-	-
Black ethnicity	3.595 (0.944-13.691)	0.061	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	2.848 (1.745-4.651)	<0.001	2.780 (1.691-4.572)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	2.763 (1.698-4.497)	<0.001	2.667 (1.626-4.374)	<0.001
Diabetes	1.337 (0.784-2.279)	0.287	-	-
Hypertension	0.937 (0.581-1.511)	0.790	-	-
AF	1.090 (0.647-1.837)	0.746	-	-
Previous stroke/ TIA	0.894 (0.526-1.521)	0.680	-	-
CHF	2.459 (0.949-6.368)	0.064	-	-
Stroke type	0.890 (0.430-1.843)	0.754	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	0.788 (0.336-1.847)	0.584	-	-
mRS on admission (as continuous variable)	1.117 (0.944-1.322)	0.197	-	-
NIHSS score on admission (as continuous variable)	1.018 (0.989-1.047)	0.228	-	-
Anaemia (baseline haemoglobin as categorical variable)	1.744 (1.055-2.883)	0.030	1.775 (1.061-2.970)	0.029

*Adjusted for age, ethnicity, presence of CKD and CHF and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{pre}, acute kidney injury diagnosed using preadmission serum creatinine; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

4.4.4.1.2 AKI^{adm}

Factors associated with AKI^{adm} in Group C are shown in Table 4-9 and are similar to the associations with AKI^{pre}. In the univariable analysis, older age, Black ethnicity, presence of CKD (ascertained using preadmission SCr and both CKD-EPI and MDRD formulae) and anaemia were all associated with AKI^{adm}.

In the multivariable analysis, factors associated with AKI^{adm} were CKD (OR 2.60, 95% CI 1.60-4.23; P<0.001 for preadmission SCr and CKD-EPI formula to calculate eGFR) and anaemia (OR 1.96, 95% CI 1.19-3.24; P=0.009). The results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Table 4-9. Binomial logistic regression analysis of factors associated with AKI^{adm} in Group C (n=443).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.013 (0.996-1.031)	0.144	-	-
Female sex	0.930 (0.583-1.483)	0.759	-	-
Black ethnicity	3.333 (0.876-12.682)	0.077	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	2.568 (1.595-4.134)	<0.001	2.599 (1.596-4.232)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	2.393 (1.488-3.849)	<0.001	2.376 (1.461-3.865)	<0.001
Diabetes	1.300 (0.770-2.197)	0.326	-	-
Hypertension	0.962 (0.603-1.534)	0.870	-	-
AF	0.794 (0.465-1.353)	0.396	-	-
Previous stroke/ TIA	0.998 (0.599-1.665)	0.995	-	-
CHF	1.365 (0.483-3.864)	0.557	-	-
Stroke type	0.711 (0.335-1.510)	0.375	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	0.886 (0.396-1.981)	0.768	-	-
mRS on admission (as continuous variable)	1.039 (0.877-1.230)	0.658	-	-
NIHSS score on admission (as continuous variable)	1.004 (0.975-1.033)	0.796	-	-
Anaemia (baseline haemoglobin as categorical variable)	1.921 (1.174-3.143)	0.009	1.960 (1.185-3.240)	0.009

*Adjusted for age, ethnicity, presence of CKD and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{adm}, acute kidney injury diagnosed using first serum creatinine on admission; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

4.4.4.1.3 AKI^{low}, AKI^{MDRD} and AKI^{EPI}

Risk factors for with AKI^{low}, AKI^{MDRD} and AKI^{EPI} are shown in Tables 4-10, 4-11 and 4-12 respectively.

Factors associated with AKI^{low} in the univariable analysis were older age, Black ethnicity, presence of CKD (ascertained using preadmission SCr and both CKD-EPI and MDRD formulae), higher disability score on admission, increased stroke severity and anaemia (Table 4-10).

In the multivariable analysis, Black ethnicity (OR 5.36, 95% CI 1.00-28.68; P=0.05), presence of CKD (OR 3.49, 95% CI 2.29-5.32; P<0.001 for CKD-EPI), increased stroke severity (OR 1.05; 95% CI 1.02-1.08: P<0.001) and anaemia (OR 2.10, 95% CI 1.34-3.31; P=0.001) remained significantly associated with AKI^{low}. The results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Factors associated with AKI^{MDRD} in the univariable analysis were age, female sex, presence of CKD (ascertained using preadmission SCr and both CKD-EPI and MDRD), diabetes, AF, CHF, haemorrhagic stroke type, higher disability score on admission and increased stroke severity (Table 4-11).

In the multivariable analysis, presence of CKD (OR 30.46, 95% CI 17.81-52.10; P<0.001 for CKD-EPI) and CHF (OR 4.10, 95% CI 1.17-14.31; P=0.03) remained significantly associated with AKI^{MDRD}. Given the high OR for CKD, the multivariable regression analysis was repeated

excluding CKD from the model. In this analysis, factors associated with AKI^{MDRD} were older age (OR 1.05, 95% CI 1.03-1.06; P<0.001), presence of diabetes (OR 1.73, 95% CI 1.09-2.76, P=0.02), CHF (OR 3.60, 95% CI 1.37-9.52; P=0.01) and increased stroke severity (OR 1.03, 95% CI 1.00-1.05; P=0.04). The results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Factors associated with AKI^{EPI} in the univariable analysis were the same as for AKI^{MDRD} (Table 4-12). In the multivariable analysis, presence of CKD (OR 29.51, 95% CI 17.35-50.18; P<0.001 for CKD-EPI) and increased stroke severity (OR 1.05, 95% CI 1.01-1.08; P=0.005) were associated with AKI^{EPI}. Similar to AKI^{MDRD}, given the high OR for CKD, the multivariable regression analysis was repeated excluding CKD from the model. In this analysis, factors associated with AKI^{EPI} were older age (OR 1.07, 95% CI 1.05-1.09; P<0.001), presence of diabetes (OR 1.79, 95% CI 1.11-2.89, P=0.02), CHF (OR 3.38, 95% CI 1.24-9.16; P=0.02) and increased stroke severity (OR 1.04, 95% CI 1.01-1.07; P=0.004). Again, the results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Thrombolysis was not associated with AKI^{pre}, nor any of the 4 surrogate methods in Group C. The relationship between AKI and thrombectomy and other radiological contrast exposure is explored in Chapter 7, section 7.4.3 of this thesis.

Table 4-10. Binomial logistic regression analysis of factors associated with AKI^{low} in Group C (n=443).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.026 (1.011-1.041)	<0.001	-	-
Female sex	1.089 (0.745-1.591)	0.660	-	-
Black ethnicity	5.180 (1.064--25.227)	0.042	5.358 (1.001-28.678)	0.050
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	3.721 (2.490-5.561)	<0.001	3.492 (2.290-5.324)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	3.822 (2.531-5.770)	<0.001	3.527 (2.291-5.430)	<0.001
Diabetes	0.842 (0.540-1.314)	0.449	-	-
Hypertension	0.785 (0.537-1.146)	0.210	-	-
AF	1.302 (0.859-1.973)	0.214	-	-
Previous stroke/ TIA	0.768 (0.505-1.169)	0.219	-	-
CHF	1.801 (0.731-4.439)	0.201	-	-
Stroke type	1.014 (0.579-1.777)	0.961	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	0.893 (0.471-1.691)	0.728	-	-
mRS on admission (as continuous variable)	1.220 (1.061-1.402)	0.005	-	-
NIHSS score on admission (as continuous variable)	1.056 (1.030-1.082)	<0.001	1.051 (1.024-1.078)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.945 (1.282-2.951)	0.002	2.102 (1.337-3.307)	0.001

*Adjusted for age, ethnicity, presence of CKD, pre-admission disability score, stroke severity and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 4-11. Binomial logistic regression analysis of factors associated with AKI^{MDRD} in Group C (n=443).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.045 (1.028-1.063)	<0.001	1.045 (1.027-1.064)***	<0.001
Female sex	1.785 (1.205-2.644)	0.004	-	-
Black ethnicity	1.370 (0.363-5.176)	0.642	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	29.890 (17.609-50.736)	<0.001	30.458 (17.809-52.094)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	33.400 (19.367-57.601)	<0.001	33.948 (19.564-58.907)	<0.001
Diabetes	1.589 (1.022-2.469)	0.040	1.732 (1.087-2.760)***	0.021
Hypertension	1.075 (0.730-1.581)	0.715	-	-
AF	1.665 (1.094-2.535)	0.017	-	-
Previous stroke/ TIA	1.072 (0.704-1.634)	0.746	-	-
CHF	3.345 (1.307-8.565)	0.012	4.097 (1.173-14.307) 3.604 (1.365-9.520)***	0.027 0.010
Stroke type	0.610 (0.331-1.124)	0.113	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	0.969 (0.507-1.851)	0.924	-	-
mRS on admission (as continuous variable)	1.179 (1.025-1.357)	0.021	-	-
NIHSS score on admission (as continuous variable)	1.037 (1.012-1.062)	0.003	1.027 (1.002-1.053)***	0.036
Anaemia (baseline haemoglobin as categorical variable)	1.251 (0.820-1.908)	0.300	-	-

*Adjusted for age, female sex, presence of CKD, diabetes, AF, CHF, stroke type, pre-admission disability score and stroke severity in a forward conditional model.

**Related variables were entered into the models separately.

***Factors associated with AKI^{MDRD} when CKD excluded from the multivariable model. Adjustments are otherwise as above.

Abbreviations: AF, atrial fibrillation; AKI^{MDRD}, acute kidney injury diagnosed from back-calculated serum creatinine using MDRD formula; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 4-12. Binomial logistic regression analysis of factors associated with AKI^{EPI} in Group C (n=443).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.066 (1.046-1.085)	<0.001	1.066 (1.045-1.087)***	<0.001
Female sex	1.539 (1.049-2.260)	0.028	-	-
Black ethnicity	1.886 (0.499-7.122)	0.349	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	29.749 (17.640-50.171)	<0.001	29.507 (17.349-50.183)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	36.206 (20.527-63.858)	<0.001	28.976 (16.198-51.837)	<0.001
Diabetes	1.540 (0.995-2.385)	0.053	1.790 (1.107-2.894)***	0.018
Hypertension	1.022 (0.699-1.495)	0.910	-	-
AF	1.800 (1.187-2.731)	0.006	-	-
Previous stroke/ TIA	1.017 (0.671-1.541)	0.938	-	-
CHF	2.904 (1.135-7.429)	0.026	3.375 (1.243-9.164)***	0.017
Stroke type	0.633 (0.350-1.144)	0.130	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	0.931 (0.491-1.763)	0.826	-	-
mRS on admission (as continuous variable)	1.223 (1.063-1.406)	0.005	-	-
NIHSS score on admission (as continuous variable)	1.050 (1.025-1.075)	<0.001	1.048 (1.014-1.082) 1.038 (1.012-1.065)***	0.005 0.004
Anaemia (baseline haemoglobin as categorical variable)	1.093 (0.719-1.661)	0.679	-	-

*Adjusted for age, female sex, presence of CKD, diabetes, AF, CHF, stroke type, pre-admission disability score and stroke severity in a forward conditional model.

**Related variables were entered into the models separately.

***Factors associated with AKI^{EPI} when CKD excluded from the multivariable model. Adjustments are otherwise as above.

Abbreviations: AF, atrial fibrillation; AKI^{EPI}, acute kidney injury diagnosed from back-calculated serum creatinine using CKD-EPI formula; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

4.5 Discussion

In the first of the two AKI study arms, I investigated the rate of AKI in patients hospitalised with acute stroke using the 'gold standard' baseline- preadmission SCr obtained between 7-365 days up to admission, compared with 4 different surrogate methods. I found that the incidence of AKI is high, at approximately 20% but varies depending upon the method used to ascertain AKI. I also explored associations with AKI and found the risk factors are generally in keeping with those reported in the literature [280]. I will now discuss the findings in turn.

4.5.1 Characteristics of Patients with and without Preadmission Serum Creatinine

In this cohort, just over half the patients had at least one preadmission SCr (53.5%), consistent with previous studies [314]. Patients who had a preadmission SCr were older, and a greater proportion were female, White and had concurrent comorbidities including CKD, diabetes, hypertension, AF, CHF and previous stroke/ TIA. In England, chronic disease monitoring with blood tests is performed widely by General Practitioners [424]. The Quality Outcomes Framework (QOF), introduced in 2004, is a pay-for-performance incentive programme which reimburses GPs for carrying out effective interventions in chronic diseases, as measured by evidence-based indicators developed by the National Institute for Health and Care Excellence (NICE) [425]. Despite being a voluntary scheme, 99% of GP practices participate, deriving approximately 8% of their income from QOF between 2017 and 2018 [426]. As part of QOF, GP practices are required to keep chronic disease registers for CKD, diabetes, hypertension, AF, CHF and stroke/ TIA, as well as other diseases such as dementia, COPD and obesity. They are also required to carry out blood test monitoring as per NICE guidelines, including

measurement of SCr at specified intervals for patients with CKD, or who are at risk of CKD [427]. My results are in keeping with widespread adherence to the practice of blood test monitoring in patients with comorbidities in the community as per QOF.

4.5.2 Comparison of preadmission SCr and admission SCr

One of the major challenges in AKI epidemiological research lies in the accurate detection of true cases of AKI. In this study, I used the 'gold standard', preadmission SCr and compared this to 4 surrogate methods. I found that first SCr on admission (AKI^{adm}) most closely agreed with preadmission SCr (AKI^{pre}) in diagnosing AKI (incidence 19.9% vs. 18.7%, McNemar P=0.63). To date, use of first SCr on admission is one of the most widely used surrogate methods in AKI studies, and the recommended method by AKIN [428]. However, as with all surrogate methods, it has limitations. For example, in some clinical situations, where the first SCr on admission is taken as the 'baseline' value, cases of community-acquired AKI (where the SCr is already elevated prior to arrival) may be missed, thus underestimating the incidence of AKI [308]. Conversely, in older and frailer patients with an acute illness, the admission SCr has been shown to be lower than the outpatient 'baseline', leading to an overestimation in the incidence of AKI [313, 422]. This was emphasised by a recent US study which reported that 45% of all hospitalised patients had a first SCr on admission less than 90% of the preadmission SCr [313].

However, my data showed that less than 25% of patients had a first SCr on admission that was less than 90% of the preadmission SCr. Furthermore, acute stroke, by its very nature, happens suddenly and patients are usually admitted to hospital promptly, imparting very little time to develop a community-acquired AKI. Patients presenting with a first acute stroke might also be less likely to have a gradually worsening health state preceding admission and therefore less likely to have a lower SCr, as might be expected in patients with conditions causing a more gradual deterioration, such as cancer. I therefore feel these are less likely to have been significant factors affecting the ascertainment of AKI in this study, although it is acknowledged that the study cohort had a high prevalence of chronic conditions.

In this study, around 25% of patients had an admission SCr greater than 110% above the preadmission 'baseline', and as mentioned above, just under 25% of patients had an admission SCr less than 90% of the preadmission SCr. This highlights the challenge of utilising different methods, in this case first SCr on admission, to diagnose AKI. The variation 10% above or below the preadmission 'baseline', demonstrated in around 50% of patients is likely to have introduced bias into the results. It is clear from AKI studies to date, that use of any surrogate method will result in some degree of bi-directional misclassification of AKI, particularly in mild AKI, which will in turn have an effect on incidence and other estimates such as risk ratios. Choice of surrogate method should be guided by the population being studied, for example, in a cohort with a high prevalence of CKD, back-calculation methods should not be used [320, 321]. In this population of stroke patients, admission SCr most closely adjudicates with

preadmission SCr, and is the only creatinine-based method that has been utilised in studies investigating AKI in patients with acute stroke to date [370].

4.5.3 Acute Kidney Injury Diagnosis

4.5.3.1 AKI^{adm} compared with AKI^{pre}

AKIN [308, 309] and ERBP [318] recommend use of first SCr on admission to ascertain AKI. However, as discussed above, admission SCr has a low sensitivity [308, 319, 320, 322] and may be a poor surrogate for a true 'steady state' or baseline as it may be altered by the acute illness leading to hospitalisation [320]. In this study, using admission SCr to diagnose AKI in our cohort (AKI^{adm}) produced a similar rate of AKI to preadmission SCr (AKI^{pre}) (19.9% vs. 18.7%, McNemar P=0.63). These rates are comparable to other published studies that utilise SCr values rather than coding to diagnose AKI in patients with acute stroke, with rates ranging from 15-27% [330, 331, 336]. However, although the absolute rates were similar, AKI^{adm} when compared to AKI^{pre} had a low sensitivity (62.7%), high specificity (90.0%) and a Kappa value indicating only moderate agreement (0.52). Furthermore, since the majority of AKI in Group C was stage 1 (83.1% for AKI^{pre} vs. 87.5% for AKI^{adm}), this is likely to have further influenced the detection of true cases of AKI.

My data are comparable with the literature reporting the low sensitivity of this method. In a US study of 4863 unselected acute hospital admissions, using first SCr on admission as a baseline to ascertain AKI (AKI^{adm}) yielded a sensitivity of 38.9% and a specificity of 94.9% [308].

Accordingly, AKI^{adm} resulted in a significantly lower AKI incidence than use of preadmission SCr (13.7% vs. 25.5%, P<0.001), which might be explained by the missed diagnosis of community-acquired AKI that subsequently improves during hospitalisation [308]. In this same study, AKI^{adm} produced a misclassification rate of 21.3%, with 4.3% being overclassified to a higher stage of AKI and 17.0% being underclassified to a lower stage. In comparison, my data showed a slightly lower overall misclassification rate of 17.4%, with 9.7% of AKI cases being overclassified and 7.7% being underclassified. This might be explained by differences in a cohort of stroke patients compared with the unselected population studied in Siew *et al*. [308].

Since the rate of AKI using AKI^{adm} most closely agreed with that of AKI^{pre}, I further compared the distribution of change between preadmission SCr and first SCr to investigate the effect on ascertainment of AKI. I found that individual patients were just as likely to have an admission SCr that was 10% higher or 10% lower than the preadmission SCr. This could potentially suggest a random effect consistent with day-to-day biological fluctuations in SCr [429, 430] or analytical variability in the laboratory [431]. I also observed that patients with a higher admission SCr had higher rates of AKI^{pre} compared with AKI^{adm} (48.2% and 20.5% respectively), whereas patients with a lower admission SCr had higher rates of AKI^{adm} compared with AKI^{pre} (33.0% and 12.0% respectively). This is consistent with the reduced ability of AKI^{adm} to detect AKI when community-acquired AKI is present and the SCr on admission is already elevated, especially at lower stages of AKI.

My findings demonstrate the practical implications of this particular method, AKI^{adm} in ascertaining AKI. Where the admission SCr is lower than the outpatient baseline, using admission SCr may misclassify some patients as having AKI when in fact AKI is absent and the SCr is merely rising back to the true baseline. The inclusion of 'false positives' may, as discussed previously, influence incidence rates and cause bias of true AKI risk factors towards the null, and as such is an important limitation of this method. The effect of using first SCr on admission compared to preadmission SCr has been highlighted in a recently published study, where a much higher proportion of patients were identified as having AKI using preadmission SCr to ascertain AKI (37,827 cases using AKI^{pre} vs. 22,568 for AKI^{adm}), in keeping with the low sensitivity of the AKI^{adm} method in detecting community-acquired AKI compared to AKI^{pre} [313]. Notably, almost 50% of hospitalised patients in this cohort had an admission SCr less than 90% of the preadmission baseline. Interestingly, older age, a history of cancer and admission to ITU were all associated with having a SCr less than 90% of the outpatient baseline, largely supporting what we know about the influence muscle mass on SCr. As survival rates from chronic diseases improve with advances in modern medicine and our population ages, further studies are required to evaluate the best method of estimating baseline SCr in these populations where preadmission SCr values are absent.

4.5.3.2 AKI^{MDRD} and AKI^{EPI} compared with AKI^{pre}

Another surrogate method for ascertaining a diagnosis of AKI is back-calculation of SCr by assigning each subject a 'low normal' eGFR of 75 mL/min/1.73m^2 using the MDRD equation, as recommended by ADQI and KDIGO [280, 281]. This method operates on the assumption

that in most clinical situations, low normal kidney function can act as a reasonable surrogate for baseline SCr [320]. In this study, I back-calculated SCr using both MDRD and CKD-EPI formulae and compared the performance of both in detecting AKI cases to AKI^{pre}. The rate of AKI was 37.0% using AKI^{MDRD}, compared with 18.7% using AKI^{pre} (McNemar P<0.001) and demonstrated weak to moderate inter-rater agreement (Kappa 0.43). The sensitivity and specificity for AKI^{MDRD} compared to AKI^{pre} was 85.5% and 74.2% respectively. Similarly, using AKI^{EPI}, the rate of AKI was 40.2% (McNemar P<0.001), with weak to moderate inter-rater agreement (Kappa 0.40) and a sensitivity and specificity of 86.7% and 70.6% respectively. Overall misclassification rates were high for both back-calculation methods (31.6%, of which 28.9% of cases were overestimated for AKI^{MDRD} and 34.8%, of which 32.1% of cases were overestimated for AKI^{EPI}). My results are comparable to those reported in Siew *et al*., which demonstrated that use of back-calculated SCr (assigning an eGFR of 75 mL/min/1.73m^2 using the MDRD formula) yielded an AKI misclassification rate of 29.5%, with 24.5% being overclassified to a higher stage and 5% being underclassified to a lower stage [308]. The authors report a sensitivity of 84.2% and specificity of 77.4%, similar to my results. The overall incidence of AKI ascertained using preadmission SCr (AKI^{pre}) reported by Siew *et al*. was 25.5%, increasing to 38.3% using AKI^{MDRD} [308].

Apart from the high rates of misclassification (predominantly overestimation) of AKI cases, another significant limitation to the back-calculation method of ascertaining AKI is worthy of discussion. Since patients are assigned a GFR at the lower limit of normal (75 mL/min/1.73m^2), this means that any patient with pre-existing CKD would be classified as having AKI using this method (as any subsequent SCr values would equate to a lower eGFR than 75

mL/min/1.73m^2). This was demonstrated in the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study, which compared the diagnosis and classification of AKI according to the RIFLE staging criteria and observed (preadmission) SCr and estimated SCr (using MDRD back-calculation) in 1314 patients who were critically ill and admitted to the ITU [320]. An 18.8% 'false positive' AKI rate was reported in the total cohort, compared with a 6.6% 'false positive' rate when CKD patients were excluded. The overall prevalence of CKD (defined as an eGFR <60 mL/min/1.73m^2) was high (46.0%) and the correlation between preadmission SCr to diagnose AKI and the GFR-75 method using MDRD was modest at best. The authors concluded that AKI^{MDRD} is a reasonable and practical surrogate approach which can be applied to a population of patients with normal preadmission renal function, but it's use is limited by the potential for misclassification of both the incidence and severity of AKI when applied to CKD patients or populations with a high prevalence of CKD. Accordingly, in this cohort of stroke patients, the prevalence of CKD was over 30% and my data confirm previous findings that the GFR-75 method produces high rates of misclassification in such a population. Consequently, the results using AKI^{MDRD} and AKI^{EPI} to determine AKI in this cohort should be interpreted with extreme caution and back-calculation methods should probably not be used. Fortunately, most patients with CKD (or indeed other chronic diseases) will have a preadmission SCr held in their medical records. However, the problem of undiagnosed CKD remains an issue which has yet to be addressed.

4.5.3.3 AKI^{low} compared with AKI^{pre}

I also explored the use of nadir or lowest SCr to ascertain AKI (AKI^{low}) and found that it performed similarly to the back-calculation methods, AKI^{MDRD} and AKI^{EPI}. The incidence of AKI^{low} in this study was 41.1% (McNemar P<0.001) and again demonstrated weak to moderate inter-rater agreement with AKI^{pre} (Kappa 0.44). The sensitivity and specificity for the AKI^{low} method compared to AKI^{pre} were 92.8% and 70.8% respectively and the overall misclassification rate was 31.8%, with a predominance of overestimation (30.0% of cases). These results suggest that in this study, nadir inpatient SCr was lower than the preadmission SCr. This might occur for a number of reasons, including administration of IV fluid causing haemodilution and a fall in SCr, possible withdrawal of ACEi or ARBs, or a reduction in SCr production in the setting of intercurrent illness [422, 423]. In the study by Siew *et al*., nadir SCr produced an AKI misclassification rate of 24.0%, with 17.9% being overclassified to a higher stage of AKI and 6.3% being underclassified to a lower stage [308]. Use of nadir SCr as a baseline yielded a sensitivity of 81.7% and specificity of 79.8%. The overall incidence of AKI ascertained using nadir SCr (AKI^{low}) was 35.9%, compared with 25.5% using AKI^{pre}. My results are broadly comparable to those reported by Siew *et al*., but in my study cohort the misclassification rate of AKI^{low} was much higher (31.8% vs. 24.0%), with a higher sensitivity (92.8% vs. 81.7%) and lower specificity (70.8% vs. 79.8%). These variances may reflect different baseline characteristics that may be a feature of this cohort of stroke patients compared to the unselected hospital population studied by Siew *et al*. As for the back-calculation methods for ascertaining AKI (AKI^{MDRD} and AKI^{EPI}), the high misclassification rate

demonstrated in this study and others in the literature [308] leads me to conclude that this method is of limited value in ascertaining rates of AKI in this particular group of patients.

In summary, I compared five methods to ascertain AKI using a 'like for like', core cohort of patients, Group C (n=443) who had a preadmission SCr, an admission SCr and at least 1 other SCr measured during the admission. In this cohort of patients hospitalised with acute stroke, the AKI^{adm} method most closely agreed with AKI^{pre} and produced the lowest misclassification rates. However, all surrogate methods resulted in bi-directional misclassification of AKI and exhibited proportional bias compared to AKI^{pre}. Use of lowest SCr and back-calculation methods significantly overestimated the rate of AKI compared with preadmission SCr and exhibited low specificity and poor inter-rater agreement. Accordingly, in this cohort of stroke patients, these methods should be used with caution.

4.5.4 Factors Associated with Acute Kidney Injury

In this cohort of patients hospitalised with acute stroke, factors that were most strongly and consistently associated with AKI in a multivariable analysis were presence of CKD and anaemia. These are in keeping with known risk factors in the literature (see Chapter 2, Table 2-2) [280]. Other known risk factors for AKI which were demonstrated in this study were older age (Groups C and B, AKI^{MDRD} and AKI^{EPI}), presence of diabetes (Groups C and B, AKI^{MDRD} and AKI^{EPI}), CHF (Groups C and B, AKI^{MDRD} and AKI^{EPI}), female sex (Group B, AKI^{MDRD}), Black ethnicity (Group C, AKI^{low}) and hypertension (Group B, AKI^{MDRD}) in multivariable regression analyses. AF was also found to be associated with AKI in multivariable models (Group B, AKI^{MDRD} and AKI^{EPI}).

Although not thought to be a direct causative factor of AKI, the presence of AF may reflect underlying cardiovascular disease, older age and CKD [115], all of which are associated with AKI [280].

Increased stroke severity was consistently associated with AKI in most of the multivariable models and across all Groups (Group C, AKI^{low}, AKI^{MDRD} and AKI^{EPI}, Group A, AKI^{pre} and Group B, AKI^{low}, AKI^{MDRD} and AKI^{EPI}). This is a key finding of this study, which adds weight to the few published studies to date that have explored and found an association between stroke severity and AKI [331, 336]. A more severe stroke might feasibly increase the risk of AKI for several reasons, as outlined in Chapter 2, sections 2.1.6 and 2.5.

Notably, in all regression analyses, entering AKI^{MDRD} and AKI^{EPI} into the models resulted in very high ORs for CKD. This highlights the problem of using back-calculation of SCr (the GFR-75 method) to determine 'baseline' SCr and ascertain a diagnosis of AKI in patients with CKD. As discussed in section 4.5.3.2, use of back-calculation methods are unsuitable for use in CKD, since all patients with CKD will be classified as having AKI using this method. It therefore follows that, as a result of the high proportion of cases misclassified as having AKI using the AKI^{MDRD} and AKI^{EPI} methods, there appears to be a very strong association with CKD. To reduce the risk of bias from misclassification of AKI, I therefore repeated the analyses, excluding CKD from the multivariable regression models and found that several other associations emerged, including older age, female sex, presence of diabetes, CHF, AF, and increased stroke severity and anaemia, in keeping with known risk factors for AKI [280].

Finally, it is noted that not all of the associations with AKI were observed across all Groups and for all methods. As previously discussed, the misclassification of AKI rates using surrogate methods and the inclusion of patients without 'real' AKI may have caused bias of true AKI risk factors towards the null. However, the regression analyses may also have been affected by a lack of power to detect associations with AKI, particularly in Group C (n=443). This 'core cohort', who had a preadmission SCr, an admission SCr and at least 1 other SCr measured during the admission, was devised to compare 'like for like' cases across all methods to ascertain AKI. Some patients in Group A (n=725) and Group B (n=808) were therefore excluded since at least 2 SCr measurements during admission were required (affecting some patients in Group A) and not all patients had a preadmission SCr (affecting some patients in Group B). The exclusion of some of these patients in order to reduce confounding may have been at the expense of powering to detect associations with AKI.

4.5.5 Limitations

One of the main limitations in this study was the number of subjects who had preadmission SCr values available for analysis (54%). This may have skewed the study population towards a more chronically unwell group, since these patients are more likely to have a SCr in the community measured prior to admission. To address this, I selected a 'core cohort' of patients (Group C) who had both a preadmission SCr value and at least 2 blood tests during admission. I also used multiple adjustments in the analyses. However, it is still possible that some residual unmeasured confounding remains. In addition, by selecting this cohort, the number of patients included for analysis was reduced, which may have limited the power to detect

associations with AKI. I also analysed and compared the results of Group A and B separately and found that the associations were not consistent across all Groups and methods of ascertaining AKI. This is likely due to both powering and the number of misclassified cases of AKI using the different surrogate methods, which may have introduced bias.

The study population is comprised of patients hospitalised with an acute stroke to a single centre and therefore AKI incidence, risk factors and outcomes may be different to an unselected hospital population with AKI in a different geographical region. Additional large, multi-centre studies using a similar methodology with linkage of EHR and SSNAP data are needed to reinforce the results of this study. I was unable to utilise data on urine output to classify AKI, since this is unreliably captured in PICS. This is likely to parallel the situation in other UK hospitals, and it is unclear whether urine output data would add any further discriminatory value to this cohort, particularly in milder AKI or patients with low SCr values. Finally, I was unable to address causality due to the observational nature of this study.

4.6 Conclusions

AKI occurs commonly in stroke patients, with an incidence of approximately 20%, depending on the method used to ascertain AKI. Older age, comorbidities including CKD, anaemia, diabetes, CHF and AF and increased stroke severity are all associated with developing AKI. Comparison of four established surrogate methods for ascertaining 'baseline' SCr with the gold standard, preadmission SCr, produced bi-directional misclassification of AKI, but first SCr

on admission most closely agreed with preadmission SCr. In cases where preadmission SCr is missing, admission SCr would appear to be a reasonable surrogate method to diagnose AKI in patients hospitalised with acute stroke. Owing to high misclassification rates of AKI, it is recommended that back-calculation methods and lowest SCr on admission should not be used in this population, where the prevalence of CKD is high. Whilst the search for superior biomarkers of AKI continues, SCr remains the mainstay of AKI diagnosis, and better surrogate methods of estimating 'baseline' renal function are needed to overcome the problem of missing preadmission SCr. These will help inform risk-prediction models and future AKI prevention trials.

CHAPTER 5 OUTCOMES OF ACUTE KIDNEY INJURY AFTER AN ACUTE STROKE

5. 1 Introduction

AKI is responsible for 1.7 million deaths per year globally, although in low and middle-income countries, the incidence of AKI is likely to be grossly underestimated [432]. Epidemiological studies have shown that even milder, reversible forms of AKI are associated with higher mortality [299, 433]. AKI is a common condition that is potentially treatable. A UK study of unselected adult admissions (both elective and non-elective) reported an overall AKI incidence of 5.4% [294]. The same study also reported increased in-hospital mortality in the AKI group (23.8% vs. 3.2% in the non-AKI group). More severe AKI was associated with increased LOS and reduced renal recovery and was the strongest independent predictor of in-hospital mortality after adjustment for age (HR 3.6, 95% CI 2.8-4.6; P<0.001 for AKI stage 3).

AKI is a syndrome which encompasses a broad range of aetiologies, including kidney-specific diseases, such as vasculitis and acute glomerular disease, systemic conditions such as hypovolaemic states or sepsis and post-renal obstruction of the urinary tract [280]. These conditions may co-exist in an individual patient, and by the same token, comorbidities that make a patient susceptible to AKI might also be simultaneously present. These factors contribute to the highly heterogeneous syndrome of AKI, which in turn has complicated the search for earlier, more accurate biomarkers to detect AKI [415]. As such the pursuit of the so-called 'kidney troponin' continues and SCr remains the only metric used in clinical practice

to diagnose and stage AKI [417-419]. Methods of ascertaining a diagnosis of AKI and their limitations are previously discussed in Chapter 2, section 2.1.5 and Chapter 4, sections 4.5.2 and 4.5.3.

5.1.1 Rationale of AKI Study Arm

Please refer to Chapter 4, section 4.1.1.

5.2 Aims of AKI Study Arm 2- Outcomes

The AKI arm of the study is subdivided further into two arms. In the second, I sought to determine the association between AKI and the following:

1) 30-day mortality;
2) 1-year mortality.

5.3 Methods

5.3.1 Study design and population

The methods for this study are outlined in full in Chapter 3. Please also refer to Chapter 4, section 4.3.1 for a brief summary of the study design and population.

5.3.2 Data collection and follow-up period

The methods for this study are outlined in full in Chapter 3.

5.3.3 Inclusion criteria

Please refer to Chapter 4, section 4.3.3.

5.3.4 Definitions

Please refer to Chapter 4, section 4.3.4 for definition of AKI and section 4.3.5 for other definitions.

5.3.5 Statistical analysis

Analyses were performed using SPSS 25.0 (SPSS Inc., Chicago IL, USA). Analyses of continuous and categorical variables and logistic regression are outlined in Chapter 4, section 4.3.6.

Time-to-event data for AKI and non-AKI groups were plotted using Kaplan-Meier curves and observed differences compared using the Log rank test [399]. Regression analysis of time-to-event data for cumulative mortality was performed using the Cox proportional hazards model and results expressed as a HR with 95% CI [400, 401].

5.4 Results

In total, 1440 hospital admissions with acute stroke occurred within the study period (December 2012 to September 2015) (see Chapter 4, Figure 4-1). After excluding readmissions, duplicates and patients with ESRD, a total of 1354 patients were included for analysis. Patients were assigned to **Group A**, **Group B** and **Group C**, as outlined in Chapter 3, section 3.14 and Chapter 4, section 4.4.

5.4.1. AKI and 30-Day Mortality

5.4.1.1 Crude 30-Day Mortality

At 30 days the overall mortality rate for the total cohort (n=1354) was 10.4% (n=141). Crude 30-day mortality rates for Groups A, B and C are shown in Table 5-1.

In Group A, 30-day mortality was significantly higher in patients with AKI^{pre} compared to patients without AKI (27.3% vs. 10.5%, P<0.001). In Group B, the mortality rate was higher in the AKI^{adm} group (20.2% vs. 12.2%, P=0.01). In Group C, mortality was higher in the AKI group when both AKI^{pre} (28.9% vs. 13.9%, P=0.001) and AKI^{adm} (23.9% vs. 14.9%, P=0.04) were used to ascertain AKI compared with patients without AKI. Mortality was also higher in the AKI group using the other three surrogate methods (AKI^{low} 24.7% vs. 11.1%, P<0.001; AKI^{MDRD} 26.2% vs. 11.1% ;P<0.001 and AKI^{EPI} 26.4% vs. 10.2%, P<0.001).

Table 5-1. Crude 30-day and 1-year mortality rates in Groups A, B and C, according to the presence or absence of AKI ascertained using preadmission SCr and 4 surrogate methods.

	Group A		
	AKI^{pre} n=88	**No AKI^{pre} n=631**	**P value**
30-day mortality	27.27% (24)	10.46% (66)	<0.001
1-year mortality	47.73% (42)	20.76% (131)	<0.001
	Group B		
	AKI^{adm} n=134	**No AKI^{adm} n=674**	**P value**
30-day mortality	20.15% (27)	12.17% (82)	0.013
1-year mortality	38.06% (51)	23.15% (156)	<0.001
	Group C		
	AKI^{pre} n=83	**No AKI^{pre} n=360**	**P value**
30-day mortality	28.92% (24)	13.89% (50)	0.001
1-year mortality	50.60% (42)	26.94% (97)	<0.001
	AKI^{adm} n=88	**No AKI^{adm} n=355**	**P value**
30-day mortality	23.86% (21)	14.93% (53)	0.044
1-year mortality	43.18% (38)	28.45% (101)	<0.001
	AKI^{low} n=182	**No AKI^{low} n=261**	**P value**
30-day mortality	24.73% (45)	11.11% (29)	<0.001
1-year mortality	50.55% (92)	18.01% (47)	<0.001
	AKI^{MDRD} n=164	**No AKI^{MDRD} n=279**	**P value**
30-day mortality	26.22% (43)	11.11% (31)	<0.001
1-year mortality	44.51% (73)	23.66% (66)	<0.001

	Group C		
	AKI^{EPI} n=178	**No AKI^{EPI} n=265**	**P value**
30-day mortality	26.40% (47)	10.19% (27)	<0.001
1-year mortality	43.26% (77)	23.40% (62)	<0.001

Abbreviations: AKI^{adm}, acute kidney injury diagnosed using first serum creatinine on admission; AKI^{EPI}, acute kidney injury diagnosed using back-calculated serum creatinine and CKD-EPI formula; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; AKI^{MDRD}, acute kidney injury diagnosed using back-calculated serum creatinine and MDRD formula; AKI^{pre}, acute kidney injury diagnosed using preadmission serum creatinine; SCr, serum creatinine.

5.4.1.2 Factors associated with 30-Day Mortality

Univariable and multivariable Cox regression models were constructed to explore factors associated with 30-day mortality for all 5 methods of ascertaining AKI in Group C (n=443), the 'core cohort', which included patients with both a preadmission SCr, a SCr on admission and at least 1 other SCr measured during admission. For closely related variables, for example CKD ascertained using both CKD-EPI and MDRD formulae, separate models were created and only one variable was entered into the model at a time.

Factors associated with 30-day Mortality in Group A (n=725) were explored. The results are displayed in Appendix 9. As outlined in Chapter 4, section 4.4.4, only the AKI^{pre} method was included in the regression model since for the surrogate methods, more than 1 SCr on admission was required to diagnose AKI, excluding some patients from the Group.

Factors associated with 30-day mortality in Group B (n=808) were similarly explored. With the exception of AKI^{pre}, all methods used to ascertain a diagnosis of AKI (AKI^{adm}, AKI^{low}, AKI^{MDRD} and AKI^{EPI}) were investigated. The results are displayed in Appendix 10. As outlined in Chapter 4, section 4.4.4, AKI^{pre} was not investigated in this Group since having a preadmission SCr was not part of the inclusion criteria for Group B and all cases of AKI^{pre} included in Group B (n=83) are already included in Group C.

5.4.1.2.1 Group C

The full univariable and multivariable associations with 30-day mortality in Group C are shown in Table 5-2. For closely related variables, for example AKI ascertained using different methods, separate models were created and only one variable was entered into the model at a time.

In the univariable analysis, older age, presence of CKD, higher disability score on admission, increased stroke severity, anaemia and presence of AKI ascertained using AKI^{pre} (OR 2.52, 95% CI 1.44-4.42; P=0.003) and all 4 surrogate methods for diagnosing AKI were associated with 30-day mortality in Group C (OR 1.79, 95% CI 1.01-3.16; P=0.046 for AKI^{adm}).

In the multivariable analysis, AKI^{pre} was associated with increased mortality at 30 days (OR 2.45; 95% CI 1.27-4.70; P=0.007). AKI^{adm} (OR 2.10, 95% CI 1.09-4.03; P=0.03), AKI^{low} (OR 1.81, 95% CI 1.02-3.22; P=0.04), AKI^{MDRD} (OR 2.42, 95% CI 1.37-4.29; P=0.002) and AKI^{EPI} (OR 2.43,

95% CI 1.37-4.32; P=0.003) were also associated with 30-day mortality in the multivariable analysis. In addition to AKI ascertained by any method, other factors associated with 30-day mortality in the multivariable analysis in Group C were older age (OR 1.03, 95% CI 1.00-1.06; P=0.04), higher disability score on admission (OR 1.51, 95% CI 1.24-1.84; P<0.001) and increased stroke severity (OR 1.11, 95% CI 1.07-1.14; P<0.001).

Table 5-2. Binomial logistic regression analysis of factors associated with 30-Day Mortality in Group C (n=443).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.05 (1.03-1.08)	<0.001	1.03 (1.00-1.06)	0.04
Female sex	0.94 (0.57-1.55)	0.81	-	-
Black ethnicity	0.62 (0.08-5.02)	0.65	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	1.79 (1.08-2.95)	0.02	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	1.67 (1.01-2.77)	0.048	-	-
Diabetes	0.83 (0.46-1.52)	0.55	-	-
Hypertension	1.44 (0.87-2.40)	0.16	-	-
AF	1.44 (0.85-2.44)	0.18	-	-
Previous stroke/ TIA	0.93 (0.54-1.62)	0.81	-	-
CHF	1.26 (0.41-3.88)	0.69	-	-
Stroke type	0.90 (0.42-1.93)	0.80	-	-
Thrombolysis	0.97 (0.41-2.26)	0.94	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
mRS on admission (as continuous variable)	1.69 (1.42-2.01)	<0.001	1.51 (1.24-1.84)	<0.001
NIHSS score on admission (as continuous variable)	1.12 (1.08-1.15)	<0.001	1.11 (1.07-1.14)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.70 (1.01-2.85)	0.047	-	-
AKI^{pre}**	2.52 (1.44-4.42)	0.003	2.45 (1.27-4.70)	0.007
AKI^{adm}**	1.79 (1.01-3.16)	0.046	2.10 (1.09-4.03)	0.03
AKI^{low}**	2.63 (1.57-4.39)	<0.001	1.81 (1.02-3.22)	0.04
AKI^{MDRD}**	2.84 (1.71-4.74)	<0.001	2.42 (1.37-4.29)	0.002
AKI^{EPI}**	3.16 (1.88-5.32)	<0.001	2.43 (1.37-4.32)	0.003

*Adjusted for age, presence of CKD, disability score on admission, stroke severity, anaemia and presence of AKI in a forward conditional model.

**In the multivariable analysis, related variables e.g. AKI^{pre} and other methods of ascertaining AKI, were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{adm}, AKI diagnosed using first serum creatinine on admission; AKI^{EPI}, acute kidney injury diagnosed from back-calculated serum creatinine using CKD-EPI formula; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; AKI^{MDRD}, acute kidney injury diagnosed from back-calculated serum creatinine using MDRD formula; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

5.4.1.3 AKI^{pre} versus AKI^{adm}

As described in Chapter 4, the surrogate method for 'baseline' SCr that most closely agreed with preadmission SCr, AKI^{pre}, in diagnosing cases of AKI was first SCr on admission, AKI^{adm}. I therefore further explored the strength of association between AKI and 30-day mortality comparing the AKI^{adm} method to the AKI^{pre} method.

Table 5-3 shows logistic univariable and multivariable associations of AKI calculated using preadmission SCr (AKI^{pre}) or first SCr on admission (AKI^{adm}) with 30-day mortality using different models:

1) Models 1 to 5 show unadjusted and adjusted ORs;
2) Models 6 to 10 include both AKI^{pre} and AKI^{adm} in a forward conditional model;
3) Models 11 to 15 include AKI^{adm} in an enter model followed by the addition of AKI^{pre}; these were constructed to explore whether AKI^{pre} adds to the model over and above AKI^{adm}.

Both AKI^{pre} and AKI^{adm} were associated with 30-day mortality in the unadjusted and adjusted models across all Groups (Table 5-3, Models 1 to 5; OR 2.64, 95% CI 1.36-5.12; P=0.004 for AKI^{pre} and OR 2.10, 95% CI 1.09-4.03; P=0.03 for AKI^{adm}, both Group C in the fully adjusted model (Model 5)).

Given that AKI^{pre} appeared to have a stronger relationship with 30-day mortality than AKI^{adm}, models were constructed adjusting for factors associated with 30-day mortality when either AKI^{pre} or AKI^{adm} were used in the multivariable model. The OR for mortality remained higher using AKI^{pre} than AKI^{adm} in all but one of the adjusted models (Models 3 to 5, Table 5-3).

Additional models were created by entering both AKI^{pre} and AKI^{adm} together in a forward conditional model. In all models, only AKI^{pre} was retained (Models 6 to 10, Table 5-3) suggesting AKI^{pre} does indeed have a stronger relationship with 30-day mortality than AKI^{adm}. I further explored this relationship by forcing AKI^{adm} into the multivariable models and then adding AKI^{pre}. In all cases AKI^{pre} was also retained in the models, suggesting that AKI^{pre} carries further information than that provided by AKI^{adm} alone (Models 11 to 15, Table 5-3).

Table 5-3. Logistic univariable and multivariable associations of AKI with 30-Day Mortality in Groups A, B and C, where AKI is ascertained using preadmission SCr (AKI^{pre}) and first SCr on admission (AKI^{adm}).

AKI^{pre} in Group A (Columns 2 and 3) and AKI^{adm} in Group B (Columns 4 and 5) are included as a comparison for Models 1 to 5.

	Group A (AKI^{pre})		**Group B (AKI^{adm})**		**Group C (AKI^{pre})**		**Group C (AKI^{adm})**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Model 1	3.21 (1.88-5.48)	<0.001	1.82 (1.13-2.95)	0.015	2.52 (1.44-4.42)	0.001	1.79 (1.01-3.16)	0.046
Model 2	2.86 (1.65-4.98)	<0.001	3.33 (0.96-2.60)	0.07	2.37 (1.33-4.22)	0.003	3.36 (0.95-3.07)	0.07
Model 3	2.66 (1.40-5.05)	0.003	1.79 (1.04-3.08)	0.04	2.64 (1.36-5.12)	0.004	2.10 (1.09-4.03)	0.03
Model 4	2.66 (1.40-5.05)	0.003	1.79 (1.04-3.08)	0.04	2.64 (1.36-5.12)	0.004	2.10 (1.09-4.03)	0.03
Model 5	2.66 (1.40-5.05)	0.003	1.79 (1.04-3.08)	0.04	2.64 (1.36-5.12)	0.004	2.10 (1.09-4.03)	0.03
Model 6	-	-	-	-	2.52 (1.44-4.42)	0.001		

	Group A (AKI^{pre})		Group B (AKI^{adm})		Group C (AKI^{pre})		Group C (AKI^{adm})	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Model 7	-	-	-	-	2.37 (1.33-4.22)	0.003		
Model 8	-	-	-	-	2.64 (1.36-5.12)	0.004		
Model 9	-	-	-	-	2.64 (1.36-5.12)	0.004		
Model 10	-	-	-	-	2.64 (1.36-5.12)	0.004		
Model 11	-	-	-	-	AKI^{adm} 1.13 (0.57-2.25) AKI^{pre} 2.37 1.21-4.62)	0.73 0.01	-	-
Model 12	-	-	-	-	AKI^{adm} 1.09 (0.54-2.22) AKI^{pre} 2.32 (1.16-4.65)	0.81 0.02	-	-

	Group A (AKI^{pre})		Group B (AKI^{adm})		Group C (AKI^{pre})		Group C (AKI^{adm})	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Model 13	-	-	-	-	AKI^{adm} 1.35 (0.61-3.01) AKI^{pre} 2.20 (1.00-4.84)	0.46 0.051	-	-
Model 14	-	-	-	-	AKI^{adm} 1.38 (0.62-3.10) AKI^{pre} 2.22 (1.00-4.91)	0.43 0.049	-	-
Model 15	-	-	-	-	AKI^{adm} 1.35 (0.60-3.02) AKI^{pre} 2.25 (1.02-4.97)	0.47 0.046	-	-

Model 1: unadjusted

Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, presence of CKD and AF, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Group A)

Model 4: adjusted for age, sex, ethnicity, presence of CKD, AF and hypertension, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Group B)

Model 5: adjusted for age, sex, ethnicity, presence of CKD, AF and hypertension, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Groups A and B)

Model 6: Model 1 + AKI^{pre} and AKI^{adm}

Model 7: Model 2 + AKI^{pre} and AKI^{adm}

Model 8: Model 3 + AKI^{pre} and AKI^{adm}

Model 9: Model 4 + AKI^{pre} and AKI^{adm}

Model 10: Model 5 + AKI^{pre} and AKI^{adm}

Model 11: Model 6 with AKI^{adm} forced into model

Model 12: Model 7 with AKI^{adm} forced into model

Model 13: Model 8 with AKI^{adm} forced into model

Model 14: Model 9 with AKI^{adm} forced into model

Model 15: Model 10 with AKI^{adm} forced into model

Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; AKI^{adm}, AKI diagnosed using first serum creatinine on admission; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CKD, chronic kidney disease; CI, confidence intervals; OR, odds ratio; SCr, serum creatinine.

5.4.1.4 AKI^{pre} versus AKI^{low}, AKI^{MDRD} and AKI^{EPI}

The strength of association between AKI and 30-day mortality, comparing the other three surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI} to AKI^{pre}, were also similarly explored.

Table 5-4 shows logistic univariable and multivariable associations of AKI calculated using preadmission SCr (AKI^{pre}) or the surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI} with 30-day mortality using different models:

1) Models 1 to 5 show unadjusted and adjusted ORs;
2) Models 6 to 10 include both AKI^{pre} and either AKI^{low}, AKI^{MDRD} or AKI^{EPI} in a forward conditional model;
3) Models 11 to 15 include AKI^{low}, AKI^{MDRD} or AKI^{EPI} in an enter model followed by the addition of AKI^{pre}; these were constructed to explore whether AKI^{pre} adds to the model over and above AKI^{low}, AKI^{MDRD} or AKI^{EPI}.

All three surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI}, were associated with 30-day mortality in the unadjusted and adjusted models (Table 5-4, Models 1 to 5; OR 1.81, 95% CI 1.02-3.22; P=0.04 for AKI^{low}, OR 2.75, 95% CI 1.52-4.97; P=0.001 for AKI^{MDRD} and OR 2.43, 95% CI 1.37-4.32; P=0.003 for AKI^{EPI} in the fully adjusted model (Model 5)).

As for AKI^{adm}, additional models were created by entering both AKI^{pre} and each of the other surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI}, into a forward conditional model (Table 5-4,

Models 6 to 10). Similar to AKI^{adm}, including both AKI^{low} and AKI^{pre} in Models 8 to 10 resulted in only AKI^{pre} being retained, suggesting that AKI^{pre} has a stronger relationship with 30-day mortality than AKI^{low} after multiple adjustments. This relationship was further explored by forcing AKI^{low} into the multivariable models and then adding AKI^{pre} (Table 5-4, Models 11 to 15). In Models 13 to 15, AKI^{pre} was also retained in the models, suggesting that AKI^{pre} carries further information than that provided by AKI^{low} alone.

When either of the back-calculation methods, AKI^{MDRD} or AKI^{EPI}, were entered into Models 6 to 10 and 11 to 15 alongside AKI^{pre}, AKI^{pre} was no longer retained in any of the models.

Table 5-4. Logistic univariable and multivariable associations of AKI with 30-Day Mortality in Group C (n=443), where AKI is ascertained using lowest SCr on admission (AKI^{low}), MDRD back-calculation of SCr (AKI^{MDRD}) and CKD-EPI back-calculation of SCr (AKI^{EPI}).

Results for AKI^{pre} in Group C (Columns 2 and 3) are included as a comparison for all models.

	Group C (AKI^{pre})		**Group C (AKI^{low})**		**Group C (AKI^{MDRD})**		**Group C (AKI^{EPI})**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Model 1	2.52 (1.44-4.42)	0.001	2.63 (1.57-4.39)	<0.001	2.84 (1.71-4.74)	<0.001	3.16 (1.88-5.32)	<0.001
Model 2	2.37 (1.33-4.22)	0.003	2.24 (1.33-3.79)	0.003	2.22 (1.31-3.77)	0.003	2.30 (1.33-3.98)	0.003
Model 3	2.64 (1.36-5.12)	0.004	1.81 (1.02-3.22)	0.043	2.75 (1.52-4.97)	0.001	2.43 (1.37-4.32)	0.003
Model 4	2.64 (1.36-5.12)	0.004	1.81 (1.02-3.22)	0.043	2.75 (1.52-4.97)	0.001	2.43 (1.37-4.32)	0.003
Model 5	2.64 (1.36-5.12)	0.004	1.81 (1.02-3.22)	0.043	2.75 (1.52-4.97)	0.001	2.43 (1.37-4.32)	0.003
Model 6	2.52 (1.44-4.42)	0.001	2.63 (1.57-4.39)	<0.001	2.84 (1.71-4.74)	<0.001	3.16 (1.88-5.32)	<0.001

	Group C (AKI^{pre})		Group C (AKI^{low})		Group C (AKI^{MDRD})		Group C (AKI^{EPI})	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Model 7	2.37 (1.33-4.22)	0.003	2.24 (1.33-3.79)	0.003	2.22 (1.31-3.77)	0.003	2.30 (1.33-3.98)	0.003
Model 8	2.64 (1.36-5.12)	0.004			2.75 (1.52-4.97)	0.001	2.43 (1.37-4.32)	0.003
Model 9	2.64 (1.36-5.12)	0.004			2.75 (1.52-4.97)	0.001	2.43 (1.37-4.32)	0.003
Model 10	2.64 (1.36-5.12)	0.004			2.75 (1.52-4.97)	0.001	2.43 (1.37-4.32)	0.003
Model 11	AKI^{adm} 1.13 (0.57-2.25) AKI^{pre} 2.37 (1.21-4.62)	0.73 0.01	AKI^{low} 2.63 (1.57-4.39) AKI^{pre} -	<0.001	AKI^{MDRD} 2.84 (1.71-4.74) AKI^{pre} -	<0.001	AKI^{EPI} 3.16 (1.88-5.32) AKI^{pre} -	<0.001
Model 12	AKI^{adm} 1.09 (0.54-2.22) AKI^{pre} 2.32 (1.16-4.65)	0.81 0.02	AKI^{low} 2.26 (1.33-3.82) AKI^{pre} -	0.002	AKI^{MDRD} 2.36 (1.38-4.02) AKI^{pre} -	0.002	AKI^{EPI} 2.35 (1.36-4.07) AKI^{pre} -	0.002

	Group C (AKI^{pre})		Group C (AKI^{low})		Group C (AKI^{MDRD})		Group C (AKI^{EPI})	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Model 13	AKI^{adm} 1.35 (0.61-3.01) AKI^{pre} 2.20 (1.00-4.84)	0.46 0.051	AKI^{low} 1.35 (0.68-2.67) AKI^{pre} 2.20 (1.04-4.67)	0.387 0.040	AKI^{MDRD} 4.54 (1.97-10.45) AKI^{pre} -	<0.001	AKI^{EPI} 3.55 (1.60-7.92) AKI^{pre} -	0.002
Model 14	AKI^{adm} 1.38 (0.62-3.09) AKI^{pre} 2.22 (1.00-4.91)	0.43 0.049	AKI^{low} 1.40 (0.71-2.77) AKI^{pre} 2.22 (1.04-4.70)	0.338 0.038	AKI^{MDRD} 4.50 (1.95-10.38) AKI^{pre} -	<0.001	AKI^{EPI} 3.61 (1.62-8.04) AKI^{pre} -	0.002
Model 15	AKI^{adm} 1.35 (0.60-3.02) AKI^{pre} 2.25 (1.02-4.97)	0.47 0.046	AKI^{low} 1.39 (0.70-2.76) AKI^{pre} 2.22 (1.04-4.70)	0.346 0.038	AKI^{MDRD} 4.44 (1.92-10.25) AKI^{pre} -	<0.001	AKI^{EPI} 3.55 (1.59-7.93) AKI^{pre} -	0.002

Model 1: unadjusted

Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, presence of CKD and AF, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Group A)

Model 4: adjusted for age, sex, ethnicity, presence of CKD, AF and hypertension, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Group B)

Model 5: adjusted for age, sex, ethnicity, presence of CKD, AF and hypertension, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 30-day mortality in Groups A and B)

Model 6: Model 1 + AKI^{pre} and AKI^{x}

Model 7: Model 2 + AKI^{pre} and AKI^{x}

Model 8: Model 3 + AKI^{pre} and AKI^{x}

Model 9: Model 4 + AKI^{pre} and AKI^{x}

Model 10: Model 5 + AKI^{pre} and AKI^{x}

Model 11: Model 6 with AKI^{x} forced into model

Model 12: Model 7 with AKI^{x} forced into model

Model 13: Model 8 with AKI^{x} forced into model

Model 14: Model 9 with AKI^{x} forced into model

Model 15: Model 10 with AKI^{x} forced into model

where AKI^{x} is the surrogate method, AKI^{low}, AKI^{MDRD} or AKI^{EPI}.

Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; AKI^{adm}, AKI diagnosed using first serum creatinine on admission; AKI^{EPI}, acute kidney injury diagnosed from back-calculated serum creatinine using CKD-EPI formula; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; AKI^{MDRD}, acute kidney injury diagnosed from back-calculated serum creatinine using MDRD formula; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CI, confidence intervals; CKD, chronic kidney disease; OR, odds ratio; SCr, serum creatinine.

5.4.2 AKI and 1-Year Mortality

5.4.2.1 Crude 1-Year Mortality

At 1 year the overall mortality rate for the total cohort (n=1354) was 19.5% (n=264). Crude 1-year mortality rates for Groups A, B and C are shown in Table 5-1.

In Group A, 1-year mortality was significantly higher in patients with AKI^{pre} compared to patients without AKI (47.7% vs 20.8%, P<0.001). In Group B, the mortality rate was higher in the AKI^{adm} group (38.1% vs 23.2%, P<0.001). In Group C, mortality was higher in the AKI group when both AKI^{pre} (50.6% vs 26.9%, P<0.001) and AKI^{adm} (43.2% vs 28.5%, P<0.001) were used to ascertain AKI compared with patients without AKI. Mortality was also higher in the AKI group using the other three surrogate methods (AKI^{low} 50.6 vs. 18.0%, P<0.001; AKI^{MDRD} 44.5 vs. 23.7% ;P<0.001 and AKI^{EPI} 43.3 vs. 24.4%, P<0.001).

5.4.2.2 Factors associated with 1-Year Mortality

Univariable and multivariable Cox regression models were constructed to explore factors associated with 1-year mortality for all 5 methods of ascertaining AKI in Group C (n=443), the 'core cohort', which included patients with both a preadmission SCr, a SCr on admission and at least 1 other SCr measured during admission. As for the 30-day mortality regression analyses, separate models were created for closely related variables and only one variable was entered into the model at a time.

Factors associated with 1-Year Mortality in Group A (n=725) were explored. The results are displayed in Appendix 11. Only the AKI^{pre} method was included in the analysis, as outlined in Chapter 4, section 4.4.4 and the previous section, 5.4.1.2 on 30-day mortality.

Factors associated with 1-Year Mortality in Group B (n=808) were similarly explored. With the exception of AKI^{pre}, all methods used to ascertain a diagnosis of AKI (AKI^{adm}, AKI^{low}, AKI^{MDRD} and AKI^{EPI}) were investigated. The results are displayed in Appendix 12. AKI^{pre} was not investigated in this Group as above.

5.4.2.2.1 Group C

A Cox regression of the full univariable and multivariable associations with 1-year mortality in Group C are shown in Table 5-5. For closely related variables, for example AKI ascertained using different methods, separate models were created and only one variable was entered into the model at a time.

In the univariable analysis, older age, presence of CKD and AF, higher disability score on admission, increased stroke severity, anaemia and presence of AKI ascertained using AKI^{pre} (HR 2.22, 95% CI 1.55-3.19; P<0.001) and all 4 surrogate methods were associated with 1-year mortality in Group C (HR 1.64, 95% CI 1.13-2.38; P=0.009 for AKI^{adm}).

In the multivariable analysis, AKI^{pre} was associated with increased mortality at 1 year (HR 1.98, 95% CI 1.37-2.85; P<0.001) after adjustment for age, presence of CKD and AF, disability score on admission, stroke severity and anaemia. AKI^{adm} (HR 1.53, 95% CI 1.05-2.23; P=0.03), AKI^{low} (HR 2.55, 95% CI 1.78-3.67; P<0.001), AKI^{MDRD} (HR 2.42, 95% CI 1.51-3.89; P<0.001) and AKI^{EPI} (HR 1.57, 95% CI 1.11-2.23; P=0.01) were also associated with 1-year mortality in the multivariable analysis. In addition to AKI ascertained by any method, other factors associated with 1-year mortality in the multivariable analysis in Group C were older age (HR 1.03, 95% CI 1.03-1.05; P<0.001), higher disability score on admission (HR 1.27, 95% CI 1.13-1.41; P<0.001), increased stroke severity (HR 1.05, 95% CI 1.03-1.07; P<0.001) and anaemia (HR 1.48, 95% CI 1.05-2.08; P=0.03).

Table 5-5. Cox regression analysis of factors associated with 1-Year Mortality in Group C (n=443).

	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.05 (1.03-1.06)	<0.001	1.03 (1.03-1.05)	<0.001
Female sex	1.06 (0.76-1.47)	0.75	-	-
Black ethnicity	1.94 (0.80-4.75)	0.15	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	1.65 (1.19-2.31)	0.003	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	1.66 (1.19-2.32)	0.003		
Diabetes	0.83 (0.55-1.24)	0.36	-	-
Hypertension	1.02 (0.73-1.43)	0.89	-	-
AF	1.42 (1.00-2.01)	0.05	-	-
Previous stroke/ TIA	0.91 (0.63-1.32)	0.64	-	-
CHF	0.98 (0.43-2.21)	0.95	-	-
Stroke type	0.85 (0.51-1.44)	0.55	-	-

	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Thrombolysis	1.03 (0.59-1.79)	0.91	-	-
mRS on admission (as continuous variable)	1.44 (1.30-1.60)	<0.001	1.27 (1.13-1.41)	<0.001
NIHSS score on admission (as continuous variable)	1.07 (1.04-1.09)	<0.001	1.05 (1.03-1.07)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.64 (1.17-2.31)	0.005	1.48 (1.05-2.08)	0.03
AKI^{pre}**	2.22 (1.55-3.19)	<0.001	1.98 (1.37-2.85)	<0.001
AKI^{adm}**	1.64 (1.13-2.38)	0.009	1.53 (1.05-2.23)	0.027
AKI^{low}**	3.39 (2.38-4.82)	<0.001	2.55 (1.78-3.67)	<0.001
AKI^{MDRD}**	2.18 (1.56-3.04)	<0.001	2.42 (1.51-3.89)	<0.001
AKI^{EPI}**	2.16 (1.55-3.02)	<0.001	1.57 (1.11-2.23)	0.012

*Adjusted for age, presence of CKD and AF, disability score on admission, stroke severity, anaemia and presence of AKI in a forward conditional model.

**In the multivariable analysis, related variables e.g. AKI^{pre} and other methods of ascertaining AKI, were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{adm}, AKI diagnosed using first serum creatinine on admission; AKI^{EPI}, acute kidney injury diagnosed from back-calculated serum creatinine using CKD-EPI formula; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; AKI^{MDRD}, acute kidney injury diagnosed from back-calculated serum creatinine using MDRD formula; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SCr, serum creatinine; TIA, transient ischaemic attack.

5.4.2.3 AKI^{pre} versus AKI^{adm}

As described in Chapter 4, the surrogate method for 'baseline' SCr that most closely agreed with AKI^{pre} in diagnosing cases of AKI was AKI^{adm}. As for 30-day mortality, I therefore further explored the strength of association between AKI and 1-year mortality, comparing AKI^{adm} to AKI^{pre}.

Table 5-6 shows Cox univariable and multivariable associations of AKI calculated using preadmission SCr (AKI^{pre}) or first SCr on admission (AKI^{adm}) with 1-year mortality using different models:

1) Models 1 to 5 show unadjusted and adjusted HRs;
2) Models 6 to 10 include both AKI^{pre} and AKI^{adm} in a forward conditional model;
3) Models 11 to 15 include AKI^{adm} in an enter model followed by the addition of AKI^{pre}; these were constructed to explore whether AKI^{pre} adds to the model over and above AKI^{adm}.

In Group A, AKI^{pre} was associated with 1-year mortality in the unadjusted and adjusted models (Table 5-6, Models 1 to 5; HR 2.00, 95% CI 1.40-2.86; P<0.001 in the fully adjusted model (Model 5)). In Group B, AKI^{adm} was also associated with 1-year mortality in both the unadjusted and adjusted models (Table 5-6, Models 1 to 5; HR 1.50; 95% CI 1.10-2.07: P=0.01 (Model 5)). Similarly, in Group C, both AKI^{pre} and AKI^{adm} were associated with 1-year mortality

in both the unadjusted and adjusted models (Table 5-6, Models 1 to 5; HR 1.90, 95% CI 1.32-2.76; P=0.001 for AKI^{pre} and HR 1.47, 95% CI 1.01-2.15; P=0.05 for AKI^{adm}, both Model 5). Similar to 30-day mortality, AKI^{pre} appeared to have a stronger relationship with 1-year mortality than AKI^{adm} and models were constructed adjusting for factors associated with 1-year mortality when either AKI^{pre} or AKI^{adm} were used in the multivariable model. The HR for mortality remained higher using AKI^{pre} than AKI^{adm} in all models (Models 2 to 5, Table 5-6).

Additional models were created by entering both AKI^{pre} and AKI^{adm} together in a forward conditional model. In all models only AKI^{pre} was retained (Models 6 to 10, Table 5-6) suggesting AKI^{pre} does indeed have a stronger relationship with 1-year mortality than AKI^{adm}. I further explored this relationship by forcing AKI^{adm} into the multivariable models and then adding AKI^{pre}. In all cases AKI^{pre} was also retained in the models, suggesting that AKI^{pre} carries further information than that provided by AKI^{adm} alone (Models 11 to 15, Table 5-6).

Table 5-6. Cox univariable and multivariable associations of AKI with 1-Year Mortality in Groups A, B and C, where AKI is ascertained using preadmission SCr (AKI^{pre}) and first SCr on admission (AKI^{adm}).

AKI^{pre} in Group A (Columns 2 and 3) and AKI^{adm} in Group B (Columns 4 and 5) are included as a comparison for Models 1 to 5.

	Group A (AKI^{pre})		**Group B (AKI^{adm})**		**Group C (AKI^{pre})**		**Group C (AKI^{adm})**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Model 1	2.74 (1.94-3.89)	<0.001	1.77 (1.29-2.42)	<0.001	2.22 (1.55-3.19)	<0.001	1.64 (1.13-2.38)	0.009
Model 2	2.43 (1.72-3.45)	<0.001	1.52 (1.11-2.09)	0.009	2.08 (1.44-2.99)	<0.001	1.55 (1.07-2.26)	0.02
Model 3	2.00 (1.40-2.86)	<0.001	1.50 (1.10-2.07)	0.01	1.98 (1.37-2.85)	<0.001	1.53 (1.05-2.23)	0.03
Model 4	2.00 (1.40-2.86)	<0.001	1.50 (1.10-2.07)	0.01	1.98 (1.37-2.85)	<0.001	1.53 (1.05-2.23)	0.03
Model 5	2.00 (1.40-2.86)	<0.001	1.50 (1.10-2.07)	0.01	1.90 (1.32-2.76)	0.001	1.47 (1.01-2.15)	0.05
Model 6	-	-	-	-	2.22 (1.55-3.19)	<0.001		

	Group A (AKI^{pre})		Group B (AKI^{adm})		Group C (AKI^{pre})		Group C (AKI^{adm})	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Model 7	-	-	-	-	2.08 (1.44-2.99)	<0.001		
Model 8	-	-	-	-	1.98 (1.37-2.85)	<0.001		
Model 9	-	-	-	-	1.98 (1.37-2.85)	<0.001		
Model 10	-	-	-	-	1.90 (1.32-2.76)	0.001		
Model 11	-	-	-	-	AKI^{adm} 1.11 (0.71-1.74) AKI^{pre} 2.10 (1.36-3.25)	0.65 0.001	-	-
Model 12	-	-	-	-	AKI^{adm} 1.07 (0.68-1.66) AKI^{pre} 2.06 (1.33-3.18)	0.78 0.001	-	-

	Group A (AKI^{pre})		Group B (AKI^{adm})		Group C (AKI^{pre})		Group C (AKI^{adm})	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Model 13	-	-	-	-	AKI^{adm} 1.09 (0.69-1.72) AKI^{pre} 2.02 (1.29-3.17)	0.70 0.002	-	-
Model 14	-	-	-	-	AKI^{adm} 1.07 (0.68-1.70) AKI^{pre} 1.96 (1.25-3.08)	0.76 0.004	-	-
Model 15	-	-	-	-	AKI^{adm} 1.06 (0.67-1.68) AKI^{pre} 2.00 (1.27-3.16)	0.81 0.003	-	-

Model 1: unadjusted

Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, presence of CKD, AF and CHF, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 1- year mortality in Group A)

Model 4: adjusted for age, sex, presence of CKD and AF, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 1-year mortality in Group B)

Model 5: Model 3 plus ethnicity

Model 6: Model 1 + AKI^{pre} and AKI^{adm}

Model 7: Model 2 + AKI^{pre} and AKI^{adm}

Model 8: Model 3 + AKI^{pre} and AKI^{adm}

Model 9: Model 4 + AKI^{pre} and AKI^{adm}

Model 10: Model 5 + AKI^{pre} and AKI^{adm}

Model 11: Model 6 with AKI^{adm} forced into model

Model 12: Model 7 with AKI^{adm} forced into model

Model 13: Model 8 with AKI^{adm} forced into model

Model 14: Model 9 with AKI^{adm} forced into model

Model 15: Model 10 with AKI^{adm} forced into model

Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; AKI^{adm}, AKI diagnosed using first serum creatinine on admission; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratio; SCr, serum creatinine.

5.4.2.4 AKI^{pre} versus AKI^{low}, AKI^{MDRD} and AKI^{EPI}

The strength of association between AKI and 1-year mortality, comparing the other three surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI} to AKI^{pre} were also similarly explored.

Table 5-7 shows Cox univariable and multivariable associations of AKI calculated using preadmission SCr (AKI^{pre}) or the surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI} with 1-year mortality using different models:

1) Models 1 to 5 show unadjusted and adjusted HRs;
2) Models 6 to 10 include both AKI^{pre} and either AKI^{low}, AKI^{MDRD} or AKI^{EPI} in a forward conditional model;
3) Models 11 to 15 include AKI^{low}, AKI^{MDRD} or AKI^{EPI} in an enter model followed by the addition of AKI^{pre}; these were constructed to explore whether AKI^{pre} adds to the model over and above AKI^{low}, AKI^{MDRD} or AKI^{EPI}.

All three surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI}, were associated with 1-year mortality in the unadjusted and adjusted models (Table 5-7, Models 1 to 5; HR 2.55, 95% CI 1.78-3.67; P<0.001 for AKI^{low}, HR 2.38, 95% CI 1.49-3.78; P<0.001 for AKI^{MDRD} and HR 1.52, 95% CI 1.06-2.16; P=0.02 for AKI^{EPI} in the fully adjusted model (Model 5)).

As for AKI^{adm}, additional models were created by entering both AKI^{pre} and each of the other surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI}, into a forward conditional model (Table 5-7,

Models 6 to 10). Similar to AKI^{adm}, including either AKI^{MDRD} or AKI^{EPI} and AKI^{pre} in Models 7 to 10 resulted in only AKI^{pre} being retained, suggesting that AKI^{pre} has a stronger relationship with 1-year mortality than AKI^{MDRD} or AKI^{EPI} after multiple adjustments. In Model 6 (unadjusted), AKI^{MDRD} or AKI^{EPI} and AKI^{pre} were both retained in the forward conditional model.

This relationship was further explored by forcing AKI^{MDRD} or AKI^{EPI} into the multivariable models and then adding AKI^{pre} (Table 5-7, Models 11 to 15). In Models 11 to 14 for AKI^{MDRD} and all Models (11 to 15) for AKI^{EPI}, AKI^{pre} was also retained in the models, suggesting that AKI^{pre} carries further information than that provided by AKI^{MDRD} or AKI^{EPI} alone.

When AKI^{low} was entered into Models 6 to 10 and 11 to 15 alongside AKI^{pre}, AKI^{pre} was no longer retained in any of the models.

Table 5-7. Cox univariable and multivariable associations of AKI with 1-Year Mortality in Group C (n=443), where AKI is ascertained using lowest SCr on admission (AKI^{low}), MDRD back-calculation of SCr (AKI^{MDRD}) and CKD-EPI back-calculation of SCr (AKI^{EPI}).

Results for AKI^{pre} in Group C (Columns 2 and 3) are included as a comparison for all models.

	Group C (AKI^{pre})		**Group C (AKI^{low})**		**Group C (AKI^{MDRD})**		**Group C (AKI^{EPI})**	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Model 1	2.22 (1.55-3.19)	<0.001	3.39 (2.38-4.82)	<0.001	2.18 (1.56-3.04)	<0.001	2.16 (1.55-3.02)	<0.001
Model 2	2.08 (1.44-2.99)	<0.001	2.94 (2.06-4.20)	<0.001	1.74 (1.24-2.45)	0.001	1.60 (1.13-2.28)	0.008
Model 3	1.98 (1.37-2.85)	<0.001	2.55 (1.78-3.67)	<0.001	2.42 (1.51-3.89)	<0.001	1.57 (1.11-2.23)	0.012
Model 4	1.98 (1.37-2.85)	<0.001	2.55 (1.78-3.67)	<0.001	2.42 (1.51-3.89)	<0.001	1.57 (1.11-2.23)	0.012
Model 5	1.90 (1.32-2.76)	0.001	2.55 (1.78-3.67)	<0.001	2.38 (1.49-3.78)	<0.001	1.52 (1.06-2.16)	0.021
Model 6	2.22 (1.55-3.19)	<0.001	3.39 (2.38-4.82)	<0.001	AKI^{MDRD} 1.80 (1.22-2.65) AKI^{pre} 1.57 (1.03-2.40)	0.003 0.035	AKI^{EPI} 1.79 (1.23-2.62) AKI^{pre} 1.61 (1.07-2.43)	0.003 0.024

	Group C (AKI^{pre})		Group C (AKI^{low})		Group C (AKI^{MDRD})		Group C (AKI^{EPI})	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Model 7	2.08 (1.44-2.99)	<0.001	2.94 (2.06-4.20)	<0.001				
Model 8	1.98 (1.37-2.85)	<0.001	2.55 (1.78-3.67)	<0.001				
Model 9	1.98 (1.37-2.85)	<0.001	2.55 (1.78-3.67)	<0.001				
Model 10	1.90 (1.32-2.76)	0.001	2.55 (1.78-3.67)	<0.001				
Model 11	AKI^{adm} 1.11 (0.71-1.74) AKI^{pre} 2.10 (1.36-3.25)	0.65 0.001	AKI^{low} 3.39 (2.38-4.82) AKI^{pre} -	<0.001	AKI^{MDRD} 1.80 (1.22-2.65) AKI^{pre} 1.57 (1.03-2.40)	0.003 0.035	AKI^{EPI} 1.79 (1.23-2.62) AKI^{pre} 1.61 (1.07-2.43)	0.003 0.024
Model 12	AKI^{adm} 1.07 (0.68-1.66) AKI^{pre} 2.06 (1.33-3.18)	0.78 0.001	AKI^{low} 2.96 (2.07-4.22) AKI^{pre} -	<0.001	AKI^{MDRD} 1.42 (0.95-2.11) AKI^{pre} 1.75 (1.15-2.67)	0.086 0.009	AKI^{EPI} 1.25 (0.83-1.86) AKI^{pre} 1.89 (1.24-2.88)	0.286 0.003

	Group C (AKI^{pre})		Group C (AKI^{low})		Group C (AKI^{MDRD})		Group C (AKI^{EPI})	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Model 13	AKI^{adm} 1.09 (0.69-1.72)	0.70	AKI^{low} 2.57 (1.77-3.73)	<0.001	AKI^{MDRD} 1.91 (1.11-3.28)	0.020	AKI^{EPI} 1.43 (0.86-2.36)	0.168
	AKI^{pre} 2.02 (1.29-3.17)	0.002	AKI^{pre} -		AKI^{pre} 1.61 (1.04-2.50)	0.034	AKI^{pre} 1.83 (1.19-2.81)	0.006
Model 14	AKI^{adm} 1.07 (0.68-1.70)	0.76	AKI^{low} 2.55 (1.75-3.70)	<0.001	AKI^{MDRD} 1.91 (1.11-3.29)	0.020	AKI^{EPI} 1.43 (0.86-2.37)	0.165
	AKI^{pre} 1.96 (1.25-3.08)	0.004	AKI^{pre} -		AKI^{pre} 1.55 (1.00-2.40)	0.048	AKI^{pre} 1.76 (1.15-2.70)	0.009
Model 15	AKI^{adm} 1.06 (0.67-1.68)	0.81	AKI^{low} 2.50 (1.72-3.64)	<0.001	AKI^{MDRD} 2.53 (1.58-4.05)	<0.001	AKI^{EPI} 1.38 (0.83-2.30)	0.209
	AKI^{pre} 2.00 (1.27-3.16)	0.003	AKI^{pre} -		AKI^{pre} -		AKI^{pre} 1.80 (1.17-2.78)	0.008

Model 1: unadjusted

Model 2: adjusted for age and sex

Model 3: adjusted for age, sex, presence of CKD, AF and CHF, stroke type, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 1-year mortality in Group A)

Model 4: adjusted for age, sex, presence of CKD and AF, disability score on admission, stroke severity and anaemia (all factors associated in univariable analysis with 1-year mortality in Group B)

Model 5: Model 3 plus ethnicity

Model 6: Model 1 + AKI^{pre} and AKI^{x}

Model 7: Model 2 + AKI^{pre} and AKI^{x}

Model 8: Model 3 + AKI^{pre} and AKI^{x}

Model 9: Model 4 + AKI^{pre} and AKI^{x}

Model 10: Model 5 + AKI^{pre} and AKI^{x}

Model 11: Model 6 with AKI^{x} forced into model

Model 12: Model 7 with AKI^{x} forced into model

Model 13: Model 8 with AKI^{x} forced into model

Model 14: Model 9 with AKI^{x} forced into model

Model 15: Model 10 with AKI^{x} forced into model

Where AKI^{x} is the surrogate method, AKI^{low}, AKI^{MDRD} or AKI^{EPI}.

Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; AKI^{adm}, AKI diagnosed using first serum creatinine on admission; AKI^{EPI}, acute kidney injury diagnosed from back-calculated serum creatinine using CKD-EPI formula; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; AKI^{MDRD}, acute kidney injury diagnosed from back-calculated serum creatinine using MDRD formula; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; HR, hazard ratio; SCr, serum creatinine.

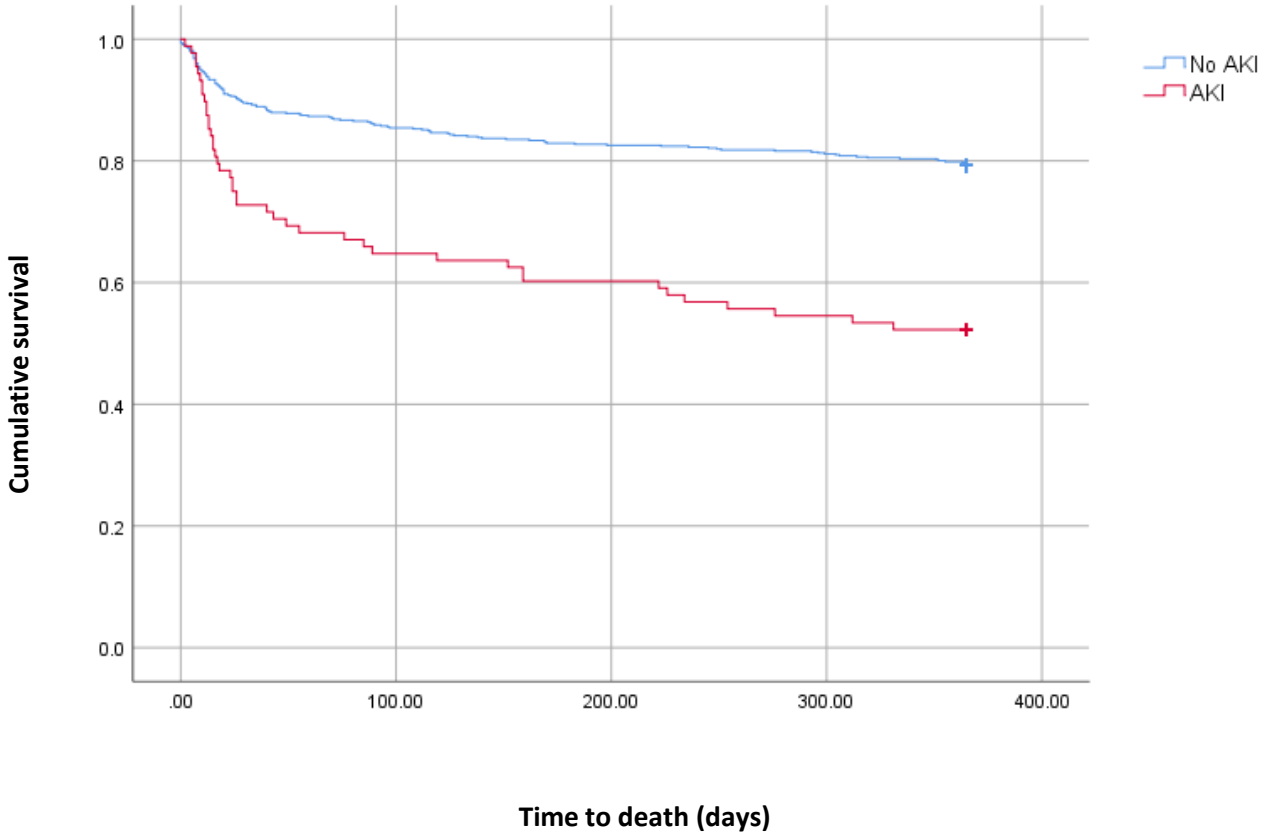
Kaplan-Meier survival curves at 1 year for the AKI versus non-AKI cohorts are displayed in Figures 5-1 to 5-7.

Results for Group A and AKI ascertained using preadmission SCr (AKI^{pre}) are shown in Figure 5-1. Results for Group B and AKI ascertained using first SCr on admission (AKI^{adm}) are shown in Figure 5-2. Results for Group C and AKI ascertained using AKI^{pre} and all 4 surrogate methods, AKI^{adm}, AKI^{low}, AKI^{MDRD} and AKI^{EPI}, are shown in Figures 5-3, 5-4, 5-5, 5-6 and 5-7 respectively.

In all Groups and across all methods of ascertaining AKI, patients who developed AKI had reduced 1-year survival compared with those who did not develop AKI.

Figure 5-1. Kaplan-Meier survival curve at 365 days for patients in Group A (n=725) with and without AKI, ascertained using AKI^{pre}.

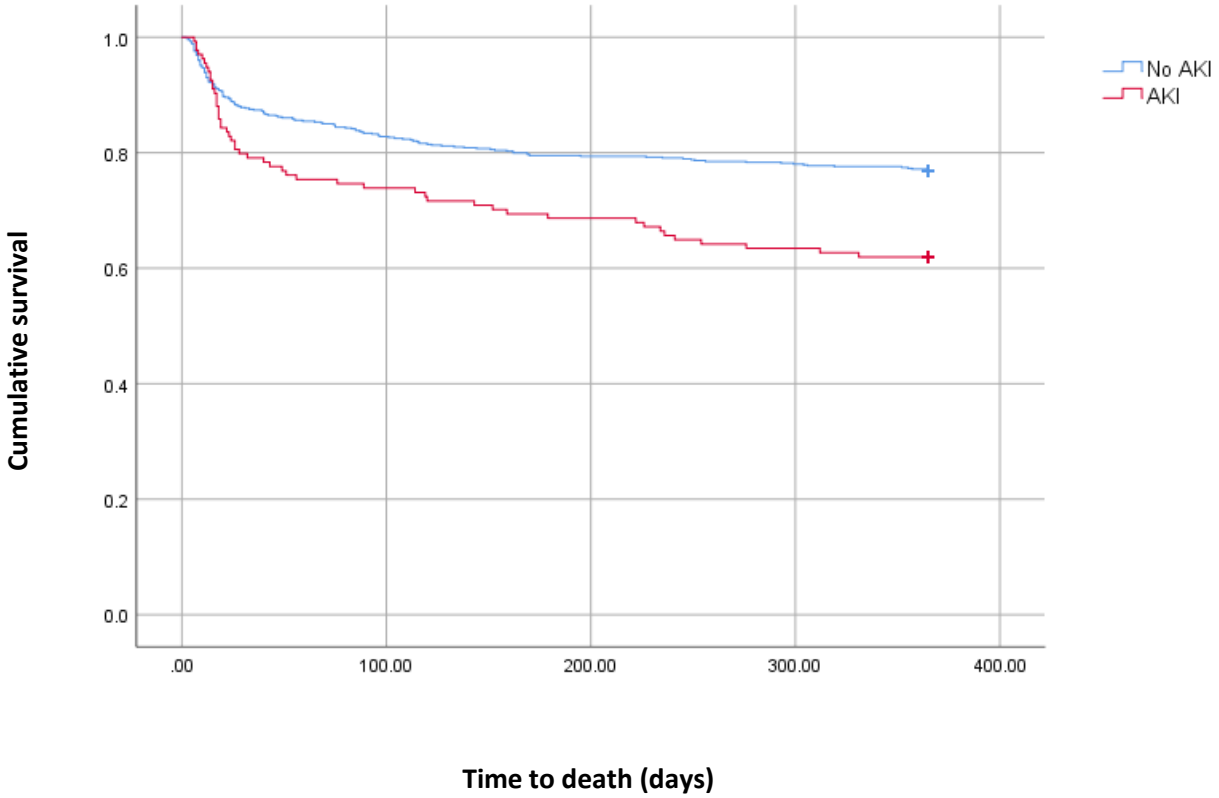
Log rank test 35.20; P<0.001.



Abbreviations: AKI, acute kidney injury; AKI^{pre}, AKI diagnosed using preadmission serum creatinine.

Figure 5-2. Kaplan-Meier survival curve at 365 days for patients in Group B (n=808) with and without AKI, ascertained using AKI^{adm}.

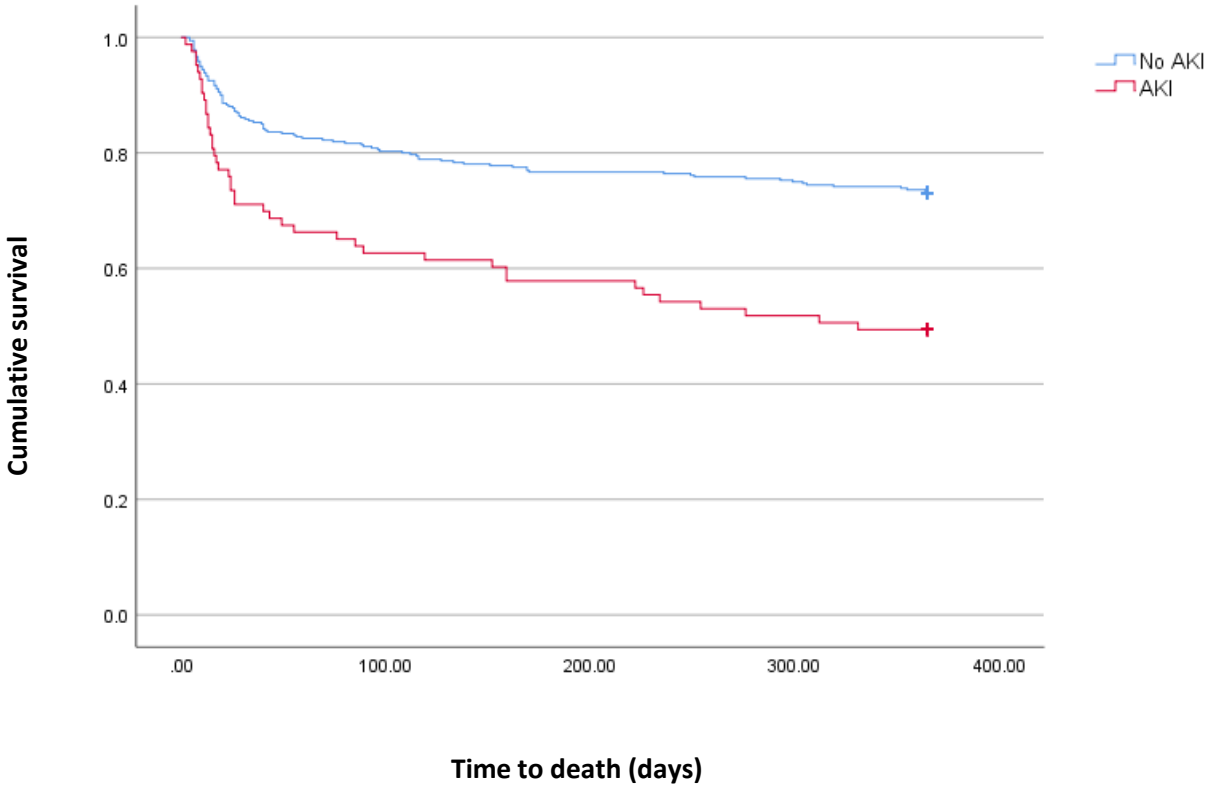
Log rank test 12.80; P<0.001.



Abbreviations: AKI, acute kidney injury; AKI^{adm}, AKI diagnosed using first serum creatinine on admission.

Figure 5-3. Kaplan-Meier survival curve at 365 days for patients in Group C (n=443) with and without AKI, ascertained using AKI^{pre}.

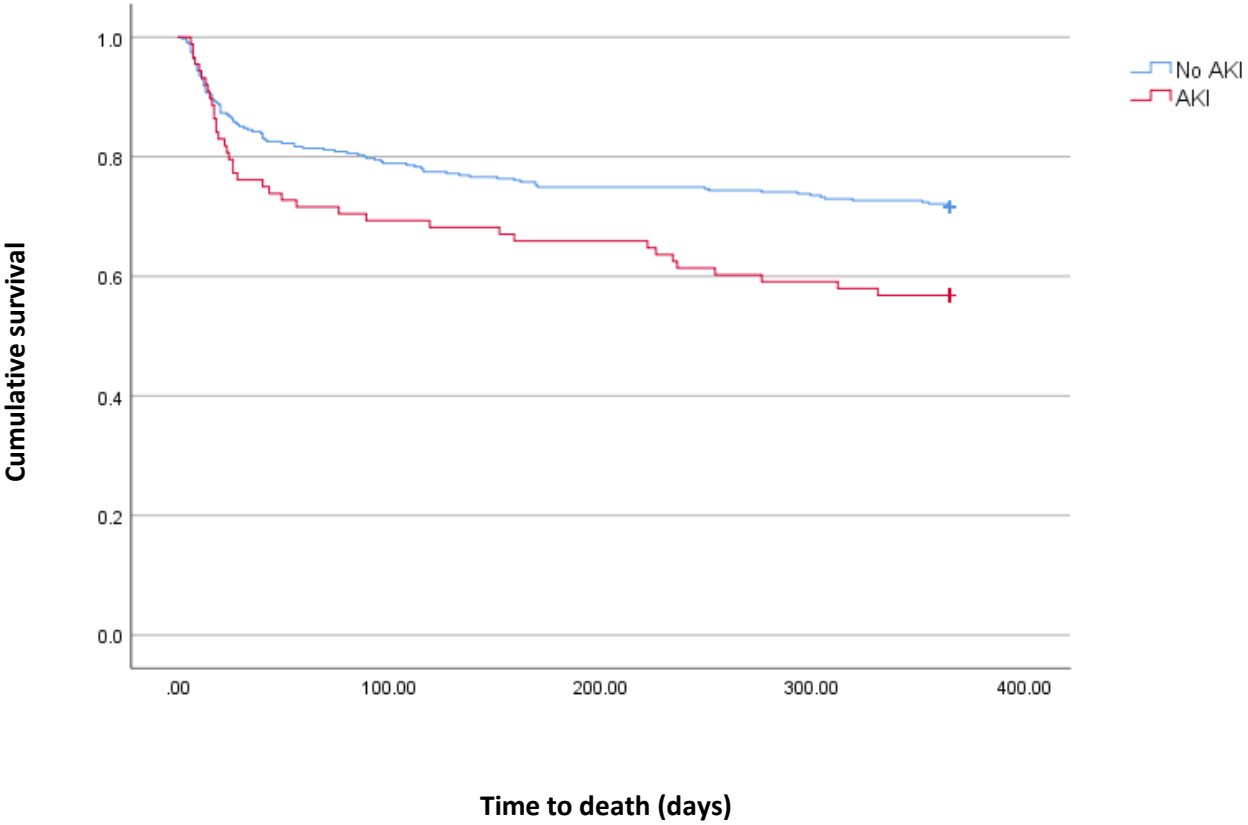
Log rank test 19.73; P<0.001.



Abbreviations: AKI, acute kidney injury; AKI^{pre}, AKI diagnosed using preadmission serum creatinine.

Figure 5-4. Kaplan-Meier survival curve at 365 days for patients in Group C (n=443) with and without AKI, ascertained using AKI^{adm}.

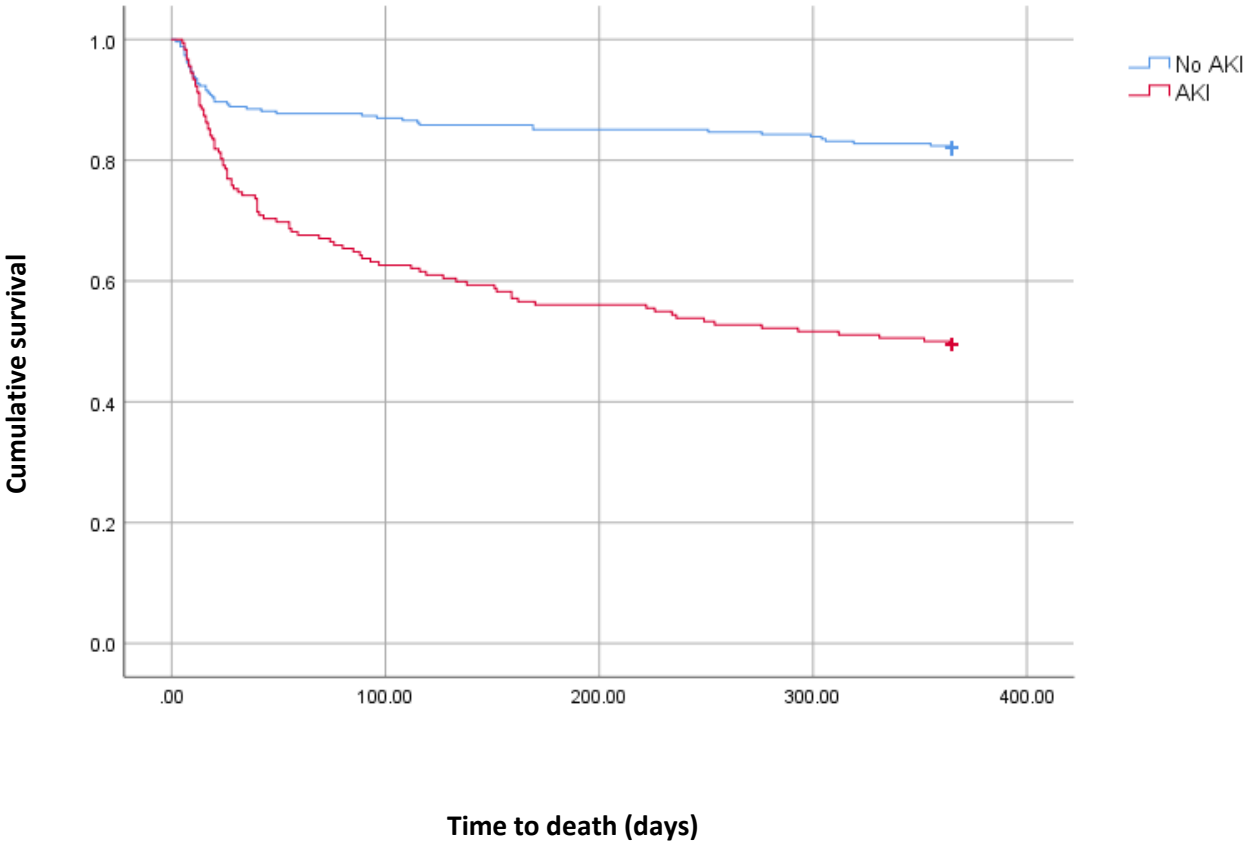
Log rank test 6.93; P=0.008.



Abbreviations: AKI, acute kidney injury; AKI^{adm}, AKI diagnosed using first serum creatinine on admission.

Figure 5-5. Kaplan-Meier survival curve at 365 days for patients in Group C (n=443) with and without AKI, ascertained using AKI^{low}.

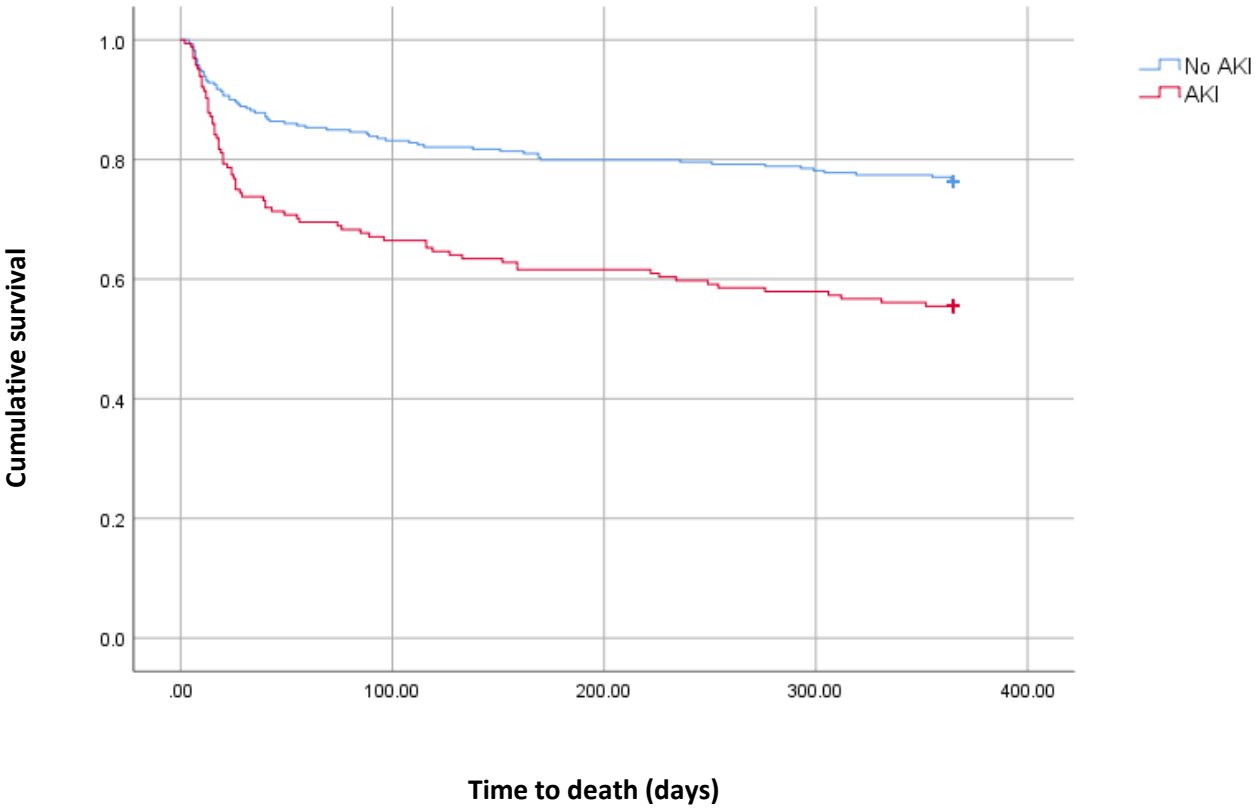
Log rank test 52.06; P<0.001.



Abbreviations: AKI, acute kidney injury; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission.

Figure 5-6. Kaplan-Meier survival curve at 365 days for patients in Group C (n=443) with and without AKI, ascertained using AKI^{MDRD}.

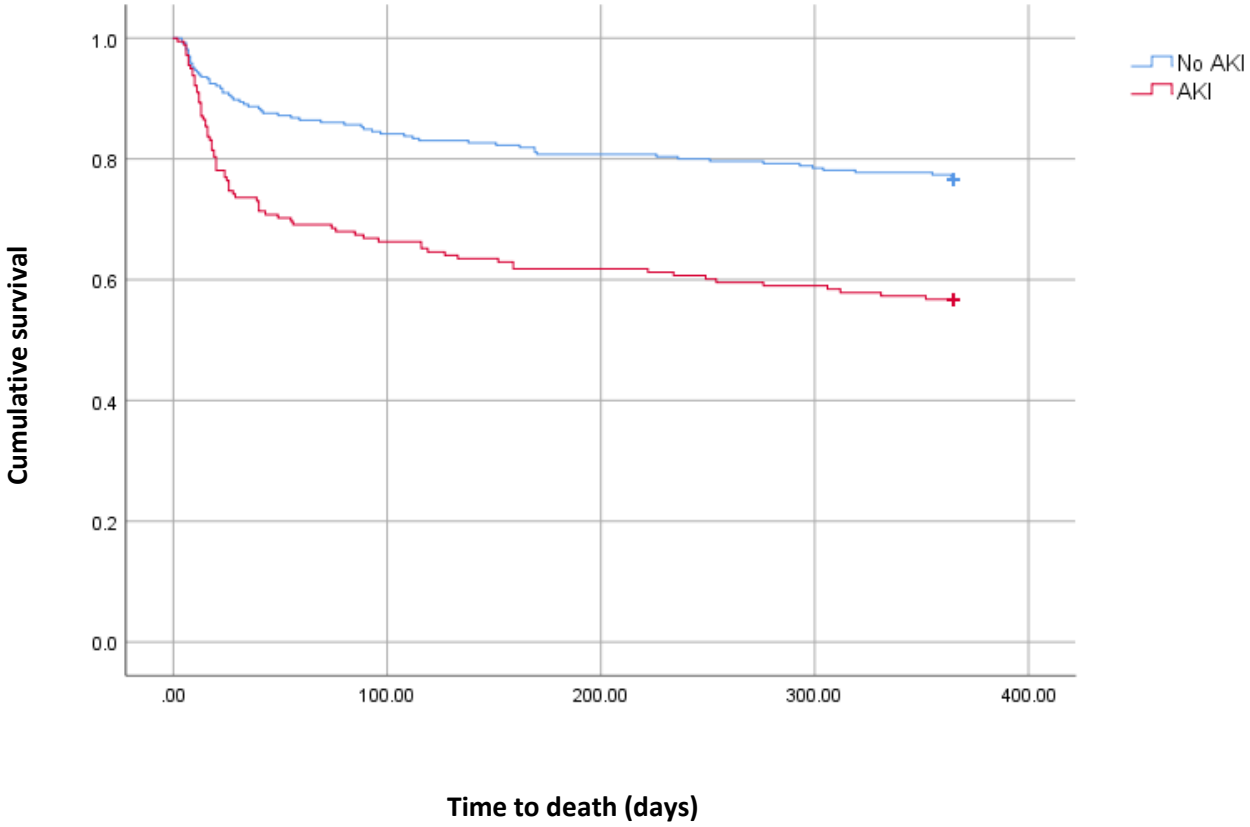
Log rank test 22.16; P<0.001.



Abbreviations: AKI, acute kidney injury; AKI^{MDRD}, acute kidney injury diagnosed from back-calculated serum creatinine using MDRD formula.

Figure 5-7. Kaplan-Meier survival curve at 365 days for patients in Group C (n=443) with and without AKI, ascertained using AKI^{EPI}.

Log rank test 21.42; P<0.001.



Abbreviations: AKI, acute kidney injury; AKI^{EPI}, acute kidney injury diagnosed from back-calculated serum creatinine using CKD-EPI formula.

5.5 Discussion

In the second of the two AKI study arms, I investigated the influence of AKI on outcomes in a cohort of stroke patients, comparing five different methods of obtaining a 'baseline' SCr to diagnose AKI- the 'gold standard', preadmission SCr, compared to 4 surrogate methods.

My results show that patients who developed AKI had higher crude 30-day mortality (28.9% vs 13.9%, P=0.001 for AKI^{pre} in Group C) and 1-year mortality (50.6% vs 26.9%, P<0.001 for AKI^{pre} in Group C), across all Groups and using all 5 methods to diagnose AKI. Having a diagnosis of AKI was associated with 30-day and 1-year mortality after multiple adjustments across all Groups and methods. Comparisons of the different methods used to ascertain AKI showed that AKI^{adm} consistently underestimated the risk of mortality at both 30 days and 1 year in the multivariable regression analyses, compared with AKI^{pre}. The other surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI} exhibited variable strength of association with 30-day and 1-year mortality compared with AKI^{pre}. I will now discuss the findings in turn.

5.5.1 30-Day Mortality

In this study, the crude 30-day mortality rate for patients with a diagnosis of AKI was significantly higher than for those without AKI, across all Groups and methods to ascertain AKI. In the multivariable regression analyses, AKI was also strongly associated with 30-day mortality across all Groups and methods to diagnose AKI. These results support the findings

of my systematic review, outlined in Chapter 2, with all studies reporting increased mortality in patients who developed AKI (pooled OR 3.13, 95% CI 1.20-8.19; I^2 95%) [370].

In addition, older age, higher disability score on admission and increased stroke severity were also found to be associated with 30-day mortality after multiple adjustments. All of these are known risk factors for mortality in stroke patients, as described in the literature [434-436]. In particular, NIHSS score is known to be a strong discriminator of mortality risk in stroke [435, 437, 438]. Interestingly, all these variables have been included in the recently developed 'Predicting Early Mortality of Ischemic Stroke' scoring system [439]. Presence of anaemia was also found to be associated with 30-day mortality in Group B in the multivariable analysis. This finding is discussed in relation to 1-year mortality in the following section, 5.5.2.

As outlined in Chapter 4, section 4.4.3, all four surrogate methods for ascertaining AKI exhibited proportional bias and bi-directional misclassification of AKI cases. AKI^{adm} most closely agreed with AKI^{pre} (AKI incidence 19.9% vs. 18.7%, P=0.63; Table 4-3, Chapter 4) and exhibited the lowest rates of misclassification (Table 4-4). The other methods produced significant misclassification, with the majority of AKI cases being overclassified (Tables 4-5, 4-6 and 4-7) and weaker agreement with AKI^{pre} compared with AKI^{adm}.

Since AKI^{adm} most closely agreed with AKI^{pre} in diagnosing AKI, it was fitting to explore the strength of association between AKI and 30-day mortality comparing AKI^{adm} to AKI^{pre}. As

demonstrated in Table 5-3, despite the similar rates of AKI diagnosed using AKI^{pre} and AKI^{adm} methods as described above, AKI^{pre} was associated with higher 30-day mortality than AKI^{adm} in all the adjusted models (except Model 2). The consistency of this finding would suggest that AKI^{pre} correctly identifies more patients with 'true' AKI than AKI^{adm}. This appears to support other studies which have shown that first SCr on admission to diagnose AKI has a low sensitivity for both hospital and community-acquired AKI, particularly mild AKI, thus underestimating the incidence of AKI [308, 319, 320]. This would lead to a weakening of the association with mortality, as observed in my analyses. Importantly, the finding that AKI^{pre} was associated with a higher 30-day mortality risk than AKI^{adm} indicates that AKI-associated mortality in acute stroke, as reported to date, probably underestimates the association, given that all of the studies that used creatinine-based definitions to diagnose AKI used first SCr on admission [330, 331, 336].

Interestingly, AKI^{pre} was also associated with higher 30-day mortality than AKI^{low} in the fully adjusted models (Table 5-4, Models 8 to 10 and 13 to 15). However, when these analyses were performed including AKI^{MDRD} and AKI^{EPI} in the regression analyses, AKI^{pre} was not retained in any of the models. These inconsistencies are likely to be explained by the high overclassification rates of AKI using these methods, leading to a stronger association with mortality. This was shown in a study by Siew *et al*., where 18.5% of deaths at 60 days were falsely associated with AKI as a result of misclassification by surrogate methods [308]. The authors compared death rates among 3 surrogate methods, first SCr on admission, lowest SCr during admission and MDRD back-calculated SCr against the 'reference standard',

preadmission SCr. They reported that use of lowest SCr or back-calculated SCr led to misclassification rates of 24.8% and 21.8% respectively, and the majority of cases were overclassified as death following AKI when no AKI had been diagnosed using preadmission SCr. Conversely, use of admission SCr led to a misclassification rate of 28.1%, with the majority of cases being underclassified as death not following AKI when in fact AKI had been diagnosed using preadmission SCr. These findings are generally in keeping with the results of this study, in which the surrogate methods, AKI^{low}, AKI^{MDRD} and AKI^{EPI}, demonstrated high rates of overclassification of AKI cases, leading to a stronger, albeit false association with 30-day mortality than AKI^{pre}. Therefore, as concluded in Chapter 4, sections 4.5.3.2 and 4.5.3.3, back-calculation methods, as recommended by KDIGO [280] and ADQI [281], as well as use of lowest SCr on admission, should probably not be used in mortality risk-prediction modelling in a cohort of hospitalised stroke patients. This is particularly significant since, due to increased age and comorbidities, the prevalence of CKD is likely to be high, as demonstrated by a rate of over 30% in this study cohort.

5.5.2 1-Year Mortality

Similar to 30-day mortality, the crude 1-year mortality rate for patients with AKI was significantly higher across all Groups and methods to ascertain AKI (50.6% vs 26.9%, $P<0.001$ for Group C, AKI^{pre}). In the multivariable regression analyses, AKI was strongly associated with 1-year mortality in all Groups and methods to diagnose AKI. As outlined in my systematic review in Chapter 2 [370], only one study reported longer-term mortality in stroke patients who developed AKI [336]. In agreement with the findings of this study, the authors report

increased crude cumulative mortality at 1 year in the AKI group (34.6% vs. 22.1%, P=0.001) [336].

Other associations with 1-year mortality were the same as those for 30-day mortality, including older age, higher disability score on admission and increased stroke severity. In addition, presence of anaemia was also consistently associated with 1-year mortality in all Groups in the multivariable analysis. Anaemia has been demonstrated to be independently associated with mortality in a variety of conditions, including CKD [440], CHF [441, 442] and ACS [443, 444]. Interestingly, a study of 8013 stroke patients investigated the relationship between anaemia and mortality and found anaemia was associated with increased odds of inpatient, 1,3 and 6-month and 1-year mortality in AIS after multiple adjustments [445]. The same authors conducted a systematic review and meta-analysis of 20 studies, which demonstrated that anaemia on admission was associated with increased mortality in both AIS and ICH [445]. Anaemia may increase the risk of mortality in acute stroke through impaired oxygen-carrying capacity via the bloodstream, which might feasibly worsen ischaemia [446]. Anaemia has also been shown to disrupt cerebral autoregulation, which may cause fluctuations in perfusion to cerebral tissue leading to hypoxia [447, 448], as well as upregulate inflammatory mediators such as nitric oxide synthase [449] and chemokine receptor CXCR4 [450], which are linked to cerebral tissue damage in the context of ischaemia [450, 451]. Furthermore, anaemic patients may be less likely to receive antiplatelets due to concerns about bleeding risk, thereby contributing to an increased risk of mortality. Future studies are needed to identify how outcomes in anaemia can be improved, but in an elderly, comorbid

cohort of acute stroke patients who exhibit high rates of AKI and CKD, care must be taken to avoid causing further harm by attempting to overcorrect anaemia with blood transfusions or erythropoiesis-stimulating agents, which are known to be associated with an increased risk of thrombosis in CKD [452].

Similar to the 30-day mortality analyses, when comparing the performance of the surrogate AKI methods against AKI^{pre} in predicting 1-year mortality, I found that AKI^{adm} consistently underestimated 1-year mortality compared to AKI^{pre} in the multivariable models (Table 5-6, Models 2 to 15). These demonstrate that AKI^{pre} has a stronger relationship with 1-year mortality than AKI^{adm}. As discussed in section 5.5.1, this is likely due to the fact that AKI^{adm} has a low sensitivity and therefore underestimates the incidence of AKI, thus weakening the relationship with mortality. Conversely, AKI^{pre} identifies more 'true' cases of AKI and therefore has a stronger and real association with 1-year mortality.

AKI^{pre} was also more strongly associated with 1-year mortality than AKI^{MDRD} and AKI^{EPI} in the adjusted models (Table 5-7, Models 7 to 10 and 11 to 14 for AKI^{MDRD}, Models 7 to 10 and 11 to 15 for AKI^{EPI}). However, when these analyses were performed including AKI^{low} in the regression analyses, AKI^{pre} was not retained in any of the models, suggesting that AKI^{low} had a stronger relationship with 1-year mortality than AKI^{pre}. Interestingly, the reverse was true for 30-day mortality, with AKI^{pre} demonstrating a stronger association with 30-day mortality compared to AKI^{low}, but a weaker association compared to AKI^{MDRD} or AKI^{EPI}. As discussed in section 5.5.1, these observations are likely to be explained by the misclassification of AKI cases

arising from use of these surrogate methods, leading to an increased or decreased strength of association with mortality in comparison to the 'gold standard', AKI^{pre}, which identifies more 'true' cases of AKI. However, the observations that AKI^{low} was more strongly associated with 1-year mortality but less strongly associated with 30-day mortality compared with AKI^{pre}, and that AKI^{MDRD} and AKI^{EPI} were less strongly associated with 1-year mortality but more strongly associated with 30-day mortality compared with AKI^{pre}, are difficult to explain and may be a result of residual confounders in the data which were not adjusted for in the regression analyses.

Due to the significant overestimation of AKI rates and the inconsistency in the multivariable regression analyses, it is reasonable to conclude, as for 30-day mortality, that back-calculation methods and lowest SCr on admission should not be used in this cohort for mortality risk modelling. These findings have important implications for the development of risk-prediction models, since variations in AKI rates may capture a different population to the one intended and mislead researchers into attributing a greater or lesser effect of AKI on outcomes than the true risk. As it stands therefore, every effort should be made to obtain a preadmission SCr in order to diagnose AKI. However, where this is missing, in a cohort of patients hospitalised with acute stroke, first SCr on admission performs best against preadmission SCr in determining AKI incidence, and acknowledging its limitation of low sensitivity, would appear to be the best currently available surrogate for predicting outcomes such as mortality.

5.5.3 Limitations

Limitations are as for the AKI incidence arm of the study (see Chapter 4, section 4.5.5).

5.6 Conclusions

In summary, AKI is associated with increased 30-day and 1-year mortality in patients hospitalised with an acute stroke. This association is consistent across all methods of ascertaining 'baseline SCr', although surrogate methods appear to underestimate the risk of death compared with AKI^{pre}. All in all, AKI^{pre} trumped surrogate methods in the regression models and as such, should remain the 'gold standard' for diagnosing AKI and predicting outcomes in future AKI studies. Of the surrogate methods, AKI^{adm} performs best against AKI^{pre} in correctly ascertaining AKI cases in this population and is therefore recommended as the preferred surrogate method for risk-prediction modelling in stroke patients. Back-calculation methods, as recommended by KDIGO, and lowest SCr on admission should not be used due to high misclassification rates of AKI, particularly when taking into account the high prevalence of CKD in the study population. Whilst SCr remains the mainstay of AKI diagnosis, further work is needed to develop better surrogate methods of estimating 'baseline' SCr to improve the detection of 'true' cases. These improvements will result in enhanced risk-prediction modelling and more accurate power estimates for AKI interventional trials.

CHAPTER 6 CHRONIC KIDNEY DISEASE: PREVALENCE, TREATMENTS AND OUTCOMES IN ACUTE STROKE

6.1. Introduction

CKD and stroke are significant public health problems that both carry an increased risk of morbidity and mortality [23]. CKD is associated with an increased risk of stroke- this is discussed extensively in Chapter 1. In the UK, the incidence of stroke in the CKD population is estimated at 12.0 per 1000 patient years, compared to 9.0 per 1000 patient years in the non-CKD population [24, 48]. Stroke is a disease of aging but patients with cerebrovascular disease also have a high prevalence of other comorbidities including CKD [23]. CKD does not distinguish between brain, cardiac, kidney or peripheral vasculature, and in common with all cardiovascular disease, both stroke events and mortality are related to the degree of renal impairment and albuminuria [68]. Patients on HD or PD are at greatest risk [453].

6.1.1 Stroke Outcomes in CKD and 'Renalism'

Patients with CKD have worse outcomes after a stroke compared with the non-CKD population [23]. Mortality increases with more severe CKD, and patients with ESRD have a 3 to 5 times higher risk than the non-CKD population [453, 454]. In the CHOICE study, which investigated incidence of stroke and outcomes in HD patients, 35% of stroke events were fatal (28% of AIS vs. 90% of ICH cases) and only 56% of patients were discharged home or to a rehabilitation facility [203]. In another study, Wang *et al*. reported a 2 to 7-fold increase in mortality in

dialysis patients hospitalised with AIS [453]. Increased rates of neurological deterioration, poor functional outcome and mortality have also been demonstrated in the non-dialysis CKD population [454-456]. Furthermore, in hospitalisations with acute stroke, CKD has been found to be an independent risk factor for both long-term mortality and cardiovascular mortality over a 10-year follow up period [353]. The persistent associations between CKD and poor outcomes are not limited to stroke (see Chapter 1, section 1.3.4).

The presence of renal disease influences clinical management and patients are less likely to undergo diagnostic procedures or interventional treatments. This may be in part be due to a lack of evidence of benefit. For example, the evidence base for cardiovascular treatments in CKD is limited since most large RCTs have excluded patients with moderate to severe CKD [375, 457]. The same is true of two recent RCTs investigating the benefit IAT in AIS [256, 257]. Interventional treatments and diagnostic imaging in stroke are discussed in more detail in Chapter 1, section 1.6.4. and Chapter 7, section 7.1. The challenge of treating cardiovascular disease in CKD patients is exacerbated by the fact that this population may derive less benefit from some treatments with an increased risk of harmful side effects. Two examples are an increased bleeding risk with antiplatelet therapy in ACS [378] and anticoagulation with warfarin for AF [115, 458].

It is perhaps not surprising therefore, that patients with CKD are less likely to receive primary or secondary preventative treatments for cardiovascular disease [459, 460]. This recognised phenomenon of underutilisation of diagnostic or therapeutic treatments due to uncertainties

about risk versus benefit is known as 'renalism'. In 2004, Chertow *et al*. showed that patients with CKD were less likely to undergo angiography than patients without CKD following an acute MI (adjusted OR 0.47, 95% CI 0.40-0.52) [461]. This may be partly explained by a change in clinical practice due to the perceived risk of CIN associated with coronary angiography and revascularisation. Unfortunately, subsequent studies have continued to show that patients with renal disease are less likely to undergo angiography [462-465] and receive aspirin, statins, beta-blockers and ACEi or ARBs in the setting of ACS [462, 466, 467]. The unbiased implementation of indicated therapy continues to be a very real challenge in patients with renal disease. In this era of advancing diagnostic techniques including CTA and interventional clot retrieval therapies for acute stroke, the same phenomenon may yet be observed in this field.

6.1.2 Relationship between stroke and CKD - UK Data

To date, there are only a handful of UK studies that have investigated the relationship between CKD and risk of stroke. In a cohort study of 19,558 patients undergoing coronary artery bypass graft surgery, Devbhandari *et al*. reported an increased risk of stroke post-operatively in patients with non-dialysis-dependent CKD (defined as SCr >200 µmol/L) in a propensity score adjusted analysis [468]. Non-dialysis CKD was also associated with increased rates of AKI, atrial arrhythmias, prolonged ventilation, LOS, in-hospital mortality and mid-term mortality. Another cohort study of 23,630 patients investigated the relationship between microalbuminuria and macroalbuminuria and stroke risk in the general population and found an increased risk of stroke after multiple adjustments (HR 1.49, 95% CI 1.13–2.14; P=0.01 for

microalbuminuria and HR 2.43, 95% CI 1.11-6.26; P=0.005 for macroalbuminuria) [469]. In the Collaborative Atorvastatin Diabetes Study (CARDS), an RCT investigating predictors of stroke and the effect of atorvastatin in 2838 patients with type 2 diabetes, microalbuminuria was found to be an independent risk factor for stroke [470].

Conversely, outcomes following stroke in CKD patients have not been well described in the UK population. In a Scottish cohort study of 2520 patients, Rowat *et al*. reported increased in-hospital mortality in stroke patients with an eGFR <60 mL/min/1.73m^2 (adjusted OR 1.59, 95% CI 1.26-2.00) [471]. The same authors conducted a systematic review of the effect of renal impairment on mortality and disability in patients with acute stroke. 31 studies were included, of which 6 were from the US and 13 from Europe. The only UK study comprised 2042 patients hospitalised with acute stroke and followed up over 7 years, and found CKD to be an independent predictor of long-term mortality (RR 1.59, 95% CI 1.32-1.92 for SCr ≥119 µmol/L) [472].

6.2 Aims and Hypotheses

This chapter comprises the CKD study arm, in which I sought to determine the following:

1) prevalence of CKD in a population of stroke patients admitted to a large tertiary centre in the UK;
2) demographic associations and risk factors for CKD;
3) the influence of CKD on 30-day and 1-year mortality;

4) the influence of CKD on treatments received for acute stroke.

The hypotheses for the CKD arm of this study are displayed in Table 6-1 below.

Table 6-1. Hypotheses for CKD arm of study.

Parameter	**Hypothesis**
Demographics	Patients with a diagnosis of CKD are older and have more underlying comorbidities than patients without CKD
Risk factors for CKD	Age, female sex, Black ethnicity, diabetes mellitus, hypertension, AF, previous stroke/ TIA and CHF are risk factors for CKD
Disability on admission	Patients with CKD have a reduced functional status (determined by admission disability score) than patients without CKD
Stroke severity	Patients with CKD present with more severe stroke than patients without CKD
Outcomes	
Mortality	Patients with a diagnosis of CKD have increased 30-day and 1-year mortality than patients without CKD
'Renalism'	Patients with a diagnosis of CKD are less likely to receive treatments for stroke including thrombolysis and IAT than patients without CKD

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; IAT, intra-arterial thrombectomy; TIA, transient ischaemic attack.

6.3. Methods

A detailed description of the study methods is given in Chapter 3. In brief, this study was of prospective, observational design and included all patients admitted with acute stroke to a single tertiary centre, QEHB, between 12 December 2012 and 30 September 2015.

Laboratory SCr values were extracted by QEHB Informatics team into an anonymised spreadsheet in Microsoft Excel. For patients within the region, whose EHR in the community was linked to PICS, all SCr values in the preceding 7-365 days leading up the index admission were extracted and the mean calculated to provide the preadmission 'baseline' renal function. Preadmission SCr data was available in 54.0% of the cohort.

Admission SCr was also extracted from PICS, available in 98.7% of the total cohort. Due to the critical nature of SCr to all the hypotheses stated above, **all** SCr values in the dataset were manually crosschecked in PICS for accuracy and completeness, as outlined in Chapter 3.

CKD was defined as an eGFR <60 mL/min/1.73m^2, calculated using both CKD-EPI and MDRD equations and further subdivided into stages as per KIDGO [41]. Both preadmission SCr and admission SCr were used to calculate eGFR. See also Chapter 3, section 3.15 for definitions of CKD.

Statistical analysis was performed as outlined in Chapter 3. For all regression analyses, where variables were closely related, separate models were created and only one variable was entered at a time.

6.4 Results

In total there were 1440 admissions with acute stroke within the study period. Repeated admissions and duplicates were excluded, leaving a total of 1375 patients eligible for inclusion in the CKD study arm. A further 18 patients with missing admission SCr were excluded, leaving 1357 in the final analysis. Patients with ESRD (n=21) were included in analyses of baseline data, CKD risk factors and stroke treatments. However, ESRD patients were excluded in the mortality analysis in an attempt to reduce confounding, since patients with ESRD on dialysis represent a unique group with different pathophysiological mechanisms contributing to cardiovascular risk and outcomes [22, 61]. As stated above, preadmission SCr was available in 54.0% (n=743) of the total cohort.

6.4.1 Baseline data

Baseline characteristics of the study cohort are presented according to presence or absence of CKD. Patients with a preadmission SCr are presented in Table 6-2 and patients with an admission SCr in Table 6-3.

The median number of preadmission SCr values was 2 (1-90, IQR 5). Using preadmission SCr and the CKD-EPI formula to ascertain CKD, the majority of CKD was stage 3 (3a 55.7% and 3b 29.7%) with <15% comprising stage 4 and 5 (8.8% and 5.7% respectively).

A higher proportion of patients with CKD were older (81.7 vs. 70.1; P<0.001 for preadmission SCr and CKD-EPI), female (61.8% vs. 42.1%; P=0.03), had more comorbidities including diabetes (29.4% vs. 21.7%; P<0.001), CHF (7.1% vs. 3.4%; P<0.001) and AF (32.8% vs. 19.0%; P<0.001), higher disability score on admission (mRS score 1 vs. 0; P=0.001) and presented with a more severe stroke (NIHSS score 4 vs. 3; P<0.001).

Table 6-2. Baseline characteristics of patients according to the presence or absence of CKD using preadmission SCr, calculated using both CKD-EPI and MDRD formulae (n=743).

CKD-EPI				**MDRD**			
	CKD (%) **296 (39.84)**	**No CKD (%)** **447 (60.16)**	**P value**		**CKD (%)** **248 (33.38)**	**No CKD (%)** **495 (66.62)**	**P value**
Age- Mean (SD)	81.69 (9.61)	70.08 (14.61)	<0.001	**Age- Mean (SD)**	81.06 (10.18)	71.52 (14.63)	<0.001
Female gender (%)	61.82	42.06	0.031	**Female gender (%)**	63.31	43.23	<0.001
Ischaemic stroke (%)	89.87	88.14	0.143	**Ischaemic stroke (%)**	88.71	88.89	0.884
NIHSS score on admission- Median (IQR)	4 (10)	3 (7)	<0.001	**NIHSS score on admission- Median (IQR)**	4 (12)	3 (6)	<0.001
mRS score on admission- Median (IQR)	1 (2)	0 (1)	0.001	**mRS score on admission- Median (IQR)**	1 (2)	0 (1)	0.003
IMD score- Mean (SD)	30.97 (15.80)	30.38 (15.18)	0.242	**IMD score- Mean (SD)**	31.32 (16.24)	30.27 (15.00)	0.036
Ethnicity (%) **White** **Asian/ Asian British** **Black/ Black British** **Mixed/ Other/ Unknown**	 87.50 7.10 3.38 2.03	 83.89 11.63 2.46 2.01	 0.026	**Ethnicity (%)** **White** **Asian/ Asian British** **Black/ Black British** **Mixed/ Other/ Unknown**	 87.50 7.66 2.82 2.02	 84.24 10.91 2.83 2.02	 0.042
Preadmission SCr (µmol/L)- Mean (SD)	140.64 (107.25)	75.92 (15.97)	<0.001	**Preadmission SCr (µmol/L)- Mean (SD)**	150.15 (114.70)	77.44 (16.23)	<0.001

CKD-EPI				**MDRD**			
	CKD (%) **296 (39.84)**	**No CKD (%)** **447 (60.16)**	**P value**		**CKD (%)** **248 (33.38)**	**No CKD (%)** **495 (66.62)**	**P value**
Preadmission eGFR (mL/min)- Mean (SD)	43.17 (13.31)	82.78 (15.39)	0.067	**Preadmission eGFR (mL/min)- Mean (SD)**	44.46 (13.48)	85.36 (20.56)	<0.001
CKD stage (%)				**CKD stage (%)**			
3a	55.74	N/A		**3a**	59.27	N/A	
3b	29.73			**3b**	26.21		
4	8.78			**4**	8.06		
5	5.74			**5**	6.45		
Comorbidities (%)				**Comorbidities (%)**			
Hypertension	53.72	51.23	0.195	**Hypertension**	50.81	52.93	0.403
Diabetes mellitus	29.39	21.70	<0.001	**Diabetes mellitus**	31.45	21.41	<0.001
CHF	7.09	3.36	<0.001	**CHF**	7.26	3.64	<0.001
Previous stroke/ TIA	31.08	29.08	0.250	**Previous stroke/ TIA**	31.05	29.29	0.332
AF	32.77	19.02	<0.001	**AF**	32.26	20.61	<0.001

Data are presented as mean (SD), median (IQR) or n (%).

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SCr, serum creatinine; SD, standard deviation; TIA, transient ischaemic attack.

Table 6-3. Baseline characteristics of patients according to the presence or absence of CKD using first SCr on admission, calculated using both CKD-EPI and MDRD formulae (n=1357).

CKD-EPI				**MDRD**			
	CKD (%) **455 (33.53)**	**No CKD (%)** **902 (66.47)**	**P value**		**CKD (%)** **368 (27.12)**	**No CKD (%)** **989 (72.88)**	**P value**
Age- Mean (SD)	81.32 (10.38)	67.49 (15.49)	<0.001	**Age- Mean (SD)**	80.77 (10.76)	68.92 (15.68)	<0.001
Female gender (%)	59.78	39.80	0.77	**Female gender (%)**	61.14	41.05	0.13
Ischaemic stroke (%)	89.89	87.36	0.006	**Ischaemic stroke (%)**	90.76	87.26	<0.001
NIHSS score on admission- Median (IQR)	4 (11)	3 (8)	<0.001	**NIHSS score on admission- Median (IQR)**	4 (12)	3 (8)	<0.001
mRS score on admission- Median (IQR)	1 (2)	0 (1)	<0.001	**mRS score on admission- Median (IQR)**	1 (2)	0 (1)	<0.001
IMD score- Mean (SD)	30.67 (16.96)	30.56 (16.37)	0.12	**IMD score- Mean (SD)**	30.66 (16.96)	30.57 (16.42)	0.17
Ethnicity (%) **White** **Asian/ Asian British** **Black/ Black British** **Mixed/ Other/ Unknown**	 87.25 7.25 3.30 2.20	 80.82 10.98 4.21 3.99	 <0.001	**Ethnicity (%)** **White** **Asian/ Asian British** **Black/ Black British** **Mixed/ Other/ Unknown**	 88.04 7.61 2.45 1.90	 81.09 10.52 4.45 3.94	 <0.001
Admission SCr (µmol/L)- Mean (SD)	134.11 (90.30)	74.85 (16.04)	<0.001	**Admission SCr (µmol/L)- Mean (SD)**	143.81 (97.68)	76.46 (16.75)	<0.001

CKD-EPI				**MDRD**			
	CKD (%) **455 (33.53)**	**No CKD (%)** **902 (66.47)**	**P value**		**CKD (%)** **368 (27.12)**	**No CKD (%)** **989 (72.88)**	**P value**
Admission eGFR (mL/min)-Mean (SD)	44.02 (13.03)	84.02 (15.53)	0.001	**Admission eGFR (mL/min)-Mean (SD)**	44.84 (12.98)	89.05 (24.51)	<0.001
CKD stage (%) **3a** **3b** **4** **5**	 57.36 27.47 10.99 4.18	 N/A		**CKD stage (%)** **3a** **3b** **4** **5**	 59.78 25.54 10.05 4.62	 N/A	
Comorbidities (%) **Hypertension** **Diabetes mellitus** **CHF** **Previous stroke/ TIA** **AF**	 52.53 27.91 7.47 27.03 29.45	 46.01 17.52 2.11 23.95 13.41	 0.35 <0.001 <0.001 0.015 <0.001	**Comorbidities (%)** **Hypertension** **Diabetes mellitus** **CHF** **Previous stroke/ TIA** **AF**	 51.36 29.08 8.15 27.72 29.89	 47.02 18.00 2.33 23.96 14.66	 0.38 <0.001 <0.001 0.006 <0.001

Data are presented as mean (SD), median (IQR) or n (%).

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; SCr, serum creatinine; SD, standard deviation; TIA, transient ischaemic attack.

6.4.2 CKD Risk Factors

Risk factors for CKD are displayed in Tables 6-4 to 6-7.

A binomial regression analysis was conducted for the following methods of ascertaining CKD:

1) preadmission SCr and CKD-EPI formula (Table 6-4);

2) preadmission SCr and MDRD formula (Table 6-5);

3) admission SCr and CKD-EPI (Table 6-6);

4) admission SCr and MDRD (Table 6-7).

Since these variables are closely related, separate regression models were created for each method.

For all four methods, older age, female sex, presence of diabetes, CHF, AF, higher disability on admission and increased stroke severity were associated with CKD in the univariable analysis. Of these, female sex, CHF and AF were most strongly associated with CKD. Anaemia was associated with CKD in the univariable analysis for all methods of ascertaining CKD except preadmission SCr and the MDRD formula used to calculate eGFR. Non-black ethnicity was associated with CKD ascertained using admission SCr but not preadmission SCr.

In the multivariable analysis, older age, female sex, presence of diabetes and CHF remained associated with CKD using all four methods outlined above. Of these, CHF was the strongest risk factor for CKD (OR 3.52, 95% CI 1.74-7.11; P<0.001 for admission SCr and CKD-EPI), followed by diabetes (OR 1.90, 95% CI 1.38-2.64; P<0.001).

AF was associated with CKD using all methods (OR 1.61, 95% CI 1.16-2.22; P=0.004 for admission SCr and CKD-EPI) except CKD ascertained using preadmission SCr and MDRD. Presence of anaemia was associated with CKD ascertained using admission SCr and CKD-EPI only (OR 1.40, 95% CI 1.01-1.94; P=0.04). Increased stroke severity was associated with CKD ascertained using admission SCr and MDRD only (OR 1.02, 95% CI 1.00-1.04; P=0.04).

Table 6-4. Binomial logistic regression analysis of factors associated with CKD, ascertained using preadmission SCr and CKD-EPI formula (n=743).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.098 (1.079-1.117)	<0.001	1.094 (1.074-1.114)	<0.001
Female sex	2.202 (1.621-2.990)	<0.001	1.622 (1.147-2.294)	0.006
Black ethnicity	1.024 (0.392-2.673)	0.962	-	-
IMD score	1.001 (0.992-1.011)	0.776	-	-
Diabetes	1.407 (0.997-1.987)	0.052	1.644 (1.108-2.438)	0.013
Hypertension	1.100 (0.815-1.484)	0.535	-	-
AF	2.176 (1.544-3.065)	<0.001	1.538 (1.046-2.261)	0.029
Previous stroke/ TIA	1.129 (0.816-1.563)	0.463	-	-
CHF	2.233 (1.123-4.438)	0.022	2.608 (1.183-5.748)	0.017
Stroke type	0.866 (0.536-1.399)	0.556	-	-
mRS on admission (as continuous variable)	1.281 (1.142-1.438)	<0.001	-	-
NIHSS score on admission (as continuous variable)	1.026 (1.006-1.047)	0.009	-	-
Anaemia (baseline haemoglobin as categorical variable)	1.162 (0.828-1.629)	0.385	-	-

*Adjusted for age, sex, presence of diabetes, AF and CHF, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 6-5. Binomial logistic regression analysis of factors associated with CKD, ascertained using preadmission SCr and MDRD formula (n=743).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.076 (1.059-1.094)	<0.001	1.075 (1.056-1.093)	<0.001
Female sex	2.240 (1.624-3.089)	<0.001	1.691 (1.194-2.395)	0.003
Black ethnicity	0.608 (0.198-1.868)	0.385	-	-
IMD score	1.003 (0.993-1.014)	0.532	-	-
Diabetes	1.573 (1.103-2.242)	0.012	1.772 (1.202-2.614)	0.004
Hypertension	0.905 (0.662-1.237)	0.532	-	-
AF	1.939 (1.367-2.751)	<0.001	-	-
Previous stroke/ TIA	1.122 (0.800-1.574)	0.504	-	-
CHF	2.115 (1.069-4.184)	0.031	2.249 (1.064-4.752)	0.034
Stroke type	1.064 (0.652-1.736)	0.804	-	-
mRS on admission (as continuous variable)	1.236 (1.100-1.388)	<0.001	-	-
NIHSS score on admission (as continuous variable)	1.035 (1.014-1.056)	0.001	-	-
Anaemia (baseline haemoglobin as categorical variable)	1.023 (0.717-1.460)	0.900	-	-

*Adjusted for age, sex, presence of diabetes, AF and CHF, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 6-6. Binomial logistic regression analysis of factors associated with CKD, ascertained using first SCr on admission and CKD-EPI formula (n=1357).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.097 (1.084-1.111)	<0.001	1.087 (1.072-1.102)	<0.001
Female sex	2.239 (1.772-2.828)	<0.001	1.514 (1.139-2.012)	0.004
Black ethnicity	0.591 (0.299-1.168)	0.130	-	-
IMD score	1.000 (0.993-1.007)	0.943	-	-
Diabetes	1.758 (1.339-2.309)	<0.001	1.904 (1.375-2.638)	<0.001
Hypertension	1.287 (1.023-1.619)	0.031	-	-
AF	2.791 (2.108-3.694)	<0.001	1.605 (1.161-2.218)	0.004
Previous stroke/ TIA	1.200 (0.925-1.557)	0.171	-	-
CHF	3.699 (2.072-6.606)	<0.001	3.518 (1.739-7.114)	<0.001
Stroke type	0.780 (0.540-1.127)	0.186	-	-
mRS on admission (as continuous variable)	1.396 (1.273-1.530)	<0.001	-	-
NIHSS score on admission (as continuous variable)	1.027 (1.012-1.043)	<0.001	-	-
Anaemia (baseline haemoglobin as categorical variable)	1.396 (1.070-1.822)	0.014	1.404 (1.014-1.944)	0.041

*Adjusted for age, sex, ethnicity, presence of diabetes, hypertension, AF and CHF, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 6-7. Binomial logistic regression analysis of factors associated with CKD, ascertained using first SCr on admission and MDRD formula (n=1357).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.079 (1.066-1.093)	<0.001	1.070 (1.056-1.084)	<0.001
Female sex	2.255 (1.756-2.896)	<0.001	1.707 (1.279-2.278)	<0.001
Black ethnicity	0.314 (0.123-0.798)	0.015	-	-
IMD score	1.000 (0.992-1.007)	0.902	-	-
Diabetes	1.793 (1.349-2.383)	<0.001	1.948 (1.406-2.700)	<0.001
Hypertension	1.173 (0.919-1.499)	0.201	-	-
AF	2.595 (1.946-3.461)	<0.001	1.569 (1.134-2.171)	0.007
Previous stroke/ TIA	1.249 (0.948-1.645)	0.114	-	-
CHF	3.687 (2.093-6.492)	<0.001	3.566 (1.852-6.865)	<0.001
Stroke type	0.696 (0.462-1.047)	0.082	-	-
mRS on admission (as continuous variable)	1.304 (1.187-1.431)	<0.001	-	-
NIHSS score on admission (as continuous variable)	1.033 (1.017-1.049)	<0.001	1.019 (1.001-1.037)	0.041
Anaemia (baseline haemoglobin as categorical variable)	1.268 (0.955-1.684)	0.100	-	-

*Adjusted for age, sex, ethnicity, presence of diabetes, AF, previous stroke/ TIA and CHF, stroke type, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

6.4.3 Stroke treatments and CKD

88.2% (n=1197) of the total cohort had AIS. Of these, 14.0% (n=167) underwent thrombolysis and 4.1% (n=49) underwent IAT. The proportion of patients with and without CKD who underwent stroke treatments is presented in the baseline imaging data results in Chapter 7, section 7.4.1. For the purposes of this analysis, the relationship between CKD and likelihood of receiving treatments for stroke was investigated by conducting a binomial regression analysis of variables associated with receiving thrombolysis, thrombectomy or the two combined. The results are displayed in Tables 6-8 to 6-10. For closely related variables, for example CKD calculated using the CKD-EPI or MDRD equation, separate models were created and only one variable was entered at a time.

Factors associated with thrombolysis are shown in Table 6-8. In the univariable model younger age, absence of diabetes or anaemia, lower disability score on admission and higher stroke severity were associated with thrombolysis.

In the multivariable analysis, younger age (OR 0.99, 95% CI 0.98-1.00; P=0.04), lower disability score on admission (OR 0.64, 95% CI 0.52-0.78; P<0.001) and increased stroke severity (OR 1.13, 95% CI 1.11-1.16; P<0.001) remained significantly associated with thrombolysis. Presence of CKD was associated with neither a lesser nor greater likelihood of receiving thrombolysis in any of the analyses, using all 4 methods to ascertain CKD as outlined above.

Table 6-8. Binomial logistic regression analysis of factors associated with thrombolysis (n=167).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	0.991 (0.981-1.001)	0.085	0.987 (0.976-0.999)	0.039
Female sex	1.037 (0.749-1.437)	0.826	-	-
Black ethnicity	0.576 (0.205-1.617)	0.295	-	-
IMD score	0.997 (0.987-1.007)	0.536	-	-
Diabetes	0.674 (0.434-1.046)	0.079	-	-
Hypertension	1.162 (0.839-1.609)	0.367	-	-
AF	1.198 (0.803-1.789)	0.376	-	-
Previous stroke/ TIA	0.990 (0.679-1.442)	0.957	-	-
CHF	0.914 (0.385-2.169)	0.838	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI) (n=743)	1.146 (0.680-1.932)	0.609	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD) (n=743)	0.998 (0.577-1.725)	0.994	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI) (n=1357)	0.900 (0.632-1.280)	0.556	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD) (n=1357)	0.899 (0.617-1.310)	0.581	-	-
mRS on admission (as continuous variable)	0.808 (0.688-0.950)	0.010	0.637 (0.521-0.779)	<0.001
NIHSS score on admission (as continuous variable)	1.112 (1.090-1.133)	<0.001	1.131 (1.106-1.156)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	0.681 (0.447-1.039)	0.074	-	-

*Adjusted for age, presence of diabetes, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Factors associated with thrombectomy are shown in Table 6-9. In the univariable analysis, younger age, male sex, absence of anaemia, absence of CKD ascertained using admission SCr (for both CKD-EPI and MDRD), lower disability score on admission and increased stroke severity were associated with undergoing thrombectomy.

In the multivariable analysis, younger age (OR 0.95, 95% CI 0.93-0.97; P<0.001), lower disability on admission (OR 0.41, 95% CI 0.23-0.72; P=0.002) and increased stroke severity (OR 1.18, 95% CI 1.14-1.23; P<0.001) remained associated with thrombectomy. CKD ascertained by any method was not associated with thrombectomy in the multivariable models.

Table 6-9. Binomial logistic regression analysis of factors associated with intra-arterial thrombectomy (n=49).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	0.959 (0.944-0.974)	<0.001	0.951 (0.933-0.970)	<0.001
Female sex	0.653 (0.367-1.160)	0.146	-	-
Black ethnicity	0.000 (0.000)	0.997	-	-
IMD score	0.995 (0.978-1.012)	0.584	-	-
Diabetes	0.574 (0.256-1.287)	0.178	-	-
Hypertension	0.719 (0.409-1.263)	0.251	-	-
AF	1.037 (0.513-2.096)	0.919	-	-
Previous stroke/ TIA	0.798 (0.405-1.570)	0.513	-	-
CHF	0.978 (0.232-4.128)	0.976	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI) (n=743)	0.406 (0.112-1.467)	0.169	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD) (n=743)	0.795 (0.247-2.561)	0.701	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI) (n=1357)**	0.320 (0.143-0.718)	0.006	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD (n=1357)**	0.437 (0.195-0.982)	0.045	-	-
mRS on admission (as continuous variable)	0.435 (0.253-0.747)	0.003	0.408 (0.233-0.715)	0.002
NIHSS score on admission (as continuous variable)	1.127 (1.094-1.161)	<0.001	1.184 (1.139-1.230)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	0.577 (0.312-1.069)	0.080	-	-

*Adjusted for age, sex, presence of CKD ascertained using admission SCr, disability score on admission, stroke severity and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Factors associated with the composite of thrombolysis and thrombectomy are displayed in Table 6-10. In the univariable analysis, younger age, absence of diabetes, lower disability score on admission and increased stroke severity were all associated with receiving the composite treatment. In the multivariable analysis, younger age (OR 0.98, 95% CI 0.97-1.00; P=0.004), lower disability score on admission (OR 0.64, 95% CI 0.53-0.77; P<0.001) and increased stroke severity (OR 1.14, 95% CI 1.12-1.16) remained significantly associated with the composite of thrombolysis and thrombectomy.

CKD ascertained by any method was not associated with the composite in either univariable or multivariable analyses.

Table 6-10. Binomial logistic regression analysis of factors associated with the composite of thrombolysis and intra-arterial thrombectomy (n=181).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	0.986 (0.977-0.996)	0.005	0.984 (0.973-0.995)	0.004
Female sex	1.026 (0.752-1.399)	0.871	-	-
Black ethnicity	0.504 (0.180-1.412)	0.192	-	-
IMD score	0.996 (0.986-1.005)	0.368	-	-
Diabetes	0.727 (0.483-1.095)	0.128	-	-
Hypertension	1.072 (0.787-1.462)	0.658	-	-
AF	1.237 (0.846-1.808)	0.272	-	-
Previous stroke/ TIA	1.058 (0.743-1.508)	0.754	-	-
CHF	0.956 (0.426-2.149)	0.914	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI) (n=743)	1.117 (0.680-1.833)	0.662	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD) (n=743)	1.094 (0.655-1.827)	0.731	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI) (n=1357)	0.847 (0.603-1.188)	0.336	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD) (n=1357)	0.874 (0.609-1.253)	0.463	-	-
mRS on admission (as continuous variable)	0.781 (0.666-0.914)	0.002	0.639 (0.528-0.773)	<0.001
NIHSS score on admission (as continuous variable)	1.118 (1.097-1.140)	<0.001	1.140 (1.117-1.164)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	0.871 (0.595-1.274)	0.476	-	-

*Adjusted for age, presence of diabetes, disability score on admission and stroke severity in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; IMD, Index of Multiple Deprivation; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

6.4.4 CKD and Mortality

6.4.4.1 30-Day Mortality

The crude mortality rate at 30 days was 10.8% (n=146) for the total cohort (n=1357). Table 6-11 shows 30-day mortality using preadmission SCr and admission SCr to ascertain CKD and both CKD-EPI and MDRD formulae. Mortality was higher in the CKD cohort using all methods to ascertain CKD (17.9% vs. 9.4%, P<0.001 for CKD ascertained using preadmission SCr and the CKD-EPI formula to calculate eGFR).

Table 6-11. Crude 30-day mortality rate according to the presence or absence of CKD, ascertained using preadmission and admission SCr and CKD-EPI and MDRD formulae.

	CKD-EPI			**MDRD**		
	CKD n= 296	**No CKD n= 447**	**P value**	**CKD n= 248**	**No CKD n= 495**	**P value**
Preadmission SCr	17.91% (53)	9.40% (42)	<0.001	18.95% (47)	9.70% (48)	<0.001
	CKD n= 455	**No CKD n= 902**	**P value**	**CKD n= 368**	**No CKD n= 989**	**P value**
Admission SCr	17.58% (80)	7.32% (66)	<0.001	18.21% (67)	7.99% (79)	<0.001

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

Associations with 30-day mortality are shown in Tables 6-12 to 6-15.

Patients with ESRD were excluded in the mortality analysis, leaving 725 patients included in the binomial regression analysis for CKD ascertained using preadmission SCr and 1337 for CKD ascertained using admission SCr.

Tables 6-12 and 6-13 show results for preadmission SCr used to ascertain CKD with CKD-EPI and MDRD formulae respectively. For both methods, factors associated with 30-day mortality in the univariable analysis were age, presence of CKD, AF, anaemia, haemorrhagic stroke type, higher disability score on admission and increased stroke severity. In the multivariable analysis, factors that remained associated with death at 30-days for CKD-EPI were age (OR 1.03, 95% CI 1.01-1.06; P=0.01), higher disability on admission (OR 1.57, 95% CI 1.31-1.87; P<0.001) and increased stroke severity (OR 1.12, 95% CI 1.09-1.16; P<0.001). CKD was not associated with 30-day mortality in the multivariable analysis. Similar results were found for CKD calculated using MDRD.

Table 6-12. Binomial logistic regression analysis of factors associated with 30-Day Mortality, with CKD ascertained using preadmission SCr and CKD-EPI formula (n=725).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.063 (1.039-1.088)	<0.001	1.031 (1.006-1.056)	0.013
Female sex	1.076 (0.692-1.673)	0.747	-	-
Black ethnicity	0.408 (0.054-3.107)	0.387	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)	2.012 (1.290-3.139)	0.002	-	-
Diabetes	0.822 (0.480-1.407)	0.474	-	-
Hypertension	1.170 (0.751-1.824)	0.488	-	-
AF	1.729 (1.078-2.772)	0.023	-	-
Previous stroke/ TIA	0.937 (0.576-1.524)	0.794	-	-
CHF	1.828 (0.774-4.318)	0.169	-	-
Stroke type	2.042 (1.136-3.673)	0.017	-	-
Thrombolysis	0.855 (0.377-1.938)	0.708	-	-
Thrombectomy	1.956 (0.535-7.150)	0.310	-	-
mRS on admission (as continuous variable)	1.773 (1.529-2.056)	<0.001	1.567 (1.314-1.869)	<0.001
NIHSS score on admission (as continuous variable)	1.141 (1.110-1.172)	<0.001	1.122 (1.089-1.155)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.799 (1.135-2.850)	0.012	-	-

*Adjusted for age, presence of CKD, AF, stroke type, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 6-13. Binomial logistic regression analysis of factors associated with 30-Day Mortality, with CKD ascertained using preadmission SCr and MDRD formula (n=725).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.063 (1.039-1.088)	<0.001	1.031 (1.006-1.056)	0.013
Female sex	1.076 (0.692-1.673)	0.747	-	-
Black ethnicity	0.408 (0.054-3.107)	0.387	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)	2.080 (1.329-3.256)	0.001	-	-
Diabetes	0.822 (0.480-1.407)	0.474	-	-
Hypertension	1.170 (0.751-1.824)	0.488	-	-
AF	1.729 (1.078-2.772)	0.023	-	-
Previous stroke/ TIA	0.937 (0.576-1.524)	0.794	-	-
CHF	1.828 (0.774-4.318)	0.169	-	-
Stroke type	2.042 (1.136-3.673)	0.017	-	-
Thrombolysis	0.855 (0.377-1.938)	0.708	-	-
Thrombectomy	1.956 (0.535-7.150)	0.310	-	-
mRS on admission (as continuous variable)	1.773 (1.529-2.056)	<0.001	1.567 (1.314-1.869)	<0.001
NIHSS score on admission (as continuous variable)	1.141 (1.110-1.172)	<0.001	1.122 (1.089-1.155)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.799 (1.135-2.850)	0.012	-	-

*Adjusted for age, presence of CKD, AF, stroke type, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Tables 6-14 and 6-15 show results for CKD ascertained using first SCr on admission and CKD-EPI and MDRD formulae respectively. For both methods, factors associated with 30-day mortality in the univariable model were age, non-Black ethnicity, presence of CKD, AF, CHF, anaemia, haemorrhagic stroke type, higher disability score on admission and increased stroke severity.

In the multivariable analysis, factors that remained associated with death at 30-days for CKD-EPI were age (OR 1.03, 95% CI 1.02-1.05; P<0.001), haemorrhagic stroke type (OR 1.93, 95% CI 1.13-3.27; P=0.016), higher admission disability score (OR 1.50, 95% CI 1.31-1.72; P<0.001), increased stroke severity (OR 1.11, 95% CI 1.08-1.13; P<0.001) and anaemia (OR 1.68, 95% CI 1.12-2.53; P=0.012). CKD was not associated with 30-day mortality in the multivariable analysis. Similar results were found for CKD calculated using MDRD.

Table 6-14. Binomial logistic regression analysis of factors associated with 30-Day Mortality, with CKD ascertained using first SCr on admission and CKD-EPI formula (n=1337).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.061 (1.044-1.078)	<0.001	1.033 (1.015-1.051)	<0.001
Female sex	1.056 (0.745-1.498)	0.759	-	-
Black ethnicity	0.171 (0.023-1.247)	0.081	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)	2.646 (1.859-3.767)	<0.001	-	-
Diabetes	0.995 (0.646-1.532)	0.981	-	-
Hypertension	1.179 (0.831-1.672)	0.355	-	-
AF	2.240 (1.525-3.290)	<0.001	-	-
Previous stroke/ TIA	1.067 (0.717-1.588)	0.748	-	-
CHF	1.873 (0.892-3.935)	0.097	-	-
Stroke type	2.142 (1.369-3.350)	0.001	1.925 (1.132-3.274)	0.016
Thrombolysis	1.044 (0.618-1.763)	0.871	-	-
Thrombectomy	1.435 (0.632-3.259)	0.388	-	-
mRS on admission (as continuous variable)	1.781 (1.587-1.999)	<0.001	1.500 (1.305-1.724)	<0.001
NIHSS score on admission (as continuous variable)	1.125 (1.102-1.149)	<0.001	1.106 (1.082-1.132)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	2.078 (1.440-2.997)	<0.001	1.684 (1.122-2.527)	0.012

*Adjusted for age, ethnicity, presence of CKD, AF, CHF, stroke type, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 6-15. Binomial logistic regression analysis of factors associated with 30-Day Mortality, with CKD ascertained using first SCr on admission and MDRD formula (n=1337).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.061 (1.044-1.078)	<0.001	1.033 (1.015-1.051)	<0.001
Female sex	1.056 (0.745-1.498)	0.759	-	-
Black ethnicity	0.171 (0.023-1.247)	0.081	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)	2.506 (1.752-3.585)	<0.001	-	-
Diabetes	0.995 (0.646-1.532)	0.981	-	-
Hypertension	1.179 (0.831-1.672)	0.355	-	-
AF	2.240 (1.525-3.290)	<0.001	-	-
Previous stroke/ TIA	1.067 (0.717-1.588)	0.748	-	-
CHF	1.873 (0.892-3.935)	0.097	-	-
Stroke type	2.142 (1.369-3.350)	0.001	1.925 (1.132-3.274)	0.016
Thrombolysis	1.044 (0.618-1.763)	0.871	-	-
Thrombectomy	1.435 (0.632-3.259)	0.388	-	-
mRS on admission (as continuous variable)	1.781 (1.587-1.999)	<0.001	1.500 (1.305-1.724)	<0.001
NIHSS score on admission (as continuous variable)	1.125 (1.102-1.149)	<0.001	1.106 (1.082-1.132)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	2.078 (1.440-2.997)	<0.001	1.690 (1.126-2.537)	0.011

*Adjusted for age, ethnicity, presence of CKD, AF, CHF, stroke type, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

6.4.4.2 1-Year Mortality

The crude mortality rate at 1 year was 19.9% (n=270) across the total cohort (n=1357). Table 6-16 shows 1-year mortality using preadmission SCr and admission SCr to ascertain CKD and both CKD-EPI and MDRD formulae. Using all methods, mortality was higher in the CKD cohort compared with the non-CKD cohort (30.7% vs. 19.7%, P<0.001 for CKD ascertained using preadmission SCr and the CKD-EPI formula to calculate eGFR).

Table 6-16. Crude 1-year mortality rate according to the presence or absence of CKD, ascertained using preadmission and admission SCr and CKD-EPI and MDRD formulae.

	CKD-EPI			**MDRD**		
	CKD n= 296	**No CKD n= 447**	**P value**	**CKD n= 248**	**No CKD n= 495**	**P value**
Preadmission SCr	30.74% (91)	19.69% (88)	<0.001	33.06% (82)	19.60% (97)	<0.001
	CKD n= 455	**No CKD n= 902**	**P value**	**CKD n= 368**	**No CKD n= 989**	**P value**
Admission SCr	30.12% (137)	14.75% (133)	<0.001	30.71% (113)	15.87% (157)	<0.001

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

Associations with 1-year mortality are shown in Tables 6-17 to 6-20. As for 30-day mortality, patients with ESRD were excluded.

Tables 6-17 and 6-18 show results for CKD calculated using preadmission SCr and CKD-EPI and MDRD formulae respectively. In a Cox regression univariable analysis, factors associated with death at 1 year for both methods were older age, presence of CKD, AF, CHF, anaemia, haemorrhagic stroke type, higher disability on admission and increased stroke severity. In addition, thrombectomy was also associated with 1-year mortality in the univariable analysis (HR 2.36, 95% CI 1.11-5.03; P=0.03).

Using the CKD-EPI formula to calculate CKD, older age (HR 1.03, 95% CI 1.01-1.04; P<0.001), higher disability score on admission (HR 1.31, 95% CI 1.19-1.45; P<0.001, more severe stroke (HR 1.07, 95% CI 1.05-1.09; P<0.001) and anaemia (HR 1.48, 95% CI 1.09-2.02; P=0.01) remained significantly associated with 1-year mortality in the multivariable analysis. CKD was not associated with 1-year mortality in the multivariable model. Similar results were found for CKD calculated using the MDRD formula.

Table 6-17. Cox regression analysis of factors associated with 1-Year Mortality, with CKD ascertained using preadmission SCr and CKD-EPI formula (n=725).

	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.050 (1.035-1.065)	<0.001	1.029 (1.014-1.044)	<0.001
Female sex	1.147 (0.851-1.546)	0.367	-	-
Black ethnicity	1.155 (0.475-2.812)	0.750	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)	1.681 (1.248-2.265)	0.001	-	-
Diabetes	0.832 (0.579-1.197)	0.323	-	-
Hypertension	0.927 (0.688-1.249)	0.618	-	-
AF	1.679 (1.226-2.299)	0.001	-	-
Previous stroke/ TIA	0.907 (0.652-1.263)	0.565	-	-
CHF	1.644 (0.914-2.955)	0.097	-	-
Stroke type	1.473 (0.964-2.250)	0.073	-	-
Thrombolysis	1.034 (0.618-1.730)	0.897	-	-
Thrombectomy	2.360 (1.108-5.030)	0.026	-	-
mRS on admission (as continuous variable)	1.513 (1.386-1.652)	<0.001	1.309 (1.185-1.445)	<0.001
NIHSS score on admission (as continuous variable)	1.091 (1.073-1.109)	<0.001	1.068 (1.050-1.086)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.824 (1.344-2.474)	<0.001	1.479 (1.085-2.016)	0.013

*Adjusted for age, presence of CKD, AF, CHF, stroke type, thrombectomy, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 6-18. Cox regression analysis of factors associated with 1-Year Mortality, with CKD ascertained using preadmission SCr and MDRD formula (n=725).

	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.050 (1.035-1.065)	<0.001	1.029 (1.014-1.044)	<0.001
Female sex	1.147 (0.851-1.546)	0.367	-	-
Black ethnicity	1.155 (0.475-2.812)	0.750	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)	1.841 (1.364-2.487)	<0.001	-	-
Diabetes	0.832 (0.579-1.197)	0.323	-	-
Hypertension	0.927 (0.688-1.249)	0.618	-	-
AF	1.679 (1.226-2.299)	0.001	-	-
Previous stroke/ TIA	0.907 (0.652-1.263)	0.565	-	-
CHF	1.644 (0.914-2.955)	0.097	-	-
Stroke type	1.473 (0.964-2.250)	0.073	-	-
Thrombolysis	1.034 (0.618-1.730)	0.897	-	-
Thrombectomy	2.360 (1.108-5.030)	0.026	-	-
mRS on admission (as continuous variable)	1.513 (1.386-1.652)	<0.001	1.309 (1.185-1.445)	<0.001
NIHSS score on admission (as continuous variable)	1.091 (1.073-1.109)	<0.001	1.068 (1.050-1.086)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.824 (1.344-2.474)	<0.001	1.479 (1.085-2.016)	0.013

*Adjusted for age, presence of CKD, AF, CHF, stroke type, thrombectomy, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SCr, serum creatinine; TIA, transient ischaemic attack.

Tables 6-19 and 6-20 show results for CKD calculated using first SCr on admission and CKD-EPI and MDRD formulae respectively. For both methods, factors associated with 1-year mortality in a univariable Cox regression analysis were older age, presence of CKD, AF, CHF, anaemia, haemorrhagic stroke type, higher disability on admission and more severe stroke.

Using the CKD-EPI formula to calculate CKD, older age (HR 1.03, 95% CI 1.02-1.04; P<0.001), AF (HR 1.33, 95% CI 1.02-1.74; P=0.04), haemorrhagic stroke type (HR 1.58, 95% CI 1.13-2.22; P=0.008), higher admission disability score (HR 1.29, 95% CI 1.19-1.39; P<0.001), more severe stroke (HR 1.07, 95% CI 1.05-1.08; P<0.001) and anaemia (HR 1.60, 95% CI 1.25-2.06; P<0.001) all remained associated with 1-year mortality in the multivariable analysis. CKD was not associated with 1-year mortality in the multivariable analysis. Similar results were found for CKD calculated using MDRD.

Table 6-19. Cox regression analysis of factors associated with 1-Year Mortality, with CKD ascertained using first SCr on admission and CKD-EPI formula (n=1337).

	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.052 (1.041-1.063)	<0.001	1.032 (1.021-1.044)	<0.001
Female sex	1.175 (0.924-1.496)	0.189	-	-
Black ethnicity	0.787 (0.389-1.590)	0.504	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)	2.260 (1.775-2.877)	<0.001	-	-
Diabetes	0.958 (0.709-1.295)	0.781	-	-
Hypertension	1.022 (0.803-1.301)	0.860	-	-
AF	2.082 (1.603-2.705)	<0.001	1.332 (1.017-1.744)	0.037
Previous stroke/ TIA	1.067 (0.810-1.403)	0.646	-	-
CHF	1.532 (0.894-2.625)	0.120	-	-
Stroke type	1.502 (1.077-2.096)	0.017	1.578 (1.125-2.215)	0.008
Thrombolysis	0.986 (0.681-1.427)	0.941	-	-
Thrombectomy	1.299 (0.728-2.319)	0.376	-	-
mRS on admission (as continuous variable)	1.530 (1.426-1.641)	<0.001	1.286 (1.187-1.394)	<0.001
NIHSS score on admission (as continuous variable)	1.086 (1.072-1.100)	<0.001	1.066 (1.052-1.081)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	2.020 (1.576-2.590)	<0.001	1.604 (1.249-2.061)	<0.001

*Adjusted for age, presence of CKD, AF, CHF, stroke type, disability score on admission, stroke severity and anaemia in a forward conditional model.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SCr, serum creatinine; TIA, transient ischaemic attack.

Table 6-20. Cox regression analysis of factors associated with 1-Year Mortality, with CKD ascertained using first SCr on admission and MDRD formula (n=1337).

	Univariable Analysis		**Multivariable Analysis***	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.052 (1.041-1.063)	<0.001	1.032 (1.021-1.044)	<0.001
Female sex	1.175 (0.924-1.496)	0.189	-	-
Black ethnicity	0.787 (0.389-1.590)	0.504	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)	2.130 (1.666-2.723)	<0.001	-	-
Diabetes	0.958 (0.709-1.295)	0.781	-	-
Hypertension	1.022 (0.803-1.301)	0.860	-	-
AF	2.082 (1.603-2.705)	<0.001	1.332 (1.017-1.744)	0.037
Previous stroke/ TIA	1.067 (0.810-1.403)	0.646	-	-
CHF	1.532 (0.894-2.625)	0.120	-	-
Stroke type	1.502 (1.077-2.096)	0.017	1.578 (1.125-2.215)	0.008
Thrombolysis	0.986 (0.681-1.427)	0.941	-	-
Thrombectomy	1.299 (0.728-2.319)	0.376	-	-
mRS on admission (as continuous variable)	1.530 (1.426-1.641)	<0.001	1.286 (1.187-1.394)	<0.001
NIHSS score on admission (as continuous variable)	1.086 (1.072-1.100)	<0.001	1.066 (1.052-1.081)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	2.020 (1.576-2.590)	<0.001	1.604 (1.248-2.062)	<0.001

*Adjusted for age, presence of CKD, AF, CHF, stroke type, disability score on admission, stroke severity and anaemia in a forward conditional model.

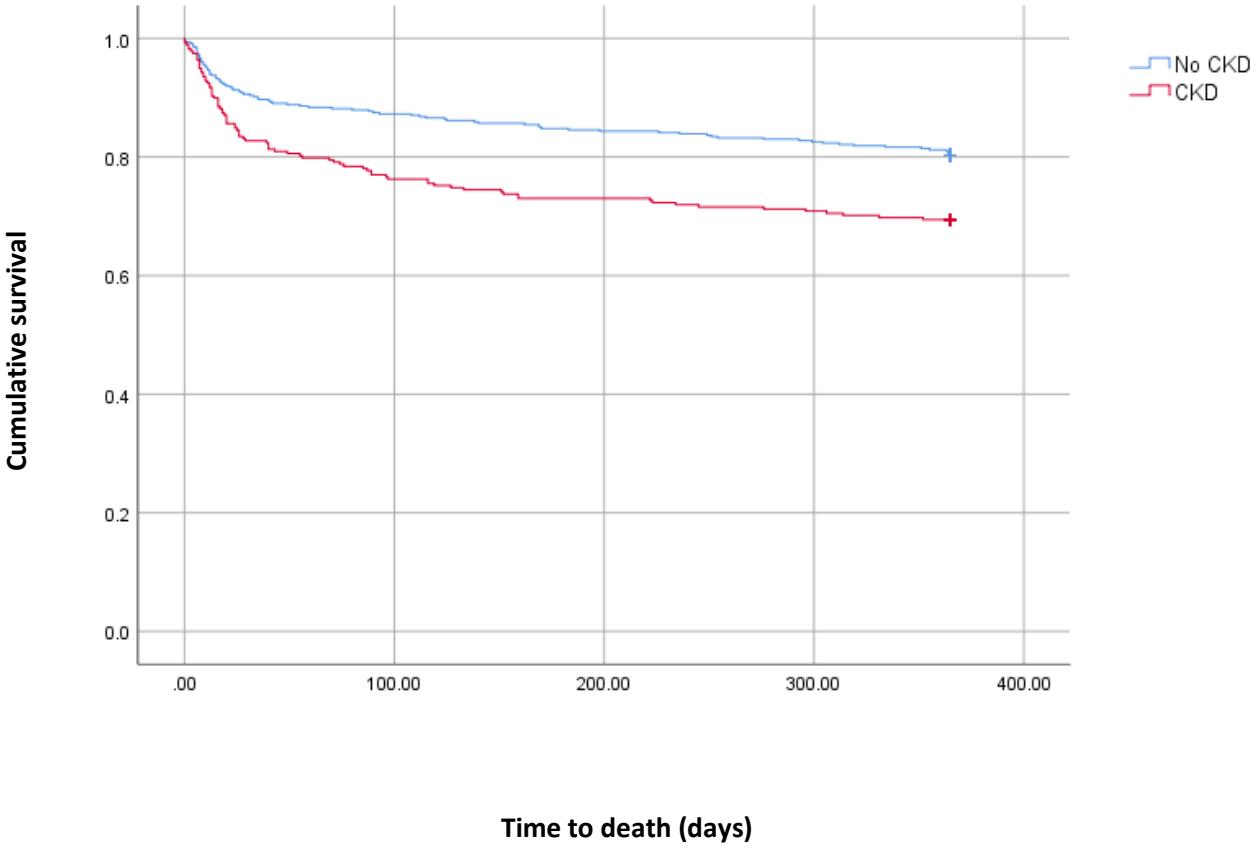
Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SCr, serum creatinine; TIA, transient ischaemic attack.

Kaplan-Meier survival curves at 1 year in the CKD versus non-CKD cohort are displayed in Figures 6-1 to 6-4.

Results for CKD calculated using preadmission SCr and CKD-EPI and MDRD formulae are shown in Figures 6-1 and 6-2 respectively. Results for CKD calculated using admission SCr and CKD-EPI and MDRD formulae are shown in Figures 6-3 and 6-4 respectively. All graphs show reduced 1-year survival in patients with a diagnosis of CKD compared with no CKD.

Figure 6-1. Kaplan-Meier survival curve at 365 days for patients with and without CKD, ascertained using preadmission SCr and CKD-EPI formula (n=725).

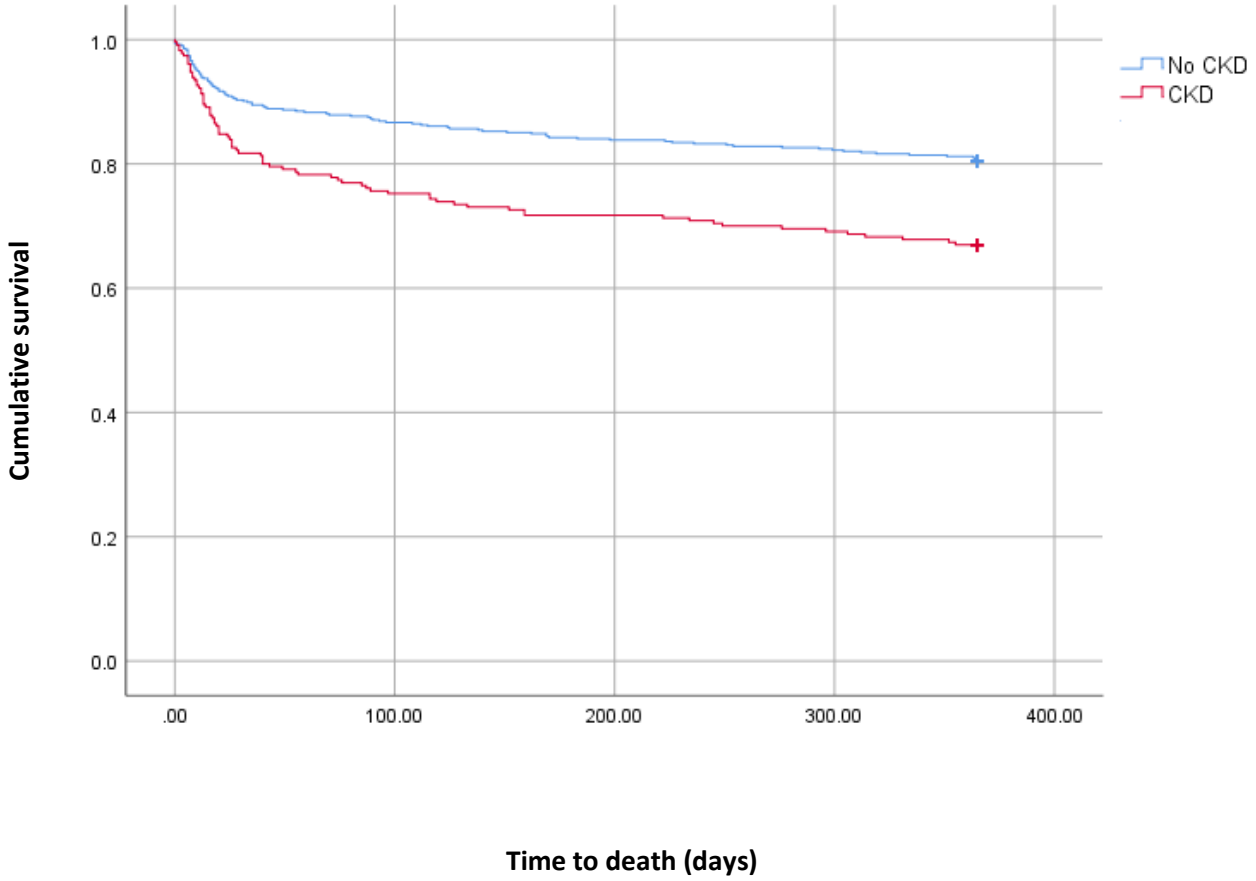
Log rank test 11.95; P=0.001.



Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SCr, serum creatinine.

Figure 6-2. Kaplan-Meier survival curve at 365 days for patients with and without CKD, ascertained using preadmission SCr and MDRD formula (n=725).

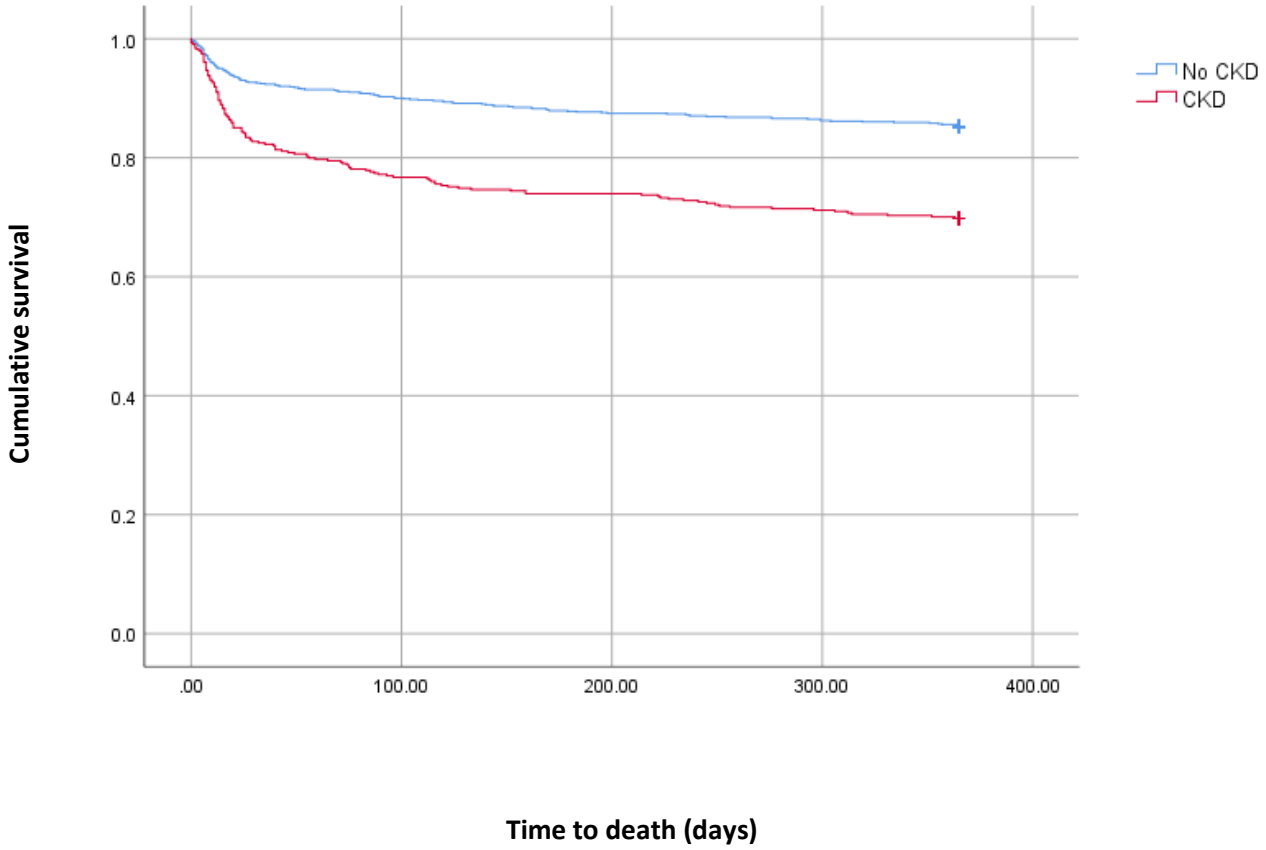
Log rank test 16.41; P<0.001.



Abbreviations: CKD, chronic kidney disease; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

Figure 6-3. Kaplan-Meier survival curve at 365 days for patients with and without CKD, ascertained using admission SCr and CKD-EPI formula (n=1337).

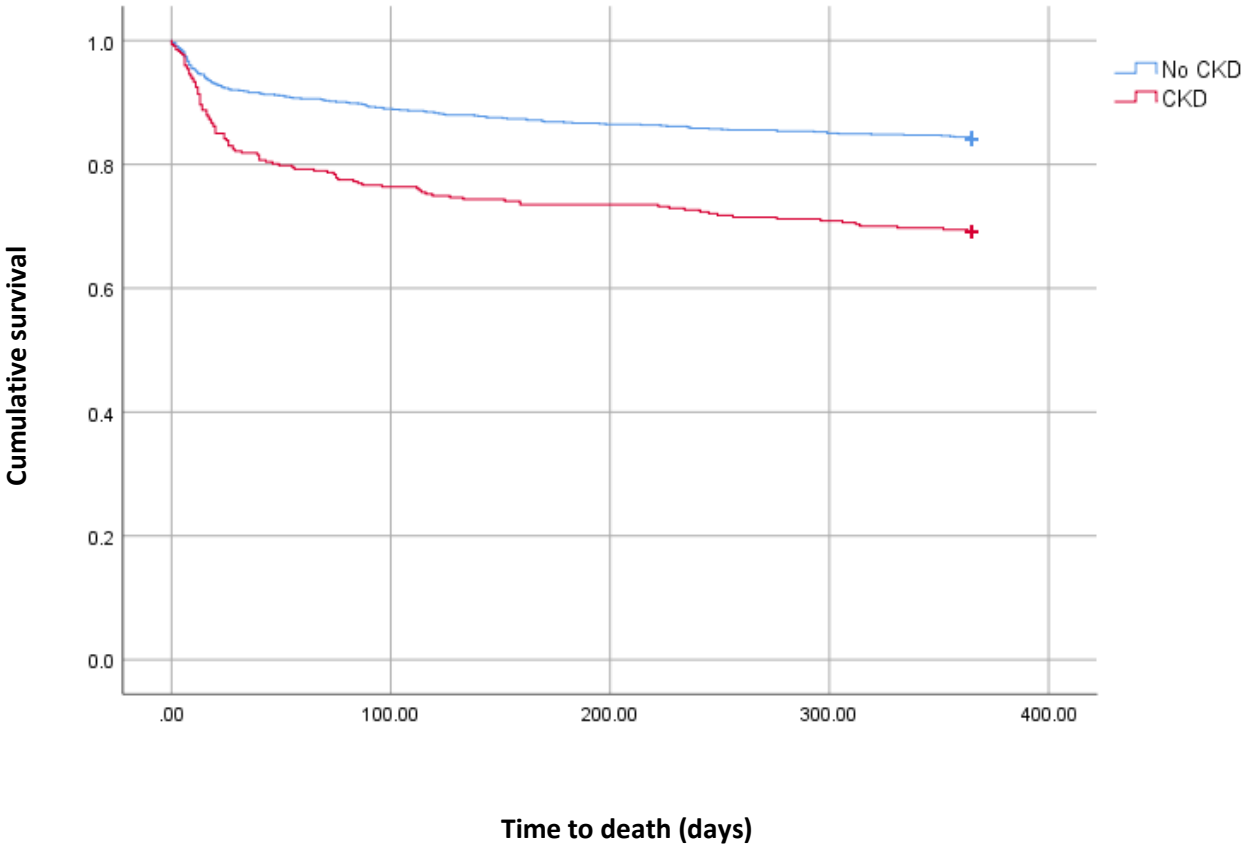
Log rank test 46.42; P<0.001.



Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; SCr, serum creatinine.

Figure 6-4. Kaplan-Meier survival curve at 365 days for patients with and without CKD, ascertained using admission SCr and MDRD formula (n=1337).

Log rank test 38.18; P<0.001.



Abbreviations: CKD, chronic kidney disease; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine.

6.5 Discussion

The large amount of data generated from this study arm has shown that CKD is common in hospitalised stroke patients (approximately 30% depending on definition used) and is associated with older age, concurrent comorbidities and increased mortality. As a whole, the results agree with the hypotheses outlined in section 6.2 and I will now discuss these in turn.

6.5.1 Baseline Demographics and CKD Risk Factors

I hypothesised that patients with a diagnosis of CKD are older and more comorbid than patients without CKD. In the multivariable regression analysis, factors associated with CKD ascertained by any method were older age, female sex and presence of diabetes. CHF was also strongly associated with CKD. In addition, AF was associated with CKD using all methods but preadmission SCr and the MDRD equation to calculate eGFR. These findings are in keeping with the bi-directional relationship exhibited between both CHF [473] and AF [117, 119] and CKD. Interestingly, AF was associated with CKD calculated using preadmission SCr and admission SCr and CKD-EPI, but only admission SCr and MDRD. This observation may be of importance since the CKD-EPI equation has been shown to predict cardiovascular risk more accurately compared to MDRD [474]. This is thought to be because CKD-EPI is a better estimate of 'true' eGFR, which therefore transforms into better risk prediction [475-478].

6.5.2 Level of Disability on Admission

The baseline data in this study showed that patients with CKD had higher disability on admission than those without CKD, in agreement with my hypothesis that CKD patients have a reduced functional status. In the univariable regression analysis for factors associated with CKD, higher admission disability was associated with CKD using all 4 methods. However, the association between disability on admission and CKD did not persist in the multivariable models for any of the methods used to ascertain CKD, signifying a weaker relationship with CKD compared with other factors entered into the model.

6.5.3 Stroke Severity

Patient with CKD were observed to have a higher median NIHSS score on admission than patients without CKD, in line with my hypothesis that CKD patients present with more severe strokes. In the univariable regression analyses, CKD was associated with increased stroke severity using all 4 methods to ascertain CKD. However, after adjustment for confounders, CKD was associated with increased stroke severity using only one method of ascertaining CKD (admission SCr and the MDRD equation to calculate eGFR). Propensity score analyses may have provided further clarification of a relationship between CKD and stroke severity but was not performed here, since matching would have significantly reduced the numbers available for analysis and potentially affected the power to detect associations with stroke severity. Nevertheless, my results demonstrate some relationship between stroke severity and CKD. This is plausible for many reasons. As discussed in Chapter 1, patients with CKD have increased cardiovascular risk and mortality and accelerated vascular calcification [22, 41, 479, 480] and

a higher prevalence of AF [112]. Small vessel disease and cerebral atrophy are also more prevalent in dialysis patients [481, 482], although these features have also been demonstrated in patients with milder stages of CKD [483-485]. Impaired homeostatic compensatory mechanisms in CKD patients, when applied to the context of brain ischaemia, might also feasibly contribute to a more severe stroke [486]. In addition, HD causes haemodynamic fluctuations which results in perfusion-related cardiovascular injury and adverse cardiac effects including reduced left ventricular function and myocardial perfusion [487, 488]. Brain tissue appears to be similarly susceptible to fluid and electrolyte shifts during HD [226]. One recent study showed that cerebral perfusion is globally and regionally reduced by factors such as increased temperature, higher ultrafiltration rate and volume and higher pH [227]. Use of cooler dialysate, by way of achieving greater haemodynamic stability during dialysis, has been shown to protect against perfusion-related brain injury [212]. This supports previous work which demonstrated that measures such as reducing dialysate temperature and ultrafiltration rate can reduce the risk of adverse cardiovascular events [210, 487-490]. These are promising targets for reducing cerebrovascular events in HD patients.

6.5.4 30-Day Mortality

In this study, crude 30-day mortality was higher in the CKD cohort compared with the non-CKD cohort, using all 4 methods to ascertain CKD. In the univariable regression analyses, CKD was associated with 30-day mortality using all methods to ascertain CKD, however this association did not persist in the multivariable models. This may be due to underpowering, although this seems unlikely as both the prevalence of CKD and crude mortality rates were

high in the study cohort. A key explanation may lie in the fact that most CKD was classified as stage 3a (58.0% compared with 27.2% stage 3b, 9.5% stage 4 and 5.2% stage 5) and patients with ESRD were excluded from the mortality analyses to reduce potential confounding (see section 6.4). Alternatively, given that CKD is strongly associated with other variables included in the model, such as age, this may have masked any relationship between CKD and 30-day mortality. The overall mean age was 72.2 years, and patients with CKD were over a decade older than those without CKD (81.2 vs. 69.5 years). Given the age of the study population, it is possible some patients may have been labelled as having CKD on the basis of age-related decline in renal function alone. In such cases, there has been some debate as to whether an abnormal eGFR represents true renal disease or is simply part of the aging process [491, 492]. These two factors may go some way to explaining the lack of association between CKD and 30-day mortality in this study in the fully adjusted models. However, the general trend does suggest that patients with CKD have higher 30-day mortality, supporting the existing literature that CKD confers worse outcomes after stroke in both dialysis [203] and non-dialysis populations [456, 493].

Associations with 30-day mortality that persisted in the multivariable analyses were older age, higher disability score on admission and increased stroke severity. These findings support the current literature on factors that are known to influence outcomes in stroke patients [494, 495]. In addition, in the multivariable analyses where CKD ascertained using admission SCr and CKD-EPI and MDRD formulae was included in the model, haemorrhagic stroke type was associated with increased 30-day mortality. Haemorrhagic stroke at presentation is generally

more severe and carries a higher mortality rate than AIS, although the latter observation appears to be time-dependent and may dissipate by 3 months [496]. Presence of anaemia was also found to be associated with 30-day mortality in multivariable analyses using admission SCr to ascertain CKD. This parallels the association between anaemia and 30-day and 1-year mortality in the AKI analyses and as discussed in Chapter 5, section 5.5.2, is a condition associated with worse outcomes in a variety of conditions, including CKD [440] and stroke [445].

6.5.5 1-Year Mortality

In this study, crude 1-year mortality was higher in the CKD cohort compared with the non-CKD cohort, using all 4 methods to ascertain CKD. Similar to the 30-day mortality results, in the univariable regression analyses, CKD was associated with 1-year mortality using all methods, however this association did not persist in the multivariable models. This may be due to underpowering, residual confounding in the data or the fact that other variables in the model such as age are strongly associated with CKD, which may have masked any relationship between CKD and 1-year mortality. However, as for the 30-day mortality results (see section 6.5.4), an important factor potentially leading to a weaker relationship between CKD and 1-year mortality is that most patients had milder CKD (85.3% stage 3). In addition, since a high proportion were elderly, this may have led to cases being classified as having CKD based on age-related decline in eGFR rather than real disease. Nevertheless, in parallel with the findings for 30-day mortality, the data do show some relationship between CKD an increased 1-year

mortality, in support of the published data which reports increased mortality after an acute stroke in CKD patients [203, 456, 497].

Associations with 1-year mortality in the Cox multivariable regression analysis were older age, higher disability score on admission and increased stroke severity using all methods to ascertain CKD. These replicate the 30-day mortality results of this study and support the current knowledge of factors known to influence outcomes in stroke patients [494, 495]. Haemorrhagic stroke type was found to be associated with 1-year mortality using admission SCr to ascertain CKD, again, replicating the 30-day mortality results. Anaemia was also found to be associated with 1-year mortality using all methods to ascertain CKD. This association goes further than the results for 30-day mortality, which found an association between anaemia and CKD ascertained using admission SCr, but not preadmission SCr. This is likely to reflect underpowering to detect and association between anaemia and 30-day mortality in the preadmission SCr cohort. Using admission SCr to ascertain CKD, presence of AF was also associated with 1-year mortality. This supports the known literature that AF is associated with worse outcomes, including increased disability and mortality after AIS, even after adjustment for older age [498]. The association between AF and 1-year mortality was not replicated in the preadmission SCr cohort, possibly due to underpowering.

6.5.6 'Renalism' and Stroke Treatments in CKD

I hypothesised that patients with CKD are less likely to receive treatments for stroke, including thrombolysis and IAT. In this study, CKD ascertained by any method was not found to be associated with a reduced likelihood of receiving thrombolysis or the composite treatment in either the univariable or multivariable analyses. However, presence of CKD ascertained using admission SCr and both CKD-EPI and MDRD was strongly associated with a reduced likelihood of undergoing thrombectomy in the univariable analysis.

In multivariable analyses, factors associated with undergoing thrombolysis, thrombectomy or the composite were younger age, lower disability on admission and increased stroke severity. The latter two findings are in keeping with the AHA/ASA treatment criteria for EVT in ischaemic stroke, outlined in Chapter 1, section 1.6.4 [81, 261]. The inverse association between CKD and thrombectomy did not persist in the multivariable analyses. This may be because the majority of patients had mild CKD, those undergoing thrombectomy were younger and this may have masked any relationship with CKD, or it may simply reflect the low overall number who underwent thrombectomy.

This study does not appear to show that patients with CKD were less likely to receive treatments for stroke and potential explanations for this are discussed above. Furthermore, it is not clear whether 'renalism' took place prior to the point of inclusion in the study. For example, patients with CKD may have been less likely to be referred to hospital or diagnosed

with a stroke due to other complicating factors, including dialysis treatment itself [23]. CKD likely represents a 'marker' of comorbidity and frailty, which may feasibly influence clinical decisions about whether to offer thrombolysis or thrombectomy in acute stroke. This discrimination has been well demonstrated in the setting of interventional treatments for cardiovascular disease [461-465]. The finding that younger patients with a lower disability score on admission were more likely to receive stroke treatments in this study adds support to this concept.

6.5.7 Limitations

In this arm of the study, a large number of factors associated with CKD were explored, including demographic associations, stroke treatments and 30-day and 1-year mortality. Unfortunately, due to missing data, other outcomes could not be analysed. For example, a significant proportion of outcome data at the point of discharge was unrecorded within SSNAP, including mRS score and discharge destination and I was therefore unable to investigate whether these outcomes differed between patients with and without CKD. Furthermore, SSNAP data on outcomes 6 months post discharge, including use of antiplatelets, anticoagulants and statins, were only available in 15% of cases. Therefore, the hypothesis that patients with CKD might be less likely to receive secondary preventative treatments for stroke (as has been demonstrated to be the case after an MI), unfortunately could not be tested in this study. Other 6-month outcomes of interest including presence of persistent AF, re-stroke, MI or other illness events requiring hospitalisation were also largely missing from SSNAP and could not be analysed.

As discussed in Chapter 4, a significant limitation was the number of subjects in the study who had preadmission SCr values available for analysis. In this study, preadmission SCr was missing in 45% of patients. As such, admission SCr was utilised as a surrogate method and could have misclassified some cases of CKD. Indeed, associations with the variables under investigation were not always consistently reproducible across all methods of ascertaining CKD. Here, the reduced power of the preadmission SCr group (compared with the admission SCr group) to detect associations with a particular outcome of interest may have influenced the results. Despite these limitations, the proportion of patients with missing preadmission SCr in this study is comparable to the literature [314] and the use of admission SCr values, which are widely available, remains a common 'surrogate' measure of baseline renal function.

A further limitation is that a significant proportion of patients in this study arm had milder CKD, which may have reduced the ability to detect an association with clinically important outcomes, including mortality in the regression models. Furthermore, CKD was entered into the models as a categorical rather than a continuous variable, which may have influenced the results. In addition, relatively low numbers of patients underwent thrombolysis and thrombectomy. As the study was not primarily powered to detect outcomes associated with these treatments, it is possible this may have affected the results and the ability to detect the possible presence of 'renalism'. As applies to all arms of this study, subjects were recruited from a single centre and further large, multi-centre studies using a similar methodology are needed to confirm the results.

6.6 Conclusions

CKD is common in stroke patients, with a prevalence of approximately 35-40%, depending on the method used to calculate eGFR. In this study, CKD was associated with older age, female sex, diabetes, CHF and AF, in agreement with known risk factors for CKD. CKD was associated with higher crude 30-day and 1-year mortality. In the univariable regression analyses, CKD was associated with increased mortality and a reduced likelihood of undergoing thrombectomy, but these associations did not persist after multiple adjustments. This study fills a gap in the UK data and generally supports the existing literature that patients with CKD have worse outcomes after a stroke. Good quality RCTs of stroke treatments which include CKD and ESRD populations are urgently needed to accurately determine risk versus benefit and help improve disability and survival in this population.

CHAPTER 7 IMAGING IN ACUTE STROKE AND RELATIONSHIP TO CHRONIC KIDNEY DISEASE

7. 1 Introduction

Radiological imaging is the first cornerstone of investigation for patients hospitalised with suspected acute stroke [81]. There are three stroke subtypes: the most common being AIS, followed by ICH and SAH, with an incidence of 87%, 10% and 3% respectively [499]. Stroke management requires rapid clinical and radiological assessment to avoid established irreversible ischaemia and loss of functioning brain tissue [500]. Non-contrast CT (NCCT) is in most cases, the most cost-effective imaging modality due to its widespread availability, rapidity and ability to detect ICH, a finding which would preclude administration of antiplatelet agents and/ or thrombolysis [501]. A number of considerations are required in determining which imaging modalities and stroke therapies have an acceptable risk-benefit profile for patients with established CKD, which are herein discussed further.

7.1.1 Thrombolysis and endovascular treatments

The benchmark National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial in 1995 demonstrated a reduction in disability at three months following thrombolysis with no significant difference in mortality compared with placebo [35]. Since then, thrombolysis with rt-PA has been widely used in clinical practice throughout the developed world. Acknowledging that the major limitation of systemic thrombolysis is poor rates of early reperfusion in LVOs [502], there have been significant developments in EVT over the last five

years [23]. In 2015, IAT via mechanical clot retrieval with second-generation stent retriever devices were shown to offer unequivocal therapeutic benefit in numerous large RCTs [253-257]. Subsequent to these results, the AHA/ASA incorporated EVT recommendations into their guidelines, which are outlined in Chapter 1, section 1.6.4 [81, 261]. Importantly, two of the landmark RCTs investigating the benefit of IAT excluded patients with CKD [256, 257] and of the other three, only one reported baseline renal function of participants in the supplementary material to the main manuscript [255]. The latest AHA/ASA guidelines advise proceeding to CTA prior to knowledge of admission SCr in those patients meeting the criteria for EVT who have no known history of CKD [81].

7.1.2 Contrast Induced Nephropathy

Contrast induced nephropathy (CIN) is defined as a 25% relative increase in SCr or 44 µmol/L (0.5 mg/dL) absolute increase from baseline within 72 hours of exposure to contrast and in the absence of an alternative causative factor [503]. Evidence from observational studies of AIS suggests that the incidence of CIN in patients undergoing contrast-enhanced brain imaging is low (approximately 3%), CTA gives additional clinical benefit and waiting for blood results to become available may result in delays in thrombectomy [504-507] [508]. Historically and presently, CKD has been identified as an important risk factor for CIN [280, 509]. The incidence of CIN in patients undergoing primary percutaneous coronary intervention is reported to be up to 20% [363, 510] with multiple studies demonstrating an adverse relationship to short and long-term outcomes [511, 512]. There is therefore a possibility that there may be unidentified confounding factors relating to the comparably low risk in stroke patients undergoing contrast

exposure. Brain perfusion imaging with CT or MRI is now recommended to aid selection of patients for mechanical thrombectomy presenting between 6 and 24 hours after symptom onset [81], following two RCTs which showed improved functional outcome at 90 days [513, 514]. With the advent of such imaging techniques and the potential to increase the scope of thrombectomy treatment, quantifying the risk of CIN in this patient group becomes all the more important. Several scoring systems have been developed for patients undergoing coronary angiography [515, 516], the most widely used of which is the Mehran scoring system [517]. However, to date, no such risk score has been developed for patients undergoing other contrast-enhanced procedures or indeed, stroke patients receiving vascular intervention.

7.1.3 Bleeding Risk in Acute Ischaemic Stroke

HT of ischaemic brain tissue results from disruption of the blood-brain-barrier and autoregulatory mechanisms following reduction in Na^+-K^+-ATPase activity and a proinflammatory response at the cellular level, the degree of which appears to be dependent on the duration of ischaemia [518-520]. It is a common phenomenon, with two studies using prospective serial radiological imaging reporting an incidence of over 40% [521, 522]. HT is a spectrum which can be further subdivided into haemorrhagic infarction and parenchymatous haematoma and classified radiographically [523]. However, it is recognised that radiographic features do not always correlate clinically and both clinical and radiological evidence of HT have been combined to improve prediction of clinical outcome [524, 525]. One of the main limitations of stroke treatments is the subsequent risk of bleeding. IV thrombolysis with a fibrinolytic agent such as rt-PA can increase the risk of both intracranial and systemic bleeding,

with reported rates of asymptomatic and symptomatic HT varying between 4.5 to 39.6% and 2.4 to 8.8% respectively [238, 526-530]. IAT may predispose to ICH as a result of reperfusion injury to ischaemic brain tissue, direct trauma to an intracranial artery (through dissection or perforation) or IA thrombolysis of the offending clot [531]. Reassuringly, recent thrombectomy trials report no significant difference between HT post-procedure compared with thrombolysis as standard care [253-259, 513, 514]. Pharmacological therapy with antiplatelets and anticoagulants also increase the risk of bleeding [532, 533]. However, in the setting of secondary prevention, the benefits of aspirin far outweigh the risk of bleeding [534]. Anticoagulation with warfarin or NOACs is recommended for patients with prior stroke with AF [535]. Evaluating the risk of stroke recurrence versus bleeding events is a challenge that has led to the use of scoring systems to guide clinical practice [153, 155, 156]. As discussed in Chapter 1, section 1.4.3, a complex coagulopathy exists in advanced CKD, with patients exhibiting both an increased bleeding risk [143, 536, 537] whilst paradoxically also being at increased risk of thrombotic events [536]. This represents a therapeutic dilemma which is particularly relevant in the treatment of cardiovascular disease and stroke. To date, there is a distinct lack of data on the risk of bleeding post thrombolysis or EVT in patients with CKD.

7.1.4 Vascular Calcification in Chronic Kidney Disease

CKD is a recognised risk factor for CVD [480, 538]. Patients with CKD are subject to the same traditional risk factors as the general population, including hypertension, hypercholesterolaemia and smoking [23]. Yet CKD itself has an independent relationship with CVD [480, 539]. Novel risk factors such as increased circulation of inflammatory cytokines and

prothrombotic factors [540, 541], uraemia, oxidative stress [542] and anaemia [543] all lead to endothelial dysfunction and contribute to increased cardiovascular risk in CKD. A further risk factor unique to CKD is the presence of CKD-MBD (see Chapter 1, section 1.4.5), which promotes arterial medial calcification (known as Mönckeberg's sclerosis), leading to increased arterial stiffness and elevated systolic BP [544]. Patients with CKD are also prone to the more typical form of atherosclerotic disease, which causes intimal arterial calcification [545]. This interplay of factors contributes to a heightened incidence of CVD in CKD, with adjusted cardiovascular mortality 10-30 times higher in ESRD compared with the general population [546]. To date, very few studies have reported intracranial artery calcification in CKD [189].

7.2 Aims and Hypotheses

This chapter comprises the imaging study arm, in which I sought to determine the following:

1) radiological contrast exposure and the risk of AKI;
2) the influence of CKD on HT of an infarct, or post-thrombolysis or thrombectomy bleeding;
3) the influence of CKD on carotid atherosclerotic disease;
4) the influence of CKD on intracranial vascular calcification.

The hypotheses for the imaging arm of this study are displayed in Table 7-1.

Table 7-1. Hypotheses for imaging arm of study.

Parameter	Hypothesis
Radiological contrast exposure	Patients undergoing contrast-enhanced imaging are at increased risk of developing AKI
Bleeding complications	
Haemorrhagic transformation of stroke	Patients with CKD are at increased risk of haemorrhagic transformation following AIS
Post thrombolysis or thrombectomy bleeding	Patients with CKD are at increased risk of bleeding post thrombolysis or intra-arterial thrombectomy in AIS
Atheromatous disease	
Carotid artery atheroma	Patients with CKD have a greater degree of carotid artery atheromatous disease compared with patients without CKD
Intracranial vascular calcification	
Vascular calcification	Patients with CKD have a greater degree of vascular calcification compared with patients without CKD

Abbreviations: AIS, acute ischaemic stroke; AKI, acute kidney injury; CKD, chronic kidney disease.

7.3. Methods

A full description of the study methods is given in Chapter 3.

For the imaging arm, all individual imaging reports were read manually. Reports were generated by a radiologist and written in prose with no standardised format, therefore it was necessary to extract and code the data using a rule-based electronic proforma in order to convert it into an analysable format. The proforma was designed in collaboration with a stroke physician and radiologist and developed in Microsoft Access (see Appendix 3). In cases of multiple or complex findings, or where there was ambiguity, clarification was sought with a neuroradiologist. Once extraction and coding was complete, the data was exported to Microsoft Excel and 10% of cases were randomly selected and manual crosschecked using PICS and IMPAX (outlined in Chapter 3, sections 3.7.2.1 and 3.7.2.3) to ensure accuracy prior to linkage to the full dataset. Unfortunately, during the data linkage process itself, imaging data from approximately half the cohort was transcribed incorrectly or missing, requiring further substantial crosschecking or in some cases repeat collection of data from scratch. Due to the nature and complexity of the imaging reports and additional unforeseen issues with data linkage, the data collection process was done manually, which was very time consuming.

Statistical analysis was performed as outlined in Chapter 3, section 3.13 using SPSS 25.0 (SPSS Inc., Chicago IL, USA).

7.4 Results

A total of 1357 patients were included in the imaging arm of the study (as for the CKD arm- see Chapter 6, section 6.4).

7.4.1 Baseline imaging data

Baseline data for the study subjects is shown in Table 7-2. Data is grouped according to the presence or absence of CKD, ascertained using first SCr on admission and the CKD-EPI formula to calculate eGFR.

Of the total cohort, 97.0% (n=1316) underwent a CT head scan, with the majority of patients having a single scan (71.9%, n=976), 33.1% (n=449) had a diffusion weighted imaging (DWI) MRI head scan (hereafter referred to as MRI) and 15.3% (n=207) had a CTA. Just over half of the cohort (50.7%, n=688) had USS Dopplers of the carotid arteries. 88.2% (n=1197) of the total cohort had an AIS. Of these, 14.0% (n=167) underwent thrombolysis and 4.1% (n=49) underwent IAT.

The raw baseline data showed that a higher proportion of patients with CKD underwent a CT head overall (98.7% vs. 96.1%, P<0.001). A lower proportion of patients with CKD had an MRI scan (20.9% vs. 39.3%, P<0.001) or CTA (8.1% vs. 18.8%, P<0.001). Fewer patients with CKD also had carotid USS Dopplers, although this did not reach statistical significance (44.2% vs 54.0%, P=0.18).

In the CKD group, a higher proportion of patients had an AIS compared with the non-CKD group (89.9% vs. 87.4%, P=0.006). Fewer patients with CKD underwent thrombectomy (1.7% vs. 5.3%, P<0.001) or a composite of thrombolysis and thrombectomy (13.4% vs. 16.0%, P=0.05). Fewer patients with CKD also underwent thrombolysis, although this did not reach statistical significance (12.7% vs. 14.6%, P=0.16).

Table 7-2. Imaging modality according to the presence or absence of CKD, as defined by an eGFR <60 mL/min/1.73m^2 calculated using first SCr on admission and CKD-EPI formula (n=1357).

Imaging Modality	**CKD (n=455)**	**No CKD (n=902)**	**P value**
CT scan	449 (98.7%)	867 (96.1%)	<0.001
No of CT scans			
1	339 (75.5%)	637 (73.5%)	
2	89 (19.8%)	180 (20.7%)	
3	17 (3.8%)	35 (4.0%)	
≥4	4 (0.9%)	15 (1.7%)	0.03
1	339 (75.5%)	637 (73.5%)	
≥2	110 (24.5%)	230 (26.5%)	0.11
MRI scan	95 (20.9%)	354 (39.3%)	<0.001
CTA	37 (8.1%)	170 (18.8%)	<0.001
Carotid USS Doppler	201 (44.2%)	487 (54.0%)	0.18
Ischaemic stroke	409 (89.9%)	788 (87.4%)	0.006

Treatment Modality	CKD (n=455)	No CKD (n=902)	P value
Thrombolysis	52 (12.7%*)	115 (14.6%*)	0.16
Thrombectomy	7 (1.7%*)	42 (5.3%*)	<0.001
Thrombolysis and thrombectomy combined	55 (13.4%*)	126 (16.0%*)	0.05

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CT/A, computerised tomography/ angiography; eGFR, estimated glomerular filtration rate; MRI, magnetic resonance imaging; SCr, serum creatinine; USS, ultrasound scan.

*****Percentages who underwent thrombolysis, thrombectomy or a composite of the two treatments are calculated using the total number of patients with ischaemic stroke as the denominator.

Data are presented as frequency and percentage.

7.4.2 Radiological features of stroke

Radiological features of stroke in the study subjects are shown in Tables 7-3 to 7-6. Patients are grouped according to the presence or absence of CKD, as for Table 7-2.

7.4.2.1 Radiological Features of Stroke on CT

Results of the radiological findings of stroke on CT are displayed in Table 7-3. Data was collected on use of iodinated contrast and radiological features of stroke on CT including stroke type (infarct or haemorrhage with further classification of haemorrhage subtype), presence of 'hyperdense artery' sign as an indication of acute arterial thrombus, age of stroke (acute versus chronic), ischaemic stroke features (embolic (acute only), large vessel (chronic only), lacunar or multiple infarcts), stroke territory and presence of vascular calcification for a

maximum of 3 CTs during the index admission. For patients exceeding this number of CTs, data on the number of scans only was collected.

Of the total cohort, 71.9% (n=976) had 1 CT, 19.8% (n=269) had 2, 3.8% (n=52) had 3 and 1.4% (n=19) had 4 or more CT scans. The majority of scans were non-contrasted (94.4%, n=1225). Infarction was seen in 76.5% (n=747) on the first CT, 90.7% (n=244) on the second CT and 94.2% (n=49) on the third CT. Haemorrhage was demonstrated in 20.4% (n=199) on first CT, 39.0% (105) on second CT and 63.5% (n=33) on third CT. Primary haemorrhage was most common, comprising 72.4% of bleeds on CT 1. The proportion of HT increased with subsequent CT scans (16.1% of bleeds on CT 1, 28.6% on CT 2 and 18.2% on CT 3).

The 'hyperdense artery' sign was seen in 17.5% (n=227) of CT scans. 11.9% (n=154) of all CT scans reported showing an acute infarct. A greater proportion of infarcts were reported as chronic (42.3%, n=548). Vascular calcification was reported in 9.7% (n=126) of CT scans.

In the CKD group, fewer patients underwent a first CT scan with contrast compared with the non-CKD group (2.1% vs. 4.7%, $P<0.001$). The crude rates of contrast administration were also lower for CKD patients undergoing a second or third CT scan, however the overall numbers were low and comparisons did not reach statistical significance in the CT2 and CT3 groups.

A greater proportion of patients with CKD had an infarct on first CT scan (79.7% vs. 74.9%, P<0.001). Conversely, patients without CKD had a higher proportion of ICH on first CT (17.4% in CKD patients vs. 22.0% in non-CKD patients, P=0.01). Patients with CKD demonstrated the 'hyperdense artery' sign more frequently (21.2% vs. 17.4%, P<0.001) and had more acute embolic infarcts (3.2% vs. 1.7%, P=0.001). They also had more chronic lacunar infarcts (25.1% vs. 22.9%, P=0.02), chronic large vessel infarcts (15.3% vs. 8.5%, P<0.001) and chronic multiple infarcts (15.6% vs. 10.5%, P<0.001). The CKD cohort also demonstrated increased crude rates of vascular calcification compared with the non-CKD cohort (13.0% vs. 10.0%, P=0.001). There were no significant differences observed in stroke territory or haemorrhage subtype between CKD and non-CKD groups on first CT scan.

Table 7-3. Radiological characteristics of stroke on CT according to the presence or absence of CKD, as defined by an eGFR <60 mL/min/1.73m^2 calculated using first SCr on admission and CKD-EPI formula (n=1357).

Radiology feature/ characteristic	**CKD (n=455)**	**No CKD (n=902)**	**P value**
CT 1	339 (75.5%)	637 (73.5%)	
Contrasted	7 (2.1%)	30 (4.7%)	
Non-contrasted	332 (97.9%)	607 (95.3%)	<0.001
Infarct	270 (79.7%)	477 (74.9%)	<0.001
Haemorrhage	59 (17.4%)	140 (22.0%)	0.01
Primary	42 (71.2%)	102 (72.9%)	
Haemorrhagic transformation	8 (13.6%)	24 (17.1%)	
Other/ not specified	9 (15.3%)	14 (10.0%)	0.91

Radiology feature/ characteristic	CKD (n=455)	No CKD (n=902)	P value
CT1			
Hyperdense artery	72 (21.2%)	111 (17.4%)	<0.001
Acute			
Embolic infarct	11 (3.2%)	11 (1.7%)	0.001
Lacunar infarct	9 (2.7%)	17 (2.7%)	0.81
Multiple infarcts	22 (6.5%)	47 (7.4%)	0.55
Chronic			
Lacunar infarct	85 (25.1%)	146 (22.9%)	0.02
Large vessel infarct	52 (15.3%)	54 (8.5%)	<0.001
Multiple infarcts	53 (15.6%)	67 (10.5%)	<0.001
Territory			
Anterior	183 (54.0%)	359 (56.4%)	
Posterior	35 (10.3%)	72 (11.3%)	
Multi-territory	5 (1.5%)	20 (3.1%)	
Venous sinus thrombosis	2 (0.6%)	0 (0%)	0.61
Calcification	44 (13.0%)	63 (10.0%)	0.001
CT2	89 (19.8%)	180 (20.8%)	
Contrasted	9 (10.1%)	21 (11.7%)	
Non-contrasted	80 (89.9%)	159 (88.3%)	0.41
Infarct	86 (96.6%)	158 (87.8%)	0.21
Haemorrhage	24 (27.0%)	81 (51.3%)	<0.001
Primary	10 (41.7%)	43 (53.1%)	
Haemorrhagic transformation	4 (16.7%)	26 (32.1%)	
Other/ not specified	10 (41.7%)	12 (14.8%)	0.89
Hyperdense artery	17 (19.1%)	19 (10.6%)	<0.001

Radiology feature/ characteristic	CKD (n=455)	No CKD (n=902)	P value
CT2			
Acute			
Embolic infarct	2 (2.3%)	3 (1.7%)	0.54
Lacunar infarct	2 (2.3%)	3 (1.7%)	0.54
Multiple infarcts	6 (6.7%)	13 (7.2%)	0.72
Chronic			
Lacunar infarct	22 (24.7%)	16 (8.9%)	<0.001
Large vessel infarct	4 (4.5%)	17 (9.4%)	0.004
Multiple infarcts	8 (9.0%)	9 (5.0%)	0.02
Territory			
Anterior	70 (78.7%)	155 (86.1%)	
Posterior	8 (9.0%)	25 (16.1%)	
Multi-territory	2 (2.3%)	6 (3.3%)	
Not specified	1 (1.1%)	0 (0%)	0.03
Calcification	9 (10.1%)	8 (4.4%)	0.001
CT3	17 (3.8%)	35 (4.0%)	
Contrasted	1 (5.9%)	4 (11.4%)	
Non-contrasted	16 (94.1%)	31 (88.6%)	0.20
Infarct	14 (82.4%)	35 (100%)	0.13
Haemorrhage	6 (42.9%)	27 (77.1%)	<0.001
Primary	3 (50.0%)	15 (55.6%)	
Haemorrhagic transformation	0 (0%)	6 (22.2%)	
Other/ not specified	3 (50.0%)	6 (22.2%)	0.28
Hyperdense artery	4 (28.6%)	4 (11.4%)	0.05

Radiology feature/ characteristic	CKD (n=455)	No CKD (n=902)	P value
CT3			
Acute			
Embolic infarct	1 (5.9%)	1 (2.9%)	0.32
Lacunar infarct	0 (0%)	0 (0%)	-
Multiple infarcts	1 (5.9%)	5 (14.3%)	0.08
Chronic			
Lacunar infarct	3 (17.7%)	5 (14.3%)	0.63
Large vessel infarct	2 (11.8%)	2 (5.7%)	0.16
Multiple infarcts	1 (5.9%)	2 (5.7%)	0.99
Territory			
Anterior	4 (23.5%)	17 (48.6%)	
Posterior	0 (0%)	3 (8.6%)	
Multi-territory	1 (5.9%)	1 (2.9%)	0.02
Calcification	2 (11.8%)	0 (0%)	<0.001

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CT, computerised tomography; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Data are presented as frequency and percentage.

7.4.2.2 Radiological Features of Stroke on MRI

Results of the radiological findings of stroke on MRI are displayed in Table 7-4.

Of the total cohort, 33.1% (n=449) underwent an MRI head scan. 81.3% (n=365) of MRI scans demonstrated an infarct and 16.9% (n=76) an ICH. 43.4% (n=33) of haemorrhages were described as primary and 44.7% (n=34) as HT. The 'hyperdense artery' sign was seen in 2.7%

(n=12) of MRI scans. 23.4% (n=105) of acute infarcts were reported as embolic, 31.0% (n=139) as multiple and 3.6% (n=16) as lacunar infarcts. 51.0% (n=229) of strokes were in the anterior circulation territory.

Patients with CKD had fewer MRI scans (20.9% vs. 39.2%, P<0.001) and a higher proportion of infarcts (87.4% vs. 79.7%, P<0.001). Conversely, patients without CKD had a higher proportion of ICH (14.7% in CKD patients vs. 17.5% in non-CKD patients, P<0.001). There was no difference in the rates of 'hyperdense artery' sign observed between groups.

Patients with CKD had an increased proportion of acute multiple infarcts on MRI (33.7% vs. 30.2%, P<0.001). They also had a higher proportion of acute lacunar infarcts, but this did not reach statistical significance (5.3% vs. 3.1%, P=0.70). The CKD cohort had a greater proportion of all types of chronic infarct on MRI (chronic lacunar infarcts 15.8% vs. 11.9%, P=0.02, chronic large vessel infarcts 12.6% vs. 4.8%, P=0.07 and chronic multiple infarcts 22.1% vs. 5.9%, P<0.001).

Table 7-4. Radiological characteristics of stroke on MRI according to the presence or absence of CKD, as defined by an eGFR <60 mL/min/1.73m^2 calculated using first SCr on admission and CKD-EPI formula (n=1357).

Radiology feature/ characteristic	CKD (n=455)	No CKD (n=902)	P value
MRI	95 (20.9%)	354 (39.2%)	<0.001
Infarct	83 (87.4%)	282 (79.7%)	<0.001
Haemorrhage	14 (14.7%)	62 (17.5%)	<0.001
Primary	4 (28.6%)	29 (46.8%)	
Haemorrhagic transformation	7 (50.0%)	27 (43.6%)	
Other/ not specified	3 (21.4%)	6 (9.7%)	0.14
Hyperdense artery	3 (3.2%)	9 (2.5%)	0.24
Acute			
Embolic infarct	20 (21.1%)	85 (24.0%)	<0.001
Lacunar infarct	5 (5.3%)	11 (3.1%)	0.70
Multiple infarcts	32 (33.7%)	107 (30.2%)	<0.001
Chronic			
Lacunar infarct	15 (15.8%)	42 (11.9%)	0.02
Large vessel infarct	12 (12.6%)	17 (4.8%)	0.07
Multiple infarcts	21 (22.1%)	21 (5.9%)	<0.001
Territory			
Anterior	45 (47.4%)	184 (52.0%)	
Posterior	30 (31.6%)	95 (26.8%)	
Multi-territory	5 (5.3%)	28 (7.9%)	
Watershed	3 (3.2%)	1 (0.3%)	<0.001

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; MRI, magnetic resonance imaging; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Data are presented as frequency and percentage.

7.4.2.3 CT Angiography Findings

Results of the radiological findings on CTA are displayed in Table 7-5.

CTA reports were analysed for presence of acute occlusive intraluminal thrombus responsible for stroke symptoms and other abnormalities, including intracranial vessel atheroma with graded degree of stenosis, presence of calcification within atheromatous plaques, calcification within the arterial smooth muscle wall (i.e. intramural) and presence of an AVM (arteriovenous malformation).

Of the total cohort, 15.3% (n=207) underwent a CTA. Acute thrombus was demonstrated in 28.0% (n=58) of CTAs and calcified plaques in 5.3% (n=11). Other abnormalities were seen in 8.7% (n=18). Of these, there were 11 cases of atheromatous plaque, 2 aneurysms (1 MCA and 1 posterior communicating artery (PCOM)), 1 AVM, 2 haemorrhages, 1 ICA dissection and 1 chronic occluding thrombus at the right carotid bifurcation.

A significantly lower proportion of patients with CKD underwent a CTA (8.1% vs. 18.8%, P<0.001). Patients with CKD had a higher proportion of acute thrombus on CTA (32.4% vs. 27.1%, P<0.001). CKD patients also had more calcified plaques demonstrated on CTA, but the overall numbers were small and this did not reach statistical significance (8.1% (n=3) vs. 4.7% (n=8), P=0.40). Amongst the CTAs showing calcified plaques, there was 1 case of mural wall calcification; this patient did not have a concurrent diagnosis of CKD.

Other CTA abnormalities were seen more frequently in the non-CKD cohort (5.4% (n=2) in CKD patients vs. 9.4% (n=16) in non-CKD patients, P<0.001). Both cases in the CKD cohort were due to atheromatous plaque.

Table 7-5. Radiological findings on CTA according to the presence or absence of CKD, as defined by an eGFR <60 mL/min/1.73m^2 calculated using first SCr on admission and CKD-EPI formula (n=1357).

Radiology feature/ characteristic	CKD (n=455)	No CKD (n=902)	P value
CTA	37 (8.1%)	170 (18.8%)	<0.001
Thrombus	12 (32.4%)	46 (27.1%)	<0.001
Calcified plaque	3 (8.1%)	8 (4.7%)	0.40
Other abnormality	2 (5.4%)	16 (9.4%)	<0.001

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; CTA, computerised tomography angiography; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.

Data are presented as frequency and percentage.

7.4.2.4 Carotid Ultrasound Doppler Findings

Results of the carotid USS Doppler findings are displayed in Table 7-6.

Carotid artery ultrasound Doppler reports were examined for atherosclerosis affecting the ICA, external carotid arteries (ECA) and common carotid arteries (CCA). Data was collected on

the presence of atherosclerotic plaques and degree of stenosis, as determined by the NASCET criteria [390, 391]. Any further description of atheromatous plaque composition was collected, as well as data on intramural calcification, where reported.

A total of 50.7% (n=688) of subjects underwent carotid Doppler scans. 12 of these were categorised as atypical reports (5 scans reported blood flow velocities alone and a further 7 examined only ICA velocities). Fewer patients in the CKD group had carotid Dopplers, although the result was not statistically significant (44.2% vs. 54.0%, P=0.18).

Of the total cohort, 56.7% had no evidence of ICA atherosclerotic disease. A total of 7.0% had ≥50% stenosis or total occlusion. 21.7% of all USS Dopplers described ICA plaque characteristics. The most common plaque description was calcified plaque (8.4%).

Fewer patients with CKD had a complete absence of ICA stenosis (49.0% vs. 59.9%, P=0.05). Patients with CKD also had a higher proportion of ≥50% stenosis or total occlusion than patients without CKD (8.0% vs. 6.7%, P<0.001). A greater proportion of patients with CKD were observed to have calcified ICA plaques, however these results did not reach statistical significance (10.4% vs. 7.6%, P=0.99). There was only 1 report of intramural ICA calcification; this was found in the left ICA of a patient with CKD.

The results for CCA and ECA disease are also displayed in Table 7-6. These are not discussed further as very low numbers of patients were found to have significant stenosis or a description of plaque characteristics. Furthermore, only ICA disease is generally considered clinically significant in stroke since it represents a potential treatment target. ICA atherosclerotic disease is considered further in section 7.4.6.

Table 7-6. Radiological characteristics of carotid artery USS Dopplers according to the presence or absence of CKD, as defined by an eGFR <60 mL/min/1.73m^2 calculated using first SCr on admission and CKD-EPI formula (n=1357).

Radiology feature/ characteristic	CKD (n=455)	No CKD (n=902)	P value
USS Doppler	201 (44.2%)	487 (54.0%)	0.18
Internal carotid artery			
No stenosis	197 (49.0%*)	583 (59.9%*)	
<10%	0 (0%*)	0 (0%*)	
10 to 19%	80 (19.9%*)	154 (15.8%*)	
20 to 29%	45 (11.2%*)	92 (9.4%*)	
30 to 39%	24 (6.0%*)	40 (4.1%*)	
40 to 49%	6 (1.5%*)	12 (1.2%*)	
50 to 59%	3 (0.7%*)	12 (1.2%*)	
60 to 69%	1 (0.2%*)	11 (1.1%*)	
70 to 79%	9 (2.2%*)	10 (1.0%*)	
80 to 89%	5 (1.2%*)	10 (1.0%*)	
90 to 99%	3 (0.7%*)	5 (0.5%*)	
Total occlusion	11 (2.7%*)	17 (1.7%*)	
Velocity reporting only	10 (2.5%*)	14 (1.4%*)	0.049
< 50% stenosis	352 (87.6%*)	881 (90.5%*)	
≥ 50% stenosis	21 (5.2%*)	48 (4.9%*)	
Total occlusion	11 (2.7%*)	17 (1.7%*)	
Velocity reporting only	10 (2.5%*)	14 (1.4%*)	<0.001
Smooth plaque	1 (0.2%*)	1 (0.1%*)	
Calcified plaque	42 (10.4%*)	74 (7.6%*)	
Mixed plaque	9 (2.2%*)	20 (2.1%*)	
Soft plaque	6 (1.5%*)	23 (2.4%*)	
Hard plaque	17 (4.2%*)	36 (3.7%*)	
Fibrous plaque	15 (3.7%*)	22 (2.3%*)	
Intramural calcification	1 (0.2%*)	0 (0%*)	
Thrombus	2 (0.5%*)	3 (0.3%*)	
Other/ not specified	10 (2.5%*)	16 (1.6%*)	0.992

Radiology feature/ characteristic	CKD (n=455)	No CKD (n=902)	P value
Common carotid artery			
No stenosis	291 (72.4%*)	749 (76.9%*)	
< 50% stenosis	94 (23.4%*)	196 (20.1%*)	
≥ 50% stenosis	2 (0.5%*)	7 (0.7%*)	
Total occlusion	0 (0%*)	1 (0.1%*)	
Velocity reporting only	8 (2.0%*)	7 (0.7%*)	0.052
Smooth plaque	2 (0.5%*)	3 (0.3%*)	
Calcified plaque	6 (1.5%*)	18 (1.8%*)	
Mixed plaque	1 (0.2%*)	0 (0%*)	
Intramural calcification	1 (0.2%*)	0 (0%*)	
Thrombus	1 (0.2%*)	1 (0.1%*)	
Other/ not specified	7 (1.7%*)	4 (0.4%*)	0.002
External carotid artery			
No stenosis	298 (74.1%*)	816 (83.8%*)	
< 50% stenosis	65 (16.2%*)	100 (10.3%*)	
≥ 50% stenosis	17 (4.2%*)	31 (3.2%*)	
Total occlusion	2 (0.5%*)	0 (0%*)	
Velocity reporting only	10 (2.5%*)	10 (1.0%*)	<0.001
Smooth plaque	0 (0%*)	0 (0%*)	
Calcified plaque	5 (1.2%*)	13 (1.3%*)	
Mixed plaque	0 (0%*)	0 (0%*)	
Intramural calcification	2 (0.5%*)	0 (0%*)	
Thrombus	1 (0.2%*)	1 (0.1%*)	
Other/ not specified	2 (0.5%*)	0 (0%*)	0.001

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; USS, ultrasound scan.

*Percentages with stenosis or plaque characteristics are calculated using the total number of patients who underwent Carotid Dopplers multiplied by 2 as the denominator (i.e. 402 and 974). This was done for the purposes of combining data from both right and left carotid vessels.

Data are presented as frequency and percentage.

7.4.3 Risk of Acute Kidney Injury following Exposure to Radiological Contrast

The risk of AKI following exposure to radiological contrast was investigated using Group C, the core cohort. This group has previously been defined in the AKI arm of the study in (see Chapter 4, section 4.4), along with exploration of factors associated with AKI including thrombolysis (section 4.4.4).

Exposure to radiological contrast was defined as undergoing any of the following: contrast-enhanced CT or CTA or thrombectomy. A binary logistic regression model was constructed to assess the relationship between contrast exposure and the risk of AKI, with results expressed as OR with 95% CI.

Associations between contrast exposure and AKI for Group C are presented in Table 7-7. In both univariable and multivariable analyses, there was no association between contrast exposure and risk of developing AKI. Similar results were found for Groups A and B (see Appendix 13 and 14 respectively).

Table 7-7. Logistic regression analysis of the relationship between radiological contrast exposure and the development of AKI^{pre} in Group C (n=443).

	Univariable Analysis		**Multivariable Analysis***	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
1 CT	1.086 (0.226-5.213)	0.917	-	-
≥2 CT	0.909 (0.301-2.745)	0.865	-	-
CTA	0.862 (0.440-1.689)	0.666	-	-
Thrombectomy	0.387 (0.049-3.039)	0.367	-	-
CT and CTA	0.939 (0.514-1.716)	0.838	-	-
All contrast exposure	0.963 (0.533-1.737)	0.899	-	-

*Adjusted for age, ethnicity, presence of CKD, CHF and anaemia (all significant variables in a binomial regression analysis of factors associated with AKI^{pre} in Group C, outlined in Chapter 4, section 4.4.4.1.1) in a forward conditional model.

Abbreviations: AKI^{pre}, acute kidney injury diagnosed using preadmission serum creatinine; CHF, congestive heart failure; CKD, chronic kidney disease; CT/A, computerised tomography/ angiography; OR, odds ratio.

7.4.4 Factors associated with Haemorrhagic Transformation or Post-Thrombolysis or Thrombectomy Bleeding in Acute Ischaemic Stroke

Of the total cohort (n=1357), 88.2% (n=1197) had AIS and were eligible for inclusion in the HT analysis. A total of 6.4% (n=77) patients had evidence of HT or post-thrombolysis or thrombectomy bleeding on CT or MRI imaging modalities. There were only 3 cases of bleeding post stroke treatments, of which 1 underwent thrombolysis alone and 2 underwent both thrombolysis and thrombectomy. Patients with CKD had lower overall crude rates of bleeding (4.40% vs. 7.49%, P<0.001 using the CKD-EPI equation to ascertain CKD and 4.19% vs. 7.30%, P<0.001 using the MDRD equation).

A binary logistic regression model was constructed to assess the relationship between putative risk factors for bleeding and HT or post-thrombolysis or thrombectomy bleeding. All factors associated with bleeding in the univariable analysis were included in the multivariable model. A P value threshold of <0.15 was selected, similar to previous multivariable regression analyses. Where variables were closely related, for example CKD ascertained using different methods, or thrombolysis and the composite of both thrombolysis and thrombectomy, separate models were created and only one variable was entered at a time. Due to the large number of significant factors in the univariable analysis, five multivariable models were created to avoid overfitting.

CKD was defined as an eGFR <60 mL/min/1.73m^2 and calculated using preadmission SCr and first SCr on admission and both CKD-EPI and MDRD formulae, as outlined in Chapter 3, section

3.15 and Chapter 6, section 6.4.2. Preadmission SCr data was available in 54.6% (n=654) of the total cohort.

Factors associated with HT or post-thrombolysis or thrombectomy bleeding in AIS in the univariable analysis are shown in Table 7-8. The strongest associations with bleeding were thrombolysis (OR 3.54, 95% CI 2.14-5.87; P<0.001), thrombectomy (OR 3.05, 95% CI 1.38-6.77; P=0.006) and a composite of thrombolysis and thrombectomy (OR 3.18, 95% CI 1.92-5.25; P<0.001). Increased stroke severity (OR 1.06, 95% CI 1.03-1.09; P<0.001) and higher INR (OR 1.50, 95% CI 0.95-2.39; P=0.09) were also associated with bleeding. In addition, younger age, male sex, absence of CKD ascertained using admission SCr, absence of diabetes, hypertension and previous stroke/ TIA, lower disability on admission and lower systolic BP were associated with bleeding in the univariable analysis.

Table 7-8. Univariable logistic regression analysis of factors associated with haemorrhagic transformation or post-thrombolysis or thrombectomy bleeding in acute ischaemic stroke (n=1197).

	Univariable Analysis	
	OR (95% CI)	**P value**
Age	0.981 (0.967-0.994)	0.006
Female sex	0.694 (0.433-1.114)	0.130
Black ethnicity	1.408 (0.491-4.033)	0.524
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI) (n=654)	1.114 (0.560-2.218)	0.758
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD) (n=654)	1.193 (0.589-2.417)	0.624
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI) (n=1197)	0.569 (0.331-0.978)	0.041
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD) (n=1197)	0.556 (0.307-1.006)	0.052
Diabetes	0.456 (0.225-0.928)	0.030
Hypertension	0.632 (0.393-1.016)	0.058
AF	1.008 (0.563-1.806)	0.979
Previous stroke/ TIA	0.314 (0.149-0.662)	0.002

	Univariable Analysis	
	OR (95% CI)	**P value**
CHF	0.969 (0.294-3.193)	0.959
Thrombolysis	3.543 (2.140-5.867)	<0.001
Thrombectomy	3.054 (1.378-6.768)	0.006
Thrombolysis and thrombectomy combined	3.177 (1.924-5.248)	<0.001
mRS on admission (as continuous variable)	0.728 (0.559-0.949)	0.019
NIHSS score on admission (as continuous variable)	1.058 (1.030-1.087)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.022 (0.596-1.753)	0.937
INR (baseline INR as categorical variable) (0 for INR <1.1, 1 for >1.1)	1.502 (0.946-2.386)	0.085
Systolic blood pressure (baseline value as categorical variable) (0 for <120 mmHg, 1 for >120 mmHg)	0.680 (0.426-1.087)	0.107
Diastolic blood pressure (baseline value as categorical variable) (0 for <80 mmHg, 1 for >80 mmHg)	0.810 (0.498-1.318)	0.396

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Factors associated with HT or post-thrombolysis or thrombectomy bleeding in AIS in the multivariable analyses are shown in Tables 7-9 to 7-13.

Model 1 (Table 7-9) is adjusted for all significant baseline comorbidities in the univariable analysis, including age, sex, presence of CKD ascertained using admission SCr, diabetes, hypertension and previous stroke/ TIA. In this model, younger age (OR 0.98, 95% CI 0.97-1.00; P=0.01) and absence of previous stroke/ TIA (OR 0.33, 95% CI 0.16-0.70; P=0.004) were associated with bleeding.

Table 7-9. Multivariable logistic regression analysis of factors associated with haemorrhagic transformation or post-thrombolysis or thrombectomy bleeding in acute ischaemic stroke (n=1197).

Model 1: *adjusted for age, sex, presence of CKD, diabetes, hypertension and previous stroke/ TIA.

	Univariable Analysis		**Multivariable Analysis***	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	0.981 (0.967-0.994)	0.006	0.982 (0.969-0.996)	0.012
Female sex	0.694 (0.433-1.114)	0.130	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and CKD-EPI)**	0.569 (0.331-0.978)	0.041	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and MDRD)**	0.556 (0.307-1.006)	0.052	-	-
Diabetes	0.456 (0.225-0.928)	0.030	-	-
Hypertension	0.632 (0.393-1.016)	0.058	-	-
Previous stroke/ TIA	0.314 (0.149-0.662)	0.002	0.330 (0.157-0.696)	0.004

**Related variables were entered into the multivariable models separately.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Model 2 (Table 7-10) is adjusted for all significant baseline comorbidities as for Model 1, and thrombolysis, thrombectomy or a composite of thrombolysis and thrombectomy and stroke severity. In this model, undergoing thrombolysis (OR 2.28, 95% CI 1.29-4.01; P=0.005) or a composite of thrombolysis and thrombectomy (OR 1.96, 95% CI 1.11-3.48; P=0.02) and increased stroke severity (OR 1.05, 95% CI 1.02-1.09; P=0.002) were associated with an increased risk of bleeding. Younger age (OR 0.98, 95% CI 0.97-1.00; P=0.008) and absence of previous stroke/ TIA (OR 0.32, 95% CI 0.15-0.67; P=0.003) were also associated with bleeding. Neither undergoing thrombectomy alone nor the presence or absence of CKD were associated with bleeding in the multivariable model.

Table 7-10. Multivariable logistic regression analysis of factors associated with haemorrhagic transformation or post-thrombolysis or thrombectomy bleeding in acute ischaemic stroke (n=1197).

Model 2: *adjusted for age, sex, presence of CKD, diabetes, hypertension, previous stroke/ TIA, thrombolysis, thrombectomy or a composite of thrombolysis and thrombectomy and stroke severity.

	Univariable Analysis		**Multivariable Analysis***	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	0.981 (0.967-0.994)	0.006	0.981 (0.966-0.995)	0.008
Female sex	0.694 (0.433-1.114)	0.130	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and CKD-EPI)**	0.569 (0.331-0.978)	0.041	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and MDRD)**	0.556 (0.307-1.006)	0.052	-	-
Diabetes	0.456 (0.225-0.928)	0.030	-	-
Hypertension	0.632 (0.393-1.016)	0.058	-	-
Previous stroke/ TIA	0.314 (0.149-0.662)	0.002	0.316 (0.149-0.673)	0.003
Thrombolysis**	3.543 (2.140-5.867)	<0.001	2.275 (1.289-4.013)	0.005
Thrombectomy**	3.054 (1.378-6.768)	0.006	-	-
Thrombolysis and thrombectomy combined**	3.177 (1.924-5.248)	<0.001	1.963 (1.107-3.482)	0.021
NIHSS score on admission (as continuous variable)	1.058 (1.030-1.087)	<0.001	1.053 (1.019-1.087)	0.002

**Related variables were entered into the multivariable models separately.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Model 3 (Table 7-11) is adjusted for all significant baseline comorbidities as for Model 1, as well as disability score on admission and stroke severity. In this model, increased stroke severity (OR 1.07, 95% CI 1.04-1.10; P<0.001), younger age (OR 0.98, 95% CI 0.96-0.99; P=0.002) and absence of previous stroke/ TIA (OR 0.31, 95% CI 0.14-0.65; P=0.002) were associated with an increased risk of bleeding. Neither the presence nor absence of CKD were associated with bleeding in the multivariable model.

Table 7-11. Multivariable logistic regression analysis of factors associated with haemorrhagic transformation or post-thrombolysis or thrombectomy bleeding in acute ischaemic stroke (n=1197).

Model 3: *adjusted for age, sex, presence of CKD, diabetes, hypertension, previous stroke/ TIA, disability score on admission and stroke severity.

	Univariable Analysis		**Multivariable Analysis***	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	0.981 (0.967-0.994)	0.006	0.978 (0.964-0.991)	0.002
Female sex	0.694 (0.433-1.114)	0.130	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and CKD-EPI)**	0.569 (0.331-0.978)	0.041	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and MDRD)**	0.556 (0.307-1.006)	0.052	-	-
Diabetes	0.456 (0.225-0.928)	0.030	-	-
Hypertension	0.632 (0.393-1.016)	0.058	-	-
Previous stroke/ TIA	0.314 (0.149-0.662)	0.002	0.307 (0.144-0.651)	0.002
mRS on admission (as continuous variable)	0.728 (0.559-0.949)	0.019	-	-
NIHSS score on admission (as continuous variable)	1.058 (1.030-1.087)	<0.001	1.071 (1.041-1.102)	<0.001

**Related variables were entered into the multivariable models separately.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Model 4 (Table 7-12) is adjusted for age, sex, presence of CKD, previous stroke/ TIA (all significant baseline comorbidities included in Model 1 except diabetes and hypertension), thrombolysis, thrombectomy or a composite of thrombolysis and thrombectomy, stroke severity and INR. In this model, thrombolysis (OR 2.60, 95% CI 1.44-4.69; P=0.002) or a composite of thrombolysis and thrombectomy (OR 2.25, 95% CI 1.24-4.07; P=0.007), higher INR (OR 1.71, 95% CI 1.04-2.80; P=0.04) and increased stroke severity (OR 1.05, 95% CI 1.02-1.09; P=0.004) were associated with an increased risk of bleeding. Younger age (OR 0.98, 95% CI 0.97-1.00; P=0.03) and absence of previous stroke/ TIA (OR 0.25, 95% CI 0.11-0.59; P=0.002) were also associated with bleeding. Neither undergoing thrombectomy alone nor the presence or absence of CKD were associated with bleeding in this model.

Table 7-12. Multivariable logistic regression analysis of factors associated with haemorrhagic transformation or post-thrombolysis or thrombectomy bleeding in acute ischaemic stroke (n=1197).

Model 4: *adjusted for age, sex, presence of CKD, previous stroke/ TIA, thrombolysis, thrombectomy or a composite of thrombolysis and thrombectomy, stroke severity and INR.

	Univariable Analysis		**Multivariable Analysis***	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	0.981 (0.967-0.994)	0.006	0.982 (0.967-0.998)	0.025
Female sex	0.694 (0.433-1.114)	0.130	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and CKD-EPI)**	0.569 (0.331-0.978)	0.041	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and MDRD)**	0.556 (0.307-1.006)	0.052	-	-
Previous stroke/ TIA	0.314 (0.149-0.662)	0.002	0.251 (0.107-0.592)	0.002
Thrombolysis**	3.543 (2.140-5.867)	<0.001	2.600 (1.440-4.694)	0.002
Thrombectomy**	3.054 (1.378-6.768)	0.006	-	-
Thrombolysis and thrombectomy combined**	3.177 (1.924-5.248)	<0.001	2.249 (1.243-4.070)	0.007
NIHSS score on admission (as continuous variable)	1.058 (1.030-1.087)	<0.001	1.050 (1.016-1.086)	0.004
INR (baseline INR as categorical variable) (0 for INR <1.1, 1 for >1.1)	1.502 (0.946-2.386)	0.085	1.705 (1.038-2.803)	0.035

**Related variables were entered into the multivariable models separately.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; MDRD, Modification of Diet in Renal Disease; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Model 5 (Table 7-13) is adjusted for age, sex, presence of CKD, previous stroke/ TIA (all significant baseline comorbidities included in Model 1 except diabetes and hypertension), thrombolysis, thrombectomy or a composite of thrombolysis and thrombectomy, stroke severity and systolic blood pressure.

In this model, undergoing thrombolysis (OR 2.46, 95% CI 1.37-4.43; P=0.003) or a composite of thrombolysis and thrombectomy (OR 2.17, 95% CI 1.20-3.92; P=0.01) and increased stroke severity (OR 1.06, 95% CI 1.02-1.09; P=0.002) were associated with an increased risk of bleeding. Younger age (OR 0.98, 95% CI 0.97-1.00; P=0.04) and absence of previous stroke/ TIA (OR 0.25, 95% CI 0.11-0.60; P=0.002) were also associated with bleeding. Neither undergoing thrombectomy alone nor the presence or absence of CKD were associated with bleeding in this model.

Table 7-13. Multivariable logistic regression analysis of factors associated with haemorrhagic transformation or post-thrombolysis or thrombectomy bleeding in acute ischaemic stroke (n=1197).

Model 5: *adjusted for age, sex, presence of CKD, previous stroke/ TIA, thrombolysis, thrombectomy or a composite of thrombolysis and thrombectomy, stroke severity and systolic blood pressure.

	Univariable Analysis		**Multivariable Analysis***	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	0.981 (0.967-0.994)	0.006	0.984 (0.969-0.999)	0.042
Female sex	0.694 (0.433-1.114)	0.130	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and CKD-EPI)**	0.569 (0.331-0.978)	0.041	-	-
CKD (eGFR <60mL/min/1.73m^2 using admission SCr and MDRD)**	0.556 (0.307-1.006)	0.052	-	-
Previous stroke/ TIA	0.314 (0.149-0.662)	0.002	0.254 (0.108-0.599)	0.002
Thrombolysis**	3.543 (2.140-5.867)	<0.001	2.461 (1.367-4.430)	0.003
Thrombectomy**	3.054 (1.378-6.768)	0.006	-	-
Thrombolysis and thrombectomy combined**	3.177 (1.924-5.248)	<0.001	2.169 (1.201-3.920)	0.010
NIHSS score on admission (as continuous variable)	1.058 (1.030-1.087)	<0.001	1.055 (1.020-1.091)	0.002
Systolic blood pressure (baseline value as categorical variable) (0 for <120 mmHg, 1 for >120 mmHg)	0.680 (0.426-1.087)	0.107	-	-

**Related variables were entered into the multivariable models separately.

Abbreviations: CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; INR, international normalised ratio; MDRD, Modification of Diet in Renal Disease; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

7.4.5 Factors associated with Vascular Calcification

All cases of vascular calcification were determined by screening through imaging reports. Descriptions of calcification affecting the cerebral, carotid or vertebral arteries on CT, CTA or USS imaging modalities met the definition and were included as cases of vascular calcification. Of 1357 subjects, a total of 14.4% (n=196) had evidence of vascular calcification. 59.2% (n=116) of calcification was described on plain CT. Patients with CKD had higher overall crude rates of vascular calcification (16.5% vs. 13.4%, P=0.008 for CKD-EPI and 17.1% vs. 13.4%, P=0.002 for MDRD).

A binary logistic regression model was constructed to assess the relationship between putative risk factors for vascular calcification. Preadmission SCr data was available in 54.3% (n=737) of the total cohort.

Factors associated with vascular calcification are shown in Table 7-14. In the univariable analysis, age (OR 1.03, 95% CI 1.01-1.04; P<0.001) and presence of diabetes (1.47, 95% CI 1.04-2.08; P=0.03) were the strongest risk factors for vascular calcification. In addition, presence of CKD ascertained using admission SCr (OR 1.27, 95% CI 0.93-1.74; P=0.13 for CKD-EPI and OR 1.33, 95% CI 0.96-1.84; P=0.09 for MDRD), AF (OR 1.35, 95% CI 0.94-1.94, P=0.11), previous stroke/ TIA (OR 1.30, 95% CI 0.93-1.82; P=0.12), female sex (OR 1.25, 95% CI 0.93-1.69; P=0.145) and lower diastolic blood pressure (OR 0.79, 95% CI 0.58-1.09; P=0.15) were also associated with calcification in the univariable analyses.

In the multivariable analysis, only age (OR 1.03, 95% CI 1.01-1.04; P<0.001) and diabetes (OR 1.44, 95% CI 1.02-2.04; P=0.04) were associated with calcification. Presence of CKD was no longer associated with calcification after multiple adjustments.

Table 7-14. Logistic regression analysis of factors associated with vascular calcification (n=1357).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.026 (1.015-1.038)	<0.001	1.026 (1.014-1.037)	<0.001
Female sex	1.252 (0.925-1.693)	0.145	-	-
Black ethnicity	0.740 (0.312-1.752)	0.493	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI) (n=737)	1.130 (0.750-1.700)	0.559	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD) (n=737)	1.096 (0.718-1.674)	0.670	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)** (n=1357)	1.274 (0.932-1.742)	0.130	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)** (n=1357)	1.329 (0.959-1.844)	0.088	-	-
Diabetes	1.469 (1.040-2.076)	0.029	1.439 (1.015-2.040)	0.041
Hypertension	1.126 (0.833-1.523)	0.440	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
AF	1.349 (0.937-1.942)	0.107	-	-
Previous stroke/ TIA	1.301 (0.932-1.818)	0.122	-	-
CHF	1.561 (0.791-3.082)	0.199	-	-
mRS pre-admission (as continuous variable)	0.999 (0.883-1.131)	0.993	-	-
NIHSS score on admission (as continuous variable)	0.992 (0.971-1.013)	0.443	-	-
Systolic blood pressure (baseline value as categorical variable) (0 for <120 mmHg, 1 for >120 mmHg)	1.122 (0.815-1.545)	0.481	-	-
Diastolic blood pressure (baseline value as categorical variable) (0 for <80 mmHg, 1 for >80 mmHg)	0.793 (0.578-1.088)	0.150	-	-

*Adjusted for age, sex, presence of CKD ascertained using admission SCr, diabetes, AF, previous stroke/ TIA and diastolic blood pressure in a forward conditional model.

**Related variables were entered into the multivariable models separately.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine, TIA, transient ischaemic attack.

7.4.6 Factors associated with Internal Carotid Artery Disease on Ultrasound

For the purposes of this analysis, atherosclerotic disease of the ICAs only was investigated, since ICA disease is an aetiological factor in anterior circulation AIS and represents a treatment target in select patients with significant carotid artery stenosis [33].

A total of 50.7% (n=688) of the total cohort (n=1357) underwent carotid Dopplers, of which 40.0% (n=275) had evidence of ICA atherosclerosis. Patients with CKD had higher overall crude rates of carotid disease (49.2% vs. 37.5%, P<0.001 for CKD-EPI and 51.6% vs. 37.8%, P=0.002 for MDRD).

A binary logistic regression model was constructed to assess the relationship between putative risk factors for atherosclerosis leading to ICA disease. Preadmission SCr data was available in 52.1% (n=357) and baseline serum cholesterol in 59.6% (n=408) of the total cohort who underwent carotid USS Dopplers.

Factors associated with ICA atherosclerotic disease are shown in Table 7-15. In the univariable analysis, age (OR 1.04, 95% CI 1.03-1.05; P<0.001), CKD ascertained using all 4 methods (OR 1.55, 95% CI 1.01-2.38; P=0.045 for preadmission SCr and CKD-EPI and OR 1.62, 95% CI 1.16-2.25; P=0.005 for admission SCr and CKD-EPI) and higher disability score on admission (OR 1.24, 95% CI 1.06-1.45; P=0.008) were most strongly associated with ICA disease. Presence of diabetes (OR 1.35, 95% CI 0.95-1.93, P=0.10) and AF (OR 1.53, 95% CI 1.00-2.36, P=0.05) were

also associated with ICA disease in the univariable analysis. Black ethnicity was inversely associated with presence of ICA atherosclerosis (OR 0.35, 95% CI 0.15-0.80; P=0.01).

In the multivariable analysis, only age (OR 1.02, 95% CI 1.01-1.04; P=0.004) remained significantly associated with ICA disease. When CKD ascertained using admission SCr was entered into the multivariable model, Black ethnicity was inversely associated with ICA disease (OR 0.36, 95% CI 0.15-0.86; P=0.02).

Table 7-15. Logistic regression analysis of factors associated with carotid artery atherosclerotic disease (n=688).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.038 (1.025-1.050)	<0.001	1.024 (1.008-1.041)	0.004
Female sex	1.195 (0.881-1.620)	0.252	-	-
Black ethnicity	0.345 (0.148-0.801)	0.013	0.363 (0.153-0.859)**	0.021
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI) (n=357)***	1.552 (1.011-2.383)	0.045	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD) (n=357)***	1.737 (1.103-2.734)	0.017	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI) (n=685)***	1.615 (1.158-2.254)	0.005	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD) (n=685)***	1.757 (1.227-2.516)	0.002	-	-
Diabetes	1.352 (0.948-1.928)	0.096		
Hypertension	1.134 (0.838-1.535)	0.415	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
AF	1.534 (0.995-2.364)	0.052	-	-
Previous stroke/ TIA	1.147 (0.803-1.638)	0.452	-	-
CHF	1.458 (0.572-3.720)	0.430	-	-
mRS pre-admission (as continuous variable)	1.240 (1.057-1.454)	0.008	-	-
NIHSS score on admission (as continuous variable)	1.006 (0.980-1.032)	0.671	-	-
Systolic blood pressure (baseline value as categorical variable) (0 for <120 mmHg, 1 for >120 mmHg)	0.937 (0.672-1.307)	0.700	-	-
Diastolic blood pressure (baseline value as categorical variable) (0 for <80 mmHg, 1 for >80 mmHg)	0.880 (0.626-1.238)	0.464	-	-
Cholesterol (baseline value as categorical variable) (0 for <5.2 mmol/L, 1 for >5.2 mmol/L)	1.204 (0.788-1.839)	0.390	-	-

*Adjusted for age, black ethnicity, presence of CKD, diabetes, AF and disability score on admission in a forward conditional model.

**In a forward conditional model with CKD ascertained using admission SCr.

***Related variables were entered into the multivariable models separately.

Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

7.5 Discussion

This study has shown that in a cohort of patients hospitalised with acute stroke, the vast majority (97.0%) underwent CT brain imaging in accordance with current stroke guidelines [81]. 33.1% of the cohort underwent an MRI head scan and 50.7% had carotid USS Dopplers performed. There were significant baseline differences between patients with and without CKD in the raw baseline data, with the CKD group exhibiting higher rates of AIS and undergoing fewer MRI, CTA and USS. Notably, patients with CKD also had lower crude rates of thrombolysis or IAT. I will now discuss these findings in more detail, starting with the baseline data and then in relation to my hypotheses outlined in section 7.2.

7.5.1 Baseline Imaging Data

7.5.1.1 CT

In this study, similar numbers of patients with and without CKD underwent a first CT head scan (75.5% vs. 73.5%). This can be explained by current stroke guidelines which advocate rapid CT imaging (ideally within 20 minutes of presentation for patients potentially eligible for thrombolysis or thrombectomy) [81], which may well be prior to blood results becoming available. The majority of CT brain scans were non-contrasted (94.4%), however patients in the CKD group undergoing a first CT were observed to undergo fewer contrast-enhanced CTs than the non-CKD group (2.1% vs. 4.7%, $P<0.001$ for CT1). The lower rates of contrast administration observed in the CKD group, even before the admitting blood results are known, could suggest other apparent clinical characteristics in these patients (for example, a

perception of increased 'frailty', age or comorbidities), which might influence clinical decisions regarding contrast administration.

Patients with CKD were observed to have more infarcts on CT (79.7% vs. 74.9%, P<0.001 for CT 1) and less haemorrhagic strokes (17.4% vs. 22.0%, P=0.01). CKD and AIS in particular, share a number of risk factors including increasing age, hypertension, diabetes and AF [23], which may account for the study findings. The CKD group also exhibited higher rates of the 'hyperdense artery' sign across first, second and third CT scans (21.2% vs. 17.4%, P<0.001 for CT 1). While this may simply be explained by the increased proportion of AIS seen in this group, this observation may represent an increased clot burden due to a procoagulant state, which manifests early on in CKD. This is characterised by a complex interplay of abnormalities of all components of Virchow's triad [115, 547], which is discussed in more detail in Chapter 1, section 1.4.3. There is also evidence that the actual physical compact structure and function of fibrin clot is altered in CKD [548, 549]. Undas *et al.* showed that HD patients produced less porous clots, initiated fibrin protofibril formation more quickly, had increased overall fibre thickness and increased clot lysis time compared with controls [549]. More recently, Lau *et al.* demonstrated similar findings in non-dialysis CKD patients (CKD stage 4) [550]. Schuett *et al.* showed that a denser clot structure is independently associated with all-cause and cardiovascular mortality in a cohort of 171 HD patients (HR 2.55, 95% CI 1.23-5.33; P=0.01 and HR 3.20, 95% CI 1.35-7.60; P<0.01 respectively) [551]. Alterations in fibrin clot properties including compact structure and impaired fibrinolysis are known to correlate with CVD [552, 553] and may also feasibly explain the increased risk of stroke in CKD. To date there are no

published studies investigating the relationship between clot structure and function and stroke in CKD populations.

CKD patients had increased numbers of all chronic infarcts reported on first CT, including lacunar infarcts. This finding supports the known association between CKD and small vessel (lacunar) strokes, thought to be due to the haemodynamic similarities between the vascular beds within the kidney and the brain, which are both susceptible to traditional atherosclerotic risk factors [554]. Furthermore, the increased proportion of chronic lacunes found in CKD patients in this study may represent 'silent strokes', which are known to occur more commonly in patients with CKD [555-559].

7.5.1.2 MRI

In contrast with the high frequency of CT in this study, only one third of the total cohort underwent a DWI MRI brain scan. A higher proportion of acute infarcts were reported and subtyped on MRI than on CT (57.9% vs. 11.9%), whereas the opposite was true for chronic infarcts (28.5% vs. 42.3%). These findings are consistent with the superior sensitivity of DWI MRI to detect hyperacute brain ischaemia by utilising apparent diffusion coefficient (ADC) mapping [560].

Patients with CKD underwent fewer MRIs than patients without CKD (20.9% vs 39.2%, $P<0.001$). The reasons for this are not clear, but this may be another example of therapeutic

nihilism or more specifically, 'renalism'. Alternatively, it may simply be that patients in the CKD group had more 'positive' findings on plain CT, therefore negating any additional diagnostic benefit of MRI. One hypothesis for the increased detection rate of infarction on CT in CKD patients could be the delayed presentation of stroke in patients with CKD and particularly ESRD, since acute neurological symptoms may be masked or mimicked by the high burden of paraesthesiae and weakness seen in these patients [23, 561] and in contrast to early infarction, subacute infarction is more likely to be detected on CT [81].

7.5.1.3 CTA

Only 15.3% of the total cohort underwent a CTA. This corresponds with the specific indications for use of this modality in acute stroke, for further characterisation of LVOs potentially amenable to thrombectomy [23, 255], accurate quantification of the degree of carotid artery stenosis and anatomical characteristics of the occluding plaque or thrombus [562, 563].

There was a significant difference in the number of patients undergoing a CTA with and without CKD (8.1% vs 18.8%, P<0.001). Due to the selective indications for this modality, these results may simply indicate that by chance, more patients in the non-CKD group met the clinical criteria for undergoing CTA. Alternatively, this could be another example of 'renalism' manifesting in this study. The perceived risk of AKI to older, frailer patients with a high prevalence of CKD, who are further debilitated by a stroke, could be a key factor in deciding whether to proceed with radiological contrast administration. Interestingly, more patients

with CKD had evidence of an acute thrombus demonstrated on CTA. This is consistent with the increased rates of 'hyperdense artery' sign observed on all CT scans in the CKD cohort and supports the increased clot burden in CKD demonstrated in previous studies, as discussed in section 7.5.1.1.

7.5.1.4 Carotid USS Dopplers

Just over half of the total cohort (50.7%) underwent USS carotid Dopplers, in which the majority (56.7%) had no disease and only 7.0% had ≥50% ICA stenosis or total occlusion. Fewer patients in the CKD group underwent carotid Dopplers, although this did not reach statistical significance. The CKD cohort had a lower proportion of complete absence of ICA disease and a higher proportion of ≥50% stenosis or total occlusion. Since patients with CKD have higher rates of cardiovascular disease, it would be reasonable to postulate that they also have higher rates of carotid artery disease (see section 7.2). However, a factor of particular relevance here is the absence of data on cigarette smoking, since smoking status was not routinely collected in EHR utilised in this study. Given that smoking is a known risk factor for atherosclerotic disease [564, 565] and AIS [33], this may have introduced significant confounding in the data. In future work, incorporating data on smoking status will allow further examination of the influence of both cigarette smoking and CKD on the development of carotid atherosclerosis, which to date, has been explored in only a handful of studies [566-568].

The CKD group had more calcified ICA plaques on USS Doppler, however the overall numbers were low and did not reach statistical significance. Nevertheless, the trend supports what we know about advanced vascular calcification in CKD [569, 570]. There was only 1 report of unilateral intramural ICA calcification and this was found in a patient with CKD. Calcification was the most common description of carotid ICA plaques in both the CKD and non-CKD cohort. This corresponds with the older age of this study cohort, which is known to be a strong risk factor for vascular calcification [571].

7.5.2 Risk of Acute Kidney Injury following Contrast Exposure

I hypothesised that patients undergoing contrast-enhanced imaging are at increased risk of developing AKI. However, this study did not show any association between contrast exposure and AKI in the regression analyses. This may be because the overall number of patients undergoing contrast-enhanced CT, CTA or thrombectomy in this study was too small to detect any association (20.6%, n=280). Alternatively, the relationship between contrast administration and the development of AKI may be weaker than historically perceived. Multiple studies have demonstrated an increased risk of AKI with contrast exposure in a variety of medical conditions [369, 572, 573], though with an apparent predominance of populations undergoing cardiac intervention [363, 510-512]. However, a recent systematic review by Aycock *et al*. comprising 28 studies and 107,335 patients reported no association between contrast-enhanced CT and AKI (OR 0.94, 95% CI 0.83-1.07; P<0.001), nor other clinically significant outcomes including the need for RRT (OR 0.83, 95% CI 0.59-1.16; P=0.24) and increased mortality (OR 1.00, 95% CI 0.73-1.36; P=0.10) [574]. In patients with acute

stroke, the majority of studies have used ICD-coding to diagnose AKI and few have investigated the risk of AKI following contrast exposure [370]. Subsequently, a large case-control study of 2299 stroke patients published in 2017 demonstrated an overall AKI rate of 1.3% and no association between use of contrast-enhanced brain imaging and the development of AKI ascertained using SCr values (OR 1.13, 95% CI 0.42-3.70; P=0.69) [508]. Shortly afterwards, a systematic review incorporating 14 studies and 6708 AIS patients undergoing CTA or CTP reported an overall AKI incidence of 3.0% (95% CI 2.0-4.0; P=0.001; I^2 65%) and no difference in the rate of AKI between the CTA/CTP group and the NCCT group in a meta-regression analysis adjusting for baseline SCr (OR 0.34, 95% CI 0.10-1.21) [575]. Interestingly, of the 6 studies that reported AKI in patients with and without CKD, the AKI rate was lower in the CKD group (2.3% vs. 3.7%) and risk of developing AKI was similar between groups (OR 0.63, 95% CI 0.35-1.12; P>0.05), although substantial heterogeneity was observed in the meta-analysis.

These data are reassuring, and perhaps call into question whether CIN really exists as a clinical syndrome. Unlike earlier studies [576, 577], both systematic reviews incorporated studies which used NCCT control groups and are therefore more likely to have accounted for other patient risk factors when attributing AKI to contrast exposure. However, as all data was observational, there was no randomisation to contrast-enhanced CT or NCCT groups, thus leading to inherent selection bias, for example, based on clinical indication for contrast-enhanced CT or renal function at the point of admission. Recognising the ethical challenges of conducting an RCT purely to ascertain the risk of CIN, the pooled results of observational

studies are, to date, the best available evidence we have for the risk of CIN in patients undergoing contrast-enhanced imaging.

Another worthy discussion point is that none of the patients included in these systematic reviews [574, 575] underwent contrast-enhanced procedures, which may impart a greater degree of technical complexity and utilise higher volumes of contrast. As such, it may not be appropriate to extrapolate these results to a different population who may be more clinically unstable and have additional risk factors for AKI. Only a handful of published studies have reported data on the risk of AKI associated with interventional stroke treatments thus far, including three case series of AIS patients undergoing contrast-enhanced CT and EVT [578-580] and a recently published retrospective analysis of 1098 patients receiving CTA/CTP and mechanical thrombectomy [581], with all reporting low AKI rates (ranging from 1.5% to 5.8%).

The results of my study show no association between contrast exposure (in the form of contrast-enhanced CT, CTA or thrombectomy) and the development of AKI after multiple adjustments, providing additional data that the risk of AKI in stroke patients undergoing contrast-enhanced CT and thrombectomy appears to be low. However, there remains a distinct lack of data in relation to stroke patients undergoing interventional treatments, and further research involving other centres is required to accurately quantify the risk of AKI, so that best use of evidence-based treatments can be applied without the anxiety of causing undue harm to patients.

7.5.3 Haemorrhagic Transformation

6.4% (n=77) of AIS patients had either HT or post-thrombolysis or thrombectomy bleeding. Amongst these, there were only 3 cases of post-thrombolysis or thrombectomy bleeding and therefore no separate analysis of bleeding post-stroke treatments could be conducted. Nonetheless, the crude rate of all bleeding events observed in this study corresponds with a bleeding rate of approximately 6% post-thrombolysis reported in a meta-analysis of open-label studies using rt-PA in non-selected patient populations [582].

I hypothesised that patients with CKD have an increased risk of HT following cerebral infarction, and an increased risk of bleeding post-thrombolysis or thrombectomy. There is good evidence that patients with advanced CKD have an increased risk of bleeding (discussed in Chapter 1, section 1.4.3 and this Chapter, section 7.1.3). This is at odds with a co-existing thrombogenic tendency, which poses a therapeutic conundrum relating to treatments for cardiovascular disease and stroke. Bos *et al*. showed that declining renal function was independently associated with an increased risk of haemorrhagic stroke in the Rotterdam Study (HR 4.10, 95% CI, 1.25-13.42 for lowest versus highest quartile of eGFR) [583]. In addition, a study of ESRD patients on dialysis demonstrated a greater than ten-fold increase in ICH compared to the general population [584]. The increased frequency of cerebral microbleeds observed in patients with CKD may also contribute to the increased risk of ICH [585].

Despite this compelling evidence, my data showed that patients with CKD had lower overall crude rates of bleeding and regression analyses demonstrated no association between the presence of CKD and bleeding. In fact, absence of CKD (ascertained using first SCr on admission) was associated with bleeding in the univariable analysis. This may be because patients with CKD in this cohort simply did not have an increased risk of bleeding. Another potential explanation, however, is the occurrence of selection bias in patients undergoing imaging to detect bleeding, possibly as a result of 'renalism'. For example, we have seen from the raw data that the CKD group had lower proportions of thrombolysis or thrombectomy. Lower numbers of CKD patients also underwent MRI, CTA and USS Dopplers. This suggests that in this group, not all cases of HT may have been picked up, since it is not always detected on imaging undertaken at the point of admission. This bias is unlikely to have affected those patients who underwent thrombolysis however, since a follow-up CT within 24 hours is recommended, precisely to rule out HT [81].

A number of other reverse associations with bleeding were demonstrated in the multivariable analyses, including younger age, absence of previous stroke/ TIA and lower disability score on admission. Similar to the absence of CKD, these associations may be due to the reduced likelihood of older, more comorbid patients undergoing stroke treatments or imaging which might detect HT.

Thrombolysis, thrombectomy or a composite of the two treatments were strongly associated with bleeding in the univariable analysis. In all multivariable models, both thrombolysis and

the composite remained strong associations, however thrombectomy alone was not associated with bleeding. It is widely known that thrombolysis increases the risk of HT and the risk increases with more severe stroke, which correlates with the size of the infarct core [586, 587]. Thrombectomy also increases the risk of bleeding, as discussed in section 7.1.3 [531]. In this study, the lack of association between thrombectomy and bleeding is likely due to the low number of thrombectomy cases (n=49).

NIHSS score has been shown to be a strong predictor of HT in the literature, since it reflects the size and severity of cerebral infarction [588]. In support of this, our study showed that increased stroke severity was independently associated with bleeding, after adjustment for stroke treatments (section 7.4.4, Models 2, 4 and 5). Higher INR was also associated with HT in the multivariable analysis (section 7.4.4, Model 4). This is in keeping with the known increased risk of ICH in the context of an elevated INR, with one study reporting a two-fold increase in the risk of ICH per 1 unit increase in INR in patients anticoagulated with warfarin [589]. Unfortunately, in this study, data on anticoagulant and antiplatelet medications at baseline was only recorded for AF cases (18.7% of the total cohort) and therefore any potential susceptibility to bleeding caused by these medications could not be adjusted for in the analyses.

7.5.4 Calcification

A higher proportion of patients with CKD had vascular calcification on CT, CTA or USS, in keeping with my hypothesis. Vascular calcification can occur as part of the normal aging process [571], however other disease states, including diabetes and CKD are known to accelerate the process [545, 590, 591]. In keeping with the literature, my data showed that older age and presence of diabetes were associated with intracranial calcification in the multivariable analyses. Although CKD ascertained using admission SCr was associated with calcification in univariable analyses, this association did not persist after multiple adjustments. Given the wide body of evidence of increased vascular calcification in patients with CKD [544, 591, 592], the lack of association in this study may potentially be explained by the relatively low numbers since it was not primarily powered to detect associations with vascular calcification. Furthermore, a high proportion of CKD in the study cohort was stage 3 (85.3%). Given the very strong association between age and vascular calcification in the literature [571], it seems likely that any weaker associations (such as mild to moderate CKD) were invariably trumped by the presence of age in the multivariable models.

7.5.5 Internal Carotid Artery Atherosclerotic Disease

Just over half the cohort underwent carotid USS Dopplers, of which 40.0% had evidence of atherosclerotic disease. Fewer patients with CKD had carotid Dopplers, although the difference between groups was not significant. In keeping with my hypothesis, patients with CKD had higher overall crude rates of ICA disease (49.2% vs. 37.5%, $P<0.001$).

Older age was associated with ICA disease in the multivariable analysis, in keeping with the known pathophysiology and risk factors for atherosclerosis [593, 594] and carotid artery disease [595]. Presence of CKD ascertained using both preadmission and admission SCr was associated with ICA disease in the univariable analysis, however this association did not persist after multiple adjustments. As discussed in section 7.5.1.4, since patients with CKD have higher rates of CVD and AIS, it is reasonable to hypothesise that they might also have increased rates of carotid artery disease. In keeping with this, some studies have demonstrated higher rates of carotid atherosclerosis in CKD patients [568, 596]. The lack of association between CKD and carotid disease here may be as a result of the low proportion of clinically significant atheromatous disease (only 7.0% of the total cohort and 8.0% of the CKD cohort had ≥50% stenosis or total occlusion), and the fact that this study was not powered to detect associations with carotid disease. In addition, the majority of CKD was mild and this may further explain the weak association. A limitation mentioned previously is the absence of data on cigarette smoking, an important risk factor for both the development of carotid disease [597]and plaque progression [598]. This may have introduced confounding since I was unable to measure, or indeed adjust for, this variable in my analyses.

7.5.6 Limitations

One of the main limitations of the imaging arm of this study was the lack of standardisation in radiology reporting. There are existing guidelines which give recommendations on necessary components to include [599, 600] and the Radiological Society of North America (RSNA) have developed more than 200 reporting templates, including CT and MRI brain imaging [601, 602].

However, due to substantial variation in complexity of both imaging modality and findings, there is no universally agreed format for standardised reporting [603]. As such, the reporting of relevant positive and negative clinical findings is left to the discretion of the reporting clinician. Since radiology reporting was not standardised, imaging data collection was extremely time-consuming due to the length, complexity and overall number of prose reports, each of which required manual interpretation. In order to simulate 'standardised' reporting, a rule-based proforma was developed to reorganise the data into a structured format for statistical analysis. Designing the proforma was a challenge in itself as large amounts of complex information had to be radically simplified. All work in the imaging arm was undertaken by one individual (myself) and despite all efforts to maintain accuracy by systematic cross-checking, there is the potential for errors, particularly in the case of longer, more complex or ambiguous reports. In addition, attempts to validate images for a particular finding of interest, for example, vascular calcification, were not performed due to time constraints and this may have led to positive findings going undetected.

In addition, a number of other factors could have affected the reporting of images. The clinical history provided by the requestor is considered by the radiologist when reporting the scan and may influence the impression formed. Furthermore, when reviewing first and subsequent reports for the same modality (usually CT), consecutive reports often only reported on new findings with no mention of any change in existing findings, which may have influenced the results. The limitations of different imaging modalities should also be considered. For example, plain CT on admission may not have detected a hyperacute infarct and a patient may

not have gone on to have subsequent scans for a number of reasons- the neurological presentation may have been unequivocal such that further imaging was not warranted, or the patient may have been too unwell or died. In addition, as a tertiary referral centre, QEHB receives inter-hospital transfers from other areas for thrombectomy. In this cohort, a number of patients were also transferred with malignant MCA infarction requiring neurosurgery. In cases of inter-hospital transfer, as the primary imaging was performed in another hospital, reports were unavailable and these patients were categorised as not undergoing a CT (though the overall number was small (3%)).

The subjective nature of reporting and other factors described in the paragraphs above, are likely to have influenced the results, although all reasonable attempts were made to adjust for residual confounding in the regression models. Another limitation is the absence of some key demographic data in the dataset. Unfortunately, information on smoking status was not available from SSNAP and recorded only sporadically in PICS. In addition, baseline medication information, namely antiplatelets and anticoagulants was only recorded for patients with AF (comprising 18.7% of the total cohort) in SSNAP. Since these factors could not be adjusted for in the analyses, there is the potential for confounding. This may be of particular relevance to the regression analyses for HT (in the case of medications), and carotid artery disease (in the case of smoking status).

Furthermore, low numbers of patients were observed to have vascular calcification and clinically significant carotid artery disease. Since the study was not powered to detect these

findings, it is conceivable that this may have affected the results and the lack of association with CKD. As previously stated, validation of reports was not performed due to time restrictions and it is possible that abnormalities may have gone undetected. In addition, cases of post-thrombolysis or thrombectomy bleeding were unanalysable as a standalone variable due to the very small numbers (n=3) and were grouped with HT of an infarct. The bleeding analysis therefore primarily relates to the number of HT events and severely limits the ability of this study to determine the relationship between CKD and bleeding risk post stroke treatments.

7.6 Conclusions

In summary, fewer patients with CKD underwent contrast-enhanced CT, MRI or USS carotid Dopplers than patients without CKD. Overall CKD patients demonstrated a higher proportion of acute and chronic infarcts on CT and MRI, as well as higher crude rates of acute thrombus on CTA, vascular calcification and ICA atherosclerotic disease, in keeping with known pathophysiological mechanisms which contribute to the increased risk of stroke in CKD patients. CKD was not associated with HT of an infarct, vascular calcification or ICA disease after multiple adjustments, however the data are limited by small event rates (in the case of bleeding), small overall numbers of patients with calcification or clinically significant carotid atherosclerosis and the fact that the majority of CKD was mild. Contrast exposure was not associated with AKI, in support of recent studies, but further work is needed to clarify the risk of CIN in stroke patients undergoing interventional procedures. This study provides further justification for the recruitment of patients with CKD and ESRD into clinical trials to determine

the efficacy and safety of stroke treatments, including bleeding risk. Better standardisation of imaging reporting is needed, but advances in information technology and automation may greatly enhance the processing of such data in the near future.

CHAPTER 8 CONCLUSIONS AND FURTHER WORK

CKD is increasingly prevalent and associated with a higher risk of CVD and stroke [22, 68]. Both CKD and stroke have shared risk factors but additional non-traditional pathophysiological mechanisms in the setting of CKD are also implicated in the increased risk of stroke observed in this population [23]. Patients with CKD have worse outcomes after an acute stroke, with the highest rates of neurological disability and mortality seen in patients with ESRD on dialysis [453, 454]. There is a lack of RCT data on cardiovascular treatments for CKD patients, particularly those with ESRD, and the current evidence base for therapy relies mainly on subgroup analyses of studies that have recruited from the general population [375]. Treatments for stroke are no exception [23], and in this era of advancements in contrast-enhanced diagnostic imaging and interventional treatments, the risk-benefit ratio in CKD populations urgently needs to be defined.

AKI and CKD exhibit a bi-directional relationship [218]. The literature on AKI incidence and outcomes after an acute stroke is sparse, but nevertheless demonstrates that AKI is associated with poor outcomes [370]. The majority of studies to date have utilised ICD-coding to diagnose AKI, which significantly underestimates incidence [370]. AKI is a heterogeneous condition with no specific treatment and general management involves early detection, correction of hypovolaemia and sepsis and avoidance of further renal insults [280]. Despite the promising results of early studies [408, 413-415], SCr is the only routinely used biomarker to detect and diagnose AKI [417-419]. Determining ‘baseline’ SCr where preadmission SCr is missing is a

significant methodological limitation of AKI diagnosis. There is a requirement to accurately detect 'true' cases of AKI cases in order to develop precise risk-prediction models and power interventional trials in AKI. Better surrogate methods for missing preadmission SCr are needed but yet to be found.

In this thesis I describe the first UK study to systematically explore the incidence of AKI and the prevalence of CKD using SCr values in a contemporaneous cohort of patients hospitalised with acute stroke, and their influence on outcomes. I have attempted to address some of the issues highlighted above, which I will now summarise in turn.

8.1 AKI Incidence and Outcomes

In Chapters 4 and 5, I present the results of the first study to investigate the incidence of AKI and outcomes in a cohort of patients with acute stroke, using preadmission SCr as a 'gold standard' baseline, compared with 4 commonly used surrogate methods. I have shown that AKI after a stroke is common, occurring in approximately 20% of patients, depending on the method used. I have also shown that older age and the presence of comorbidities including CKD, anaemia, diabetes, CHF and AF are associated with AKI, in agreement with known risk factors for AKI [280]. Importantly, I have shown that increased stroke severity is associated with the development of AKI across all Groups, using 4 of the 5 methods to ascertain AKI (except AKI^{adm}). This adds further support to the few studies which have reported an association between stroke severity and AKI to date [370]. Patients who developed AKI also

had significantly higher 30-day and 1-year mortality after multiple adjustments, using all five methods to diagnose AKI.

Missing preadmission SCr values are a recognised problem in AKI research and in these circumstances, surrogate methods are used to avoid selection bias. However, this study showed that 4 commonly used surrogate methods to estimate 'baseline' renal function all bi-directionally misclassify AKI. In my study, first SCr on admission performed best against preadmission SCr and gave a comparable incidence of AKI, but exhibited low sensitivity, in keeping with the known limitations of the AKI^{adm} method reported in the literature. The other 3 surrogate methods for ascertaining AKI exhibited poor agreement and high misclassification rates of AKI (predominantly overclassification) and should be used with extreme caution, particularly in a population with a high prevalence of CKD, as applies to this study cohort. Acknowledging its limitations, in circumstances where all reasonable attempts to obtain a preadmission SCr have been made and these are unavailable, admission SCr would appear to be a reasonable surrogate for diagnosing AKI in a cohort of stroke patients.

Similarly, use of first SCr on admission to diagnose AKI consistently underestimated 30-day and 1-year mortality compared with preadmission SCr. In all regression analyses where AKI^{adm} and AKI^{pre} were entered into the models together, AKI^{pre} was retained, suggesting that it carries further information than that provided by AKI^{adm} alone. Similar results were demonstrated for the association between AKI^{low} and 30-day mortality, and for the association between AKI^{MDRD} and AKI^{EPI} and 1-year mortality, when AKI^{pre} was added simultaneously to

the models. Owing to the identification of more 'true' AKI cases, preadmission SCr therefore appears to trump other methods of diagnosing AKI in predicting mortality. As such, AKI^{pre} should remain the preferred method of ascertaining 'baseline' SCr to diagnose AKI in future studies. In circumstances where attempts to obtain a preadmission SCr have not been fruitful, based on closest agreement of AKI incidence, first SCr on admission appears to be the best surrogate method for mortality prediction in a cohort of stroke patients. Due to the high rates of misclassification demonstrated by lowest SCr and back-calculation methods, these are unsuitable for use in risk-prediction models applied to a stroke population with a high prevalence of CKD.

8.1.1 Future directions

As it stands, the retrospective ascertainment of a change in SCr is the only measure for diagnosing AKI in routine clinical practice. Further studies are urgently needed to find superior biomarkers of AKI which more closely correspond to 'real time' renal function and degree of injury, which might translate into improved risk prediction and earlier diagnosis. Although some biomarkers such as NGAL [604], TIMP-2 and IGFBP7 [416, 605, 606] have demonstrated potential, they are hampered by the heterogeneous syndrome of AKI which frequently requires individualisation of biomarker panels for different settings [607]. As such, a movement away from SCr towards tissue-based definitions of renal injury is now on the cards and the Kidney Precision Medicine Project has been set up using kidney biopsy specimens to create a tissue 'atlas' [608]. It is hoped that projects such as this will enhance our understanding of AKI biomarkers and through incorporation into clinical practice, facilitate the

drive towards 'personalised' medicine in the future. In the meantime, whilst SCr remains the mainstay of AKI diagnosis, there is still work to be done in determining the optimal surrogate methods of ascertaining 'baseline' renal function where preadmission SCr is missing. Going forward, recruitment of hospitalised stroke patients from other UK centres into a national study is needed to confirm the results of this single-centre study. It is hoped that the findings will facilitate the development of risk-prediction models and help inform future AKI prevention trials, with the ultimate goal of improving clinical outcomes in stroke patients who develop AKI.

8.2 Stroke Treatments and Outcomes in CKD

In Chapter 6, I present the results of the first UK study to systematically investigate the role of CKD, and how it is defined, on outcomes in the era of modern stroke treatments. I have shown that CKD is associated with older age, female sex, diabetes, CHF and AF, in keeping with known risk factors for CKD [41]. I have also shown that CKD is associated with increased 30-day and 1-year mortality in the univariable analyses. Stroke affects an already vulnerable and comorbid population and CKD confers an additive risk in this group. My data appear to support the findings of previous studies that CKD is associated with worse outcomes after an acute stroke, as well as adding to the sparsity of UK data. However, in this study, CKD was not associated with an increased risk of death after multiple adjustments. This may be explained by the high mean age of the study population (which may have trumped CKD in the regression models) and the fact that the majority of CKD was mild.

The concept of 'renalism' has been discussed extensively in this thesis. In this study, younger patients with a lower disability score on admission were more likely to receive thrombolysis or IAT, which appears to align with this concept. However, presence of CKD did not affect the likelihood of receiving stroke treatments after multiple adjustments. The number of patients who received treatments was relatively low and thus, the lack of association may have been due to underpowering. It is also not known whether 'renalism' took place before the point of inclusion in the study, for example patients with CKD or ESRD may have been less likely to be referred to hospital or diagnosed with a stroke due to diverting factors such as an increased symptom burden or being on dialysis [23].

8.2.1 Future directions

This retrospective, observational study of a cohort of stroke patients in the West Midlands has laid the foundations for further research into outcomes of CKD patients hospitalised with acute stroke. The next natural step is to conduct a multi-centre study in the UK utilising SSNAP data, linkage of SCr values through EHR and outcome data through HES. In particular, recruiting larger numbers of patients with more severe CKD may shed further light on outcomes in this group of interest in this period of advancing diagnostic imaging and stroke treatments. Despite the efforts of health professionals to improve health outcomes in CKD patients, there is still much work to be done globally. The American Society of Nephrology Research Advocacy Committee estimates that for every 500 USD spent annually on research for each cancer patient, the National Institutes of Health spent only 30 USD per CKD patient [609]. This lack of research investment is reflected in the fact that survival in patients with

ESRD has not improved significantly over the past few decades, in comparison to the substantial progress made in many medical specialities, such as Cardiology and Human Immunodeficiency Virus medicine [609]. Large RCTs are needed in this patient population in order to clarify the risk-benefit conundrum which contributes to therapeutic nihilism ('renalism') in these patients. In parallel to the field of Cardiology, there are very few or no high quality evidence-based recommendations that exist to guide the management of acute stroke in CKD and ESRD patients [23], which is further compounded by the lack of investment into therapeutic and technological advances. Part of this responsibility lies with encouraging medical industries, who have historically excluded patients with CKD, to recruit patients more representative of our aging, comorbid population into randomised trials. Better methods of risk stratifying patients with CKD, for example, the risk of bleeding, may also help clinicians decide who to treat in this era of rapidly developing therapies for stroke. It is hoped that new legislation, such as the US' CKD Improvement in Research and Treatment Act (H.R. 2644) [610], will influence a renewed drive in research in the field of Nephrology.

8.3 Imaging Findings and Relationship to CKD

In Chapter 7, I present the results of the first study to investigate the use of imaging modalities in acute stroke and their relationship to CKD. I have shown that the vast majority of patients undergo a NCCT scan, as per current stroke guidelines [81]. Patients with a diagnosis of CKD had fewer contrast-enhanced CT, CTA, MRI and USS carotid Doppler scans. CKD patients had a higher proportion of ischaemic strokes and exhibited higher crude rates of the 'hyperdense artery' sign, vascular calcification, acute thrombus and carotid atherosclerotic disease. After

multiple adjustments, no association was found between CKD and the risk of HT of an infarct, vascular calcification or carotid artery disease. However, these results were limited by the fact that small numbers of patients had advanced CKD or indeed, clinically significant carotid atherosclerosis. Although it cannot be proven from this observational study, this lack of association may also suggest the presence of 'renalism', which may have affected the utilisation of specific imaging modalities (and stroke treatments) offered to patients with CKD. Interestingly, there was no association between exposure to radiological contrast and the development of AKI after multiple adjustments. This suggests that the risk of CIN in stroke patients is low, in keeping with several published studies [504, 508, 575]. However, most data on CIN in stroke populations thus far relates to contrast-enhanced imaging, and more research is needed to clarify the risk of CIN in stroke patients undergoing interventional treatments, who may be exposed to different AKI risk factors.

Unfortunately, despite the vast amount of time spent collecting, verifying and analysing the imaging data, the results of this arm of the study are not entirely consistent and should be interpreted within the confines of the data. Such limitations lie in both reporting and data collection, as well as the intrinsic limitations of each imaging modality. However, the general trend of the data does support current knowledge about the pathophysiological mechanisms which lead to an increased risk of stroke in CKD populations, including a thrombogenic disposition and accelerated vascular calcification [23].

8.3.1 Future directions

To the best of my knowledge, this is the first study which has attempted to characterise the features of acute stroke on radiological imaging and their relationship with CKD. However, one of the main limitations was the methodology, which almost entirely relied on manual data collection. This was extremely time consuming and is impractical for use in future studies, especially where larger numbers of patients are involved. In this era of advancing technology, improved automation systems and the increasing use of artificial intelligence may in the future, make lighter work of processing tasks where interpretation of complex information is required, such as radiological imaging reports, or even the images themselves. This has already been demonstrated in the field of Ophthalmology, where automated retinal imaging analysis systems have been developed to detect diabetic retinopathy [611] and have been shown to achieve comparable sensitivity to that of human graders [612]. Recently, a study showed that natural language processing and machine learning algorithms were able to accurately define whether imaging reports are compliant with standardised reporting templates, compared with manual auditing [613]. Such studies hold great promise for achieving new limits in medical care through improved cost-effectiveness, accessibility and efficiency. Discussions are currently underway with UHBFT's Health Informatics Department about how automated processing of complex imaging reports can be scaled up. It is hoped that progress in this area will facilitate data capture for analysis in a large multi-centre study.

8.4 Final thoughts

In this study, I have utilised and linked several EHR datasets in order to investigate the scale of renal dysfunction and how it influences outcomes in a contemporaneous population with acute stroke. The huge potential of capturing EHR data for research has already been demonstrated in the field of AKI [303, 321]. Similarly, eResearch provides a valuable opportunity to study CKD, and with the increasing use of 'big data', better validation and refinement processes and the integration of clinically relevant information, has the potential to be harnessed to develop precise risk-prediction models and inform clinical trials.

The next question is whether the results from this study can be reproduced in a large multi-centre study in the UK. This is feasible, since SSNAP comprises a UK-wide data collection programme. In particular, the observation that AKI ascertained using first SCr on admission performs best against preadmission SCr in predicting mortality is promising but needs to be confirmed in other geographical populations before firm conclusions can be drawn about its use in risk-prediction modelling in stroke patients. In addition, observations about CKD and the risk of mortality, as well as other clinically important outcomes, such as length of stay and readmission rates require further investigation, ideally including patients with more advanced CKD. Notably, less than 5% of patients underwent thrombectomy in this study, and it is hoped that a large multi-centre study will clarify the risk of AKI in stroke patients undergoing interventional treatments- an area in which data is currently lacking. Furthermore, it is recognised that underpowering and a lack of standardisation of radiology reporting were significant limitations in the imaging arm. Local plans to develop automated processing of

imaging data will, in future, greatly enhance efficiency in data collection, negating the need for reports to be screened manually by individuals. This will facilitate data capture of large numbers of stroke admissions and increase the power to detect associations with CKD.

Patients with CKD represent a heterogeneous group with unique risk factors. As such, there is no cure and hopes for treatment rest on increased investment in technology and industry, as well as recruitment of this historically neglected patient cohort into large RCTs. From these trials, as well as through observational studies like that outlined in this thesis and proposed above, it is anticipated that the generation of high-quality evidence will help guide treatment decisions and allay concerns about risk versus benefit, thus reducing the problem of therapeutic nihilism which continues to blight these patients.

Appendices

Appendix 1. Data collection proforma for studies included in systematic review.

Date of screening:

Author(s):	
Title:	
Year of publication:	
Country of publication:	
Publication type:	Journal article/ Other (specify)

Study Eligibility

	Inclusion Criteria	Exclusion Criteria
Type of study	• Observational- retrospective/ prospective etc.	
Participants	• Patients hospitalized with acute stroke	

Types of outcome/ measure(s)	• AKI incidence • Mortality • Disability • Length of stay • Further stroke • Further CVS event • Factors associated with AKI in stroke patients • Other:	
Type of intervention(s) (if any)		

Include □ **Exclude** □

Reason(s) for exclusion:

……
……
……

Study inclusion criteria	

Study exclusion criteria	
Stroke definition e.g. clinical, CT with/ without contrast, first stroke vs any stroke	
AKI definition e.g. creatinine values (which ones? e.g. baseline vs imputed values) vs coding, which classification e.g. RIFLE, AKIN Did the study measure urine output?	
Setting	Source e.g. multi-centre, hospital, University teaching hospital
Study outcome(s) (including duration)	
Study intervention(s) (including duration)	
Study control (including duration) (if applicable)	

Duration of follow up	
Compliance/ Loss to f/u (if applicable)	
Matching of intervention(s) (if applicable)	
Similarity between groups (if applicable)	e.g. numbers, dropouts, age, sex
Statistical analysis	
Request for further information Clarification of methods Clarification of results Funding source	

Results

<table>
<tr><td colspan="6">1. Participants (entire group) n=</td></tr>
<tr><td>Age:</td><td colspan="3">Mean (SD)</td><td>Median (range)</td><td></td></tr>
<tr><td>Ethnicity:</td><td>Caucasian</td><td>Afro-Caribbean</td><td>South Asian</td><td>Chinese</td><td>Other</td></tr>
<tr><td colspan="6">Comorbidities</td></tr>
<tr><td>Ischaemic heart disease:</td><td colspan="5"></td></tr>
<tr><td>Congestive heart failure:</td><td colspan="5"></td></tr>
<tr><td rowspan="2">Chronic kidney disease (with stages, if given):</td><td>1</td><td colspan="2">2</td><td colspan="2">3a</td></tr>
<tr><td>3b</td><td colspan="2">4</td><td colspan="2">5 or 5D</td></tr>
<tr><td>Diabetes mellitus:</td><td colspan="5"></td></tr>
<tr><td>Hypertension:</td><td colspan="5"></td></tr>
<tr><td>Atrial fibrillation (or other CV embolic condition):</td><td colspan="5"></td></tr>
<tr><td>Previous stroke/ TIA:</td><td colspan="5"></td></tr>
</table>

ACEi or ARB			
Stroke type:	Ischaemic (Territory if given e.g. total/ partial anterior circulation, posterior, lacunar)	Haemorrhagic	SAH/ other
Clinical parameters			
Serum creatinine (including units, mg/dL or µmol/L):			
eGFR (if given)			
Acute kidney injury			
Outcomes			
Short-term mortality (e.g. 30-day or in-hospital mortality)			
Intermediate mortality (e.g. 3 months)			
Long-term mortality (e.g. 1 year)			
Re-stroke or other cardiac event (if given)			
Disability (and scale of measurement e.g. modified Rankin Scale)			

Length of stay					
Risk factors for AKI identified in the study e.g. age, presence of comorbidities					
2. Participants (subgrouped e.g. with or without AKI) n= Please specify _____					
Age:	Mean (SD)			Median (range)	
Ethnicity:	Caucasian	Afro-Caribbean	South Asian	Chinese	Other
Comorbidities					
Ischaemic heart disease:					
Congestive heart failure:					
Chronic kidney disease (with stages, if given):	1	2	3a		
	3b	4	5 or 5D		
Diabetes mellitus:					
Hypertension:					

Atrial fibrillation (or other CV embolic condition):			
Previous stroke/ TIA:			
ACEi or ARB			
Stroke type:	Ischaemic (Territory if given e.g. total/ partial anterior circulation, posterior, lacunar)	Haemorrhagic	SAH/ other
Clinical parameters			
Serum creatinine (including units, mg/dL or µmol/L):			
eGFR (if given)			
Outcomes			
Short-term mortality (e.g. 30-day or in-hospital mortality)			
Intermediate mortality (e.g. 3 months)			
Long-term mortality (e.g. 1 year)			
Re-stroke or other cardiac event (if given)			
Disability (and scale of measurement e.g. modified Rankin Scale)			

Length of stay	

3. Participants (subgrouped e.g. with or without AKI) n= Please specify _____					
Age:	Mean (SD)			Median (range)	
Ethnicity:	Caucasian	Afro-Caribbean	South Asian	Chinese	Other
Comorbidities					
Ischaemic heart disease:					
Congestive heart failure:					
Chronic kidney disease (with stages, if given):	1		2	3a	
	3b		4	5 or 5D	
Diabetes mellitus:					
Hypertension:					
Atrial fibrillation (or other CV embolic condition):					
Previous stroke/ TIA:					

ACEi or ARB			
Stroke type:	Ischaemic (Territory if given e.g. total/ partial anterior circulation, posterior, lacunar)	Haemorrhagic	SAH/ other
Clinical parameters			
Serum creatinine (including units, mg/dL or µmol/L):			
eGFR (if given)			
Outcomes			
Short-term mortality (e.g. 30-day or in-hospital mortality)			
Intermediate mortality (e.g. 3 months)			
Long-term mortality (e.g. 1 year)			
Re-stroke or other cardiac event (if given)			
Disability (and scale of measurement e.g. modified Rankin Scale)			
Length of stay			

Loss to follow up/ missing data/ other comments:

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Reasons for exclusion/ loss to follow up:

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Appendix 2. SSNAP core dataset parameters.

	Parameters
Section 1 **Demographics/ Onset/ Arrival**	Hospital, patient audit number, hospital number, NHS number, surname, forename, date of birth, gender, postcode, ethnicity Diagnosis of stroke or TIA or other Inpatient at time of stroke Date/ time of onset/ awareness of symptoms Arrival by ambulance/ ambulance trust/ CAD number Date/ time patient arrived in hospital First ward patient was admitted to (MAU/AAU/CDU, Stroke Unit, ITU/CCU/HDU, other) Date/ time patient arrived on Stroke Unit/ did not stay on Stroke Unit

Section 2 **Case mix/ First 24 hours**	Comorbidities: CHF/ hypertension/ AF/ diabetes/ previous stroke/ TIA If AF- on antiplatelet/ anticoagulation prior to admission mRS before stroke NIHSS score on arrival including breakdown (level of consciousness (including questions and commands), best gaze, visual, facial palsy, motor arm (left and right), motor leg (left and right), limb ataxia, sensory, best language, dysarthria, extinction and inattention) Date/ time of first brain imaging after stroke/ not imaged Stroke type (infarction or primary intracerebral haemorrhage) Was patient thrombolysed? If not, reason (not available/ outside thrombolysis service hours/ unable to scan quickly enough/ none/ haemorrhagic stroke/ arrived outside thrombolysis time window/ stroke too mild or severe/ contraindicated medication/ symptom onset time unknown (wake-up stroke)/ symptoms improving/ age/ comorbidity/ patient or relative refusal/ other medical reason)

	Date and time of thrombolysis Complications post thrombolysis (symptomatic intracranial haemorrhage/ angioedema/ extracranial bleed/ other NIHSS score 24 hours post thrombolysis Date and time of first swallow screen, if not performed in first 4 hours reason why
Section 3 **Assessments- First 72 hours**	Decision in first 72 hours that patient for palliative care/ date of decision/ is patient on end of life pathway? Date/ time first assessed by nurse trained in stroke management/ no assessment in first 72 hours Date/ time first assessed by stroke specialist consultant physician/ no assessment in first 72 hours Date and time of first swallow screen, if not performed in first 72 hours reason why Date/ time first assessed by occupational therapist, if not performed in first 72 hours reason why

	Date/ time first assessed by physiotherapist, if not performed in first 72 hours reason why Date/ time communication first assessed by speech and language therapist, if not performed in first 72 hours reason why Date/ time of formal swallow assessment by speech and language therapist or other professional trained in dysphagia assessment, if not performed in first 72 hours reason why
Section 4 **This admission**	Date/ time patient arrived at this hospital First ward patient was admitted to at this hospital (MAU/AAU/CDU, Stroke Unit, ITU/CCU/HDU, other) Date/ time patient arrived on Stroke Unit at this hospital/ did not stay on Stroke Unit Patient considered to require physiotherapy/ occupational therapy/ speech and language therapy/ psychology at any point this admission, how many days/ minutes of therapy did patient receive during hospital stay

	Date rehabilitation goals agreed or no goals, reason if no goals (not known/ patient refused/ organisational reasons/ patient medically unwell for entire admission/ patient has no impairments/ patient considered to have no rehabilitation potential)
Section 5 **Patient Condition in First 7 days**	Patient's worst level of consciousness in first 7 days following initial admission with stroke (based on NIHSS level of consciousness score) Did patient develop a urinary tract infection in first 7 days following initial admission with stroke (defined by positive culture or clinically treated) Did patient receive antibiotics for newly acquired pneumonia in first 7 days following initial admission with stroke
Section 6 **Assessments- By discharge**	Date/ time first assessed by occupational therapist, if no assessment by discharge reason why Date/ time first assessed by physiotherapist, if no assessment by discharge reason why Date/ time communication first assessed by speech and language therapist, if no assessment by discharge reason why

	Date/ time of formal swallow assessment first assessed by speech and language therapist or other professional trained in dysphagia assessment, if no assessment by discharge reason why Date urinary continence plan made, if no plan reason why Patient identified as being at high risk of malnutrition following nutritional screening, if yes seen by dietician/ not seen by dietician Patient screened for mood using validated tool, if no reason why Patient screened for cognition using a simple standardised measure, if no reason why Decision by discharge that patient for palliative care/ date of decision/ is patient on end of life pathway? Date rehabilitation goals agreed or no goals
Section 7 **Discharge/ Transfer**	Did patient die in hospital/ discharged to care home/ discharged home/ discharged somewhere else/ transferred to another hospital or bed-based rehabilitation setting If patient died in hospital, date of death

	Did patient die on Stroke Unit Which hospital was patient transferred to Date/ time of discharge/ transfer from Stroke Unit Date/ time of discharge/ transfer from hospital Date patient considered by multidisciplinary team to no longer require inpatient rehabilitation mRS at discharge/ transfer If discharged to care home was patient previously a resident/ not previously a resident If not previously a resident, is the new arrangement temporary/ permanent If discharged home is the patient living alone/ not living alone/ unknown Patient discharged with Early Supported Discharge multidisciplinary team, stroke or neurology specific/ non-specialist /none

	Patient discharged with multidisciplinary community rehabilitation team, stroke or neurology specific/ non-specialist /none Patient requires help with activities of daily living If yes what support received (paid carers/ informal carers/ paid and informal carers/ paid care services unavailable/ patient refused) At point of discharge number of visits per week social services will provide or not known Documented evidence that patient is in AF on discharge If yes patient taking anticoagulation on discharge or discharged with a plan to start anticoagulation within the next month Documented evidence of joint care planning between health and social care for post discharge management Documentation of a named person for the patient and/or carer to contact after discharge
Section 8	Did patient have a follow-up assessment at 6 months post discharge (plus or minus 2 months), yes/ no/ died within 6 months of discharge

Six month/ post admission follow up	Date of follow-up, how was follow-up carried out, in person/ telephone/ online/ by post Which professional carried out the follow-up assessment, GP/ stroke coordinator/ therapist/ other/ district or community nurse/ voluntary services employee/ secondary care clinician/ other Did patient give consent for their identifiable information to be included in SSNAP, yes/ no/ patient not asked Patient screened for mood, behaviour or cognition since discharge using a validated tool If yes, was the patient identified as needing support If yes, has the patient received psychological support for mood, behaviour or cognition since discharge Where is the patient living, home/ care home/ other mRS score Is the patient in persistent, permanent or paroxysmal AF? Is the patient taking an antiplatelet/ anticoagulant/ lipid lowering/ antihypertensive

	Since their initial stroke, has the patient had a stroke/ myocardial infarction/ other illness requiring hospitalisation

Abbreviations: AAU, acute admissions/ assessment unit; AF, atrial fibrillation; CAD, Computer Aided Despatch; CCU, coronary care unit; CDU, clinical decisions unit; CHF, congestive heart failure; HDU, high dependency unit; ITU, intensive care unit; mRS, modified Rankin Scale; MAU, medical assessment unit; NIHSS, National Institutes of Health Stroke Scale; SSNAP, Sentinel Stroke National Audit Programme; TIA, transient ischaemic attack.

Appendix 3. Rule-based imaging data collection proforma developed in Microsoft Access.

Patient Number	**Patient ID**
Hospital Number	**Date of birth**
First arrival time/ date	**Discharge time/ date**
CT scan Yes □ No□	**Number of CT scans** 1 □ 2 □ 3 □ ≥4 □

CT1		
CT1 Contrast Yes □ No□	CT1 Stroke Yes □ No□	CT1 Infarct Yes □ No□
CT1 Haemorrhage Yes □ No□	CT1 Haemorrhage Primary haemorrhage □ OR Haemorrhagic transformation □	CT1 Multiple/ embolic infarcts □
CT1 Hyperdense artery Yes □ No□	CT1 Hyperdense artery Specify site	CT1 Small vessel or lacunar infarct □
CT1 Acute □	CT1 Subacute □	CT1 Reported chronic/ old □
CT1 Reported chronic/ old Small vessel or lacunar infarct □	CT1 Reported chronic/ old Large vessel infarct □	CT1 Reported chronic/ old Multiple infarcts □
CT1 Reported chronic/ old Infarct size/ distribution not reported □	CT1 Reported 'established' □	CT1 Age of infarct not reported □
CT1 Territory Anterior □ Posterior □	CT1 Territory if posterior Cerebellum □ OR Brainstem □ OR Cerebellum and brainstem □ OR Pure occipital lobe □	CT1 Presence of calcification □
CT2		
CT2 Contrast Yes □ No□	CT2 Stroke Yes □ No□	CT2 Infarct Yes □ No□

CT2 Haemorrhage Yes □ No□	CT2 Haemorrhage Primary haemorrhage □ OR Haemorrhagic transformation □	CT2 Multiple/ embolic infarcts □
CT2 Hyperdense artery Yes □ No□	CT2 Hyperdense artery Specify site	CT2 Small vessel or lacunar infarct □
CT2 Acute □	CT2 Subacute □	CT2 Reported chronic/ old □
CT2 Reported chronic/ old Small vessel or lacunar infarct □	CT2 Reported chronic/ old Large vessel infarct □	CT2 Reported chronic/ old Multiple infarcts □
CT2 Reported chronic/ old Infarct size/ distribution not reported □	CT2 Reported 'established' □	CT2 Age of infarct not reported □
CT2 Territory Anterior □ Posterior □	CT2 Territory if posterior Cerebellum □ OR Brainstem □ OR Cerebellum and brainstem □ OR Pure occipital lobe □	CT2 Presence of calcification □
CT3		
CT3 Contrast Yes □ No□	CT3 Stroke Yes □ No□	CT3 Infarct Yes □ No□
CT3 Haemorrhage Yes □ No□	CT3 Haemorrhage Primary haemorrhage □ OR Haemorrhagic transformation □	CT3 Multiple/ embolic infarcts □
CT3 Hyperdense artery Yes □ No□	CT3 Hyperdense artery Specify site	CT3 Small vessel or lacunar infarct □
CT3 Acute □	CT3 Subacute □	CT3 Reported chronic/ old □
CT3 Reported chronic/ old Small vessel or lacunar infarct □	CT3 Reported chronic/ old Large vessel infarct □	CT3 Reported chronic/ old Multiple infarcts □
CT3 Reported chronic/ old Infarct size/ distribution not reported □	CT3 Reported 'established' □	CT3 Age of infarct not reported □
CT3 Territory Anterior □ Posterior □	CT3 Territory if posterior Cerebellum □ OR	CT3 Presence of calcification □

	Brainstem □ OR Cerebellum and brainstem □ OR Pure occipital lobe □	
MRI Yes □ No□	MRI Stroke Yes □ No□	MRI Infarct Yes □ No□
MRI Haemorrhage Yes □ No□	MRI Haemorrhage Primary haemorrhage □ OR Haemorrhagic transformation □	MRI Multiple/ embolic infarcts □
MRI Hyperdense artery Yes □ No□	MRI Hyperdense artery Specify site	MRI Small vessel or lacunar infarct □
MRI Acute □	MRI Subacute □	MRI Reported chronic/ old □
MRI Reported chronic/ old Small vessel or lacunar infarct □	MRI Reported chronic/ old Large vessel infarct □	MRI Reported chronic/ old Multiple infarcts □
MRI Reported chronic/ old Infarct size/ distribution not reported □	MRI Reported 'established' □	MRI Age of infarct not reported □
MRI Territory Anterior □ Posterior □	MRI Territory if posterior Cerebellum □ OR Brainstem □ OR Cerebellum and brainstem □ OR Pure occipital lobe □	MRI Presence of calcification □
CTA Yes □ No□	CTA Abnormality Yes □ No□	CTA Thrombus Yes □ No□
CTA Territory of abnormality	CTA Other abnormality free text	
USS Carotid Dopplers Yes □ No□	USS carotid Dopplers Standardised report Yes □ No□	
Right common carotid artery <50% stenosis □ ≥50% stenosis □	Right internal carotid artery <10% stenosis □ 10-19% □	Right external carotid artery <50% stenosis

Total occlusion □	20-29% □ 30-39% □ 40-49% □ 50-59% □ 60-69% □ 70-79%□ 80-89% □ 90-99% □ Total occlusion □	≥50% stenosis Total occlusion
Right common carotid artery Other finding free text	Right internal carotid artery Other finding free text	Right external carotid artery Other finding free text
Left common carotid artery <50% stenosis □ ≥50% stenosis □ Total occlusion □	Left internal carotid artery <10% stenosis □ 10-19% □ 20-29% □ 30-39% □ 40-49% □ 50-59% □ 60-69% □ 70-79% □ 80-89% □ 90-99% □ Total occlusion	Left external carotid artery <50% stenosis □ ≥50% stenosis □ Total occlusion □
Left common carotid artery Other finding free text	Left internal carotid artery Other finding free text	Left external carotid artery Other finding free text
Additional comments Free text		

Abbreviations: CT/A, computerised tomography/ angiography; MRI, magnetic resonance imaging; USS, ultrasound scan.

Appendix 4. Group A- factors associated with AKI^{pre}.

In the univariable analysis, older age, female sex, presence of CKD (ascertained using preadmission SCr and both CKD-EPI and MDRD formulae), higher disability score on admission, increased stroke severity and anaemia were all associated with AKI^{pre}. Thrombolysis was not associated with AKI^{pre}.

In the multivariable analysis, presence of CKD (OR 2.61, 95% CI 1.63-4.18; P<0.001 for CKD-EPI), increased stroke severity (OR 1.03, 95% CI 1.00-1.06; P=0.04) and anaemia (OR 1.67; 95% CI 1.03-2.70: P=0.04) were associated with AKI^{pre}. The results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Binomial logistic regression analysis of factors associated with AKI^{pre} in Group A (n=725).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.020 (1.002-1.038)	0.029	-	-
Female sex	1.406 (0.897-2.205)	0.137	-	-
Black ethnicity	2.264 (0.721-7.104)	0.161	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	2.771 (1.754-4.376)	<0.001	2.611 (1.632-4.177)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	2.702 (1.719-4.248)	<0.001	2.694 (1.695-4.283)	<0.001
Diabetes	1.295 (0.787-2.132)	0.309	-	-
Hypertension	0.961 (0.615-1.501)	0.860	-	-
AF	1.240 (0.754-2.039)	0.397	-	-
Previous stroke/ TIA	0.864 (0.525-1.423)	0.565	-	-
CHF	1.861 (0.787-4.399)	0.157	-	-
Stroke type	0.995 (0.493-2.010)	0.990	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	1.060 (0.485-2.318)	0.884	-	-
mRS on admission (as continuous variable)	1.192 (1.021-1.392)	0.027	-	-
NIHSS score on admission (as continuous variable)	1.037 (1.010-1.065)	0.007	1.029 (1.001-1.058)	0.041
Anaemia (baseline haemoglobin as categorical variable)	1.748 (1.093-2.796)	0.020	1.668 (1.032-2.695)	0.037

*Adjusted for age, sex, presence of CKD, disability score on admission, stroke severity and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{pre}, acute kidney injury diagnosed using preadmission serum creatinine; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 5. Group B- factors associated with AKI^{adm}.

Similar to AKI^{pre} in Group A, univariable associations with AKI^{adm} in Group B were older age, female sex, presence of CKD (ascertained using admission SCr and both CKD-EPI and MDRD formulae), higher disability score on admission and anaemia. In contrast to AKI^{pre} in Group A, Black ethnicity and presence of AF were associated with AKI^{adm} and stroke severity was not associated with AKI^{adm} in the univariable model. Undergoing thrombolysis was inversely associated with AKI^{adm} in Group B in the univariable analysis (OR 0.60, 95% CI 0.31-1.15; P=0.12).

In the multivariable analysis, presence of CKD (OR 2.29, 95% CI 1.56-3.37; P<0.001 for CKD-EPI) and anaemia (OR 1.56, 95% CI 1.04-2.36; P=0.03) remained significantly associated with AKI^{adm}. The results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Binomial logistic regression analysis of factors associated with AKI^{adm} in Group B (n=808).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.020 (1.006-1.033)	0.003	-	-
Female sex	1.127 (0.777-1.633)	0.529	-	-
Black ethnicity	1.974 (0.855-4.577)	0.111	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)**	2.303 (1.582-3.353)	<0.001	2.291 (1.557-3.372)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)**	2.278 (1.554-3.339)	<0.001	2.239 (1.512-3.318)	<0.001
Diabetes	1.180 (0.757-1.838)	0.465	-	-
Hypertension	1.055 (0.728-1.528)	0.778	-	-
AF	1.453 (0.949-2.225)	0.085	-	-
Previous stroke/ TIA	1.120 (0.730-1.718)	0.605	-	-
CHF	1.389 (0.552-3.494)	0.485	-	-
Stroke type	0.769 (0.438-1.351)	0.361	-	-

	Univariable Analysis		Multivariable Analysis*	
	Odds Ratio (95% CI)	**P value**	**Odds Ratio (95% CI)**	**P value**
Thrombolysis	0.596 (0.309-1.148)	0.122	-	-
mRS on admission (as continuous variable)	1.142 (0.997-1.307)	0.055	-	-
NIHSS score on admission (as continuous variable)	1.004 (0.981-1.028)	0.717	-	-
Anaemia (baseline haemoglobin as categorical variable)	1.627 (1.083-2.442)	0.019	1.564 (1.036-2.362)	0.033

*Adjusted for age, sex, ethnicity, presence of CKD and AF, thrombolysis, disability score on admission and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{adm}, acute kidney injury diagnosed using first serum creatinine on admission; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 6. Group B- factors associated with AKI^{low}.

Univariable associations with AKI^{low} were older age, female sex, presence of CKD (ascertained using admission SCr and both CKD-EPI and MDRD formulae), AF, CHF, higher disability score on admission, increased stroke severity and anaemia.

In the multivariable analysis, presence of CKD (OR 3.92, 95% CI 2.85-5.40; P<0.001 for CKD-EPI), increased stroke severity (OR 1.05, 95% CI 1.03-1.07; P<0.001) and anaemia (OR 1.86, 95% CI 1.31-2.64; P=0.001) remained significantly associated with AKI^{low}. The results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Binomial logistic regression analysis of factors associated with AKI^{low} in Group B (n=808).

	Univariable Analysis		**Multivariable Analysis***	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.027 (1.017-1.038)	<0.001	-	-
Female sex	1.295 (0.974-1.722)	0.076	-	-
Black ethnicity	1.565 (0.745-3.289)	0.237	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)**	4.054 (2.986-5.505)	<0.001	3.921 (2.848-5.398)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)**	4.702 (3.399-6.505)	<0.001	4.489 (3.198-6.299)	<0.001
Diabetes	0.867 (0.608-1.236)	0.430	-	-
Hypertension	0.962 (0.724-1.279)	0.790	-	-
AF	1.847 (1.314-2.597)	<0.001	-	-
Previous stroke/ TIA	0.997 (0.713-1.394)	0.987	-	-
CHF	2.265 (1.057-4.856)	0.036	-	-
Stroke type	1.276 (0.857-1.899)	0.230	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	0.957 (0.614-1.491)	0.846	-	-
mRS on admission (as continuous variable)	1.215 (1.088-1.356)	0.001	-	-
NIHSS score on admission (as continuous variable)	1.055 (1.036-1.075)	<0.001	1.049 (1.028-1.070)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.887 (1.365-2.610)	<0.001	1.861 (1.311-2.641)	0.001

*Adjusted for age, sex, presence of CKD, AF and CHF, disability score on admission, stroke severity on admission and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{low}, acute kidney injury diagnosed using lowest serum creatinine on admission; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 7. Group B- factors associated with AKI^{MDRD}.

Factors associated with AKI^{MDRD} in the univariable analysis were older age, female sex, presence of CKD (ascertained using admission SCr and both CKD-EPI and MDRD formulae), diabetes, hypertension, AF, previous stroke/ TIA, CHF, haemorrhagic stroke type, higher disability score on admission, increased stroke severity and anaemia.

In the multivariable analysis, presence of CKD (OR 35.17, 95% CI 22.87-54.09; P<0.001 for CKD-EPI) and anaemia (OR 1.64, 95% CI 1.03-2.62; P=0.04) remained significantly associated with AKI^{MDRD}. When CKD calculated by MDRD was included in the multivariable model, older age (OR 1.02, 95% CI 1.01-1.04; P=0.008) and hypertension (OR 1.61, 95% CI 1.02-2.56; P=0.04) were also associated with AKI^{MDRD}. Given the high OR for CKD, the multivariable regression analysis was repeated excluding CKD from the model. In this analysis, factors associated with AKI^{MDRD} were older age (OR 1.05, 95% CI 1.03-1.06; P<0.001), female sex (OR 1.77, 95% CI 1.23-2.52; P=0.002), diabetes (OR 1.80, 95% CI 1.22-2.66; P=0.003), AF (OR 1.56, 95% CI 1.06-2.28; P=0.02) CHF (OR 3.42, 95% CI 1.49-7.82; P=0.004), increased stroke severity (OR 1.02, 95% CI 1.00-1.04; P=0.03) and anaemia (OR 1.61, 95% CI 1.10-2.37; P=0.02).

Binomial logistic regression analysis of factors associated with AKI^{MDRD} in Group B (n=808).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.058 (1.044-1.072)	<0.001	1.023 (1.006-1.041)¥ 1.048 (1.033-1.062)***	0.008 <0.001
Female sex	1.911 (1.410-2.589)	<0.001	1.765 (1.234-2.524)***	0.002
Black ethnicity	0.702 (0.296-1.665)	0.422	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)**	32.795 (21.657-49.663)	<0.001	35.171 (22.868-54.092)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-MDRD)**	47.406 (30.418-73.881)	<0.001	45.116 (27.757-73.330)	<0.001
Diabetes	1.825 (1.284-2.595)	0.001	1.802 (1.220-2.662)***	0.003
Hypertension	1.280 (0.949-1.726)	0.105	1.613 (1.017-2.559)¥	0.042
AF	2.384 (1.684-3.373)	<0.001	1.557 (1.063-2.281)***	0.023
Previous stroke/ TIA	1.448 (1.029-2.036)	0.033	-	-
CHF	4.252 (1.933-9.351)	<0.001	3.416 (1.492-7.820)***	0.004

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Stroke type	0.630 (0.398-0.996)	0.048	-	-
Thrombolysis	1.034 (0.652-1.640)	0.886	-	-
mRS on admission (as continuous variable)	1.284 (1.147-1.437)	<0.001	-	-
NIHSS score on admission (as continuous variable)	1.030 (1.011-1.050)	0.002	1.023 (1.002-1.044)***	0.034
Anaemia (baseline haemoglobin as categorical variable)	1.547 (1.106-2.162)	0.011	1.638 (1.025-2.618) 1.614 (1.097-2.374)***	0.039 0.015

*Adjusted for age, sex, presence of CKD, diabetes, hypertension, AF, previous stroke/ TIA and CHF, stroke type, disability score on admission, stroke severity on admission and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

***Factors associated with AKI^{MDRD} when CKD excluded from the multivariable model. Adjustments are otherwise as above.

¥ Factors associated with AKI^{MDRD} when CKD ascertained using MDRD included in the multivariable model.

Abbreviations: AF, atrial fibrillation; AKI^{MDRD}, acute kidney injury diagnosed from back-calculated serum creatinine using MDRD formula; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 8. Group B- factors associated with AKI^{EPI}.

Factors associated with AKI^{EPI} in the univariable analysis were the same as for AKI^{MDRD}. In the multivariable analysis, older age (OR 1.03, 95% CI 1.01-1.05; P=0.001) and presence of CKD (OR 34.34, 95% CI 21.81-54.07; P<0.001 for CKD-EPI) remained significantly associated with AKI^{EPI}. Similar to AKI^{adm}, given the high OR for CKD, the multivariable regression analysis was repeated excluding CKD from the model. In this analysis, factors associated with AKI^{EPI} were older age (OR 1.07, 95% CI 1.05-1.08; P<0.001), diabetes (OR 1.91, 95% CI 1.29-2.83; P=0.001), AF (OR 1.50, 95% CI 1.03-2.19; P=0.04), CHF (OR 3.76, 95% CI 1.59-8.93; P=0.003) and increased stroke severity (OR 1.03, 95% CI 1.01-1.05; P=0.008). The results were not significantly affected when CKD calculated by MDRD was included in the multivariable model.

Binomial logistic regression analysis of factors associated with AKI^{EPI} in Group B (n=808).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.073 (1.058-1.088)	<0.001	1.029 (1.012-1.048) 1.069 (1.053-1.084)***	0.001 <0.001
Female sex	1.676 (1.248-2.250)	0.001	-	-
Black ethnicity	0.878 (0.394-1.955)	0.750	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)**	44.855 (29.296-68.678)	<0.001	34.337 (21.807-54.065)	<0.001
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)**	68.133 (41.527-111.786)	<0.001	56.888 (33.787-95.784)	<0.001
Diabetes	1.800 (1.272-2.548)	0.001	1.913 (1.294-2.828)***	0.001
Hypertension	1.292 (0.965-1.731)	0.085	-	-
AF	2.554 (1.810-3.604)	<0.001	1.497 (1.025-2.187)***	0.037
Previous stroke/ TIA	1.409 (1.007-1.971)	0.045	-	-
CHF	4.372 (1.950-9.799)	<0.001	3.763 (1.586-8.925)***	0.003

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Stroke type	0.636 (0.408-0.990)	0.045	-	-
Thrombolysis	0.943 (0.597-1.487)	0.800	-	-
mRS on admission (as continuous variable)	1.353 (1.209-1.513)	<0.001	-	-
NIHSS score on admission (as continuous variable)	1.036 (1.018-1.055)	<0.001	1.028 (1.007-1.050)***	0.008
Anaemia (baseline haemoglobin as categorical variable)	1.459 (1.048-2.029)	0.025	-	-

*Adjusted for age, sex, presence of CKD, diabetes, hypertension, AF, previous stroke/ TIA and CHF, stroke type, disability score on admission, stroke severity on admission and anaemia in a forward conditional model.

**Related variables were entered into the models separately.

***Factors associated with AKI^{EPI} when CKD excluded from the multivariable model. Adjustments are otherwise as above.

Abbreviations: AF, atrial fibrillation; AKI^{EPI}, acute kidney injury diagnosed from back-calculated serum creatinine using CKD-EPI formula; CHF, congestive heart failure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 9. Group A- factors associated with 30-Day Mortality.

Univariable and multivariable logistic regression models were constructed to explore factors associated with 30-day mortality in Group A (n=725). For closely related variables, namely CKD ascertained using both CKD-EPI and MDRD formulae, separate models were created and only one variable was entered into the model at a time.

In the univariable analysis, older age, presence of CKD and AF, haemorrhagic stroke type, higher disability score on admission, increased stroke severity, anaemia and presence of AKI, ascertained using AKI^{pre} (OR 3.21, 95% CI 1.88-5.48; P<0.001) were all associated with 30-day mortality in Group A.

In the multivariable analysis, older age (OR 1.03, 95% CI 1.01-1.06; P=0.02), higher disability score on admission (OR 1.57, 1.31-1.88; P<0.001), increased stroke severity (OR 1.12, 95% CI 1.09-1.15; P<0.001) and presence of AKI, ascertained using AKI^{pre} (OR 2.66, 95% CI 1.40-5.05; P=0.003) all remained significantly associated with 30-day mortality in Group A.

Binomial logistic regression analysis of factors associated with 30-Day Mortality in Group A (n=725).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.06 (1.04-1.09)	<0.001	1.03 (1.01-1.06)	0.02
Female sex	1.08 (0.70-1.68)	0.73	-	-
Black ethnicity	0.43 (0.06-3.29)	0.42	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	2.01 (1.29-3.32)	0.002	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	2.08 (1.33-3.26)	0.001	-	-
Diabetes	0.83 (0.48-1.41)	0.48	-	-
Hypertension	1.18 (0.76-1.84)	0.47	-	-
AF	1.72 (1.07-2.76)	0.02	-	-
Previous stroke/ TIA	0.95 (0.58-1.54)	0.82	-	-
CHF	1.81 (0.77-4.28)	0.18	-	-
Stroke type	2.02 (1.12-3.36)	0.02	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	0.86 (0.38-1.96)	0.72	-	-
mRS on admission (as continuous variable)	1.77 (1.53-2.05)	<0.001	1.57 (1.31-1.88)	<0.001
NIHSS score on admission (as continuous variable)	1.14 (1.11-1.17)	<0.001	1.12 (1.09-1.15)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.80 (1.13-2.84)	0.01	-	-
AKI^{pre}	3.21 (1.88-5.48)	<0.001	2.66 (1.40-5.05)	0.003

*Adjusted for age, presence of CKD and AF, stroke type, disability score on admission, stroke severity, anaemia and presence of AKI in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 10. Group B- factors associated with 30-Day Mortality.

Full univariable and multivariable associations with 30-day mortality in Group B (n=808) were performed. For closely related variables, separate models were created and only one variable was entered into the model at a time.

Univariable associations were the same as for Group A, with the addition of Black ethnicity and hypertension. Haemorrhagic stroke type was not associated with death in Group B in the univariable analysis.

AKI^{adm} was associated with 30-day mortality in the univariable analysis (OR 1.82; 95% CI 1.13-2.95: P=0.02) in Group B. This association persisted after adjustment for age, ethnicity, presence of CKD, hypertension, AF, disability score on admission, stroke severity and anaemia (OR 1.73, 95% CI 1.01-2.96; P=0.046). In addition to AKI^{adm}, other factors associated with 30-day mortality in Group B in the multivariable model were older age (OR 1.03, 95% CI 1.01-1.05; P=0.002), higher disability score on admission (OR 1.45, 95% CI 1.24-1.69; P<0.001), increased stroke severity (OR 1.09, 95% CI 1.07-1.12; P<0.001) and presence of anaemia (OR 1.70, 95% CI 1.06-2.73; P=0.03).

Binomial logistic regression analysis of factors associated with 30-Day Mortality in Group B (n=808).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Age	1.06 (1.04-1.08)	<0.001	1.03 (1.01-1.05)	0.002
Female sex	0.87 (0.58-1.34)	0.51	-	-
Black ethnicity	0.22 (0.03-1.65)	0.14	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)**	2.44 (1.62-3.67)	<0.001	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)**	2.30 (1.52-3.48)	<0.001	-	-
Diabetes	0.96 (0.58-1.58)	0.87	-	-
Hypertension	1.44 (0.96-2.16)	0.08	-	-
AF	1.94 (1.25-3.02)	0.003	-	-
Previous stroke/ TIA	1.07 (0.67-1.72)	0.77	-	-
CHF	1.79 (0.71-4.53)	0.22	-	-
Stroke type	0.93 (0.52-1.68)	0.82	-	-

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Thrombolysis	0.92 (0.48-1.75)	0.79	-	-
mRS on admission (as continuous variable)	1.69 (1.48-1.94)	<0.001	1.45 (1.24-1.69)	<0.001
NIHSS score on admission (as continuous variable)	1.10 (1.07-1.13)	<0.001	1.09 (1.07-1.12)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.96 (1.28-3.00)	0.002	1.70 (1.06-2.73)	0.03
AKI^{adm}	1.82 (1.13-2.95)	0.02	1.73 (1.01-2.96)	0.046

*Adjusted for age, ethnicity, presence of CKD, hypertension and AF, disability score on admission, stroke severity, anaemia and presence of AKI in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{adm}, AKI diagnosed using first serum creatinine on admission; CHF, congestive heart failure; CI, confidence intervals; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 11. Group A- factors associated with 1-Year Mortality.

Univariable and multivariable Cox regression models were constructed to explore factors associated with 1-year mortality in Group A (n=725). For closely related variables, for example CKD ascertained using both CKD-EPI and MDRD formulae, separate models were created and only one variable was entered into the model at a time.

In the univariable analysis, older age, presence of CKD, AF and CHF, haemorrhagic stroke type, disability score on admission, increased stroke severity, anaemia and presence of AKI, ascertained using AKI^{pre} (HR 2.74, 95% CI 1.94-3.89; P<0.001) were all associated with 1-year mortality in Group A.

In the multivariable analysis, older age (HR 1.03, 95% CI 1.02-1.05; P<0.001), higher disability score on admission (HR 1.30, 95% CI 1.17-1.43; P<0.001), increased stroke severity (HR 1.07, 95% CI 1.05-1.08; P<0.001), anaemia (HR 1.55, 95% CI 1.14-2.11; P=0.005) and presence of AKI, ascertained using AKI^{pre} (HR 2.00; 95% CI 1.40-2.86: P<0.001) all remained significantly associated with 1-year mortality in Group A.

Cox regression analysis of factors associated with 1-Year Mortality in Group A (n=725).

	Univariable Analysis		**Multivariable Analysis***	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.05 (1.03-1.07)	<0.001	1.03 (1.02-1.05)	<0.001
Female sex	1.16 (0.86-1.56)	0.34	-	-
Black ethnicity	1.22 (0.50-2.98)	0.66	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and CKD-EPI)**	1.68 (1.25-2.26)	0.001	-	-
CKD (eGFR <60 mL/min/1.73m^2 using preadmission SCr and MDRD)**	1.84 (1.37-2.49)	<0.001		
Diabetes	0.84 (0.58-1.20)	0.34	-	-
Hypertension	0.93 (0.69-1.26)	0.64	-	-
Atrial fibrillation	1.67 (1.22-2.29)	0.001	-	-
Previous stroke/ TIA	0.92 (0.66-1.27)	0.60	-	-
Congestive heart failure	1.63 (0.91-2.93)	0.10	-	-
Stroke type	1.46 (0.95-2.23)	0.08	-	-

	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Thrombolysis	1.04 (0.62-1.75)	0.87	-	-
mRS on admission (as continuous variable)	1.51 (1.38-1.65)	<0.001	1.30 (1.17-1.43)	<0.001
NIHSS score on admission (as continuous variable)	1.09 (1.07-1.11)	<0.001	1.07 (1.05-1.08)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.82 (1.34-2.47)	<0.001	1.55 (1.14-2.11)	0.005
AKI^{pre}	2.74 (1.94-3.89)	<0.001	2.00 (1.40-2.86)	<0.001

*Adjusted for age, presence of CKD, AF and CHF, stroke type, disability score on admission, stroke severity, anaemia and presence of AKI in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AKI^{pre}, AKI diagnosed using preadmission serum creatinine; CKD, chronic kidney disease; CI, confidence intervals; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD; Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 12. Group B- factors associated with 1-Year Mortality.

Cox regression analyses of the full univariable and multivariable associations with 1-year mortality in Group B (n=808) were performed. For closely related variables, separate models were created and only one variable was entered into the model at a time.

In the univariable analysis, older age, presence of CKD and AF, higher disability score on admission, stroke severity, anaemia and presence of AKI, ascertained using AKI^{adm} (HR 1.77, 95% CI 1.29-2.42; P<0.001) were all associated with 1-year mortality in Group B.

In the multivariable analysis, AKI^{adm} was associated with increased 1-year mortality after multiple adjustments (HR 1.50, 95% CI 1.10-2.07; P=0.01). In addition to AKI^{adm}, other factors associated with 1-year mortality in Group B in the multivariable model were older age (HR 1.04, 95% CI 1.02-1.05; P<0.001), higher disability score on admission (HR 1.25, 95% CI 1.14-1.37; P<0.001), increased stroke severity (HR 1.05, 95% CI 1.04-1.07; P<0.001) and presence of anaemia (HR 1.53, 95% CI 1.15-2.03; P=0.003).

Cox regression analysis of factors associated with 1-Year Mortality in Group B (n=808).

	Univariable Analysis		**Multivariable Analysis***	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Age	1.05 (1.04-1.06)	<0.001	1.04 (1.02-1.05)	<0.001
Female sex	1.03 (0.79-1.36)	0.82	-	-
Black ethnicity	0.90 (0.42-1.91)	0.79	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and CKD-EPI)**	2.06 (1.57-2.70)	<0.001	-	-
CKD (eGFR <60 mL/min/1.73m^2 using admission SCr and MDRD)**	2.01 (1.52-2.65)	<0.001		
Diabetes	0.96 (0.68-1.35)	0.81	-	-
Hypertension	1.19 (0.91-1.57)	0.20	-	-
AF	1.85 (1.38-2.48)	<0.001	-	-
Previous stroke/ TIA	1.17 (0.86-1.60)	0.32	-	-
CHF	1.19 (0.59-2.41)	0.63	-	-
Stroke type	0.84 (0.56-1.27)	0.42	-	-

	Univariable Analysis		Multivariable Analysis*	
	HR (95% CI)	**P value**	**HR (95% CI)**	**P value**
Thrombolysis	0.83 (0.53-1.31)	0.43	-	-
mRS on admission (as continuous variable)	1.46 (1.35-1.58)	<0.001	1.25 (1.14-1.37)	<0.001
NIHSS score on admission (as continuous variable)	1.06 (1.05-1.08)	<0.001	1.05 (1.04-1.07)	<0.001
Anaemia (baseline haemoglobin as categorical variable)	1.82 (1.37-2.41)	<0.001	1.53 (1.15-2.03)	0.003
AKI^{adm}	1.77 (1.29-2.42)	<0.001	1.50 (1.10-2.07)	0.012

*Adjusted for age, presence of CKD and AF, disability score on admission, stroke severity, anaemia and presence of AKI in a forward conditional model.

**Related variables were entered into the models separately.

Abbreviations: AF, atrial fibrillation; AKI^{adm}, AKI diagnosed using first serum creatinine on admission; CHF, congestive heart failure; CKD, chronic kidney disease; CI, confidence intervals; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; SCr, serum creatinine; TIA, transient ischaemic attack.

Appendix 13. Logistic regression analysis of the relationship between radiological contrast exposure and the development of AKI^{pre} in Group A (n=725).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
1 CT	1.025 (0.229-4.587)	0.974	-	-
≥2 CT	1.026 (0.351-2.996)	0.963	-	-
CTA	0.949 (0.496-1.815)	0.875	-	-
Thrombectomy	0.546 (0.071-4.229)	0.563	-	-
CT and CTA	1.064 (0.596-1.900)	0.833	-	-
All contrast exposure	1.110 (0.629-1.957)	0.719	-	-

*Adjusted for age, sex, presence of CKD, disability score on admission, stroke severity and anaemia (all significant variables in a binomial regression analysis of factors associated with AKI^{pre} in Group A, outlined in Appendix 4) in a forward conditional model.

Abbreviations: AKI^{pre}, acute kidney injury diagnosed using preadmission serum creatinine; CKD, chronic kidney disease; CT/A, computerised tomography/ angiography; OR, odds ratio.

Appendix 14. Logistic regression analysis of the relationship between radiological contrast exposure and the development of AKI^{adm} in Group B (n=808).

	Univariable Analysis		Multivariable Analysis*	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
1 CT	1.267 (0.467-3.438)	0.642	-	-
≥2 CT	1.034 (0.472-2.265)	0.934	-	-
CTA	0.601 (0.344-1.050)	0.074	-	-
Thrombectomy	0.549 (0.164-1.836)	0.330	-	-
CT and CTA	0.731 (0.454-1.177)	0.197	-	-
All contrast exposure	0.691 (0.432-1.103)	0.122	-	-

*Adjusted for age, sex, ethnicity, presence of CKD and AF, thrombolysis, disability score on admission and anaemia (all significant variables in a binomial regression analysis of factors associated with AKI^{adm} in Group B, outlined in Appendix 5) in a forward conditional model.

Abbreviations: AKI^{adm}, acute kidney injury diagnosed using first serum creatinine on admission; AF, atrial fibrillation; CKD, chronic kidney disease; CT/A, computerised tomography/ angiography; OR, odds ratio.

List of References

1. Organisation, W.H. *Global Health Observatory Data: Mortality and Global Health Estimates*. 2016 1 May 2019]; Available from: https://www.who.int/gho/mortality_burden_disease/en/.
2. Collaborators, G.B.D.C.o.D., *Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2018. **392**(10159): p. 1736-1788.
3. Feigin, V.L., et al., *Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study.* Neuroepidemiology, 2015. **45**(3): p. 161-76.
4. DALYs, G.B.D. and H. Collaborators, *Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2018. **392**(10159): p. 1859-1922.
5. Murray, C., *The Global Burden of Disease*. Global Burden of Disease and Injury Series. Vol. 1. 1996, Cambridge, MA: Harvard School of Public Health.
6. Evaluation, I.f.H.M.a. *Global Burden of Disease Study 2017 (GBD 2017) Disability Weights*. 2017 [cited 2020 3 May 2020]; Available from: http://ghdx.healthdata.org/record/ihme-data/gbd-2017-disability-weights.
7. Rankin, J., *Cerebral vascular accidents in patients over the age of 60. II. Prognosis.* Scott Med J, 1957. **2**(5): p. 200-15.
8. Banks, J.L. and C.A. Marotta, *Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis.* Stroke, 2007. **38**(3): p. 1091-6.
9. Dawson, J., et al., *Association between disability measures and healthcare costs after initial treatment for acute stroke.* Stroke, 2007. **38**(6): p. 1893-8.
10. Eriksson, M., et al., *Functional outcome 3 months after stroke predicts long-term survival.* Cerebrovasc Dis, 2008. **25**(5): p. 423-9.
11. Slot, K.B., et al., *Impact of functional status at six months on long term survival in patients with ischaemic stroke: prospective cohort studies.* BMJ, 2008. **336**(7640): p. 376-9.
12. Organisation, W.H. *Global Burden of Disease 2004 Update: Disability Weights for Diseases and Conditions.* 2004 [cited 2020 3 May 2020]; Available from: https://www.who.int/healthinfo/global_burden_disease/GBD2004_DisabilityWeights.pdf.
13. Stouthard MEA, E.-B.M., Bonsel GJ, *Disability weights for diseases: A modified protocol and results for a Western European region.* Eur J Public Health, 2000. **10**(1): p. 24-30.
14. Hong, K.S. and J.L. Saver, *Quantifying the value of stroke disability outcomes: WHO global burden of disease project disability weights for each level of the modified Rankin Scale.* Stroke, 2009. **40**(12): p. 3828-33.
15. Hong, K.S., *Disability-adjusted life years analysis: implications for stroke research.* J Clin Neurol, 2011. **7**(3): p. 109-14.
16. Benjamin, E.J., et al., *Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association.* Circulation, 2019. **139**(10): p. e56-e528.
17. Patel A, B.V., King D, Quayyum Z, Wittenberg R, Knapp M, *Current, future and avoidable costs of stroke in the UK. Executive summary Part 1: Burden of stroke in the next 20 years and potential returns from increased spending on research.* 2017, Stroke Association: London.

18. Patel A, B.V., King D, Quayyum Z, Wittenberg R, Knapp M, *Current, future and avoidable costs of stroke in the UK. Executive summary Part 2: Burden of stroke in the next 20 years and potential returns from increased spending on research.* 2017, Stroke Association: London.
19. Jorgensen, H.S., et al., *Acute stroke care and rehabilitation: an analysis of the direct cost and its clinical and social determinants. The Copenhagen Stroke Study.* Stroke, 1997. **28**(6): p. 1138-41.
20. Caro, J.J., K.F. Huybrechts, and I. Duchesne, *Management patterns and costs of acute ischemic stroke : an international study. For the Stroke Economic Analysis Group.* Stroke, 2000. **31**(3): p. 582-90.
21. Specogna, A.V., et al., *Hospital treatment costs and length of stay associated with hypertension and multimorbidity after hemorrhagic stroke.* BMC Neurol, 2017. **17**(1): p. 158.
22. Gansevoort, R.T., et al., *Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention.* Lancet, 2013. **382**(9889): p. 339-52.
23. Arnold, J., D. Sims, and C.J. Ferro, *Modulation of stroke risk in chronic kidney disease.* Clin Kidney J, 2016. **9**(1): p. 29-38.
24. Kerr, M., et al., *Estimating the financial cost of chronic kidney disease to the NHS in England.* Nephrol Dial Transplant, 2012. **27 Suppl 3**: p. iii73-80.
25. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-128.
26. Wolfe, C.D., *The impact of stroke.* Br Med Bull, 2000. **56**(2): p. 275-86.
27. Coresh, J., et al., *Prevalence of chronic kidney disease in the United States.* JAMA, 2007. **298**(17): p. 2038-47.
28. Silverwood, R.J., et al., *Cognitive and kidney function: results from a British birth cohort reaching retirement age.* PLoS One, 2014. **9**(1): p. e86743.
29. Cole, W., *A physico-medical essay concerning the late frequency of apoplexies together with a general method of their prevention and cure : in a letter to a physician*. 1689, Oxford.
30. Aho, K., et al., *Cerebrovascular disease in the community: results of a WHO collaborative study.* Bull World Health Organ, 1980. **58**(1): p. 113-30.
31. Sacco, R.L., et al., *An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2013. **44**(7): p. 2064-89.
32. Writing Group, M., et al., *Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association.* Circulation, 2016. **133**(4): p. e38-360.
33. Kernan, W.N., et al., *Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2014. **45**(7): p. 2160-236.
34. Adams, H.P., Jr., et al., *Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment.* Stroke, 1993. **24**(1): p. 35-41.
35. National Institute of Neurological, D. and P.A.S.S.G. Stroke rt, *Tissue plasminogen activator for acute ischemic stroke.* N Engl J Med, 1995. **333**(24): p. 1581-7.
36. *The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group.* Lancet, 1997. **349**(9065): p. 1569-81.
37. Shea, A.M., et al., *Characteristics of nontraumatic subarachnoid hemorrhage in the United States in 2003.* Neurosurgery, 2007. **61**(6): p. 1131-7; discussion 1137-8.
38. Sacco, S., et al., *Incidence, case-fatalities and 10-year survival of subarachnoid hemorrhage in a population-based registry.* Eur Neurol, 2009. **62**(3): p. 155-60.

39. Biotti, D., et al., *Trends in case-fatality rates in hospitalized nontraumatic subarachnoid hemorrhage: results of a population-based study in Dijon, France, from 1985 to 2006.* Neurosurgery, 2010. **66**(6): p. 1039-43; discussion 1043.
40. van Gijn, J. and G.J. Rinkel, *Subarachnoid haemorrhage: diagnosis, causes and management.* Brain, 2001. **124**(Pt 2): p. 249-78.
41. KDIGO, *KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease.* Kidney Int Suppl, 2013. **3**(1): p. 136-150.
42. Levey, A.S., et al., *The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report.* Kidney Int, 2011. **80**(1): p. 17-28.
43. Hill, N.R., et al., *Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis.* PLoS One, 2016. **11**(7): p. e0158765.
44. Mills, K.T., et al., *A systematic analysis of worldwide population-based data on the global burden of chronic kidney disease in 2010.* Kidney Int, 2015. **88**(5): p. 950-7.
45. Excellence, N.I.f.H.a.C., *Quality and Outcomes Framework (QOF) Indicator Development Programme Chronic Kidney Disease Briefing Paper*. 2014.
46. Marilyn Roth, P.R., Jennifer Mindell, *Health Survey for England - 2010, Respiratory health: Chapter 8- Kidney disease and renal function*. 2010, Health Survey for England.
47. Stevens, P.E., et al., *Chronic kidney disease management in the United Kingdom: NEOERICA project results.* Kidney Int, 2007. **72**(1): p. 92-9.
48. de Lusignan, S., et al., *Creatinine fluctuation has a greater effect than the formula to estimate glomerular filtration rate on the prevalence of chronic kidney disease.* Nephron Clin Pract, 2011. **117**(3): p. c213-24.
49. Stephanie J MacNeill, D.F., Katharine Evans, James F Medcalf *UK Renal Registry 20th Annual Report: Chapter 2 UK Renal Replacement Therapy Adult Prevalence in 2016: National and Centre-specific Analyses.* Nephron Clin Pract, 2018. **139**: p. 47-74.
50. Stevens, L.A., G. Viswanathan, and D.E. Weiner, *Chronic kidney disease and end-stage renal disease in the elderly population: current prevalence, future projections, and clinical significance.* Adv Chronic Kidney Dis, 2010. **17**(4): p. 293-301.
51. Tonelli, M. and M. Riella, *Chronic kidney disease and the aging population.* Am J Physiol Renal Physiol, 2014. **306**(5): p. F469-72.
52. Davies, D.F. and N.W. Shock, *Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males.* J Clin Invest, 1950. **29**(5): p. 496-507.
53. Aitken, G.R., et al., *Change in prevalence of chronic kidney disease in England over time: comparison of nationally representative cross-sectional surveys from 2003 to 2010.* BMJ Open, 2014. **4**(9): p. e005480.
54. System, U.S.R.D., *Annual Data Report 2018 Epidemiology of Kidney Disease in the United States*. 2018.
55. Zoccali, C., A. Kramer, and K.J. Jager, *Chronic kidney disease and end-stage renal disease-a review produced to contribute to the report 'the status of health in the European union: towards a healthier Europe'.* NDT Plus, 2010. **3**(3): p. 213-224.
56. Murphy, D., et al., *Trends in Prevalence of Chronic Kidney Disease in the United States.* Ann Intern Med, 2016. **165**(7): p. 473-481.
57. Liyanage, T., et al., *Worldwide access to treatment for end-stage kidney disease: a systematic review.* Lancet, 2015. **385**(9981): p. 1975-82.
58. Dalrymple, L.S., et al., *The risk of infection-related hospitalization with decreased kidney function.* Am J Kidney Dis, 2012. **59**(3): p. 356-63.
59. Pimentel, A., et al., *Fractures in patients with CKD-diagnosis, treatment, and prevention: a review by members of the European Calcified Tissue Society and the European Renal Association of Nephrology Dialysis and Transplantation.* Kidney Int, 2017. **92**(6): p. 1343-1355.

60. Kerr, M., *Chronic Kidney Disease in England: The Human and Financial Cost*. 2017, NHS Kidney Care.
61. Tonelli, M., et al., *Chronic kidney disease and mortality risk: a systematic review.* J Am Soc Nephrol, 2006. **17**(7): p. 2034-47.
62. Chronic Kidney Disease Prognosis, C., et al., *Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis.* Lancet, 2010. **375**(9731): p. 2073-81.
63. Astor, B.C., et al., *Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts.* Kidney Int, 2011. **79**(12): p. 1331-40.
64. Gansevoort, R.T., et al., *Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts.* Kidney Int, 2011. **80**(1): p. 93-104.
65. van der Velde, M., et al., *Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts.* Kidney Int, 2011. **79**(12): p. 1341-52.
66. Viasus, D., et al., *Epidemiology, clinical features and outcomes of pneumonia in patients with chronic kidney disease.* Nephrol Dial Transplant, 2011. **26**(9): p. 2899-906.
67. Eckardt, K.U., et al., *Evolving importance of kidney disease: from subspecialty to global health burden.* Lancet, 2013. **382**(9887): p. 158-69.
68. Masson, P., et al., *Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis.* Nephrol Dial Transplant, 2015. **30**(7): p. 1162-9.
69. Sanchez-Perales, C., et al., *Ischaemic stroke in incident dialysis patients.* Nephrol Dial Transplant, 2010. **25**(10): p. 3343-8.
70. Gerstein, H.C., et al., *Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals.* JAMA, 2001. **286**(4): p. 421-6.
71. Ibsen, H., et al., *Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy: the LIFE Study.* Kidney Int Suppl, 2004(92): p. S56-8.
72. Klausen, K., et al., *Very low levels of microalbuminuria are associated with increased risk of coronary heart disease and death independently of renal function, hypertension, and diabetes.* Circulation, 2004. **110**(1): p. 32-5.
73. Hallan, S., et al., *Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The HUNT II Study.* Arch Intern Med, 2007. **167**(22): p. 2490-6.
74. Hemmelgarn, B.R., et al., *Relation between kidney function, proteinuria, and adverse outcomes.* JAMA, 2010. **303**(5): p. 423-9.
75. Longenecker, J.C., et al., *Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study.* J Am Soc Nephrol, 2002. **13**(7): p. 1918-27.
76. Goodkin, D.A., et al., *Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS).* J Am Soc Nephrol, 2003. **14**(12): p. 3270-7.
77. Seliger, S.L., et al., *Elevated risk of stroke among patients with end-stage renal disease.* Kidney Int, 2003. **64**(2): p. 603-9.
78. Herrington, W., et al., *Evidence for the prevention and treatment of stroke in dialysis patients.* Semin Dial, 2015. **28**(1): p. 35-47.
79. Moody, W.E., et al., *Understanding the effects of chronic kidney disease on cardiovascular risk: are there lessons to be learnt from healthy kidney donors?* J Hum Hypertens, 2012. **26**(3): p. 141-8.
80. Demarin, V., Zikic M and Zikic T., *Stroke: a historical overview and contemporary management.* Curr Top Neurol Psychiatr Relat Discip, 2011. **19**(2): p. 15-23.

81. Powers, W.J., et al., *2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association.* Stroke, 2018. **49**(3): p. e46-e110.
82. Lewington, S., et al., *Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.* Lancet, 2002. **360**(9349): p. 1903-13.
83. Cheung, A.K., et al., *Effects of Intensive BP Control in CKD.* J Am Soc Nephrol, 2017. **28**(9): p. 2812-2823.
84. Drazner, M.H., *The progression of hypertensive heart disease.* Circulation, 2011. **123**(3): p. 327-34.
85. Agarwal, R., et al., *Pre- and postdialysis blood pressures are imprecise estimates of interdialytic ambulatory blood pressure.* Clin J Am Soc Nephrol, 2006. **1**(3): p. 389-98.
86. Agarwal, R. and A.D. Sinha, *Cardiovascular protection with antihypertensive drugs in dialysis patients: systematic review and meta-analysis.* Hypertension, 2009. **53**(5): p. 860-6.
87. Heerspink, H.J., et al., *Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: a systematic review and meta-analysis of randomised controlled trials.* Lancet, 2009. **373**(9668): p. 1009-15.
88. McCallum, W. and M.J. Sarnak, *Blood pressure target for the dialysis patient.* Semin Dial, 2019. **32**(1): p. 35-40.
89. Palmer, B.F. and W.L. Henrich, *Recent advances in the prevention and management of intradialytic hypotension.* J Am Soc Nephrol, 2008. **19**(1): p. 8-11.
90. Reiss, A.B., et al., *Cholesterol Metabolism in CKD.* Am J Kidney Dis, 2015. **66**(6): p. 1071-82.
91. Visconti, L., et al., *Lipid disorders in patients with renal failure: Role in cardiovascular events and progression of chronic kidney disease.* J Clin Transl Endocrinol, 2016. **6**: p. 8-14.
92. Ferro, C.J., et al., *Lipid management in patients with chronic kidney disease.* Nat Rev Nephrol, 2018. **14**(12): p. 727-749.
93. Cholesterol Treatment Trialists, C., et al., *Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials.* Lancet, 2010. **376**(9753): p. 1670-81.
94. Cholesterol Treatment Trialists, C., et al., *The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials.* Lancet, 2012. **380**(9841): p. 581-90.
95. Cholesterol Treatment Trialists, C., et al., *Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials.* Lancet, 2015. **385**(9976): p. 1397-405.
96. Baigent, C., M.J. Landray, and D.C. Wheeler, *Misleading associations between cholesterol and vascular outcomes in dialysis patients: the need for randomized trials.* Semin Dial, 2007. **20**(6): p. 498-503.
97. Steenkamp, R., R. Pyart, and S. Fraser, *Chapter 5 Survival and Cause of Death in UK Adult Patients on Renal Replacement Therapy in 2016.* Nephron, 2018. **139 Suppl 1**: p. 117-150.
98. Saran, R., et al., *US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States.* Am J Kidney Dis, 2019. **73**(3S1): p. A7-A8.
99. Tonelli, M., et al., *Effect of pravastatin on cardiovascular events in people with chronic kidney disease.* Circulation, 2004. **110**(12): p. 1557-63.
100. Shepherd, J., et al., *Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study.* J Am Coll Cardiol, 2008. **51**(15): p. 1448-54.
101. Ridker, P.M., et al., *Rosuvastatin for primary prevention among individuals with elevated high-sensitivity c-reactive protein and 5% to 10% and 10% to 20% 10-year risk. Implications of*

the Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial for "intermediate risk". Circ Cardiovasc Qual Outcomes, 2010. **3**(5): p. 447-52.
102. Wanner, C., et al., *Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis.* N Engl J Med, 2005. **353**(3): p. 238-48.
103. Fellstrom, B.C., et al., *Rosuvastatin and cardiovascular events in patients undergoing hemodialysis.* N Engl J Med, 2009. **360**(14): p. 1395-407.
104. Baigent, C., et al., *The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial.* Lancet, 2011. **377**(9784): p. 2181-92.
105. Cholesterol Treatment Trialists, C., et al., *Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials.* Lancet Diabetes Endocrinol, 2016. **4**(10): p. 829-39.
106. KDIGO, *Kidney Disease Improving Global Outcomes: Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease.* Kidney Int Suppl, 2013. **3**(3): p. 259-305.
107. Disease, G.B.D., I. Injury, and C. Prevalence, *Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017.* Lancet, 2018. **392**(10159): p. 1789-1858.
108. Kirchhof, P., et al., *2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS.* Eur Heart J, 2016. **37**(38): p. 2893-2962.
109. Goldstein, L.B., et al., *Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.* Stroke, 2011. **42**(2): p. 517-84.
110. Flint, A.C., et al., *Detection of paroxysmal atrial fibrillation by 30-day event monitoring in cryptogenic ischemic stroke: the Stroke and Monitoring for PAF in Real Time (SMART) Registry.* Stroke, 2012. **43**(10): p. 2788-90.
111. Lau, Y.C., et al., *Atrial Fibrillation and Thromboembolism in Patients With Chronic Kidney Disease.* J Am Coll Cardiol, 2016. **68**(13): p. 1452-1464.
112. Soliman, E.Z., et al., *Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC).* Am Heart J, 2010. **159**(6): p. 1102-7.
113. Hobbs, F.D., et al., *A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.* Health Technol Assess, 2005. **9**(40): p. iii-iv, ix-x, 1-74.
114. Tonelli, M., S.A. Karumanchi, and R. Thadhani, *Epidemiology and Mechanisms of Uremia-Related Cardiovascular Disease.* Circulation, 2016. **133**(5): p. 518-36.
115. Potpara, T.S., C.J. Ferro, and G.Y.H. Lip, *Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction.* Nat Rev Nephrol, 2018. **14**(5): p. 337-351.
116. Alonso, A., et al., *Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study.* Circulation, 2011. **123**(25): p. 2946-53.
117. Watanabe, H., et al., *Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study.* Am Heart J, 2009. **158**(4): p. 629-36.
118. Bansal, N., et al., *Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease.* Circulation, 2013. **127**(5): p. 569-74.
119. Bansal, N., et al., *Atrial Fibrillation and Risk of ESRD in Adults with CKD.* Clin J Am Soc Nephrol, 2016. **11**(7): p. 1189-96.
120. Calenda, B.W., et al., *Stroke risk assessment in atrial fibrillation: risk factors and markers of atrial myopathy.* Nat Rev Cardiol, 2016. **13**(9): p. 549-59.
121. Schlaich, M.P., et al., *Sympathetic activation in chronic renal failure.* J Am Soc Nephrol, 2009. **20**(5): p. 933-9.

122. Khatib, R., et al., *Blockade of the renin-angiotensin-aldosterone system (RAAS) for primary prevention of non-valvular atrial fibrillation: a systematic review and meta analysis of randomized controlled trials.* Int J Cardiol, 2013. **165**(1): p. 17-24.
123. Healey, J.S., C.A. Morillo, and S.J. Connolly, *Role of the renin-angiotensin-aldosterone system in atrial fibrillation and cardiac remodeling.* Curr Opin Cardiol, 2005. **20**(1): p. 31-7.
124. Keller, C., et al., *Association of kidney function with inflammatory and procoagulant markers in a diverse cohort: a cross-sectional analysis from the Multi-Ethnic Study of Atherosclerosis (MESA).* BMC Nephrol, 2008. **9**: p. 9.
125. Krane, V. and C. Wanner, *Statins, inflammation and kidney disease.* Nat Rev Nephrol, 2011. **7**(7): p. 385-97.
126. Gupta, J., et al., *Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC.* Clin J Am Soc Nephrol, 2012. **7**(12): p. 1938-46.
127. Ghosh, A.K. and D.E. Vaughan, *PAI-1 in tissue fibrosis.* J Cell Physiol, 2012. **227**(2): p. 493-507.
128. Mercier, E., et al., *Tissue factor coagulation pathway and blood cells activation state in renal insufficiency.* Hematol J, 2001. **2**(1): p. 18-25.
129. Levin, A. and R.N. Foley, *Cardiovascular disease in chronic renal insufficiency.* Am J Kidney Dis, 2000. **36**(6 Suppl 3): p. S24-30.
130. Edwards, N.C., et al., *Diffuse interstitial fibrosis and myocardial dysfunction in early chronic kidney disease.* Am J Cardiol, 2015. **115**(9): p. 1311-7.
131. Foley, R.N., et al., *Left ventricular hypertrophy in new hemodialysis patients without symptomatic cardiac disease.* Clin J Am Soc Nephrol, 2010. **5**(5): p. 805-13.
132. Bansal, N., C.Y. Hsu, and A.S. Go, *Intersection of cardiovascular disease and kidney disease: atrial fibrillation.* Curr Opin Nephrol Hypertens, 2014. **23**(3): p. 275-82.
133. Wang, M.C., et al., *Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease.* Am J Kidney Dis, 2005. **45**(3): p. 494-501.
134. Lutz, J., et al., *Haemostasis in chronic kidney disease.* Nephrol Dial Transplant, 2014. **29**(1): p. 29-40.
135. Chen, S.C., et al., *Echocardiographic parameters are independently associated with rate of renal function decline and progression to dialysis in patients with chronic kidney disease.* Clin J Am Soc Nephrol, 2011. **6**(12): p. 2750-8.
136. Olesen, J.B., et al., *Stroke and bleeding in atrial fibrillation with chronic kidney disease.* N Engl J Med, 2012. **367**(7): p. 625-35.
137. Friberg, L., M. Rosenqvist, and G.Y. Lip, *Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study.* Eur Heart J, 2012. **33**(12): p. 1500-10.
138. Banerjee, A., et al., *A prospective study of estimated glomerular filtration rate and outcomes in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project.* Chest, 2014. **145**(6): p. 1370-1382.
139. Guo, Y., et al., *Sequential changes in renal function and the risk of stroke and death in patients with atrial fibrillation.* Int J Cardiol, 2013. **168**(5): p. 4678-84.
140. Go, A.S., et al., *Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study.* Circulation, 2009. **119**(10): p. 1363-9.
141. Wetmore, J.B., et al., *Atrial fibrillation and risk of stroke in dialysis patients.* Ann Epidemiol, 2013. **23**(3): p. 112-8.
142. Wetmore, J.B., et al., *Stroke and the "stroke belt" in dialysis: contribution of patient characteristics to ischemic stroke rate and its geographic variation.* J Am Soc Nephrol, 2013. **24**(12): p. 2053-61.
143. Jalal, D.I., M. Chonchol, and G. Targher, *Disorders of hemostasis associated with chronic kidney disease.* Semin Thromb Hemost, 2010. **36**(1): p. 34-40.

144. Mant, J., et al., *Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial.* Lancet, 2007. **370**(9586): p. 493-503.
145. Diener, H.C., et al., *Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial.* Lancet Neurol, 2012. **11**(3): p. 225-31.
146. Tereshchenko, L.G., et al., *Comparative Effectiveness of Interventions for Stroke Prevention in Atrial Fibrillation: A Network Meta-Analysis.* J Am Heart Assoc, 2016. **5**(5).
147. Apostolakis, S., et al., *Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial.* Eur Heart J, 2013. **34**(46): p. 3572-9.
148. Banerjee, A., et al., *Renal impairment and ischemic stroke risk assessment in patients with atrial fibrillation: the Loire Valley Atrial Fibrillation Project.* J Am Coll Cardiol, 2013. **61**(20): p. 2079-87.
149. Roldan, V., et al., *Does chronic kidney disease improve the predictive value of the CHADS2 and CHA2DS2-VASc stroke stratification risk scores for atrial fibrillation?* Thromb Haemost, 2013. **109**(5): p. 956-60.
150. Chao, T.F., et al., *Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis.* Heart Rhythm, 2014. **11**(10): p. 1752-9.
151. Wang, T.K., et al., *Relationships between Anticoagulation, Risk Scores and Adverse Outcomes in Dialysis Patients with Atrial Fibrillation.* Heart Lung Circ, 2016. **25**(3): p. 243-9.
152. Lip, G.Y., et al., *Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation.* Chest, 2010. **137**(2): p. 263-72.
153. Pisters, R., et al., *A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey.* Chest, 2010. **138**(5): p. 1093-100.
154. Ng, K.P., et al., *Atrial fibrillation in CKD: balancing the risks and benefits of anticoagulation.* Am J Kidney Dis, 2013. **62**(3): p. 615-32.
155. Gage, B.F., et al., *Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF).* Am Heart J, 2006. **151**(3): p. 713-9.
156. Fang, M.C., et al., *A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study.* J Am Coll Cardiol, 2011. **58**(4): p. 395-401.
157. Murphy M., et al., *Modified HASBLED Bleeding Risk Score in Dialysis Patients With Atrial Fibrillation.* Circulation, 2015. **132**: p. A12014.
158. Yoon, C.Y., et al., *Warfarin Use in Patients With Atrial Fibrillation Undergoing Hemodialysis: A Nationwide Population-Based Study.* Stroke, 2017. **48**(9): p. 2472-2479.
159. Ocak, G., et al., *Performance of bleeding risk scores in dialysis patients.* Nephrol Dial Transplant, 2019. **34**(7): p. 1223-1231.
160. Dahal, K., et al., *Stroke, Major Bleeding, and Mortality Outcomes in Warfarin Users With Atrial Fibrillation and Chronic Kidney Disease: A Meta-Analysis of Observational Studies.* Chest, 2016. **149**(4): p. 951-9.
161. Jun, M., et al., *Warfarin Initiation, Atrial Fibrillation, and Kidney Function: Comparative Effectiveness and Safety of Warfarin in Older Adults With Newly Diagnosed Atrial Fibrillation.* Am J Kidney Dis, 2017. **69**(6): p. 734-743.
162. Abbott, K.C., et al., *Atrial fibrillation in chronic dialysis patients in the United States: risk factors for hospitalization and mortality.* BMC Nephrol, 2003. **4**: p. 1.
163. Bonde, A.N., et al., *Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study.* J Am Coll Cardiol, 2014. **64**(23): p. 2471-82.

164. Genovesi, S., et al., *Warfarin use, mortality, bleeding and stroke in haemodialysis patients with atrial fibrillation.* Nephrol Dial Transplant, 2015. **30**(3): p. 491-8.
165. Knoll, F., et al., *Coumarins and survival in incident dialysis patients.* Nephrol Dial Transplant, 2012. **27**(1): p. 332-7.
166. Chen, J.J., et al., *Anti-platelet or anti-coagulant agent for the prevention of ischemic stroke in patients with end-stage renal disease and atrial fibrillation--a nation-wide database analyses.* Int J Cardiol, 2014. **177**(3): p. 1008-11.
167. Shen, J.I., et al., *Outcomes After Warfarin Initiation in a Cohort of Hemodialysis Patients With Newly Diagnosed Atrial Fibrillation.* Am J Kidney Dis, 2015. **66**(4): p. 677-88.
168. Findlay, M.D., et al., *Risk Factors of Ischemic Stroke and Subsequent Outcome in Patients Receiving Hemodialysis.* Stroke, 2015. **46**(9): p. 2477-81.
169. Tan, J., et al., *Warfarin use and stroke, bleeding and mortality risk in patients with end stage renal disease and atrial fibrillation: a systematic review and meta-analysis.* BMC Nephrol, 2016. **17**(1): p. 157.
170. Chan, K.E., et al., *Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation.* J Am Soc Nephrol, 2009. **20**(10): p. 2223-33.
171. Wizemann, V., et al., *Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy.* Kidney Int, 2010. **77**(12): p. 1098-106.
172. Andrews, J., et al., *Warfarin Use Is Associated With Progressive Coronary Arterial Calcification: Insights From Serial Intravascular Ultrasound.* JACC Cardiovasc Imaging, 2018. **11**(9): p. 1315-1323.
173. Koos, R., et al., *Relation of circulating Matrix Gla-Protein and anticoagulation status in patients with aortic valve calcification.* Thromb Haemost, 2009. **101**(4): p. 706-13.
174. Galloway, P.A., et al., *Vitamin K antagonists predispose to calciphylaxis in patients with end-stage renal disease.* Nephron, 2015. **129**(3): p. 197-201.
175. Connolly, S.J., et al., *Dabigatran versus warfarin in patients with atrial fibrillation.* N Engl J Med, 2009. **361**(12): p. 1139-51.
176. Patel, M.R., et al., *Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.* N Engl J Med, 2011. **365**(10): p. 883-91.
177. Granger, C.B., et al., *Apixaban versus warfarin in patients with atrial fibrillation.* N Engl J Med, 2011. **365**(11): p. 981-92.
178. Giugliano, R.P., et al., *Edoxaban versus warfarin in patients with atrial fibrillation.* N Engl J Med, 2013. **369**(22): p. 2093-104.
179. Nielsen, P.B., et al., *Renal function and non-vitamin K oral anticoagulants in comparison with warfarin on safety and efficacy outcomes in atrial fibrillation patients: a systemic review and meta-regression analysis.* Clin Res Cardiol, 2015. **104**(5): p. 418-29.
180. Steffel, J., et al., *The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation.* Eur Heart J, 2018. **39**(16): p. 1330-1393.
181. January, C.T., et al., *2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons.* Circulation, 2019. **140**(2): p. e125-e151.
182. Palmer, S.C., et al., *Antiplatelet agents for chronic kidney disease.* Cochrane Database Syst Rev, 2013(2): p. CD008834.
183. Antithrombotic Trialists, C., *Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients.* BMJ, 2002. **324**(7329): p. 71-86.

184. Tanrikulu, A.M., et al., *Aspirin resistance in patients with chronic renal failure.* J Nephrol, 2011. **24**(5): p. 636-46.
185. Capodanno, D. and D.J. Angiolillo, *Antithrombotic therapy in patients with chronic kidney disease.* Circulation, 2012. **125**(21): p. 2649-61.
186. KDIGO, *KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD).* Kidney Int Suppl, 2017. **7**(1): p. 1-59.
187. Ferro, C.J., et al., *Is lowering phosphate exposure the key to preventing arterial stiffening with age?* Heart, 2009. **95**(21): p. 1770-2.
188. Chue, C.D., et al., *Arterial stiffness in chronic kidney disease: causes and consequences.* Heart, 2010. **96**(11): p. 817-23.
189. Bugnicourt, J.M., et al., *High prevalence of intracranial artery calcification in stroke patients with CKD: a retrospective study.* Clin J Am Soc Nephrol, 2009. **4**(2): p. 284-90.
190. Townsend, R.R., *Arterial Stiffness in CKD: A Review.* Am J Kidney Dis, 2019. **73**(2): p. 240-247.
191. Palmer, S.C., et al., *Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis.* JAMA, 2011. **305**(11): p. 1119-27.
192. Block, G.A., et al., *CKD-mineral and bone disorder and risk of death and cardiovascular hospitalization in patients on hemodialysis.* Clin J Am Soc Nephrol, 2013. **8**(12): p. 2132-40.
193. Gutierrez, O.M., et al., *Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis.* N Engl J Med, 2008. **359**(6): p. 584-92.
194. Isakova, T., et al., *Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease.* JAMA, 2011. **305**(23): p. 2432-9.
195. Cozzolino, M., et al., *Is chronic kidney disease-mineral bone disorder (CKD-MBD) really a syndrome?* Nephrol Dial Transplant, 2014. **29**(10): p. 1815-20.
196. Navaneethan, S.D., et al., *Benefits and harms of phosphate binders in CKD: a systematic review of randomized controlled trials.* Am J Kidney Dis, 2009. **54**(4): p. 619-37.
197. Chertow, G.M., et al., *Baseline characteristics of subjects enrolled in the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) trial.* Nephrol Dial Transplant, 2012. **27**(7): p. 2872-9.
198. Block, G.A., et al., *Effect of Etelcalcetide vs Placebo on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: Two Randomized Clinical Trials.* JAMA, 2017. **317**(2): p. 146-155.
199. Block, G.A., et al., *Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis With Secondary Hyperparathyroidism: A Randomized Clinical Trial.* JAMA, 2017. **317**(2): p. 156-164.
200. Murray, A.M., et al., *Incidence of stroke before and after dialysis initiation in older patients.* J Am Soc Nephrol, 2013. **24**(7): p. 1166-73.
201. Eckardt, K.U., et al., *High cardiovascular event rates occur within the first weeks of starting hemodialysis.* Kidney Int, 2015. **88**(5): p. 1117-25.
202. Toyoda, K., et al., *Stroke in patients on maintenance hemodialysis: a 22-year single-center study.* Am J Kidney Dis, 2005. **45**(6): p. 1058-66.
203. Sozio, S.M., et al., *Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study.* Am J Kidney Dis, 2009. **54**(3): p. 468-77.
204. Foley, R.N., et al., *Long interdialytic interval and mortality among patients receiving hemodialysis.* N Engl J Med, 2011. **365**(12): p. 1099-107.
205. Georgianos, P.I., et al., *Adverse effects of conventional thrice-weekly hemodialysis: is it time to avoid 3-day interdialytic intervals?* Am J Nephrol, 2015. **41**(4-5): p. 400-8.
206. Power, A., *Stroke in dialysis and chronic kidney disease.* Blood Purif, 2013. **36**(3-4): p. 179-83.

207. Maduell, F., et al., *High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients.* J Am Soc Nephrol, 2013. **24**(3): p. 487-97.
208. Group, F.H.N.T., et al., *In-center hemodialysis six times per week versus three times per week.* N Engl J Med, 2010. **363**(24): p. 2287-300.
209. Culleton, B.F., et al., *Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial.* JAMA, 2007. **298**(11): p. 1291-9.
210. Selby, N.M., et al., *Dialysis-induced regional left ventricular dysfunction is ameliorated by cooling the dialysate.* Clin J Am Soc Nephrol, 2006. **1**(6): p. 1216-25.
211. Selby, N.M. and C.W. McIntyre, *A systematic review of the clinical effects of reducing dialysate fluid temperature.* Nephrol Dial Transplant, 2006. **21**(7): p. 1883-98.
212. Eldehni, M.T., A. Odudu, and C.W. McIntyre, *Randomized clinical trial of dialysate cooling and effects on brain white matter.* J Am Soc Nephrol, 2015. **26**(4): p. 957-65.
213. Hsu, C.Y., et al., *The risk of acute renal failure in patients with chronic kidney disease.* Kidney Int, 2008. **74**(1): p. 101-7.
214. Grams, M.E., et al., *A Meta-analysis of the Association of Estimated GFR, Albuminuria, Age, Race, and Sex With Acute Kidney Injury.* Am J Kidney Dis, 2015. **66**(4): p. 591-601.
215. Coca, S.G., K.C. Cho, and C.Y. Hsu, *Acute kidney injury in the elderly: predisposition to chronic kidney disease and vice versa.* Nephron Clin Pract, 2011. **119 Suppl 1**: p. c19-24.
216. Pannu, N., *Bidirectional relationships between acute kidney injury and chronic kidney disease.* Curr Opin Nephrol Hypertens, 2013. **22**(3): p. 351-6.
217. Chawla, L.S., et al., *Acute kidney injury and chronic kidney disease as interconnected syndromes.* N Engl J Med, 2014. **371**(1): p. 58-66.
218. Coca, S.G., S. Singanamala, and C.R. Parikh, *Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis.* Kidney Int, 2012. **81**(5): p. 442-8.
219. Odutayo, A., et al., *AKI and Long-Term Risk for Cardiovascular Events and Mortality.* J Am Soc Nephrol, 2017. **28**(1): p. 377-387.
220. Liu, M., et al., *Acute kidney injury leads to inflammation and functional changes in the brain.* J Am Soc Nephrol, 2008. **19**(7): p. 1360-70.
221. Herget-Rosenthal, S., et al., *Uremic toxins in acute kidney injury.* Semin Dial, 2009. **22**(4): p. 445-8.
222. Kelly, K.J., *Acute renal failure: much more than a kidney disease.* Semin Nephrol, 2006. **26**(2): p. 105-13.
223. Grams, M.E. and H. Rabb, *The distant organ effects of acute kidney injury.* Kidney Int, 2012. **81**(10): p. 942-948.
224. Vasan, R.S., et al., *Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study.* Circulation, 2003. **107**(11): p. 1486-91.
225. Cohen, G. and W.H. Horl, *Retinol binding protein isolated from acute renal failure patients inhibits polymorphonuclear leucocyte functions.* Eur J Clin Invest, 2004. **34**(11): p. 774-81.
226. McIntyre, C.W. and D.J. Goldsmith, *Ischemic brain injury in hemodialysis patients: which is more dangerous, hypertension or intradialytic hypotension?* Kidney Int, 2015. **87**(6): p. 1109-15.
227. Polinder-Bos, H.A., et al., *Hemodialysis Induces an Acute Decline in Cerebral Blood Flow in Elderly Patients.* J Am Soc Nephrol, 2018. **29**(4): p. 1317-1325.
228. Wiesholzer, M., et al., *Incidence of stroke among chronic hemodialysis patients with nonrheumatic atrial fibrillation.* Am J Nephrol, 2001. **21**(1): p. 35-9.
229. Drew, D.A. and M.J. Sarnak, *Ischemic and hemorrhagic stroke: high incidence in hemodialysis and peritoneal dialysis patients.* Am J Kidney Dis, 2014. **63**(4): p. 547-8.

230. *How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. Stroke Unit Trialists Collaboration.* Stroke, 1997. **28**(11): p. 2139-44.
231. Stroke Unit Trialists, C., *Organised inpatient (stroke unit) care for stroke.* Cochrane Database Syst Rev, 2013(9): p. CD000197.
232. McKinney, J.S., et al., *Comprehensive stroke centers may be associated with improved survival in hemorrhagic stroke.* J Am Heart Assoc, 2015. **4**(5).
233. Stroke Units Tralists Collaboration, *How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. Stroke Unit Trialists Collaboration.* Stroke, 1997. **28**(11): p. 2139-44.
234. Stroke Unit Trialists, C., *Organised inpatient (stroke unit) care for stroke.* Cochrane Database Syst Rev, 2013. **9**: p. CD000197.
235. Balami, J.S., et al., *The exact science of stroke thrombolysis and the quiet art of patient selection.* Brain, 2013. **136**(Pt 12): p. 3528-53.
236. Prabhakaran, S., I. Ruff, and R.A. Bernstein, *Acute stroke intervention: a systematic review.* JAMA, 2015. **313**(14): p. 1451-62.
237. Wardlaw, J.M., et al., *Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis.* Lancet, 2012. **379**(9834): p. 2364-72.
238. Wahlgren, N., et al., *Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study.* Lancet, 2007. **369**(9558): p. 275-82.
239. Shobha, N., et al., *Thrombolysis at 3-4.5 hours after acute ischemic stroke onset--evidence from the Canadian Alteplase for Stroke Effectiveness Study (CASES) registry.* Cerebrovasc Dis, 2011. **31**(3): p. 223-8.
240. Tan Tanny, S.P., et al., *Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke: experience from Australian stroke center.* Stroke, 2013. **44**(8): p. 2269-74.
241. Agrawal, V., et al., *In-hospital outcomes with thrombolytic therapy in patients with renal dysfunction presenting with acute ischaemic stroke.* Nephrol Dial Transplant, 2010. **25**(4): p. 1150-7.
242. Lyrer, P.A., et al., *Renal function and outcome among stroke patients treated with IV thrombolysis.* Neurology, 2008. **71**(19): p. 1548-50.
243. Naganuma, M., et al., *Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA registry.* Cerebrovasc Dis, 2011. **31**(2): p. 123-9.
244. Power, A., et al., *Renal impairment reduces the efficacy of thrombolytic therapy in acute ischemic stroke.* Cerebrovasc Dis, 2013. **35**(1): p. 45-52.
245. Ma, H., et al., *Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke.* N Engl J Med, 2019. **380**(19): p. 1795-1803.
246. Marshall, R.S., *Image-Guided Intravenous Alteplase for Stroke - Shattering a Time Window.* N Engl J Med, 2019. **380**(19): p. 1865-1866.
247. Gonzalez, R.G., et al., *Good outcome rate of 35% in IV-tPA-treated patients with computed tomography angiography confirmed severe anterior circulation occlusive stroke.* Stroke, 2013. **44**(11): p. 3109-13.
248. Broderick, J.P., et al., *Endovascular therapy after intravenous t-PA versus t-PA alone for stroke.* N Engl J Med, 2013. **368**(10): p. 893-903.
249. Khandelwal, P., D.R. Yavagal, and R.L. Sacco, *Acute Ischemic Stroke Intervention.* J Am Coll Cardiol, 2016. **67**(22): p. 2631-44.
250. Ciccone, A., et al., *Endovascular treatment for acute ischemic stroke.* N Engl J Med, 2013. **368**(10): p. 904-13.

251. Kidwell, C.S., et al., *A trial of imaging selection and endovascular treatment for ischemic stroke.* N Engl J Med, 2013. **368**(10): p. 914-23.
252. Khatri, P., et al., *State of acute endovascular therapy: report from the 12th thrombolysis, thrombectomy, and acute stroke therapy conference.* Stroke, 2015. **46**(6): p. 1727-34.
253. Berkhemer, O.A., et al., *A randomized trial of intraarterial treatment for acute ischemic stroke.* N Engl J Med, 2015. **372**(1): p. 11-20.
254. Campbell, B.C., et al., *Endovascular therapy for ischemic stroke with perfusion-imaging selection.* N Engl J Med, 2015. **372**(11): p. 1009-18.
255. Goyal, M., et al., *Randomized assessment of rapid endovascular treatment of ischemic stroke.* N Engl J Med, 2015. **372**(11): p. 1019-30.
256. Saver, J.L., et al., *Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke.* N Engl J Med, 2015. **372**(24): p. 2285-95.
257. Jovin, T.G., et al., *Thrombectomy within 8 hours after symptom onset in ischemic stroke.* N Engl J Med, 2015. **372**(24): p. 2296-306.
258. Mocco, J., et al., *Aspiration Thrombectomy After Intravenous Alteplase Versus Intravenous Alteplase Alone.* Stroke, 2016. **47**(9): p. 2331-8.
259. Bracard, S., et al., *Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial.* Lancet Neurol, 2016. **15**(11): p. 1138-47.
260. Meurer, W.J., et al., *Rapid Systematic Review: Intra-Arterial Thrombectomy ("Clot Retrieval") for Selected Patients with Acute Ischemic Stroke.* J Emerg Med, 2017. **52**(2): p. 255-261.
261. Powers, W.J., et al., *2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association.* Stroke, 2015. **46**(10): p. 3020-35.
262. Kwolek, C.J. and R.S. Crawford, *Training the next generation of vascular specialists: current status and future perspectives.* J Endovasc Ther, 2009. **16 Suppl 1**: p. I42-52.
263. Bhaskar, S., et al., *Reperfusion therapy in acute ischemic stroke: dawn of a new era?* BMC Neurol, 2018. **18**(1): p. 8.
264. G., E., *A history of urolithiasis.* Clin Rev Bone Min Metab, 2004. **2**: p. 172-185.
265. Eknoyan, G. and J. Nagy, *A history of diabetes mellitus or how a disease of the kidneys evolved into a kidney disease.* Adv Chronic Kidney Dis, 2005. **12**(2): p. 223-9.
266. Eknoyan, G., *Emergence of the concept of acute renal failure.* Am J Nephrol, 2002. **22**(2-3): p. 225-30.
267. Eknoyan, G., *The origins of nephrology--Galen, the founding father of experimental renal physiology.* Am J Nephrol, 1989. **9**(1): p. 66-82.
268. Richards, A.N., *Direct observations of change in function of the renal tubule caused by certain poisons.* Trans Assoc Am Phys, 1929(44): p. 64-67.
269. Richards, A.N., *Process of urine formation.* Proc R Soc Med Hist, 1938(126): p. 398-432.
270. Bywaters, E.G. and D. Beall, *Crush Injuries with Impairment of Renal Function.* Br Med J, 1941. **1**(4185): p. 427-32.
271. Oliver, J., D.M. Mac, and A. Tracy, *The pathogenesis of acute renal failure associated with traumatic and toxic injury; renal ischemia, nephrotoxic damage and the ischemic episode.* J Clin Invest, 1951. **30**(12:1): p. 1307-439.
272. Smith, H.W., *The Kidney: Structure and Function in Health and Disease*. 1951, New York: Oxford University Press.
273. Giebisch, G., *Homer W. Smith's contribution to renal physiology.* J Nephrol, 2004. **17**(1): p. 159-65.
274. Henderson, L.W., *A Tribute to Willem Johan Kolff, M.D., 1912–2009.* J Am Soc Nephrol, 2009. **20**(5): p. 923-924.

275. Morrissey, M., *Willem J Kolff (1911-2009): physician, inventor and pioneer: father of artificial organs.* J Med Biogr, 2012. **20**(3): p. 136-8.
276. Swann, R.C., Merrill, J.P., *The clinical course of acute renal failure.* Medicine, 1953. **32**: p. 215-292.
277. Epstein, M., *John P. Merrill: the father of nephrology as a specialty.* Clin J Am Soc Nephrol, 2009. **4**(1): p. 2-8.
278. Schreiner, G.E., *Acute renal failure: the dawn of dialysis and the roaring 50s.* Nephrol Dial Transplant, 1994. **9 Suppl 4**: p. 1-8.
279. Murray, P.T., et al., *A framework and key research questions in AKI diagnosis and staging in different environments.* Clin J Am Soc Nephrol, 2008. **3**(3): p. 864-8.
280. Kellum, J.A., Lameire, N., Aspelin, P., Barsoum, R. S., Burdmann, E. A., Goldstein, S. L., Herzog, C. A., Joannidis, M., Kribben, A., Levey, A. S., MacLeod, A. M., Mehta, R. L., Murray, P. T., Saraladevi N., Opal, S. M., Schaefer, F., Schetz, M., Uchino, S. Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group., *KDIGO clinical practice guideline for acute kidney injury.* Kidney Int Suppl, 2012. **2**(1): p. 1-138.
281. Bellomo, R., et al., *Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group.* Crit Care, 2004. **8**(4): p. R204-12.
282. Mehta, R.L., et al., *Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury.* Crit Care, 2007. **11**(2): p. R31.
283. Praught, M.L. and M.G. Shlipak, *Are small changes in serum creatinine an important risk factor?* Curr Opin Nephrol Hypertens, 2005. **14**(3): p. 265-70.
284. Lameire, N.H., et al., *Acute kidney injury: an increasing global concern.* Lancet, 2013. **382**(9887): p. 170-9.
285. Hsu, C.Y., et al., *Community-based incidence of acute renal failure.* Kidney Int, 2007. **72**(2): p. 208-12.
286. Hsu, R.K., et al., *Temporal changes in incidence of dialysis-requiring AKI.* J Am Soc Nephrol, 2013. **24**(1): p. 37-42.
287. Rewa, O. and S.M. Bagshaw, *Acute kidney injury-epidemiology, outcomes and economics.* Nat Rev Nephrol, 2014. **10**(4): p. 193-207.
288. Siew, E.D. and A. Davenport, *The growth of acute kidney injury: a rising tide or just closer attention to detail?* Kidney Int, 2015. **87**(1): p. 46-61.
289. Susantitaphong, P., et al., *World incidence of AKI: a meta-analysis.* Clin J Am Soc Nephrol, 2013. **8**(9): p. 1482-93.
290. Liano, F., et al., *The spectrum of acute renal failure in the intensive care unit compared with that seen in other settings. The Madrid Acute Renal Failure Study Group.* Kidney Int Suppl, 1998. **66**: p. S16-24.
291. Metcalfe, W., et al., *Acute renal failure requiring renal replacement therapy: incidence and outcome.* QJM, 2002. **95**(9): p. 579-83.
292. Chertow, G.M., et al., *Acute kidney injury, mortality, length of stay, and costs in hospitalized patients.* J Am Soc Nephrol, 2005. **16**(11): p. 3365-70.
293. Khan, F. and J.F. Pallant, *Use of the International Classification of Functioning, Disability and Health (ICF) to identify preliminary comprehensive and brief core sets for multiple sclerosis.* Disabil Rehabil, 2007. **29**(3): p. 205-13.
294. Selby, N.M., et al., *Use of electronic results reporting to diagnose and monitor AKI in hospitalized patients.* Clin J Am Soc Nephrol, 2012. **7**(4): p. 533-40.
295. Silver, S.A., et al., *Cost of Acute Kidney Injury in Hospitalized Patients.* J Hosp Med, 2017. **12**(2): p. 70-76.

296. Abosaif, N.Y., et al., *The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability.* Am J Kidney Dis, 2005. **46**(6): p. 1038-48.
297. Chang, C.H., et al., *Acute kidney injury enhances outcome prediction ability of sequential organ failure assessment score in critically ill patients.* PLoS One, 2014. **9**(10): p. e109649.
298. Kerr, M., et al., *The economic impact of acute kidney injury in England.* Nephrol Dial Transplant, 2014. **29**(7): p. 1362-8.
299. Hoste, E.A., et al., *RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis.* Crit Care, 2006. **10**(3): p. R73.
300. Lewington, A.J., J. Cerda, and R.L. Mehta, *Raising awareness of acute kidney injury: a global perspective of a silent killer.* Kidney Int, 2013. **84**(3): p. 457-67.
301. Tan, S.S., G. Gao, and S. Koch, *Big Data and Analytics in Healthcare.* Methods Inf Med, 2015. **54**(6): p. 546-7.
302. Appelbe B, B.D., *eResearch - paradigm shift or propaganda?* Journal of Research and Practice in Information Technology, 2007. **39**: p. 83-90.
303. Kellum, J.A., D.R. DeAlmeida, and V.J. Watzlaf, *eResearch: the case of acute kidney injury.* Intensive Care Med, 2013. **39**(3): p. 522-3.
304. James, M. and N. Pannu, *Methodological considerations for observational studies of acute kidney injury using existing data sources.* J Nephrol, 2009. **22**(3): p. 295-305.
305. Siew, E.D., et al., *Optimizing administrative datasets to examine acute kidney injury in the era of big data: workgroup statement from the 15(th) ADQI Consensus Conference.* Can J Kidney Health Dis, 2016. **3**: p. 12.
306. Grams, M.E., et al., *Performance and limitations of administrative data in the identification of AKI.* Clin J Am Soc Nephrol, 2014. **9**(4): p. 682-9.
307. Go, A.S., et al., *The assessment, serial evaluation, and subsequent sequelae of acute kidney injury (ASSESS-AKI) study: design and methods.* BMC Nephrol, 2010. **11**: p. 22.
308. Siew, E.D., et al., *Commonly used surrogates for baseline renal function affect the classification and prognosis of acute kidney injury.* Kidney Int, 2010. **77**(6): p. 536-42.
309. Siew, E.D., et al., *Estimating baseline kidney function in hospitalized patients with impaired kidney function.* Clin J Am Soc Nephrol, 2012. **7**(5): p. 712-9.
310. Matheny, M.E., et al., *Laboratory test surveillance following acute kidney injury.* PLoS One, 2014. **9**(8): p. e103746.
311. Siew, E.D. and M.E. Matheny, *Choice of Reference Serum Creatinine in Defining Acute Kidney Injury.* Nephron, 2015. **131**(2): p. 107-12.
312. Leaf, D.E., et al., *Excessive diagnostic testing in acute kidney injury.* BMC Nephrol, 2016. **17**: p. 9.
313. Liu, K.D., et al., *Acute Kidney Injury Ascertainment Is Affected by the Use of First Inpatient Versus Outpatient Baseline Serum Creatinine.* Kidney Int Rep, 2018. **3**(1): p. 211-215.
314. Bernier-Jean, A., et al., *Diagnosis and outcomes of acute kidney injury using surrogate and imputation methods for missing preadmission creatinine values.* BMC Nephrol, 2017. **18**(1): p. 141.
315. Myers, G.L., et al., *Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program.* Clin Chem, 2006. **52**(1): p. 5-18.
316. Levey, A.S., et al., *Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values.* Clin Chem, 2007. **53**(4): p. 766-72.
317. Levey, A.S., et al., *A new equation to estimate glomerular filtration rate.* Ann Intern Med, 2009. **150**(9): p. 604-12.

318. Ad-hoc working group of, E., et al., *A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy.* Nephrol Dial Transplant, 2012. **27**(12): p. 4263-72.
319. Lafrance, J.P. and D.R. Miller, *Defining acute kidney injury in database studies: the effects of varying the baseline kidney function assessment period and considering CKD status.* Am J Kidney Dis, 2010. **56**(4): p. 651-60.
320. Bagshaw, S.M., et al., *A comparison of observed versus estimated baseline creatinine for determination of RIFLE class in patients with acute kidney injury.* Nephrol Dial Transplant, 2009. **24**(9): p. 2739-44.
321. Joyce, E.L., et al., *eResearch in acute kidney injury: a primer for electronic health record research.* Nephrol Dial Transplant, 2019. **34**(3): p. 401-407.
322. Broce, J.C., et al., *Hospital-acquired acute kidney injury: an analysis of nadir-to-peak serum creatinine increments stratified by baseline estimated GFR.* Clin J Am Soc Nephrol, 2011. **6**(7): p. 1556-65.
323. Sawhney, S., et al., *Maximising Acute Kidney Injury Alerts--A Cross-Sectional Comparison with the Clinical Diagnosis.* PLoS One, 2015. **10**(6): p. e0131909.
324. Levey, A.S., et al., *A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group.* Ann Intern Med, 1999. **130**(6): p. 461-70.
325. Zavada, J., et al., *A comparison of three methods to estimate baseline creatinine for RIFLE classification.* Nephrol Dial Transplant, 2010. **25**(12): p. 3911-8.
326. Kellum, J.A., et al., *Classifying AKI by Urine Output versus Serum Creatinine Level.* J Am Soc Nephrol, 2015. **26**(9): p. 2231-8.
327. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* PLoS Med, 2009. **6**(7): p. e1000097.
328. Wells GA, S.B., O'Connell D, Peterson J, Welch V, Losos M, et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses.* [cited 2017 03/03/2017]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
329. Serghiou, S. and S.N. Goodman, *Random-Effects Meta-analysis: Summarizing Evidence With Caveats.* JAMA, 2019. **321**(3): p. 301-302.
330. Covic, A., et al., *The impact of acute kidney injury on short-term survival in an Eastern European population with stroke.* Nephrol Dial Transplant, 2008. **23**(7): p. 2228-34.
331. Khatri, M., et al., *Acute kidney injury is associated with increased hospital mortality after stroke.* J Stroke Cerebrovasc Dis, 2014. **23**(1): p. 25-30.
332. Lin, S., et al., *Characteristics, treatment and outcome of ischemic stroke with atrial fibrillation in a Chinese hospital-based stroke study.* Cerebrovasc Dis, 2011. **31**(5): p. 419-26.
333. Mohamed, W., et al., *Which Comorbidities and Complications Predict Ischemic Stroke Recovery and Length of Stay?* Neurologist, 2015. **20**(2): p. 27-32.
334. Saeed, F., et al., *Acute renal failure is associated with higher death and disability in patients with acute ischemic stroke: analysis of nationwide inpatient sample.* Stroke, 2014. **45**(5): p. 1478-80.
335. Saeed, F., et al., *Acute renal failure worsens in-hospital outcomes in patients with intracerebral hemorrhage.* J Stroke Cerebrovasc Dis, 2015. **24**(4): p. 789-94.
336. Tsagalis, G., et al., *Long-term prognosis of acute kidney injury after first acute stroke.* Clin J Am Soc Nephrol, 2009. **4**(3): p. 616-22.
337. Nadkarni, G.N., et al., *Dialysis Requiring Acute Kidney Injury in Acute Cerebrovascular Accident Hospitalizations.* Stroke, 2015. **46**(11): p. 3226-31.

338. Waikar, S.S., et al., *Validity of International Classification of Diseases, Ninth Revision, Clinical Modification Codes for Acute Renal Failure.* J Am Soc Nephrol, 2006. **17**(6): p. 1688-94.
339. Jannot, A.S., et al., *The Diagnosis-Wide Landscape of Hospital-Acquired AKI.* Clin J Am Soc Nephrol, 2017. **12**(6): p. 874-884.
340. Silver, S.A. and G.M. Chertow, *The Economic Consequences of Acute Kidney Injury.* Nephron, 2017.
341. Bedford, M., et al., *What is the real impact of acute kidney injury?* BMC Nephrol, 2014. **15**: p. 95.
342. Lassnigg, A., et al., *Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study.* J Am Soc Nephrol, 2004. **15**(6): p. 1597-605.
343. Goldenberg, I., M. Chonchol, and V. Guetta, *Reversible acute kidney injury following contrast exposure and the risk of long-term mortality.* Am J Nephrol, 2009. **29**(2): p. 136-44.
344. James, M.T., et al., *Associations between acute kidney injury and cardiovascular and renal outcomes after coronary angiography.* Circulation, 2011. **123**(4): p. 409-16.
345. Weisbord, S.D., *AKI and medical care after coronary angiography: renalism revisited.* Clin J Am Soc Nephrol, 2014. **9**(11): p. 1823-5.
346. Hsu, R.K. and C.Y. Hsu, *The Role of Acute Kidney Injury in Chronic Kidney Disease.* Semin Nephrol, 2016. **36**(4): p. 283-92.
347. Kumar, S., M.H. Selim, and L.R. Caplan, *Medical complications after stroke.* Lancet Neurol, 2010. **9**(1): p. 105-18.
348. Prosser, J., et al., *Predictors of early cardiac morbidity and mortality after ischemic stroke.* Stroke, 2007. **38**(8): p. 2295-302.
349. Simmons, E.M., et al., *Plasma cytokine levels predict mortality in patients with acute renal failure.* Kidney Int, 2004. **65**(4): p. 1357-65.
350. Lisowska-Myjak, B., *Uremic toxins and their effects on multiple organ systems.* Nephron Clin Pract, 2014. **128**(3-4): p. 303-11.
351. Himmelfarb, J., et al., *Oxidative stress is increased in critically ill patients with acute renal failure.* J Am Soc Nephrol, 2004. **15**(9): p. 2449-56.
352. Basi, S., et al., *Insulin resistance in critically ill patients with acute renal failure.* Am J Physiol Renal Physiol, 2005. **289**(2): p. F259-64.
353. Tsagalis, G., et al., *Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality.* Nephrol Dial Transplant, 2009. **24**(1): p. 194-200.
354. Chawla, L.S., et al., *Association between AKI and long-term renal and cardiovascular outcomes in United States veterans.* Clin J Am Soc Nephrol, 2014. **9**(3): p. 448-56.
355. Wu, V.C., et al., *The impact of acute kidney injury on the long-term risk of stroke.* J Am Heart Assoc, 2014. **3**(4).
356. Reinecke, H., et al., *Dilemmas in the management of atrial fibrillation in chronic kidney disease.* J Am Soc Nephrol, 2009. **20**(4): p. 705-11.
357. Sinnaeve, P.R., et al., *Stroke prevention in elderly patients with atrial fibrillation: challenges for anticoagulation.* J Intern Med, 2012. **271**(1): p. 15-24.
358. Moscucci, M., et al., *Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE).* Eur Heart J, 2003. **24**(20): p. 1815-23.
359. Moretti, C., et al., *Impact on prognosis of periprocedural bleeding after TAVI: mid-term follow-up of a multicenter prospective study.* J Interv Cardiol, 2014. **27**(3): p. 293-9.
360. Wattanakit, K., et al., *Chronic kidney disease increases risk for venous thromboembolism.* J Am Soc Nephrol, 2008. **19**(1): p. 135-40.
361. Rath, C.E., J.A. Mailliard, and G.E. Schreiner, *Bleeding tendency in uremia.* N Engl J Med, 1957. **257**(17): p. 808-11.

362. Castaldi, P.A., M.C. Rozenberg, and J.H. Stewart, *The bleeding disorder of uraemia. A qualitative platelet defect.* Lancet, 1966. **2**(7454): p. 66-9.
363. Narula, A., et al., *Contrast-induced acute kidney injury after primary percutaneous coronary intervention: results from the HORIZONS-AMI substudy.* Eur Heart J, 2014. **35**(23): p. 1533-40.
364. Gargiulo, G., et al., *Moderate and severe preoperative chronic kidney disease worsen clinical outcomes after transcatheter aortic valve implantation: meta-analysis of 4992 patients.* Circ Cardiovasc Interv, 2015. **8**(2): p. e002220.
365. Bagshaw, S.M., et al., *Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes.* Clin J Am Soc Nephrol, 2007. **2**(3): p. 431-9.
366. Bihorac, A., et al., *Long-term risk of mortality and acute kidney injury during hospitalization after major surgery.* Ann Surg, 2009. **249**(5): p. 851-8.
367. Coca, S.G., et al., *Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis.* Am J Kidney Dis, 2009. **53**(6): p. 961-73.
368. Karkouti, K., et al., *Acute kidney injury after cardiac surgery: focus on modifiable risk factors.* Circulation, 2009. **119**(4): p. 495-502.
369. Wang, H.E., et al., *Acute kidney injury and mortality in hospitalized patients.* Am J Nephrol, 2012. **35**(4): p. 349-55.
370. Arnold, J., et al., *Incidence and impact on outcomes of acute kidney injury after a stroke: a systematic review and meta-analysis.* BMC Nephrol, 2018. **19**(1): p. 283.
371. Luengo-Fernandez, R., J. Leal, and A. Gray, *UK research spend in 2008 and 2012: comparing stroke, cancer, coronary heart disease and dementia.* BMJ Open, 2015. **5**(4): p. e006648.
372. Slyter, H., *Ethical challenges in stroke research.* Stroke, 1998. **29**(8): p. 1725-9.
373. Bernhardt, J., et al., *Advances in Stroke 2017.* Stroke, 2018. **49**(5): p. e174-e199.
374. Physicians, R.C.o. *Sentinel Stroke National Audit Programme (SSNAP)*. 2015 02/02/2019]; Available from: https://www.strokeaudit.org/.
375. Ng, K.P., J.N. Townend, and C.J. Ferro, *Randomised-controlled trials in chronic kidney disease--a call to arms!* Int J Clin Pract, 2012. **66**(10): p. 913-5.
376. Perkovic, V. and B. Neal, *Trials in kidney disease--time to EVOLVE.* N Engl J Med, 2012. **367**(26): p. 2541-2.
377. Chue, C.D., et al., *Cardiovascular effects of sevelamer in stage 3 CKD.* J Am Soc Nephrol, 2013. **24**(5): p. 842-52.
378. Palmer, S.C., et al., *Effects of antiplatelet therapy on mortality and cardiovascular and bleeding outcomes in persons with chronic kidney disease: a systematic review and meta-analysis.* Ann Intern Med, 2012. **156**(6): p. 445-59.
379. Melloni, C., et al., *Impact of chronic kidney disease on long-term ischemic and bleeding outcomes in medically managed patients with acute coronary syndromes: Insights from the TRILOGY ACS Trial.* Eur Heart J Acute Cardiovasc Care, 2016. **5**(6): p. 443-454.
380. Shroff, G.R., R. Stoecker, and A. Hart, *Non-Vitamin K-Dependent Oral Anticoagulants for Nonvalvular Atrial Fibrillation in Patients With CKD: Pragmatic Considerations for the Clinician.* Am J Kidney Dis, 2018. **72**(5): p. 717-727.
381. Johnston, S.C., et al., *Effect of a US National Institutes of Health programme of clinical trials on public health and costs.* Lancet, 2006. **367**(9519): p. 1319-27.
382. Benson, K. and A.J. Hartz, *A comparison of observational studies and randomized, controlled trials.* N Engl J Med, 2000. **342**(25): p. 1878-86.
383. Concato, J., N. Shah, and R.I. Horwitz, *Randomized, controlled trials, observational studies, and the hierarchy of research designs.* N Engl J Med, 2000. **342**(25): p. 1887-92.
384. Thadhani, R. and M. Tonelli, *Cohort studies: marching forward.* Clin J Am Soc Nephrol, 2006. **1**(5): p. 1117-23.

385. Williams, J.G., et al., *Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.* Health Technol Assess, 2003. **7**(26): p. iii, v-x, 1-117.
386. van Staa, T.P., et al., *The opportunities and challenges of pragmatic point-of-care randomised trials using routinely collected electronic records: evaluations of two exemplar trials.* Health Technol Assess, 2014. **18**(43): p. 1-146.
387. Arnold, J.J., et al., *Acute Care QUAliTy in chronic Kidney disease (ACQUATIK): a prospective cohort study exploring outcomes of patients with chronic kidney disease.* BMJ Open, 2015. **5**(4): p. e006987.
388. England, N. *Digital Technology: Connected Digital Systems- Acute Global Digital Exemplars*. 04/03/2019]; Available from: https://www.england.nhs.uk/digitaltechnology/connecteddigitalsystems/exemplars/acute-global-digital-exemplars/.
389. von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.* Epidemiology, 2007. **18**(6): p. 800-4.
390. North American Symptomatic Carotid Endarterectomy Trial, C., et al., *Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis.* N Engl J Med, 1991. **325**(7): p. 445-53.
391. Grant, E.G., et al., *Carotid artery stenosis: grayscale and Doppler ultrasound diagnosis--Society of Radiologists in Ultrasound consensus conference.* Ultrasound Q, 2003. **19**(4): p. 190-8.
392. Government, D.f.C.a.L. *English indices of deprivation 2010*. 2010 25/09/2015]; Available from: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2010.
393. Jurawan, N., et al., *Hospital acquired Acute Kidney Injury is associated with increased mortality but not increased readmission rates in a UK acute hospital.* BMC Nephrol, 2017. **18**(1): p. 317.
394. Burns, E.M., et al., *Variation in reoperation after colorectal surgery in England as an indicator of surgical performance: retrospective analysis of Hospital Episode Statistics.* BMJ, 2011. **343**: p. d4836.
395. Ferro, C.J., et al., *Fracture risk and mortality post kidney transplantation.* Clin Transplant, 2015.
396. Mc, N.Q., *Note on the sampling error of the difference between correlated proportions or percentages.* Psychometrika, 1947. **12**(2): p. 153-7.
397. Tripepi, G., et al., *Linear and logistic regression analysis.* Kidney Int, 2008. **73**(7): p. 806-10.
398. Norton, E.C., B.E. Dowd, and M.L. Maciejewski, *Odds Ratios-Current Best Practice and Use.* JAMA, 2018. **320**(1): p. 84-85.
399. Jager, K.J., et al., *The analysis of survival data: the Kaplan-Meier method.* Kidney Int, 2008. **74**(5): p. 560-5.
400. van Dijk, P.C., et al., *The analysis of survival data in nephrology: basic concepts and methods of Cox regression.* Kidney Int, 2008. **74**(6): p. 705-9.
401. Tolles, J. and R. Lewis, *Time-to-event analysis.* JAMA, 2016. **315**: p. 1046-1047.
402. Bland, J.M. and D.G. Altman, *Statistical methods for assessing agreement between two methods of clinical measurement.* Lancet, 1986. **1**(8476): p. 307-10.
403. Giavarina, D., *Understanding Bland Altman analysis.* Biochem Med (Zagreb), 2015. **25**(2): p. 141-51.
404. Dwyer, A.J., *Matchmaking and McNemar in the comparison of diagnostic modalities.* Radiology, 1991. **178**(2): p. 328-30.

405. Saunders, C.L., et al., *Accuracy of routinely recorded ethnic group information compared with self-reported ethnicity: evidence from the English Cancer Patient Experience survey.* BMJ Open, 2013. **3**(6).
406. Uchino, S., *Creatinine.* Curr Opin Crit Care, 2010. **16**(6): p. 562-7.
407. Waikar, S.S., K.D. Liu, and G.M. Chertow, *Diagnosis, epidemiology and outcomes of acute kidney injury.* Clin J Am Soc Nephrol, 2008. **3**(3): p. 844-61.
408. Murray, P.T., et al., *Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference.* Kidney Int, 2014. **85**(3): p. 513-21.
409. Mishra, J., et al., *Amelioration of ischemic acute renal injury by neutrophil gelatinase-associated lipocalin.* J Am Soc Nephrol, 2004. **15**(12): p. 3073-82.
410. Mori, K., et al., *Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury.* J Clin Invest, 2005. **115**(3): p. 610-21.
411. Ichimura, T., et al., *Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury.* J Biol Chem, 1998. **273**(7): p. 4135-42.
412. Wu, H., et al., *IL-18 contributes to renal damage after ischemia-reperfusion.* J Am Soc Nephrol, 2008. **19**(12): p. 2331-41.
413. Zhang, A., et al., *Diagnosis and prognosis of neutrophil gelatinase-associated lipocalin for acute kidney injury with sepsis: a systematic review and meta-analysis.* Crit Care, 2016. **20**: p. 41.
414. Su, L.J., et al., *Predictive value of cell cycle arrest biomarkers for cardiac surgery-associated acute kidney injury: a meta-analysis.* British Journal of Anaesthesia, 2018.
415. Alge, J.L. and J.M. Arthur, *Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications.* Clin J Am Soc Nephrol, 2015. **10**(1): p. 147-55.
416. Kashani, K., et al., *Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury.* Crit Care, 2013. **17**(1): p. R25.
417. Thomas, M.E., et al., *The definition of acute kidney injury and its use in practice.* Kidney Int, 2015. **87**(1): p. 62-73.
418. Pickering, J.W. and Z.H. Endre, *The definition and detection of acute kidney injury.* J Renal Inj Prev, 2014. **3**(1): p. 21-5.
419. Malhotra, R. and E.D. Siew, *Biomarkers for the Early Detection and Prognosis of Acute Kidney Injury.* Clin J Am Soc Nephrol, 2017. **12**(1): p. 149-173.
420. Organisation, W.H. *WHO Mortality Database*. [cited 9 March 2017; Available from: http://www.who.int/healthinfo/mortality_data/en/.
421. Kim, S. and W. Lee, *Does McNemar's test compare the sensitivities and specificities of two diagnostic tests?* Stat Methods Med Res, 2014. **26**(1): p. 142-154.
422. Doi, K., et al., *Reduced production of creatinine limits its use as marker of kidney injury in sepsis.* J Am Soc Nephrol, 2009. **20**(6): p. 1217-21.
423. Wilson, F.P., et al., *Creatinine generation is reduced in patients requiring continuous venovenous hemodialysis and independently predicts mortality.* Nephrol Dial Transplant, 2012. **27**(11): p. 4088-94.
424. Elwenspoek, M.M.C., et al., *Are guidelines for monitoring chronic disease in primary care evidence based?* BMJ, 2019. **365**: p. l2319.
425. Sutcliffe, D., et al., *NICE and the Quality and Outcomes Framework (QOF) 2009-2011.* Qual Prim Care, 2012. **20**(1): p. 47-55.
426. Digital, N. *NHS Payments to General Practice - England, 2017/18*. 2018 9 July 2019]; Available from: https://digital.nhs.uk/data-and-information/publications/statistical/nhs-payments-to-general-practice/england-2017-18.

427. Excellence, N.I.f.H.a.C. *Chronic kidney disease in adults: assessment and management (Clinical guideline CG182)*. 2014 9 July 2019]; Available from: https://www.nice.org.uk/guidance/cg182.
428. De Rosa, S., S. Samoni, and C. Ronco, *Creatinine-based definitions: from baseline creatinine to serum creatinine adjustment in intensive care.* Crit Care, 2016. **20**: p. 69.
429. Toffaletti, J.G. and E.H. McDonnell, *Variation of serum creatinine, cystatin C, and creatinine clearance tests in persons with normal renal function.* Clin Chim Acta, 2008. **395**(1-2): p. 115-9.
430. Reinhard, M., E.J. Erlandsen, and E. Randers, *Biological variation of cystatin C and creatinine.* Scand J Clin Lab Invest, 2009. **69**(8): p. 831-6.
431. Delanaye, P., E. Cavalier, and H. Pottel, *Serum Creatinine: Not So Simple!* Nephron, 2017. **136**(4): p. 302-308.
432. Mehta, R.L., et al., *International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology.* Lancet, 2015. **385**(9987): p. 2616-43.
433. Uchino, S., et al., *An assessment of the RIFLE criteria for acute renal failure in hospitalized patients.* Crit Care Med, 2006. **34**(7): p. 1913-7.
434. Nedeltchev, K., et al., *Predictors of early mortality after acute ischaemic stroke.* Swiss Med Wkly, 2010. **140**(17-18): p. 254-9.
435. Smith, E.E., et al., *Risk score for in-hospital ischemic stroke mortality derived and validated within the Get With the Guidelines-Stroke Program.* Circulation, 2010. **122**(15): p. 1496-504.
436. Myint, P.K., et al., *Important factors in predicting mortality outcome from stroke: findings from the Anglia Stroke Clinical Network Evaluation Study.* Age Ageing, 2017. **46**(1): p. 83-90.
437. Weimar, C., et al., *Age and National Institutes of Health Stroke Scale Score within 6 hours after onset are accurate predictors of outcome after cerebral ischemia: development and external validation of prognostic models.* Stroke, 2004. **35**(1): p. 158-62.
438. Fonarow, G.C., et al., *Relationship of national institutes of health stroke scale to 30-day mortality in medicare beneficiaries with acute ischemic stroke.* J Am Heart Assoc, 2012. **1**(1): p. 42-50.
439. Gattringer, T., et al., *Predicting Early Mortality of Acute Ischemic Stroke.* Stroke, 2019. **50**(2): p. 349-356.
440. Babitt, J.L. and H.Y. Lin, *Mechanisms of anemia in CKD.* J Am Soc Nephrol, 2012. **23**(10): p. 1631-4.
441. Groenveld, H.F., et al., *Anemia and mortality in heart failure patients a systematic review and meta-analysis.* J Am Coll Cardiol, 2008. **52**(10): p. 818-27.
442. Anand, I.S. and P. Gupta, *Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies.* Circulation, 2018. **138**(1): p. 80-98.
443. Lawler, P.R., et al., *Anemia and mortality in acute coronary syndromes: a systematic review and meta-analysis.* Am Heart J, 2013. **165**(2): p. 143-53 e5.
444. Mamas, M.A., et al., *Relationship Between Anemia and Mortality Outcomes in a National Acute Coronary Syndrome Cohort: Insights From the UK Myocardial Ischemia National Audit Project Registry.* J Am Heart Assoc, 2016. **5**(11).
445. Barlas, R.S., et al., *Impact of Hemoglobin Levels and Anemia on Mortality in Acute Stroke: Analysis of UK Regional Registry Data, Systematic Review, and Meta-Analysis.* J Am Heart Assoc, 2016. **5**(8).
446. Shahar, A. and M. Sadeh, *Severe anemia associated with transient neurological deficits.* Stroke, 1991. **22**(9): p. 1201-2.
447. Tomiyama, Y., et al., *Hemodilution, cerebral O2 delivery, and cerebral blood flow: a study using hyperbaric oxygenation.* Am J Physiol, 1999. **276**(4): p. H1190-6.

448. van Bommel, J., et al., *Intestinal and cerebral oxygenation during severe isovolemic hemodilution and subsequent hyperoxic ventilation in a pig model.* Anesthesiology, 2002. **97**(3): p. 660-70.
449. McLaren, A.T., et al., *Increased expression of HIF-1alpha, nNOS, and VEGF in the cerebral cortex of anemic rats.* Am J Physiol Regul Integr Comp Physiol, 2007. **292**(1): p. R403-14.
450. Felszeghy, K., et al., *Dexamethasone downregulates chemokine receptor CXCR4 and exerts neuroprotection against hypoxia/ischemia-induced brain injury in neonatal rats.* Neuroimmunomodulation, 2004. **11**(6): p. 404-13.
451. Moro, M.A., et al., *Role of nitric oxide after brain ischaemia.* Cell Calcium, 2004. **36**(3-4): p. 265-75.
452. Palmer, S.C., et al., *Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease.* Ann Intern Med, 2010. **153**(1): p. 23-33.
453. Wang, H.H., et al., *Risk of stroke in long-term dialysis patients compared with the general population.* Am J Kidney Dis, 2014. **63**(4): p. 604-11.
454. Ovbiagele, B., *Chronic kidney disease and risk of death during hospitalization for stroke.* J Neurol Sci, 2011. **301**(1-2): p. 46-50.
455. Yahalom, G., et al., *Chronic kidney disease and clinical outcome in patients with acute stroke.* Stroke, 2009. **40**(4): p. 1296-303.
456. Kumai, Y., et al., *Proteinuria and clinical outcomes after ischemic stroke.* Neurology, 2012. **78**(24): p. 1909-15.
457. Johnston, N., H. Dargie, and A. Jardine, *Diagnosis and treatment of coronary artery disease in patients with chronic kidney disease: Ischaemic heart disease.* Heart, 2008. **94**(8): p. 1080-8.
458. Kalra, P.A., et al., *Which anticoagulants should be used for stroke prevention in non-valvular atrial fibrillation and severe chronic kidney disease?* Curr Opin Nephrol Hypertens, 2018. **27**(6): p. 420-425.
459. Kalra, P.R., et al., *Impact of chronic kidney disease on use of evidence-based therapy in stable coronary artery disease: a prospective analysis of 22,272 patients.* PLoS One, 2014. **9**(7): p. e102335.
460. Zachariah, D., et al., *The impact of age and chronic kidney disease on secondary prevention post-primary percutaneous coronary intervention.* QJM, 2014. **107**(3): p. 185-92.
461. Chertow, G.M., S.L. Normand, and B.J. McNeil, *"Renalism": inappropriately low rates of coronary angiography in elderly individuals with renal insufficiency.* J Am Soc Nephrol, 2004. **15**(9): p. 2462-8.
462. Han, J.H., et al., *Chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes.* Am J Med, 2006. **119**(3): p. 248-54.
463. Charytan, D.M., et al., *Clinical presentation of myocardial infarction contributes to lower use of coronary angiography in patients with chronic kidney disease.* Kidney Int, 2007. **71**(9): p. 938-45.
464. Goldenberg, I., et al., *Relation between renal function and outcomes in patients with non-ST-segment elevation acute coronary syndrome: real-world data from the European Public Health Outcome Research and Indicators Collection Project.* Arch Intern Med, 2010. **170**(10): p. 888-95.
465. Szummer, K., et al., *Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome: data from the SWEDEHEART register.* J Intern Med, 2010. **268**(1): p. 40-9.
466. Leung, K.C., et al., *Contrast-associated AKI and use of cardiovascular medications after acute coronary syndrome.* Clin J Am Soc Nephrol, 2014. **9**(11): p. 1840-8.
467. Nauta, S.T., et al., *Decline in 20-year mortality after myocardial infarction in patients with chronic kidney disease: evolution from the prethrombolysis to the percutaneous coronary intervention era.* Kidney Int, 2013. **84**(2): p. 353-8.

468. Devbhandari, M.P., et al., *Effect of risk-adjusted, non-dialysis-dependent renal dysfunction on mortality and morbidity following coronary artery bypass surgery: a multi-centre study.* Eur J Cardiothorac Surg, 2006. **29**(6): p. 964-70.
469. Yuyun, M.F., et al., *Microalbuminuria and stroke in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study.* J Intern Med, 2004. **255**(2): p. 247-56.
470. Hitman, G.A., et al., *Stroke prediction and stroke prevention with atorvastatin in the Collaborative Atorvastatin Diabetes Study (CARDS).* Diabet Med, 2007. **24**(12): p. 1313-21.
471. Rowat, A., C. Graham, and M. Dennis, *Renal dysfunction in stroke patients: a hospital-based cohort study and systematic review.* Int J Stroke, 2014. **9**(5): p. 633-9.
472. MacWalter, R.S., et al., *Does renal dysfunction predict mortality after acute stroke? A 7-year follow-up study.* Stroke, 2002. **33**(6): p. 1630-5.
473. House, A.A., et al., *Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference.* Kidney Int, 2019. **95**(6): p. 1304-1317.
474. Matsushita, K., et al., *Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate.* JAMA, 2012. **307**(18): p. 1941-51.
475. Matsushita, K., et al., *Risk implications of the new CKD Epidemiology Collaboration (CKD-EPI) equation compared with the MDRD Study equation for estimated GFR: the Atherosclerosis Risk in Communities (ARIC) Study.* Am J Kidney Dis, 2010. **55**(4): p. 648-59.
476. Stevens, L.A., et al., *Comparison of the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) study equations: risk factors for and complications of CKD and mortality in the Kidney Early Evaluation Program (KEEP).* Am J Kidney Dis, 2011. **57**(3 Suppl 2): p. S9-16.
477. Skali, H., et al., *Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation.* Am Heart J, 2011. **162**(3): p. 548-54.
478. White, S.L., et al., *Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations: the AusDiab (Australian Diabetes, Obesity and Lifestyle) Study.* Am J Kidney Dis, 2010. **55**(4): p. 660-70.
479. Moe, S.M. and N.X. Chen, *Mechanisms of vascular calcification in chronic kidney disease.* J Am Soc Nephrol, 2008. **19**(2): p. 213-6.
480. Sarnak, M.J., et al., *Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention.* Circulation, 2003. **108**(17): p. 2154-69.
481. Drew, D.A., et al., *Anatomic brain disease in hemodialysis patients: a cross-sectional study.* Am J Kidney Dis, 2013. **61**(2): p. 271-8.
482. Tsuruya, K., et al., *Brain atrophy in peritoneal dialysis and CKD stages 3-5: a cross-sectional and longitudinal study.* Am J Kidney Dis, 2015. **65**(2): p. 312-21.
483. Martinez-Vea, A., et al., *Silent cerebral white matter lesions and their relationship with vascular risk factors in middle-aged predialysis patients with CKD.* Am J Kidney Dis, 2006. **47**(2): p. 241-50.
484. Khatri, M., et al., *Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS).* Stroke, 2007. **38**(12): p. 3121-6.
485. Makin, S.D., et al., *Cerebral small vessel disease and renal function: systematic review and meta-analysis.* Cerebrovasc Dis, 2015. **39**(1): p. 39-52.

486. Castro, P., et al., *Chronic kidney disease and poor outcomes in ischemic stroke: is impaired cerebral autoregulation the missing link?* BMC Neurol, 2018. **18**(1): p. 21.
487. Selby, N.M., et al., *Occurrence of regional left ventricular dysfunction in patients undergoing standard and biofeedback dialysis.* Am J Kidney Dis, 2006. **47**(5): p. 830-41.
488. McIntyre, C.W., et al., *Hemodialysis-induced cardiac dysfunction is associated with an acute reduction in global and segmental myocardial blood flow.* Clin J Am Soc Nephrol, 2008. **3**(1): p. 19-26.
489. Jefferies, H.J., et al., *Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning).* Clin J Am Soc Nephrol, 2011. **6**(6): p. 1326-32.
490. Odudu, A., et al., *Randomized Controlled Trial of Individualized Dialysate Cooling for Cardiac Protection in Hemodialysis Patients.* Clin J Am Soc Nephrol, 2015. **10**(8): p. 1408-17.
491. Locatelli, F. and P. Pozzoni, *Chronic kidney disease in the elderly: is it really a premise for overwhelming renal failure?* Kidney Int, 2006. **69**(12): p. 2118-20.
492. James, M.T., B.R. Hemmelgarn, and M. Tonelli, *Early recognition and prevention of chronic kidney disease.* Lancet, 2010. **375**(9722): p. 1296-309.
493. Putaala, J., et al., *Factors associated with impaired kidney function and its impact on long-term outcome in young ischemic stroke.* Stroke, 2011. **42**(9): p. 2459-64.
494. Adams, H.P., Jr., et al., *Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST).* Neurology, 1999. **53**(1): p. 126-31.
495. Kelly-Hayes, M., et al., *The influence of gender and age on disability following ischemic stroke: the Framingham study.* J Stroke Cerebrovasc Dis, 2003. **12**(3): p. 119-26.
496. Andersen, K.K., et al., *Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors.* Stroke, 2009. **40**(6): p. 2068-72.
497. Toyoda, K. and T. Ninomiya, *Stroke and cerebrovascular diseases in patients with chronic kidney disease.* Lancet Neurol, 2014. **13**(8): p. 823-33.
498. Lamassa, M., et al., *Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project).* Stroke, 2001. **32**(2): p. 392-8.
499. Benjamin, E.J., et al., *Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association.* Circulation, 2018. **137**(12): p. e67-e492.
500. Saver, J.L., *Time is brain--quantified.* Stroke, 2006. **37**(1): p. 263-6.
501. Wardlaw, J.M., et al., *Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life.* Stroke, 2004. **35**(11): p. 2477-83.
502. Bhatia, R., et al., *Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action.* Stroke, 2010. **41**(10): p. 2254-8.
503. Morcos, S.K., H.S. Thomsen, and J.A. Webb, *Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR).* Eur Radiol, 1999. **9**(8): p. 1602-13.
504. Josephson, S.A., W.P. Dillon, and W.S. Smith, *Incidence of contrast nephropathy from cerebral CT angiography and CT perfusion imaging.* Neurology, 2005. **64**(10): p. 1805-6.
505. Aulicky, P., et al., *Safety of performing CT angiography in stroke patients treated with intravenous thrombolysis.* J Neurol Neurosurg Psychiatry, 2010. **81**(7): p. 783-7.
506. Lima, F.O., et al., *Functional contrast-enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy.* AJNR Am J Neuroradiol, 2010. **31**(5): p. 817-21.
507. Ehrlich, M.E., et al., *Safety of Computed Tomographic Angiography in the Evaluation of Patients With Acute Stroke: A Single-Center Experience.* Stroke, 2016. **47**(8): p. 2045-50.

508. Demel, S.L., et al., *Association Between Acute Kidney Disease and Intravenous Dye Administration in Patients With Acute Stroke: A Population-Based Study.* Stroke, 2017. **48**(4): p. 835-839.
509. Stacul, F., et al., *Contrast induced nephropathy: updated ESUR Contrast Media Safety Committee guidelines.* Eur Radiol, 2011. **21**(12): p. 2527-41.
510. Marenzi, G., et al., *Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction.* J Am Coll Cardiol, 2004. **44**(9): p. 1780-5.
511. James, M.T., et al., *Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis.* Circ Cardiovasc Interv, 2013. **6**(1): p. 37-43.
512. Rear, R., R.M. Bell, and D.J. Hausenloy, *Contrast-induced nephropathy following angiography and cardiac interventions.* Heart, 2016. **102**(8): p. 638-48.
513. Nogueira, R.G., et al., *Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct.* N Engl J Med, 2018. **378**(1): p. 11-21.
514. Albers, G.W., et al., *Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging.* N Engl J Med, 2018. **378**(8): p. 708-718.
515. Maioli, M., et al., *Preprocedural score for risk of contrast-induced nephropathy in elective coronary angiography and intervention.* J Cardiovasc Med (Hagerstown), 2010. **11**(6): p. 444-9.
516. Tziakas, D., et al., *Development of an easily applicable risk score model for contrast-induced nephropathy prediction after percutaneous coronary intervention: a novel approach tailored to current practice.* Int J Cardiol, 2013. **163**(1): p. 46-55.
517. Mehran, R., et al., *A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation.* J Am Coll Cardiol, 2004. **44**(7): p. 1393-9.
518. Komotar, R.J., et al., *The role of complement in stroke therapy.* Adv Exp Med Biol, 2008. **632**: p. 23-33.
519. Rossi, D.J., J.D. Brady, and C. Mohr, *Astrocyte metabolism and signaling during brain ischemia.* Nat Neurosci, 2007. **10**(11): p. 1377-86.
520. Khatri, R., et al., *Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke.* Neurology, 2012. **79**(13 Suppl 1): p. S52-7.
521. Hornig, C.R., W. Dorndorf, and A.L. Agnoli, *Hemorrhagic cerebral infarction--a prospective study.* Stroke, 1986. **17**(2): p. 179-85.
522. Okada, Y., et al., *Hemorrhagic transformation in cerebral embolism.* Stroke, 1989. **20**(5): p. 598-603.
523. Fiorelli, M., et al., *Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort.* Stroke, 1999. **30**(11): p. 2280-4.
524. Multicenter Acute Stroke Trial--Europe Study, G., et al., *Thrombolytic therapy with streptokinase in acute ischemic stroke.* N Engl J Med, 1996. **335**(3): p. 145-50.
525. Berger, C., et al., *Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic?* Stroke, 2001. **32**(6): p. 1330-5.
526. *Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. The NINDS t-PA Stroke Study Group.* Stroke, 1997. **28**(11): p. 2109-18.
527. Hacke, W., et al., *Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators.* Lancet, 1998. **352**(9136): p. 1245-51.
528. Clark, W.M., et al., *Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial.*

Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA, 1999. **282**(21): p. 2019-26.
529. Hacke, W., et al., *Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke.* N Engl J Med, 2008. **359**(13): p. 1317-29.
530. group, I.S.T.c., et al., *The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial.* Lancet, 2012. **379**(9834): p. 2352-63.
531. Sussman, E.S. and E.S. Connolly, Jr., *Hemorrhagic transformation: a review of the rate of hemorrhage in the major clinical trials of acute ischemic stroke.* Front Neurol, 2013. **4**: p. 69.
532. Gorelick, P.B. and S.M. Weisman, *Risk of hemorrhagic stroke with aspirin use: an update.* Stroke, 2005. **36**(8): p. 1801-7.
533. He, J., et al., *Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials.* JAMA, 1998. **280**(22): p. 1930-5.
534. Halvorsen, S., et al., *Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis.* J Am Coll Cardiol, 2014. **64**(3): p. 319-27.
535. January, C.T., et al., *2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society.* J Am Coll Cardiol, 2014. **64**(21): p. e1-76.
536. Boccardo, P., G. Remuzzi, and M. Galbusera, *Platelet dysfunction in renal failure.* Semin Thromb Hemost, 2004. **30**(5): p. 579-89.
537. Molino, D., D. De Lucia, and N. Gaspare De Santo, *Coagulation disorders in uremia.* Semin Nephrol, 2006. **26**(1): p. 46-51.
538. National Kidney, F., *K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification.* Am J Kidney Dis, 2002. **39**(2 Suppl 1): p. S1-266.
539. Mann, J.F., et al., *Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: the HOPE randomized trial.* Ann Intern Med, 2001. **134**(8): p. 629-36.
540. Ridker, P.M., M.J. Stampfer, and N. Rifai, *Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease.* JAMA, 2001. **285**(19): p. 2481-5.
541. Weiner, D.E., et al., *Inflammation and cardiovascular events in individuals with and without chronic kidney disease.* Kidney Int, 2008. **73**(12): p. 1406-12.
542. Cachofeiro, V., et al., *Oxidative stress and inflammation, a link between chronic kidney disease and cardiovascular disease.* Kidney Int Suppl, 2008(111): p. S4-9.
543. Vlagopoulos, P.T., et al., *Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: the impact of chronic kidney disease.* J Am Soc Nephrol, 2005. **16**(11): p. 3403-10.
544. Shroff, R., D.A. Long, and C. Shanahan, *Mechanistic insights into vascular calcification in CKD.* J Am Soc Nephrol, 2013. **24**(2): p. 179-89.
545. Demer, L.L. and Y. Tintut, *Vascular calcification: pathobiology of a multifaceted disease.* Circulation, 2008. **117**(22): p. 2938-48.
546. Foley, R.N., P.S. Parfrey, and M.J. Sarnak, *Clinical epidemiology of cardiovascular disease in chronic renal disease.* Am J Kidney Dis, 1998. **32**(5 Suppl 3): p. S112-9.
547. Watson, T., E. Shantsila, and G.Y. Lip, *Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited.* Lancet, 2009. **373**(9658): p. 155-66.
548. Sjoland, J.A., et al., *Fibrin clot structure in patients with end-stage renal disease.* Thromb Haemost, 2007. **98**(2): p. 339-45.

549. Undas, A., et al., *Altered fibrin clot properties in patients on long-term haemodialysis: relation to cardiovascular mortality.* Nephrol Dial Transplant, 2008. **23**(6): p. 2010-5.
550. Lau, Y.C., et al., *Altered fibrin clot structure in patients with atrial fibrillation and worsening renal function.* Thromb Haemost, 2016. **116**(3): p. 408-9.
551. Schuett, K., et al., *Clot Structure: A Potent Mortality Risk Factor in Patients on Hemodialysis.* J Am Soc Nephrol, 2017. **28**(5): p. 1622-1630.
552. Fatah, K., et al., *Proneness to formation of tight and rigid fibrin gel structures in men with myocardial infarction at a young age.* Thromb Haemost, 1996. **76**(4): p. 535-40.
553. Collet, J.P., et al., *Altered fibrin architecture is associated with hypofibrinolysis and premature coronary atherothrombosis.* Arterioscler Thromb Vasc Biol, 2006. **26**(11): p. 2567-73.
554. Lau, W.L., B.N. Huisa, and M. Fisher, *The Cerebrovascular-Chronic Kidney Disease Connection: Perspectives and Mechanisms.* Transl Stroke Res, 2017. **8**(1): p. 67-76.
555. Kobayashi, S., et al., *Asymptomatic cerebral lacunae in patients with chronic kidney disease.* Am J Kidney Dis, 2004. **44**(1): p. 35-41.
556. Seliger, S.L., et al., *Cystatin C and subclinical brain infarction.* J Am Soc Nephrol, 2005. **16**(12): p. 3721-7.
557. Ikram, M.A., et al., *Kidney function is related to cerebral small vessel disease.* Stroke, 2008. **39**(1): p. 55-61.
558. Wada, M., et al., *Cerebral small vessel disease and chronic kidney disease (CKD): results of a cross-sectional study in community-based Japanese elderly.* J Neurol Sci, 2008. **272**(1-2): p. 36-42.
559. Shima, H., et al., *Decreased kidney function is a significant factor associated with silent cerebral infarction and periventricular hyperintensities.* Kidney Blood Press Res, 2011. **34**(6): p. 430-8.
560. Lansberg, M.G., et al., *Evolution of apparent diffusion coefficient, diffusion-weighted, and T2-weighted signal intensity of acute stroke.* AJNR Am J Neuroradiol, 2001. **22**(4): p. 637-44.
561. Power, A., et al., *Screening for transient ischemic attacks in hemodialysis patients.* J Nephrol, 2013. **26**(5): p. 919-24.
562. Bartlett, E.S., et al., *Quantification of carotid stenosis on CT angiography.* AJNR Am J Neuroradiol, 2006. **27**(1): p. 13-9.
563. Douglas, V., M. Shamy, and P. Bhattacharya, *Should CT Angiography be a Routine Component of Acute Stroke Imaging?* Neurohospitalist, 2015. **5**(3): p. 97-8.
564. Howard, G., et al., *Cigarette smoking and progression of atherosclerosis: The Atherosclerosis Risk in Communities (ARIC) Study.* JAMA, 1998. **279**(2): p. 119-24.
565. Messner, B. and D. Bernhard, *Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis.* Arterioscler Thromb Vasc Biol, 2014. **34**(3): p. 509-15.
566. Turkmen, K., et al., *Coronary flow velocity reserve and carotid intima media thickness in patients with autosomal dominant polycystic kidney disease: from impaired tubules to impaired carotid and coronary arteries.* Clin J Am Soc Nephrol, 2008. **3**(4): p. 986-91.
567. Tanaka, M., et al., *Chronic kidney disease and carotid atherosclerosis.* J Stroke Cerebrovasc Dis, 2012. **21**(1): p. 47-51.
568. Kajitani, N., et al., *Chronic kidney disease is associated with carotid atherosclerosis and symptomatic ischaemic stroke.* J Int Med Res, 2018. **46**(9): p. 3873-3883.
569. Russo, D., et al., *Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis.* Kidney Int, 2011. **80**(1): p. 112-8.
570. London, G.M., et al., *Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality.* Nephrol Dial Transplant, 2003. **18**(9): p. 1731-40.
571. Leopold, J.A., *Vascular calcification: an age-old problem of old age.* Circulation, 2013. **127**(24): p. 2380-2.

572. Lafrance, J.P. and D.R. Miller, *Acute kidney injury associates with increased long-term mortality.* J Am Soc Nephrol, 2010. **21**(2): p. 345-52.
573. Grams, M.E., et al., *Acute Kidney Injury After Major Surgery: A Retrospective Analysis of Veterans Health Administration Data.* Am J Kidney Dis, 2016. **67**(6): p. 872-80.
574. Aycock, R.D., et al., *Acute Kidney Injury After Computed Tomography: A Meta-analysis.* Ann Emerg Med, 2018. **71**(1): p. 44-53 e4.
575. Brinjikji, W., et al., *Neurons Over Nephrons: Systematic Review and Meta-Analysis of Contrast-Induced Nephropathy in Patients With Acute Stroke.* Stroke, 2017. **48**(7): p. 1862-1868.
576. Katzberg, R.W. and R. Lamba, *Contrast-induced nephropathy after intravenous administration: fact or fiction?* Radiol Clin North Am, 2009. **47**(5): p. 789-800, v.
577. Radiology, A.C.o., *ACR Manual on Contrast Media*. 2020, ACR Committee on Drugs and Contrast Media. p. 1-131.
578. Loh, Y., et al., *The risk of acute radiocontrast-mediated kidney injury following endovascular therapy for acute ischemic stroke is low.* AJNR Am J Neuroradiol, 2010. **31**(9): p. 1584-7.
579. Sharma, J., et al., *Risk of contrast-induced nephropathy in patients undergoing endovascular treatment of acute ischemic stroke.* J Neurointerv Surg, 2013. **5**(6): p. 543-5.
580. Jia, Z.Y., et al., *Risk of Acute Kidney Injury with Consecutive, Multidose Use of Iodinated Contrast in Patients with Acute Ischemic Stroke.* AJNR Am J Neuroradiol, 2019. **40**(4): p. 652-654.
581. Weber, R., et al., *Incidence of Acute Kidney Injury After Computed Tomography Angiography+/-Computed Tomography Perfusion Followed by Thrombectomy in Patients With Stroke Using a Postprocedural Hydration Protocol.* J Am Heart Assoc, 2020. **9**(4): p. e014418.
582. Graham, G.D., *Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data.* Stroke, 2003. **34**(12): p. 2847-50.
583. Bos, M.J., et al., *Decreased glomerular filtration rate is a risk factor for hemorrhagic but not for ischemic stroke: the Rotterdam Study.* Stroke, 2007. **38**(12): p. 3127-32.
584. Iseki, K., et al., *Evidence for high risk of cerebral hemorrhage in chronic dialysis patients.* Kidney Int, 1993. **44**(5): p. 1086-90.
585. Ovbiagele, B., et al., *Association of chronic kidney disease with cerebral microbleeds in patients with primary intracerebral hemorrhage.* Stroke, 2013. **44**(9): p. 2409-13.
586. Lansberg, M.G., et al., *Risk factors of symptomatic intracerebral hemorrhage after tPA therapy for acute stroke.* Stroke, 2007. **38**(8): p. 2275-8.
587. Wahlgren, N., et al., *Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST).* Stroke, 2008. **39**(12): p. 3316-22.
588. Kidwell, C.S., et al., *Predictors of hemorrhagic transformation in patients receiving intra-arterial thrombolysis.* Stroke, 2002. **33**(3): p. 717-24.
589. Hylek, E.M. and D.E. Singer, *Risk factors for intracranial hemorrhage in outpatients taking warfarin.* Ann Intern Med, 1994. **120**(11): p. 897-902.
590. Shanahan, C.M., et al., *Medial localization of mineralization-regulating proteins in association with Monckeberg's sclerosis: evidence for smooth muscle cell-mediated vascular calcification.* Circulation, 1999. **100**(21): p. 2168-76.
591. Cozzolino, M., et al., *Vascular calcification and uremia: what do we know?* Am J Nephrol, 2008. **28**(2): p. 339-46.
592. Cannata-Andia, J.B., et al., *Vascular calcifications: pathogenesis, management, and impact on clinical outcomes.* J Am Soc Nephrol, 2006. **17**(12 Suppl 3): p. S267-73.
593. Kannel, W.B., *Blood pressure as a cardiovascular risk factor: prevention and treatment.* JAMA, 1996. **275**(20): p. 1571-6.

594. Weber, C. and H. Noels, *Atherosclerosis: current pathogenesis and therapeutic options.* Nat Med, 2011. **17**(11): p. 1410-22.
595. Mathiesen, E.B., O. Joakimsen, and K.H. Bonaa, *Prevalence of and risk factors associated with carotid artery stenosis: the Tromso Study.* Cerebrovasc Dis, 2001. **12**(1): p. 44-51.
596. Ohara, T., et al., *Impact of chronic kidney disease on carotid atherosclerosis according to blood pressure category: the Suita study.* Stroke, 2013. **44**(12): p. 3537-9.
597. de Weerd, M., et al., *Prediction of asymptomatic carotid artery stenosis in the general population: identification of high-risk groups.* Stroke, 2014. **45**(8): p. 2366-71.
598. Herder, M., et al., *Risk factors for progression of carotid intima-media thickness and total plaque area: a 13-year follow-up study: the Tromso Study.* Stroke, 2012. **43**(7): p. 1818-23.
599. Radiology, A.C.o., *ACR practice guideline for communication of diagnostic imaging findings.* 2014: American College of Radiology, Reston.
600. Radiologists, T.R.C.o., *Standards for the Reporting and Interpretation of Imaging Investigations Second Edition*. 2018: The Royal College of Radiologists, London.
601. America, R.S.o.N. *RSNA Informatic Reporting*. 2018 [cited 2018 26/10/2018]; Available from: http://www.radreport.org/index.php.
602. Kahn, C.E., Jr., M.E. Heilbrun, and K.E. Applegate, *From guidelines to practice: how reporting templates promote the use of radiology practice guidelines.* J Am Coll Radiol, 2013. **10**(4): p. 268-73.
603. Radiology, E.S.o., *Good practice for radiological reporting. Guidelines from the European Society of Radiology (ESR).* Insights Imaging, 2011. **2**: p. 93-96.
604. Zarbock, A., et al., *Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial.* JAMA, 2016. **315**(20): p. 2190-9.
605. Bihorac, A., et al., *Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication.* Am J Respir Crit Care Med, 2014. **189**(8): p. 932-9.
606. Hoste, E.A., et al., *Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers.* Nephrol Dial Transplant, 2014. **29**(11): p. 2054-61.
607. Parikh, C.R. and S.G. Mansour, *Perspective on Clinical Application of Biomarkers in AKI.* J Am Soc Nephrol, 2017. **28**(6): p. 1677-1685.
608. Diseases, N.I.o.D.a.D.a.K. *Kidney Precision Medicine Project (KPMP)*. 2016 28 July 2019]; Available from: https://www.niddk.nih.gov/research-funding/research-programs/kidney-precision-medicine-project-kpmp.
609. Yaseen, M., et al., *Impact of Recent Clinical Trials on Nephrology Practice: Are We in a Stagnant Era?* Kidney Dis (Basel), 2019. **5**(2): p. 69-80.
610. Congress, t.U.S., *H.R.2644 - Chronic Kidney Disease Improvement in Research and Treatment Act of 2017.* 2017.
611. Abramoff, M.D., et al., *Automated analysis of retinal images for detection of referable diabetic retinopathy.* JAMA Ophthalmol, 2013. **131**(3): p. 351-7.
612. Tufail, A., et al., *Automated Diabetic Retinopathy Image Assessment Software: Diagnostic Accuracy and Cost-Effectiveness Compared with Human Graders.* Ophthalmology, 2017. **124**(3): p. 343-351.
613. Guimaraes, C.V., et al., *Comparison Between Manual Auditing and a Natural Language Process With Machine Learning Algorithm to Evaluate Faculty Use of Standardized Reports in Radiology.* J Am Coll Radiol, 2018. **15**(3 Pt B): p. 550-553.