Chronic Kidney Disease: Comparing Trends in Primary and Secondary Care

Masters by Research Thesis

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ABSTRACT

Background

Chronic kidney disease is a serious and complex medical condition which affects a significant number of people in the UK. Guidance from NICE currently recommends referral of CKD patients at stages G4-5 but the guidelines themselves are not based on strong evidence.

Objectives

To compare progression rates for CKD G3 patients in primary and secondary care groups to determine whether or not earlier referral should be supported.

Methods

We categorised 1,345 patients with stage G3 CKD into primary and secondary care and further subdivided secondary care into non-renal and renal groups. Baseline differences between primary and secondary care groups were explored via Student t-tests and chi-squared analyses. Baseline exploratory analysis of potential relationships between eGFR and other variables was done via simple linear and multiple regression modelling. Longitudinal trends were described using linear mixed effects modelling and chi-squared tests were used to compare differences in all-cause mortality and end-stage renal disease rates.

Results

The overall trend was an improvement in renal function by 1.26 ml/min/1.73 m^2 per year over an average follow up period of 2.84 years. Trends for primary, non-renal secondary and renal secondary care were 1.84, 0.87 and -0.17 ml/min/1.73 m^2 per year respectively. The relative risk of all-cause mortality was 2.49 times greater for secondary care patients compared to primary care ($p<0.001$).

Conclusions

The management of CKD G3 patients in primary care is able to defer renal decline for at least 2.84 years. Most patients who are at higher risk of progression are already identified and referred to secondary care. Overall this supports current NICE guidelines on referral.

CHAPTER 1: INTRODUCTION

This chapter aims to introduce and explore the literature surrounding stage 3 chronic kidney disease (CKD) especially with regards to the impact that the condition has on health. We then investigate the evidence underpinning UK guidelines on CKD in order to outline our rationale that the evidence underpinning them, especially those relating to referral, is poor and that research on which care setting is best for stage 3 CKD patients is currently lacking.

1.1 Definition of Chronic Kidney Disease

Chronic kidney disease, previously known as chronic renal failure or chronic renal insufficiency, is defined as "abnormalities of kidney structure or function, present for more than 3 months, with implications for health"[1]. This is the international definition first used by the Kidney Disease Improving Global Outcomes (KDIGO) initiative in 2012 and that which is currently used by the National Institute of Clinical Excellence (NICE)[1,2]. It encompasses all people identified as having a glomerular filtration rate (GFR) below 60 ml/min/1.73 m^2 on more than one occasion separated by a minimum of 90 days plus anyone with markers of kidney damage regardless of their GFR measurements.

1.2 Classification of Chronic Kidney Disease

CKD is classified into categories by both glomerular filtration rate (GFR) and albumin to creatinine ratio (ACR) into five and three groups respectively[1,2].

GFR category, denoted by the letter 'G', has thresholds ranging from ≥ 90 ml/min/1.73 m^2 for G1 to < 15 ml/min/1.73 m^2 for G5. As mentioned above, the threshold for diagnosis in the absence of additional markers of kidney damage is 60 ml/min/1.73 m^2; below which

people would fall into a classification of G3, G4 or G5. Category G3 has been further subdivided into 3a (GFR 45-59 ml/min/1.73m^2) and 3b (30-44 ml/min/1.73m^2) to underline the higher risk of adverse outcomes for those in the latter category. For those with a classification of G1 or G2, additional markers of kidney disease must be present. Accepted markers include 'albuminuria (ACR more than 3 mg/mmol), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, and a history of kidney transplantation.'

As more accurate measurements of GFR are not practical in every day clinical practice, estimated GFR (eGFR) values calculated from serum creatinine measurements are usually used to categorise patients instead. Table 1 outlines the full classification by GFR below.

Table 1: GFR Categories in CKD (KDIGO Classification)

GFR Category	GFR (ml/min/1.73 m^2)	Terms
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

ACR category, denoted by the letter 'A' was introduced into international classification system in 2012 by KDIGO. This classification by ACR ranges from A1 (ACR < 3 mg/mmol) to A3 (> 30 mg/mmol) and allows patients to be delineated by increasing albuminuria and therefore by increasing risk of CKD progression. Table 2 outlines the categorisation by ACR and its equivalent investigation results below.

Table 2: ACR Categories in CKD (KDIGO Classification)

Category	AER (mg/24 hours)	ACR (approximate equivalent) (mg/mmol)	(mg/g)	Terms
A1	< 30	< 3	< 30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased
A3	> 300	> 30	> 300	Severely increased

1.3 Epidemiology of Chronic Kidney Disease

1.3.1 Incidence and Prevalence of CKD

The narrative of chronic kidney disease is frequently described as 'silent' in the early stages of the disease, with cases of CKD often identified opportunistically from routine blood tests as opposed to the specific investigation of symptomatic patients. The most common cause of CKD worldwide is diabetes mellitus so it is no surprise that for CKD some of the highest prevalence rates are often found in more developed countries such as the USA[3]. More than 20,000,000 Americans have CKD which is equivalent to more than 10% of the population with suggested rates estimated to be as high as 16.8%[4]. Similar figures have been determined in UK populations with 13% of the total population estimated to have CKD stages 3-5[5]. There is strong evidence showing rising CKD prevalence in the USA from 1988-1994 to 1999-2006; which may be explained in part by increasing prevalence rates of diabetes mellitus and hypertension[6]. However, figures from the National Health and Nutrition Examination Survey (NHANES) 2007-2012 and from the Health Survey for England (HSE) 2010 support an overall reduction in prevalence rates for America and the UK in more recent years[4,5] and for all subgroups by age and sex with the exception of the subgroup of men aged 65-74 years old whose prevalence increased[5]. Despite this small improvement in prevalence figures, CKD still presents a large problem with regards to its undiagnosed burden of disease[7]. In the UK only 4.3% of UK adults had a diagnosis of CKD in 2010-2013[8,9] which when compared to the aforementioned 13% estimated prevalence rate is an underdiagnosis of almost 9%. This may have future implications especially given the expected rise in global CKD prevalence from predictions of the increasing prevalence of risk factors such as diabetes, hypertension and cardiovascular disease in developing countries[3].

There are several demographic risk factors which influence the likelihood of developing chronic kidney disease including age, sex and ethnicity. Cross-sectional studies have

demonstrated that prevalence of CKD increases exponentially with age[6,10,11], which has prompted debate over whether or not chronic kidney disease is a pathological phenomenon or is conversely a resulting part of the normal ageing process. However regardless, this association between increasing age and increasing CKD prevalence is important in light of an ageing population which is likely to increase the existing burden of chronic kidney disease. Prevalence of chronic kidney disease is higher overall in women compared to men with an estimated 25% of women and 20% of men aged 65-74 thought to have CKD worldwide. The most recent figures from the UK show a 1% difference in prevalence between men and women demonstrated by figures of 6% and 7% for men and women respectively[5]. On the other hand, the relationship between ethnicity and CKD development is not as clear cut. Compared to white populations, non-white ethnic groups have lower or similar prevalence rates of CKD but may be at higher risk of progressive disease or adverse renal events[12]. This is especially true for black ethnic groups and may be explained by genetic differences between different races or linked to other confounding factors such as socioeconomic status and reduced access to healthcare[12–15].

The relationship between smoking status and CKD has been better researched and documented than for other lifestyle factors. There is good evidence to support cigarette smoking as a risk factor for developing CKD in both diabetic and non-diabetic patients[16–18]. The relative risk of CKD development for current smokers compared to the total population is 2.5 times higher and has been shown to have an attributable risk of 31% according to a prospective study in 2003[16]. In patients with type 2 diabetes the underlying mechanism for increasing CKD development risk in smokers is linked to the development of microalbuminuria. This has been independently and significantly associated with CKD development in patients with either a previous or current smoking history[17].

1.3.2 Incidence and Prevalence of End-Stage Renal Disease

End-stage renal disease (ESRD), a term used synonymously with renal failure, is the final stage in CKD and quantitatively refers to when GFR falls below 15 ml/min/1.73 m^2. It marks a patient's necessity for life-saving renal replacement therapy (RRT) in the interim period before potential renal transplantation. Diabetes, hypertension and glomerulonephritis are the most common underlying causes of CKD which lead to renal failure with incidence rates of 153, 99, and 23.7 cases per million people respectively[19]. However, the majority of patients with CKD will never reach ESRD outcompeted instead by the risk of death which may result from cardiovascular complications. For patients with stage G3 CKD the proportion who reach renal failure is low as demonstrated by incidence rates of 1.3-2% after five years[20,21]. This increases to 4% after ten years[20] but may be higher as one study published a figure of 34.6% in a non-Caucasian population[22].

Risk factors associated with the development of renal failure include being of non-white ethnicity and the underlying cause for CKD. We have known for a long time that prevalence of ESRD is higher in non-white populations[23], in spite of reduced prevalence rates for CKD itself. This higher incidence of progression is thought to be attributed to an increased prevalence of risk factors such as type 2 diabetes in South Asians and hypertension in Afro-Caribbeans; as well as a greater prevalence of diseases which are of higher risk of progression e.g. chronic interstitial nephritis and focal glomerulosclerosis. However, compared to Caucasians there is a relative lack of knowledge with regards to the prevalence of early stage CKD in non-white ethnic groups.

The lifestyle factors obesity, physical inactivity and smoking have also been linked to an increased risk of developing ESRD[18]. Patients with self-reported low levels of physical activity are twice as likely to develop ESRD or die from CKD-related causes. In the same cross-sectional study, morbid obesity was shown to have a similar albeit weaker relationship

which was at least partly influenced by the presence of the co-morbidities diabetes and hypertension. However, although these associations exist following adjustment for many confounding factors, we cannot disregard the fact that CKD itself can reduce a person's physical activity and that these risk factors are also directly linked with cardiovascular risk. There is evidence to support smoking cigarettes as a risk factor for developing CKD in both diabetic and non-diabetic patients[16–18]. The number of cigarettes smoked potentially exhibits a dose-response relationship with risk of ESRD and CKD-related death whereby the increasing number of cigarettes smoked per day increased the combined risk[18]. However, this association did not persist in separate analysis focusing on ESRD which supports the theory that smokers are less likely to reach ESRD and instead die of cardiovascular complications to which smoking is a major risk factor.

Worldwide, there are 2 million patients in receipt of treatment for ESRD of which more than 80% are treated in more affluent countries including the USA, Japan, Germany, Brazil and Italy[24]. This pattern is likely to be explained by having ageing populations with high prevalences of hypertension and diabetes alongside unrestricted access to well-structured healthcare systems. Projections based on the increasing ageing populations in both India and China predicts a disproportionate rise in the incidence of ESRD[3]. Overall, this would lead to a greater number of deaths due to the lack of treatment resources and facilities for ESRD; an issue currently problematic for lower and middle income countries worldwide[24].

1.4 Global Burden of CKD and its Complications

In 2010 the Global Burden of Disease Study ranked CKD 18th in the list of causes of total number of global deaths; a position rise of 9 places from its 27th position ranking in 1990. The age-standardised annual death rate increased from 15.7 per 100,000 to 16.3 per

100,000 over the 2 decade period; an 82% increase in years of life lost due to premature death[25]. In CKD, the most common causes of mortality are due to cardiovascular events such as myocardial infarction or stroke but CKD itself has many complications beyond those of a cardiovascular nature. These include but are not limited to anaemia, electrolyte imbalances and acid-base disturbance; all of which contribute to the overall costs of CKD and its complications which was estimated to be between £1.44 to £1.45 billion pounds in 2009-2010 (approximately 1.3% of the NHS total budget)[26].

1.4.1 Vascular Risk

It was first pointed out in 1974 by Lindner et al.[27] that CKD patients suffer from an increased risk of cardiovascular morbidity and mortality through the accelerated development of atherosclerosis, a disease process whereby vascular damage is caused by cholesterol and fat deposition within the walls thereby narrowing the arteries throughout the body. The potential cardiovascular complications from this process include ischaemic heart disease, myocardial infarction (MI), stroke, and peripheral vascular disease. CKD patients may also suffer from arteriosclerosis followed by the possible development of structural heart abnormalities which may culminate in heart failure[28] which is in fact the most common cardiovascular complication in CKD patients[29]. Vascular disease itself is also a risk factor for CKD progression, a relationship that will be explored further in section 2.1.3.

In recent years it has become widely accepted that CKD itself is an independent risk factor for cardiovascular disease, an association often explained by the presence of several "traditional" and/or "non-traditional" risk factors. "Traditional" risk factors are those which are linked to CVD in "normal" patients and include older age, diabetes, hypertension and dyslipidaemia. "Non-traditional" risk factors are more specific to CKD patients. Examples

include volume overload, metabolic abnormalities, albuminuria and anaemia to name a few[28].

There is substantial evidence showing that the prevalence of CVD in CKD patients is directly correlated with the CKD severity and exhibits a dose-response relationship in this regard. Evidence from meta-analysis also shows that once GFR declines below 60 ml/min/1.73 m^2, the risk of death due to cardiovascular causes increases exponentially[30], a pattern that has also been observed independently with regards to stroke risk[31]. In patients receiving renal replacement therapy, mortality rates are 10-20 times higher than those without CKD following adjustment by gender and age[32]. Unsurprisingly, having a prior history of cardiovascular event puts patients at high risk of subsequent mortality when compared to patients with no previous history[33].

The development of heart failure is common in the pathogenesis of CKD and the prevalence is as high as 40% in CKD patients[34]. Compared to people with normal levels of renal function, adults with CKD (eGFR less than 60 ml/min/1.73 m^2) are at three times greater risk of developing heart failure[35]. This association is particularly pertinent for those starting renal replacement therapy, as the presence of heart failure at this stage is an independent predictor of increased mortality in both the short[36] and long term[37,38]. In fact overall, the three year survival rate of patients with ESRD who are diagnosed with heart failure is as low as 13% from the date of diagnosis[39].

1.4.2 Anaemia

Interstitial cells within the kidneys are responsible for the synthesis of erythropoietin, a hormone which acts within red bone marrow to stimulate the proliferation of red blood cells. With increasing CKD severity, synthesis of this hormone is reduced which typically

causes anaemia of a normochromic, normocytic variety. This anaemia is also seen in other chronic diseases but in CKD concurrent iron deficiency is common due to either bleeding or poor dietary intake which, alongside the "functional iron deficiency" state caused by inhibition of iron release from the liver, may cause a hypochromic, microcytic picture instead.

Anaemia itself may be quantitatively defined as a haemoglobin level below a certain threshold depending on the cut-offs used (see Box 1). Thus estimated total prevalence rates are highly variable depending on the clinical definition ranging from 2.9% using the NICE definition to 13.8% with the KDIGO definition within the same study[40].

Anaemia Definitions

KDIGO[1]:

- men and postmenopausal women <13g/dl
- premenopausal women <12 g/dl

K/DOQI[81]:

- men and postmenopausal women <12 g/dl
- premenopausal women <11 g/dl

Other / NICE[2]:

- Hb <11 g/dl

Box 1: Clinical definitions of anaemia from the WHO, KDOQI and NICE

However, regardless of the definitions used, as GFR declines so do haemoglobin levels leading to increasing prevalence of anaemia with increasing CKD stage in both diabetic and non-diabetic CKD patients[41]. Figures from the NHANES III study show that prevalence is two-fold greater in people with CKD compared to those without: 15.4% prevalence to 7.6% respectively[41]. The risk of developing anaemia is also greater for those with diabetes, demonstrated by the prevalence of diabetes being almost two times greater in patients with low haemoglobin compared to those with normal levels[42]. In ESRD, 68% of patients are anaemic[43] which not only reduces quality of life[44] but also increases incidence rates of heart failure[37] and myocardial infarction[45]. If left untreated, anaemia can have dire consequences for all CKD patients and has been associated with higher rates of hospitalisation and mortality following both renal and cardiovascular events[46,47].

1.4.3 Metabolic Acidosis and Metabolic Bone Disease

In CKD, as renal function declines and nephron loss increases, the tight control and regulation of acid-base balance can go awry. Normally, homeostasis of acid-base balance involves 3 main processes: intra and extracellular buffering, alveolar ventilation, and renal excretion of hydrogen (H^+) ions. In CKD, it is the latter of these processes which when impaired leads to the retention of H^+ and therefore metabolic acidosis. The underlying mechanism for this impairment is mostly due to an overall reduction in urinary ammonia production which acts as a buffer for H^+ by combining with it to form ammonium which can then be excreted; although less commonly patients with CKD may also suffer from the urinary loss of bicarbonate ions[48]. In chronic metabolic acidosis, the reabsorption of bone releases base to buffer the excess of acid by releasing calcium, phosphate and carbonate which can later lead to osteopoenia and renal osteodystrophy[49]. Besides metabolic bone disease, chronic acidosis may also lead to a number of other deleterious consequences including muscle catabolism, systemic inflammation and reduced albumin synthesis [50–52] to name but a few.

Metabolic acidosis has been shown to increase the risk of progression in non-dialysis dependent patients with CKD[53]. Evidence comes from several observational studies which have demonstrated an association between reduced serum bicarbonate levels and adverse renal events, defined as progression to ESRD, eGFR decline of 50% or a predefined reduction in eGFR compared to baseline values depending on the study[53–55]. Low serum bicarbonate levels are also significantly associated with increased mortality rates in both non-dialysis dependent[54,56,57] and dialysis dependent patients[58]. Evidence from the Modification of Diet in Renal Disease (MDRD) study also shows an increased risk of renal failure for patients with lower serum bicarbonate levels.

1.4.4 Volume Overload

Fluid overload is a common complication for patients especially in the later stages of chronic kidney disease and is closely linked to disturbances of sodium balance. There are two underlying mechanisms which may predispose a patient to fluid overload: either a reduction in the kidney's ability to concentrate or dilute urine or the abnormal handling of solutes leading to the retention of water. With regards to the former mechanism, the dysregulation of water balance can occur independently of sodium concentration. In normal renal function, urine concentration is controlled by the secretion of anti-diuretic hormone released from the posterior pituitary which promotes the retention of water by increasing its reabsorption in the collecting ducts. Normal production of this hormone is unchanged in CKD but as renal function deteriorates the kidneys become less able to dilute or concentrate urine which eventually leads to the development of isothenuria, whereby urine osmolality becomes equal to that of protein-free plasma. At any stage of CKD, if intake of water exceeds the ability of the kidneys to excrete it, then fluid overload may occur and can lead to the development of further complications such as peripheral oedema, pulmonary oedema and congestive heart failure. Overload due to poor excretion of sodium does not normally become an issue until GFR deteriorates beyond the threshold of 25 ml/min/1.75 m^2 [59].

There is extensive evidence which illustrates the associated risk of mortality with fluid overload in patients receiving dialysis[60,61] likely resulting from the development of cardiorenal syndrome in which fluid overload causes hypertension, puts extra strain on the heart and predisposes to heart failure later on[62]. The association of increased mortality is also present in late-stage predialysis patients in terms of both all-cause and cardiovascular mortality[63]. However, although it is accepted that fluid overload develops early on in CKD, evidence from this subgroup of patients especially those with early stage CKD is lacking.

1.4.5 Electrolyte Disturbances

The dysfunction of homeostatic mechanisms which control electrolyte balance may lead to abnormalities in serum sodium and potassium levels. Most commonly this is due to impaired water homeostasis which can cause both high (hypernatraemia) and low sodium levels (hyponatraemia), although hypernatraemia is a lot less common and only tends to happen when fluid intake is reduced alongside intercurrent illness. Normally compensatory mechanisms which are external to the renal system are able to maintain the balance of electrolytes in the face of deteriorating renal function so imbalances are not common until the later stages of CKD (GFR < 10-25 ml/min/1.73 m^2)[64].

Hyponatraemia is typically caused by the dilutional effect of fluid overload, the mechanisms of which have been mentioned above, but may also be a side effect of diuretic use especially thiazide diuretics. A low serum sodium level is an independent predictor of increased mortality and increased length of hospital admission in hospitalised patients without CKD[65] but evidence from CKD patients is limited. Waikar et al.[66] demonstrated a significant association between lower serum sodium levels and increased risk of all-cause death in CKD patients receiving haemodialysis, although this was not significant when analysis was restricted to cardiovascular mortality only. Hyponatraemia also increases the risk of infection leading to hospitalisation in haemodialysis patients[67] but there is little to no evidence exploring hypernatraemia in dialysis patients. Despite this, in non-dialysis patients serum sodium levels have been shown to exhibit a U-shaped relationship with mortality which means that high sodium levels are also harmful[68].

With regards to potassium homeostasis, hyperkalaemia may result from reduced potassium excretion which decreases proportionately to GFR decline, although extra-renal compensatory mechanisms may be able to maintain potassium homeostasis at eGFR levels as low as 10 ml/min/1.73 m^2 [59]. Hyperkalaemia itself is a potentially life-threatening medical

condition that can cause dangerous cardiac arrhythmias that may lead to death in both CKD non-CKD patients. In CKD patients, hyperkalaemia is most commonly caused by interference in the renin-angiotensin-aldosterone system, often as a side-effect of medical intervention to reduce risk of progression with the use of blood pressure (BP) controlling drugs such as ACE inhibitors, angiotensin receptor blockers and potassium-sparing diuretics or aldosterone antagonists[69,70], but my also result from potassium shift into the extracellular space resulting from metabolic acidosis[71]. As CKD progresses and GFR falls, the odds of developing hyperkalaemia increase alongside an increasing odds of mortality[72]. It is associated with an increased risk of death in hospitalised patients and has also been shown to be significantly more prevalent in patients with CKD than the general population: prevalence up to 40-50% compared to 2-3% respectively[73].

1.4.6 Vitamin D and Secondary Hyperparathyroidism

The kidneys play an important role in vitamin metabolism; converting 25(OH)D into its active form $1,25(OH)_2D$. In turn, $1,25(OH)_2D$ helps to regulate bone metabolism through its effects to promote an increase in serum calcium by the stimulation of bone osteoclastic activity, absorption in the small intestine, reabsorption in the distal convoluted tubules of the kidneys and suppression of the parathyroid glands[74]. In chronic kidney disease, the pathological development of secondary hyperparathyroidism results from elevated fibroblast growth factor 23 (FGF-23) which leads to a reduction in $1,25(OH)_2D$ and thus reduction in serum calcium levels. Low circulating serum calcium then promotes the synthesis and secretion of parathyroid hormone which can culminate in the development of secondary hyperparathyroidism[75]. As with all previously mentioned complications of CKD, the prevalence of secondary hyperparathyroidism increases with declining renal function as can be shown by a prevalence of 40-80% for patients with stages 3-4 which increases to 95%

for those with stage 5[74]. High serum calcium and phosphorous levels due to secondary hyperparathyroidism are also associated with vascular calcification which itself causes increased morbidity and mortality. It is, however, worth noting that high levels of parathyroid hormone are often present in the absence of abnormal calcium and/or phosphate levels and can be detected in the early stages of CKD: 12% of patients with eGFR greater than 80 ml/min/1.73 m^2 and 56% of those with eGFR less than 60 ml/min/1.73 m^2 [76].

1.5 Evolution of Relevant CKD Guidelines

It is widely accepted within the renal specialist community that recommendations made by NICE guidelines are not based on particularly strong evidence. The following section aims to investigate the relevant guidelines and the evidence underpinning them by exploring their evolution from 2008 to 2014; focusing on the management and interventions aimed to assist in the amelioration of progressive decline in renal function and its consequences (e.g. bone metabolism problems).

1.5.1 Who should be tested?

Guidelines 1.1.27-1.1.29 focus on which patients should be candidates for CKD testing. Recommendations amended from 2008 promote regular testing for at risk patients using known nephrotoxic medications such as lithium, non-steroidal anti-inflammatory drugs (NSAIDs), cyclosporin or tacrolimus, although no evidence was reviewed to underpin this guideline instead relying on advice from the British National Formulary to provide guidance on the frequency of testing[2]. Following a review of the evidence on potential risk factors for progression, a new guideline 1.1.28 (see Box 2 below) was added in 2014 and lists the risk factors, the presence of which would support testing for CKD. The evidence reviewed was

based mostly on several large-scale cross-sectional studies and a few cohort studies but no randomised controlled trials (RCT)[2]. Cross-sectional studies of note include the American NHANES III[77], Australian Ausdiab study[11] and a large Norwegian study[10] using data from the HUNT II study[78]. Guideline 1.1.29 (see Box 2) was amended to outline risk factors for which evidence supporting progression was deemed to not be strong enough to recommend testing e.g. gender, ethnicity and obesity (without metabolic syndrome)[2]. However, whilst conclusions regarding gender[10,11,77], ethnicity[17,77] and obesity[18,79] were inconsistent between studies, the studies reviewed to examine the relationship between age and CKD all support increasing age as a risk factor[10,11,77]. In fact, there is evidence which shows 93% of CKD stages 3-5 can be identified from screening people either greater than 55 years old, hypertensive or diabetic[80]. The recommendation to include age in guideline 1.1.29 instead of 1.1.28 is therefore unsupported by the evidence.

1.1.28 Offer testing for CKD using eGFRcreatinine and ACR to people with any of the following risk factors:

- diabetes
- hypertension
- acute kidney injury (see recommendation 1.3.9)
- cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
- structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
- multisystem diseases with potential kidney involvement – for example, systemic lupus erythematosus
- family history of end-stage kidney disease (GFR category G5) or hereditary kidney disease
- opportunistic detection of haematuria **[new 2014]**

1.1.29 Do not use age, gender or ethnicity as risk markers to test people for CKD. In the absence of metabolic syndrome, diabetes or hypertension, do not use obesity alone as a risk marker to test people for CKD. **[2008, amended 2014]**

Box 2: NICE Guidelines on who should be offered CKD testing from CG182

1.5.2 Classification

As previously mentioned NICE currently recommends the use of a 5 stage classification system which was initially conceived in 2002 by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI)[2,81]. The subdivision of stage 3 into 3a (GFR 45-59 ml/min/1.73m^2) and 3b (30-44 ml/min/1.73m^2) was a change first suggested by NICE in 2008 and later incorporated into the KDIGO guidelines in 2012[1,2]. With evidence supporting proteinuria as an important risk factor for CKD progression, 2008 NICE guidelines also recommended the use of the suffix 'P' to signify significant proteinuria at any stage, defined as ACR >30 mg/mmol or PCR > 50 mg/mmol, but this has since been superseded by the ACR categories of staging recommended in the 2012 KDIGO report and later adopted by NICE in 2014[1,2]. This followed increasing evidence for the now widely accepted view that albuminuria increases the risk of CKD progression independently of eGFR values.

1.5.3 Frequency of Monitoring

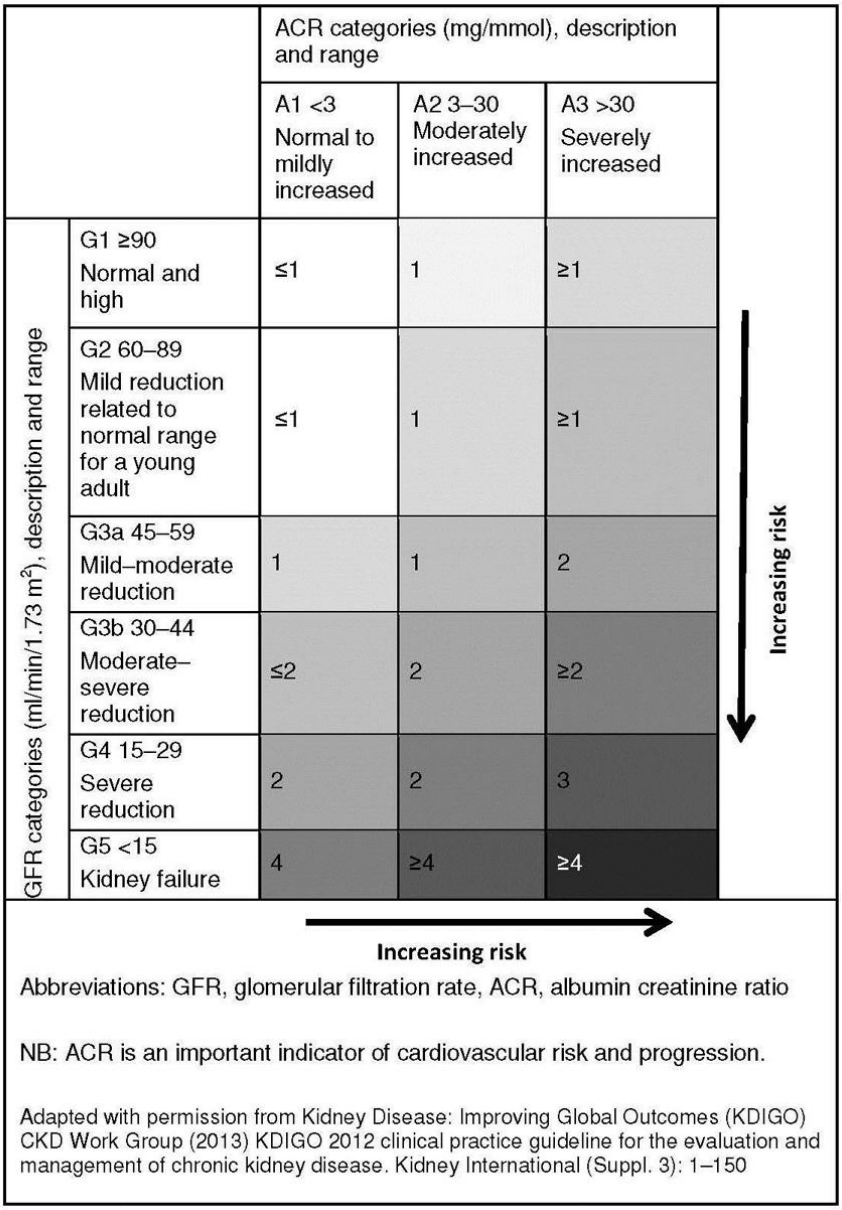
Defining progression of CKD has previously been considered a difficult problem to address, due in part to the subsequently refuted belief that CKD as a disease always followed a linear progression pattern. It is now more widely accepted that having CKD is not inherently associated with further deterioration in renal function, that many patients will not develop end-stage renal disease and that those that do often follow a non-linear trajectory. This only makes the task of identifying patients at greater risk of adverse outcomes more arduous.

Prior to 2014, the NICE guidance on the suggested frequency of monitoring kidney function in CKD was based solely on the opinions of those within the guideline development group (GDG); not on evidence (see table 3).

Table 3: Table showing the suggested frequency of monitoring according to CG73 (2008)

Measurement of eGFR: how often?		
Annually in all at-risk groups.		
During intercurrent illness and peri-operatively in all patients with CKD.		
Exact frequency should depend on the clinical situation. The frequency of testing may be reduced where eGFR levels remain very stable but will need to be increased if there is rapid progression.		
Stage	eGFR range (ml/min/1.73m^2)	Typical testing frequency
1 and 2	≥60 + other evidence of kidney disease	12 monthly
3a and 3b	30-59	6 monthly
4	15-29	3 monthly
5	<15	6 weekly

In 2014, NICE reviewed 11 retrospective cohort studies looking into progression and mortality rates for CKD and various risk factors which showed associations between progressive decline in eGFR or increasing ACR and increased mortality or risk of progression to ESRD[82–87]. This was incorporated into current 2014 guidelines (guideline 1.3) so ACR is now a risk factor for which more frequent monitoring is recommended as well as deteriorating GFR (see Figure 1). The guideline also advises that monitoring should also be determined on an individual basis according to underlying cause of CKD, comorbidities, intercurrent illness and their agreed upon management/treatment plan. However, further advice on how to incorporate these risk factors into a monitoring plan is not provided.



GFR categories (ml/min/1.73 m²), description and range	ACR categories (mg/mmol), description and range		
	A1 <3 Normal to mildly increased	A2 3–30 Moderately increased	A3 >30 Severely increased
G1 ≥90 Normal and high	≤1	1	≥1
G2 60–89 Mild reduction related to normal range for a young adult	≤1	1	≥1
G3a 45–59 Mild–moderate reduction	1	1	2
G3b 30–44 Moderate–severe reduction	≤2	2	≥2
G4 15–29 Severe reduction	2	2	3
G5 <15 Kidney failure	4	≥4	≥4

Abbreviations: GFR, glomerular filtration rate, ACR, albumin creatinine ratio

NB: ACR is an important indicator of cardiovascular risk and progression.

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

Figure 1: Table Showing the Suggested Annual Frequency of Monitoring GFR (by GFR and ACR Category) for People with CKD (NICE Guidelines adapted from KDIGO)

1.5.4 Defining Progression

Evidence reviewed in 2014 led to an update on the definition of accelerated progression which previously defined progression based on an absolute drop in eGFR by either 5 ml/min/1.73 m^2 within a twelve month period or 10 ml/min/1.73 m^2 within a five year period. It now supports the updated recommendations that define progression as either an absolute drop of 15 ml/min/1.73 m^2 in 1 year or a 'sustained decrease in GFR of 25% or

more and a change in GFR category within 12 months' as both were associated with greater mortality risk[82] and the latter an up to five-fold increased risk of progression to ESRD[83]. Although several cohort studies reviewed can support the notion that risk of ESRD disease increases with decreasing eGFR[83,85–87], the suggested 25% decrease in GFR is solely based on a single retrospective large-scale cohort study[83] as other studies could not provide a quantitative threshold at which one would be at a significantly increased risk of adverse outcomes and therefore form the basis on which to define progression.

Otherwise, the guidelines relating to the identification of progression remain largely unchanged as evidence underpinning them has not been reviewed since 2008. Both the original and current guidelines recommend using at least three GFR measurements over a period greater than three months in order to identify progression as well as repeating GFR measurements within two weeks of newly reduced GFR findings in order to exclude acute causes for deterioration. The current 2014 guideline (1.3.4) is an amalgamation of two prior 2008 recommendations whereby examples given for these causes of acute deterioration have also been reworded: 'acute kidney injury or initiation of ACE inhibitor/ARB therapy' has been replaced by 'acute kidney injury or starting renin–angiotensin system antagonist therapy.' The 2014 GDG accepted that the trajectory of an individual's GFR decline is potentially non-linear and aimed to 'highlight intervention strategies that can be chosen based on current rate of decline to slow progression' by adding 'and take this into account when planning intervention strategies' to the recommendation (1.3.6) which otherwise remains largely unaltered from 2008. Box 3 outlines the current NICE guideline on progression below.

1.3.3 Define accelerated progression of CKD as:

- a sustained decrease in GFR of 25% or more and a change in GFR category within 12 months **or**
- a sustained decrease in GFR of 15 ml/min/1.73 m^2 per year. **[new 2014]**

1.3.4 Take the following steps to identify the rate of progression of CKD:

- Obtain a minimum of 3 GFR estimations over a period of not less than 90 days.
- In people with a new finding of reduced GFR, repeat the GFR within 2 weeks to exclude causes of acute deterioration of GFR – for example, acute kidney injury or starting renin–angiotensin system antagonist therapy. **[2008, amended 2014]**

1.3.5 Be aware that people with CKD are at increased risk of progression to end-stage kidney disease if they have either of the following:

- a sustained decrease in GFR of 25% or more over 12 months **or**
- a sustained decrease in GFR of 15 ml/min/1.73 m^2 or more over 12 months. **[2008, amended 2014]**

1.3.6 When assessing CKD progression, extrapolate the current rate of decline of GFR and take this into account when planning intervention strategies, particularly if it suggests that the person might need renal replacement therapy in their lifetime. **[2008, amended 2014]**

Box 3: NICE guidelines on CKD Progression from CG182

1.5.5 Risk Factors

Guideline 1.3.7 (see Box 4) lists the risk factors for potential CKD progression and advises that patients with them should have their health optimised. Further guidance on how to do this is not directly addressed with the exception of chronic NSAID use for which additional advice is provided in guideline 1.3.8, a recommendation leftover from 2008. The addition of guideline 1.3.7 in 2014 followed a review of evidence on CKD and ethnicity, obesity, smoking, cardiovascular disease, acute kidney injury, urinary tract obstruction or chronic NSAID use but not hypertension, diabetes mellitus or proteinuria as these were already well-established risk factors for progression. Evidence from a single pooled analysis of the prospective longitudinal cohort studies (Atherosclerosis Risk in Communities and Cardiovascular Health Study) provided good evidence to support the inclusion of CVD as an independent risk factor for renal function deterioration[88]. Current 2014 guidance includes

both smoking and ethnicity in spite of the cohort and case-control studies reviewed being deemed as 'not conclusive' by the GDG. Obesity was also omitted as a risk factor because the single case-series reviewed yielded no significant results[89]. Furthermore, the inclusion of urinary outflow obstruction within the current guidelines was completely unsupported by a non-existent evidence base at that time. Zero studies were reviewed which meant that its inclusion was based instead on the clinical judgement of the GDG from which consensus agreed that untreated outflow obstruction could cause CKD.

1.3.7 Work with people who have any of the following risk factors for CKD progression to optimise their health:

- cardiovascular disease
- proteinuria
- acute kidney injury
- hypertension
- diabetes
- smoking
- African, African-Caribbean or Asian family origin
- chronic use of NSAIDs
- untreated urinary outflow tract obstruction. **[new 2014]**

1.3.8 In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible decrease in GFR. Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression. **[2008]**

Box 4: NICE guidelines on risk factors for CKD progression from CG182

1.5.6 Blood Pressure Control

Despite good evidence supporting blood pressure control as an intervention to ameliorate the risk of progression and risk of cardiovascular events, the optimal target range for patients with CKD remains poorly defined by the international community as shown by the lack of consensus between guidelines. 2002 K/DOQI guidelines[81] advise maintaining blood pressure below 130/80 mmHg whereas 2008 SIGN guidelines[90] only focus on a systolic target

of <130 mmHg if proteinuric (1g/day) and the more recent 2012 KDIGO guidelines[1] recommend a target of <140/90 mmHg. Currently the NICE guidelines[2] on blood pressure targets recommend a systolic target range of 120-139 mmHg and a diastolic target <90 mmHg for patients with CKD but a lower target of 120-129/80 mmHg is advised for patients with diabetes or ACR ≥ 70 mg/mmol. However, as no review of the evidence was conducted in 2014, these guidelines remain unchanged from 2008 and are therefore supported by literature at least 8 years old[91].

With regards to the pharmacological management options for controlling blood pressure, an extensive review of studies on antihypertensive therapy use in CKD patients was conducted in order to determine which drugs were the most cost-effective and clinically suitable options to recommend.[91] This led to the addition of guidelines 1.6.3, 1.6.4 and 1.6.5 alongside an amendment to guideline 1.6.8 in 2014 (see Box 5) which promote renin-angiotensin system (RAS) inhibition through the use of low-cost angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) or direct renin inhibitors for people with CKD and the following caveats:

- diabetes mellitus with an ACR ≥ 3mg/mmol
- hypertension with and ACR ≥30 mg/mmol
- ACR greater ≥ 70 mg/mmol

Choice of antihypertensive agent

1.6.3 Offer a low-cost renin–angiotensin system antagonist to people with CKD and:

- diabetes and an ACR of 3 mg/mmol or more (ACR category A2 or A3)
- hypertension and an ACR of 30 mg/mmol or more (ACR category A3)
- an ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease)[4]. **[new 2014]**

1.6.4 Do not offer a combination of renin–angiotensin system antagonists to people with CKD. **[new 2014]**

1.6.5 Follow the treatment recommendations in Hypertension (NICE guideline CG127) for people with CKD, hypertension and an ACR of less than 30 mg/mmol (ACR categories A1 and A2), if they do not have diabetes. **[new 2014]**

1.6.8 Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment serum potassium concentration is greater than 5.0 mmol/litre. **[2008, amended 2014]**

Box 5: NICE guidelines on antihypertensive therapy from CG182

Combinations of RAS inhibitors are not recommended by NICE guideline 1.6.4 which is supported by RCTs which reported either no significant benefit or adverse effects of combined ACE inhibitor and ARB therapy compared to ACE inhibitor or ARB therapy alone[92–94]. Otherwise guideline 1.6.5 recommends that patients should follow the standard NICE guidelines for hypertension outlined in NICE guideline CG127[95] i.e. commence an ACE inhibitor or calcium channel blocker first-line depending on age and ethnicity. The amendment to guideline 1.6.8 acknowledges the risk of hyperkalaemia in CKD often as a side effect of RAS inhibitors by not recommending the commencement of them in patients who have serum potassium greater than 5.0 mmol/l. However it was also stated that 'there was little evidence to guide formulation of recommendations' with regards to serum potassium.[91]

1.5.7 Reducing Cardiovascular Risk

Advice on the amelioration of cardiovascular risk through statin therapy is no longer included within the NICE CKD guideline (CG182)[2] but has instead been incorporated into a separate section within the recommendations on lipid modification (CG181)[96] as of 2014. Guideline 1.3.27 from this advises offering a starting dose of 20 mg of atorvastatin to reduce cardiovascular risk in patients with CKD; dose to be increased if a minimum 40% reduction in non-high density lipoprotein (HDL) cholesterol is not observed with a given GFR ≥ 30 ml/min/1.73m^2. Specialist advice should be sought when considering augmenting the dose of atorvastatin for patients within CKD GFR categories G4 and G5. Statin intolerance also welcomes specialist advice as statins are the only lipid-lowering drug recommended within the guideline[96], although there were no trials comparing statins and other lipid-lowering therapies[97]. Overall, these recommendations are underpinned by poor quality (level 1) evidence from three meta-analyses[98–100], two of which had significant heterogeneity[99,100]. With regards to slowing progression and proteinuria reduction no consensus was found between these studies but the largest study did find a significant reduction in cardiovascular risk[100] which therefore forms the basis for the recommendation of statin therapy in CKD. CKD patients are known to be at high risk of cardiovascular and cerebrovascular events and are shown to be more likely to suffer from atrial fibrillation (AF)[101]. Anti-platelet or anticoagulant therapy is normally used to reduce cardiovascular risk but in CKD patients this has its own risks as increasing CKD severity is associated with increasing risk of bleeding and Warfarin use has been linked to CKD progression. NICE attempted to answer the question of 'For people with CKD, what is the clinical and cost effectiveness of oral antiplatelet and anticoagulant therapy in reducing cardiovascular disease?' by reviewing the evidence in 2014[91]. Unfortunately there were no RCTs found which directly addressed this question as, although there were trials which explored the use of anti-platelet and anticoagulant therapy, none had been specifically designed to explore the relationship in CKD patients. Trials

reviewed therefore included CKD patients as a subgroup and most as a post-hoc analysis. Following this review of newer poor quality evidence, the original recommendation to offer anti-platelets remains unchanged from 2008 but now acknowledges the increased risk of all bleeding, not just minor (see Box 6). Apixiban may also be considered instead of warfarin in patients with eGFR 30-50 ml/min/1.73 m^2 with AF but this based on findings from a single study[102] which then supported the incorporation of guideline TA275[103] into CG182[2] as evidence was based on the same trial population.

Oral antiplatelets and anticoagulants

1.6.16 Offer antiplatelet drugs to people with CKD for the secondary prevention of cardiovascular disease, but be aware of the increased risk of bleeding. [new 2014]

1.6.17 Consider apixaban in preference to warfarin in people with a confirmed eGFR of 30–50 ml/min/1.73 m^2 and non-valvular atrial fibrillation who have 1 or more of the following risk factors:

- prior stroke or transient ischaemic attack
- age 75 years or older
- hypertension
- diabetes mellitus
- symptomatic heart failure. **[new 2014]**

Box 6: NICE guidelines on antiplatelet and anticoagulant use from CG182

1.5.8 Bone Metabolism, Osteoporosis and CKD-MBD

Guidelines 1.7.1, 1.7.2 and 1.7.3 pertain to the identification and treatment of osteoporosis in CKD patients but have not had their evidence reviewed, and therefore have not been updated, since 2008. They are underpinned by cross-sectional study evidence only which show that calcium levels decrease and phosphate levels increase in advanced CKD[76,104]. However, despite the statistical significance of these findings, they were deemed not to be clinically significant by the GDG. The guidelines reflect this by not recommending investigation of patients until eGFR drops below 30 ml/min/1.73 m^2; although treatment

with bisphosphonates is recommended if osteoporosis is diagnosed at any GFR stage (see Box 7)[91].

Bone metabolism and osteoporosis

1.7.1 Do not routinely measure calcium, phosphate, parathyroid hormone (PTH) and vitamin D levels in people with a GFR of 30 ml/min/1.73 m^2 or more (GFR category G1, G2 or G3). [2008]

1.7.2 Measure serum calcium, phosphate and PTH concentrations in people with a GFR of less than 30 ml/min/1.73 m^2 (GFR category G4 or G5). Determine the subsequent frequency of testing by the measured values and the clinical circumstances. Where doubt exists, seek specialist opinion. [2008]

1.7.3 Offer bisphosphonates if indicated for the prevention and treatment of osteoporosis in people with a GFR of 30 ml/min/1.73 m^2 or more (GFR category G1, G2 or G3). **[2008]**

Box 7: NICE guidelines on the investigation and management of bone disorders from CG182

In depth advice on managing CKD-MBD is stated to be 'beyond the scope' of NICE guidelines so doctors are advised to 'seek advice from your local renal service' if unsure about what to do[91]. Guidelines 1.7.4 to 1.7.7 were added in 2014, relate to vitamin D supplementation and are based on low-moderate quality RCT evidence from a review of 8 small trials conducted between 1988 and 2011[91,105–108]. Using vitamin D supplementation as primary prevention of CKD-MBD is not recommended by the guidelines as evidence didn't support clinical benefit in the absence of vitamin D deficiency. Also despite inactivated vitamin D being most commonly prescribed in the UK, there were no trials reviewed using inactive vitamin D and trials on activated forms showed inconclusive results and were associated with causing hypercalcaemia[91,105–108]. However, despite this, active vitamin D is recommended for persistent CKD-MBD symptoms in patients with GFR < 30 ml/min/1.73 m^2 as the GDG attributed more weight to the physiological impairment to vitamin D activation which occurs with worsening renal function. Guideline 1.7.7 does however acknowledge this risk by recommending monitoring of calcium and phosphate levels in patients receiving alfacalcidol or calcitriol.[91]

1.5.9 Anaemia

Guideline 1.7.8 within CG182[2] recommends testing haemoglobin in patients with eGFR below 45 ml/min/1.73m^2 in order identify anaemia; defined as a haemoglobin level < 110 g/L. It also signposts doctors to separate guidelines on anaemia management in CKD (NG8)[109] which despite being published in June 2015, much of the evidence has not been reviewed since 2011 or even 2006. According to NG8[109], CKD should be investigated and managed if patients are either symptomatic or have a measured haemoglobin result < 110 g/L. It makes no statement regarding a threshold of eGFR below which testing for anaemia should be carried out unlike guideline 1.7.8 in CG182[2] but instead suggests that anaemia of CKD should be suspected and investigated in anaemic patients with eGFR < 60 ml/min/1.73 m^2. The threshold of 45 ml/min/1.73 m^2 is based on results from a single large UK cross-sectional study which shows a sharp rise in anaemia prevalence from stage G3b onwards[40]. It was published in 2007 so will not have been considered in the formulation of NG8; whose guideline on the diagnostic role of GFR has not been reviewed since 2006[109].

Evidence on determining iron status in CKD patients and starting iron therapy was reviewed in 2015 leading to the creation of new guidelines on testing and management[110]. Of eleven studies reviewed, only two were RCTs[111,112] with the remaining nine being diagnostic accuracy reviews. Guidelines 1.1.3 and 1.1.4 from NG8 recommend using the percentage of hypochromic red blood cells, not transferrin or ferritin levels, to assess iron status; with a level > 6% being suggestive of iron deficiency[109]. However the generalisability of the evidence underpinning these guidelines is questionable as 10/11 studies were conducted on patients with ESRD[110]. The guidelines on haemoglobin target ranges were last reviewed in 2011 and are unclear regarding what to aim for when treating anaemia of CKD in patients not being treated with erythropoietic stimulating agents (ESAs). It states that ‘patient preferences’, ‘symptoms and comorbidities’ and ‘the required treatment’ are all factors that

should be considered when determining the optimal haemoglobin levels but provides no suggested levels so one may assume correction is to within normal limits[109].

Additional guidance on managing anaemia with ESAs and blood transfusions is also found within NG8 but will not be discussed here as these are not commonly used to manage patients with stage G3 CKD, the primary focus of our study.

1.5.10 Metabolic Acidosis

As with the guidelines on CKD-MBD, in depth advise on managing metabolic acidosis is stated to be 'beyond the scope of this guideline' (guideline 1.7.9)[2]. The only recommendation made by NICE, an addition in 2014, advises considering treating with sodium bicarbonate if patients in CKD stages 4-5 have a serum bicarbonate concentration less than 20 mmol/L. This is underpinned by poor quality evidence from two RCTs which both had inadequate randomisation and allocation concealment[113,114].

1.6 Referral Criteria to Secondary Care

NICE have stated 'there was no evidence to guide recommendations on who should be referred' which highlights a lack of high quality evidence within the field of renal research relating specifically to when to refer CKD patients to secondary care, although admittedly this is a difficult question to search for[91]. In the absence of this evidence, the guidance is instead based on 'the recommendations in other guidelines on who should be referred' as well as 'the aims and benefits of referral from their own professional standpoint', with 'their' referring to members of the NICE Guideline Development Group[91].

NICE guidelines are similar to recommendations outlined in the internationally recognised 2012 KDIGO report but with a few differences. KDIGO recommends that all CKD patients with ACR category 3 (A3) should be referred whereas NICE guideline 1.5.2 has the added

caveat of haematuria alongside category A3[1,91]. In the absence of haematuria, NICE also recommends referral at an ACR level greater than 70mg/mmol instead of the 30mg/mmol suggested by KDIGO[91]. The reason for the discrepancy between guidelines is currently unexplained especially considering that the evidence underpinning KDIGO referral criteria was rated as 'moderate' as opposed to the stated 'no evidence' supposedly underpinning NICE guideline 1.5.1-1.5.5[1,91].

The NICE referral criteria are outlined in the box below.

1.5.1 Take into account the individual's wishes and comorbidities when considering referral. **[2008]**

1.5.2 People with CKD in the following groups should normally be referred for specialist assessment:

- GFR less than 30 ml/min/1.73 m^2 (GFR category G4 or G5), with or without diabetes
- ACR 70 mg/mmol or more, unless known to be caused by diabetes and already appropriately treated
- ACR 30 mg/mmol or more (ACR category A3), together with haematuria
- sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months
- hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (see also Hypertension [NICE guideline CG127])
- known or suspected rare or genetic causes of CKD
- suspected renal artery stenosis. **[2008, amended 2014]**

1.5.3 Consider discussing management issues with a specialist by letter, email or telephone in cases where it may not be necessary for the person with CKD to be seen by the specialist. **[2008]**

1.5.4 Once a referral has been made and a plan jointly agreed (between the person with CKD or their carer and the healthcare professional), it may be possible for routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic. If this is the case, criteria for future referral or re-referral should be specified. **[2008]**

1.5.5 People with CKD and renal outflow obstruction should normally be referred to urological services, unless urgent medical intervention is required – for example, for the treatment of hyperkalaemia, severe uraemia, acidosis or fluid overload. **[2008]**

Box 8:NICE guidelines on the CKD Referral Criteria from CG182

1.7 Summary

Chronic kidney disease, a disease with numerous potential complications, is a serious medical condition which affects large numbers of people both in the UK and worldwide. Despite advances in the understanding and management of CKD and its complications, the burden of this disease continues to rise and is predicted to continue alongside projections of a worldwide ageing population. The National Institute of Clinical Excellence has formulated guidelines aimed to assist UK clinicians manage and reduce progression in patients with this condition; but it is accepted that these guidelines are not based on high quality evidence. RCTs are considered the gold-standard study design within the field of medical research but exploration of the evidence underpinning these guidelines showed a lack of RCT evidence as most guidelines are based evidence from lesser study designs such as cohort or cross-sectional studies. However, this is not surprising as nephrology has a poor RCT publication rate[115] (see Figure 2). With regards to the referral criteria, it was stated that 'there was no evidence to guide recommendations' which currently recommend referral at CKD stages G4-5; not stage G3[91]. As there is no evidence underpinning this recommendation we therefore pose the question of under which care setting do CKD stage G3 patients receive the best care?

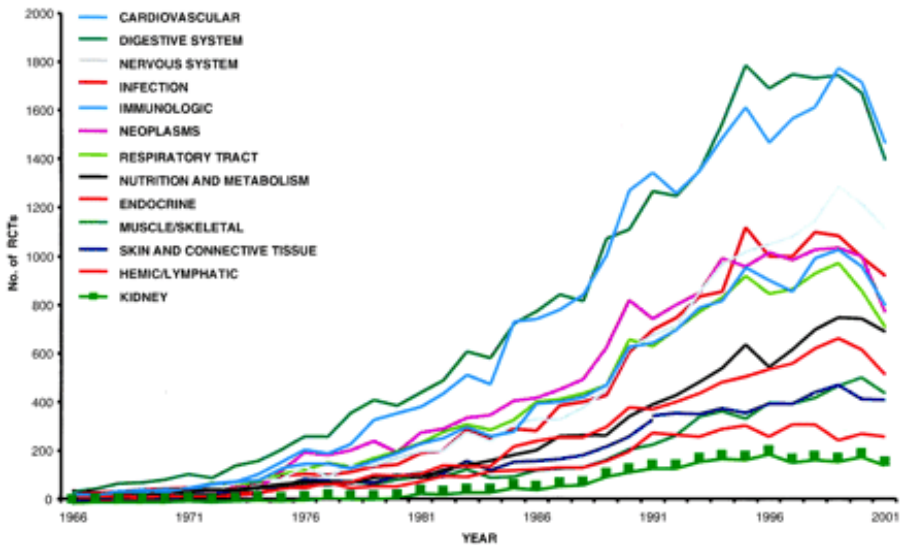


Figure 2: Number of randomized controlled trials (RCT) published in nephrology and 12 other specialties of internal medicine from 1966 to 2002 (replicated from The Number, Quality, and Coverage of Randomized Controlled Trials in Nephrology - Strippoli et al.)

CHAPTER 2: CHRONIC KIDNEY DISEASE PROGRESSION

In this chapter we explore the subject of progression in chronic kidney disease by investigating the main risk factors associated with CKD progression as well as the interventions which have the potential to slow this progression down. We then focus on the impact of secondary care referral on progression rates and mortality in order to explore the potential benefits which may be provided by secondary care in lieu of primary care.

2.1 Risk Factors for CKD Progression

2.1.1 Diabetes

There are several different pathological mechanisms by which diabetes can lead to the development of renal damage and therefore chronic kidney disease. Both metabolic and haemodynamic changes have already been implicated in causing diabetic nephropathy but oxidative stress, endothelial damage and inflammation also play a role in the pathophysiology[116]. The first step in the pathogenesis of diabetic glomerulosclerosis is afferent arteriole dilation which leads to an increase in pressure within the glomerulus and then glomerular hyperfiltration. Progressive thickening of the basement membrane then occurs due to the deposition of extra-cellular matrix in a process known as hyalinosis. Mesangial cells expand, protein kinase is activated and subsequent inflammation may cause additional secondary damage. The development of glomerular hypertension and its subsequent hyperfiltration state increases the permeability of the membrane which allows albumin to pass into the urine resulting in microalbuminuria which is recognised as an early manifestation of diabetic nephropathy. Diabetes is also a condition known to accelerate the development of atherosclerosis which can contribute to the development of renal artery stenosis. Reduced blood flow to the kidneys themselves can then cause ischaemia which can

result in necrosis of renal tissue, therefore outlining another pathological mechanism by which diabetes can cause CKD.

As previously mentioned, diabetic nephropathy is the leading cause of ESRD which is quantified in the SHARP study as relative risk of three when compared to other primary causes of renal disease[117]. Its natural disease progression is associated with the development of hypertension and proteinuria, risk factors also independently linked with progression of CKD and to be discussed in further detail below. However despite this, the increased risk of adverse renal outcomes (ESRD or 40% eGFR reduction) when compared to those with hypertensive nephropathy was not found to be significantly associated with levels of blood pressure or proteinuria[118], therefore supporting diabetes as an independent risk factor for progression. Individuals with type 1 diabetes have been shown to naturally have highly variable rates of GFR decline without intervention which range from 2-20 ml/min/year with the overall rate approximated at 12 ml/min/year[119,120]. Additionally, without intervention, 80% of those with type 1 diabetes and microalbuminuria will progress to clinical albuminuria within 10-15 years[121]. Compared to patients without diabetes, there is strong evidence which shows that patients with diabetes are more likely to progress to end stage renal disease at all GFR stages of CKD and this risk substantially increases once eGFR declines below the threshold of 45 ml/min/1.73 m^2.[122] However, in spite of this, those with diabetic nephropathy are still more likely to outcompeted by the risk of mortality and die from both cardiovascular and non-cardiovascular causes than reach ESRD[122].

2.1.2 Hypertension

The relationship between hypertension and CKD is complex and bidirectional in nature as hypertension is both a cause of CKD and consequence of it. For most patients with essential hypertension renal damage starts to occur in the form of benign nephrosclerosis which

usually does not affect the glomerulus and instead causes a slow ischaemic nephron loss. Autoregulatory dilatation and constriction of the afferent arteriole usually maintains fairly a constant pressure within the glomerular capillaries but over time chronic hypertension leads to remodelling of these vessels. Should the threshold for the compensatory ability of the afferent arteriole be exceeded, then patients may develop a "malignant" nephrosclerosis which causes damage to the glomerulus as well as its supplying blood vessels[123]. Similarly to diabetic glomerulosclerosis, this may lead to hyperfiltration, thus causing proteinuria, and subsequent hyaline deposition.

With regards to progression, hypertension is known to independently accelerate the progression rate of CKD with observational evidence showing increasing incidence of ESRD in CKD patients with blood pressure greater than 130/80 mmHg[124–126]; as well as evidence showing reduced incidence rates of serum creatinine elevation in patients with more intensively controlled blood pressure[127]. As levels of blood pressure increase, patients are increasingly more likely to initially develop CKD[16] and to then later progress to ESRD which is demonstrated by increasing incidence rates at higher stages of hypertension in both men and women[124]; although conversely, systolic blood pressure levels below 110 mmHg have also been associated with increased risk of progression in nondiabetic patients independently of proteinuria[126]. Although strong observational evidence associates both systolic and diastolic blood pressure levels with the development of ESRD[124,125], the contribution of raised systolic, as opposed to diastolic, blood pressure is thought to be the main contributor to causing renal damage. This is supported by a meta-analysis which demonstrated no significant relationship for diastolic BP after accounting for systolic BP[126] and also by another study showing no difference in ESRD rates based on diastolic BP targets[128]. Compared to other causes of primary kidney disease, patients with hypertensive nephropathy are at greater risk of cardiovascular mortality alongside diabetes, as previously mentioned.

2.1.3 Vascular Disease

We already know that chronic kidney disease increases cardiovascular risk with the majority of CKD patients dying from a cardiovascular event as opposed to succumbing to a progressive decline in renal function; a trend which is true even in the earlier stages of CKD. Prevalence rates of both arterial vascular disease, cardiomyopathy and heart failure are high in patients with CKD and are especially high in patients with renal failure[34,37,129–131]. The latter is demonstrated by figures from a Canadian prospective cohort study which showed that almost three quarters (74%) of patients starting dialysis had left ventricular hypertrophy and almost one third had evidence of cardiac failure[131].

However, like with many other risk factors associated with CKD, the relationship between CKD and CVD potentially goes both ways. Analysis of pooled data from the ARIC Study[35] and Cardiovascular Health Study[132] showed that history of CVD at baseline was independently associated with increased likelihood of developing CKD and that patients who developed CKD were 10% more likely to have CVD than those who did not[88]. Progression defined as an increase in serum creatinine level by more than 35.4 µmol/L was also significantly more likely to occur in patients with CVD at baseline over a mean study period of nine years[88]; thus supporting the bidirectional relationship that patients with CKD are not only more likely to develop CVD but conversely patients with CVD are at increased risk of initially developing CKD and progressing if CKD is already present. On the other hand, it should be noted that this possibly causal association between CVD and CKD may at least in part due to confounding between shared risk factors such as hypertension and diabetes; although atherosclerotic changes affecting renal vessels could also explain the decline in renal function.

2.1.4 Proteinuria

Proteinuria is a well-established promoter of progression in chronic kidney disease in patients with and without diabetes, and has been identified as the most important predictor of ESRD when compared to other potential clinical predictors such as BP and haematuria[133]. The pathogenetic mechanisms by which proteinuria, via both glomerular and tubulointerstitial injury, induces progressive decline in renal function include mesangial damage and protein accumulation within proximal tubule lysosomes. This accumulation then damages tubular cells and leads to overexpression of pro-inflammatory markers which eventually culminates in fibrosis and consequent decline in GFR. Proteinuria is often present in conjunction with other risk factors such as age, diabetes mellitus, and hypertension which have been independently associated with it[11].

In more recent years the focus on proteinuria has narrowed to concentrate on albumin as the main contributor to renal damage and progression in CKD. Although worsening albuminuria itself is linked with declining renal function[134], strong evidence from meta-analyses have shown albuminuria to be independently associated with either accelerated progression rates or increased risk of ESRD and mortality in various different population groups at all stages of eGFR[122,135–137]. It is clearly demonstrated by the inclusion of albuminuria within the classification of CKD, that severity of albuminuria can be used as a discriminator for identifying patients at increased risk of progression. This is supported by findings from Gansevoort et al.[135] whose systematic review on over one million patients from general and high risk populations associated worsening albuminuria with increasing rates of eGFR decline. For those with eGFR levels between 30-59 ml/min/1.73m^2, all albumin to creatinine ratio categories were predictive of progression but for those with GFR stage 4 only ACR measurements greater than 10 mg/g were found to be predictive. However as normal urinary albumin loss is estimated to be 10 mg/g on average, this falls within the normal range and is not a particularly clinically significant finding. Similarly,

increasing ACR has been strongly associated with increased risk of progression to end-stage renal disease across stratified eGFR categories between 15-59 ml/min/1.73 m^2 but is unable to accurately predict ESRD risk at eGFR >60 ml/min/1.73 m^2 [135]. As mentioned above, for patients with both type 1 and type 2 diabetes, albuminuria is often the first clinical marker of renal dysfunction so unsurprisingly, of those with higher ACR levels, patients are more likely to be diabetic[138]. Despite this, when comparing patients with and without diabetes, the relative risk of progression to ESRD does not seem to be a significant difference between groups which therefore suggests absence of an additional interaction effect between albuminuria and diabetes[122]. Likewise, a similar relationship was noted between hypertension, albuminuria and mortality whereby, although the absolute risk of death increased in those with higher ACR and higher blood pressure, relative risks between hypertensive and non-hypertensive groups with regards to ESRD risk did not significantly differ[136].

2.2 Slowing Progression of CKD

2.2.1 Glycaemic Control

In diabetic patients, blood pressure control, albuminuria reduction and good glycaemic control are all potential intervention goals which may lead to reduction of progressive renal decline[139]. In this section we will focus on glycaemic control as albuminuria reduction and blood pressure control will be discussed later on.

Evidence from several studies demonstrates that poor glycaemic control increases the risk of developing diabetic nephropathy and that good control can therefore delay the onset of developing renal dysfunction[140,141]. However, for many years it was uncertain whether or not intervention could alter the course of progression once patients developed microalbuminuria as results from several poor-quality observational studies showed no

evidence of improvement[142–144]. Strong evidence from one of the largest and most robust trials, the Diabetes Control and Complications Trial (DCCT)[145], provided results which support the theory that more intensive glycaemic control can prevent progression of diabetic nephropathy, especially in patients with type 1 diabetes mellitus. Intensive therapy was shown to cause a significant reduction in HbA1c by 1.9% for the intensive treatment group in comparison to the conventional treatment group after two months. This lead to a lower incidence of microalbuminuria (albumin excretion rate ≥ 28 μg/min) and was also associated with a 15% relative reduction in albumin excretion rate after twelve months. Despite this, in patients with type 2 diabetes there is conflicting evidence on whether or not more stringent glycaemic control improves renal outcomes. Of two large clinical trials on patients with type 2 diabetes, the largest and most recent found a 20% reduction in the rate of new-onset or declining nephropathy alongside a reduction in microalbuminuria when comparing intense to standard control[146] whereas the other reported no reduction in the risk of adverse renal events for the more intensively controlled group[147]. Regardless, the benefits of more intensive blood glucose control may be outweighed by the risk of harm. More intensive therapy is not only linked to increased rates of hypoglycaemia[146] but has also been associated with increased cardiovascular morbidity and mortality in patients with CKD[148].

2.2.2 Managing Hypertension

There is extensive RCT evidence from studies on CKD patients which demonstrates the benefits of lowering blood pressure for those with hypertension and CKD[149]. Blood pressure control not only ameliorates the risk of adverse cardiovascular events but also reduces the rate of progressive decline in renal function. The benefits of antihypertensive therapy are such that there is strong recent evidence which shows hypertensive patients on treatment

do not exhibit greater rates of ESRD or mortality when compared to normotensive patients[136].

However, with regards to determining the optimal BP target, as previously mentioned, RCT studies do not meet a consensus. While it is accepted that controlling hypertension to a normal BP goal of less than 140/90 mm Hg reduces risk of CKD progression in both diabetic and non-diabetic patients[150], evidence on whether or not more intensive BP control at systolic goals less than 130 mm Hg can reduce the progression of chronic kidney disease is inconsistent. The MDRD study was unable to show a statistically significant benefit for a more intensive blood pressure target of less than 125/75 mm Hg, compared to the usual control target of less than 140/90 mm Hg, despite clinically significant findings which showed patients with higher levels of proteinuria progressed to ESRD at a rate that was 32% lower in the lower BP group compared to the standard BP control group after 10 years[151]. Results from the more recent REIN-2 trial in 2005 which defined the BP of the intensive treatment group as systolic BP <130 mm Hg plus diastolic BP <80 mm Hg and standard treatment as diastolic BP < 90 mm Hg did not show any clinically or statistically significant differences[152]. Rates of progression to ESRD were similar in both the intensive treatment and standard treatment groups, although the mean difference in BP between the two groups was only 4.1/2.8 mm Hg[152]. Similarly, results from the AASK trial demonstrated no significant differences in a cohort of African American patients, with regards to either the rate of GFR deterioration (relative eGFR reduction of 50% or absolute reduction of 25 ml/min/1.73m^2) or risk of adverse outcomes (ESRD or death) between lower and usual BP control groups[153]. This contrasts with analysis of results from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) Study which showed a statistically significant 6.7% reduction in the risk of progression to ESRD for every 10 mm Hg decrease in systolic blood pressure[150]. A similar but slightly larger relationship was also seen in the Irbesartan Diabetic Nephropathy Trial (IDNT)[149] which associated a systolic decrease of 20 mm Hg with

a 47% reduction in adverse renal outcomes. However, it was also noted that lowering systolic blood pressure in CKD patients to below 120 mm Hg did not confer any additional benefit with regards to preventing progression of CKD but additionally had an adverse outcome by increasing the proportion of all-cause deaths[149] which were cardiovascular in nature[154]. More robust evidence from meta-analysis does however associate low BP with increased risk of progression but not until systolic blood pressure is below 110 mm Hg, not 120 mm Hg. The lowest risk of progression was also found in the group with systolic BP between 110-129 mm Hg[126], which contrasts results of individual RCTs some of which were discussed above.

There is extensive RCT evidence which supports the use of ACE inhibitors in order to ameliorate cardiovascular risk and to slow the progression of renal function decline in CKD[155–160]. ACE inhibitors like ramipril and fosinopril not only help to reduce blood pressure but also reduce albuminuria in diabetic and non-diabetic CKD patients with albuminuria[157,158]. This contributes to their beneficial effect of reducing the risks of progressive decline or ESRD[155]. Meta-analysis has shown that the combination of blood pressure control and albuminuria reduction does not fully explain the overall reduction in CKD progression as the relative risks for ESRD and doubling of serum creatinine were 0.69 and 0.70 respectively even following adjustment for systolic blood pressure and proteinuria[155]. ACE inhibition therefore provides additional benefits beyond the effect on blood pressure and albuminuria.

For patients with diabetic nephropathy, the benefits of ARB and ACEi use have been widely studied[161]. There is strong evidence supporting the use of ARBs; as investigated by Brenner et al. and Lewis, E. et al. in the IDNT[162] and RENAAL[163] studies. The angiotensin receptor blockers Losartan and Irbesartan are associated with relative reductions in CKD progression rates by 25% and 33% respectively[162,163]. The RENAAL study also reported that the risk of progressing to ESRD was 28% lower in the Losartan group which approximately equates to

deferring the need for dialysis or transplantation by 2 years[162]. Similarly to evidence on ACEi use in non-diabetic patients, the benefit of ARB use in limiting renal disease progression seems to exceed that attributable to its effect solely on lowering BP. However, ACE inhibitors are still the superior hypertensive drug class for diabetic patients as they demonstrate improved survival rates not seen with ARBs[161].

Whilst there is evidence from large clinical trials that using two RAS blocking drugs enhances the antiproteinuric effect of antihypertensive monotherapy, dual inhibition has not been shown to have any additional benefit for patients with CKD[164]. The risk of progression, ESRD or death does not improve with dual inhibition and instead has been shown to have adverse effects such as increased risks of hyperkalaemia, hypotension[165] and acute kidney injury[94]. Renal function may also deteriorate[164].

2.2.3 Reducing Cardiovascular Risk

In the management of CKD, the main methods of reducing cardiovascular risk are through antihypertensive therapy, as discussed above, as well as statin therapy.

Statins have not been shown to reduce the progression rate of CKD in all patients but have been shown by one meta-analysis to slow the rate of eGFR decline in patients with CKD alongside cardiovascular disease by a rate reduction of 1.22 ml/min/1.73 m^2 per year[99]. The use of statins is able to significantly reduce low density lipoprotein (LDL) levels and triglyceride levels leading to a significant reduction in total protein in patients with CKD[100]. This in turn may lead to reductions in albuminuria or proteinuria which Douglas et al.[98] suggests could be via the reduction of pre-existing endothelial dysfunction and by reducing vasoconstriction. For patients with pre-existing macroalbuminuria (or proteinuria >300 mg per day) statins can significantly reduce their levels of proteinuria or albuminuria but for proteinuric patients with an excretion rate below the threshold of 300mg per day

reductions were not deemed to be statistically significant[98]. Although, these studies show that statins are able to reduce albuminuria and the rate of eGFR decline in patients with macroalbuminuria and pre-existing cardiovascular disease respectively[98,99], statins have fewer significant benefits for the total CKD population. This is demonstrated by results from a more recent meta-analysis which did not show any significant improvement in risk of progression to ESRD, although it did show a 23% reduction in risk of cardiovascular events[166]. With regards to the reduction in CKD progression rate observed by Sandhu et al.[99] in patients with comorbid cardiovascular disease, it is likely that the benefit observed was attributable to the effect of Atorvastatin which has been shown to have superior lipid-lowering effects than other statins as well as Cerivastatin[100]. However, regardless of whether statins do or do not lead to reductions in CKD progression rates in all CKD patients, there is no denying their ability to reduce risk of cardiovascular events[166] and subsequent mortality[100].

2.2.4 Proteinuria Reduction

The main method of proteinuria reduction is through the use of RAS inhibitors especially ACE inhibitors as discussed above. It was previously thought that reducing protein intake would provide benefits with regards to proteinuria reduction but low protein diets are no longer recommended.

2.3 Impact of Secondary Care Referral

2.3.1 Secondary Care and Progression Rates

Only a few studies have explored the effect that nephrology care has on the progression rates of chronic kidney disease. Three studies published in 1999, 2002 and 2006 by Feest et

al.[167], Joss et al.[168] and Jones et al.[169] respectively do this by using regression analysis to assess the rate of declining kidney function pre-referral and post-referral to nephrology clinics. Patients with diabetic nephropathy who receive care from a diabetic-renal clinic for at least 1 year are likely to see a slower rate of deterioration in renal function which was quantified as 0.25 ml/min per month improvement in creatinine clearance from baseline to 3 years post-referral; although this difference was not found to be significant within a shorter time frame[168]. Otherwise, overall, referral to nephrology clinic was associated with an improvement in renal progression rates which have been quantified as either a reduction in the rate of eGFR decline from -5.4 ml/min/1.73m^2 to -0.35ml/min/1.73m^2 per year [169] or as a change in the slope of reciprocal serum creatinine measurements over time from -2.6 x 10^{-6} to -1.5 x 10^{-6} [167] in a mixed patient cohort and diabetic only cohort respectively. Despite this average improvement in renal decline of up 5 ml/min/1.73 m^2 per year[169], a large proportion of patients see no improvement at an individual level as demonstrated by 45% of patients who were identified as having a progressive rate of decline before referral continuing to progress at the same or an accelerated rate following referral[169]. Similarly, one cohort study published results which actually satisfied the concept of ecological fallacy whereby an association that exists at a population level does not exist at an individual level. Here, the slowed rate of deterioration was found to be significant in analysis of the whole group but was only significant in individual analyses for 39% of patients[167]. In theory this may be due to the variable progression patterns which differ between individuals or perhaps due to a significant proportion of patients in secondary care who have a propensity for steeper renal decline as a result of worse or more complex underlying disease. However, the differences in risk factors between 'fast' and 'slow' progressor groups were not statistically significant in a study which compared the two[168]. There was however, an increase in ACE inhibitor use to 81% from 50% which contributed to an absolute reduction in systolic blood pressure by 10 mmHg but again this was not statistically significant[168]. This is also

inconsistent with the findings by Jones et al. who found that lower systolic blood pressure was significantly associated with non-progression[169].

2.3.2 Timing of Secondary Care Referral

There are multiple studies on how the timing of nephrology referral affects patient outcomes in patients with end-stage renal disease, usually in terms of mortality. Later referral is associated with a dose-response relationship with poorer patient prognosis as demonstrated by mortality rates at one, two and three years post first dialysis which show an increasing risk of mortality: 4.3%, 9.5% and 13.3% at year one; 14.6%, 22,4% and 27.6% at year two and 26.3%, 32.7% and 37.0% at year three for 'early', 'intermediate' and 'late' referral groups respectively[170]. This relationship between timing of referral and mortality rates is supported by several international cohort studies[171–176] plus a meta-analysis of 12,018 patients which quantified the increased relative mortality risk as 1.99 in patients referred 'late' compared to 'early' referrals[177]. This figure is only generalisable for mortality risk for up to one year due to differences in follow-up periods for included studies[177] although the improved survival of 'early' referral patients has been shown to be valid for up to 5 years follow-up[174,178].

Unsurprisingly, patients in late referral groups are more likely to be in a poorer state of health at the start of RRT compared to 'early' referrals as demonstrated by Jungers et al. whose 'late' referral patients had a substantially increased risk of requiring emergency dialysis due to uraemia (88% of late referral patients)[179]. Patients have also been noted to have a higher burden of co-morbid disease plus more abnormal baseline characteristics e.g. raised blood pressure, low levels of haemoglobin, reduced serum calcium and raised serum phosphate[172]. These factors are likely to increase the mortality risk experienced by 'late' referral patients and contribute to the more frequent complications of dialysis and

prolonged stays in hospital[180]. Patients referred 'late' or just lacking pre-ESRD nephrology care may also miss out on benefits such as education on dialysis modality which could influence patient choice and therefore be responsible for the reduced uptake of initial peritoneal dialysis compared to haemodialysis in late referral groups in some studies[180]. Permanent vascular access is also less likely to have been obtained prior to commencement of dialysis which may in turn lead to increased risk of complications such as sepsis[179]. Patients referred late are also less likely to receive or even be put on the waiting list for both living or cadaveric renal transplantation[173,180,181]. The greatest difference in transplant rates is noted to be within the first 3 months of referral[181] which is likely due to poorer health in the early stages of dialysis in combination with limited time to adequately prepare the patient for transplantation. However, differences in transplantation rates remain significantly different for at least 2 years after initiating dialysis[181].

Early referral not only has clinical benefits but an economic one too. The costs of care in both the 6 months preceding and 12 months following initiation of RRT are lower in patients referred early compared to late referrals[182]. This is likely to be due to a number of factors such as the increased expenditures from prolonged hospitalisation in late referral patients[183].

2.3.3 Duration and Frequency of Secondary Care

Cohort studies on the duration and quantity of nephrology care show that a longer duration of nephrology care is associated with better outcomes in end-stage renal disease. Following any duration of nephrology care patients are more likely to have favourable values of clinical markers such as serum albumin and haemoglobin, increased uptake of peritoneal dialysis and already established permanent vascular access as well as better access to renal transplantation[184]. The most favourable outcomes are found in patients with at least twelve

months of nephrology care[184] although any duration of nephrology care before the initiation of dialysis can ameliorate the risk of mortality[185]. The frequency of visits to the nephrologist can also affect the mortality of patients with end-stage renal disease. Patients who had more than five visits in twelve months had a 15% improved survival rate[171]. However, the number of visits is no doubt inextricably linked with timing of the referral to nephrology care which would inevitably limit the possible number of nephrology visits which are feasible within the time available. Therefore the improved survival rate observed may again be due differences between early and late referrals which are evidently associated with increased mortality.

2.4 Summary

Chronic kidney disease is a complex condition in which complications of the disease may also cause it and/or accelerate its progression. This bidirectional relationship exists for the previously explored risk factors hypertension[126], cardiovascular disease[35] and proteinuria[133]; all of which are associated with an increased risk of progression[88,126,133]. The main methods of reducing the effects of these risk factors and therefore decreasing progression rates are through the control of blood pressure as well as blood sugar for diabetic patients[145,149]. Statin therapy especially the use of Atorvastatin can reduce the risk of cardiovascular mortality but may or may not reduce progression rates of CKD as results from meta-analyses are inconsistent[99,100,166]. Proteinuria/albuminuria reduction may also be achieved through the use of antihypertensive agents such as ACE inhibitors which are a first-line hypertensive agent due to their enhanced effect on reducing progression rates[2,155].

Optimising the management of these risk factors, the goal of nephrology specialist care, overall is associated with slowing the decline of CKD although there may be a significant proportion of individuals in which this is not achieved[167,169]. Earlier referral to specialist care

has been shown to improve patient outcomes[170]. Any input from nephrology may increase survival rates but patients with a longer duration of care or more frequent visits are more likely to have better clinical biomarker values and reduced mortality[171,184]. However, currently the evidence on the timing of referral to specialist care, duration of care and frequency of care has been conducted on patients with or approaching ESRD. The generalisability of these findings to patients with CKD stage G3 patients is therefore questionable and thus highlights a gap in the current evidence base which we hope to explore.

CHAPTER 3: OBJECTIVES

3.1 General Aim

To investigate what the effect of care provided in different settings has on patients with CKD stage G3. In doing so we hope to provide evidence to either support or refute current NICE referral recommendations.

3.2 Specific Objectives

The key question we are aiming to answer is as follows:

- What are the differences, if any, between CKD progression rates under primary care, renal secondary care and non-renal secondary care?

Other aims of this thesis are to answer the following questions:

- What are the differences, if any, between mortality rates under primary care, renal secondary care and non-renal secondary care?
- What are the differences, if any, between rates of end-stage renal disease under primary care, renal secondary care and non-renal secondary care?

CHAPTER 4: METHODS

4.1 Data Sources

The majority of the data for this dissertation was provided from two sources: the pathology database in the Royal Lancaster Infirmary and the EMIS database from Queen Square; a local GP practice. Raw data from each source was extracted by a single member of staff located within the pathology department or GP practice and then sent to the researcher and author of this work. A complete dataset was provided from Queen Square but the data from pathology was initially incomplete in two regards. Firstly, the pathology IT system underwent a system update in late 2010 so only data from January 2011 onwards was available for collection. Secondly, the pathology database only contains extractable data on the biochemical test results for patients treated in the Morecambe Bay area as well as some limited basic demographic information. The researcher was therefore required to collect further information on renal diagnoses, co-morbidities, medications and type of specialty care from an alternative source. This was done by accessing the electronic patient record via the program Lorenzo to view the records of patients who had been previously identified to be within the initial entry criteria of the research.

Patients were initially categorised into primary or secondary care based on which database their records came from. There were 48 patients with records from both databases who were subsequently categorised as secondary care. Secondary care patients were subdivided into non-renal and renal care based on additional data collected as mentioned above.

4.2 Entry Criteria

The entry criteria were as follows:

- 2x eGFR measurements between 30-59 which are >90 days apart

    - Date of entry (‘diagnosis’) to be the date of the first measurement
- Both eGFR measurements to be within 01/04/2006 – 31/03/2014
- Age > 18 years old
- No active malignancy

4.3 Manual Data Collection

In order to gain a usable data set from a secondary care patient cohort which would not only be suitable for analysis but also be of a feasible size for manual data collection, the secondary care cohort for the study was limited to those treated in the Royal Lancaster Infirmary outpatient department. Thus, the manual data collection was restricted to patients who attended the Royal Lancaster Infirmary outpatient department only.

Electronic patient records were accessed by conducting searches in Lorenzo using patient NHS numbers. Data was extracted by the researcher and author of this work by reading outpatient clinic letters written by medical consultants to GPs. These were only accessed if they fell within the study period of 01/01/2011 – 31/04/2014. Data was collected on date of death, medical specialty, renal replacement therapy type and date, renal diagnosis, number of antihypertensive medications by type as well as the co-morbidities: hypertension, diabetes and cardiovascular disease. Ideally the data was to be extracted from the single most recent letter. However, as the letter style varied greatly between specialties and the consultants within them, letters often contained inconsistent amounts of extractable data so additional letters were read from most to least recent until the information was gathered. For example if the most recent letter contained all the desired information, no further letters would be read. However if the most recent letter only contained information on co-morbidities with no reference to medication, less recent letters would be accessed until medications were mentioned and the missing data would be extracted from that letter. If data was deemed to still be missing following scrutiny of all clinic letters in the allocated

study period, the researcher would then access the most recent hospital discharge summary to 31/04/2014 to provide this data if possible. Information on specialty type was then gathered by reading the full list of clinic letters and noting there origin by medical specialty.

4.4 Reformatting

The data provided from both primary and secondary care required considerable reformatting and cleaning. This task was undertaken with the use of both Microsoft Excel and R: an open-source statistical software. The cleaning process involved the removal of data rows in multiple sweeps; leaving only data suitable for analysis in the final data set. For the secondary care data reformatting mostly consisted of data removal. Initially rows were removed if the patient had no eGFR values which reduced the data set from 1,302,469 rows to 555,324. Patients without two eGFR values were then excluded followed by those whose values were not more than 90 days apart as they therefore did not meet the entry criteria. As mentioned above, the dataset was then restricted to patients treated in the Royal Lancaster Infirmary outpatient department.

On the other hand, the primary care data provided only included patients who had already met the entry criteria so reformatting instead consisted of converting the data into long format suitable for analysis as opposed to the exclusion of rows. Once combined with the secondary care data set, patients with active malignancy were also removed.

Additionally, all eGFR values above 60 ml/min/1.73 m^2 had to be calculated from serum creatinine measurements as the eGFR values were capped at this threshold. We did this using the MDRD equation which generated values which were comparable to our existing data set. Ranges of the data parameters were then inspected and if values were deemed to be clinically implausible that value only was also removed.

Figure 3 summarises the process of data cleaning.

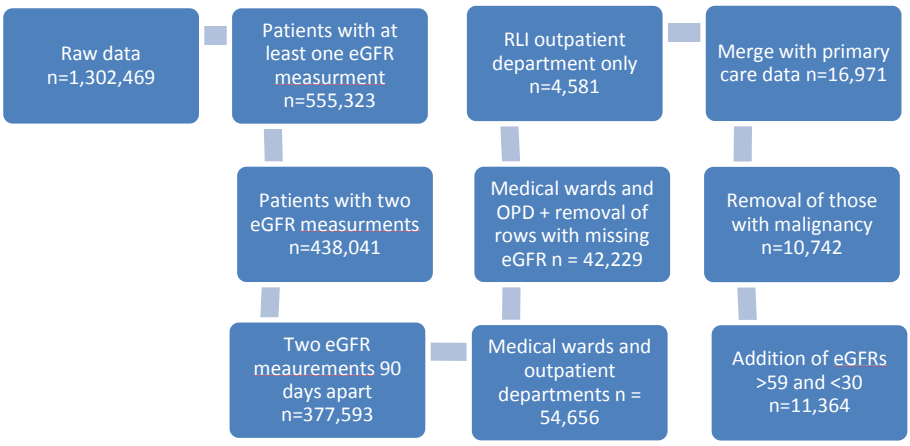


Figure 3: Flow diagram of the data cleaning process

4.5 Statistical Software

All data manipulation and analyses undertaken within this dissertation were performed using R, an open-source statistical software. The following additional packages were also installed to aid with these processes:

"reshape2"

"ggplot"

"gridExtra"

"nlme"

"mvtnorm"

4.6 Simple Linear Modelling

In order to describe the relationship between two variables, one of the most common techniques is regression analysis. When modelling a continuous output, the most basic form of regression may be represented by the simple linear model which describes a straight line relationship between x, an input variable and y, an output variable.

$$y = \alpha + \beta x \quad (1)$$

Here the intercept of the line is denoted by α and the gradient of the line by β. A positive value of β shows a relationship whereby an increase in x leads to an increase in y. Conversely a negative value of β shows the inverse of this relationship; with increasing x leading to a decrease in y. The remaining possible value for β is 0 which represents no relationship between the input and output variables x and y. This mathematical model (1) represents a perfect linear relationship and therefore cannot represent experimental data which is affected by random variation, often due to repeated measurements or experimental error. The statistical linear model (2) extends the mathematical model by adding the variable Z to represent this unpredictable random variation in experimental data.

$$Y = \alpha + \beta x + Z \quad (2)$$

Z measures the difference between the 'line of best fit', $Y = \alpha + \beta x$, and an experimental result. Overall it should have a mean of zero and assumes independence between subjects. As Z is a random variable, y must also be affected by random variation so Y is capitalised in the statistical model to also show its stochastic nature[186].

Simple linear modelling was used to explore the relationships between eGFR and other potential explanatory variables at baseline. Continuous variables included age, albumin to creatinine ratio, haemoglobin, corrected calcium, albumin, alkaline phosphatase and phosphate. Binary variables included gender, ethnicity, smoking status, hypertension, cardiovascular disease and diabetes. Results can be found in sections 5.2 and 5.3.

There a number of limitations to the simple linear model:

1. It cannot model relationships between a continuous output variable, y, and a categorical input variable, x, with more than two categories.

2. Only one input variable can be modelled at a time so the simple linear model cannot account for multiple risk factors

3. The model makes the assumption that measurements are independent of each other. This is not the case in longitudinal analysis where a single subject had repeated measurements over time. Thus a simple linear model cannot model longitudinal data.

4.7 Multiple Linear Regression

A multiple linear regression model is an extension of the simple linear model which tries to predict the relationship between a single output (dependent variable) and more than one input (explanatory) variable. In theory a multiple regression model may include an arbitrary number of explanatory variables and is therefore represented by the following equation:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_k x_k + Z \quad (3)$$

As in the simple linear model β_0 represents the intercept and Z represents the random variation. β_1 represents the change in y for every unit change in x_1 when all other explanatory variables ($x_2 \ldots x_k$) equal zero and likewise, β_2 represents the same relationship for the variable x_2. k represents the total number of input variables in the model[187]. It is worth noting that in contrast to the simple linear model, multiple regression models are also able to incorporate categorical input variables with more than one outcome; not solely those which are continuous or binary.

The 3 main situations in which you may want to perform a multiple regression analysis are:

1. To explore the relationship between two variables by removing the effects of the other variables which are not considered important.

2. To explore the relationships between multiple variables when limited knowledge is available on which variables have prognostic interest.
3. To develop a model which predicts an outcome of interest from several explanatory variables[188].

For this research, the third scenario is the most relevant. There are however several different methods which may be employed in order to develop a multiple regression model[188].

In this thesis, a forwards stepwise approach was used in order to try to construct a model to predict eGFR values at baseline.

Initially all possible explanatory variables were fitted in order to construct a model with which all associations could be compared and therefore guide the order of which to add variables. A 'null model' with variables which were always to be included was then created. These often include variables already known to affect the outcome but our 'null model' only included the demographic variables age, gender and ethnicity. The variables deemed to have the greatest statistical (smallest p-values) and/or clinical significance were then added one at a time until an additional variable made no significant improvement to the model at the 5% level ($p<0.05$). This was evaluated by maximum likelihood testing which is discussed in section 4.10.

4.8 Linear Mixed Effects Modelling

The main aim of this study is to compare the progression rates over time between primary and secondary care patients. As this uses longitudinal data, we cannot assume independence between measurements for the same individual patient, as previously done

when constructing simple linear and multiple regression models. Linear mixed effects models provide a solution to this problem.

A linear mixed effects model allows for non-independence between experimental results by including both explanatory variables, henceforth referred to as 'fixed' effects, and 'random' effects with which to predict the outcome variable. The 'fixed' effects are those which have been measured and controlled in the experiment whereas 'random' effects refer to the unpredictable stochastic variation that is present within a study. Within health research this is often because of between-individual random variation due to differences between a patients underlying propensity to respond both at baseline and as a trajectory over a longer time period. A random intercept and random slope model in the form of

$$Y_{ij} = \alpha + \beta t_{ij} + U_i + V_i t_{ij} + Z_{ij} \quad (4)$$

predicts the outcome variable for the i^{th} subject at the j^{th} measurement. Here, U denotes the random variation in the intercept and V denotes the random variation in the slope[189]. U therefore represents the variation in baseline level of response between individual subjects and V represents the variation in their response over time.

4.9 Residual Analysis

Once a model has been constructed, it should be tested for its 'goodness-of-fit'. By analysing the residuals we are studying how well the constructed model can predict the outcomes seen in the observed data. A single residual value is calculated by subtracting the predicted or fitted value from the model from the observed value: $y_{obs} - y_{fit}$ .The assumption that residual values are normally distributed around a mean of zero can be verified by creating and inspecting the shape of a histogram of residuals.

A plot of the residuals against model-fitted values should show no relationship or recognisable pattern which therefore demonstrates a good fit for the model. Visualisation of this plot can also identify outliers within the study[186].

4.10 Likelihood

The probability density function for a given set of parameter values show us that some data are more likely to be generated than others. The likelihood function is a reversal of this relationship which instead represents the probability of generating the observed data from a given parameter value, θ[190]. The value of θ which is most likely to generate the observed data is that which maximises the likelihood function and is known as the maximum likelihood estimate (MLE). For any other value of θ, we can conclude that its likelihood will be smaller than that of the MLE. A quantitative test of how many times smaller this is may be given by the likelihood ratio. If set to the MLE, this will take a value of 1 and less than 1 for any other value of the parameter. The likelihood ratio can then be used to evaluate the performance of two competing statistical models and provide a formal guide to advise rejection or acceptance of the more complex model.

By convention and computational convenience, the test statistic often denoted as D is calculated from the logarithm of the likelihood; which is also maximised by the MLE of the likelihood function.

$$D = 2 \times [L(\text{likelihood for alternative model}) - L(\text{likelihood for null/simpler model})] \quad (5)$$

This value may be referred to as the deviance or likelihood ratio statistic and can be interpreted for statistical significance by using a standard chi-squared test; whereby a p-value below the given threshold for significance promotes the acceptance of the more complex model[189]. This technique was implemented at every stage of model construction.

CHAPTER 5: CROSS-SECTIONAL ANALYSIS RESULTS

5.1 Description of the Study Population

The following section aims to describe the study population with regards to distribution of demographic characteristics, co-morbidities and baseline biomarker data. Statistical significance was determined by conducting either a student's t-test or a chi-squared test depending on the nature of the data (t-test for continuous and chi-squared for binomial data). The threshold for determining significance was a p-value less than 0.05.

The total study sample included 1345 patients with CKD stage G3 at entry of whom 62.8% (n=845) were female compared to 37.2% (n=500) male. The patients with known ethnicity were almost exclusively white; with only 10 patients being of non-white ethnicity (see Table 4). With regards to smoking history 398, 320 and 85 patients were classed as non-smokers, ex-smokers and current smokers respectively. However, there were a significant number of missing values for this risk factor.

Table 4: Number of Patients by Ethnicity and Smoking Status

Ethnicity	**White**	**Non-White**	**Not Stated**	
	984	10	351	
Smoking Status	**Current**	**Ex-smoker**	**Non-smoker**	**Unknown**
	85	320	398	542

From the total sample, 51.7% (n=695) and 48.3% (n=650) of patients were categorised into primary care or secondary care groups respectively. Those who had seen a secondary care specialist at least once within the study period were categorised as secondary care, otherwise patients were primary care.

Of the co-morbidities, a history of hypertension was the most prevalent followed by history of cardiovascular disease and then diabetes, with prevalence rates of 56.7% (n=762), 38.7% (n=521) and 35.8% (n=481), respectively. The distribution of comorbidities by care group and gender is outlined in Table 5 below.

Table 5: Prevalence of Comorbidities by Gender and Care Group

Comorbidity	Total Population (n=1345)	Male (n=500)	Female (n=845)	Primary Care (n=695)	Secondary Care (n=650)
Hypertension (%)	762 (56.7)	290 (58.0)	472 (55.9)	447 (64.3)	315 (48.5)
CVD (%)	521 (38.7)	235 (47.0)	286 (33.8)	280 (40.3)	241 (37.1)
Diabetes (%)	481 (35.8)	212 (42.4)	269 (31.8)	221 (31.8)	260 (40.0)

Table 19 (see appendix) shows the mean, median, standard deviation (SD), range and interquartile range for each biomarker under study for the total population, males, females, primary care and secondary care. There are relatively large differences between the mean and median values for ACR and ALP which suggests that the data for these biomarkers may not be normally distributed. This can be seen by visualising the histograms found in Figures 4 and 5 which additionally show eGFR as another variable with a non-normal distribution at baseline. In order explore the potential multiplicative effect, as opposed to additive effect, of ACR, ALP and eGFR at baseline we performed a transformation on to a logarithmic scale. These histograms may be found in the appendix (Figure 12).

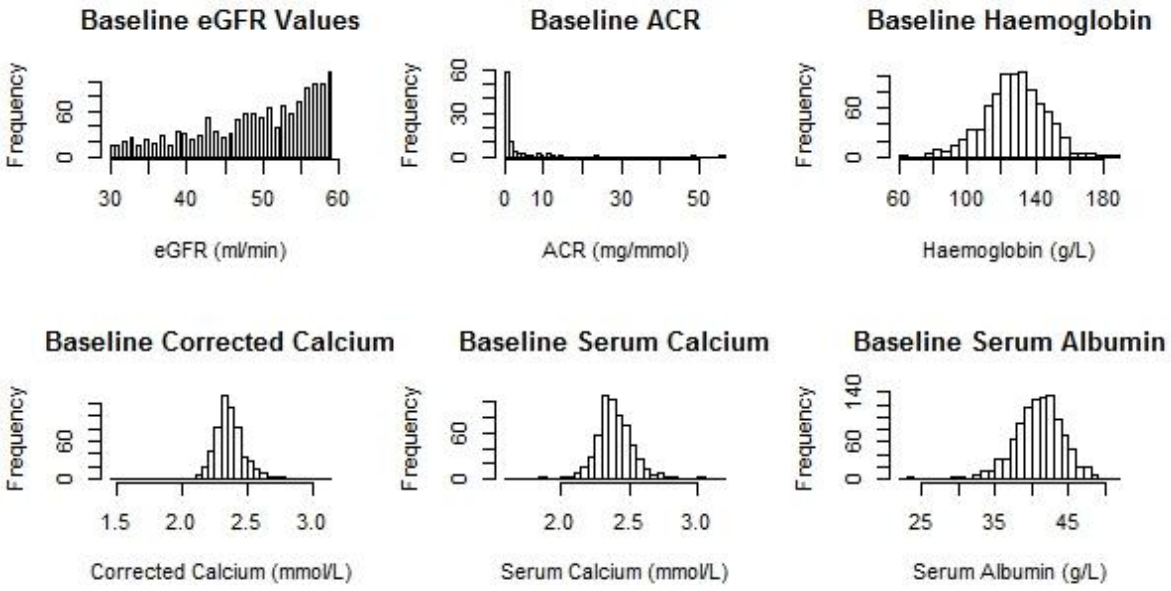


Figure 4: Histograms showing the distribution of values at baseline for the biomarker variables eGFR, ACR, Hb, Corrected Calcium, Serum Calcium and Serum Albumin

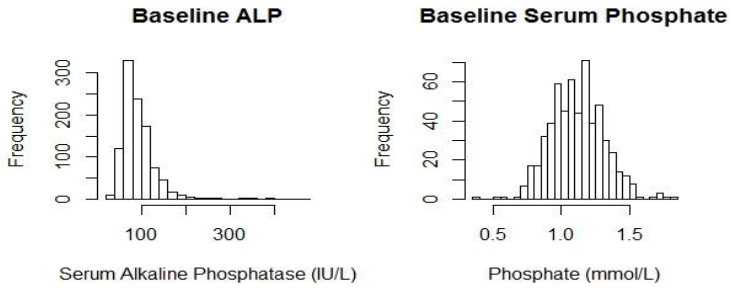


Figure 5: Histograms showing the distribution of values at baseline for the biomarker variables ALP and serum phosphate

In order to test whether differences between continuous variables for the care groups were significant, student's t-tests were conducted.

The average age of the total sample was 75.6 years at baseline but age differed significantly between the genders. On average, the female sample is significantly older than the male sample; with mean values of 76.1 and 74.7 years respectively and a p-value of 0.048. A similar relationship was also demonstrated between primary and secondary care patients whose average ages were 79.1 and 71.8 years respectively with a p-value of less than 0.001. No significant difference was found in the gender distribution between the care groups (p=0.057).

Table 6: Description of baseline characteristics and biomarker data for the study population as a whole and then divided into primary and secondary care

	Total Population	Primary Care	Secondary Care	p-value	95% Confidence Interval
Number (%)	1345	695	650		
Age in years (SD)	75.6 (12.2)	79.1 (11.17)	71.8 (12.26)	<0.001	5.946-8.460
eGFR (SD)	49.23 (8.03)	52.16 (6.17)	46.10 (8.59)	<0.001	5.253-6.863
ACR (SD)	3.78 (10.01)	2.01 (7.14)	8.49 (14.65)	0.047	0.080-12.880
Haemoglobin (SD)	128.7 (17.52)	132.8 (15.27)	124.1 (18.12)	<0.001	6.430-10.916
Corrected Calcium (SD)	2.37 (0.13)	2.35 (0.10)	2.39 (0.14)	<0.001	0.020-0.059
Serum Calcium (SD)	2.40 (0.14)	2.39 (0.11)	2.40 (0.16)	0.727	-0.026-0.018
Albumin (SD)	41.35 (3.48)	42.05 (3.01)	40.56 (3.78)	<0.001	1.069-1.906
ALP (SD)	94.62 (43.15)	89.13 (36.77)	100.7 (48.62)	<0.001	6.317-16.899
Phosphate (SD)	1.12 (0.20)	1.12 (0.19)	1.13 (0.20)	0.718	-0.039-0.027

As one might expect, there were significant differences observed between primary and secondary care for the majority (75%) of the biomarker variables. These are laid out in Table 6. Secondary care patients had worse renal function at baseline as demonstrated by a mean eGFR value significantly lower than that for primary care: 46.10 compared to 52.16 ml/min/1.73 m^2 with a p-value of less than 0.001. Similarly, average haemoglobin levels of 132.8 and 124.1 g/L for primary and secondary care respectively were significantly different at the 0.1% significance level. Albuminuria levels were higher in secondary care: 8.49 compared to 2.01 mg/mmol but at a lower significance level (p-value of 0.047). There were higher ALP levels in secondary care of 100.7 mmol/L compared to 89.1 mmol/l in primary care with a p-value of less than 0.001. On average, corrected calcium levels were 2.35 and 2.39 mmol/L for primary and secondary care respectively with a p-value less than 0.001. Serum albumin was significantly lower in the secondary care group with mean values for primary and secondary care of 42.05 and 40.56 g/L respectively and a p-value less than 0.001.

Table 7 below shows the number of patients with each comorbidity within primary and secondary care. In order to ascertain whether or not observed differences were statistically significant, p-values were determined by conducting chi-squared tests. For both hypertension and cardiovascular disease, significant differences in the proportion of patients with these comorbidities between primary and secondary care groups were present. 64.3% of primary care patients compared to 48.5% of secondary care patients had hypertension at a significance level of 0.1%; which shows a greater prevalence of hypertension in the primary care group. A similar relationship was demonstrated for cardiovascular disease with a 40.3% and 37.1% prevalence demonstrated for primary and secondary care respectively; although this was at a lesser significance level (p=0.002). Conversely, proportionally there were fewer patients with diabetes in the primary care group compared to the secondary care group: 31.8% and 40.0% for primary and secondary care respectively with a p-value of 0.057.

However, as this is just above the threshold of 0.05, no statistically significant difference was found in the prevalence of diabetes between the two groups.

Table 7: Prevalence of co-morbidities by total population and then split by care group

Comorbidity	Total Population (n=1345)	Primary Care (n=695)	Secondary Care (n=650)	p-value
Hypertension (%)	762 (56.7)	447 (64.3)	315 (48.5)	<0.001
CVD (%)	521 (38.7)	280 (40.3)	241 (37.1)	0.002
Diabetes (%)	481 (35.8)	221 (31.8)	260 (40.0)	0.057

Out of 1345 patients, 91 (6.8%) had a renal diagnosis other than diabetic or hypertensive nephropathy. Obstructive nephropathy was the most common followed by those with previous nephrectomy and then glomerulonephritis which accounted for 30.8%, 23.1% and 19.8% of those with an additional renal diagnosis respectively. PKD and RAS accounted for 6.6% and 7.7% respectively with the remaining 11 'other' diagnoses consisting of patients with granulomatosis with polyangiitis, Alport syndrome, and congenital abnormalities such as absence or medullary sponge kidney. As might be expected, there were significant differences between the distribution of these primary renal diseases between primary and secondary care. Table 8 shows the number of patients with each renal diagnosis within primary and secondary care below. As with comorbidities mentioned above, p-values were calculated by chi-squared tests in order to determine the significance levels of the observed differences.

Table 8: Prevalence of renal diagnoses by total population and then split by care group

Renal Diagnosis	Total Population (n=1345)	Primary Care (n=695)	Secondary Care (n=650)	p value
RAS (%)	7 (0.5)	0 (0)	7 (1.1)	0.018
PKD (%)	6 (0.4)	0 (0)	6 (0.9)	0.033
Obstructive Nephropathy (%)	28 (2.1)	20 (2.9)	8 (1.2)	0.054
Glomerulonephritis (%)	18 (1.3)	0 (0)	18 (2.8)	<0.001
Previous Nephrectomy (%)	21 (1,6)	0 (0)	21 (3.2)	<0.001
Other (%)	11 (0.8)	2 (0.3)	9 (1.4)	0.054
Total (%)	91 (6.8)	22 (3.2)	69 (10.6)	<0.001

With the exception of obstructive nephropathy, all renal diagnoses were more prevalent in the secondary care group. In fact, 100% of those diagnosed with renal artery stenosis, polycystic kidney disease, glomerulonephritis and previous nephrectomy were in receipt of secondary care; albeit at varying levels of significance. The differences between primary and secondary care for PKD and RAS were significant at the 5% level with p-values of 0.018 and 0.033 respectively whereas glomerulonephritis and previous nephrectomy had statistical significance at a greater level of 0.1% ($p<0.001$). The diagnoses for which some patients were being treated under primary care only were not significant at the 5% level as both obstructive nephropathy and 'other' renal diagnosis had a p-value of 0.054 which is just above the threshold for significance at 0.05.

Overall, if we accept the premise that in general patients in secondary care have been referred for a reason and therefore exhibit more complicated health issues, we might expect patients in secondary care to be younger and have a greater burden of renal or co-morbid disease. At baseline this is true for our study population with regards to average age and burden of renal disease as patients in secondary care were both significantly more likely to have a renal diagnosis and be younger compared to primary care patients; thus supporting this premise. However, with regards to the distribution of comorbid disease such as diabetes, hypertension and diabetes there was no clear cut distinction suggesting a higher prevalence in secondary care; although the burden is likely to have been underestimated in secondary care due to missing data. Regardless, the significant differences found baseline should be adjusted for before we can compare progression rates between care groups.

5.2 Simple Linear Modelling of Continuous Variables

Simple linear models were constructed between potential continuous explanatory variables and eGFR (the response variable) in order to investigate the relationships between them and

their potential effects on renal function. The variables included were age as well as the biomarkers albumin to creatinine ratio, haemoglobin, corrected calcium, serum albumin, alkaline phosphatase and serum phosphate. Table 9 outlines the results below.

Table 9: Results of simple linear models of eGFR against potential continuous explanatory variables

Variable	Coefficient	Standard Error	p-value
Age	-0.021	0.018	0.242
ACR	-0.010	0.063	0.879
Haemoglobin	0.132	0.016	<0.001
Corrected Calcium	-6.536	2.733	0.017
Albumin	0.426	0.070	<0.001
ALP	-0.015	0.006	0.008
Phosphate	-5.159	1.812	0.005

For the variable age, the linear model coefficient was -0.021 which would show that per year increase in age eGFR declines by 0.021 ml/min/1.73 m^2 but the effect is not significant (p=0.242).

The result for albumin-creatinine ratio again shows no relationship between it and eGFR. The linear model coefficient was -0.010 and the p-value was not significant (p=0.879).

The linear model coefficient for haemoglobin was 0.132 which suggests that every unit (g/L) decrease in haemoglobin predicts a decrease in eGFR by 0.13 ml/min/1.73 m^2. The result is significant at the 0.1% significance level (p<0.001).

Per unit increase in corrected calcium, an eGFR decline of 6.54 ml/min/1.73 m^2 is predicted by the linear model coefficient of -6.536. This result is just above the threshold for significance at the 1% level but is significant at the 5% level (p=0.017). However we cannot interpret this result as both extremes of calcium are linked with progression; a non-linear relationship which cannot be captured by a linear model.

There is a significant positive relationship between serum albumin levels and renal function. According to the simple linear model, for every 1 mg/mmol increase in albumin levels predicts an increase in eGFR by 0.43 ml/min/1.73 m^2 with significance at the 0.1% level ($p<0.001$).

The linear model for ALP shows a significant negative relationship between ALP and eGFR whereby a unit increase in ALP predicts a reduction in eGFR by 0.02 ml/min/1.73 m^2 ($p=0.008$).

A significant relationship was found between serum phosphate and renal function at baseline. The linear model coefficient of -5.159 demonstrates a negative relationship. Per unit increase in serum phosphate, eGFR decreases by 5.16 ml/min/1.73 m^2 ($p=0.005$).

Overall, significant relationships were found between eGFR and five out of seven of the continuous explanatory variables investigated. Positive relationships were identified for haemoglobin and serum albumin whereas the relationships between corrected calcium, ALP and serum phosphate were negative. Surprisingly, no significant relationships were identified for age and albumin-creatinine ratio as reduced eGFR is more common with increasing age and ACR itself is associated with CKD disease progression. However, within the data set there are a lot of missing values for ACR which could explain this missed association.

5.3 Simple Linear Modelling of Categorical Variables

In order to explore the relationship between the response variable eGFR and categorical explanatory variables with two outputs, simple linear models were constructed in order to measure the association between them. The table below shows the results of these for the variables male gender, white ethnicity, positive history of smoking, hypertension, cardiovascular disease and diabetes.

Table 10: Results of simple linear models of eGFR against potential categorical explanatory variables

Variable	Coefficient	Standard Error	p-value
Gender (Male)	-0.158	0.453	0.727
Ethnicity (White)	2.041	2.623	0.437
Smoking (Positive History)	-0.528	0.484	0.276
Hypertension	0.144	0.442	0.744
CVD	-0.863	0.449	0.055
Diabetes	-0.804	0.457	0.078

For male gender, the linear model coefficient was -0.158 which suggests that males have marginally lower eGFR values at baseline than females. However, this was not significant (p=0.727) and would have been of limited to no clinical relevance regardless.

Being of white ethnicity was not found to be significantly associated with better renal function at baseline than non-white ethnicity. The linear model coefficient was 2.041 which suggests that white patients within the study sample would on average have eGFR values 2.04 ml/min/1.73 m^2 greater than those of non-white ethnicity (p=0.437).

Patients with a history of smoking had eGFR values which were on average 0.53 ml/min/1.73 m^2 worse than patients who had never smoked. This was not found to be significant (p= 0.276).

The linear model coefficient for hypertension was 0.144 suggesting a slight improvement in eGFR for those with a history of hypertension. This was not statistically significant (p=0.744).

History of cardiovascular disease had a coefficient value of -0.863 which on average suggests that those with a history of cardiovascular disease have slightly worse eGFR values at baseline than those without. However this was just above the 5% significant level (p=0.055).

On average, patients with diabetes have eGFR 0.80 ml/min/1.73 m^2 lower than patients without as demonstrated by its linear model coefficient of -0.804. This relationship was not found to be significant (p=0.078).

Overall, there were no statistically significant relationships discovered between eGFR and any of the binary variables. The lack of significant associations found between having a history of hypertension, cardiovascular disease or diabetes and renal function at baseline is perhaps a little surprising especially considering the causative nature of the relationship between hypertension or diabetes and chronic kidney disease. However, as previously mentioned, the burden of these comorbidities may not be accurate.

5.4 Multiple Linear Regression Modelling

Using the same baseline data as in sections 5.2 and 5.3, we now develop a multiple regression model for eGFR. A forwards stepwise regression approach was implemented and example R code may be found in the appendix. Initially a 'full model' using all potential explanatory variables was constructed with the exceptions of the biomarker ACR and categorical variable smoking status, which were omitted due to their high proportions of missing values (93.3% for ACR, 40.2% for smoking status).

The table below shows the results of a model with main effects only, using data from 512 patients.

Table 11: Coefficients for the full multiple regression model for eGFR (ACR and smoking omitted)

Variable	Coefficient	Standard Error	p value
(Intercept)	52.868	10.501	<0.001
Care (Secondary)	-7.435	0.877	<0.001
Age	-0.058	0.031	0.064
Gender (Male)	-1.576	0.754	0.037
Ethnicity (Not Stated)	2.846	3.319	0.392
Ethnicity (White)	4.301	3.227	0.183
Haemoglobin	0.073	0.023	0.001
Corrected Calcium	-2.025	2.856	0.479
Albumin	0.071	0.108	0.512
ALP	-0.010	0.008	0.224
Phosphate	-4.797	1.863	0.010
Hypertension	-0.985	0.710	0.166
CVD	0.770	0.747	0.303
Diabetes	0.232	0.758	0.759

Care group was both statistically and clinically significant within the model summarised in Table 11; with patients in secondary care having a 7.435 ml/min/1,73 m^2 lower eGFR at baseline than primary care patients ($p<0.001$). In order to explore this association further, a second model was constructed which also accounted for any potential interaction effects between care group and other potential explanatory variables. Table 12 outlines the results below.

Table 12: Coefficients for the full multiple regression model for eGFR accounting for interaction effects between care group and other explanatory variables

Variable	Coefficient	Standard Error	p value
(Intercept)	54.793	18.579	0.003
Care (Secondary)	-9.090	20.969	0.665
Age	-0.053	0.031	0.093
Gender (Male)	-1.412	0.757	0.063
Ethnicity (Not Stated)	2.526	3.307	0.445
Ethnicity (White)	3.873	3.216	0.229
Haemoglobin	0.083	0.044	0.064
Corrected Calcium	-6.976	5.796	0.229
Albumin	0.088	0.201	0.661
ALP	-0.000	0.020	0.992
Phosphate	-0.288	3.269	0.930
Hypertension	1.450	1.235	0.241
CVD	-0.357	1.234	0.772
Diabetes	1.482	1.243	0.234
Care*Haemoglobin	-0.008	0.051	0.867
Care*Corrected Calcium	5.858	6.657	0.379
Care*Albumin	-0.025	0.236	0.917
Care*ALP	-0.008	0.022	0.730
Care*Phosphate	-6.045	3.959	0.127
Care*Hypertension	-3.704	1.507	0.014
Care*CVD	1.879	1.531	0.220
Care*Diabetes	-2.384	1.555	0.126

The only significant interaction effect captured in this model was between care group and hypertension ($p=0.014$). Refitting without the non-significant interactions gave the model summarised in Table 13. We call this the ‘full model’.

Table 13: Coefficients for the full multiple regression model for eGFR accounting for interaction effect between care group and hypertension only

Variable	Coefficient	Standard Error	p value
(Intercept)	50.633	10.451	<0.001
Care (Secondary)	-5.102	1.182	<0.001
Age	-0.055	0.031	0.072
Gender (Male)	-1.529	0.749	0.042
Ethnicity (Not Stated)	2.917	3.295	0.376
Ethnicity (White)	4.302	3.203	0.180
Haemoglobin	0.076	0.023	<0.001
Corrected Calcium	-2.188	2.836	0.441
Albumin	0.077	0.107	0.474
ALP	-0.007	0.008	0.338
Phosphate	-4.747	1.849	0.011
Hypertension	1.816	1.190	0.128
CVD	0.719	0.742	0.333
Diabetes	0.059	0.754	0.938
Care*Hypertension	-4.244	1.454	0.004

We now define the 'null model' to include only the demographic variables age, gender and ethnicity. Other variables were then added in turn; the order of which to add next being based on the judgement of both the statistical and clinical significance of the variables from the 'full model', until further additions did not give a significant improvement in the fit. This resulted in the successive adding of care group, haemoglobin, phosphate and hypertension. The next variable, cardiovascular disease, made no statistically significant improvement to the model. Table 14 below shows the characteristics of the model prior to the inclusion of CVD.

Table 14: Coefficients for the multiple regression model prior to refitting for eGFR

Variable	Coefficient	Standard Error	p value
(Intercept)	46.947	5.644	<0.001
Age	-0.052	0.030	0.081
Gender (Male)	-1.355	0.724	0.062
Ethnicity (Not Stated)	3.231	3.272	0.324
Ethnicity (White)	4.586	3.178	0.150
Care (Secondary)	-5.280	1.163	<0.001
Haemoglobin	0.080	0.021	<0.001
Phosphate	-4.578	1.831	0.013
Hypertension	1.941	1.163	0.097
Care*Hypertension	-4.373	1.441	0.003

In this model care group was the most clinically and statistical significant variable included with a coefficient of -5.280 and a p value of less than 0.001 which shows that secondary care is a predictor of lower eGFR values. Each unit increase in haemoglobin predicted an eGFR decline of 0.08 ml/min/1.73 m^2 at the 0.1% significance level ($p<0.001$). Conversely phosphate shows a negative association whereby a single unit increase in phosphate predicts a reduction in eGFR by 4.58 ml/min/1.73 m^2. This was also statistically significant but at a lesser significance level of 1% ($p=0.013$). Surprisingly, in this model hypertensive patients were predicted to have better eGFR values at baseline by 1.94 ml/min/1.73 m^2 which although not found to be statistically significant as its p value was just above the threshold of significance ($p=0.097$), may be clinically significant and did make a statistically significant improvement to the model. Accounting for the interaction effect between care group and hypertension reduced the magnitude of the care group coefficient to -4.373.

In order to test the assumption that residual values are normally distributed, a histogram was constructed and inspected (see Figure 6 below). On visualisation, although not a perfect fit, it does seem to show a normal distribution; meaning that the assumption has been met in this model.

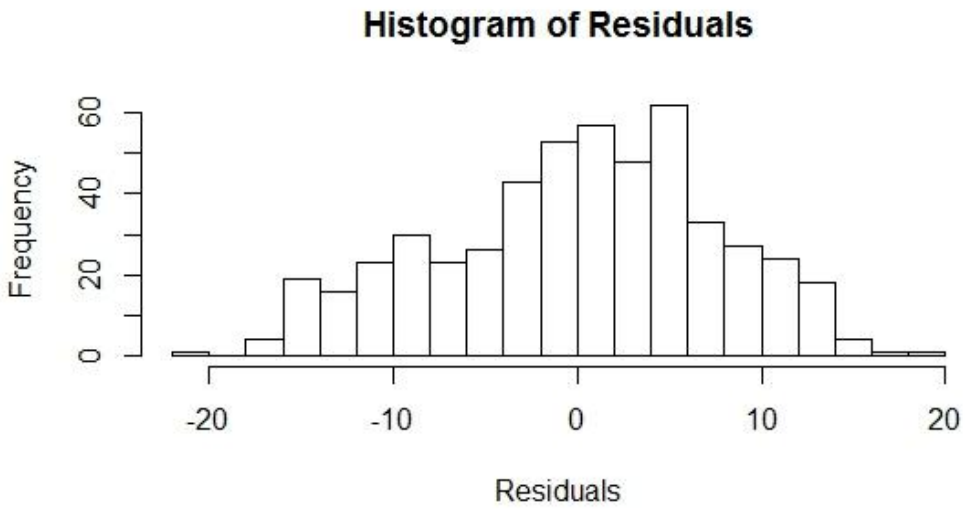


Figure 6: Histogram of residual values for the constructed model

Plots of the residuals against the fitted values were constructed to evaluate the adequacy / goodness of fit of the model constructed. As previously mentioned, no demonstrable pattern should be seen; thus indicating good fit. Overall, the residual plot for the constructed multiple regression model shows no obvious discernible pattern of residuals and therefore shows satisfactory fit for the model (see Figure 7).

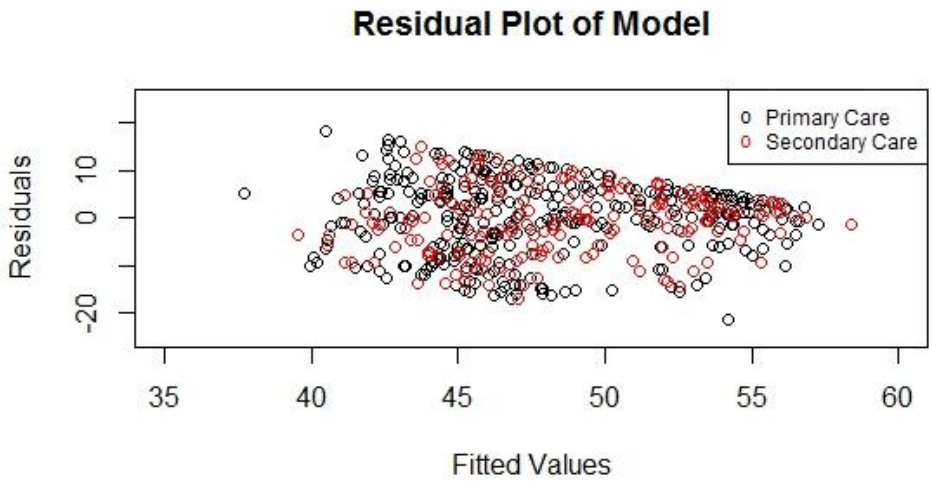


Figure 7: Plot of fitted values against residuals divided by care group

It does however show a slight linearity between fitted and residual values which suggests that the model may have a propensity to underestimate higher eGFR values and overestimate lower values. It was suggested that this may possibly be due to uncaptured interaction effects between care group and the other biomarker variables which were not accounted for in the current model. However, comparison of the distribution of residuals for primary and secondary care patients shows no particular pattern and extending the current model to account for interaction between care group and haemoglobin or phosphate yielded no significant results; thus not supporting this theory. It is therefore more likely that this linear appearance is due to having an entry criterion which restricts baseline eGFR to between 30-59 ml/min/1.73 m^2.

Overall, the final multiple regression model included the following variables: age, gender, ethnicity, care group, haemoglobin, phosphate, and hypertension. A significant interaction effect between care group and hypertension was present and accounted for within the model which demonstrated the absence of systematic error and satisfactory fit through the lack of discernible pattern of residuals (Figure 7).

CHAPTER 6: LONGITUDINAL ANALYSIS RESULTS

6.1 Description of Longitudinal Data

Here we aim to describe the data available for longitudinal analysis and provide the results of the initial exploratory analysis.

As the main outcome variable of interest eGFR had no missing values due to the entry criteria, a record was considered to be incomplete if there were missing values for the non-eGFR biomarker variables: haemoglobin, corrected calcium, albumin, alkaline phosphatase and phosphate. Similarly to in the multiple regression modelling performed in the cross-sectional analysis, albumin to creatinine ratio was omitted again due to its high proportion of missing values (85.6%).

Of the 11,364 records provided from 1,345 patients, there were only 4,530 complete records from 1,094 patients. Table 15 shows the number of complete records available per patient.

Table 15: Breakdown of patients by number of complete records available

Number of Complete Records	1-5	6-10	11-15	14-20	>20
Number of Patients	844	149	70	25	6

Between one and five complete records were available for 844 patients of which 282 patients had only one complete record. 149 patients had six to ten complete records, 70 patients had between 11-15 complete records and 25 patients had 14-20. Only 6 had more than 20 complete records with the maximum number of complete records being 37. The mean number of complete records was 4.14, SD 4.11. 251 patients had zero complete records so were subsequently excluded from the linear mixed effects modelling to be discussed later. The ungrouped breakdown of complete patient records can be found in the appendix (Table 20).

Figure 8 shows the eGFR trajectories of a random sample of 50 patients overall and then split by care group. Here we can see that eGFR has different patterns in different patients. Whilst some patients demonstrate small variations in eGFR between measurements, others vary by over 50 ml/min/1.73 m^2. Overall trajectories are also variable with some patients demonstrating improvement in renal function over time, others demonstrating progressive decline and others no particular change. There seems to be no obvious difference between patient trajectory patterns when comparing primary and secondary care. However, it should be noted that the lack of data beyond 3.3 years for most patients in secondary care is due to the available data being restricted to a shorter period of time as previously mentioned in section 4.1.

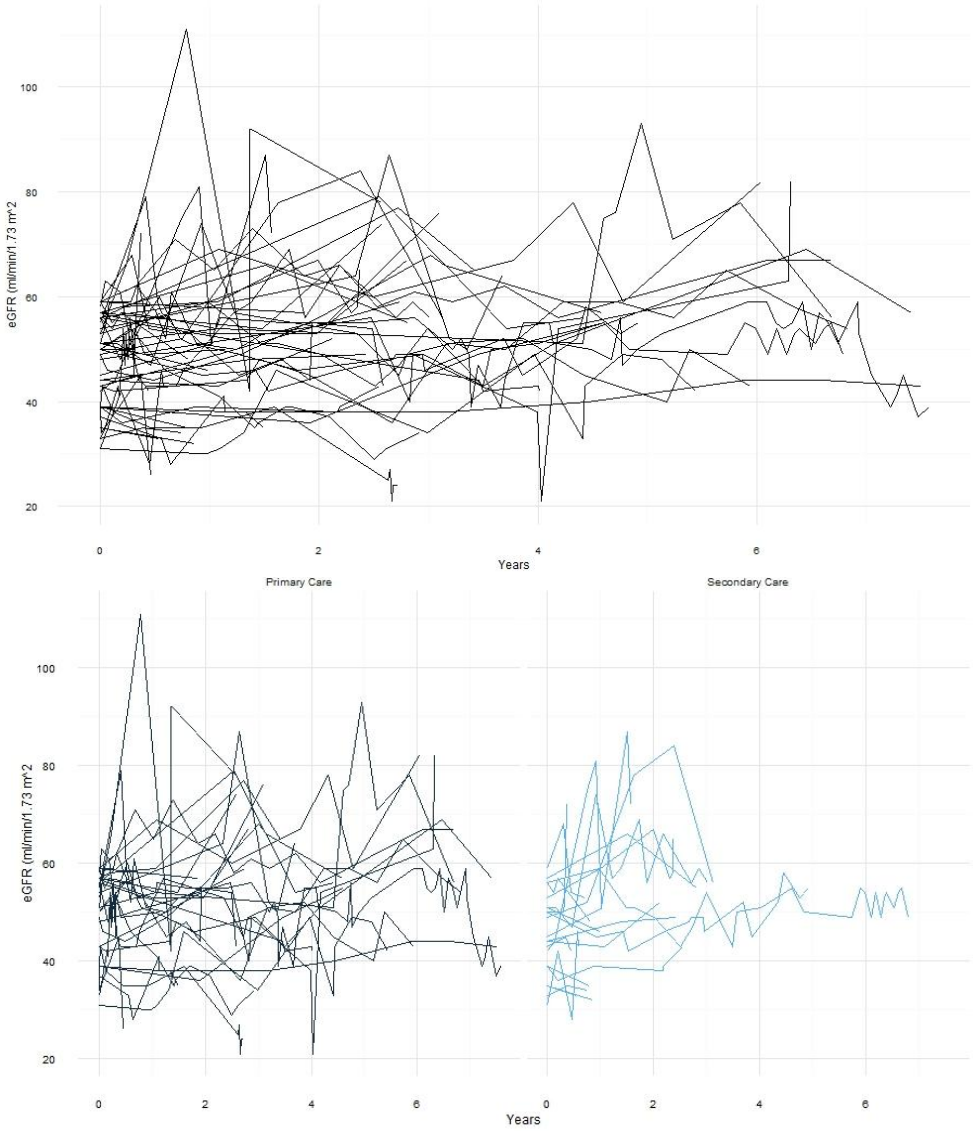


Figure 8: Spaghetti plots showing the eGFR trajectories of a random sample of 50 patients and then split by care group

6.2 Preliminary Linear Mixed Effects Modelling

In order to investigate any potential differences between primary and secondary care patients in a longitudinal analysis, we attempted to construct two different linear mixed effects models: one for primary care and another for secondary care. We did this by initially constructing normal multiple regression models which allowed us to exclude variables which were not likely to be significant in the mixed effects model and then converting these multiple regression models to linear mixed effects models in order to account for the non-independence between longitudinal measurements. Variables which were no longer significant post-conversion were excluded from the mixed effects model. Tables 16 and 17 show the characteristics of the mixed effects models for primary and secondary care respectively.

Table 16: Linear mixed effects model for primary care only

Fixed Effects	Value	SE	p-value	Random	SD	Corr
Intercept	76.807	6.719	<0.001	Intercept	5.505	
Age	-0.280	0.036	<0.001	Time	2.914	0.322
Gender(Male)	0.107	0.809	0.895	Residual	7.861	
Ethnicity (Unknown)	10.800	3.819	0.005			
Ethnicity (White)	13.230	3.797	<0.001			
Time (years)	1.822	0.185	<0.001			
Diabetes	15.852	5.875	0.007			
Albumin	-0.184	0.107	0.086			
Phosphate	-7.604	1.204	<0.001			
Diabetes:Albumin	-0.334	0.138	0.016			

The primary care mixed effects model included 2,827 complete records from 568 patients. It shows that for every per year increase in a patients baseline age, eGFR declines by 0.28 ml/min/1.73 m^2 ($p<0.001$). Males had a marginally higher eGFR (0.10 ml/min/1.73 m^2) than females but this was not statistically significant ($p=0.895$). Patients of white ethnicity had eGFR values 13.23 ml/min/1.73m^2 greater than those of non-white ethnicity and this was statistically significant ($p<0.001$). Each single unit increase in phosphate predicted a 7.60

ml/min/1.73 m^2 reduction in eGFR (p<0.001). The model shows a significant interaction effect between diabetes and albumin levels whereby albumin levels are predictive of diabetes effect on patients' renal function. Surprisingly, per unit increase in albumin is associated with a 0.33 ml/min/1.73 m^2 reduction in eGFR for diabetic patients only. However, overall relationship between diabetes and eGFR is likely to be positive. Based on the mean albumin level of primary care patients (41.21 g/L), those with diabetes have eGFR values 2.09 ml/min/1.73 m^2 greater than patients without diabetes. Albumin does not have a significant effect on its own.

Overall, patients in primary care seemed to show improvement in renal function over time with an eGFR increase of 1.82 ml/min/1.73 m^2 per year.

Table 17: Linear mixed effects model for secondary care only

Fixed Effects	Value	SE	p-value	Random	SD	Corr
Intercept	61.165	6.435	<0.001	Intercept	8.708	
Age	-0.109	0.041	0.007	Time	3.529	0.125
Gender(Male)	-0.645	0.975	0.509	Residual	6.660	
Ethnicity (Unknown)	-0.043	5.373	0.994			
Ethnicity (White)	1.546	5.212	0.767			
Time (years)	0.827	0.321	0.010			
Diagnosis (RAS)	-11.348	4.142	0.006			
Diagnosis (Nephrectomy)	-3.631	2.649	0.171			
Diagnosis (PKD)	1.713	4.898	0.723			
Diagnosis (Other)	-6.675	3.639	0.067			
Diagnosis (Obstructive Nephropathy)	-7.276	4.686	0.121			
Diagnosis (Glomerulonephritis)	-5.793	2.601	0.026			
Phosphate	-9.549	1.273	<0.001			
Haemoglobin	0.037	0.018	0.047			
Hypertension	-2.202	0.946	0.020			

The secondary care mixed effects model was fitted to 1,703 complete records from 526 patients. It shows that for every per year increase in a patients baseline age, eGFR declines by 0.11 ml/min/1.73 m^2 (p=0.007). Males had a marginally reduced eGFR which was 0.65 ml/min/1.73 m^2 lower than females but this was not statistically significant (p=0.509).

Patients of white ethnicity had eGFR values 1.55 ml/min/1.73m^2 greater than those of non-white ethnicity but again this was statistically significant (p=0.767). Each single unit increase in phosphate predicted a 9.55 ml/min/1.73 m^2 reduction in eGFR (p<0.001). For secondary care patients, two renal diagnoses were associated with having poorer renal function. Patients with either renal artery stenosis or glomerulonephritis had poorer eGFR than those without by 11.35 ml/min/1.73 m^2 (p=0.006) and 5.79 ml/min/1.73 m^2 (p=0.026) respectively. The results from other renal diagnoses within the model were not significant at the 5% level. Per unit increase in haemoglobin was associated with a 0.04 ml/min/1.73 m^2 improvement in renal function (p=0.047). Patients with hypertension had eGFR which was 2.20 ml/min/1.73 m^2 lower than those without (p=0.020). No significant interaction effects between variables were found.

Overall, patients in secondary care show a 0.83 ml/min/1.73 m^2 improvement in renal function per year (p=0.010).

If we compare the intercepts of both models, patients in primary care are likely to have a higher starting level of eGFR: 76.81 ml/min/1.73 m^2 for primary care compared to 61.17 ml/min/1.73 m^2 in secondary care. Only age and serum phosphate were found to be significant in both models and whilst the magnitude of the effect of age is slightly greater in primary care, the effect of phosphate is greater in secondary care. Surprisingly patients with diabetes are likely to have better renal function, dependent on their albumin levels, than those without in primary care only. Conversely, whilst no interaction effects were found in secondary care, additional different variables were found to be significant. Having an existing renal diagnosis specifically renal artery stenosis or glomerulonephritis, poorer haemoglobin levels and having hypertension were significantly associated with poorer renal function in secondary care. By identifying the different variables which were statistically significant for one model but not the other e.g. diabetes in the primary care model, we have identified some variables which may potentially interact with care group in the overall

combined population model. These include diabetes, diabetes*albumin, renal diagnosis, haemoglobin and hypertension.

6.3 Final Mixed Effects Modelling

We created a linear mixed effects model for the total study population by adding the variable care group and then automatically including the baseline demographic variables such as age, gender and ethnicity plus any variable which was found to be significant in either the primary or secondary care model. Potential interaction effects between care group and the variables unique to one model as discussed above were explored for statistical significance before deeming the variable as insignificant and excluding it. Hypertension as a variable was recoded to account for the treatment effect of antihypertensive agents which have been shown to reduce progression rates to the same level as those without hypertension. The new binary variable for hypertension instead refers to patients diagnosed with hypertension but receiving no antihypertensive therapy instead of the crude previous delineation of diagnosis of hypertension or not. Similarly we recoded care group into a three-way categorical variable by splitting secondary care patients into those who were seeing a renal specialist or not. This was to allow us to make a more in depth comparison of the effect of secondary care on renal function. The characteristics of the overall model can be found below in Table 18.

Table 18: Linear mixed effects model for total population

Fixed Effects	Value	SE	p-value	Random	SD	Corr
Intercept	74.604	5.983	<0.001	Intercept	6.854	
Age	-0.214	0.027	<0.001	Time	2.964	0.249
Gender(Male)	-0.122	0.628	0.856	Residual	7.458	
Ethnicity (Unknown)	4.860	3.111	0.118			
Ethnicity (White)	7.164	3.069	0.020			
Time (years)	1.834	0.186	<0.001			
Diagnosis (RAS)	-6.642	3.721	0.075			
Diagnosis (Nephrectomy)	-3.230	2.346	0.169			
Diagnosis (PKD)	4.509	4.304	0.295			

Diagnosis (Other)	-4.422	2.853	0.121
Diagnosis (Obstructive Nephropathy)	-0.780	1.963	0.691
Diagnosis (Glomerulonephritis)	-0.042	2.383	0.986
Phosphate	-7.910	0.885	<0.001
Haemoglobin	0.058	0.014	<0.001
Albumin	-0.278	0.108	0.010
Untreated Hypertension	-1.582	0.821	0.054
Diabetes	16.693	5.851	0.004
Care (Secondary Non-renal)	-0.389	6.433	0.952
Care (Secondary – renal)	-12.374	10.356	0.232
Time:Care (Secondary Non-renal)	-0.960	0.400	0.017
Time:Care (Secondary Renal)	-2.005	0.651	0.002
Albumin:Diabetes	-0.344	0.137	0.012
Diabetes:Care (Secondary Non-renal)	-17.196	9.113	0.059
Diabetes:Care (Secondary Renal)	-17.917	13.414	0.182
Albumin:Diabetes (without):Care (Secondary Non-renal)	-0.065	0.154	0.672
Albumin:Diabetes (with):Care (Secondary Non-renal)	0.243	0.154	0.672
Albumin:Diabetes (without):Care (Secondary Renal)	-0.022	0.248	0.930
Albumin:Diabetes (with):Care (Secondary Renal)	0.372	0.208	0.074

The total population mixed effects model was fitted to 4,530 complete records from 1,094 patients. It shows that for every per year increase in a patients baseline age, eGFR declines by 0.21 ml/min/1.73 m^2 ($p<0.001$). Males had a marginally reduced eGFR which was 0.12 ml/min/1.73 m^2 lower than females but this was not statistically significant (p=0.856). Patients of white ethnicity had eGFR values 7.16 ml/min/1.73m^2 greater than those of non-white ethnicity and this was statistically significant (p=0.020). Despite being significant in the secondary care model, results from the total population model show no specific renal diagnosis significantly affects renal function at the 5% level. However, patients with renal artery stenosis had poorer eGFR than those without by 6.64 ml/min/1.73 m^2 although this

was just above the threshold for significance (p=0.075). Each single unit increase in phosphate predicted a 7.91 ml/min/1.73 m^2 reduction in eGFR (p<0.001). Per unit increase in haemoglobin was associated with a 0.06 ml/min/1.73 m^2 improvement in renal function (p<0.001). Patients with untreated hypertension had eGFR which was 1.58 ml/min/1.73 m^2 lower than those without but this was just above the threshold for statistical significance (p=0.058).

Similarly to the primary care model, interaction effects were observed involving diabetes in either a two-way interaction between albumin or in a potential three-way interaction also involving care group. Individually the variables care group, diabetes and albumin were all associated with significant effects on renal function. Each single unit increase in albumin was significantly associated with a 0.28 ml/min/1.73 m^2 increase in eGFR (p=0.010). Without accounting for the interaction between diabetes and albumin, having diabetes in primary care was associated with a statistically significant increase in eGFR by 16.69 ml/min/1.73 m^2 (p=0.004); in contrast to secondary care in which a diagnosis of diabetes was associated with 0.50 ml/min/1.73 m^2 (p=0.059) and 1.22 ml/min/1.73 m^2 (p=0.182) reduction in eGFR depending whether patients were under non-renal or renal specialist care respectively. The interaction effect between albumin and diabetes associates a per unit increase in albumin with a 0.34 ml/min/1.73 m^2 reduction in eGFR if diabetic which would reduce the beneficial effect of diabetes on renal function to 2.36 ml/min/1.73 m^2 based on a mean albumin level for primary care of 41.68 g/L. In contrast to this finding, increasing albumin levels and thus better nutritional status, were associated with improvements in eGFR by 0.37 ml/min/1.73 m^2 per unit increase in albumin in diabetic patients under renal specialist care although this was just above the threshold for statistical significance (p=0.074). The interaction between albumin and diabetes in the secondary non-renal care group was not remotely significant but there is an almost significant interaction between secondary non-renal care and diabetes

which associates diabetes with worse renal function than those without by 0.50 ml/min/1.73 m^2.

No additional interaction effects were found between care group and any other variables.

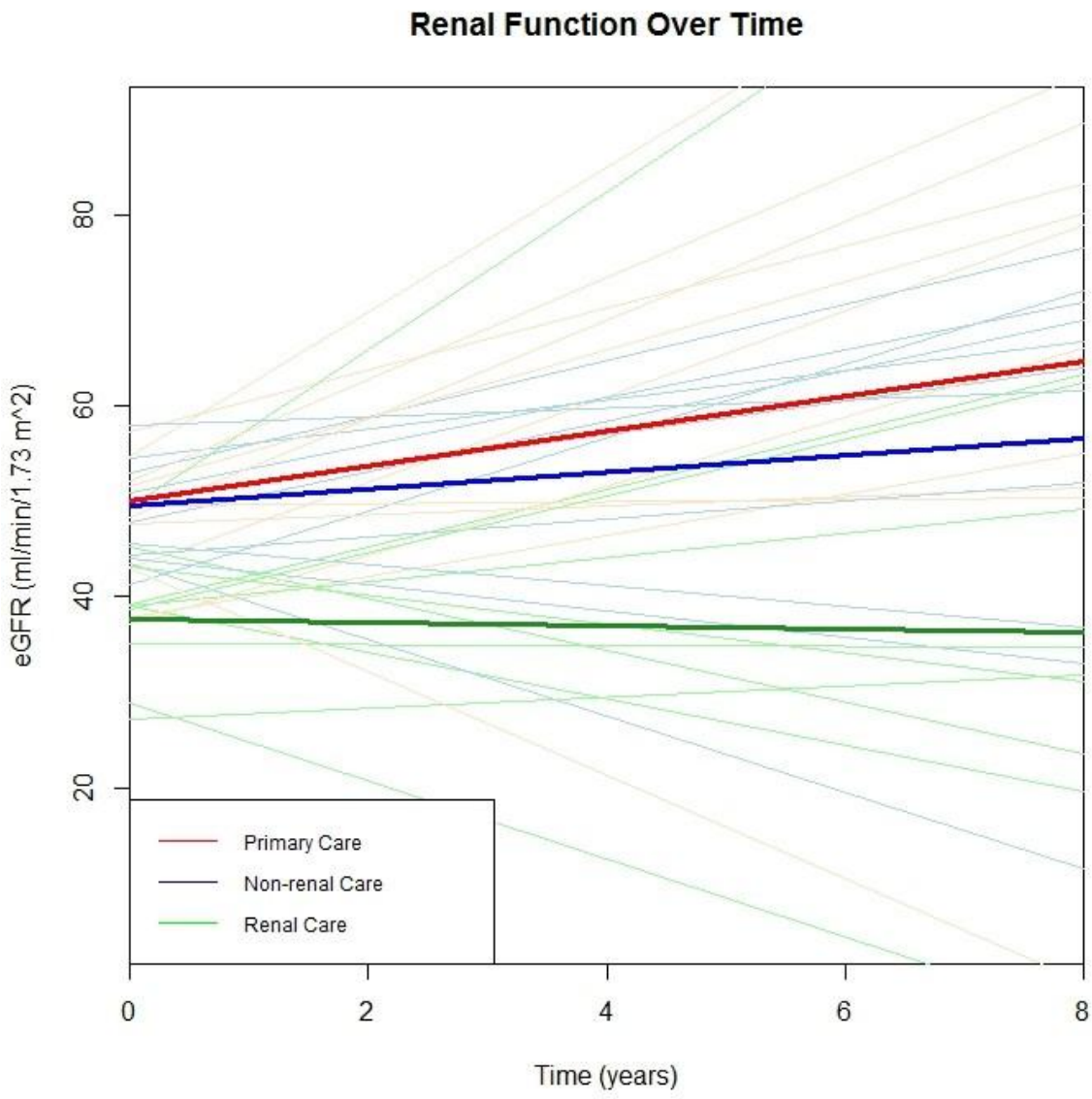


Figure 9: Plot showing the overall eGFR trajectories of primary care, secondary non-renal care and secondary renal care patients with 15 simulated individual patient trajectories per group

Figure 9 above shows the trends of renal function over time by care group based on a starting eGFR of 50 ml/min/1.73 m^2 for primary care patients. The bold red, blue and green lines show the overall trajectories for primary, secondary non-renal and secondary renal care respectively. Additionally there are 15 simulated patient lines included for each care

group. Secondary care patients under non-renal specialists had a non-significant difference in baseline renal function compared to primary care patients which was -0.39 ml/min/1.73 m^2 (p=0.952). Patients receiving care from renal specialists also had worse renal function at baseline which was 12.37 ml/min/1.73 m^2 lower than primary care patients but again this was not significant (p=0.232) .The overall trajectories of primary care patients and secondary non-renal patients showed improvement in renal function. In primary care this was an improvement in eGFR by an average of 1.83 ml/min/1.73 m^2 per year (p<0.001) but in non-renal secondary care patients renal function improved by a lesser rate of 0.87 ml/min/1.73 m^2 per year. In contrast, patients who received care from a renal specialist showed a decline in renal function by a rate of 0.17 ml/min/1.73 m^2 per year.

The weighted average for the study population was 1.26 ml/min/1.73 m^2.

6.4 Residual Diagnostics

Figures 10 and 11 are plots used for the residual diagnostics for the combined model. Figure 11 shows no clear pattern and Figure 10 shows a normal distribution of residuals which therefore demonstrates a good fit for the model and thus the absence of systematic error. However as Figure 11 shows increasing variance with increasing fitted values, if we had not been constrained by time pressures we would have liked to log-transform the output variable eGFR in order to reduce the variability and therefore improve the model fit. Residual diagnostics for the primary and secondary care only models can be found in the appendix (Figures 13-16).

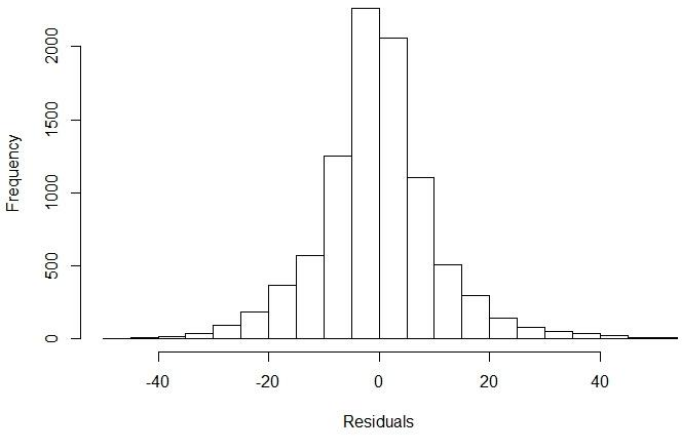


Figure 10: Histogram of residual values for the total population linear mixed effects model

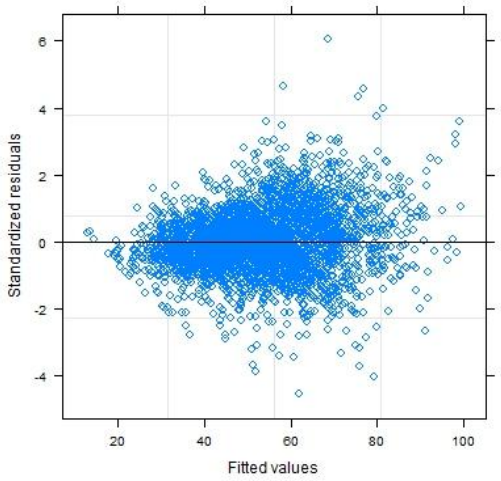


Figure 11: Residual plot for the total population mixed effects model

6.5 Patient Mortality, Progression to ESRD and Initiation of RRT

Overall there were 227 patient deaths over the study period of up to 8 years of which 152 were primary care patients and 75 were secondary care. Crude mortality rates for the respective groups are therefore 16.9%, 21.9% and 11.5% for the total population, primary care and secondary care. As primary care patients had a study period greater than that of secondary care, we then restricted analysis of primary care patients to those who died within the first 3.3 years (the study period for secondary care) in order to make figures comparable. Comparable mortality rates were 7.4% (n=100), 4.3% (n=30) and 10.8% (n=70) for the total population, primary care and secondary care respectively. The difference in mortality rate between primary and secondary care is equivalent to a 2.49 times increased risk of death for the secondary care group (95% CI = 1.65-3.77). This was significantly different at the 0.1% level. Of the secondary patients who died, only 10% (n=7) were under renal specialist care. The relative risk of death for renal compared to non-renal patients in secondary care was 0.50 (95% CI = 0.23-1.06).

In total 10 patients progressed to ESRD in the study period which is a total population incidence rate of 0.74%. According to our data, most of these patients were under primary care (60%, n=6) and those under secondary care were split evenly between non-renal (20%,

n=2) and renal specialists (20%, n=2). Crude rates for the incidence of ESRD in primary and secondary care were 0.86% and 0.62% respectively. Once restricted to a period of 3.3 years the incidence rates of ESRD were 0.30% (n=4), 0.14% (n=1) and 0.46% (n=3) respectively for the total population, primary care and secondary care. The relative risk for secondary care compared to primary care was 3.21 (95% CI = 0.33-30.76) but this was not significant. However, renal secondary care patients were 8.92 times more likely to progress to ESRD than non-renal secondary care patients (95% CI = 0.81-97.61) but as the confidence interval includes 1 this result cannot be seen as statistically significant.

Of the patients who progressed to ESRD we know that one went on to receive haemodialysis and then renal transplantation and that another also had a transplant but additional data on the other patients is missing. We therefore cannot make any comparisons or conduct any analyses between care groups for RRT.

6.6 Summary

Patients with CKD stage G3 not under renal specialist care show an overall improvement in renal function over time which is equivalent to improvements of 1.83 ml/min/1.73 m^2 or 0.87 ml/min/1.73 m^2 per year in eGFR for primary care and non-renal secondary care patients respectively. Conversely, patients receiving renal specialist care decline at an overall rate of 0.17 ml/min/1.73 m^2 per year. Increasing age, non-white ethnicity, higher phosphate levels, lower haemoglobin levels and higher albumin levels were significantly associated with poorer renal function whilst surprisingly diabetes was associated with greater renal function in primary care which to some extent may be influenced by albumin levels. Patients in secondary care have a significantly increased risk of mortality compared to primary care patients which is equivalent to a relative risk of 2.5 although a substantial portion of this risk

may be attributed to patients in non-renal secondary care. Similarly, those who progress to ESRD are more likely to be under secondary care specifically renal care.

CHAPTER 7: DISCUSSION AND CONCLUSIONS

7.1 Discussion

This is the first study to attempt to compare patterns of renal function in CKD G3 patients in different care settings so we have no other literature with which to directly compare our results.

Patients in secondary care have worse biomarker values at baseline

With the exceptions of serum calcium and phosphate levels, patients in secondary care had biomarkers which were both significantly different and suggestive of worse or slightly further progressed disease compared to primary care patients.

Haemoglobin levels were significantly lower for secondary care patients which is suggestive of a higher prevalence of anaemia in secondary care patients although levels were within normal parameters (132.8 g/L in primary care and 124.1 g/L for primary and secondary care respectively). Albuminuria levels at baseline support the notion that secondary care patients are at greater risk of progression as on average secondary care patients had albuminuria 6.48 mg/mmol greater than primary care patients. There may also be a greater prevalence of metabolic acidosis and therefore perhaps CKD metabolic bone disease in the secondary care population which can be inferred by the higher ALP levels in secondary care of 100.7 mmol/L compared to 89.1 mmol/l in primary care. Lower albumin results in secondary care compared to primary care suggest that secondary care patients have poorer nutritional status. On average, corrected calcium levels were 2.35 mmol/L and 2.39 mmol/L for primary and secondary care respectively. Although this difference was statistically significant, as CKD may cause both hypo- and hypercalcaemia, the clinical interpretation of these results is difficult. This could be due to a greater prevalence of secondary hyperparathyroidism in the secondary care group or due to the presence of a solitary individual with worse disease.

However, as the spread of data for secondary care is greater than primary care this is hard to determine.

Overall trends of renal function are significantly different between care groups.

At baseline patients in secondary care had eGFR which was 6.06 ml/min/1.73 m^2 significantly worse on average than patients in primary care. This difference is likely to be due to having a higher proportion of patients with worse renal function in renal secondary care as results from longitudinal analysis suggest that on average renal secondary care patients have eGFR which is 12.37 ml/min/1.73 m^2 worse than patients under primary care. Although this finding was not statistically significant, this difference is large enough to be clinically significant unlike the difference of -0.39 ml/min/1.73 m^2 for patients in non-renal secondary care which is statistically significant but unlikely to be clinically relevant. The total population demonstrated an average improvement of 1.26 ml/min/1.73 m^2 per year over a mean follow up period of 2.84 years. Both primary care patients and non-renal secondary care patients demonstrated improvements in renal function over time by rates of 1.83 ml/min/1.73 m^2 per year and 0.87 ml/min/1.73 m^2 per year respectively. This is in contrast to a decline in renal function demonstrated by patients seeing renal specialists in secondary care by 0.17 ml/min/1.73 m^2 per year.

There are three possible ways to interpret these findings:

1. Patients in renal specialist care are deteriorating because the care they receive is different to that provided by the other care groups
2. Patients under renal specialist secondary care themselves have a greater propensity to decline
3. Patients in renal secondary care are further along in the disease process

To even consider the first interpretation would be ill-advised as previous studies have shown the benefits of nephrology care with regards to slowing progression rates, increasing survival and increasing access to transplantation in patients with ESRD. We therefore focus on trying to explore the latter two explanations.

Differences in renal function trends between care groups cannot be attributed to a greater burden of comorbid disease in secondary care patients.

It may be assumed that patients in secondary care have a greater burden of comorbid disease or more complex health needs and therefore have worse health than patients in primary care. However, according to our data, with regards to the prevalence of hypertension and cardiovascular disease the reverse was true. Primary care patients had significantly higher prevalence rates of these comorbidities which were 15.8% and 3.2% higher for hypertension and cardiovascular disease respectively in comparison to secondary care. For diabetes prevalence rates were greater in secondary care but this was not found to be statistically significant. Additionally, hypertension and cardiovascular disease did not have a significant impact on renal function within the linear mixed effects model which would suggest that for CKD stage G3 patients either these risk factors do not affect renal function or perhaps that the management of these risk factors had already been optimised. As there is already extensive literature which demonstrates the relationship between hypertension or vascular disease as risk factors for progression in CKD patients, we therefore propose the latter explanation but cannot ignore that the burden of comorbid disease likely to have been underestimated in secondary care.

Diabetes was shown to have a more complex relationship with renal function in the linear mixed effect model which shows that it may or may not be dependent on albumin levels and care group. Contradictorily, it seems to suggest that better nutritional status was associated

with worse renal function of diabetic patients in primary care but improved renal function in patients in secondary care under renal specialists. We cannot discount that this finding may just be the result of statistical artefact but the author of this work deems the interpretation of this to be beyond their current level of knowledge on the subject and would therefore like to consult the specialist renal community before commenting on this finding.

Differences in renal function trends between care groups cannot be attributed to a greater burden of known progressive renal diseases.

We know from previous studies that the underlying aetiology of chronic kidney disease can have an impact on patient survival and likelihood of progression to end-stage renal disease[117,118]. Preliminary modelling seemed to support this within the secondary care model as diagnoses of renal artery stenosis and glomerulonephritis were significantly associated with comparatively worse renal function to those without by 11.35 ml/min/1.73 m^2 and 7.28 ml/min/1.73 m^2 respectively. Renal diagnosis had no significance within the primary care model but this was not surprising as the greatest burden of patients with these was within secondary care. Despite being significant in secondary care, within the total population model no specific renal diagnoses demonstrated a significant impact on renal function. The effect of renal artery stenosis was the closest to being significant with a p-value of 0.075 and lesser negative effect on renal function compared the secondary care model of 6.64 ml/min/1.73 m^2. As the effects on renal function from different renal diagnoses were not significant within the full model, we cannot attribute the differences in pattern of renal progression to differences in burden of known progressive renal diagnoses for our study population. However, it is possible that this lack of significance is due to the small number of patients with each diagnosis within our cohort.

Differences in renal function trends between care groups cannot be attributed to differences in antihypertensive therapy use.

Untreated hypertension was shown to have an adverse effect on renal function. Patients with untreated hypertension on average had renal function which was 1.58 ml/min/1.73 m^2 worse than patients who did not. Although this was just above the level for statistical significance (p=0.054), this finding is supported by extensive evidence showing the benefits of antihypertensive therapy especially ACE inhibitors and ARBs which reduce progression rates and also reduce albuminuria[126,152,153,155]. However, the lack of interaction with time or care group for this variable showed that it did not increase the rate of progression and that its effect was similar in all care groups. This finding is perhaps a little surprising, considering that antihypertensive therapy is often the main method of ameliorating renal progression so a lack of treatment would in theory promote faster deterioration in renal function. It is worth noting that in our study diagnoses of untreated hypertension were given based on written records of patient diagnoses not on clinical blood pressure measurements. Thus, it is entirely plausible that some patients categorised as having untreated hypertension did not have a current diagnosis of hypertension and therefore did not require anti-hypertensive therapy. If this was the case, the eGFR patterns may have counteracted the increased progression rates which may have been demonstrable and therefore explain the lack of increased progression rates seen in patients with untreated hypertension.

Stage G3 CKD is not inherently progressive.

As far as we are aware, this is the first study to demonstrate a small overall population level improvement for patients with CKD stage G3. These results therefore add to the growing theory that chronic kidney disease is not an inherently progressive condition and that there is a lot of variability between individuals. This hypothesis was first speculated following the

Modification of Diet in Renal Disease[151] study which observed improvement or non-progression of renal decline in up to 19% of patients with GFR 25-55 ml/min/1.73 m^2 over the two year study period. A more recent longitudinal observation study which focused solely on patients with CKD stage G3 (GFR 30-59 ml/min/1.73 m^2) for an average of four years demonstrated an even greater proportion of favourable outcomes as 27% of patients showed no evidence of progressive decline[20]. In fact, the proportion of non-progressing CKD 3 patients may be even greater as one retrospective cohort study has shown that up to 48.1% of patients with CKD 3 did not progress and instead showed either maintenance or improvement in renal function over a 10 year follow-up period[22]. Even higher rates of non-progression have been found in up to 96% of a UK population of patients with CKD stage G3 who demonstrated non-progression rates of 76% alongside an improvement rate of up to 20% of those studied between 2001 to 2004[191].

Our study population showed an overall improvement in renal function by 1.26 ml/min/1.73 m^2.

We cannot ignore the fact that published evidence shows an overall decline in renal function at a population level which is in contradiction to our findings. Other studies showed rates of renal function decline between 1.0-5.4 ml/min/1.73 m^2 per year[20,192,193]. This suggests that within our study perhaps there were a larger proportion of non-progressing or improving patients than compared to other studies but unfortunately as we did not conduct analyses of individual patient trajectories we cannot confirm this assumption. Additionally as we do not know how many patients within our study population maintained stable renal function or improved we cannot directly compare our figures to those of the studies mentioned above. It is therefore possible that the overall improvement in renal function demonstrated by our results may be instead be due to significant improvements in renal function in a smaller

proportion of patients which made the overall relationship positive as opposed to negative; thereby satisfying the definition of ecological fallacy. However, this alternative explanation seems highly improbable considering the number of patients included in our study.

The all-cause mortality rate for a follow-up period of up to 3.3 years was 7.4% for the total population.

This figure follows similar findings published by other clinical studies which have reported all-cause mortality rates for patients with stage G3 CKD from as low as 6% after a follow up period of three years[193] to as high as 32% and 51% after five and ten years respectively[20]. Although we cannot directly comment on the rate of cardiovascular mortality, evidence from other studies has shown varying figures from as low as 2% in a secondary care cohort after three years[193] to 4% and 21% in a general population after thirteen and ten years respectively.

Secondary care patients had a significantly increased risk of all-cause mortality.

Our study shows that all-cause mortality rates for patients under primary care or secondary care are 4.3% and 10.8% respectively which confers to a significant increased relative risk of 2.49 for patients in secondary care. Of the patients who died in secondary care compared to primary, the majority (90%) of patients had been seeing non-renal specialists although differences were not deemed to be statistically significant (RR=0.50, 95% CI = 0.23-1.06). This suggests that patients with CKD stage G3 who are at higher risk of all-cause mortality are more likely to be under secondary care but not necessarily under renal specialists and therefore that the increased risk of mortality in secondary care may be due to other non-CKD related risk factors or co-morbidities in patients seeing non-renal specialists. The all-cause mortality rate attributable to CKD stage G3 patients under renal specialists may be

quantified as 5.8% which is 1.5% more than primary care patients. This is similar to the rate of all-cause mortality rate of 6% from a patient cohort under nephrology care[193] as previously mentioned above.

The ESRD rate for a follow-up period of up to 3.3 years was 0.30 % for the total population.

Our study demonstrated a very low rate of end-stage renal disease of only 0.74% for the complete follow up period of up to 8 years which reduced to 0.30% when restricted to 3.3 years follow up. These figures are especially small in comparison to study with a ten year follow up of nephrology patients which published that just over one in four patients started dialysis[22]. However as the study patient population was from South Korea their results may not be generalisable to western populations which is demonstrated by a study showing a high rate of ESRD which outcompeted mortality risk in a population of patients from eastern Asia[193].

There was no significant difference between rates of ESRD between the different care groups.

The incidence rate for our renal secondary care population was 1.68% after 3.3 years which although notably higher than the overall secondary care rate of 0.46% is in keeping with similar incidence rates reported in CKD stage G3 patients of 1.3-2% after 5 years and 4% after ten years[20,21]. Although there was a non-significant difference in risk of ESRD between primary and secondary care patients in our study, figures show lower rates in primary compared to secondary care of 0.14% and 0.46% respectively. This is consistent with two studies which show lower rates of ESRD in general populations compared to secondary care[80,193].

Patients with CKD G3 are at greater risk of all-cause mortality than progression to ESRD.

Similarly to results from other studies[20,21], our findings support the risk of mortality being greater than the risk of ESRD in patients with CKD stage G3. This was true for all care settings which show that risk of ESRD was outcompeted by risk of mortality. We can quantify this as increased absolute risks of 7.10%, 4.17% and 10.34% for the total population, primary and secondary care respectively for a follow up period of 3.3 years.

7.2 Clinical Impact

The rationale behind our study was that NICE guidelines[2] are currently based on poor evidence; especially those which pertain to when to refer patients for specialist care which on the whole recommend referral at stages 4-5 not stage G3. Here we revisit the advice provided by the National Institute of Clinical Excellence within the context of our findings to explore whether they support or refute current referral recommendations/practices.

We have shown that within our study, patients in primary and non-renal secondary care showed overall improvements in renal function over time whilst secondary care patients under renal specialists showed an overall decline. This suggests that in primary care patients with stage G3 CKD are receiving good care from GPs which is not only able to reduce progression and maintain stable renal function for at least 2.84 years but perhaps also improve renal function in some patients. The lack of significant association between hypertension and eGFR in different care groups supports this and implies that overall hypertension was adequately controlled in all groups through the use of antihypertensive therapy. Our study therefore supports the current recommendation to refer patients for 'GFR less than 30 ml/min/1.73 m^2 (GFR category G4 or G5), with or without diabetes'[2] therefore promoting referral at CKD stages G4-5.

On the other hand, we could not explain the worsening of renal secondary care patients via greater burdens of co-morbid hypertension, cardiovascular disease or known progressive renal diseases for the renal secondary care group as these were not significantly associated with eGFR. However, if we also take into account the worse starting baseline renal function for secondary care groups especially renal patients it suggests that perhaps patients in secondary care under renal specialists were further along in their individual disease progression than primary care patients. Our results suggest that the start of deterioration occurs after 2.84 years. As the lack of association with comorbidities known to cause progression alludes to management being satisfactory in all care settings, we hypothesise that independently of existing comorbidities, patients with an increased propensity to decline have already been referred to secondary care by GPs. We also suggest that primary care management of CKD is able to defer renal decline in most patients for at least 2.84 years. The NICE recommendations[2] for identifying these patients as those who either suffer from a 'sustained decrease in GFR of 25% or more, and a change in GFR category or sustained decrease in GFR of 15 ml/min/1.73 m^2 or more within 12 months', 'known or suspected rare or genetic causes of CKD', 'hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses' or 'suspected renal artery stenosis' is supported by this hypothesis. The referral of RAS patients is also demonstrated by our study as 100% were in secondary care. However as there were still individual patients who progressed to ESRD under primary care, it is possible that some patients with progressive renal deterioration were not referred.

It is clear from the overall trajectory of renal improvement and within primary and non-renal secondary care that patients who can be diagnosed with stage G3 CKD will not necessarily

progress and that a large proportion of patients may in fact improve over an average time period of 2.84 years. This brings into focus an additional question of whether the diagnostic definition of "abnormalities of kidney structure or function, present for more than 3 months, with implications for health"[2] should have its time period of three months extended for patients with CKD stage G3 in the absence of other markers of renal dysfunction. One study using the K/DOQI[81] staging criteria explored this relationship for patients with stage G3 by comparing rates of ESRD and improvement within diagnostic categories from 3 months to 12 months[194]. It found that extending the category from 3 months up to 12 months only increased the incidence rate of ESRD from 4.2% in the 3 month cohort to 4.6% in the 12 month cohort whilst the proportions of patients with improvement decreased. The observed 0.1 ml/min/1.73 m^2 per year increase in renal decline observed between 3 month and 6 month cohorts was non-significant. This suggests that increasing the arbitrarily defined period for diagnosing patients with stage G3 CKD up to 6 months may reduce the number of patients undergoing unnecessary investigation for CKD without significantly affecting progression rates. However, the evidence from our study is not strong enough to support this recommendation.

7.3 Limitations of the Study

Capping of eGFR values greater than 60 ml/min/1.73 m^2 meant that we had to calculate these values within our data set by using the MDRD equation on serum creatinine measurements. Ideally we would have used the exact equation used by the laboratory but this could not be provided within the timescale of this project. We cannot deny that by using MDRD calculated values we have introduced an element of bias into our data set. Although the MDRD equation is known to underestimate GFR ≥60 ml/min/1.73 m^2 [195], we do not know how this compares with the data provided from the laboratory so the true rates of eGFR

improvement/decline may have been over or underestimated. Despite this, we know that the overall relationships of slight improvement or decline are still valid as these trends were still present when using data with eGFR figures capped at 60 ml/min/1,73 m^2.

Initially the data underpinning our study from secondary care was incomplete as it lacked information on comorbidities, and outcomes such as death or commencement of RRT. As previously mentioned this data was collected manually from outpatient clinic letters. Admittedly this method of data collection is not the most robust of data collection techniques as the data available to the collector was dependent on how individual consultants wrote their clinic letters. It is therefore likely that the burden of comorbidities within secondary care patients has been underestimated as information may have been missing from letters.

Unfortunately we were unable to use portions of our data due to missing information within the data set. The most significant knock-on effect of this was the exclusion of albumin creatinine ratio from our baseline and longitudinal modelling as its inclusion excluded the majority of our patient records. As a well-known independent predictor of renal decline in CKD patients, this risk factor is important in identifying patients at increased risk of progression so being unable to account for this means that we were not able to compare the effects of albuminuria between care groups. This does not however affect the validity of our results on progression rates which was the main objective of our study.

Due to the time constraints applied to this study, we were unable to quantify the duration of secondary care or frequency of visits to secondary care specialists. This means that we defined our primary and secondary groups based on a crude delineation of whether or not

patients had attended a specialist clinic or not. Although we know that any amount of secondary renal care is beneficial to patients with CKD, this research was conducted on patients with ESRD and therefore may not be generalisable to patients with stage G3 CKD. There may be a minimum amount of secondary care required before conferring benefit to patients in patients with stage G3 which we have therefore not been able to account for or explore with our study. This means we may not have compared the true effects of care on CKD stage G3 patients as some patients in secondary are may not have had any meaningful intervention at the time of their inclusion within the study.

As our study compared primary and secondary care by using data from a single primary care practice, it is possible that results may not be generalisable to the whole of primary care. However, as the practice had twelve GPs we are likely to have captured the effects of potential differences in referral practices between doctors which, alongside a fairly large patient population, we believe supports our results as generalisable.

7.4 Suggestions for Further Research

We believe that we have identified an area which is severely lacking in evidence. Existing published studies often not only focus on patients with CKD stages G4-5 not stage G3 but the majority of studies focus on specific patient cohorts such as primary or secondary care which make direct comparisons between the two care settings difficult.

Studies on patients with ESRD have already shown the benefits of secondary care referral by demonstrating reductions in the rate of decline as well as decreased mortality rates in individuals post-referral earlier to specialist care. However as we cannot generalise the

findings of these studies to patients with CKD stage G3 we suggest that similarly designed studies should be carried out which follow patients with CKD stage G3 pre and post-referral to secondary care so we can directly measure the potential benefits that secondary care can provide. Similar studies with longitudinal designs could also investigate the frequency of visits and the overall duration of care which could provide evidence on which to base criteria for the frequency of monitoring / follow-up in secondary care.

Unfortunately our study was only able to make a crude comparison between patients who had been to secondary care and those who had not so could not shed any light on the impact of patient transitions between care groups. Guideline 1.5.4 from CG182 advises that patients referred to specialist care may be discharged back to primary care for 'routine follow-up to take place at the patient's GP surgery rather than in a specialist clinic'. If doctors follow this advice, patients are therefore likely to transition between care settings: a variable which we have not managed to account for. In light of this, we propose that further studies could either study the patterns of transition between primary and secondary care and how this affects renal function for patients with CKD stage G3 or make less crude comparison than our study has. This could be done by comparing rates from periods when patients are known to have been in one care setting as opposed to an extended period of several years in which a patient was known to have visited a specialist at least once in the overall period.

As previously mentioned some of the limitations of this study included being unable to account for albuminuria due to the missingness of the variable within the data set as well as limited generalisability from studying patients from only one GP practice and one hospital trust. Similar research should therefore be repeated on data sets which can include

albuminuria and also explore relationships in patients from a wide variety of different GP practices to increase the generalisability of results.

During our longitudinal analysis we discovered an interesting association between albumin and diabetes which contradictorily seems to suggest that better nutritional status was associated with worse renal function of diabetic patients in primary care but improved renal function in patients in secondary care under renal specialists. Although this finding may be due to statistical artefact, a potential clinical explanation for this finding is beyond the current knowledge and understanding of the author but following a brief search for relevant literature, there seems to be limited evidence exploring albumin levels in diabetic patients with CKD which therefore underpins this as the final suggested area for future research.

7.5 Conclusion

Chronic kidney disease is a complex and diverse condition which affects a growing number of people worldwide. Its complications are numerous ranging from anaemia to metabolic bone disease and hyperparathyroidism. Without intervention patients with CKD are at risk of developing end-stage renal disease requiring dialysis or transplantation or may instead suffer from cardiovascular events which result in patients being at increased risk of mortality. Whilst diabetes is the leading cause of ESRD, hypertension, vascular disease and albuminuria have relationships which are bidirectional in nature. They are both associated with causing or accelerating the progression of CKD and are also complications of renal dysfunction. Managing these risk factors through the use of antihypertensive agents, statin therapy and control of hyperglycaemia have been shown to improve patient outcomes by reducing CKD progression or reducing mortality risk. Specialists in secondary care aim to optimise the management of patient risk factors and this has already been shown to benefit

patients with ESRD by reducing rates of renal decline. Current UK guidelines from the National Institute of Clinical Excellence recommend referral of patients with CKD at stages G4-5 but these guidelines are based on 'no evidence' and the professional opinion of members of the Guideline Development Group only and other guidelines are not based on strong evidence. This proffered the question of whether patients with CKD stage G3 should be referred to secondary care or whether current management is adequate in primary care.

Overall we found that for patients with CKD stage G3, renal function was stable and showed a slight improvement of 1.26 ml/min/1.73 m^2 per year for an average follow up period of 2.84 years. Patients in primary care showed slight rates of improvement in eGFR whilst renal secondary care patients declined overall which suggests that the care provided in primary care is able to maintain stable renal function and defer the start of deterioration. Renal secondary care patients showed a small overall rate of decline and had worse renal function at baseline which in the context of an overall population improvement implies that patients in renal care were potentially already further along in the CKD disease process than those in primary care. This also suggests that perhaps primary care is able to defer renal decline in CKD G3 patients for up to 2.84 years.

Our findings support current NICE guidelines regarding the referral of patients to secondary care at stages G4-5 as on average CKD stage G3 patients did not progress. As patients in secondary care under renal specialist care had an overall decline in renal function, it suggests that patients with progression were already seeing nephrologists. This suggests that overall, the referral guidelines seem to be able to adequately identify patients at risk of progression. However as we did not conduct individual analyses we do not know to what extent this is assumption is valid. Furthermore, there is evidence which suggests that some progressing patients were not identified by general practitioners which may be inferred from the presence patients who progressed to end-stage renal disease in the primary care cohort. Further research on the effect of referral practices on CKD stage G3 patients should

therefore be conducted to identify other potential criteria for progression in this disease which has wide variability within patients.

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APPENDIX A – Figures and Tables

Table 19: Baseline mean, median, SD, IQR and range at baseline for the total population and by gender and care group

Biomarker		Total Population	Male	Female	Primary Care Only	Secondary Care Only
eGFR	Mean	49.23	49.13	49.29	52.16	45.97
	Median	51.00	51.0	51.0	54.0	47.0
(ml/min)	SD	8.03	8.03	8.03	6.17	8.58
	Interquartile Range	43.0-56.0	43-56	44.0-56.0	49.0-57.0	39.0-53.0
	Range	30.0-59.0	30.0-59.0	30.0-59.0	31.0-59.0	30.0-59.0
ACR	Mean	3.775	6.51	1.28	2.01	8.84
	Median	0.61	0.84	0.50	0.45	1.68
(mg/mmol)	SD	10.10	13.98	2.46	7.14	14.87
	Interquartile Range	0.30-1.62	0.3-4.78	0.30-1.00	0.30-1.03	0.51-10.2
	Range	0.10-56.20	0.11-56.20	0.30-14.66	0.10-56.20	0.11-55.16
Hb	Mean	128.7	131.9	125.4	132.8	124.1
	Median	129.0	133.0	127.0	133.0	124.0
(g/L)	SD	17.52	19.20	16.04	15.27	18.37
	Interquartile Range	117-140	120-146	116-136	123-143	113-136
	Range	62.0-187.0	78-187	62-166	62-182	78-187
Corrected Calcium	Mean	2.37	2.35	2.39	2.35	2.39
	Median	2.36	2.34	2.37	2.33	2.37
	SD	0.13	0.12	0.13	0.10	0.14
(mmol/L)	Interquartile Range	2.30-2.43	2.28-2.40	2.31-2.44	2.29-2.39	2.31-2.45
	Range	1.49-3.11	2.03-3.01	1.49-3.11	2.14-2.88	1.49-3.11
Serum Calcium	Mean	2.396	2.37	2.41	2.39	2.40
	Median	2.39	2.36	2.40	2.38	2.40
	SD	0.14	0.14	0.15	0.11	0.16
(mmol/L)	Interquartile Range	2.32-2.47	2.31-2.44	2.33-2.49	2.32-2.46	2.32-2.49
	Range	1.61-3.16	1.86-3.01	1.61-3.16	2.03-2.80	1.61-3.16
Albumin	Mean	41.35	41.42	41.30	42.05	40.53
	Median	42.0	42.0	42.0	42.0	41.0
(g/L)	SD	3.48	3.61	3.40	3.01	3.85
	Interquartile Range	39.0-44.0	39.0-44.0	39.0-43.0	40.0-44.0	39.0-43.0
	Range	22.0-52.0	24.0-49.0	22.0-52.0	30.0-52.0	22.0-49.0
ALP	Mean	94.62	91.32	96.54	89.13	101.7
	Median	84.0	80.50	87.0	81.0	89.0
(IU/L)	SD	43.15	42.25	43.59	36.77	49.89
	Interquartile Range	69.0-110.0	65.8-106.0	72.0-111.0	68.0-103.0	71.0-118.0
	Range	30.0-465.0	31.0-385.0	30.0-465.0	31.0-465.0	30.0-413.0
Phosphate	Mean	1.12	1.07	1.16	1.12	1.12
	Median	1.12	1.07	1.15	.10	1.12
(mmol/L)	SD	0.20	0.19	0.19	0.19	0.20
	Interquartile Range	0.99-1.25	0.93-1.20	1.01-1.29	0.99-1.25	0.99-1.25
	Range	0.38-1.81	0.38-1.60	0.70-1.81	0.38-1.60	0.55-.81

Table 20: Table of Complete Records

Number of Complete Records	Number of Patients
1	282
2	241
3	153
4	104
5	64
6	57
7	24
8	29
9	18
10	21
11	22
12	19
13	16
14	7
15	6
16	6
17	8
18	6
19	4
20	1
21	3
24	1
31	1
37	1

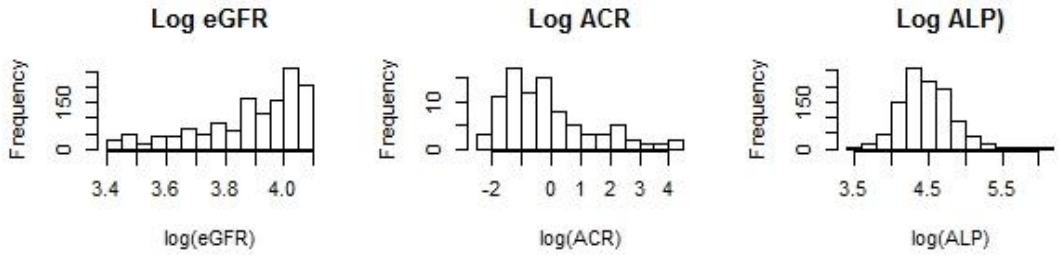

Figure 12: Baseline histograms of eGFR. ACR and ALP following log-transformation

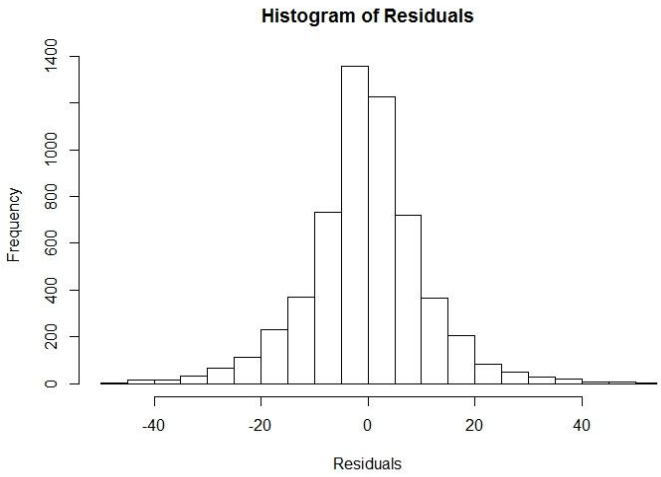

Figure 13: Histogram of residual values for the secondary care linear mixed effects model

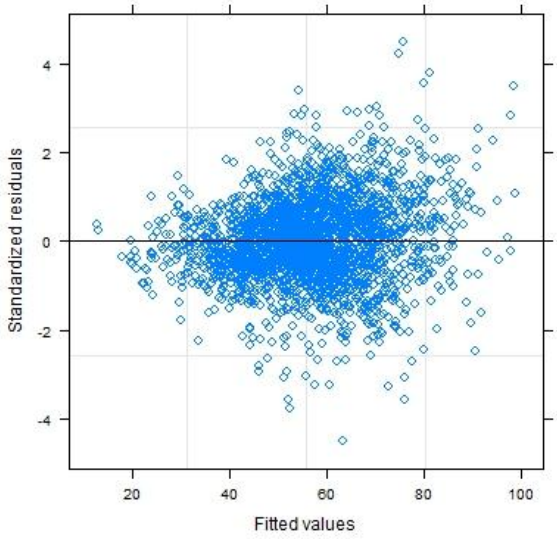

Figure 13: Residual plot for the secondary care mixed effects model

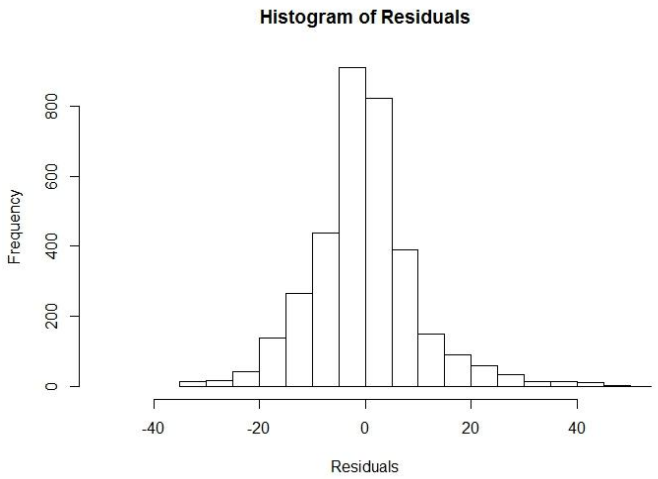

Figure 14: Histogram of residual values for the secondary care linear mixed effects model

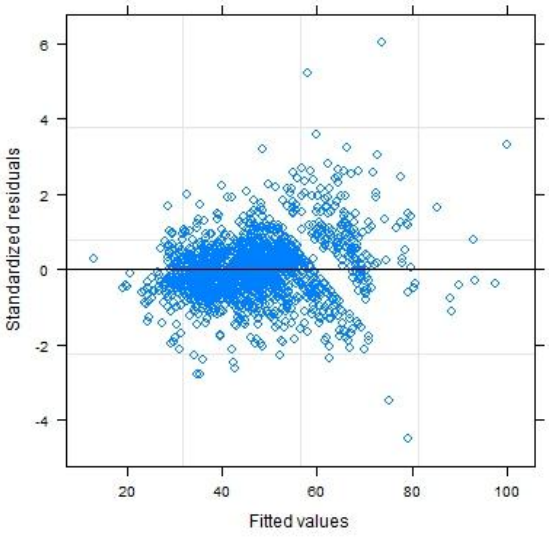

Figure 16: Residual plot for the secondary care mixed effects model

APPENDIX B – R Script Examples

Simple Linear Models

```
Base<-read.csv(file.choose())
attach(Base)

lmage<-lm(Base$eGFR~Base$Age)
summary(lmage)
lmACR<- lm(Base$eGFR~Base$ACR)
summary(lmACR)
lmHb<-lm(Base$eGFR~Hb)
summary(lmHb)
lmAdjcalc<-lm(eGFR~Adj.Calc)
summary(lmAdjcalc)
lmalb<-lm(Base$eGFR~Base$Alb)
summary(lmalb)
lmALP<-lm(eGFR~ALP)
summary(lmALP)
lmPhos<-lm(eGFR~Phos)
summary(lmPhos)
lmmf<-lm(Base$eGFR~as.factor(Base$Gender))
summary(lmmf)
lmeth<- lm(Base$eGFR~as.factor(Base$Eth))
summary(lmeth)
lmsmoke<-lm(Base$eGFR~as.factor(Base$Smoking))
summary(lmsmoke)
lmHTN<-lm(Base$eGFR~as.factor(Base$HTN))
summary(lmHTN)
lmCVD<-lm(Base$eGFR~as.factor(Base$CVD))
summary(lmCVD)
lmDiab<-lm(Base$eGFR~as.factor(Base$Diab))
summary(lmDiab)
```

Multiple Regression Models

```
Base<- read.csv(file.choose())
data<-Base[,c(2:4,11,14,15,17:22,40)]
data<-na.omit(data)

# model with all variables
fit<-lm(data$eGFR~as.factor(data$Care)+data$Age+as.factor(data$Gender)+
        as.factor(data$Eth)+data$Hb+data$Adj.Calc+data$Alb+data$ALP+
        data$Phos+as.factor(data$HTN)+as.factor(data$CVD)+as.factor(data$Diab))

summary(fit)

# final model
fit8<-lm(data$eGFR~data$Age+as.factor(data$Gender)+as.factor(data$Eth)+
         as.factor(data$Care)*as.factor(data$HTN)+data$Hb+data$Phos)

# significance test
anova(fit7,fit8)

# residual diagnostics
plot(fit8$fitted.values, fit8$resid, main="Residual Plot of Model",
    xlab="Fitted Values",ylab="Residuals",xlim=c(35,60),ylim=c(-25,25))
points(fit8$fitted.values[take], fit8$resid[take], col = "red")
legend("topright",c("Primary Care","Secondary
Care"),pch=c("o","o"),col=c("black","red"),cex=0.75)

hist(fit8$residuals,breaks=20, main="Histogram of Residuals",xlab="Residuals")
```

Linear Mixed Effects Models

```
all<-read.csv(file.choose())
library("nlme", lib.loc="C:/Program Files/R/R-3.2.3/library")

# model with all variables
fit<-lme(fixed = eGFR~Age+Gender+Eth+as.factor(Diagnosis)+
        (Day+Hb+as.factor(HTN)+Phos+as.factor(Diab)+(as.factor(Diab):Alb))*as.factor(Care),
         random = ~Day|ID, data=all,na.action=na.omit, method="ML"))

summary(fit)

# final model
fit10<-lme(fixed =
eGFR~Age+Gender+Eth+as.factor(Diagnosis)+Hb+Alb+Phos+as.factor(hyp)+(Day+
       as.factor(Diab)+(as.factor(Diab):Alb))*as.factor(NewCare), random = ~Day|ID,
       data=new,na.action=na.omit,method="ML")

summary(fit10)

# significance test
anova(fit9,fit10)

# residual diagnostics
plot.lme(fit10)
hist(fit10$residuals, breaks=25,main="Histogram of Residuals",xlab="Residuals")
```

Spaghetti Plots Script

```
all<-read.csv(file.choose())

library(ggplot2, lib="C:/R/Rpackages")
library(reshape2, lib="C:/R/Rpackages")
library(gridExtra, lib="C:/R/Rpackages")

# spaghetti plot of all patients
ggplot(all,aes(x=Day,y=eGFR,group=ID))+
  geom_line()+
  theme_minimal()+
  xlab("Years")+ylab("eGFR (ml/min/1.73m^2)")

# spaghetti plot of random sample (n=50)
ids <- data.frame(sample(unique(all$ID), 50))
colnames(ids)<-"ID"
samp<-all[all$ID %in% ids$ID,]

ggplot(samp,aes(x=Day,y=eGFR,group=ID))+
  geom_line()+
  xlab("Years")+ylab("eGFR (ml/min/1.73 m^2")+
  theme_minimal()+
  theme(legend.position="none")+
  facet_grid(. ~ Care,labeller=labeller(Care = labels))
```

Figure 9 Script

```
library("mvtnorm", lib="C:/R/Rpackages")

alpha1<-50 # intercept
beta<- 1.834 # slope parameter for time
SDU<-6.854 # std dev of random intercept
SDV<-2.964 # std dev of random slope
rho<-0.249 # correlation between random slope and intercept
Vmat1<-matrix(c(SDU*SDU,rep(SDU*SDV*rho,2),SDV*SDV),2,2)

n<-15 # number of samples required
RE1<-rmvnorm(n,sigma=Vmat1) # simulate samples
years<-c(0,8) # time-range to be plotted
fixed1<-alpha1+beta*years
random1<-matrix(0,n,2)

alpha2<-49.6 # intercept
beta2<- 0.874 # slope parameter for time
SDU<-6.854 # std dev of random intercept
SDV<-2.964 # std dev of random slope
rho<-0.249 # correlation between random slope and intercept
Vmat2<-matrix(c(SDU*SDU,rep(SDU*SDV*rho,2),SDV*SDV),2,2)

n<-20 # number of samples required
RE2<-rmvnorm(n,sigma=Vmat2) # simulate samples
years<-c(0,8) # time-range to be plotted
fixed2<-alpha2+beta2*years
random2<-matrix(0,n,2)

alpha3<-37.6 # intercept
beta3<- -0.171 # slope parameter for time
SDU<-6.854 # std dev of random intercept
SDV<-2.964 # std dev of random slope
rho<-0.249 # correlation between random slope and intercept
```

```
Vmat3<-matrix(c(SDU*SDU,rep(SDU*SDV*rho,2),SDV*SDV),2,2)

n<-20 # number of samples required
RE3<-rmvnorm(n,sigma=Vmat3) # simulate samples
years<-c(0,8) # time-range to be plotted
fixed3<-alpha3+beta3*years
random3<-matrix(0,n,2)

for (i in 1:n) {
  random1[i,]<-(RE1[i,1]+RE1[i,2]*years)+fixed1
  random2[i,]<-(RE2[i,1]+RE2[i,2]*years)+fixed2
  random3[i,]<-(RE[i,1]+RE3[i,2]*years)+fixed3
}
ylim<-c(5,90)
xlim<-c(0,8)# make space for all the lines!
plot(years,fixed1,type="l",col="red",lwd=3,xlim=xlim,ylim=ylim,xlab="Time
(years)",ylab="eGFR (ml/min/1.73 m^2)",
     main="Renal Function Over Time",xaxs="i")

for (i in 1:n) {
  lines(years,random1[i,],col="bisque")
  lines(years,random2[i,],col="lightblue")
  lines(years,random3[i,],col="palegreen")
}
lines(years,fixed2,col="blue",lwd=3)
lines(years,fixed3,col="forestgreen",lwd=3)
lines(years,fixed1,col="red",lwd=3)
legend("bottomleft",col=c("red","blue","green"),legend=c("Primary Care","Non-renal Care ",
                                        "Renal Care"),lwd=c(1,1,1),cex=0.75)
```