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The Natural History of Acute Kidney Injury and its relationship to Chronic Kidney Disease.

by

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ABSTRACT

Background: The natural history of Acute Kidney Injury (AKI) in hospitalized patients is poorly characterized in the literature. Its relationship to the development of de novo chronic kidney disease (CKD) and the progression of known CKD is unclear particularly in patients outside of the intensive care setting. This study was designed to explore the natural history of AKI in the general hospital population to better characterize its relationship to CKD.

Methods: This is a single centre prospective observational study. Subjects were recruited over 17 months from Nov. 2009 to April 2011 from unselected admissions to Queen Alexandra Hospital Portsmouth, a large UK general hospital. Follow up was scheduled at 6 months post-discharge to assess the primary outcomes of recovery of renal function and mortality. Additional follow up was carried out at 12 months to assess mortality. The study consisted of three groups: Group 1 with previous baseline eGFR ≥ 60 mls/min who developed an AKI, Group 2 with a background of CKD (defined by at least two eGFRs < 60 mls/min) who developed an AKI, and Group 3 a control group consisting of those with previous CKD who did not sustain an AKI. Baseline function was derived from records over the previous year while AKI was defined by the AKIN criteria. Extensive baseline data was recorded on each patient. To explore the impact of different definitions of loss of function: failure to recover function after six months was defined as a fall in eGFR of 5mls/min, a fall of 10mls/min and as a fall of 25% of eGFR from baseline.

Results: 401 patients were recruited. 375 patients were recruited with AKI (Group 1 n=190, Group 2 n=185) with 26 CKD controls in Group 3. Mean age was 67 in Group 1 and 77 in Group 2. At 6 months mortality in the AKI group was 12.6% while in the AKI/CKD group it was 24.3%. After 12 months mortality in the AKI group was 16.3% while in the AKI/CKD group it was 30.2%. 20.8% of the AKI group and 14.8% of the AKI/CKD group demonstrated a fall in eGFR of at least 25% from baseline after 6 months. During the 6 months after discharge 40% of the AKI group and 43% of the AKI/CKD group were readmitted and of these 12.1% and 19.8% experienced another AKI.

Conclusions: AKI in hospitalised patients carries a poor prognosis in the long-term. AKI is contributing to the incident CKD population and to the progression of known CKD. At least some patients with AKI are characterised by recurrent episodes and this may represent an important factor in CKD progression in the general population. In this study the AKIN definition performed poorly at predicting the key outcomes.

Presentations/Publications

Parts of this work have been presented at the following national and international conferences:

Ref: **Uniacke MD**, Lewis RJ, Harris S, Roderick PJ
'Does Acute Kidney Injury (AKI) cause or worsen Chronic Kidney Disease (CKD)?' (Poster) American Society of Nephrology , Philadelphia Nov. 2011

Ref: **Uniacke MD**, Lewis RJ, Harris S, Roderick PJ
'Does the cause of 'Pre-renal' AKI in a general hospital setting make a difference to outcomes?' (Poster) ERA-EDTA Congress Paris, France May 24-27th 2012.

Ref: **Uniacke MD**, Lewis RJ, Harris S, Roderick PJ
'Does the cause of 'Pre-renal' AKI in a general hospital setting make a difference to outcomes?' (Abstract) Nephrol. Dial. Transplant. (2012) 27(suppl 2)

Ref: **Uniacke MD**, Lewis RJ, Harris S, Roderick PJ
'Defining the contribution of AKI to the incidence and progression of CKD' (Poster) Renal Association Conference, Newcastle, 12-14 June 2012

In addition an article entitled 'The Natural History of AKI and its relationship to CKD' is being drafted for submission for publication.

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DECLARATION OF AUTHORSHIP

I, Mark Uniacke

declare that the thesis entitled

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and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

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List of abbreviations

ADQI – Acute Dialysis Quality Initiative

AKI – Acute Kidney Injury

AKIN – Acute Kidney Injury Network

ANZIC – Australia and New Zealand Intensive Care

APACHE – Acute Physiology and Chronic Health Evaluation

ARF – Acute Renal Failure

ASN – American Society of Nephrology

ATN – Acute Tubular Necrosis

ATP – Adenosine Triphosphate

CG – Cockcroft and Gault

CKD – Chronic Kidney Disease

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration

CV – Coefficient of Variation

ECMO – Extracorporeal Membrane Oxygenation

eGFR – estimated Glomerular Filtration Rate

ESRD – End Stage Renal Disease

FACTT - Fluid and Catheter Treatment Trial

FeNA – Fractional Excretion of Sodium

GFR – Glomerular Filtration Rate

HSE – Health Survey for England

HES – Hospital Episode Statistics

HIV – Human Immunodeficiency Virus

HCT – Haematopoietic Cell Transplantation

ICD – International Classification of Diseases

IDMS – Isotope dilution mass spectrometry

ITU – Intensive Therapy Unit

KDIGO – Kidney Disease Improving Global Outcomes

KDOQI - Kidney Disease Outcomes Quality Initiative

mRNA – messenger Ribonucleic Acid

MDRD – Modification of Diet in Renal Disease

NCEPOD – National Confidential Enquiry into Patient Outcomes and Deaths

NHANES – National Health and Nutrition Examination Survey

NICE – National Institute for Helath and Clinical Excellence]

NSAID – Non-steroidal anti-inflammatory Drug

NGAL – Neutrophil Gelatinase Associated Lipocalin

NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases

PAH – Para-aminohippurate

PENIA – Particle-enhanced nephelometric immunoassay

QOF – Quality Outcomes Framework

RAS – Renin Angiotensin-Aldosterone System

RIFLE – Risk Injury Failure Loss End Stage Renal Disease

RRT – Renal Replacement Therapy

SF-36 – Short Form 36

TNF – Tumor Necrosis Factor

USRDS – United States Renal Data System

VA – Veterans Affairs

Chapter 1: Introduction

Acute Kidney injury (AKI) is a complex heterogeneous condition. It involves the rapid loss of renal function over hours to days secondary to a pathological process causing damage to the kidney. It can arise in isolated forms due to a single cause but is most commonly seen in the setting of other acute conditions where it forms a part of the 'syndrome' of acute illness. Until recently, AKI was recognised as an important marker of the gravity of the underlying disease but was not felt to be directly responsible for the outcomes [1-3]. Recent publications have highlighted the high incidence of AKI. They have demonstrated many important independent effects of AKI on clinical outcomes and health care resource use. As a result, AKI has become an area of increasing importance for research and public health policy making.

The increased focus on AKI has paralleled a growing interest in Chronic Kidney Disease (CKD). CKD is now well established as a major public health concern. Whilst in some cases CKD can progress to End Stage Kidney Disease the primary absolute risk associated with CKD is an increase in cardiovascular morbidity and mortality [4,5]. The Health Survey for England 2010 reported a CKD prevalence of 6% in adults. The prevalence rises significantly with age and evidence from the US suggests that it is increasing [6,7]. This has been linked to rises in the prevalence of some of its underlying determinants such as diabetes, hypertension and obesity. Changes in demographics due to the aging population may also be contributing [7]. A key question in this area is whether or not AKI is contributing to the incidence of CKD.

1.1 AKI is common and its incidence is rising

The descriptive epidemiology of AKI is unclear from the literature. The principal reason for this is due to the marked heterogeneity of published studies. Until very recently there has been no consensus definition of AKI. This has made extrapolation and comparison of published work difficult. This will be discussed further in Chapter 2. However, it is known that AKI is common with estimates of its frequency in hospitalised patients ranging from 7 – 10% in the developed world [8,9]. AKI is particularly important in the intensive care population where studies show its incidence to be over 30% [10-12]. The incidence of AKI appears to be rising. For example, Xue et al described an increase of up to 11% per year between 1992 and 2001 in US Medicare beneficiaries [13]. The authors suggest this may in part be due to an increased recognition of the condition and a change in coding practices. However, it has also been found in several different study populations in the US and was also recognised by Bagshaw et al in

Australian intensive care units [8,13-17]. The rising incidence is more likely due to the increased use of complex interventions in increasingly older and sicker comorbid patients. This has included a greater use of drugs and contrast agents that are toxic to the kidney [15].

1.2 AKI is associated with significant morbidity and mortality

It has been recognised for decades that AKI is associated with significantly increased mortality in the hospital population [18-21]. Mortality figures vary in the literature depending on the definition of AKI used and the population studied. Contemporary work using a new consensus definition has shown it to be around 15% in hospitalised patients [22-24]. Mortality varies with AKI severity and the severity of the underlying illness such that in the intensive care setting mortality rates over 70% have been reported [25]. A high mortality is maintained even with adjustment for the severity of underlying illness and comorbidities. In addition it has been shown to extend well beyond the acute illness and even small acute changes in kidney function have been associated with an increase in mortality in various settings [26,27].
Notwithstanding the influence of confounding factors, AKI appears to be an independent risk factor for adverse outcomes. The reason for this is unclear. It has been postulated that the effects of the fluid and metabolic disturbances associated with the AKI may be impairing the immune system and organ function [28,29]. This topic will be revisited in Chapter 2.

In addition to its effects on mortality, survivors of AKI have been shown to have an increased length of hospital stay compared to those without AKI [24,30-32]. Furthermore, there is evidence that those who do survive hospitalisation with AKI are more likely to be discharged to a rehabilitation or nursing home facility rather than to their own homes. In some populations studied there appears to be an increased risk of rehospitalisation [16,17,24,33,34]. In addition to the cost in terms of patient morbidity and mortality, AKI is placing an increasing burden on the healthcare economy.

1.3 AKI is preventable and management is suboptimal

There is emerging evidence that AKI itself is managed poorly and may be preventable. In 2002, Stevens et al reported findings from East Kent where they found that 37.5% of cases of AKI were iatrogenic and may have been preventable. They found that the initial assessment of these patients was often suboptimal, and key steps in

investigation and initial management were lacking [35]. The National Confidential Enquiry into Patient Outcomes and Deaths (NCEPOD) examined these findings further in 2009 and published a report highlighting the process of care of patients who died in hospital with a primary diagnosis of AKI. Only 50% of patients included in this enquiry were felt to have had a standard of care that was considered 'good' by the Advisory Panel [36]. More recently, a study using information from Hospital Episode Statistics (HES) in England and Wales found that patients with AKI presenting to hospitals without nephrology cover had a higher mortality [37].

1.4 AKI is now a research priority

In 2002 the Acute Dialysis Quality Initiative (ADQI) Group proposed a graded classification system for AKI known as the RIFLE criteria in an attempt to standardise the definition of AKI and facilitate research [38]. Following this, the Acute Kidney Injury Network (AKIN) was formed in 2004 with a mandate 'to facilitate international, interdisciplinary, and inter-societal collaborations to ensure progress in the field of AKI and obtain the best outcomes for patients with or at risk for AKI'. They proposed the AKIN definition for AKI [39].

In 2005 the American Society of Nephrology Renal Research Report recognised significant gaps in knowledge relating to AKI. The natural history and spectrum of AKI were unclear, knowledge of the risk factors for AKI was limited, and the causes were not defined. In addition, it was recognised that data on the long-term outcomes of AKI and its influence on Chronic Kidney Disease was particularly limited [40]. In the same year, Chertow et al published a landmark study identifying the increased mortality, length of stay and costs associated with AKI. They called for the prevention and effective treatment of AKI to be made a national priority in the United States [32].

The recognition of AKI has not been restricted to nephrology and intensive care circles. In 2008 the Centre for Disease Control (CDC) published a report on the hospitalisation and discharge diagnoses for kidney diseases in the USA between 1984 and 2005. They found that much of the observed change in reported kidney disease was the result of increases in hospitalisation for AKI. They highlighted a need for research to determine the causes for this and to examine the risk for CKD and ESRD associated with AKI [41].

1.5 AKI and its relationship to CKD

Considerable interest has developed recently regarding the relationship between AKI and the development and progression of CKD. CKD is recognised as an important risk

factor for AKI. Studies have consistently shown that up to a third of AKI patients had evidence of pre-existing CKD [30,42-44]. However, the relationship between AKI and subsequent CKD is unclear. Although it has long been appreciated that AKI may lead to permanent renal damage [49], the clinical perception has been that recovery from AKI, when it occurs, has no important long-term sequelae. This may be because many of the studies examining renal recovery after AKI used independence from dialysis as an endpoint and once this was achieved it was felt to be 'adequate' [45,46]. Despite this perception there are now concerns that AKI may be contributing to the development and progression of CKD. In 2008 AKIN rated investigating the relationship between AKI and CKD as one of the top three research priorities in the field [47]. More recently, the Kidney Disease Improving Global Outcomes (KDIGO) consortium has published AKI Guidelines and highlighted the need for 'research with follow up beyond discharge to better understand the clinical consequences of AKI in patients with and without underlying CKD' [48].

1.6 The purpose of this research

It has been known for over 60 years that recovery of kidney function is not complete after an episode of severe AKI [49]. Despite extensive research in recent years, the relationship between milder episodes of AKI and CKD in the general hospital population remains unclear [50]. In addition, studies in this area to date have been retrospective in nature. They have lacked baseline clinical data and have been subject to many methodological flaws. As a result, the natural history of AKI remains poorly characterized.

The aim of this research was to explore the natural history of AKI and in particular its relationship to CKD in the general hospital population. The study was designed around the hypothesis that AKI can cause CKD in those with previously normal function and may worsen pre-existing CKD. This hypothesis was tested by conducting a prospective observational study of general hospitalised patients who sustained an AKI. The aim was to have an adequate follow up period to assess the impact of the AKI on baseline kidney function. The prospective design allowed for the collection of extensive baseline data in order to explore the risk factors for the outcomes in question.

This study contributes to the existing literature in the field in several ways. Judging from the available published data, this is the only prospective study completed to date specifically designed to explore AKI and its medium-term (6 months) effects on renal function. It has been undertaken in the general hospital setting and is not restricted to the intensive care population. The use of the AKIN definition allows for the exploration

of the effects of milder degrees of AKI. The methods used and the findings will contribute to future AKI research design.

1.7 Outline of the thesis

This thesis begins with a thorough review of the current knowledge of the natural history of AKI in Chapter 2. This is followed by a literature review of the outcomes of kidney function after an AKI episode in Chapter 3. The study design and methods are presented in Chapter 4 followed by results and analysis in Chapters 5, 6 and 7. Finally, Chapter 8 contains a discussion of the findings together with the strengths and limitations of the study and future research directions.

1.8 Literature sources

It is important to note that the recent surge of interest in AKI has resulted in a dramatic expansion of the literature. The present study was undertaken between 2009 and 2011 and during this period the number of new AKI articles exceeded 2,500 per year [51]. As a result a single systematic search of the literature for the purpose of the reviews contained in Chapters 2 and 3 would rapidly have become out-dated. The literature reviewed was therefore compiled from multiple Medline searches undertaken during the course of the study. This was consolidated by undertaking a broad systematic search of the Medline and Embase databases in January 2012. The search strategy used is outlined in Appendix 1. It was developed using an iterative process with keywords relevant to the natural history of AKI and spanned the period 1990 to 2011. The references within the articles reviewed were also consulted for any relevant studies prior to this period. In addition to this more formal search, regular email alerts from the major critical care and nephrology journals were used to identify newly published articles. Using these methods a database of over 150 cohort studies in AKI was built. The reviews in Chapters 2 and 3 are as comprehensive as possible accounting for the rapidly changing literature base in AKI.

Chapter 2: Background

2.1 Basic Structure and Functions of the kidney

2.1.1 Kidney Anatomy

The functioning unit of the kidney is the nephron and there are over a million in each kidney. The nephron is made up of a glomerulus and a tubule system. The glomerulus consists of a tuft of capillaries that receive blood from the systemic circulation through the afferent arteriole and drain through the efferent arteriole. Blood is filtered across the glomerular basement membrane into the space in Bowman's Capsule to form an ultrafiltrate of plasma. This is the early stage of urine formation. The ultrafiltrate passes through the tubules before leaving the kidney through the collecting tubule which drains into the ureter. During its passage through the tubules the ultrafiltrate is subjected to selective secretion and reabsorption of electrolytes and other solutes by the cells lining the tubules. Through this regulated process the kidney is able to maintain water, electrolyte and acid/base balance. The final urine that is produced is concentrated according to the prevailing physiological conditions and is excreted along with the metabolic waste it contains through the ureter into the bladder.

2.1.2 Functions of the Kidney

The kidneys are an important regulator of body homeostasis. The five principle functions of the kidney are outlined in Figure 2.1. The kidney primarily regulates fluid and electrolyte balance, acid/base balance, and excretes metabolic waste products. These include urea and creatinine which are the surrogates currently used to measure kidney function in clinical practice. In addition to the functions directly related to the filtration of blood, the kidney also produces a number of important hormones and has some metabolic functions for example the metabolism of insulin. In the context of an AKI, the most important impact is on the ability of the kidney to filter blood to excrete metabolic waste and maintain fluid and electrolyte balance.

Figure 2.1 Principle functions of the kidney.

Functions of the Kidney

1. Maintenance of body fluid balance.
2. Maintenance of electrolyte balance.
3. Maintenance of Acid/Base balance.
4. Elimination of metabolic waste products.
5. Endocrine functions:
   - production of Erythropoetin
   - production of Renin
   - production of Calcitriol (Vitamin D)

2.2 Measurement of Kidney Function

2.2.1 Glomerular Filtration Rate (GFR)

The most important measure of kidney function is the Glomerular Filtration Rate (GFR). The GFR is the rate in unit time at which fluid is filtered by the glomerulus and is widely accepted as the best overall index of kidney function [52]. The driving force for filtration is the glomerular capillary hydrostatic pressure. This ultimately depends on cardiac output and an effective circulating volume. The oncotic pressure due to plasma proteins within the filtered blood and the hydrostatic pressure in Bowman's space oppose this pressure. The difference between the opposing pressures is the net filtration pressure. In addition to the net filtration pressure the GFR is also determined by the glomerular filtration coefficient which reflects the permeability and the surface area of the basement membrane across which the fluid is filtered. In men the GFR averages 125mls/min or 180L/day while in women it averages 110mls/min or 160L/day [53]. Any of the determinants of GFR mentioned above may be altered in disease states. In particular, approximately 25% of cardiac output is used to drive filtration. The kidneys are therefore very 'vascular' organs which is why they are susceptible to conditions that change haemodynamics. The level of GFR and its magnitude of change over time are vital to the detection of kidney disease, understanding its severity, and for making decisions about diagnosis, prognosis, and treatment [52]. In AKI the GFR is generally decreased and the ability of the kidney to carry out the functions outlined above is compromised.

2.2.2 Measurement of GFR

The glomerular filtration rate can be expressed in terms of the renal clearance. The renal clearance of a substance is the volume of plasma from which all the substance is removed and excreted into the urine in unit time [54]. This can be measured by using a substance as a filtration marker and by calculating the rate at which it is excreted in the urine and dividing this by the plasma concentration according to the following formula:

$C_x = U_x V / P_x$

where U_x is the urine concentration of the substance, V the urine flow rate, and P_x the plasma concentration of the substance. In order to measure GFR in this way the substance must be cleared from the plasma solely by glomerular filtration. It should not be metabolised, synthesised, or stored by the kidneys and neither should it be reabsorbed or secreted by the renal tubules. In addition, it should not be bound to plasma proteins that might hinder its filtration [53]. The polysaccharide inulin is classically recognised as the ideal filtration marker and its use is considered the 'gold standard' for measuring GFR. After an intravenous infusion, the plasma inulin concentration can be measured together with its concentration in a timed urine sample. The use of inulin as a filtration marker can give an accurate measurement of the GFR. However, the need for an intravenous infusion and a difficult chemical assay makes it impractical for use in clinical practice [55].

As an alternative to inulin, several radioactive isotopes have been developed and used as filtration markers. All can be given as a single injection and thus avoid the need for a continuous infusion. These include ^{125}I-Iotholamate, ^{51}Cr-EDTA and ^{99m}Tc-DTPA. ^{125}I-Iothalamate is known to be comparable to inulin as a filtration marker and can be assayed accurately and precisely in a laboratory. For this reason it has been used in clinical trials assessing progression of renal disease [56]. Iotholamate and Iohexol are also available as nonradioactive filtration markers and levels are measured by X-ray fluorescence assay or high performance liquid chromatography.

While the methods described above are the most accurate available for measuring GFR they are invasive and time consuming. In everyday clinical practice, measurement of serum urea and creatinine remain the mainstay for determining changes in renal function. Serum creatinine together with a urine collection can be used to estimate GFR by measuring creatinine clearance while several equations have been developed to estimate GFR based on serum creatinine alone. The use of creatinine as a marker of

renal function and subsequent employment in estimating equations is subject to limitations that are discussed below.

2.2.3 Urea as a filtration marker

Urea is a nitrogenous waste product excreted by the kidneys and can serve as a crude marker of filtration. It is the main by-product of the oxidation of amino acids in protein catabolism. An elevated plasma urea level suggests impairment of renal function [54]. Its use as a marker is limited by significant variation that can occur in its levels on a day-to-day basis. Protein intake and levels of hydration can affect urea levels. It may also be elevated in other situations such as an upper gastrointestinal bleed owing to the absorption of degraded blood products from the gastrointestinal tract. As a result of these limitations it is not generally used in the setting of acute kidney injury. In addition it is not used in any of the GFR estimating equations in current use.

2.2.4 Creatinine as a filtration marker

Despite numerous limitations serum creatinine remains the mainstay for assessing renal function in clinical practice and is widely employed in estimating equations to determine GFR. Creatinine has been in use as a filtration marker since endogenous levels were first measured in the 1930's [55]. The obvious advantage of using an endogenous filtration marker is that it does not require the administration of a test compound [57].

Creatinine is a cyclic anhydride of creatine and is the metabolic end product of creatine metabolism in muscle. Creatine is produced primarily in the liver and transported to muscle cells where it is phosphoralated to creatine phosphate that then acts as a storage depot for muscle energy [57]. Creatinine possesses many of the attributes of a perfect filtration marker described above. It is freely filtered and not protein bound. In addition, it is not metabolised by the kidney and it is physiologically inert [55]. However, there are a number of issues that limit creatinines ability to reflect GFR accurately which are related to its production, its renal handling and its measurement. These issues need to be kept in mind when interpreting renal function expressed in terms of creatinine excretion and are of great importance in AKI. They follow the same principles of biological and analytical variation of any analyte.

2.2.4 (i) Creatinine Production

In the steady state the production of creatinine from creatine occurs at a constant rate [58]. It stems from this that influences on the size of the creatine pool will lead to proportionate changes in creatinine production. Muscle mass is the most important determinant of the size of the creatine pool and so age and sex have dominant effects on creatinine production because of their effects on muscle mass [55]. Muscle mass decreases with age and hence creatinine production falls [59]. Muscle mass in women is lower than it is in men and so creatinine production and excretion is lower in women [60]. Racial differences have also been identified. African Americans have been shown to have higher serum creatinine levels for any given GFR than non-African Americans [61]. In addition, creatinine production will be lower in individuals with muscle wasting conditions such as mytonic dystrophy or in those who have had an amputation. In these situations serum creatinine and its associated clearance are unlikely to be an accurate reflection of GFR.

Serum creatinine can also be influenced by dietary intake of meat. Reducing or eliminating the meat content of the diet reduces creatinine excretion by 10-30%. It has been shown that serum creatinine levels are lower in vegetarians [62]. After a meal of cooked meat, serum creatinine levels rise substantially and peak within the first two hours after the meal. Normal levels are not regained until between 12 and 24 hours after the meat load [63-65].

Trauma and exercise have also been shown to increase serum creatinine levels [55]. In animal models it has been recently demonstrated that creatinine production is reduced in the setting of sepsis [66]. There have been additional reports of a diurnal variation in serum creatinine concentration with levels being higher in the afternoon [67].

2.2.4 (ii) Renal handling of creatinine

Although creatinine is freely filtered it does not pass through the renal tubules unaltered. In 1935 Shannon demonstrated that at low plasma concentrations of creatinine the creatinine clearance is 30 to 45% higher than the inulin clearance in healthy volunteers. The active secretion of creatinine by tubular cells accounts for this difference [68].

Shamesh et al took these findings further in 1985 by demonstrating that there is progressive fractional hypersecretion of creatinine by renal tubules in glomerular disease and that this hypersecretion increases as the glomerular disease worsens [69]. In

the setting of low urine flow rates some reabsorption of creatinine may also occur due to its passive back-diffusion from the lumen to the blood [55].

In addition to the secretion and reabsorption of creatinine by the renal tubules the handling of creatinine is further complicated by extrarenal metabolism. This is undetectable in normal subjects. However, in those with chronic kidney disease it has been shown that creatinine production exceeds the rate of accumulation of serum creatinine and its excretion in the urine. This 'creatinine deficit' is eliminated via extrarenal routes. This is thought to mainly involve its release into the gut where it is degraded by bacterial flora in a similar manner to urea and uric acid [70].

The direct relationship between serum creatinine concentration and the GFR is also an important consideration. At near normal levels of renal function, large changes in GFR correspond to small changes in serum creatinine concentration. Enger et al and others demonstrated that patients with up to a 50% fall in GFR may still have serum creatinine concentrations in the near normal range [57,71].

In pregnancy creatinine generation remains unchanged however there is up to a 50% increase in GFR from the first trimester onwards which leads to decreases in the concentration of serum creatinine [55]. The implication of this in the setting of AKI is that a serum creatinine considered normal in the nonpregnant state may in fact represent significant renal injury.

2.2.4 (iii) Creatinine measurement

Creatinine is easily measured in serum, plasma or urine. The standard method used is the Jaffe reaction. Creatinine reacts directly with picrate ion under alkaline conditions to form an equimolar complex whose orange-red colour is detected and quantified. This method has been modified over the years to separate 'true creatinine' from noncreatinine chromogens which accounted for up to 20% of the colour reaction. Several enzymatic methods are now available in addition to a kinetic alkaline picrate method. Elevated serum bilirubin levels have been shown to interfere with these techniques and result in a reduced serum creatinine concentration [72].

Like any biochemical test these methods are associated with a degree of intraindividual analytical variation that can be expressed as a coefficient of variation. Data from the NHANES 3 study showed that the analytical variation for creatinine was 1%. However, when the biological variation described above was also taken into account the total coefficient of variation for an individual was 6.9% [73].

In addition to intraindividual variation, variation can also occur between laboratories. This may be due to differences in calibration of the analyser or due to different analysis techniques. This has implications for comparing results from different laboratories particularly in clinical trials. In recent years efforts have been made to standardise the reporting of results by calibrating to a single standardized serum creatinine based on gold standard methods. The primary reference is assigned values based on isotope dilution mass spectrometry (IDMS). IDMS traceable creatinine measurements have been in use in the UK since April 2006 [74]. Prior to the introduction of IDMS calibrated creatinine measurements quite large differences were observed in results between different laboratories [75].

2.2.4 (iv) Drug influences on creatinine measurement

Numerous drugs influence renal handling of creatinine and its serum concentration. In renal insufficiency, tubular secretion of creatinine can account for as much as 60% of the total amount of creatinine excreted. Complete inhibition of this pathway could result in a doubling of the serum creatinine concentration [55]. Cimetidine is known to be potent inhibitor of creatinine secretion by the tubules and is used for this purpose experimentally [76]. Probenecid, trimethoprim and calcitriol have also been described in this manner and can result in increases in serum creatinine concentration in the absence of renal damage.

Volume depletion due to diuretic treatment can lead to an increase in serum creatinine concentration. Certain drugs can also influence renal haemodynamics such as RAS-blockers and NSAIDS both of which reduce renal blood flow.

2.2.4 (v) Creatinine Clearance

Carrying out a timed urine collection and applying the clearance formula ($C_x = U_x V/P_x$) described above can measure the clearance of creatinine. However, creatinine clearance is subject to the same limitations associated with serum creatinine. It has been shown to overestimate 'true' GFR measured by inulin clearance [69]. Timed urine collections are inconvenient for patients and frequently inaccurate. Inaccuracies can result from incomplete bladder emptying and failure to collect the entire specimen [55]. This method was commonly used in clinical practice however it has been replaced by estimated GFR over the past decade. A recent report by Kagoma et al showed a 23.5% reduction in the use of creatinine clearance since the introduction of eGFR reporting [77].

2.2.5 Cystatin C as a marker of renal function

Due to the many limitations with the use of creatinine as a marker of renal function there have been efforts to find better alternatives. Cystatin C is one such alternative that has been extensively studied.

Cystatin C is a non-glycosylated polypeptide and is part of the cystatin superfamily. These proteins inhibit cysteine proteinases and play a key role in protection against tissue injury during the course of an insult. It is released from all nucleated cells. In addition to its role as a cysteine proteinase inhibitor it also has properties that modulate the immune system and it has antibacterial and antiviral effects. Cystatin C is almost completely filtered by the glomerulus. It is then taken up by proximal tubular cells which catabolise virtually all of it. It can be found in all body fluids. Elevations in its serum levels occur almost exclusively in the setting of a reduced GFR and this drew attention to it as a potential filtration marker. Its levels can be measured by immunoassay with rabbit antibodies against human cystatin C and a fully automated particle-enhanced nephelometric immunoassay (PENIA) is now available [78].

Cystatin C possesses properties that in theory would make it a better filtration marker than creatinine. Age, sex, and race have been shown to have less influence on it [52]. In addition, it appears to be unaffected by dietary protein intake and muscle mass [79-80]. Two meta-analyses in the past decade have suggested that cystatin C is superior to creatinine as a marker of kidney function [81,82]. However, there is evidence that its measurement is influenced by other factors such as body mass index, the presence of diabetes and inflammation [52]. Cystatin C alone has been incorporated into GFR estimating equations but these have not been show to be superior to those based on serum creatinine. More recently, the two have been combined together and have shown more promise at estimating renal function [80,83]. At present Cystatin C is considered a possible alternative to creatinine however it is not widely used. It is costly to measure and in the absence of evidence that it significantly improves outcomes these costs are difficult to justify [84].

2.2.6 GFR estimating equations

There are several reasons why an estimation of GFR is useful in clinical practice. Firstly, it allows adjustment of drug doses in patients with impaired renal function. Secondly, it enables physicians to establish the presence of and monitor CKD. It has gained additional importance over the past decade with the recognition that CKD increases the risk of cardiovascular mortality in addition to being a precursor to ESRD [4].

GFR estimating equations are derived from regression analysis in which the level of measured GFR is related to the serum concentration of an endogenous filtration marker. It is also related to observed clinical and demographic variables that serve as surrogates for the non-GFR determinants of the serum concentration [85]. At present, serum creatinine based equations are the mainstay in clinical practice.

As discussed above, age, sex, race, and body weight are surrogates that can influence creatinine generation from muscle. These can be adjusted for in estimating equations and so they can provide a more accurate estimate of measured GFR than serum creatinine alone. In addition, the estimates are provided in the same units as GFR which simplifies clinical decision making [85]. However, like serum creatinine from which they are derived, the estimating equations are subject to variation and bias. A key assumption in their development is that renal function is in the steady state [55]. Therefore they cannot be used in the setting of AKI where creatinine may be acutely rising or falling. The equations only capture the average relationships between the marker and its non-GFR determinants and this relationship may vary over time [86]. Another key issue to take into consideration is the population from which the equations are derived. This can influence their generalizability and can account for bias in their interpretation. For example, the MDRD equation was developed in a population with CKD and has been found to perform less well at higher levels of GFR in those without CKD [87].

The first widely accepted estimating equations was proposed by Cockcroft and Gault in 1976 [60]. This equation was derived from investigation of 249 patients, mainly men, who had no history of renal disease and is an estimate of creatinine clearance rather than GFR itself. It accounts for age and weight in its calculation and required a correction for use in women:

C_{cr} = [140 – age] x weight / 7.2 x serum creatinine (mg/L)

The CG formula has seen widespread use but has several limitations. It has been shown to underestimate clearance at higher levels of GFR and to overestimate clearance at lower levels [88].

2.2.6 (i) MDRD eGFR

Levey et al presented the Modification of Diet in Renal Disease equation in 1999 [89]. This was developed using data from the MDRD study in which GFR was measured using ^{125}I-iotholamate. All of the population studied had CKD and this accounts for

some of the limitations of the equation. In the original paper describing its development, the MDRD eGFR was found to be more accurate at measuring GFR than measured creatinine clearance or the CG equation. An advantage of the MDRD equation is that it does not need a weight measurement and so can be readily calculated by a laboratory. The equation has since been modified including an adjustment for use with creatinine values standardised to IDMS:

$GFR = 175 \times \text{Serum Creatinine}^{-1.154} \times \text{age}^{-0.203} \times 1.212(\text{if black}) \times 0.742(\text{if female})$.

In addition adjustment needs to be made for racial differences. It was discussed earlier that serum creatinine values have been found to be higher in blacks and so adjustment is now made for those of black Afro-Caribbean origin.

Since its introduction the MDRD formula has been applied in more diverse populations in a number of studies where it has demonstrated reasonably good performance at levels of GFR < 60mls/min. However at higher levels its performance was poor and it was found to underestimate GFR. In one study the overall performance of the equation expressed as P_{30} was found to be 83% [90]. This means that 83% of measurements are within 30% of the measured GFR. Another study by Botev et al comprising mainly European Caucasian subjects found that the equation had an overall P_{30} accuracy of 70% and that approximately 60% of the study population was correctly defined by the K/DOQI-CKD classification. Despite these limitations in accuracy it has been deemed acceptable for routine decision-making in clinical practice. As a result the MDRD equation has been widely adopted as the means to estimate GFR [74,91].

A key issue with the MDRD equation is its ability to monitor progression of renal disease in the individual. This is relevant to the study described in this thesis. Despite its inaccuracy in terms of estimating true GFR its ability to identify relative changes in function is important in longitudinal studies. Tent et al described the renal function outcomes in 253 consecutive living kidney donors who had GFR measured with ^{125}I-Iotholamate four months before and two months after donation. This was compared with the MDRD eGFR, CG estimation of creatinine clearance, and the CKD -EPI eGFR discussed below. All three equations significantly underestimated true GFR at both time points prompting the authors to caution the use of estimating equations in healthy individuals. However, while the equations underestimated the absolute measured eGFR decline the percentage decrease of MDRD and CKD-EPI were proportionally equal to the change in measured GFR [92]. In terms of the coefficient of variation (CV) within an individual, the CV for MDRD eGFR was reported as 6.7% [93]. Evidence suggests that eGFR is not accurate at estimating the absolute true GFR level

however in terms of relative change it appears to mirror changes in the true GFR with less than 10% intraindividual variation.

2.2.6 (ii) CKD – EPI eGFR

The CKD – EPI equation to estimate GFR was introduced by the Chronic Kidney Disease Epidemiology Collaboration in 2009 [94]. This equation was developed to improve on the performance of the MDRD equation particularly at higher levels of GFR. With CKD –EPI adjustments are made leading to higher eGFR at lower creatinine levels. In addition, the relationship between GFR and sex varies according to the level of serum creatinine whereas in the MDRD equation it was constant. Concordance of estimated and measured GFR stages was 69% for the CKD –EPI equation versus 64% for the MDRD equation. When applied to the NHANES study data the CKD –EPI equation led to a reduction in the estimated prevalence of CKD from 13.1% to 11.5% primarily due to a lower prevalence of Stage 3 CKD. The authors concluded that while precision remains a problem, the CKD –EPI equation has lower bias than the MDRD eGFR at higher levels of GFR [94]. Compared to the MDRD formula, CKD-EPI improves bias substantially in those under 65 years of age. However there is little change in performance for those older than 65 years of age [95]. The elderly make up a substantial proportion of the CKD population and so further evaluation of this formula is required before it is widely adopted. Nevertheless, some authors have recommended that it should replace the MDRD equation in routine practice [95].

2.2.6 (iii) GFR measurement and AKI

Estimating equations for GFR are not valid in AKI as they are derived under the assumption that the patient is in a steady state without acute changes in serum creatinine. Despite its many limitations there is still a consensus that serum creatinine together with urine output if available should form the basis of all diagnostic criteria in AKI [48]. Urine output has been included in diagnostic criteria because it is known that decreases in urine output often herald renal dysfunction before serum creatinine increases [39]. However, its precise role in the diagnosis of AKI is poorly characterised. Considerable renal injury may be present in certain conditions such as glomerulonephritis in the absence of any changes in urine output [48].

It is of particular relevance to AKI that up to 50% of GFR may be lost before the creatinine level begins to rise. Measurements of serum creatinine are therefore of little value in determining the degree of renal impairment in AKI. Simulation studies by Bjornsson in the 1970's demonstrated that following acute changes in renal function,

the concentration of serum creatinine continues to rise or fall until new steady state levels are reached. The time required to reach the new steady state is dependent on the half-life of serum creatinine. This in turn is dependent on clearance, so a longer period of time will be needed to reach steady state when the GFR is falling rather than rising [57]. The delay in reaching steady state has such an effect that it is possible for the creatinine level to continue to rise even after the GFR has started to recover [55].

The limitations associated with using serum creatinine for diagnosing AKI have been the driving force behind the quest to develop new biomarkers that can more accurately reflect the timing and extent of injury during AKI. These biomarkers will be discussed further later in the chapter.

2.3 Defining AKI

In the past decade two widely accepted definitions and classification systems of AKI have been developed. Firstly, the RIFLE criteria which were introduced in 2004 by the Acute Dialysis Quality Initiative Group (ADQI Group) and secondly, the AKIN criteria introduced by the Acute Kidney Injury Network in 2007 [39,96]. In order to fully understand these definitions and their limitations it is necessary to discuss why defining AKI is considered so important. In addition, it is important to discuss the reasoning behind any definition of AKI.

2.3.1 Acute Renal Failure becomes AKI

Bellomo et al were the first to put the concept of kidney 'injury' forward in 2001. While acknowledging that this was a matter of semantics they felt that the term 'injury' was more useful to describe the initial phase of kidney malfunction [97]. The Acute Kidney Injury Network (AKIN) has adopted the term Acute Kidney Injury. There were several reasons for this: firstly, the recognition that relatively modest changes in serum creatinine were associated with adverse outcomes suggested that the syndrome should encompass more than just outright kidney failure. Secondly, it was felt that the term 'injury' more accurately conveyed the associated pathophysiology than the term 'failure'. Finally, it was recognised that the word 'kidney' was more accessible than the Latin derived 'renal' by the general public [98].

2.3.2 The need to define and classify AKI

It has been recognised that there are significant gaps in the understanding of the natural history of AKI. The 2005 Amercian Society of Nephrology (ASN)

Renal research report identified a number of important areas in clinical AKI that needed further work [40]:

- The incidence and prevalence were unknown
- The natural history and spectrum of AKI was unknown
- The causes of AKI were not defined
- The variations in processes of care were unknown
- There was no data on long-term outcomes, particularly progression to CKD
- Information was required to inform the design and conduct of multicentre interventional studies
- Benchmarks for disease patterns and their management were needed

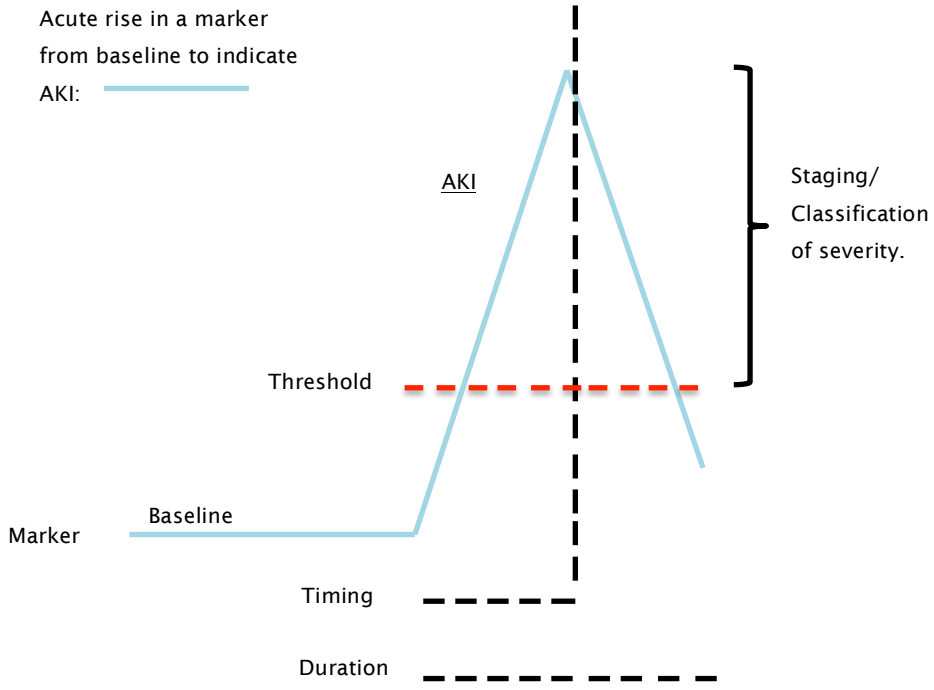
One of the principal barriers to progress in these areas was recognised as the lack of a consensus definition and classification system for AKI [38,97]. This problem had been apparent in the literature for many years. In a 1991 study on the immediate and long-term prognosis in acute renal failure in the elderly, Gentric et al found comparison with other studies difficult because of the use of different creatinine values as the cut-off to define AKI [19]. In 1994 Novis et al attempted to perform a systematic review of 26 studies published between 1965 and 1989 in order to examine preoperative risk factors for postoperative renal failure. No two studies used the same definition for acute renal failure and the authors concluded that the literature was not adequate to support a comprehensive quantitative review [99].

In a 2002 review Kellum et al referred to more than 35 different quantitative definitions of AKI and concluded that a standardised classification system was mandatory for the advancement of clinical research in the prevention and treatment of AKI [38]. In 2001, Bellomo et al highlighted that there were too many essentially arbitrary biochemical “cut-off values” for serum creatinine in the definition of AKI leaving one unable to come to any conclusions when comparing clinical research [97]. Observational research relevant to this current study carried out between 1990 and 2011 revealed 42 different definitions of AKI and these are outlined in Appendix 2. Some of these definitions were similar in terms of the creatinine cut-off used but they then differed in other areas such as the cut-off for baseline renal function. It is notable that some used an absolute increase in creatinine, for example a rise > 0.3mg/dl, while others used a relative increase such as a rise of 30%. This potentially has important implications when the level of baseline kidney function is considered. In addition, some studies even used a fall in estimated GFR to define AKI [124].

2.3.3 Considerations when defining AKI

A number of factors needed to be taken into account when defining AKI and these ultimately determine the usefulness of any definition. These factors are illustrated in the diagram in Figure 2.2. The first and most important consideration is to establish what marker should be used to measure kidney function.

Figure 2. 2 Diagram illustrating the various factors that need to be accounted for in any definition of AKI. A marker of kidney function (in yellow) begins at a baseline level and peaks across a threshold level to indicate an AKI has occurred.



There are only two physiological functions that are unique to the kidney that can be easily measured in clinical practice and these are the production of urine and renal solute clearance. Renal solute clearance reflects glomerular filtration rate and serum creatinine remains the most useful measure of this function despite its many limitations. While no single creatinine value corresponds to a given GFR across all patients, changes in creatinine levels are clinically and physiologically useful in determining the presence of AKI [128]. For these reasons the current definition and classification systems of AKI are based on serum creatinine as the main marker of renal function.

Urine output has also been included as a marker in the current definitions and has some advantages over biochemical markers. However, it also has notable limitations. It is more sensitive to changes in haemodynamics than biochemical markers such as serum creatinine because changes in urine output can become apparent long before biochemical markers change. However, it is far less specific. Severe cases of AKI can exist despite maintaining normal urine output [128]. Measurement of urine output in practice is an additional problem. Accurate measurement requires a urinary catheter and this is not always available in cases of AKI particularly the milder ones.

The next consideration in any definition is the baseline from which the AKI is measured. This is not only important from the point of view of outcomes such as recovery of function but will also influence how the threshold to define AKI is defined and interpreted. Many patients with AKI will have pre-existing CKD. The implication of this is that the absolute decrease in renal function required to reach a level consistent with the diagnosis of AKI will be less than that of a patient without pre-existing kidney disease. To overcome this problem, developers of the current definitions included relative changes in creatinine rather than an absolute change [38]. An additional important concern is that many patients with AKI will not have a known baseline on record.

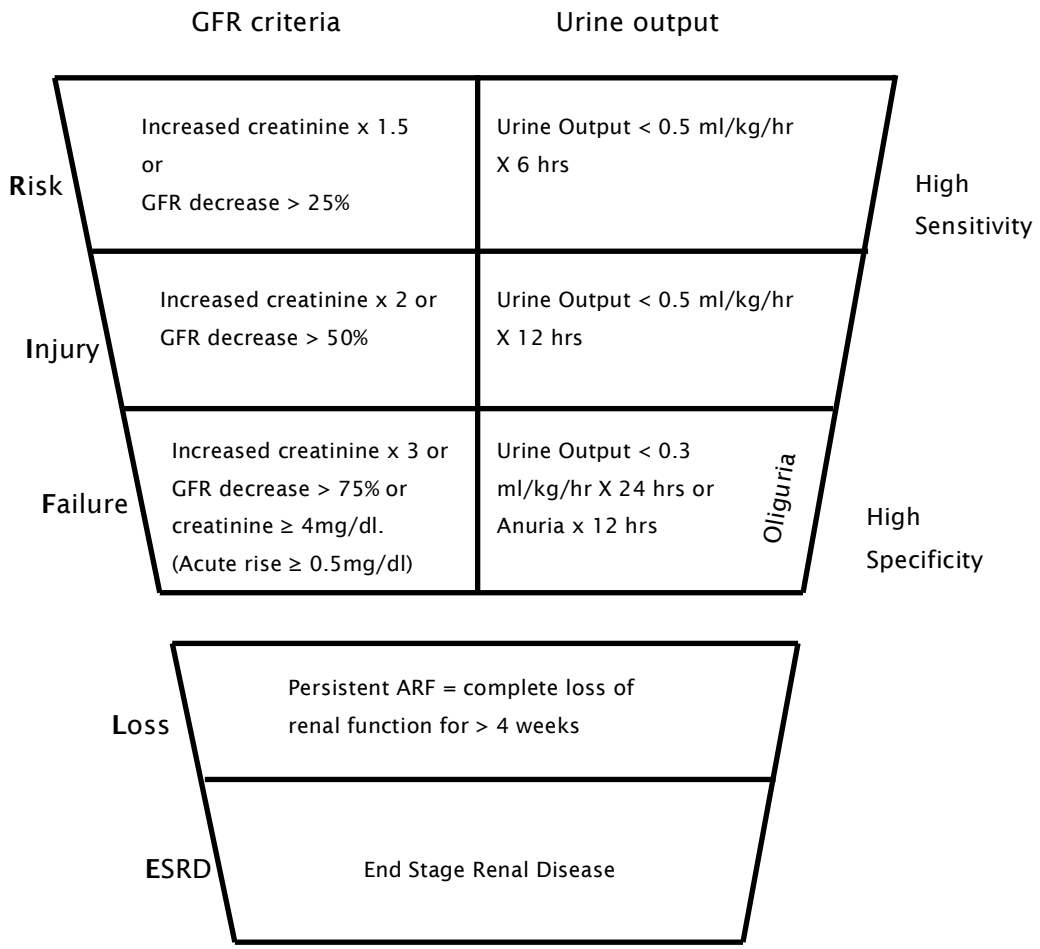
Another consideration is the choice of threshold for the marker beyond which AKI is defined. This is largely arbitrary but needs to be set so that it is sensitive enough to detect milder cases of AKI. The issues surrounding the importance of sensitivity and specificity to any definition of AKI were recognised in the development of the current definitions [38,96]. In proposing the RIFLE definition, the ADQI Group advocated using a multilevel classification system to separate mild (or early) and severe (or late) cases. This allowed the classification to detect those whose renal function was mildly affected (high sensitivity but limited specificity) and those whose function was severely affected (high specificity but limited sensitivity).

A final consideration in any definition is the timing and duration of the injury. These will also influence the sensitivity and specificity of the definition when it is applied in practice [38]. For example, if a sudden decline in function is defined as less than 48 hours this will be far less sensitive at detecting AKI than say a 7 day time frame.
All of the above factors need to be considered in the development of a suitable definition of AKI. However, it is widely recognised that no consensus definition will ever be perfect [38].

2.3.4 The RIFLE Classification

The Rifle Classification was introduced by the ADQI Group in 2004 and is illustrated in its original format in Figure 2.3 [96].

Figure 2. 3. The Rifle Classification [96].



The RIFLE classification uses two separate markers of renal dysfunction. Firstly, renal excretory capacity measured by either serum creatinine or GFR and secondly, urine output. Either or both of these markers may be used to place the patient in the worst classification possible. Changes in excretory capacity are measured from baseline and when this was unknown the ADQI group suggested using an estimate of baseline function by back calculating from an assumed eGFR of 75mls/min. The definition uses a multilevel staging system with three stages of dysfunction; risk, injury and failure, and two outcomes; loss and end stage renal disease. It was proposed that when the

failure stage is reached and there is a background of CKD then this stage should be designated RIFLE-Fc with the 'c' indicating CKD. In a similar manner, if the failure stage is reached and the urine output criteria have been used then this should be designated RIFLE – Fo. The overall classification was presented as an inverted pyramid to indicate the larger numbers of patients that would be included in the milder stages owing to greater sensitivity [96]. In 2008 Ricci et al concluded that RIFLE was a simple and useful clinical tool for detecting and stratifying the severity of AKI. In addition, it also appeared to predict outcomes with a stepwise increase in relative risk for death with each of the three stages Risk, Injury, and Failure [129].

The RIFLE criteria have a number of limitations. Firstly, it is largely based on changes in serum creatinine and the limitations of this are well-recognised [130-132]. It included a fall in GFR in addition to changes in serum creatinine and as discussed earlier this is not valid in the setting of acutely changing renal function [131,132]. Secondly, urine output is not available in all settings. It is not reliable in retrospective studies and these have made up the bulk of AKI research to date. In a pooled analysis of the studies reviewed by Ricci et al only 12% of patients had the urine output criteria applied to them. The authors also found that the relative risk for death among studies that used both creatinine and urine output was lower than in those using the creatinine criteria alone [129]. This finding suggests that there is an imbalance between the creatinine and urine output criteria [131]. A third limitation of the criteria is the need to use a baseline creatinine or GFR level that in many cases will not be available. The ADQI group suggested using an estimate of the baseline but this has been heavily criticised and will be discussed further in section 2.3.7. A fourth issue raised by some authors is that the criteria do not take into account the nature and site of the injury bearing in mind the heterogeneous nature of AKI [130-132]. Finally, around the time that the RIFLE classification was being introduced evidence was emerging that even small increments in serum creatinine were associated with adverse outcomes [32,133-135]. These increments were much smaller than would be picked up by the Risk category of RIFLE which requires a 50% increase in serum creatinine. In 2007 Coca et al carried out a meta-analysis to look specifically at the prognostic importance of a small decrement in kidney function. They found that even very small increases in serum creatinine, of the order of 10% to 24% or 0.3 to 0.4 mg/dl (26 to 35μmol/l) were associated with approximately a 2-fold risk of short-term death [27].

2.3.5 The AKIN Definition

In 2007 the Acute Kidney Injury Network put forward the AKIN definition of AKI [39]. This represented a modification of the RIFLE criteria and an effort to solve some of the problems with RIFLE outlined above. The AKIN definition is illustrated in Figure 2.4.

Figure 2. 4 AKIN Definition and staging system [39].

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in Creat. of ≥ 0.3mg/dl (≥26.4µmol/l) or increase to ≥ 150% to 200% (1.5 fold to 2 fold) from baseline.	< 0.5ml/kg/hr for more than 6 hours
2	Increase in Creat. to > 200% to 300% (>2 to 3 fold) from baseline	< 0.5mls/kg/hr for more than 12 hours
3	Increase in Creat. to > 300% (>3 fold) from baseline or a Creat. of ≥4.0mg/dl (≥354µmol/l) with an acute increase of at least o.5mg/dl (44µmol/l).	< 0.3mls/kg/hr for 24 hours or anuria for 12 hours

The AKIN definition was designed to account for smaller increments in serum creatinine and hence the first stage includes an increase of 0.3mg/dl or 26.4µmol/l. The original proposal stipulated that a 48 hour time frame should be applied for the acute rise in serum creatinine. AKIN proposed that this would ensure the process was acute and representative of a clinically relevant time period. In addition, it was proposed that the diagnostic criteria should only be applied after an optimal state of hydration was achieved. This was to account for the influence of volume status on serum creatinine levels. However, there was no proposal on how this might be achieved. The group retained the use of urine output criteria but with recognition of the limitations of this as a marker of renal dysfunction. The group did not include any stipulation regarding pre-existing renal impairment or CKD but recognised that the criterion for elevation of creatinine of 0.3mg/dl would need to be validated in this population.

AKIN retained the multilevel classification approach used in RIFLE and divided AKI into three stages that could be used to classify AKI over a 7 day period. The Loss and ESRD categories were removed as these were considered outcomes of AKI and not relevant to the definition itself. They stipulated that anyone requiring renal replacement therapy should automatically fall into Stage 3 and this would account for the variation in practices regarding the timing of RRT start up. The GFR criteria used in RIFLE were also eliminated to avoid its incorrect use in AKI [39].

The AKIN definition partially addressed some of the limitations associated with RIFLE however issues still remain [131]. Firstly, while efforts were made to exclude easily reversible causes of creatinine elevation such as volume depletion the definition still does not account for the nature of the renal injury [24]. Application of the volume repletion component of the definition has proved problematic particularly in retrospective studies. In one of the first validation studies of the AKIN definition in an intensive care population, Barrantes et al found that only 123 of 213 patients had complete information on a fluid challenge at the time of their AKI although all had met the criteria of a rise in creatinine of 0.3mg/dl [136]. Barrantes et al defined a fluid challenge as having received at least 500mls of fluid at the time of the creatinine rise and whether or not this actually represents volume repletion is open to question. Secondly, the AKIN definition remains dependent on rises in serum creatinine. At present there is no way around this issue. A third problem with the AKIN definition has been the 48 hour timeframe. In another study by Barrantes et al in a general hospital population, 209 cases out of 6033 were excluded because of an unspecified timeframe or one beyond 48 hours despite meeting the creatinine criteria. These cases were analysed separately and were found to have outcomes similar to the AKI cases included in the study [24]. This suggests that this aspect of the definition may miss clinically relevant cases of AKI. Ostermann et al also noted problems with the timeframe when applying the definition to a large cohort of intensive care patients. The authors expressed concern that such a narrow time window would miss cases with a slower rise in creatinine that may be clinically relevant [137]. The original proposal for the AKIN definition also stated that at least two creatinine measurements were required in the 48 hour timeframe in order to make the diagnosis of AKI – it was hoped that this would reduce the need for a baseline creatinine which was shown to be a problem with the RIFLE criteria. This poses difficulties for diagnosing AKI at the time of admission to hospital. However the AKIN definition did state that the criteria should be used in the context of the clinical presentation.

2.3.6 RIFLE compared to AKIN

Following the introduction of the AKIN definition, a key question was whether or not it offered any improvement on the RIFLE classification of AKI. Since its introduction over a dozen publications have appeared in the literature conducting some form of comparison between the two definitions in adult populations. These publications are summarised in Appendix 3. The general consensus in the literature is that the AKIN criteria offer no clear advantage over the RIFLE criteria [150]. The key difference is that more patients are diagnosed in the milder Stage 1 of AKIN than its counterpart Risk in the RIFLE classification. This increased sensitivity at the milder end of the AKI spectrum is not surprising as it was the intention of the AKIN group to do this by including a lower threshold for the diagnosis of AKI [39].

The interpretation of the rules attached to the AKIN definition and their application have led to a few notable problems. These relate mainly to the 48 hour timeframe used in the AKIN definition. For example, Ando et al in their study on AKI after stem cell transplantation found contrary to other studies, that RIFLE appeared to be more sensitive than AKIN at detecting AKI. In their study, RIFLE diagnosed 52.6% with AKI as opposed to 46.6% diagnosed by AKIN. The reason for this difference was that many patients in the study did not have more than one blood sample taken in a 48 hour period and so by rigidly applying the need to have two serum creatinine measurements in 48 hours many cases of AKI could not be classified [147].

It was the intention of the AKIN group that by requiring two creatinine measurements within 48 hours it would negate the need to have a known baseline. Engleberger et al clearly demonstrated the problems with this approach. In their study looking at AKI after cardiac surgery it was found that 9.6% of patients classified as AKIN stage 1 had no AKI according to RIFLE. It was found that these patients actually had a fall in serum creatinine post-operatively due to fluid therapy however the rise in creatinine was taken from this new nadir level during the 48 hour window. In fact none of these patients had a rise of > 0.3mg/dl if the pre-operative creatinine was used. Strict application of the AKIN rules can therefore potentially over diagnose AKI [146].

Haase et al noted some differences between the two definitions in how they assigned cases to various stages of AKI. They noted that 13 patients were classified as AKIN stage 1 but went beyond this to the Injury Class in RIFLE [143]. This disparity again comes down to how the definition is interpreted. They stuck rigidly to the 48 hour timeframe and those who were assigned to AKIN stage 1 remained in that group. However their function deteriorated further over the course of the next few days resulting in them

being assigned a higher RIFLE class. This is an error in interpretation of the definition because AKIN did not intend for the 48 timeframe to be a limit for the staging of the AKI and clearly stated, albeit in small print, that the staging could take place over the course of 7 days.

Joannidis et al also found similar problems. In their study, RIFLE classified close to 7% more patients as having AKI. These were mainly patients who presented with significantly increased creatinine values compared to the estimated baselines and so were classified by RIFLE. However, they did not progress any further during the 48 hour window of observation and so did not strictly meet AKIN criteria [140].

Strict application of the AKIN 48 hour rule would make it virtually impossible to diagnose adequately community acquired AKI which is evident on admission to hospital. In addition, using the first serum creatinine in the 48 hour period as representative of baseline function will not always be accurate as was demonstrated by Engleberger above. It is notable that outside of the comparison studies summarised in Appendix 3 many of the observational studies which have used the AKIN definition have used an adapted version.

During the course of this research 33 observational studies applying the AKIN criteria were reviewed and are summarised in Appendix 4. All but four of these studies were retrospective in nature. Direct application of the AKIN definition was carried out in 16 studies (48%). In the others, the definition was either adapted or the precise methods were unclear. As an example of this approach, Kramer et al used the definition of a rise in serum creatinine by 0.3mg/dl or a 50% rise from a pre-operative stable baseline to any creatinine taken up to the point of discharge from hospital. There was no timeframe specified nor was there any form of staging used [161]. 15 studies defined a time point from which to measure a stable baseline level of kidney function. There was considerable variation in the definitions of baseline used and this will be discussed further in the next section. Just four studies formally applied the urine output criteria to define AKI. Only one study in an ITU population by Mandelbaum et al managed to record urine output on all patients [170]. Bucovic et al and Fonseca et al had urine outputs on 58.9% and 57.5% of patients respectively [166,177]. Finally, only one study by Minejima et al attempted to insure the patients were adequately hydrated at the time of the AKI. They defined dehydration by a rapid decline in the patients weight or if the serum creatinine or urea normalized within 48 hours following administration of fluids. It was found that 18 patients were excluded by applying this definition of dehydration, which compares to 43 patients actually recruited as cases of AKI [176]. However, the validity of excluding these patients in this study can be called into question. There is evidence

that adverse outcomes occur even with this type of transient azotemia [180]. This will be discussed in more detail later.

In summary, the AKIN definition has been widely adopted. However, it has not been precisely applied in any study. There appears to be considerable variation in its application particularly in relation to the 48 hour timeframe. Many studies have attempted to define a stable baseline from which the rise in creatinine can be measured but these also show much variation.

2.3.7 Defining the baseline level of kidney function

There has been considerable inconsistency in the literature on what determines baseline kidney function. 146 observational studies were reviewed during the course of this research using the search strategy outlined in Appendix 1. 30 different definitions for baseline kidney function were found in use during the past decade and are summarised in Appendix 5. In addition to this, 56 studies had not clearly specified what baseline if any was used.

Baseline kidney function is important for a number of reasons and is arguably more important than the arbitrary thresholds of serum creatinine used as a cut off to determine the presence of an AKI. Any threshold chosen for AKI must be determined relative to some baseline (see Figure 2.3). A patient presenting for the first time with a raised serum creatinine may have CKD or it could be an AKI and the only way of knowing this is to use a baseline as reference. Without a reasonably accurate baseline, cases of CKD could be misclassified as AKI. This would in turn lead to bias in reported incidences and outcomes. CKD has been recognised as an important risk factor for AKI for many years and close to a third of patients with AKI in contemporary studies have evidence of CKD prior to the AKI. [42,43].

The ADQI group attempted to address the problem of baseline function when they introduced the RIFLE classification. They recognised that any definition of AKI should consider a change from baseline and it should include classifications for CKD. They also recognised that many patients may present with acute renal dysfunction but without any baseline measure of kidney function. They suggested that one option to circumvent this would be to calculate a theoretical baseline serum creatinine value assuming a given normal GFR [96]. From this arose the practice of back estimating serum creatinine for a given eGFR of 75mls/min using the MDRD formula. This approach that can be found in many publications in the literature (see Appendix 5).

The Acute Kidney Injury Network did not make any specific recommendations regarding the assessment of baseline kidney function. In fact it could be argued that the AKIN approach was a step backwards. The AKIN definition requires two serum creatinine measurements within 48 hours with which to diagnose AKI and it was hoped that this would reduce the need for a baseline creatinine [39]. This aspect of the definition has proved problematic as discussed above and cannot be reasonably applied to a patient presenting with an acute illness and a raised serum creatinine. For this reason many studies have adapted the definition and devised their own definition of baseline function or simply used the back estimation previously recommended by the ADQI group.

Several studies have been conducted to assess the impact of various definitions of baseline kidney function [196-200]. In 2009 Bagshaw et al published a study comparing the use of a known pre-morbid baseline creatinine level with a back estimation derived by solving the MDRD equation for an eGFR of 75mls/min. The authors found that by using a back estimation 18.8% of patients were classified as having an AKI when they had not. These false positives were primarily due to patients with CKD being classified as AKI. The authors concluded that back estimation should not be used in those with suspected CKD [196]. This however is very difficult to assess especially in older patients.

Siew et al reviewed 4863 adult patients with a known outpatient creatinine in the year prior to the index admission that served as a reference baseline. They studied the effects of using several different surrogates for baseline function including back estimation, the minimum serum creatinine available during the first seven days of hospitalisation, and the first serum creatinine available on admission. The overall incidence of AKI using the known baseline as a reference was 25.5%. This was considerably higher when an estimated baseline or when the minimum inpatient level was used reaching 38.3% and 35.9% respectively. In the case of using the first admission serum creatinine the incidence fell to 13.7%. The use of different methods also resulted in different mortality rates. For example, the higher incidence rate associated with the imputed baseline resulted in a lower mortality. This would be expected to have a significant impact in populations enriched with CKD such as the elderly or those with diabetes [199].

One option in observational studies would be to classify only those who had a known baseline serum creatinine although this would exclude an important and selective group with no prior results. The question then is what kind of time frame should be used for obtaining this serum creatinine from the patient records. La France et al studied the impact of using different baseline assessment periods and compared those

with a creatinine on admission with a period extending back 3months, 6 months and 12 months. Extending the baseline assessment period back to twelve months resulted in an incremental increase in the cumulative incidence of AKI from 12.5% to 18.3%. The cases added tended to be milder and have a lower mortality. The authors highlighted that differences in baseline assessment periods had the potential to severely bias results [197].

A notable feature of some studies listed in Appendix 5 is that they used more than one definition of baseline function and even in one study by Hoste et al there were three. The most common approach was to use a known baseline when available and to back estimate the rest. For example, Cruz et al used a known pre-morbid baseline creatinine from an unspecified period prior to the index admission and when this was not available an estimate using an eGFR of 75mls/min was used. 22% of patients had an estimated baseline [186]. The problem with this approach is that these two essentially separate cohorts were analysed together adding to any potential bias in the results.

In summary, progress has been made in trying to achieve a consensus definition of AKI and most studies in the literature are now using either the RIFLE definition or some form of the AKIN definition. However, this is a process that is still in evolution. There is still a lack of consensus on other aspects of AKI such as the definition of baseline function that are contributing to study heterogeneity.

2.3.8 KDIGO 2012

In March 2012 KDIGO (Kidney Disease: Improving Global Outcomes) released a clinical practice guideline for AKI. They recognised that two similar definitions of AKI are in use in the literature namely the RIFLE classification and the AKIN definition and stated that there was a need for a single definition for practice, research and public health. KDIGO also recognised that there is the potential for a bidirectional misclassification of AKI cases between the RIFLE and AKIN definitions and that cases that were missed by either definition also had poor outcomes. For this reason they felt that there was strong rational for the use of both RIFLE and AKIN criteria to identify patients with AKI. A new hybrid definition of AKI has therefore been proposed which has some minor modifications and possesses features of both definitions and is shown in Figure 2.5 [48]. In figure 2.5 it can be seen that the new KDIGO definition includes the 0.3mg/dl rise in 48 hours seen in AKIN but also the 50% rise over 7 days seen in RIFLE. For clarity, KDIGO specified that to reach Stage 3 by a serum creatinine > 4.0mg/dl, it should be required that this is reached by a rise of ≥0.3mg/dl within 48 hours rather than a rise of 0.5mg/dl over an unspecified time period.

Figure 2. 5 The 2012 KDIGO definition and staging of AKI which combines features of both the RIFLE and AKIN definitions [48].

AKI is defined as any of the following:

An increase in serum creatinine by ≥0.3mg/dl (≥26.5µmol/l) within 48 hours
or
An increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days
or
A urine volume < 0.5ml/kg/hr for 6 hours

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline or ≥0.3mg/dl (≥26.5µmol/l) increase	<0.5ml/kg/hr for 6-12 hours
2	2.0 -2.9 times baseline	<0.5 ml/kg/hr for ≥12 hours
3	3.0 times baseline or an increase in serum creatinine to ≥4.0mg/dl (≥353.6µmol/l) or initiation of RRT	<0.3ml/kg/hr for ≥24 hours or anuria for ≥ 12 hours.

The combination of the RIFLE and AKIN thresholds seems to be a logical evolution in the definition of AKI but there remain some issues regarding baseline function. There will be some cases where a baseline is not known and in this instance a back estimate as described earlier may be used provided there is no evidence of CKD. In doing this however, there is still the risk of misclassifying patients. KDIGO felt that by using all available clinical data it should be possible to arrive at an accurate estimate of baseline. This type of dynamic interpretation can occur in clinical practice but may be difficult to apply in the research setting. In addition, as mentioned earlier, the time period from which a known pre-morbid level of function is taken may also influence outcomes. This aspect of function was not addressed by KDIGO. KDIGO has stressed that clinical judgement must be used in applying the definition of AKI.

2.3.9 New Biomarkers for AKI

As interest in the definition and natural history of AKI has grown, there has been increasing interest in the development of new biomarkers for AKI. The limitations of serum creatinine and urine output for the detection of AKI have been discussed. More sensitive and specific markers of renal injury and dysfunction could offer several advantages:

1. They could allow the diagnosis of AKI before a rise in creatinine is detected.
2. Better stratification for severity may be possible.
3. They may provide prognostic indicators.

In 2005 the ASN Renal Research Report cited these points as reasons to prioritise the development of new biomarkers [40]. Earlier diagnosis of AKI could offer several advantages. Chief among them would be the ability to offer targeted therapy at an earlier stage [48]. It is well recognised in the literature that several agents that showed promise for the treatment of AKI in animal models failed in human trials [201]. Most notable is Anaratide, a synthetic analogue of Atrial Natriuetic Peptide, that was shown to improve renal function and renal histopathology in laboratory animals but later failed to show an improvement in the overall rate of dialysis-free survival in critically ill patients with acute tubular necrosis [202].

One of the reasons put forward for the failure of therapeutic trials in humans is the fact that we rely on serum creatinine as a marker of renal dysfunction. Renal injury is already well established by the time a rise in serum creatinine is detected and hence any treatment may be too late [40,201,203].

Over 20 different candidate biomarkers can be found in the literature and the area continues to grow as a result of new technologies such as functional genomics and proteomics [201,204,205]. These markers are illustrated in Figure 2.6. Urinary NGAL is one of the markers which is showing great promise but for the present none of these markers can be recommended for routine clinical use [48,205]. Given the heterogeneous nature of AKI it is unlikely that any one marker would suffice on its own for the detection of AKI and so a panel of markers may well be needed.

Figure 2.6 Candidate biomarkers which have been used for the early diagnosis and assessment of AKI.

Candidate biomarkers for AKI	Abbreviation
Cystatin C	
Prohormone of atrial natriuretic peptide	ProANP(1-98)
Neutrophil Gelatinase Associated Lipocalin	NGAL
Neutrophil CD11b	
Interleukin 18	IL-18
Interleukin-6	IL-6
Interleukin-8	IL-8
Interleukin-10	IL-10
Kidney Injury Molecule – 1	KIM-1
N-acetyl-β- D-glucosaminidase	NAG
Matrix Metalloproteinase – 9	MMP-9
Glutathione-S-transferase	GST
π-GST	
α-GST	
γ–Glutamyl Transpeptidase	γ–GT
Alkaline Phosphatase	AP
Lactate Dehydrogenase	LDH
α-Microglobulin	
Retinol Binding Protein	RBP
β-2-Microglobulin	
MicroRNA – 210	miRNA-210
Monocyte chemoattractant protein -1	MCP-1
L type fatty acid binging protein	L-FABP

2.4 Epidemiology of AKI

The epidemiology of AKI remains difficult to ascertain from the literature [48]. The table in Appendix 6 contains a list of the observational studies carried out on AKI that were reviewed during this research. There are considerable differences in the definitions of AKI, the majority are from single centres or derived from databases, and the populations studied are diverse.

A review of the data summarised in Appendix 6 indicates that AKI is more common in the elderly with an average age of 66 years in the studies reviewed. There is also a male predominance with an average of 63% in these cohorts.

2.4.1 Incidence

Marked differences are found in the incidences reported for similar populations depending on whether or not cases with baseline CKD were included. Few studies have calculated population based incidence rates so at best the incidence of AKI can be expressed in terms of crude risk or cumulative incidence.

In studies using the RIFLE or AKIN definitions the incidences range between 3 and 18% and so interpreted together the overall incidence of AKI is probably somewhere in the region of 10% of hospitalised patients depending on the population studied with up to 1% requiring renal replacement therapy.

Appendix 7 contains summary tables of contemporary observational studies with AKI incidences for the overall general population including hospital and community acquired cases (Table A7.1), critical care (Table A7.2), and specific critical care groups (Table A7.3). The incidence in studies using coded data ranges from 0.7 to 3.1% and this is much less than that reported from studies using a formal definition of AKI [42,224,230]. Coded discharge summaries use ICD-9 codes and are known to have a poor sensitivity and so will under report the incidence of AKI [15]. Ali et al reported an incidence rate of 2147 per million population per year in northern Scotland using the RIFLE classification [187]. Bedford et al reported an annual incidence of 7007 per million population in the Kent region using the AKIN definition [238]. This marked difference between these incidence rates is due mainly to the inclusion of milder cases of AKI using the AKIN definition.

Many studies have been undertaken applying the RIFLE or AKIN definitions in the critical care setting and relevant studies are summarised in Table A7.2 (Appendix 7).

The incidence of AKI in critical care has a broad range between 10.8 and 67%. Averaging the available figures gives an incidence in the region of 40% with up to 30% of AKI cases requiring renal replacement therapy depending on the population studied. The broad range in incidence in the critical care setting can be accounted for by local admission policies but in addition the patient mix is likely to have a significant effect. Table A7.3 (Appendix 7) summarises contemporary studies where the incidences reflect specific patient groups within critical care. It can be seen that there is a broad range reflecting the underlying illness. Licker et al reported an incidence of just 6.8% in patients undergoing lung surgery while an incidence as high as 78% was reported by Lin et al in patients receiving extracorporeal membrane oxygenation (ECMO) [211,234].

Finally, there is evidence in the literature that the incidence of AKI is increasing. In 2002 Nash et al conducted a single centre study of hospital acquired AKI in the US and reported an incidence of 7.2%. This study was carried out in 1996 and mirrored exactly a study carried out in the same hospital in 1979 that reported an incidence of 4.9% [8,239]. Xue et al reported on the incidence and mortality of AKI in Medicare beneficiaries in the US between 1992 and 2001 and found that the incidence rates were increasing by approximately 11% per year. They felt that the increase in admission for sepsis could partly account for this [13]. However, in addition to this, multiple new drugs have been introduced that can affect renal function, new surgical procedures have been introduced, and there has been a change in the pattern of use of radiographic contrast media as was demonstrated by Nash et al in their cohort [8]. It is not possible to assess the influence of changes in the age profile of patients in the study by Nash et al as this data was not provided in the original study conducted by Hou et al. In the study by Xue et al the increased incidence during the 1992 to 2001 period was confirmed after adjustment for age, gender and race [13].

2.4.2 Hospital compared to Community Acquired AKI

In terms of epidemiology, some authors have divided AKI into community acquired AKI, hospital acquired AKI, and AKI occurring in critical care settings [48,240]. The division between community and hospital acquired AKI is an important distinction to make, as evidence exists that the causes and outcomes may differ [107,110,206,241]. In 2004 Sesso et al reported on a population of elderly patients with AKI and found that hospital acquired cases were more likely to be due to prerenal causes and have a significantly higher mortality [110]. However, very few studies have looked at these specific populations [8,23,107,174,190,206]. Community acquired AKI is usually defined as AKI that occurs in the community and is evident at the point of admission to hospital [206]. The key insult or insults have occurred in the community which contrasts with hospital acquired cases

where the insults occur at some point during the hospital stay. Some studies purporting to be community based have in fact included hospital acquired cases in their final cohorts [20,101]. In the case of studies looking specifically at hospital acquired cases there have been differences in how this has been defined. Kwon et al defined hospital acquired AKI as that occurring during hospitalisation and excluded those presenting in the first 48 hours of admission [190]. Broce et al calculated hospital acquired cases from rises in creatinine from the nadir level in the first three days of hospitalisation [23].

There is evidence that community acquired cases are in the majority [107,110,168]. Obialo et al compared the incidences of the two in a population of African Americans and found community acquired cases were 3.5 times more common [107]. Pannu et al in a broader population based study reported that 60% of cases of AKI had achieved their highest serum creatinine within 48 hours of admission [168]. Finally, Murugan et al recently reported on non-severe community acquired pneumonia and found that two thirds of patients with AKI had already developed it at the time of hospital admission [31]. Overall, while there are clear differences between the two types of AKI in the literature it is difficult to clearly distinguish between the two from an epidemiological point of view. As can be seen in Appendix 6 the majority of hospital- based studies have included community cases.

2.4.3 AKI around the world

Appendix 6 also illustrates that the majority of AKI studies in the English speaking literature are from Europe or North America. South America, Asia, and Australasia are also represented but to a lesser extent. There is very little information available on AKI in Africa. The aetiology of AKI in Africa is considerably different from that in developed countries, infections such as Malaria and HIV, nephrotoxins, obstetric and surgical complications predominate. AKI appears to be a considerable burden on resources in African countries but little if anything is known about its epidemiology [242].

2.5 Causes, Risk Factors and pathophysiology of AKI

AKI is a syndrome rather than a single disease entity and its aetiological pathway is complex. It can consist of an interaction between risk factors that make an individual susceptible to developing an AKI and the definitive insult that causes the AKI. Often more than one insult may occur in the same patient particularly in the elderly [18,106,243,244]. In some cases the distinction between being a susceptibility factor and a causative insult is unclear. For example, dehydration could be considered a risk or susceptibility

factor in some settings whereas in others it may be the definitive cause if severe enough. In this section those factors traditionally considered insults will be discussed under 'causes of AKI' while susceptibility factors will be discussed under the heading of 'risk factors'. It should nonetheless be remembered that there is some overlap. The interaction between cause and risk is difficult to decipher from the literature because the risk factors for AKI are incompletely understood and very few studies have thoroughly explored the cause of AKI [48,245,246].

2.5.1 Causes of AKI

The many causes of AKI are traditionally divided into Prerenal, Intrinsic and Postrenal causes. This is outlined in Appendix 8 [48,244]. Prerenal is defined as a functional decline in glomerular filtration associated with renal hypoperfusion. Renal hypoperfusion is generally described to occur in the context of a loss of effective circulating or arterial volume. Intrinsic refers to causes that lead to structural damage to the kidney that includes the many causes of acute nephritis. Postrenal refers to obstruction of urine outflow from the kidney and urinary tract and is sometimes simply called Obstructive renal failure [244,247]. It is important to note that while this division is useful during the initial assessment of patients with AKI there is often overlap between these divisions.

It is not possible to precisely describe the contribution of the many causes of AKI listed in Appendix 8 to its epidemiology. There are a number of reasons for this. The first relates to the description and classification of the causes. For example, acute tubular necrosis figures prominently as a cause of AKI in most observational studies that report aetiology. It is generally classified as intrinsic but for the most part it is predominantly due to prolonged ischaemic injury and so represents the severe end of the prerenal spectrum. The problem with this diagnosis is that it is usually based on clinical grounds and so there is subjectivity in classification. The distinction often comes down to whether the AKI is volume responsive or not volume responsive [20,226]. However, this distinction between functional AKI due to prerenal causes and structural ATN is known to be difficult to make [248]. The methods used to describe them in the literature differ considerably. Some authors have preferred to retain the concept of 'Prerenal AKI' while others have avoided it completely and used terms such as hypovolaemia, hypotension, ischaemic or hypoxic [44,186,247,249]. Coupled with this problem are other issues surrounding classification that have evolved in recent years. AKI associated with sepsis has traditionally been linked with reduced renal perfusion and so has been included in the prerenal causes. In more severe cases it has been classified as Septic ATN in some studies [20,45]. However, there is now evidence that the pathophysiological mechanisms involved in septic AKI are far more complex and there

may even be increased renal perfusion in some cases. This has led some authors to separate sepsis as an aetiology [248]. Current literature is therefore confused and difficult to compare. Authors have attempted their own classification of aetiology that has lead to widely differing reporting [8,44,106,108,186,190,208,226,235,236,250-252].

A second reason for the difficulty in describing the cause of AKI is due to the small number of studies that have attempted to report on it in detail. In recent years observational studies on AKI have been dominated by retrospective reviews of hospital records and databases. While this approach offers large patient numbers the baseline clinical data are incomplete or even absent and therefore potential aetiological factors cannot be accurately described. Of 128 observational studies carried out between 2000 and 2011 that were reviewed just 22 were prospective in nature. Only 13 of these studies attempted to describe the distribution of causes. The remaining studies either did not report aetiology or the focus was on a particular cause of AKI such as sepsis, the use of contrast or post-surgery. Therefore an overall picture of AKI aetiology could not be given [25,117,216]. The studies that did attempt to report aetiology came from diverse populations and no two of them used the same method for describing and reporting the aetiology as described above.

Finally, the aetiology of AKI is probably multifactorial in many cases. Many of the causes outlined in Appendix 8 overlap with each other in the same patient making accurate description of aetiology very difficult. In the Madrid Acute Renal Failure Study Liano et al found that more than one aetiology could be attributed to the overall cause in 16% of patients [20]. In a study of elderly patients with AKI, Kohli et al found 31 different combinations of causes in their cohort [106]. Metcalfe et al reported up to three insults in each patient in a cohort with AKI who required renal replacement therapy [236]. It is also likely that the definition of AKI used in these studies will have influenced the reporting of aetiology. For example, the AKIN definition will detect much milder cases of AKI and this may alter the reporting of aetiology.

AKI aetiology is poorly described and understood. The syndrome of AKI is used as an umbrella term for a wide variety of overlapping causes and there is a lack of consensus on how these should be described. Appendix 9 contains a summary of thirteen prospective studies reviewed which attempted to describe the causes of AKI in various cohorts. It can be clearly seen that it would not be possible to cross tabulate these reports for comparison owing to the differences in classification and reporting. However, some deductions can be made from these data. Postrenal obstructive causes of AKI make up a very small proportion of AKI in all settings. In the intensive care setting postrenal causes contribute to < 2% of cases while in the overall hospital

population it is likely to be somewhere in the region of 2-10% depending on the population studied. The distinction between prerenal and intrinsic causes are less clear but it can be deduced that the spectrum of prerenal failure due to reduced renal perfusion extending to ischaemic ATN makes up the large majority of cases of AKI. Using the figures provided in Appendix 9 it is likely to be around 85%. These overlap with other causes. Sepsis appears to contribute in over 50% of cases in all settings while medications, radiocontrast and post surgery are also important contributors. In the case of most of these contributors the pathophysiological mechanisms appear to be similar and related to renal ischaemia. However, their contribution will depend on the population studied. Kohli et al reported that medications contributed in 66% of cases in an elderly population while Nash et al found medications contributed in just 16% of a general hospital population [8,106]. Primary intrinsic diseases such as acute glomerulonephritis and interstitial nephritis are very uncommon. Using the figures provided by Nash and Liano for general hospital populations they are likely to make up < 5% of cases [8,20].

There is also evidence that the aetiology of AKI has changed in the past 50 years. A publication by KG Lowe in the Lancet in 1952 illustrates the very different causes attributed to renal failure in that era. Figure 2.7 outlines the causes listed by Lowe for his series of 14 patients from the Hammersmith Hospital in London [49]. 36% of the cases are obstetric related while a further 29% are related to haemolytic transfusion reactions. With modern medical care the latter cause is now virtually unheard of. Turney et al conducted an extensive review of cases of AKI in Leeds between 1956 and 1988. They found that obstetric causes made up 20-30% of cases between 1956 and 1970 but by the 1980s this cause had become rare however it remained an important cause in the young. In addition, they found that the incidence of trauma related AKI had fallen from 11.3% in the 1960s to 2.8% in the 1980s. The authors attributed these findings to improved medical care. There was a marked increase in general medical cases of AKI which could be attributed to the aging population and increased use of medications toxic to the kidney together with more advanced medical and surgical procedures [253]. These have already been used to account for the rising incidence in AKI noted in the past decade. While the aetiology of AKI has changed in the western world as a result of improvements in medical management over the past fifty years some of the causes that were prominent in the 1950s remain a problem in the developing world. A recent publication from Pakistan by Ali et al reported that obstetric-related AKI continues to make up 9-11% of their AKI series [126].

Figure 2.7 List of causes of AKI, more specifically ATN, by KG Lowe in the Lancet 1952. The causes are described exactly as they were in the original article and demonstrate the different aetiologies in that era [49].

Case	Age	Cause of ATN
1	38	Post abortion
2	27	Post abortion
3	24	Post abortion
4	27	Post abortion
5	38	Unexplained episode of intravascular haemolysis following delivery of anencephalic monster
6	24	Haemolytic transfusion reaction
7	42	Haemolytic transfusion reaction
8	23	Haemolytic transfusion reaction
9	41	Haemolytic transfusion reaction
10	30	Anuria, following concealed accidental haemorrhage
11	21	Mercury poisoning
12	39	Posthaemorrhagic shock
13	19	Posthaemorrhagic shock
14	54	Myanesin poisoning

2.5.2 Prerenal AKI and Acute Tubular Necrosis (ATN)

2.5.2(i) Defining Prerenal AKI and ATN

Prerenal AKI (also referred to as Prerenal azotemia) is classically defined as a decrease in GFR resulting from renal hypoperfusion, which is rapidly reversible when the underlying cause is corrected [98]. The body can adapt to reduced renal blood flow to a certain extent, but if the ischaemia is prolonged, adaptive mechanisms fail and cellular injury ensues [247]. This has been referred to as the stage of renal decompensation [254]. With established cellular injury the AKI is no longer rapidly reversible and at this point ATN is said to be present. ATN describes the clinical situation in which there is adequate renal perfusion but GFR is not maintained [48,255]. Based on animal models the transition from Prerenal to ATN appears to be at least in part dependent on the duration of ischaemia, with increasing cellular damage seen with greater duration of hypoperfusion [249]. This may explain the variability in AKI severity seen in clinical

practice and underscores the need to view Prerenal and ATN as part of the same continuum [256,257].

2.5.2(ii) Pathophysiology of Prerenal AKI and ATN

Current understanding of the mechanisms involved in prerenal AKI and its evolution to ATN are largely based on animal models, chiefly the rat. Although widely quoted in the literature these pathological processes need to be interpreted with caution in the context of human AKI. Human AKI is poorly depicted by most animal models [249]. The rat kidney possesses fundamental differences to its human counterpart. It has a well-developed medullary outer strip, which is not the case in humans, and in addition the vascular bundle in the inner strip is more complex [255]. Several rat models have been utilized in basic science research, particularly the warm ischaemia-reflow model, but none have any direct resemblance to the findings in human AKI. In the warm ischaemia-reflow model extensive tubular destruction is seen particularly in the proximal tubules. This is not the case in human AKI [255]. In fact, in human AKI, overt tissue injury is more focal and limited. It tends to be concentrated in distal medullary tubule segments and the inflammatory component is not prominent [249]. The limited nature of the damage seen histologically in human AKI is not accurately reflected in animal models and the term acute tubular necrosis is in some ways a misnomer. Part of the problem may be that in animal models hypoxic ischaemic damage is simulated by total cessation of blood flow to the kidney. However, in clinical practice most cases of ‘hypoxic’ AKI are characterized by compromised renal microcirculation and oxygenation that is related to systemic haemodynamic disturbance, sustained critical hypoxaemia, or to various nephrotoxins that cause renal dysfunction by disrupting oxygenation. The latter includes radiocontrast agents and NSAIDS. In these settings, in contrast to the animal models, renal blood flow never ceases completely, and oxygen consumption for residual tubular transport persists [249]. Despite their limitations, animal models have nevertheless provided some basis for understanding the processes involved [255].

In response to reduced effective circulating volume several neurohumural processes come into play in order to compensate for the disturbance. There is an increase in activity of the renin-angiotensin-aldosterone system. Angiotensin II increases both afferent and efferent arteriole vascular resistance through vasoconstriction and in the early stages this is concentrated on the efferent arteriole. This has the effect of increasing glomerular capillary pressure and so maintains GFR. In addition there is increased adrenergic activity which appears to have its effects through Angiotensin II and there is also increased release of Antidiuretic hormone [254]. The vasoconstrictor

effects of Angiotensin II and adrenergic nerve stimulation are buffered by vasodilation promoted by Nitric Oxide and Prostaglandins [254]. All of these mechanisms serve to retain salt and water and maintain an effective circulating volume. In later stages Angiotensin II causes severe vasoconstriction of both the afferent and efferent arterioles. This leads to a reduction in nephron plasma flow and hence a reduction in GFR.

Another mechanism which comes into play in the early stages of the prerenal injury is tubuloglomerular feedback. Reduced proximal tubular reabsorption owing to injury leads to an increase in the delivery of sodium chloride to the macula densa cells of the nephron which cause a feedback to increase afferent vasoconstriction and hence reduce GFR even further [254]. It is thought by some that the reduction in GFR that is seen in these early stages of AKI may actually be an adaptive response to protect the kidney. The renal medulla is known to operate at low oxygen tensions and is sensitive to reductions in oxygen supply. By reducing GFR the kidney reduces the demands on the medullary tubule cells for transport activity and hence their oxygen requirements [249]. This has led some to suggest that efforts to increase GFR in this setting may actually put the kidney at more risk [249,257].

It is clear from the description above that prerenal AKI does not involve a simple ischaemic injury. Nevertheless, the most widely accepted cause for the more advanced stages of renal damage in this setting involves the reduction of oxygen supply to cells which leads to a depletion of cellular ATP. ATP is vital for essential cellular processes [258]. The cells most susceptible to this process are tubular epithelial cells. They have a high oxygen and ATP demand in order to carry out transport functions and they operate in an environment with already low oxygen tension. In addition they are vulnerable to higher concentrations of toxic substances as these are transported into the urine [259]. Liberthal et al have demonstrated that the extent of ATP reduction determines the fate of the cells affected. With moderate reductions cells undergo apoptosis while with more severe reduction necrosis of cells occurs [260]. This difference in the outcome of cells may explain why in animal models where ischaemia tends to be more complete, necrosis predominates, whereas in human AKI necrosis is limited. Indeed, apoptosis is now considered to be one of the most important mechanisms in human AKI. Oxidative stress leads to the release of reactive oxygen species from mitochondria which can activate apoptotic pathways and also lead to direct cellular damage. In addition, renal tubular cells also express cell surface receptors of the tumor necrosis factor (TNF) superfamily that also induce apoptosis. This is part of the basis for the theory that removal of circulating cytokines such as TNF-α, particularly in the setting of sepsis, could preserve organ function. Apoptosis is known to promote

fibrosis and this could account for some of the long-term sequelae of AKI including its possible progression to CKD [258].In addition to the direct ischaemic damage described above, cell death leads to desquamation of cells into the tubular lumen where they can form casts and cause obstruction.
In summary, the processes involved in prerenal AKI and ATN are complex and incompletely understood. They lead to epithelial and endothelial cell death, intratubular obstruction, changes in local blood flow and immunological responses. The relative contribution of each of these processes to the injury is unclear but may depend on the type and severity of the injury along with individual susceptibility [258]. Why some patients with prerenal AKI appear to reverse quickly and others do not and progress to ATN is an important question but at present the answer is unclear. It is likely to be at least partly due to the severity and the duration of the injury but in addition patients may possess predisposing factors. Intensified medullary hypoxia has been demonstrated in various settings that may increase the risk of cellular damage. These include patients taking NSAIDS, those after radiocontrast administration, in diabetes, and in those with CKD [249].

2.5.2(iii) Differentiating Prerenal AKI from ATN

There is no universal definition of when Prerenal AKI should be considered to have progressed to ATN but it is generally considered to have occurred if the AKI does not reverse within 24 to 72 hours [180,261]. Distinguishing between reversible prerenal AKI and established ATN is important in clinical practice. Prerenal AKI is generally reversed using fluid resuscitation. However, in the setting of ATN when GFR is not maintained, continued fluid resuscitation can be detrimental and lead to fluid overload and potentially increased mortality [262]. Apart from the initial response to a volume challenge a number of additional methods have been explored in order to differentiate between prerenal and ATN. The fractional excretion of sodium (FeNa) has been shown at least in some settings to be useful. This is the percentage of sodium filtered by the kidney that is excreted in the urine [263]. In prerenal AKI sodium handling by the kidney is preserved, as opposed to ATN where it is impaired and associated with increased sodium losses in the urine. A fractional excretion of sodium < 1% has been shown to indicate the presence of prerenal AKI and hence the potential for reversibility [263]. However, the usefulness of FeNa is reduced in certain settings particularly in patients who have been administered diuretics, diabetics with glucosuria, advanced CKD, and in sepsis [261,264]. These have limited its use in clinical practice. Urine microscopy may also be a useful tool in determining the presence of ATN. As outlined above ATN is associated with the release of tubular cells and casts into the urine. A recent study by Perazella et al confirmed that using urine microscopy to detect the presence of casts or

renal tubular epithelial cells had a strong positive predictive value for a final diagnosis of ATN [265]. Finally, there is some evidence that the use of Doppler ultrasound may be useful in detecting the presence of ATN although this has little support in clinical practice and requires more investigation [266,267].

2.5.3 Septic AKI

Sepsis is one of the most important contributing factors to AKI. It has traditionally been viewed that AKI in the setting of sepsis is due to impaired renal perfusion and is part of the prerenal/ATN spectrum. While some of the mechanisms of cellular injury discussed in relation to ischaemic AKI may take place in the setting of sepsis, the evidence base to support any firm conclusion about the processes involved is lacking. Bellomo et al have pointed out that the understanding of septic AKI is limited and that the knowledge of the pathophysiological mechanisms are based on animal models subjected to ischaemia or toxins and not to sepsis itself [248,268]. Evidence has been emerging that septic AKI may not fit the ischaemia model. Langenberg et al conducted experiments using female Merino sheep as animal models of septic AKI and found that at least in hyperdynamic sepsis there was marked renal vasodilation and a marked increase in renal blood flow [269]. This is contrary to what one would expect with the prerenal/ATN model. Indeed there is evidence from post-mortem studies that ATN may not be the pathological endpoint of septic AKI. Over 90% of one series of septic patients were found to have normal renal histology [248]. Another recent study by Benes et al using a porcine animal model demonstrated that in some animals there was an increase in renal vascular resistance associated with AKI. These were predominately animals with normodynamic haemodynamics and not the hyperdynamic circulation seen in Langenberg's study. However, AKI was preceded by an early and marked inflammatory response with oxidative stress suggesting that more complex mechanisms may be in play [270]. In summary, septic AKI appears to share some of the pathophysiological mechanisms associated with ischaemic AKI however it is incompletely understood and inflammatory mechanisms may also play an important role. This supports the approach taken by some authors to separate sepsis as an individual cause of AKI. Nevertheless the reduced renal perfusion model should not be completely ignored in sepsis. Despite the findings that in some septic patients the renal blood flow is increased there is still strong evidence in the literature that early goal directed resuscitation of septic patients to restore haemodynamics reduces the risk of AKI [195].

2.5.4 Risk factors for developing AKI

There is a complex interaction between known insults and risk factors in the development of AKI. As is the case with the causes of AKI, the risk factors for AKI are also incompletely understood [246]. KDIGO have recently put forward the need for better delineation of risk for hospital- and community- acquired AKI as a research recommendation. KDIGO have referred to them as susceptibility factors and Figure 2.8 lists these factors according to the 2012 KDIGO Clinical Practice Guideline for Acute Kidney Injury [48].

Figure 2.8 AKI Susceptibilities according to KDIGO 2012 [48].

AKI Susceptibilities
Dehydration or volume depletion
Advanced age
Female gender
Black Race
CKD
Chronic Diseases (heart, lung, liver)
Diabetes Mellitus
Cancer
Anaemia

AKI risk factors have not been extensively studied and few studies have conducted an adjusted analysis to thoroughly explore them. Many of the studies that have reviewed risk factors in any detail have been limited to specific populations such as cardiac surgery and therefore it is difficult to extrapolate their findings [222,223]. Appendix 10 contains a summary of 14 studies from the past decade from various populations that conducted an analysis of the risk factors for AKI adjusted for potential confounders such as age, sex, and comorbidities. It is evident that increased age and the presence of baseline CKD are consistent risk factors in most of the populations studied. The presence of comorbid illnesses and in particular diabetes, hypertension and vascular disease are also important. There appears to be little to support including female sex as a susceptibility factor as KDIGO has done. Of the fourteen studies shown in table 2.9 only four have found a sex association following adjusted analysis and three of these favoured male sex as a risk factor rather than female. In addition there is evidence from animal models that male hormones may exacerbate the effects of renal ischaemia/reperfusion injury [272]. With regard to CKD there is evidence that the association with AKI is a graded one. Hsu et al demonstrated that even with a baseline eGFR in the range of 45-49mls/min there was a twofold increased adjusted odds ratio

of AKI and this risk then increased sharply for increasing severity of baseline kidney disease [271]. There is also recent evidence that those with albuminuria have an increased risk of AKI. This is likely to be linked to the risks associated with CKD [30,231,273]. A study by Grams et al demonstrated that an eGFR of 60mls/min had adjusted relative hazards for AKI nearly twice as high as those with eGFR 75mls/min. This is a stronger and earlier signal for an adverse outcome than that seen in studies of eGFR with death or cardiovascular disease [274].

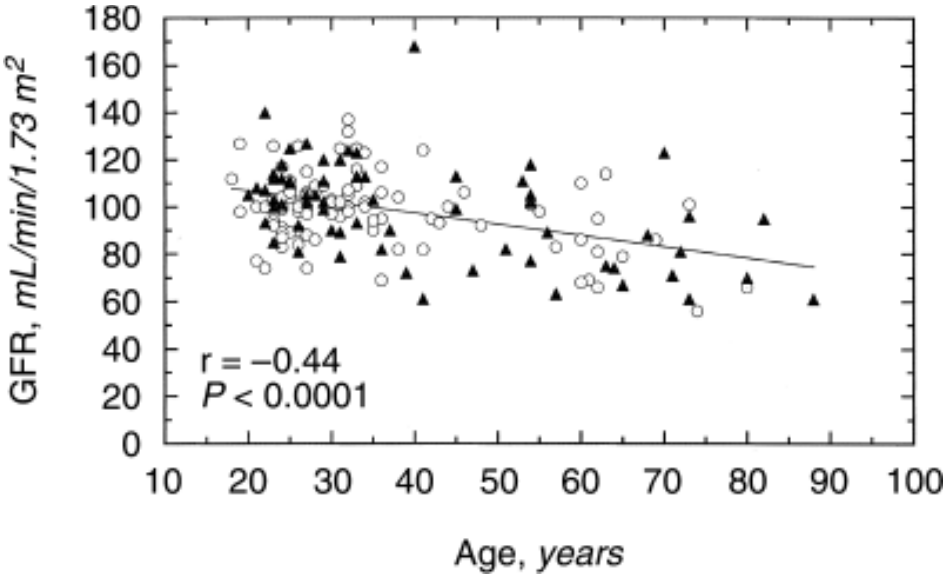
2.5.5 AKI and the elderly

Epidemiological studies show that AKI is more common in the elderly and that increasing age is an important risk factor for AKI. The reason for this strong link between age and the development of AKI is complex and not completely understood [275]. There are a number of likely overlapping factors that make elderly people vulnerable to developing an AKI. Firstly, there is a general loss of function with age. Secondly, there is impaired sodium and water handling which makes elderly people vulnerable to dehydration. Finally, there is an increased prevalence of comorbidities with age and these bring with them increased exposure to potentially nephrotoxic medications and procedures [245]. In addition to these factors, age-related changes in cardiovascular haemodynamics can lead to a reduction in cardiac output and hence renal perfusion [276]. Renal atherosclerosis is also likely to play a role.

The loss of function that occurs with age has been known for decades and is illustrated in Figure 2.9. How much of this is actually due to senescence and how much of it is due to other factors such as accumulated vascular disease remains unclear. There is good evidence of specific age-related changes within the kidney. For example, in experimental animals collagen accumulates in the kidney with age and has been linked with increased gene transcription [277]. One of the hallmarks of the aging kidney is considered to be increasing glomerulosclerosis and as much as 30% of glomeruli have been found to be sclerosed in apparently healthy elderly patients. This compares to less than 10% that would be expected in those under 40 years of age [278,279]. However, the association between age and glomerulosclerosis is not clear-cut and Kasiske showed that atherosclerosis is also likely to play an important role [280]. Along similar lines, in 1950 Davies and Shock published a widely cited paper on the decline in GFR that occurs with age and this has become part of nephrology dogma. They reported a gradual reduction in GFR from the third decade onwards such that by the ninth decade the GFR has fallen by nearly 50%. They were initially careful to exclude patients with hypertension, coronary artery disease and known renal disease. However, examination of their study cohort reveals that a large number of patients in the older age

categories had a history of atherosclerosis suggesting their results may have been confounded [281,282]. Facts such as these have led some to conclude that age-related glomerulosclerosis is indicative of subclinical renal injury from comorbid conditions leading to atherosclerosis and is not entirely due to increasing aging per se [281].

Figure 2. 9 GFR measured by inulin clearance plotted as a function of age in 164 healthy individuals. Reprinted by permission from Macmillan Publishers Ltd:[Kidney International][425],Copyright 2003.



In addition to the fall in GFR with aging other factors have been recognised including a reduction in renal blood flow, increased glomerular basement membrane permeability and a reduction in renal mass [276]. There also appear to be changes in the activity and/or responsiveness to vasoactive mediators. There is an impaired ability to autoregulate renal blood flow and this can lead to a fall in GFR even when the magnitude of the acquired renal insult is relatively modest [276,281]. Elderly patients will also have increased sensitivity to medications that can affect renal blood flow such as NSAIDS and RAS-blockers [244]. The former inhibit the vasodilatory effects of prostaglandins while the latter inhibit angiotensin II mediated efferent arteriole vasoconstriction and so reduce glomerular capillary pressure and hence GFR. It is not uncommon that such medications are used together in the elderly and they may also be combined with diuretic use and so the effects are potentiated. Finally, renal salt and water handling is altered with age. The elderly are characterised by a reduced ability to concentrate and dilute urine and so their ability to conserve and excrete sodium and water is diminished. This may be because of age related reductions in vasoactive mediators such as plasma renin and aldosterone. This increases their

vulnerability to developing an AKI in situations where salt and fluid depletion occur and make them more prone to dehydration [244,281]. This is potentially exacerbated by the use of diuretics.

2.6 AKI and Outcomes

There are a number of measurable outcomes which may be relevant to AKI. These include short and long-term mortality, hospital length of stay as well as patient morbidity. In addition, the burden of AKI in terms of costs to healthcare systems has been estimated in a number of populations. More recently there has been interest in the long-term impact of AKI on kidney function and its relationship to the incidence and progression of CKD. The association with CKD is the focus of this thesis and will be discussed in more detail in Chapter 3.

2.6.1 AKI and Mortality

AKI is associated with a high mortality in hospitalised patients. However, it was traditionally perceived that the presence of AKI reflected the severity of the underlying illness rather than having a direct negative role itself. This led to the well-known nephrological idiom that patients ' die with AKI and not from AKI'. There is now substantial evidence in the literature that this is not the case and that AKI alone is an important negative prognostic factor [26,240].

2.6.1 (i) Hospital and Short-term mortality

Observational studies have shown that AKI is associated with a significantly increased risk of hospital mortality. This is illustrated in Appendix 11, which summarises the mortality outcomes from contemporary studies carried out over the past decade that contained a control group without AKI. Most importantly this association remains significant even with adjustment for other factors known to increase mortality. As expected, mortality is highest in the intensive care setting. Table 2.1 lists observational studies carried out in the general intensive care setting using the RIFLE or AKIN definitions to define AKI. There is a broad mortality range from 13 – 56% but the average mortality is 33%. Two of these studies carried out a clear multivariate adjustment with factors such as age, gender, illness severity defined by the APACHE II score, and comorbidities. Even with adjustment AKI remained a potent predictor of hospital mortality maintaining a three to four fold increased odds of death [136,139].

Table 2.1 Hospital or ITU mortality reported for general intensive care patients by contemporary studies using the RIFLE and AKIN definitions. Mortality is given for those with and without AKI. In the studies by Bagshaw and Lopes data was available for both definitions.

Author (Year)	AKI Definition	Hospital/ ITU Mortality	
		AKI	No AKI
Hoste (2006)	RIFLE	13.3%	5.5%
Ostermann (2007)	RIFLE	36%	8.4%
Ostermann (2008)	AKIN	40.4%	16.9%
Cruz (2007)	RIFLE	36.3%	-
Bagshaw (2008)	AKIN	24.5%	8.5%
	RIFLE	24.2%	8.9%
Lopes (2008)	AKIN	39.8%	8.5%
	RIFLE	41.3%	11%
Barrantes (2008)	AKIN	45.8%	16.4%
Garzotto (2011)	RIFLE	28.8%	8.1%
Clec'h (2011)	RIFLE	27.6%	8.7%
Mandelbaum (2011)	AKIN	16%	6.7%
Fonseca (2011)	AKIN	32.1%	7.3%

It is likely that the ITU case-mix and local intensive care policies account for the broad range in reported mortalities. Appendix 11shows that the cohort studied and underlying severity of illness can have an important impact on mortality. For example, studies that have reported specifically on those with septic AKI in critical care have reported mortalities in a range closer to 50 – 70% [25,119,195,218]. Koreny et al reported a mortality of 87% in a cohort with cardiogenic shock while Li et al reported a mortality of 67% with pancreatitis [109,217].

When the general hospital population has been studied the mortality is in the region of 15% but again there is a broad range in the literature depending on the population studied [22-24]. Murugan et al reported on a cohort with pneumonia and found mortality to be 11% which is significantly higher than the 1.3% found in those without AKI [31]. On the other hand, in a cohort that had general surgery the mortality was much higher with AKI at 26.4% compared to 2.5% in controls [154].

2.6.1 (ii) Factors influencing mortality

Numerous factors have been shown to influence mortality [26]. Figure 2.10 lists the factors that may influence the hospital mortality outcomes associated with AKI.

AKI severity

The severity of the underlying AKI has been shown to be directly linked to hospital mortality. For example, in the general intensive care setting Cruz et al found a graded increased risk of mortality with worsening RIFLE class. Using the Risk group as a reference the adjusted odds ratio for the Injury class was 2.2 and this increased to 4.9 for the Failure class [186]. These findings have also been reported in general hospital admissions. Uchino et al reported on the incidence and outcomes of AKI occurring in all admissions to an urban academic hospital in which only 14.7% were admitted to intensive care. They found that all RIFLE classes were significant predicators of hospital mortality with a steady increase with RIFLE class. After adjustment, the odds ratio for hospital death was 2.9 for the Risk class, 6.8 for Injury, and 8.0 for Failure [183]. The studies mentioned have all based severity of AKI on increasing stage according to the rise in serum creatinine. An increased mortality has also been found when severity has been expressed in terms of urine output. Oliguria has traditionally been seen as a marker of AKI severity and studies have demonstrated that mortality is higher in those who have oliguria during the AKI episode compared to those who do not [2,228,284,285].

AKI Duration

AKI duration has been shown to influence outcomes in a variety of populations [22,160,162,163]. In a 2010 study involving post-operative AKI in diabetic veterans Coca et al found that for each AKI stage, longer duration of AKI was significantly associated with a graded higher rate of mortality. They found that the mortality rate for those with severe AKI (AKIN Stage 3) but of short duration (< 2 days) was nearly 50% lower than the mortality associated with mild AKI (Stage 1) but of longer duration. They postulated that duration may discriminate between patients with 'prerenal' AKI without true injury and those with true 'intrinsic' renal damage [163]. This may well be the case but there is also good evidence that even mild transient AKI is associated with worse outcomes than no AKI [180].

The presence of pre-existing CKD

Pre-existing CKD also appears to modulate the outcomes of AKI. Studies have reported a lower mortality in patients who have pre-existing CKD [42,43,119,121,168,228]. For example, in a cohort of patients from the intensive care setting Khosla et al found that patients with pre-existing CKD had a mortality 9% lower than those without a history of CKD despite being older and having more comorbidities [121]. Numerous reasons have been suggested to explain this phenomenon. Khosla et al postulated that the process of care may be different in patients with CKD and indeed demonstrated that these patients received earlier nephrology referral. This may have resulted in better management [121]. Ali et al also reported earlier referral in a Scottish general hospital cohort and in addition they found that patients with CKD were more likely to have renal imaging performed [187]. Another reason that could explain better hospital outcomes in patients with CKD is that they may require a lesser burden of acute illness in order to reach the same level of AKI. Two studies that reported better outcomes in CKD patients found that the phenomenon disappeared when adjustment was made for severity of the acute illness [119,286]. Finally, the effect of small rises in creatinine of 0.3mg/dl used in the AKIN definition on patients with lower levels of GFR remains unclear [48]. It is possible that different thresholds are needed to accurately define AKI at these levels and this may also partly explain the lower mortality in the CKD group in some studies. Some evidence to support this theory has been provided by Broce et al who conducted an analysis of nadir to peak serum creatinine increments and stratified them for baseline eGFR. In their fully adjusted model they found that the odds ratio for inhospital mortality became significant with a creatinine increment of just 0.2mg/dl in those with a baseline eGFR ≥ 60mls/min. On the other hand, the odds ratio for mortality did not become significant in those with an eGFR < 30mls/min until an increment in creatinine of 0.5mg/dl was reached [23].

Hospital-acquired AKI

Several studies have demonstrated that the mortality is higher in patients who develop their AKI in hospital [107,110,206,241]. Sesso et al reported mortality rate of 59% in a cohort of elderly patients with hospital –acquired AKI compared to 41% in the community-acquired group [110]. This is likely to be related to the underlying illness severity and type of AKI. At present there has been little work conducted on this area of AKI [48].

Cause of AKI

Several studies have shown that the outcomes for AKI are worse when the cause is due to sepsis [103,227]. In the intensive care setting Bagshaw et al demonstrated that septic AKI had a significantly higher crude ITU and hospital mortality compared to non-septic AKI (19.8% v 13.4%). With adjustment for covariates the odds of death remained marginally higher in the septic group with an odds ratio of 1.54 compared to 1.43 [227]. Overall however, there has been little work done on the influence of the underlying cause on mortality outcomes. This is partly due to the fact that the majority of recent studies in AKI have been retrospective and have lacked the clinical data needed to classify the episodes by cause.

General management

In terms of AKI management it has already been alluded to that early nephrology referral in hospital may improve outcomes. In addition there is evidence that the basic clinical management of the AKI is important. Grams et al used data from the FACTT trial which looked at conservative versus liberal fluid management in patients with acute lung injury. They demonstrated that post-AKI fluid balance was significantly associated with mortality in both crude and adjusted analysis [287].

Figure 2.10 Factors that may influence the mortality associated with AKI.

Influencing Factor	Effect on AKI mortality
AKI severity	Graded increase in mortality
Duration of AKI	Graded increase in mortality
Underlying CKD	Associated with reduced mortality
Setting	Hospital acquired AKI associated with increased mortality
Cause of AKI	Sepsis associated with increased mortality
General AKI management	Accumulated positive fluid balance associated with increased mortality

2.6.1 (iii) Long-term mortality following recovery from AKI

The mortality associated with AKI is not confined to the hospital setting. Few studies have reported long-term outcomes after AKI (see Appendix 11). However, there is evidence that patients who survive AKI have a higher rate of long-term mortality and

that this is also consistent across every clinical setting [26]. Ishani et al studied the outcomes of 29388 individuals who underwent cardiac surgery and followed them for just over five years. They found a graded increased mortality according to the severity of AKI after three months with an adjusted hazard ratio for death at three months of 5.0 in the group with a rise in creatinine > 100% from baseline. This increased mortality risk attenuated over time but remained elevated after five years [127]. Similar results are found in studies that included outcomes in a general hospital population. For example, La France et al presented data on over two years of follow up of patients from the US Veterans Affairs database who were alive 90 days after discharge. The mortality in those who had sustained an AKI was 29.8% while in those without an AKI it was 16.1% during the follow up period. In a Cox Proportional Hazards model adjusted for age, sex, race, comorbidities, medication use, and post-discharge eGFR categories the hazard ratio for all-cause mortality in those with AKI was 1.41 [9]. While these findings do not imply causality, studies that have performed multivariate analysis have shown that the strength of association between AKI and mortality is similar to or greater than other established risk factors such as diabetes, peripheral vascular disease, and chronic obstructive lung disease [26].

2.6.1 (iv) Trends in mortality from AKI

There is evidence in the literature from several different populations that despite a rising incidence of AKI the mortality appears to be falling [13,14,16,17]. In the United States, Xue et al studied the outcomes of AKI using a 5% Sample of Medicare Beneficiaries. AKI was defined by ICD -9 codes. Between 1992 and 2001 there was a declining trend in mortality at 90 days after discharge despite the incidence rising by 11% per year. The authors felt that this reflected improvements in hospital care [13]. Similarly, using the ANZIC ITU database in Australia and New Zealand, Bagshaw et al found that the adjusted odds ratio for mortality associated with AKI fell from 1.54 to 1.33 between 1996 and 2005. The authors were unsure of what could account for this decline. It may be due to an improvement in the overall care of ITU patients or by specific interventions or therapies such as improved renal replacement therapy [16]. Finally, Swaminathan et al used the US National Inpatient Sample Database to study the outcomes of patients that underwent coronary bypass surgery between 1988 and 2003. Despite an increase in comorbid disease burden in this cohort mortality in the AKI group fell from 39.5% to 17.9%. They attributed this to improved care [17].

2.6.2 AKI is a major healthcare burden

Appendix 6 demonstrates that AKI is associated with a significantly prolonged length of stay in hospital. This is evident in every clinical setting. In the general hospital setting this can be anywhere from 3 to 9 days [22,31,32]. Few studies have analysed this phenomenon in depth, but in those that have, AKI remains a potent risk factor for prolonged length of stay even with adjustment for age and comorbidities [23,24,32,136]. Length of stay appears to be influenced by the severity of the AKI episode. Chertow et al demonstrated that larger increases in creatinine in a US Medicare population were associated with longer relative increases in hospital length of stay [32]. The reasons for this increased length of stay are unclear from the literature but it is reasonable to propose that it is related to illness severity. It may also be related to the fact that in clinical practice patients who demonstrate a rise in serum creatinine are often retained in hospital for monitoring until the creatinine settles.

Studies have demonstrated that AKI is associated with an increased risk of discharge to extended care facilities [17,22-23,224,227]. For example, in their study on non-critically ill hospitalised patients with AKI, Barrantes et al found that AKI was associated with an odds ratio of 3.0 of discharge to an extended care facility after adjustment for age, sex, race and comorbidities. In this study 43.1% of AKI patients were discharged to care as opposed to 20.3% in the control group [24]. Similarly, in another cohort of hospitalised patients, Liangos et al found a two fold higher adjusted odds of discharge to a care facility [224]. Swaminathan et al showed similar results after cardiac surgery however, they also demonstrated a significant increase in baseline comorbidities suggesting that the underlying level of frailty may be playing an important role in these findings [17].

There is emerging evidence that patients who survive their episode of AKI are at an increased risk of readmission to hospital. There are several recent studies in the literature illustrating this [30,34,288-290]. Allaudeen et al conducted a retrospective study to identify factors associated with readmission within 30 days for general medical patients. After multivariate analysis an episode of AKI was independently associated with readmission [290]. There also appears to be a graded association between readmission and the severity of the AKI at least in some cases [34]. Grams et al reported on the outcomes of a large cohort of patients taking part in the Atherosclerosis Risk in Communities Study. They found that patients with an AKI hospitalisation at any point during the follow up period had more hospitalisations for any cause (6.0 hospitalisations over 7 years) than there counterparts without an AKI hospitalisation (1.3 hospitalisations over 8 years) [30].

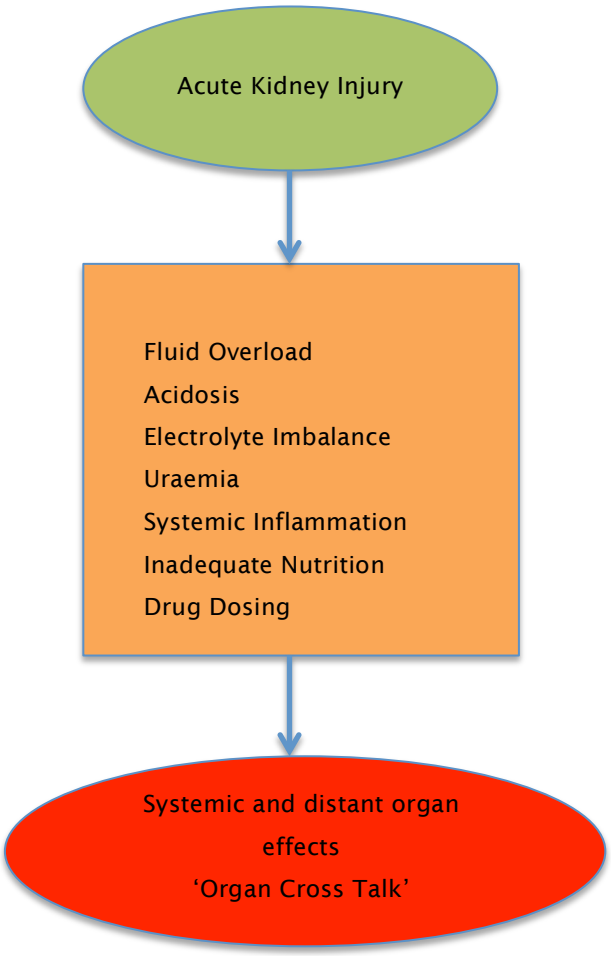
Finally, very few studies have addressed the issue of quality of life after AKI however there is some suggestion that this too may be adversely affected [252,291,292]. Johansen et al recently reported on the health utility of 60-day survivors of severe AKI involved in the Acute Renal Failure Trial Network Study. This study enrolled adults in critical care units who had AKI attributable to acute tubular necrosis plus sepsis or additional organ failure. They used the Health Utilities Index Mark 3 to derive an overall health related quality of life score in 60- day survivors of AKI who had required RRT in the ITU. 27% of respondents at 60 days had health states that would be considered by the general population to be equivalent to or worse than death [291]. Another recent ITU based study by van Berendoncks et al used the SF-36 score to assess quality of life in AKI survivors at a mean of 20.3 months after hospital discharge. The SF-36 is a generic measure of health status with a physical component summary and a mental component summary. They found that the physical component health-related quality of life of the SF-36 score in the AKI survivors was lower compared to age-matched general populations. On the other hand, the mental health-related quality of life was found to be the same as in the general population [252]. These findings need to be interpreted with caution. The reduced physical component may reflect a greater severity of illness or burden of comorbid disease rather than the AKI itself.

In summary, in addition to increased short and long-term mortality, AKI is associated with prolonged hospital stay, a tendency for multiple readmissions to hospital in the long-term, an increased risk of needing extended care after hospital discharge, and possibly a reduced quality of life. This is a considerable burden to the healthcare system if the estimated incidence of AKI in the general hospital population is between 10 and 20%. As a result, several studies have reviewed the costs of AKI over the past decade [32,293,294]. In 2005 Chertow et al reviewed the impact of AKI in a US hospital population. As expected there was an increased cost associated with AKI episodes and in multivariate analysis these costs were found to increase in accordance with the severity of the AKI. They estimated for their own hospital that AKI was consuming roughly 5% of the overall hospital budget and offered a conservative estimate that AKI was costing the United States healthcare system more than $10 billion annually [32]. NHS Kidney care recently offered estimates for the NHS. They estimated that the total yearly cost of AKI (including acute admissions, critical care, and renal replacement therapy) was up to £620 million annually based on 2009-2010 budget figures. This is more than the cost of lung cancer and skin cancer combined [295].

2.6.3 The pathological mechanisms underlying AKI Outcomes

AKI remains a highly complex syndrome and association does not necessarily imply causality despite the efforts of researchers to adjust for established risk factors. As a result there has been a surge of work over the past decade in both humans and experimental animals that has provided good evidence that the pathophysiology of AKI may be having direct independent effects on outcomes. AKI is associated with numerous pathophysiological consequences and these are illustrated in Figure 2.

Figure 2.11 Consequences of AKI that may account for systemic and distant organ effects leading to adverse outcomes.



Some of the consequences of AKI such as fluid and electrolyte imbalances can have obvious direct clinical effects while others such as systemic inflammation and uraemic toxins have a more subtle influence through distant organ dysfunction. Some authors

refer to the effects of AKI on distant organs as distant 'organ cross talk' or 'multiorgan cross talk' [29,247,296]. Changes have been described in virtually every organ system as a result of the uraemic milleu seen in AKI [297].

2.6.3 (i) Fluid overload

Intravenous fluid resuscitation is one of the mainstays of treatment of AKI particularly those with oliguria. Patients with AKI will have reduced free water clearance and this combined with aggressive fluid resuscitation can lead to accumulation of fluid [29]. Bouchard et al reviewed the outcomes associated with fluid overload in 618 patients in critical care with AKI. They demonstrated that fluid accumulation resulting in a positive fluid balance is a frequent event in critically ill patients with AKI. Moreover, they showed that fluid-overloaded patients had a significantly higher mortality and the effects of this were maintained over 60 days. The association between fluid overload and mortality was highly significant even after adjustment for severity of illness and the need for dialysis. They also found that cumulative fluid overload may be associated with decreased likelihood of renal recovery [262]. Fluid overload can result in a broad range of complications that could account for increased morbidity and mortality. These include the development of tissue oedema, ascites and intra-abdominal hypertension, pleural effusion and pulmonary oedema [29].

2.6.3 (ii) Acidosis

Metabolic acidosis frequently occurs in the setting of AKI particularly in more severe cases. Acute acidosis is known to affect a number of organ systems and in particular the cardiovascular system where reductions in cardiac output and contractility can be seen [298]. In addition, acidosis has been found to increase nitric oxide production that leads to vasodilation and so may contribute to haemodynamic instability in critically ill patients [299,300]. Acidosis also appears to have important effects on immune function and contributes to increased inflammation and an impaired immune response although the processes involved are poorly understood at present [298,300].

2.6.3 (iii) Uraemic Toxins

A consequence of renal failure is the inability of the kidneys to excrete metabolic waste products that can then accumulate as uraemic retention solutes. There are currently well over 100 uraemic retention solutes recognised and some are known to have an adverse biologic impact. For example, guanidine compounds are small water-

soluble solutes that have been implicated in neurotoxicity, inhibition of inducible nitric oxide synthase and stimulation of leukocytes [301].

Until recently, interest in uraemic toxins has primarily involved their link to the adverse effects of CKD particularly their cardiovascular effects. However, there is now growing interest in the impact of uraemic toxins in AKI [302]. Uraemic toxins are known to play a role in blunting immune responses and endothelial cell dysfunction and it is likely that they play a role in the systemic effects of AKI as well. Rabb et al demonstrated in animal models of ischaemia/reperfusion injury that AKI is associated with downregulation of pulmonary epithelial sodium channels, Na,K-ATPase and aquaporin 5. These features were seen in animals after bilateral nephrectomy and not after unilateral nephrectomy. This led the authors to conclude that they must result from systemic effects mediated by uraemic toxins [303].

2.6.3 (iv) Inflammation

AKI is associated with a profound inflammatory reaction in the kidneys and systemic circulation [29]. Several authors have demonstrated marked derangement of elements of immune and inflammatory responses that may be having a direct effect on distant organ function. Much of this work has been carried out in animal models. Kelly et al demonstrated increased levels of TNF-α, interleukin-1 and intercellular adhesion molecule-1 mRNA in heart tissue after renal ischaemia. After 48 hours, functional changes in the heart included increased left ventricular end diastolic diameter, increased left ventricular end systolic diameter, and decreased fractional shortening leading the authors to conclude that these effects may be important in the morbidity and mortality observed clinically [304]. To complement these findings there is some evidence from human studies that cardiovascular outcomes are worse long-term in patients with AKI [26].

The interaction between the lungs and the kidney in the setting of AKI has attracted interest because of its implications in critical care. Kramer et al demonstrated that there was an increase in macrophage- mediated pulmonary vascular permeability in the setting of renal ischaemia [305]. Klein et al demonstrated that features of lung injury seen in AKI such as pulmonary oedema, increased capillary leak and leukocyte infiltration are reduced in animals deficient in interlukin- 6 [306]. Interleukin-6 levels have been shown to be elevated significantly in patients with AKI and can predict mortality [307]. In addition interleukin-10 has also been implicated in mediating systemic inflammation and lung changes in the setting of renal ischaemia [308]. In human studies Murugan et al

showed that patients with AKI who developed severe sepsis with pneumonia had higher concentrations of interleukin-6, 10, and TNF-α at presentation [31].

2.6.3 (v) Nutritional imbalance

AKI is associated with a hypercatabolic state and it interferes with the metabolism of macronutrients [309]. This is thought to contribute to the nutritional depletion of ill patients particularly those in critical care. However, very little work has been done on this area to date. In addition to the hypercatabolic state, patients with AKI receiving renal replacement therapy will have additional losses of amino acids and proteins in the dialysate together with water soluble vitamins such as vitamin C, thiamine, and folic acid [29].

2.6.3 (vi) Deranged drug handling

Alterations in drug metabolism in AKI are complex and are currently poorly understood. This is largely due to the fact that there is no mandate to conduct pharmacokinetic studies in AKI prior to drug approval [310]. It is quite likely that drug metabolism is significantly altered in AKI and this may have a number of knock on effects through underdosing or overdosing particular drugs. This may be particularly important in the case of antimicrobials in the setting of acute illness and sepsis [29].

Chapter 3: AKI and its relationship to CKD

3.1 Introduction

Chronic kidney disease (CKD) denotes persistent structural or functional damage to the kidneys. Like AKI, it results from a heterogeneous group of disorders that affect the kidneys and the variation in its expression is related to its different causes and pathology, severity, and rate of progression [311]. In the past decade CKD has come to the forefront as a major public health problem and is an important cause of death in the industrialized world [312]. CKD is a chronic non-communicable disease. It epitomizes the epidemiological shift to the "age of degenerative and man-made diseases" described by Omran that developed countries and increasingly developing countries are now facing [313].

The evolution in our understanding of AKI has paralleled the growing importance of CKD. This is not by coincidence as the two are inherently linked. As discussed in Chapter 2, CKD renders people susceptible to sustaining an AKI and up to one third of hospitalized patients with AKI have a history of CKD. In addition, there has been considerable interest in the bidirectional association between AKI and CKD. On the one hand CKD confers a risk of developing an AKI: on the other, AKI appears to be associated with causing incident CKD and may augment its progression. This chapter will explore the current evidence base relating to this issue.

3.2 Defining and staging CKD

In 2002 KDOQI (Kidney Disease Outcomes Quality Initiative), which was established by the US National Kidney Foundation, released a proposal for the definition and staging of CKD. This was later endorsed by an international review board representing KDIGO (Kidney Disease Improving Global Outcomes) in 2004 [314,315]. This definition was based on estimated GFR and the presence or absence of other evidence of kidney damage for three months or more. This time frame was arbitrarily included on the assumption that most acute kidney injury has resolved by three months. The rationale behind formally defining and staging CKD was to facilitate its earlier recognition and management [314].

In the UK the National Institute for Health and Clinical Excellence (NICE) published CKD guidelines in 2008 [74]. The five stages of GFR were modified slightly by splitting Stage 3 into Stages 3A and 3B. This was done on the basis that prevailing evidence suggested

that the adverse outcomes from CKD increased at levels of GFR below 45mls/min. The staging system with the NICE modification is illustrated in Figure 3.1.

Figure 3.1 Stages of Chronic Kidney Disease (NICE 2008 [74])

Stage	GFR (ml/min/1.73m^2)	Description
1	≥90	Normal or increased GFR, with other evidence of kidney damage
2	60-89	Slight decrease in GFR, with other evidence of kidney damage
3A 3B	45-59 30-44	Moderate decrease in GFR, with or without other evidence of kidney damage
4	15-29	Severe decrease in GFR, with or without other evidence of kidney damage
5	<15	Established renal failure

The definition and staging system introduced by KDOQI has led to a major shift in the focus of kidney disease management. End stage kidney failure and its treatment with renal replacement therapy had for decades been the defining role of nephrology. Recognition of the earlier stages of CKD has changed the emphasis to one of prevention and early recognition [312,316].

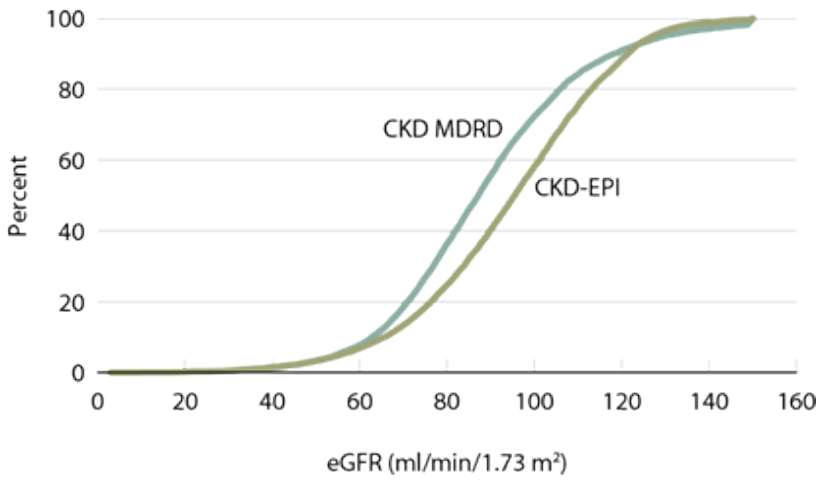
3.3 The epidemiology of CKD

The 2010 Health Survey of England reported the overall prevalence of moderate to severe CKD (Stages 3-5) as 6% using the abbreviated MDRD equation to estimate GFR. It was higher in women and it increased with age in both sexes from 1-2% in those aged 16-44 to over 30% in those aged over 75 [6]. Prevalence estimates have also been

reported in other countries although they cannot be directly compared to the HSE data because of differences in methodology and reporting. The US NHANES IV data reported an overall prevalence for CKD stages 1- 4 of 13.1% for the period 1999 – 2004. NHANES III had reported a prevalence of 10% for the period 1988-1994 and the increase in prevalence between the two periods had been attributed in part to the increasing prevalence of diabetes, hypertension and obesity. Data on CKD stage 5 was excluded from NHANES but assuming this is small for comparison with the HSE data, the prevalence of stages 3-4 were 8% [7]. It should be noted however that NHANES IV used the abbreviated MDRD equation to estimate GFR and when this is replaced by the CKD-EPI equation it results in a reduction in prevalence from 13.1% to 11.5% overall [94]. The MDRD equation will tend to place more individuals in CKD Stage 3 owing to underestimating higher levels of GFR and this influence can be seen in Figure 3.2. The revised prevalence figure of 11.5% is now being quoted for the US population [311]. Chadban et al reported the prevalence of either proteinuria, haematuria, and/or reduced GFR in the Australian population as 16%. This study used the Cockcroft and Gault equation to estimate GFR which may be overestimating the prevalence [317].

The rise in the prevalence of CKD recognized in the USA was one of the driving forces behind implementing formal recognition and preventive strategies for CKD [315]. There is no historical HSE data with which to compare however some indication of the prevalence of CKD over time in the UK can be obtained from QOF data. The Quality and Outcomes Framework (QOF) has been in existence since 2004 with data submitted on a yearly basis from primary care. The 2010/11 QOF data revealed a national prevalence of registered CKD stages 3-5 in persons over 18 of 4.3% . This is compared to a prevalence of 4.1% in 2008/2009 [318].

Figure 3. 2 Cumulative eGFR distribution curves of NHANES participants from 2001-2008 by method used to estimate GFR (USRDS 2011 [319]).



3.4 Aetiology and Outcomes of CKD

The aetiology of CKD is complex and poorly characterized in the literature. It is clear that certain uncommon conditions such as rapidly progressive glomerulonephritis can cause chronic irreversible damage. However, it usually develops in an insidious fashion in susceptible individuals and is associated with conditions that overlap as risk factors and true causes [311]. For example, hypertension is often perceived as a cause but it is also a secondary consequence of CKD and a known risk factor for disease progression. In many cases the cause of CKD is unknown. The primary method for making a definitive diagnosis of the cause is a renal biopsy. However this is not carried out in the majority of cases as it is an invasive procedure that generally does not alter clinical management. Consequently there is no clear delineation of the causes of CKD in the general population. However, the diversity and indeed the uncertainty can be found in those presenting for renal replacement therapy. Figure 3.3 lists causes attributed to the population starting RRT in the UK from the 2009 cohort described by the UK Renal Registry [320]. It can be seen that diabetic nephropathy figures prominently in all age groups but in the elderly over the age of 65 renal vascular disease becomes more prominent. However, in more than a quarter of patients there is no known cause.
In the developed world, CKD is generally associated with old age, diabetes, hypertension, and cardiovascular disease [311]. It is now recognized as a part of the metabolic syndrome milieu [321]. The nephropathy associated with diabetes mellitus is well characterized however in the others the process appears to involve progressive age related vascular pathology but is incompletely understood [322-324]. The end result in all cases is replacement of renal tissue with extracellular matrix, culminating in organ fibrosis [325].

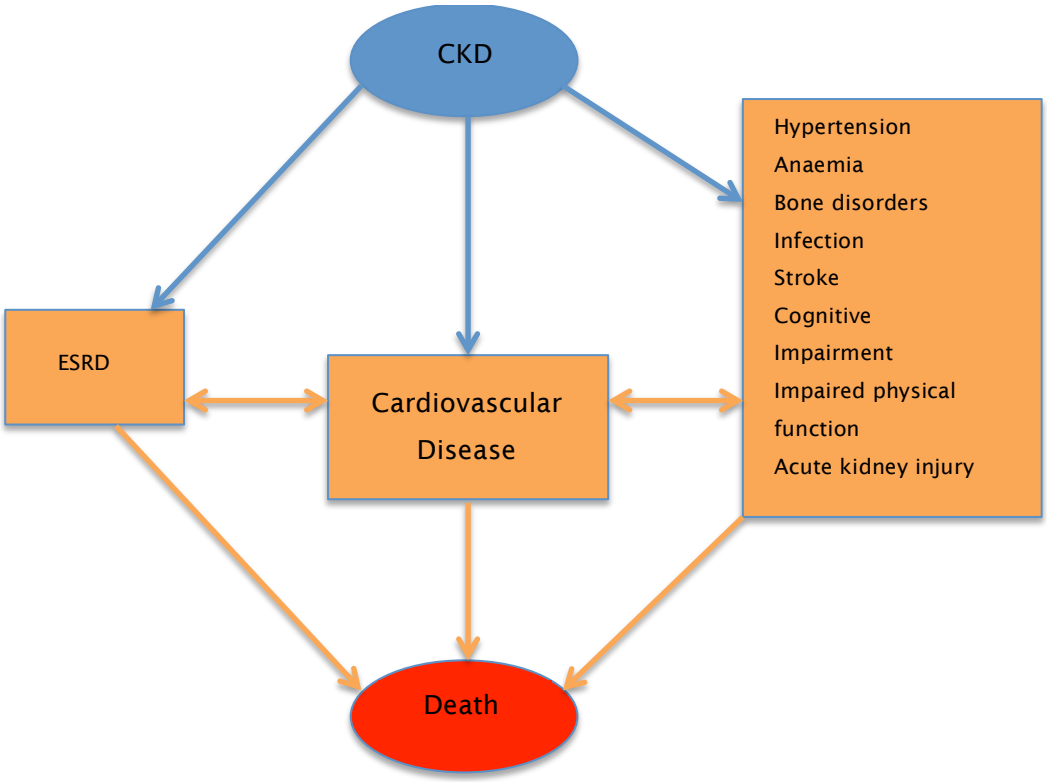
Figure 3. 3 Percentage distribution of primary renal disease diagnosis by age in the 2009 UK Renal Registry cohort starting RRT [320].

Diagnosis	Age < 65	Age > 65	All Patients
Diabetes	27.3	23.2	25.3
Glomerulonephritis	16.0	6.9	11.5
Pyelonephritis	7.1	7.6	7.3
Hypertension	6.0	7.9	6.9
Polycystic kidney disease	10.2	3.1	6.7
Renal Vascular Disease	2.0	10.4	6.1
Other	16.5	14.4	15.5
Uncertain Aetiology	15.0	26.6	20.7

The importance of CKD from a public health viewpoint lies in its outcomes. The first is progression over time to end stage renal disease which requires substantial input from health services in both renal replacement therapy and end of life care. The second important outcome of CKD is cardiovascular disease. This contributes to considerable morbidity and mortality in the general population.

Figure 3.4 illustrates the outcomes associated with CKD. End stage renal disease is important from a patient and healthcare point of view however only a very small proportion of those with CKD will ever reach this stage. Drey et al performed a retrospective cohort study of all new cases of CKD from the Southampton and South-West Hampshire Health Authority and found an annual incidence of 1701 per million population but only 4% were accepted to renal replacement therapy during 5.5 years of follow up. In this study CKD was defined as a persistently elevated serum creatinine above 150µmol/l and so would have underestimated the incidence of CKD stage 3 particularly in the elderly population. Therefore in today's currency the proportion reaching ESRD would be even smaller [326]. In a large US cohort, Keith et al found that just 1.1% and 1.3% of CKD stages 2 and 3 progressed to requiring renal replacement therapy during a similar follow up period. The majority of patients appear either to remain stable over time or at least progress very slowly and die from another cause - particularly cardiovascular disease [327-329]. The risk of progressing to ESRD has been shown to increase exponentially at lower levels of eGFR. In addition, higher levels of albuminuria have been shown to independently increase the risk of progression to ESRD [330].

Figure 3. 4 Illustration of the outcomes of CKD.



There is evidence that cardiovascular disease is a leading causes of mortality in those with CKD and this mortality risk increases with lower levels of GFR [4,326,327]. In a large US cohort, Go et al found that the adjusted hazard ratio for cardiovascular events increased inversely with the estimated GFR from 1.4 for an eGFR of 45 to 59 mls/min to 3.4 for an eGFR of < 15mls/min [4]. CKD is now recognized as an independent risk factor for cardiovascular events [5,312]. Impaired kidney function and uraemia are associated with many physiological abnormalities that can account for this. Alterations of mineral metabolism and expression of mineral regulating proteins have been linked with increased arterial calcification. This is responsible for stiffening of the arteries leading to increased left ventricular afterload and hypertrophy as well as abnormal coronary perfusion [331,332]. CKD has also been independently linked to increased inflammatory and procoagulant biomarkers which may be important mediators in the overall process [333]. More recently the role of renal insufficiency in modulating the activity of macrophages and rendering them proatherogenic has been examined [334]. CKD has been linked with numerous other adverse outcomes, including an increased risk of cerebrovascular disease and stroke, impaired cognitive function and impaired physical function [335-337]. In addition evidence exists that CKD increases the risk of fractures and some cancers [338,339]. CKD has also recently been linked to an increased risk of hospitalization with pneumonia that may be contributing to the increased

mortality [340]. Another recent study, by Daratha et al reported that patients with CKD after an index hospitalisation for any cause were at increased risk of subsequent hospitalizations. The top three reasons for readmission were heart failure, ischaemic heart disease and AKI [341]. It has already been discussed that CKD is an important risk factor for the latter.

3.5 CKD Progression

It is well established that more advanced stages of CKD are associated with adverse outcomes [342]. As a result, the progression of CKD and the factors influencing this is an area of major interest to the medical community. Several factors can contribute to the progression of CKD. With early identification and treatment, some of these can be modified to slow or arrest the progression and improve outcomes [314]. However, it should be noted that there is good evidence that not everyone with CKD will progress and this suggests that there may also be unidentified genetic or environmental factors involved [327,328].

The association of diabetes, hypertension and proteinuria with declining renal function has been demonstrated in numerous longitudinal and interventional studies [343-346]. In addition to these well-known risk factors, associations have also been made with the presence of cardiovascular disease, smoking, race, and the chronic use of non-steroidal anti-inflammatory drugs [74]. The mechanisms involved in CKD progression are complex. Regardless of the cause of the inciting injury there appears to be a final common pathway in all cases of CKD resulting in a phenotype of tissue destruction, inflammation and scarring. Cell damage and activation leads to inflammation and cytokine imbalance which contributes to fibrosis, mesangial and vascular contraction [347]. In addition to maladaptive inflammatory and cellular responses alteration of renal haemodynamics may also be important. Renal hyperfiltration has been associated with sclerosis of the glomeruli and maneuvers to reduce this, such as the use of RAS blockers, have been shown to be effective [348].

Renal function declines slowly with age but the rates reported are variable depending on the population used [74]. There is some controversy over whether CKD in older people represents a disease or is a benign phenomenon [349]. In the Nijmegen Biomedical Study a reference population of healthy subjects was selected without a history of known hypertension, diabetes, cardiovascular or renal diseases. In these subjects the rate of decline in GFR was approximately 0.4mls/min/year [350]. In the Balitmore Longitudinal Study of Aging, Lindman et al reported an age related decline of 0.75mls/min year although the so-called ‘normal’ group in the study contained individuals with diabetes

[351]. Following a review of the available literature NICE concluded that a decrease of more than 2mls/min/year is more than can be accounted for by age alone, and therefore accounting for variation in measurement, NICE defined a clinically significant progression in CKD as a decline in eGFR of more than 5mls/min/year.

It is notable that in compiling the 2008 CKD Guidelines the NICE group listed AKI as a factor associated with the progression of CKD but no studies were found examining this association at the time [74]. KDOQI also recognised AKI as a potential risk factor for CKD when the original staging system for CKD was produced in 2002 [314].

3.6 AKI and the incidence and progression of CKD

Historically recovery of renal function after an AKI episode has been thought of in terms of recovering enough function to no longer require renal replacement therapy. As this is achieved in most survivors it led to the perception that the functional prognosis after AKI was good or even completely reversible [127,352]. The long-term functional impact of AKI was not considered important. This perception has changed dramatically over the past decade as the influence of CKD on adverse outcomes has become appreciated.

AKI is very common in hospitalised patients and therefore if it is causing incident CKD and contributing to its progression this will have major public health implications. The incidence of AKI appears to be rising and so could add considerably to the burden on healthcare resources. It could be partly responsible for the rising prevalence noted in CKD as well as contributing to the ESRD population.

It is intuitive that an episode of AKI may lead to some degree of permanent loss of renal function and may potentiate pre-existing pathology [324]. It has recently been highlighted that every experienced nephrologist will come across a case where an individual with advanced kidney failure has been precipitated onto dialysis following an AKI episode [50]. In addition, there is literature containing examples of patients who have not recovered function fully after an AKI [49,353-356]. However, the precise nature of the link between AKI and functional outcomes has not been actively studied until very recently. In the following sections the historical, experimental, and contemporary evidence for the AKI/CKD association is reviewed.

3.6.1 Historical Evidence

There has been evidence in the literature for over sixty years that AKI has the potential to cause a persistent loss of renal function. While these early studies were carried out in an era when the causes of AKI were quite different from today they nevertheless provided a valuable insight into the recovery patterns after episodes of severe AKI. All of the studies reviewed below undertook careful laboratory renal clearance measurements and one even performed follow- up renal biopsies. Arguably, they are more accurate than contemporary studies that have relied solely on serum creatinine measurements and eGFR.

In 1952, KG Lowe produced one of the first follow up series after an episode of severe AKI [49]. It contained 14 women with a mean age of 28 years and all had experienced an episode of severe acute kidney injury with anuria or severe oliguria attributed to acute tubular necrosis. The causes of AKI in this series were listed in Figure 2.9. The author was careful to point out that none had had an illness before or after the AKI episode that may have influenced renal function at follow up. They were followed up after variable time periods but up to 3 years. All had para-aminohippurate (PAH), thiosulphate and creatinine clearances measured. Lowe found generally good renal recovery up to six months which was then sustained. However, in some cases it was sustained at a lower level than normal suggesting that CKD was a consequence of the AKI. Lowe speculated that there might be residual scarring and vascular damage following AKI.

In 1956 Finkenstaedt and Merrill published a series of 16 patients treated in Boston [355]. All had survived an episode of severe anuric AKI. These patients were selected from a larger series for evaluation because they had no history of cardiovascular or renal disease. The mean age was 31 years and they were followed up after a mean period of 18 months. In 7 cases measurements of renal function were taken on more than one occasion during follow up. As with Lowes series they found that good functional recovery was established by six months and that function was maintained thereafter. However, inulin clearances in the majority of patients were below normal at follow up leading the authors to conclude that there may have been permanent damage after the AKI. They found no evidence for a progressive diminution of function over time and neither did they find any correlation between the severity or duration of AKI and the outcome.

Finally, Price and Palmer published a series of 14 patients that were followed up at various time points up to 10 years after an episode of severe AKI requiring dialysis [356].

In 6 cases inulin clearance was reduced at follow-up and in five of these there was also a reduction in renal blood flow measured by PAH clearance. The authors carried out follow-up renal biopsies in some of these patients. These showed an increase in glomerulosclerosis compared to normal along with tubular atrophy and basement membrane thickening. These are all features of chronic kidney disease. There were also areas of chronic inflammation and focal interstitial fibrosis that led the authors to conclude that there could be a continuing 'process' that may have correlated with a subsequent decline in function noted in some patients.

3.6.2 Experimental Evidence

There is much experimental evidence in studies on animal models that lend plausibility to AKI having a causal role in the development and progression of CKD. The animal models that have been used have universally involved induction of ischaemic or toxic damage to the kidney. These models have been criticised by some as being a poor analogue of human AKI particularly in the case of septic AKI [248,357]. Nevertheless histological findings in animal models in the aftermath of AKI are remarkably similar to those found in humans with CKD.

Fox published one of the earliest studies looking at the recovery pattern of ATN in experimental animals in 1967. Using a mouse model, it was demonstrated that recovery was followed by progressive deterioration in renal function accompanied by a reduction in renal size and interstitial fibrosis [358]. More recently, Pagtalunan et al conducted a detailed study of the effects of ischaemic injury in a rat model. They found that animals subjected to ischaemic injury showed an initial recovery phase that was incomplete and this was followed by further deterioration in function. Urinary protein excretion was markedly increased in the animals subjected to ischaemic injury. They hypothesized that the addition of tubular injury caused by proteinuria might account for the progressive loss of function. Histological examination on follow up revealed widespread tubulointerstitial injury accompanied by patchy interstitial fibrosis, infiltration with inflammatory cells and occasional calcification. The findings were largely made up of features generally associated with CKD [359]. In a similar rat model, Forbes et al demonstrated a marked increase in the deposition of collagen type III 180 days after the ischaemic episode. This increase was not seen early in the course of the recovery period. The authors felt that these findings supported the hypothesis that ischaemia may have long-term implications [360].

Basile et al have demonstrated a now well-recognized phenomenon of 'vascular dropout' after ischaemic injury. In a rat model they have showed that there is a

significant reduction in microvasculature density after ischaemia in the kidney. The extent of the vessel loss was influenced by the duration of ischaemia and was most prominent in the outer medulla [361]. The loss of renal microvessels after AKI may contribute to tissue hypoxia and promote progressive damage. In more recent work the same group have demonstrated that the dropout phenomenon results from an impaired regenerative capacity in the damaged vasculature associated with endothelial cell phenotypic transition [362].

Finally, using an obese-diabetic rat model, Kelly et al have demonstrated that after bilateral renal ischaemia rats with obesity diabetes were characterized by progressive chronic kidney disease, increased proteinuria, and increased renal expression of proinflammatroy mediators. Leukocyte numbers in these kidneys were markedly increased for months after the renal injury. Intrarenal blood flow velocity was decreased and similar to the work of Basile et al they demonstrated reduced microvascular density. They concluded that accelerated persistent renal inflammation is a critical element of progressive renal failure complicated by AKI and coined the term 'postischaemic inflammatory syndrome of diabetic nephropathy' [363]. In a follow up study the same group tested the hypothesis that administration of an anti-inflammatory agent would ameliorate the functional decline. In a similar rat model they administered mycophenolate mofitel and demonstrated that the reduction in renal inflammation improved long-term renal function, microvascular dysfunction, fibrosis and apoptosis and thus confirmed the role for inflammation at least in the diabetic kidney [363].

The evidence from animal models that AKI may contribute to CKD is compelling. Whether or not the findings can be extrapolated to humans is open to debate. At present the pathological processes involved are incompletely understood and are the subject of hypothesis rather than fact [324]. There are many pathological pathways along which AKI and CKD may be intertwined and these pathways may well overlap. However, one recent hypothesis concerning focal ischaemic injuries is worth mentioning. Venkatachalam et al speculated that because systemic blood pressure can fluctuate abnormally in the setting of decreased renal mass and impaired autoregulation, microenvironments in the kidney supplied by sclerotic arterioles may be vulnerable to hypoxia and ischaemia. They pointed out that there is some evidence for this phenomenon in rat models of hypertension and that recurring acute tubule damage in microenvironment foci could be contributing to disease progression even without overt clinical episodes of AKI [324]. If this hypothesis is correct it would provide some basis for the findings that relatively minor AKI episodes could be contributing to CKD progression.

3.6.3 Contemporary Evidence

A systematic search of Medline and Embase databases for the period 1990 - 2011 was carried out to identify cohort studies reporting renal function outcomes after an episode of AKI in adults. Using the search strategy described in Chapter 1 studies reporting clear functional outcomes from the point of hospital discharge to any follow-up time point were reviewed in depth and are presented in summary in Appendix 12. A total of 73 studies were found.

A striking feature of the studies summarized in Appendix 12 is the marked clinical and methodological heterogeneity and this makes it very difficult to carry out any meaningful comparison. The study cohorts were drawn from a wide variety of populations and different clinical circumstances which may have influenced reported outcomes. For example, four studies reported the incidence of CKD after AKI in patients who had undergone haematopoietic cell transplantation (HCT) [147,375,391,394]. It is known from autopsy series that acute renal dysfunction in this population is characterized by renal tubulitis that may be related to graft versus host disease [375,396]. This represents a very different renal insult to that which the general hospital population would be subjected. In addition, many of these patients are treated with cyclosporine during follow-up that may also have caused a reduction in renal function. Using the HCT population to generalize the outcomes of the hospital population as a whole would therefore be inappropriate. In terms of the study population it is also notable that no study has separated the populations into those of community origin or hospital origin. Given the differences in causes and outcomes in these groups it is possible there may be significant differences in functional outcomes.

3.6.3 (i) Methodological Issues

The varying study designs and methods that have been employed by different authors has led to substantial differences in reported outcomes. Indeed some of the methodological issues have prompted some to question the validity of the conclusions being made [357]. The majority (78%) of the studies are retrospective. Therefore, they generally lack patient level clinical data and so adequate exploration of the potential causes, confounders, and severity of the AKI cannot be undertaken. In addition retrospective studies are known to be vulnerable to ascertainment bias during follow up. They rely on outpatient follow up blood samples having been performed and so eligible patients are likely to represent those that are arguably at a higher risk of incident CKD and CKD progression. A total of 52 studies (71%) have follow up for a period beyond discharge. Seven of these were prospective in nature but all seven were

either based in intensive care populations or included cases of AKI that required renal replacement therapy only. Therefore there is no study currently in the literature reporting the prospective follow up of AKI in a general hospital population.
The definition of baseline kidney function would be considered crucial to any conclusions drawn regarding the recovery of kidney function after AKI. However, of the 73 studies included in Appendix 12, 25 of them did not specify a clear baseline definition. Another 10 studies used a combination of baselines that included estimates. In all, there are 13 definitions of baseline function. On top of this wide variation in baseline definition a total of 17 different definitions of AKI itself have been used.

Finally, there is no consensus on how to define recovery of kidney function after AKI. In the 73 studies reviewed there are 19 different definitions of renal function outcomes after AKI. These are summarised in Appendix 13 . In some cases no definition of recovery was used.

Different approaches have been taken in studies to record the evolution of renal function after an episode of AKI. Some use a threshold below which recovery is defined as complete. However the thresholds are widely variable. For example in the same year Bihorac et al defined recovery as a serum creatinine < 50% above baseline while Thakar et al defined it as < 25% above baseline [155,189]. This level of variation in thresholds has the potential to report very different outcomes.

Five different approaches have been used to define progression of CKD. Several studies expressed this as a progression to ESRD. ESRD is a very uncommon outcome occurring in < 1% of survivors and gives no information of progression in those who do not reach it [34,42,168,188,383,389]. James et al used this outcome together with a doubling of serum creatinine [231]. Two studies defined progression as advancement to CKD stage 4 [365,369]. Ishani et al used a similar approach but simply defined progression as advancement to the next CKD stage [127]. This approach by Ishani is potentially problematic as no threshold for the decline in GFR was specified. Therefore small changes in eGFR across the CKD stage thresholds, for example from an eGFR of 61 to 59 mls/min, would be recorded as progression. Such changes in function may not be outside what would be expected from analytical variation. Finally, James et al defined rapid progression as a decline in eGFR > 4mls/min/year [230]. This is the only study to have defined a specific fall in eGFR. A fall of 4mls/min/year is less than that specified by NICE in their definition of rapid progression and whether or not it represents true progression when the variation in measurements is taken into account is open to question.

It was discussed in Chapter 2 that patients have an increased risk of readmission to hospital after AKI and hence a repeat AKI may occur. Thakar et al reviewed this phenomenon in a cohort of diabetic patients. They found that repeat episodes of AKI occur in up to one third of AKI patients who survive their initial hospitalisation. Moreover, each AKI episode was found to double the risk of advanced CKD in a cumulative fashion [34]. No other study has accounted for this in their reporting. Therefore outcomes reported in relation to a single AKI episode may be confounded by overestimating prognosis. Whether or not the effect reported by Thakar in the VA diabetic population is applicable to the general population is unknown.

Only one study has compared the decline in renal function after an AKI to any decline that was occurring prior to the index AKI episode. James et al reviewed the recovery patterns after AKI in a cohort of patients who had undergone coronary angiography. The decline in function was compared before and after the AKI In a subgroup of patients who also had eGFR measurements that spanned a minimum of 1 year during the pre-angiography period. The annual rate of decline before and after the angiography was unchanged in those without AKI or with mild AKI. Mild AKI in this study was defined as an increase in serum creatinine of 50-99% or by > 0.3mg/dl [230]. The population studied by James et al is restricted to those that underwent angiography and so is quite specific and limited to a single AKI insult. It is unknown if this is extendable to other populations but it differs from the findings reported in other studies to date. For example, Newsome et al reported a marked increase risk of ESRD in those with an AKI where the creatinine had risen by only 0.1mg/dl [383]. This is a much smaller rise in creatinine than that used by James et al which showed no influence on disease progression. It raises the possibility that there were additional factors influencing the outcomes in Newsome's study. AKI and CKD share many risk factors and these findings raise concerns that there may be residual confounding in studies particularly relating to the milder levels of AKI.

3.6.3. (ii) Incident CKD

The general consensus in the literature at present is that AKI may be causing CKD in some populations and represents an important prognostic marker for the development of future CKD. This certainly appears to be true for severe cases of AKI however in the case of milder AKI episodes its role needs further characterisation. Differences in study population and methodology have led to some conflicting results and some authors have questioned the precise causative role of AKI in this phenomenon [357]. Table 3.1 summarises contemporary studies published between 2008 and 2012 which reported long-term functional outcomes after an episode of AKI. All of these studies attempted

to distinguish between those with and without CKD at baseline. Studies involving haematopoietic cell transplantation (HCT) only were excluded from this summary for the reasons outline earlier in this section.

Table 3. 1 Contemporary studies reporting functional outcomes after AKI when baseline CKD has been excluded.

Author (Year)	Setting	Study Type	AKI Definition	Duration of follow up	Outcome
Ponte (2008)[386]	Hospital ATN	Retrospective	Creat. Rise > 2mg/dl	8 years	61.1% had some degree of CKD 1.1% on RRT
Schiffl (2008)[388]	ITU ATN only	Prospective	RRT	5 years	86% normal function 9% CKD 5% RRT 1% of total cohort required RRT at 5 years
Ishani (2009)[42]	Hospital Medicare	Retrospective	ICD-9 codes	2 years	Adjusted HR of ESRD AKI – 13.0 AKI/CKD – 41.2 CKD only – 8.4
Triverio (2009)[392]	ITU	Randomised controlled trial	RRT	3 years	40% had CKD at follow up
Van Kuijk (2010)[124]	Vascular Surgery	Retrospective	> 10% fall in CKD-Epi RIFLE	5 years	Adjusted RR of CKD with temporary decline in function 3.4 RR 3.6 with persistent decline.

Author (Year)	Setting	Study Type	AKI Definition	Duration of follow up	Outcome
Ishani (2011)[127]	Cardiac Surgery	Retrospective	Stratified rises in creat. From 0% to > 100%	5 years	Graded increased risk of incident CKD (adjusted HR 2.33) and progression
Siew (2011)[389]	Hospital AKI survivors	Retrospective	AKIN	1 year	50.2% had returned to baseline < 1% of cohort required RRT
Bucaloiu (2012)[194]	Hospital Recovered AKI	Retrospective	50% rise in creatinine from baseline	3.3 years	HR of de novo CKD 1.91

There are some notable methodological issues with the studies summarized in Table 3.1. There are also important differences between the results reported. Ponte et al reported some degree of CKD in 61.1% of patients with hospital ATN after 8 years of follow up [386]. In contrast to this, Schiffl et al reported that 86% of ATN survivors had normal function after 5 years [45]. This is despite the fact that Schiffl's group included only those who had dialysis and so the AKI was more severe. It is difficult to account for these differences. There may be a degree of survivor bias in Schiffl's group but equally well there are likely to have been differences in the baseline characteristics of the patients and the aetiology of the ATN episode. The survivors in Schiffl's study appear to have had a low burden of comorbid disease with a Charlson Score of 0.7. Ponte did not specify this in detail but did report that 81.3% of survivors had some degree of comorbidity. Detail on aetiology was also lacking in Ponte's study but it is apparent that 13.6% of the cohort had ATN attributed to sepsis. This compares to 35% of survivors in the Schiffl study. These conflicting results would suggest that other factors have an important influence on the outcomes. This raises questions about the precise role of AKI in causality. How can an apparently milder level of AKI described by Ponte be associated with poorer functional outcomes than the more severe AKI episodes described by Schiffl if AKI has a direct causal role in this phenomenon? It is

worth noting however that neither study accounted for repeat AKI episodes during follow up.

In the 2011 study by Ishani et al involving patients who had undergone cardiac surgery, it is notable that the very mild AKI class with a rise in creatinine from 0 - 24% was found to have a hazard ratio for the development of CKD of 2.1 [147]. This is surprising as the rise in creatinine within this class may not have been outside the threshold of individual and analytical variation. It raises some important questions. Ishani used a single creatinine to define baseline function and this may not have been enough to rule out baseline CKD particularly at levels close to the defined threshold of 60ml/min. As discussed earlier they did not specify the fall in eGFR necessary to define the decline in function. The results may therefore have been confounded by minor variations around the 60ml/min threshold. Ishani's results are also difficult to reconcile with the results reported by James et al discussed earlier. James defined mild AKI as a rise in creatinine of 50-99% and yet found no change in the rate of decline of renal function during follow up [230]. While Ishani provides compelling evidence that AKI is associated with incident CKD at the more severe end of the AKI spectrum, the milder end is less clear.

In the study by Siew et al, after 1 year of follow up 50% of those who had a baseline level of function > 60mls/min were found to have an eGFR < 60mls/min. Of the 50% who showed a decline in function into a CKD category the vast majority (96%) were in CKD stage 3 [389]. Siew et al did not specify a decline in eGFR necessary to define disease progression and so the question remains how many of those with apparently incident CKD were actually on the cusp of the CKD stage 3 threshold before the AKI. The median baseline eGFR of Siews entire cohort was 56mls/min. This indicates that those classified as 'normal' are likely to have been quite close to the 60mls/min CKD stage 3 threshold. This issue also raises another important question. Is the definition of "normal' with a baseline eGFR above 60mls/min appropriate when exploring outcomes such as incident CKD? For example it could be argued that a patient with say an eGFR of 65mls/min already has reduced renal function.

3.6.3 (iii) CKD Progression

Substantial evidence exists supporting an association between AKI and the progression of CKD. However, as with incident CKD there are similar methodological issues in the studies reported. As discussed earlier different approaches have been taken in the literature to describing the progression of CKD after AKI. Some studies have defined it in terms of the risk of developing ESRD while others have taken the approach of

describing the risk of progression across a specific threshold of CKD stage during follow up. It could be argued that at best AKI can be interpreted as a marker of risk in these studies.

One of the first studies to describe the risk of progression to ESRD was reported by Newsome et al in 2008. This study used a dataset of patients admitted to hospital with the diagnosis of acute myocardial infarction. Patients over 65 years of age who had sustained an acute decline in renal function during hospitalisation were linked to the USRDS during follow up to identify those who developed ESRD. AKI was defined as an increase in serum creatinine of 0.1, 0.2, 0.3 to 0.5, or 0.6 to 3.0 mg/dl. The baseline serum creatinine was taken from the initial creatinine measured on hospital admission. For each level of rise in serum creatinine there was an increased risk of ESRD during four years of follow up. After adjustment for demographic characteristics the hazard ratio for a rise in creatinine of 0.1mg/dl was 1.45 and this increased in a graded manner to 3.26 for a rise of 0.6 to 3.0mg/dl. However, it is notable that ESRD was an uncommon outcome in this cohort. After ten years of follow up the incidence rate of ESRD was 3.8 per 1000 person-years whereas the incidence rate for death was 154.7 per 1000 person years [383].

In 2009 several studies were published which came to a similar conclusion as Newsome. Ishani et al described an adjusted hazard ratio of 41.2 for the development of ESRD after AKI on CKD in a sample of US Medicare patients. This study relied entirely on coded data [42]. At the same time Wald et al reviewed the outcomes of survivors of AKI in intensive care that had required RRT. After three years of follow up there was an increased risk of developing ESRD in the RRT group compared to non-AKI controls with a hazard ratio of 3.26 [393]. Hsu et al reported a similar study that used the Kaiser Permanente database in Northern California. It involved patients who had a pre-existing baseline eGFR < 45mls/min who were hospitalized between 1996 and 2003. AKI was defined as a peak inpatient creatinine > 50% above baseline and requiring dialysis. Over 7 years of follow up the adjusted hazard ratio for the development of ESRD was 1.47 [188]. It is notable that in this study the hazard ratio did not reach statistical significance. It also included only patients who had at least CKD stage 4 who were already at a high risk of progressing to ESRD.

In the same year Amdur et al used the Veterans Affairs database in the US to describe the progression to CKD stage 4 after an AKI episode from a mean baseline eGFR which lay between 80 to 85mls/min. Using ATN and ARF codes they found an increased risk of progression to CKD stage 4 with a hazard ratio of 6.64 for the ATN group and 4.03 for the ARF group during 75 months of follow up [365]. Lo et al used a similar definition

of progression in disease in hospital survivors who had required RRT. All patients with an eGFR < 45mls/min were excluded. The adjusted hazard ratio for progression to CKD stage 4 was 28.1 [120].

Several more studies in 2010 demonstrated an increased risk of ESRD after AKI. Lafrance et al reviewed data from the British Columbia CKD register during the period 2002 to 2007. This study included only patients who had a baseline eGFR < 30mls/min. During 19 months of follow up the adjusted relative risk of ESRD in those who were hospitalised with an AKI was 2.33 [125]. In another Canadian study James et al reviewed the outcomes of patients who had sustained an AKI in a cohort of over 900,000 Alberta residents. They found an increased risk of a composite outcome of ESRD or doubling of serum creatinine in those with AKI. However, this increased risk appeared to be greatest in those with higher baseline GFR. For those with a baseline eGFR < 30mls/min and heavy proteinuria admission to hospital with AKI did not further increase the risk of the composite outcome. This finding was unexplained. The study was retrospective and used routine coding to identify the occurrence of AKI. Therefore there was no indication of the type or severity of AKI in these patients. It is possible that the AKI episodes in those with advanced CKD were not severe enough to alter the outcomes [231]. James et al published another study in the same year that explored the kidney function outcomes in those who sustained an AKI following coronary angiography. They defined rapid progression of CKD as a fall in eGFR of > 4mls/min per year. In the non-AKI control group the adjusted mean rate of decline in kidney function was 0.2mls/min/year. This increased to 0.8mls/min/year in those with mild AKI and 2.8mls/min/year in those with moderate or severe AKI [230]. This study is notable for a number of reasons. Firstly, those with a greater number of serum creatinine measurements during follow up had an increased rate of decline in eGFR. This suggests that ascertainment bias may be an issue in this type of study. However, the authors found that the relative increase in rate of decline and odds of rapid progression were comparable across all strata to those seen in their primary analysis. Secondly, the authors compared the rate of decline of kidney function prior to the AKI to the decline afterwards. In those with moderate or severe AKI there was a statistically significant increase in the rate of decline in renal function after the AKI episode. However, this was not the case in those with mild AKI where the rate of decline was found to be similar in both periods.

Finally, Choi et al reported another study in 2010 looking at the risk of ESRD this time in a cohort of patients registered with HIV. AKI was defined using the AKIN criteria and it was reported that AKI increased the risk of ESRD in graded manner according to AKIN stage from 1.37 for AKIN 1, 3.8 for AKIN 2, to 20.36 for AKIN 3. There was no

increased risk found in those with AKIN 1 who recovered fully by the time of discharge [165].

In 2011 Ishani et al studied the outcomes after AKI in a cohort of patients who had undergone cardiac surgery. Progression of CKD was defined as progression to the next CKD stage. Among the subjects with CKD at baseline who did not experience an AKI the incidence of CKD progression was 26.4%. Following an AKI episode the proportion progressing to the next CKD stage increased in a graded manner according to the magnitude of the AKI [127]. Also in 2011 Pannu et al explored the influence of baseline CKD on outcomes after AKI. They used the same Alberta database as James et al and defined AKI using the AKIN criteria. The impact of AKI was found to increase as eGFR decreased irrespective of the severity of AKI. The adjusted hazard ratio for death or ESRD in those with a baseline eGFR < 30mls/min who sustained an AKIN stage 3 AKI was 4.04. ESRD was uncommon during the two years of follow up in this study. The increased hazard ratio for the composite outcome of death or ESRD associated with progressively severe AKI at lower levels of eGFR was attributed primarily to increased mortality [168].

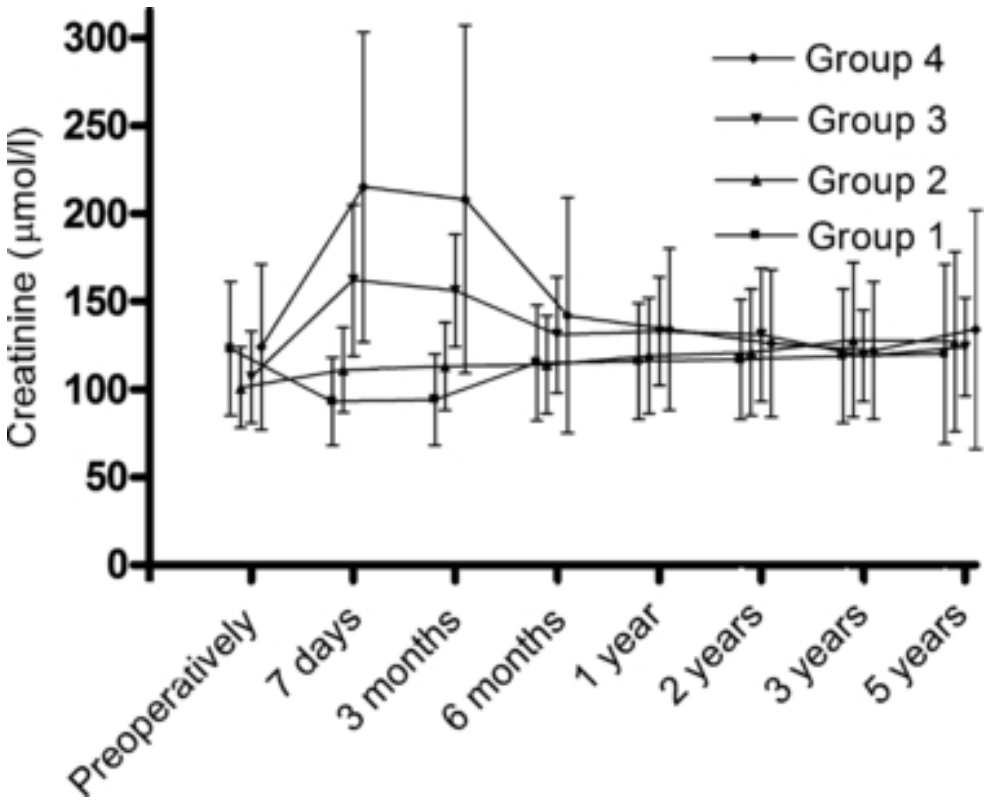
Finally, Thakar et al reported the outcomes of a cohort of diabetics from the US Veterans Affairs database that had sustained an AKI during hospitalization. AKI was defined using AKIN criteria and all patients with an eGFR < 30mls/min at baseline were excluded. The primary outcome was progression to CKD stage 4 during just under four years of follow up. The adjusted hazard ratio for progression was 3.56. 30% of patients in the cohort had experienced 2 or more AKI episodes during follow up and the risk of CKD progression was doubled in a cumulative manner [34]. This suggests that the hazard ratios attributed to AKI in the other studies discussed above are likely to be confounded by his phenomenon.

3.6.3 (iv) Negative Studies

The findings described in the previous sections have not been consistent in every study reporting AKI outcomes. Gude et al studied the outcomes of 585 patients who had undergone a heart transplant in Norway between 1983 and 2007. 145 (25%) patients experienced an AKI in the post-operative period. 71 of these required dialysis but all survivors were dialysis free at the time of hospital discharge. Patients were followed up for a mean of 6.6 years. Renal function was expressed in terms of the mean serum creatinine and patients were divided into four groups. Group 1 were those with no AKI who showed an improvement in creatinine during the first 7 days post-operatively. Group 2 were patients with no AKI who increased their creatinine but not

above the level of AKIN stage 1. Group 3 increased their creatinine above the level of AKIN stage 1 while Group 4 required dialysis. Figure 3.5 illustrates the mean creatinine for each of these groups during the follow up period. As expected the levels were separated in the immediate post-operative period however, after three months they began to converge. After two years there was no statistical difference between the groups. The authors concluded that AKI did not predict future functional outcomes [159]. It is unclear why these findings contrast with the findings reported in other AKI studies. The transplant population is quite specific and would have been subjected to further nephrotoxic agents such as cyclosporine that may have influenced results. There may also have been a degree of survivor bias in that those who were more likely to have not recovered function may have died during follow up.

Figure 3.5 Evolution of the mean serum creatinine following heart transplant in the study by Gude et al. Reprinted by permission from John Wiley and Sons:[Clinical Transplantation][159], Copyright 2010 John Wiley and Sons A/S.



In a 2005 study from Sheffield, Abosaif et al applied the RIFLE criteria to a cohort of 183 patients with AKI in the intensive care unit. Renal function was again expressed in terms of mean serum creatinine. After 6 months follow up the mean serum creatinine

had actually improved in all the RIFLE groups. For example in the Failure Class the mean baseline was recorded as 2.4 mg/dl while after 6 months of follow up it was 1.7mg/dl. This apparent improvement led the authors to conclude that the percentage change in serum creatinine levels mainly predicts short-term ITU survival, but does not impact on longer- term renal survival [181]. Abosaif et al used the serum creatinine on admission to ITU as the baseline level. This is likely to have already been elevated in many patients due to AKI and will overestimate the true baseline. In addition, the authors included only those patients who had impaired function on admission to ITU, excluding those developing AKI later during the ITU stay. This latter group is known to have worse outcomes as discussed in Chapter 2. There may also be a degree of survivor bias at the point of follow up.

Another study by Van Berendoncks et al using survivors of dialysis requiring AKI in the intensive care setting reported similar findings to those discussed above. They found that the mean creatinine clearance at the point of discharge from hospital did not differ from that found at follow up after 1 year. Some clue to the reasons behind this finding is the wide variation in the evolution of renal function after discharge that was described in this study.13 patients discharged on dialysis became dialysis independent while 7 additional patients developed ESRD [252]. It is possible that the changes in function in the opposite directions of recovery and decline may cancel each other out to leave the mean unchanged. This may also partly explain the findings in the study by Gude and Abosaif.

3.6.3 (v) Published Meta-Analyses of recovery after AKI

There have been three studies published to date that have conducted a meta-analysis of functional outcomes after AKI [26,352,397]. Schmitt et al conducted a meta-analysis of published literature to determine the incidence of non-recovery of kidney function after AKI as a function of age. They included studies published between 2000 and 2007 that reported a clear definition of renal recovery of function, assessed renal recovery as a primary or secondary outcome, and reported the participant's age. 17 studies were included in this meta-analysis and included the pooled data of 5,529 participants. In keeping with the findings in the literature discussed earlier in this section, the study populations and clinical settings showed marked heterogeneity. 12 of the 17 studies examined patients with only severe dialysis requiring AKI. 10 of the studies had data only for recovery at the time of hospital discharge. The authors found heterogeneous definitions of AKI and renal recovery but the most striking methodological issue was that few studies included data on baseline kidney function and so this could not be included in meta-regression analysis. Without this the

definition of recovery is essentially meaningless. The authors found that 31.3% of elderly patients over 65 years of age failed to recover function after AKI compared to 26% in patients under 65 years of age. Heterogeneity was significant with an I^2 Index of 55%. The authors attempted to reduce the heterogeneity by pooling studies according to the definition of renal recovery. When independence of RRT was used to define recovery results showed a strong effect of age with a relative risk of 1.56. Overall the authors concluded that recovery after an episode of AKI is approximately 28% less likely to occur in the elderly over the age of 65 years [397]. The validity of this conclusion is questionable given the marked heterogeneity encountered in the studies. Nevertheless, independence from RRT is a more robust outcome and age was strongly associated with this. The authors could not explain the effect of age on recovery. It may relate to the effects of age itself on kidney function or may be related to the increased number of comorbidities encountered in this age group.

In 2009 Coca et al published a meta-analysis that attempted to characterize the relations between AKI and the long-term outcomes of CKD, cardiovascular disease, and death. They included studies from 1985 onwards with at least 6 months of follow-up of patients after a defined AKI episode. 27 studies from a total of 48 analyzed provided data on the incidence of CKD or ESRD in patients who survived hospitalisation with AKI. 21 of these studies included patients with CKD. 23 reported ESRD as an outcome while 11 reported some form of CKD as an outcome but definitions varied. The rate of CKD after AKI was reported as 7.8 per 100 patient years while that for ESRD was 4.9 per 100 patient years. The authors were unable to calculate the relative risks as no study had compared outcomes with a group of controls without AKI. This meta-analysis highlighted all of the methodological issues discussed earlier in this section [26].

Finally, Coca et al conducted a second meta-analysis in 2011 and attempted to estimate the risk for CKD and ESRD after an episode of AKI. This is something they were unable to do in the 2009 analysis. 13 studies published between 2006 and 2011were included in the analysis all of which were retrospective. The authors found that the pooled adjusted hazard ratio for CKD after an episode of AKI was 8.8 and for ESRD it was 3.1. In keeping with the previous meta-analysis the reported heterogeneity was very high with an I^2 Index > 75%. The authors were unable to reduce the statistical heterogeneity to below 75% with deletion of studies from the pooled analysis [397]. The results of this analysis are therefore of questionable validity. In deriving the pooled relative risk of CKD after AKI, Coca et al used seven studies from markedly different populations including two from the general hospital population [231,365], two containing those with haemopoetic bone marrow transplantation only [147,394], one from cardiac surgery [127], one from coronary angiography [230], and one from a group of RRT survivors

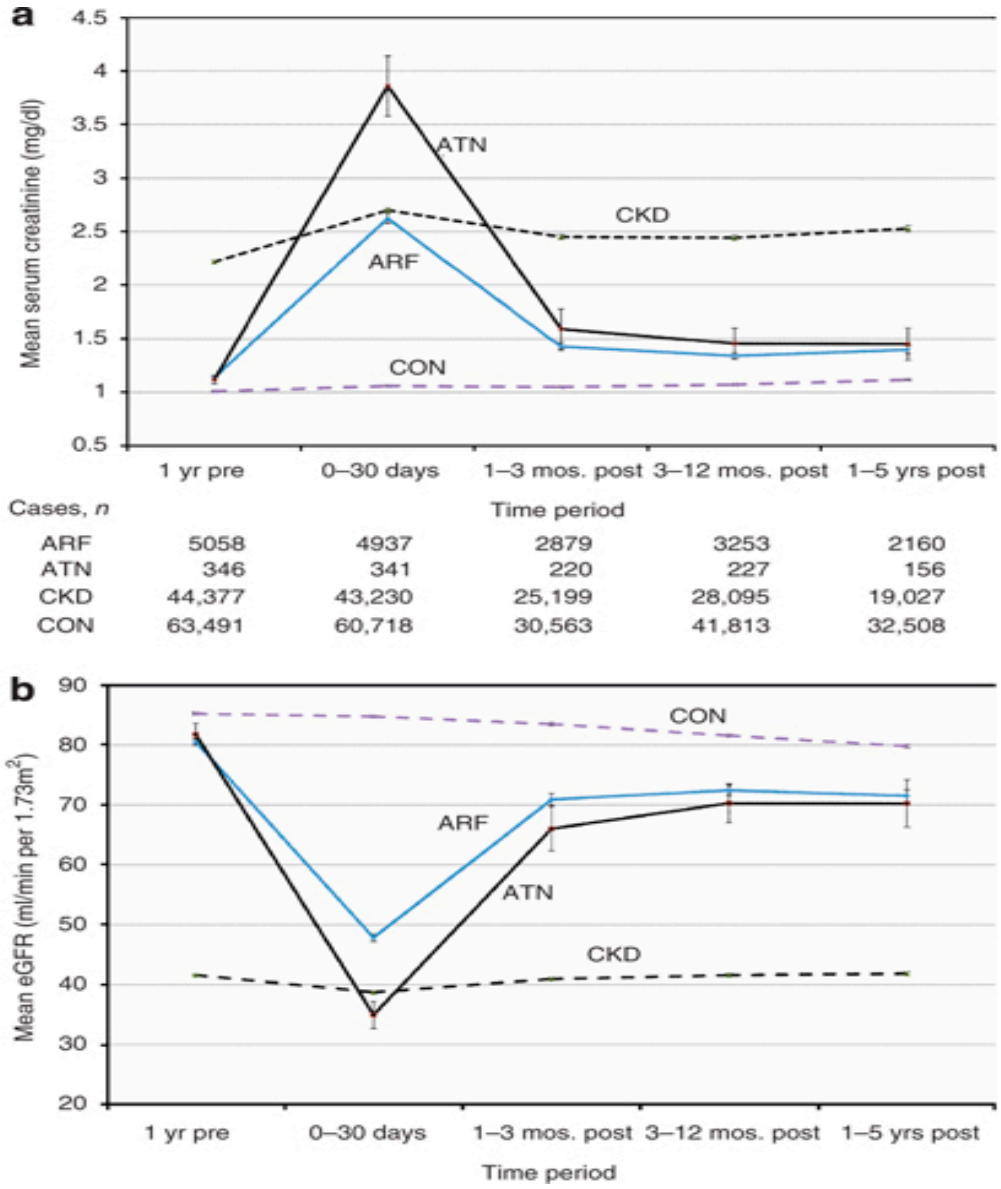
[120]. The authors were careful to describe the findings in this study as an 'association' and did not suggest that AKI was playing a causal role [352]. They felt that residual confounding may still be a problem. For example, six (nearly half) of the studies included in the analysis used ICD-9 codes for ascertainment of important confounders such as CKD, diabetes, hypertension, and heart disease. Therefore they are likely to have under-reported them.

3.7 Recovery Patterns after AKI

Many of the studies summarized in Appendix 12 reported the state of recovery at the point of discharge from hospital. There is clear evidence that recovery continues to occur in some patients after hospital discharge. Therefore an assessment of function at discharge will not be an accurate reflection of the final outcome. The question is how much time should be given before deciding a patient has reached their maximum point of recovery?

Several studies have reported a rough approximation for the recovery timeframe and it appears that recovery continues for between 3 and 6 months after the AKI episode and the function then plateaus [46,159,365,388]. Figure 3.5 has already illustrated this type of pattern of recovery in those with AKI after a heart transplant [159]. Figure 3.6 illustrates the recovery pattern presented by Amdur et al. This study involved patients from the US Veterans Affairs system who had been coded for either ATN or ARF at the time of discharge from hospital. The ATN group in this case is likely to represent a more severe form of AKI however it is demonstrated that in all cases of AKI the point of maximal recovery appears to occur roughly between three and six months [365]. Based on the available evidence it appears that six months would be a reasonable time point from which to follow up patients after AKI to assess its immediate impact on kidney function. However, in the longer-term there is likely to be a further decline in function particularly those with CKD.

Figure 3.6 Recovery patterns after AKI demonstrated by Amdur et al in patients coded for ATN or ARF at the time of discharge from hospital. Reprinted by permission from Macmillan Publishers Ltd:[Kidney International][365], copyright 2009.



Cases, *n*					
ARF	5058	4937	2879	3253	2160
ATN	346	341	220	227	156
CKD	44,377	43,230	25,199	28,095	19,027
CON	63,491	60,718	30,563	41,813	32,508

Several of the studies discussed earlier demonstrated an increased risk of progression of CKD after an episode of AKI. The pathological process involved is unknown. Figure 3.7 illustrates the outcomes of patients in the study by James et al after coronary angiography. The patients included had a baseline eGFR<90mls/min. This study demonstrated an increased rate of decline in kidney function after moderate to severe AKI [230]. Whether the increased rate of decline is due to the effects of the AKI episode itself is unknown.

Figure 3.7 The decline in renal function after an episode of AKI reported by James et al in patients who had undergone coronary angiography. Reprinted by permission from Macmilan Punlishers Ltd:[Kidney International][230], copyright 2010.

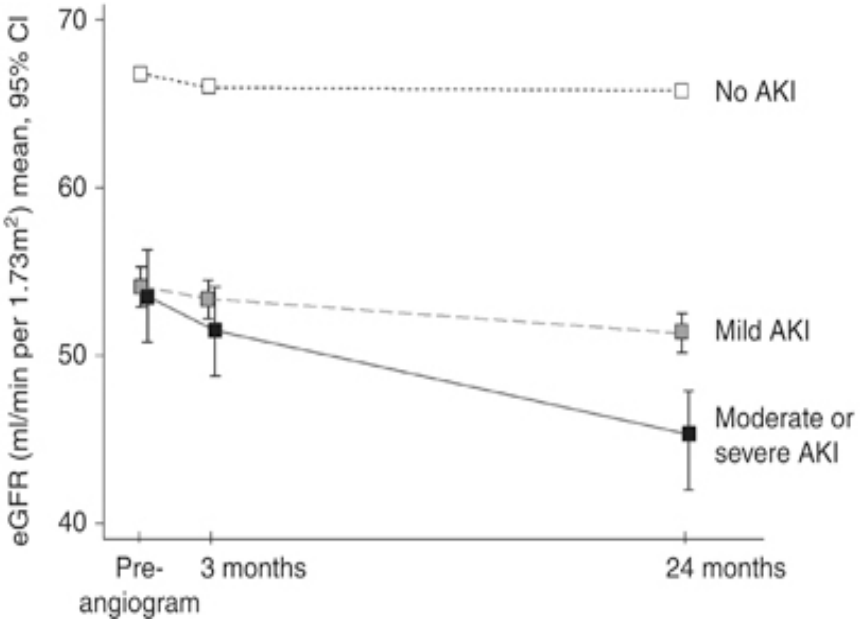
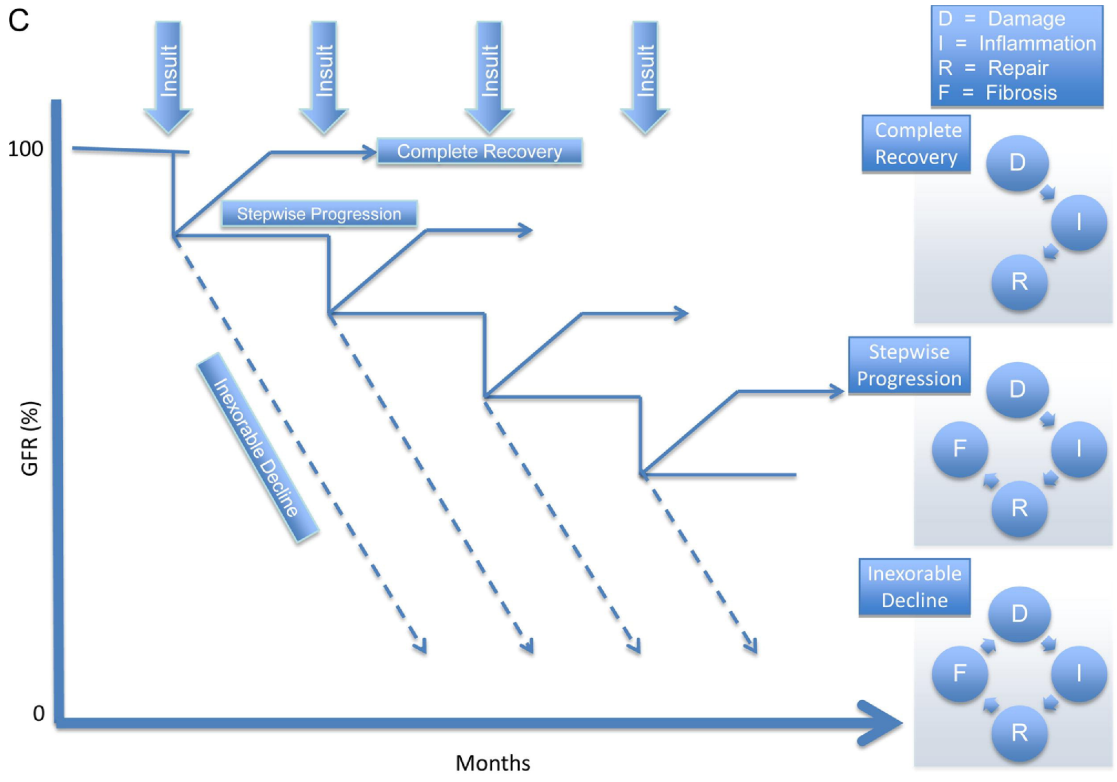


Figure 3.7 gives the impression of a smooth process of decline after the AKI however as with virtually all of the studies to date, James et al did not account for inter-current events during follow up. It is likely to be far more complex. As discussed earlier patients may be at an increased risk of another AKI after their initial episode and the pathway may be one of repeated step-downs in function rather than a steady decline. This hypothesis was illustrated recently by Bedford et al and is shown in Figure 3.8 [398]. This graph shows the possible outcomes after an episode of AKI. Firstly, there may be complete recovery. Secondly, AKI may initiate a relentless process of repair and fibrosis causing progressive CKD, or thirdly repeat AKI episodes may cause gradual step-downs in function. In addition to the possible effects of the AKI itself on function, during any prolonged follow up period the patient will be subject to the effects of aging and inter-current illnesses. The latter may be associated with medication changes that could influence kidney function. For example, the starting of an ACE Inhibitor could result in a decline in GFR. No study to date has taken these issues into account. Overall the precise influence of any single AKI episode on long-term renal function is unclear and is currently only the subject of hypothesis and speculation. It appears unlikely that a single episode is responsible for the long-term outcomes reported in studies to date and it may be that a single AKI can only be considered a poor prognostic marker.

Figure 3.8 Hypothetical patterns of decline in renal function associated with AKI [398]. Reprinted with permission from Elselvier, Copyright 2012.



3.7.1 Factors influencing recovery of renal function after AKI

Factors that may influence the recovery of renal function after an AKI episode have been reviewed by several studies and are listed in Figure 3.9. These factors are poorly characterized in the literature and their interpretation is complicated by the fact that they overlap with the risk factors for the progression of CKD itself.

Older age has been consistently shown to be associated with less likelihood of recovery after AKI [21,122,194,369,386]. This association appears to be a strong one and was confirmed in the meta-analysis by Schmitt [397]. The reason for this increased risk of non-recovery is unclear but is likely to be related to the reduction in renal reserve that occurs with aging together with a rising burden of comorbidities.

The effect of baseline kidney function on recovery has been poorly studied, but some studies have reported a paradoxical effect in that patients with lower baseline GFR may actually show better recovery after an AKI episode. James et al found that the risk of the composite outcome of ESRD or doubling of serum creatinine was higher in those with AKI but this risk grew progressively smaller with lower baseline eGFR or heavier proteinuria [231]. Similarly, LaFrance et al found that the risk of the composite outcome of

death or ESRD was lower in those with an eGFR between 10 and 20mls/min than at higher levels [125]. Several reasons could account for these findings. Firstly, it is possible that the definition of AKI that has been used in these studies is not appropriate at lower levels of eGFR where the relative changes in creatinine may not represent the same extent of injury. For example, an increase in creatinine of 0.3mg/dl according to the AKIN definition is likely to represent a far greater injury in someone with a normal baseline creatinine compared to a higher baseline. Another important factor is the interpretation of these statistics in terms of the absolute and relative risks. For example in the study by Wald et al, the absolute risk of ESRD in those without AKI and decreased baseline GFR was 9.8% and this increased to 18.4% for those with AKI and decreased baseline. On the other hand for those with normal baseline and no AKI the risk was 0.4% and this increased to 4.6% with AKI [393]. This represents more than a ten-fold increased risk compared to the two-fold increase at lower levels on account of the extremely low probability of ESRD in those with normal baseline that do not sustain an AKI. Hence the relative risks at normal levels of renal function are higher but the absolute risk difference is lower [352]. Overall it is unclear from the literature how the baseline level of function is influencing outcomes.

The impact of the cause of the AKI on recovery is an important consideration. However, owing to the fact that the majority of studies published to date are retrospective they have lacked the patient level data necessary to define the cause. Bagshaw et al reported the 90 day follow up of patients who had required RRT in the ITU and found that the adjusted odds of recovery were increased in those who had septic shock [366]. This suggests that the cause may be relevant to outcomes however Piccini et al reported the opposite in their study of intensive care patients with AKI defined by RIFLE. In this study patients with sepsis appeared to be less likely to recover function [251]. No other studies reviewed have reported the influence of cause on outcomes and so it remains poorly characterized. Along similar lines the impact of community versus hospital acquired AKI on outcomes has not been reported.

Several studies have reported an increased risk of non-recovery with higher burdens of comorbidities [122,194,366,369]. In particular congestive cardiac failure, diabetes mellitus, and a low serum albumin. These findings are arguably non-specific as they are risk factors that would be shared with CKD for poor outcomes in general.

Gender may play a role in renal recovery. Bagshaw et al found that the odds of recovery were increased in males [366]. Many studies have shown that the severity of the AKI is linked with recovery [155,186,190,230,369]. For example, James et al demonstrated a clear

increased risk of decline in renal function after AKI in those with moderate to severe AKI compared to those with mild AKI and this has been illustrated in Figure 3.7 [230]. The clinical management of AKI is likely to be very relevant to functional outcomes. No study to date has reviewed this in any detail.

Figure 3.9 Factors that may be influencing recovery after an episode of AKI.

Factors associated with AKI recovery	Influence
Older Age	Recovery less likely
Baseline function	Unclear
AKI cause	Unclear
Gender	Males may show better recovery
Comorbidities	Increased risk of non-recovery - Diabetes - Heart Failure - Low albumin
AKI Severity	Graded increased risk of non-recovery
AKI management	Unclear

It is notable that Schiffl et al has published the only prospective study to date carrying out an assessment of potential risk factors for functional recovery. This study followed up patients who had required RRT in the ITU for one year. The authors found that after multivariate analysis neither age, gender, comorbidity, severity of illness, cause of ATN nor mode of RRT were independently associated with partial recovery of function from an episode of ATN [388]. However, this study may have lacked the power to draw any firm conclusions from these findings. The original cohort consisted of 425 patients but only 25% of these survived the five years of follow up.

Finally, there is some evidence that the demographics of recovery have changed in recent decades. McCarthy et al reported the outcomes of patients who required dialysis in their intensive care unit during two separate periods from 1977 to 1979 and then 1991 to 1992. They found that the overall survival had improved in the later era and this was despite an increase in the age and burden of comorbidities of the patients. The authors attributed this to improved ITU management. However, in relation to recovery from the need for dialysis the later era faired worse. In the earlier period 96% of patients (22 of 23) had recovered to come off dialysis after one year compared to 78% (29 of 37) in the later period [382]. These findings indicate the important role of age and comorbidities with regard to recovery. In addition, these

findings highlight the important implications of AKI in the modern era. If more patients are surviving the hospitalisation and AKI is playing a causal role in the incidence and progression of CKD its contribution to the CKD population will be increasing.

3.8 Summary

The precise nature of the association between AKI and CKD is still debated in the literature [50,357,398,399]. However, there is agreement that rigorous prospective studies are needed to better characterize the AKI/CKD interaction [50,399]. There are many problems with the current body of evidence:

- Many of the risk factors for AKI are shared with CKD itself and so separating the two along a causal pathway is difficult. Some authors have suggested that AKI may simply serve as a prognostic marker for the development of CKD in those who are already at high risk and destined to develop it. AKI in this sense may simply represent a failed 'stress test' [352,399].
- There is a lack of consensus in the literature on the definition of baseline kidney function, AKI itself, and the definition and evaluation of recovery and progression. Indeed many studies have failed to adequately define baseline function or have used estimates. This may have resulted in AKI occurring on top of previously unrecognized CKD and then being reported as having caused CKD.
- There is conflicting evidence in the literature particularly in relation to the outcomes of milder episodes of AKI. Some studies have demonstrated an increased risk of progressive disease even after a very mild AKI. In the only study to review the slope of decline of renal function before and after the AKI episode there was no increased decline in function demonstrated for mild cases of AKI [230].
- Studies to date have focused on follow up at a single time point to assess renal function and have done this retrospectively. They have not taken into account the effects of inter-current medical events and in particular repeat episodes of AKI. There is now evidence that up to one third of patients may experience a repeat AKI. As such a single index AKI cannot be said to result in the outcomes reported and it is likely that the evolution of function after an AKI is far more complex.
- There is currently no prospective study in the literature of general hospital based patients with follow up beyond discharge. As a result the natural history of AKI and its relationship to CKD is unclear because of a lack of patient level data. Many important issues remain and these include the association of

different AKI causes with recovery, the risk factors for non-recovery, and the association of hospital based versus community based AKI with recovery.

In recent years researchers have focused on trying to establish a link between AKI and CKD. It appears that this link has never been in doubt and what is actually needed is more focused studies to better describe its characteristics and ascertain if the outcomes are modifiable. This cannot be done without a proper description of the clinical history of the condition and it is hoped this present research will provide this.

Chapter 4: Methods

4.1 Introduction

The aim of this research was to study the natural history of AKI in the general hospital population with a focus on its relationship to the aetiology and progression of CKD. This was achieved by conducting a prospective observational study. This chapter describes the overall study design as it was outlined in the original study proposal beginning with these objectives. During the course of the study, particularly during the initial recruitment period, some amendments to the original design occurred. Where necessary, these amendments are outlined in detail within the relevant section in this chapter.

4.2 Ethical Approval

Ethical approval for this study was obtained from the Milton Keynes Research Ethics Committee on the 30th September 2009. REC Ref. 09/H0603/26.

4.3 Objectives

This study was designed to answer the following questions:

1. In patients with moderate to severe CKD (stages 3-4) does AKI lead to a clinically significant persistent reduction in kidney function?
2. To what extent does AKI in patients who previously did not have moderate to severe CKD (eGFR ≥ 60) lead to incident moderate to severe CKD?
3. What is the relationship between the severity of AKI and progression of pre-existing moderate to severe CKD or the occurrence of moderate to severe CKD in those who previously did not have it in hospitalized patients?
4. What socio-demographic and clinical factors predict persistent loss of function after AKI both in individuals previously without moderate to severe CKD and those with pre-existing moderate to severe CKD?

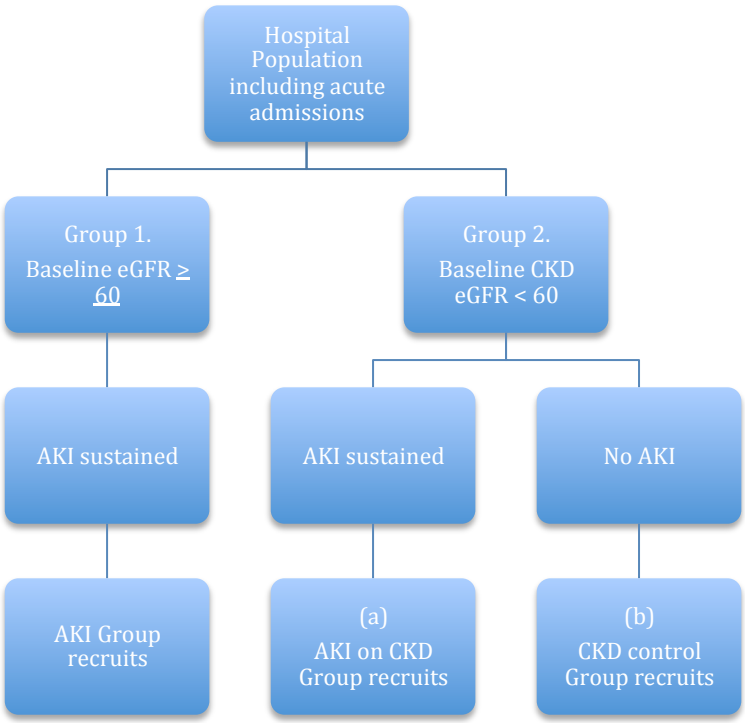
4.4 Design

This study was a prospective observational cohort study. It was proposed that patients would be followed up at 6 and 12 months after recruitment.

The study consisted of two main recruitment arms (see Figure 4.1):

1. The AKI Group – patients who had no history of moderate to severe CKD (eGFR ≥ 60) and sustained an AKI either on admission to hospital or during their hospital stay.
2. The AKI on CKD Group – patients in whom a history of pre-existing moderate to severe CKD was identified. Subjects in this population fell into two groups (a) those that had CKD and then sustained an episode of AKI either on admission to hospital or during their hospital stay, and (b) those that had a history of CKD but did not sustain an AKI during their hospital stay. It was proposed that patients in Group (a) would be studied to ascertain the effects of AKI on their pre-existing CKD, while those in Group (b) would serve as a control group.

Figure 4.1 Flow chart of study recruitment arms.



4.5 Sample Sizes

Group 2 AKI on CKD Group

Based on existing evidence of disease progression in those with stable CKD progression in the CKD control group was not expected to exceed a 5% fall in eGFR over the course of twelve months. For 80% power at the 5% level with a 2 sided test, in order to detect a difference of 10% in absolute terms i.e. 15% in the AKI on CKD Group, then 160 patients would be needed per group. Allowing for attrition due to losses to follow up (death, moved away, non-response to follow up checks) the projected number required was rounded up to 250 patients per group. Several assumptions were made to arrive at this final number. The inhospital and follow up mortality after an episode of AKI reported in the literature while designing this study was widely variable. Stevens et al reported a 1 year mortality of 65% in a UK sample however this study included largely severe AKI with all cases having a serum creatinine > 300µmol/l [35]. Ali et al reported a 6 month mortality of 50% [187]. We therefore assumed a mortality rate of roughly 50% at one year and assuming a drop out rate in the region of 5% the rounded figure of 250 was adopted.

Group 1 AKI Group

The AKI group was expected to have fewer co-morbid diseases and particularly would be lacking the influence of known CKD. Thus the mortality was expected to be substantially lower than in the AKI on CKD group. It was therefore assumed the overall attrition rate would be approximately 30%. It was decided to also aim to recruit 250 in this group. With this number and 70% follow-up, the 95% confidence limits would be ± 2.9% if the observed percentage developing moderate to severe CKD was 4%.

4.6 Definitions

4.6.1 Baseline Renal function

Pre-existing moderate to severe CKD

Subjects had at least two eGFR readings < 60mls/min over the previous twelve months at least three months apart that did not differ by more than 5mls/min.

Pre-existing eGFR ≥ 60 (not moderate to severe CKD)

Subjects had at least one eGFR ≥ 60mls/min within the previous twelve months.

4.6.2 Acute Kidney Injury

AKI was defined using the Acute Kidney Injury Network Definition (AKIN) definition which was outlined in Chapter 2, Figure 2.5 [39].

The original AKIN stipulated that the criteria be used in the context of the clinical presentation and following adequate fluid resuscitation when applicable [39]. As there is no reliable or validated way of assessing fluid status this was not applied in this study. No study to date where the AKIN definition has been employed has attempted to apply rigorous assessment of fluid status.

In this study it was intended to record urine output when this information was available. However, as this study was designed to include patients outside of the intensive care setting where urine output is generally not reliably recorded only the serum creatinine criteria were used in patient recruitment. Finally, the 48 hour timeframe was not applied to patients with AKI evident on admission to hospital as the precise timing was unknown.

4.6.3 Progression of CKD

Significant progression in CKD was considered to have occurred if there was a sustained fall in eGFR ≥ 5mls/min from baseline at the time of follow up.

4.6.4 Discussion on definitions

A discussed in Chapter 3, a key question in AKI research design is how to define progressive or incident CKD. This study uses the definition of progression in CKD recommended by the National Institute for Health and Clinical Excellence [74]. It was also applied to the definition of baseline kidney function in those with previous CKD.
The first arm of the study containing patients without moderate to severe CKD is intended to represent those with 'normal' baseline function. What constitutes normal function in terms of eGFR is subject to debate. However, a threshold was required and that of an eGFR ≥ 60 has been widely applied in the literature previously.

4.7 Setting and Population

Recruitment took place in a single centre at Queen Alexandra Hospital Portsmouth (Portsmouth Hospitals NHS Trust).

Portsmouth Hospitals NHS trust is an acute trust, which accepts unselected admissions, serving a population of approximately 600,000. It is a non-tertiary district general hospital but includes the regional tertiary renal service. There is no cardiothoracic, neurosurgical, or trauma service on site. The catchment area includes the city of Portsmouth with a population of approximately 200,000. Records from the Centre for Demography at the Office for National Statistics for 2009 show that the ethnic origin of Portsmouth City is 88.8% White with 4.9% Asian or Asian British and 2.2% Black or Black British. Data from the Quality Outcomes Framework database for 2011 shows that Portsmouth City Teaching Primary Care Trust has a prevalence of registered CKD of 2.9% compared to the UK prevalence of 3.4% [318]. These data relate to registered cases only and so will underestimate the true prevalence.

4.8 Study Inclusion Criteria

All patients over 16 years of age admitted to hospital who met the definition of AKI, either with or without moderate to severe CKD.

4.9 Study Exclusion Criteria

The following groups were excluded from the study:

1. Patients already receiving renal replacement therapy including renal transplants.
2. Patients with malignancy whose prognosis was considered by the clinicians managing them to be less than one year.
3. Patients who lacked the capacity to give informed consent and were unlikely to regain this capacity before discharge from hospital; largely older individuals with dementia.

During recruitment, the exclusion criterion pertaining to terminal illness above was found to be too restrictive as it did not account for other illnesses such as severe heart failure, lung disease, or liver failure where the prognosis was equally poor. It was

therefore amended to include anyone with terminal illness of any cause where the prognosis was considered by the clinicians managing them to be less than one year.

4.10 Case Identification and Recruitment

The entire study, from case identification to recruitment, data recording, follow up and administration was undertaken by the author.

The steps involved in screening for potential recruits and the recruitment process itself are outlined in Figure 4.2.

4.10.1 Screening and Recruitment

Step 1: The hospital biochemistry laboratory provided a daily list of patients who had an eGFR < 60mls/min from the previous day. The eGFR was determined using the abbreviated MDRD formula [89]. This list contained the patient names and hospital numbers together with their location within the hospital and their eGFR. The biochemistry laboratory ran a computer program so that this list printed daily onto a specified printer to which the author had access for the duration of the study.

The Queen Alexandra Hospital Laboratory processes over 4,000 biochemistry samples per day. The list of patients with an eGFR<60mls/min served as a filter to identify subjects potentially suitable for inclusion. The laboratory computer algorithm was set up to automatically filter samples from origins that would be unsuitable for recruitment. This included the dialysis unit, the outpatient department, and those received from general practice.

Step 2: All hospital laboratory results are recorded on a system called APEX. Referring to the list provided by the laboratory the author screened each case individually on APEX to ascertain if the eGFR represented an acute change in renal function using the associated serum creatinine. By applying the AKIN criteria patients were identified as having an AKI. Blood test records from the previous year were then reviewed to identify cases that met the definition of baseline kidney function as defined above. All cases potentially suitable for recruitment were recorded on an Excel spreadsheet throughout the study which served as a record of the screening process.

Step 3: After generating the list of potential recruits the wards on which the patients were staying were visited to review their suitability. The medical notes were reviewed and the case discussed with the managing team to insure that the patient did not meet

any of the exclusion criteria. If suitable for recruitment, a short invitation to participate in the study was given to the patient before approaching them.

Step 4: Patients expressing an initial interest were given an information sheet to inform them about the study and what it involved. A separate information sheet was used for each of the groups recruited to the study. A copy of each information sheet can be viewed in Appendix 14.

Between steps 3 and 4 if a patient was found to be unsuitable or did not want to take part this was recorded on the screening spreadsheet and the reason why. Those suffering from acute confusion which was expected to settle with treatment of their underlying illness were retained on the screening list and reviewed again after a few days to assess if they had improved to the point where they could be recruited.

Step 5: If they agreed to take part the patient was asked to sign a consent form and was assigned a study identification number designated by the order of their recruitment. Three copies of this consent form were made. One was retained for the study records, one placed in the patients' notes and one given to the patient to keep along with the information sheet. A copy of the consent form, which was universal for all groups in the study, can be viewed in Appendix 15.

Step 6: A study review form specifically designed for the study was used to record all of the baseline data required. This information was obtained from the patient themselves, hospital notes, laboratory records, and radiology records. No intervention took place with regard to the management of the patient. The study review form used can be found in Appendix 16 and is discussed in detail below.

Step 7: Patients recruited to the study were recorded on an Excel spreadsheet with one spreadsheet for each group in the study. This recorded their study identification number, date of recruitment and the projected dates for follow up in order to keep track of the follow up process. Having been recorded in this manner a letter was sent to the patients' general practitioner informing them of their involvement in the study. All data on the study review form was later transferred to an SPSS database for data analysis.

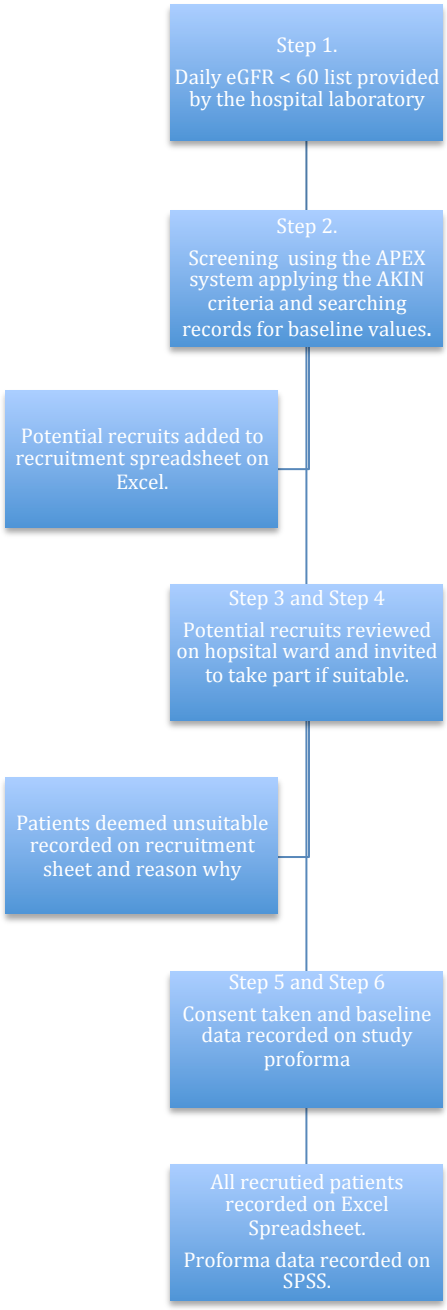


Figure 4.2 Flowchart of recruitment process.

4.10.2 Recruitment Study Review Form

The study review form went through multiple revisions during the initial recruitment period before the final version used throughout the study was established. The form submitted with the original study proposal (Version 2) and the final version used (Version 11) can be viewed in Appendix 16.

Problems with the original review form included:

1. The original was designed without accounting for the fact that data would eventually be transferred to an SPSS database for analysis. There were open-ended questions that would not be amenable to statistical analysis on SPSS. The form was revised to dichotomize the data recording where possible and a tick box format was adopted.
2. Certain aspects of the original were time-consuming. It was planned to record baseline blood results along with discharge data on the form. This was abandoned as it was taking up valuable time and the information was easily accessible on the hospital APEX system.
3. Recording hospital discharge data such as blood pressure made the study unfeasible for a single individual. To capture these data the subject's status in the hospital needed to be monitored and the ward staff requested to alert the investigator when the time of discharge arrived. It then required a second visit to the ward to collect this data. Initially the option of requesting the managing team to record this data was explored. This would have required a significant change to the site approvals for the study and it was unclear how reliable the process would be. It was decided that the discharge data was not necessary for the questions being asked in this study. Discharge blood test results and the inhospital outcome could be obtained from the hospital computer system so this section of the original form was abandoned.
4. Whilst reworking the form a number of additional pieces of information were added as outlined below. This included information on the patients' social situation.

4.10.3 AKI Study Review Form Summary and Explanation

Section 1. Patient Details

This section recorded simple information including the study identification number, admission date, age and sex. The group the patient was assigned to was also recorded. To facilitate analysis, the groups were stratified by AKIN stage and in the case of CKD patients the CKD stage was also stratified by the KDOQI classification described in Chapter 3.

Section 2. Pre – admission details

This section recorded the subjects comorbidities and for this the Charlson Index were used [400]. The most appropriate way to record comorbid illness in this population was

unclear at the time of designing this study however the Charlson Index has been widely used in the literature in AKI studies [168,231,235,352,393]. For this study the original index as described by Charlson has not been modified and is outlined in Appendix 17. This index consists of 19 medical conditions weighted by scores from 1 – 6. A sum score is then calculated to yield the total comorbidity score. With regard to patients included in the CKD arms of the study these automatically started with a score of 2.

In addition to the comorbidities listed in the Charlson index other parameters were added to this section because they were felt relevant to AKI. These included a history of obesity and measures to calculate Body Mass Index. A smoking history was recorded together with a history of hypertension and the number of antihypertensives in use. An effort was made to record some sociodemographic information. This included whether or not they lived alone or required carers.

To record an indicator of the subjects' functional capacity prior to the AKI the Katz index was included. After reviewing the literature the Katz index, using a modified version from the US Gerontology Society, was chosen because of its simplicity. This is a simple numbered scale from 1-6 scoring 1 or 0 for bathing, dressing, toileting, transferring, continence and feeding. It has been validated by Brorsson [401].

Finally, the pre-admission details section recorded a list of the medications taken prior to the AKI with a focus on the indication for the use of RAS-blockers. In addition other potentially nephrotoxic drugs such NSAIDS were recorded.

Section 3 AKI Details

This section recorded essential details surrounding the period when the AKI occurred. It included the admitting specialty and timing of the AKI including whether it occurred in hospital or was found on admission. Data recorded included whether or not a urine dipstick and renal ultrasound were performed. It was originally planned to request a urine Albumin Creatinine Ratio at this point however after reviewing the literature no evidence was found that this test would be valid in the setting of an AKI. If the subject had documented hypotension within 72 hours of the AKI this was noted and the nadir blood pressure recorded.

An effort was also made to record urine output. This is notoriously difficult as many patients do not have a urinary catheter placed at the time of an AKI. The urine records are also dependent on the nursing staff recording them. This section was later

simplified to record if a patient was oliguric (urine output < 300mls/day) or anuric in the 72 hours prior to the AKI or afterward.

As discussed earlier, no validated way exists to assess hydration status and this element of the AKIN definition has not been used. A record of the clinical impression of the subject's fluid status at the time of the AKI was included in this section of the review form to explore this area.

Finally, to record the clinical condition of the patient at the time of the AKI the MEWS System was used (Modified Early Warning System). The MEWS system relies on recording baseline parameters such as temperature and heart rate and is used on all patients routinely in Queen Alexandra Hospital. It is presented as a MEWS score and is easily accessible. The MEWS system has been reviewed and validated by several authors [402]. It was felt that using a more complex scoring system such as APACHE II which is used commonly in the intensive care setting would overcomplicate the data collection process.

Section 4 AKI Type

This section was used to record further baseline data on the nature of the AKI. AKI has been traditionally divided into Pre-renal, Intrinsic, and Post-renal causes and this continues in the recent KDOQI AKI Guidelines [48]. This approach was maintained in this study but greater detail was required for the pre-renal type. This was to insure that the data could be reproducible and would allow further exploration of this area in the analysis.

Traditional pre-renal causes were divided. In the case of sepsis a rigorous definition was used adapted from the American College of Chest Physicians and Society of Critical Care Medicine 2001 International Sepsis definitions conference [403]. A minimum of two criteria were required to diagnose an infection associated AKI – a documented or suspected infection with a clear focus and one feature of the systemic inflammatory response syndrome. Culture status was recorded but was not essential for diagnosis. By definition, as there was an AKI present, these patients automatically fell into the category of severe sepsis with organ dysfunction regardless of their overall clinical state.

Intrinsic AKI was only recorded if there was biopsy evidence or a high clinical suspicion recorded by a consultant nephrologist. The latter was bearing in mind that not all patients are suitable for biopsy. Obstructive AKI required radiological evidence.

Finally, the review sheet ended with a record of any formal review by the renal service, admission to intensive care, or any form of renal replacement therapy.

4.10.4 Discussion on recruitment

An initial period of recruitment to this study began in November 2009 and continued through to December 2009. During this time the methods outlined were put into practice and the recruitment process was assessed. Many problems were identified with the original design during this period and recruitment was suspended in December 2009 in order to address these issues.

1. The recruitment study review form

As outlined above extensive changes were made to the study review form.

2. Feasibility of recruitment numbers

Pilot Study
To aid the design of this study a pilot was undertaken from 16/03/2008 to 24/03/2008 inclusive. The purposes of this pilot were as follows:

1. To establish how the data collection would be undertaken.
2. To estimate the duration of the data collection process on a daily basis, ensuring it would be within reasonable time limits.
3. To estimate how many patients could potentially be enrolled during the study time period, ensuring that projected numbers could be achieved.

The pilot was carried out using the same conditions specified in the protocol and illustrated earlier in Figure 4.2. The time it took to conduct this process was recorded on a daily basis together with the numbers of potential recruits. A sample of the cases was reviewed on the wards and data was recorded on the study review form. The time taken to conduct these reviews was also recorded.

It took an average of 64 minutes per day to review the eGFR list provided by the laboratory. An average of 5 cases per day met the study criteria and were suitable for review (range 1-8). 15 cases meeting the AKI Group criteria were identified and 21 cases meeting the AKI on CKD Group criteria. Based on these numbers it was estimated that there would be roughly 277 AKI Group cases over 6 months and 388 AKI on CKD cases over 6 months that would be available for recruitment. It was

originally proposed that recruitment would take place over 6 months and so it was felt that these numbers were adequate as there would be lee way to extend the recruitment period. During the pilot it took on average twenty minutes to review the cases and taken with the time it took to review the eGFR list it was felt that the process would be manageable.

In hindsight, there were several problems with these assumptions which became readily apparent when actual recruitment to the study began.

1. The time estimate for reviewing one eGFR list was accurate however it was not considered that there would be three lists present on a Monday after a weekend.
2. The pilot demonstrated a marked range of daily cases from 1 to 8. It is likely that if the pilot was carried on for longer it may have given a better indication of how many cases would be eligible. An extreme example would be three days of 8 cases over a weekend leading to 24 cases to be reviewed on a Monday.
3. The time estimate for reviewing the patients did not account for time spent locating them within the hospital. It was also a rough overview of the time needed to recruit and did not actually involve explaining the study to the patients and the time needed to obtain consent.
4. The distribution of the AKIN Criteria stages was not taken into account.

Taking these issues into consideration a longer and more thorough pilot study may have altered the approach to the recruitment process from the outset.

Problems with recruitment numbers

When recruitment began in November 2009 the numbers of cases meeting the recruitment criteria after screening were far higher than was anticipated from the pilot study. In addition, the list of potential recruits was overwhelmed by the milder AKIN Stage 1 cases in both the AKI Group and the AKI on CKD Group.

After recruitment was temporarily suspended in December 2009 screening continued on a daily basis during the months that followed in order to explore ways of dealing with this problem. To preserve the integrity of the selection process it was decided to adopt a randomization process for the AKIN stage 1 cases. In the case of the AKI on CKD Group it was found that the overwhelming numbers were in the CKD stage 3A

group. CKD Stage three was therefore split to 3A and 3B and the 3A Group was added to the randomization process.

Various levels of randomization were assessed in order to find the most appropriate that would keep the numbers of all AKIN Stages at a roughly similar level. A 1:5 randomization was settled upon and a 1:5 random number list was generated from a program freely available online (www.randomizer.org). Using this list the AKIN stage 1 subjects screened were selected at random yielding one fifth the number of potential recruits from the sample.

3. Work load on the wards

Several issues became apparent during the recruitment of the patients that meant the workload was too much for a single individual and contributed to the recruitment time period being extended significantly.

1. Queen Alexandra Hospital officially opened a large extension to the hospital in October 2009. Many services which had been based at another trust site were moved to the new hospital and this may have contributed to an increase in the numbers of AKI cases within the hospital. The hospital itself was now one of the largest in the region with close to 1400 beds making even getting around it time consuming. These issues were not factored into the planning at the time of the pilot study.
2. Patients were frequently found to have moved wards within the hospital and so were not present on the wards that the eGFR list indicated they should be on. This resulted in the need to frequently log back on to the hospital computer system to locate the patients and so more time was spent.
3. With regard to patient movement the Medical Assessment Unit and Surgical Assessment Unit were found to be particularly problematic. Patients that appeared on the list with an AKI who were located on the assessment units were frequently moved to another location in the hospital by the time they were reviewed. It was eventually decided to stop attempting to recruit patients on the assessment units and to wait for them to appear on the list at ward locations within the hospital. This resulted in some patients being missed as they were discharged directly from the assessment units back into the community.
4. The original plan to speak to the admitting team prior to approaching the patients also had to be abandoned. The presence of the ward teams was found to be erratic as most covered more than one ward. Considerable time was

wasted looking for members of the ward team or trying to contact them through the hospital bleep system. It was eventually decided to make an assessment of the patient suitability directly from the notes and by speaking to the nursing staff involved in their care.

5. The timing of visiting the wards was also an unseen issue when recruitment began. Ward rounds tended to take place in the morning at various times and it was felt to be inappropriate to approach patients while these were taking place as it hampered patient care. Likewise, it was felt to be inappropriate to approach patients around mealtimes. Considerable organisation was required to overcome these problems. A list of ward round times for each ward was kept to minimize disruption and lunchtimes were spent screening the days eGFR list rather than approaching patients.
6. Mondays proved to be particularly problematic in terms of recruitment as there were three eGFR lists to be reviewed and more than double the number of patients. The only way around this problem working as a single individual was to come to the hospital at weekends during recruitment in order to screen the lists and have them ready for the following Monday.
7. The actual time it took to recruit each patient was also greatly underestimated by the original pilot. The information sheet was four pages long and it could take over an hour at times to explain everything to the patients and obtain informed consent.

4. The CKD Control Group and Recruitment Problems

In the study design it was planned that for each AKI on CKD patient recruited another patient with CKD without an AKI would be recruited using the same baseline function criteria. These would be matched for age, sex and CKD stage as well as relevant comorbidities such as diabetes and hypertension. It was proposed to screen for them while doing the daily eGFR list. The recruitment of controls proved to be extremely difficult for a number of reasons which resulted in numbers for this group not reaching anywhere near the original target.

The problems with CKD control recruitment included:

1. Matching for the specified criteria was simply not possible for one person to juggle while also trying to screen for patients with AKI. The original proposal was overmatching the samples. It was eventually simplified to match for just age and CKD stage but even this proved to be onerous.
2. There was an inevitable time delay between recruiting a patient and then trying to match them with another suitable control. It was found in many cases that

those selected had already been discharged. Presumably, this was influenced by the fact that these patients were not as unwell as the patients who had experienced an AKI. Indeed, the length of hospital stay was eventually found to be considerably different in the results analysis.

3. Some patients who were successfully recruited went on to have an AKI during their hospital stay and switched arms in the study. To overcome this an attempt was made to observe patients for a few days to ensure stability prior to recruiting them however again this resulted in many being discharged early.

Overall, the control population in this study was not feasible under the circumstances. The workload was too much for one person and was not helped by the study design. Ideally, in order to recruit controls of this type one would need a process of blanket recruitment of all with CKD. This would require far more resources and was beyond the scope of this study. Personal communication with a member of the ASSESS AKI group in the United States who are currently undertaking a study of a very similar design has revealed that they are also experiencing problems recruiting controls.

4.11 Serum Creatinine and EGFR Measurements

All blood tests carried out in this study and used in the analysis of renal function were carried out in the same laboratory in Queen Alexandra Hospital. Tests were done using the Jaffe Method described in Chapter 2 using a Beckman Coulter Analyser – Unicel DXC 800. The laboratory runs continuous automated quality control testing of this analyser up to seven times per day to ensure the accuracy of its calibration. This is one of the strengths of this study as it eliminates interlaboratory variation in the measurement of serum creatinine and hence eGFR calculation.

4.12 Overall Timeframe of the Study

The original timeframe allotted for this project was two years. It was proposed that recruitment would take place over the first six months. Patients would then be followed up once at six months and again at twelve months taking the time for the study up to 18 months. This would allow six months for data analysis.

As outlined above the recruitment process was far more onerous than expected and the time needed considerably longer. After a period of recruitment in November and December 2009 it was put on hold in order to rectify the problems encountered. This was further hampered by a period of compassionate leave for the author so that formal recruitment did not recommence until May 2010. At this stage a radical revision of

follow up plans was undertaken. It was recognized that follow up of twelve months for each patient was unlikely to be possible in the timeframe remaining. It was thus shortened to a single six month follow up for each patient. The basis for doing this was researched and found to be reasonable. A review of the literature revealed several studies where the recovery pattern of patients after an AKI was illustrated. It was found that recovery continued for up to three months after the AKI but plateaued from six months onwards. This was described in detail in Chapter 3. It was therefore felt to be reasonable to conduct a single follow up at six months in order to answer the questions the study was asking.

The overall timeframe for the study therefore was:

Recruitment - November 2009 to April 2011

Follow up - complete in October 2011.

4.13 Follow up Process

After discharge from hospital a letter was sent to the patients general practitioner informing them of the patients recruitment to the study.

The follow up information planned were

1. A serum Creatinine with eGFR
2. A urine Albumin creatinine ratio
3. A list of current medications
4. Weight

The two groups had separate follow up plans:

AKI on CKD Group

Patients with pre-existing CKD under current guidelines should be undergoing monitoring by their general practitioners at least on a yearly basis and in more severe cases on a six monthly basis. It was agreed with the ethics panel and the local Primary Care Trusts that it would be reasonable to request that the general practitioner conduct a follow up blood test for renal function with serum creatinine and eGFR together with a urine ACR. The letter to the GP explained this and requested that the blood tests be timed for six months after the patients AKI. A reminder was sent to the

practice one month before the due date with a proforma requesting they provide confirmation that the blood test and urine sample had been requested. A letter was also sent to the patient reminding them that the tests would be due.

This overall process was helped considerably by the fact that many patients were already booked for monitoring blood tests by their general practice. Responses to requests were initially found to be slow but the overall response rate was excellent. For those where no response was received the patient was eventually telephoned directly and given the option of coming to the renal unit to have the tests done. In a number of cases the patients were willing to take part but not to come to the hospital. In this situation the author called directly to their homes to take the blood sample and record the necessary information.
Many GP practices performed the blood test but did not provide a urine ACR. It was felt that this was because in patients without diabetes the general practitioners did not feel that it was indicated. These tests are not without cost. Rather than pursuing this matter it was decided to abandon the need for a urine ACR. The study participants for the most part did not have a baseline ACR performed at any stage prior to the AKI and without anything to compare with the follow up sample would be futile in terms of results analysis.

AKI Group

Patients without CKD prior to the AKI would not be expected to be having monitoring at their GP practice. For this reason it was agreed that these patients would be followed up in the hospital renal unit by the author. A reminder was posted to the patients one month prior to the due date with an appointment to attend the renal unit for follow up. This was quickly found to be an impractical way of making contact with the patients and non-attendance was high. The letter to the patient was revised and rather than sending a set appointment they were reminded of the follow up due and told that they would be contacted directly by telephone to make the appointment. This was successful and with this method few patients were missed. Those that were unprepared to return as in the AKI on CKD Group were offered a follow up visit at home.

Prior to contacting any patient before follow up the hospital computer system was consulted to see if the patients were still alive.

After follow up a brief report was posted to each general practitioner informing them of the end of the study. Where necessary a brief report was given if the patient had

particularly severe CKD and in a few cases the general practitioner was advised to refer the patients to the renal unit for formal review in the event that there were concerns about ongoing care. An example of such a letter from the study is shown in Appendix 18.

4.14 Review of pre-admission details

To facilitate exploration of admission patterns and recurrent episodes of AKI a retrospective review of hospital and biochemistry records was carried out. In addition, previous biochemistry records were used to calculate the eGFR slope during the three years prior to the index AKI.

4.14.1 Hospital admissions prior to the index AKI

Portsmouth Hospitals NHS Trust records all hospital admission on a computer database called PAS. The PAS system was reviewed for all patients recruited to the study to record admission during the year prior to the index AKI.

4.14.2 Possible previous AKI episodes

The hospital APEX system was used to review all of the biochemistry records of each recruit extending back four years from the index AKI. Any rises in creatinine that met the AKIN criteria for AKI were recorded.

4.14.3 eGFR slope prior to the AKI

In order to explore the influence of prior renal function on outcomes further, a regression line was used to calculate the eGFR slope for each patient prior to the index AKI. A uniform approach was taken in each case to create the regression line. Hospital biochemistry records were retrospectively reviewed over the three years prior to the baseline eGFR at six monthly intervals. If an outpatient eGFR was present in the three months on either side of each six month interval then this was selected for inclusion. If more than one was available then the highest was chosen. Therefore over the three years reviewed a patient could have a maximum of seven eGFR results to create a regression line from which to calculate the slope. The slope of the regression line was calculated using SPSS.

4.15 Confidentiality and Data Protection

Strict confidentiality and data protection was carried out throughout the study and good clinical practice standards were observed.

Each patient recruited to the study was assigned a Study Identification number which was used throughout. Patient details with this study number were kept in a separate file with no clinical data attached. All data was recorded on password protected computers using the study number only so no link could be made to the patients involved. All files pertaining to the study were stored in the research laboratory of the Wessex Renal and Transplantation Service at Queen Alexandra Hospital which is locked when unoccupied by research staff.

4.16 Data Analysis

Data was analysed using SPSS 19 with help and advice from Dr. Scott Harris from the Department of Public Health Sciences and Clinical Statistics at the University of Southampton.

The data are presented as percentages, mean ± standard deviation or median with interquartile range where appropriate. The groups were compared using the Chi-squared test or Fishers Exact Test for categorical data. Continuous data was compared using the independent samples T-test if normally distributed with 95% Confidence Intervals or if non-parametric the Mann – Whitney U test. Categorical data was tested using the Chi-squared test for trend while continuous data was compared using the method of one-way Analysis of Variance or the Kruskall - Wallis test where appropriate. A p-value of <0.01 is taken as significant. Univariate and multivariate binary logistic regression analysis was carried out to explore the factors influencing the study outcomes. Univariate data is presented as the Beta coefficient, odds ratio with 95% confidence interval and p value. Multivariate analysis was carried out on a priori factors of interest.

Chapter 5: Results 1 – Study Population

5.1 The AKI population

This study was designed to evaluate the impact of AKI on CKD. To do this a rigorous definition of baseline renal function was used and is described fully in Chapter 4. This restricted recruitment to those who had previous measurements of their kidney function on record. Therefore the sample is not representative of the entire AKI population. The recruitment process is outlined here to describe how the study population was obtained in order to facilitate interpretation of the results.

Figure 5.1 shows the framework of recruitment of the study population which took place in two stages. Firstly, the screening stage during which patients with an eGFR < 60 meeting the study criteria were identified. This was followed by the recruitment stage during which eligible patients were reviewed and recruited. Two groups did not fit into this framework and may have represented additional AKI cases that were not identified by this study:

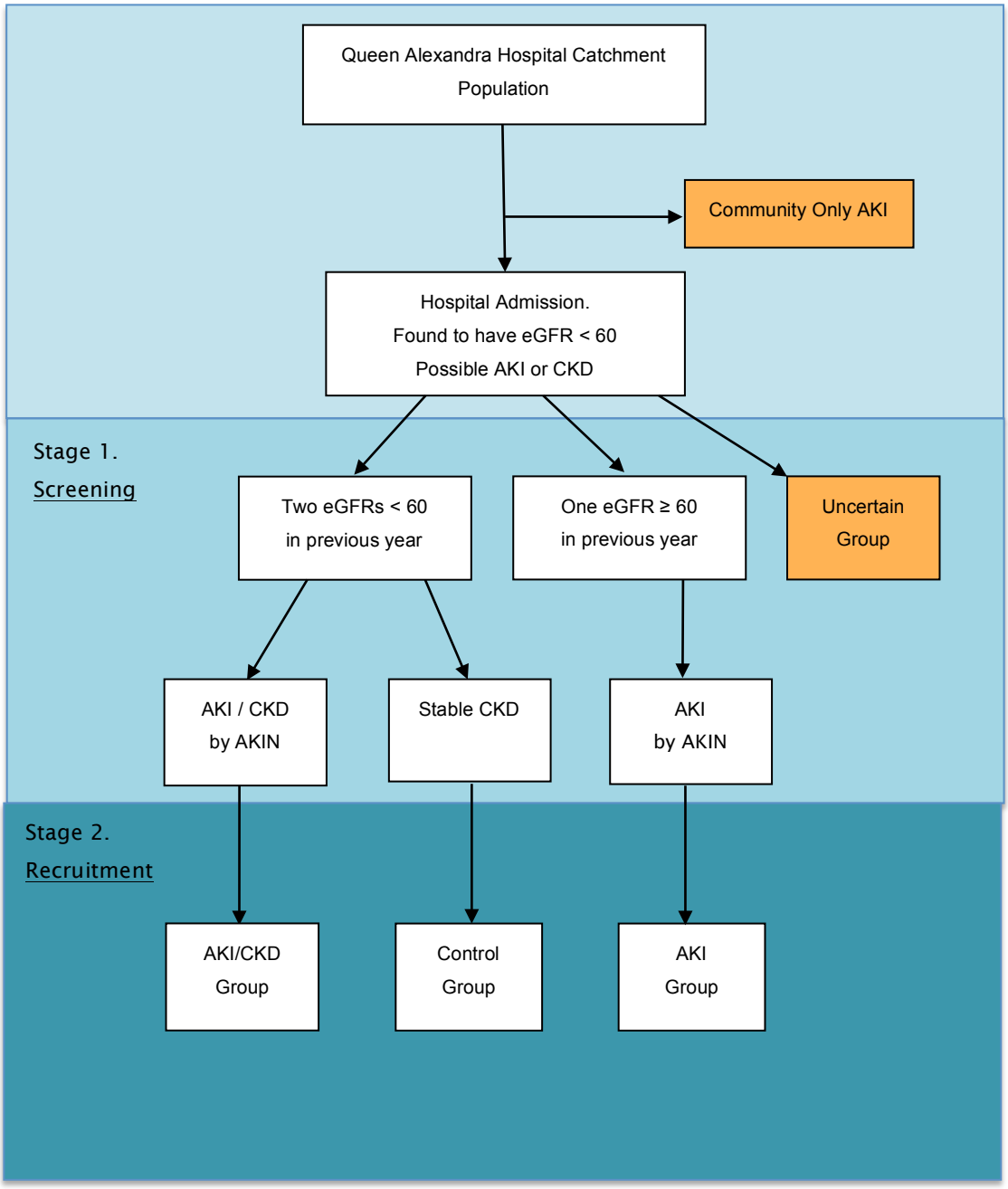
1. Community Only AKI

AKI is known to occur in the community in patients who are not admitted to hospital. This group could not be studied. Therefore the impact of these AKI episodes cannot be assessed. The blood test records for the four years preceding the index admission of all 401 patients recruited for this study were retrospectively reviewed. Just two patients had evidence of a rise in serum creatinine meeting the AKIN definition that occurred in the community without an admission to hospital. This represents < 0.5% of the sample and as these patients represent those most vulnerable to sustaining an AKI this figure serves as a crude indicator that this group may be very small.

2. Uncertain Group not meeting study criteria

Patients in the Uncertain group were found to have an eGFR < 60 during the index hospitalization but did not meet the study criteria for baseline kidney function and so could not be classified into any of the groups eligible for recruitment. These could have fallen into one of the groups outlined in Table 5.1. Firstly, there were those with an eGFR < 60 but no values on record in the previous year. These may have represented an AKI, AKI/CKD or may have been stable CKD. As outlined in Chapter 2 many studies used a back calculation in this scenario.

Figure 5.1. Flowchart illustrating the stages leading to recruitment of the study population.



Secondly, those with an eGFR < 60 with just one previous value < 60 on record. These may have been in the stable CKD group or could have been AKI/CKD. Thirdly, there were some with two or more previous values < 60 but these were differing by more than 5mls/min or were not more than three months apart. These may have included those with a rapid progression of CKD in the absence of AKI or may have been AKI/CKD. Finally, during the screening stage another group was identified that did not meet the 48 hour rise in creatinine in hospital specified by the AKIN definition. In this

group the rise in creatinine tended to be slow and delayed sometimes by several days and may have fluctuated. These may or may not have also had an AKI.

Table 5.1. Outline of potential diagnoses within the Uncertain Group.

a. Hospital eGFR < 60 but no previous values	- possible AKI possible AKI/CKD possible stable CKD
b. Hospital eGFR < 60 with one previous value < 60	- possible stable CKD possible AKI/CKD
c. eGFR < 60 with ≥ 2 previous values < 60 but differing by > 5mls/min or < 3 mts apart	- possible AKI/CKD possible rapid progression of CKD
d. Those meeting baseline criteria but not AKIN timeframe within hospital	- possible AKI

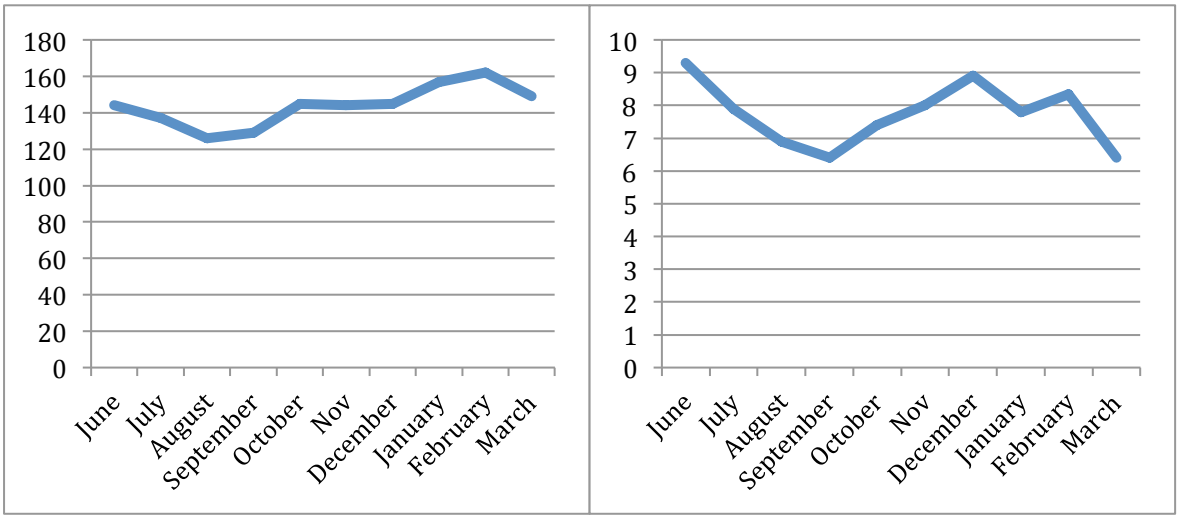
Analysis of the screening data outlined in more detail below revealed that this uncertain group comprised approximately 15% of the eGFR < 60 tests screened. Those found to meet study criteria for AKI in the two groups accounted for just over 5% of the samples screened while the remaining approximately 80% had stable CKD according to study criteria. It must be highlighted that these proportions are estimates.

5.2 Stage 1 – Screening of laboratory eGFR tests

The daily lists of eGFRs < 60 provided by the laboratory were reviewed to ascertain the numbers screened. Eight of the original screening lists were missing – these were not printed at the time of screening because of occasional transient power outages within the hospital which shut down the printer. The average number screened per day for the rest of that month was substituted in their place. In total 44,655 tests with eGFR <60 were screened. This excludes cases where a patient had more than one eGFR on the same day. However, it does not account for the repeats that would have occurred during the patients hospital stay and likewise does not account for repeat admissions during the study period. Chapter 6 contains information on the admission patterns of the recruits in the study during follow up where it was found that over 40% in each group was readmitted at least once. Given the large numbers of tests involved and the fact that the screening of the eGFR lists was performed by hand it was not possible to

monitor this repeat sampling. Only the cases who were already recruited could be excluded if they were readmitted. Repeat sampling and readmissions are likely to contribute significantly to the overall number of tests screened. It therefore must be highlighted that the tests do not represent patient numbers and are likely to considerably overestimate actual patient numbers. The total of 44,655 gives an average of 144 eGFRs < 60 screened per day during the study period. There was some evidence of seasonal variation in numbers during the study and this is illustrated in Figure 5.2.

Figure 5.2. On the left is shown the seasonal variation of the numbers identified with eGFR < 60 on a daily basis per month. On the right is the mean number of patients eligible for recruitment on a daily basis per month. Both graphs demonstrate the increase in available numbers and hence AKI during the winter months.



5.2.1 Uncertain Group estimation

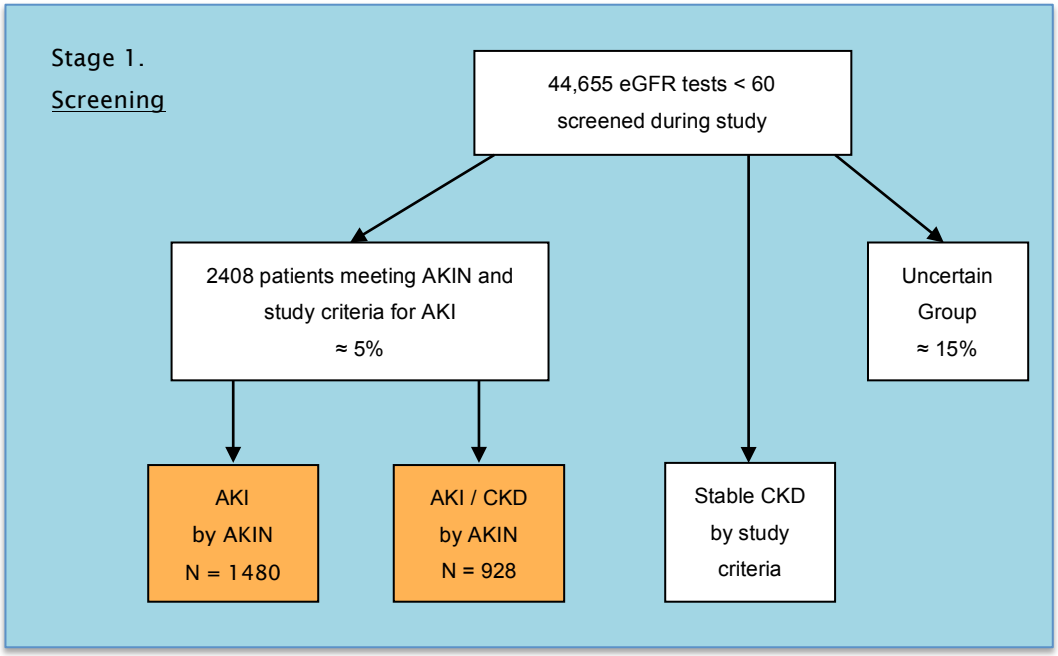
During the screening process the tests falling into the four uncertain groups described in Table 5.1 were highlighted. To estimate the numbers in this group three random days were selected from each full month of the recruitment period from June 2010 through to March 2011. The random selection was undertaken using a standard table of random numbers and all months of the recruitment period were sampled to account for the seasonal variation demonstrated above. In the thirty randomly selected days there was a total of 4506 tests with eGFRs < 60 screened and of these 592 tests did not meet study criteria because of a lack of previous results while 88 tests were in the delayed category. This was 13% and 1.9% of the total respectively. Therefore a crude estimate of 15% of the tests screened fell into the uncertain group. As mentioned earlier, the 44655 tests screened did not exclude cases where a patient had more than one test during their hospital stay and so the actual proportion of patients in this

group cannot be reasonably estimated but it can be inferred from the 15% test estimate that this group was not small.

5.2.2 Eligible patients following initial screening

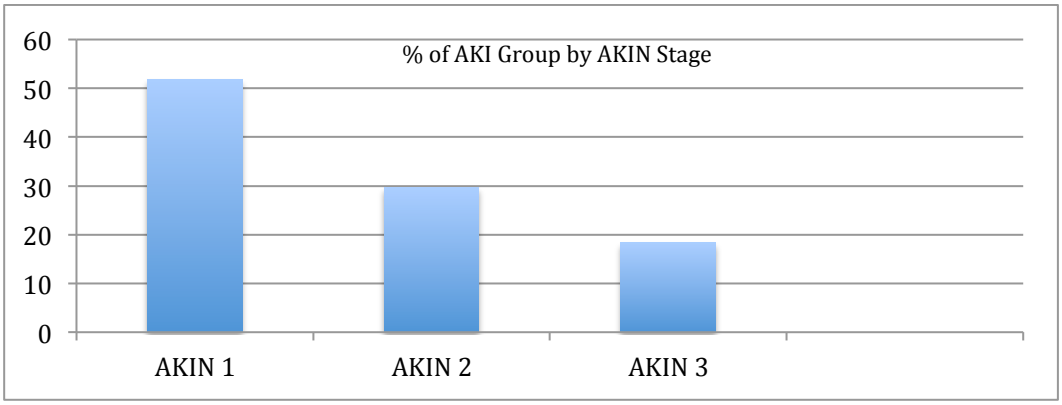
A total of 2408 patients met the study criteria for either the AKI group or the AKI/CKD group after screening the 44655 eGFR tests. 61.4% (n=1480) of these were in the AKI group and 38.5% (n=928) were in the AKI/CKD group. This is illustrated in the flow chart in Figure 5.3.

Figure 5.3. Flowchart highlighting the 2408 patients meeting study criteria for the two AKI groups during screening.



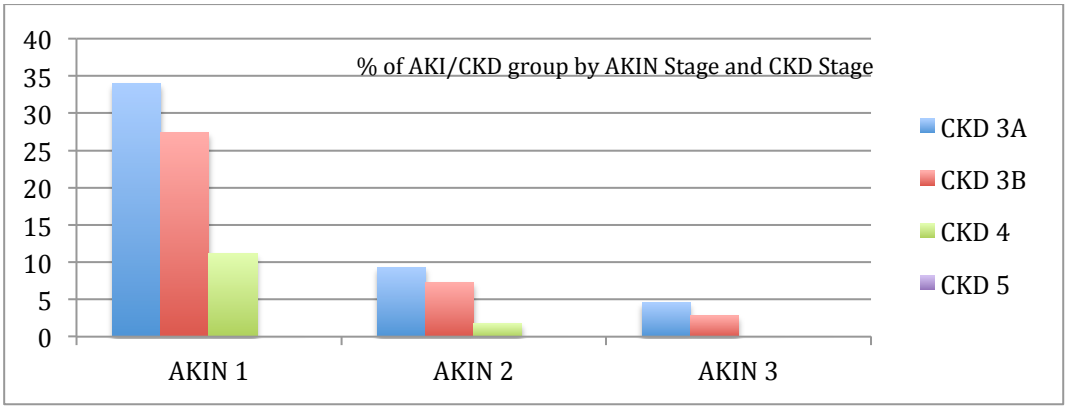
The distribution of the eligible patients according to AKIN stage in each of the groups is illustrated in Figure 5.4 and Figure 5.5. In the case of the AKI/CKD group the distribution is divided according to CKD stage. This clearly illustrates that over 60% in both groups were in the milder AKIN Stage 1 without sampling of this group.

Figure 5.4. Distribution of the screened AKI group by % AKIN stage.



	AKI Group (N=1480)
AKIN Stage	No. %
1	769 (51.9)
2	439 (29.6)
3	272 (18.4)

Figure 5.5. Distribution of the screened AKI/CKD group by % AKIN Stage.



	AKI/CKD Group	(N=928)	
CKD Stage	AKIN 1 (No. %)	AKIN 2 (No.%)	AKIN 3 (No.%)
3A	316 (34)	87 (9.3)	43 (4.6)
3B	255 (27.4)	68 (7.3)	26 (2.8)
4	104 (11.2)	17 (1.8)	2 (<.01)
5	10 (.01)	0	0
Total	685 (73.8)	172 (18.5)	71 (7.7)

To explore the distribution of the CKD stages by AKIN stage it was necessary to combine CKD Stage 4 and CKD Stage 5 because of the smaller numbers. This is illustrated in Table 5.2. The Chi-Squared test for trend was used to compare the CKD stages. A significant difference was found in the distribution of the AKIN stages according to CKD stage (p=0.005). A significantly larger portion of CKD stage 4/5 was in the milder AKIN stage 1.

Table 5.2. Distribution of the screened AKI/CKD group with AKIN stage expressed as N(%) of each CKD Stage. CKD Stages 4 and 5 are merged.

	AKI/CKD Group	(N=928)		
CKD Stage	AKIN 1	AKIN 2	AKIN 3	Total
3A N(%)	316 (70.8))	87 (19.5)	43 (9.6)	446
3B N(%)	255 (73)	68 (19.4)	26 (7.4)	349
4/5 N(%)	114 (85.7)	17 (12.7)	2 (0.02)	133
Total	685	172	71	928

5.3 Stage 2 – Recruitment of eligible patients

The flowchart in Figure 5.6 provides a summary of the recruitment stage of the study.

5.3.1 Random Sampling of AKIN Stages 1

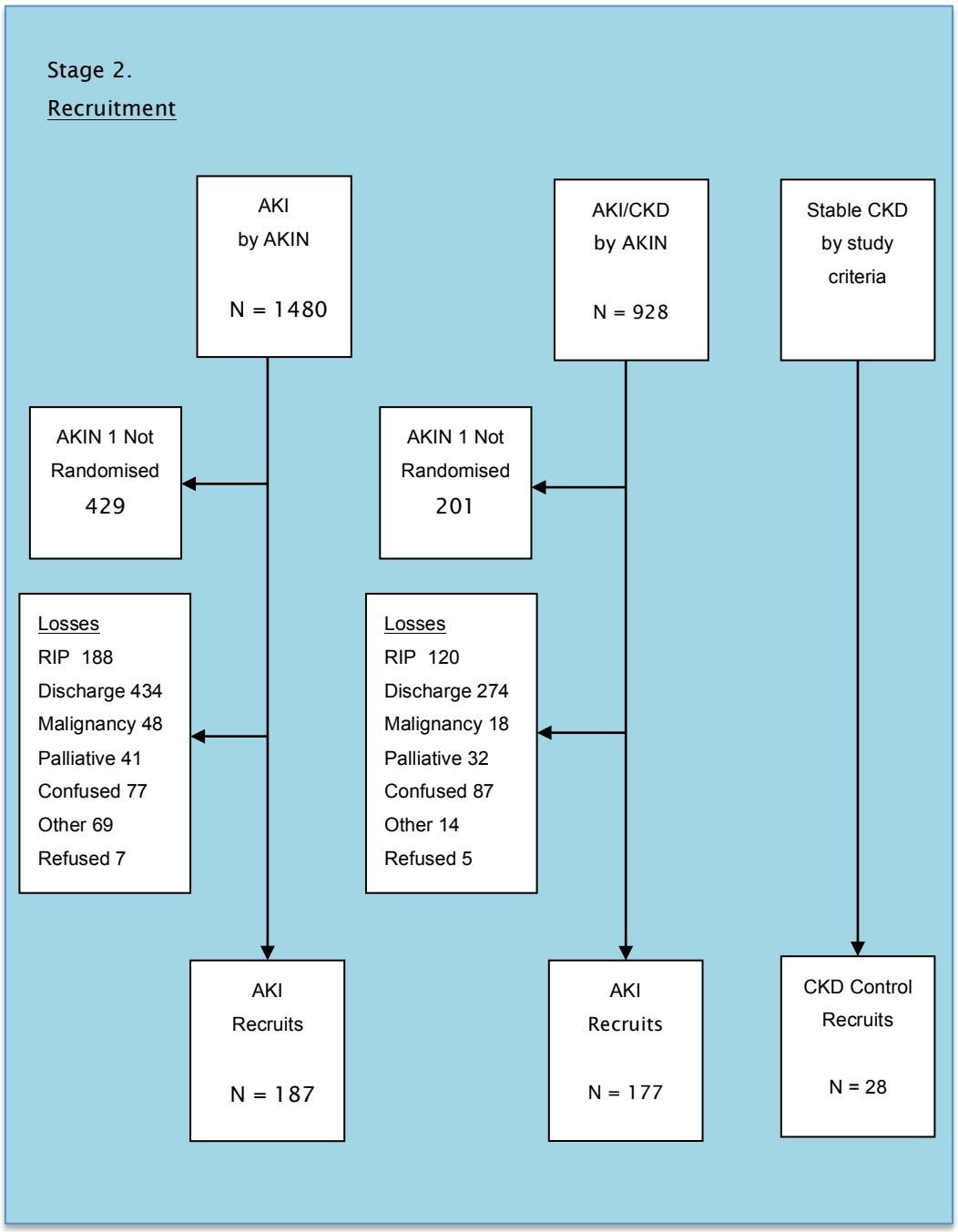
It was necessary to randomly sample AKIN Stage 1 in this study and the rationale for this can is outlined here. Figure 5.4 and Figure 5.5 illustrate how the majority of eligible patients in both groups were in the milder AKIN stage 1. As there was scope to recruit at most between 15 and 20 patients per week by a single investigator there was a danger that the recruited cohort would be overwhelmed by AKIN stage 1. This in theory would be the group least likely to show the impact on CKD incidence and progression that was being studied. Therefore random sampling of AKIN Stage 1 in the AKI group and the AKIN 1/CKD stage 3A cases in the AKI/CKD group took place. This resulted in the deliberate over-sampling of AKIN stages 2 and 3.

5.3.2 Problems with random sampling of AKIN Stage 1

A formal review of the recruitment process and numbers obtained was undertaken in December 2010. A key finding was that the AKIN stage 1 numbers were far lower than expected. For example, in the AKI group 538 AKIN stage 1 cases had been found to be

eligible and 102 of these were randomised for potential recruitment. Just 11 patients from this group were actually recruited. The reason for this was found to be the high discharge rate in this group prior to them being reviewed. 59 (58%) of those randomised had been discharged by the time they were approached for review, some within 24 hours. This may be explained by the fact that these patients were less sick and had milder kidney injuries but also the milder injury may not have been recognised by the clinical team. However, it was also found that 18 (17.6%) of the randomised cases had died in hospital before they could be recruited. As the natural losses in this group were so high it was decided to abandon the randomisation process for the remainder of the study. Random sampling was therefore carried out for the first seven months of the recruitment period from the 25th May 2010 to 24th December 2010 and abandoned for the remaining three months.

Figure 5 6 Flowchart illustrating how the recruited groups were derived from the eligible patients.



5.3.3 Recruitment losses

Figure 5.6 shows that there were considerable losses from the eligible group with 2044 lost during the recruitment period. Table 5.3 summarizes the reasons for these losses.

Table 5.3 Losses from the eligible groups during recruitment.

Losses from eligible group	N = 2044	No. (%)
Death	308 (15.1)	
Discharged	708 (34.6)	
Declined to take part	12 (.006)	
Confused/dementia	164 (8.0)	
Advanced malignancy	66 (3.2)	
Palliative	73 (3.6)	
Other	83 (4.1)	
AKIN 1 Not randomised due to sampling	630 (30.8)	

As expected, a large proportion was not randomised from the AKIN 1 group during the first seven months of recruitment. Another large proportion of patients (34.6%) was discharged prior to being able to review them. This includes 228 (32.2% of total discharged) that were lost while the investigator was on compassionate leave. As mentioned earlier, there is a concern that some cases were discharged without the clinical team recognising the importance of the AKI. On several occasions the investigator had to intervene and inform the clinical team that they had discharged patients with an evolving AKI that required them to call the patients and get them to return. One of these patients had a severe AKI requiring a formal renal review.
A substantial portion of the eligible group had died by the time the investigator approached them. The 'Other' group included a wide variety of reasons for being unsuitable for recruitment including several patients under mental health section, overseas visitors and even one prisoner awaiting deportation. Very few patients in the population (0.006%) declined to participate.

5.3.4 The Sampling Fraction

An effort was made to establish the sampling fraction of each AKIN Stage subgroup recruited. This is relevant to any conclusions that can be drawn from comparisons within and between groups. It also illustrates the effect of the random sampling and losses described above. It proved impossible to derive this with 100% accuracy and so the proportion is expressed as an adjusted estimate. The reason that an estimate has to be used is because of a small shift that occurred between groups following recruitment. This is a feature of prospective recruitment whereby a patient found to be eligible for a particular subgroup on a given day continued to evolve after recruitment and progressed to a higher AKIN stage. The proportions expressed are therefore only estimates as there would have been a similar small shift within the losses from each

eligible group that cannot be quantified. The proportions sampled from those eligible for each AKIN stage are outlined in Table 5.4 and Table 5.5 for the AKI and AKI/CKD groups respectively.

In the AKI Group it can be seen that there were 769 patients found to be eligible from the screening process. The total recruited was 45 and when added to the losses including those not randomly sampled the total is 767. The difference is accounted for by two patients that were screened as AKIN stage 1 and recruited but who continued to evolve immediately after recruitment and progressed to AKIN stage 3. The proportion sampled is therefore calculated by taking the 45 recruits for this stage as a proportion of 767 instead of 769 and gives 5.9%. In a similar manner ten patients shifted from AKIN stage 2 to stage 3 and so the sampled proportion of 16.3% is calculated from the adjusted total. For AKIN stage 3 the total eligible was increased by the 12 that shifted from lower groups when doing the calculation. Table 5.4 illustrates that the proportion of each AKIN stage in the AKI group differs from how it is distributed in the population studied. Just 5.9% of eligible AKIN stage 1 patients were recruited as opposed to 25.4% of those eligible for AKIN stage 3. AKIN stage 1 is therefore under represented in the final cohort and this needs to be accounted for when discussing the generalizability of the results obtained in the study.

In the AKI/CKD group the same phenomenon occurred with 14 patients shifting from AKIN stage 1 to higher stages so adjustments were necessary as described above. 14.3% of those eligible for AKIN stage 1 were recruited, 27.7% of AKIN stage 2 and 40% of AKIN stage 3. Like the AKI group this highlights the difference in the proportions of AKIN stage in the final cohort compared to the population studied.

Table 5.4 The adjusted sampling estimate for each AKIN Stage of the AKI group accounting for losses and adjusted for the stage shift following recruitment.

	AKIN Stage 1	AKIN Stage 2	AKIN Stage 3
	N(%)	N(%)	N(%)
No. Eligible	769	439	272
Death	38(5)	85(19)	65(24)
Discharge	182(24)	171(39)	81(30)
Malignancy	14(2)	17(4)	17(6)
Palliative	10(1)	18(4)	13(5)
Dementia	21(3)	38(9)	18(7)
Refused	0	2	5
Others	28(4)	28(6)	13(5)
Not Randomised	429		
Recruited	45	70	72
Total	767	429	284
Number shifting to higher stage after recruitment	2	10	
Number added to group after shift from lower stage			12
Adjusted Sampling Estimate	5.9%	16.3%	25.4%

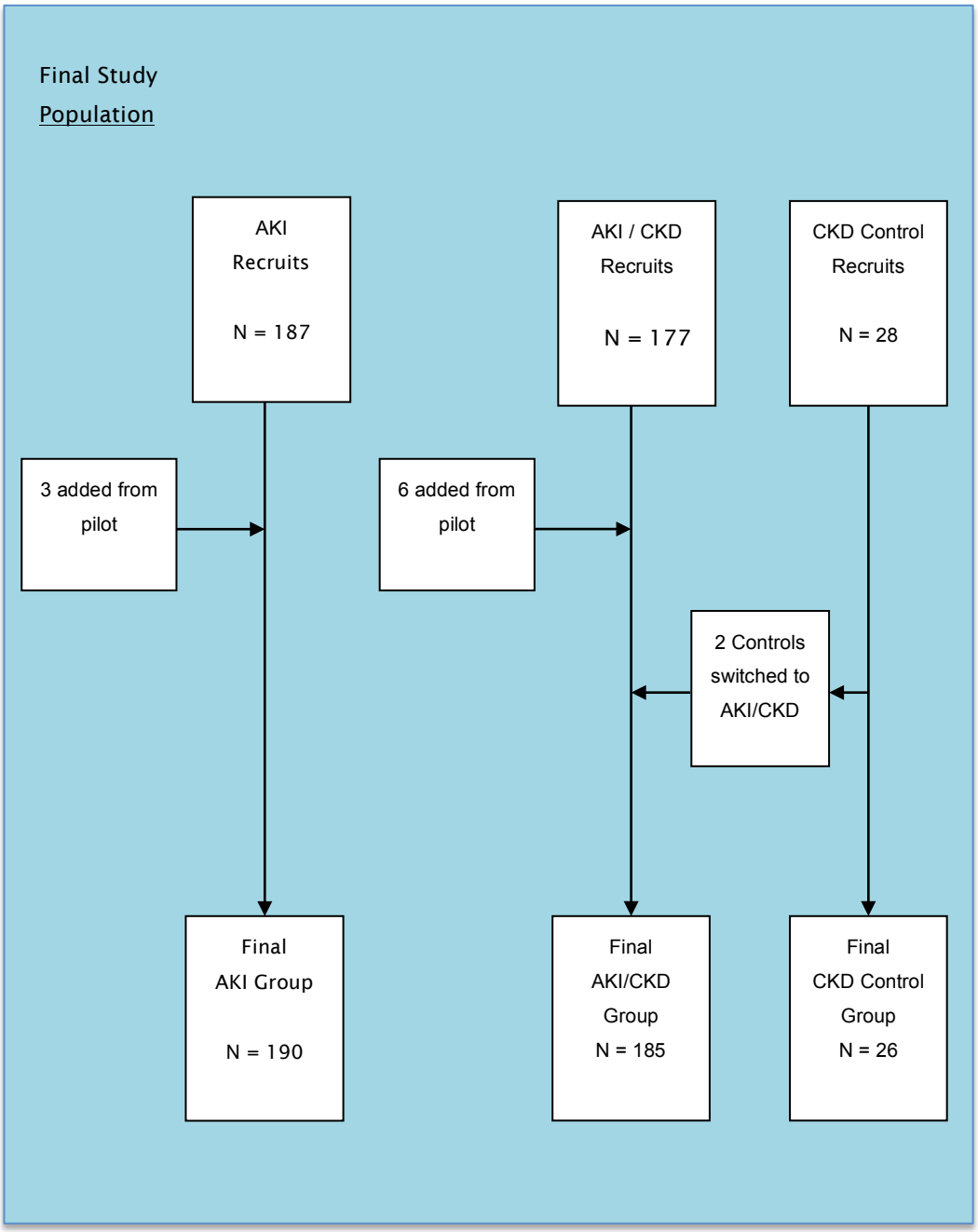
Table 5.5 The adjusted sampling estimate for each AKIN Stage of the AKI /CKD group accounting for losses and adjusted for the stage shift following recruitment.

	AKIN Stage 1	AKIN Stage 2	AKIN Stage 3
	N(%)	N(%)	N(%)
No. Eligible	685	172	71
Death	64(9)	41(24)	15(21)
Discharge	199(29)	56(33)	19(27)
Malignancy	15(2)	0	3(4)
Palliative	24(4)	4(2)	4(6)
Dementia	60(9)	21(12)	6(8)
Refused	3	1	1
Others	9	5	0
Not Randomised	201		
Recruited	96	49	32
Total	671	177	80
Number shifting to higher stage after recruitment	14		
Number added to group after shift from lower stage		5	9
Adjusted Sampling Estimate	14.3%	27.7%	40%

5.4 The Final Study Population

The final AKI study population consisted of 375 patients together with 26 CKD controls taking the total to 401. The assembly of this population is summarised in Figure 5.7. The original pilot in November 2009 recruited 9 patients – 6 for the AKI/CKD group and 3 for the AKI group. These were added to the final cohort. In addition 2 patients that were originally recruited to the CKD control group were later switched to the AKI/CKD group as they were found to have sustained an AKI during their admission after recruitment.

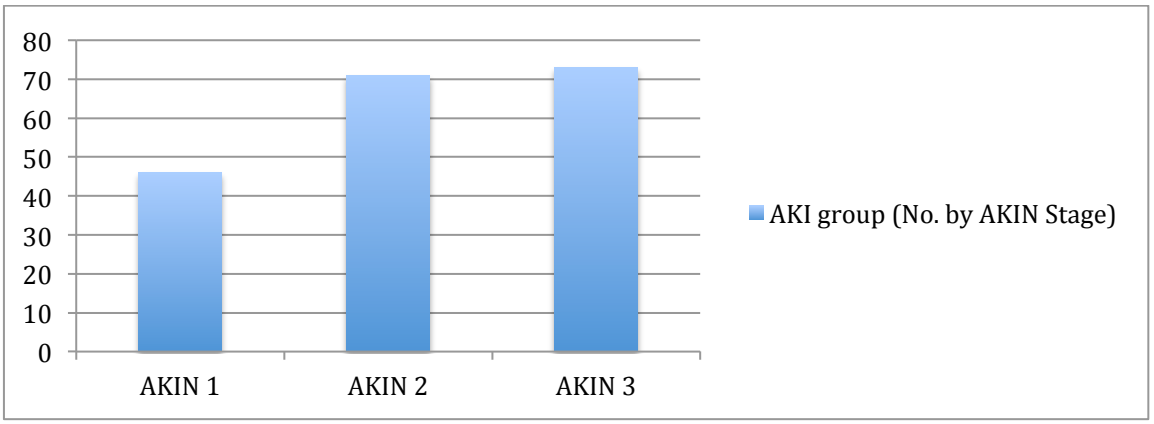
Figure 5.7 Flowchart illustrating the assembly of the final study population.

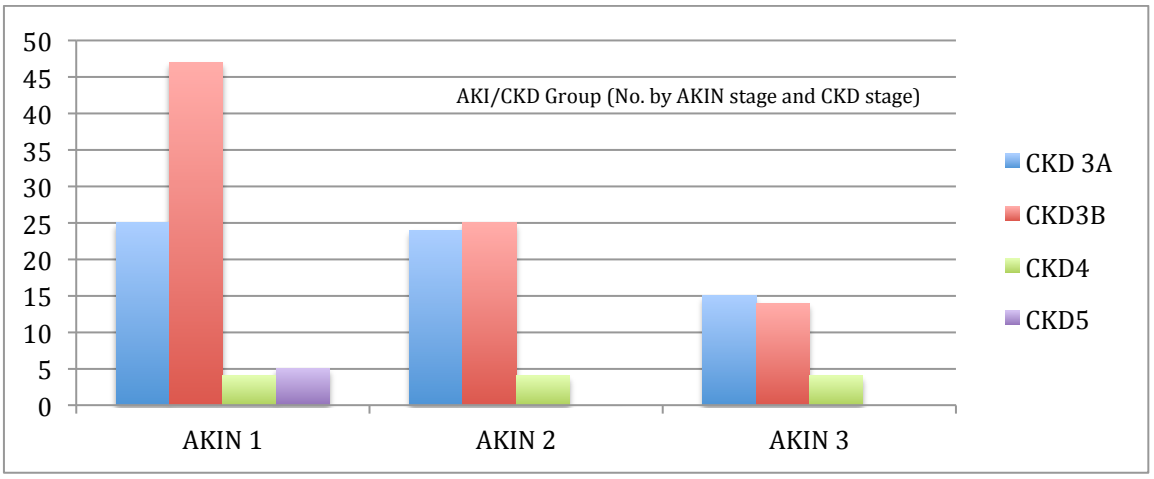


The distribution of the final AKI cohort of 375 patients by AKIN stage is illustrated in Figure 5.8. The distribution of the sample is notable for the deliberate under sampling of AKIN stage 1which can be contrasted with the actual eligible numbers illustrated in Figures 5.4 and 5.5 earlier in the chapter. In Figure 5.8 the AKI/CKD group is also distributed by CKD stage. It is notable that in the three AKIN stages of the AKI/CKD group there were very few of the higher CKD stages 4 and 5. For this reason, during analysis of the data the CKD stages will be merged for each AKIN subgroup.

Figure 5.8 Distribution of the Final AKI Cohort by AKIN stage. The AKI/CKD group is also distributed by CKD stage.

		AKI Group N = 190	AKI/CKD Group N=185
AKIN Stage No, %	1	46 (24.2)	99 (53.51)
	2	71 (37.4)	53 (28.64)
	3	73 (38.4)	33 (17.83)





Chapter 6: Baseline Characteristics, AKI and Outcomes

6.1 Baseline characteristics of Study Population

6.1.1 The AKI and AKI/CKD Groups

Table 6.1 outlines the baseline characteristics of the final AKI and AKI/CKD cohorts. As the AKIN stage 1 subgroup was deliberately under sampled in both groups the baseline characteristics of the AKIN stages within both groups were compared to assess if comparison of the overall groups is valid. These data are presented in Table 6.2 and Table 6.3.

Table 6.1 Comparison of the baseline characteristics of the AKI and AKI/CKD groups.

		AKI Group N = 190	AKI/CKD Group N=185	P
Age,ys, Median (IQR)		**68 (59-75)**	**75 (72-84)**	**<0.001**
Gender, Male, %		58.4	47.6	0.04
Ethnicity, Caucasian %		98.9	100	
Social History, N(%)	Lives Alone	62 (32.6)	82 (44.3)	0.02
Mean, SD	Katz Index	5.86 (0.65)	5.66 (0.88)	0.02
Comorbidities No., (%) unless stated				
	Hypertension	**123 (64.7)**	**164 (88.6)**	**<0.001**
	No. Antihypertensives Mean, SD	**1.13 (1.08)**	**1.62 (0.99)**	**<0.001**
	Coronary Heart Disease	39 (20.5)	56 (30.3)	0.03
	Heart Failure	**10 (5.3)**	**46 (24.9)**	**<0.001**
	Cerebrovasc. Dis.	**17 (8.9)**	**39 (21.1)**	**0.001**
	Peripheral Vascular Disease	15 (7.9)	28 (15.1)	0.03
	Dementia	0	4 (2.2)	0.06
	Chronic Lung Dis.	25 (13.2)	40 (21.6)	0.03
	Peptic Ulcer Dis.	0	0	
	Rheumatic. Dis	11 (5.8)	13 (7)	0.62
	Mild Liver Disease	0	2 (1.1)	0.24

		AKI Group N = 190	AKI/CKD Group N=185	P
	Diabetes without Complications	41 (21.6)	29 (15.7)	0.14
	Diabetes with Complications	**15 (7.9)**	**53 (28.6)**	**0.001**
	Diabetes Overall	**56 (29.5)**	**82 (44.3)**	**0.003**
	Hemiplegia	1 (0.5)	0	
	Neoplasia	13 (6.8)	18 (9.7)	0.31
	Severe Liver Dis.	5 (2.6)	0	0.06
	Leukaemia	0	1 (0.5)	
	Metastases	0	0	
	Lypmhoma	0	4 (2.2)	0.06
	AIDS	0	0	
Comorbidity Score	Charlson Score Mean, SD	**1.24 (1.25)**	**4.19 (1.48)**	**<0.001**
Other Risk Factors	Smoking History (Current and past)	99 (52.1)	107 (57.8)	0.27
	BMI Mean, SD	28.16 (7.76) (n=153)	29.08 (6.71) (n=145)	0.27
Medications prior to AKI N(%)				
On Ace Inhibitor		76 (40)	92 (49.7)	0.06
On ARB		**24 (12.6)**	**48 (25.9)**	**0.001**
On RAS blocker		**99 (52.1)**	**137 (74.1)**	**<0.001**
Indication for RAS Blockade N(%)				
	Previous M.I.	**27 (27.2)**	**46 (33.5)**	**<0.001**
	Heart Failure	**7 (7.1)**	**31 (22.6)**	**<0.001**
	Diabetes with microalbuminuria	**14 (14.1)**	**32 (23.4)**	**<0.001**
	Hypertension	**95 (96)**	**132 (96.4)**	**<0.001**
	More than 1 indication	**37 (37.4)**	**81 (59.1)**	**0.001**
Aspirin		**59 (31.1)**	**86 (46.5)**	**0.002**
NSAID		**31 (16.3)**	**13 (7)**	**0.005**
Furosemide		**32 (16.8)**	**98 (53)**	**<0.001**
Bendroflumethiaz.		22 (11.6)	22 (11.9)	0.93
Spironolactone		**6 (3.2)**	**29 (15.7)**	**<0.001**
Trimethoprim		5 (2.6)	10 (5.4)	0.17
Statin		**75 (39.5)**	**105 (56.8)**	**0.001**
Metformin		32 (16.8)	34 (18.4)	0.69
Beta Blocker		**41 (21.6)**	**76 (41.1)**	**<0.001**
Calcium Ch.		38 (20)	45 (24.3)	0.31
Alpha Blocker		7 (3.7)	18 (19.7)	0.02
Allopurinol		12 (6.3)	19 (10.3)	0.16
PPI		57 (30)	68 (36.8)	0.17

There are significant differences between the AKI and AKI/CKD groups. The AKI/CKD group is older and more likely to be living alone. The differences between the scores in the Katz Index indicate a greater degree of dependency in this group. The AKI/CKD group also carries a much greater burden of comorbid illness which is reflected in the higher Charlson Score. When the Charlson Index is divided into separate comorbidities it demonstrates more cardiac failure, cerebrovascular disease and diabetes with complications within the group. There is also more history of hypertension. Nevertheless, the AKI Group itself is also characterized by a burden of comorbid disease with a mean Charlson score of 1.24.

As expected with the quite marked difference in comorbidities, the baseline medications in the groups are also significantly different. The AKI/CKD group is characterised by a greater use of cardiovascular medications including aspirin, furosemide, spironolactone, statins, Beta-blockers and blockers of the renin-angiotensin system. The only medications which more common in the AKI group are NSAIDS. This may be because those with known CKD are routinely advised to avoid NSAIDS in clinical practice.

It is clear from the comparisons made in Tables 6.2 and 6.3 that there was no significant difference between the baseline characteristics of the three AKIN stages within either group. This makes it unlikely that the under sampling of AKIN stage 1 had an effect on the baseline characteristics of the overall groups which would have questioned the validity of the between group analysis and its generalisability.

Table 6.2 Baseline Characteristics and comparison of the AKIN stages within the AKI Group.

	AKI Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 46	N = 71	N = 73	
Age,ys,				
Median (IQR)	69 (60–74)	69 (62-80)	65 (57-75)	0.16
Gender, Male,N%	33 (71.7)	39 (54.9)	39 (53.4)	0.11
Social History, N(%)				
Lives Alone	10 (21.7)	28 (39.4)	24 (32.9)	0.14
Comorbidities				
No., (%) unless stated				
Hypertension	28 (60.9)	50 (70..4)	45 (61.6)	0.45
No. Antihypertensives	0.96 (0.96)	1.18 (1.09)	0.96 (0.96)	0.21
Mean, SD				

	AKI Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 46	N = 71	N = 73	
Coronary Disease	9 (19.6)	13(18.3)	17 (23.3)	0.75
Heart Failure	**0**	**8 (11.3)**	**2 (2.7)**	**0.01**
Cerebrovas. Dis.	5 (10.9)	8 (11.3)	4 (5.5)	0.42
Peripheral Vascular Disease	6 (13)	5 (7)	4 (5.5)	0.31
Dementia	0	0	0	
Chronic Lung Dis.	9 (19.6)	8 (11.3)	8 (11)	0.34
Peptic Ulcer Dis.	0	0	0	
Rheumatic. Dis	0	5 (7)	6 (8.2)	0.15
Mild Liver Disease	0	0	0	
Diabetes without Complications	10 (21.7)	17 (23.9)	14 (19.2)	0.79
Diabetes with Complications	4 (8.7)	6 (8.5)	5 (6.8)	0.91
Diabetes Overall	14 (30.4)	23 (32.4)	19 (26)	0.69
Hemiplegia	0	1 (1.4)	0	
Neoplasia	3 (6.5)	4 (5.6)	6 (8.2)	0.82
Severe Liver Dis.	0	0	5 (6.8)	
Leukaemia	0	0	0	
Metastases	0	0	0	
Lypmhoma	0	0	0	
AIDS	0	0	0	
Charlson Score Mean, SD	1.26 (1.27)	1.21 (1.2)	1.26 (1.27)	0.98
Smoking History (Current and past)	26 (56.5)	35 (49.3)	38 (52.1)	0.75
BMI				0.82
Mean, SD	28.13 (8.92)	27.71 (7.03)	28.13 (8.92)	
Medications prior to AKI N(%)				
On Ace In. N(%)	17 (37)	29 (40.8)	30 (41.1)	
On ARB N(%)	9 (19.6)	8 (11.3)	7 (9.6)	
On RAS blocker N(%)	25 (54.3)	37 (52.1)	37 (50.7)	0.93
Aspirin	15 (32.6)	20 (28.2)	24 (32.9)	0.80
NSAID	10 (21.7)	10 (14.1)	11 (15.1)	0.51
Furosemide	5 (10.9)	14 (19.7)	13 (17.8)	0.44
BZF	9 (19.6)	9 (12.7)	4 (5.5)	0.06
Spironolactone	0	3 (4.2)	3 (4.1)	0.37
Trimethoprim	1 (2.2)	3 (4.2)	1 (1.4)	0.55
Statin	21 (45.7)	28 (39.4)	26 (35.6)	0.55
Metformin	8 (17.4)	28 (39.4)	26 (35.6)	0.62

	AKI Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 46	N = 71	N = 73	
Beta Blocker	10 (21.7)	19 (26.8)	12 (16.4)	0.32
Calcium Ch.	10 (21.7)	15 (21.1)	13 (17.8)	0.83
Alpha Blocker	1 (2.2)	3 (4.2)	3 (4.1)	0.82
Allopurinol	4 (8.7)	1 (1.4)	7 (9.6)	0.09
PPI	17 (37)	19 (26.8)	21 (28.8)	0.48

Table 6.3 Baseline characteristics and comparison of the AKIN stages within the AKI/CKD group.

	AKI/CKD Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 99	N = 53	N = 33	
Age,ys, Median (IQR)	79 (71-84)	77 (72-83)	80 (75-85)	0.47
Gender,Male,N%	50 (50.5)	23 (43.4)	15 (45.5)	0.68
Social History, N(%)				
Lives Alone	46 (46.5)	23 (43.4)	13 (39.4)	0.77
Comorbidities No., (%) unless stated				
Hypertension	88 (88.9)	46 (86.8)	30 (90.9)	0.84
No. Antihypertensives Mean, SD	1.61 (1.08)	1.64 (0.9)	1.64 (0.93)	0.68
Coronary Disease	27 (27.3)	20 (37.7)	9 (27.3)	0.38
Heart Failure	21 (21.2)	17 (32.1)	8 (24.2)	0.34
Cerebrovas. Dis.	22 (22.2)	8 (15.1)	9 (27.3)	0.37
Peripheral Vascular Disease	12 (12.1)	10 (18.9)	6 (18.2)	0.47
Dementia	1 (1)	2 (3.8)	1 (3)	0.49
Chronic Lung Dis.	22 (22.2)	9 (17)	9 (27.3)	0.52
Peptic Ulcer Dis.	0	0	0	
Rheumatic. Dis	4 (4)	7 (13.2)	2 (6.1)	0.11
Mild Liver Disease	1 (1)	0	1 (3)	0.42
Diabetes without Complications	13 (13.1)	10 (18.9)	6 (18.2)	0.59
Diabetes with Complications	29 (29.3)	15 (28.3)	9 (27.3)	0.97
Diabetes Overall	42 (42.4)	25 (47.2)	15 (45.5)	0.85
Hemiplegia	0	0	0	

	AKI/CKD Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 99	N = 53	N = 33	
Neoplasia	7 (7.1)	5 (9.4)	6 (18.2)	0.18
Severe Liver Dis.	0	0	0	
Leukaemia	0	0	1 (3)	
Metastases	0	0	0	
Lypmhoma	2 (2)	1 (1.9)	1 (3)	0.93
AIDS	0	0	0	
Charlson Score Mean, SD	4 (1.5)	4.34 (1.41)	4.55 (1.44)	0.27
Smoking History (Current and past)	51 (51.5)	36 (67.9)	20 (60.6)	0.14
BMI Mean, SD	28.57 (6.46)	29.58 (7.17)	30.11 (6.91)	0.93
Medications prior to AKI N(%)				
On Ace In. N(%)	53 (53.5)	26 (49.1)	13 (39.4)	
On ARB N(%)	19 (19.2)	17 (32.1)	12 (36.4)	
On RAS blocker N(%)	70 (70.7)	42 (79.2)	25 (75.8)	0.51
Aspirin	44 (44.4)	24 (45.3)	18 (54.5)	0.59
NSAID	7 (7.1)	3 (5.7)	3 (9.1)	0.83
Furosemide	50 (50.5)	27 (50.9)	21 (63.6)	0.39
BZF	11 (11.1)	8 (15.8)	3 (9.1)	0.66
Spironolactone	15 (15.2)	9 (17)	5 (15.2)	0.95
Trimethoprim	6 (6.1)	2 (3.8)	2 (6.1)	0.82
Statin	50 (50.5)	33 (62.3)	22 (66.7)	0.17
Metformin	14 (14.1)	15 (28.3)	5 (15.2)	0.09
Beta Blocker	37 (37.4)	23 (43.4)	16 (48.5)	0.49
Calcium Ch.	28 (28.3)	6 (11.3)	11 (33.3)	0.03
Alpha Blocker	8 (8.1)	5 (9.4)	5 (15.2)	0.49
Allopurinol	13 (13.1)	4 (7.5)	2 (6.1)	0.38
PPI	37 (37.4)	17 (32.1)	14 (42.4)	0.62

6.1.2 AKI/CKD group and the CKD Controls

The characteristics of the CKD control group alongside the AKI/CKD Group are outlined in Table 6.4. The groups are similar in terms of age and sex but there is a trend toward more diabetes overall and a greater burden of comorbid illness in the AKI/CKD group (p=0.011). The only significant differences between these groups is a greater tendency to use furosemide and blockers of the renin-angiotensin system in

the AKI/CKD group. These findings must be interpreted with caution in the presence of such low numbers in the control group.

Table 6.4 Baseline Characteristics of the AKI/CKD Group compared to the CKD Control Group.

		AKI/CKD Group N=185	CKD Control Group N=26	P
Age,ys, Median (IQR)		75 (72-84)	78 (74-85)	0.98
Gender, Male, %		47.6	38.5	0.41
Social History, N(%)	Lives Alone	82 (44.3)	13 (52)	0.47
	Katz Index	5.66	5.85 (0.78)	0.32
Comorbidities No., (%) unless stated				
	Hypertension	164 (88.6)	21 (80.8)	0.33
	No. Antihypertensives Mean, SD	1.62 (0.99)	1.35	0.19
	Coronary Heart Disease	56 (30.3)	9 (34.6)	0.65
	Heart Failure	46 (24.9)	3 (11.5)	0.21
	Cerebrovas. Dis.	39 (21.1)	3 (11.5)	0.31
	Peripheral Vascular Disease	28 (15.1)	1 (3.8)	0.22
	Dementia	4 (2.2)	1 (3.8)	0.49
	Chronic Lung Dis.	40 (21.6)	3 (11.5)	0.30
	Peptic Ulcer Dis.	0	0	
	Rheumatic. Dis	13 (7)	3 (11.5)	0.43
	Mild Liver Disease	2 (1.1)	0	
	Diabetes without Complications	29 (15.7)	2 (7.7)	0.38
	Diabetes with Complications	53 (28.6)	3 (11.5)	0.09
	Diabetes Overall	82 (44.3)	5 (19.2)	0.02
	Hemiplegia	0	0	
	Neoplasia	18 (19.7)	3 (11.5)	0.73
	Severe Liver Dis.	0	0	
	Leukaemia	1 (0.5)	0	
	Metastases	0	0	
	Lymphoma	4 (2.2)	0	
	AIDS	0	0	
Comorbidity Score	Charlson Score Mean, SD	**4.19 (1.48)**	**3.42 (1.13)**	**0.01**
Other Risk Factors	Smoking History (Current and past)	107 (57.8)	17 (65.4)	0.46

		AKI/CKD Group N=185	CKD Control Group N=26	P
	BMI Mean, SD	29.08 (6.71) (n=145)	29.58 (7.2) (n=18)	0.77
Medications prior to AKI N(%)				
On Ace In. N(%)		92 (49.7)	7 (26.9)	0.03
On ARB N(%)		48 (25.9)	5 (19.2)	0.46
On RAS blocker N(%)		**137 (74.1)**	**12 (46.2)**	**0.003**
Indication for RAS Blockade N(%)				
	Previous M.I.	46 (33.5)	4 (15.4)	
	Heart Failure	31 (22.6)	1 (3.8)	
	Diabetes with microalbuminuria	32 (23.4)	2 (7.7)	
	Hypertension	132 (96.4)	10 (38.5)	
	More than 1 indication	81 (59.1)	6 (23.1)	
Aspirin		86 (46.5)	10(38.5)	0.44
NSAID		13 (7)	2 (7.7)	1
Furosemide		**98 (53)**	**6 (23)**	**0.004**
BZF		22 (11.9)	5 (19.2)	0.29
Spironolactone		29 (15.7)	2 (7.7)	0.38
Trimethoprim		10 (5.4)	0	0.62
Statin		105 (56.8)	14 (53.8)	0.78
Metformin		34 (18.4)	2 (7.7)	0.27
Beta Blocker		41.1 (76)	11 (42.3)	1
Calcium Ch.		45 (24.3)	5 (19.2)	0.57
Alpha Blocker		18 (19.7)	1 (3.8)	0.48
Allopurinol		19 (10.3)	0	0.14
PPI		68 (36.8)	12(46.2)	0.36

6.2 AKI Details

6.2.1 AKI Details – AKI and AKI/CKD Groups

Table 6.5 compares additional clinical details relating to baseline kidney function and the AKI episode recorded at the time of recruitment between the AKI group and the AKI/CKD group. In the AKI group it is notable that an ACR was available at baseline in 24.2% of patients. Just over 80% of these were diabetic. Of those with an ACR available, 16 patients had evidence of microlbuminuria and these make up 8.4% of the AKI

group. All of these patients had diabetes suggesting that there may have been some degree of early diabetic nephropathy present.

In the AKI group 60% were admitted under a medical specialty while 68% of the AKI/CKD group were medical (p=0.128). In the case of surgical admissions 15% of the AKI/CKD group were admitted as elective cases compared to 41% of the AKI group (p=0.001). There was a trend toward a greater percentage of the AKI episodes in the AKI/CKD group being present on admission and hence having occurred in the community (73% v 62%, p=0.025).A more detailed analysis of the admission and inhospital AKI episodes in each group is presented later in this chapter.

There was no difference in the distribution of the primary causes of the AKI between the groups. Over 95% in each group had a mechanism that would have been described as 'Prerenal" AKI. The most common causal mechanism was 'hypoperfusion' with 46% and 42% in the AKI and AKI/CKD groups respectively. Sepsis accounted for 23% of the AKI group cases and 31% of the AKI/CKD group cases (p=0.057). Complex cases with more than one causal insult recorded accounted for 28% and 26% of the respective groups.
In terms of the clinical findings and basic investigations performed there were no significant differences between the groups. There was a trend toward more fluid overload in the AKI/CKD group which could be expected given the more prominent history of cardiac failure in this group at baseline (p=0.019). There was also a trend that patients in the AKI/CKD group were less likely to have had their urine output measured during the episode (p=0.035). Approximately 50% or less of each group had a urine dipstick performed at the time of the episode and one third in each group had a renal ultrasound.

Table 6. 5 Comparison of baseline clinical details relating to renal function and the AKI episode between the AKI and AKI/CKD groups.

		AKI Group N = 190	AKI/CKD Group N=185	P
Function	ACR available N(%)	**46 (24.2)**	**117 (63.24)**	**<0.001**
	Abnormal ACR N(%)	**16 (8.4)**	**56 (30.2)**	**<0.001**
	Normal ACR N(%)	**30 (15.8)**	**61 (32.9)**	**<0.001**
	No ACR available N(%)	**144 (75.8)**	**68 (36.7)**	**<0.001**
	Baseline Creatinine			
	Mean (SD)	**75.5 (15.5)**	**147.3 (70.9)**	**<0.001**
	Baseline eGFR			
	Mean (SD)	**77.9 (9.9)**	**39.6 (12.2)**	**<0.001**
	Peak Creatinine			
	Median (IQR)	**180 (143-251)**	**242 (190-341)**	**<0.001**

		AKI Group N = 190	AKI/CKD Group N=185	P
Admitting Specialty N(%)	Medicine	114 (60%)	125 (67.6)	0.128
	Surgery	74 (38.9)	60 (32.4)	0.316
	Obs/Gynae	2 (1.1)	0	0.499
Surgical	Elective	**30(40.5)**	**9(15)**	**0.001**
	Emergency	**44(59.5)**	**51(85)**	**0.001**
AKI N(%)	On Admission	118 (62.1)	135 (73)	0.025
	Age of admission group			
	Median (IQR)	**68.5 (58.7-75.5)**	**79 (71-84)**	**0.007**
Cause on admission N(%)	Septic	38 (22.2)	45 (33.3)	0.849
	Hypoperfusion	44 (37.3)	54 (40)	0.659
	Nephrotoxic	1 (0.8)	1 (0.7)	1
	Complex	30 (25.4)	35 (25.9)	0.927
	Pure Intrinsic	2 (1.7)	0	0.217
	Pure Obstructive	3 (2.5)	0	0.1
AKI N(%)	In hospital	72 (37.9)	50 (27)	0.025
	Age of in hospital group			
	Median (IQR)	67.5 (60-75.8)	80 (75.5-86)	0.011
Cause of in hospital cases N(%)	Septic	**5 (6.9)**	**13 (26)**	**0.004**
	Hypoperfusion	43 (59.7)	24 (48)	0.201
	Nephrotoxic	0	0	
	Complex	24 (33.3)	13 (26)	0.386
	Pure Intrinsic	0	0	
	Pure Obstructive	0	0	
Primary cause overall N(%)	Septic	43 (22.6)	58 (31.4)	0.057
	Hypoperfusion	87 (45.8)	78 (42.2)	0.479
	Nephrotoxic	1 (0.5)	1 (0.5)	1
	Complex	54 (28.4)	48 (25.9)	0.590
	Pure Intrinsic	2 (1.1)	0	0.499
	Pure Obstructive	3 (1.6)	0	0.248
Urine Dip performed N(%)		88 (46.3)	94 (50.8)	0.384
Ultrasound Performed N(%)		70 (36.8)	64 (34.6)	0.650
Fluid Status N(%)	Dry	146 (76.8)	129 (69.7)	0.119

		AKI Group N = 190	AKI/CKD Group N=185	P
	Euvolaemic	32 (16.8)	31 (16.8)	0.982
	Overloaded	12 (6.3)	25 (13.5)	0.019
Urine Output N(%)				
	Normal	123 (64.7)	113 (61.1)	0.464
	Oliguria	31 (16.3)	18 (9.7)	0.059
	Anuria	1 (0.5)	3 (1.6)	0.366
	Not done	35 (18.4)	51 (27.6)	0.035
Hypotension N(%)	None	44 (23.2)	53 (28.6)	
Systolic Pressure	101 - 110	33 (17.4)	35 (18.9)	
	91 - 100	52 (27.4)	48 (25.9)	
	81 - 90	37 (19.5)	36 (19.5)	
	< 80	24 (12.6)	13 (7)	
	Overall			
	>90	129 (67.9)	136 (73.5)	0.232
	<90	61 (32.1)	49 (26.4)	

6.2.2 AKI Details – AKI Group by AKIN Stage

Table 6.6 outlines the clinical details relating to baseline kidney function and the AKI episode of the AKI Group divided by AKIN stage. There were no differences found in baseline kidney function between the three stages. There were no significant differences between admitting specialties although there was a trend toward the more severe AKIN stage 3 occurring under medical specialties (p=0.071). There was significantly more AKIN stage 3 evident on admission to hospital as opposed to occurring in hospital (p=0.007). Of the admission cases, there were no significant differences in causal mechanism though there was a trend toward more hypoperfusion cases in AKIN stage 1 with more complex cases in AKIN stage 3. No differences were found between the cases occurring in hospital with regard to cause. With admission and inhospital cases combined, significantly more of the milder AKIN 1 cases were due to hypoperfusion causes (p=0.004). The overall trend indicates that more severe AKI episodes were associated with complex causes or sepsis.

As expected, the more severe the AKI, the more likely the patient was to have had a urine dip or renal ultrasound performed. In addition, the severe cases were significantly more likely to be clinically dehydrated or have oliguria. No differences were found in nadir blood pressure levels at the time of the AKI between the three stages.

Table 6.6 AKI clinical details of the AKI Group with comparison of AKIN stages.

	AKI Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 46	N = 71	N = 73	
Function N(%)				
ACR available	10 (21.7)	23 (32.4)	13 (17.8)	0.112
Abnormal ACR	4 (8.7)	8 (11.3)	4 (5.5)	0.337
Normal ACR	6 (13)	15 (21.1)	9 (12.3)	
No ACR available	36 (78.3)	48 (67.6)	60 (82.3)	
Baseline Creatinine Mean (SD)	83.17 (11.4)	74.37 (14.49)	71.88 (17.16)	0.301
Baseline eGFR Mean (SD)	74.67 (8.88)	78.15 (9.95)	79.67 (9.54)	0.331
Peak Creatinine Median IQR	**133.5 (118-149)**	**179 (152-216)**	**294 (228-425)**	**<0.001**
Admitting Specialty N(%)				
Medicine	21 (45.7)	45 (63.4)	48 (65.8)	0.071
Surgery	24 (52.2)	26 (36.6)	24 (32.9)	0.232
Obs/Gynae	1 (2.2)	0	1 (1.4)	0.501
Surigcal				
Elective	10(41.7)	11(42.3)	9(37.5)	0.933
Emergency	14(58.3)	15(57.7)	15(62.5)	
On Admission	**22 (47.8)**	**41 (57.7)**	**55 (75.3)**	**0.007**
Age of admission group Median (IQR)	70 (62 to 74)	71 (59 to 81)	65 (55 to 75)	0.248
Cause on admission N(%)				
Septic	7 (31.8)	14 (34.1)	17 (30.9)	0.944
Hypoperfusion	13 (59.1)	16 (39)	15 (27.3)	0.032
Nephrotoxic	0	0	1 (1.8)	0.561
Complex	1 (4.5)	11 (26.8)	18 (32.7)	0.036
Pure Intrinsic	0	0	2 (3.6)	0.312
Pure Obstructive	1 (4.5)	0	2 (3.6)	0.429
In hospital	**24 (52.1)**	**30 (42.3)**	**18 (24.7)**	**0.007**
Age of in hospital group Median (IQR)	68 (55 to 75)	68 (63 to 80	65 (59 to 74)	0.574
Cause in hospital N(%)				
Septic	1 (42.)	2 (6.7)	2 (11.1)	0.679

	AKI Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 46	N = 71	N = 73	
Hypoperfusion	17 (70.8)	16 (53)	10 (55.6)	0.392
Nephrotoxic	0	0	0	
Complex	6 (25)	12 (40)	6 (33.3)	0.509
Pure Intrinsic	0	0	0	
Pure Obstructive	0	0	0	
Primary cause overall N(%)				
Septic	8 (17.4)	16 (22.5)	19 (26.2)	0.548
Hypoperfusion	**30 (65.2)**	**32 (45.1)**	**25 (34.2)**	**0.004**
Nephrotoxic	0	0	1 (1.4)	0.447
Complex	7 (15.2)	23 (32.4)	24 32.9)	0.074
Pure Intrinsic	0	0	2 (2.7)	0.198
Pure Obstructive	1 (2.2)	0	2 (2.7)	0.391
Urine Dip performed N(%)	18 (39.1)	28 (39.4)	42 (57.5)	0.05
Ultrasound Performed N(%)	**10 (21.7)**	**16 (22.5)**	**44 (60.3)**	**<0.001**
Fluid Status N(%)				
Dry	**28 (60.9)**	**56 (78.9)**	**62 (84.9)**	**0.009**
Euvolaemic	**15 (32.6)**	**11 (15.5)**	**6 (8.2)**	**0.002**
Overloaded	3 (6.5)	4 (5.6)	5 (6.8)	0.954
Urine Output N(%)				
Normal	**35 (76.1)**	**53 (74.6)**	**35 (47.9)**	**0.001**
Oliguria	**3 (6.5)**	**7 (9.9)**	**21 (73)**	**0.001**
Anuria	0	0	1 (1.4)	0.447
Not done	8 (17.4)	11 (15.5)	16 (21.9)	0.597
Systolic Pressure				
>90	33 (71.7)	53 (74.6)	43 (58.9)	0.105
<90	13 (28.3)	18 (25.4)	30 (41.1)	

6.2.3 AKI Details – AKI/CKD Group by AKIN Stage

Table 6.7 outlines the clinical details relating to baseline kidney function and the AKI episode of the AKI/CKD Group divided by AKIN stage. Findings are similar to those found in the AKI group. There were no differences found in baseline kidney function between the three groups and no differences between admitting specialties. Like the AKI group, there was a trend toward the more severe AKIN stage 3 being found on admission (p=0.033). No differences were found in the cause of the AKI between the three stages either on admission or in hospital.

More severe AKI cases were more likely to have had a urine dip and renal ultrasound. The severe cases were more likely to have had oliguria but no differences were found between stages with regard to nadir blood pressure at the time of the AKI.

Table 6.7 AKI clinical details of the AKI/CKD Group with comparison of AKIN stages.

	AKI/CKD Group			
	AKIN 1 N = 99	AKIN 2 N = 53	AKIN 3 N = 33	**p**
Function N(%)				
ACR available	63 (63.6)	31 (58.5)	23 (69.7)	0.573
Abnormal ACR	30 (30.3)	19 (35.8)	7 (21.2)	0.08
Normal ACR	33 (33.3)	12 (22.6)	16 (48.5)	
No ACR Available	36 (36.4)	22 (41.5)	10 (30.3)	
Baseline Creatinine Mean (SD)	157.86 (83.3)	131.43 (43.9)	140.85 (61.19)	0.724
Baseline eGFR Mean (SD)	37.37 (11.85)	42.74 (11.69)	41.42 (13.13)	0.464
Peak Creatinine Mean (SD)	**210 (172-254)**	**294 (239-348)**	**436 (332-713)**	**<0.001**
Admitting Specialty N(%)				
Medicine	65 (65.66)	36 (67.92)	24 (72.72)	0.752
Surgery	34 (34.34)	17 (32.07)	9 (27.27)	
Obs/Gynae	0	0	0	
Surigcal				
Elective	5(14.7)	2(3.8)	2(22.2)	0.775
Emergency	29(85.3)	15(88.2)	7(77.8)	
AKI N(%)				
On Admission	67 (67.68)	38 (71.69)	30 (90.9)	0.033
Age of admission group				
Median (IQR)	78 (71-83)	77 (71.8-84.3)	79.5 (74-84.3)	0.504
Cause on admission N(%)				
Septic	21 (31.3)	12 (31.6)	12 (40)	0.680
Hypoperfusion	30 (44.8)	16 (42.1)	8 (26.7)	0.231
Nephrotoxic	0	0	1 (3.3)	0.172
Complex	16 (23.9)	10 (26.3)	9 (30)	0.815
Pure Intrinsic	0	0	0	
Pure Obstructive	0	0	0	

	AKI/CKD Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 99	N = 53	N = 33	
AKI N(%)				
In hospital	32 (32.32)	15 (28.3)	3 (9.09)	0.033
Age of in hospital group				
Median (IQR)	80.5 (76-86.8)	80 (72-82)	82	0.465
Cause in hospital N(%)				
Septic	7 (21.9)	5 (33.3)	1 (33.3)	0.675
Hypoperfusion	18 (56.3)	5 (33.3)	1 (33.3)	0.298
Nephrotoxic	0	0	0	
Complex	7 (21.9)	5 (33.3)	1 (33.3)	0.675
Pure Intrinsic	0	0	0	
Pure Obstructive	0	0	0	
Primary cause overall N(%)				
Septic	28 (28.28)	17 (32.07)	13 (39.39)	0.487
Hypoperfusion	48 (48.48)	21 (39.62)	9 (27.27)	0.092
Nephrotoxic	0	0	1 (3)	0.099
Complex	23 (23.23)	15 (28.3)	10 (30.3)	0.651
Pure Intrinsic	0	0	0	
Pure Obstructive	0	0	0	
Urine Dip performed N(%)	42 (42.42)	30 (56.6)	22 (66.67)	0.033
Ultrasound Performed N(%)	**23 (23.23)**	**18 (33.96)**	**23 (69.69)**	**<0.001**
Fluid Status N(%)				
Dry	62 (62.62)	41 (77.36)	26 (78.79)	0.078
Euvolaemic	23 (23.23)	5 (9.43)	3 (9)	0.041
Overloaded	14 (14.14)	7 (13.2)	4 (12.12)	0.955
Urine Output N(%)				
Normal	**73 (73.73)**	**29 (54.72)**	**11 (33.33)**	**<0.001**
Oliguria	**2 (2)**	**5 (9.43)**	**11 (33.33)**	**<0.001**
Anuria	**0**	**0**	**3 (9.09)**	**0.001**
Not done	24 (24.24)	19 (35.85)	8 (24.24)	0.279
Systolic Pressure				
>90	72 (72.73)	42 (79.25)	22 (66.67)	0.423
<90	27 (27.27)	11 (20.75)	11 (33.33)	

6.2.4 AKI Details – Community AKI and Hospital AKI

Tables 6.8 and 6.9 outline the comparisons made between the community acquired cases of AKI which were present on admission and the hospital acquired AKI cases in the AKI group and AKI/CKD group respectively. In the AKI group, Table 6.8 shows that

there were no age or sex differences found however there was a trend toward a greater burden of comorbidity in the admission group. There were more admission cases found under medical specialties. This might be expected given that a large portion of the surgical group were elective and already in hospital at the time of their AKI. More of the admission cases were caused by sepsis while more of the in hospital cases were recorded as hypoperfusion. This again may reflect the elective surgical portion of this group with perioperative low blood pressure as a cause. The admission group was more likely to have had a urine dipstick recorded or renal ultrasound ($p<0.001$). Finally, there were significantly more nadir blood pressures < 90 systolic recorded in the inhospital group. This may be that the low pressures were missed in the admission group whilst in the community however it parallels the finding of more hypoperfusion AKI in hospital.

In the AKI/CKD group the findings were broadly similar although there was no difference in the burden of comorbidities as was found in the AKI group. In addition, unlike the AKI group there were no differences found in nadir blood pressure between the admission and inhospital cases.

Table 6.8 Comparison of the admission and inhospital AKI cases in the AKI Group.

		AKI Group On Admission N = 118	AKI Group In Hospital N = 72	P
Age				
Median (IQR)		68.5 (58.7-75.5)	67.5 (60-75.8)	0.740
Male N(%)		71 (60.2)	40 (55.6)	0.531
Charlson Score				
Mean(SD)		1.42(1.28)	.94(1.16)	0.012
Function	ACR available N(%)	33 (28)	13 (18.1)	0.122
	Abnormal ACR N(%)	12 (10.2)	4 (5.6)	1.0
	Normal ACR N(%)	21 (17.8)	9 (12.5)	1.0
	No ACR available N(%)	85 (72)	59 (81.9)	0.122
	Baseline Creatinine Mean (SD)	76.21 (16.26)	74.44 (14.27)	0.448
	Baseline eGFR Mean (SD)	77.35 (10.04)	78.79 (9.07)	0.320
	Peak Creatinine Median (IQR)	190 (152-255)	162 (130-247)	0.40
Admitting Specialty N(%)	Medicine	**90 (76.3)**	**24 (33.3)**	**<0.001**

		AKI Group On Admission N = 118	AKI Group In Hospital N = 72	P
	Surgery	28 (23.7)	46 (63.9)	
	Obs/Gynae	0	2 (2.8)	
Surigcal	Elective	**1(3.6)**	**29(63)**	**<0.001**
	Emergency	27(96.4)	17(37)	
Primary cause N(%)				
	Septic	**38 (22.2)**	**5 (6.9)**	**<0.001**
	Hypoperfusion	**44 (37.3)**	**43 (59.7)**	**0.003**
	Nephrotoxic	1 (0.8)	0	1.0
	Complex	30 (25.4)	24 (33.3)	0.241
	Pure Intrinsic	2 (1.7)	0	0.527
	Pure Obstructive	3 (2.5)	0	0.290
Urine Dip performed N(%)		**69 (58.5)**	**19 (26.4)**	**<0.001**
Ultrasound Performed N(%)		**55 (46.6)**	**15 (20.8)**	**<0.001**
Fluid Status N(%)	Dry	97 (82.2)	49 (68.1)	0.025
	Euvolaemic	14 (11.9)	18 (25)	0.019
	Overloaded	7 (5.9)	5 (6.9)	0.781
Urine Output N(%)				
	Normal	71 (60.2)	52 (72.2)	0.092
	Oliguria	22 (18.6)	9 (12.5)	0.266
	Anuria	0	1 (1.4)	0.199
	Not done	25 (21.2)	10 (13.9)	0.208
Systolic Pressure				
	>90	**89 (75.4)**	**40 (55.6)**	**0.004**
	<90	29 (24.6)	32 (44.4)	

Table 6.9 Comparison of the admission and inhospital AKI cases in the AKI/CKD Group.

		AKI/CKD Group On Admission N = 135	AKI /CKD Group In Hospital N = 50	P
Age				
Median (IQR)		79 (71-84)	80 (75.5-86)	0.105
Male N(%)		68 (50.4)	20 (40)	0.210
Charlson Score				
Mean(SD)		4.27(1.52)	3.98(1.35)	.230
Function	ACR available N(%)	90 (66.7)	27 (54)	0.113
	Abnormal ACR N(%)	47 (34.8)	9 (18)	0.085
	Normal ACR N(%)	43 (31.9)	18 (36)	0.085
	No ACR available N(%)	45 (33.3)	23 (46)	0.113
	Baseline Creatinine			
	Mean (SD)	153.57 (80.41)	130.2 (28.25)	0.046
	Baseline eGFR			
	Mean (SD)	39.17 (13.25)	40.88 (8.88)	0.4
	Peak Creatinine			
	Median (IQR)	255 (190-391)	223.5 (187-277)	0.024
Admitting				
Specialty N(%)	Medicine	**103 (76.3)**	**22 (44)**	**<0.001**
	Surgery	32 (23.7)	28 (56)	
	Obs/Gynae	0	0	
Surigcal	Elective	3(9.3)	6(21)	0.192
	Emergency	29(91)	22(79)	
Primary cause N(%)				
	Septic	45 (33.3)	13 (26)	0.340
	Hypoperfusion	54 (40)	24 (48)	0.328
	Nephrotoxic	1 (0.7)	0	1.0
	Complex	35 (25.9)	13 (26)	0.992
	Pure Intrinsic	0	0	
	Pure Obstructive	0	0	
Urine Dip performed N(%)		**80 (59.3)**	**14 (28)**	**<0.001**
Ultrasound Performed N(%)		53 (39.3)	11 (22)	0.028
Fluid Status N(%)	Dry	**102 (75.6)**	**27 (54)**	**0.005**
	Euvolaemic	17 (12.6)	14 (28)	0.013
	Overloaded	16 (11.9)	9 (18)	0.277

		AKI/CKD Group On Admission N = 135	AKI /CKD Group In Hospital N = 50	P
Urine Output N(%)				
	Normal	83 (61.5)	30 (60)	0.854
	Oliguria	15 (11.1)	3 (6)	0.298
	Anuria	2 (1.5)	1 (2)	0.804
	Not done	35 (25.9)	16 (32)	0.412
Systolic Pressure				
	>90	99 (73.3)	37 (74)	0.927
	<90	36 (26.7)	13 (26)	

6.2.5 AKI Details – AKI/CKD Group and Controls

Table 6.10 outlines the comparison between the AKI/CKD group and the CKD controls. Findings here must be interpreted with caution given the low number in the control group. Overall, few differences were found between the groups. Baseline kidney function was similar. As might be expected, patients in the control group were more likely to be euvolaemic and to have a normal urine output. There were no differences found in nadir blood pressure readings between the two groups.

Table 6.10 Comparison of baseline details between AKI/CKD group and the CKD Control group.

		AKI/CKD Group N=185	CKD Control Group N=26	P
Function	ACR available N(%)	117 (63.24)		
	Abnormal ACR N(%)	56 (30.2)		
	Normal ACR N(%)	61 (32.9)		
	No ACR available N(%)	68 (36.7)		
	Baseline Creatinine			
	Mean (SD)	147.3 (70.9)		
	Baseline eGFR			
	Mean (SD)	39.6 (12.2)	41.85 (12.18)	0.388
	Peak Creatinine			
	Median (IQR)	242 (190-341)		
Admitting Specialty N(%)	Medicine	125 (67.6)		
	Surgery	60 (32.4)	8 (30.76)	0.865
	Obs/Gynae	0	0	

		AKI/CKD Group N=185	CKD Control Group N=26	P
Surgical	Elective	9(15)	2(25)	0.471
	Emergency	51(85)	6(75)	
Urine Dip performed N(%)		94 (50.8)	8 (30.8)	0.056
Ultrasound Performed N(%)		**64 (34.6)**	**2 (7.7)**	**0.006**
Fluid Status N(%)	Dry	**129 (69.7)**	**9 (34.6)**	**<0.001**
	Euvolaemic	**31 (16.8)**	**15 (57.7)**	**<0.001**
	Overloaded	25 (13.5)	2 (7.7)	0.405
Urine Output N(%)				
	Normal	**113 (61.1)**	**24 (92.3)**	**0.002**
	Oliguria	18 (9.7)	0	0.137
	Anuria	3 (1.6)	0	1
	Not done	51 (27.6)	2 (7.7)	0.03
Systolic Pressure				
	>90	136 (73.5)	21 (80.8)	0.427
	<90	49 (26.4)	5 (19.2)	

6.3 Preadmission Details

Later in this chapter the readmission pattern of the AKI recruits is outlined. To facilitate exploration of this phenomenon a retrospective review was carried out of each recruit to record admissions in the year prior to the index AKI. In addition, hospital biochemistry records were reviewed to record any rises in serum creatinine that met the study criteria for AKI during the previous four years. This retrospective search was limited to admissions and biochemistry recorded on the Portsmouth Hospitals NHS Trust database and therefore may have missed episodes that occurred elswhere. These data are outlined in Table 6.11. During the year prior to the index admission, 32.1% of the AKI group and 42.7% of the AKI/CKD group were admitted to hospital at least once while 5.3% and 20.5% of each group respectively had evidence of an AKI meeting AKIN criteria occurring during admission. This was significantly higher in the AKI/CKD group ($p<0.001$). Extending the search back to four years the proportion of patients who had evidence of a previous AKI increased to 8.9% in the AKI group and 34.6% in the AKI/CKD group.

6.3.1 eGFR slope prior to study AKI

In order to explore the influence of prior renal function on outcomes further, a regression line was used to calculate the eGFR slope for each patient prior to the index AKI. The method used to calculate this has been described in Chapter 4. In the case of the AKI group 169 patients (89%) had two or more outpatient eGFR results (range 2-7, median 5). In the AKI/CKD group 183 patients (99%) had two or more results (range 2-7, median 5). The mean change in eGFR slope over the three years in the AKI group was +1.21mls/min/year while in the AKI/CKD group the mean change was -3.16mls/min/year (p<0.001). The influence of the eGFR slope on outcomes is explored further in regression analysis in Chapter 7.

Table 6.11 Basic preadmission details for the AKI and AKI/CKD groups.

		AKI Group N = 190	AKI/CKD Group N=185	p
Before study AKI N(%)				
	Adm. prev. 12 mts	61 (32.1)	79 (42.7)	0.034
	AKI prev 12 mts	**10 (5.3)**	**38 (20.5)**	**<0.001**
	AKI prev 4 yrs	**17 (8.9)**	**64 (34.6)**	**<0.001**
		N=169	N=183	
eGFR slope mls/min/year Mean(SD)		**1.21(4.90)**	**-3.16 (5.45)**	**<0.001**

6.4 Hospital Outcomes – AKI Group and AKI/CKD Group

Table 6.12 compares the hospital outcomes of the AKI and AKI/CKD groups, followed by an analysis of the outcomes in each group divided by AKIN stage in Tables 6.13 and 6.14.

6.4.1 Hospital mortality

16 patients (8.6%) in the AKI/CKD group and 7 patients (3.7%) in the AKI group died whilst in hospital (p=0.045). In the AKI group the mortality pattern was consistent with the severity of the AKIN stage but did not reach statistical significance (p=0.137). In the AKI/CKD group mortality did not correlate with AKIN stage as it was significantly

higher in AKIN stage 2 (p=0.007). However, as the mortality is low in both groups there is insufficient power to draw any firm conclusions regarding the ability of AKIN to predict mortality.

6.4.2 Recovery of function at hospital discharge

The mean change in eGFR at discharge compared to baseline, described as 'Delta eGFR', was significantly different between the groups. The mean change was -11.75 in the AKI group while in the CKD group the mean change was +0.11 (p<0.001). This is illustrated in the Box-Whisker plot in Figure 6.1 below. The changes did not reach significance by AKIN stage in each group. However, there was a trend toward a more negative change with increasing AKIN stage. When viewed as a failure to recover function according to the study criteria of a fall in eGFR of >5mls/min, 52.6% of the AKI group had not recovered and 31.4% of the AKI/CKD group had not recovered (p<0.001). Lack of recovery was not significantly different between AKIN stages in either group and this is illustrated graphically in Figure 6.2 and Figure 6.3 respectively.

Figure 6.1 Box-whisker plots of the mean change in eGFR (Delta eGFR) at the time of discharge from hospital in the AKI and AKI/CKD groups.

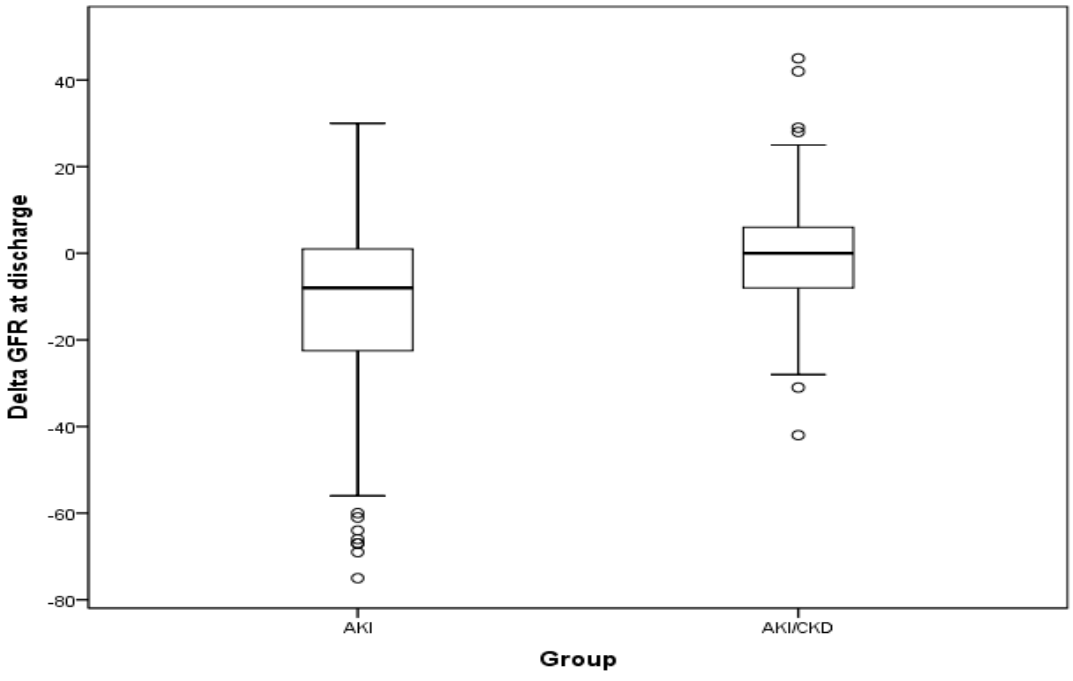


Figure 6. 2 Graphical illustration of recovery of eGFR to within 5mls/min of baseline at the time of discharge in the AKI group. The red bars represent the proportion failing to recover in each AKIN stage.

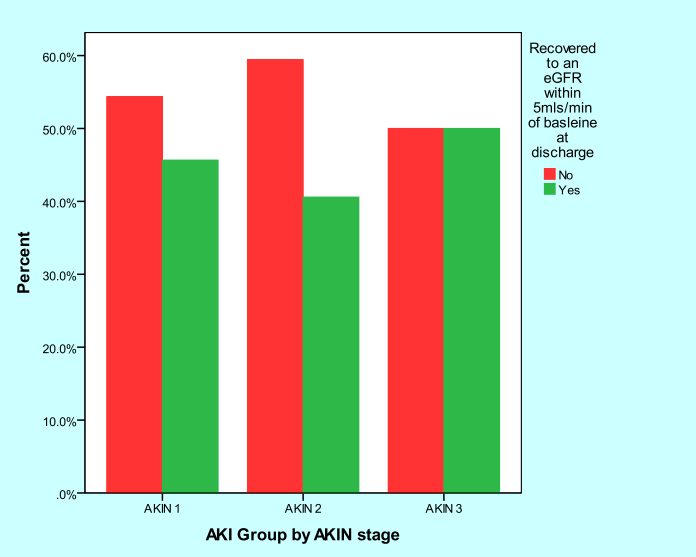
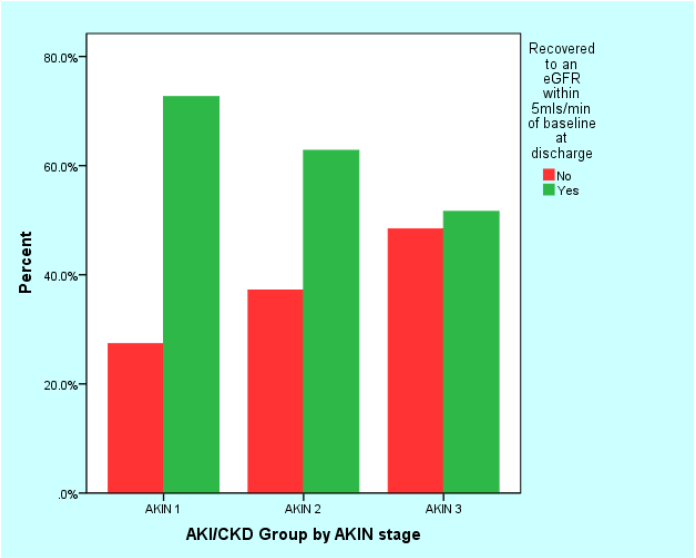


Figure 6.3 Graphical illustration of recovery of eGFR to within 5mls/min of baseline at the time of discharge in the AKI/CKD group. The red bars represent the proportion failing to recover in each AKIN stage.



The time taken for the serum creatinine to fall below the level of AKIN stage 1 was taken as the time to recover. The median time for this to occur in the AKI group was 3 days compared to 4 days in the AKI/CKD group (p=0.021). The time to recover function was predicted by AKIN stage in both groups.

6.4.3 Length of hospital stay

The median length of hospital stay in the AKI group was 10 days compared to 12 days in the AKI/CKD group (p=0.04). This is likely to be accounted for by the increased age and burden of comorbidities in the AKI/CKD group at baseline. There was no significant difference in length of hospital stay according to AKIN stage in either group.

6.4.4 General management

There was a trend toward a greater proportion of the AKI group (14.2% v 7%) being managed in intensive care (p=0.024). Although numbers were low, there was a trend toward more of the AKI group receiving renal replacement therapy in the ITU (48% v 23%, p=0.019). These differences may reflect differing thresholds for admission and less aggressive management in the AKI/CKD group which was older and had more comorbidity.

Overall, 8.4% (n=16) patients in the AKI group and 5.4% (n=10) patients in the AKI/CKD group received renal replacement therapy during their hospital stay. All of the AKI group had recovered sufficiently to come off dialysis at the time of discharge from hospital while 3 patients (1.6%) in the AKI/CKD group remained on dialysis at the time of discharge.

Only 3 patients from the entire cohort (0.8%) received a renal biopsy. All of these were from the AKI group. One showed features of a rapidly progressive glomerulonephritis, one had features consistent with scleroderma kidney, while one had non-specific features felt most likely to be due to acute tubular necrosis.

As a part of the clinical management of the AKI, over 90% of patients in each group who had been taking RAS-blockers had them stopped by the admitting team.

It is notable that significantly more of the AKI/CKD group received a formal review by the renal team in hospital although most had no review (20.5% v 8.9%, p=0.002). Within the AKI group all of these reviews were requested in patients with AKIN stage 3 but accounted for only 23% of this stage. On the other hand, in the AKI/CKD group 12% of AKIN stages 1 and 2 received a renal consultation in hospital while more than 77% of AKIN stage 3 received one. The reasons for these marked differences are unclear but may reflect a greater awareness of renal disease in those with established and documented CKD.

Finally, the discharge summaries of each patient were reviewed after the patients left the hospital to assess the ICD-10 coding practices. In the AKI group 38.9% had an AKI coded on their discharge summary while 50.8% of the AKI/CKD group were coded (p=0.021). The code used in the majority of cases in both groups was N17.9 – ARF unspecified. This again likely reflects the greater recognition of renal problems in those with established CKD. When divided by AKIN stage coding improved significantly with increasing AKIN stage however nearly 40% of the most severe AKIN stage 3 in the AKI group were still not coded. The coding is derived from the discharge summary to the general practitioner. These findings indicate that a large proportion of patients who have a severe AKI in hospital are discharged without their general practitioners being informed.

Table 6.12 Hospital Outcomes and comparison of the AKI Group and AKI/CKD Group.

		AKI Group N = 190	AKI/CKD Group N=185	P
ITU Admission N(%)		27 (14.2)	13 (7)	0.024
	Dialysis in ITU N(%)	13 (48)	3(23.07)	0.019
Renal Review N(%)		**17 (8.9)**	**38 (20.5)**	**0.002**
Renal Review by AKIN Stage N(%)	Stage 1	0	11 (12.2)	
	Stage 2	0	6 (12.2)	
	Stage 3	17 (23%)	21 (77.7)	
Total dialysed N(%)		16 (8.4)	10 (5.41)	0.250
RASB stopped N(%)		91 (90.1)	131 (92.3)	0.556
Biopsy N(%)		3 (1.6)	0	0.248
Hospital mortality N(%)		7 (3.7)	16 (8.6)	0.045
Mortality by AKIN N(%)	Stage 1	0	4 (4)	
	Stage 2	2 (2.8)	10 (18.9)	
	Stage 3	5 (6.8)	2 (6)	
Overall LOS, Median (IQR)		10 (6-19)	12 (8-23.5)	0.04
LOS by AKIN Median (IQR)	Stage 1	9 (5-15.25)	12 (8-24)	
	Stage 2	9 (6-17)	13 (7-26)	
	Stage 3	13 (7-34.25)	12 (10-22)	
Delta eGFR @ D/C Mean (SD)		**-11.75 (21.1)**	**+0.11 (12.7)**	**<0.001**

		AKI Group N = 190	AKI/CKD Group N=185	P
Delta by AKIN				
Mean (SD)	Stage 1	-6.26 (16.1)	+0.99 (10.3)	
	Stage 2	-10.33 (17.7)	-0.35 (14.8)	
	Stage 3	-16.91 (25.7)	-2.18 (16.3)	
Not recovered N(%)				
		100 (54.64)	**57 (33.7)**	**<0.001**
By AKIN %	Stage 1	25 (54.35)	26 (27.3)	
	Stage 2	39 (56.52)	16 (37.2)	
	Stage 3	36 (52.94)	15 (48.38)	
Dialysis @ D/C N(%)				
		0	3 (1.6)	0.110
Duration of recovery Median (IQR)				
		3 (3-5)	4 (3-7)	0.020
	Stage 1	2 (2-3)	4 (2-6)	
	Stage 2	3 (3-5)	5 (4-6)	
	Stage 3	5 (3-9.8)	7 (4-9)	
AKI coded @ D/C N%				
		74 (38.9)	94 (50.8)	0.021
By AKIN N%	Stage 1	4 (8.7)	38 (38.38)	
	Stage 2	25 (35.21)	27 (50.94)	
	Stage 3	45 (61.64)	29 (87.9)	

Table 6.13 Hospital Outcomes in AKI Group divided by AKIN stage.

	AKI Group			
	AKIN 1 N = 46	AKIN 2 N = 71	AKIN 3 N = 73	**p**
ITU Admission N(%)	4 (8.69)	7 (9.86)	16 (21.92)	0.055
Dialysis in ITU N(%)	**0**	**0**	**13 (17.81)**	**<0.001**
Renal Review N(%)	**0**	**0**	**17 (23.29)**	**<0.001**
Total dialysed N(%)	**0**	**0**	**16 (21.92)**	**<0.001**
RASB stopped N(%)	20 (80)	35 (92.1)	36 (94.74)	0.139
Biopsy N(%)	0	0	3 (4.11)	0.087
Hospital mortality N(%)	0	2 (2.82)	5 (6.85)	0.137
Overall LOS, Median (IQR)	9 (5-15.25)	9 (6-17)	13 (7-34.25)	0.066
Delta eGFR @ D/C Mean (SD)	-6.26 (16.1)	-10.33 (17.7)	-16.91 (25.7)	0.014
Not recovered N(%)	25 (54.35)	39 (56.52)	36 (52.94)	0.914
Dialysis @ D/C N(%)	0	0	0	
Duration of recovery Median (IQR)	**2 (2-3)**	**3 (3-5)**	**5 (3-9.8)**	**,0.001**
AKI coded @ D/C N%	**4 (8.7)**	**25 (35.21)**	**45 (61.64)**	**<0.001**

Table 6.14 Hospital Outcomes in AKI/CKD Group divided by AKIN stage.

	AKI/CKD Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 99	N = 53	N = 33	
ITU Admission N(%)	4 (4.04)	5 (9.43)	4 (12.12)	0.209
Dialysis in ITU N(%)	**0**	**0**	**3 (0.09)**	**0.001**
Renal Review N(%)	**11 (12.2)**	**6 (12.2)**	**21 (77.7)**	**<0.001**
Total dialysed N(%)	**0**	**0**	**10 (5.41)**	**<0.001**
RASB stopped N(%)	65 (89.04)	41 (97.62)	25 (92.59)	0.253
Biopsy N(%)	0	0	0	
Hospital mortality N(%)	**4 (4.04)**	**10 (18.87)**	**2 (6.06)**	**0.007**
Overall LOS, Median (IQR)	12 (8-24)	13 (7-26)	12 (10-22)	0.947
Delta eGFR @ D/C Mean (SD)	+0.99 (10.3)	-0.35 (14.8)	-2.18 (16.3)	0.353
Not recovered N(%)	26 (27.3)	16 (37.21)	15 (48.39)	0.114
Dialysis @ D/C N(%)	**0**	**0**	**3 (9.68)**	**0.001**
Duration of recovery Median (IQR)	**4 (2-6)**	**5 (4-6)**	**7 (4-9)**	**<0.001**
AKI coded @ D/C N%	**38 (38.38)**	**27 (50.94)**	**29 (87.88)**	**<0.001**

A further comparison was made between the hospital outcomes of the AKI/CKD group and the CKD controls. This is outlined in Table 6.15. As the control numbers are small interpretation of these data are difficult. However, an important finding was a significant difference in the hospital length of stay. The median length of stay was 5 days longer in the AKI/CKD group (p=0.002). It is also notable that of those who were taking RAS blockers in the CKD control group 73% had these stopped during their admission. This may reflect increased awareness on the part of the clinical team of the risk of AKI.

Table 6.15 Hospital Outcome comparison between the AKI/CKD Group and CKD Controls.

	AKI/CKD Group N=185	CKD Control Group N=26	P
ITU Admission N(%)	13 (7)	0	0.376
Renal Review N(%)	**38 (20.5)**	**0**	**0.006**
RASB stopped N(%)	131 (92.3)	8 (72.7)	0.065
Hospital mortality N(%)	16 (8.6)	1 (3.8)	0.701
Overall LOS, Median (IQR)	**12 (8-23.5)**	**7 (4.5-14)**	**0.002**
Delta eGFR @ D/C Mean (SD)	+0.11 (12.7)	+2.4 (-11-12)	0.374
Dialysis @ D/C N(%)	3 (1.6)	0	1

6.5 Outcomes after 6 months follow up

Figure 6.4 Flowchart illustrating the outcomes from recruitment of each group and available numbers in each group for functional analysis after follow up.

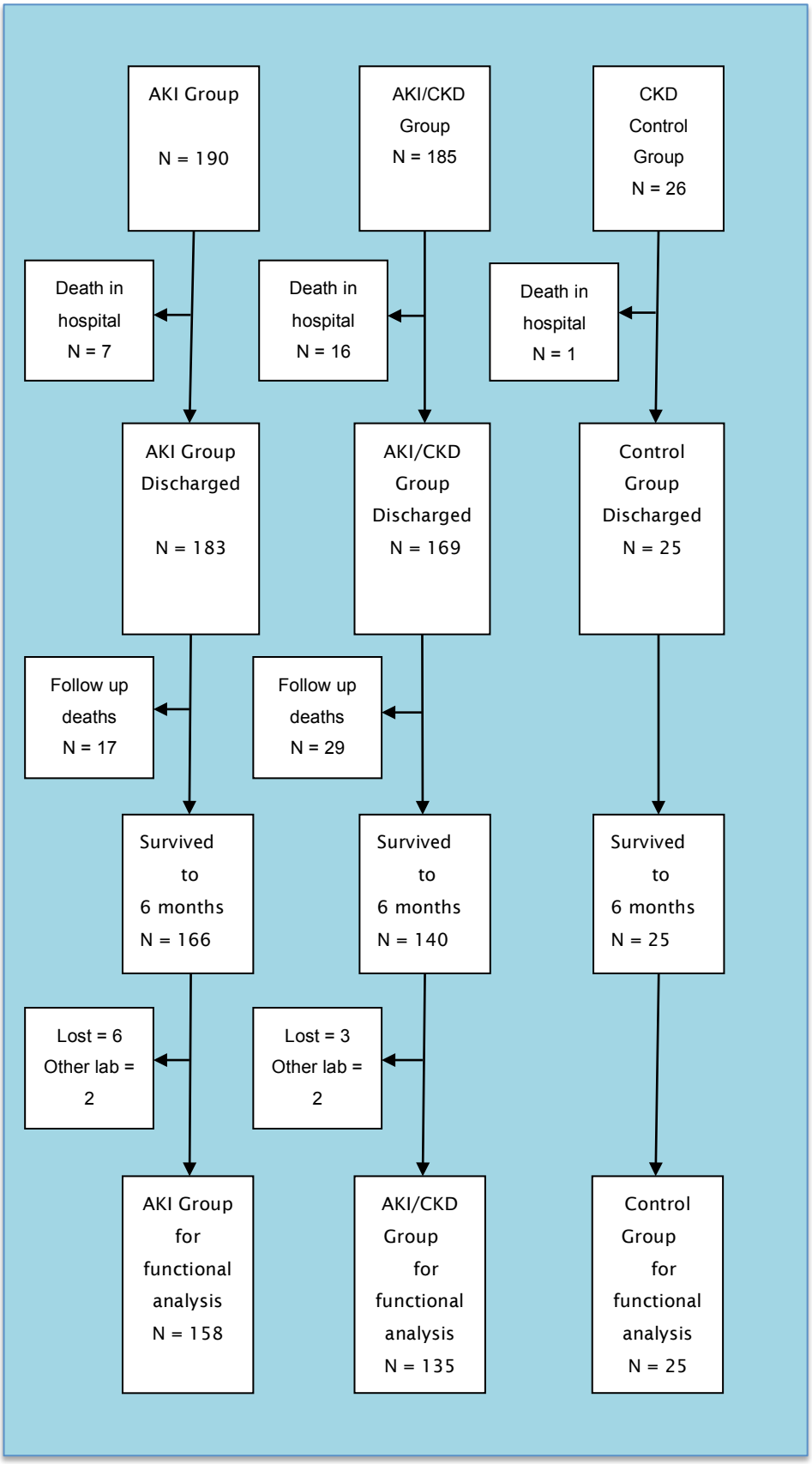


Figure 6.4 describes the outcomes of each group from recruitment through to the follow up at 6 months. Most importantly it describes the numbers in each group available for functional analysis at discharge and again after follow up. In the AKI group contact was lost with 6 patients while in the AKI/CKD group contact was lost with only 3 patients. NHS records and patients general practice was checked to confirm these patients were still alive but they have been removed from the respective groups for the final functional analysis. In addition, 2 patients in each of the groups had moved from the area and while blood test results were provided by their general practice these too were removed from the final analysis as they were performed in a different laboratory. This made a total of 158 (83%) available for follow up of renal function in the AKI group and 135 (73%) in the AKI/CKD group. The overall follow up data for the AKI group and AKI/CKD group is outlined in Table 6.12 and a comparison between the groups is presented. In addition, Tables 6.17 and 6.18 outline the same follow up data divided by AKIN stage for each group respectively.

The median follow up time for each group was 7 months (interquartile range 6-8 months). No patients were followed up before six months.

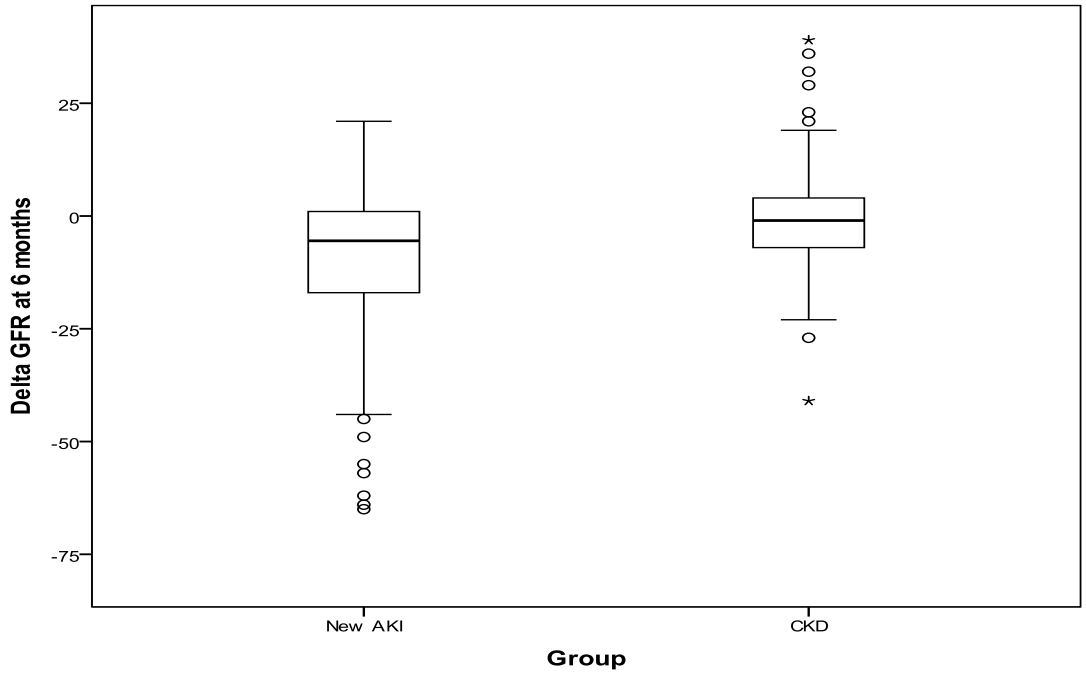
6.5.1 Mortality after 6 months

A formal survival analysis using the Kaplan Meier method was not undertaken as all patients were followed for the same length of time. Mortality is therefore expressed as a simple comparison of proportions. The overall mortality including in hospital was 24.3% in the AKI/CKD group and 12.6% in the AKI group (p=0.003). When divided by AKIN stage there was no mortality difference between stages in the AKI group while in the AKI/CKD group there was significantly increased mortality in AKIN stage 2. Overall, the AKIN stages do not appear to predict mortality on follow up in this study.

6.5.2 Recovery of function after 6 months

Similar to the findings at discharge there was a significant difference in delta eGFR after follow up between the groups. In the AKI group, eGFR fell by a mean of 8.88mls/min while in the AKI/CKD group the fall was 0.47mls/min (p<0.001). These are illustrated in the box-whisker plot in Figure 6.5 below. The fall in eGFR did not reach significance by AKIN stage in the AKI group though there was a trend toward a worsening fall with increasing stage (p=0.044). In the AKI/CKD group there was no significant difference between the AKIN stages according to the change in eGFR.

Figure 6.5 Box-whisker plots of the mean change in eGFR (Delta eGFR) from baseline after 6 months of follow up in the AKI and AKI/CKD groups.



After at least six months follow up it was found that 53% of the AKI group and 34% of the AKI/CKD group had failed to recover within 5mls/min of baseline kidney function. This failure to recover was found across all AKIN stages and is illustrated graphically in Figure 6.6 for the AKI and AKI/CKD groups.

The original study protocol defined failure to recover function as a fall of at least 5mls/min in eGFR. This could arguably be subject to error. The relative percentage fall in function would be much less at higher levels of eGFR and in addition there may be within-subject variation. Therefore in order to strengthen the findings the definition of recovery was expanded to allow for possible variation and error.

Firstly, the criterion for failure to recover was expanded to a fall in eGFR of at least 10mls/min or more. This was chosen as it is above the reported within-individual variation in eGFR of 6.7mls/min discussed in Chapter 2 and so reduces the likelihood of a chance fall due to within subject and analytical variation. In this case the pattern of findings was similar between the groups but was attenuated with 41% in the AKI group failing to recover and 19% of the AKI/CKD group. This is illustrated graphically in Figures 6.7 for the AKI and AKI/CKD groups.

Secondly, the criteria put forward by the ASSESS AKI study group was applied [404]. In the AKI group a fall of at least 25% of baseline eGFR together with progression to at least CKD stage 3 was required. 19.6% of cases failed to recover function according to this definition and thus indicates not only a loss of function after an AKI episode but also progression into the moderate to severe CKD category. In the AKI/CKD group, a 50% fall in baseline eGFR was required to define CKD progression. Only 3.7% of patients satisfied this definition. The ASSESS AKI definition outcomes are illustrated in Figures 6.8.

Finally, as the event rates were so low in the AKI/CKD group with a fall of 50% both groups were examined using a general definition of a fall in eGFR of 25%. In the case of the AKI group the proportion that failed to recover was 20.8%. In the AKI/CKD group 14.8% showed a fall of at least 25% in eGFR. These findings are illustrated in Figures 6.9 for each group.

The study therefore supports the hypothesis that AKI is contributing to the progression of moderate to severe CKD and is causing loss of function in those without moderate to severe CKD. Further strength is added to these findings when the comparison between the outcomes in the AKI/CKD group and CKD controls are examined. These are shown in Table 6.19. Despite the low numbers in the CKD control group there is a difference in functional outcomes. This is not readily apparent when a definition of a fall in eGFR of 5mls/min is used as the outcome, however when it is extended to 10mls/min the difference approaches statistical significance (p=.016) with 20% of the AKI/CKD group reaching this endpoint but none in the CKD control group.

Figure 6.6 Graphical illustration of the percentage of patients with a fall in eGFR of 5mls/min or more from baseline after 6 months (in red) in the AKI and AKI/CKD groups.

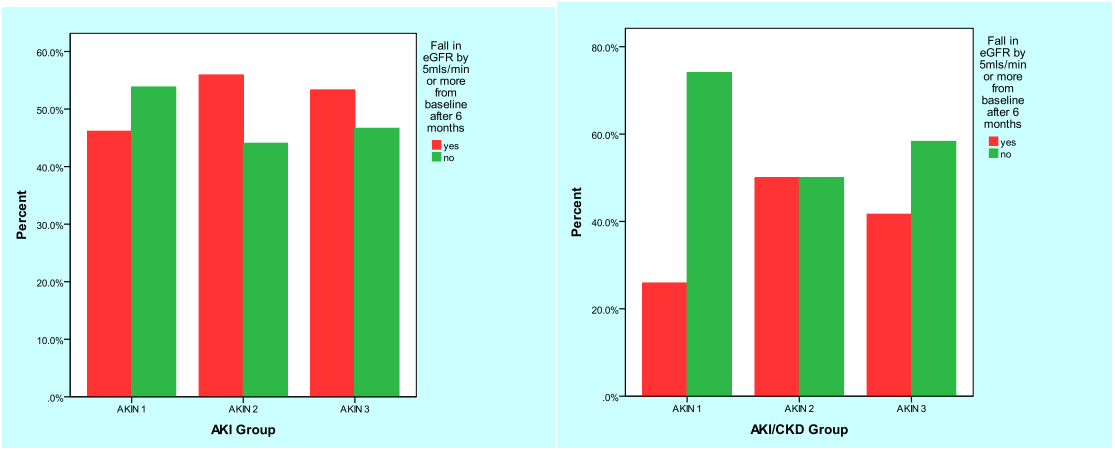


Figure 6.7 Graphical illustration of the percentage of patients with a fall in eGFR of 10mls/min or more from baseline after 6 months (in red) in the AKI and AKI/CKD groups.

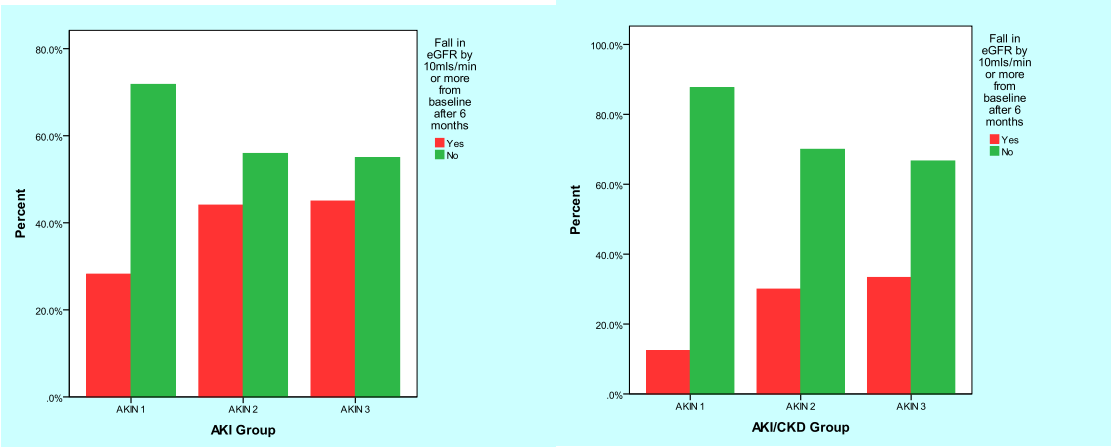


Figure 6. 8 Graphical illustration of the percentage of patients with a fall in eGFR according to the ASSESS AKI criteria from baseline after 6 months – a fall of 25% in eGFR and reaching at least CKD stage 3 in the AKI group and a fall in eGFR of at least 50% in the AKI/CKD group.

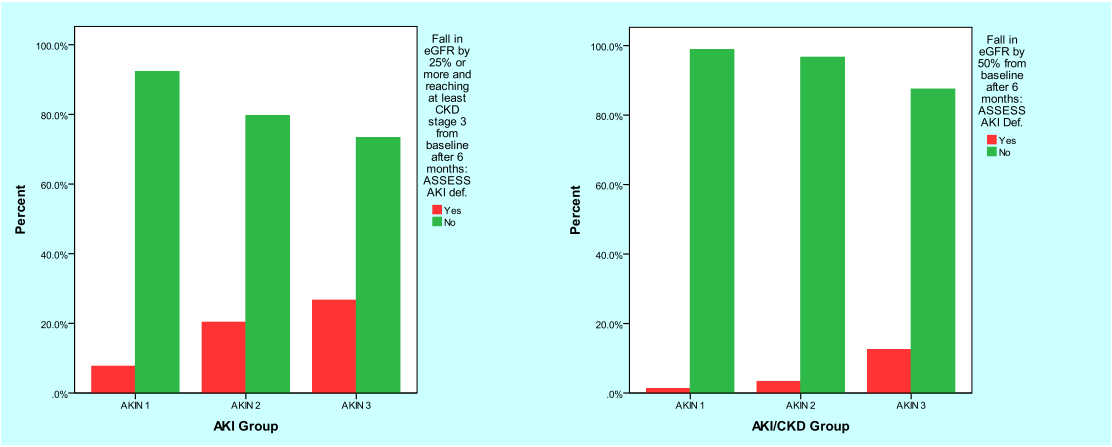
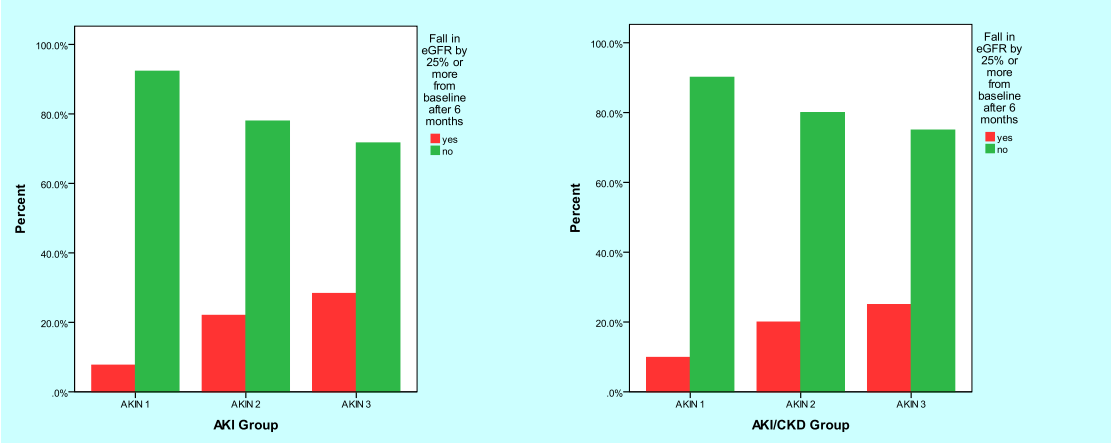


Figure 6.9 Graphical illustration of the percentage of patients with a fall in eGFR of at least 25% from baseline after 6 months in the AKI and AKI/CKD groups.



Dialysis after 6 months

In the AKI group 16 patients received renal replacement therapy during their AKI episode. Two of these patients died in hospital and another died during follow up. The remaining 13 patients remained independent of dialysis at the time of follow up. Of these, 6 returned to within 5mls/min of baseline function and were considered to have recovered fully. The remaining 7 (54%) patients who did not recover demonstrated a fall of at least 10mls/min in eGFR while 3 (23%) had a fall of at least 25% from baseline and reached CKD stage 3.

In the AKI/CKD group 10 patients received renal replacement therapy during the AKI episode. Two of these died in hospital. Three patients were discharged requiring dialysis and one of these died during follow up. During follow up another patient from the AKI/CKD group started dialysis but had not required dialysis during their AKI. Therefore after 6 months 3 patients from the AKI/CKD group were dialysis dependent which account for 1.6% of the original AKI/CKD cohort or 2.1% of survivors.

6.5.3 Sensitivity analysis for AKI Group

One potential limitation in any study of the impact of AKI on baseline function is the definition of baseline function itself. In this study baseline function in the AKI group was defined as at least one eGFR ≥ 60mls/min measured as an outpatient in the year prior to the index AKI. Given the variation that can occur in eGFR measurement it is possible that some patients may have been misclassified. It was noted during the extended review of previous results when calculating the eGFR slope described earlier that some patients in the AKI group had evidence of an eGFR below 60 mls/min at some point over the three years prior to the chosen baseline despite having no evidence of this during the year immediately prior to the AKI. In addition, some patients with diabetic nephropathy manifested by evidence of microalbuminuria may have an eGFR above the 60mls/min threshold i.e. lie in CKD stages 1 or 2. As shown in Table 6.5 8.4% of patients in the AKI group had evidence of microalbuminuria. It is therefore possible that some of the lack of recovery found in the AKI group may have occurred in patients who already had evidence of CKD.

The hospital biochemistry database was searched for each patient in the AKI group over the three year period prior to their study baseline eGFR for any evidence of an eGFR recorded as < 60mls/min in the outpatient setting. At least one was found in 28 patients (14.7%). These were combined with those with evidence of microalbuminuria which brought the total up to 38 patients (20%). Although by definition at least two

eGFR values < 60mls/min are needed to define CKD these patients were removed from the original cohort and this new group of 152 patients was analysed separately to assess if this would make any difference to the outcomes found. The outcomes in this group are outlined in Table 6.20 and are compared to the outcomes found in the subgroup of 38 patients removed. It can be seen that no significant difference was found in mortality or in recovery of function using any of the definitions described. The 38 patients in the original cohort are therefore unlikely to be distorting the results.

Table 6.16 Follow up data after 6 months for the AKI and AKI/CKD groups with between group analysis.

		AKI Group	AKI/CKD Group	P
		N = 158	N=135	
Time to follow up eGFR in months Median (IQR)		7 (6-8)	7 (6-8)	0.422
Over all Mortality N(%)		**24 (12.6)**	**45 (24.3)**	**0.003**
Mortality by AKIN N(%)				
	Stage 1	5 (10.9)	17 (17.1)	
	Stage 2	9 (12.7)	21 (39.6)	
	Stage 3	10 (13.7)	7 (21.2)	
Mortality by CKD Stage N(%)	Stage 3A		14 (21.9)	
	Stage 3B		27 (31.4)	
	Stage 4		4 (12.1)	
Delta eGFR @ 6mts Mean (SD)		**-8.88 (16.5)**	**-0.47 (11.5)**	**<0.001**
Delta by AKIN	Stage 1	-4 (11.52)	-0.13 (9.15)	
	Stage 2	-8.51 (14.26)	-1.5 (15.36)	
	Stage 3	-12.42 (20.24)	-0.32 (13.67)	
Failure to recover by study criteria Fall in eGFR >5mls/min N(%)		**83 (52.5)**	**46 (34.1)**	**0.002**
By AKIN N(%)	Stage 1	18 (46.15)	21 (25.92)	
	Stage 2	33 (55.93)	15 (50)	
	Stage 3	32 (53.33)	10 (41.67)	

		AKI Group	AKI/CKD Group	
		N = 158	N=135	P
Fall in eGFR >10 mls/min N(%)		**64 (40.5)**	**27 (20)**	**<0.001**
By AKIN N(%)	Stage 1	11 (28.2)	10 (12.3)	
	Stage 2	26 (44.1)	9 (30)	
	Stage 3	27 (45)	8 (33.33)	
ASSESS AKI Criteria Fall 25% and to CKD N(%)		31 (19.6)		
By AKIN N(%)	Stage 1	3 (7.7)		
	Stage 2	12 (20.34)		
	Stage 3	16 (26.67)		
50% fall in eGFR in CKD Group N(%)			5 (3.7)	
Fall in eGFR by ≥25% N(%)		33(20.8)	20(14.8)	
By AKIN N(%)	Stage 1	3 (7.7)	8 (9.9)	
	Stage 2	13 (22)	6 (24)	
	Stage 3	17 (28.3)	6 (33)	
Total on Dialysis @ 6mts N(%)		0	3 (2.1)	0.101
	On dialysis since d/c N(%)	0	2 (1.4)	
	Started dialysis since d/c N(%)	0	1 (0.7)	
On RASB after 6mts N(%)	AKI: N=155 AKI/CKD: N=119	67 (43.2)	60 (50.4)	0.237
	On RASB after 6mts who were on it at time of AKI N(%)	59 (73)	59 (65.5)	0.247
Readmitted N(%)		71 (40.1)	72 (43.1)	0.572
Another AKI in 6mts N(%)		23 (12.1)	36 (19.5)	0.082
Failing to recover by study criteria with another AKI N(%)		7(8.4)	9(19.6)	0.093
Failing to recover by study criteria with readmission N(%)		27 (32.5)	20 (43.5)	0.216

Table 6.17 Follow up data for the AKI group divided by AKIN stage.

	AKI Group			
	AKIN 1	AKIN 2	AKIN 3	**p**
	N = 46	N = 71	N = 73	
Time to follow up eGFR in months Median (IQR)	7 (6-8)	7 (6-8)	7 (6-8)	
Over all Mortality N(%)	5 (10.9)	9 (12.7)	10 (13.7)	0.903
Delta eGFR @ 6mts Mean (SD)	-4 (11.52)	-8.51 (14.26)	-12.42 (20.24)	0.044
Failure to recover by study criteria Fall in eGFR >5mls/min N(%)	18 (46.15)	33 (55.93)	32 (53.33)	0.630
Fall in eGFR >10 mls/min N(%)	11 (28.2)	26 (44.1)	27 (45)	0.196
ASSESS AKI Criteria Fall 25% and to CKD N(%)	3 (7.7)	12 (20.34)	16 (26.67)	0.066
Total on Dialysis @ 6mts N(%)	0	0	0	
On RASB after 6mts N(%)	18 (46.2)	25 (43.9)	24 (40.7)	0.860
On RASB after 6mts who were on it at time of AKI N(%)	15 (71.4)	22 (73.3)	22 (75.9)	0.938
Readmitted N(%)	18 (41.9)	23 (34.3)	30 (44.8)	0.451
Another AKI in 6mts N(%)	6 (13)	8 (11.3)	9 (12.3)	0.994
Failing to recover by study criteria with another AKI N(%)	2 (11.1)	3 (9.1)	2 (6.3)	0.826
Failing to recover by study criteria with readmission N(%)	6 (33.3)	9 (27.3)	12 (37.5)	0.677

Table 6.18 Follow up data for the AKI/CKD group divided by AKIN stage.

	AKI/CKD Group			
	AKIN 1 N = 99	AKIN 2 N = 53	AKIN 3 N = 33	**p**
Time to follow up eGFR in months Median (IQR)	**7 (6-8)**	**7 (7-8.25)**	**6 (6-7)**	**0.002**
Over all Mortality N(%)	**17 (17.1)**	**21 (39.6)**	**7 (21.2)**	**0.008**
Delta eGFR @ 6mts Mean (SD)	-0.13 (9.15)	-1.5 (15.36)	-0.32 (13.67)	0.337
Failure to recover by study criteria Fall in eGFR >5mls/min N(%)	21 (25.92)	15 (50)	10 (41.67)	0.041
Fall in eGFR >10 mls/min N(%)	10 (12.3)	9 (30)	8 (33.3)	0.023
ASSESS AKI Criteria 50% fall in eGFR in CKD Group N(%)	1 (1.2)	1 (3.3)	3 (12.5)	0.037
Total on Dialysis @ 6mts N(%)	1 (1.2)	0	2 (7.4)	0.087
On dialysis since d/c N(%)	0	0	2 (7.4)	
Started dialysis since d/c N(%)	1 (1.2)	0	2 (7.4)	
On RASB after 6mts N(%)	36 (50)	14 (56)	10 (45.5)	0.766
On RASB after 6mts who were on it at time of AKI N(%)	35 (66)	14 (66.7)	10 (62.5)	0.959
Readmitted Y/N N(%)	43 (45.3)	18 (42.9)	11 (36.7)	0.709
Another AKI in 6mts N(%)	**18 (18.2)**	**13 (24.5)**	**5 (15.2)**	**0.008**
Failing to recover by study criteria with another AKI N(%)	4 (19)	4 (26.7)	1 (10)	0.587
Failing to recover by study criteria with readmission N(%)	10 (47.6)	6 (40)	4 (40)	0.874

Table 6.19 Comparison of outcomes of the AKI/CKD group and CKD control group after 6 months of follow up.

		AKI/CKD Group N=185	CKD Control Group N=26	P
Time to follow up eGFR in months Median (IQR)		7 (6-8)	6 (6-7.75)	0.323
Over all Mortality N(%)		45 (24.3)	1 (3.8)	0.02
Delta eGFR @ 6mts Mean (SD)		-0.47 (11.5)	+ 1.46 (7.48)	0.432
Total on Dialysis @ 6mts N(%)		3 (2.1)	0	
Fall in eGFR >5mls/min N(%)		46 (34)	4 (16.7)	.091
Fall in eGFR >10 mls/min N(%)		27 (20)	0	.016
Fall in eGFR by ≥25% N(%)		20 (14.8)	0	.044
On RASB after 6mts N(%)		60 (50.4)	7 (38.9)	0.328
	On RASB after 6mts who were on it at time of AKI N(%)	59 (65.5)		
Readmitted N(%)		72 (43.1)	10 (40)	0.769
AKI in 6mts N(%)		36 (19.5)	3 (11.5)	0.423

Table 6.20 The AKI group split into those with and without evidence of at least one eGFR < 60mls/min during the three years prior to the chosen baseline and/or evidence of microalbuminuria. Comparison of the outcomes in these subgroups after 6 months is made and no difference can be seen between them in terms of mortality or functional recovery.

		AKI Group	AKI Group without previous eGFR < 60 and/or raised ACR	AKI Group with previous eGFR < 60 and/or raised ACR	P
		N = 190	N=152	N= 38	
Over all Mortality N(%)		24 (12.6)	21(13.8)	3(7.9)	0.326
Mortality by AKIN					
N(%)	Stage 1	5 (10.9)	5 (13.1)	0	
	Stage 2	9 (12.7)	7 (13.4)	2 (10.52)	
	Stage 3	10 (13.7)	9 (14.5)	1(9.0)	
Failure to recover by study criteria		N=158	N=123	N=35	
Fall in eGFR >5mls/min N(%)		83 (52.5)	63 (51.2)	20 (57.1)	0.536
By AKIN N(%)	Stage 1	18 (46.15)	15 (48)	3 (37.5)	
	Stage 2	33 (55.930	23 (54.7)	10 (58.8)	
	Stage 3	32 (53.33)	25 (50)	7 (70)	
Fall in eGFR >10 mls/min N(%)		64 (40.5)	50 (40.7)	14 (40)	0.945
By AKIN N(%)	Stage 1	11 (28.2)	10 (32)	1 (12.5)	
	Stage 2	26 (44.1)	19 (45)	7 (41.1)	
	Stage 3	27 (45)	21 (42)	6 (60)	
ASSESS AKI Criteria					
Fall 25% and to CKD N(%)		31 (19.6)	22(17.9)	9 (25.7)	0.304
By AKIN N(%)	Stage 1	3 (7.7)	3 (9.7)	0	
	Stage 2	12 (20.34)	7 (16.6)	5 (29.4)	
	Stage 3	16 (26.67)	12(24)	4 (40)	

Table 6.16 outlines the comparison of the AKI/CKD group and the CKD control group after 6 months. Again the small numbers in the control group make it difficult to draw any firm conclusion from these data. There was a trend toward a higher mortality in the AKI/CKD group (p=0.02). It is notable that the mean change in eGFR in the control group was +1.46mls/min compared to -0.47mls/min in the AKI/CKD group although

this difference did not reach statistical significance possibly because of a lack of power.

Table 6.21 Comparison of outcomes of the AKI/CKD group and CKD control group after 6 months of follow up.

		AKI/CKD Group N=185	CKD Control Group N=26	P
Time to follow up eGFR in months Median (IQR)		7 (6-8)	6 (6-7.75)	0.323
Over all Mortality N(%)		45 (24.3)	1 (3.8)	0.02
Delta eGFR @ 6mts Mean (SD)		-0.47 (11.5)	+ 1.46 (7.48)	0.432
Total on Dialysis @ 6mts N(%)		3 (2.1)	0	
Fall in eGFR >5mls/min N(%)		46 (34)	4 (16.7)	.091
Fall in eGFR >10 mls/min N(%)		27 (20)	0	.016
Fall in eGFR by ≥25% N(%)		20 (14.8)	0	.044
On RASB after 6mts N(%)		60 (50.4)	7 (38.9)	0.328
	On RASB after 6mts who were on it at time of AKI N(%)	59 (65.5)		
Readmitted N(%)		72 (43.1)	10 (40)	0.769
AKI in 6mts N(%)		36 (19.5)	3 (11.5)	0.423

6.5.4 Evolution of kidney function after AKI

There are two paradoxical findings described in the results above that required further exploration. Firstly, at the time of discharge from hospital it was found that the mean change of eGFR in the AKI/CKD group was positive 0.11mls/min. This contrasts with the finding that 31.4% of the group had not recovered function. Secondly, it is notable that there was little difference between the proportion who failed to recover function

at discharge according to the study criteria and the proportion who failed to recover after 6 months of follow up. For example, in the AKI group, 52.6% of patients were found to have failed to recover within 5mls/min of baseline function at the time of discharge from hospital while after 6 months follow up this figure was unchanged at 52.5%. A similar pattern was seen in the AKI/CKD group. If it is presumed these are the same people this is a surprising finding as some degree of recovery would be expected to have occurred.

To resolve these issues each group at the time of discharge was divided into three subgroups. Those whose function remained unchanged at discharge and so remained within ± 5mls/min of baseline, those with a fall of ≥ 5mls/min and hence failure to recover, and those who showed a gain of function with a rise in eGFR from baseline ≥ 5mls/min. The mean change in eGFR was calculated for each of the subgroups and the results of these for both the AKI group and AKI/CKD group are illustrated in Table 6.22. As expected there is an overall fall in the mean eGFR in the group that failed to recover within 5mls/min of baseline. This is attenuated in the overall mean change in eGFR by a rise in eGFR in the subdivision that apparently gains function at the time of discharge. This is most marked in the AKI/CKD group and explains why the overall mean change is positive 0.11 mls/min despite finding that more than 30% failed to recover.

The outcome for each subgroup was then explored after the 6 months of follow up to assess how the position of patients within these subgroups may have changed and this is illustrated in Table 6.23 and Table 6.24 for the AKI and AKI/CKD groups respectively. It can be seen that in both groups a marked exchange between the subdivisions takes place between discharge and follow up. For example, in the AKI group at the time of discharge 100 patients fell into the failure to recover division. After 6 months 36% of these that were available for analysis had recovered to join either the ‘gain’ or ‘no change’ divisions. However, a similar number from the ‘gain’ and ‘no change’ groups at discharge switch to the failure to recover group after 6 months and balance this.

This explains the finding in the results described in this chapter that there appeared to be no overall change in the percentage that recovered at follow up. The answer lies in the fact that the patients in this subdivision at follow up are not entirely the same patients that were in the subdivision at discharge.

Table 6.22 Mean change in eGFR at discharge in each group in subdivisions of a gain in eGFR , no change, and a fall in eGFR together with the overall mean change.

	Mean change in Discharge eGFR (±SD)	Overall mean mean change at discharge (±SD)
AKI Group		
Gain in eGFR ≥ 5mls/min	+14.24 (7.5)	
No change ± 5mls/min	+0.16 (1.9)	
Fall in eGFR ≥ 5 mls/min	-26.43 (16.6)	
		-11.75 (21.1)
AKI/CKD Group		
Gain in eGFR ≥ 5mls/min	+ 13.75 (9.1)	
No change ± 5mls/min	-0.66 (2.5)	
Fall in eGFR ≥ 5 mls/min	-12.31 (7.6)	
		+0.11 (12.7)

Table 6. 23 AKI Group divided by functional status at discharge into a gain in eGFR of ≥5mls/min, no change ±5mls/min, and a fall of ≥5mls/min relative to baseline. The status of each of these divisions after 6 months of follow up is tabulated.

eGFR status at discharge from hospital relative to baseline	eGFR status after 6 months of follow up relative to baseline			
	RIP/Lost	Gain of ≥5mls/min N(%)	No change N(%)	Fall of ≥ 5mls/min N(%)
Gain of ≥5mls/min N=34	4	10(33)	9 (30)	11(37)
No change N=49	10	1 (3)	23 (58)	15 (38)
Fall of ≥5mls/min N= 100	11	16 (18)	16 (18)	57 (64)

Table 6. 24 AKI/CKD Group divided by functional status at discharge into a gain in eGFR of ≥5mls/min, no change ±5mls/min, and a fall of ≥5mls/min relative to baseline. The status of each of these divisions after 6 months of follow up is tabulated.

eGFR status at discharge from hospital relative to baseline	eGFR status after 6 months of follow up relative to baseline			
	RIP/Lost	Gain of ≥5mls/min N(%)	No change N(%)	Fall of ≥ 5mls/min N(%)
Gain of ≥5mls/min N=51	11	17(44)	17 (44)	6(13)
No change N=61	11	10 (20)	27 (54)	13 (26)
Fall of ≥5mls/min N= 57	12	4 (9)	14(31)	27 (60)

6.5.5 Repeat hospitalisation and repeat AKI during follow up

During the six months following the AKI 40% of the AKI group and 43% of the AKI/CKD group were readmitted to hospital at least once. No difference was found in readmission rates according to AKIN stage within the groups. 19.5% of the AKI/CKD group had evidence of another AKI episode meeting AKIN criteria while 12.1% of the AKI group had another AKI episode. When divided by AKIN stage there was no difference in repeat AKI rate between stages in the AKI group while in the AKI/CKD group more repeat episodes occurred in AKIN stage 2. The AKIN stages did not predict readmission or repeat AKI according to stage during follow up.

To assess the influence of repeat AKI episodes on recovery patterns the numbers who failed to recover according to study criteria and had a repeat AKI episode were explored. In the AKI group 8.4% of those who failed to recover had a repeat episode while in the AKI/CKD group 19.6% had a repeat episode (p=0.093). No differences were found according to AKIN stage in either group.

The finding that a substantial proportion of both groups experienced repeat AKI episodes is important when viewed together with the preadmission findings. 5.3% of the AKI group and 20.5% of the AKI/CKD group also showed evidence of an AKI in the 12 months prior to the index AKI. Of the 23 patients in the AKI group who had a repeat AKI during follow up, 3 patients (13%) had evidence of an AKI in the previous 12 months. Of the 36 patients in the AKI/CKD group who had a repeat episode, 7 patients (19.4%) had an AKI during the previous 12 months. This suggests that at least in some patients particularly in the AKI/CKD group, AKI is a recurrent phenomenon. Whether or not repeat AKI episodes predicted failure to recover function will be explored further using regression analysis in Chapter 7.

6.5.6 Use of ACE inhibitors at the time of follow up

52.1% of the AKI Group and 74.1% of the AKI/CKD group were on RAS-blockers at the time of their AKI. These were stopped in over 90% in each group at the time of the AKI as a part of their clinical management. The status in relation to the use of RAS-blockers after 6 months was available in all but 6 patients in the AKI group and 18 patients in the AKI/CKD group. Missing data was not made available by the general practitioner at the time of follow up.

After follow up, 43% of the AKI group (N=155) and 50% of the AKI/CKD group (N=119) were on RAS-blockers. Comparison was made between the status of those prior to the AKI and after follow up. It was found that of the survivors at 6 months who were on RAS blockers before the AKI, 73% in the AKI group and 65.5% in the AKI/CKD group were on them after follow up. This indicates that many of those who had their RAS blocker medication discontinued at the time of the AKI did not have them restarted. There was no difference between AKIN stages in each group in this regard.

6.6 Comparison of outcomes between community-acquired and hospital-acquired AKI

Tables 6.25 and 6.26 compare the hospital and 6 month outcomes between those cases where AKI was present on admission, and hence community- acquired, and cases with hospital -acquired AKI in each of the two groups. There is a trend toward increased mortality both in hospital and at 6 months in community-acquired cases in the AKI group. There is no difference in mortality at either time point in the AKI/CKD group. In terms of failure to recover function there is no significant difference in this outcome either at hospital discharge or after 6 months between hospital and community acquired cases in either group.

Table 6.25 Hospital and 6 month outcomes of those with AKI present on admission (Community AKI) compared to hospital-acquired AKI in the AKI group.

	AKI Group Admission AKI N = 118	AKI Group Hospital AKI N = 72	P
Hospital mortality N(%)	7(5.9)	0	.035
Not recovered function at discharge N(%)	58 (52.2)	42 (58.3)	.420
	N=98	N=68	
Over all 6 month Mortality N(%)	20 (16.9)	4 (5.5)	.024
Fall in eGFR >5mls/min N(%)	47 (50)	36 (56)	.440
Fall in eGFR >10 mls/min N(%)	38 (40.4)	26 (40.6)	.980
Fall in eGFR by ≥25% N(%)	24 (25.5)	9 (14)	.082

Table 6.26 Hospital and 6 month outcomes of those with AKI present on admission (Community AKI) compared to hospital-acquired AKI in the AKI/CKD group.

	AKI/CKD Group Admission AKI N = 135	AKI Group Hospital AKI N = 50	P
Hospital mortality N(%)	11(8.1)	5(10)	.891
Not recovered function at discharge N(%)	47 (37.9)	10 (22.2)	.057
	N=102	N=38	
Over all 6 month Mortality N(%)	33 (24.4)	12 (24)	.956

	AKI/CKD Group Admission AKI N = 135	AKI Group Hospital AKI N = 50	P
Fall in eGFR >5mls/min N(%)	34 (34.3)	12 (33.3)	.913
Fall in eGFR >10 mls/min N(%)	21 (21.2)	6 (16.6)	.559
Fall in eGFR by ≥25% N(%)	16 (16.1)	4(11.1)	.465

6.7 12 month mortality

The mortality status on all patients at 12 months was obtained using NHS tracing. In the AKI group a further 7 patients died between 6 and 12 months. In the AKI/CKD group a further 11 patients died during this period. This brings the total mortality at 12 months to 16.3% in the AKI group and 30.2% in the AKI/CKD group. These data are outlined in Table 6.27 and are divided by AKIN stage.

Table 6.27 Mortality at 12 months in the AKI and AKI/CKD groups overall and divided by AKIN stage.

		AKI Group N = 190	AKI/CKD Group N=185	P
Over all Mortality at 12 months N(%)		**31 (16.3)**	**56 (30.2)**	**0.001**
Mortality by AKIN Stage N(%)	Stage 1	16 (15.7)	26 (26.2)	
	Stage 2	9 (16.7)	22 (41.5)	
	Stage 3	6 (17.6)	8 (24.2)	

6.8 Summary of key findings

1. 53% of the AKI group and 34% of the AKI/CKD group failed to recover their eGFR to within 5mls/min of baseline. 20.8% of the AKI group and 14.8% of the AKI/CKD group demonstrated a fall in eGFR of at least 25% from baseline. Therefore this study demonstrates clearly that AKI causes de novo CKD in those with a baseline eGFR > 60mls/min and progression of CKD in those who already have it.

2. Those in the AKI/CKD were older and had a greater burden of comorbidities. In both groups, the majority had an AKI in which the primary insult occurred in the community and was evident on admission to hospital – 62% in the AKI group and 73% in the AKI/CKD group. In over 95% of cases the cause of the AKI in each group was pre-renal. Sepsis was prominent in both groups with 23% in the AKI group and 31% in the AKI/CKD group. More than one causal insult was found in 28% of the AKI group and 26% of the AKI/CKD group.

3. Hospital mortality was 3.7% in the AKI group and 8.6% in the AKI/CKD group. AKIN staging did not predict hospital mortality. Comparing the AKI/CKD group to the CKD controls the median length of hospital stay was significantly longer. At 6 months mortality in the AKI group was 12.6% while in the AKI/CKD group it was 24.3%. AKIN staging did not predict mortality.

4. After 12 months of follow up mortality in the AKI group was 16.3% while in the AKI/CKD group it was 30.2%. This clearly demonstrates the poor prognostic significance of an AKI.

5. The findings also demonstrate a pattern of repeat admission and repeat AKI in this cohort. During the 6 months after discharge 40% of the AKI group and 43% of the AKI/CKD group were readmitted and of these 12.1% and 19.8% experienced another AKI.

Chapter 7: Results 3 – Regression analysis

7.1 Introduction

In this chapter the data are explored further using binary logistic regression analysis. Univariate analysis was preformed on a variety of clinical variables to assess their influence on mortality at 6 and 12 months after the index AKI and recovery of function. In addition, the combined outcome of death or failure to recover defined by a fall in eGFR of 5mls/min was explored. Finally, the influence of recovery of function at discharge, readmission, and repeat AKI during follow up was explored. The univariate analysis was then followed by multivariate logistic regression which is described later in this chapter. The findings presented are discussed at length in Chapter 8.

7.2 Univariate analysis

7.2.1 Mortality

Tables 7.1 and 7.2 outline the univariate binary logistic regression analysis using mortality at 6 and 12 months respectively as the dependent variables. Results are described for both the AKI and the AKI/CKD groups. In Tables 7.3 and 7.4 the factors that reached the study level of significance (P<.01) in each group are summarised.

7.2.1 (i) Preadmission variables

Admission to hospital during the 12 months prior to the index AKI increased the odds of mortality in both groups. This approached statistical significance for mortality at 12 months in the AKI group (p=0.037). In the AKI group a history of a previous AKI during the 4 years prior to the index AKI increased the odds of mortality significantly at 6 months (OR 4.697, p=0.006). The significance of this finding was reduced at 12 months (p=0.034). In the AKI/CKD group a history of a previous AKI did not significantly influence mortality.

The slope of decline in eGFR over the three years prior to the index AKI was not found to influence either 6 or 12 month mortality in the AKI or the AKI/CKD groups. In addition the influence of baseline eGFR did not reach significance in either group.

7.2.1 (ii) Baseline variables

Increasing age and Charlson comorbidity score significantly increased the odds of mortality at both 6 and 12 months in the AKI group. However in the AKI/CKD group the findings were less clear except at 12 months where age increased the odds of mortality (P=.029). Sex did not appear to influence mortality in either group.

A potentially important finding was that use of RAS-blockers prior to the AKI had a protective effect in the AKI/CKD group and this approached statistical significance at 6 months (OR .468, 95% C.I .227 - .965, p=0.04). The use of furosemide increased the odds of mortality in both groups and this reached statistical significance at 12 months in the AKI group (p=0.004). This effect is presumably related to underlying comorbidities that required the use of furosemide and indeed it was reduced with adjustment for age and Charlson score.

Increased body mass index reduced the odds of mortality for the AKI/CKD group at 12 months (OR .933, 95 C.I. .876-.995, p=0.034). A surprising finding was that a history of previous hypertension appeared to exert a protective effect in the AKI/CKD group particularly for 6 month mortality (OR .375, 95% C.I. .146 - .960, p=0.041). Given the large proportion of patients using RAS blockers in this group (74%), adjustment was made for their use and the effect was reduced (OR .540, 95% C.I. .176 – 1.653, p=0.281).

7.2.1 (iii) AKI related variables

The variable that appeared to exert the strongest influence on mortality was the admitting specialty in the AKI/CKD group. When admission was under a medical specialty the odds of mortality was increased and this was statistically significant at 6 and 12 months. Those who had evidence of AKI on admission to hospital and hence had community acquired AKI in the AKI group had increased odds of mortality at both 6 and 12 months. This approached significance at both time points (p=0.029 and p=0.025 respectively). This effect was not found in the AKI/CKD group.

AKIN stage did not prove to be a predictor of mortality in the AKI group perhaps because of insufficient power in the study. In the AKI/CKD group increased AKIN stage did predict mortality and reached statistical significance overall (p=0.01). Interestingly, AKIN stage 2 had the highest odds ratio. The reason for this increased risk compared to stage 3 is unclear. As demonstrated in Table 6.3, there was no significant difference

between these groups in terms of baseline function or AKI details. This finding is therefore likely to be due to chance.
The cause of AKI appeared not to have an influence in either group although in the AKI/CKD group the odds of mortality were increased for septic and complex AKI at 12 months (p=.062).

ITU admission did not predict mortality in either group. This is most likely bias from the selection of younger fitter patients for intensive care. A formal renal review at the time of the AKI had no influence on mortality at either time point. Finally, in the case of those who recovered to baseline by the time of discharge from hospital, the longer it took to recover increased the odds of mortality in the AKI group at 12 months (p=0.023).

Table 7.2 Univariate binary logistic regression analysis using mortality at 6 months as the dependent variable for the AKI and AKI/CKD groups.

	AKI Group				**AKI/CKD Group**			
	B	**OR**	**95% CI**	**Sig.**	**B**	**OR**	**95% CI**	**Sig.**
PreAKI ACR	-.107	.898	(.905 - 1.145)	.386	-.001	.999	(.990 – 1.008)	.860
eGFR slope	-.028	.972	(.884 – 1.070))	.566	.023	1.023	(.961 – 1.089)	.475
Admit. In prev.								
12 months	1.265	3.545	(1.472 - 8.557)	.379	.569	1.766	(.898 – 3.475)	.099
AKI in prev.								
12 months	1.674	5.333	(1.386 – 20.529)	.015	-.602	.134	(.506 – 2.584)	.748
AKI in prev.								
4 years	**1.547**	**4.697**	**(1.551 – 14.224)**	**.006**	-.074	.838	(.456 – 1.890)	.929
Baseline eGFR	.034	1.034	(.989 – 1.082)	.143	-.007	.993	(.966 – 1.021)	.638
Age	**.059**	**1.061**	**(1.019 – 1.104)**	**.004**	.033	1.034	(.994 – 1.075)	.098
Sex	.402	1.495	(.606 – 3.686)	.383	.652	1.919	(.958 – 3.844)	.066
Charlson Score	**.509**	**1.664**	**(1.2 – 2.308)**	**.002**	.057	1.059	(.844 – 1.329)	.622
Diabetes	.206	1.229	(.493 – 3.062)	.658	-.607	.545	(.270 – 1.100)	.090
Hypertension	.098	1.103	(.446 – 2.729)	.832	-.981	.375	(.146 - .960)	.041
Smoking hist.	-.096	.908	(.386 – 2.138)	.825	.365	1.441	(.719 – 2.888)	.304
BMI	-.031	.970	(.906 – 1.038)	.379	-.042	.959	(.898 – 1.025)	.215
RASB preAKI	-.096	.908	(.386 – 2.138)	.825	-.758	.468	(.227 - .965)	.040
Aspirin	-.102	.903	(.353 – 2.309)	.831	.127	1.136	(.580 – 2.225)	.710
NSAID	-.351	.704	(.197 – 2.522)	.590	-.606	.545	(.116 – 2.559)	.442
Furosemide	1.085	2.958	(1.141 – 7.669)	.026	.623	1.865	(.931 – 3.735)	.079
Statin	-.522	.593	(.233 – 1.509)	.273	.176	1.192	(.602– 2.361)	.614
Betablocker	.469	1.599	(.614 – 4.165)	.337	.062	1.064	(.539 – 2.102)	.858
Allopurinol	-.490	.613	(.076 – 4.970)	.646	.118	1.125	(.382 – 3.317)	.831
PPI	-.046	.955	(.373 – 2.447)	.924	.182	1.200	(.602 – 2.391)	.604

	AKI Group				AKI/CKD Group			
AKI present on admission	1.244	3.469	(1.135 – 10.603)	.029	.024	1.025	(.480 – 2.187)	.950
Medical	.783	2.187	(.826 – 5.793)	.115	1.644	5.176	(1.924 – 13.926)	.001
AKIN Stage				.903				**.010**
AKIN 1 (ref)		1.00				1.00		
AKIN 2	.174	1.190	(.372 – 3.806)	.769	1.152	3.165	(1.482 – 6.761)	.003
AKIN 3	.264	1.302	(.415 – 4.083)	.651	.261	1.299	(.485– 3.476)	.603
BP < 90	.675	1.963	(.823 – 4.680)	.128	-.650	.522	(.224 – 1.217)	.132
AKI Cause				.834				.262
Hypoperfusion (ref)		1.00				1.00		
Septic	.222	1.249	(.422 – 3.697)	.688	.639	1.895	(.844 – 4.256)	.121
Complex	.292	1.339	(.493 – 3.636)	.567	.529	1.698	(.718 – 4.013)	.228
ITU admission	.544	1.722	(.584 – 5.085)	.325	-.606	.545	(.116 – 2.559)	.442
Renal review	-.897	.408	(.052 – 3.222)	.395	-.044	.957	(.414-2.210)	.918
AKI duration	.077	1.080	(.978 – 1.193)	.130	.017	1.017	(.944 – 1.095)	.664

Table 7.3 Univariate binary logistic regression analysis using mortality at 12 months as the dependent variable for the AKI and AKI/CKD groups.

	AKI Group				AKI/CKD Group			
	B	**OR**	**95% CI**	**p**	**B**	**OR**	**95% CI**	**p**
PreAKI ACR	-.074	.929	(.779 – 1.107)	.409	-.001	.999	(.991 – 1.008)	.891
eGFR slope	-.016	.984	(.900 – 1.075)	.720	.018	1.019	(.961 – 1.080)	.538
Admit. In prev. 12 months	.834	2.303	(1.052 – 5.041)	.037	.529	1.697	(.901 – 3.195)	.101
AKI in prev. 12 months	1.329	3.778	(.999 – 14.729)	.050	.077	1.080	(.500 – 2.333)	.844
AKI in prev. 4 years	1.172	3.229	(1.095 – 9.520)	.034	-.042	.959	(.495 – 1.857)	.900
Baseline eGFR	.025	1.026	(.985 – 1.068)	.220	.007	1.007	(.981 – 1.033)	.605
Age	**.059**	**1.060**	**(1.023 – 1.099)**	**.001**	.042	1.043	(1.004 – 1.083)	.029
Sex	.018	1.018	(.467 – 2.220)	.965	.377	1.457	(.773 – 2.748)	.245
Charlson Score	**.405**	**1.499**	**(1.117 – 2.012)**	**.007**	.119	1.126	(.910 – 1.394)	.274
Diabetes	.332	1.393	(.618 – 3.140)	.424	-.510	.600	(.314 – 1.146)	.122
Hypertension	.160	1.174	(.517 – 2.664)	.702	-.624	.536	(.212 – 1.355)	.187
Smoking hist.	-.178	.837	(.388 – 1.808)	.651	.277	1.319	(.694 – 2.510)	.398
BMI	-.010	.990	(.936 – 1.047)	.728	-.069	.933	(.876 - .995)	.034
RASB preAKI	-.024	.977	(.452 – 2.110)	.952	-.571	.565	(.283 – 1.127)	.105
Aspirin	-.114	.892	(.383 – 2.076)	.791	-.106	.899	(.479 – 1.688)	.740
NSAID	-.691	.501	(.142 – 1.765)	.282	-.923	.397	(.085 – 1.855)	.240
Furosemide	**1.285**	**3.164**	**(1.518 – 8.603)**	**.004**	.775	2.171	(1.131 – 4.168)	.020

	AKI Group				AKI/CKD Group			
Statin	-.551	.576	(.250 – 1.332)	.197	-.082	.922	(.490 – 1.734)	.800
Betablocker	.284	1.328	(.545 – 3.238)	.533	.105	1.111	(.588 – 2.097)	.746
Allopurinol	-.802	.448	(.056 – 3.606)	.451	-.217	.805	(.275 – 2.355)	.692
PPI	-.055	.946	(.406 – 2.205)	.946	.155	1.168	(.612 – 2.228)	.638
AKI present on admission	1.084	2.957	(1.149 – 7.609)	.025	-.111	.895	(.444 – 1.801)	.755
Medical	.765	2.148	(.906 – 5.096)	.083	**1.585**	**4.882**	**(2.053 – 11.607)**	**<.001**
AKIN Stage				.523				.110
AKIN 1 (ref)		1.00				1.00		
AKIN 2	.609	1.838	(.608 – 5.556)	.281	.689	1.993	(.983 – 4.038)	.056
AKIN 3	.575	1.777	(.588 – 5.365)	.308	-.107	.898	(.360 – 2.240)	.818
BP < 90	.349	1.418	(.639 – 3.147)	.391	-.388	.678	(.322 – 1.427)	.306
AKI Cause				.565				.062
Hypoperfusion (ref)		1.00				1.00		
Septic	.357	1.429	(.536 – 3.808)	.476	.788	2.199	(1.021 – 4.737)	.044
Complex	.469	1.599	(.650 – 3.932)	.307	.844	2.325	(1.042 – 5.186)	.039
ITU admission	.456	1.577	(.579 – 4.297)	.373	-.923	.397	(.085 – 1.855)	.240
Renal review	-.412	.662	(.144 – 3.053)	.597	-.080	.923	(.422 – 2.022)	.842
AKI duration	.112	1.118	(1.016 – 1.230)	.023	.005	1.005	(.935 – 1.081)	.885

Table 7.3 Summary of factors that reached the study threshold of significance (p<.01) in the AKI or AKI/CKD groups on univariate analysis with mortality at 6 months as the dependent variable.

	AKI Group			AKI/CKD Group		
Factor	**OR**	**95% C.I.**	**Sig.**	**OR**	**95% C.I.**	**Sig**
AKI in previous 4 years	4.697	(1.551 – 14.224)	**.006**	.838	(.456 – 1.890)	.929
Age	1.061	(1.019 – 1.104)	**.004**	1.034	(.994 – 1.075)	.098
Charlson Score	1.664	(1.2 – 2.308)	**.002**	1.059	(.844 – 1.329)	.622
Medical Admission	2.187	(.826 – 5.793)	.115	5.176	(1.924 – 13.926)	**.001**

Table 7.4 Summary of factors that reached the study threshold of significance (p<.01) in the AKI or AKI/CKD groups on univariate analysis with mortality at 12 months as the dependent variable.

	AKI Group			AKI/CKD Group		
Factor	**OR**	**95% C.I.**	**Sig.**	**OR**	**95% C.I.**	**Sig**
Age	1.060	(1.023 – 1.099)	**.001**	1.043	(1.004 – 1.083)	.029
Charlson Score	1.499	(1.117 – 2.012)	**.007**	1.126	(.910 – 1.394)	.274
Furosemide	3.164	(1.518 – 8.603)	**.004**	2.171	(1.131 – 4.168)	.020
Medical Admission	2.148	(.906 – 5.096)	.083	4.882	(2.053 – 11.607)	**<.001**

7.2.2 Recovery of function

Tables 7.5 outlines the univariate binary logistic regression analysis for failure to recover function according to the original study criteria defined by a fall in eGFR of 5mls/min from baseline. Tables 7.6 and 7.7 outline the same data for the definition extended to a fall in eGFR of 10mls/min and a fall of 25%. Results are described for both the AKI and the AKI/CKD groups. In Table 7.8 the factors that reached the study level of significance (P<.01) in each group are summarised.

7.2.2 (i) Preadmission variables

The strongest finding among the preadmission variables and the most surprising is a protective effect associated with an increased slope of decline in eGFR during the three years prior to the index AKI. In the AKI group this was highly significant when using the definition of a fall in eGFR of 5mls/min (OR .879, 95% C.I. .800 to .965, p=.007). Using the same definition in the AKI/CKD group there was also a protective effect but it did not reach the same level of significance (OR .920, 95% C.I. .851 to .995, p=0.036). This protective effect persisted with extension of the definition of failure to recover to a fall of 10mls/min but was lost when a fall of 25% from baseline was used.

A lower baseline eGFR also appeared to exert a protective effect. In the AKI/CKD group this was highly significant for a fall in eGFR of 10mls/min (OR .944, 95% C.I. .908 to .982, p=.005). However, when failure to recover function was defined as a fall in eGFR of 25% this effect disappears.

7.2.2 (ii) Baseline variables

None of the baseline variables appear to have a substantial impact on recovery of function. In the AKI group increasing age raised the odds of failure to recover but this did not reach significance (OR 1.026, 95% C.I. 1.001-1.051, p=.040). This was not the case in the AKI/CKD group. In both groups the burden of comorbidities at baseline did not appear to influence the recovery outcome.

RAS-blocker use was associated with increased odds of failure to recover in the AKI group. For a fall in eGFR of 25% this association was strongest and approached statistical significance (OR 2.337, 95% C.I. 1.028 to 5.312, p=0.043). Conversely, in the AKI/CKD group the association was less clear. A potentially important observation is that there is a trend toward a protective effect with the use of aspirin or a statin at the time of the AKI. In the case of the AKI/CKD group this approached significance using a definition of a fall in eGFR of 5mls/min in the case of a statin (OR .472, 95% C.I. .229 to .973, p=.042).

7.2.2 (iii) AKI related variables

The severity of the AKI defined by the AKIN stage appeared to be predictive of non-recovery in both groups although this did not reach statistical significance presumably due to insufficient power. This trend with increasing AKIN stage becomes much clearer using the definition of a fall of 25% in eGFR.

Having a nadir BP < 90 systolic recorded at the time of the AKI appears to exert a protective effect in terms of recovery. In the AKI group this approached statistical significance for a fall in eGFR of 5mls/min (OR .439, 95% C.I. .218 to .884, p=.021).

Finally, obtaining a formal renal review while in hospital increased the odds of failure to recover function. This effect was clearest when the definition of a fall of 25% is used and in the case of the AKI group is highly significant (OR 4.680, p=.005). This is likely to be a form of bias by indication, reflecting the severity of the AKI. However, in clinical practice many renal reviews are simply single assessments and so it raises important questions about the follow up of patients after hospital discharge.

Table 7.5 Univariate binary logistic regression analysis for failure to recover function according to the original study criteria defined by a fall in eGFR of 5mls/min from baseline. Results are shown for the AKI group and the AKI/CKD group.

	AKI Group				AKI/CKD Group			
	B	**OR**	**95% CI**	**Sig.**	**B**	**OR**	**95% CI**	**Sig.**
PreAKI ACR	-.038	.963	(.874 – 1.060)	.442	.009	1.009	(.999 – 1.019)	.068
eGFR slope	**-.129**	**.879**	**(.800 - .965)**	**.007**	-.084	.920	(.851 - .995)	.036
Admit. In prev.								
12 months	.311	1.365	(.673 – 2.770)	.389	.039	1.040	(.501 – 2.159)	.916
AKI in prev.								
12 months	-.523	.593	(.096 – 3.647)	.572	-.254	.776	(.310 – 1.938)	.587
AKI in prev.								
4 years	-1.428	.240	(.048 – 1.193)	.081	-.149	.862	(.406 – 1.831)	.699
Baseline eGFR	.000	1.000	(.967 – 1.034)	.985	-.036	.965	(.936 - .994)	.019
Age	.025	1.026	(1.001 – 1.051)	.040	-.004	.996	(.964 – 1.029)	.816
Sex	-.279	.757	(.401 – 1.426)	.389	-.020	.981	(.481 – 1.999)	.957
Charlson Score	-.093	.911	(.699 – 1.187)	.490	-.079	.924	(.729 – 1.171)	.513
Diabetes	-.266	.766	(.385 – 1.525)	.448	.112	1.119	(.549 – 2.281)	.757
Hypertension	.609	1.838	(.945 – 3.574)	.073	.478	1.612	(.415 – 6.271)	.491
Smoking hist.	-.519	.595	(.317 – 1.118)	.107	-.078	.925	(.451 – 1.899)	.832
BMI	.023	1.024	(.974 – 1.076)	.359	.000	1.000	(.943 – 1.060)	1.000
RASB preAKI	.549	1.732	(.921 – 3.257)	.088	-.091	.913	(.382 – 2.180)	.837
Aspirin	-.148	.665	(.441 – 1.687)	.665	-.647	.524	(.253 – 1.086)	.082
NSAID	-.391	.676	(.294 – 1.555)	.357	.924	2.520	(.726 – 8.753)	.924
Furosemide	-.118	.889	(.361 – 2.189)	.798	-.154	.857	(.420 – 1.747)	.671
Statin	-.070	.932	(.495 – 1.756)	.828	-.752	.472	(.229 - .973)	.042
Betablocker	.115	1.122	(.510 – 2.469)	.774	.577	1.781	(.865 – 3.667)	.117
Allopurinol	-.108	.897	(.249 – 3.231)	.868	.081	1.084	(.341 – 3.445)	.891
PPI	-.026	.975	(.494 – 1.921)	.941	-.393	.675	(.316 – 1.441)	.310
AKI present on admission	-.251	.778	(.411 – 1.472)	.440	.045	1.046	(.466 – 2.346)	.913
Medical	-.522	.593	(.311 – 1.130)	.112	.194	1.214	(.509 – 2.898)	.662
AKIN Stage				.631				.045
AKIN 1 (ref)		1.00				1.00		
AKIN 2	.393	1.481	(.657 – 3.338)	.344	1.050	2.857	(1.195 – 6.829)	.018
AKIN 3	.288	1.333	(.594 – 2.993)	.486	.713	2.041	(.788 – 5.285)	.142
BP < 90	-.823	.439	(.218 - .884)	.021	-.153	.858	(.392 – 1.877)	.702
AKI Cause				.748				.835
Hypoperfusion (ref)		1.00				1.00		
Septic	-.309	.734	(.328 – 1.641)	.451	.049	1.050	(.448 – 2.463)	.911
Complex	-.064	.938	(.443 – 1.984)	.866	.262	1.300	(.543 – 3.112)	.556

	AKI Group				AKI/CKD Group			
ITU admission	.309	1.362	(.546 – 3.397)	.508	.523	1.687	(.486 – 5.855)	.410
Renal review	1.099	3.000	(.923 – 9.748)	.068	-.254	.776	(.310 – 1.938)	.587
AKI duration	.049	1.050	(.953 – 1.158)	.322	.033	1.033	(.912 – 1.171)	.606

Table 7.6 Univariate binary logistic regression analysis for failure to recover function defined by a fall in eGFR of 10mls/min from baseline. Results are shown for the AKI group and the AKI/CKD group.

	AKI Group				AKI/CKD Group			
	B	**OR**	**95% CI**	**p**	**B**	**OR**	**95% CI**	**p**
PreAKI ACR	-.084	.920	(.807 – 1.048)	.210	-.001	.999	(.989 – 1.009)	.869
eGFR slope	-.097	.907	(.831 - .990)	.029	-.092	.912	(.833 - .998)	.045
Admit. In prev. 12 months	.208	1.231	(.606 – 2.502)	.565	1.068	2.909	(1.224 – 6.914)	.016
AKI in prev. 12 months	-1.030	.357	(.039 – 3.271)	.362	.432	1.540	(.573 – 4.137)	.392
AKI in prev. 4 years	-1.768	.171	(.021 – 1.399)	.100	.512	1.669	(.706 – 3.941)	.243
Baseline eGFR	-.008	.992	(.959 – 1.027)	.662	**-.057**	**.944**	**(.908 - .982)**	**.005**
Age	.019	1.019	(.994 – 1.044)	.137	-.020	.296	(.945 – 1.017)	.296
Sex	-.632	.532	(.275 – 1.029)	.061	.001	1.000	(.430 – 2.326)	1.000
Charlson Score	-.235	.790	(.598 – 1.045)	.099	.064	1.066	(.809 – 1.405)	.650
Diabetes	-.341	.711	(.349 – 1.451)	.349	.560	1.751	(.744 – 4.123)	.199
Hypertension	.340	1.405	(.712 – 2.773)	.327	1.081	2.948	(.364 – 23.895)	.311
Smoking hist.	-.551	.576	(.303 – 1.094)	.092	.076	1.079	(.458 – 2.543)	.862
BMI	.024	1.024	(.974 – 1.076)	.351	.010	1.010	(.943 – 1.082)	.768
RASB preAKI	-.166	1.181	(.624 – 2.236)	.610	.879	2.410	(.669 – 8.674)	.178
Aspirin	-.153	.858	(.432 – 1.706)	.662	-.338	.713	(.303 – 1.678)	.439
NSAID	-.789	.454	(.180 – 1.149)	.096	.446	1.562	(.385 – 6.334)	.532
Furosemide	-.203	.816	(.321 – 2.076)	.670	-.111	.895	(.385 – 2.081)	.796
Statin	-.297	.743	(.388 – 1.422)	.369	-.487	.614	(.263 – 1.434)	.260
Betablocker	.238	1.268	(.575 – 2.800)	.238	.754	2.125	(.905 – 4.990)	.084
Allopurinol	.411	1.508	(.418 – 5.439)	.530	.097	.888	(.285 – 4.263)	.888
PPI	.069	1.071	(.538 – 2.134)	.844	-.374	.422	(.276 – 1.714)	.422
AKI present on admission	-.008	.992	(.519 – 1.894)	.980	.297	1.346	(.495 – 3.660)	.560
Medical	-.522	.593	(.311 – 1.130)	.112	.194	1.214	(.509 – 2.898)	.662
AKIN Stage				.203				
AKIN 1 (ref)		1.00				1.00		.029
AKIN 2	.696	2.006	(.843 – 4.770)	.115	1.113	3.043	(1.093 – 8.470)	.033
AKIN 3	.734	2.083	(.878 – 4.937)	.096	1.267	3.550	(1.210 – 10.416)	.021
BP < 90	-.389	.677	(.333 – 1.379)	.283	.379	1.461	(.603 – 3.542)	.401

	AKI Group				AKI/CKD Group			
AKI Cause				.326				.048
Hypoperfusion (ref)		1.00				1.00		
Septic	-.205	.815	(.351 – 1.892)	.634	1.216	3.375	(1.245 – 9.149)	.017
Complex	.444	1.559	(.732 – 3.319)	.250	.369	1.446	(.457 – 4.581)	.530
ITU admission	.449	1.566	(.634 – 3.867)	.331	-.128	.875	(.179 – 4.331)	.875
Renal review	**1.647**	**5.192**	**(1.592 – 16.931)**	**.006**	-.118	.888	(.302 – 2.611)	.830
AKI duration	.090	1.094	(.987 – 1.212)	.086	-.004	.957	(.852 – 1.164)	.957

Table 7.7 Univariate binary logistic regression analysis for failure to recover function defined by a fall in eGFR of 25% from baseline. Results are shown for the AKI group and the AKI/CKD group.

	AKI Group				AKI/CKD Group			
	B	**OR**	**95% CI**	**p**	**B**	**OR**	**95% CI**	**p**
PreAKI ACR	-.056	.945	(.826 – 1.082)	.413	.007	1.007	(.999 – 1.015)	.092
eGFR slope	-.063	.939	(.855 – 1.031)	.188	-.050	.951	(.868 – 1.042)	.283
Admit. In prev. 12 months	.192	1.212	(.522 – 2.814)	.654	1.286	3.619	(1.336 – 9.805)	.011
Baseline eGFR	.013	1.013	(.972 – 1.056)	.534	.017	1.017	(.981 – 1.056)	.359
Age	.040	1.040	(1.005 – 1.077)	.024	-.026	.975	(.936 – 1.014)	.207
Sex	**-1.200**	**.301**	**(.122 - .745)**	**.009**	.087	1.091	(.422 – 2.820)	.858
Charlson Score	-.062	.940	(.676 – 1.307)	.713	-.047	.954	(.696 – 1.309)	.772
Diabetes	.425	1.529	(.679 – 3.443)	.425	.087	1.091	(.422 – 2.820)	.858
Hypertension	1.031	2.805	(1.079 – 7.291)	.034	.698	2.010	(.245 – 16.488)	.516
Smoking hist.	-.482	.618	(.285 – 1.341)	.223	-.606	.545	(.210 – 1.420)	.214
BMI	-.001	.999	(.942 – 1.060)	.975	.031	1.031	(.957 – 1.111)	.417
RASB preAKI	.849	2.337	(1.028- 5.312)	.043	.053	1.055	(.323 – 3.448)	.929
Aspirin	.436	1.546	(.697 – 3.430)	.284	-.353	.702	(.267 – 1.846)	.474
NSAID	-1.355	.258	(.058 – 1.151)	.076	.269	1.309	(.261 – 6.557)	.744
Furosemide	-.199	.820	(.257 – 2.612)	.737	-.017	.983	(.380 – 2.540)	.971
Statin	.345	1.412	(.653 – 3.051)	.381	-.606	.545	(.210 – 1.420)	.214
Betablocker	.767	2.153	(.895 – 5.181)	.087	.921	2.512	(.951 – 6.633)	.063
Allopurinol	.522	1.686	(.411 – 6.909)	.468	.965	2.625	(.735 – 9.378)	.137
PPI	-.005	.995	(.432 – 2.293)	.991	-.332	.718	(.257 – 2.007)	.527
AKI present on admission	.740	2.095	(.901 – 4.871)	.086	.433	1.542	(.479 – 4.964)	.468
Medical	.157	1.170	(.535 – 2.560)	.694	.549	1.732	(.621 – 4.830)	.294
AKIN Stage				.064				.138
AKIN 1 (ref)		1.00				1.00		
AKIN 2	1.221	3.391	(.898 – 12.810)	.072	.825	2.281	(.719 – 7.238)	.162
AKIN 3	1.557	4.744	(1.287 – 17.492)	.019	1.112	3.042	(.937 – 9.874)	.064
BP < 90	-.787	.455	(.174 – 1.189)	.108	-.313	.731	(.247 – 2.167)	.573

	AKI Group				AKI/CKD Group			
AKI Cause				.875				.573
Hypoperfusion (ref)		1.00				1.00		
Septic	.074	1.077	(.388 – 2.990)	.887	.542	1.719	(.553 – 5.346)	.350
Complex	.243	1.275	(.505 – 3.215)	.607	.521	1.684	(.517 – 5.488)	.387
ITU admission	.126	1.134	(.385 – 3.342)	.819	.269	1.309	(.261 – 6.557)	.744
Renal review	**1.543**	**4.680**	**(1.604 – 13.656)**	**.005**	.651	1.918	(.660 – 5.576)	.231
AKI duration	-.018	.982	(.848 – 1.137)	.807	.091	1.095	(.918 – 1.307)	.313

Table 7.8 Summary of factors that reached the study threshold of significance (p<.01) in the AKI or AKI/CKD groups on univariate analysis with failure to recover function using the thresholds of a fall of 5mls/min, 10mls/min, and 25% from baseline eGFR.

		AKI Group			AKI/CKD Group		
	Factor	**OR**	**95% C.I.**	**Sig.**	**OR**	**95% C.I.**	**Sig**
Fall in eGFR by 5mls/min							
	eGFR Slope	.879	(.800 - .965)	**.007**	.920	(.851 - .995)	.036
Fall in eGFR by 10mls/min							
	Baseline eGFR	.992	(.959 – 1.027)	.662	.944	(.908 - .982)	**.005**
Fall in eGFR by 25%							
	Sex	.301	(.122 - .745)	**.009**	1.091	(.422 – 2.820)	.858
	Renal Review	4.680	(1.604 – 13.656)	**.005**	1.918	(.660 – 5.576)	.231

7.2.3 Combined outcome of failure to recover and mortality

Table 7.9 outlines the univariate binary logistic regression analysis for the combined outcome of failure to recover function using the original study definition of a fall in eGFR of 5mls/min and mortality at 6 months. In Table 7.10 the factors that reached the study level of significance (P<.01) in each group are summarised.

7.2.3 (i) Preadmission variables

The most striking feature in this analysis is again the protective effect evident with an increasing slope of decline in eGFR prior to the index AKI. In the AKI group this is highly significant (OR .883, 95% C.I. .808 - .965, p=.006). This effect is less marked in the AKI/CKD group (p=.200). Due to insufficient statistical power the influence of previous AKI episodes on the combined outcome is difficult to interpret. A reduced baseline eGFR appears to have a protective effect in the AKI/CKD group (OR .973, 95% C.I. .939 to .997. p=0.028).

7.2.3 (ii) Baseline variables

In the baseline variables age is the strongest predictor of the combined outcome. In the AKI group the effect of increased age reaches statistical significance (OR 1.010, p=.005). None of the other baseline variables analysed gave a clear indication of an influence on the combined outcome.

7.2.3 (iii) AKI related variables

Admission to a medical specialty increases the risk of the combined outcome in the AKI/CKD group (OR 2.145, 95% C.I. 1.137 to 4.046, p=.018). AKIN stage did not clearly predict the outcome in the AKI group presumably due to insufficient statistical power. In the case of the AKI/CKD group the stage was significant although the risk was highest in AKIN stage 2 (overall p=0.001). The influence of AKI cause on the combined outcome was unclear and results for both groups did not reach significance. It is likely that that there were insufficient numbers to demonstrate any clear associations.

Table 7.9 Univariate binary logistic regression analysis for the combined outcome of failure to recover function defined by a fall in eGFR of 5mls/min and mortality at 6 months. Results are shown for the AKI group and the AKI/CKD group.

	AKI Group				AKI/CKD Group			
	B	**OR**	**95% CI**	**Sig.**	**B**	**OR**	**95% CI**	**Sig.**
PreAKI ACR	-.051	.950	(.863 – 1.046)	.295	.007	1.007	(.998 – 1.017)	.117
eGFR slope	**-.124**	**.883**	**(.808 - .965)**	**.006**	-.037	.964	(.912 – 1.020)	.200
Admit. In prev. 12 months	.597	1.816	(.939 – 3.514)	.076	.308	1.361	(.751 – 2.468)	.310
AKI in prev. 12 months	.355	1.426	(.345 – 5.890)	.624	-.110	.895	(.434 – 1.847)	.765
AKI in prev. 4 years	-.242	.785	(.272 – 2.266)	.655	-.150	.861	(.465 – 1.594)	.633

	AKI Group				AKI/CKD Group			
Baseline eGFR	.007	1.007	(.977 – 1.038)	.662	-.028	.973	(.949 - .997)	.028
Age	**.032**	**1.033**	**(1.010 – 1.056)**	**.005**	.011	1.011	(.982 – 1.041)	.460
Sex	-.329	.720	(.395 – 1.312)	.283	.334	1.396	(.775 – 2.515)	.266
Charlson Score	.046	1.047	(.827 – 1.326)	.702	-.023	.977	(.803 – 1.190)	.820
Diabetes	-.189	.828	(.435 – 1.575)	.565	-.242	.785	(.435 – 1.417)	.422
Hypertension	.547	1.727	(.928 – 3.214)	.085	-.288	.750	(.299 – 1.880)	.539
Smoking hist.	-.481	.618	(.340 – 1.122)	.114	.103	1.108	(.610 – 2.012)	.735
BMI	.011	1.011	(.969 – 1.056)	.608	-.014	.987	(.939 – 1.037)	.593
RASB preAKI	.454	1.575	(.869 – 2.853)	.134	-.495	.610	(.307 – 1.210)	.157
Aspirin	-.159	.853	(.453 – 1.608)	.624	-.379	.685	(.380 – 1.235)	.208
NSAID	-.427	.652	(.297 – 1.431)	.287	.470	1.600	(.503 – 5.094)	.426
Furosemide	.228	1.256	(.559 – 2.822)	.581	.197	1.218	(.677 – 2.194)	.511
Statin	-.181	.835	(.458 – 1.523)	.556	-.450	.638	(.351 – 1.160)	.141
Betablocker	.231	1.260	(.603 – 2.634)	.539	.405	1.500	(.824 – 2.730)	.184
Allopurinol	-.184	.832	(.244 – 2.832)	.768	.080	1.084	(.418 – 2.809)	.869
PPI	-.036	.965	(.508 – 1.833)	.912	-.197	.821	(.448 – 1.506)	.524
AKI present on admission	-.002	.998	(.542 – 1.837)	.995	.046	1.047	(.540 – 2.028)	.892
Medical	-.197	.821	(.448 – 1.503)	.522	.763	2.145	(1.137 – 4.046)	.018
AKIN Stage				.589				**.001**
AKIN 1 (ref)	1.00				1.00			
AKIN 2	.389	1.475	(.685 – 3.178)	.321	1.332	3.789	(1.832 – 7.837)	.000
AKIN 3	.314	1.370	(.640 – 2.930)	.418	.725	2.065	(.902 – 4.729)	.086
BP < 90	-.528	.590	(.314 – 1.108)	.101	-.389	.678	(.348 – 1.319)	.252
AKI Cause				.808				.486
Hypoperfusion (ref)	1.00				1.00			
Septic	-.235	.791	(.372 – 1.679)	.541	.330	1.391	(.695 – 2.787)	.351
Complex	-.005	.995	(.490 – 2.020)	.989	.401	1.493	(.717 – 3.108)	.284
ITU admission	.394	1.483	(.627 – 3.509)	.370	.130	1.139	(.367 – 3.533)	.822
Renal review	.898	2.455	(.768 – 7.848)	.130	-.181	.834	(.401 – 1.735)	.628
AKI duration	.066	1.069	(.974 – 1.173)	.161	.061	1.063	(.957 – 1.181)	.257

Table 7.10 Summary of factors that reached the study threshold of significance (p<.01) in the AKI or AKI/CKD groups on univariate analysis with the combined outcome of mortality and failure to recover function defined by a fall in eGFR of 5mls/min at 6 months as the dependent variable.

	AKI Group			AKI/CKD Group		
Factor	**OR**	**95% C.I.**	**Sig.**	**OR**	**95% C.I.**	**Sig**
eGFR Slope	.883	(.808 - .965)	**.006**	.964	(.912 – 1.020)	.200
Age	1.033	(1.010 – 1.056)	**.005**	1.011	(.982 – 1.041)	.460

7.2.4 Analysis of recovery at discharge, readmission and repeat AKI

Table 7.11 through to table 7.15 outline the univariate analysis of recovery at discharge, readmission during follow up, and repeat AKI during follow up using the outcomes already covered. As patients who died during admission were not exposed to these events they were removed from this analysis.

7.2.4 (i) Recovery at discharge

Recovery of function at the time of discharge was defined as a return to within 5mls/min of baseline. Patients who achieved this were significantly less likely to show a decline in function after 6 months according to any of the definitions reviewed. In addition patients who recovered function at discharge were significantly less likely to reach the combined endpoint of failure to recover within 5mls/min of baseline or death at 6 months. Recovery of function appears to have little effect on the outcome of mortality at 6 months.

7.2.4 (ii) Readmission

Readmission at some point during the 6 months of follow up was associated with an increased risk of mortality in both the AKI and AKI/CKD groups. In terms of functional recovery at 6 months the findings are less clear as are the combined outcomes of death and recovery within 5mls/min of baseline.

7.2.4 (iii) Repeat AKI

In the AKI group the occurrence of a repeat AKI during follow up was one of the strongest predictors of mortality on univariate analysis. The odds ratio for mortality at 6 months in the AKI group was 8.647 (95% C.I. 2.507 to 29.821, p=.001). In the AKI/CKD group, repeat AKI had a similar effect but was not as strong (OR 2.762 95% C.I. 1.162 to 6.568, p=.022). However, there was no significant influence of repeat AKI episodes on functional recovery. This was surprising but may have been due to insufficient power in the study.

Table 7.11 Univariate binary logistic regression analysis of survivors to discharge using mortality at 6 months as the dependent variable.

	AKI Group				AKI/CKD Group			
	B	OR	95% CI	Sig.	B	OR	95% CI	Sig.
Recovered at d/c	.076	1.079	(.397 – 2.932)	.882	-.041	.960	(.414 – 2.229)	.925
Readmission	1.309	3.702	(1.094 – 12.530)	.035	.934	2.545	(1.116 – 5.804)	.026
Repeat AKI	2.157	8.647	(2.507 – 29.821)	.001	1.016	2.762	(1.162 – 6.568)	.022

Table 7.12 Univariate binary logistic regression analysis of survivors to discharge using a fall in eGFR of more than 5mls/min at 6 months as the dependent variable.

	AKI Group				AKI/CKD Group			
	B	OR	95% CI	Sig.	B	OR	95% CI	Sig.
Recovered at d/c	-1.080	.339	(.177 - .651)	.001	-1.724	.178	(.082 - .390)	.000
Readmission	-.324	.723	(.377 – 1.387)	.330	.266	1.305	(.633 – 2.694)	.471
Repeat AKI	-.513	.599	(.216 – 1.662)	.325	.182	1.200	(.480 – 2.998)	.696

Table 7.13 Univariate binary logistic regression analysis of survivors to discharge using a fall in eGFR of more than 10mls/min at 6 months as the dependent variable.

	AKI Group				AKI/CKD Group			
	B	OR	95% CI	Sig.	B	OR	95% CI	Sig.
Recovered at d/c	-1.109	.330	(.167 - .651)	.001	-1.580	.206	(.084 - .502)	.001
Readmission	-.240	.787	(.404 – 1.533)	.481	.645	1.905	(.814 – 4.462)	.138
Repeat AKI	-.546	.579	(.194 – 1.732)	.328	.357	1.429	(.506 – 4.037)	.501

Table 7.14 Univariate binary logistic regression analysis of survivors to discharge using a fall in eGFR of more than 25% at 6 months as the dependent variable.

	AKI Group				AKI/CKD Group			
	B	OR	95% CI	Sig.	B	OR	95% CI	Sig.
Recovered at d/c	-2.885	.056	(.013 - .244)	.000	-1.572	.208	(.076 - .567)	.002
Readmission	-.152	.859	(.382 – 1.930)	.712	.515	1.674	(.645 – 4.349)	.290
Repeat AKI	-.232	.793	(.214 – 2.940)	.728	.172	1.187	(.359 - 3931)	.778

Table 7.15 Univariate binary logistic regression analysis of survivors to discharge using the combined outcome of a fall in eGFR of more than 5mls/min at 6 months and mortality as the dependent variable.

	AKI Group				AKI/CKD Group			
	B	OR	95% CI	Sig.	B	OR	95% CI	Sig.
Recovered at d/c	-.959	.383	(.207 - .710)	.002	-1.331	.264	(.133 - .525)	.000
Readmission	-.105	.900	(.484 – 1.673)	.739	.537	1.712	(.916 – 3.199)	.092
Repeat AKI	.030	1.030	(.425 – 2.500)	.947	.571	1.770	(.831 – 3.767)	.139

7.3 Multivariate analysis

Multivariate binary logistic regression analysis was undertaken to further explore the factors that may be influencing the outcomes found in this study. Factors used in the regression modelling were selected a priori. Variables identified in the literature as having an influence on the outcomes were reviewed. In addition the results of the univariate analysis carried out for this study were taken into account.

7.3.1 Mortality

In chapter 2 several factors were identified in the literature that may have an influence on mortality after an AKI episode (see Figure 2.11). In this study the strongest predictors of mortality in the AKI group found on univariate analysis included increasing age, higher Charlson comorbidity score, a history of a previous AKI, and finally the presence of AKI on admission i.e. community acquired AKI. In the AKI/CKD group the use of RAS blockers at the time of the AKI appeared to have a protective effect while AKIN stage and AKI occurring in medical admissions appeared to be associated with an increased risk.

Based on theses observations the five principal variables selected for exploration were AKI stage, AKI cause, the use of RAS blockers, the presence of AKI on admission, and if the AKI was medical. For uniformity the same variables were used in both the AKI and AKI/CKD groups. Each variable was adjusted in stages for age (model 2), age and sex (model 3), and age,sex, Charlson score and hypertension (model 4). Hypertension was added as this was considered an important comorbid factor but is not part of the Charlson Index. Model 4 was then adjusted for AKI cause (model 5), the use of RAS blockers (model 6), AKI on admission (model 7) and AKIN stage (model 8). A total of eight models were explored for each variable and can be found in Appendix 19. An outline of the findings are presented here and will be discussed further in Chapter 8.

7.3.1 (i) AKIN stage

In the AKI group AKIN stage did not appear to be a useful predictor of mortality at either follow up time point. In the AKI/CKD group the influence of AKIN stage reaches statistical significance. However, in all models the odds of death at 6 months is higher in AKIN stage 2. As discussed earlier, this is likely to be due to chance or a lack of power in the study. There is a notable increase in risk in model 6 when adjustment for the use of RAS blockers is made. At 12 months the increased risk of mortality associated with AKIN stage is attenuated and no longer significant. In the case of AKIN stage 3 the odds are actually reversed in terms of risk relative to the reference AKIN stage 1.

7.3.1 (ii) AKI Cause

In the models used to assess AKI cause, Hypoperfusion AKI was used as the reference level. In the univariate analysis AKI cause had no influence on mortality in the AKI group. This persisted with adjustment for all covariates in multivariate analysis.

In the AKI/CKD group both septic AKI and Complex AKI increase the odds of death at 12 months but this influence was not found at 6 months. At 12 months in model 8 where adjustment is also made for AKIN stage in addition to age,sex and comorbidities, septic AKI has an odds ratio of 2.405 while complex AKI has one of 2.871 (overall p=0.03).

7.3.1 (iii) Use of RAS blockers

In the AKI group the use of RAS blockers at the time of the AKI was not found to affect mortality at 6 or 12 months.

In the AKI/CKD group the unadjusted model for 6 month mortality showed a protective effect for the use of RAS blockers which approached statistical significance (OR .468, 95% C.I. .227 to .965, p=0.04). This protective effect persists with adjustment for age and sex but is attenuated substantially with adjustment for comorbidities in model 4. At 12 months this apparent protective effect in the unadjusted model is lost.

7.3.1 (iv) AKI on admission

Patients who had community acquired AKI evident at the time of admission were compared to the hospital acquired cases as a reference. Community AKI appears to have a strong influence on mortality in the AKI group. In all models the findings approached statistical significance. In model 2 with adjustment for age alone, community AKI was associated with an odds ratio for death at 6 months of 3.975 (p=0.018). This influence was reduced only marginally with adjustment for comorbidities, however it was reduced substantially with adjustment for AKIN stage in model 8. This suggests that the severity of the AKI may play an important role in these findings. For 12 month mortality the findings are similar.

In the AKI/CKD group the results are less convincing and difficult to interpret both at 6 and 12 months. Community AKI appears not to have the same impact.

7.3.1 (v) Medical admission

In the AKI group the admitting specialty whether medical or surgical did not influence mortality at 6 or 12 months. In the AKI/CKD group the influence of medical admission on mortality was strong. For 6 month mortality the unadjusted odds ratio was 5.176 (p=.001). This was reduced with adjustment in model 4 but remained highly significant (OR 4.476, p=0.004). These findings persisted even with adjustment for AKI cause in model 6 and AKIN stage in model 8. The findings were similar but with increased significance levels in the 12 month mortality analysis

7.3.1 (vi) Supplementary modelling

Univariate analysis showed that patients who had evidence of an AKI during the 12 month and four year periods prior to the index episode in the AKI group had a significantly increased risk of mortality at 6 months. In those with evidence of an AKI in the previous four years regardless of its severity the odds ratio for mortality at 6 months was 4.697 (95% C.I. 1.551 – 14.224, p=.006). This was not found to be the case in the AKI/CKD group.

To explore this finding further multivariate analysis was carried out to adjust for age, sex, and comorbidities. This is illustrated in Table 7.16. It can be seen that this influence persisted even with adjustment for comorbidities in model 4.

Table 7.16 Multivariate analysis exploring the relationship between mortality at 6 months and a history of at least one previous AKI episode during the 4 years prior to the index AKI in the AKI group.

	OR	95% C. I.	P	OR	95% C.I.	P
		Model 1 (Unadjusted)			Model 2	
AKI in Previous 4 years						
No (ref)	1.00			1.00		
Yes	4.697	(1.551 – 14.224)	.006	6.018	(1.783 – 20.310)	.004
		Model 3			Model 4	
No (ref)	1.00			1.00		
Yes	6.049	(1.777 – 20.591)	.004	3.895	(1.076 – 14.095)	.038

Model 1 – unadjusted Model 3 – adjusted for age and sex

Model 2 – adjusted for age Model 4 – adjusted for age, sex, Charlson Score and hypertension

7.3.2 Recovery of function

The risk factors for failure to recover function after an episode of AKI were discussed in Chapter 3 (see Figure 3.9). In this study a number of additional factors appeared to have an important influence on univariate analysis. A greater slope of decline in eGFR during the three years prior to the AKI episode appears to have a paradoxical protective effect in both the AKI and AKI/CKD groups. In the AKI group the use of RAS blockers appears to increase the risk of non-recovery whereas in the AKI/CKD group the trend was toward a protective effect. The recording of a nadir blood pressure < 90 systolic at the time of the AKI appears to have a protective effect in the AKI group.

Based on these findings and using existing literature six variables were chosen for analysis including AKIN stage, AKI Cause, the use of RAS blockers, pre-AKI slope of decline in eGFR, nadir BP at the time of the AKI, and the presence of the AKI on admission to hospital. As with the mortality analysis, for the purpose of uniformity the same variables were used in both the AKI and AKI/CKD groups. The results of this analysis can be found in Appendix 20 for each group using the three definitions of

failure to recover function covered in the univariate analysis – a fall in eGFR of 5mls/min, a fall of 10mls/min, and a fall of 25% from baseline. An outline of the main findings is presented here.

7.3.2 (i) AKIN Stage

In the AKI group the odds of failure to recover function increase with increasing AKIN stage although this is apparent as a trend only. This influence becomes clearer as the definition of failure to recover function is extended from a fall of 5mls/min to a fall of 10mls/min and a fall of 25%. In the case of a fall in eGFR of 25% from baseline the odds of failing to recover in model 4 with AKIN stage 2 was 4.356 and this increases to 7.748 with AKIN stage 3 (p=.015).

A similar pattern is seen in the AKI/CKD group. However, using the definition of a fall in eGFR of 5mls/min the highest odds are seen in AKIN stage 2. This is reversed when the definition is extended. For example, in model 4 the odds of a fall in eGFR of 5mls/min are 3.015 and 2.270 for AKIN stage 2 and 3 respectively. This reverses in model 4 for the odds of a fall in eGFR of 25% to 2.444 and 3.508.

7.3.2 (ii) AKI Cause

The influence of the cause of AKI on functional outcomes is unclear from these data. It is notable that in the fall of 25% models there is a marked drop in the odds of failure to recover when adjustment for AKIN stage is made suggesting that AKI severity is important in these outcomes rather than the cause per se.

In the AKI/CKD group there is a clear trend of an increased risk associated with septic and complex AKI although the effects of using different definitions of recovery are again seen. With all definitions a fall in the odds ratios is noted when adjustment for AKIN severity is made.

7.3.2 (iii) Use of RAS blockers

In the AKI group there appears to be an increased risk of a failure to recover function in those using RAS-blockers at baseline. In the case of a fall of 25% from baseline the unadjusted odds of this occurring was 2.337 (95% C.I. 1.028 – 5.312, p=.043). The influence becomes uncertain when adjustment for age, sex, and comorbidities is made. In the AKI/CKD group the influence of RAS blockers on recovery is unclear.

7.3.2 (iv) Pre-AKI slope of decline in function

An increasing slope of decline in eGFR during the three years prior to the index AKI appears to have substantial protective effect in terms of recovery. This paradoxical finding is evident in both groups but is most marked in the AKI group. In the AKI group the odds ratio for a fall in eGFR of 5mls/min is .877 (95% C.I. .798 to .964, p= .006) in model 4 with adjustment for age, sex, and comorbidities. This protective effect is evident for all definitions of recovery although the significance is lost as the definition is extended to a fall of 25%. For the AKI/CKD group there is again a protective effect and in the case of a fall in eGFR of 5mls/min the odds ratio was .906 in model 4 (95% C.I. .833 to .986, p=.022).

7.3.2 (v) Nadir blood pressure < 90 systolic

The influence of having had a nadir BP of < 90 systolic was explored in these models because of the finding that this may reduce the odds of non-recovery on univariate analysis. While this finding appears to be counter-intuitive there may be some basis for it. Evidence exists that remote ischaemic pre-conditioning can have a protective effect on the kidney [405].

In the AKI group having had a systolic pressure recorded < 90 at the time of the AKI appears to have a substantial protective effect in terms of failure to recover function. For a fall in eGFR of 5mls/min the odds ratio was .377 in model 5 where adjustment is made for age, sex, comorbidities and AKIN stage (95% C.I. .180 to .787, p=.009). Using the definition of a fall of 25% these findings are similar (OR .308 95% C.I> .108 to .880, p=.028).

In the AKI/CKD group the results are less clear. The odds ratios for a fall of 5mls/min also suggest a protective effect but this is only a trend.

7.3.2 (vi) AKI on admission

An AKI which was evident on admission was shown earlier to be associated with a higher mortality in the AKI group but findings were less clear in the AKI/CKD group. In this analysis the outcomes of recovery of function were explored in this subgroup of patients. In both groups the results of these data are difficult to interpret and did not reach significance.

7.3.2 (vii) Supplementary modelling

On univariate analysis it was shown that statin use at the time of the AKI may have a protective effect in terms of recovery of function in the AKI/CKD group when the definition of a fall in eGFR of 5mls/min is used (OR .472, 95% C.I. .229 to .973, p=0.042). This was not observed in the AKI group. As this is a potentially important finding and has been the subject of much interest in the literature recently it was explored further in multivariate analysis [118,169,406,407]. Table 7.17 summarises the results of the various models explored in relation to statin therapy. In model 4 with adjustment for age, sex, Charlson score and a history of hypertension the association between statin therapy and a reduced risk of a failure to recover increases. It increases further when this model is adjusted for AKIN stage in model 5 (OR.358, 95% C.I. .159 - .806, p=.013). Further consideration was given to other factors that could be potentially acting as covariates in this association and so in model 6 additional adjustments are made for the use of aspirin therapy and in model 7 for the use of RAS blockers. These medications theoretically may also be having a protective effect. In the case of aspirin therapy the association is weakened and loses significance. Results are largely unaltered by adjustment for the use of RAS blockade. Finally in model 8 adjustment is made for the slope of decline in eGFR prior to the AKI and this does not alter the findings appreciably.

Table 7.17 Multivariate analysis of statin therapy at the time of the AKI with a fall in eGFR of more than 5mls/min after 6 months as the dependent variable.

	Model 1 (Unadjusted)			Model 2		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**
On Statin						
No (ref)	1.00			1.00		
Yes	.472	(.229 - .973)	.042	.040	(.226 - .966)	.040
		Model 3			**Model 4**	
No (ref)	1.00			1.00		
Yes	.466	(.225 - .965)	.040	.440	(.207 - .938)	.033
		Model 5			**Model 6**	
No (ref)	1.00			1.00		
Yes	.358	(.159 - .806)	.013	.506	(.229 – 1.120)	.093
		Model 7			**Model 8**	
No (ref)	1.00			1.00		
Yes	.451	(.210 - .970)	.042	.443	(.205 - .959)	.039

Model 1 – unadjusted
Model 2 – adjusted for age
Model 3 – adjusted for age and sex
Model 4 – adjusted for age, sex, Charlson Score and hypertension
Model 5 – model 4 and AKIN stage
Model 6 – model 4 and aspirin
Model 7 – model 4 and RASB
Model 8 – model 4 and eGFR slop

7.3.3 Combined outcome of failure to recover and mortality

Multivariate binary logistic regression analysis for the combined outcome of failure to recover function defined by a fall in eGFR of 5mls/min or more and mortality at 6 months in the AKI and AKI/CKD was also undertaken. This explored the same six factors described for the analysis of recovery of function described above. The modelling can be found in Appendix 21 while an outline of the findings is presented here.

7.3.3 (i) AKIN stage

In the AKI group there is a trend for an increased risk of the combined outcome according to AKIN stage in all models although none reach statistical significance. The association is stronger in the AKI/CKD group. In this case the odds are highest in AKIN stage 2. In model 4 with adjustment for age, sex, and comorbidities the odds ratios for

the combined outcome were 3.823 and 2.116 for AKIN stage 2 and AKIN stage 3 respectively (p=.001).

7.3.3 (ii) AKI Cause

In the AKI group the influence of cause on the combined outcome is unclear from these data. In the AKI/CKD group there is a trend for an increased risk in the septic and complex cases though none reach significant levels.

7.3.3 (iii) Use of RAS blockers

The influence of the use of RAS blockers on the combined outcomes is also unclear from these data. No firm conclusions can be reached most likely due to insufficient power in the study.

7.3.3 (iv) Pre-AKI slope of decline in function

In the AKI group an increasing slope of decline in eGFR during the three years prior to the index AKI is associated with a reduced risk of the combined outcome that reaches statistical significance in all of the models tested. A similar pattern is observed in the AKI/CKD group though the association is weaker and does not reach significance.

7.3.3 (v) AKI on admission

In both groups the association between an admission AKI and the combined outcome is weak and it is not possible to draw any conclusions.

7.4 Analysis of recovery at discharge, readmission and repeat AKI

Multivariate analysis was also undertaken to explore the influence of recovery at discharge, readmission during follow up, and repeat AKI during follow up on 6 month outcomes. The full models can be found in Appendix 22 for mortality at 6 months and Appendix 23 for recovery of function after 6 months. The findings are outlined below. As with the univariate analysis patients who died in hospital who were not exposed to these events were excluded.

7.4.1 Mortality

In both groups recovery at discharge appears to have little effect on mortality at 6 months.

Patients who were readmitted to hospital during the 6 month follow up period showed an increased risk of mortality in both groups. In the AKI group the odds ratio for mortality at 6 months was 3.702 (95% C.I. 1.094 to 12.530, p=.035). This fell marginally with adjustment for age, sex, and comorbidities in model 4 (OR 3.149). Adjustment for additional variables in models 5 to 8 had little impact.
In the AKI/CKD group findings were similar across all groups. In model 4 with adjustment for age, sex, and comorbidities the odds ratio for death at 6 months was 2.313 (95% C.I. .976 to 5.482, p=.057).

The occurrence of a repeat AKI was one of the strongest predictors of mortality at 6 months in both groups particularly in the AKI group. In model 4 with adjustment for age, sex, and comorbidities the odds ratio for death at 6 months in the AKI group was 8.260 (95% C.I. 1.953 to 34.938, p=.004). Adjustment for additional variables had little effect on this finding. In the AKI/CKD the pattern was similar although the strength of the association fell with adjustment for comorbidities in model 4.

7.4.2 Recovery of function

Appendix 23 contains the full models used for recovery of function for each group using the three definitions of failure to recover function already described.

7.4.2 (i) Recovered at discharge

Patients who had recovered function at the time of discharge showed a reduced likelihood of meeting the criteria for failure to recover function after 6 months of follow up in both groups. This association was strong and remained largely unchanged after adjustment in the regression models. In the AKI group the odds ratio for a fall in eGFR of 5mls/min or more after 6 months was .366 in model 4 with adjustment for age, sex, and comorbidities (95% C.I. .188 to .715, p=.003). The same model in the AKI/CKD group revealed an odds ratio of .160 (95% C.I. .071 to .362, p<.001).

7.4.2 (ii) Readmission

In the AKI group the data on hospital readmission is difficult to interpret. In the AKI/CKD group the findings are similar. There may be a trend toward an increased risk of failure to recover but no firm conclusions can be drawn.

7.4.2 (iii) Repeat AKI

The occurrence of a repeat AKI during follow up was not shown to have any impact on recovery using these data but it is highly likely that the study was underpowered to demonstrate this. In the AKI/CKD group the influence of a repeat AKI appears to be strongest and there is a consistent trend toward an increased risk of non-recovery for all of the recovery definitions used.

7.5 Summary

Table 7.18 summarises the findings presented in this chapter. It highlights the factors found to have a significant influence on the outcomes studied in univariate analysis using the study threshold of P<0.01. In addition, factors that may also be of interest (P<0.05) which have been highlighted in the chapter are included.

Table 7.18 Summary of factors found to have an influence on the study outcomes in univariate analysis.

Outcome	AKI Group	OR	P	AKI/CKD Group	OR	P
6 Month Mortality	AKI in prev. 12 mths	5.333	.015	Hypertension Hx.	.375	.041
	AKI in prev. 4 years	4.697	.006	Use of RASB pre-AKI	.468	.040
	Age	1.061	.004	Medical Admission	1.644	.001
	Charlson Score	1.664	.002	AKIN Stage		.010
	Use of Furosemide	2.958	.026			
	AKI on admission	3.469	.029			
12 Month Mortality	Admitted in prev. 12 mths.	2.303	.037	Age	1.043	.029
				Use of Furosemide	2.171	.020
	AKI in prev. 12 mths	3.778	.050	Medical Admission	4.882	<.001
	AKI in prev. 4 years	3.229	.034			
	Age	1.060	.001			
	Charlson Score	1.499	.007			
	Use of Furosemide	3.164	.004			
	AKI on admission	2.957	.025			
	AKI duration	1.118	.023			

Fall in eGFR by 5mls/min	eGFR Slope	.879	.007	eGFR Slope	.920	.036
	Age	1.026	.040	Baseline eGFR	.965	.019
	BP < 90	.439	.021	Statin use	.472	.042
				AKIN Stage		.045
Fall in eGFR by 10mls/min	eGFR Slope	.907	.029	eGFR Slope	.912	.045
	Renal Review	5.192	.006	Baseline eGFR	.944	.005
				AKIN Stage		.029
				AKI Cause		.048
Fall in eGFR of 25%	Age	1.040	.024	Admitted in prev. 12	3.619	.011
	Male Sex	.301	.009	mths.		
	Hypertension	2.805	2.805			
	Use of RASB	2.337	2.337			
	Renal Review	4.680	.005			
Combined mortality and fall 5mls/min	eGFR Slope	.883	.006	AKIN Stage		.001
	Age	1.033	.005			

Chapter 8: Summary and Discussion

8.1 Introduction

In this chapter the principal findings of this study are discussed. The focus will initially be on the recovery of function after an episode of AKI. This will be followed by the other outcomes of clinical interest including hospital length of stay and mortality after AKI. The performance of the AKIN staging system will also be reviewed. Many additional findings were identified and these will be discussed under the separate headings of contributions to the natural history of AKI, management practices in AKI, and methodological issues. The chapter ends with a review of the study strengths and limitations together with an outline of future research directions.

8.2 Recovery of renal function after acute kidney injury

It was highlighted in Chapter 3 that the natural history of AKI and its relationship to CKD is poorly characterized in the literature. The findings in this study substantially improve the understanding of this natural history.

8.2.1 General summary of findings

At the time of hospital discharge 52.6% of survivors in the AKI group and 31.4% in the AKI/CKD group had failed to recover function to within 5mls/min of baseline ($p<.001$). In the AKI group 8.4% had required dialysis during hospitalisation but all of the survivors recovered sufficiently to remain independent of dialysis at discharge. In the AKI/CKD group 5.4% required dialysis in hospital and 3 remained dialysis-dependent at discharge (1.8% of survivors).

After 6 months of follow up 53% of the AKI group and 34% of the AKI/CKD group had failed to recover ($p=0.002$). During follow up one of the patients dependent on dialysis in the AKI/CKD group died and another started dialysis. Therefore 3 patients were dialysis dependent at follow up (2.1% of survivors). This suggests that AKI may be contributing to the incident dialysis population.

As a fall in eGFR of 5mls/min at a single time point could be attributed to individual and analytical variation, the definition of failure to recover was extended to a fall of 10mls/min and a fall of 25% from baseline. The overall proportions in the AKI and

AKI/CKD groups that failed to recover function according to each definition are summarised in Table 8.1. A substantial proportion of hospitalised patients failed to recover function across all AKIN stages. The definition of failure to recover proposed by the ASSESS AKI study consortium was also applied and tested [4]. Results showed that 19.6% of patients in the AKI group had a fall in eGFR of 25% from baseline and progressed to at least CKD stage 3. In the AKI/CKD group the ASSESS study defines progression as a fall in eGFR of at least 50% from baseline. In this study only 3.7% of survivors demonstrated this. It is likely that the event rates in the ASSESS study for progression of CKD will be low and may under-report the phenomenon.

The findings in this study relating to the AKI/CKD group are strengthened when comparison is made to the CKD control group. 20% of the AKI/CKD group demonstrated a fall of at least 10mls/min while none in the control group did (p=0.016). No attempt was made to recruit a control group for the AKI group however it is highly unlikely that 20% of a group of controls would have progressed to CKD stage 3 within 6 months as was found in this study. Overall, the results in this study confirm that AKI across all its stages of severity is associated with incident CKD and progression of underlying CKD.

It is accepted in the literature that in severe cases of AKI there is a persistent decline in renal function in some individuals. The position on milder episodes of AKI remains subject to debate. This is largely due to the methodologies used in recent studies [50,357]. It is possible, particularly where estimates of baseline function have been used, that patients with pre-existing CKD stages 3-5 are misclassified as having an eGFR > 60mls/min. Therefore in the case of mild episodes of AKI the failure to recover function may represent a return to the true baseline. Additional sensitivity analysis was undertaken which involved searching the records of all patients extending back three years from the time the study baseline level was selected. 14.7% of patients in the group had at least one eGFR < 60 mls/min taken as an outpatient during this period. 8.4% of patients, all of whom were diabetic, had evidence of microalbuminuria on ACR measurement. These patients were removed from the analysis, however this did not alter the overall findings significantly. Even when the ASSESS AKI definition is applied 7.7% of patients in the mild AKIN stage 1 demonstrated a fall in eGFR of 25% and progression to at least CKD stage 3 after 6 months.

This study was able to investigate the influence of repeat episodes of AKI during the follow up period. This did not have a major influence on the findings. In the AKI Group with AKIN stage 1, 66% of patients who failed to recover according to the study criteria did not have a repeat episode recorded. None of those in AKIN stage 1 who met the

more rigorous ASSESS AKI criteria and demonstrated reaching CKD stage 3 had a repeat episode. Therefore with every effort made to ensure the classification of patients was correct this study shows unequivocally that even so called mild AKI episodes may result in a substantial decline in renal function.

Table 8.1 Summary of the proportions of patients in the AKI and AKI/CKD Groups who failed to recover function after 6 months according to each of the definitions of failure to recover explored in this study.

Fall in eGFR from baseline	AKIN Stage	AKI Group N = 158	AKI/CKD Group N = 135
By 5mls/min, N%		83(52.5)	46(34.1)
	1	18(46.1)	21(25.9)
	2	33(55.9)	15(50)
	3	32(53.3)	10(41.7)
By 10mls/min, N%		64(40.5)	27(20)
	1	11(28.2)	10(12.3)
	2	26(44.1)	9(30)
	3	27(45)	8(33.3)
By 25%, N%		33(20.8)	20(14.8)
	1	3(7.7)	8(9.9)
	2	13(22)	6(24)
	3	17(28.3)	6(33)

8.2.2 Findings in the context of current literature

The literature currently does not contain a prospective study of AKI in general hospitalised patients with systematic follow up beyond hospital discharge. No study to date has reviewed the outcomes in those with and without CKD in the detail that this study has done. Therefore there is little with which to compare the results of this study. Most contemporary work involves the retrospective review of clinical databases with a focus on expressing long-term function in terms of the relative risk of progression of CKD or progressing to ESRD. Ultimately most of these studies maybe flawed as they do not take into account the occurrence of repeat AKI episodes during

follow up. For example, Ishani et al reported the incidence of CKD after AKI in patients following cardiac surgery. They reported the overall incidence during over five years of follow up. While this study confirmed an increased risk of CKD after an AKI episode it did not take into account repeat episodes or inter-current medical events during the five-year follow up period. Therefore it is difficult to attribute these findings to a single AKI event [127].

Kwon et al have published the only prospective study of AKI defined by AKIN staging to date. They found that 50% of patients had not returned to baseline function at the time of discharge form hospital [190]. This study had only 96 patients and did not present follow up beyond discharge. In addition, it was restricted to hospital acquired AKI only and did not distinguish between those with and without CKD. However, the result is not too dissimilar to the overall finding in this study of a failure to recover at discharge in 45% of patients with and without CKD at baseline.

8.2.3 Outcomes in those with and without pre-existing CKD

This study provides an important insight into the quite marked differences in outcomes between those with and without CKD who sustain an AKI. As discussed above a significantly larger proportion of patients in the AKI group failed to recover function (53% v 34%, p = .002). This may partly be explained by a degree of survivor bias, as mortality in the AKI/CKD group was significantly higher. However, this alone is unlikely to explain the large difference in recovery patterns. The same large difference in recovery was seen at the time of discharge from hospital despite the mortality difference between the groups not reaching significance. Bagshaw et al made a similar observation in a study of ITU patients who had undergone renal replacement therapy. A higher pre-RRT serum creatinine was associated with reduced odds of recovery [366]. One explanation could be that the relative severity of the AKI and the severity of the underlying illness in the AKI group were greater and more likely to result in a lack of recovery. As those with CKD already have impaired function the same relative rise in serum creatinine might take a far lesser injury. Similar reasoning can be used to explain the lower hospital mortality in those with CKD and AKI compared to those without CKD and AKI found in some studies [168,228]. For example, Pannu et al in a study involving Canadian hospitalized patients found an adjusted hazard ratio for death in hospital of 10.62 in those with AKIN stage 3 and a baseline eGFR > 60mls/min, whereas those with AKIN stage 3 and a baseline eGFR < 60 had a significantly lower adjusted hazard ratio of 4.71 [168]. If the hypothesis that the CKD group have a lesser injury is correct then it raises the point that the use of the same creatinine based

estimates of changes in renal function in those with and without CKD is likely to be incorrect as a measure of AKI severity.

If the differences in recovery are not entirely due to differences in severity then another possible explanation is that the pathological processes involved are different. It is possible that an AKI episode on a normal kidney excites a more vigorous inflammatory response than one on an already damaged kidney where response mechanisms may be blunted or protective mechanisms may already be up-regulated.

Finally, it was noted during this study that significantly more patients in the AKI/CKD group received a formal nephrology review. It is conceivable that better AKI management may have improved outcomes. However the referral rate would be insufficient to account for the outcomes in all of the patients. In addition, regression analysis did not reveal any influence of referral on functional outcomes.

No study to date has described these differences in this detail. Ali et al separated their cohort into an AKI and AKI/CKD group in a retrospective review of AKI in hospitalised patients defined by the RIFLE criteria. They reported that 92.5% of patients in the AKI group had full recovery at 90 days compared to 65% in the AKI/CKD group [187]. This is contrary to the results reported in this present study and indeed the recovery appears to be substantially better. The explanation for the differences lies in the definitions used. Ali et al defined full recovery of function as a return to below a threshold serum creatinine of 150µmols/litre. Below this threshold still represents CKD in many patients and it is likely to have grossly overestimated recovery in the AKI group.

Two studies by Lo et al and James et al have reported the risk for CKD in those with and without decreased baseline GFR. Coca et al reviewed these studies in a meta-analysis [120,230,352]. The relative risk for CKD was higher in those without decreased baseline GFR and this supports the findings in this study. In a similar manner the relative risk for ESRD was found by Coca et al to be higher in those with AKI and without decreased baseline function. This latter finding was accounted for by Coca et al by the fact that the difference between the absolute risks for ESRD in those without decreased baseline function with and without AKI was far greater than the difference between the absolute risk for ESRD in those with decreased baseline function. This is because ESRD is an extremely uncommon event in those without decreased baseline function and no AKI. Hence the relative risk is higher. While this is a valid argument in the case of ESRD, it does not hold up as robustly in the case of the risk for CKD and certainly would not explain the findings in this study.

8.2.4 Recovery patterns after AKI

Another interesting finding in this study is the impact of expressing changes in function in terms of the mean change in eGFR. In the AKI/CKD group it was shown in Figure 6.17 that a large proportion of patients have a mean increase in eGFR at the time of discharge that balances the mean fall derived from those who have failed to recover. This resulted in a positive mean change of 0.11mls/min despite the study showing that over 30% had failed to recover. This finding may explain why some studies in the literature which were discussed in Chapter 3 reported no change in renal function at the time of follow up because they expressed changes in function in terms of the mean of the overall group [159,181,252].

A novel aspect of this study is the clear demonstration of the complex nature of recovery patterns that follow an AKI. In Chapter 6 it was shown that 38% of those who had recovered completely at discharge had progressed to a fall in eGFR of more than 5mls/min after 6 months. In the AKI/CKD group 21% of patients demonstrated this phenomenon. Therefore recovery at discharge is a poor predictor of recovery after 6 months. In this study the positive predictive values for the AKI and AKI/CKD groups were only 62% and 79% respectively. There are several possible explanations for this finding. Firstly, patients may have lost muscle mass during their acute illness and hence have a lower serum creatinine. This would not reflect their true renal function. Loss of function may be masked on discharge only to manifest during follow up when they have regained their muscle mass. Secondly, patients may have received vigorous fluid resuscitation during their admission that again may result in a lowering of the serum creatinine through dilution. Finally, over 90% of patients in both groups had their RAS-blockers discontinued. This almost certainly would have led to an increase in GFR in many patients and if these drugs were recommenced during follow up a fall in GFR would be noted.

Defining these patterns has important clinical implications. While it was shown in multivariate regression analysis that recovery at discharge increased the odds of being in the recovered group at follow up this is not universal. Even in the patients who have recovered function it may be advisable to repeat their renal function after discharge. It also highlights that recovery of function at discharge should not be used as an endpoint in AKI studies. The question then arises regarding the appropriate duration of any follow up period. Amdur et al demonstrated that recovery of AKI peaks between 3 and 6 months [365]. This was expressed in terms of the mean creatinine of the overall group and would have included patients exhibiting a decline in function that have been identified in this study. It follows that those who show a decline in function following

discharge are also likely to stabilise between 3 and 6 months if the mean has stabilised. Therefore the 6 month follow up point used in this study seems reasonable. A recent NIDDK workshop report on the design of AKI clinical trials suggested using recovery of function at 60-90 days as a suitable endpoint [408]. This needs to be reconsidered in light of the findings discussed here.

8.2.5 Readmission and repeat AKI episodes

One of the most important findings described in this study is the pattern of admission and repeat AKI episodes that occurs. A review of hospital records revealed that 32% of patients in the AKI group had at least one admission to hospital in the 12 months prior to the index AKI. In the AKI/CKD group this figure was 43%. Likewise during the 6 month follow up period 40% of the AKI group was readmitted to hospital at least once while 43% of the AKI/CKD group was readmitted. These findings highlight the vulnerable nature of these patients and this is reflected in the substantial comorbidity load evident in both groups at baseline. It is worth noting however, that this study was limited by design to those with previous serum creatinine values on record in order to calculate baseline function. This approach will be bias to these more vulnerable patients as they are more likely to have previous blood tests. Therefore it may not describe the complete natural history of AKI. AKI occurring in possibly younger fitter patients without blood test records will not have been included and these may not exhibit repeat admissions. In this study approximately 15% of those screened fell into this group.

A pattern of recurrent AKI episodes was evident in both groups associated with repeat admissions. In the AKI group 8.9% had at least one AKI during the four years prior to the index AKI while 34.6% of the AKI/CKD group showed evidence of this. During follow up 12% of the AKI group had at least one repeat episode while 20% of the AKI/CKD group experienced one. It is likely that these episodes are in themselves contributing to the decline in renal function in these patients. It highlights the fact that the vast majority of contemporary studies on AKI that have reported long-term functional outcomes are likely to be influenced by this phenomenon. At present only one study, by Thakar et al, has taken this into account. In this study of AKI in hospitalised diabetic patients that were under observation for over 60 months the authors reported more than 2 AKI episodes occurring in 30% of patients during the period of observation. They found that one AKI episode increased the risk of progressing to CKD stage 4 with a hazard ratio of 3.56 and each subsequent AKI episode doubled this risk in a cumulative fashion [34].

This study failed to show a significant influence of these repeat episodes on recovery of function after 6 months follow up in logistic regression analysis of survivors to discharge. However while failure to recover was common it is likely the study was underpowered. Nevertheless this study clearly demonstrates that this phenomenon occurs in general hospitalised patients and not just in diabetics.

8.2.6 Influence of the slope of decline in eGFR prior to the AKI

This study describes the slope of decline in renal function prior to the AKI episode. This revealed a mean slope of +1.21mls/min/year in the AKI group while in the AKI/CKD group this was -3.16mls/min/year. In Chapter 3 the natural progression of CKD was discussed and it was noted that the NICE review group considered a decline in GFR of more than 2mls/min/year to be more than could be explained by aging alone [74]. The study by Hemmelgarn et al reviewed the rate of decline in renal function in a large elderly population over 66 years in Canada and reported a rate of decline of 0.8 and 1.4 mls/min/year in women and men without diabetes. In those with diabetes these figures rose to 2.1 and 2.7 mls/min/year [409]. The decline of 3.16mls/min/year identified in this AKI/CKD population is therefore higher. This raises some important questions. Chief among these is whether or not this population represents a subset of the population that by virtue of their comorbidities and other risk factors are vulnerable to repeat AKI episodes and a more rapid decline in renal function. AKI could therefore be more than just a marker of future decline but an important variable in 'rapid progressors' similar to proteinuria. Another important question that stems from this is whether or not prevention of these AKI episodes or better management and follow up can arrest or slow this functional decline.

James et al have reported the only study to date that has examined the rate of decline in renal function after an AKI episode. In a population who had undergone coronary angiography they found that the mean annual rate of decline in eGFR during a mean follow up of 2.5 years was 0.1mls/min/year in those who did not have an AKI, 1.0mls/min/year in those with a mild AKI (AKIN stage 1), and 3.1mls/min/year in those with moderate to severe AKI (AKIN stages 2 and 3). With adjustment for age, sex and comorbidities, including the presence of proteinuria, the rate of decline in the moderate to severe group was 2.8mls/min/year. In addition, they compared this to the slope of decline during the year prior to the AKI episode and found that the rate of decline was unchanged in the mild AKI group but had increased by 1.8mls/min/year in the moderate/severe group [230]. James et al used only a 12 month time period with which to calculate the slope prior to the AKI episode which is unlikely to be an accurate reflection of the true trajectory particularly when such small changes are being

recorded [410]. Their study was also limited to a very specific population after coronary angiography where the cause of the AKI was more likely to be contrast related. Nevertheless their findings lend some support to the findings in this study discussed above.

An unexpected finding was the influence of the slope of decline on recovery of function after 6 months. Univariate logistic regression analysis revealed a reduced risk of failure to recover function according to the study criteria of a fall in eGFR of 5mls/min. This was most marked in the AKI group where the odds ratio was .879 (95% C.I. .800 to .965, p=.007) but was also evident in the AKI/CKD group (OR .920, 95% C.I. .851 to .995, p=.036). This protective effect persisted when the definition of recovery was extended to a fall of 10mls/min/year but was lost when failure to recover function was defined by a fall of 25% in eGFR from baseline. The finding of reduced odds of failing to recover persisted in every model on multivariate analysis. This effect is counter-intuitive however there may a plausible explanation. It was previously highlighted that recovery of function appears to be better in those with pre-existing renal impairment. This might be explained by differences in the relative severities of the AKI episodes themselves. The same idea could be applied to those with pre-existing evidence of a decline in function. This is not suggesting that AKI does not worsen these cases but rather that the AKI episode necessary to bring this about needs to be more severe when expressed in terms of changes in serum creatinine. This theory is supported by the finding that the protective effect exerted by a steeper decline in function prior to the AKI episode is lost when the definition of recovery is extended to the more robust definition of fall in eGFR of 25% from baseline. To achieve this greater decline in function a more severe AKI may be needed. Another interesting feature of this analysis is that adjustment for AKIN stage in the multivariate models had little if any impact on the findings. This does not rule out the theory that AKI severity is the key to these findings. Instead it may be another example of how measuring acute renal dysfunction and injury by changes in serum creatinine could be inaccurate and not truly reflect the extent of the underlying injury.

8.2.7 Factors influencing failure to recover function

Regression analysis was used to explore factors that may influence failure to recover function after an AKI episode. The strongest factor was the slope of decline in eGFR prior to the episode as discussed above. Notably, the occurrence of at least one AKI episode during the 12 month and 4 year periods prior to the index AKI did not appear to increase the risk of failure to recover function. This suggests that repeat episodes in themselves may not be enough to cause progression of renal disease but rather the

relative severity of the underlying renal injury with the episode that is important. Baseline eGFR did not predict the outcome of failure to recover function in the AKI group. However in the AKI/CKD group on univariate analysis, for a fall in eGFR of 5mls/min, reduced baseline eGFR had a protective effect with an (OR .965, 95% C.I. .936 to .994, p=0.019). With a fall in eGFR of 10mls/min this became highly significant (p=.005). The lack of influence of baseline on recovery in the AKI group is unsurprising as this group has relatively normal kidney function. In the AKI/CKD group the finding of a protective effect fits with the earlier theory that pre-existing CKD requires a more severe AKI (as expressed by changes in creatinine) to cause any lasting impact on function.

Increasing age was found to increase the risk of failure to recover in the AKI group but not in the AKI/CKD group. A possible explanation for this is that all of the AKI/CKD group encompassed a smaller age range (median 75years, IQR 72-84). Overall gender was not found to have an influence on recovery in either group although in the AKI group for a fall in eGFR of 25% from baseline male sex showed a marked protective effect (OR .301, 95%C.I. .122 to .745, p=.009). This was unaffected by adjustment for age, comorbidities and AKIN stage. Bagshaw et al reported a similar finding in a Canadian population of ITU survivors who had undergone renal replacement therapy [366]. The reason for this protective effect in males is unclear but there may be a degree of survivor bias as over two thirds of the deaths in the AKI group at 6 months were male.

The baseline level of comorbidity expressed by the Charlson score in this study was not found to influence recovery of function in either group. The use of RAS-blockers at the time of the AKI episode does not appear to influence recovery in either group. In the AKI group when the definition of a fall of 25% in eGFR is used the use of RAS blockers was found to increase the risk of non-recovery on univariate analysis (OR 2.337 95% C.I. 1.028 to 5.312, p=0.043). However, this effect was lost with adjustment for increasing age.

A potentially important finding in this study was a reduced risk of failing to recover in the AKI/CKD group in those taking a statin although the finding may be due to chance. This was found on univariate analysis when the definition of a fall in eGFR of 5mls/min was used but was not found when the other recovery definitions were used. On multivariate analysis this protective effect increased with adjustment for age, sex, Charlson Score and hypertension. It increased further when AKIN stage was added to this model (OR .358, 95% C.I. .159 - .806, p=.013). The only factor that was found to

reduce the protective effect associated with statin therapy was the addition of aspirin to the models.

There is a sound theoretical basis for a possible protective effect of statin therapy in the setting of AKI and this has been demonstrated in experimental animals. Statins increase Nitric Oxide synthesis, and reduce both inflammation and the production of reactive oxygen species. On this background, Sabbatini et al studied the impact of low dose atorvastatin in aging rats subjected to ischemic AKI. Atorvastatin was found to independently increase the expression of endothelial NO synthase (eNOS)-mRNA expression with a resulting increase in nitric oxide production. Nitric oxide can reduce vasoconstriction and Sabbatini et al demonstrated that in treated experimental animals atorvastatin significantly attenuated the ischaemic tubular injury found on histological examination [411]. In another study using experimental animals Yasuda et al reported that simvastatin improved sepsis- induced AKI. This occurred through a reversal of the reduced intra-renal microvascular perfusion induced by the AKI and a reduction in renal tubular hypoxia. Like Sabbatini et al the authors found a reduction in tubular damage [412].

Observational work has been undertaken examining the impact of statin therapy on the occurrence of AKI but reports have been mixed. Mithani et al conducted a retrospective review of patients who underwent cardiac surgery and found that the use of statins did not lower the risk of postoperative AKI [169]. Conversely, in another retrospective study, Billings et al showed a lower incidence of AKI after cardiac surgery in those given statin therapy early postoperatively in both chronic and naïve statin users [406]. Prowle et al found that short-term perioperative use of atorvastatin was not associated with a reduced risk of post-operative AKI [413]. These reports are specific to cardiac surgery patients. Molnar et al reviewed a large population of patients following major elective surgery of any kind and found that after adjustment for patient and surgical characteristics statin therapy was associated with 16% lower odds of AKI [407]. Whelten et al reviewed the immediate outcomes after vascular surgery. In 2170 patients they found that post operative AKI occurred in 664(34%) and of these 47% had a complete recovery within 3 days. The use of statin therapy did not reduce the risk of AKI but did improve the odds of complete recovery by day three [118].

Work to date has largely focused on the ability of statin therapy to prevent AKI and not on long-term recovery of function. While Whelten et al did not find a reduced risk of AKI the fact that statin therapy increased the chances of recovery, albeit in the first three days, may be important. Statins may not prevent AKI events from occurring but they may attenuate them. The findings in this study might support this theory as the

protective effect was lost when more severe failure to recover was considered. This is presumably because they had a more severe injury that outweighed any potential beneficial effects.

Follow up findings may also be related to the chronic use of statins in the aftermath of the AKI episode. However, data on the influence of statin therapy on the progression of CKD are conflicting [414]. There is some evidence in the literature that statins may slow the progression of CKD. Sandhu et al conducted a meta-analysis of 27 trials of statins that reported kidney function outcomes and found that statin therapy reduced proteinuria modestly and resulted in a small reduction in the rate of kidney function decline. This was most marked in those with cardiovascular disease [415]. Conversely, the recent SHARP study did not report a beneficial effect on progression of renal disease in those on statin therapy over nearly 5 years of follow up using the endpoint of a doubling of serum or creatinine or reaching ESRD [416]. No study to date has looked at the subset of CKD patients who have experienced an AKI episode. As experimental evidence suggests that some of the benefit of statin therapy may lie in its effects on reducing renal ischaemia, this may be the patient group that could show a benefit. This is an area that needs further work.

This study showed no difference in recovery outcomes depending on whether the AKI was community acquired (present on admission) or hospital acquired. Increasing AKIN stage resulted in an increased risk of failing to recover function in both groups but this finding varied with the definition of recovery used. In the AKI group, using a fall in eGFR of 5mls/min as failure to recover, AKIN stage was not useful at predicting this outcome. However for a fall in eGFR of 25% from baseline the association was much clearer. In model 4 with adjustment for age, sex, and comorbidities the adjusted OR ratio of failure to recover for AKIN stage 2 was 4.356 (95% C.I. 1.077 – 17.621) which increased to 7.748 for AKIN stage 3 (95% C.I. 1.922 – 31.323. overall p=.015). This finding supports a theory raised earlier. It may be that a fall in eGFR of 5mls/min is not adequate to describe this phenomenon as it may be heavily influenced by individual and analytical variation and could be too weak to reflect true injury.

In chapter 3 it was highlighted that the influence of cause of AKI on recovery of function was unclear from the literature. In this study when the cause of the AKI is divided into hypoperfusion, septic and complex causes, the recovery outcomes were not significantly different. There is a trend toward an increased risk of failing to recover in the septic and complex groups but this trend is attenuated by adjustment for AKIN stage. This suggests that AKI severity rather than cause per se is the important factor.

A curious finding in this study is that the risk of failing to recover function appears to be reduced in those who have had a nadir blood pressure recorded < 90 systolic at the time of the AKI. In the AKI group this effect was found to be substantial and persisted in all of the multivariate models explored. For a fall in eGFR of 5mls/min the odds ratio was .377 when adjustment was made for age, sex, comorbidities and AKIN stage (95% C.I. .180 to .787, p=.009). Using the definition of a fall of 25% these findings are similar (OR .308 95% C.I> .108 to .880, p=.028). In the AKI/CKD group this protective effect was weaker and apparent only as a trend. The finding that significantly reduced blood pressure is protective seems counter-intuitive. However, the effects of remote ischemia pre-conditioning are well described in the literature. It is known that transient non-lethal ischaemia applied to an organ or tissue protects another organ or tissue from subsequent lethal ischaemic injury. This phenomenon is thought to be due to alterations in the expression of signalling mechanisms in the inflammatory cascade. These alterations persist and protect other tissue and organs from repeat ischaemia. This concept has been applied in practice in patients undergoing cardiac surgery. Venugoppal et al recently reported a secondary analysis of two randomised controlled trials in which remote ischaemic pre-conditioning, involving three 5 minute cycles of right forearm ischaemia using a blood pressure cuff, was applied to patients about to undergo cardiac surgery. They found that pre-conditioning reduced the risk of AKI [405].

There is some evidence in the literature that the duration of the AKI may have an impact on outcomes. Coca et al studied a group of diabetic patients who had sustained an AKI after cardiac surgery. They found that the duration of the AKI was significantly associated with mortality in a dose dependent manner [163]. They did not report on functional outcomes. In this study the duration of the AKI episode was defined as the time taken to recover to a creatinine value that was below the threshold for AKIN stage 1. The duration to reach this point was not found to influence function after 6 months of follow up.

Finally, patients who had a formal review by the renal team were studied. On univariate analysis it was found that those in the AKI group who had a review were at a significantly increased risk of failing to recover function after follow up. This was associated with an odds ratio of a fall in eGFR of 25% from baseline after 6 months of 4.68 (1.604-13.656, p=.005). This is almost certainly related to the severity of the illness and underlying AKI. However, it is worth highlighting because in clinical practice many of these renal reviews are for advice only and patients do not receive subsequent follow up.

8.3 Mortality

As discussed in Chapter 2, it is well established in the literature that AKI is independently associated with increased hospital and long-term mortality. This study highlights the high mortality associated with AKI in both those with and without underlying CKD.

8.3.1 General Summary of findings

At 6 months mortality reached 24% in the AKI/CKD group and 12.6% in the AKI group (p=.003). When the AKI/CKD group was compared to the CKD control group mortality was higher and approached statistical significance despite the low numbers in the control group (p=.02). It would not be appropriate to generalise these results to the general population as this study was designed primarily to explore the impact of AKI on kidney function. The study cohort was enriched with more severe AKIN stages through the under-sampling of AKIN stage 1.Nevertheless it provides an insight into the poor outcomes that can be expected with AKI.

8.3.2 Outcomes in those with and without pre-existing CKD

In this study hospital mortality was higher in the AKI/CKD group compared to the AKI group (8.6% v 3.7%, p=.045). This is not unexpected given that this group was significantly older and had more comorbidities. Many previous studies have associated AKI/CKD with a lower mortality. Those studies were largely set either in the intensive care setting or in severely ill patients where patient selection and underlying illness severity are likely to have played an important role. This is supported by the findings by Cerda et al who found a lower mortality in the CKD group in a group of critically ill patients requiring renal replacement therapy. This was effectively removed when adjustment was made for illness severity [286]. The findings in this study are in keeping with the findings of Ali et al who also found a higher mortality in hospital in those with pre-existing CKD [187].

8.3.3 Factors influencing mortality outcomes

Regression analysis demonstrated several notable findings when examining mortality 6 months after the AKI episode. Univariate analysis demonstrated that an increasing slope of decline in eGFR prior to the AKI did not influence mortality outcomes. This is surprising given that CKD progression is associated with a higher mortality in the general population [4]. The study may have been underpowered to detect this

association and in addition the follow up period may have been too short. However, the slope of decline was found to have a protective effect in terms of recovery of function. It was highlighted in Chapter 3 that incident CKD and progression of CKD may account for the increased mortality after an AKI episode. If the slope of decline is associated with a reduced risk of failing to recover function then this might explain the lack of association with mortality at least in the aftermath of an AKI episode.

In the AKI group univariate analysis revealed an increased risk of mortality associated with an admission to hospital in the 12 months preceding the index AKI. In addition those who had evidence of an AKI in the 4 years prior to the index AKI were found to be at a significantly increased risk of dying in the following 6 months (OR 4.697, 95% C.I. 1.551 – 14.224, p=.006). This apparent cumulative effect is at least partly due to the presence of underlying comorbidities as it is weakened when adjustment is made for increasing Charlson Score (OR 2.898, 95% C.I. .887 – 9.468). This association was not found in the AKI/CKD group. This may have implications for clinical practice as a history of a previous AKI is easily identifiable. It may identify a subgroup of patients that will benefit from preventive strategies and aggressive management of their AKI. This area needs further study.

Increasing age was found to be an important risk factor for mortality in the AKI group (p=.004) but not in the AKI/CKD group. As discussed earlier, this may be due to the tighter age range evident in the AKI/CKD group and perhaps a lack of power in the study. Likewise, increasing Charlson comorbidity score was found to have a strong influence on mortality in the AKI group but not in the AKI/CKD group. In the AKI/CKD group most patients had a high comorbidity load (mean Charlson Score 4.19) and it is likely the patient numbers in this group were insufficient to detect any differences. Gender did not influence mortality in either group.

RAS-blockers did not influence mortality in the AKI group. In the AKI/CKD group, univariate analysis revealed a reduced odds of mortality at 6 months in those taking RAS-blockers (OR .468 95% C.I. .227 - .965, p=.04). This protective effect was reduced when adjustment was made for age, sex, and co-morbidities. It is possible that this effect is due to the their use in patients with less co-morbidity and therefore possible more likely to recover. Nevertheless this finding is important as 35% of those who had their RAS blocker stopped at the time of their AKI in the AKI/CKD group did not have them restarted during follow up. This may be because it was felt to be clinically inappropriate. On the other hand it may be an oversight on the part of the managing physicians. If there is a protective effect then these patients are being denied a drug that may be conferring longer-term benefit. This needs further exploration.

With regard to the other medications reviewed in this study it is notable that the use of statin therapy was not associated with mortality in either group. This study is likely to have been underpowered to detect any association.

The setting of the AKI appears to have an important influence on mortality outcomes in both groups. In the AKI group, community acquired AKI evident on admission to hospital was associated with a more than 3 fold increased risk of mortality at 6 months (OR 3.469, 95% C.I. 1.135 – 10.603, p=.029). This was not the case in the AKI/CKD group. The increased risk in the AKI group was weakened when adjustment was made for comorbidities and AKIN stage. This suggests that AKI severity may be partly responsible for this finding. In the AKI/CKD group admission under a medical specialty was strongly associated with an increased risk of mortality. This was not influenced by adjustment in any of the multivariate models. The explanation for this finding may that patients selected to be suitable for surgery are likely to be younger and fitter. Therefore they will have better outcomes. In addition the nature of the AKI and the underlying illness are likely to be more severe in medical patients compared to elective surgical patients.

AKIN stage was not found to predict mortality outcomes in the AKI group. In the AKI/CKD group AKIN staging was associated with an increased risk of mortality. However, the highest risk was found in AKIN stage 2 in all of the models analysed. Numerous studies in the literature have found an increased mortality with increasing AKIN stage [155,167,170]. However, others have not. In a validation study in the intensive care setting Ostermann et al found that only AKIN stage 3 predicted mortality [137]. These findings will be discussed further below.

In terms of the cause of the AKI episode, this did not appear to have a strong influence on mortality outcomes at 6 months in either group. In the AKI/CKD group septic AKI and complex AKI were associated with an increased risk of mortality at 12 months and this association persisted even with adjustment for comorbidities and AKIN stage. There is limited evidence in the literature associating AKI cause with mortality outcomes. Bagshaw et al demonstrated an increased risk of mortality in septic cases in intensive care [227]. This study is the first to look at longer-term outcomes in relation to cause and it appears that this has little influence on 6 month outcomes. Although an association was found in the AKI/CKD group at 12 months, medical events in the months prior to this time point are not known and so making a causal link with AKI cause is tenuous at best.

In this study AKI duration was defined as the time taken for the rise in creatinine to return to levels below the threshold for AKIN stage 1. Duration was not found to influence 6 month mortality in either group on univariate analysis. Several studies in the literature, albeit in quite specific patient groups, have associated a longer duration of AKI with increased mortality. Some have concluded that it adds additional prognostic information [160,162,163]. For example, using the same definition of duration as this study, Coca et al found that increasing duration of AKI increased long-term mortality in a cohort of diabetic surgical patients even with adjustment for AKI severity [163]. This study may have lacked the power to demonstrate this association or it may be that this association does not exist in a more diverse general hospital population.

8.4 Combined outcome of failure to recover function and mortality at 6 months

In the AKI group logistic regression showed that an increasing slope of decline in eGFR prior to the AKI episode had a strong protective effect on the combined outcome of mortality or a fall in eGFR of 5mls/min or more from baseline. This was the strongest influencing factor. On univariate analysis the odds ratio for the combined outcome was .883 (95% C.I. .808 to .965, p=.006). This was largely unaffected by adjustment in the multivariate models. This association was not found in the AKI/CKD group.

Increasing age was found to increase the risk of the combined outcome in the AKI group but not in the AKI/CKD group. On univariate analysis lower baseline eGFR was associated with a reduced risk of the combined outcome in the AKI/CKD group but not in the AKI group. This fits with the earlier findings for the individual outcomes and supports the theory that the relative impact of the AKI episode may be different in the AKI/CKD group.

Admission under a medical specialty appears to increase the risk of the combined outcome in the AKI/CKD group but not in the AKI group. AKIN stage had no influence on the combined outcome in the AKI group. In the AKI/CKD group AKIN stage was associated with an increased risk. This persisted with adjustment for comorbidities in multivariate analysis. However, the highest risk was associated with AKIN stage 2.

8.5 Length of hospital stay

In this study the median length of hospital stay in the AKI/CKD group was significantly longer than that of the CKD control group (12 days v 7 days, p=.002). This is the first

study to demonstrate this in a prospective review of general hospitalised patients. It confirms the findings of numerous retrospective studies. This is one of the key issues highlighting AKI as a major drain on healthcare resources [32].

8.6 Contributions to the natural history of AKI

8.6.1 AKI Group compared to the AKI/CKD group

This study highlights numerous differences in characteristics and outcomes of the AKI group and AKI/CKD group.

Both groups are substantially different at baseline. The AKI/CKD group is older and has a greater comorbidity burden. As a result the AKI/CKD group showed differences in terms of the medications in use. In the case of RAS blockers, 74% of the AKI/CKD group were taking these compared to 52% in the AKI group ($p<.001$). Baseline characteristics also appear to influence the setting of the AKI episode in each group. In the AKI/CKD group significantly more patients in the surgical category were emergencies (85% v 59.5%, $p=0.001$). This will have an influence on the nature and management of the AKI episodes rendering any meaningful comparison impossible. More of the AKI/CKD group had a history of previous AKI episodes. In addition, mortality was higher at all time points in the AKI/CKD group however functional recovery in this group appears to be better.

These differences highlight the need to separate these groups carefully in the design of AKI studies. As discussed earlier, the relative effects of each AKI stage on those with pre-existing CKD may be quite different to those with normal renal function and this may account for the better recovery patterns in the AKI/CKD group. The possibility also exists that the pathological responses of an already impaired kidney to an AKI insult may be different to those seen in a normal kidney. These issues raise questions about the appropriateness of using the same definition of AKI in each of these groups. It highlights how biomarkers that reflect actual injury rather than relative changes in function may be more suitable for studying AKI.

8.6.2 Community-acquired AKI compared to Hospital-acquired AKI

The recent NCEPOD report in the UK, AKI: Adding Insult to Injury, identified a good overall standard of care in only 50% of patients with AKI. This fell to 30% in cases that occurred in hospital [36]. KDIGO recently identified the need to better delineate the risk for hospital-and community-acquired AKI [48]. If better management of AKI is to be

achieved an improved understanding of the epidemiology and natural history of these subsets of the AKI population is needed.

This is the first study to examine the differences in characteristics and outcomes between community and hospital acquired AKI in the same population. It was highlighted in Chapter 2 that the epidemiology of community and hospital-acquired AKI is unclear in the literature. KDIGO suggested that hospital-acquired cases are 5 to 10 times more common however there is a lack of evidence to support this claim in the literature [48]. In fact community – acquired AKI appears to be more common in some studies [107,110,168]. In this study it is not possible to give a clear description of the relative proportions that are community or hospital-acquired. In the overall cohort community-acquired cases are more common with over two thirds of cases being evident on admission (67.4%). However, examination of the distribution of admission cases by AKIN stage in each group revealed a trend toward there being more AKIN stage 1 in the hospital-acquired subset. This means that the under-sampling of AKIN stage 1 used in the recruitment in this study would have underestimated the number of hospital-acquired cases. Nevertheless, as there were no significant differences found in the baseline characteristics between stages in either group it is possible to comment on the general differences between community and hospital –acquired cases.

There was no age difference found between these subsets in either group. There was a trend toward there being a greater burden of comorbidity in the community-acquired cases in the AKI group. In both groups a significant majority of the community – acquired cases were admitted under a medical specialty. In the AKI group there were significantly more septic AKI cases on admission (p=.001) while more perfusional cases were found in the hospital –acquired subset (p=.003). No difference in the distribution of causes were found in the AKI/CKD group. In terms of management practices the findings in this study are in keeping with the NCEPOD report [36]. Patients with AKI present on admission were more likely to have had a urine dipstick and renal ultrasound in both groups.

No differences in recovery patterns were found between the subsets in either group. In the AKI group mortality was higher in community – acquired cases both in hospital and after 6 months. This finding would not have been affected by the under-sampling of AKIN stage 1. More of these cases would have been in the hospital-acquired subset and so would have increased the mortality difference even further. The only study with which to compare this finding is that of Sesso et al who found an increased mortality in hospital-acquired AKI in the elderly [110]. The finding that community acquired cases in this study have a higher mortality may have important practice implications. In

addition to implementing preventive strategies within hospitals, community management by general practitioners will also need to be addressed.

8.6.3 The influence of AKI cause on outcomes

In this study an effort was made to describe the causes of AKI clearly and to examine their influence on outcomes. The traditional 'pre-renal' variety of AKI was divided into septic, hypoperfusion and complex cases. This was done because as discussed in Chapter 2, evidence exists that there may be differences in the pathology and outcomes in relation to the septic causes.

In Chapter 6 it was seen that at baseline there was no difference in the distribution of causes between the AKI and AKI/CKD groups. Approximately 40% of cases in each group were hypoperfusion indicating that the primary cause was due to a haemodynamic disturbance. Between one quarter and one third of cases in each group were septic in origin while a quarter of cases had more than one primary cause and fell into the complex category. This latter finding is in keeping with the literature. Liano et al found more than one aetiology in 16% of cases of AKI in hospital [20]. Complex cases included cases of obstruction and nephrotoxic AKI. The latter was made up largely of contrast-induced AKI. In fact all of the contrast-related cases in both groups were considered to be complex and had at least one additional cause associated with it. Pure intrinsic AKI was very uncommon making up just 1.7% of the AKI group and no case was found in the AKI/CKD group.

In terms of outcomes, the cause of the AKI episode was not found to have a marked influence. Cause did not influence mortality in the AKI group. In the AKI/CKD group there was a trend toward an increased mortality in the septic and complex cases at 12 months but not at 6 months. Recovery of function was not influenced by cause in either group.

8.6.4 Recurrent AKI episodes

An important finding in this study was a pattern of repeat AKI episodes evident both before the AKI and during follow up. Thakar et al recently detected this phenomenon in a study of diabetic patients but it has not been described in a general hospitalised cohort [34].

In this study a review of records up to four years prior to the index AKI revealed that 8.9% of the AKI group and 34.6% of the AKI/CKD group had had a previous AKI that

met AKIN criteria (p=.001). During the 6 month follow up period 8.4% of survivors in the AKI group and 19.6% of the AKI/CKD group had at least one more such AKI episode. This included cases that occurred solely in the community. Of those who had demonstrated a fall in eGFR of at least 5mls/min after 6 months 8.4% in the AKI group and 19.6% in the AKI/CKD group had had a repeat AKI episode. These episodes may also be contributing to the outcomes found.

Logistic regression was used to assess their impact in patients who had survived to discharge. A repeat AKI episode was found to be one of the strongest predictors of mortality at 6 months in the AKI group. In the unadjusted model the odds of death were increased nearly 9 fold (OR 8.647, 95% C.I. 2.507 to 29.821, p=.001). This was largely unaffected by adjustment in multivariate models. The influence was weaker in the AKI/CKD group and was lost when adjustment was made for comorbidities in the multivariate analysis. There was surprisingly no influence found on recovery of function in either group. The overall event rates were low however and it is likely that the study lacked the numbers to demonstrate any significant differences in recovery outcomes.

This finding is very important. Other than the study by Thakar et al no study to date has considered the influence of repeat AKI episodes. Therefore all of the recent reports of long-term outcomes in AKI studies are potentially flawed and the effects of individual AKI episodes and the relative risks associated with them are overestimated. AKI epidemiology needs to take account of the multiple nature of these events and further work needs to be done to better understand their potential cumulative effect.

8.7 Management Practices

This study has identified a number of areas in the management of AKI in hospitalised patients that need further review as they have important implications for clinical practice.

8.7.1 General management

The NCEPOD report identified a number of deficiencies pertaining to the basic management of AKI patients who had died in hospital. This report involved patients who were coded as having a death associated with AKI and so were almost certainly at the more severe end of the spectrum. 33% of patients were found to have had inadequate basic investigations. This included no urine dipstick in 14% and no renal ultrasound in 18% [36].

This study was carried out during the two years after the publication of the NCEPOD report. Despite this the deficiencies described by NCEPOD are evident and in fact appear worse because milder episodes of AKI are included. Urine dipstick measurement was performed in only 46% of the AKI group and 51% of the AKI/CKD group. When the groups were divided by AKIN stage there were still a substantial number not having this basic investigation even in AKIN stage 3. In the AKI group only 58% of AKIN stage 3 had a urine dipstick while 60% in the AKI/CKD group had one. 36.8% in the AKI group and 34.6% in the AKI/CKD group had a renal ultrasound performed. In clinical practice it would not be considered appropriate to perform a renal ultrasound in many of the milder cases of AKI. However, when divided by AKIN stage it was shown that even in AKIN stage 3 only 60% of the AKI group and 70% of the CKD group had an ultrasound. In the case of a fall in eGFR of 25% from baseline after 6 months (the most severe reduction in function reviewed) 42% of the AKI group who reached this endpoint did not have an ultrasound performed at the time of their AKI (p=.007). Finally, in this study accurate urine output measurement was missing in a large proportion of patients in each group. While this may have implications for management it also highlights how urine output is of limited use in the definition of AKI in general hospitalised patients.

8.7.2 Nephrology Referral

One of the key findings in the NCEPOD report on acute kidney injury related to referral practices. Of the 561 AKI cases reviewed only 31% had been referred for nephrology advice and management. It was the opinion of the advisory team that a further 20% should have been referred for specialist opinion [36].

Evidence exists that nephrology referral and support may alter outcomes. Meier et al recently reported the outcomes of 4296 non-critically ill patients that had sustained an AKI. They divided patients into those who had not received a referral, those who had a late referral defined as greater than 5 days after the onset of the AKI, and those who had an early referral. In that study referral rates were high which probably reflects local practices. In total 78% of patients were referred for nephrology review. The authors found that mortality was significantly higher in those who had no referral or a late referral compared to those who had an early referral [174]. It is likely that nephrology referral improves AKI management and may prevent deterioration to a higher AKI stage. Further support for this can be found in a recent study by Abraham et al who found that the mortality associated with AKI in hospitals in England was significantly higher in those hospitals without onsite nephrology cover [37].

In this study 8.9% of patients in the AKI Group were reviewed by a nephrologist while in the AKI/CKD group 20.5% had a review (p=.002). When divided by AKIN stage it was found that in the AKI group no patient in AKIN stages 1 or 2 were referred. This leaves 23% of AKIN stage 3 having had a review. In the case of the AKI/CKD group 12% in each of AKIN stages 1 and 2 received a referral and 78% in AKIN stage 3. In regression analysis renal referral was not found to influence mortality outcomes although the numbers may have been insufficient to demonstrate a difference. In the AKI group having had a referral was strongly associated with an increased risk of a fall in eGFR of 10mls/min or a fall of 25% from baseline after 6 months follow up. This was unaffected by adjustment for age, sex, and comorbidities. In the case of a fall in eGFR of 25% the odds in those who had a referral was 5.362 (95% C.I. 1.656 – 17.359, p=.005) This is likely to reflect AKI severity and the severity of the underlying illness.

These findings highlight key issues concerning referral practices. A significantly larger proportion of the AKI/CKD group was referred to nephrology. This study has demonstrated that functional recovery is actually worse in the AKI group. The increased referral rate may be because there is a greater awareness of renal disease in the CKD population. Some of these CKD patients were already known to the renal service and this may have prompted earlier referral. Regardless, it is concerning that over three quarters of AKIN stage 3 in the AKI group did not receive a nephrology review. This appears to contravene the National Service Framework for Renal Services in the UK which states that patients experiencing an AKI are entitled to clinically appropriate care in partnership with specialised renal teams [417].

8.7.3 AKI coding practices

International Classification of Diseases codes are used in many countries to record and classify patient diagnoses at the time of death or discharge from hospital. Their use has formed the basis of numerous contemporary retrospective AKI studies in the literature. The accuracy of this coding system is dependent on the teams managing the patients and it is known to under-report certain diagnoses. Waikar et al conducted a study of coding practices in relation to AKI in a US hospital and found that ICD-9 codes failed to identify a large proportion of clinically significant changes in serum creatinine. Patients who had a rise in creatinine of at least 100% from baseline during their hospital stay were identified. The authors found that the sensitivity of the codes for this definition was only 35.4% while the specificity was 97.7% [418]. However, the accuracy of coding will clearly be dependent on local practices.

In this study patient records were reviewed after death or discharge from hospital to ascertain what coding if any was used in relation to the AKI episode. During the course of this study ICD-9 codes were in use in Queen Alexandra Hospital. In the case of the AKI group only 38.9% had an AKI related code while 50.8% of the AKI/CKD group had one (p=.021). When the AKI group is divided by AKIN stage 8.7%, 35.2%, and 61.6% were coded for AKIN stages 1,2, and 3 respectively. In the AKI/CKD group these figures were 38.4%, 50.9% and 87.9% respectively. The code used in the vast majority of cases was ICD-9:N17.9 – ARF unspecified.

These findings have important implications. A large proportion of patients who had an AKI during their hospital admission do not have this recorded at discharge. The most worrying finding is that nearly 40% of the more severe AKIN stage 3 in the AKI group are not recorded. In the majority of cases the discharge summary from which these codes are derived is the sole communication with the patients general practitioner after discharge. The findings indicate that general practitioners are not being made aware of a large proportion of patients with a severe AKI. This raises questions regarding the quality of the follow up these patients receive at least in relation to the hospital in which this study took place. However, there is no reason to believe that this is not the case at a national level. Another important implication is that the codes used in the hospital discharge summaries are used to determine the tariff for that hospital episode. While many of these AKI episodes will be bundled with the primary diagnosis and not influence the tariff, it is still possible that the tariffs may be incorrect and therefore the hospital may not be remunerated appropriately for the episode. Finally, routine discharge data have been used to identify AKI in many studies and so are likely to underestimate AKI.

8.7.4 Use of RAS-blockers

The use of RAS blockers is generally considered in clinical practice to contribute to the causes of AKI. This is based on their effect of reducing GFR. As a result it is now common practice to discontinue their use in those at risk of or experiencing an AKI. Several studies have demonstrated an increased risk of AKI in those taking RAS blockers in different settings to support this practice [116,220,419,420]. Thakar et al reported an increased risk in a cohort that had undergone gastric bypass surgery while Akram et al reported an increased risk in those with community – acquired pneumonia [116,220]. However, in the setting of cardiac surgery the findings have been conflicting. Arora et al demonstrated an increased risk of AKI after cardiac surgery while Yoo et al showed no increase in the risk [152,421]. Benedetto et al actually demonstrated a reduced risk of

AKI after on-pump bypass surgery in the RAS blockade group [422]. The reason for the differences in these studies is unclear.

While RAS blockers may be associated with an increased risk of AKI, their influence on outcomes have not been studied in detail. In the study by Akram et al the use of RAS-blockers was found to have no effect on adverse outcomes [220].

This study gives an insight into current practices in the use of RAS blockers at the time of an AKI episode and reviews their influence on outcomes. At baseline the use of RAS blockers was considerable in both groups. 52% of the AKI Group and 74% of the AKI/CKD group were on a RAS-blocker (p<.001). It is notable that when the AKI/CKD group was compared to the non-AKI CKD controls there was a significant difference in their use with only 46% of controls taking them (p=.003).

At the time of the AKI episode over 90% of patients had their RAS blocker discontinued. However, an important finding is that of those who were taking them at baseline only 73% of the AKI group and 66% of the AKI/CKD group were taking them after 6 months of follow up. The reason why the drugs were not restarted is unclear. It is likely that in some cases they were not deemed to be clinically necessary. In 50% of the AKI group and 71% of the AKI/CKD group the original indication for the RAS blocker was hypertension. However it is also possible that they were not restarted as an oversight on the part of the admitting team. This could have an impact on long-term outcomes particularly in those with cardiac failure or diabetics with proteinuria.

The use of RAS blockers at the time of the AKI had no influence on mortality after 6 months in the AKI group. However in the AKI/CKD group in univariate analysis RAS blocker use was found to be associated with a reduced 6 month mortality (OR .468, 95% C.I. .227 to .965, p=.040). This protective influence was lost with adjustment for age, sex, and comorbidities in the multivariate analysis. In the AKI group RAS blocker use was found to be associated with an increased risk of having a fall in eGFR by 25% after 6 months in univariate analysis. This effect was lost in the multivariate models. RAS blockers were not found to influence functional outcomes in the AKI/CKD group after 6 months.

The finding that RAS blockers may reduce mortality in the AKI/CKD group is a weak association at best. There are many potential confounding issues not least of which is the fact that the RAS blockers were not restarted in some patients. Nevertheless it highlights some important issues. This study has demonstrated that a large proportion of patients on RAS blockers do not have them restarted after hospital discharge. If

there is the potential for a protective effect in terms of mortality in the AKI/CKD group then this practice needs to be reviewed. This is an area that clearly needs further study.

8.8 Methodological issues

Chapters 2 and 3 highlighted several methodological issues hampering current AKI research. These included the definitions of baseline kidney function, that of AKI itself, and of recovery of function. This study adds to the current literature as it has further examined these areas and may aid in the design of future studies.

8.8.1 Definition of baseline kidney function

Up to 30 different definitions of baseline function have been used in AKI research. The definition of baseline kidney function is important because it effectively anchors the definition of AKI and provides a longitudinal reference point [423]. This is crucial in any study of the functional outcomes of AKI. The lack of a consensus definition of baseline function contributes to study heterogeneity and potentially confounds the reports of long-term functional outcomes after AKI [424].

In the design of this study close attention was paid to the identification of baseline function resulting in one of the most rigorous definitions used to date. Despite the rigorous approach taken in defining baseline potential problems were identified. During the retrospective review of biochemistry records it was found that 14.7% of patients selected for the AKI Group had at least one eGFR measured as an outpatient < 60mls/min when the search was extended back over a three year period from the chosen baseline. In addition 8.4% of patients were found to have evidence of microalbuminuria prior to their admission. It therefore could not be said with certainty that these patients did not already have underlying CKD. Sensitivity analysis in this study revealed no differences in outcomes in this group of patients however it remains a potential source of confounding.

Siew et al examined several different methods of estimating baseline kidney function. This included the mean outpatient value, the most recent outpatient value, the nadir outpatient value, and the most recent inpatient value. They concluded that using the mean outpatient serum creatinine from values taken during the previous 7 – 365 days most closely approximated a nephrologist-adjudicated estimation of baseline function. This assumed that the nephrologist estimation was the correct estimate or gold

standard. This was an unusual study because the authors suspected that the nephrologists had used a similar averaging method themselves and therefore the study was essentially comparing like with like. They found that by extending the search for outpatient values back to 2 years the numbers available for assessment increased but the accuracy of the estimation was reduced. They did not report if the fall in accuracy was due to under- or overestimation of baseline [424].

Choosing the average value within the previous 12 months would seem to be a reasonable approach. However, based on the findings in this study care should be exercised to ensure that there is no evidence of renal dysfunction in those who are being classified as not having CKD. In addition previous evidence of microalbuminuria may need to be taken into account.

Finally, it is important to note that while it is necessary to define baseline function this will inevitably result in missing cases of AKI where no baseline can be defined which was approximately 15% in this study. As a result any conclusions drawn from AKI research cannot be generalised to the entire population.

8.8.2 Definition of AKI

Overall the AKIN staging system was found in this study to be a poor predictor of key outcomes. There were also clear differences in its performance between the AKI and AKI/CKD groups.

In regression analysis AKIN staging did not predict mortality in the AKI group. In addition, AKIN stage did not predict failure to recover function when the original study definition of a fall in eGFR of at least 5mls/min was used. For a fall of 10mls/min or 25% from baseline AKIN stage 3 appeared to predict this outcome and this became stronger with adjustment for age, sex and comorbidities. But as AKIN stage 2 remained unclear within the regression modelling the staging system as a whole was unsatisfactory.

The system performed slightly better in the AKI/CKD group. At 6 months it appeared to predict mortality however the highest odds on regression analysis were associated with AKIN stage 2 and this was unaffected by adjustment in any of the models used in multivariate analysis. Where failure to recover function was concerned the findings were mixed. For a fall in eGFR of 5mls/min AKIN appeared predictive of this outcome however it was strongest in AKIN stage 2. It performed well when the definition of a fall of 10mls/min was used with the odds increasing with increasing stage.

The performance of AKIN was therefore disappointing. The study may have lacked sufficient power to demonstrate any clear differences between the stages. However several studies in the literature have also failed to demonstrate a strong association between staging and outcomes. In an intensive care validation study Ostermann et al showed that only AKIN stage 3 predicted mortality (Ostermann 2008). Kwon et al reported a similar result in a cohort of general hospitalised patients (Kwon 2010). While it has been demonstrated in at least one study that AKI severity influences functional outcomes no study to date has looked specifically at the ability of AKIN staging to predict these outcomes [369].

One possibility for the poor performance of the AKIN system is that it is entirely reliant on changes in serum creatinine. It was discussed at length in Chapter 2 that creatinine is an imperfect marker of renal dysfunction and it is possible that as a result the AKIN stages do not reflect the true underlying injury. This highlights the need to develop better biomarkers of renal injury.

Finally, it is worth noting that in this study the urine output criteria specified by the AKIN definition were not used. There are many potential problems associated with the use of urine output as discussed in Chapter 2. Chief among these are concerns about the accuracy of output measurement on wards where often patients will not have a urinary catheter in situ. It was decided from the outset that urine output would not be relied upon in the definition of AKI in this study. Nevertheless an effort was made to record urine output at the time of the AKI where possible. In 18.4% of cases in the AKI group no records had been kept of urine output. In the AKI/CKD group this figure reached 27.6%. Many of the cases where an output chart was maintained relied upon periodic measurement of urine collections provided by the patient. Therefore the accuracy of these results could be drawn into question. Overall, based on the findings in this study it is unlikely that urine output will ever play a significant role in AKI research in the non-critically ill where it would not be routine or appropriate to insert a urinary catheter.

8.8.3 Defining recovery of function

It was highlighted in Chapter 3 that the recovery that occurs after an episode of AKI remains poorly characterised in the literature. To date the methodological issues surrounding this aspect of AKI research have not been addressed in any detail. In this respect the work carried out in this study adds to the literature in terms of AKI research design.

Two key issues are relevant to the assessment of recovery after an AKI episode. The first is the appropriate timeframe after which patients should be followed up and the second is the definition of recovery itself. In addition to these issues there is also the problem of repeat AKI episodes that may occur during the follow up period.

The timeframe of follow up was discussed in Chapter 3. Based on the evidence available recovery appears to peak between 3 and 6 months after the AKI and then plateaus. For this reason a 6 month follow up point was chosen in this study. In addition to straight-forward recovery of function this study identified another group of patients who appear to have recovered at the time of discharge from hospital but show a decline in function during follow up. This phenomenon may be explained by several factors including the loss of muscle mass during the acute illness or vigorous rehydration. These may reduce serum creatinine and mask any sustained kidney injury in hospital. One thing that has been made clear from this study is that while renal function is measured using serum creatinine as a marker, recovery at the point of discharge from hospital should not be used as an endpoint in any study. This practice continues in contemporary literature [426].

The question of how to define recovery after an episode of AKI has not been addressed in the literature. There are currently 19 different approaches to defining the recovery of function and progression of CKD in the literature. These widely differing definitions have the potential to report very different outcomes. Consequently, there is marked heterogeneity in the literature rendering cross-validation of studies difficult [352]. It has already been mentioned that the recent NIDDK reports on AKI study design suggested that recovery could be used as a suitable endpoint in AKI clinical trials. However, no recommendations were given on how to define recovery [408].

This study explored several different definitions of recovery. The outcome of a fall in eGFR of at least 5mls/min was reached in over 50% of the AKI group and 34% of the AKI/CKD group after 6 months. When the definition is extended to 10mls/min the proportions reaching this endpoint are reduced to 41% and 20% respectively and these fall further if a fall of 25% from baseline is used. This impact of broadening the definition might be expected. However, in doing so, this study has identified how this variation can result in very different findings when data is analysed. For example, in the AKI/CKD group when the AKIN staging system was explored in regression analysis, broadening the definition from a fall of 5mls/min to a fall of 25% from baseline had the effect of completely reversing the findings in relation to the AKIN stages.

The question then arises as to which definition should be used. The definition should be clinically meaningful and ideally should be shown to influence outcomes such as mortality. At present no data exists which might help solve this problem. During the analysis in this study the effect of the different definitions of recovery at 6 months on 12 month mortality was explored, however the event rates were too low to show any differences. Therefore at present the decision on which definition is best needs to be made based on what is known about CKD and CKD progression.

The NICE CKD Guidelines define rapid progression of CKD as a fall of more than 5mls/min/year [74]. Stevens et al defined 'rapid progressors' as having a fall of > 4mls/min/year which was also the definition used by KDOQI in the 2002 CKD clinical practice guidelines [314,410]. James et al used this latter definition in a recent study exploring outcomes following an AKI episode after coronary angiography [230]. These definitions are likely to be appropriate only when follow up is carried out over a prolonged period of time with multiple measurements. In addition, intra-individual variation in eGFR measurement is more than 5mls/min and therefore a fall in eGFR of 5mls/min or less at a single time point is unlikely to be accurate or clinically meaningful. It is clear from this argument that a fall of 25% from baseline would be the most robust and least likely to give false positives. However, it is more likely to miss clinically significant changes in function. Therefore if it is applied in a clinical trial, patients who may benefit from an intervention may be missed. In both groups in this study a fall of 10mls/min correlated well with AKIN staging. This definition is above intra-individual variation if follow up is taken at a single time point and therefore may be the most appropriate. In the case of multicentre studies intra-laboratory analytical variation will also need to be considered and therefore the argument may lean toward using the most robust definition such as a fall of 25% in eGFR from baseline. This is open to debate and is an area that needs further work.

The ASSESS AKI study group are currently exploring the natural history of AKI [404]. In this study the authors opted for the more robust definition of recovery. They require a fall in eGFR of 25% from baseline and progression to at least CKD stage 3 in the AKI group and a fall of at least 50% from baseline in the AKI/CKD group. In this study there was little difference between a fall of 25% from baseline and this outcome if the definition also required reaching a least CKD stage 3 (20.8% v 19.6%). In the case of a fall of 50% in the AKI/CKD group only 3.7% reached this. The event rates in the ASSESS AKI study are therefore going to be low in the AKI/CKD group and will arguably under-report the phenomenon and the study will lack power.

8.8.4 Recruitment of controls for the AKI/CKD group

During this study it became apparent that the study design made recruitment of adequate numbers in the CKD control group extremely difficult if not impossible. The reasons for this were discussed in Chapter 4. In summary, there was an inevitable time delay between recruitment of the AKI/CKD patient and efforts to recruit a matched control. Consequently, many of the intended controls had been discharged from hospital. This may have been influenced by the fact that these patients were less ill than their AKI counterparts. In addition patients who were recruited as controls may have then gone on to have an AKI themselves and so switched arms in the study. An attempt was made to overcome this by waiting a few days to ensure that patients remained stable, however many were discharged in the interim. This aspect of the study was not anticipated but it is information for the design of future AKI research. The only reasonable way around these problems would be to recruit every patient with CKD as they came into hospital and direct them into either a stable CKD arm or an AKI/CKD arm. However, this would require vastly more resources than were available for this study. Personal communication with one of the investigators involved in the US ASSESS AKI study revealed that they are having similar problems with the recruitment of controls.

8.9 Strengths and weaknesses of this study

This study has much strength over and above the work that has been previously published in this area. To date no prospective study in general hospitalised patients that has been specifically designed to explore recovery of renal function after an episode of AKI has been published.

The prospective nature of this study allowed for the systematic follow up of patients. This removes concerns about ascertainment bias that have been raised about the retrospective studies carried out to date [357]. A nephrologist reviewed each case recruited into this study and this removes some uncertainty about the clinical diagnosis. In addition, the prospective nature of the study allowed for the real-time collection of extensive clinical data. This ability has been lacking in recent AKI research. All creatinine measurements were carried out in the same laboratory using the same analyser. This will have considerably reduced the influence of analytical variation. This study also had a relatively low attrition rate. Unlike many studies that were confined to the critical care environment, this study covers the broader hospital population and therefore the findings are more generalisable from a clinical viewpoint.

The extensive baseline and clinical data allows for a more thorough understanding of the natural history of the syndrome. Examples include the distinction between community and hospital-acquired AKI, any influence of the causes of AKI on outcomes, and recovery patterns following the AKI episode including repeat AKI episodes. Above all else, the detail in this study has helped draw a clear distinction between those with and without pre-existing CKD who sustain an AKI. This was recently highlighted by KDIGO as a research priority [48]. An additional strength of this study is that it has facilitated the exploration of AKI research methodology. To date this has not been studied in detail in a prospective manner.

As with any study there are also weaknesses. This is a single centre study in a largely Caucasian UK population and therefore the results may not be generalisable to every population. The sample size was also limited. Queen Alexandra Hospital is a large district general hospital and does not have a number of specialist services onsite. In particular there is no cardiothoracic service and it does not offer trauma services. This could have influenced the case mix and the outcomes reported. The AKI group in this study lacked a control group. However this study was designed to explore the natural history of recovery of function and the factors influencing this and so a control group was not necessary per se.

The definition of AKI relied on the measurement of serum creatinine which is an imperfect marker of renal function. However, there is currently no better alternative. The definition of baseline kidney function has been highlighted as an important aspect of AKI research design however this inevitably results in missing patients who have no baseline available. These patients are likely to be younger and fitter. This also limits the generalisability of the results. Patients in this study were followed up at a single time point and it may be argued that it cannot be proven that any failure to recover found was sustained. In addition, a single follow up measurement may be confounded by intra-individual variation. To address the problem that intra-individual variation may have affected the findings, this study explored several different definitions of recovery. Intra-individual variation is unlikely to have influenced the extended definition using a fall in eGFR of 10mls/min and even less so when a fall in eGFR of 25% was used.

In order to prevent the study cohort being saturated with milder AKIN stage 1, random sampling of this group was undertaken. This will not have influenced the primary aim of this study to explore the recovery of function. However it does mean that some of the findings in this study need to be interpreted with caution. For example, the overall mortality for each group is likely to overestimate the true mortality figure associated with AKI because the milder cases have been removed. In addition there were

considerable losses during the recruitment phase of this study. It was shown in Chapter 5 that close to a third of patients in each group were discharged and so could not be assessed. It is therefore uncertain what happens to this group in terms of mortality or recovery of function. Finally, the design of this study allowed only for recruitment of patients who had an AKI that resulted in an eGFR < 60. It is possible that some patients may have had an AKI above this threshold. For example, a fall in eGFR from 90 to 65 may also be clinically significant but will not have been recorded in this study.

8.9 Future Research Directions

The field of AKI is rapidly evolving and numerous areas requiring further investigation and research have been identified during the course of this study. Some of the more important areas are summarised here:

1. The use of RAS blockers in this population needs to be further explored. It appears from the literature that RAS blockers increase the risk of AKI. However this study has raised several important questions. Do RAS blockers influence long-term outcomes in this group? Should they be restarted after an AKI episode and in whom? This study identified a possible protective effect in terms of mortality in the AKI/CKD group and yet it was found that RAS blockers were not restarted in a large proportion of patients. In addition a possible adverse effect on functional recovery was identified in the AKI group. What if any is the meaning of this?
2. This study identified the possible important influence of repeat AKI episodes in this population. This area needs further exploration as it may be a key aspect of CKD progression in the general population.
3. The definition of recovery of function needs further work. Most importantly work needs to be done to identify what levels of failure to recover are clinically meaningful in order to be applied in AKI clinical trials. This could involve looking longer term in those who have not recovered function to assess mortality outcomes.
4. The influence of different relative changes in serum creatinine in those with CKD need to be explored further. In this study recovery of function was significantly better in the AKI/CKD group. Is this because there are different pathological processes in play or is it because the relative changes in function expressed by creatinine reflect injury differently in those with and without CKD?
5. This study has highlighted the need for a better marker of renal injury than serum creatinine alone. This work is ongoing in many centres.

6. This study clearly demonstrated an increased length of hospital stay in the AKI/CKD group compared to controls. This raises several questions. Are patients remaining in hospital simply to wait for their creatinine to fall and could this be modifiable? Would a nephrology review facilitate earlier discharge? Could patients be discharged earlier before the creatinine has settled and leave follow up for primary care? This area needs to be explored further as it may reduce the burden of AKI on the healthcare system.

8.11 Final Summary

This study has demonstrated that recovery of function is incomplete after 6 months follow up in a substantial portion of hospitalised patients who have sustained an AKI. In those without pre-existing CKD stage 3-5 21% experienced a fall in eGFR of at least 25% while in those with CKD stages 3-5 15% experienced a fall of at least 25% in eGFR. AKI is therefore contributing to the incident CKD population and to the progression of CKD. In addition this study has demonstrated a pattern of repeat admissions and repeat AKI episodes in these patients. There may be a cumulative effect in terms of loss of function and it lends some support to the theory of Bedford et al that progression of CKD at least in some may be due to step-downs in function as a result of repeated AKI episodes. AKI may be an important marker of CKD progression in much the same way as proteinuria. This has important practice implications. It highlights the importance of AKI prevention and management not only in hospital but also in the community. In addition, it raises important questions regarding the follow up of these patients in the aftermath of their AKI episode.

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Appendix 1

The strategy used to carry out a broad search of the Medline and Embase databases for studies relevant to the natural history of AKI.

1) incidence.tw
2) cause$.tw
3) aetiology.tw
4) (risk adj factor$).tw
5) definition.tw
6) classification.tw
7) progression.tw
8) survival.tw
9) (follow adj up).tw
10) outcome$.tw
11) (recovery adj3 function).tw
12) mortality.tw
13) or/1-12
14) kidney failure, chronic/
15) chronic kidney disease.mp
16) 14 or 15
17) 13 or 16
18) 18 exp Acute kidney injury/
19) 19 exp Kidney tubular necrosis, acute/
20) 18 or 19
21) 17 and 20
22) limit 21 to (humans and yr="1990-2011" and "all adult(19 plus years) and journal article)

Appendix 2

42 different definitions of AKI found in observational research between 1990 and 2011. Creatinine (Creat.) expressed in mol/l or mg/dl. Some of these were unique to the particular study while others have been used in more than one study.

Author (Year)	**Definition of AKI**
Gentric et al (1991)[19]	Rise in Creat. to > 120
Tran et al (1993)[100]	Rise in Creat. to > 280 or twofold rise if history of CKD present
Feest et al (1993)[101]	Rise in Creat. to > 500
Bhandari et al (1996)[102]	Rise in Creat. to > 600 or RRT
Neveu et al (1996)[103]	Rise in Creat. to > 310 or 100% increase if CKD present
Khan et al (1997)[104]	Rise in Creat. to > 300
Barreti et al (1997)[2]	Rise in Creat. by > 30%
Baraldi et al (1998)[21]	Rise in Creat. to > 2.0 or twofold rise if history CKD present
Behrend et al (1999)[105]	Rise by at least 0.9 to at least 2.0 if baseline < 2.0 or rise by 1.5 if baseline > 2.0
Kohli et al (2000)[106]	Rise in Creat. to > 178 or if CKD present a rise > 132.6
Obialo et al (2000)[107]	Rise in Creat. by 0.5 to at least 2.0
Guerin et al (2000)[108]	Rise in Creat. to > 300 or urine output < 500mls/24hrs or need for RRT
Stevens et al (2001)[35]	Rise in Creat. to > 300 and/or a rise in urea to > 40 or a 50% rise in Creat. if CKD present and baseline < 250
Nash et al (2002)[8]	Stratified starting from a rise of 0.5 if baseline < 1.9
Koreny et al (2002)[109]	Urine output < 20mls/hr and 50% rise in Creat.
Sesso et al (2004)[110]	Rise in Creat. by > 0.5
Mehta et al (2004)[43]	Rise in Creat. > 0.5 if baseline < 1.5 or a rise > 1.0 if baseline 1.5 to 5.0

Author (Year)	Definition of AKI
Yegenaga et al (2004)[25]	Rise in Creat. to > 2.0
Loef et al (2005)[111]	Rise in Creat. by > 25%
Uchino et al (2005)[112]	RRT or a rise in Urea to > 30
Franceschini et al (2005)[113]	Rise in Creat. by 0.5 if baseline < 2.0, by 1.0 if baseline 2 to 4.9 or by 1.5 if baseline > 5.0
Thakar et al (2005)[114]	30% decline in GFR
Thakar et al (2007)[14]	> 50% fall in GFR
Kheterpal et al (2007)[115]	At least a 37.5% fall in Cr/Cl to < 50mls/min
Thakar et al (2007)[116]	A rise in Creat. > 50%
Bagshaw et al (2007)[16]	A rise in Creat. to > 133 or urine output < 410mls/24hrs
Weisbord et al (2008)[117]	Stratified by % rise in Creat. from 25 to 100%
Welten et al (2008)[118]	> 10% fall in Cr/Cl
Oppert et al (2008)[119]	Rise in Creat. by 100%
Lo et al (2009)[120]	RRT and at least a 50% rise in Creat.
Khosla et al (2009)[121]	Rise in Creat. > 0.5 if baseline < 1.5 or by > 1.0 if baseline > 1.5
Tian et al (2009)[22]	Rise in Creat. > 0.3
Mehta et al (2010)[122]	Risein Creat. by > 50% or by 0.7
Engleberger et al (2010)[123]	Rise in Creat. by > 2.0 and at least twofold from baseline
Van Kuijk et al (2010)[124]	Decline in CKD-EPI eGFR by > 10%
La France et al (2010)[125]	Fall in GFR of 25% or by > 5mls/min
Ali et al (2011)[126]	25% rise in Urea or Creat. or Creat. rise to > 1.5 or Urea rise to > 55 in 24 hrs
Broce et al (2011)[23]	Rise in Creat. by increments of 0.1
Ishani et al (2011)[127]	Stratified by % rise in Creat.
Multiple studies	RRT requirement
Multiple studies	RIFLE definition
Multiple Studies	AKIN definition

Appendix 3

Summary of publications with comparison of the RIFLE Classification and AKIN definition of AKI. The table includes the numbers of patients in each study together with the percentage with AKI as defined by each definition. In addition the AuROC for predicting mortality for each definition is included where available.

Author (Year)	**Country**	**Setting**	**Number of patients**	**AKI – RIFLE (%)**	**AKI-AKIN (%)**	**Mortality ROC-RIFLE**	**Mortality ROC-AKIN**
Bagshaw (2008)[138]	Australia/New Zealand	General ITU	120,123	36.1	37.1	0.66	0.67
Lopes (2008)[139]	Portugal	General ITU	662	43.8	50.4	0.93	0.97
Joannidis (2009)[140]	International (SAPS 3)	General ITU	14,356	35.5	28.5	_	_
Jiang (2011)[141]	China	General ITU	524	18.1	25.8	0.73	0.78
Kim (2012)[142]	Korea	Sepsis/Septic Shock ITU	291	62.9	65.6	_	_
Haase (2009)[143]	Australia	Post Cardiac Surgery	282	45.8	44.7	0.91	0.94
Robert (2010)[144]	USA	Post Cardiac Surgery	24747	31	30	0.78	0.79
Yan (2010)[145]	China	Post Cardiac Surgery	67	81	85	0.74	0.80
Engleberger (2011)[146]	USA	Post Cardiac Surgery	4836	18.9	26.3	0.80	0.82
Ando (2010)[147]	Japan	Post HSCT	249	52.6	46.6	0.65	0.64
Han (2011)[148]	China	Haemorrhagic Fever	120	79.2	82.5	_	_
Garner (2012)[149]	UK	General Hospital	1315	7.1	9.5	_	_

Appendix 4

Observational studies using the AKIN definition since its introduction in 2007. Study type is given as retrospective or prospective. Studies using variants of the AKIN definition are noted as 'adapted' or unclear.

Author (Year)	Study Type	Setting	AKIN Criteria Used	Stable Baseline Reference Y/N	Urine Output Y/N	Volume Status Assessed Y/N
Massoudy (2008)[151]	Retrospective	Cardiac Surgery	AKIN	Y	N	N
Arora (2008)[152]	Retrospective	Cardiac Surgery	Adapted	Y	N	N
Ostermann (2008)[137]	Retrospective	ITU	AKIN	N	N	N
Parikh (2008)[153]	Retrospective	Acute M.I.	Adapted	N	N	N
Abelha (2009)[154]	Retrospective	Post surgery	AKIN	Y	Y	N
Barrantes (2009)[24]	Retrospective	General Hospital	AKIN	N	N	N
Thakar (2009)[155]	Retrospective	ITU	Adapted	N	N	N
Machado (2009)[156]	Retrospective	ITU	AKIN	N	N	N
Zhu (2010)[157]	Retrospective	Post Liver Transplant	Unclear	N	N	N
James (2010)[158]	Retrospective	Post angiography	Adapted	Y	N	N
Gude (2010)[159]	Retrospective	Post Heart Transplant	Adapted	Y	N	N
Brown (2010)[160]	Retrospective	Cardiac Surgery	Adapted	Y	N	N
Kramer (2010)[161]	Retrospective	Cardiac Surgery	Adapted	Unclear	N	N
Swaminathan (2010)[162]	Retrospective	Cardiac Surgery	Adapted	Y	N	N
Coca (2010)[163]	Retrospective	Post surgery	Adapted	Y	N	N
Anzai (2010)[164]	Prospective	Acute M.I.	Adapted	N	N	N
La France (2010)[9]	Retrospective	VA hospital admissions	Adapted	N	N	N

Author (Year)	Study Type	Setting	AKIN Criteria Used	Stable Baseline Reference Y/N	Urine Output Y/N	Volume Status Assessed Y/N
Choi (2010)[165]	Retrospective	HIV Register	Adapted	Y	N	N
Fonseca (2011)[166]	Retrospective	ITU	AKIN	N	Y	N
Li (2011)[167]	Retrospective	Cardiac Surgery	AKIN	Y	N	N
Pannu (2011)[168]	Retrospective	General Hospital	Adapted	Y	N	N
Mithani (2011)[169]	Retrospective	Cardiac Surgery	AKIN	Unclear	N	N
Mandelbaum (2011)[170]	Retrospective	ITU	AKIN	N	Y	N
Thakar (2011)[34]	Retrospective	US VA Diabetics	Adapted	N	N	N
Lombardi (2011)[171]	Retrospective	ITU ventilated patients	AKIN	N	N	N
Medve (2011)[172]	Prospective	ITU	AKIN	N	Unclear	N
Mori (2011)[173]	Retrospective	Aortic Arch Surgery	AKIN	Y	N	N
Meier (2011)[174]	Retrospective	General Hospital	AKIN but unclear	Y	Unclear	N
Lakhal (2011)[175]	Retrospective	ITU contrast	AKIN	Y	N	N
Minejima (2011)[176]	Prospective	Vancomycin patients	AKIN	Y	N	Y
Bucovi (2011)[177]	Retrospective	ATN cases	AKIN but unclear	N	Y	N
Martin-Loech (2011)[178]	Prospective	ITU	AKIN	N	N	N
Li (2011)[179]	Retrospective	Neuro ITU	AKIN	N	Unclear	N

Appendix 5

Table illustrating the 30 different definitions of baseline renal function in use in the AKI literature over the past decade. Some of these definitions were used in more than one study.

Author (Year)	**Definition of baseline kidney function.**
Obialo (2000)[107]	Any serum creatinine < 150µmol/l in the previous 12 months defined as normal.
Nash (2002)[8]	Lowest in hospital serum creatinine.
Sesso (2004)[110]	Any previously normal serum creatinine with no timeframe specified.
Yegenaga (2004)[25]	The creatinine on the first day of sepsis in septic patients if < 2mg/dl.
Abosaif (2005)[181]	Lowest in hospital serum creatinine or from records up to three months before admission.
Hoste (2006)[182]	A back estimate using eGFR 75mls/min if no history of CKD or the lowest of the hospital admission creatinine or ITU admission creatinine.
Uchino (2006)[183]	The last hospital discharge serum creatinine or a back estimate using an eGFR of 75mls/min.
Kheterpal (2007)[115]	A pre-operative serum creatinine within 30 days of surgery.
Coca (2007)[185]	The lowest serum creatinine within 5 days of hospital admission.
Cruz (2007)[186]	Any pre-morbid serum creatinine without specified timeframe or a back estimate using an eGFR of 75mls/min.
Ali (2007)[187]	A serum creatinine in the previous 6 months or the recovery level.

Author (Year)	Definition of baseline kidney function.
Weisbord (2008)[117]	The most recent outpatient serum creatinine within 60 days of admission.
Lopes (2008)[139]	A back estimate using an eGFR of 75mls/min for all patients.
Hsu (2009)[188]	The last outpatient eGFR before admission with no specified timeframe.
Kheterpal (2009)[184]	A pre-operative serum creatinine within 90 days of surgery.
Bihorac (2009)[189]	The lowest of either the lowest measured serum creatinine at hospital admission or a back estimate using an eGFR of 75mls/min.
Kwon (2010)[190]	Either the last hospital discharge serum creatinine, the last outpatient serum creatinine or the lowest in hospital serum creatinine.
Hata (2010)[191]	With a history of CKD the lowest in hospital value otherwise a back estimate using an eGFR of 75mls/min.
Bennet (2010)[192]	The discharge serum creatinine level.
Anzai (2010)[164]	The admission serum creatinine level.
La France (2010)[9]	The lowest serum creatinine between 3 months before the index admission and hospital discharge.
Choi (2010)[165]	The most recent outpatient serum creatinine with no timeframe specified or the first creatinine on admission.
James (2010)[158]	The last outpatient serum creatinine within 6 months of admission.

Author (Year)	Definition of baseline kidney function.
Murugan (2010)[31]	A known pre-morbid serum creatinine with no specified timeframe or the lower of either a back estimate using eGFR 75mls/min or the lowest creatinine during admission.
Palmieiri (2010)[193]	The earliest available creatinine available on admission. If this was elevevated with no preadmission level then a back estimate using eGFR 75mls/min was used.
Engleberger (2010)[124]	The last serum creatinine before surgery.
Pannu (2011)[168]	The mean eGFR from all outpatient serum creatinines within 6 months of admission.
Meier (2011)[174]	The last outpatient value more than 30 days before the index admission or the average of all values between 30 and 365 days before admission.
Bucaloiu (2012)[194]	The lowest serum creatinine between three months before admission and 30 days after discharge.
Plataki (2011)[195]	A value within the last three months of admission or a back estimate using eGFR 75mls/min.

Appendix 6

Summary of the observational studies reviewed from 1990 onwards which contain figures for the risk/incidence of AKI in various populations and where available the % requiring renal replacement therapy. Study type is single center, multicenter (Multi) or derived from a database (Data). Mean age and % male is included where available. A basic summary of the definition used is provided. In addition, where the information is available, there is confirmation if patients with CKD were fully included in the cohort and their proportion of the total. Missing data was either not provided in the publication or was unclear.

Author (Year)	Country	Study Type	Setting	Patient Number	Mean Age	% Male	Definition summary	CKD Y/N	Incidence /Risk	RRT
Kaufman (1991)[206]	USA	Single	Community	100			Cr. rise > 177	Y	1% of admissions	
Metha (2010)[122]	USA	Single	Cardiac Surgery	10415	68	70	Cr. Rise > 50%	N	20%	
Elhmidi (2011)[207]	Germany	Single	AV valve implants	234	82	33	RIFLE	Y	19.6%	10.3%
Nash (2002)[8]	USA	Single	Hospital	4622		54	Cr. rise by 0.5	Y 45%	7.2%	
Yegenaga (2004)[25]	Belgium	Single	ITU sepsis	217	65	72	Cr. Rise > 177	N	13%	45% of AKI
Thakar (2007)[14]	USA	Single	Cardiac Surgery	31677			50% fall in eGFR	Y 42%	5.9%	1.8%
Coca (2007)[185]	USA	Single	Burns	304	45	68	RIFLE	N	26.6%	
Engleberger (2010)[123]	USA	Single	Cardiac Surgery	12096	68	71	RRT or rise x 2	N	6%	2.1%
Pannu (2011)[168]	Canada	Data	Community + Hospital	43008			AKIN	Y 33%	18.3%	
Koreny (2002)[109]	Austria	Single	Cardiogenic shock	118		67	Cr. Rise > 50%	Y	33%	
Cole (2000)[208]	Australia	Multi	ITU	135	63	66	Need for RRT	Y		13.4/ 100,000/yr
Guerin (2000)[108]	France	Multi	ITU	14116	64	65	Cr. Rise to > 300	Y	7.7%	

Author (Year)	Country	Study Type	Setting	Patient Number	Mean Age	% Male	Definition summary	CKD Y/N	Incidence /Risk	RRT
Falvo (2008)[209]	USA	Single	Cardiac Surgery	1085				Y	37%	2%
Kheterpal (2007)[115]	USA	Single	Surgery	15102	59	56	CrCl < 50	N	0.8%	0.1%
Kheterpal (2009)[184]	USA	Data	Surgery	75952	65	57	Rise > 2mg/dl	Y	1%	
Bihorac (2009)[189]	USA	Single	ITU Surgery	10518	62	56	RIFLE	N	32%	6%
Gaudino (2005)[210]	Italy	Single	Cardiac Surgery	6542	75	42	RRT	Y 44.9%		1.1%
Brown (2010)[160]	USA	Single	Cardiac Surgery	4837	67	71			39%	
Kramer (2010)[161]	USA	Single	Cardiac Surgery	668			AKIN		45%	1.5%
Swaminathan (2010)[162]	USA	Single	Cardiac Surgery	1113	72	66	AKIN	N	10.8%	
Licker (2011)[211]	Swiss	Single	Lung Surgery	1345	67	80	RIFLE		6.8%	
Mithani (2011)[169]	USA	Single	Cardiac Surgery	2104			AKIN	N	24%	
Kagoya (2011)[212]	Japan	Single	Stem cell transplants	207			RIFLE		76.3%	
Obialo (2000)[107]	USA	Single	Community + Hospital	100			Cr. rise by 0.5	N	0.69%	
Weisbord (2008)[117]	USA	Single	Contrast AKI	421	69	96 VA	% rise	Y	7.7%	0.2%
Parikh (2008)[153]	USA	Data	Acute MI	147007			AKIN	Y	19.4%	
Ishani (2011)[127]	USA	Data	Cardiac Surgery	29388			% Rise	Y	32%	
Machado (2009)[156]	Brasil	Data	Cardiac Surgery	817	61	65	AKIN	Y	48.5%	7.8%
Fang (2010)[213]	China	Single	Community + Hospital	176155			AKIN		3.19%	
Garzotto (2011)[214]	Italy	Multi	ITU	576	66	59	RIFLE	Y	65.7%	8,3%

Author (Year)	Country	Study Type	Setting	Patient Number	Mean Age	% Male	Definition summary	CKD Y/N	Incidence /Risk	RRT
Swaminathan (2007)[17]	USA	Data	Cardiac Surgery	10275			Coded	N	3.95%	
Ostermann (2007)[11]	UK/ Germany	Data	ITU	41972			RIFLE	Y	35.8%	
Barrantes (2008)[136]	USA	Single	ITU	471	69	50	AKIN		31.5%	
Thakar (2009)[155]	USA	Data	ITU	325395			AKIN	Y 38%	22%	0.9%
Marenzi (2010)[215]	Italy	Single	Cardiogenic Shock	97	69	71	RIFLE	Y	55%	13.4%
Mandelbaum (2011)[170]	USA	Single	ITU	14524			AKIN	Y	57%	
Li (2011)[167]	Taiwan	Single	Cardiac Surgery	964			AKIN	Y	19.8%	7%
Hata (2010)[191]	Japan	Single	ITU Heart Failure	376	73	57	RIFLE	Y 18%	73%	
Tallgren (2007)[216]	Finland	Single	AAA Surgery	69	72	87	RIFLE	N	22%	
Bennet (2010)[192]	UK Scotland	Data	Fractured Femur	177	85	48	RIFLE	Y	16%	
Loef (2005)[111]	Holland	Single	Cardiac Surgery	843	65	74	Cr. Rise of 25%	Y	17.2%	
Uchino (2005)[112]	Inter-national	Multi	ITU	29269	67	64	RRT or urea > 30	Y	5.7%	4.2%
Anzai (2010)[164]	Japan	Single	Acute MI	195	69	77	AKIN	Y	22%	
Li (2010)[217]	China	Single	Pancreatitis	228	57	60	Cr. rise > 177	Y	18.4%	
Fonseca (2011)[166]	Colombia	Single	ITU	794			AKIN	Y	39.8%	12.4%
Hoste (2003)[218]	Belgium	Single	ITU Surgical	185	62	66	Cr. Rise > 2.0	Y	16.2%	
Ali (2007)[187]	UK Scotland	Multi	Community + Hospital	562	76	54	RIFLE	Y 16%	2147 pmp	8% of AKI

Author (Year)	Country	Study Type	Setting	Patient Number	Mean Age	% Male	Definition summary	CKD Y/N	Incidence /Risk	RRT
Ishani (2009)[42]	USA	Data	Community + Hospital	233803	80	48	Code	Y 34.3%	3.1%	
Grams (2010)[30]	USA	Data	Community + Hospital	11,200	65	52	Code	Y 28%	4/1000 pt years	
La France (2010)[9]	USA	Data	Community + Hospital	82711	66	97 VA	AKIN	Y	9.6%	
Liano (1996)[20]	Spain	Multi	Community + Hospital	748			Cr. rise > 177	N	209pmp/yr	
Behrend (1999)[105]	USA	Single	Coronary Care	106	69	53	Cr. Rise > 2.0	Y 21%	4%	
Clermont (2002)[219]	USA	Single	ITU	254	59		Cr. rise by 0.5	Y	17.2%	11%
Franceschini (2005)[113]	USA	Single	HIV	754		80	Cr. rise by 0.5	Y	5.9/1000 person yrs	
Thakar (2005)[114]	USA	Single	Cardiac Surgery	31677			Fall in GFR by 30%	Y	17.4%	1.7%
Feest (1993)[101]	UK	Multi	Community + Hospital	125		72	Cr. Rise > 500		140.5pmp	
Palmieri (2010)[193]	USA	Single	ITU Burns	60	46	82	RIFLE		53.3%	
Akram (2010)[220]	UK Scotland	Single	Community Pneumonia	1241			RIFLE	Y	18%	2.4%
Hobson (2009)[221]	USA	Single	Cardiac Surgery	2973	64	63	RIFLE	N	43%	6%
Karkouti (2009)[222]	Canada	Multi	Cardiac Surgery	3460			RIFLE	Y	34%	
James (2011)[33]	Canada	Data	Coronary angio	14782			AKIN	Y	9.6%	
Chertow (1997)[223]	USA	Multi	Cardiac Surgery	43642			RRT	N		1.1%
Thakar (2011)[34]	USA	Single	Diabetes	3679			AKIN	N	29%	
Liangos (2006)[224]	USA	Data	Community + Hospital	29 million	73	52	Codes	Y	1.9%	7.5% of AKI
Thakar (2007)[116]	USA	Single	Gastric Surgery	491	43	17	Cr. Rise > 50%		8.5%	4.7%

Author (Year)	Country	Study Type	Setting	Patient Number	Mean Age	% Male	Definition summary	CKD Y/N	Incidence /Risk	RRT
Cruz (2007)[186]	Italy	Multi	ITU	2164			RIFLE	Y	10.8%	30.3% of AKI
Arora (2008)[152]	USA	Multi	Cardiac Surgery	1358	69	79	AKIN		40.2%	
Mittalhenkle (2008)[225]	USA	Data	Elderly	5731	75	63	Codes	N	3.9% over 10 years	
Hsu (2009)[188]	USA	Data	Community + Hospital	39805	67	57	RRT	Y		2.7%
Van Kuijk (2010)[124]	Holland	Single	Vascualr Surgery	1308	64	72	> 10%fall in CKD-EPI	N	38%	
Plataki (2011)[195]	USA	Single	ITU Septic	390	68	54	RIFLE	N	61%	
Broce (2011)[23]	USA	Single	Hospital only	29645			AKIN	Y	15.3%	
Lombardi (2011)[171]	Multi-national	Data	ITU Ventilation	2783	61	64	AKIN	Y	28.8%	
Gude (2010)[159]	Norway	Single	Heart Transplants	585	52		AKIN	Y	25%	12%
Bagshaw (2005)[226]	Canada	Multi	ITU	5693	67	60	RRT	Y	11/100000 /yr or 4.2%	
Hoste (2006)[182]	USA	Single	ITU	5383	63	56	RIFLE	Y	67%	4.1%
Ostermann (2008)[137]	UK/ Germany	Data	ITU	7898	62		AKIN	Y	35.4%	
Lopes (2008)[139]	Portugal	Single	ITU	662	64	66	AKIN	Y	50.4%	
Bagshaw (2008)[227]	AusNZ	Data	ITU Septic	14039	67	55	RIFLE	Y	42.1%	
Clec'h (2011)[12]	France	Data	ITU	8639	66	59	RIFLE	Y	32.9%	19%
Silvester (2001)[228]	Australia	Multi	ITU	299	61	70	RRT	Y 34.1%		8/100000/ year
Metnitz (2002)[229]	Austria	Data	ITU	17126	63		RRT	N		4.9%

Author (Year)	Country	Study Type	Setting	Patient Number	Mean Age	% Male	Definition summary	CKD Y/N	Incidence /Risk	RRT
Choi (2010)[165]	USA	Data	HIV	17325			AKIN	Y	18%	
James (2010)[230]	USA	Data	Coronary angio	11249		67	AKIN	Y	7.6%	
Coca (2010)[163]	USA	Data	Surgery Diabetic	35302			AKIN	Y	17.8%	
Murugan (2010)[31]	USA	Multi	Community Pneumonia	1836	73	51	RIFLE	Y	34%	
James (2010)[231]	Canada	Data	Community + Hospital	920985			Code	Y	0.7%	<0.01%
Tran (1993)[100]	Holland	Single	Pancreatitis	267	60	57	Cr. Rise to > 280	Y	16%	
Kolli (2010)[232]	USA	Multi	Cardiac Surgery	1359			AKIN	Y 20.4%	40.2%	15.2%
vanNoorgate (2003)[233]	Belgium	Single	Cardiac Surgery	82			RRT	Y		2.3%
Lin (2006)[234]	Taiwan	Single	ITU ECMO	46			RIFLE	Y	78%	34.8%
Prescott (2007)[44]	UK Scotland	Multi	Hospital RRT	809			RRT	Y 25%		286pmp/ year
Welten (2008)[118]	Holland	Single	Surgery	1944	68	78	Fall in CrCl >10%	Y	34%	2.4%
Bagshaw (2008)[10]	AusNz	Data	ITU	120123			RIFLE	Y	36.1%	
Oppert (2008)[119]	Germany	Multi	ITU Sepsis	401	71	63	Cr. Rise by 100%	Y	41.4%	4.2% of AKI
La France (2010)[125]	Canada	Data	CKD	6862	68	55	Fall in GFR by 5mls/min	Y all	44.9% over 19mts	
Uchino (2010)[180]	Australia	Single	Community + Hospital	3641	74	55	RIFLE	Y	18.1%	1%
Kwon (2010)[190]	Korea	Single	Hospital	96	63	60	AKIN	Y	1.2%	
Hegarty (2005)[235]	UK	Multi	Community + Hospital	28	65	68	Cr. > 500 Single org	Y 36%	125pmp/ year	

Author (Year)	Country	Study Type	Setting	Patient Number	Mean Age	% Male	Definition summary	CKD Y/N	Incidence /Risk	RRT
Khan (1997)[104]	UK Scotland	Single	Community + Hospita	310			Cr. Rise >300	N	620pmp/ year	
Stevens (2001)[35]	UK	Multi	Community + Hospital	288	73	64	Cr. Rise >300	N	545pmp/ year	
Metcalfe (2002)[236]	UK Scotland	Multi	Hospital RRT	89	71		RRT	Y		203pmp/ year
Barretti (1997)[2]	Brasil	Single	Hospital	200	51	64	Cr. Rise by 30%		4.9/1000 admissions	51%
Bagshaw (2008)[237]	AusNZ	Multi	ITU Trauma	1711			RIFLE	Y	18.1%	
Abelha (2009)[154]	Portugal	Single	Surgery	1166	68	64	AKIN	N	7.5%	
Meier (2011)[174]	Swiss	Single	Hospital Non-critical	4296	61	55	AKIN	Y	4.12%	

Appendix 7

Table A7. 1 Summary of contemporary AKI observational studies reporting incidences for the general hospital population. These studies used consensus definitions AKIN and RIFLE or Codes from hospital discharge summaries.

Author (Year)	Country	Patient Number	Definition	CKD Incl. Y/N	Incidence /Risk	Incidence Rate	RRT
James (2010)[231]	Canada	920985	Coded	Y	0.7%	-	<0.01%
Uchino (2010)[180]	Australia	3641	RIFLE	Y	18.1%	-	1%
Liangos (2006)[224]	USA	29 million	Coded	Y	1.9%	-	-
Ali (2007)[187]	UK Scotland	562	RIFLE	Y 16%	-	2147pmp	8% of AKI
Ishani (2009)[42]	USA	233803	Coded	Y 34.3%	3.1%	-	-
LaFrance (2010)[9]	USA	82711	AKIN	Y	9.6%	-	-
Pannu (2011)[168]	Canada	43008	AKIN	Y 33%	18.3%	-	-
Fang (2010)[213]	China	176155	AKIN	-	3.19%	-	-
Bedford (2011)[238]	UK	44266	AKIN	Y	5.7%	7007pmp	-

Table A7.2 Summary of contemporary AKI studies from the critical care setting that reported incidences. These studies applied the RIFLE or AKIN criteria.

Author (Year)	Country	Patient Number	Definition	CKD Incl. Y/N	Incidence /Risk	Incidence Rate	RRT
Garzotto (2011)[214]	Italy	576	RIFLE	Y	65.7%	-	8.3%
Ostermann (2007)[11]	UK/ Germany	41972	RIFLE	Y	35.8%	-	-
Barrantes (2008)[136]	USA	471	AKIN	-	31.5%	-	-
Thakar (2009)[155]	USA	325395	AKIN	Y	22%	-	0.9%
Mandelbaum (2011)[170]	USA	14524	AKIN	Y	57%	-	-
Fonseca (2011)[166]	Colombia	794	AKIN	Y	39.8%	-	-
Cruz (2007)[186]	Italy	2164	RIFLE	Y	10.8%	-	30.3% of AKI
Hoste (2006)[182]	USA	5383	RIFLE	Y	67%	-	4.1%
Ostermann (2008)[137]	UK/ Germany	7898	AKIN	Y	35.4%	-	-
Lopes (2008)[139]	Portugal	662	AKIN	Y	50.4%	-	-
Clec'h (2011)[12]	France	8639	RIFLE	Y	32.9%	-	19%
Bagshaw (2008)[10]	AusNZ	120123	RIFLE	Y	36.1%	-	-

Table A7.3 Summary of contemporary studies focusing on AKI in specific patient groups in critical care.

Author (Year)	Country	Patient Number	Patient Type	Definition	CKD Incl. Y/N	Incidence /Risk	RRT
Bihorac (2009)[189]	USA	10518	General Surgical	RIFLE	N	32%	6%
Licker (2011)[211]	Swiss	1345	Lung Surgery	RIFLE	-	6.8%	-
Hata (2010)[191]	Japan	376	Heart Failure	RIFLE	Y	73%	-
Palmieri (2010)[193]	USA	60	Burns	RIFLE	-	53.3%	-
Plataki (2011)[195]	USA	390	Septic	RIFLE	N	61%	-
Lombardi (2011)[171]	Multi-national	2783	Mechanical Ventilation	AKIN	Y	28.8%	-
Bagshaw (2008)[227]	AusNZ	14039	Septic	RIFLE	Y	42.1%	-
Lin (2006)[234]	Taiwan	46	On ECMO	RIFLE	Y	78%	34.8%
Bagshaw (2008)[237]	AusNZ	1711	Trauma	RIFLE	Y	18.1%	-

Appendix 8

Illustration of the division of the causes of AKI into prerenal, intrinsic and postrenal causes with examples. This list is by no means exhaustive (Sharfuddin 2011, KDIGO 2012)

Prerenal causes of AKI	
Intravascular volume depletion	- haemorrhage - burns - gastrointestinal fluid losses e.g diarrhoea - salt-wasting renal disease - diuretics - nephrotic syndrome - advanced liver disease -
Reduced Cardiac Output	Any cause of myocardial dysfunction - ischaemic heart disease and myocardial infarction - arrhythmias - valvular heart disease - pulmonary disease e.g pulmonary embolism - sepsis
Systemic vasodilation	- drugs - anaphylaxis - sepsis - advanced liver disease
Renal Vasoconstriction	- Drugs eg. NSAIDS, Calcineurin inhibitors, ACE inhibitors, noradrenaline - sepsis - hepatorenal syndrome - radiocontrast agents
Mechanical occlusion of renal arteries	- thrombotic occlusion - trauma

Intrinsic causes of AKI	
Acute tubular necrosis (ATN)	e.g. prolonged prerenal ischaemia, toxins such as radiocontrast and aminoglycosides, pigmenturia with rabdomylosis
Glomerulonephritis	e.g rapidly progressive glomerulonephritis due to vasculitis
Interstitial nephritis	e.g drugs such as NSAIDS, Omeprazole or idiopathic such as TINU syndrome
Infiltration	e.g sarcoidosis
Infections	e.g malaria
Intratubular Causes	e.g light chains
Postrenal causes of AKI	
Intrinsic obstruction of pelviureters	e.g. stones, tumours
Extrinsic obstruction of pelviureters	e.g pelvic malignancy, retroperitoneal fibrosis
Bladder obstruction	e.g. prostatic hypertrophy, bladder tumours
Urethral obstruction	e.g. urethral stricture

Appendix 9

Summary of thirteen prospective studies reviewed from the period 2000 - 2011 that reported causes contributing to the aetiology of AKI. The summary illustrates the diverse and overlapping reporting of aetiology in each cohort that makes it impossible to conduct any reasonable comparisons.

Author (Year)	Population	AKI Definition	Aetiology of AKI as reported
Kwon (2010)[190]	Hospital acquired AKI	AKIN	Infection 30.2%
			Reduced circulating volume 2.1%
			Diuretics 31%
			SIRS 24%
			Sepsis 9.3%
			ARB/ACEi 4.2%
			Chemotherapy 7.3%
			Contrast 6.2%
			Operation 20.8%
Guerin (2000)[108]	ITU	Creat. > 300 or RRT	Pre-renal 12%
			Renal Artery Thrombosis 1%
			Obstructive 2%
			ATN - Ischaemic 54%
			- Endogenous toxic 4%
			- Exogenous toxic 4%

Author (Year)	Population	AKI Definition	Aetiology of AKI as reported
			- Mixed 21%
			Undetermined 3%
Cruz (2007)[186]	ITU	RIFLE	Prerenal 38%
			Sepsis 25.6%
			Ischaemic ATN 14.5%
			Contrast 0.4%
			Nephrotoxic ATN 5.6%
			Other 5.1%
Bagshaw (2005)[226]	ITU	RRT	Prerenal 15%
			Intra-renal 85% - ATN 75%
			- Glomerular 5%
			- Interstitial 4%
			- Vascular 14%
			Post-renal 0.4%
Cole (2000)[208]	ITU	RRT	Ischaemia/Low BP 40.6%
			Sepsis 5.1%
			Septic Shock 45.8%
			Rhabdomyolysis 5.1%
			Other 3.4%

Author (Year)	Population	AKI Definition	Aetiology of AKI as reported	
Kholi (2000)[106]	Elderly	Creat.rise > 176.8	Drugs	66%
			Sepsis	45.7%
			Reduced renal perfusion	45.7%
			Septic shock	8.5%
			Surgery	25.4%
			Radiocontrast	16.9%
Prescott (2007)[44]	Hospital	RRT	Sepsis	48%
			Hypotension	25%
			Post-surgical	21.5%
			Hypovolaemia	22.6%
			Toxins and drugs	12.5%
			Hepato-renal syndrome	7.5%
			Myocardial infarction	6.3%
			Rhabdomyolysis	5.6%
			Glomerulonephritis	3%
			Obstruction	5.2%
Albright (2000)[250]	Hospital	RRT	Post-operative	39%
			Radiocontrast	26%
			Sepsis	18%
			Atheroembolic	8%

Author (Year)	Population	AKI Definition	Aetiology of AKI as reported	
			Prerenal	71%
			Hepatorenal syndrome	12%
			Multiorgan failure	25.7%
			Drug toxicity	21%
			Obtstructive	3%
			Rhabdomyolysis	3%
Metcalfe (2002)[236]	Hospital	RRT	Sepsis	69%
			Surgery	25%
			Obstruction/hypotension	13.5%
			Hypovolaemia	9.6%
			Pancreatitis/nephrotoxins	6%
			Gastrointestinal haemorrhage	4%
Nash (2002)[8]	Hospital	Creat. Rise > 0.5	Reduced renal perfusion	38.7%
			Medications	16%
			Contrast	11.3%
			Post-operative	9.2%
			Sepsis	6.6%
			Liver-transplant	3.7%
			Heart – transplant	2.1%
			Obstruction	1.8%
			Hepato-renal syndrome	1.8%

Author (Year)	Population	AKI Definition	Aetiology of AKI as reported	
			Rhabdomyolysis	1%
			Glomerulonephritis	0.8%
			Artifactual	0.8%
			Nephrectomy	0.8%
			Interstitial nephritis	0.5%
			Atheroembolic	0.5%
			Hypercalcaemia	0.5%
Van Berendoncks (2010)[252]	ITU	Creat. Rise > 2.0	Pre-renal	49.7%
			Renal (42.4%) : ATN	84.4%
			Acute GN	5.9%
			AIN	4.7%
			Systemic Dis.	3.9%
			Post-renal	0.8%
			Acute on Chronic	7%
Piccinni (2011)[251]	ITU	RIFLE	Hypovolaemia	29.5%
			Sepstic shock	13.5%
			Surgery	12.1%
			Cardiogenic shock	11.8%

Author (Year)	Population	AKI Definition	Aetiology of AKI as reported	
Liano (1996)[20]	General Hospital	Creat. Rise to > 177	ATN	45%
			Prerenal	21%
			Obtructive	10%
			Acute on Chronic	12.7%
			Interstitial nephritis	2%
			Vasculitis	1.5%
			Vascular	1%
			Primary glomerulonephritis	1.5%
			Secondary glomerulonephritis	1.6%
			Other	3.5%

Appendix 10

Summary of the risk factors for AKI provided by studies that have carried out adjusted analysis from the past decade.

Author (Year)	Setting and AKI definition	Risk Factors for AKI	
Hoste (2003)[218]	ITU Septic Patients Creat. Rise to > 2.0mg/dl	PH < 7.3	Creatinine > 1.0mg/dl
Bagshaw (2005)[226]	ITU Need for RRT	Age ≥ 65 Male Sex if ≥ 65 years Heart Disease Stroke COPD	Diabetes Cancer Connective Tissue Disease CKD Alcohol abuse
Gaudino (2005)[210]	Cardiac Surgery Need for RRT	Age > 70 Type of surgery Hypertension Vasculopathy	Emergency surgery CPB time > 120 mins Preop. Creat > 2.1mg/dl
Hoste (2006)[182]	ITU RIFLE	Age CKD Medical admission Trauma GI Disease	Malignancy SOFA Score Blacks for RIFLE Class Failure
Kheterpal (2007)[115]	Surgery CrCl ≤ 50mls/min	Age Emergency surgery BMI Liver Disease	High risk surgery Peripheral vascular Disease COPD
Coca (2007)[185]	Burns RIFLE	Inhalational Injury Catheter infection Sepsis	Note: Age and female sex by univariate analysis only
Mittalhenkle (2008)[225]	Elderly > 65 years Cardiovascular Health Study ICD – 9 Codes	CKD Age Male Sex Nonwhite Race	Hypertension Diabetes Smoking
Bagshaw (2008)[237]	ITU RIFLE	Age > 65 Female Sex	Comorbid Disease

Author (Year)	Setting and AKI definition	Risk Factors for AKI	
Hsu (2008)[271]	Hospitalised with history of CKD RRT	Lower baseline GFR Diabetes Hypertension	Proteinuria
Kheterpal (2009)[184]	Surgery	Age > 56 years Male Sex Emergency Surgery Type of surgery Diabetes	CCF Ascites Hypertension CKD
Karkouti (2009)[222]	Cardiac Surgery RIFLE	Age BSA Diabetes Hypertension Atrial Fibrillation LV dysfunction	Preop IABP CKD Anaemia Thrombocytopenia Blood Transfusion
Marenzi (2010)[215]	Cardiogenic Shock post infarction Rise > 25% from baseline	Age > 75 years LVEF < 40% Use of ventilation	SOFA score
Li (2010)[217]	Severe Pancreatitis Creat. Rise > 177	CKD hypoxaemia	Acute coronary syndrome
Elhmidi (2011)[207]	Aortic valve implants RIFLE	Preoperative serum creatinine level	
Fonseca (2011)[166]	ITU AKIN	Age Sepsis	Heart Failure Vasopressor use

Appendix 11

Summary of the outcome data from the AKI observational studies reviewed that possessed a control group. Outcomes are expressed in terms of length of hospital stay (or ITU stay where stated) as well as in hospital mortality and follow up mortality. Where the information was provided the adjusted mortality risk for AKI is also given.

Author (Year)	Population Setting	AKI Definition	Length of Stay days	Inhospital Mortality % AKI v Control	Follow up mortality
Yegenaga (2004)[25]	ITU Sepsis	Rise > 2.0mg/dl	23 v 15	72 v 24	-
Elhmidi (2011)[207]	AV Implants	RIFLE	11.7 v 8.7	15.2 v 7.7	35.6 v 14.3 at 6mts
Thakar (2007)[14]	Cardiac Surgery	> 50% fall in GFR	-	27.1 v 2.2	-
Tian (2009)[22]	Medical Admissions	AKIN	14 v 5	14.8 v 1.3	-
Pannu (2011)[168]	Hospital with CKD	AKIN	-	24 v 4	-
Koreny (2002)[109]	Cardiogenic Shock	50% rise in Creat.	-	87 v 53 Adjusted OR 6.5	-
Guerin (2000)[108]	ITU	Cr. Rise > 300	-	66 v 15	-
Falvo (2008)[283]	Cardio-thoracic ITU	Used 6 definitions	21 v 8.6 in ITU	18 v 2	-
Gaudino (2005)[210]	Cardiac Surgery	RRT	-	40.5 v 6.4	-
Brown (2010)[160]	Cardiac Surgery	AKIN	-	15.3 v 2.3	-
Fang (2010)[213]	General hospital	AKIN	-	19.68 v 2.84	-
Garzotto (2011)[214]	ITU	RIFLE	7 v 3 in ITU	28.8 v 8.1 in ITU	-
Palmieri (2010)[193]	Burns ITU	RIFLE	42 v 25	34.4 v 0 Adjusted OR for RIFLE F = 3.21	-

Author (Year)	Population Setting	AKI Definition	Length of Stay days	Inhospital Mortality % AKI v Control	Follow up mortality
Liangos (2006)[224]	General hospital	ICD -9 codes	7 v 3	21.3 v 2.3	-
Cruz (2007)[186]	ITU	RIFLE	-	36.3 v 13.4 Adjusted OR for RIFLE F = 4.9	-
Plataki (2011)[195]	Septic Shock	RIFLE	9 v 8.5	49 v 34	-
Broce (2011)[23]	Hospital AKI	Rise from 0.1	8 v 4	14.8 v 1.7	-
Lombardi (2011)[171]	ITU ventilated	AKIN	19 v 20	55 v 38 Adjusted OR 1.65	-
Hoste (2006)[182]	ITU	RIFLE	9 v 6	13.3 v 5.5 Adjusted HR 1.7	-
Bagshaw (2007)[16]	ITU	Rise > 133	14 v 11	42.7 v 13.4 Adjusted OR 1.23	-
Osterman (2008)[137]	ITU	AKIN	7 v 2 in ITU	40.4 v 16.9	-
Lopes (2008)[139]	ITU	AKIN	-	39.8 v 8.5 Adjusted OR 3.59	-
Bagshaw (2008)[227]	ITU Septic	RIFLE	17 v 12	29.7 v 12.6 Adjusted OR 1.54	-
Clec'h (2011)[12]	ITU	RIFLE	-	27.6 v 8.7	-
Metnitz (2002)[229]	ITU	RRT	-	62.8 v 15.6	-
Osterman (2007)[11]	ITU	RIFLE	-	56.8 v 8.4 Adjusted OR increased by RIFLE class	-
Barrantes (2008)[136]	ITU	AKIN	14 v 9	45.8 v 16.4 Adjusted OR 3.7	-
Marenzi (2010)[215]	MI with shock	RIFLE	11 v 8	50 v 2.2 Adjusted RR 17.0	-
Mandel-baum (2011)[170]	ITU	AKIN	-	16 v 6.7 Adjusted OR increased by AKIN stage	-

Author (Year)	Population Setting	AKI Definition	Length of Stay days	Inhospital Mortality % AKI v Control	Follow up mortality
Hata (2010)[191]	Heart Failure	RIFLE	48 v 25	10 v 1	-
Bennet (2010)[192]	Fractured Femur	RIFLE	-	19 v 0	41 v 13 at 120 days
Loef (2005)[111]	Cardiac Surgery	Rise in Creat. By 25%	5.4 v 1.4	14.5 v 1.1 Adjusted HR 1.6	-
Li (2010)[217]	Pancreatitis	Rise > 177	57 v 49	66.6 v 14.5	-
Fonseca (2011)[166]	ITU	AKIN	-	32.1 v 7.3	-
Hoste (2003)[218]	ITU Septic	Rise in Creat. to > 2.0mg/dl	-	56.7 v 28.4	-
Behrend (1999)[105]	Coronary Care Unit	Rise in Creat. to > 2.0mg/dl	-	50 v 8	-
Clermont (2002)[219]	ITU	Rise in Creat > 0.5mg/dl	11 v 4 in ITU	34 v 9	-
Thakar (2005)[114]	Cardiac Surgery	Fall in GFR by 30%	-	5.9% v 0.4% for non – RRT patients	-
Murugan (2010)[31]	Pneumonia	RIFLE	8 v 5	11 v 1.3	24 v 9.8 at 90 days
Barrantes (2009)[24]	Hospital	Rise > 0.3mg/dl	7.9 v 3.7	14.8 v 1.5	-
Tran (1993)[100]	Pancreatitis	Rise > 280	-	81% v *5	-
Kohli (2000)[106]	Hospital Elderly	Rise > 178	-	25.4 v 12.7	-
Van den Noorgate (2003)[233]	Cardiac Surgery	RRT	-	56 v 3.7	-
Bagshaw (2008)[138]	ITU	RIFLE AKIN	-	24.2 v 8.9 24.5 v 8.5	-

Author (Year)	Population Setting	AKI Definition	Length of Stay days	Inhospital Mortality % AKI v Control	Follow up mortality
Oppert (2008)[119]	ITU Septic Shock	Rise in Creat. By 100%	38 v 30	67.3 v 42.8	-
Bagshaw (2008)[237]	ITU Trauma	RIFLE	-	16.7 v 7.8 Adjusted OR 1.8	-
Abelha (2009)[154]	General Surgery	AKIN	16 v 13	26.4 v 2.5	35.6 v 9.5 at 6mts

Appendix 12

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Abosaif (2005)[181]	UK	ITU Admission	Retro	183	Y	Y	Two used Preadmission or lowest during adm.	RIFLE	none	-	6 months	Expressed as Mean Creat.. Overall fell by 0.5mg/dl	Apparent improvement
Albright (2000)[250]	USA	ITU	Trial	66	N excluded Cr. > 3.0	N	Two used Preadmission or baseline during adm.	RRT	7 days off dialysis	-	30 days	59% off RRT at 30 days	Only 18% of deaths had recovered
Ali (2011)[126]	Pakistan	Obstetric	Retro	100	Unclear	N	Unclear. Normal = Creat< 1.5l	25% rise or Creat. rise > 1.5mg/dl	Normal < 1.5mg/dl	23% normal on d/c	-	-	No link to baseline function
Ali (2007)[187]	UK	Hospital	Retro	562	Y	N	Preadmission < 150 μmol/l	RIFLE	Full, partial, or failure relative to 150μmol/l threshold	-	90 days	AKI group – 93% full, 7% partial, 0.6% none CKD group – 65% full, 29% partial, 6% none	AKI group likely contained CKD stage 3. Recovery defined by threshold so inaccurate

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Alric (2003)[364]	France	EVR AAA Repair	Retro	315	Y	Y	Preoperative	> 20% rise in creatinine from baseline Creat. > 103 defined CKD	Return to 'normal' Not defined	-	3 months then 3 years and 5 years	At 3 mts 20.3% of CKD group with persistent decline and 6.1% of normal group	At 3 years 6% of normal group had persistent decline and 16% at 5 years. For CKD group 44% for each time point.
Amdur (2009)[365]	USA	VA Hospital	Retro	113,272	Y	Y	Preadmission	ICD-9 Codes for AKI and ARF	Entry to CKD-4	-	75 months	Hazard Ratio ATN – 6.64 ARF – 4.03	97.8% men
Ando (2010)[147]	Japan	Hemato. Cell Transplant	Retro	158	N	Y	Pre- transplant	> 2 fold increase in serum creatinine	CKD	-	3 years	Adjusted OR of CKD 9.91	-
Bagshaw (2005)[226]	Canada	ITU	Retro	240	Y If Creat > 150μmol/l	N	unclear	RRT	Off RRT	68% off RRT at d/c	1 year	78% off RRT	63% of those on RRT at follow up had history of CKD

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Bagshaw (2006)[366]	Canada	ITU	Retro	240	Y If Creat > 150μmol/l	N	unlcear	RRT	Off RRT	-	90 days	72% off RRT	Adjusted odds of recovery increased if Male or septic shock. Reduced with higher Charlson score
Bahar (2005)[367]	Turkey	Cardiac Surgery	Retro	116	Y	N	Preoperatvie	RRT	Not defined Return to 'normal'	87.5% had not recovered 4.7% on dialysis	6 years	15% not recovered with CKD 24% on RRT	
Barratt (2000)[368]	UK	Surgical AAA Repair	Retro	65	Y	N	Admission	Creat. Rise > 600 or RRT	Not defined clearly	16 survivors 69% failed to recover 6% on RRT	-	-	

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Bhandari (1996)[102]	UK	Hospital	Prosp	1095	N	N	Unclear	RRT	Off RRT	16.7% on RRT	-	-	Outcome influenced by cause
Baraldi (1998)[21]	Italy	Hospitalised Medical Pts	Retro	109	Y	N	Preadmission when available	Rise > 2.0mg/dl or doubling if CKD	Not defined	-	? 1 month	32% full recovery 49% partial 19% RRT	Elderly appeared at greater risk of no recovery.
Bihorac (2009)[189]	USA	ITU Major Surgery	Retro	10518	N	Y	Lowest in hospital or estimated	RIFLE	Complete < 50% above baseline	56% complete, 41% partial, 3% on HD	-	-	-
Bucaloiu (2012)[194]	USA	Hospital Reversible AKI	Retro	1610	N All excluded including history of proteinuria	Y Matched	Lowest from 3 months before to 30 days after admission	50% rise in Creat. relative to baseline	eGFR within at least 90% of baseline within 90 days of AKI	-	3.3 years	De novo CKD Hazard Ratio 1.91	Risk factors: Older age, CCF, AKI stage, albumin preadmission
Bucuvic (2011)[177]	Brazil	Hospital ATN	Retro	477	Y	N	Unclear	AKIN	Not defined	96.9% complete or partial	-	-	-

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Chawla (2011)[369]	USA	VA Hospital	Retro	5351	N	Y	Preadmission otherwise excluded	ICD-9 Codes + RIFLE	Entry to CKD-4	-	Mean 2.4 years	CKD-4 AKI – 14% Con – 9%	Predictors: Older age, Low albumin, Diabetes, AKI severity.
Chertow (1995)[370]	USA	ITU	Retro	132	Y	N	unlcear	RRT	Off RRT	67% off RRT	-	-	-
Choi (2010)[165]	USA	VA HIV registry	Retro	17325	Y	Y	Preadmission or first inpatient	AKIN	Decrase in Creat. below AKIN 1	-	5.7 years	Adjusted Hazard Ratio for ESRD by AKIN stage 1: 1.37 2: 3.8 3: 20.36	No increased risk in Stage 1 who have recovered at discharge
Chugh (1994)[371]	India	Hospital	Retro	113	Unclear	N	Unclear	RRT	Off RRT	-	3 months	44% off RRT	
Coca (2010)[163]	USA	VA Surgical Diabetics	Retro	35302	Y	Y	Preoperative	AKIN	Within 0.2mg/dl of baseline	71% recovered at discharge	-	-	

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Cosentin (1994)[372]	USA	ITU	Retro	363	Y	N	unclear	RRT	Off RRT	34% on RRT at d/c	-	-	-
Cruz (2007)[186]	Italy	ITU	Prosp.	2164	Y	Y	Preadmission or estimated	RIFLE	Creat. < 1.5mg/dl or return to baseline	36% recovered at time of ITU d/c	-	-	Recovery linked to AKI severity
Fonseca (2011)[166]	Colombia	ITU	Retro	794	Y	Y	Unclear	AKIN	Full = Creat. Returns to normal	67.9% full 3.5% partial 22.9% no recovery	-	-	-
Gentric (1991)[19]	France	Elderly > 65	Retro	46	Unclear	N	Unclear	Creat. Rise > 120	Total = Creat. < 100	20% total recovery at discharge	39 months	56% normal 37% CKD 7% RRT	No reference to baseline
Gonwa (2001)[373]	USA	Liver Transplants	Retro	1535	Y	Y	Preoperative	RRT	Off RRT	-	1 year	16% on RRT	-

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Gruberg (2000)[374]	USA	Coronary angio	Retro	439	All CKD Cr. > 1.8mg/dl	Y	Preoperative	Creat. Rise > 25%	Off RRT	-	1 year	18% of RRT group	-
Gude (2010)[159]	Norway	Heart Transplants	Retro	585	Y	Y	Preoperative	AKIN	Need for RRT	-	6.6 years	AKI did not predict ESRD	By 2 years there was no difference in Creat. between groups
Hingoran (2007)[375]	USA	Hemato. Cell Transplant	Retro	1635	N	Y	Pretransplant normal	Creat. Rise > 2.0mg/dl	De novo CKD	-	Max 540 days	CKD in 23% of AKI group and 17% of no AKI group HR 1.7	Increased risk with AKI but many shared risk factors between groups
Hobson (2009)[221]	USA	Cardiac Surgery	Retro	2973	N	Y	Lowest on admission or estimated	RIFLE	Complete = return to <50% above baseline None = RRT	60% complete, 37% partial, 3% non	-	-	-

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Hsu (2009)[188]	USA	Hospital	Retro	39805	All with eGFR < 45	Y	Taken from > 30 days from admission to 365 days	RRT	ESRD	-	7 years	Adjusted HR of ESRD 1.47	
Ishani (2009)[42]	USA	Hospital Medicare	Retro	233,803	Y	Y	Coded for CKD	ICD-9 Codes	ESRD	-	2 years	Adjusted HR: AKI – 13.0 AKI/CKD – 41.2 CKD only – 8.4	Without a history of recognized CKD 72% had CKD within 2 years after AKI
Ishani (2011)[127]	USA	Cardiac Surgery	Retro	29388	Y	Y	Preoperative within 30 days	Stratified in rises from 0% to > 100%	Progress to next CKD stage or reaching CKD staging if previously normal	-	5 years	Graded increased risk of incident CKD (adjusted HR 2.33) and progress-ion	Risk persisted over 5 years

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
James (2010)[231]	Canada	Hospital	Retro	920985	Y	Y	Mean of previous 6 months	Coded	ESRD or doubling of serum creatinine	-	35 months	Increased risk of composite outcome of ESRD or doubling of creat.	-
James (2010)[230]	Canada	Coronary Angiogram	Retro	14782	Y	Y	Preangio Within 6 months	Mild = rise in Creat > 0.3mg/dl or 50-99% Mod/sev = Rise > 100%	Sustained loss of function = Creat > 50% or 0.3mg/dl above baseline up to 3 months Prog. = decline > 4mls/min In GFR /yr	-	2.5 years	Odds of decline at 3 months Mild – 4.74 Mod/Sev - 17.31. Adjusted rate of decline increased in AKI group	Severity predicted decline Rate of decline in Mild group no different to year pre AKI but increased for Mod/Severe
Jones (1998)[376]	UK	ITU ventilated	Retro	408	Y	Y	unclear	RRT	Off RRT	-	6 months	8% on RRT	-

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Kholi (2000)[106]	India	Hospital Acquired Elderly	Prosp	4176	Y	Y	Admission Creat. If stable	Creat. Rise > 178	Not defined	86.3% complete, 13.6% deranged	-	-	-
Korkeila (2000)[377]	Finland	ITU	Retro	62	Unclear	N	Unclear	RRT	Off RRT at 6 months	82% off RRT	6 months	85% off RRT	Follow up continued to 5 years
Kwon (2010)[190]	Korea	Hosptial acquired	Prosp	96	Y	N	Preadmission or lowest in hospital	AKIN	Return to baseline	50% recovered	-	-	AKIN stage predicted recovery
La France (2010)[125]	USA	CKD Register GFR < 30	Retro	6562	All	Y	Lowest between 3 months before and discharge	AKIN RRT excluded	eGFR decrease < 10% follow up from 90 days	-	19 months	Adjusted RR of ESRD 2.33 in AKI group	No account of readmissions or reaki
Landoni (2006)[378]	Italy	Cardiac Surgery	Retro	7846	Y	Y	preoperative	RRT	Off RRT	-	3.5 years	91% off RRT	

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Liano (2007)[46]	Spain	Hospital ATN	Retro	187	Y but Cr > 3mg/dl excluded	N	Amission but poorly defined	Rise in Creat. > 2mg/dl	Total= Creat < 1.4mg/dl Partial= Creat > 1.4 but lower than peak	-	12 years	19% with CKD 2% on RRT	58 survivors evaluated
Lin (2009)[379]	Taiwan	ITU Post-op	Retro	342	Y	N	Unclear	RRT	Off RRT	-	90 days	84.7% off RRT at 90 days	50% had come off RRT by 14 days Recovery predicted by lower baseline Creat., lower SAPS ii score and use of CRRT
Lines (2011)[380]	UK	ITU	Retro	821	Y	N	Within 3 months of admission 52%	RRT	Need for RRT and mean increase in Creat.	6.5% on RRT Mean increase in Creat from 111 to 127	1 year	Mean increase from 127 at discharge to 134	

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Lins (2006)[381]	Belgium	ITU	Retro	145	N	N	Unclear	Creat. Rise to > 2mg/dl	-	31.7% had eGFR > 60	1 year	No change in mean serum creatinine	
Lo (2009)[120]	USA	Hospital RRT survivors from 30days after d/c	Retro	703	N Excluded GFR < 45	Y	Outpatient eGFR	RRT with Creat. Rise of > 50%	Progress to CKD 4 or beyond	9% on RRT at d/c	33 months	Adjusted hazard for progress CKD 28.1	Higher risk for those with baseline GFR > 60 RR 54.0 But lower absolute risk
Loef (2005)	Holland	Cardiac Surgery	Retro	843	Y	Y	Preoperative	Creat. Rise > 25%	Return to baseline	68% returned to baselin	-	-	-
Mccarthy (1996)[382]	USA	ITU Two eras 1970's versus 1990's	Retro	142	N excluded Cr. > 5.0mg/dl	N	Unclear	RRT	Off RRT	45% in 1970s 35% in 1990s	1 year	96% in 1970's 78% in 1990's	

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Mehta (2010)[122]	USA	Cardiac Surgery	Retro	2083	N Excluded Creat. > 2mg/dl	Y	Preoperative	Creat. Rise > 50% or > 0.7mg/dl from baseline	Complte = return to baseline	33.7% returned to baseline at d/c	-	-	Predictors of failure to recover: Age, CVD, CCF.
Morgera (2002)[292]	Germany	ITU	Retro	979	Unclear	N	Unclear	RRT	-	-	938 days	Missing data 10% on RRT 46% with CKD	
Nash (2002)[8]	USA	Hospital	Prosp	332	Y	Y	Lowest in hospital	Creat. Rise from 0.5mg/dl	Complete or partial not defined	39% complete recovery. 22.6% partial recovery. 2.7% on dialysis	-	-	-
Newsom (2008)[383]	USA	Elderly Myocardial Infarction	Retro	87094	Y	Y	First on admission	Stratified increases in creat.	ESRD	-	4 years	Adjusted HR 3.26	Hazard graded by severity of AKI

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Ojo (2003)[384]	USA	Organ Transplants	Retro		Y	Y	Preoperative	50% reduction from baseline GFR or RRT	CKD defined as eGFR < 29 or ESRD	-	36 months	Relative risk of CKD post AKI 2.13	Risk of CKD increased if older, female, HTN, DM, postop AKI
Pannu (2011)[168]	Canada	Hospital	Retro	7856	Y	Y	Outpatient within 6 months	AKIN	ESRD	-	2 years	Graded increased hazard of death or ESRD	ESRD was very uncommon
Parames (2004)[385]	USA	Liver Transplant	Retro	1602	N	Y	preoperative	RRT	Off RRT or CKD	-	6 years	23% on RRT 46% with CKD	Baseline CKD not defined Risk for ESRD= Creat > 1.7mg/dl at 1 year, use of Cyclosporin, diabetes

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Picinni (2011)[251]	Italy	ITU	Prosp	576	Y	Y	Lowest in previous 3 months or estimate	RIFLE	Complete= Creat at ITU d/c < 120% of baseline	59.4% complete at death or d/c, 13.5% partial	-	-	Sepsis patients less likely to recover function
Ponte (2008)[386]	Spain	Hospital ATN	Retro	187	Excluded Cr > 1.4mg/dl but 25% CKD 3	N	Unclear	Creat rise > 2mg/dl	Return to baseline	38.4% recovered to baseline	8 years	61.1% had some degree of renal failure 1.1% on RRT	Multivariate Model predictors of CKD: Age, Comorbidity GFR at d/c Follow up time
Prescott (2007)[44]	UK Scotland	National RRT sample	Prosp	809	Y	N	Cr. > 150 = CKD otherwise normal Not all had baseline	RRT	Off RRT	-	90 days	Of CKD group 53% on RRT Of previous normal group 13% on RRT	

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Salmanul (2003)[387]	USA	VA Hospital	Retro	916	Y	N	Pre-AKI but unclear	Stratified by % rise in Creat.	Return to baseline	-	Up to 9 years	Prior normal function with mild AKI recovered 60% recovered in mod/sev group	
Schiffl (2006)[45]	Germany	ITU ATN only	Prosp	425	N Excluded Creat. > 1.3mg/dl	N	Preadmission but unclear	RRT	Complete= return to baseline	57% had complete recovery. 33% mild/mod renal failure Cr. > 1.3 but < 3.0. 10% severe Cr. 3-6 but no RRT	I year	1 patient on RRT = <1% of survivors No info. on function	No adjusted predictors of complete or partial recovery

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Schiffl (2008)[388]	Germany	ITU ATN only	Prosp	425	N Excluded Creat. > 1.3mg/dl	N	Preadmission but unclear	RRT	Complete= return to baseline ± 10%	-	5 years	86% normal 9% CKD 5% RRT !%of total cohort needed RRT at 5 years	No patient discharged with recovery showed a decline in function over the 5 years of follow up
Siew (2011)[389]	USA	VA Hospital AKI survivors	Retro	32929	Y	N	7 – 365 days before AKI	AKIN	At 1 year improved= eGFR > 60	All had eGFR <60 at 30 days	1 year	With baseline > 60 50.2% had improved to > 60 < 1% of cohort needed RRT	-
Silvester (2001)[228]	Australia	ITU	Prosp	299	Y	N	Preadmission	RRT	Off RRT	8.7% on RRT at d/c	-	-	-

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Soares (2006)[390]	Brazil	ITU Oncology	Prosp	309	Y	N	unclear	Bellomo Criteria Rise in Creat from > 1.44mg/dl	Failure to recover = ESRD or CKD	-	6 months	8% on RRT 26% with CKD	Baseline function unclear
Thakar (2009)[155]	USA	VA ITU	Retro	325395	Y	Y	Lowest in ITU	AKIN	Complete= < 25% above baseline	56,5% complete	-	-	Recovery graded by severity of AKI
Thakar (2011)[34]	USA	VA Diabetics	Retro	3679	N Excluded GFR < 30	Y	Last outpatient	AKIN	Developing CKD Stage 4 CKD	-	3.8 years	Adjusted HR 3.56 of outcome	Risk cumulative Risk factors: Proteinuria, HTN, Female, Higher baseline creatine

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Touzot (2010)[391]	France	Hemato. Cell Transplant	Retro	123	unclear	Y	unclear	RIFLE	Reaching CKD eGFR <60	-	2 years	40% had CKD at follow up AKI odds ratio 4.54	Age > 45, AKI, GFR<90 predicted CKD
Triverio (2009)[392]	Swiss	ITU	RCT	206	Y	N	Creat. one month prior to AKI	RRT	Complete= ±10% of baseline GFR Partial =not on RRT	36% complete at d/c. 60% partial, 4.4% RRT	3 years	50% with normal function had CKD at f/u	
Uchino (2005)[112]	Multi-national	ITU	Prosp	29269	Y	Y	unclear	RRT or Urea rise > 30	Off RRT	13% on RRT at discharge	-	-	-
Van Beren-doncks (2010)[252]	Belgium	ITU AKI survivors	Prosp	595	Y	N	unclear	Creat rise > 2.0mg/dl	Off RRT	16% on RRT aat d/c	3 years	Function expressed as mean Creat. With no change from disch. to follow up	-

Author (Year)	Country	Setting	Study Type	Patient Number	CKD Included	Controls without AKI Y/N	Baseline Definition	AKI Definition	Recovery Definition or failure to recover	Hospital Outcome % survivors	Follow up	Follow up Outcome % survivors	Notes
Wald (2009)[393]	Canada	ITU survivors	Retro	3769	Y	Y	none	RRT coded	Off RRT	-	3 years	HR fo ESRD 3.26	-
Weiss (2006)[394]	USA	Hemato. Cell Transplant	Retro	122	N	Y	Pre-transplant	Graded by rise in Creat. And % fall in GFR	Decrease in GFR 25%	-	1 year	Adjusted OR 32.8	-
Wu (2011)[395]	Taiwan	ITU Major Surgery	Prosp	9425	Y	Y	First on admission or nadir in hospital	RIFLE	< 50 % above baseline	AKI 86.7% recovered AKI/CKD 72.3% recovered RRT 2%	5 years	HR for ESRD AKI/CKD 123 HR increased with AKI severity	CKD patients without recovery at discharge had highest risk of ESRD
Van Kuijk (2010)[124]	Holland	Vascular Surgery	Retro	1308	N	Y	Preoperative	> 10% fall in CKD-Epi eGFR	Within 10% of baseline GFR	-	5 years	Adjusted RR of CKD with temp. decline in function 3.4 RR 3.6 with	Functional decline predicted by RIFLE stage

Appendix 13

19 different definitions of recovery of renal function found in the literature for the period 1990-2012.

Author (Year)	Definition of Recovery/Progression
Abosaif (2005)[181]	Expressed as change in mean serum creatinine.
Albright (2000)[250]	7 days off renal replacement therapy
Ali (2011)[126]	Normal function = creatinine < 1.5mg/dl
Ali (2007)[187]	Full recovery if creatinine < 150µmol/l
Amdur (2009)[365]	Progression to CKD stage 4
Bagshaw (2005)[226]	Off renal replacement therapy
Bihorac (2009)[189]	Recovered if creatinine < 50% above baseline
Bucaloiu (2012)[194]	eGFR ±10% of baseline
Choi (2010)[165]	Fall in creatinine to below threshold of AKIN stage 1
Coca (2010)[163]	Creatinine within 0.2mg/dl of baseline
Gentric (1991)[19]	Total recovery = creatinine < 100µmol/l
Hingorani (2007)[375]	Lack of recovery = de novo CKD with eGFR < 60mls/min
Ishani (2011)[127]	Lack of recovery = progression to next CKD stage

Author (Year)	Definition of Recovery/Progression
James (2010)[231]	Rapid progression = fall in eGFR > 4mls/min/year
Korkeila (2000)[377]	Recovery = off renal replacement therapy at 6 months
Liano (2007)[46]	Total recovery = creatinine < 1.4mg/dl
Piccini (2008)[251]	Total recovery = creatinine < 120% of baseline
Thakar (2009)[155]	Creatinine < 25% above baseline
Weiss (2006)[394]	Failure to recover = decrease in GFR by 25%

Appendix 14

Information sheets used in the study:

1. AKI Group
2. AKI/CKD Group
3. Control Group

Study: Natural history of Acute Kidney Injury and its relationship to Chronic kidney Disease.

Patient Information Sheet

Introduction

We would like to invite you to take part in our research study which is explained in this information sheet. Before you decide to take part we would like you to understand why the research is being done and what it will involve for you if you take part. Our researcher who is a medical doctor and a member of the kidney team will go through the information sheet with you and answer any questions you may have. This should not take any more than twenty minutes. You do not need to make a decision immediately but can think about it for 24 hours if you wish. You can also talk to others about the study if you wish.

Part 1 of this information sheet will tell you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

We would encourage you to ask any questions you may have especially if something is not clear.

Part 1.

1. What is the purpose of this study?

The purpose of this study is to improve our knowledge of kidney disease and how it behaves. Kidney disease is very common. Many people have some kidney impairment which is often simply watched by their doctors. Sometimes when people become unwell for other reasons their kidney impairment can deteriorate. It generally appears to get better but we do not know if this will result in more impairment in the future. This study hopes to answer this question by comparing your kidney function now with its future values.

In this study we will be looking at three different groups of patients. The first are people who experience some impairment in their kidney function for the first time during their hospital stay. We want to observe these people to see if their kidney

function recovers fully after their illness has settled. The second group are people who have existing kidney impairment who experience a further decline in their kidney function during their illness. We will observe these to see if the further impairment of their kidney function results in any permanent decline in their function. We will then have a third group who have existing impairment but do not have a further decline during their illness. This group is called a control group and we will compare these with group two to see if there are differences.

This study will involve monitoring only and will not mean any changes in your usual treatment or affect the treatment you currently need.

2. Why have you been invited to take part?

During this stay in hospital your doctors have done some blood tests to help monitor your condition. It has been noted in these blood tests that you have some kidney impairment. The doctors are watching this closely. We can see from some of your older blood tests that this kidney impairment has not been present before. This places you in the first group mentioned above. We would like to observe your kidney function to see how it changes in the future.

3. Do I have to take part?

It is up to you to decide if you wish to take part in this study. Whatever you decide will have no effect on the standard of care you receive. We will describe the study and go through this information sheet with you. If you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason.

4. What will happen to me if I take part?

This type of study will involve monitoring only. It will involve the recording of information and will not affect the standard treatment you need in any way. In the beginning, we will record your previous kidney function and how it has been affected by your current illness. We will also record from your medical records your medical history which will include previous illnesses to see how these have influenced your kidney condition. When you are discharged from hospital we will record your final blood test results. After you are discharged we will write to your GP and tell them you are part of this study.

We will then wish to record your kidney function again after six months and after twelve months. We will write to you in the future when it is time to check your kidney function again and invite you to attend a clinic appointment in the renal outpatients department of this hospital. At these appointments we will take a blood sample to check your kidney function and also a urine sample. In addition we will check your blood pressure and record the medications you are taking at that time. You will be part of this study for a total of one year. When the study is complete we will write to your GP to let them know the study is over and outline your condition at that time. All of your results will be recorded anonymously and will be identified by number only.

5. Will there be any expenses or payments?

You will not be paid for taking part in this study and it is purely voluntary. If you have any difficulty getting transport for the follow up appointments we will be happy to pay for a taxi to bring you to the hospital.

6. What will I have to do?

The good news is that you will have to do very little. You will not be receiving any additional treatments and we will not expect you to change your lifestyle in any way. Our only request is that you attend for the two follow up appointments at six months and twelve months. Your GP may wish to see you more frequently than this but that would not be part of this study.

7. Are there any risks to me by taking part?

We do not see any risks to you as a result of taking part in this study. It is possible that during follow up we may identify a significant decline in your kidney function. In the event of this happening we will inform your GP in writing.

8. Are there any possible benefits from taking part?

This study will involve monitoring only and will not involve any treatment. It is not designed to have any affect on your condition. The information gathered from this study will improve our knowledge of kidney disease which may help improve the treatment of the condition in the future.

9. What happens when the study ends?

You participation in the study will end after the second follow up appointment in one year. The information recorded during the study will be stored anonymously in our confidential database and will not be linked to you by name. We may use your NHS number to link to NHS hospital records for statistics purposes. All information will be analysed to produce reports on the subject. We will be happy to provide you with a brief report on the results of the study if you request this.

If the information in Part 1 interests you and you are considering taking part please read the additional information in Part 2 before making a decision.

Part 2

1. What will happen if I do not want to carry on with the study?

You can withdraw from this study at any time if you wish. If you withdraw we will need to let your GP know. We will need to record your withdrawal but all information gathered on you will be removed from our database.

2. What if there is a problem?

If you have a concern about any aspect of this study our principal researcher will do their best to answer your questions and can be contacted at the address and number given at the end of this document. If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study the normal NHS complaints mechanisms are available to you.

3. Will the information recorded on me be kept confidential?

All information collected about you during the course of this study will be kept strictly confidential. It will be stored by number only and will not be identifiable to you. We will record your personal contact details separately and this will include your hospital and NHS numbers, name, date of birth, contact address and telephone number as well as your GP contact details. We will ask you to sign a consent form to allow us access to this information.

4. What will happen to any samples that I give?

During the follow up you will have routine blood and urine testing performed. These samples will be performed in our hospital laboratory in a standard manner. We will not be storing samples for the purposes of this study.

5. What will happen to the results of this study?

Once the results of this study have been gathered and analysed, we will publish them in medical journals in order to add to the knowledge of kidney disease so that others can learn from it.

6. Who is organising and funding the research?

This research is being organised by a team from the Wessex Renal and Transplant Unit with help form the Health Care Research Unit of the University of Southampton School of Medicine. It is funded by the local Renal Research Fund. The researcher conducting this study is paid a fixed salary which is independent of whether you take part in the study or not.

7. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called an ethics committee, to protect your interests. This study has been reviewed and given favourable opinion by Milton Keynes Research Ethics Committee.

Study: Natural history of Acute Kidney Injury and its relationship to Chronic kidney Disease.

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Introduction

We would like to invite you to take part in our research study which is explained in this information sheet. Before you decide to take part we would like you to understand why the research is being done and what it will involve for you if you take part. Our researcher who is a medical doctor and a member of the kidney team will go through the information sheet with you and answer any questions you may have. This should not take any more than twenty minutes. You do not need to make a decision immediately but can think about it for 24 hours if you wish. You can also talk to others about the study if you wish.

Part 1 of this information sheet will tell you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

We would encourage you to ask any questions you may have especially if something is not clear.

Part 1.

1. What is the purpose of this study?

The purpose of this study is to improve our knowledge of kidney disease and how it behaves. Kidney disease is very common. Many people have some kidney impairment which is often simply watched by their doctors. Sometimes when people become unwell for other reasons their kidney impairment can deteriorate. It generally appears to get better but we do not know if this will result in more impairment in the future. This study hopes to answer this question by comparing your kidney function now with its future values.

In this study we will be looking at three different groups of patients. The first are people who experience some impairment in their kidney function for the first time during their hospital stay. We want to observe these people to see if their kidney function recovers fully after their illness has settled. The second group are people who

have existing kidney impairment who experience a further decline in their kidney function during their illness. We will observe these to see if the further impairment of their kidney function results in any permanent decline in their function. We will then have a third group who have existing impairment but do not have a further decline during their illness. This group is called a control group and we will compare these with group two to see if there are differences.

This study will involve monitoring only and will not mean any changes in your usual treatment or affect the treatment you currently need.

2. Why have you been invited to take part?

During this stay in hospital your doctors have done some blood tests to help monitor your condition. It has been noted in these blood tests that your kidneys are not working as well as they normally do. The doctors are watching this closely. We can see from some of your older blood tests that your kidneys have been impaired before this illness. This places you in the second group mentioned above and we would like to observe your kidney function to see what affect this illness will have on it in the future.

3. Do I have to take part?

It is up to you to decide if you wish to take part in this study. Whatever you decide will have no effect on the standard of care you receive. We will describe the study and go through this information sheet with you. If you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason.

4. What will happen to me if I take part?

This type of study will involve monitoring only. It will involve the recording of information and will not affect the standard treatment you need in any way. In the beginning, we will record your previous kidney function and how it has been affected by your current illness. We will also record from your medical records your medical history which will include previous illnesses to see how these have influenced your kidney condition. When you are discharged from hospital we will record your final blood test results. After you are discharged we will write to your GP and tell them you are part of this study.

We will then wish to record your kidney function again after six months and after twelve months. Your GP will review you at these times and take a blood sample and a

urine sample. We will also need a measure of your blood pressure at these times as well as a list of your medications. These visits should not take any longer than fifteen minutes and in most cases would be expected as routine in somebody with some kidney impairment.

You will be part of this study for a total of one year. When the study is complete we will write to your GP to let them know the study is over and outline your condition at that time. All of your results will be recorded anonymously and will be identified by number only.

5. Will there be any expenses or payments?

You will not be paid for taking part in this study and it is purely voluntary.

6. What will I have to do?

The good news is that you will have to do very little. You will not be receiving any additional treatments and we will not expect you to change your lifestyle in any way. Our only request is that you attend for the two follow up appointments with your GP at six months and twelve months. Your GP may wish to see you more frequently than this but that would not be part of this study.

7. Are there any risks to me by taking part?

We do not see any risks to you as a result of taking part in this study. It is possible that during follow up we may identify a significant decline in your kidney function. In the event of this happening we will inform your GP in writing and recommend appropriate action.

8. Are there any possible benefits from taking part?

This study will involve monitoring only and will not involve any treatment. It is not designed to have any affect on your condition. The information gathered from this study will improve our knowledge of kidney disease which may help improve the treatment of the condition in the future.

9. What happens when the study ends?

You participation in the study will end after the second follow up appointment in one year. The information recorded during the study will be stored anonymously in our confidential database and will not be linked to you by name. We may use your NHS number to link to NHS hospital records for statistics purposes. The information will be analysed to produce reports on the subject. We will be happy to provide you with a brief report on the results of the study if you request this.

If the information in Part 1 interests you and you are considering taking part please read the additional information in Part 2 before making a decision.

Part 2

1. What will happen if I do not want to carry on with the study?

You can withdraw from this study at any time if you wish. If you withdraw we will need to let your GP know that we will not be requiring your follow up information. We will need to record your withdrawal but all information gathered on you will be removed from our database.

2. What if there is a problem?

If you have a concern about any aspect of this study our principal researcher will do their best to answer your questions and can be contacted at the address and number given at the end of this document. If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study the normal NHS complaints mechanisms are available to you.

3. Will the information recorded on me be kept confidential?

All information collected about you during the course of this study will be kept strictly confidential. It will be stored by number only and will not be identifiable to you. We will record your personal contact details separately and this will include your hospital and NHS numbers, name, date of birth, contact address and telephone number as well as your GP contact details.

4. What will happen to any samples that I give?

During the follow up you will have routine blood and urine testing performed. These samples will be performed in our hospital laboratory in a standard manner. We will not be storing samples for the purposes of this study.

5. What will happen to the results of this study?

Once the results of this study have been gathered and analysed, we will publish them in medical journals in order to add to the knowledge of kidney disease so that others can learn from it.

6. Who is organising and funding the research?

This research is being organised by a team from the Wessex Renal and Transplant Unit with help form the Health Care Research Unit of the University of Southampton School of Medicine. It is funded by the local Renal Research Fund. The researcher conducting this study is paid a fixed salary which is independent of whether you take part in the study or not.

7. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called an ethics committee, to protect your interests. This study has been reviewed and given favourable opinion by Milton Keynes Research Ethics Committee.

Study: Natural history of Acute Kidney Injury and its relationship to Chronic kidney Disease.

Patient Information Sheet

Introduction

We would like to invite you to take part in our research study which is explained in this information sheet. Before you decide to take part we would like you to understand why the research is being done and what it will involve for you if you take part. Our researcher who is a medical doctor and a member of the kidney team will go through the information sheet with you and answer any questions you may have. This should not take any more than twenty minutes. You do not need to make a decision immediately but can think about it for 24 hours if you wish. You can also talk to others about the study if you wish.

Part 1 of this information sheet will tell you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

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In this study we will be looking at three different groups of patients. The first are people who experience some impairment in their kidney function for the first time during their hospital stay. We want to observe these people to see if their kidney function recovers fully after their illness has settled. The second group are people who

have existing kidney impairment who experience a further decline in their kidney function during their illness. We will observe these to see if the further impairment of their kidney function results in any permanent decline in their function. We will then have a third group who have existing impairment but do not have a further decline during their illness. This group is called a control group and we will compare these with group two to see if there are differences.

This study will involve monitoring only and will not mean any changes in your usual treatment or affect the treatment you currently need.

2. Why have you been invited to take part?

During this stay in hospital your doctors have done some blood tests to help monitor your condition. It has been noted from these blood tests that you have some kidney impairment. The doctors are watching this closely. We can see from some of your older blood tests that your kidneys have been impaired like this before but it has not changed. Your kidney impairment has not been affected by your current illness. This places you in the third group mentioned above, the control group, and we would like to observe your kidney function to see what will happen to it in the future.

3. Do I have to take part?

It is up to you to decide if you wish to take part in this study. Whatever you decide will have no effect on the standard of care you receive. We will describe the study and go through this information sheet with you. If you agree to take part, we will ask you to sign a consent form. You are free to withdraw at any time, without giving a reason.

4. What will happen to me if I take part?

This type of study will involve monitoring only. It will involve the recording of information only and will not affect the standard treatment you need in any way. In the beginning, we will record your previous kidney function and how it has been affected by your current illness. We will also record from your medical records your medical history which will include previous illnesses to see how these have influenced your kidney condition. When you are discharged from hospital we will record your final blood test results. After you are discharged we will write to your GP and tell them you are part of this study.

We will then wish to record your kidney function again after six months and after twelve months. Your GP will review you at these times and take a blood sample and a urine sample. We will also need a measure of your blood pressure at these times as well as a list of your medications. These visits should not take any longer than fifteen minutes and in most cases would be expected as routine in somebody with some kidney impairment.

You will be part of this study for a total of one year. When the study is complete we will write to your GP to let them know the study is over and outline your condition at that time. All of your results will be recorded anonymously and will be identified by number only.

5. Will there be any expenses or payments?

You will not be paid for taking part in this study and it is purely voluntary.

6. What will I have to do?

The good news is that you will have to do very little. You will not be receiving any additional treatments and we will not expect you to change your lifestyle in any way. Our only request is that you attend for the two follow up appointments with your GP at six months and twelve months. Your GP may wish to see you more frequently than this but that would not be part of this study.

7. Are there any risks to me by taking part?

We do not see any risks to you as a result of taking part in this study. It is possible that during follow up we may identify a significant decline in your kidney function. In the event of this happening we will inform your GP in writing and recommend appropriate action.

8. Are there any possible benefits from taking part?

This study will involve monitoring only and will not involve any treatment. It is not designed to have any affect on your condition. The information gathered from this study will improve our knowledge of kidney disease which may help improve the treatment of the condition in the future.

9. What happens when the study ends?

You participation in the study will end after the second follow up appointment in one year. The information recorded during the study will be stored anonymously in our confidential database and will not be linked to you by name. We may use your NHS number to link to NHS hospital records for statistics purposes. All information will be analysed to produce reports on the subject. We will be happy to provide you with a brief report on the results of the study if you request this.

If the information in Part 1 interests you and you are considering taking part please read the additional information in Part 2 before making a decision.

Part 2

1. What will happen if I do not want to carry on with the study?

You can withdraw from this study at any time if you wish. If you withdraw we will need to let your GP know that we will not be requiring your follow up information. We will need to record your withdrawal but all information gathered on you will be removed from our database.

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If you have a concern about any aspect of this study our principal researcher will do their best to answer your questions and can be contacted at the address and number given at the end of this document. If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during this study the normal NHS complaints mechanisms are available to you.

3. Will the information recorded on me be kept confidential?

All information collected about you during the course of this study will be kept strictly confidential. It will be stored by number only and will not be identifiable to you. We will record your personal contact details separately and this will include your hospital number and NHS number, name, date of birth, contact address and telephone number as well as your GP contact details.

4. What will happen to any samples that I give?

During the follow up you will have routine blood and urine testing performed. These samples will be performed in our hospital laboratory in a standard manner. We will not be storing samples for the purposes of this study.

5. What will happen to the results of this study?

Once the results of this study have been gathered and analysed, we will publish them in medical journals in order to add to the knowledge of kidney disease so that others can learn from it.

6. Who is organising and funding the research?

This research is being organised by a team from the Wessex Renal and Transplant Unit with help form the Health Care Research Unit of the University of Southampton School of Medicine. It is funded by the local Renal Research Fund. The researcher conducting this study is paid a fixed salary which is independent of whether you take part in the study or not.

7. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called an ethics committee, to protect your interests. This study has been reviewed and given favourable opinion by Milton Keynes Research Ethics Committee.

Appendix 15

Copy of the patient consent form used in the study.

Patient Identification Number: ……

Consent Form

Study: Natural History of Acute Kidney Injury and its relationship to Chronic Kidney Disease.

Chief Investigator: Dr. Mark Uniacke

Please Initial Box

1. I confirm that I have read and understand the information sheet dated ……. (version ……) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that the researcher will have access to my medical notes and that data collected during the study will be stored confidentially. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in this study. ☐

5. I agree to take part in the above study. ☐

_____	_____	_____
Name of patient	Date	Signature

_____	_____	_____
Name of person taking consent	Date	Signature

When completed the original will be kept in the medical notes and two copies should be made, one for the participant and one for the research file.

Appendix 16

Study Review Forms:

1. Original version used in research proposal (Version 2)
2. Final Version used in the study (Version 11)

AKI Study review form

1. Patient Details

Patient Study ID number……. Admission Date : ……..

Age…….

Sex…….

2. Pre - Admission

Comorbidities (Based on Charlson Index)

Tick if the patient has a history or active disease

Myocardial Infarction

Congestive Heart Failure

Peripheral Vascular Disease

Cerebral Vascular Disease

Dementia

Chronic Lung Disease

Rheumatological Disease

Peptic Ulcer Disease

Mild Liver Disease

Inflammatory bowel disease

Diabetes without complications

Hemiplegia

Diabetes with complications

Neoplasia

Moderate / severe liver disease

Metastatic Disease

Leukemia

Lymphoma

Human Immunodeficiency Virus

Additional backround information

Any previous known renal or urological problems

Smoking History Current Ex-smoker Never No data

Alcohol/ Illicit drug History.....

Herbal / Alternative therapies

Regular medications pre-admission

Previous blood results available

	Date		**Date**	
Urea				
Creat.				
Na				
K				
Ca.				
Albumin				
Urate				
Chol.				
CRP				
Hb.				

Previous Urine Dipstick/ PCR / ACR Date……Values…….

…… ……

…… ……

If previously known to have CKD what was the diagnosis/ presumed diagnosis of the cause (indicate which) ……..

3. Admission Details

Specialty –

Initial Diagnosis –

Final Diagnosis –

Notes:

4. AKI Details

Date noted: …… In Hospital…….
On admission…….

Treatment given prior to AKI

……
……
……
……..

Was team aware of problem?

.....

Bloods at the time the AKI was noted

Urea	Ca.	pH
Creat.	Alb	HCO3
Na	CRP	
K	WCC	

Fluid status ……..

Input / Output records Yes No

Blood pressure …….....
…….
……..

Urine Dipstick PCR/ACR (specify)
Microscopy

Action taken if any
……
……
……

Ultrasound Yes No Result……
……
……
Renal Size Right Left

Other investigations if any …….
……
……

Outcome/Notes
……
……..
……..

5. Hospital Discharge

Bloods at time of discharge

Urea Ca.
Creat. Alb.
Na
K

Discharge blood pressure

Discharge urine dipstick / ACR

Discharge Medications

……

……

……

……

.....

AKI Study Review Form

1. Patient Details

Study I.D. ☐☐☐ Admission Date : ☐☐/☐☐/☐☐

Age ☐☐ Sex Male ☐ Female ☐

Group: New AKI1 ☐ AKI1 C3A ☐ AKI2 C3A ☐ AKI3 C3A ☐

AKI2 ☐ C3B ☐ C3B ☐ C3B ☐

AKI3 ☐ C4 ☐ C4 ☐ C4 ☐

C5 ☐ C5 ☐ C5 ☐

CKD Control ☐

2. Pre - Admission

Comorbidities

Myocardial Infarction ☐ Congestive Heart Failure ☐

Peripheral Vascular Disease ☐ Cerebral Vascular Disease ☐

Dementia	☐	Chronic Lung Disease	☐
Rheumatological Disease	☐	Peptic Ulcer Disease	☐
Mild Liver Disease	☐	Diabetes without complications	☐
Hemiplegia	☐	Diabetes with complications	☐
Neoplasia	☐	Moderate / severe liver disease	☐
Metastatic Disease	☐	Leukemia	☐
Lymphoma	☐	AIDS	☐

Additional backround information

Obesity: ☐ Weight ☐☐☐ Height ☐☐☐

Smoking: Current/ Ex. ☐ Never ☐

Hypertension: Yes ☐ No ☐

Number of antihypertensives: 1.☐ 2.☐ 3.☐ 4. or more ☐

Previous known renal or urological problems Yes ☐ No ☐

Comment:

coding ☐☐

Age at which they left full time education? ☐☐

Do they live alone? Yes ☐ No ☐ Do carers call? ☐

Katz Index (Tick if independent and score 1)

Bathing ☐ Dressing ☐ Toileting ☐

Transfer ☐ Continence ☐ Feeding ☐

Score ☐

Regular medications pre-admission

_____☐☐_____☐☐

_____☐☐_____☐☐

_____☐☐_____☐☐

_____☐☐_____☐☐

_____☐☐_____☐☐

What was the indication for the ACE/ARB :

Previous M.I. ☐ CCF ☐ DM/Alb. ☐

Hypertension ☐ **Unknown** ☐

3. AKI Details

Specialty : Medical ☐ Surgical ☐ Obstetric ☐

_____☐☐ _____☐☐

Working Diagnosis on Admission after Consultant review:

_____

_____ ☐☐

When AKI was noted: On Admission ☐ In hospital ☐ Date _____

Urine Dipstick:Yes ☐ No ☐

Blood ☐ Protein ☐

Most recent pre-admission PCR/ACR (Specify): ☐☐☐☐ .....

Ultrasound performed: Yes ☐ No ☐

Clinical impression of fluid status at time of AKI

Dry ☐ Euvolaemic ☐ Overloaded ☐

Documented Hypotension within 72hrs of AKI/@ad: Yes ☐ No ☐ N/A ☐

Urine Output in previous 24hrs ☐☐☐☐mls Not measured ☐ N/A ☐

☐☐☐mls/hr Peri – AKI documented Anuria ☐ Oliguria ☐ No ☐

Highest MEWS score in previous 72 hours/ On Admission

Systolic BP ☐ Heart Rate ☐ Resp. Rate ☐

Temperature ☐ AVPU ☐ Sats ☐ O2 therapy ☐

Total ☐☐

4. AKI Type

Pre-renal ☐ Intrinsic ☐ Post- renal ☐

Pre-renal (loss of effective circulating volume)

1. Sepsis ☐ Features: Pyrexial ☐ Rigors ☐ Hypotension ☐

WCC>12 ☐ Neutropenic ☐ Clear focus ☐

_____

Culture Positive

Urine ☐ Blood ☐ Sputum ☐ Swab ☐

2. other causes of ECV loss

Diarrhoea ☐ Vomiting ☐ Cardiac ☐ _____

Blood Loss ☐ Other ☐ _____

Was subject within 48hrs of a surgical procedure Yes ☐ No ☐

_____☐☐

Relevant drugs taken within 48hrs of AKI

ACEi ☐ ARB ☐ NSAID ☐

Diuretic ☐ _____other ☐ _____☐☐

Management of AKI: ACE/ARB stopped ☐ NSAID stopped ☐

Diuretic stopped ☐ other_____☐

Intrinsic

Biopsy Proven ☐ _____

High Clinical Suspicion ☐ _____

Post-renal detail

Renal Review Obtained **Yes** ☐ No ☐

ITU admission Yes ☐ No ☐

Filtered / HD Yes ☐ No ☐

Appendix 17

Outline of the Charlson Comorbidity Score with the weights attached to each condition. The total score is calculated from the sum of the weights for each condition a patient has. For example a history of congestive heart failure and diabetes with end organ damage carries a score of 3.

Assigned weights for diseases	Conditions
1	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascualr disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease
	Diabetes without complications
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukaemia
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS

Appendix 18

Example of letter sent to a patients General Practitioner in the event that there were concerns regarding ongoing care.

Study: Natural history of Acute Kidney Injury and its relationship to Chronic Kidney Disease.

Re
Study I.D. NHS No.

Recruitment date: February 2011.

Dear Dr. ,

During an admission to Queen Alexandra Hospital in February of last year your patient ……. was kind enough to consent to be enrolled in the above major research study which has been conducted by the regional renal unit at Queen Alexandra Hospital. The purpose of this study is to assess the impact of acute kidney injury on chronic kidney disease.

In this case ……sustained a significant Stage 3 AKI at the time of his admission. Prior to admission his baseline kidney function on record showed a serum creatinine of 83µmol/l (eGFR 79) on the 29/07/2010. His AKI peaked at a creatinine of 512µmol/l during his February admission whilst under the endocrinology team. It was at that point he was recruited into this study. At that time he had a normal renal ultrasound and the usual screening tests for AKI were negative. This included a negative autoimmune screen and negative screening for myeloma. His working diagnosis was a pre-renal type AKI due to an underlying urinary tract infection combined with the use of an ACE inhibitor. The ACE inhibitor was put on hold during the admission.

…… returned to me for follow up in the study in September when he showed evidence of sustained loss of renal function with a serum creatinine of 159µmol/l and eGFR 37. In hindsight he had evidence of microalbuminuria on record in 2010 and I suspect the AKI has unmasked a degree of underlying diabetic nephropathy. I note that he had further blood tests in November when his creatinine was 183µmol/l (eGFR 31) and a urine ACR of 25.1.

This study has been purely observational and participation has now ended. The purpose of this letter is to draw your attention to the renal issues outlined above which I am sure you are already monitoring. ……. ACE inhibitor was discontinued in

the context of the AKI however I can see no reason why this cannot be restarted. He has microalbuminuria and renal impairment and ACE inhibition would be beneficial in this setting. It would obviously have to be restarted with care and a repeat blood test should be performed a week after restarting it. I think that this renal disease is likely to progress in the longer term and would recommend a formal renal referral when he reaches CKD stage 4.

Yours Sincerely

_____

Dr. Mark Uniacke

Appendix 19

Multivariate logistic regression models used to explore a priori factors of interest in the AKI and AKI/CKD Groups with 6 month and 12 month mortality as the dependent variables.

A19.1 : AKI Group and 6 month mortality.

A19.2 : AKI/CKD Group and 6 month mortality.

A19.3 : AKI Group and 12 month mortality.

A19.4 : AKI/CKD Group and 12 month mortality.

Table A19.1 Multivariate analysis of the AKI group with 6 month mortality as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage			.903			.761			.710			.802
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	1.190	(.372 – 3.806)	.769	1.062	(.323 – 3.498)	.921	1.157	(.345 – 3.874)	.813	1.151	(.331 – 3.998)	.825
AKIN 3	1.302	(.415 – 4.803)	.651	1.455	(.449 – 4.715)	.532	1.585	(.480 – 5.229)	.449	1.479	(.431 – 5.072)	.534
AKI Cause			.834						.933			.851
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	1.249	(.422 – 3.697)	.688	1.094	(.359 – 3.337)	.874	1.142	(.372 – 3.505)	.817	.891	(.271 – 2.927)	.849
Complex	1.339	(.493 – 3.636)	.567	1.188	(.423 – 3.334)	.744	1.210	(.431 – 3.395)	.718	1.256	(.434 – 3.640)	.674
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.908	(.386 – 2.138)	.825	.735	(.303 – 1.779)	.494	.671	(.271 – 1.662)	.389	.680	(.207 – 2.235)	..525
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	3.469	(1.135 – 10.603)	.029	3.975	(1.261 – 12.530)	.018	3.869	(1.223–12.239)	.021	3.074	(.951 – 9.933)	.061
Medical admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.187	(.826 – 5.793)	.115	2.055	(.760 – 5.555)	.156	2.015	(.744 – 5.462)	.168	1.662	(.591 – 4.674)	.336

Model 1 – unadjusted

Model 2 – adjusted for age

Model 3 adjusted for age and sex

Model 4 adjusted for age,,sex, Charlson score and hypertension

Table A19.1 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage			.773			.803			.963			
AKIN 1 (ref)	1.00			1.00			1.00					
AKIN 2	1.116	(.309 – 4.029)	.867	1.144	(.328 – 3.989)	.833	1.068	(.298 – 3.830)	.920			
AKIN 3	1.526	(.409 – 5.692)	.529	1.476	(.428 – 5.094)	.538	1.183	(.332 – 4.217)	.796			
AKI Cause						.832			.604			.863
Hypoperfusion (ref)				1.00			1.00			1.00		
Septic				.850	(.254 – 2.839)	.792	.613	(.178 – 2.117)	.439	.804	(.234 – 2.765)	.729
Complex				1.246	(.429 – 3.615)	.686	1.175	(.391 – 3.527)	.774	1.140	(.372 – 3.490)	.819
On RAS Blocker												
No (ref)	1.00						1.00			1.00		
Yes	.669	(.203 – 2.205)	.509				.698	(.213 – 2.282)	.552	.679	(.205 – 2.250)	.527
AKI on admission												
No (ref)	1.00			1.00						1.00		
Yes	3.723	(1.102 – 12.575)	.034	3.060	(.946 – 9.898)	.062				2.988	(.909 – 9.824)	.072
Medical admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.701	(.585 – 4.940)	.329	1.648	(.585 – 4.640)	.344	1.346	(.462 – 3.922)	.586	1.610	(.562 – 4.619)	.375

Model 5 – adjusted for age, sex, Charlson Score, hypertension and AKI cause

Model 6 - adjusted for age, sex, Charlson Score, hypertension and use of RAS Blockers

Model 7 - adjusted for age, sex, Charlson Score, hypertension and AKI present on admission.

Model 8 - adjusted for age, sex, Charlson Score, hypertension and AKIN Stage.

Table A19.2 Multivariate analysis of the AKI group with 12 month mortality as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.523			.471			.483			.532
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	1.838	(.608 – 5.556)	.281	1.685	(.542 – 5.239)	.368	1.680	(.532 – 5.302)	.376	1.699	(.525 – 5.502)	.376
AKIN 3	1.777	(.588 – 5.365)	.308	2.036	(.652 – 6.356)	.221	2.031	(.642 – 6.427)	.228	1.953	(.601 – 6.351)	.266
AKI Cause			.565			.732			.736			.679
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	1.429	(.536 – 3.808)	.476	1.265	(.460 – 3.478)	.648	1.256	(.455 – 3.467)	.659	1.040	(.360 – 3.008)	.942
Complex	1.599	(650 – 3.932)	.307	1.448	(.569 – 3.682)	.437	1.445	(.568 – 3.678)	.440	1.500	(.577 – 3.900)	.405
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.977	(.452 – 2.110)	.952	.782	(.351 – 1.742)	.547	.790	(.349 – 1.793)	.574	.820	(.280 – 2.401)	.717
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.957	(1.149 – 7.609)	.025	3.395	(1.276 – 9.033)	.014	3.507	(1.304 – 9.432)	.013	2.920	(1.068 – 7.987)	.037
Medical admission												
No (ref)	1.00			1.00								
Yes	2.148	(.906 – 5.096)	.083	2.044	(.843 – 4.957)	.114	2.068	(.851 – 5.029)	.109	1.741	(.696 – 4.354)	.235

Model 1 – unadjusted

Model 2 – adjusted for age

Model 3 adjusted for age and sex

Model 4 adjusted for age,,sex, Charlson score and hypertension

Table A19.2 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.585			.537			.730			
AKIN 1 (ref)	1.00			1.00			1.00					
AKIN 2	1.590	(.476 – 5.309)	.451	1.687	(520 – 5.473)	.384	1.578	(.475 – 5.244)	.457			
AKIN 3	1.932	(.556 – 6.716)	.300	1.948	(.598 – 6.344)	.269	1.557	(.463 – 5.235)	.474			
AKI Cause						.684			.501			.800
Hypoperfusion (ref)				1.00			1.00			1.00		
Septic				1.021	(.350 – 2.977)	.970	.708	(.233 – 2.151)	.543	.900	(.299 – 2.711)	.851
Complex				1.487	(.571 – 3.871)	.416	1.407	(.524 – 3.774)	.498	1.286	(.475 – 3.485)	.621
On RAS Blocker												
No (ref)	1.00						1.00			1.00		
Yes	.833	(.283 – 2.455)	.740				.820	(.280 – 2.398)	.716	.833	(.280 – 2.479)	.742
AKI on admission												
No (ref)	1.00			1.00						1.00		
Yes	3.474	(1.214 – 9.942)	.020	2.922	(1.068 – 7.997)	.037				2.777	(.999 – 7.722)	.050
Medical admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.728	(.671 – 4.455)	.257	1.735	(.694 – 4.340)	.238	1.359	(.522 – 3.537)	.530	1.616	(.637 – 4.097)	.312

Model 5 – adjusted for age, sex, Charlson Score, hypertension and AKI cause.

Model 6 - adjusted for age, sex, Charlson Score, hypertension and use of RAS Blockers.

Model 7 - adjusted for age, sex, Charlson Score, hypertension and AKI present on admission.

Model 8 - adjusted for age, sex, Charlson Score, hypertension and AKIN Stage.

Table A19.3 Multivariate analysis of the AKI/CKD group with 6 month mortality as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.010			.007			.009			.012
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	3.165	(1.482 – 6.761)	.003	3.337	(1.543 – 7.219)	.002	3.274	(1.502 – 7.133)	.003	3.249	(1.462 – 7.220)	.004
AKIN 3	1.299	(.485 – 3.476)	.603	1.264	(.468 – 3.415)	.644	1.235	(.454 – 3.362)	.679	1.240	(.444 – 3.465)	.682
AKI Cause			.262			.234			.182			.184
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	1.895	(844 – 4.256)	.121	1.987	(.878 – 4.494)	.099	2.148	(.935 – 4.938)	.072	2.035	(.861 – 4.809)	.105
Complex	1.339	(718 – 4.013)	.228	1.676	(705 – 3.984)	.243	1.716	(.715 – 4.118)	.227	2.004	(814 – 4.937)	.131
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.468	(227 - 965)	.040	.477	(.230 - .989)	.047	.485	(.232 – 1.013)	.054	.713	(.290 – 1.757)	.463
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.025	(.480 – 2.187)	.950	1.119	(.519 – 2.415)	.774	1.187	(.545 – 2.582)	.666	1.098	(.496 – 2.432)	.818
Medical admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	5.176	(1.924 – 13.926)	.001	4.932	(1.826 – 13.323)	.002	4.702	(1.732–12.763)	.002	4.476	(1.624-12.331)	.004

Model 1 – unadjusted

Model 2 – adjusted for age

Model 3 adjusted for age and sex

Model 4 adjusted for age,,sex, Charlson score and hypertension

Table A19.3 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.010			.009			.012			
AKIN 1 (ref)	1.00			1.00			1.00					
AKIN 2	3.175	(1.409 – 7.154)	.005	3.477	(1.539 – 7.855)	.003	3.236	(1.455 – 7.196)	.004			
AKIN 3	.934	(.315 – 2.767)	.902	1.287	(.458 – 3.613)	.632	1.211	(.424 – 3.458)	.721			
AKI Cause						.211			.185			.191
Hypoperfusion (ref)				1.00			1.00			1.00		
Septic				1.980	(.834 – 4.701)	.122	2.035	(.861 – 4.808)	.105	2.070	(.849 – 5.051)	.110
Complex				1.963	(.795 – 4.851)	.144	2.002	(.811 – 4.940)	.132	2.036	(806 – 5.143)	.133
On RAS Blocker												
No (ref)	1.00						1.00			1.00		
Yes	.759	(.302 – 1.912)	.559				.701	(283 – 1.737)	.443	.586	(.230 – 1.494)	.263
AKI on admission												
No (ref)	1.00			1.00						1.00		
Yes	1.016	(.451 – 2.291)	.969	1.139	(.510 – 2.545)	.752				1.098	(.477 – 2.527)	.826
Medical admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	4.174	(1.500 – 11.612)	.006	4.404	(1.590-12.204)	.004	5.174	(1.777–15.063)	.003	4.887	(1.710-13.964)	.003

Model 5 – adjusted for age, sex, Charlson Score, hypertension and AKI cause.

Model 6 - adjusted for age, sex, Charlson Score, hypertension and use of RAS Blockers.

Model 7 - adjusted for age, sex, Charlson Score, hypertension and AKI present on admission.

Model 8 - adjusted for age, sex, Charlson Score, hypertension and AKIN Stage.

Table A19.4 Multivariate analysis of the AKI/CKD group with 12 month mortality as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.110			.079			.087			.111
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	1.993	(.983 – 4.038)	.056	2.109	(1.025 – 4.341)	.043	2.072	(1.004 – 4.275)	.049	1.957	(.938 – 4.084)	.074
AKIN 3	.898	(.360 – 2.240)	.818	.861	(.341 – 2.178)	.753	.848	(.335 – 2.151)	.729	.794	(.307 – 2.052)	.633
AKI Cause			.062			.053			.044			.037
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	2.199	(1.021 – 4.737	.044	2.351	(1.078 – 5.127)	.032	2.456	(1.120 – 5.427)	.025	2.290	(1.021 – 5.136)	.044
Complex	2.325	(1.042 – 5.186)	.039	2.310	()1.025 – 5.204	.043	2.348	(1.038 – 5.311)	.040	2.736	(1.182 – 6.330)	.019
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.565	(.283 – 1.127)	.105	.578	(.286 – 1.166)	.126	.586	(.290 – 1.185)	.137	.743	(.317 – 1.741)	.494
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.895	(.444 – 1.801)	.755	.995	(.488 – 2.029)	.988	1.027	(.501 – 2.102)	.943	.952	(.459 – 1.978)	.896
Medical admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	4.882	(2.053 – 11.607)	.000	4.625	(1.932 – 11.070)	.001	4.507	(1.877–10.820)	.001	4.196	(1.732–10.161)	.001

Model 1 – unadjusted

Model 2 – adjusted for age

Model 3 adjusted for age and sex

Model 4 adjusted for age,,sex, Charlson score and hypertension

Table A19.4 continued

	Model 5			Model 6			Model 7			Model 8		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.071			.094			.112			
AKIN 1 (ref)	1.00			1.00			1.00					
AKIN 2	1.852	(.871 – 3.936)	.109	2.047	(.971 – 4.312)	.060	1.958	(.937 – 4.089)	.074			
AKIN 3	.573	(.209 – 1.575)	.280	.810	(.312 – 2.100)	.664	.794	(.301 – 2.093)	.641			
AKI Cause						.043			.035			.030
Hypoperfusion (ref)				1.00			1.00			1.00		
Septic				2.248	(.998 – 5.064)	.050	2.304	(1.026 – 5.176)	.043	2.405	(1.054 – 5.488)	.037
Complex				2.694	(1.161 – 6.251)	.021	2.763	(1.192 – 6.405)	.018	2.871	(1.220 – 6.756)	.016
On RAS Blocker												
No (ref)	1.00						1.00			1.00		
Yes	.759	(.302 – 1.912)	.559				.745	(.316 – 1.757)	.501	.671	(.282 – 1.596)	.367
AKI on admission												
No (ref)	1.00			1.00						1.00		
Yes	.864	(.407 – 1.836)	.704	.981	(.469 – 2.053)	.960				.998	(.470 – 2.120)	.995
Medical admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	3.877	(1.583 – 9.496)	.003	4.150	(1.704 – 10.108)	.002	5.221	(2.015–13.527)	.001	4.391	(1.788–10.781)	.001

Model 5 – adjusted for age, sex, Charlson Score, hypertension and AKI cause.

Model 6 - adjusted for age, sex, Charlson Score, hypertension and use of RAS Blockers.

Model 7 - adjusted for age, sex, Charlson Score, hypertension and AKI present on admission.

Model 8 - adjusted for age, sex, Charlson Score, hypertension and AKIN Stage.

Appendix 20

Multivariate logistic regression models used to explore a priori factors of interest in the AKI and AKI/CKD Groups using failure to recover function after 6 months as the dependent variable. Modeling is presented for the three definitions of faiure to recover explored in the study – a fall in eGFR by 5mls/min, a fall of 10mls/min, and a fall of 25% from baseline.

A20.1 : AKI Group for a fall in eGFR of 5mls/min after 6 months.

A20.2 : AKI/CKD Group for a fall in eGFR of 5mls/min after 6 months.

A20.3 : AKI Group for a fall in eGFR of 10mls/min after 6 months.

A20.4 : AKI/CKD Group for a fall in eGFR of 10mls/min after 6 months.

A20.5 : AKI Group for a fall in eGFR of 25% from baseline after 6 months.

A20.6 : AKI/CKD Group for a fall in eGFR of 25% from baseline after 6 months.

Table A20.1 AKI Group models with fall in eGFR of 5mls or more after 6 months as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.631			.608			.567			.599
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	1.481	(.657 – 3.338)	.344	1.418	(.623 – 3.228)	.405	1.470	(.640 – 3.376)	.364	1.449	(.625 – 3.361)	.387
AKIN 3	1.333	(.594 – 2.993)	.486	1.483	(.649 – 3.388)	.350	1.523	(.662 – 3.499)	.322	1.497	(.646 – 3.468)	.347
AKI Cause			.748			.662			.681			.719
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	.734	(.328 – 1.641)	.451	.689	(.304 – 1.560)	.371	.694	(.306 – 1.573)	.381	.711	(.312 – 1.620)	.416
Complex	.938	(.443 – 1.984)	.866	.933	(.436 – 1.998)	.859	.900	(.417 – 1.941)	.789	.900	(.415 – 1.953)	.790
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.732	(.921 – 3.257)	.088	1.511	(.786 – 2.905)	.216	1.484	(.764 – 2.885)	.244	1.419	(.589 – 3.418)	.435
GFR slope preAKI	.879	(.800 - .965)	.007	.876	(.797 - .962)	.006	.876	(.797 - .962)	.006	.877	(.798 - .964)	.006
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.439	(.218 - .884)	.021	.417	(.205 - .852)	.016	.412	(.202 - .843)	.015	.404	(.196 - .831)	.014
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.778	(.411 – 1.472)	.440	.808	(.423 – 1.543)	.518	.805	(.421 – 1.538)	.511	.803	(.416 – 1.549)	.512

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A20.1 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage						.346			.586			.591
AKIN 1 (ref)				1.00			1.00			1.00		
AKIN 2				1.396	(.533 – 3.653)	.497	1.468	(.632 – 3.408)	.372	1.491	(.625 – 3.557)	.368
AKIN 3				2.059	(.778 – 5.452)	.146	1.505	(.649 – 3.492)	.341	1.537	(.629 – 3.756)	.346
AKI Cause			.624			.505			.733			
Hypoperfusion (ref)	1.00			1.00			1.00					
Septic	.661	(.285 – 1.536)	.336	.558	(.199 – 1.563)	.267	.718	(.314 – 1.640)	.432			
Complex	.816	(.366 – 1.818)	.619	.716	(.292 – 1.759)	.467	.912	(.419 – 1.984)	.817			
On RAS Blocker												
No (ref)	1.00			1.00						1.00		
Yes	1.439	(.596 – 3.477)	.419	2.232	(.840 – 5.930)	.107				1.496	(.609 – 3.672)	.380
GFR slope preAKI	.875	(.796 - .962)	.006				.861	(.781 - .950)	.003	.859	(.777 - .950)	.003
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.377	(.180 - .787)	.009	.530	(.233 – 1.204)	.129	.399	(.193 - .824)	.013	.351	(.165 - .747)	.007
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.744	(.376 – 1.474)	.397	1.121	(.527 – 2.381)	.767	.790	(.408 – 1.529)	.483	.873	(.430 – 1.774)	.708

Model 5 – adjusted for age, sex, Charlson Score, hypertension, and AKIN stage.

Model 6 – adjusted for age, sex, Charlson Score, hypertension, and Pre-AKI slope.

Model 7 – adjusted for age, sex, Charlson Score, hypertension, and use of RAS blockers.

Model 8 – adjusted for age, sex, Charlson Score, hypertension, and cause.

Table A20.2 AKI/CKD Group models with fall in eGFR of 5mls or more after 6 months as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage			.045			.045			.044			.033
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	2.857	(1.195 – 6.829)	.018	2.851	(1.192 – 6.816)	.018	2.867	(1.197 – 6.866)	.018	3.015	(1.244 – 7.303)	.015
AKIN 3	2.041	(.788 – 5.285)	.142	2.044	(.789 – 5.296)	.141	2.072	(.795 – 5.401)	.136	2.270	(.852 – 6.050)	.101
AKI Cause			.835			.833			.829			.889
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	1.050	(.448 – 2.463)	.911	1.034	(.436 – 2.449)	.940	1.031	(.434 – 2.446)	.945	1.004	(.415 – 2.427)	.993
Complex	1.300	(.543 – 3.112)	.556	1.297	(.542 – 3.106)	.559	1.301	(.542 – 3.121)	.556	1.227	(.507 – 2.970)	.650
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.913	(.382 – 2.180)	.837	.916	(.383 – 2.191)	.844	.917	(.383 – 2.196)	.846	.681	(.243 – 1.903)	.463
GFR slope preAKI	.920	(.851 - .995)	.036	.907	(.834 - .986)	.022	.907	(.834 - .986)	.022	.906	(.833 - .986)	.022
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.858	(.392 – 1.877)	.702	.862	(.394 – 1.886)	.709	.862	(.394 – 1.886)	.710	.802	(.362 – 1.776)	.586
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.046	(.466 – 2.346)	.913	1.033	(.457 – 2.335	.937	1.032	(.455 – 2.339)	.941	1.086	(.476 – 2.479)	.845

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A20.2 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage						.022			.025			
AKIN 1 (ref)				1.00			1.00			1.00		
AKIN 2				3.573	(1.422 – 8.980)	.007	3.237	(1.317 – 7.956)	.010	2.993	(1.233 – 7.267)	.015
AKIN 3				2.034	(.729 – 5.676)	.175	2.315	(.865 – 6.199)	.095	2.291	(.850 – 6.172)	.101
AKI Cause			.934			.908			.882			
Hypoperfusion (ref)	1.00			1.00			1.00					
Septic	.917	(.368 – 2.281)	.852	.939	(.378 – 2.334)	.892	.980	(.403 – 2.379)	.964			
Complex	1.110	(.446 – 2.764)	.823	1.168	(.474 – 2.877)	.736	1.223	(.505 – 2.965)	.655			
On RAS Blocker												
No (ref)	1.00			1.00						1.00		
Yes	.560	(.194 – 1.616)	.283	.703	(.249 – 1.988)	.507				.676	(.241 – 1.897)	.457
GFR slope preAKI	.894	(.817 - .979)	.015				.907	(.834 - .987)	.023	.906	(.833 - .986)	.022
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.741	(.327 – 1.677)	.471	.825	(.367 – 1.856)	.642	.825	(.370 – 1.840)	.638	.800	(.355 – 1.802)	.590
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.030	(.436 – 2.432)	.947	1.083	(.466 – 2.518)	.853	1.121	(.488 – 2.575)	.788	1.099	(.477 – 2.534)	.824

Model 5 – adjusted for age, sex, Charlson Score, hypertension, and AKIN stage.

Model 6 – adjusted for age, sex, Charlson Score, hypertension, and Pre-AKI slope.

Model 7 – adjusted for age, sex, Charlson Score, hypertension, and use of RAS block

Model 8 – adjusted for age, sex, Charlson Score, hypertension, and cause.

Table A20.3 AKI Group models with fall in eGFR of 10 mls or more after 6 months as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage			.203			.172			.111			.100
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	2.006	(.843 – 4.770)	.115	1.941	(.811 – 4.642)	.136	2.208	(.904 – 5.393)	.082	2.337	(.936 – 5.831)	.069
AKIN 3	2.083	(.878 – 4.937)	.096	2.268	(.944 – 5.447)	.067	2.512	(1.026 – 6.152)	.044	2.604	(1.042 – 6.506)	.041
AKI Cause			.326			.294			.415			.386
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	.815	(.351 – 1.892)	.634	.780	(.334 – 1.826)	.567	.798	(.338 – 1.883)	.607	.828	(.346 – 1.981)	.671
Complex	1.559	(.732 – 3.319)	.250	1.567	(.731 – 3.359)	.248	1.458	(.673 – 3.160)	.339	1.542	(.700 – 3.394)	.282
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.181	(.624 – 2.236)	.610	1.050	(.543 – 2.034)	.884	.948	(.482 – 1.865)	.878	.853	(.343 – 2.121)	.732
GFR slope preAKI	.907	(.831 - .990)	.029	.905	(.829 - .989)	.027	.905	(.828 - .989)	.027	.909	(.830 - .996)	.040
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.677	(.333 – 1.379)	.283	.662	(.323 – 1.355)	.259	.639	(.310 – 1.320)	.227	.622	(.298 – 1.297)	.205
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.992	(519 – 1.894)	.980	1.024	(.533 – 1.966)	.944	1.010	(.523 – 1.949)	.977	1.066	(.543 – 2.093)	.854

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A20.3 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage						.057			.100			.153
AKIN 1 (ref)				1.00			1.00			1.00		
AKIN 2				2.313	(.827 – 6.472)	.110	2.337	(.935 – 5.843)	.069	2.301	(.892 – 5.937)	.085
AKIN 3				3.430	(1.243 – 9.463)	.017	2.613	(1.044 – 6.541)	.040	2.449	(.924 – 6.487)	.072
AKI Cause			.484			.453			.388			
Hypoperfusion (ref)	1.00			1.00			1.00					
Septic	.707	(.285 – 1.750)	.453	.580	(.200 – 1.679)	.315	.826	(.345 – 1.977)	.667			
Complex	1.276	(.563 – 2.892)	.560	1.186	(.490 – 2.873)	.705	1.538	(.698 – 3.387)	.286			
On RAS Blocker												
No (ref)	1.00			1.00						1.00		
Yes	.848	(.336 – 2.137)	.726	1.184	(.453 – 3.097)	.730				.916	(.360 – 2.335)	.855
GFR slope preAKI	.909	(.828 - .997)	.042				.906	(.826 - .994)	.037	.890	(807 - .981)	.018
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.557	(.262 – 1.186)	.129	.797	(.350 – 1.818)	.590	.623	(.298 – 1.300)	.207	.601	(.280 – 1.288)	.190
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.933	(.460 – 1.893)	.848	1.633	(.761 – 3.503)	.208	1.072	(.545 – 2.109)	.839	1.171	(.562 – 2.441)	.674

Model 5 – adjusted for age, sex, Charlson Score, hypertension, and AKIN stage.

Model 6 – adjusted for age, sex, Charlson Score, hypertension, and Pre-AKI slope.

Model 7 – adjusted for age, sex, Charlson Score, hypertension, and use of RAS blockers.

Model 8 – adjusted for age, sex, Charlson Score, hypertension, and cause.

Table A20.4 AKI/CKD Group models with fall in eGFR of 10 mls or more after 6 months as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage			.029			.029			.028			.023
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	3.043	(1.093 – 8.470)	.033	3.030	(1.084 – 8.473)	.035	3.056	(1.090 – 8.564)	.034	3.263	(1.141 – 9.329)	.027
AKIN 3	3.550	(1.210 – 10.416)	.021	3.627	(1.227 – 10.723)	.020	3.697	(1.239–11.035)	.019	3.974	(1.289–12.253)	.016
AKI Cause			.048			.065			.064			.101
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	3.375	(1.245 – 9.149)	.017	3.219	(1.174 – 8.824)	.023	3.242	(1.180 – 8.910)	.023	2.969	(1.064 – 8.289)	.038
Complex	1.446	(.457 – 4.581)	.530	1.434	(.452 – 4.549)	.541	1.422	(.447 – 4.526)	.551	1.353	(.421 – 4.349)	.612
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.410	(.669 – 8.674)	.178	2.502	(.689 – 9.088)	.163	2.507	(.689 – 9.116)	.163	1.868	(.440 – 7.927)	.397
GFR slope preAKI	.912	(.833 - .998)	.045	.888	(.806 - .978)	.016	.888	(.806 - .978)	.016	.880	(.795 - .974)	.014
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.461	(.603 – 3.542)	.401	1.514	(.620 – 3.698)	.362	1.514	(.620 – 3.698)	.362	1.440	(.583 – 3.557)	.429
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.346	(.495 – 3.660)	.560	1.264	(.460 – 3.475)	.650	1.267	(.459 – 3.499)	.648	1.343	(.483 – 3.735)	.572

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A20.4 continued

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage						.026			.032			.030
AKIN 1 (ref)				1.00			1.00			1.00		
AKIN 2				3.912	(1.309 – 11.693)	.015	3.710	(1.226–11.225)	.020	4.090	(1.335–12.532)	.014
AKIN 3				3.455	(1.046 – 11.414)	.042	3.466	(1.048–11.463)	.042	3.244	(.944 – 11.155)	..062
AKI Cause			.145			.132			.086			
Hypoperfusion (ref)	1.00			1.00			1.00					
Septic	2.722	(.938 – 7.895)	.065	2.871	(.988 – 8.342)	.053	3.126	(1.107 – 8.826)	.031			
Complex	1.162	(.348 – 3.881)	.807	1.276	(.386 – 4.215)	.689	1.360	(.421 – 4.393)	.607			
On RAS Blocker												
No (ref)	1.00			1.00						1.00		
Yes	1.572	(.361 – 6.851)	.547	1.940	(.459 – 8.199)	.368				2.164	(.484 – 9.680)	.313
GFR slope preAKI	.875	(.784 - .976)	.017				.879	(.793 - .974)	.014	.880	(.791 - .979)	.019
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.364	(.538 – 3.463)	.513	1.538	(.605 – 3.909)	.365	1.371	(.552 – 3.406)	.496	1.921	(.725 – 5.086)	.189
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.163	(.399 – 3.387)	.782	1.327	(.462 – 3.813)	.599	1.302	(.466 – 3.639)	.614	1.135	(.396 – 3.249)	.814

Model 5 – adjusted for age, sex, Charlson Score, hypertension, and AKIN stage.

Model 6 – adjusted for age, sex, Charlson Score, hypertension, and Pre-AKI slope.

Model 7 – adjusted for age, sex, Charlson Score, hypertension, and use of RAS blockers.

Model 8 – adjusted for age, sex, Charlson Score, hypertension, and cause.

Table A20.5 AKI Group models with fall in eGFR of 25% or more after 6 months as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.064			.033			.016			.015
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	3.391	(.898 – 12.810)	.072	3.186	(.831 – 12.217)	.091	4.223	(1.068– 16.705	.040	4.356	(1.077–17.621)	.039
AKIN 3	4.744	(1.287 – 17.492)	.019	5.670	(1.501 – 21.421)	.011	7.318	(1.861– 28.766	.004	7.748	(1.922–31.232)	.004
AKI Cause			.875			.861			.936			.913
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	1.077	(.388 – 2.990)	.887	1.001	(.353 – 2.839)	.998	1.128	(.384 – 3.314)	.827	1.203	(.404 – 3.582)	.739
Complex	1.275	(.505 – 3.215)	.607	1.278	(.495 – 3.297)	.612	1.191	(.449 – 3.163)	.725	1.206	(.450 – 3.233)	.709
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.337	(1.028 – 5.312)	.043	1.966	(.849 – 4.555)	.115	1.716	(.729 – 4.042)	.216	1.350	(.440 – 4.145)	.600
GFR slope preAKI	.939	(.855 – 1.031)	.188	.935	(.850 – 1.028)	.165	.932	(.844 – 1.029)	.161	.941	(.851 – 1.041)	.236
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.455	(.174 – 1.189)	.108	.423	(.159 – 1.124)	.084	.390	(.144 – 1.057)	.064	.399	(.146 – 1.086)	.072
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.095	(.901 – 4.871)	.086	2.276	(.962 – 5.383)	.061	2.211	(.925 – 5.286)	.074	2.197	(.905 – 5.332)	.082

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A20.5 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage						.016			.016			.026
AKIN 1 (ref)				1.00			1.00			1.00		
AKIN 2				5.000	(1.164 – 21.479)	.030	4.320	(1.068–17.472)	.040	5.093	(1.180–21.991)	.029
AKIN 3				7.976	(1.948 – 32.665)	.004	7.626	(1.890–30.775)	.004	7.982	(1769– 36.016)	.007
AKI Cause			.858			.639			.907			
Hypoperfusion (ref)	1.00			1.00			1.00					
Septic	.761	(.235 – 2.459)	.648	1.762	(.528 – 5.876)	.357	1.209	(.406 – 3.601)	.733			
Complex	.775	(.271 – 2.214)	.634	1.088	(.371 – 3.187)	.878	1.218	(.452 – 3.281)	.697			
On RAS Blocker												
No (ref)	1.00			1.00						1.00		
Yes	1.200	(.371 – 3.886)	.761	1.724	(.542 – 5.478)	.356				1.593	(.481 – 5.280)	.446
GFR slope preAKI	.948	(.856 – 1.050)	.307				.932	(.841 – 1.033)	.177	.912	(817 – 1.019)	.102
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.308	(.108 - .880)	.028	.352	(.117 – 1.058)	.063	.397	(.145 – 1.082)	.071	.415	(.147 – 1.171)	.097
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.767	(.700 – 4.458)	.228	2.591	(1.008 – 6.659)	.048	2.195	(.904 – 5.333)	.083	2.108	(.808 – 5.500)	.128

Model 5 – adjusted for age, sex, Charlson Score, hypertension, and AKIN stage.

Model 6 – adjusted for age, sex, Charlson Score, hypertension, and Pre-AKI slope.

Model 7 – adjusted for age, sex, Charlson Score, hypertension, and use of RAS blockers.

Model 8 – adjusted for age, sex, Charlson Score, hypertension, and cause.

Table A20.6 AKI/CKD Group models with fall in eGFR of 25% or more after 6 months as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.138			.134			.136			.105
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	2.281	(.719 – 7.238)	.162	2.267	(.709 – 7.246)	.167	2.270	(.709 – 7.267)	.167	2.444	(.748 – 7.981)	.139
AKIN 3	3.042	(.937 – 9.874)	.064	3.126	(.952 – 10.268)	.060	3.135	(.946 – 10.388)	.062	3.508	(1.023–12.036)	.046
AKI Cause			.573			.651			.653			.738
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	1.719	(.553 – 5.346)	.350	1.555	(.489 – 4.945)	.454	1.567	(.491 – 4.995)	.448	1.458	(.445 – 4.774)	.533
Complex	1.684	(.517 – 5.488)	.387	1.653	(.504 – 5.421)	.407	1.639	(.497 – 5.400)	.417	1.533	(.461 – 5.095)	.486
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.055	(.323 – 3.448)	.929	1.096	(.332 – 3.623)	.881	1.090	(.329 – 3.610)	.888	.742	(.196 – 2.810)	.661
GFR slope preAKI	.951	(.868 – 1.042)	.283	.928	(.844 – 1.019)	.119	.927	(.844 – 1.019)	.118	.927	(.843 – 1.019)	.115
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.731	(.247 – 2.167)	.573	.763	(.255 – 2.277)	.627	.763	(.256 – 2.280)	.629	.707	(.235 – 2.132)	.538
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.542	(.479 – 4.964)	.468	1.417	(.434 – 4.625)	.563	1.438	(.438 – 4.717)	.549	1.550	(.468 – 5.130)	.473

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A20.6 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage						.126			.095			.124
AKIN 1 (ref)				1.00			1.00			1.00		
AKIN 2				2.661	(.801 – 8.847)	.110	2.607	(.782 – 8.697)	.119	2.391	(.729 – 7.845)	.151
AKIN 3				3.188	(.897 – 11.329)	.073	3.570	(1.037–12.295)	.044	3.362	(.969 – 11.665)	.056
AKI Cause			.874			.794			.750			
Hypoperfusion (ref)	1.00			1.00			1.00					
Septic	1.271	(.376 – 4.298)	.699	1.376	(.411 – 4.603)	.605	1.429	(.434 – 4.704)	.557			
Complex	1.354	(.396 – 4.628)	.628	1.472	(.437 – 4.958)	.533	1.529	(.460 – 5.081)	.489			
On RAS Blocker												
No (ref)	1.00			1.00						1.00		
Yes	.631	(.160 – 2.484)	.510	.744	(.197 – 2.814)	.663				.761	(.198 – 2.924)	.691
GFR slope preAKI	.931	(.845 – 1.026)	.151				.926	(.842 – 1.019)	.115	.929	(.844 – 1.022)	.128
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.650	(.211 – 2.000)	.452	.720	(.237 – 2.191)	.563	.739	(.240 – 2.271)	.597	.767	(.245 – 2.403)	.649
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.374	(.400 – 4.714)	.614	1.509	(.451 – 5.055)	.504	1.576	(.475 – 5.234)	.457	1.504	(.448 – 5.055)	.509

Model 5 – adjusted for age, sex, Charlson Score, hypertension, and AKIN stage.

Model 6 – adjusted for age, sex, Charlson Score, hypertension, and Pre-AKI slope.

Model 7 – adjusted for age, sex, Charlson Score, hypertension, and use of RAS blockers.

Model 8 – adjusted for age, sex, Charlson Score, hypertension, and cause.

Appendix 21

Multivariate logistic regression models used to explore a priori factors of interest in the AKI and AKI/CKD Groups using the combined outcome of mortalty and a fall in eGFR of 5mls/min or more from baseline as the dependent variable.

A21.1 : AKI Group models for the combined outcome.

A21.2 : AKI/CKD Group models for the combined outcome.

Table A21.1 AKI Group models with combined outcome of death or fall in GFR of 5mls/min or more at 6 months

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
AKIN Stage			.589			.517			.466			.488
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	1.475	(.685 – 3.178)	.321	1.369	(.625 – 3.000)	.432	1.430	(.647 – 3.160)	.377	1.405	(.633 – 3.122)	.404
AKIN 3	1.370	(.640 – 2.930)	.418	1.580	(.720 – 3.471)	.254	1.639	(.741 – 3.625)	.223	1.622	(.730 – 3.606)	.235
AKI Cause			.808			.690			.711			.721
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	.791	(.372 – 1.679)	.541	.715	(330 – 1.550)	.395	.721	(.332 – 1.568)	.409	.725	(.333 – 1.580)	.419
Complex	.995	(.490 – 2.020)	.989	.933	(451 – 1.933)	.853	.907	(.436 – 1.885)	.793	.903	(.433 – 1.882)	.785
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.575	(.869 – 2.853)	.134	1.312	(.706 – 2.438)	.391	1.269	(.675 – 2.385)	.459	1.250	(.543 – 2.875)	.600
GFR slope preAKI	.883	(.808 - .965)	.006	.880	(.804 - .963)	.006	.880	(.804 - .963)	.006	.879	(.803 - .962)	.005
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.590	(.314 – 1.108)	.101	.581	(.304 – 1.110)	.100	.574	(.300 – 1.099)	.094	.577	(.301 – 1.106)	.098
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.998	(.542 – 1.837)	.995	1.024	(.549 – 1.912)	.940	1.017	(.544 – 1.900)	.957	1.014	(.536 – 1.919)	.966

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A21.1 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage						.282			.479			.471
AKIN 1 (ref)				1.00			1.00			1.00		
AKIN 2				1.535	(.612 – 3.851)	.361	1.428	(.641 – 3.179)	.383	1.442	(.632 – 3.293)	.385
AKIN 3				2.149	(.837 – 5.521)	.112	1.629	(.733 – 3.623)	.231	1.694	(.725 – 3.957)	.224
AKI Cause			.600			.357			.733			
Hypoperfusion (ref)	1.00			1.00			1.00					
Septic	.666	(.300 – 1.480)	.319	.497	(.185 – 1.336)	.166	.731	(.335 – 1.595)	.431			
Complex	.810	(.379 – 1.729)	.585	.695	(.294 – 1.640)	.406	.910	(.436 – 1.898)	.801			
On RAS Blocker												
No (ref)	1.00			1.00						1.00		
Yes	1.270	(.550 – 2.933)	.576	1.964	(.777 – 4.964)	.153				1.311	(.561 – 3.067)	.532
GFR slope preAKI	.879	(.802 - .962)	.005				.866	(.789 - .952)	.003	.864	(.785 - .950)	.003
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.530	(.272 – 1.034)	.062	.636	(.297 – 1.364)	.245	.574	(.299 – 1.100)	.094	.529	(.271 – 1.035)	.063
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.928	(.479 – 1.799)	.826	1.326	(.638 – 2.758)	.450	1.010	(.533 – 1.913)	.976	1.139	(.574 – 2.263)	.710

Model 5 – adjusted for age, sex, Charlson Score, hypertension, and AKIN stage.

Model 6 – adjusted for age, sex, Charlson Score, hypertension, and Pre-AKI slope.

Model 7 – adjusted for age, sex, Charlson Score, hypertension, and use of RAS blockers.

Model 8 – adjusted for age, sex, Charlson Score, hypertension, and cause.

Table A21.2 AKI/CKD Group models with combined outcome of death or fall in GFR of 5mls/min or more at 6

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage			.001			.001			.001			.001
AKIN 1 (ref)	1.00			1.00			1.00			1.00		
AKIN 2	3.789	(1.832 – 7.837)	.000	3.818	(1.843 – 7.908)	.000	3.758	(1.811 – 7.798)	.000	3.823	(1.829 – 7.989)	.000
AKIN 3	2.065	(.902 – 4.729)	.086	2.061	(.898 – 4.728)	.088	2.043	(.889 – 4.697)	.092	2.116	(.912 – 4.910)	.081
AKI Cause			.486			.468			.441			.416
Hypoperfusion (ref)	1.00			1.00			1.00			1.00		
Septic	1.391	(.695 – 2.787)	.351	1.422	(.707 – 2.859)	.323	1.470	(.727 – 2.971)	.284	1.474	(.725 – 2.997)	.284
Complex	1.493	(.717 – 3.108)	.284	1.495	(.718 – 3.115)	.283	1.496	(.716 – 3.126)	.284	1.539	(731 – 3.241)	.256
On RAS Blocker												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.610	(.307 – 1.210)	.157	.613	(.308 – 1.218)	.162	.614	(.308 – 1.224)	.166	.612	(.266 – 1.405)	.247
GFR slope preAKI	.964	(.912 – 1.020)	.200	.967	(.913 – 1.025)	.261	.968	(.914 – 1.026)	.276	.968	(.914 – 1.026)	.271
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.678	(.348 – 1.319)	.252	.669	(.343 – 1.304)	.238	.667	(.341 – 1.304)	.236	.681	(.345 – 1.347)	.270
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.047	(.540 – 2.028)	.892	1.085	(.556 – 2.119)	.810	1.128	(.575 – 2.214)	.726	1.118	(.568 – 2.202)	.747

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A21.2 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
AKIN Stage						.002			.001			.002
AKIN 1 (ref)				1.00			1.00			1.00		
AKIN 2				3.775	(1.783 – 7.994)	.001	4.298	(2.012 – 9.183)	.000	3.730	(1.778 – 7.823)	.000
AKIN 3				2.026	(.867 – 4.731)	.103	2.226	(.952 – 5.208)	.065	1.858	(.786 – 4.391)	.158
AKI Cause			.604			.473			.493			
Hypoperfusion (ref)	1.00			1.00			1.00					
Septic	1.400	(.665 – 2.947)	.376	1.406	(.685 – 2.887)	.353	1.405	(.686 – 2.879)	.353			
Complex	1.366	(.629 – 2.969)	.431	1.525	(.718 – 3.239)	.272	1.492	(.706 – 3.154)	.295			
On RAS Blocker												
No (ref)	1.00			1.00						1.00		
Yes	.455	(.188 – 1.099)	.080	.632	(.272 – 1.469)	.286				.638	(.275 – 1.481)	.296
GFR slope preAKI	.961	(.904 – 1.021)	.199				.973	(.917 – 1.032)	.358	.972	(.916 – 1.030)	.334
Nadir BP < 90 Sys												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.683	(.336 – 1.389)	.292	.708	(.357 – 1.404)	.323	.719	(.361 – 1.434)	.349	.724	(.361 – 1.451)	.362
AKI on admission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.022	(.498 – 2.095)	.953	1.212	(.608 – 2.418)	.585	1.164	(.587 – 2.308)	.664	1.081	(.546 – 2.141)	.823

Model 5 – adjusted for age, sex, Charlson Score, hypertension, and AKIN stage.

Model 6 – adjusted for age, sex, Charlson Score, hypertension, and Pre-AKI slope.

Model 7 – adjusted for age, sex, Charlson Score, hypertension, and use of RAS blockers.

Model 8 – adjusted for age, sex, Charlson Score, hypertension, and cause.

Appendix 22

Multivariate logistic regression models used to explore the influence of recovery at discharge, readmission and repeat AKI in the AKI and AKI/CKD Groups using mortality at 6 months as the dependent variable.

A22.1 : AKI Group models.

A22.2 : AKI/CKD Group models.

Table A22.1 AKI group models of survivors to discharge with mortality at 6 months as the dependent variable.

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.079	(.397 – 2.932)	.882	1.185	(.426 – 3.297)	.745	1.262	(.449 – 3.547)	.659	1.002	(.338 – 2.966)	.997
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	3.702	(1.094 – 12.530)	.035	3.801	(1.114 – 12.973)	.033	3.801	(1.108–13.041)	.034	3.149	(.880 – 11.269)	.078
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	8.647	(2.507 – 29.821)	.001	9.239	(2.619 – 32.599)	.001	9.285	(2.607–33.076)	.001	8.260	(1.953–34.938)	.004

Table A22.2 AKI/CKD group models of survivors to discharge with mortality at 6 months as the dependent

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.960	(.414 – 2.2229)	.925	.900	(.384 – 2.112)	.809	.855	(.362 – 2.020)	.720	.901	(.372 – 2.183)	.817
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.545	(1.116 – 5.804)	.026	2.590	(1.131 – 5.933)	.024	2.426	(1.047 – 5.622)	.039	2.313	(.976 – 5.481)	.057
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.762	(1.162 – 6.568)	.022	2.816	(1.176 – 6.740)	.020	2.617	(1.079 – 6.347)	.033	2.422	(.976 – 6.009)	.056

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A22.1 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.984	(.327 – 2.966)	.977	1.060	(.356 – 3.158)	.916	.955	(.317 – 2.879)	.935	.991	(.334 – 2.937)	.987
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	3.245	(.904 – 11.647)	.071	3.065	(.855 – 10.986)	.085	2.862	(.781 – 10.483)	.112	3.228	(.897 – 11.616)	.073
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	7.758	(1.800 – 33.433)	.006	7.724	(1.819 – 32.793)	.006	8.044	(1.778– 6.398)	.007	8.401	(1.970–35.830)	.004

Table A22.2 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.924	(.378 – 2.254)	.861	.947	(.387 – 2.314	.904	.928	(.379 – 2.273)	.871	.909	(.370 – 2.237)	.836
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.160	(.902 – 5.171)	.084	2.327	(.976 – 5.547)	.057	2.326	(.980 – 5.518)	.055	2.428	(1.016 – 5.805)	.046
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	2.202	(.877 – 5.532)	.093	2.384	(.952 – 5.971)	.064	2.396	(.964 – 5.958)	.060	2.283	(.913 – 5.712)	.078

Model 5 – adjusted for age, sex, Charlson Score, hypertension and AKI cause.

Model 6 - adjusted for age, sex, Charlson Score, hypertension and use of RAS Blockers.

Model 7 - adjusted for age, sex, Charlson Score, hypertension and AKI present on admission.

Model 8 - adjusted for age, sex, Charlson Score, hypertension and AKIN Stage.

Appendix 23

Multivariate logistic regression models used to explore the influence of recovery at discharge, readmission and repeat AKI in the AKI and AKI/CKD Groups using failure to recover function after 6 months according to the three definitions explored in the study as the dependent variables

A23.1 : AKI Group models for a fall in eGFR of 5mls/min or more after 6 months.

A23.2 : AKI/CKD Group models for a fall in eGFR of 5mls/min or more after 6 months.

A23.3 : AKI Group models for a fall in eGFR of 10mls/min or more after 6 months.

A23.4 : AKI/CKD Group models for a fall in eGFR of 10mls/min or more after 6 months.

A23.5 : AKI Group models for a fall in eGFR of 25% or more after 6 months.

A23.6 : AKI/CKD Group models for a fall in eGFR of 25% or more after 6 months.

Table A23.1 AKI Group models of survivors to discharge with a fall in eGFR of 5mls/min or more at follow up as

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.339	(.177 - .651)	.001	.346	(.179 - .670)	.002	.347	(.179 - .671)	.002	.366	(.188 - .715)	.003
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.723	(.377 – 1.387)	.330	.777	(.400 – 1.508)	.456	.770	(.396 – 1.497)	.440	.827	(.412 – 1.664)	.595
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.599	(.216 – 1.662)	.325	.645	(.229 – 1.821)	.408	.655	(.232 – 1.854)	.426	.713	(.241 – 2.110)	.541

Table A23.2 AKI/CKD Group models of survivors to discharge with a fall in eGFR of 5mls/min or more at follow up

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.178	(.082 - .390)	.000	.178	(.081 - .390)	.000	.173	(.078 - .384)	.000	.160	(.071 - .362)	.000
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.305	(.633 – 2.694)	.471	1.299	(.629 – 2.686)	.480	1.319	(.628 – 2.768)	.464	1.321	(.628 – 2.779)	.463
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.200	(.480 – 2.998)	.696	1.197	(.479 – 2.993)	.700	1.209	(.477 – 3.068)	.689	1.255	(.491 – 3.207)	.635

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A23.1 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.352	(.178 - .696)	.003	.366	(.187 - .715)	.003	.389	(.178 - .853)	.018	.363	(.185 - .714)	.003
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.806	(.393 – 1.652)	.555	.859	(.424 – 1.742)	.674	1.020	(.982 – 1.060)	.297	.834	(.412 – 1.686)	.612
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.697	(.233 – 2.083)	.518	.744	(.250 – 2.216)	.596	1.020	(.982 – 1.060)	.310	.718	(.241 – 2.137)	.551

Table A23.2 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.154	(.067 - .353)	.000	.161	(.071 - .367)	.000	.146	(.062 - .343)	.000	.163	(.070 - .377)	.000
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.329	(.625 – 2.826)	.459	1.346	(.637 – 2.843)	.436	.978	(.942 – 1.016)	.251	1.450	(.670 – 3.136)	.345
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.242	(.476 – 3.242)	.658	1.206	(.468 – 3.108)	.698	.977	(.941 – 1.015)	.230	1.242	(.469 – 3.293)	.663

Model 5 – adjusted for age, sex, Charlson Score, hypertension and AKI cause.

Model 6 - adjusted for age, sex, Charlson Score, hypertension and use of RAS Blockers.

Model 7 - adjusted for age, sex, Charlson Score, hypertension and AKI present on admission.

Model 8 - adjusted for age, sex, Charlson Score, hypertension and AKIN Stage.

Table A23.3 AKI Group models of survivors to discharge with a fall in eGFR of 10mls/min or more at follow up as

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.330	(.167 - .651)	.001	.336	(.170 - .666)	.002	.334	(.168 - .665)	.002	.359	(.178 - .723)	.004
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.787	(.404 – 1.533)	.481	.830	(.423 – 1.630)	.589	.805	(.407 – 1.591)	.532	.980	(.478 – 2.012)	.957
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.579	(.194 – 1.732)	.328	.613	(.203 – 1.851)	.386	.643	(.211 – 1.963)	.438	.828	(.258 – 2.653)	.750

Table A23.4 AKI/CKD Group models of survivors to discharge with a fall in eGFR of 10mls/min or more at follow

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.206	(.084 - .502)	.001	.208	(.085 - .509)	.001	.202	(.081 - .499)	.001	.201	(.080 - .503)	.001
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.905	(.814 – 4.462)	.138	1.856	(.789 – 4.368)	.156	1.904	(.794 – 4.565)	.149	1.940	(.805 – 4.678)	.140
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.429	(.506 – 4.037)	.501	1.415	(.498 – 4.017)	.515	1.431	(.495 – 4.139)	.509	1.452	(.494 – 4.267)	.498

Model 1 – unadjusted.

Model 2 – adjusted for age.

Model 3 – adjusted for age and sex.

Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A23.3 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.359	(.175 - .735)	.005	.358	(.177 - .722)	.004	.333	(.148 - .749)	.008	.356	(.174 - .726)	.005
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.924	(.439 – 1.945)	.835	.961	(.464 – 1.990)	.915	.984	(.428 – 2.262)	.971	1.000	(.481 – 2.081)	.999
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.867	(.264 – 2.849)	.814	.807	(.250 – 2.612)	.721	.702	(.183 – 2.700)	.607	.843	(.258 – 2.751)	.777

Table A23.4 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.210	(.083 - .532)	.001	.184	(.072 - .467)	.000	.172	(.065 - .455)	.000	.222	(.086 - .571)	.002
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.707	(.691 – 4.217)	.246	1.898	(.786 – 4.585)	.154	1.758	(.704 – 4.390)	.227	2.292	(.909 – 5.782)	.079
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.175	(.383 – 3.602)	.778	1.546	(.520 – 4.593)	.433	1.512	(.503 – 4.549)	.462	1.514	(.492 – 4.656)	.470

Model 5 – adjusted for age, sex, Charlson Score, hypertension and AKI cause.

Model 6 - adjusted for age, sex, Charlson Score, hypertension and use of RAS Blockers.

Model 7 - adjusted for age, sex, Charlson Score, hypertension and AKI present on admission.

Model 8 - adjusted for age, sex, Charlson Score, hypertension and AKIN Stage.

Table A23.5 AKI Group models of survivors to discharge with a fall in eGFR of 25% or more at follow up as the

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.056	(.013 - .244)	.000	.054	(.012 - .238)	.000	.052	(.012 - .232)	.000	.054	(.012 - .244)	.000
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.859	(.382 – 1.930)	.712	.939	(.411 – 2.147)	.882	.881	(.379 – 2.048)	.769	.947	(.392 – 2.293)	.905
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.793	(.214 – 2.940)	.728	.896	(.236 – 3.396)	.871	.983	(.251 – 3.855)	.980	1.080	(.259 – 4.507)	.916

Table A23.6 AKI/CKD Group models of survivors to discharge with a fall in eGFR of 25% or more at follow up as

	Model 1 (Unadjusted)			Model 2			Model 3			Model 4		
	OR	95% C. I.	P	OR	95% C.I.	P	OR	95% C.I.	P	OR	95% C.I.	P
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.208	(.076 - .567)	.002	.210	(.076 - .576)	.002	.200	(.071 - .558)	.002	.194	(.069 - .547)	.002
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.674	(.645 – 4.349)	.290	1.609	(.614 – 4.213)	.333	1.609	(.603 – 4.293)	.343	1.621	(.606 – 4.334)	.336
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.187	(.359 – 3.931)	.778	1.170	(.351 – 3.903)	.799	1.151	(.338 – 3.917)	.822	1.223	(.354 – 4.222)	.750

Model 1 – unadjusted.
Model 2 – adjusted for age.
Model 3 – adjusted for age and sex.
Model 4 – adjusted for age, sex, Charlson Score and hypertension.

Table A23.5 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.052	(.011 - .242)	.000	.053	(.012 - .242)	.000	.064	(.014 - .296)	.000	.050	(.011 - .232)	.000
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.807	(.313 – 2.081)	.657	.981	(.401 – 2.400)	.966	.871	(.328 – 2.318)	.783	.962	(.382 – 2.422)	.934
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.248	(.289 – 5.397)	.766	1.133	(.268 – 4.782)	.865	1.107	(.248 – 4.952)	.894	1.140	(.257 – 5.057)	.863

Table A23.6 continued.

	Model 5			Model 6			Model 7			Model 8		
	OR	**95% C. I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**	**OR**	**95% C.I.**	**P**
Recovered at d/c												
No (ref)	1.00			1.00			1.00			1.00		
Yes	.192	(.067 - .549)	.002	.195	(.069 - .552)	.002	.180	(.062 - .521)	.002	.217	(.075 - .623)	.005
Readmission												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.564	(.579 – 4.226)	.378	1.661	(.617 – 4.474)	.315	1.491	(.546 – 4.070)	.436	1.883	(.683 – 5.192)	.221
Repeat AKI												
No (ref)	1.00			1.00			1.00			1.00		
Yes	1.110	(.313 – 3.931)	.872	1.190	(.341 – 4.149)	.785	1.257	(.361 – 4.378)	.719	1.292	(.364 – 4.590)	.692

Model 5 – adjusted for age, sex, Charlson Score, hypertension and AKI cause.

Model 6 - adjusted for age, sex, Charlson Score, hypertension and use of RAS Blockers.

Model 7 - adjusted for age, sex, Charlson Score, hypertension and AKI present on admission.

Model 8 - adjusted for age, sex, Charlson Score, hypertension and AKIN Stage.