# Optimising care in chronic kidney disease with risk prediction tools and better hyperkalaemia management

---

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Biology, Medicine and Health

2021

Ibrahim Ali

School of Medical Sciences
Division of Cardiovascular Sciences

---

## LIST OF CONTENTS

**WORD COUNT: 53,982**

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ACEi: | angiotensin converting enzyme inhibitor |
| ADPKD: | autosomal dominant polycystic kidney disease |
| AKCS: | Advanced Kidney Care Service clinic |
| AKI: | acute kidney injury |
| ARB: | angiotensin receptor blocker |
| AUC: | area under the curve |
| BMI: | body mass index |
| CI: | confidence interval |
| CKD: | chronic kidney disease |
| CKD-EPI: | chronic kidney disease epidemiology collaboration |
| CVD: | cardiovascular disease |
| CVE: | cardiovascular event |
| DBP: | diastolic blood pressure |
| ΔeGFR: | delta estimated glomerular filtration rate |
| DM: | diabetes mellitus |
| eGFR: | estimated glomerular filtration rate |
| ESRD: | end-stage renal disease |
| Hb: | haemoglobin |
| HDL: | high density lipoprotein |
| HF: | heart failure |
| HFrEF: | heart failure with reduced ejection fraction |
| HR: | hazard ratio |
| KDIGO: | Kidney Disease Improving Global Outcomes |
| KFRE: | Kidney Failure Risk Equation |
| LDL: | low density lipoprotein |
| MI: | myocardial infarction |
| MRA: | mineralocorticoid receptor antagonist |
| NICE: | National Institute for Health and Care Excellence |
| OR: | odds ratio |
| PVD: | peripheral vascular disease |
| RAASi: | renin-angiotensin-aldosterone system inhibitor |
| ROC: | receiver operator characteristic curve |

| | |
|---|---|
| RRT: | renal replacement therapy |
| SBP: | systolic blood pressure |
| SKS: | Salford Kidney Study |
| uACR: | urine albumin:creatinine ratio |
| uPCR: | urine protein:creatinine ratio |
| UK: | United Kingdom |

## ABSTRACT

Chronic kidney disease (CKD) is a highly prevalent condition worldwide that is associated with major health consequences. Patients with progressive and advanced disease can experience significant multi-system complications as well as an increased risk of end-stage renal disease (ESRD) and mortality.

Using data from the Salford Kidney Study, an ongoing observational cohort study of non-dialysis patients with CKD stages 3 to 5, this thesis aimed to explore two major research themes related to optimising CKD care. The first was risk prediction in CKD: the capacity to accurately risk stratify patients in order to enable timely, targeted treatment to those most likely to sustain adverse outcomes. The second concerned better hyperkalaemia management: effectively negating the occurrence of hyperkalaemia can facilitate continuation and optimisation of renin-angiotensin-aldosterone system inhibitors (RAASi), which are well-established renoprotective agents.

Results chapters 4 to 8 focused on areas in the field of risk prediction. Chapter 4 highlighted the differential impact of risk determinants in different primary renal disease groups with emphasis on ESRD and mortality for those with rapid linear progression and those with stable disease. Those progressing rapidly can be further differentiated with respect to clinical endpoints by their pattern of progression, detailed in chapter 5. Chapter 6 reinforced the need to account for the rate and pattern of CKD progression when attempting to identify novel biomarkers of disease. Risk prediction tools exist such as the Kidney Failure Risk Equation (KFRE), designed to predict the 2- and 5-year risk of ESRD in patients with CKD stages 3-5. Chapter 7 demonstrated that the KFRE is not wholly accurate when used for risk prediction in transplant recipients but does have clinical utility in those with advanced CKD as analysed in chapter 8. This provides compelling evidence for shifting towards risk-based tools to guide decision-making in clinical practice. With respect to hyperkalaemia management, chapter 9 emphasised the efficacy of patiromer, a novel potassium binder, in maintaining normokalaemia. This effect was harnessed to successfully up-titrate RAASi dosing in patients with symptomatic heart failure attending a bespoke hyperkalaemia clinic, which was described in chapter 10.

Whilst all the studies in this thesis have helped to deepen our understanding in the field of CKD care, the strength of the KFRE for risk prediction in advanced CKD and the real-world experience of the effectiveness of oral potassium binders have emerged as major findings. This will hopefully provide optimism for future research into tackling the heterogeneity and complexity of CKD management so as to improve long-term patient prognosis.

## DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

## COPYRIGHT STATEMENT

i. The author of this thesis (including any appendices and/or schedules to this thesis) owns certain copyright or related rights in it (the "Copyright") and s/he has given the University of Manchester certain rights to use such Copyright, including for administrative purposes.

ii. Copies of this thesis, either in full or in extracts and whether in hard or electronic copy, may be made **only** in accordance with the Copyright, Designs and Patents Act 1988 (as amended) and regulations issued under it or, where appropriate, in accordance with licensing agreements which the University has from time to time. This page must form part of any such copies made.

iii. The ownership of certain Copyright, patents, designs, trademarks and other intellectual property (the "Intellectual Property") and any reproductions of copyright works in the thesis, for example graphs and tables ("Reproductions"), which may be described in this thesis, may not be owned by the author and may be owned by third parties. Such Intellectual Property and Reproductions cannot and must not be made available for use without the prior written permission of the owner(s) of the relevant Intellectual Property and/or Reproductions.

iv. Further information on the conditions under which disclosure, publication and commercialisation of this thesis, the Copyright and any Intellectual Property and/or Reproductions described in it may take place is available in the University IP Policy (see http://documents.manchester.ac.uk/DocuInfo.aspx?DocID=2442 0), in any relevant Thesis restriction declarations deposited in the University Library, the University Library's regulations (see http://www.library.manchester.ac.uk/about/regulations/) and in the University's policy on Presentation of Theses

## ABOUT THE AUTHOR

I completed my undergraduate medical training at Imperial College London in 2010. I spent the next four years in London for foundation and core medical training before embarking on specialist training in renal and general internal medicine in Manchester in 2014.

Whilst in Manchester, my first foray into postgraduate academic research was through undertaking an MSc in Medical Education at the University of Manchester. Whilst the research was qualitative in nature, it gave me valuable experience in obtaining ethical approval from a research ethics committee, conducting literature reviews and writing effectively in an academic manner.

The subsequent appeal of performing research in nephrology came naturally during my training. I was particularly interested in chronic kidney disease and how it progresses differently in different patients, even in advanced stages, and the momentum of this intellectual stimulation inevitably led me to enrol into a PhD programme of research.

There has been much to reflect and celebrate from my PhD experience. I have developed new skills in applying research methodology and performing statistical analyses. The latter has been entirely self-directed, and I have grown in confidence over the years in utilising statistical software effectively. There has also been success through the publication of several peer-reviewed articles that have arisen from this thesis as well as the opportunity to present the research on an international stage. Most importantly, however, I have enjoyed having the time to explore the medical literature, contemplate ideas, and finally execute research hypotheses through effective collaboration with other enthusiastic researchers. This process has been rewarding and my experiences will serve me in good stead as I continue to mature as an academic researcher.

## JOURNAL FORMAT PRESENTATION

### Justification

This thesis is presented in the journal format as individual research studies outlined in the results chapters have been published in peer-reviewed journals. This is the case for results chapters 4 to 9, whilst chapter 10 is awaiting submission.

### Orientation to thesis layout

The Introduction section (chapter 1) provides an overview and critical appraisal of the literature and is supported by a peer-reviewed publication in the field of risk prediction in CKD. Chapter 1 provides the basis for the overarching research aims that are explicitly detailed in chapter 2, which also highlights the context for how each of the research studies align with each other. The Methods section in chapter 3 summarises the key research methodology utilised throughout the thesis and precedes the Results section, which comprises chapters 4 to 10. The final Discussion section (chapter 11) reviews the key findings and discusses the scope for future research.

## PUBLICATIONS FROM THIS THESIS AND CONTRIBUTION OF AUTHORS

Chapters 1, 2, 3 and 11 were all conceived and written by the main author (Ibrahim Ali) with editorial review from the main supervisor, Professor Philip Kalra. The individual research studies presented in results chapters 4 to 10 would not have been possible without the support and involvement from several co-authors, and their contributions are detailed below alongside each publication.

**Chapter 1**

**Risk prediction in chronic kidney disease**

Ibrahim Ali, Philip Kalra

Curr Opin Nephrol Hypertens. 2019;28:513-518. DOI: 10.1097/MNH.0000000000000553

Ibrahim Ali conceived the study and wrote the manuscript.
Philip Kalra critically revised the manuscript.

**Chapter 4**

**Predictive factors of rapid linear renal progression and mortality in patients with chronic kidney disease**

Ibrahim Ali, Rajkumar Chinnadurai, Sara T. Ibrahim, Darren Green, Philip A. Kalra

BMC Nephrol. 2020;21:345. DOI: https://doi.org/10.1186/s12882-020-01982-8

Ibrahim Ali conceived the study design, undertook data collection, performed statistical analyses and wrote the manuscript.
Rajkumar Chinnadurai performed linear regression analyses.
Sara T. Ibrahim supported with patient selection into the study.
Darren Green and Philip A. Kalra critically revised the manuscript.

**Chapter 5**

**Adverse outcomes associated with rapid linear and non-linear patterns of chronic kidney disease progression**

Ibrahim Ali, Rajkumar Chinnadurai, Sara T. Ibrahim, Philip A. Kalra

BMC Nephrol. 2021;22:82. DOI: https://doi.org/10.1186/s12882-021-02282-5

Ibrahim Ali and Philip A. Kalra conceived the study. Ibrahim Ali performed data collection, statistical analyses and wrote the manuscript.
Rajkumar Chinnadurai performed linear regression analyses.
Sara T. Ibrahim supported with patient selection into the study.
Philip A. Kalra critically revised the manuscript.

**Chapter 6**

**A paradigm to discover biomarkers associated with chronic kidney disease progression**

Ibrahim Ali, Sara T. Ibrahim, Rajkumar Chinnadurai, Darren Green, Maarten Taal, Tony D. Whetton and Philip A. Kalra

Biomarker Insights. 2020;15:1-5. DOI: https://doi.org/10.1177/1177271920976146

Ibrahim Ali and Philip A. Kalra conceived the study. Ibrahim Ali undertook data analysis and wrote the manuscript.
Rajkumar Chinnadurai provided data from linear regression analyses.
Sara T. Ibrahim provided support in patient selection.
Darren Green, Maarten Taal, Tony D. Whetton and Philip A. Kalra critically revised the manuscript.

**Chapter 7**

**A validation of the 4-variable and 8-variable kidney failure risk equation in transplant recipients in the United Kingdom**

Ibrahim Ali, Philip A. Kalra

BMC Nephrol. 2021;22:57. DOI: https://doi.org/10.1186/s12882-021-02259-4

Ibrahim Ali conceived the study, performed statistical analyses and wrote the manuscript.

Philip A. Kalra critically revised the manuscript.

**Chapter 8**

**A validation study of the kidney failure risk equation in advanced chronic kidney disease according to disease aetiology with evaluation of discrimination, calibration and clinical utility**

Ibrahim Ali, Rosemary L. Donne, Philip A. Kalra

BMC Nephrol. 2021;22:194. DOI: https://doi.org/10.1186/s12882-021-02402-1

Ibrahim Ali conceived the study, undertook data collection, performed statistical analyses and wrote the manuscript.

Rosemary L. Donne and Philip A. Kalra critically revised the manuscript.

**Chapter 9**

**The role of patiromer: comparing OPAL-HK data with untreated real-world patients in the United Kingdom – a retrospective, propensity-matched analysis**

Ibrahim Ali, Rajkumar Chinnadurai, Georgiana Cornea, Michele Intorcia, Philip A. Kalra

PLoS ONE 15(8): e0237467. DOI: https://doi.org/10.1371/journal.pone.0237467

Ibrahim Ali undertook data collection, performed statistical analyses and wrote the manuscript.

Rajkumar Chinnadurai performed the propensity-matched analysis.

Georgiana Cornea, Michele Intorcia and Philip A. Kalra conceived the study and critically revised the manuscript.

## Chapter 10

## Experience of a bespoke hyperkalaemia clinic to facilitate prescribing of renin-angiotensin-aldosterone system inhibitors in patients with heart failure with reduced ejection fraction

Ibrahim Ali, Darren Green, Paul Kalra, Philip A. Kalra

*Planned for submission*

Ibrahim Ali undertook data collection, performed statistical analyses and wrote the manuscript.

Philip A. Kalra conceived the study and critically revised the manuscript along with Darren Green and Paul Kalra.

## ACKNOWLEDGEMENTS

Firstly, I wish to give my sincere thanks to my main supervisor, Professor Philip Kalra. His unrelenting buoyant enthusiasm and encouragement has been truly inspiring. He has always sought for me to succeed in all aspects of my career for which I am very grateful.

I wish to also thank my co-supervisor, Professor Darren Green, for his valuable support and guidance over the years.

A special mention goes to Dr Rosemary Donne, with whom insightful discussions surrounding CKD care established the intellectual curiosity to pursue research in this field in the first place.

I am grateful to the contribution of all my co-authors, but I wish to give specific recognition to my early collaborators, Drs Rajkumar Chinnadurai and Sara T. Ibrahim, who provided much-needed initial assistance for me to launch my research work. I am also thankful to Emma Flanagan who was instrumental in data collection for chapter 7.

Finally, I wish to thank all the research nurses for their role in making the SKS a continued success and to the patients in the SKS, without whom this research would not have been achievable.

## DEDICATION

This work is dedicated to my family.

To my sister, for providing me with plenty of laughter.

To my wife, for her undying love and devotion.

To my children, for making my heart swell with joy and happiness.

To my parents, who have made significant sacrifices in their lives to give me the best opportunity to thrive in mine.

I am eternally grateful to all of them.

# CHAPTER 1

# INTRODUCTION

## 1.1 Preface

This chapter provides a critical appraisal of CKD epidemiology, the risk factors associated with progressive disease, the emerging role of biomarkers to help risk-stratify patients and the evidence for clinical risk prediction tools. This section is supported by a published review article on risk prediction in CKD (in which the references have been modified to fit the sequential flow of the introduction). Following this, the chapter discusses the evidence for novel oral potassium-binding agents to facilitate renin-angiotensin-aldosterone system inhibitors as a means to retard CKD progression.

## 1.2 CHRONIC KIDNEY DISEASE DEFINITION AND CLASSIFICATION

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) international guidelines defines chronic kidney disease (CKD) as *"abnormalities of kidney structure or function, present for ≥3 months, with implications for health and is classified based on cause, GFR category, and albuminuria category."* [1]

The guidelines have produced a colour-coded grid (Table 1.1) that incorporates six categories of glomerular filtration rate (GFR) with three categories of albuminuria and serves to highlight prognostic information.

**Table 1.1** KDIGO classification and prognosis of CKD

| | | | **Albuminuria category (mg/mmol)** | | |
|---|---|---|---|---|---|
| | | | **A1** | **A2** | **A3** |
| | | | <3 | 3-30 | >30 |
| **GFR category (ml/min/1.73m$^2$)** | **G1** | >90 | | | |
| | **G2** | 60-89 | | | |
| | **G3a** | 45-59 | | | |
| | **G3b** | 30-44 | | | |
| | **G4** | 15-29 | | | |
| | **G5** | <15 | | | |

**Green: low risk; yellow: moderate risk; orange: high risk; red: very high risk.**
The colouring used is a representation of the pooled adjusted relative risks for each categorical variable of estimated GFR and albuminuria, drawn from a meta-analysis. Outcomes include progressive CKD, acute kidney injury (AKI), end-stage renal failure and cardiovascular and all-cause mortality. Modified and reproduced with permission from KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3:i-150.

This current classification is in sharp contrast to the 2002 classification developed by the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) [2], which described 5 stages of CKD severity based on the GFR (Table 1.2).

**Table 1.2** CKD classification based on NFK KDOQI guidelines

| Stage | Description | GFR (ml/min/1.73m$^2$) |
|---|---|---|
| **1** | Kidney damage with normal or ↑ GFR | ≥90 |
| **2** | Kidney damage with mild ↓ GFR | 60-89 |
| **3** | Moderate ↓ GFR | 30-59 |
| **4** | Severe ↓ GFR | 15-29 |
| **5** | Kidney failure | <15 (or dialysis) |



The 2002 classification is recognised as being the first to provide an internationally recognised, uniform definition of CKD. However, the 2012 guidelines significantly expand on the former classification in four ways. Firstly, emphasis is placed on defining the underlying cause of CKD, which is of importance with respect to offering treatment and predicting long-term events that are disease-specific. Secondly, it separates stage 3 into two categories: G3a (45-59 ml/min/1.7.3m$^2$) and G3b (30-44 ml/min/1.73m$^2$), a subdivision first proposed in the 2008 National Institute of Clinical Excellence (NICE) guidelines on CKD [3]. Thirdly, it considers grades of albuminuria and, fourthly, provides prognostic information on CKD outcomes. In making these changes, it adopts the findings summarised in a number of meta-analyses, which demonstrate that lower eGFR and higher levels of albuminuria are independently associated with progression to end-stage renal disease (ESRD) as well as cardiovascular and all-cause mortality, regardless of the aetiology of CKD [4]. As a result, the heat-map shown in Table 1.1 provides a valuable representation of the relationship of eGFR and albuminuria on the adverse health consequences faced by patients with CKD.

This recognition has prompted many investigators such as Eckardt et al [5] to argue that nephrology has evolved as a subspecialty. From treating the few with life-threatening ESRD, who require specialist intervention such dialysis and transplantation, nephrology has drawn attention to the previously neglected large cohort of patients in the population who have CKD, a condition felt to be benign until eGFR reached levels of less than 15ml/min/1.73m$^2$.

Thus, through a better understanding of the risk profile of patients with CKD, the introduction of the 2012 classification has helped to highlight CKD as a major public health concern, prompting healthcare institutions worldwide to confront the scale of the problem and improve patient outcomes.

## 1.3 THE SCALE OF THE PROBLEM

A number of studies have provided prevalence estimates for CKD in the United Kingdom (UK). The New Opportunities for Early Renal Intervention by Computerised Assessment (NEOERICA) [6] study used primary care computer records in the regions of Manchester, Kent and Surry to extract serum creatinine measurements on 38,262 patients. It found an overall CKD prevalence for stages 3 to 5 of 8.5%, with a greater prevalence amongst females of 10.6% compared with 5.8% in males. In addition, the Health Survey for England (HSE) [7], which monitors health behaviours, risk factors and trends in disease in England, showed in 2016 that 15% of adults aged over 35 years had CKD stage 1 to 5 with 7% at stages 3 to 5. When using the Office for National Statistics population data from 2009, NEOERICA and HSE estimates the number of people in the UK with CKD at approximately 3.6 million and 2.7 million people respectively.

In 2016, Hill et al [8] published a systematic review and meta-analysis of global CKD prevalence by analysing data from 100 studies that were conducted in 74 populations worldwide. It reported a global mean prevalence of 13.4% for CKD stages 1 to 5 and 10.6% for stages 3 to 5. The greatest proportion of individuals were at CKD stage 3 at 7.6%, whereas <1% had CKD stages 4 or 5. Prevalence of CKD was shown to increase with age: from the studies measuring CKD stages 3 to 5, the mean prevalence increased in each decile age category, ranging from 13.7% in those in their 30s to 27.9% in those in their 70s.

Interestingly, the 2017 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) estimated there were almost 700 million people with CKD, representing a global prevalence of 9.1% [9], lower than that reported by Hill et al [8]. This is likely

explained by the fact the GBD excludes clinic-based studies in which the prevalence of high-risk patients with lower eGFR may overestimate the burden of CKD. Nonetheless, both the meta-analysis by Hill et al [8] and the GBD report [9] have important limitations that hinder obtaining an accurate prevalence of CKD.

### 1.3.1 Challenges in determining CKD prevalence

One of the main challenges in determining CKD prevalence from epidemiological studies centres on the inaccuracies that are key to the methodological calculation of eGFR. For instance, creatinine is a biomarker used to determine eGFR but is affected by non-GFR determinants [10] such as muscle mass, ingestion of meat, and drugs such as trimethoprim, which affects creatinine tubular secretion. Furthermore, measuring creatinine without the use of a standardised assay, calibrated to an isotope dilution mass spectrometry method can cause marked differences in creatinine values [10]. In the American study of NHANES (National Health and Nutrition Examination Survey) III [11], using two different creatinine assays caused a variation in creatinine of 20.3μmol/l. This, unsurprisingly, impacted on CKD prevalence by almost four-fold, whereby the estimate for those with CKD stage 3 varied from 3.2% to 12.5%.

A second challenge regards the formulae used to calculate eGFR. The two commonly used methods include the Modification of Diet in Renal Disease (MDRD) study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). The CKD-EPI equation is more accurate than the MDRD equation at reflecting the measured GFR at values more than 60ml/min/1.73m$^2$ [12]. The MDRD equation, in comparison, systematically underestimates the values corresponding to CKD stages 1 and 2 and as a consequence overestimates CKD prevalence by designating more individuals as having CKD stage 3a.

In a meta-analysis of 1.1 million adults from 25 different population cohorts, Matsushita et al [13] showed that, when compared with the MDRD equation, the CKD-EPI re-classified 24.4% of the population to a higher CKD stage with better renal function, and this contributed to a reduction in CKD prevalence for stages 3 to 5 from 8.7% to 6.3%. Significantly, those that were reclassified to a better CKD stage showed lower incidence rates of ESRD, cardiovascular mortality and all-cause mortality even after adjusting for confounders. Similar findings have been demonstrated by others including Skali et al

[14] and White et al [15]. Therefore, the ability to better predict eGFR and the risk of future outcomes has led guidelines to advocate the use of CKD-EPI in favour of MDRD [16].

In returning back to the meta-analysis by Hill et al [8], which included only studies that used MDRD or CKD-EPI formulas, only 12 had in fact used the more accurate CKD-EPI formula. With respect to creatinine assays, 36 studies did not explicitly clarify if the measurements were standardised or calibrated to a reference method. Such limitations, however, are perhaps not as significant as compared with the fact that the vast majority of studies only performed a single creatinine measure in estimating CKD prevalence. In fact, only 5 of the 100 studies in the meta-analysis measured serum creatinine at two different time points in an attempt to fulfil the KDIGO definition of *chronicity*, defined as the persistence of abnormalities for ≥3 months. This is also a shortfall of the GBD report, which in its cross-sectional design, only takes account of single eGFR and albuminuria values. Single measurements are prone to being influenced by non-GFR determinants and can inaccurately label an individual with CKD when they may in fact have an acute kidney injury (AKI), and which may normalise on repeat testing once the offending cause has been treated.

Indeed, Gharbi et al [17] showed how misclassification can occur if repeat samples are not undertaken. In their Moroccan cohort of 10,524 individuals, prevalence was 1.6% in those with an eGFR of less than 60ml/min/1.73m$^2$. In this small cohort of CKD, repeat sampling after 3 months resulted in 32% of those initially classified as stage 3a and 7.8% of those with stage 3b being re-classified with an eGFR of more than 60ml/min1.73m$^2$. Studies, therefore, that do not meet the criteria of chronicity are susceptible to producing overestimates of prevalence.

Such limitations have led Delanaye et al [18] to question whether the threat of a global epidemic of CKD exists in the midst of studies tending to overestimate prevalence. At a population level, however, repeated tests impact on feasibility, increase costs and increase the risk of individual dropout. The US renal data system (USRDS), which provides cross-sectional data on CKD prevalence based on data from NHANES and the Behavioural Risk Factors Surveillance System (BRFSS), recognise this limitation but argue that obtaining true estimates from only two readings can also result in either

under or over-estimation [19]. As a consequence, single measures of creatinine are deemed to be a pragmatic and credible way of providing CKD estimates at the population level.

In the UK, the Quality Improvement in CKD (QICKD) study [20] nonetheless attempted to provide a nationwide prevalence estimate based on two serum creatinine results at least 3 months apart. Figures from 930,997 patients across 129 general practices revealed a prevalence of 5.4%, corresponding to approximately 2.8 million people with CKD stages 3 to 5.

It is clear, therefore, that although the true prevalence of CKD may not be accurately determined, it is nonetheless a common condition that merits close attention, not least because of the adverse health outcomes and high economic cost it inflicts.

### 1.3.2 Health outcomes and financial costs

CKD is not a benign condition, as the 2012 KDIGO guidelines neatly illuminates. It is associated with a multitude of complications, which affect almost every organ system (Table 1.3), the clinical sequelae of many resulting in poor health outcomes [21].

The most concerning complication faced by patients with CKD is the high burden of cardiovascular disease. For instance, Go et al [22] conducted a longitudinal study of 1,120,295 adult members of the Kaiser Permanente Renal Registry within San Francisco. Primary outcomes included all-cause mortality, cardiovascular events and hospitalisation. Cardiovascular events were defined as hospitalisation for coronary artery disease, heart failure, ischaemic stroke or peripheral artery disease. Over a median follow-up of 2.84 years, the study showed that age-standardised rates for all outcomes significantly increased with progressive renal impairment.

**Table 1.3** Complications of CKD [21]

| | |
|---|---|
| **Homeostatic disruption** | **Dermatological** |
| Fluid overload | Pruritis, dry skin, pigmentation |
| Acidosis | |
| Hyperkalaemia | **Gastrointestinal** |
| | Anorexia, nausea |
| **Cardiovascular** | Vomiting, diarrhoea |
| Coronary artery disease | Malnutrition |
| Myocardial infarction | Peptic ulceration |
| Heart failure | |
| Peripheral vascular disease | **Endocrine** |
| Arrhythmias | Secondary and tertiary |
| | hyperparathyroidism |
| **Haematological** | |
| Anaemia | **Neurological** |
| Coagulopathy | Ischaemic stroke |
| | Cognitive impairment |
| **Immunological** | Depression |
| Impaired immunity | Peripheral and autonomic neuropathy |
| | Restless leg syndrome |
| **Sexual** | |
| Sexual dysfunction, reduced fertility | **Musculoskeletal** |
| | Gout |

The strong link between CKD and cardiovascular events has been further supported by Meisinger et al [23] who showed those with CKD stages 3 to 4 had a higher risk of myocardial infarction (MI): the hazard ratio (HR) in women was 1.67 (95% confidence interval [CI] 1.07-2.61) and 1.51 in men (95% CI 1.09-2.10). Furthermore, Weiner et al [24] showed that CKD was an independent risk factor for stroke in CKD stages 3 to 4, with a HR of 1.22 (95% CI 1.02-1.44).

Incorporating these risks into the UK's QICKD prevalence study, 12,334 excess MIs and 6,733 excess strokes occurred in patients with CKD in 2009-10 [25]. The financial

expenditure from these events was estimated to be more than £177 million. This, however, is only a small percentage of the financial burden of CKD on the NHS, which was estimated to be £1.45 billion in 2009-10. This takes into account direct costs of care delivered by general practice, secondary care consultations, hospital admissions and indirect costs associated with the excess morbidity imposed on those with CKD from stroke and MI.

What is most striking from this cost is that over half the total expenditure is spent on care associated with dialysis and transplantation. Thus, although patients with ESRD account for less than 1% of the population, they consume a disproportionate amount of the healthcare budget, and this is representative of the scale of the problem in developed countries. In fact, costs of renal replacement therapy (RRT) render them unaffordable in many developing countries.

The adverse health and economic implications of CKD has been met with a strong response from the international renal community. In 2017, the International Society of Nephrology (ISN) [26] published a global kidney health atlas in an attempt to understand and remedy the wide variations in CKD care across the world. The report advocated for the systematic implementation of a variety of public health strategies to improve CKD care globally. These included screening programmes to detect and manage CKD earlier, creating and maintaining renal registries to analyse and monitor disease burden and raising awareness at the government level to prioritise attention towards CKD. The overarching aim is to deliver optimal care to patients earlier and retard the progression towards ESRD, the effect of which would mean prolonging better health, reducing mortality and lowering long-term healthcare costs.

It is important, therefore, to recognise CKD not simply as a generic term that encompasses a multitude of heterogeneous diseases but to conceptualise it as an embodiment of *risk* – a risk of progression and poor outcomes.

## 1.4 CONCEPTUALISING CKD RISK

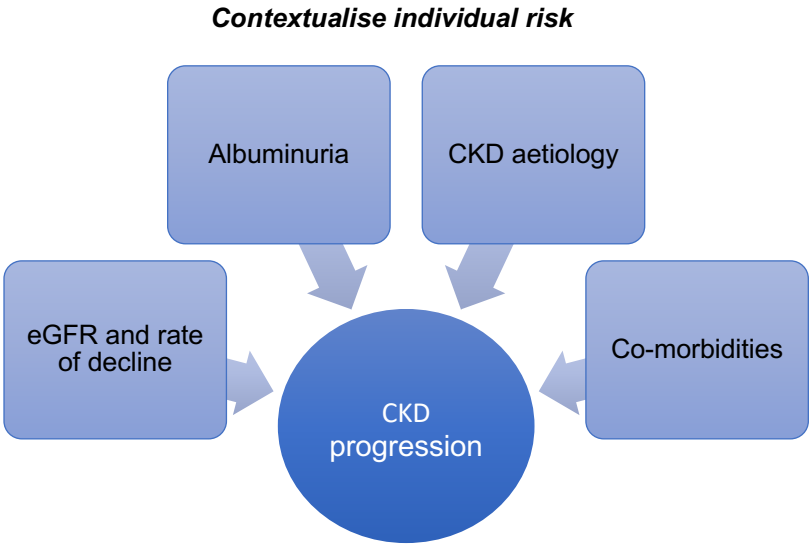
Although the 2012 KDIGO classification raises awareness of the health risks imposed by CKD, it does have a number of limitations. Firstly, it does not take account of age and its effect on renal function. CKD prevalence increases with age but whether this is diagnostic of actual pathological kidney disease or merely age-related kidney decline is difficult to elucidate. The aging process can potentially cause renal senescence, which describes the age-dependent processes leading to scarring of the kidney architecture [10]. It is therefore viewed as a physiologically normal state for an elderly individual as opposed to an active 'disease' phenomenon. KDIGO nonetheless does not include age-related thresholds as they recognise that lower eGFR and higher levels of albuminuria contribute to increased risk of adverse outcomes in elderly patients and thus all individuals should be deemed to have CKD without age-specific thresholds [1].

But the magnitude of the effect of age on adverse outcomes has been shown to be different between elderly and young patients. For instance, O'Hare et al [27] showed that the absolute risk of mortality across all CKD stages was higher in elderly patients but that the adjusted relative risk with moderate reductions in eGFR was in fact lower. The 2012 classification is modelled on relative risk as opposed to absolute risk, which is why Nahas and Kwaja [28] regard this as a limitation. The classification assumes, for instance, that the relative risk of adverse events in a 75-year-old with CKD G4 A2 is comparative to a 25-year-old with CKD 3b A3, whereas in fact the long-term prognosis for these two patients is markedly different.

Importantly, the KDIGO classification does not provide any measure of an individual's risk of progression over time, providing instead only a snapshot of their risk profile at a given time. Finding strategies to better predict those who will progress towards ESRD is an important concern in clinical practice and one that depends on viewing CKD on a continuous spectrum of risk [29]. In essence, patients become susceptible to the development of CKD in the presence of risk factors. Over time, progressive damage to the kidneys causes reduced eGFR, which may progress to ESRD and finally death. Various complications (as outlined in Table 1.3) can arise at different points, although are more likely to occur at advanced stages of CKD and confer significant morbidity

and mortality on patients. This continuum highlights the need to contextualise individual risk in those who have not yet reached ESRD, which involves screening for and addressing modifiable risk factors implicated in the development and progression of CKD (Figure 1.1).

**Figure 1.1** Conceptualise risk based on factors associated with CKD progression




## 1.5 CKD RISK FACTORS

There are several risk factors associated with both the development of CKD and its progression (Table 1.4), and a number of these are discussed below.

**Table 1.4** Risk factors associated with CKD

| | |
|---|---|
| Age | Metabolic syndrome |
| Ethnicity | Smoking |
| Gender | Cardiovascular disease |
| Low birth weight | Primary renal disease |
| Reduced eGFR | NSAIDs |
| Albuminuria | Lead exposure |
| Diabetes mellitus | Anaemia |
| Hypertension | AKI |

### 1.5.1 Age

Epidemiological studies have shown that the incidence of CKD increases with age [30, 31]. In a longitudinal cohort study, Fox et al [32] determined risk factors that predict the onset of CKD. The study was composed of 2,585 individuals from the Framingham Offspring Study who had been recruited between 1978-1982 and who underwent a repeat examination between 1998-2001. Over a mean follow-up of 18.5 years, increasing age was predictive for the development of CKD with an odds ratio (OR) of 2.36 per 10-year age increment (95% CI 2.00-2.78).

Interestingly, increased age appears to provide a protection against progressive CKD and delay the onset of RRT. For instance, in a cohort of 920 patients with CKD stages 4 or 5, age was inversely related to the risk of initiating RRT: in those ≥65 years, the adjusted relative risk for RRT was 0.7 (95% CI 0.6-0.9) compared with those who were less than 45 years old [33].

Therefore, although increased age may contribute to an increased incidence of CKD, it does not appear to be a major contributor to progressive CKD.

### 1.5.2 Gender

A number of longitudinal studies have shown that gender plays a role in the risk of progressive CKD with a greater risk experienced by male patients. Eriksen and Ingebretsen [34] showed that being male was associated with more rapidly declining renal function and progression to ESRD. This was also shown by Evans et al [33] who discovered that being male imposed an adjusted HR of 1.59 (95% CI 1.35-1.88) of reaching RRT sooner compared to being female.

There are, however, studies that have concluded that gender does not impact on renal outcomes [35, 36]. Despite these studies, a meta-analysis by Neugarten et al [37] concluded a positive association between male gender and progressive CKD exists but the exact mechanism behind this observation is unclear.

### 1.5.3 Ethnicity

CKD is more prevalent in ethnic minorities including South Asians, Native Americans and Hispanics [19], in part explained by the higher incidence of other CKD risk factors,

genetic predisposition and behavioural and socio-economic differences compared to their Caucasian counterparts.

Poor renal outcomes have been observed in those of black race. In the Racial Differences in Stroke Cohort Study (REGARDS) [38], racial difference between black and white participants were observed at different levels of renal function: the OR of a black individual with eGFR 50-59ml/min/1.73m$^2$ compared with a white individual was 0.42 (95% CI 0.4-0.46) but this increased significantly to 1.73 (95% CI 1.02-2.94) and 4.19 (95% CI 1.9-9.24) at eGFRs of 10-19ml/min/1.73m$^2$ and less than 10ml/min/1.73m$^2$ respectively. Thus, higher rates of ESRD in black patients with comparatively fewer rates at earlier stages of CKD suggest that black race is an important mediator of progression.

This heightened risk to ESRD in black patients has also been shown by Kilberd and Clase [39] who revealed that by age 56 years, black Americans experienced a cumulative risk of ESRD that was equivalent to the lifetime risk of ESRD in the white population. It is not surprising, therefore, that the USRDS 2015 data show an adjusted incidence rate ratio of 3.0 for the development of ESRD in black patients compared with white patients [19].

### 1.5.4 Reduced eGFR

Individuals with a lower degree of renal function as indicated by their eGFR have been shown to be at risk of further decline. For instance, in the study by Eriksen and Ingebretsen [34], patients with CKD stage 3 faced a HR of 2.5 (95% CI 1.89-3.31) for the development of ESRD for each decrement of 10ml/min/1.73m$^2$ in eGFR. Furthermore, Fox et al [32] discovered that individuals with an eGFR of less than 90ml/min/1.73m$^2$ at baseline were three times more likely to develop CKD than those whose renal function was normal. This alludes to the notion, described in experimental studies, that after a critical threshold of nephron loss, maladaptive and progressive changes that perpetuate renal injury continue to occur [40].

However, findings from the MDRD study [41] contradict this notion of linear, homogeneous pattern of deterioration. The study followed 840 patients with eGFR ranging from 15-55ml/min/1.73m$^2$ and found that over a period of 3.5 years, 85% had a

decline in renal function regardless of their baseline eGFR, whereas the remaining 15% in fact showed an improvement in eGFR.

### 1.5.5 Low birth weight

Low birth weight has been reported to have two major implications for CKD. Firstly, as proposed by the Barker hypothesis [42], low birth weight increases future risk of cardiovascular disease, diabetes and hypertension, all of which are antecedents to CKD and are linked with progressive disease.

Secondly, low birth weight correlates well with reduced nephron number and volume [43] and this inherited nephron loss has been viewed to be an important determinant of future long-term renal outcomes. For instance, Lackland et al [44] used registry data of 1,230 patients with ESRD in South Carolina to conduct a retrospective, case-control study to determine the effect of low birth weight on future risk of ESRD. The study showed that low birth weight (<2500g) was positively associated with ESRD irrespective of gender, race or cause of renal failure.

A potential underlying mechanism to explain this positive correlation has been proposed by Brenner and Mackenzie [45]. They suggest that lower nephron volume predisposes to glomerular hyperfiltration, which increases the risk of glomerulosclerosis that further reduces nephron number and potentiates chronic injury.

### 1.5.6 Albuminuria

Several studies highlight the strong association of risk associated with albuminuria and progressive CKD [31, 46, 47]. For instance, Halbesma et al [46] followed-up 6,984 patients from the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, a population-based cohort in Denmark. Over 4.2 years, the study found that macroalbuminuria at baseline, defined as albuminuria of >300mg/day, was associated with the biggest impact on renal decline with an eGFR change of -7.2ml/min/1.73m$^2$, compared with -2.3ml/min/1.73m$^2$ in the control population.

Other prospective studies in the CKD population, including MDRD [41], have demonstrated similar findings that higher degrees of proteinuria are linked with worse renal outcomes.

In a meta-analysis [48] of 11 clinical studies and 1,860 patients with non-diabetic CKD, baseline proteinuria was a strong independent risk factor for CKD progression. Importantly, the analysis showed that angiotensin converting enzyme inhibitors (ACEi) helped reduce proteinuria, but that whilst on treatment, the most recent level of proteinuria could be used to guide prognosis: higher levels of proteinuria increased the risk for the combined outcome of doubling of serum creatinine or the onset of ESRD with a relative risk of 5.56 (95% CI 3.87-9.78) for every 1g/day increase in proteinuria.

Overall, therefore, quantifying albuminuria or proteinuria is important in predicting risk in screening programmes in the general population, in those with CKD and in those with CKD who receive anti-proteinuric treatment.

### 1.5.7 Diabetes mellitus

Diabetes is a very strong independent risk factor for CKD [41] and diabetic nephropathy is the most common cause of ESRD in America. In the Multiple Risk Factor Intervention Trial (MRFIT) [49], 332,544 male participants were recruited from 18 cities in America. Over an average follow-up of 16 years, men with diabetes had an age-adjusted incidence of all-cause ESRD of 199.8 per 100,000 person years compared to 13.7 per 100,000 person years in those without diabetes.

Further evidence from randomised controlled trials shows that achieving better glycaemic control in both type 1 and type 2 diabetes retards CKD progression. For instance, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study [50], 11,140 male participants aged 35-57 years were randomly assigned to either intensive glycaemic control or standard treatment. Over a median follow-up of 5 years, there was a 21% reduction in the rate of CKD in those in the intensive arm (HR 0.79; 95% CI 0.66-0.93).

### 1.5.8 Hypertension

Hypertension is both a cause and consequence of kidney disease and, along with diabetes, is a major contributor to the burden of ESRD worldwide. Several observational studies have shown hypertension is linked with progressive CKD [31, 32, 51, 52]. For instance, the MRFIT study [49] showed that higher levels of blood

pressure were independently associated with ESRD: readings of ≥210mmHg systolic or 120mmHg diastolic conveyed a relative risk of 22.1 compared with those with optimal blood pressure control of less than 120/80mmHg.

Controlling hypertension is at the forefront of CKD management not least because it is also an important risk factor for cardiovascular disease such as stroke and coronary artery disease. Achieving lower blood pressure targets have been shown to be of benefit in reducing the risk of progressive disease, especially in those patients with higher levels of proteinuria, as highlighted in the MDRD [41] and African American Study of Kidney Disease and Hypertension (AASK) [53]. In the latter study, a lower blood pressure target of less than 130/80mmHg proved to be of benefit in retarding progression on CKD and ESRD but was notably only applicable in patients with a urine protein:creatinine ratio of more than 0.22.

Hypertension has strong interactions with albuminuria and diabetes. For instance, albuminuria is an early marker of diabetic renal disease, hypertension is associated with both albuminuria and diabetes, and all are associated with cardiovascular mortality, CKD progression and ESRD. Optimal blood pressure control has been extensively studied in the diabetic population. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [54] randomised 4,733 diabetic patients to intensive blood control of <120mmHg systolic or to standard therapy of <140mmHg systolic. There was no significant difference in the degree of albuminuria between the two groups, of which the median value lies within the A2 category of the KDIGO guidelines. Importantly, there was no significant difference in the primary composite outcomes of non-fatal MI, non-fatal stroke or cardiovascular mortality.

The Steno-2 study [55] randomised 160 diabetic patients with persistent albuminuria to receive a multi-component interventional strategy or standard therapy. The intervention group received better glycaemic and lipid control, aspirin for primary prevention, renin-angiotensin-aldosterone system blockade and their target blood pressure was <130/80mmHg. After an average follow-up period of 7.8 years, the trial found better cardiovascular outcomes for the intervention cohort and a 56% reduction (relative risk 0.44; 95% CI 0.25-0.77) in incident diabetic nephropathy, defined as a urinary albumin

excretion rate of >300mg/day. This equates to a urine albumin:creatinine ratio (uACR) of 30mg/mmol.

The studies described above highlight a differential effect of different blood pressure targets on CKD and cardiovascular (CVD) outcomes, which appear to be modulated by the level of albuminuria in patients with or without diabetes. This variance forms the basis of KDIGO guidance recommending a target blood pressure of <130/80mmHg in those whose uACR is >30mg/mmol and <140/80mmHg where uACR is <30mg/mmol [55].

### 1.5.9 Obesity, dyslipidaemia and metabolic syndrome

Obesity can produce direct structural and functional changes to the nephron and can cause a glomerulopathy that is characterised by proteinuria and histological appearances in keeping with focal segmental glomerulosclerosis [57]. Obesity itself, however, has also been shown to be a risk factor for progressive CKD in prospective population-based observational studies. For instance, Fox et al [32] showed that obesity, defined as a body mass index (BMI) of more than 30kg/m$^2$, produced an OR of 1.21 (95% CI 1.06-1.39) for predicting the development of CKD. In addition, a retrospective cohort study [58] of 320,252 adults in Northern California, followed-up for 15-35 years, showed that BMI was an independent risk factor for developing ESRD when other confounders were adjusted for. The risk increased in a stepwise manner with higher levels of BMI: when compared to normal BMI, the relative risk was 3.57 (95% CI 3.05-4.18) in those with a BMI of 30-34.9kg/m$^2$ and 7.07 (95% CI 5.37-9.31) in those with a BMI ≥40kg/m$^2$.

Dyslipidaemia is a common finding in patients with CKD, characterised by elevated triglycerides and low-density lipoproteins (LDL) and low levels of high-density lipoprotein (HDL) cholesterol particles. There is a growing body of evidence that point to dyslipidaemia being a risk factor for both the development and progression of CKD. For example, the Atherosclerosis Risk in Communities (ARIC) study [59] demonstrated an increased risk of incident CKD in those who had elevated triglycerides and low HDL levels. In the MDRD study [41], lower levels of HDL cholesterol were associated with a more rapid decline in renal function in those with CKD.

Treating patients with lipid-lowering medications, particularly statins, may provide some benefit to retarding progression. For instance, in a post-hoc analysis of the Cholesterol and Recurrent Events (CARE) study [60], patients who had suffered a previous MI and who had an eGFR of <40ml/min/1.73m$^2$, experienced a slower rate of renal decline whilst on pravastatin treatment. Furthermore, a meta-analysis [61] of 13 small trials comprising 384 patients concluded that treatment with lipid-lowering agents was significantly associated with a slower rate of renal decline of 0.156ml/min/month (95% CI 0.026-0.285ml/min/month) compared to non-treatment.

Both centripetal obesity and dyslipidaemia are features of the metabolic syndrome, which is also characterised by hypertension and insulin resistance. The metabolic syndrome has been shown to influence CKD progression as shown by Kurella et al [62]. In their longitudinal study of 10,096 non-diabetic patients, the OR for metabolic syndrome being associated with the development of CKD was 1.43 (95% CI 1.18-1.73).

### 1.5.10 Smoking

Several studies have drawn attention to the negatively potent effect of smoking on CKD outcomes [63-68]. In the multivariate analysis in the cohort study by Fox et al [32], smoking was positively linked with the development of CKD with an overall OR of 1.42 (95% CI 1.06-1.91). In addition, in a population-based prospective study of 23,534 participants residing in Maryland, Haroun et al [51] found that smoking was strongly associated with the risk of ESRD or death due to kidney disease with a HR of 2.4 (95% CI 1.5-4.0) in men and 2.9 (95% CI 1.7-5.0) in women.

In those with CKD, multiple studies have shown that smoking independently increases the risk of progression in diabetic and non-diabetic renal disease, such as hypertension [66], glomerulonephritis [67] and polycystic kidney disease [68]. Smoking, therefore, is recognised to have an additive effect, in the setting of other risk factors, of accelerating renal decline.

### 1.5.11 Cardiovascular disease

There is a significant overlap in risk factors that contribute to CVD and CKD such as albuminuria, diabetes, hypertension, dyslipidaemia and smoking. In addition, non-traditional risk factors, often unique to advanced CKD, have also been postulated to

play a role in the relationship between CKD and CVD such as endothelial dysfunction, vascular calcification, anaemia, hyperparathyroidism, volume overload, left ventricular hypertrophy, diastolic dysfunction, myocardial fibrosis and a pro-inflammatory state [21].

The overlap in risk factors can explain to some extent the adverse cardiovascular outcomes in patients with CKD as well as the risk of CKD progression in those with established CVD. This has been highlighted in the study by Fox et al [32] and in a Canadian observational cohort study [69]. In the latter study of 313 adults, established CVD (defined as previous MI, angina, bypass surgery, angioplasty, transient ischaemic attack, stroke, peripheral vascular disease and heart failure) proved to be an independent risk for progression to ESRD with a relative risk of 1.58 (95% CI 1.006-2.482).

### 1.5.12 Primary renal disease

Although patients with the same underlying disease will progress variably, dependent on other predictive factors of progression, patients who have autosomal dominant polycystic kidney disease (ADPKD) have been shown to advance more rapidly compared with other causes of CKD. For instance, in the MDRD study [41], there were 200 patients with ADPKD, 256 with glomerular disease (which included diabetic nephropathy) and 384 with miscellaneous or unknown pathologies. The study showed that in those with ADPKD, in whom the baseline eGFR was 25-55ml/min/1.73m$^2$, the mean eGFR declined fastest at a rate of 3.56ml/min/1.73m$^2$/yr when compared to those with other diseases. Locatelli et al [70] found similar results by showing that patients with ADPKD were more likely to reach the primary endpoint of doubling of serum creatinine or initiating dialysis.

### 1.5.13 Non-steroidal anti-inflammatory drug (NSAID) use and lead exposure

NSAIDs can cause both acute and chronic deteriorations in renal function. Long-term use is known to cause chronic interstitial nephritis and is recognised as a risk factor for CKD progression, as highlighted in a case-control study by Perneger et al [71]. In this study, a higher lifetime exposure of NSAIDs was associated with an almost 9-fold increased risk of developing ESRD: OR 8.8 (95% CI 1.1-71.8).

Lead is a nephrotoxic agent, which can result in lead nephropathy, a condition that classically causes chronic interstitial nephritis in individuals with a history of prolonged lead exposure. Low-level exposure is also associated with CKD as highlighted in a prospective study by Yu et al [72], which showed blood lead levels were associated with a dose-dependent decline in renal function.

### 1.5.14 Anaemia

Anaemia is a known complication of CKD (Table 1.3) but studies suggest it is also an independent risk factor for CKD progression. For instance, baseline anaemia was found to increase the risk of progression to ESRD in diabetic patients in the Reduction in Endpoints in non-insulin dependent diabetes with the Angiotensin II Antagonist Losartan (RENAAL) study [73].

Studies have also shown that correcting anaemia with erythropoietin (EPO) treatment can delay CKD progression. Gouva et al [74] conducted a randomised controlled trial that showed a 63% reduction of the composite endpoint of the doubling of creatinine, RRT and death when EPO was initiated once haemoglobin dropped to <11.6g/dl as opposed to <9g/dl.

### 1.5.15 AKI

CKD and AKI are closely linked. Patients with CKD are more susceptible to episodes of AKI [75, 76] and patients who have AKI are at increased risk of CKD progression regardless of their baseline eGFR. A meta-analysis of 13 studies by Coca et al [77] revealed that AKI increased the risk of CKD with a pooled adjusted HR of 8.8 (95% CI 3.1-25.5) for the risk of reaching ESRD. The meta-analysis also showed that the greater the severity of AKI, the higher the risk imposed for progression, and this has been shown in other studies. For instance, Lo et al [78] showed that patients who have dialysis-requiring AKI and who recover within 30 days of discharge face a 28-times increase in their risk of developing CKD (adjusted HR 28.1; 95% CI 21.1-37.6).

Repeated episodes of AKI also aggravate risk as shown by Thakar et al [79]. In their cohort of 3,679 diabetic patients, followed-up from January 1999 to December 2008, 530 patients had one episode of AKI, of which 157 sustained ≥2 AKI episodes. In their multivariate analysis, patients with one episode of AKI had a 3.56-fold increase in their

risk of developing CKD stage 4, HR 3.56 (95% CI 2.76-4.61), and this risk doubled with each AKI event (HR 2.02; 95% CI 1.78-2.30).

AKI episodes are clearly a marker of risk for CKD progression and the mechanisms postulated have been based on AKI insults creating structural sequelae such as tubulointerstitial fibrosis and glomerulosclerosis, which promote chronic functional deterioration.

### 1.5.16 Future prospects

Several risk factors have been described that are associated with CKD development or progression or both. However, efforts are ongoing to gain a holistic and complete understanding of CKD pathogenesis. To that end, there has been significant attention on the discovery of novel biomarkers that may help unravel the pathways of disease progression but also provide utility for diagnosis and risk prediction of CKD in clinical practice. Biomarkers uncovered using proteomic techniques offers a promising lead in this area.

## 1.6 PROTEOMICS AND CKD

### 1.6.1 Introduction

There are approximately 19,000 to 20,000 protein-coding genes in the human genome but there are likely over 1 million individual protein molecules when post-translational modifications occur [80]. Proteomics refers to the study and analysis of proteins in order to better understand their relationship in biological systems in health and disease states. By identifying and quantifying protein molecules, proteomics is providing a means of ever-expanding discovery of the mechanistic pathways that define underlying diseases.

In general, proteomics involves techniques such as capillary electrophoresis combined with mass spectrometry to separate, isolate and quantify individual proteins and peptides [82]. The spectra analysis then requires modification into a meaningful format to allow further validation with protein database searches to accurately identify the

isolated proteins before finally undertaking a comprehensive large-scale analysis of the output using bioinformatic tools.

Using such techniques, there have been advances in characterising the kidney proteome, the entire expressed protein composition of the kidney. Miyamoto et al [82] achieved identifying over 6,000 specific proteins expressed by the normal human glomerulus and classified them according to a named biological function and their interaction in cellular pathways. The work has contributed to an international collaboration, the Human Kidney and Urine Proteome Project [83], to compile protein databases important to the kidney.

It is evident how the application of proteomics would benefit nephrology care. Molecular signals that denote renal injury may arise in conjunction with the development of structural or functional changes within the kidney, which may exacerbate CKD progression. Several pathophysiological processes contribute to CKD such as oxidative stress, endothelial dysfunction, ischaemic injury, inflammation and fibrotic cell activation [21]. If protein signals that relate specifically to some or all of these processes are detected prior to permanent renal injury, then proteomics offers unique possibilities in early diagnosis, risk prediction, monitoring of treatment efficacy and timely management to reverse or retard disease progression [84].

For instance, Figure 1.2 highlights how a biomarker can help predict CKD risk progression in clinical practice. In this example, the emergence of new protein signals that are known to be associated with CKD progression helps herald a significant clinical event: a phase of progressive decline that confers an increased risk of adverse CKD complications and an earlier onset of RRT. Biomarkers could therefore add significant utility to our current model (Figure 1.3) for predicting future eGFR trajectory.

**Figure 1.2** Role of biomarkers in predicting stability or rapid, progressive decline

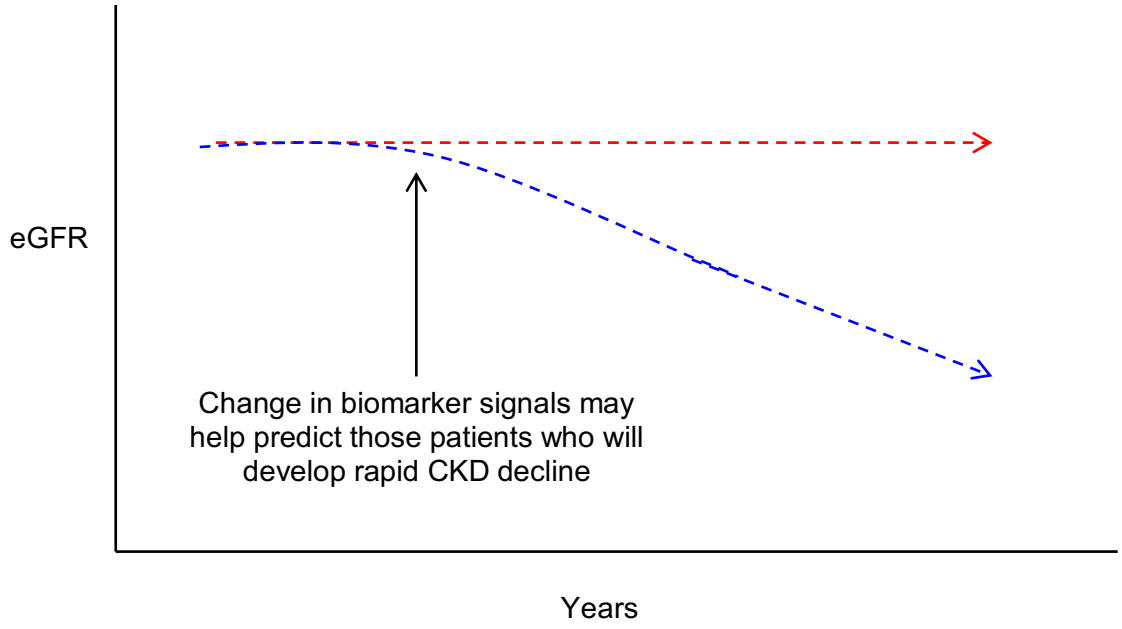
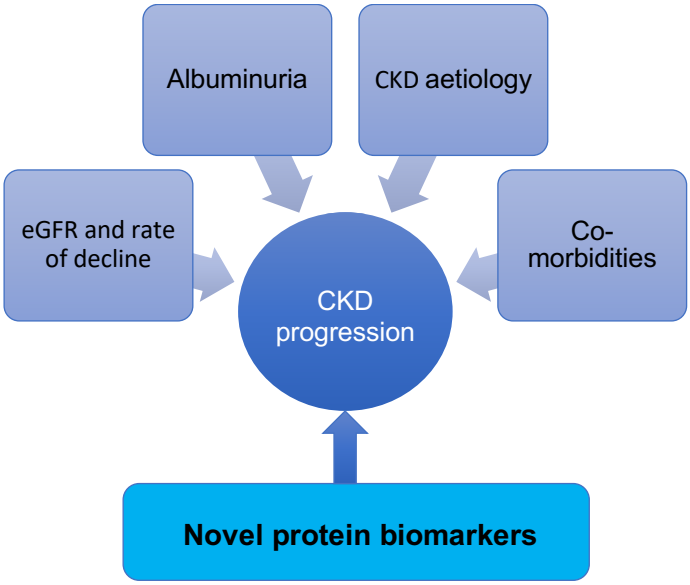



**Figure 1.3** The addition of protein biomarkers for risk prediction in clinical practice



It is of course equally possible that along with the detection of proteins that drive progression, there is a reduction of, or disappearance of markers associated with protecting the kidney from injury. Regardless, a change in an individual's biomarker profile to one that predicts progressive disease should alert clinicians to considering a different management approach sooner rather than later. This may involve more frequent outpatient monitoring, alteration of pharmacological therapies to stabilise renal function and timely pre-emptive discussions regarding the prospect of RRT.

What is also striking is the glimpse protein biomarkers provide with respect to the underlying pathophysiological processes underpinning stability or progression. Discovering novel biomarkers that signal rapid renal decline may provide insight into unravelling key biological pathways that could hold targets for future therapies to help preserve renal function.

There is clearly a pressing need for alternative biomarkers of renal function other than creatinine-based eGFR equations and albuminuria, the most commonly utilised biomarkers across the full gamut of nephrological conditions. Although they are easily measured, widely accessible and can predict disease progression, cardiovascular events and mortality, they are prone to important limitations. Both are non-specific markers of renal impairment, typically becoming deranged after late manifestations of renal damage have occurred. Furthermore, serum creatinine is affected by several non-GFR determinants such as ingestion of cooked meat, drugs and muscle mass. It is no surprise therefore that novel biomarkers that deliver excellent clinical applicability are highly sought to help transform investigation and management of renal disease.

Over the last decade, many biomarkers have been discovered that show promise in detecting and predicting CKD progression and a number of these are discussed in detail below.

### 1.6.2 Urine CKD273 classifier

The urinary peptidome is an attractive focus for proteomics for several reasons [84]. Firstly, testing urine is non-invasive compared to obtaining blood or tissue samples. Secondly, the peptides within the urine are largely derived from the kidney, which makes it specific to identifying disease processes. Finally, the peptides are products of

proteolytic activity that have already occurred prior to urine reaching the bladder and are thus in a more steady and stable state for analysis after voiding.

Using the capillary electrophoresis and mass spectrometry approach, Good et al [85] discovered 273 urine peptides that could differentiate between 230 patients with various causes and stages of CKD and 379 subjects who were healthy controls. This so-called CKD273 classifier was validated by the investigators on an independent, blinded cohort of 110 patients with CKD and 34 healthy individuals and demonstrated a sensitivity of 85.5% and 100% specificity. It has also been shown to demonstrate unique patterns [86] in patients with IgA nephropathy, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), minimal change disease and ANCA-associated vasculitis.

In addition to diagnosis, other investigators have been able to demonstrate its applicability in disease progression and therapeutic monitoring. For example, using similar techniques as Good et al [85], Roscioni et al [87] performed a case-control study of diabetic patients and analysed whether the CKD273 classifier could predict patients who, with preserved renal function, would progress to develop worsening albuminuria. The urine samples in a total of 44 case-control pairs were analysed; cases were those patients who suffered an albuminuria stage transition in two consecutive visits – either from normal albuminuria to microalbuminuria or from microalbuminuria to macroalbuminuria – and controls were patients who had no change. Proteomic analysis of the biomarker was undertaken from the patients' visit prior to them experiencing an albuminuria transition. The study showed that CKD273 classifier was significantly associated with albuminuria change. For instance, in the group of the 24 case-control pairs who shifted from micro- to macroalbuminuria, the adjusted OR was 1.35 (95% CI 1.02-1.79) and the area under the receiver operative curve (AUC) was 0.94. This performed better than combining urinary albumin excretion and eGFR for predicting risk.

These findings support work by Zürbig et al [88] who, in a retrospective analysis of 35 diabetic patients, showed that the CKD273 classifier positively predicted the onset of macroalbuminuria over a 5-year follow-up in patients who were initially normoalbuminuric. In addition, it was able to predict this 4.9±2.2 years earlier

compared with 3.4±2.1 years for patients who developed microalbuminuria prior to developing macroalbuminuria.

Further value for CKD273 is supported in a larger, retrospective cohort study of 522 patients from 9 different centres worldwide [89]. Over an average follow-up of 54±24 months, the CKD273 classifier was better associated with eGFR and predicted progression better than albuminuria and eGFR combined; the AUC improving to 0.831 from 0.758.

The studies described above suggest that urinary proteomics can help stratify diabetic and non-diabetic patients who are likely to progress and importantly relay this message at earlier stages of disease. Despite being limited by small patient numbers, they do demonstrate strong statistical correlations between CKD273 classifier with important outcome measures. In addition, they consistently find similar peptide markers in these at-risk patients, such as a reduction in urinary collagen fragments. This may reflect the downregulation of matrix metalloproteinases [90], which would normally promote collagen deposition within the kidney microarchitecture, and which is a characteristic feature of the non-reversible histological findings of glomerulosclerosis and interstitial fibrosis.

CKD273 also shows potential to assess response to treatment. For instance, Andersen et al [91] obtained 22 urine samples from subjects who participated in the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA2) trial, which demonstrated the renoprotective benefit of irbesartan 300mg in hypertensive, diabetic patients with microalbuminuria. In their study, the peptide pattern changed from matching overt diabetic nephropathy to becoming akin to normoalbuminuric patients after a 2-year period of taking irbesartan when compared to controls. Thus, the renoprotective benefit of irbesartan in diabetic patients was demonstrated by changes within the urinary proteome.

Further work in assessing biomarker changes to treatment has been undertaken in patients with ANCA-associated vasculitis. Haubitz et al [92] analysed the urinary proteome in 18 patients with ANCA-associated vasculitis compared with 425 control subjects, 200 of whom were healthy volunteers with the remaining diagnosed with

CKD of various aetiologies, including IgA nephropathy, diabetic nephropathy, FSGS, minimal change and membranous nephropathy. They were able to demonstrate a differential pattern of peptide expression in patients with vasculitis compared with the control subjects and between patients with active vasculitic disease and those in remission. It was interesting that up-regulation of fragments relating to $\alpha_1$-antitrypsin and albumin were observed in those with active disease, which has been postulated to reflect an inflammatory state. The most common peptides, however, were haemoglobin products. This could correspond with the presence of non-visible haematuria that is often present in patients with vasculitis. Intriguingly, however, it was the N- and C-terminal fragment of haemogoblin that provided specific discrimination for vasculitis compared with other causes of non-visible haematuria, and this may be a result of specific protease activity that is upregulated only in active vasculitis.

The investigators completed their study by monitoring patients who were initiated on immunosuppressive therapy and analysed their urine prior to treatment and at 1, 3 and 6 months. They showed that the urinary peptide analysis changed with time as treatment began to successfully bring patients into remission, which was correlated by improvement in other routine markers of disease activity such as the ANCA titre and C-reactive protein levels.

This raises the potential scope of urinary markers to pre-empt, support and guide decisions on treatment in those with specific renal disease. This would especially be of value in aiding decisions surrounding immunosuppressive treatments. It may also prove a surrogate way to assess disease activity without the need to reflexively proceed with a renal biopsy. Glassock [93] argues, however, that the renal biopsy will remain a gold-standard investigation for diagnosis and prognosis in nephrology but there may be instances where, in the presence of contraindications to an invasive biopsy, clinicians could rely on biomarkers to make informed clinical decisions.

A number of other biomarkers have materialised in the area of CKD diagnosis and progression, including NGAL, KIM-1, FGF-23 and cystatin C, which are discussed below.

### 1.6.3 NGAL and KIM-1

NGAL (neutrophil gelatinase-associated lipocalin) and KIM-1 (kidney injury molecule-1), both tubular proteins, are upregulated in the context of kidney injury. Both have been shown to be highly predictive markers of AKI in varying clinical contexts [94, 95]. In the setting of CKD, several studies have shown their influence on CKD progression. Bolignano et al [96] showed in a cohort of 96 patients that serum and urine NGAL levels were independently associated with CKD progression, with higher levels indicative of faster progression. Peralta et al [97] designed a case-control study of 686 subjects and showed that the highest levels of KIM-1 were associated with an increased risk of developing CKD, with an OR of 2.02 (95% CI 1.15-3.56). In a larger, prospective cohort of 1,982 patients drawn from the Chronic Renal Insufficiency Standards Implementation Study (CRISIS), Alderson et al [98] showed that higher levels of serum NGAL and KIM-1 were independent markers for the progression towards ESRD over a median follow-up of 29.5 months with HRs of 1.25 (95% CI 1.10-1.43) and 1.35 (95% CI 1.14-1.59) respectively, for every 1 standard deviation higher serum concentration.

### 1.6.4 FGF-23

FGF-23 (fibroblast growth factor-23), a protein released by osteoblasts, plays a role in phosphate homeostasis [99], and studies have shown it to be an important marker for the future risk of adverse outcomes. For instance, Isakova et al [99] highlighted the increased risk of ESRD and mortality of higher levels of FGF-23 in a cohort of 3,879 patients who had CKD stages 2 to 4. This has been further supported by work by Alderson et al [100], who showed that higher serum FGF-23 levels at baseline in 463 patients with CKD was independently associated with progression to ESRD, cardiovascular events and mortality, with HRs of 1.35 (95% CI 1.001-1.820), 1.74 (95% CI 1.303-1.305) and 1.06 (95% CI 1.006-1.117) respectively.

### 1.6.5 Cystatin C

Cystatin-C, a protein released by all nucleated cells and freely filtered by the glomerulus is more favoured as an endogenous marker of renal function than serum creatinine as it does not share the same limitations as creatinine [101] and has been shown to predict CKD and cardiovascular outcomes [102, 103]. Shlipak et al [103] showed that in a cohort of 4,663 elderly patients with preserved renal function, cystatin

C was strongly associated with MI, stroke, heart failure, cardiovascular death and all-cause mortality over a median follow-up of 9.3 years. Creatinine, conversely, was only significantly associated with cardiovascular death. Furthermore, subjects with higher levels of cystatin C at baseline were approximately four times more likely to develop progressive CKD after a 4-year follow-up (HR 4.53; 95% CI 3.25-5.38). Thus, cystatin C provided better prediction of CKD and CVD outcomes than serum creatinine in a cohort of patients who were ≥65 years old. The authors highlight the advantage therefore lies in the ability to detect a cohort of patients in a pre-clinical state of progression, a state that is potentially amenable to pre-emptive, targeted therapy.

Using a cohort of 5,352 patients drawn from 13 different studies, Inker et al [104] developed equations to estimate GFR, which were then validated in a separate 1,119 subjects. It showed that the CKD-EPI equation that combined both serum creatinine and cystatin C levels was the best to estimate GFR in contrast to CKD-EPI equations that use either creatinine or cystatin C alone. The authors suggested that given cystatin C can provide a more precise measure of renal function, it could be measured as a confirmatory test in those shown to have low eGFR based on serum creatinine. This has now become part of NICE guidance [16], which states cystatin C should be measured in patients who have a creatinine-based eGFR of 45-59ml/min/1.73m$^2$ but have no other markers of renal disease. Cystatin C, therefore, has become one of a few recently discovered biomarkers to enter into clinical practice.

### 1.6.6 Future prospects

A number of biomarkers have been described but they represent a small fraction of a compelling array of biomarkers that have surfaced in the pursuit of better understanding CKD [105]. They have been studied to help unravel underlying pathophysiological processes, achieve earlier diagnosis, and provide better estimates of the risk of progression, the threat of cardiovascular outcomes and the likelihood of treatment success.

It is argued that to fully encompass the complex, pathophysiological determinants of disease, a combination of biomarkers, as opposed to a single biomarker, will likely best serve future clinical practice. Indeed, Agarwal et al [106] showed that different biomarkers were associated with different CKD outcomes. In their study of 67 US

veterans with diabetic kidney disease, they showed that urinary C-terminal FGF-23 was significantly associated with eGFR decline whereas the presence of plasma VEGF (vascular endothelial growth factor) had the strongest association with the development of ESRD.

However, there are very few biomarkers that have entered into clinical practice because they have yet to provide robust or substantially incremental value above and beyond routine clinical markers. A key exception is cystatin C, which has garnered acceptance for confirmatory testing of CKD. Another major breakthrough in biomarker discovery in the last decade has been the discovery of the M-type phospholipase A2 receptor (PLA2R) [107] as the antigen target in idiopathic membranous nephropathy, which was identified using proteomic technologies. Testing for the IgG4 autoantibody that targets PLA2R has proved beneficial in differentiating primary and secondary causes of membranous nephropathy and serial testing can help monitor treatment efficacy. In this case, anti-PLA2R fits several criteria for an ideal biomarker, which may be related to the fact it directly *causes* a specific disease state.

In contrast, the pathophysiological roles of many novel biomarkers have not been elucidated. Whether they are causally implicated in disease pathology is unclear. In addition, biomarker studies have several methodological limitations including small patient numbers, retrospective study designs, varying definitions of CKD progression, and the fact only a single baseline biomarker is used to quantify future risk in longitudinal studies. All these issues highlight significant pitfalls in establishing the potential value of a biomarker. Nonetheless, novel biomarkers continue to be added to the growing literature [108] and there remains enthusiasm for ongoing robust research into biomarker discovery.

In addition to identifying potentially meaningful biomarkers, studies must also extensively validate them across different patient cohorts in a prospective manner in order to confirm their clinical utility. Further collaborative work across other disciplines of transcriptomics, metabolomics and genomics will no doubt also be necessary if the advent of personalised medicine is to be truly realised.

### 1.6.7 The need for renal prognosis scores

In the pursuit of achieving personalised renal care, the question of how the multitude of risk factors in an individual interact and affect long-term outcomes in CKD is an important one. A multi-hit hypothesis may be important in predisposing patients to develop CKD, whereby several risk factors overcome renal compensatory mechanisms, resulting in CKD propagation. This is consistent with the study by Fox et al [32] that showed an increased risk of progression occurred in those with a higher burden of known risk factors.

Therefore, when contextualising an individual's risk of progression, it is important to take account of all the contributing factors as they may have additive or multiplicative effects on risk. KDIGO [1] recommends reviewing a patient's eGFR and albuminuria category, the aetiology of CKD and all other risk factors to determine renal prognosis. However, as shown in Figure 1.1, an equally important consideration is the rate of decline in predicting prognosis. The average rate of eGFR decline with age is estimated to be 0.75-1.00 ml/min/1.73m$^2$/yr after the age of 40 [109]. Rapid progression has not been strictly defined with some suggesting that a rate of 4ml/min/1.73m$^2$/yr should be considered fast [110]. NICE guidance reports that rapid progression should be based on *"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/1.73m$^2$ per year"* [16]. This encompasses a high-risk cohort of patients that are more likely to face the prospect of RRT.

Consider then a 60-year-old male patient with diabetic nephropathy at CKD stage 3b with an eGFR of 38ml/min/1.73m$^2$ and significant (A3) albuminuria of 166mg/mmol. He has poorly controlled glycaemic control, hypertension, dyslipidaemia, prior history of MI, is a current smoker and his renal trajectory has been declining at an annual rate of almost 5ml/min/1.73m$^2$. It would not be difficult to estimate his risk of CKD progression and ESRD to be very high and matched equally by his risk for future cardiovascular events. However, CKD progresses in an often heterogeneous, non-linear fashion [110], and this poses significant uncertainty for clinicians in how best to deliver patient-centred care.

Indeed, at a population level, the vast majority of patients with CKD will in fact never progress to ESRD. In a large cohort of 27,998 patients with CKD, Keith et al [111] showed that the risk of progression to RRT over 5 years was 0.9%, 1.1% and 17.6% in patients with CKD stages 2, 3 and 4 respectively but their risk of death, mainly from cardiovascular disease, was markedly higher at 19.5%, 24.3% and 45.7%. The findings raise two important points. Firstly, aggressively managing cardiovascular risk factors and CVD is critical for patients with CKD whatever their stage. Secondly, given a large proportion of patients are likely to remain stable, especially at earlier stages of CKD, finding strategies to predict those who will progress is necessary to help anticipate and favourably alter a patient's renal prognosis earlier. Addressing this issue requires quantification of patients' risk of future outcomes. This will hopefully inform the frequency of monitoring required and allow aggressive and timely interventions to be offered to high-risk individuals, who have the most to gain from therapy in terms of risk reduction. This targeted approach will also likely represent a more efficient use of specialist resources, as the majority of patients deemed to have stable disease could be managed in primary care. The key underlying aim of this approach would nonetheless remain the same: prevent over-treatment of those likely to have stable disease and prevent delaying treatment for those likely to progress.

A means to accurately obtain a quantifiable measure of risk is not offered by the KDIGO 2012 guidelines but a number of renal prediction models have emerged and offer promising value for the care of patients with CKD.

## 1.7 CKD RISK PREDICTION MODELS

In conjunction with public health efforts to promote healthier lifestyles and attempt to reduce the burden of modifiable risk factors at a population level, a high-risk, targeted approach provides value to individuals who are likely to have the worst outcomes. Risk prediction models are important in this regard for several clinical reasons. Instead of subjectively conceptualising risk, a quantifiable, validated measure can be obtained from a risk calculation. This can be used as a tool to educate and inform patients of their risk and motivate them to adhere to treatment plans, especially given that CKD is largely asymptomatic until advanced stages. In addition, prediction models can also

help anticipate future events and, importantly, provide an evidence-based measure to guide appropriate management decisions.

A number of renal prediction formulas have been created, which calculate estimates of risk in different patient cohorts. Kshirsagar et al [112] developed a model to help predict risk of incident CKD in patients over 45 years old. In their study, they combined data from two separate non-current cohort studies, the ARIC study and Cardiovascular Health Study, totalling 14,155 participants. They determined baseline variables that were implicated in incident CKD in 9,470 patients over a period of 4-9 years, and then validated them in a separate 4,624 patients to create three, points-based algorithms to predict risk. In the best-fitting model, 10 variables were identified, including age, gender, ethnicity, anaemia, hypertension, diabetes, history of cardiovascular disease, history of heart failure, peripheral vascular disease and HDL-C levels. The removal of ethnicity and HDL-C levels provided an 8-variable, simplified model that still maintained discrimination with the AUC of 0.69. The study, however, was limited by the lack of any urine markers in the patient population, namely albuminuria, and by the fact incident CKD was defined as a single eGFR reading of $<60ml/min/1.73m^2$, which as discussed previously tends to overestimate the true prevalence of CKD. Despite these limitations, however, the algorithms do show potential in stratifying patients at a population level.

Screening for Occult Renal Disease (SCORED) [113] is another scoring tool for risk screening the general population. Using cross-sectional data of 8,530 subjects from the NHANES database, Bang et al [113] developed a points-based system to predict incident CKD in patients over 20 years old. Risk factors utilised in the model included age, sex, hypertension, diabetes, history of cardiovascular disease, heart failure, peripheral vascular disease, anaemia and proteinuria. A score of $\geq 4$ was used as the cut-off mark to highlight increased risk. This produced good sensitivity of 92% and a negative predictive value of 99%, but this was concomitantly associated with low specificity of 68% and a positive predictive value of only 18%.

Importantly, SCORED has been externally validated in a number of other studies, including ARIC and two other patient cohorts [114] with cardiovascular risk factors, the Enhancing Recovery in Coronary Heart Disease (ENRICHED) and the Vitamin

Intervention for Stroke Prevention (VISP) studies, all of which demonstrated the SCORED tool to have moderate-to-high AUC values. In addition, a key clinical application devised from SCORED is a questionnaire-based screening tool, aimed to help raise awareness of CKD amongst patients and clinicians and to guide further decisions on monitoring and future care.

Alongside scores to help risk prediction within the general population, investigators have focused on predicting future risk of adverse events in those with established CKD. Given diabetic nephropathy is the commonest cause of ESRD in developed countries, Keane et al [73] devised a risk calculation to predict progression of CKD in diabetic patients. They used data from the RENAAL trial, which included 1,513 patients with diabetes, followed for a mean of 3.4 years and found that uACR, serum albumin, serum creatinine and haemoglobin can be incorporated into a formula to predict risk. Those with albuminuria, hypoalbuminaemia, higher serum creatinine and anaemia had the highest risk of adverse outcomes. Interestingly, hypertension was not an independent risk factor, and this was likely explained by the fact that blood pressure was very well controlled in both intervention groups in the trial and therefore was masked as a contributor within the multivariate analysis. Glycaemic control was also not found to be contributory, but the authors discussed that HbA1c levels were separately utilised in models that helped predict a composite risk of ESRD and mortality. The major limitation with the study by Keane et al [73] is the lack of validation in other patient cohorts, which is a common problem found with several prediction tools. To date, the Kidney Failure Risk Equation (KFRE) [115] has gained the most leverage in the field of risk prediction at it has been extensively validated.

The KFRE predicts the risk of ESRD in patients with CKD stages 3 to 5. It was first developed in a cohort of 3,449 patients, drawn from the health records of a Canadian hospital and then validated on 4,942 patients taken from the British Columbia CKD registry. The analysis showed that being male, younger, with a lower eGFR, higher uACR, higher serum phosphate and lower levels of calcium, bicarbonate and albumin contributed the most risk for CKD progression. In comparison to this 8-variable model, a 4-variable equation incorporating only age, sex, eGFR and uACR was also shown to perform very well in predicting risk of future ESRD.

A significant feature of the KFRE is that it has undergone external validation in 31 cohorts [116], comprising a total of 721,357 patients across 30 countries and 4 continents. There was a high level of discrimination demonstrated by the 4-variable and 8-variable equations throughout the 31 cohorts under investigation. Calibration, the ability of a model to predict observed outcomes, was reasonably good and increased with the inclusion of a calibration factor for studies conducted outside of North America.

There are several advantages to the KFREs. Firstly, they provide accurate, extensively validated risk prediction models for patients with CKD across diverse populations. Secondly, they utilise measurable parameters routinely tested in clinical practice. Thirdly, they provide a timeline measure, quoting a 2- and 5-year risk of ESRD, which is highly relevant in making decisions for the preparation of RRT. Fourthly, the prediction models can be accessed online or integrated into electronic health records to support decision-making, especially in outpatient care. Whilst the KFRE is a promising tool, there is scope for further research to refine our ability to better risk stratify patients.

The KFRE has a few shortcomings that are worth reviewing. Firstly, it only corroborated risk for patients with eGFR <60ml/min/1.73m$^2$, thus excluded those with stages 1 and 2, a group of patients who remain at risk of progression in the presence of predictive risk factors.

Secondly, the authors recognised that there were missing data from several cohort studies that could not be used to validate the 8-variable equation. Since the data from previous epidemiological studies were not designed to specifically develop prediction models, concerns have been raised regarding the accuracy and completeness of the data. However, it is arguable that this is reflective of day-to-day clinical practice and may not be as significant as ensuring the model is still capable of accurately predicting outcomes.

Thirdly, only 2-year and 5-year risk scores are available and obtaining risk scores for a longer period of time may be desirable to better quantify the contribution of modifiable risk factors. For example, the QRISK2 [117] score calculates the risk of developing

incident coronary heart disease, stroke and transient ischaemic attack over the next 10 years based on several measurable parameters. It is endorsed by NICE for use in the UK and is extensively utilised in primary care settings to help trigger behavioural and medication changes to lower the toll of cardiovascular risk.

Finally, it is interesting that other contributing risk factors such as diabetes, hypertension or smoking do not provide any additional discriminatory information on a patient's risk of ESRD in this model. It may be that these factors have a more powerful effect on cardiovascular outcomes as opposed to CKD progression, or it may be that the surrogate markers of eGFR and albuminuria sufficiently measure their impact on progression. It is equally possible that there are other pathophysiological processes that are yet undetermined, which could account for how these risk factors interact and cause progressive disease.

Thus, there is scope for further development and refinement. Whether or not it will result in improved outcomes for patients remains to be explored. However, given the scarcity of meaningful prediction tools in nephrology, this current model begins to fill an unmet challenge of enhancing, improving and supporting decisions for patients with renal disease. In contrast to nephrology, there are several scoring systems used across the medical community, each one shown to be of benefit in specific clinical conditions. For instance, the CURB-65 [118] predicts the 30-day mortality of patients who suffer community-acquired pneumonia, and the MELD score [119] provides a 3-month mortality score for hospitalised patients with cirrhosis. These scores, amongst others, are widely used to aid clinical decision-making. Many have been updated over the years and have become more precise, such as the $CHADS_2$ score, which provides an annual risk of developing stroke in patients with atrial fibrillation. This score was amended into the $CHA_2DS_2$-VASc score [120] due to the inclusion of other validated stroke risk factors and is recommended by NICE in deciding whether anticoagulation should be initiated for stroke prevention.

The routine uptake, however, of renal prediction scores has not yet occurred on an international level. Searching for an ideal prediction model for CKD progression, nonetheless, remains an active field of ongoing research given the foreseeable benefits it

may bring to patient care. A published review article of the latest developments in this field follows next.

## 1.8 RISK PREDICTION IN CHRONIC KIDNEY DISEASE

Ibrahim Ali, Philip Kalra
Curr Opin Nephrol Hypertens. 2019;28:513-518.
DOI: 10.1097/MNH.0000000000000553

### 1.8.1 Abstract

**Purpose of review**

Accurate risk stratification in patients with CKD is highly desirable to help guide earlier, targeted treatment in high-risk individuals. In this review, we report recent developments in our understanding of risk factors and risk prediction in patients with CKD.

**Recent findings**

A large meta-analysis has shown that conventional cardiovascular risk factors continue to play an important role in disease progression and adverse outcomes in patients with advanced CKD (eGFR ≤30ml/min/1.73m$^2$). Several studies have shed light on novel biomarkers in CKD, including peptides (LG1M), genes (*MUC1*) and metabolic factors (urinary oxalate excretion). Cortical oxygenation measured by BOLD-MRI also provides a novel radiological measure predictive of future eGFR decline. A new risk prediction score for patients with CKD G4-5 has been developed, offering an aid to decision-making in these patients.

**Summary**

Ongoing work across various disciplines continues to unravel the determinants of CKD progression. A few notable risk prediction tools in CKD have now surfaced but whether they can be utilised to offer improved care remains a key unanswered question.

### 1.8.2 Introduction

Chronic kidney disease (CKD) is not benign. Regardless of the aetiology of CKD, lower eGFR and higher albuminuria are independent risk factors for progression to end-stage renal disease (ESRD), non-fatal and fatal cardiovascular events (CVE) and all-cause mortality [4].

The global adult prevalence of CKD is estimated between 10-14% [8], and in light of the adverse health outcomes and the associated high economic burden, the International Society of Nephrology has published an updated treatise promoting a variety of public health measures to improve CKD care worldwide [121]. Along with population-based health measures, however, a targeted approach is essential to reduce the risk in individuals expected to have the worst outcomes. Given that many patients have heterogeneous eGFR trajectories, risk prediction tools in CKD offers a promising means to better identify patients at risk of major events and therefore help guide treatment in a pre-emptive manner.

In this review we discuss the progress made in investigating risk factors in CKD, the emergence of new risk prediction tools, and the allied work searching for novel biomarkers that could help refine our predictive ability as well as uncover pathophysiological pathways that may offer targets for therapeutic intervention.

### 1.8.3 Conventional risk factors in advanced CKD

The CKD Prognosis Consortium undertook the largest epidemiological study to date assessing the impact of traditional risk factors on outcomes in those with CKD G4-5 [4]. Compared with patients at earlier stages of CKD, little was known as to how conventional risk factors determine outcomes in advanced CKD.

The study included 28 CKD cohorts, comprising 185,024 patients across 30 countries. The mean age was 70 years, 69% were male, mean eGFR was 24ml/min/1.73m$^2$, median urine albumin:creatinine ratio (uACR) was 48mg/g and the mean follow-up 3.3 years. Nine variables were studied (age, sex, ethnicity, systolic blood pressure, diabetes, smoking, history of cardiovascular disease, eGFR and uACR) and adjusted pooled hazard ratios acquired for 3 primary outcomes – renal replacement therapy (RRT), CVE and all-cause mortality.

The authors showed that traditional risk factors were associated with an increased risk of all three adverse outcomes but there was a differentiating relationship between risk factors and outcomes. For instance, lower eGFR and higher albuminuria were significantly associated with all three outcomes but the risk association for these factors was highest for reaching RRT. Older age increased the risk of CVE and mortality but not RRT. This most likely reflects the competing risk of death in older patients and that older patients are more likely to opt for conservative management. When patients were stratified into two age groups (<65 and >65 years), the presence of diabetes was significantly associated with RRT and CVE in younger patients, and male sex contributed to a higher risk of RRT in the older subgroup. With respect to ethnicity, Black race was associated with progression to RRT but not for CVE or mortality. Smoking was significantly associated with mortality but not RRT, a finding shown previously [123].

The study also shows the negative impact of a history of cardiovascular disease (previous myocardial infarction, percutaneous coronary intervention, bypass surgery, heart failure or stroke) in advanced CKD on future outcomes. Firstly, a history of cardiovascular disease conveys the highest risk for future CVE, and if a new CVE does occur, patients are twice as likely to reach RRT or die. Thus, individuals with a high cardiovascular risk profile are those destined to have the worst outcomes. This highlights the need to consider maximal, secondary cardiovascular prevention therapy in patients with advanced CKD.

Due to a lack of data, the authors could not assess whether other traditional risk factors such as obesity [58] or dyslipidaemia [124] played a predictive role in in this meta-analysis of patient cohorts. In addition, it would have been interesting to determine whether other measurable factors such as anaemia [74], hyperuricaemia [125], hypoalbuminaemia [126] and hyperphosphataemia [127] play an equally relevant role in these patients. Notwithstanding, the consortium have robustly highlighted that well-known risk factors continue to remain a threat to patients as they progress to later stages of CKD.

### 1.8.4 Novel biomarkers in CKD

Several novel biomarkers have been recently reported in the literature and are discussed below.

#### *1.8.4.1 Fibrosis*

Nielsen et al investigated the role of laminin γ1 chain (LAMC1), an integral structural protein of the glomerular basement membrane, on CKD outcomes [128]. The authors developed a novel immunoassay targeting LG1M, a degradation fragment of LAMC1, generated by matrix metalloproteinase (MMP)-9, an enzyme upregulated in fibrosis. The study population included 492 patients taken from the Renal Impairment in Secondary Care cohort, who had a median eGFR of 26.5ml/min/1.73m$^2$ (IQR 19.4-34.6). Over a median follow-up of 3.5 years, the study showed that higher serum LG1M levels were associated with ESRD and that higher urine LG1M was associated with mortality. However, as has been seen with several previous biomarker studies of CKD progression, neither reached statistical significance when adjusted for other prognostic factors including eGFR and albuminuria.

#### *1.8.4.2 Angiogenesis*

There is a growing body of evidence that suggests dysregulated angiogenesis has a role in CKD pathogenesis, contributing to an increased risk of progression and mortality. More recently, Anderson et al [129] reported the association between a potent angiogenic factor, VEGF-A, and a higher risk of having CKD in a cross-sectional study of 201 patients with CKD compared with control participants, in which CKD was defined as eGFR<60ml/min/1.73m$^2$ or albuminuria of >30mg/24hrs. A systematic review [130] has also been recently published that highlights a number of anti-angiogenic factors, including circulating endostatin, vasohibin-1 and pigment epithelium-derived factor (PEDF), may be implicated in either CKD initiation or progression.

#### *1.8.4.3 Advanced glycation end products (AGEs) and skin autofluorescence (SAF)*

AGEs are derived from proteins, amino acids or lipids that are glycated by reducing sugars and reflect a state of oxidative stress. They have been implicated in CKD pathogenesis and a review on this topic has been provided recently by Rabbani and Thornalley [131].

SAF, a well-validated marker of estimating AGE accumulation in skin, has been studied in patients with CKD and found to represent a risk predictor for CKD progression. In a recent study of 245 patients with atherosclerotic risk factors [132], higher SAF levels were independently associated with rapid renal decline (defined as an absolute eGFR loss rate of >3ml/min/1.73m$^2$) over 2 years follow-up and was especially predictive of renal decline in patients <65 years, male, obese and with earlier stages of CKD (G1-2). A major limitation to this work is that albuminuria was not measured and therefore not controlled for in the multivariate analysis, and hence the independent usefulness of SAF over traditional risk factors is uncertain.

#### *1.8.4.4 Radiological factors*

Blood oxygenation level-dependent magnetic resonance imaging (BOLD-MRI) can non-invasively quantify renal tissue oxygenation as a result of altered paramagnetic characteristics of oxygenated and deoxygenated haemoglobin. The technique provides a cortical R2* value to represent cortical oxygenation and an R2* slope to denote corticomedullary differences in oxygenation. Pruijm et al [133] report the novel finding that reduced cortical oxygenation (higher R2* values) and reduced corticomedullary differences in oxygenation (lower R2* slope) can predict progressive renal decline (eGFR loss of >3ml/min/1.73m$^2$) over an average of 3 years follow-up. Receiver operator characteristics for a major renal event (reaching ESRD or a creatinine increase >30%) showed an area under the curve (AUC) of 0.71 for cortical R2* and 0.80 for the R2* slope. Although proteinuria provided a stronger association (AUC 0.83), the combination of all three parameters increased the AUC further to 0.89. There are limitations to the use of BOLD-MRI but this study provides a platform to further evaluate and improve its performance in predicting CKD outcomes.

In contrast to the cost and limited availability of MRI, ultrasound-based imaging is cheap and routinely performed. Kuo et al [134] developed an artificial intelligence (AI) based automation of renal ultrasound images that focused on interpreting kidney length. In their study of 1299 patients under regular renal follow-up in Taiwan, they showed their algorithm had a reasonable correlation of 0.74 for predicting continuous eGFR values. In addition, the AUC at the cut-off threshold of <60ml/min/1.73m$^2$ was excellent at 0.90, surpassing the predictive ability of experienced nephrologists, and provides encouraging initial data on the application of AI in imaging techniques.

Whether such tools can provide information on future progression or adverse outcomes is yet to be studied. However, the possibility that repeated imaging could replace the need for invasive biopsy to assess progression is an attractive one for patient safety.

#### *1.8.4.5 Metabolic factors*

High oxalate levels are known to be nephrotoxic: disorders of oxalate metabolism (primary hyperoxaluria), over-ingestion of oxalate or its metabolic precursors such as ethylene glycol, or increased oxalate gut absorption can all produce renal failure. In light of these associations, a recent study explored whether measuring urinary excretion of oxalate may be a risk factor for CKD progression [135]. The authors showed that in a prospective study of 3123 patients with CKD G2-4 within the Chronic Renal Insufficiency Cohort, higher 24-hour urinary oxalate levels were independently associated with progression, defined as a composite of incident ESRD or eGFR loss of >50%. The study, however, did not measure plasma oxalate levels nor could it ascertain the mechanism by which oxalate homeostasis was most affected; for instance, whether diet, altered gut handling or altered metabolism due to CKD were contributing. Nonetheless, it does provide a novel observation that elevated urinary oxalate identifies patients at risk of CKD progression and offers the treatment prospect of lowering oxalate in this patient group.

At least two studies have sought to determine a metabolic risk tool for CKD prediction. One evaluated the application of a metabolic severity z-score (MetS) on CKD risk [136]. The MetS provides a sex- and race-specific (Hispanic, non-Hispanic black, non-Hispanic white) normally distributed z-score that takes account of the risk factors in the metabolic syndrome (hypertension, glucose intolerance, dyslipidaemia and obesity). A z-score of 2 is 2 standard deviations from the mean, corresponding to the 97.7% percentile. The study focused on 2627 African-American participants within the Jackson Heart Study without baseline diabetes and showed that higher MetS were associated with eGFR decline over an 8 year period, but this was only observed in female subjects. The cause for the sex differences remains unclear but suggests a complex interplay of risk factors exists in different ethnic populations.

In another study, nuclear magnetic resonance spectroscopy was performed in 4640 patients from the German Chronic Kidney Disease study who had a mean eGFR of 49.4

ml/min/1.73m$^2$. The study provided multiple metabolite signals that were incorporated into a metabolic risk tool to predict ESRD, which affected 4% of the patient cohort over a mean follow-up of 3.7 years [137]. The most important contributors to the model included creatinine, high-density lipoprotein, valine, acetyl groups of glycoproteins and $Ca^{2+}$-EDTA. The AUC of 0.87 was, however, only marginally better than using the Kidney Failure Risk Equation (KFRE) in this cohort.

*1.8.4.6 Genetic factors*

In a Spanish cohort of 2245 CKD patients, 5 single nucleotide polymorphisms (SNPs) of proteins related to CKD mineral bone disease were found to improve CKD detection defined as an eGFR<60ml/min/1.73m$^2$ [138]. These included genes encoding for osteopontin, matrix metalloproteinase 3, osteocalcin, matrix Gla protein and *CYP24A1*, an enzyme involved with Vitamin D metabolism. This cohort was almost entirely Caucasian. In contrast, in an ethnically diverse population-based cohort of 41,041 participants in the Population Architecture using Genomics and Epidemiology study, a novel locus near *NMT2*, encoding for a protein (N-myristoyltransferase) that regulates the function of other signalling proteins, was found to be associated with CKD G3-4 [139].

Xu et al [140] undertook genotyping and RNA-sequencing of 280 kidney transcriptomes from the Transcriptome of Renal Human Tissue study and The Cancer Genome Atlas. They uncovered 35 genes that were significantly associated with CKD. However, only one was found to be causally linked to CKD – *MUC1*, which encodes mucin1, a glycoprotein found on the apical surface of epithelial cells in many organs that serves a role in mucosal defence against pathogens. Interestingly, mutations in *MUC1* cause medullary cystic kidney disease type 1 and could therefore serve as a potential avenue for further research into CKD pathophysiology.

A high genetic risk score incorporating 53 SNPs was significantly associated with incident CKD G3a in a Swedish population-based cohort of 2301 participants followed-up over a mean of 16.6 years [141]. Although it failed to be of discriminatory value in addition to standard clinical risk factors, it did help reclassify 21% of patients accurately within the same cohort. The study, however, was limited by a single eGFR being used to diagnose CKD and a lack of adjustment for albuminuria.

Most recently, Stanzick et al undertook a genome-wide association meta-analysis of over 1 million patients derived from the CKD Genetics Consortium and the UK Biobank. They identified 424 gene loci associated with creatinine-based eGFR (i.e., a quantifiable measure of kidney function), of which 201 were novel [142]. The researchers validated their findings by showing that these loci are specifically associated with kidney function as more than 80% of them were also associated with other measures of kidney function, namely cystatin-based eGFR and serum urea, the latter of which was previously shown to have genetic correlation with serum creatinine in a genome-wide analysis of patients from the UK Household Longitudinal Study [143]. Through fine-mapping analytic techniques, the work by Stanzick et al has uncovered a novel group of 23 genes that map onto specific causal proteins, providing compelling new groundwork for experimental studies to explore the mechanistic aetiology of CKD.

### 1.8.5 Clinical risk prediction tools

The KFRE remains the most extensively validated risk prediction tool for estimating ESRD in those with CKD G3-5 [116], and study protocols have been published to ascertain whether it can guide optimal CKD care in both secondary and primary care settings [144][145]. Nonetheless, risk prediction tools for various CKD outcomes continue to be explored and evaluated in different clinical contexts.

Ravizza et al [146] show that an algorithm derived from the electronic health records of 417,912 patients with diabetes had a strong ability to predict CKD over a 3-year period (AUC 0.79). The algorithm, incorporating 7 variables (age, body mass index, creatinine, eGFR, albumin, glucose and HbA1c) performed better than 4 clinical datasets that have studied CKD risk in diabetic patients. This finding highlights that real-world data can generate meaningful risk assessment tools and, in contrast to prospective clinical trials, may represent a cost-effective means to enhance evidence-based practice.

A Japanese study of 296 patients with biopsy-proven diabetic nephropathy evaluated the performance of the KFRE combined with a biopsy-based diabetic nephropathy score (D-score) in predicting the 3-year risk of ESRD [147]. The KFRE had an AUC of 0.78, weaker than reported from its original validation cohorts, and this only improved marginally to 0.80 with the addition of the D-score. The study therefore raises two issues. First, the KFRE has scope for further refinement, certainly in Japanese patients

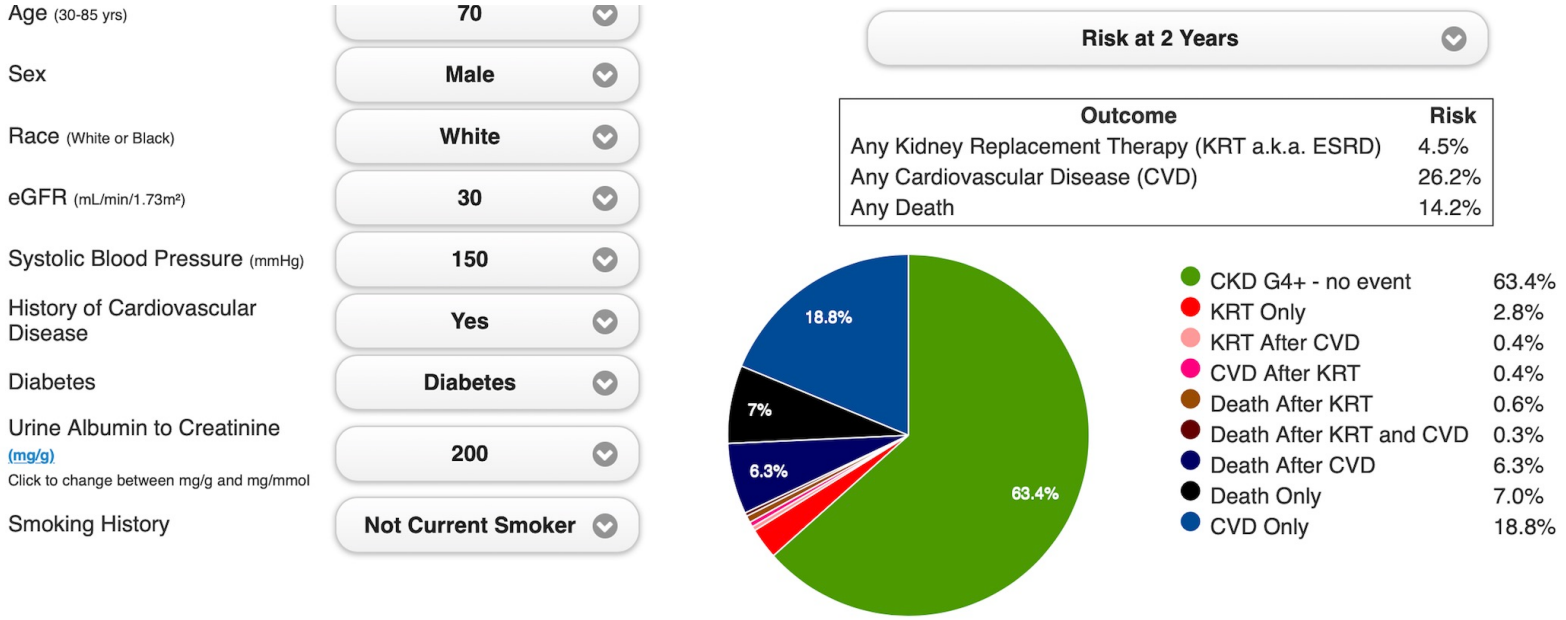
with diabetes; secondly, prognostication of diabetic disease from a renal biopsy is not significantly improved beyond simple clinical parameters.

Finally, using the 9 risk factors from their original meta-analysis, the CKD Prognosis Consortium have developed a risk calculator that provides a 2- and 4-year estimate of the timing of RRT, non-fatal CVE or mortality and their relation to each other in CKD patients [148]. A hypothetical use of the online calculator is shown in Figure 1.4. The risk tool compared well with the KFRE but supplements it with information on CVE and mortality in those with an eGFR <30ml/min/1.73m$^2$. Further work to refine the calculator is proposed to help account for a degree of unexplained variation in the risk between cohorts but for now it provides a valuable pictorial representation of risk outcomes to both clinicians and patients.

### 1.8.6 Conclusion

Significant progress continues to be made with respect to CKD risk prediction, from discovering novel biomarkers to developing accessible calculators to predict adverse outcomes. Future research in CKD risk prediction requires two simultaneous goals. The first is to continue to unravel the mechanistic pathways of novel risk factors implicated in CKD progression in order to identify new therapeutic targets. Secondly, further development and refinement of risk prediction tools, supported by novel biomarker discovery, should be evaluated to assess clinical utility in improving patient care. A multi-disciplinary, collaborative approach is therefore required to realise the advent of personalised medicine in CKD risk prediction.

**Figure 1.4** CKD Prognosis Consortium risk calculator estimating the risk of adverse events at 2 years



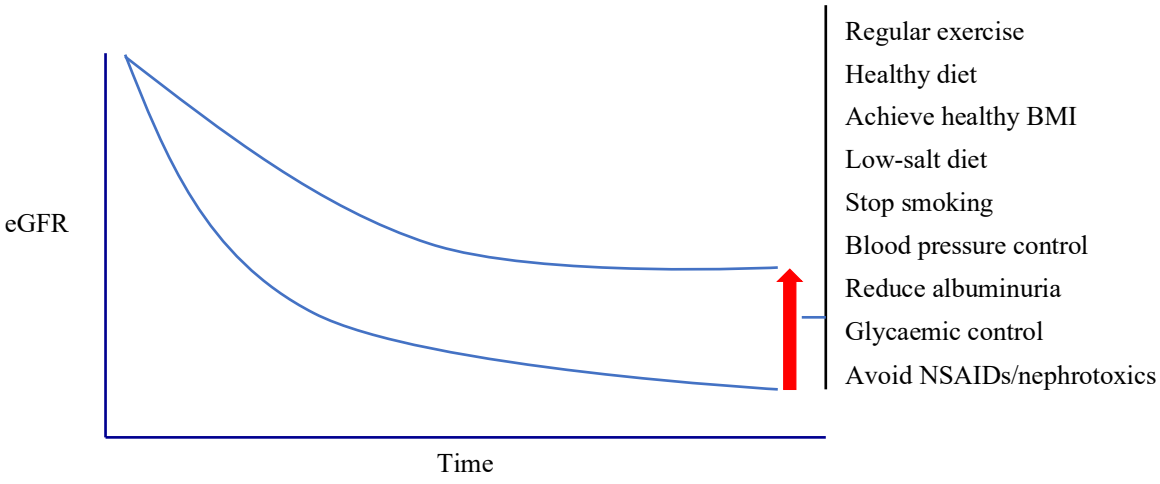

The variables are of a 70-year-old male, eGFR of 30ml/min/1.73m$^2$, systolic blood pressure of 150mmHg, history of cardiovascular disease, presence of diabetes, urine ACR of 200mg/g and not a current smoker [149].

## 1.9 RETARDING CKD PROGRESSION

The advancement of omic technologies, biomarker detection and risk prediction all need to be simultaneously met with a better understanding of CKD pathophysiology. This will provide the means to offer novel therapeutic targets that could stabilise or reverse progression and remains the ultimate goal of CKD care.

The management ethos to limit CKD progression is to concurrently treat the underlying cause of CKD if known and address the multitude of other modifiable risk factors that can contribute to progressive disease [1]. Given that several risk factors overlap with those associated with CVD, CKD management reflects a convergence of treatment pathways that aim to modify cardiovascular risk (Figure 1.5). These include lifestyle measures such as regular exercise, salt restriction, smoking cessation and achieving a healthy BMI.

**Figure 1.5** Measures to retard CKD progression are integrated with CVD risk reduction



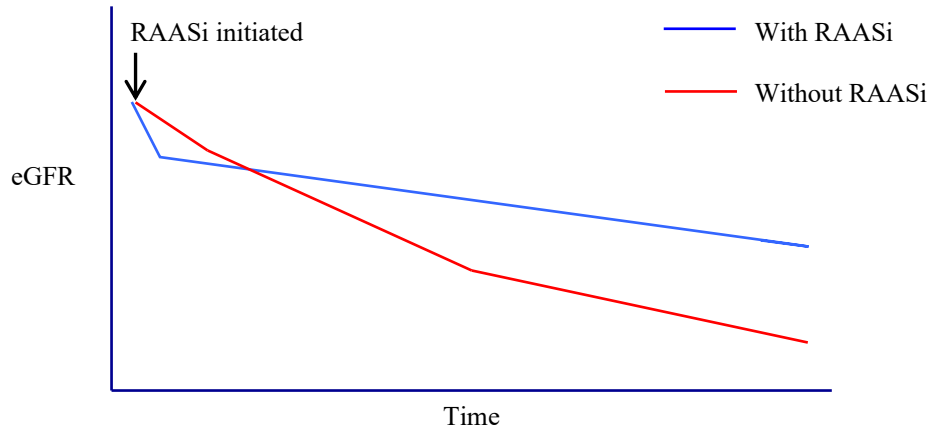

### 1.9.1 The role for renin-angiotensin-aldosterone system inhibitors

Along with lifestyle changes, the medical treatment paradigm of retarding CKD progression, in general, lies in controlling blood pressure and reducing albuminuria. Renin-angiotensin-aldosterone system inhibitors (RAASi), including ACEi and angiotensin receptor blockers (ARB), lie at the cornerstone of CKD management given they are able to influence both blood pressure and albuminuria [1]. Their mechanism of action involves arterial vasodilation, which causes a reduction in systemic blood

pressure. At the level of glomerulus, they cause efferent arteriolar dilatation, which causes the intra-glomerular pressure to drop, and this is believed to reduce albuminuria.

The benefit of ACEi and ARBs has been shown to improve renal and cardiovascular outcomes in patients with CKD who are hypertensive and proteinuric. In a meta-analysis of 11 randomised controlled trials, Jafar et al [150] showed that ACEi use resulted in a 31% reduction in the development of ESRD (HR 0.69; 95% CI 0.51-0.94) and the benefit was most marked in those with higher levels of albuminuria. In a separate meta-analysis [151] of 45,758 patients across 25 trials, ACEi/ARB therapy was associated with a lower risk of cardiovascular outcomes in CKD patients when compared with placebo or other anti-hypertensive medications. These long-term effects occur despite an initial fall in eGFR (Figure 1.6).

**Figure 1.6** Altering the trajectory of CKD progression with RAASi




Although initiation, or up-titration, of RAASi agents may cause a deterioration in eGFR, it confers long-term renoprotection. NICE guidance recommends that blood tests should be performed 1-2 weeks after initiating or up-titrating RAASi therapy. A change in eGFR of less than 25% or serum creatinine increase of less than 30% permits safe continuation of these agents [16].

The reno- and cardioprotection afforded by ACEi/ARB therapy, however, has been postulated to be mediated beyond their impact on blood pressure and albuminuria alone. Indeed, experimental studies have highlighted that tissue injury can occur through RAAS activation by inflammatory processes, oxidative stress and fibrosis, and these can be blunted by RAASi therapy [152, 153].

In clinical practice, however, a major hindrance to the long-term use of RAASi medications is the development of hyperkalaemia. Hyperkalaemia, therefore, plays an indirect role in CKD progression as it often prevents the administration and/or maximal use of renoprotective drugs. Treatments to help control hyperkalaemia are therefore important in order to deliver optimal care in CKD.

### 1.9.2 Clinical importance of hyperkalaemia

Potassium is the main intracellular cation in the human body. Hyperkalaemia, defined in most observational studies as >5mmol/L, has been shown to be prevalent in approximately 2-3% of the general population [154] but it can affect more than 50% in those with advanced stages of CKD [153]. This is because the kidneys play a major role in electrolyte homeostasis, and hence why poor renal function, typically CKD stages 3b and lower, is the most common predisposing factor for hyperkalaemia. Other risk factors include diabetes, heart failure, acidosis and RAASi medications, which in combination therapy increase the risk of hyperkalaemia further [1].

Importantly, both hypo- and hyperkalaemia are harmful to the patient as they can trigger malignant electrophysiological changes within the myocardium that can lead to a cardiac arrest. As a consequence, patients who are discovered to have marked dyskalaemia from clinic blood tests require urgent emergency department attendance, re-checking of blood tests and possible inpatient management, all of which drives healthcare costs [156].

In a meta-analysis of 27 patient cohorts, comprising 1,217,986 patients followed-up for an average of nearly 7 years, Kovesdy et al [157] showed a U-shaped distribution of baseline serum potassium levels with ESRD, cardiovascular and all-cause mortality. Patients with potassium in the range of 4-4.5mmol/L experienced the least risk. In contrast, when compared to a potassium level of 4.2mmol/L, the adjusted HR for all-cause mortality for a potassium level of 5.5mmol/L and 3.0mmol/L was 1.22 (95% CI 1.15-1.29) and 1.49 (95% CI 1.26-1.76) respectively.

A major limitation with this study was the use of a single baseline potassium result to predict the risk of future adverse events. It therefore did not take into account

fluctuations of potassium over time or the impact the potassium level may have had when obtained as close to an event as possible. However, the findings were nonetheless consistent across all cohorts, and these were adjusted for multiple confounders including eGFR. Furthermore, the U-shaped association of potassium with all-cause mortality has also been shown in studies that have assessed time-varying potassium levels with clinical outcomes. This method was undertaken in the Renal Research Institute CKD (RRI-CKD) study [158] of 820 patients with an average eGFR of 25.4ml/min/1.73m$^2$, in which a potassium of ≤4mmol/l and >5.5mmol/l was associated with the greatest risk of mortality when compared with those in the range 4-5.5mmol/l over a 2.6-year follow-up.

Derangements in potassium can therefore have important long-term health consequences. But with respect to CKD management, it is mainly hyperkalaemia that imposes a restriction on the use of renoprotective RAASi agents. Strategies to overcome hyperkalaemia include a potassium-restricted diet, administering sodium bicarbonate if acidosis is present or a diuretic if the patient is fluid overloaded [56] and reducing or withdrawing RAASi therapy. In a single-centre study, Yildrim et al [159] showed that hyperkalaemia was the commonest reason for discontinuation of RAASi agents. Upon withdrawal, clinicians may be averse to re-starting the RAASi therapy for fear of hyperkalaemia recurrence or may prescribe a low-dose and fail to up-titrate. Not achieving the maximal therapeutic doses of RAASi has been shown to be detrimental to patient care. In the prospective Renoprotection of Optimal Antiproteinuric Doses (ROAD) study [160] of 360 non-diabetic, proteinuric patients, maximal doses of benazepril and losartan produced an approximately 50% reduction in endpoints of doubling of creatinine, ESRD or death. In addition, Epstein et al [161] found that patients with CKD stages 3-4 who discontinued RAASi therapy faced twice the risk of death compared to those who continued taking treatment.

Ideally, therefore, managing hyperkalaemia without the need to discontinue RAASi therapy is of critical importance. Recently, the emergence of well-tolerated and efficacious novel potassium-binding agents, such as patiromer (Veltassa®) and sodium zirconium cyclosilicate (SZC, Lokelma®), have provided an ideal solution to hyperkalaemia management. These agents are now recommended as part of the

measures to control hyperkalaemia in international guidelines for patients with CKD receiving RAASi therapy [162].

### 1.9.3 Patiromer

Patiromer is a non-absorbed, potassium-binding polymer that non-specifically binds potassium for calcium along the gastrointestinal tract [163]. It has been shown in a number of trials to be effective in achieving control of hyperkalaemia and permitting the continuation of anti-RAAS medications (Table 1.5).

The AMETHYST-DN study [164] was a phase 2, multi-centre, randomised controlled trial that evaluated the efficacy of patiromer to normalise serum potassium levels. In total, 306 diabetic patients were stratified according to mild or moderate hyperkalaemia and randomised to different initiating doses of patiromer. The study showed that there were significant reductions in serum potassium at 4 weeks across the two strata and these reductions were maintained on monthly blood tests until the end of the 1-year follow-up.

The OPAL-HK trial [165] also studied the efficacy of patiromer. This was a two-part, multi-centre, randomised controlled trial. The study participants were adults aged 18-80 years with CKD stages 3 to 5 and who were receiving one or more RAASi medications. A total of 243 subjects were recruited of whom 97% had hypertension, 57% had diabetes, 42% had heart failure and 25% had a previous MI. Thus, the cohort represented a high-risk group of patients most likely to benefit from RAASi therapy.

The first part of the study consisted of a 4-week dose-varying, single-arm treatment phase for patients whose potassium was 5.1-6.5mmol/L. At the end of 4 weeks, patiromer had resulted in a mean change in serum potassium of -1.01±0.03mmol/L (95% CI -1.07 to -0.95) with 76% of the total cohort reaching normal potassium levels. The second part of the study was a randomised, 8-week withdrawal phase. In this part, 107 participants were chosen who had a baseline potassium between 5.5-6.5mmol/L and whose potassium had reduced to a range of 3.8-5.1mmol/L at the end of the part 1 of the study. They were randomly assigned to continue with patiromer or switch to placebo. In this phase of the trial, 60% of the patients in the placebo arm had a recurrent hyperkalaemic episode of ≥5.5mmol/L, compared with 15% in the patiromer group.

Importantly, only 6% patients receiving patiromer had to discontinue RAASi therapy compared with 56% of patients within the placebo group.

In the 4-week, double-blind, randomised, placebo-controlled PEARL-HF [166] trial, the efficacy of patiromer at maintaining normokalaemia was evaluated in patients with chronic heart failure who had a serum potassium between 4.3-5.1mEq/L at screening. In addition, they also had to have either (i) CKD (defined as an eGFR <60ml/min/min/1.73m$^2$) and be receiving an ACEi, ARB or beta-blocker, or (ii) have had discontinuation of ACEi, ARB, mineralocorticoid antagonist or beta-blocker due to RAASi-associated hyperkalaemia in the preceding 6 months. This study showed that patients randomised to patiromer at a high dose of 25.2g/day experienced significantly reduced serum potassium levels compared to those receiving placebo, and a higher proportion of patients receiving patiromer were able to safely up-titrate spironolactone from 25mg/day to 50mg/day (91% in patiromer arm compared to 74% in the placebo arm; p=0.019).

The AMBER trial [167] was another double-blind, randomised, placebo-controlled trial whose primary endpoint was the difference in the proportion of patients in the patiromer and placebo groups who were still receiving spironolactone at 3 months. This study exclusively enrolled patients with CKD (eGFR 25-45ml/min/1.73m$^2$) and showed that 86% of patients in the patiromer arm remained on spironolactone compared with only 66% patients in the placebo arm; p<0.001.

In summary, these trials have demonstrated the efficacy of patiromer to normalise potassium and promote RAASi enablement. Importantly, they all reported that patiromer was very well tolerated with mild-to-moderate gastrointestinal symptoms being the major side effect. This is particularly welcome given historic potassium binders such as sodium polystyrene sulfonate (SPS) were poorly tolerated due to their gastrointestinal side effect profile and SPS is well known to cause the serious adverse complication of intestinal necrosis [163].

**Table 1.5** Trials of patiromer and SZC and the impact on RAASi therapy

| | **Trials involving patiromer** | | | | **Trial involving SZC** |
|---|---|---|---|---|---|
| | **AMETHYST-DN [164]** | **OPAL-HK [165]** | **PEARL-HF [166]** | **AMBER [167]** | **ZS-005 [168]** |
| Patient numbers | 306 (all received patiromer) | 243 (all received patiromer in treatment phase) | 120 (55 randomised to patiromer) | 295 (148 randomised to patiromer) | 746 (all received SZC) |
| Placebo arm | No | Yes (in withdrawal phase) | Yes | Yes | No |
| [1]Diabetes, % | 100% | 57% (in treatment phase) | 27% | 50% | 64% |
| [1]Heart failure, % | 35% | 42% (in treatment phase) | 100% | 43% | 15% |
| [1]CKD, % | 89% (stages 3-5) | 100 (stages 3-4) | 50% (stages 3-5) | 100% (stages 3-4) | 74% (stages 3-5) |
| [1]Mean eGFR, ml/min/1.73m$^2$ | 40.6 (±50.7) | 35.4 (±16.2) | 84 (±35) | 35.4 (±7.3) | 47 (±32) |
| [1]RAASi at baseline, % | 100% | 100% | 98% | 100% | 65% |
| RAASi optimisation | **Study protocol** 100% of patients remained on RAASi whilst on patiromer treatment | **Exploratory endpoint** 94% of patient receiving patiromer continued RAASi vs. 44% in placebo group (during randomised withdrawal phase) | **Secondary endpoint** 91% of patients receiving patiromer up-titrated spironolactone from 25mg/day to 50mg/day vs. 74% in placebo group | **Primary endpoint** 86% of patients receiving patiromer remained on spironolactone vs. 66% in placebo group | **Exploratory endpoint** 87% of patients on RAASi continued or increased RAASi dose |

[1]Relates to % in patients receiving a potassium binder

### 1.9.4 Sodium zirconium cyclosilicate (SZC)

SZC is another non-absorbed potassium binder, which exchanges potassium for sodium and hydrogen cations in the gastrointestinal tract. It has been shown to be efficacious at achieving normokalaemia. In the HARMONIZE trial [169], 258 ambulatory patients with a serum potassium of ≥5.1mEq/L received SZC 10g three times a day in an initial open-label 48-hour correction phase. Of these patients, 237 achieved normokalaemia (3.5-5.0mEq/L) and were subsequently randomised in the maintenance phase of the trial to receive SZC at doses of 5, 10 and 15g or placebo daily for 28 days. The trial demonstrated that SZC had a significant effect at reducing potassium levels acutely with a mean change in serum potassium of -0.5mEq/L (95% CI -0.6 to -0.5) at 4 hours, with normokalaemia achieved in 98% (95% CI 96% to 99%) of patients by 48 hours. In the randomised maintenance phase, the proportion of patients with a mean potassium of <5.1mEq/L was significantly higher in those receiving SZC compared to those receiving placebo: 80%, 90% and 94% for those receiving 5, 10 and 15g respectively, compared to 46% receiving placebo; p-value <0.001. The efficacy of SZC to reduce potassium acutely and maintain its effect over 28 days was similarly reproduced in the HARMONIZE-Global study, which evaluated SZC in ethnically diverse populations from Russia, Taiwan, South Korea and Japan [170].

Importantly, SZC, like patiromer, has evidence to show it can permit RAASi enablement by maintaining normokalaemia: a multicentre, open-label study of SZC was recently conducted in patients with hyperkalaemia [168]. After achieving normokalaemia (3.5-5.0mmol/L), 746 patients were enrolled into a 12-month maintenance phase during which time a mean serum potassium of ≤5.1mmol/L and ≤5.5mmol/L was achieved in 88% and 99% of patients respectively. Amongst the 483 patients who were receiving RAASi, 87% continued on the same dose or received a dose increase.

Similar to patiromer, SZC also has a good safety profile, with reported adverse events such as oedema and nausea being only mild-to-moderate in nature and not necessitating treatment cessation [168].

### 1.9.5 Future prospects

Further trials evaluating the impact of patiromer and SZC in patients with CKD on major clinical endpoints such as ESRD, cardiovascular and all-cause mortality, would be highly desired. For now, given the appeal of enabling RAASi continuation, these agents should be used routinely as part of hyperkalaemia management.

## 1.10 SUMMARY

This literature review has appraised the importance of recognising CKD as a continuum of risk that is associated with poor health outcomes. Efforts to better understand and mitigate this risk has generated a wealth of research, from better phenotypic characterisation of progressive renal decline to developing accurate clinical risk prediction tools. In the future, biomarker discovery will likely play a major role in offering patients a precise and personalised risk-based assessment and help uncover new therapeutic targets to improve CKD outcomes. Currently, there is much enthusiasm for novel potassium binders, which can safeguard RAASi continuation by preventing hyperkalaemia, and this will undoubtedly help in optimising CKD care for high-risk patients.

## 1.11 REFERENCES


1. KDIGO. Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3:i-150.
2. National Kidney Foundation. Definition and classification of stages of chronic kidney disease. Am J Kidney Dis. 2002;39:S46-75.
3. NICE. Chronic kidney disease. Early identification and management of chronic kidney disease in adults in primary and secondary care. 2008. Available at: www.impakt.org.uk/resources/MANAGE1/NICE_CKD_Guidelines/NICE_CKD_Guidelines.pdf. [Accessed 14 Aug 2018].
4. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011;80:17-28.
5. Eckardt KU, Coresh J, Devuyst O, et al. Evolving importance of kidney disease: from subspecialty to global health burden. Lancet. 2013;382:158-169.
6. Stevens PE, O'Donoghue DJ, de Lusignan S, et al. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int. 2007;72:92-99.
7. Health Survey for England. Summary of key findings. 2006. Available at: https://files.digital.nhs.uk/pdf/s/q/hse2016-summary.pdf. [Accessed 14 Aug 2018]
8. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. PLoS ONE. 2016;11:e0158765.
9. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395:709-733.
10. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. Nature. 2017;13:104-114.
11. Coresh J, Eknoyan G, Levey AS. Estimating the prevalence of low glomerular filtration rate requires attention to the creatinine assay calibration. J Am Soc Nephrol.2002;13:2811–2812.
12. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612.

13. Matsushita K, Mahmoodi BK, Woodward M. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. JAMA. 2012;307:1941-1951.
14. Skali H, Uno H, Levey AS, et al. Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. Am Heart J. 2011;162:548-554.
15. White SL, Polkinghorne KR, Atkins RC, et al. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations. Am J Kidney Dis. 2010;55:660-670.
16. NICE. Chronic kidney disease in adults: assessment and management. 2015. Available at: https://www.nice.org.uk/guidance/cg182, [Accessed 14 Aug 2018].
17. Gharbi MB, Elseviers M, Zamd M et al. Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid 'over'- and 'under'-diagnosis of CKD. Kidney Int. 2016;89:1363–1371.
18. Delanaye P, Glassock RJ, De Broe ME. Epidemiology of chronic kidney disease: think (at least) twice! Clin Kidney J. 2017;10:370-374.
19. USRDS. Incidence, prevalence, patient characteristics, and treatment modalities. 2017. Available at: https://www.usrds.org/2017/view/v2_01.aspx. [Accessed 14 Aug 2018].
20. de Lusignan S, Tomson C, Harris K, et al. Creatinine fluctuation has a greater effect than the formula to estimate glomerular filtration rate on the prevalence of chronic kidney disease. Nephron Clin Pract. 2011;117:c213–24.
21. Steddon S, Ashman N. Oxford Handbook of Nephrology and Hypertension. Oxford, UK; 2014.
22. Go AS, Glenn M, Chertow MD, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Eng J Med. 2004;351:1296-1305.
23. Meisinger C, Döring A, Löwel H. Chronic kidney disease and risk of incident myocardial infarction and all-cause and cardiovascular disease mortality in middle-aged men and women from the general population. Eur Heart J. 2006;27:1245-1250.

24. Weiner DE, Tighiouart H, Levey AS, et al. Lowest systolic blood pressure is associated with stroke in stages 3 to 4 chronic kidney disease. J Am Soc Nephrol. 2007;18:960-966.
25. NHS England. Chronic kidney disease in England: the human and financial cost. 2012. Available at: https://www.england.nhs.uk/improvement-hub/wp-content/uploads/sites/44/2017/11/Chronic-Kidney-Disease-in-England-The-Human-and-Financial-Cost.pdf. [Accessed 14 Aug 2018].
26. ISN Global Kidney Health Atlas. 2017. Available at: https://www.theisn.org/scroller-content/689-isn-global-kidney-health-atlas. [Accessed 14 Aug 2018].
27. O'Hare AM, Bertenthal D, Covinsky KE, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? J Am Soc Nephrol. 2006;17:846-853.
28. Nahas M, Khwaja A. Epidemiology, natural history, and pathophysiology of chronic kidney disease. In: Johnson RJ, Feehally J, Floege J, editors. Comprehensive Clinical Nephrology, Philadelphia; 2015. P.916-918.
29. Levey AS, Stevens LA, Coresh J. Conceptual model of CKD: applications and implications. Am J Kidney Dis. 2009;53:S4-16.
30. Weller JM, Wu SC, Ferguson CW, et al. End-stage renal disease in Michigan. Incidence, underlying causes, prevalence, and modalities of treatment. Am J Nephrol. 1985;5:84–95.
31. Iseki K, Iseki C, Ikemiya Y, et al. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int. 1996;49:800–805.
32. Fox CS, Larson MG, Leip EP, et al. Predictors of new-onset kidney disease in a community-based population. JAMA. 2004;291:844-850.
33. Evans M, Fryzek JP, Elinder CG, et al. The natural history of chronic renal failure: results from an unselected, population-based, inception cohort in Sweden. Am J Kidney Dis. 2005;46:863–870.
34. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int. 2006;69:375–382.
35. Silbiger S, Neugarten J. The impact of gender on the progression of chronic renal disease. Am J Kidney Dis. 1995;25:515–533.

36. Jafar TH, Schmid CH, Stark PC, et al. The rate of progression of renal disease may not be slower in women compared with men: a patient-level meta-analysis. Nephrol Dial Transplant. 2003;18:2047–2053.
37. Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. J Am Soc Nephrol. 2000;11:319-329.
38. McCellan W, Warnock DG, McClure L, et al. Racial Differences in the Prevalence of Chronic Kidney Disease among Participants in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Cohort Study. J Am Soc Nephrol. 2006;17:1710-1715.
39. Kiberd BA, Clase CM. Cumulative risk for developing end-stage renal disease in the US population. J Am Soc Nephrol. 2002;13:1635–1644.
40. Hostetter TH, Olson JL, Rennke HG et al. Hyperfiltration in remnant nephrons: a potentially adverse response to renal ablation. Am J Physiol. 1981;241:F85–F93.
41. Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease study. Kidney Int. 1997;51:1908-1919.
42. Barker DJ. Fetal origins of coronary heart disease. BMJ. 1995;311:171–174.
43. Hughson M, Farris AB, Douglas-Denton R, et al. Glomerular number and size in autopsy kidneys: The relationship to birth weight. Kidney Int. 2003;63:2113-2122.
44. Lackland DT, Bendall HE, Osmond C, et al. Low birth weights contribute to the high rates of early-onset chronic renal failure in the Southeastern United States. Arch Intern Med. 2000;160:1472-1476.
45. Brenner BM, Mackenzie HS. Nephron mass as a risk factor for the progression of renal disease. Kidney Int. 1997;52:124-127.
46. Halbesma N, Kuiken DS, Brantsma AH, et al. Macroalbuminuria is a better risk marker than low estimated GFR to identify individuals at risk for accelerated GFR loss in population screening. J Am Soc Nephrol. 2006;17:2582–2590.
47. Imai E, Horio M, Yamagata K, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433–441.
48. Jafar TH, Stark PC, Schmid CH, et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. Kidney Int. 2001;60:1131–1140.

49. Brancati FL, Whelton PK, Randall BL, et al. Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. JAMA. 1997;278:2069-2074.
50. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008;358:2560–2572.
51. Haroun MK, Jaar BG, Hoffman SC, et al. Risk factors for chronic kidney disease: a prospective study of 23 534 men and women in Washington County, Maryland. J Am Soc Nephrol. 2003;14:2934–2941.
52. Klag MJ, Whelton PK, Randall BL, et al. Blood pressure and end-stage renal disease in men. N Engl J Med. 1996;334:13–18.
53. Appel LJ, Wright JT, Jr, Greene T, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010;363:918–929.
54. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575–1585.
55. Gaede P, Lund-Andersen H, Parving HH, et al. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med. 2008;358:580–591.
56. KDIGO. Clinical Practice Guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2012;2:i-414.
57. Appel GB, D'Agati VD. Primary and secondary (non-genetic) causes of focal segmental glomerulosclerosis. In: Johnson RJ, Feehally J, Floege J, editors. Comprehensive Clinical Nephrology, Philadelphia; 2015. P.916-918.
58. Hsu C, McCulloch CE, Iribarren C, et al. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144:21-28.
59. Munter P, Coresh J, Smith JC, et al. Plasma lipids and risk of developing renal dysfunction: The Atherosclerosis Risk In Communities. Kidney Int. 2000;58:293–301.
60. Onelli M, Moye L, Sacks FM, et al. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. J Am Soc Nephrol. 2003;14:1605–1613.
61. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: a meta-analysis. Kidney Int. 2001;59:260–269.

62. Kurella M, Lo JC, Chertow GM. Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults. J Am Soc Nephrol. 2005;16:2134–2140.
63. Briganti EM, Branley P, Chadban SJ, et al. Smoking is associated with renal impairment and proteinuria in the normal population: the AusDiab Kidney Study. Am J Kidney Dis. 2002;40:704-712.
64. Pinto-Sietsma SJ, Mulder J, Janssen WM, et al. Smoking is related to albuminuria and abnormal renal function in non-diabetic persons. Ann Intern Med. 2000;133:585-591.
65. Orth SR, Schroeder T, Ritz E, et al. Effects of smoking on renal function in patients with type 1 and type 2 diabetes mellitus. Nephrol Dial Transplant. 2005;20:2414–2419.
66. Regalado M, Yang S, Wesson DE. Cigarette smoking is associated with augmented progression of renal insufficiency in severe essential hypertension. Am J Kidney Dis. 2000;35:687–694.
67. Stengel B, Couchoud C, Cenee S, et al. Age, blood pressure and smoking effects on chronic renal failure in primary glomerular nephropathies. Kidney Int. 2000; 57:2519–2526.
68. Orth SR, Stockmann A, Conradt C, et al. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. Kidney Int. 1998;54:926–931.
69. Levin A, Djurdjev O, Barrett B, et al. Cardiovascular disease with chronic kidney disease: getting to the heart of the matter. Am J Kidney Dis. 2001;38:1398-1407.
70. Locatelli F, Marcelli D, Comelli M, et al. Proteinuria and blood pressure as causal components of progression to end-stage renal failure. Nephrol Dial Transplant. 1996;11:461-467.
71. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and non-steroidal anti-inflammatory drugs. N Engl J Med. 1994;331:1675–1679.
72. Yu CC, Lin JL, Lin-Tan DT. Environmental exposure to lead and progression of chronic renal diseases: a four-year prospective longitudinal study. J Am Soc Nephrol. 2004;15:1016–1022.
73. Keane WF, Zhang Z, Lyle PA, et al. Risk scores for predicting outcomes in patients with type 2 diabetes and nephropathy: the RENAAL study. Clin J Am Soc Nephrol. 2006;1:761–767.

74. Gouva C, Nikolopoulos P, Ioannidis JP, et al. Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Kidney Int. 2004;66:753–760.
75. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. Clin J Am Soc Nephrol. 2008;3:844–861.
76. Hsu CY, Ordonez JD, Chertow GM, et al. The risk of acute renal failure in patients with chronic kidney disease. Kidney Int. 2008;74:101–107.
77. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;8:442-448.
78. Lo L, Go A, Chertow G, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int. 2009;76:893–899.
79. Thakar CV, Christianson A, Himmelfarb J, et al. Acute kidney injury episodes and chronic kidney disease in diabetes mellitus. Clin J Am Soc Nephrol. 2011;6:2567-2572.
80. Hallan SI. The possibilities to improve kidney health with proteomics. *C*lin J Am Soc Nephrol. 2017;12:e06200617.
81. Chen L, Su W, Chen H, et al. Proteomics for biomarker identification and clinical application in kidney disease. In: Edelstein C, editor. Biomarkers of Kidney Disease, UK; 2017. P.119-224.
82. Miyamoto M, Yoshida Y,Taguchi I, et al. In-depth proteomic profiling of the normal human kidney glomerulus using two-dimensional protein prefractionation in combination with liquid chromatography-tandem mass spectrometry. J Proteome Res. 2007;6:3680-3690.
83. Human Kidney and Urine Proteome Project. 2007. Available at: http://www.hkupp.org. [Accessed 14 Aug 2018].
84. Pena MJ, Mischak H, Heerspink HJL. Proteomics for prediction of disease progression and response to therapy in diabetic kidney disease. Diabetologia 2016;59:1819-1831.
85. Good DM, Zürbig P, Argilés A, et al. Naturally occurring human urinary peptides for use in diagnosis of chronic kidney disease. Mol Cell Proteomics. 2010;9:2424-2437.
86. Siwy J, Zürbig P, Argilés A, et al. Noninvasive diagnosis of chronic kidney disease using urinary proteome analysis. Nephrol Dial Transplant. 2017;32:2079-2089.

87. Roscioni SS, de Zeeuw D, Hellemons ME, et al. A urinary peptide biomarker set predicts worsening of albuminuria in type 2 diabetes mellitus. Diabetologia. 2013;56:259–267.
88. Zürbig P, Jerums G, Hovind P, et al. Urinary proteomics for early diagnosis in diabetic nephropathy. Diabetes. 2012;61:3304–3313.
89. Siwy J, Schanstra JP, Argilés A, et al. Multicentre prospective validation of a urinary peptidome-based classifier for the diagnosis of type 2 diabetic nephropathy. Nephrol Dial Transplant. 2014;29:1563–1570.
90. Pontillo C, Zhang ZU, Schanstra JP, et al. Prediction of chronic kidney disease stage 3 by CKD273, a urinary proteomic biomarker. Kideny Int Rep. 2017;2:1066-1075.
91. Andersen S, Mischak H, Zürbig P, et al. Urinary proteome analysis enables assessment of renoprotective treatment in type 2 diabetic patients with microalbuminuria. BMC Nephrol. 2010;11:29.
92. Haubitz M, Good DM, Woywodt A, et al. Identification and validation of urinary biomarkers for differential diagnosis and evaluation of therapeutic intervention in ANCA-associated vasculitis. Mol Cell Proteomics. 2009;8:2296–2307.
93. Glassock RJ. Con: Kidney biopsy: an irreplaceable tool for patient management in nephrology. Nephrol Dial Transplant. 2015;30:528-531.
94. Haase M, Bellomo R, Devarajan P, et al. Accuracy of neutrophil gelatinase associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009;54:1012-1024.
95. Liangos O, Tighiouart H, Perianayagam M, et al. Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. Biomarkers. 2009;14:423-431.
96. Bolignano D, Lacquaniti A, Coppolino G, et al. Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clin J Am Soc Nephrol. 2009;4:337–344.
97. Peralta CA, Katz R, Bonventre JV, et al. Associations of urinary levels of kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) with kidney function decline in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis. 2012;60:904–911.

98. Alderson HV, Ritchie JP, Pagano S, et al. The associations of blood kidney injury molecule-1 and neutrophil gelatinase–associated lipocalin with progression from CKD to ESRF. Clin J Am Soc Nephrol. 2016;11:2141–2149.
99. Isakova T, Xie H, Yang W, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. JAMA. 2011;305:2432–3439.
100. Alderson HV, Ritchie JP, Middleton R, et al. FGF-23 and osteoprotegerin but not Fetuin-A are associated with death and enhance risk prediction in non-dialysis chronic kidney disease stages 3-5. Nephrology. 2016;21:566-573.
101. Roos JF, Doust J, Tett SE, et al. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children – a meta-analysis. Clin Biochem. 2007;40:383-391.
102. Taglieri N, Koenig W, Kaski JC. Cystatin C and Cardiovascular Risk. Clin. Chem. 2009;55:1932–1943.
103. Shlipak MG, Katz R, Sarnak MJ, et al. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. Ann Intern Med. 2006;145:237-246.
104. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367:20-29.
105. Peters KE, Davis WA, Ito J, et al. Identification of novel circulating biomarkers predicting rapid decline in renal function in type 2 diabetes: the Fremantle Diabetes Study Phase II. Diabetes Care. 2017;40:1548-1555.
106. Agarwal R, Duffin KL, Laska DA, et al. A prospective study of multiple protein biomarkers to predict progression in diabetic chronic kidney disease. Nephrol Dial Transplant. 2014;29:2293-2302.
107. Beck LH, Bonegio RGB, Lambeau G, et al. M-type phospholipase $A_2$ receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med. 2009;36:11-21.
108. Taal MW, Brenner BM. Predicting initiation and progression of chronic kidney disease: developing renal risk scores. Kidney Int. 2006;70:1694-1705.
109. Stevens LA, Coresh J, Greene T, et al. Assessing kidney function – measured and estimated glomerular filtration rate. N Engl J Med. 2006;354:2473–2483.
110. Li L, Astor BC, Lewis J, et al. Longitudinal progression trajectory of GFR among patients with CKD. Am J Kidney Dis. 2012;59:504-512.

111. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organisation. Arch Intern Med. 2004;164:659-663.
112. Kshirsagar AV, Bang H, Bomback AS, et al. A simple algorithm to predict incident kidney disease. Arch Intern Med. 2008;168:2466-2473.
113. Bang H, Vupputuri S, Shoham DA, et al. Screening for Occult Renal Disease (SCORED): a simple prediction model for chronic kidney disease. Arch Intern Med. 2007;167:374–381.
114. Bang H, Mazumdar M, Newman G, et al. Screening for kidney disease in vascular patients: Screening for Occult Renal Disease (SCORED) experience. Nephrol Dial Transplant. 2009;24:2452–2457.
115. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305:1553-1559.
116. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: a meta-analysis. JAMA. 2016;315:164-174.
117. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008;336:1475-1482.
118. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax. 2003;58:377-382.
119. Botta F, Giannini E, Romagnoli P, et al. MELD scoring system is useful for predicting prognosis in patients with liver cirrhosis and is correlated with residual liver function: a European study. Gut. 2003;52:134-139.
120. van dem Ham HA, Klungel OH, Singer DE, et al. Comparative performance of ATRIA, $CHADS_2$ and $CHA_2DS_2$-VASc risk scores predicting stroke in patients with atrial fibrillation. JACC. 2015;66:1851-1859.
121. ISN Global Kidney Health Atlas. 2019. Available at: https://www2.theisn.org/GKHA. [Accessed 1 June 2019].
122. Evans M, Grams ME, Sang Y, et al. Risk Factors for Prognosis in Patients with Severely Decreased GFR. Kidney Int Rep. 2018;3:625–637.
123. Staplin N, Haynes R, Herrington WG, et al. Smoking and adverse outcomes in patients with CKD: The Study of Heart and Renal Protection (SHARP). Am J Kidney Dis. 2016;68:371–380.

124. Voskamp PWM, Diepen MV, Dekker FW, et al. Dyslipidemia and risk of renal replacement therapy or death in incident pre-dialysis patients. Scientific Reports. 2018;8:3130.
125. Oh TR, Choi HS, Kim CS, et al. Hyperuricemia has increased the risk of progression of chronic kidney disease: propensity score matching analysis from the KNOW-CKD study. Scientific Reports. 2019;9:6681.
126. Lang J, Katz R, Ix JH, et al. Association of serum albumin levels with kidney function decline and incident chronic kidney disease in elders. Nephrol Dial Transplant. 2017;33:986-992.
127. McGovern AP, Lusignan SD, Vlymen JV, et al. Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study. PLoS ONE. 2013;8:e74996.
128. Nielsen SH, Rasmussen DGK, Brix S, et al. A novel biomarker of laminin turnover is associated with disease progression and mortality in chronic kidney disease. PLoS ONE. 2018;13:e0204239.
129. Anderson CE, Hamm LL, Batuman G, et al. The association of angiogenic factors and chronic kidney disease. BMC Nephrol. 2018;19:117.
130. Tanabe K, Sato Y, Wada J. Endogenous antiangiogenic factors in chronic kidney disease: potential biomarkers of progression. Int. J. Mol. Sci. 2018;19:1859.
131. Rabbani N, Thornalley PJ. Advanced glycation end products in the pathogenesis of chronic kidney disease. Kidney Int 2018;93:803–813.
132. Wang C-C, Shen M-Y, Chang K-C, et al. Skin autofluorescence is associated with rapid renal function decline in subjects at increased risk of coronary artery disease. PLoS ONE 2019;14:e0217203.
133. Pruijm M, Milani B, Pivin E, et al. Reduced cortical oxygenation predicts a progressive decline of renal function in patients with chronic kidney disease. Kidney Int. 2018;93:932–940.
134. Kuo C, Chang C, Liu K, et al. Automation of the kidney function prediction and classification through ultrasound-based kidney imaging using deep learning. npj Digital Medicine. 2019;2:29.
135. Waikar SS, Srivastata A, Palsson R, et al. Association of urinary oxalate excretion with the risk of chronic kidney disease progression. JAMA Intern Med. 2019; 179:542-551.

136. DeBoer MD, Filipp SL, Musani SK, et al. Metabolic syndrome severity and risk of CKD and worsened GFR: The Jackson Heart Study. Kidney Blood Press Res. 2018;43:555-567.
137. Zacharias HU, Altenbuchinger M, Schultheiss UT, et al. A novel metabolic signature to predict the requirement of dialysis or renal transplantation in patients with chronic kidney disease. J. Proteome Res. 2019;18:1796−1805.
138. Valls J, Cambray S, Pérez-Guallar C, et al. Association of candidate gene polymorphisms with chronic kidney disease: results of a case-control analysis in the Nefrona Cohort. Front. GeneT. 2019;10:118.
139. Lin BM, Nadkarni GN, Tao R, et al. Genetics of chronic kidney disease stages across ancestries: The PAGE Study. Front. Genet. 2019;10:494.
140. Xu X, Eales JM, Akbarov A, et al. Molecular insights into genome-wide association studies of chronic kidney disease-defining traits. Nat Commun. 2018;4800.
141. Schulz C, Engström G, Christensson A, et al. Genetic Predisposition for Renal Dysfunction and Incidence of CKD in the Malmö Diet and Cancer Study. Kidney Int Rep. 2019;4:1143-1151.
142. Stanzick KJ, Li Y, Schlosser P, et al. Discovery and prioritization of variants and genes for kidney function in >1.2 million individuals. Nat Commun. 2021;12**:** 4350.
143. Prins BP, Kuchenbaecker KB, Bao Y, et al. Genome-wide analysis of health-related biomarkers in the UK Household Longitudinal Study reveals novel associations. Nature Scientific Reports. 2017;7:11008.
144. Hemmelgarn BR, Smekal MD, Weaver RG, et al. Implementation and evaluation of a risk-based approach to guide chronic kidney disease care: protocol for a multiphase mixed-methods study. Can. J. Kidney Health Dis. 2018;5:1-10.
145. Harasemiw O, Drummond N, Singer A, et al. Integrating risk-based care for patients with chronic kidney disease in the community: study protocol for a cluster randomized trial. Can J Kidney Health Dis. 2019;6:12054358119841611.
146. Ravizza S, Huschto T, Adamov A, et al. Predicting the early risk of chronic kidney disease in patients with diabetes using real-world data. Nat Med. 2019;25:57-59.

147. Yamanouchi M, Hoshino J, Ubara Y, et al. Value of adding the renal pathological score to the kidney failure risk equation in advanced diabetic nephropathy. PLoS ONE. 2018;13:e0190930.
148. Grams ME, Sang Y, Ballew SH, et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int. 2018;93:1442–1451.
149. Chronic Kidney Disease Prognosis Consortium. Timing of clinical outcomes in CKD with severely decreased GFR. Available at: http://ckdpcrisk.org/lowgfrevents/. [Accessed 18 June 2019].
150. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease. A meta-analysis of patient-level data. Ann Intern Med. 2001;17:73-87.
151. Balamuthusamy S, Srinivasan L, Verma M, et al. Renin angiotensin system blockade and cardiovascular outcomes in patients with chronic kidney disease and proteinuria: a meta-analysis. Am Heart J. 2008;155:791-805.
152. Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. EMBO Mol Med. 2010;2:247-257.
153. Crowley SD, Rudemiller NP. Immunologic effects of the renin-angiotensin system. J Am Soc Nephrol. 2017;28:1350-1361.
154. Hughes-Austin JM, Rifkin DE, Beben T, et al. The relation of serum potassium concentration with cardiovascular events and mortality in community-living individuals. Clin J Am Soc Nephrol. 2017;12:245–252.
155. Sarafidis PA, Blacklock R, Wood E, et al. Prevalence and factors associated with hyperkalaemia in predialysis patients followed in a low-clearance clinic. Clin J Am Soc Nephrol. 2012;7:1234-1241.
156. Betts KA, Woolley JM, Mu F, et al. The cost of hyperkalaemia in the United States. Kidney Int Rep. 2017;13:385-393.
157. Kovesdy CP, Matsushita K, Sang Y, et al. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. Eur Heart J. 2018;39:1535-1542.
158. Korgaonkar S, Tilea A, Gillespie BW, et al. Serum potassium and outcomes in CKD: insights from the RRI-CKD cohort study. Clin J Am Soc Nephrol. 2010;5:762-769.

159. Yildirim T, Arici M, Piskinpasa S, et al. Major barriers against renin-angiotensin-aldosterone system blocker use in chronic kidney disease stages 3-5 in clinical practice: a safety concern? Ren Fail. 2012;34:1095-1099.
160. Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal antiproteinuric doses (ROAD) study: a randomised controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol. 2007;18:1889-1898.
161. Epstein M, Reaven NL, Funk SE, et al. Evaluation of the treatment gap between clinical guidelines and the utilisation of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care. 2015;21:S212-20.
162. KDIGO. Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98:S1-S115.
163. Georgianos PI, Agarwal R. Revisiting RAAS blockade in CKD with newer potassium-binding drugs. Kidney Int. 2018;93:325-334.
164. Bakris GL, Pitt B, Weir MR, et al. Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. JAMA. 2015;314:151–161.
165. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372:211–221.
166. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. European Heart Journal. 2011;32:820-828.
167. Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2019;394:1540-1550.
168. Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalaemia. A 12-months phase 3 study. Clin J Am Soc Nephrol. 2019;14:798-809.
169. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalaemia. The HARMONIZE randomised clinical trial. JAMA. 2014;312:2223-2233.

170. Zannad F, Hsu BG, Maeda Y, et al. Efficay and safety of sodium zirconium cyclosilicate for hyperkalaemia: the randomised, placebo-controlled HARMONIZE-Global study. ESC Heart Failure. 2020;7:55-65.

# CHAPTER 2

# AIMS AND OBJECTIVES

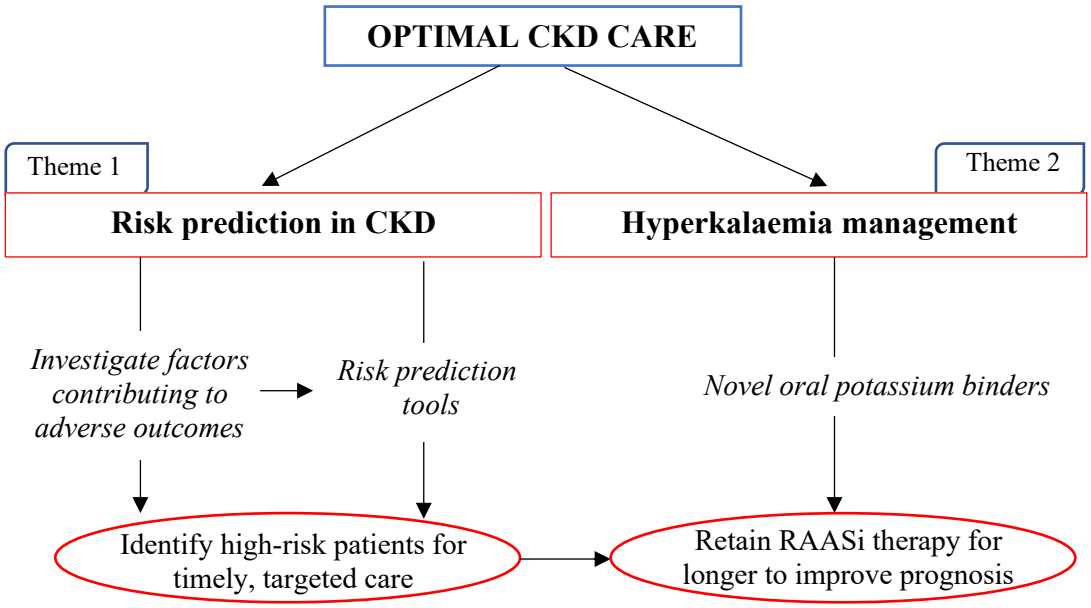
## 2.1 Preface

Based on the literature review of chapter 1, this chapter highlights the two broad research themes of this thesis: risk prediction in CKD and hyperkalaemia management. It also outlines the specific aims of each research study and contextualises them within the framework of the thesis. The specific research questions, aimed to address gaps in the literature, are also specified for each study.

## 2.2 OVERARCHING RESEARCH THEMES

Two interconnected research themes have been identified to be crucial to delivering optimal CKD care (Figure 2.1). The first lies in the domain of CKD risk prediction, specifically with regards to investigating the differential impact of factors responsible for poor CKD outcomes, which can inform the development and refinement of risk prediction calculators in identifying vulnerable patients at threat of adverse outcomes. Through accurate risk stratification tools can targeted treatment be offered, for instance through optimisation of RAASi therapy, which has remained a cornerstone of patient care thanks to its reno- and cardioprotective properties. However, the occurrence of hyperkalaemia undercuts the ability of patients benefiting from long-term RAASi therapy. This is why the second research theme focuses on improving hyperkalaemia care, principally through novel oral potassium binders. As is shown in Figure 2.1, a concerted effort has made to explore both these interconnecting research themes, given their important clinical implications.

**Figure 2.1** Overarching research themes of this thesis



## 2.3 THEME 1: RISK PREDICTION IN CKD

### Chapter 4

*Aim*

To establish the phenotypic risk profile of patients who progress rapidly in a linear manner.

*Context*

There have been relatively few studies in patients progressing linearly, but they arguably represent a prototypic cohort of CKD progression and thus this chapter serves as a gateway into the research theme of risk prediction.

*Research questions*

1. What are the predictive factors of rapid linear CKD progression?
2. Are these factors differentially expressed in different types of renal disease?
3. What are the factors associated with mortality prior to ESRD in rapid linear progressors compared to those with stable CKD?
4. What is the survival probability of rapid linear progressors compared with stable patients with respect to a combined endpoint of ESRD or mortality prior to ESRD?

### Chapter 5

*Aim*

To determine whether the pattern of rapid progression influences adverse patient outcomes.

*Context*

This work further develops the analyses of chapter 4 by exploring two patterns of progression, linear and non-linear, in patients with rapid progression to further delineate patients' risk of adverse outcomes.

*Research questions*

1. What are the factors responsible for patients progressing rapidly in a linear and non-linear fashion?

2. Does the pattern of rapid progression differentially affect outcomes of ESRD and mortality prior to ESRD?

**Chapter 6**

*Aim*

To develop a methodological paradigm for biomarker discovery in the field of CKD progression by focusing on accurately characterising the rate and pattern of patients' eGFR trajectory.

*Context*

This work was borne out of the methodological groundwork made in the preceding chapters to categorise and define the nature of CKD progression in individual patients. The importance of this methodology was clearly apparent when the literature reporting biomarkers associated with CKD progression was scrutinised. Defining CKD progression was an often overlooked and limiting issue in biomarker research and this provided the stimulus for formulating this chapter.

*Research questions*

1. What are the limiting factors in biomarker research interested in CKD progression?
2. How can these factors be overcome to establish a new paradigm to drive accurate biomarker discovery?

**Chapter 7**

*Aim*

To determine the predictive accuracy of the Kidney Failure Risk Equation (KFRE) in predicting graft failure in transplant recipients.

*Context*

This chapter marks a shift in direction in the research theme towards assessing the KFRE as a risk prediction tool in clinical practice. Transplant recipients were chosen as there was emerging evidence from a few studies that the KFRE had potential in accurately predicting graft failure but whether this was replicable for a UK-based patient cohort required investigating.

*Research question*

Can the 4- and 8-variable KFRE provide accurate risk prediction of graft failure in transplant recipients in the UK?

**Chapter 8**

*Aim*

To evaluate the predictive performance of the KFRE in a cohort of patients with advanced CKD and according to disease aetiology.

*Context*

Upon completion of chapter 7, the research spotlight of the KFRE was placed on those with advanced CKD. Decision-making in these patients is typically dependent on eGFR thresholds and the notion that the KFRE could be more informative to patient care than an eGFR-based strategy was explored.

*Research questions*

1. What is the discrimination and calibration performance of the 4- and 8-variable KFRE in predicting ESRD in an advanced CKD cohort?
2. In evaluating clinical utility, can a risk-based strategy to patient care provide advantages over an eGFR-based strategy?

## 2.4 THEME 2: HYPERKALAEMIA MANAGEMENT

### Chapter 9

*Aim*

To provide further evidence of the efficacy of the novel potassium binder, patiromer, at achieving normokalaemia by using a real-world patient cohort as a control arm to the first phase of the OPAL-HK study.

*Context*

This study is the first of two chapters within the theme of managing hyperkalaemia by way of oral potassium binders and looks at reinforcing the trial data of the OPAL-HK study with a real-world patient analysis.

*Research question*

What is the efficacy of patiromer when the uncontrolled first phase of the OPAL-HK study is matched with a real-world patient cohort?

### Chapter 10

*Aim*

To prospectively evaluate the ability of potassium binders to enable RAASi prescribing in patients with heart failure reviewed in a bespoke hyperkalaemia clinic.

*Context*

The knowledge from trial data that potassium binders can achieve normokalaemia provided the genesis for this study to assess the clinical experience of using these medications in patients most likely to benefit from RAASi optimisation. Whilst not exclusively dedicated to patients with CKD, the vast majority of the patient cohort in this study had CKD stages 3a-5.

*Research question*

Can potassium binders enable RAASi initiation or up-titration in patients with heart failure?

# CHAPTER 3

# METHODS

## 3.1 Preface

This chapter provides an overview of the methodology used to conduct the research in this thesis. As this thesis is presented in the alternative format, there will be overlap of text between this chapter and the methods section of individual results chapters.

Herein, specific attention is given to describing the study design, data collection, clinical endpoints and ethical approval for the Salford Kidney Study (SKS), which provided the patient population for all but one of the analyses in the results chapters. Given the wide scope of the SKS protocol, only aspects that are pertinent to the thesis methodology are described.

Furthermore, an overview of the statistical techniques used in this thesis is provided and the rationale for specific approaches in different studies is also explained. Details of the specific analyses relevant to each results chapter are provided within the methods section of that study.

## 3.2 THE SALFORD KIDNEY STUDY (SKS)

### 3.2.1 Study design and setting

The SKS is a single-centre, ongoing, prospective, observational cohort study of adult patients referred to the renal services at Salford Royal NHS Foundation Trust [1]. Patient recruitment has been ongoing since 2002 and the current SKS database has approximately 3500 patients, making it one of the largest international epidemiological studies involved in all aspects of CKD care and research.

The renal service at Salford Royal NHS Foundation Trust serves a direct population of approximately 240,000 people in the City of Salford and this is included in the overall 1.55 million catchment in the surrounding North West region of the UK, which also includes the local authorities of Bolton, Bury, Oldham, Rochdale and Wigan.

Based on the 2011 census [2], Salford, Wigan and Bury have a predominantly white population (≥90%). In comparison, white British residents account for just under 80% of the population in Oldham, Bolton and Rochdale, which are areas that serve a more ethnically diverse population, especially those of Indian, Pakistani and Bangladeshi heritage.

Importantly, Public Health England data from 2019 reveal that all six local authorities have higher rates of obesity, smoking, cardiovascular mortality and all-cause mortality in those under 75 years of age and lower life expectancies compared with the national average in England [3-8]. In particular, Salford fares the worst within the region in terms of life expectancy, which is lower by 2.4 years and 2.3 years in male and female residents respectively. Set within this population of poor health outcomes, participants within the SKS represent a high-risk cohort in which the determinants of adverse CKD outcomes can be ideally analysed.

### 3.2.2 Inclusion and exclusion criteria

The inclusion criteria into SKS for non-dialysis CKD patients include:

- Age ≥ 18 years at the time of consent
- Referred to or under the care of renal services at Salford Royal Hospital
- eGFR <60ml/min/1.73m$^2$ recorded in the preceding 12 months
- Able to give written informed consent for participation

Exclusion criteria include:

- Age ≤18 years at the time of consent
- Not known to have CKD nor to have had an episode of AKI with eGFR <60ml/min/1.73m$^2$
- Unable to give written informed consent for participation

Patients deemed suitable for enrolment are provided with a patient information sheet and if they are willing to participate, written informed consent is obtained at the next clinic visit by a trained research nurse.

### 3.2.3 Data collection

A wide variety of clinical data is obtained at recruitment and updated on an annual basis by dedicated research nurses and trained clinical research fellows using detailed questionnaires and reference to clinical care records where needed. All aspects of data collection are performed at patients' routine clinic visits to avoid the need for repeated attendances.

#### *3.2.3.1 Demographics*

Demographic data include age, sex, ethnicity, height, weight and smoking history.

#### *3.2.3.2 Primary renal disease*

The primary renal disease was coded based on the 1995 European Renal Association – European Dialysis and Transplant Association disease codes [9].

#### *3.2.3.3 Comorbidities*

Baseline co-morbid data include a history of type 1 or 2 diabetes mellitus, hypertension (>140/90mmHg or taking anti-hypertensive therapy at recruitment), heart failure (diagnosed clinically or if the left ventricular ejection fraction is <50% or there is presence of diastolic dysfunction on echocardiogram), myocardial infarction (treated by coronary revascularisation or managed medically), stroke (diagnosed clinically and/or radiologically) and peripheral vascular disease (defined as symptoms of claudication, presence of distal ischaemic ulcers or previous revascularisation treatment).

#### *3.2.3.4 Medications*

Medication history is coded for anti-platelet and statin therapy as well as the number and type of anti-hypertensive agent, including ACEi, ARB, mineralocorticoid antagonist (MRA), renin inhibitors, alpha-blockers, beta-blockers, dihydro- and non-dihydropyridine calcium channel antagonists, loop or thiazide diuretics and centrally-acting agents. All other prescribed medications are documented as free text.

#### *3.2.3.5 Blood pressure*

Blood pressure is measured at routine clinic visits using a validated, automated sphygmomanometer and an appropriately sized inflation cuff. The average of two readings taken after five minutes of rest is recorded.

#### *3.2.3.6 Laboratory data*

Blood and urine samples are taken at recruitment and on an annual basis when patients attend for a routine renal clinic visit. All samples are analysed in the laboratories of Salford Royal NHS Foundation Trust. Blood measurements utilised in this thesis include potassium (mmol/L), bicarbonate (mmol/L), urea (mmol/L), creatinine (umol/L), calcium (mmol/L), phosphate (mmol/L), alkaline phosphatase (U/L), albumin (g/L), C-reactive protein (mg/L), total cholesterol (mmol/L), high-density lipoprotein (mmol/L) and haemoglobin (g/L).

With respect to determining renal function, serum creatinine is measured using a calibrated Jaffe method traceable to an isotope dilution mass spectrometry reference measurement procedure. This permitted the GFR to be estimated using the CKD-EPI equation [10], given as:

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

where:

$S_{cr}$ is serum creatinine in μmol/L, κ is 61.9 for females and 79.6 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of $S_{cr}/\kappa$ or 1, and max indicates the maximum of $S_{cr}/\kappa$ or 1.

The CKD-EPI equation was favoured in this thesis as per recommendations from international guidelines that recognise it is more precise than the MDRD equation at higher eGFRs [4].

Along with blood measurements, a spot urine sample is also processed to determine the uPCR (mg/mmol). Prior to 2007, 24-hour urinary collections were routinely performed, and in these instances, the urine protein (g/L) was divided by the urine creatinine (mmol/L) and multiplied by 1000 to obtain an accompanying uPCR.

Further samples including EDTA whole blood, serum and citrate plasma are collected, centrifuged and bio-banked at -80$^{o}$C in the Salford Biological Repository for future biomarker and genomic research.

### 3.2.4 Study endpoints

Patients continue to participate in the SKS until death, withdrawal of consent or loss to follow-up. Clinical endpoints include all-cause mortality and ESRD, defined as either initiation of chronic haemodialysis, peritoneal dialysis, receiving a pre-emptive renal transplant or attendance in the conservative care clinic. The date of death was available from the hospital's electronic patient record.

### 3.2.5 Data storage

Each patient in the SKS is assigned a unique patient identification number and all data are stored in a password-protected Microsoft Access database within the Trust's computer server. Handling and extracting data are undertaken as per the Trust's policy on data protection and information governance.

### 3.2.6 Ethical approval

The SKS received ethical approval from the North West Greater Manchester South Research Ethics Committee (REC15/NW/0818).

### 3.2.7 Rationale for using the SKS

The large cohort size, detailed phenotypic data, the volume of longitudinal laboratory measurements and prevalence of major endpoints, including all-cause mortality and ESRD, means the SKS database is perfectly suited to address the research aims and objectives of this thesis. A key advantage is the ability to utilise all laboratory results taken during patients' outpatient clinic visits in addition to their annual SKS review. This was particularly important to help characterise eGFR trajectories over time, which was essential to results chapters 4, 5 and 6, which focus on specific patterns of CKD progression and their impact on long-term outcomes.

Results chapter 8 relies on routinely collected data necessary to validate the KFRE in an advanced CKD population and the SKS provided a sizeable patient cohort for this analysis.

Whilst there is no specific alteration to management for patients enrolled in the SKS, care for all patients align with existing national and international guidelines [11,12]. Hence, analyses of real-world practices with respect to management of ambulatory hyperkalaemia, as performed in chapters 9 and 10, are adequately supported by the SKS cohort. Of note, patients with an eGFR >60ml/min/1.73m$^2$ were included for the analysis in chapter 10 as the SKS protocol had been updated with ethical approval at the time to permit enrolment of patients with CKD stages 1 and 2.

The analysis in chapter 7 exploring the accuracy of the KFRE in transplant recipients is the only one not to draw exclusively upon the SKS because the subgroup cohort of transplant recipients was not large enough at the time of the study. The study presented in this chapter included patients who were nonetheless under renal care at Salford Royal NHS Foundation Trust and was therefore registered with the Research and Innovation department of the Northern Care Alliance NHS Group (Ref: S20HIP57). As it was a retrospective study using routinely collected laboratory tests and used fully anonymised

data, the need for individual patient consent was waived by the Research and Innovation review committee.

## 3.3 AN OVERVIEW OF STATISTICAL ANALYSES

Statistical analyses were performed using SPSS (Version 25.0) (IBM SPSS, Chicago, IL) licensed to the University of Manchester, or R version 4.0.2 (The R Foundation for Statistical Computing Platform).

### 3.3.1 Descriptive statistics

As is standard with statistical methods, all analyses in this thesis present continuous data as mean (± standard deviation) or median (± interquartile range) values for parametric and non-parametric data respectively. Categorical data are presented as absolute numbers (percentage). To compare the mean values between two groups, independent Student's t-test was used, whereas a paired t-test was used for non-independent, matched data. To compare the median values between two groups, the Mann-Whitney U test was calculated. Chi-squared testing was utilised for comparisons between categorical data. Statistical significance was defined as a p-value of $<0.05$ in all analyses.

### 3.3.2 Characterising CKD progression

Results chapters 4 and 5 explore how different trajectories of eGFR impact on future outcomes. This required a systematic two-step process: firstly, calculation of the change in eGFR over time (ΔeGFR) and, secondly, a mechanism to characterise the nature of that change as either linear or non-linear.

#### *3.3.2.1 The ΔeGFR*

Calculation of the ΔeGFR for each patient in the SKS was achieved by applying ordinary least-squares linear regression to all their outpatient eGFR values during their study follow-up and provided an annual change in eGFR (±ml/min/1.73m$^2$/yr). This is a validated approach as long as patients have at least 4 eGFR values over 2 years [13,14].

In chapter 4, rapid progression was defined as a ΔeGFR of <-4ml/min/1.73m$^2$/yr (in other words, losing more than 4ml/min/1.73m$^2$/yr), a cut-off that had been used in previous studies. However, patient selection was expanded for the subsequent analysis in chapter 5, in which rapid progressors were defined by a ΔeGFR of <-3ml/min/1.73m$^2$/yr. This latter threshold has been shown to be associated with worse outcomes compared to stable disease [15,16] and widened our selection of high-risk patients.

#### *3.3.2.2 Verifying linear or non-linear trajectory*

Once the ΔeGFR had been calculated for all patients, determining whether patients progress in a linear or non-linear manner was performed by visual inspection of eGFR-time graphs (essentially a scatterplot of eGFR values on the y-axis and time on the x-axis), which is a strategy that has been used elsewhere [17]. Two clinicians undertook this task independently in order to reduce bias. This systematic approach enabled the linear ΔeGFR slope to be corroborated and facilitated patient selection with either linear or non-linear patterns of progression.

In chapter 4, the visual verification of linearity was also quantified with the 95% CIs of the ΔeGFR values. With this calculation, the lower the 95% CI, the greater the degree of linearity of the eGFR trajectory. This methodological approach was strengthened in the analysis in chapter 5 in which the $R^2$ coefficient of determination was preferentially calculated. This is an accessible measure of linearity specific to linear regression and helped demonstrate how close the eGFR values fit the linear regression slope; an $R^2$ value of 1 demonstrates a perfect fit of the linear regression line to the data. This objective measure provided a further safeguard for the robust classification of patients with linear or non-linear CKD progression in this specific study.

### 3.3.3 Survival analysis

In chapter 4, univariate and multivariate Cox proportional hazards regression were used to determine the hazard ratios with 95% CIs of the factors associated with mortality prior to ESRD in rapid progressors and stable patients. Kaplan-Meier curves graphically visualised survival probability at a given timepoint and used log-rank testing to compare survival between patient groups.

In the subsequent study in chapter 5, the survival analysis was modified in recognition of the results in chapter 4 in that rapid progressors faced high rates of both ESRD and all-cause mortality. As such, these clinical endpoints were therefore treated as competing events. To ensure accurate analyses when accounting for competing risks, construction of cumulative incidence function curves was undertaken and a Fine-Gray competing risk hazard model was performed. The latter is analogous to the Cox proportional hazards model and provides the subdistribution hazard ratio for each covariate within a competing risk model.

### 3.3.4 Validation of the KFRE performance

felt

Analyses evaluating the performance of the KFRE to predict ESRD relied upon two key statistical elements: discrimination and calibration. In both chapters 7 and 8, discrimination was assessed by the area under the receiver operator characteristic curve. Calibration is typically presented as calibration plots and can be created in a variety of ways. In chapter 7, it was done by splitting the predicted risk scores into decile risk groups on the x-axis with the observed frequency of actual events in each decile group plotted on the y-axis. This approach was chosen to align with a previous study in a similar patient cohort [18], which was necessary to allow a more direct comparison of the study findings.

In the subsequent analysis performed in chapter 8, the calibration plot was based on a published review of prediction modelling [19], in which the predicted risk scores were plotted on the x-axis, the binary outcome of ESRD (1=yes, 0=no) plotted on the y-axis, and a smoothing function then applied to visualise the estimated observed probability. This method provided a clearer and more accurate depiction of calibration than utilising decile risk groups, which has been criticised for being arbitrary and less precise [20].

The statistical entities of discrimination and calibration are however unable to offer insight into the clinical utility of a prediction tool or the clinical consequences of its use. This is why decision curve analyses were specifically performed in chapter 8 to add an important layer of understanding on the role of the KFRE in clinical practice. All aspects of the statistical analyses to assess the KFRE, including decision curve analyses, are discussed in further detail in the relevant results chapters.

## 3.4 REFERENCES


1. NHS Health Research Authority. Salford Kidney Study. Available at: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/salford-kidney-study/. [Accessed 6 June 2021].
2. Office for National Statistics. 2011 Census data catalogue. Available at: https://www.ons.gov.uk/census/2011census/2011censusdata/2011censusdatacatalogue. [Accessed 6 June 2021].
3. Public Health England. Salford: local authority health profile 2019. Available at: https://fingertips.phe.org.uk/static-reports/health-profiles/2019/E08000006.html?area-name=Salford. [Accessed 6 June 2021].
4. Public Health England. Bolton: local authority health profile 2019. Available at: https://fingertips.phe.org.uk/static-reports/health-profiles/2019/E08000001.html?area-name=Bolton. [Accessed 6 June 2021].
5. Public Health England. Wigan: local authority health profile 2019. Available at: https://fingertips.phe.org.uk/static-reports/health-profiles/2019/E08000010.html?area-name=Wigan. [Accessed 6 June 2021].
6. Public Health England. Rochdale: local authority health profile 2019. Available at: https://fingertips.phe.org.uk/static-reports/health-profiles/2019/E08000005.html?area-name=Rochdale. [Accessed 6 June 2021].
7. Public Health England. Oldham: local authority health profile 2019. Available at: https://fingertips.phe.org.uk/static-reports/health-profiles/2019/E08000004.html?area-name=Oldham. [Accessed 6 June 2021].
8. Public Health England. Bury: local authority health profile 2019. Available at: https://fingertips.phe.org.uk/static-reports/health-profiles/2019/E08000002.html?area-name=Bury. [Accessed 6 June 2021].
9. ERA-EDTA registry. ERA-EDTA PRD coding system. Available at: https://era-edta-reg.org/prd.jsp. [Accessed 6th June 2021].
10. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612.
11. The Renal Association. Guidelines and commentaries. Available at: https://renal.org/health-professionals/guidelines/guidelines-commentaries. [Accessed 6 June 2021].

12. KDIGO. Guidelines. Available at: https://kdigo.org/guidelines/. [Accessed 6 June 2021].
13. Levey AS, Greene T, Schluchter MD, et al. Glomerular filtration rate measurements in clinical trials. Modification of Diet in Renal Disease Study Group and the Diabetes Control and Complications Trial Research Group. J Am Soc Nephrol. 1993;4:1159–1171.
14. Stringer S, Sharma P, Dutton M, et al. The natural history of, and risk factors for progressive Chronic Kidney Disease (CKD): the Renal Impairment in Secondary care (RIISC) study; rationale and protocol. BMC Nephrol. 2013;14:95.
15. Shlipak MG, Katz R, Kestenbaum B, et al. Rapid decline of kidney function increases cardiovascular risk in the elderly. J Am Soc Nephrol. 2009;20:2625-2630.
16. Matsushita K, Selvin E, Bash LD, et al. Change in estimated GFR associates with coronary heart disease and mortality. Clin J Am Soc Nephrol. 2009;20:2617-2624.
17. Agarwal R, Duffin K, Laska DA, et al. A prospective study of multiple protein biomarkers to predict progression in diabetic chronic kidney disease. Nephrol Dial Transplant. 2014;29:2293-2302.
18. Tangri N, Ferguson TW, Wiebe C, et al. Validation of the Kidney Failure Risk Equation in kidney transplant recipients. Can J Kidney Health Dis. 2020;7:1-9.
19. Au EH, Francis A, Bernier-Jean A, et al. Prediction modelling – part 1: regression modelling. Kidney Int. 2020;97:877-884.
20. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. Epidemiology. 2010;21:128-138.

# CHAPTER 4

## PREDICTIVE FACTORS OF RAPID LINEAR RENAL PROGRESSION AND MORTALITY IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Ibrahim Ali, Rajkumar Chinnadurai, Sara T. Ibrahim, Darren Green, Philip A. Kalra
BMC Nephrol. 2020;21:345.
DOI: https://doi.org/10.1186/s12882-020-01982-8

## 4.1 ABSTRACT


**Background**

Risk factors predictive of rapid linear chronic kidney disease (CKD) progression and its associations with end-stage renal disease (ESRD) and mortality requires further exploration, particularly as patients with linear eGFR trajectory represent a clear paradigm for understanding true CKD progression.

**Methods**

A linear regression slope was applied to all outpatient estimated glomerular filtration rate (eGFR) values for patients in the Salford Kidney Study who had ≥2 years follow-up, ≥4 eGFR values and baseline CKD stages 3a-4. An eGFR slope (ΔeGFR) of ≤-4ml/min/1.73m$^2$/yr defined rapid progressors, whereas -0.5 to +0.5ml/min/1.73m$^2$/yr defined stable patients. Binary logistic regression was utilised to explore variables associated with rapid progression and Cox proportional hazards model to determine predictors for mortality prior to ESRD.

**Results**

There were 157 rapid progressors (median ΔeGFR -5.93ml/min/1.73m$^2$/yr) and 179 stable patients (median ΔeGFR -0.03ml/min/1.73m$^2$/yr). Over 5 years, rapid progressors had an annual rate of mortality or ESRD of 47 per 100 patients compared with 6 per 100 stable patients. Factors associated with rapid progression included younger age, female gender, higher diastolic pressure, higher total cholesterol:high density lipoprotein ratio, lower albumin, lower haemoglobin and a urine protein:creatinine ratio of >50g/mol. The latter three factors were also predictive of mortality prior to ESRD, along with older age, smoking, peripheral vascular disease and heart failure.

**Conclusions**

There is a heterogenous interplay of risk factors associated with rapid linear CKD progression and mortality in patients with CKD. Furthermore, rapid progressors have high rates of adverse outcomes and require close specialist monitoring.

## 4.2 BACKGROUND

Chronic kidney disease (CKD) is an important public health concern given that lower estimated glomerular filtration rate (eGFR) and increasing albuminuria are common and are independent risk factors associated with progression to end-stage renal disease (ESRD), cardiovascular events and all-cause mortality [1].

Accurately stratifying patients with CKD who are at risk of progression could enable earlier, targeted treatment in an effort to stabilise renal decline and reduce future adverse outcomes [2]. Data from epidemiological studies have been used to create risk calculators for the prediction of outcomes such as ESRD and mortality in patients with CKD [3,4]. However, they have yet to be implemented in routine clinical practice and require further refinement [5]. One particular omission from current prediction tools involves quantifying the rate of change in renal function in patients over time, which can help conceptualise an individual's risk profile more meaningfully [6,7]. Although a number of studies have explored the association of various risk factors on different rates of progression [8-10], there is a lack of data focusing exclusively on patients with a consistent linear rate of progression and the associations with adverse outcomes such as ESRD and mortality. These patients warrant attention as their linear eGFR trajectory represents a clear paradigm for understanding true CKD progression.

In this study we focus on patients with a linear pattern of progression stratified into two groups – rapid progressors or stable patients – defined by their rate of eGFR change. We aimed to (1) determine factors predictive of rapid linear CKD progression; (2) evaluate whether these factors are different depending upon the underlying disease aetiology; (3) determine the variables associated with mortality prior to ESRD in rapid progressors and stable patients and (4) explore how the rate of the eGFR trajectory impacts on outcomes of ESRD and mortality.

## 4.3 METHODS

### 4.3.1 Patient population

The Salford Kidney Study (SKS) is a prospective observational cohort study based in the United Kingdom that has been recruiting patients with non-dialysis dependent CKD since 2002. Any patient referred to the renal services at Salford Royal NHS Foundation Trust who is ≥18 years old with an eGFR of <60ml/min/1.73m$^2$ is eligible for recruitment.

### 4.3.2 Baseline covariates

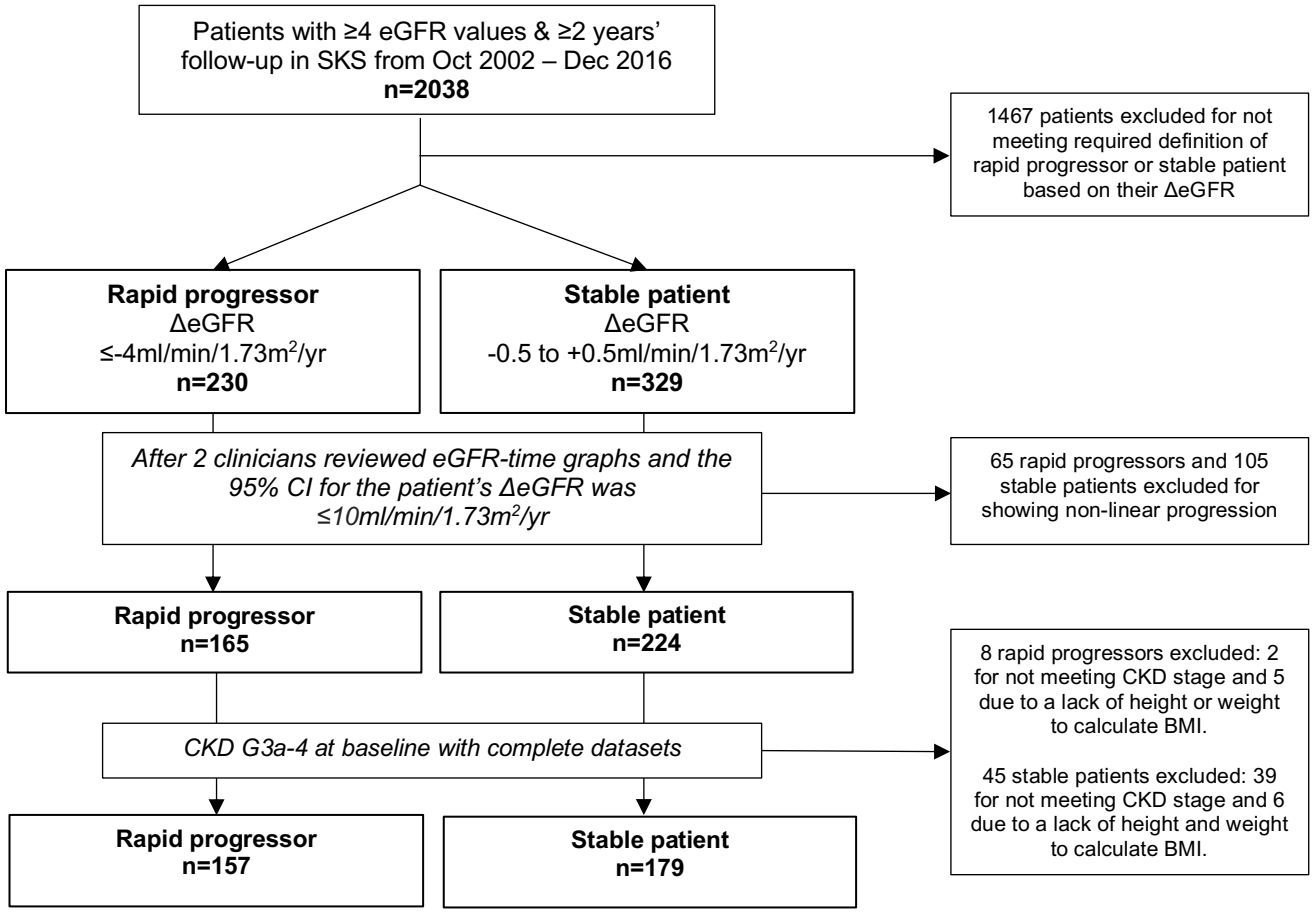
All covariates were measured at the point of recruitment into SKS. Demographic data in this analysis included age, gender, ethnicity, history of current or past smoking, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP). Co-morbidities included hypertension, diabetes mellitus (DM), myocardial infarction (MI), peripheral vascular disease (PVD), stroke and heart failure (HF). Medications of interest included use of angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blockers (ARB) and statins. Laboratory values included serum creatinine, eGFR calculated using the CKD-EPI equation, bicarbonate, urea, calcium, phosphate, alkaline phosphatase, albumin, total cholesterol:high density lipoprotein (HDL) ratio, C-reactive protein, haemoglobin (Hb) and urine protein:creatinine ratio (uPCR), where uPCR values of <15g/mol, 15-50g/mol and >50g/mol categorised patients into albuminuria grades of A1, A2 and A3 respectively, based on international guidelines [11]. Subsequent blood tests performed at routine clinic visits were accessible via the hospital's electronic patient record and were used to define a patient's rate of progression.

### 4.3.3 Inclusion criteria and study outcomes

Patient selection into this study was performed retrospectively and involved 2 stages (Figure 4.1). First, linear regression was applied to all outpatient eGFR values for patients with at least 4 eGFR measurements and 2 years follow-up [12,13] in order to obtain a delta (Δ) eGFR slope (ml/min/1.73m$^2$/yr). The outpatient eGFR values used to calculate the ΔeGFR for each patient represent all the tests performed in clinic as part of a patient's renal follow-up. Rapid progression was defined as a ΔeGFR of ≤-4ml/min/1.73m$^2$/yr (i.e., losing more than 4ml/min/1.73m$^2$/yr) [10,14]. Stable patients

were defined as a ΔeGFR of -0.5 to +0.5ml/min/1.73m$^2$/yr as this small range centred on a zero rate of change. Second, visual inspection of the eGFR-time graphs, a methodology that has been used previously [15], helped to corroborate the linear pattern of progression, and patients with non-linear progression were excluded. This phase was performed by two clinicians independently as a means to ensure reproducibility. We also calculated the 95% confidence intervals (CI) for the ΔeGFR of each patient. Those with a smaller size interval are by definition expected to have a more consistent linear pattern than those with larger intervals. We therefore set a cut-off 95% CI of ≤10ml/min/1.73m$^2$/yr for each patient as a quantitative marker of eGFR linearity. Finally, only patients with baseline CKD G3a-4 (eGFR 15 to <60ml/min/1.73m$^2$) comprised the final cohort. Patient data was reviewed until 31$^{st}$ December 2019 for study outcomes including reaching ESRD or death prior to ESRD. ESRD was defined as initiation of chronic haemodialysis or peritoneal dialysis, receiving a renal transplant or initiating follow-up in the conservative care clinic.

**Figure 4.1** Patient selection from the SKS



### 4.3.4 Statistical analysis

Continuous data is presented as median ± interquartile range; categorical data as number (percentage). To compare variables between rapid progressors and stable patients, Mann-Whitney U or chi-squared test were used for continuous and categorical variables respectively. Binary logistic regression modelling was used to determine predictors associated with rapid CKD progression across all patients and in three specific conditions: diabetic nephropathy, glomerulonephritis of any cause and hypertensive nephropathy. These conditions were selected as patient numbers permitted appropriate analysis. Cox proportional hazards ratios with 95% CIs were calculated to determine factors implicated in mortality prior to ESRD in both rapid progressors and stable patients. The assumption of proportional hazards was assessed by the non-significance of each time-by-variable interaction (an interaction between a variable and a linear function of time) in both patient groups. Kaplan-Meier survival curves for ESRD and mortality prior to ESRD used Log Rank significance testing. To account for competing risks, the competing event was censored in survival analyses [16]. All multivariate models used a forward stepwise elimination procedure [17] incorporating the following 22 baseline clinical variables: age, gender, SBP, DBP, BMI, hypertension, DM, smoking, MI, PVD, stroke, HF, ACEi/ARB use, statin use, eGFR, bicarbonate, calcium, phosphate, albumin, Hb, total cholesterol:HDL ratio and A3 proteinuria. Statistical significance in all analyses was defined as $p<0.05$. Analyses were undertaken using SPSS (Version 25.0) (IBM SPSS, Chicago, IL) licensed to the University of Manchester.

### 4.3.5 Ethics approval and consent to participate

The Salford Kidney Study was granted ethical approval by the North West Greater Manchester South Research Ethics Committee (REC15/NW/0818). Participants provided written consent to participate.

## 4.4 RESULTS

### 4.4.1 Baseline characteristics

A total of 157 patients with rapid linear progression and 179 stable patients comprised the final cohort (Table 4.1). There was no disagreement between the two clinicians during visual inspection of the eGFR-time graphs with respect to selecting patients with linear progression. Quantitatively, eGFR linearity was reflected in the average 95% CI of the ΔeGFR for rapid progressors of only 2.0ml/min/1.73m$^2$ /yr and 1.7ml/min/1.73m$^2$/yr in stable patients.

The two patient groups demonstrated a clear separation in ΔeGFR: rapid patients progressed at a median rate of -5.93ml/min/1.73m$^2$/yr (with the median upper and lower 95% CIs of -5.41 to -7.42), whereas the eGFR changed at a rate of only -0.03ml/min/1.73m$^2$/yr (median 95% CIs 0.81 to -0.89) in stable patients ($p<0.001$). This was despite the baseline eGFR being lower in the stable group (28ml/min/1.73m$^2$ versus 34ml/min/1.73m$^2$; $p<0.001$). Each patient group had the same large number of eGFR measurements per patient (median of 25), with the frequency of monitoring higher for rapid progressors: median of 47 (24-91) days between eGFR testing in contrast to 84 days (38-135) in stable patients; $p<0.001$. The median follow-up time for the whole cohort was 5.3 years but rapid progressors had a much shorter follow-up of 3.9 years compared with 7.5 years in stable patients.

There was a significantly higher proportion of younger, female patients with higher blood pressure amongst the rapid progressors. In contrast, stable patients had a higher proportion with cardiovascular co-morbidity, including a history of MI and HF. There was no difference between the groups with respect to ACEi, ARB or statin use. Autosomal dominant polycystic kidney disease (ADPKD) was the commonest primary renal disease in rapid progressors, accounting for 33% of cases in this group, whereas there were more patients with renovascular disease or obstructive nephropathy in the stable group. Rapid progressors also had markedly higher levels of proteinuria and this was reflected in the majority of patients being categorised with A3 proteinuria.

**Table 4.1** Baseline characteristics of rapid progressors and stable patients

| Variable | Rapid progressor (n=157) | Stable patient (n=179) | P-value |
|---|---|---|---|
| Age (years) | 54.0 (43.5-64.0) | 68.4 (58.8-76.5) | **<0.001** |
| Men, *n* (%) | 81 (52) | 128 (72) | **<0.001** |
| Caucasian, *n* (%) | 152 (97) | 174 (97) | 0.833 |
| Systolic blood pressure (mmHg) | 144 (133-157) | 137 (122-148) | **0.001** |
| Diastolic blood pressure (mmHg) | 82 (74-91) | 74 (66-80) | **<0.001** |
| Hypertension, *n* (%) | 151 (96) | 168 (94) | 0.332 |
| Diabetes, *n* (%) | 41 (26) | 67 (37) | **0.027** |
| Body mass index (kg/m$^2$) | 28.0 (24.5-32.0) | 28.0 (24.5-32.2) | 0.925 |
| Past/current smoking history, *n* (%) | 100 (64) | 122 (68) | 0.389 |
| Myocardial infarction, *n* (%) | 5 (3) | 25 (14) | **0.002** |
| Peripheral vascular disease, *n* (%) | 8 (5) | 11 (6) | 0.375 |
| Stroke, *n* (%) | 11 (7) | 5 (3) | 0.138 |
| Heart failure, *n* (%) | 2 (1) | 10 (6) | **0.047** |
| ACEi/ARB, *n* (%) | 112 (71) | 118 (66) | 0.286 |
| Statin, *n* (%) | 92 (58) | 116 (65) | 0.243 |
| CKD stage 3, *n* (%) | 109 (69) | 78 (44) | **<0.001** |
| CKD stage 4, *n* (%) | 48 (31) | 101 (56) | **<0.001** |
| Years follow-up | 3.9 (2.9-5.0) | 7.5 (5.7-9.8) | **<0.001** |
| **Primary renal disease** | | | |
| Diabetic nephropathy, *n* (%) | 31 (20) | 39 (22) | 0.646 |
| ADPKD, *n* (%) | 52 (33) | 2 (1) | **<0.001** |
| Hypertensive nephropathy, *n* (%) | 11 (7) | 17 (10) | 0.410 |
| Renovascular disease, *n* (%) | 3 (2) | 14 (8) | **0.014** |
| Obstructive uropathy, *n* (%) | 7 (4) | 17 (9) | **0.038** |
| Glomerulonephritis, *n* (%) | 26 (17) | 24 (13) | 0.418 |
| Other causes, *n* (%) | 21 (13) | 39 (22) | **0.045** |
| Unknown, *n* (%) | 6 (4) | 27 (15) | **<0.001** |

| **Laboratory results** | | | |
|---|---|---|---|
| Creatinine (umol/l) | 171 (145-201) | 193 (157-238) | **<0.001** |
| eGFR-EPI (ml/min/1.73m$^2$) | 34 (28-41) | 28 (22-37) | **<0.001** |
| eGFR measurements, *n* | 25 (16-36) | 24 (15-38) | 0.960 |
| Days between eGFR measurements, *n* | 47 (24-91) | 84 (39-135) | **<0.001** |
| ΔGFR (±ml/min/1.73m$^2$/yr) | -5.930 ( -7.345 to -4.810) | -0.030 (-0.290 to 0.170) | **<0.001** |
| Bicarbonate (mmol/L) | 22.5 (20.2-25.0) | 23.0 (20.7-24.9) | 0.354 |
| Urea (mmol/L) | 12.0 (9.6-15.0) | 13.4 (10.8-17.6) | **0.001** |
| Calcium (mmol/L) | 2.31 (2.21-2.37) | 2.28 (2.21-2.37) | 0.350 |
| Phosphate (mmol/L) | 1.16 (1.03-1.29) | 1.05 (0.93-1.21) | **<0.001** |
| Alkaline phosphatase (mmol/L) | 78 (59-95) | 83 (65-104) | **0.025** |
| Albumin (g/L) | 41 (38-44) | 44 (42-46) | **<0.001** |
| Total cholesterol/HDL ratio | 3.55 (2.75-4.46) | 3.17 (2.48-4.06) | **0.007** |
| C-reactive protein (mg/L) | 2.8 (1.2-7.3) | 2.5 (1.0-5.7) | 0.234 |
| Haemoglobin (g/L) | 122 (113-134) | 129 (119-137) | **0.006** |
| Urine protein:creatinine ratio (g/mol) | 102 (28-289) | 17 (9-36) | **<0.001** |
| - A1 proteinuria (<15g/mol) | 16 (10) | 76 (42) | **<0.001** |
| - A2 proteinuria (15-50g/mol) | 44 (26) | 73 (41) | **0.005** |
| - A3 proteinuria (>50g/mol) | 107 (64) | 30 (17) | **<0.001** |

Continuous data are presented as median (interquartile range) and categorical variables presented as number (percentage).

P-value calculated by Mann-Whitney test for continuous data and Chi-squared test for categorical data.

### 4.4.2 Factors associated with rapid linear CKD progression

Univariate binary logistic analysis of the factors associated with rapid linear progression are presented in Table 4.2.

**Table 4.2** Univariate analysis of factors associated with rapid progression

| | Rapid progression | |
|---|---|---|
| **Variable** | **Univariate model OR (95% CI)** | **P-value** |
| Age (per year) | 0.942 (0.925-0.958) | **<0.001** |
| Female | 0.425 (0.271-0.667) | **<0.001** |
| Systolic blood pressure (per 1mmHg) | 1.018 (1.007-1.030) | **0.002** |
| Diastolic blood pressure (per 1mmHg) | 1.066 (1.044-1.088) | **<0.001** |
| Body mass index (per 1kg/$m^2$) | 1.002 (0.965-1.040) | 0.911 |
| Hypertension | 1.648 (0.595-4.564) | 0.337 |
| Diabetes mellitus | 0.591 (0.370-0.943) | **0.027** |
| Smoking | 0.820 (0.521-1.289) | 0.389 |
| Myocardial infarction | 0.651 (0.383-1.106) | 0.112 |
| Peripheral vascular disease | 0.635 (0.279-1.450) | 0.281 |
| Stroke | 1.267 (0.618-2.596) | 0.518 |
| Heart failure | 0.984 (0.520-1.863) | 0.961 |
| ACEi/ARB | 1.287 (0.809-2.046) | 0.287 |
| Statin | 0.769 (0.494-1.195) | 0.243 |
| eGFR (per 1ml/min/1.73$m^2$) | 1.057 (1.032-1.082) | **<0.001** |
| Bicarbonate (per 1mmol/L) | 0.966 (0.906-1.031) | 0.297 |
| Calcium (per 0.1mmol/L) | 1.516 (0.318-7.212) | 0.601 |
| Phosphate (per 0.1mmol/L) | 7.896 (2.513-24.807) | **<0.001** |
| Albumin (per 1g/L) | 0.835 (0.784-0.889) | **<0.001** |
| Total cholesterol:HDL ratio | 1.259 (1.069-1.482) | **0.006** |
| Haemoglobin (per 1g/L) | 0.982 (0.968-0.996) | **0.011** |
| A3 proteinuria | 8.250 (4.963-13.712) | **<0.001** |

In multivariate analysis, younger age, female gender, higher DBP, lower albumin, higher total cholesterol:HDL ratio, lower Hb and A3 proteinuria were all independently associated with rapid progression (Table 4.3). A3 proteinuria imparted the highest adjusted odds ratio (OR) of being a rapid progressor: 7.66, 95% CI 3.77-15.6, $p<0.001$.

**Table 4.3** Predictors of rapid linear progression based on multivariate binary logistic regression modelling

| Variable | Adjusted OR | 95% CI | P-value |
|---|---|---|---|
| Age (per year) | 0.958 | 0.936-0.980 | <0.001 |
| Male | 0.300 | 0.154-0.585 | 0.002 |
| DBP (per 1mmHg) | 1.063 | 1.033-1.093 | <0.001 |
| Total cholesterol:HDL ratio | 1.346 | 1.047-1.730 | 0.020 |
| Albumin (per 1g/L) | 0.912 | 0.842-0.987 | 0.023 |
| Hb (per 1g/L) | 0.956 | 0.935-0.979 | 0.004 |
| A3 proteinuria | 7.661 | 3.772-15.560 | <0.001 |

### 4.4.3 Factors associated with progression in specific conditions

The baseline characteristics of patients with diabetic nephropathy, glomerulonephritis of any cause and hypertensive nephropathy are provided in Table 4.4. Different combinations of clinical factors were associated with rapid progression in these specific conditions (Table 4.5). A3 proteinuria conferred the highest adjusted OR across all the diseases but differentiating factors for rapid progression included lower Hb in diabetic nephropathy (OR 0.96, 95% CI 0.93-0.98, p=0.002), lower albumin in glomerulonephritis (OR 0.89, 95% CI 0.82-0.97, p=0.005), and older age in hypertensive nephropathy (OR 1.06, 95% CI 1.01-1.11, p=0.023).

**Table 4.4** Baseline characteristics of rapid progressor patients with diabetic nephropathy, glomerulonephritis and hypertensive nephropathy

| Variable | Diabetic nephropathy (n=31) | Glomerulonephritis (n=26) | Hypertensive nephropathy (n=11) |
|---|---|---|---|
| Age (years) | 58.2 (51.0-67.1) | 60 (44.9-65.6) | 69.9 (56.5-74.1) |
| Men, *n* (%) | 21 (68) | 14 (54) | 10 (91) |
| Caucasian, *n* (%) | 30 (97) | 26 (100) | 11 (100) |
| Systolic blood pressure (mmHg) | 150 (132-161) | 144 (137-165) | 150 (143-164) |
| Diastolic blood pressure (mmHg) | 76 (70-83) | 81 (73-90) | 80 (71-89) |
| Hypertension, *n* (%) | 31 (100) | 26 (100) | 11 (100) |
| Diabetes, *n* (%) | 31 (100) | 5 (19) | 1 (9) |
| Body mass index (kg/m$^2$) | 31.1 (27.3-33.3) | 31.9 (25.5-36.7) | 28.1 (27.1-29.6) |
| Past/current smoking history, *n* (%) | 21 (68) | 18 (69) | 5 (45) |
| Myocardial infarction, *n* (%) | 4 (13) | 0 (0) | 0 (0) |
| Peripheral vascular disease, *n* (%) | 4 (13) | 0 (0) | 1 (9) |
| Stroke, *n* (%) | 5 (16) | 0 (0) | 2 (18) |
| Heart failure, *n* (%) | 2 (6) | 0 (0) | 1 (9) |
| ACEi/ARB, *n* (%) | 24 (77) | 22 (85) | 7 (64) |
| Statin, *n* (%) | 27 (87) | 18 (69) | 7 (64) |
| Years follow-up | 3.6 (3.0-4.4) | 4.2 (2.5-5.4) | 4.2 (3.1-4.7) |
| **Laboratory results** | | | |
| Creatinine (umol/L) | 169 (154-195) | 157 (124-171) | 189 (153-200) |
| eGFR-EPI (ml/min/1.73m$^2$) | 34 (27-40) | 39 (34-42) | 33 (28-39) |
| eGFR measurements, *n* | 26 (15-38) | 26 (18-48) | 29 (23-41) |
| ΔGFR (±ml/min/1.73m$^2$/yr) | -5.656 (-6.571 to -4.714) | -6.474 (-8.856 to -5.708) | -5.543 (-6.727 to -5.127) |
| Bicarbonate (mmol/L) | 22.6 (21.5-24.7) | 21.9 (20.1-25.6) | 23.2 (20.9-24.7) |
| Urea (mmol/L) | 13.0 (10.7-15.7) | 11.7 (9.4-15.9) | 13.4 (11.6-14.3) |

| | | | |
|---|---|---|---|
| Calcium (mmol/L) | 2.31 (2.22-2.39) | 2.28 (2.21-2.39) | 2.32 (2.28-2.38) |
| Phosphate (mmol/L) | 1.19 (1.04-1.36) | 1.17 (1.07-1.31) | 1.05 (0.91-1.13) |
| Alkaline phosphatase (mmol/L) | 94 (79.5-110) | 68.5 (58.0-93.8) | 69 (60-84) |
| Albumin (g/L) | 39 (37-42) | 39 (35-42) | 41 (39-44) |
| Total cholesterol:HDL ratio | 3.52 (2.74-4.92) | 4.04 (3.16-4.46) | 2.87 (2.66-4.12) |
| C-reactive protein (mg/L) | 3.1 (1.4-7.3) | 2.7 (1.2-5.1) | 2.8 (2.0-8.0) |
| Haemoglobin (g/L) | 118 (105-125) | 129 (110-137) | 123 (115-127) |
| Urine protein:creatinine ratio (g/mol) | 269 (107-446) | 270 (153-490) | 130 (67-186) |
| - A1 proteinuria (<15g/mol) | 0 (0) | 0 (0) | 1 (9) |
| - A2 proteinuria (15-50g/mol) | 4 (13) | 2 (8) | 1 (9) |
| - A3 proteinuria (>50g/mol) | 27 (87) | 24 (92) | 9 (82) |

**Table 4.5** Predictors of rapid linear progression based on binary logistic regression modelling in different causes of CKD

| Variable | Diabetic nephropathy | | | Glomerulonephritis | | | Hypertensive nephropathy | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | P-value | OR | 95% CI | P-value | OR | 95% CI | P-value |
| Age (per year) | | | | | | | 1.055 | 1.007-1.105 | 0.023 |
| A3 proteinuria | 13.393 | 4.510-39.771 | <0.001 | 26.120 | 5.253-129.864 | <0.001 | 11.530 | 2.335-56.930 | 0.003 |
| Albumin (per 1g/L) | | | | 0.888 | 0.817-0.965 | 0.005 | | | |
| Hb (per 1g/L) | 0.958 | 0.933-0.984 | 0.002 | | | | | | |
| Body mass index (per 1kg/$m^2$) | | | | 1.120 | 1.036-1.212 | 0.001 | | | |

### 4.4.4 Factors associated with mortality in rapid linear progressors and stable patients

Univariate analyses of the clinical factors associated with mortality in rapid progressors and stable patients are presented in Tables 4.6 and 4.7 respectively. In multivariate analysis, older age, male gender, a lack of ACEi/ARB blockade, MI, acidosis and anaemia were significantly associated with mortality prior to ESRD in rapid progressors. Older age and anaemia were also contributory in stable patients but smoking, PVD, HF and A3 proteinuria were specifically relevant in this patient cohort (Table 4.8).

**Table 4.6** Univariate analysis using Cox proportional hazards to evaluate factors associated with mortality prior to ESRD in rapid progressors

| | **In rapid progressors** | |
|---|---|---|
| **Variable** | **Univariate model OR (95% CI)** | **P-value** |
| Age (per year) | 1.094 (1.060-1.128) | **<0.001** |
| Female | 1.075 (0.505-2.286) | 0.852 |
| Systolic blood pressure (per 1mmHg) | 1.007 (0.988-1.027) | 0.480 |
| Diastolic blood pressure (per 1mmHg) | 0.958 (0.930-0.986) | **0.003** |
| Body mass index (per 1kg/$m^2$) | 0.964 (0.896-1.036) | 0.318 |
| Hypertension | 21.635 (0.004-127098.803) | 0.487 |
| Diabetes mellitus | 2.344 (1.105-4.969) | **0.026** |
| Smoking | 1.289 (0.567-2.930) | 0.544 |
| Myocardial infarction | 2.995 (1.716-5.226) | **<0.001** |
| Peripheral vascular disease | 7.923 (2.535-24.758) | **<0.001** |
| Stroke | 1.627 (0.539-4.915) | 0.388 |
| Heart failure | 1.628 (0.847-3.127) | 0.144 |
| ACEi/ARB | 0.417 (0.193-0.903) | **0.026** |
| Statin | 2.439 (1.022-5.816) | **0.044** |
| eGFR (per 1ml/min/1.73$m^2$) | 0.932 (0.890-0.975) | **0.003** |
| Bicarbonate (per 1mmol/L) | 0.919 (0.810-1.042) | 0.189 |
| Calcium (per 0.1mmol/L) | 1.450 (0.100-20.985) | 0.785 |
| Phosphate (per 0.1mmol/L) | 0.652 (0.093-4.594) | 0.668 |
| Albumin (per 1g/L) | 0.955 (0.899-1.013) | 0.128 |
| Total cholesterol:HDL ratio | 1.060 (0.813-1.381) | 0.668 |
| Haemoglobin (per 1g/L) | 0.963 (0.939-0.987) | **0.003** |
| A3 proteinuria | 1.709 (0.751-3.892) | 0.202 |

**Table 4.7** Univariate analysis using Cox proportional hazards to evaluate factors associated with mortality prior to ESRD in stable patients

| | In stable patients | |
|---|---|---|
| **Variable** | **Univariate model OR (95% CI)** | **P-value** |
| Age (per year) | 1.086 (1.058-1.115) | **<0.001** |
| Female | 1.077 (0.643-1.803) | 0.779 |
| Systolic blood pressure (per 1mmHg) | 1.001 (0.989-1.012) | 0.914 |
| Diastolic blood pressure (per 1mmHg) | 0.970 (0.949-0.992) | **0.007** |
| Body mass index (per 1kg/$m^2$) | 0.969 (0.929-1.012) | 0.158 |
| Hypertension | 1.082 (0.394-2.969) | 0.879 |
| Diabetes mellitus | 1.838 (1.158-2.916) | **0.010** |
| Smoking | 1.555 (0.913-2.649) | 0.104 |
| Myocardial infarction | 1.411 (0.899-2.213) | 0.134 |
| Peripheral vascular disease | 1.696 (1.037-2.776) | **0.035** |
| Stroke | 1.258 (0.724-2.186) | 0.416 |
| Heart failure | 2.807 (1.753-4.493) | **<0.001** |
| ACEi/ARB | 0.810 (0.502-1.306) | 0.387 |
| Statin | 1.518 (0.907-2.542) | 0.113 |
| eGFR (per 1ml/min/1.73$m^2$) | 0.980 (0.957-1.005) | 0.111 |
| Bicarbonate (per 1mmol/L) | 1.055 (0.986-1.128) | 0.119 |
| Calcium (per 0.1mmol/L) | 1.106 (0.165-6.245) | 0.986 |
| Phosphate (per 0.1mmol/L) | 3.142 (0.939-10.511) | 0.063 |
| Albumin (per 1g/L) | 0.887 (0.837-0.939) | **<0.001** |
| Total cholesterol:HDL ratio | 0.959 (0.783-1.174) | 0.685 |
| Haemoglobin (per 1g/L) | 0.965 (0.950-0.981) | **<0.001** |
| A3 proteinuria | 1.258 (0.676-2.342) | 0.469 |

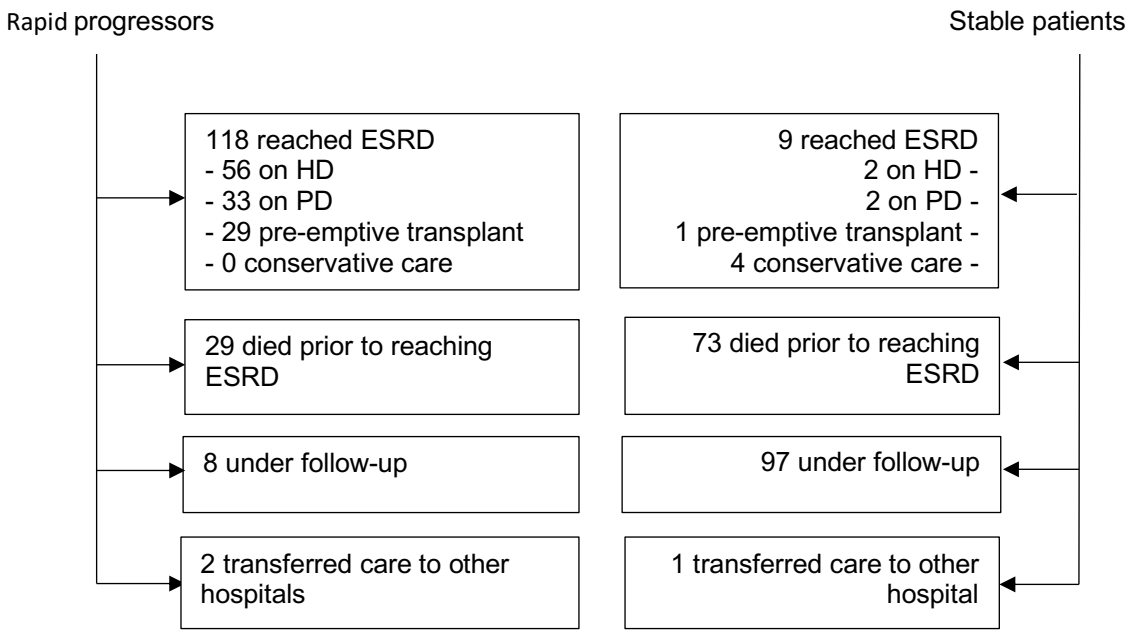
**Table 4.8** Multivariate Cox proportional hazards ratio for predictive factors for mortality prior to ESRD

| | IN RAPID PROGRESSOR | | | IN STABLE PATIENT | | |
|---|---|---|---|---|---|---|
| **Variable** | **HR** | **95% CI** | **P-value** | **HR** | **95% CI** | **P-value** |
| Age (per year) | 1.176 | 1.117-1.238 | <0.001 | 1.091 | 1.061-1.121 | <0.001 |
| Male | 3.501 | 1.382-8.867 | 0.008 | | | |
| Smoking | | | | 1.834 | 1.015-3.314 | 0.045 |
| ACEi/ARB | 0.222 | 0.081-0.610 | 0.004 | | | |
| MI | 3.711 | 1.739-7.918 | 0.001 | | | |
| PVD | | | | 2.014 | 1.173-3.458 | 0.011 |
| HF | | | | 2.423 | 1.468-4.000 | 0.001 |
| Bicarbonate (per mmol/L) | 0.838 | 0.717-0.979 | 0.026 | | | |
| Hb (per 1g/L) | 0.918 | 0.885-0.952 | <0.001 | 0.964 | 0.947-0.981 | <0.001 |
| A3 proteinuria | | | | 2.554 | 1.333-4.894 | 0.005 |

### 4.4.5 Impact of ΔeGFR on ESRD and mortality

Over a cumulative follow-up of 2366 patient-years in the combined cohort of rapid progressors and stable patients, 127 patients reached ESRD, 102 died prior to ESRD and 105 remained under nephrology follow-up (Figure 4.2).

**Figure 4.2** Outcomes for rapid progressors and stable patients



Kaplan-Meier analysis revealed significantly worse outcomes were faced by rapid progressors, compared with stable patients, for reaching ESRD (censored at death) or mortality prior to ESRD (Figure 4.3 and Figure 4.4), and this is further illustrated in Figure 4.5 for the combined endpoint of ESRD and mortality prior to ESRD (censored at the last clinic visit, until 31st December 2019). Over the first 5 years of follow-up, rapid progressors reached ESRD at an average rate of 34 per 100 patients per year compared with 0.2 stable patients per 100 per year. Rapid progressors also faced higher rates of mortality over this time period at a rate of 10 per 100 patients per year, compared with 6 per 100 per year amongst stable patients.

**Figure 4.3** Kaplan Meier curve for probability of survival from ESRD

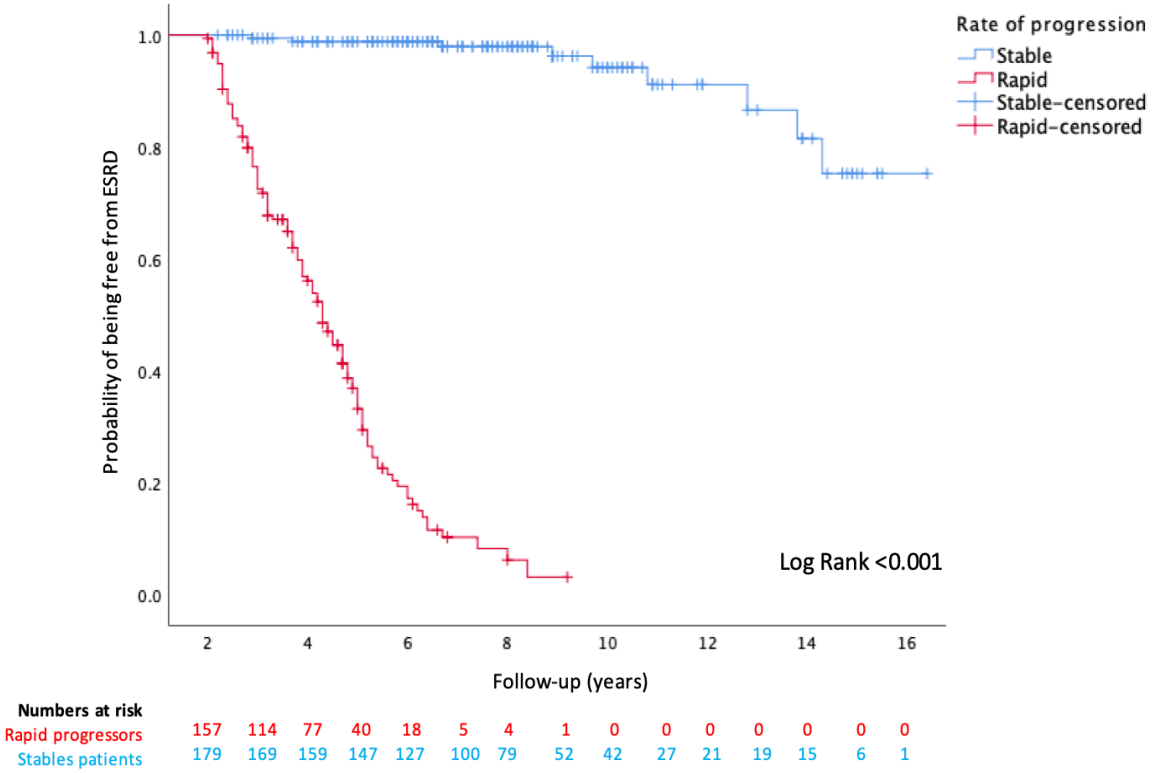


**Figure 4.4** Kaplan Meier curve for probability of survival from death prior to ESRD

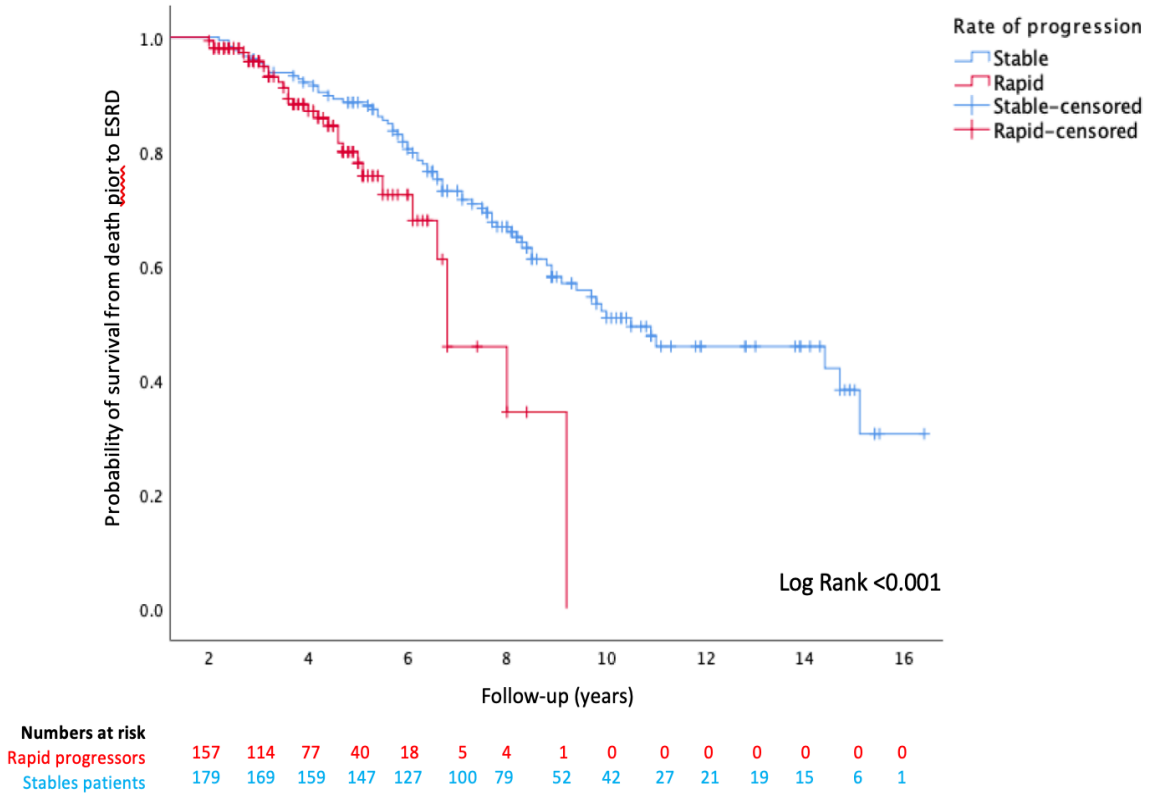
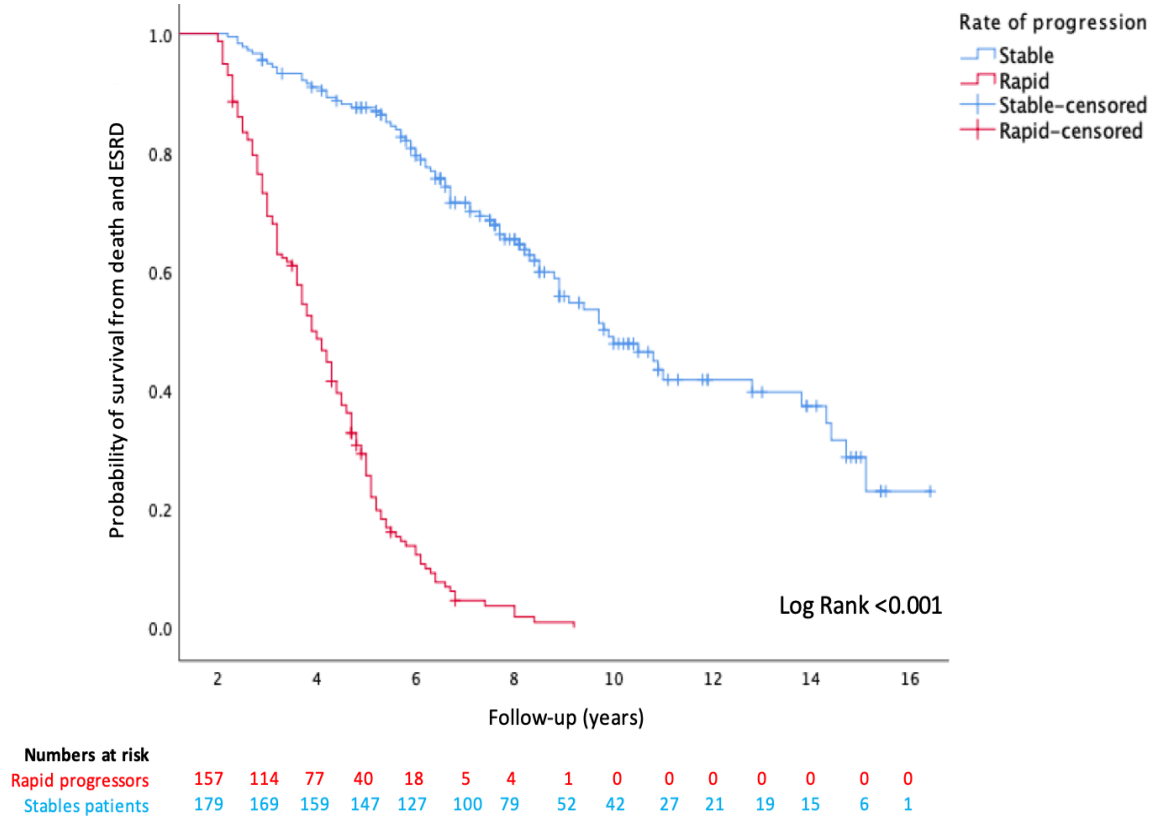



**Figure 4.5** Kaplan Meier curve for probability of survival from ESRD or death prior to ESRD



## 4.5 DISCUSSION

This study highlights several risk factors predictive of rapid linear progression, which are uniquely expressed in different renal diseases. We also highlight distinct clinical factors associated with mortality prior to ESRD in rapid progressors compared with stable patients. Interventions targeting modifiable factors should be prioritised, especially in rapid progressors, given the significant burden of adverse outcomes experienced by this patient cohort.

### 4.5.1 Predictive factors associated with progression

Studies have shown that younger age [17], dyslipidaemia [18], lower albumin [19], lower Hb [20] and proteinuria [21] are associated with CKD progression and all these factors were predictive of patients having rapid linear progression in our analysis. The observation of younger patients at more at risk of progression may be due to the underlying age differences in CKD aetiology [22]. Indeed, in our cohort, a third of the rapid progressors were patients with ADPKD, in whom the median age was 51 (44.8-56.5) years [data not shown], compared to 68.4 (58.8-76.5) years in the stable cohort as a whole.

Of note, we also found female gender to have a positive association with rapid linear progression. Studies that explored gender differences in CKD have found conflicting results: some found male sex confers more risk [23,24] whereas other studies suggest the opposite [25,26]. The exact reason for why sex differences exist in patients with CKD is not clearly understood and remains an area for further research.

We also interestingly found that higher DBP was more important than SBP in predicting rapid progression. Although historic studies have highlighted a role of DBP in progression, more recent ones have focussed on the importance of SBP alone [17], or of both SBP and DBP [27], with respect to renal outcomes. We did find higher SBP was associated with rapid progression in the univariate analysis (Table 4.2), but it was not significant after adjustment of other covariates. Further work may be required to better understand the clinical implications of DBP in those with advanced CKD, an issue recently identified by the renal community warranting further review [28].

CKD aetiology is important in predicting future progression and our study highlights the well-known association of ADPKD being most commonly linked with rapid linear progression [29] as a consequence of the progressive nature of cyst enlargement and destruction of healthy renal architecture. The higher proportion of stable patients with renovascular disease or obstructive nephropathy in our study is likely reflective of successful treatment interventions that remove ongoing renal injury in these conditions, minimising the risk of developing tubular atrophy and interstitial fibrosis and thus improving long-term renal outcomes.

What is perhaps less well understood is the interplay of factors in the pathogenesis of rapid linear progression in other primary renal disease states. This is shown in the differential impact of exposures on three renal conditions (Table 4.5). For instance, rapid progressors with diabetic nephropathy were more likely to be anaemic and have A3 proteinuria, whereas rapidly progressing patients diagnosed with glomerulonephritis were more likely to have lower albumin and severe proteinuria, which is indicative of active disease and perhaps inflammation driving renal decline. Higher BMI was also associated with rapid progression in those with glomerulonephritis, but this is likely confounded by patients who were taking immunosuppressive agents such as steroids which can raise BMI.

### 4.5.2 Predictive factors associated with mortality

There was an unsurprising representation of cardiovascular risk factors such as older age, male gender, smoking, PVD, HF and A3 proteinuria associated with mortality in both patient groups. However, these factors impacted the two patient groups in different ways. For instance, rapid progressors who had suffered a prior MI were less likely to survive, whereas there was a significant risk of mortality amongst stable patients who had suffered PVD or HF. Whether these differences are directly attributable to pathophysiological processes underlying different rates of progression requires further exploration. A3 proteinuria did not impact mortality in rapid progressors but was important for those who had stable disease. This may be due to the potentially greater role severe proteinuria plays on the competing risk of ESRD in rapid progressors. Notably, use of ACEi/ARB was found to reduce the mortality risk in rapid progressors specifically. Although the beneficial effect of ACEi/ARB on mortality at different CKD

stages has been highlighted in prior studies [30,31], we show this benefit extends to those with a defined rate of rapid CKD progression. Potential protective mechanisms include favourable haemodynamic changes [32] on the cardiovascular system but also anti-inflammatory effects of renin-angiotensin-aldosterone blockade [33], which may be of particular relevance in the inflammatory milieu of rapid CKD progression.

### 4.5.3 Clinical implications

There are several clinical implications of our findings. Firstly, there is a pressing need for accurate risk stratification that aids prognostication of adverse clinical outcomes in patients with CKD. Developing risk prediction calculators that take account of CKD aetiology or the rate of prior eGFR change, both of which are important determinants that influence future eGFR trajectory [34], would be desirable.

Secondly, our data clearly demonstrate that those with rapid linear progression are an especially vulnerable group of patients that suffer significantly higher annual rates of ESRD or mortality compared to their stable counterparts. Translating this to clinical practice requires assessment of patients' rate of eGFR decline based on prior blood tests, and those progressing rapidly should be offered prompt, vigorous management of modifiable risk factors and closer follow-up monitoring to mitigate future harm.

Finally, we highlight that stable CKD is also not benign. In our cohort, stable patients were older with a higher burden of cardiovascular disease, and although only 5% of patients reached ESRD, 40% of patients died. It underscores previous work showing that older patients are more likely to have stable disease, but that the absolute risk of death in this CKD subgroup remains high, largely as a consequence of cardiovascular disease [35], and this was also borne out in our study. Therefore, an equally important aspect of optimal CKD care, regardless of the rate of progression, requires addressing modifiable cardiovascular risk factors given their association with mortality [21].

### 4.5.4 Strengths and limitations

Although several studies have investigated factors predictive of progression, our study has the advantage of providing a closer perspective of those with linear rates of progression using a robust methodological approach to patient selection. Each patient had a large number of eGFR measurements taken over a long follow-up period and this

helped to precisely characterise patients' eGFR trajectories. This consequently permitted a robust analysis of patients with different rates of progression, based on their ΔeGFR slope, which was corroborated by visually inspecting each patients' eGFR-time graphs and confirmed quantitatively by assessing the spread of the 95% CIs of the ΔeGFR in each patient group. Our systematic approach therefore ensured only patients with true linear CKD progression were selected. Our findings also largely support the established literature in describing key determinants of CKD progression and mortality, and in doing so also provides evidence that the phenotypic profile of those with true linear progression is also shared with those with other rates of variable, non-linear progression described in the wider literature.

Our work also has limitations. The analysis was limited to specific ΔeGFR changes to define rapid and stable disease but did not consider the outcomes of other rates of progression, such as those between -0.5 to -4ml/min/1.73m$^2$/yr or those with larger, positive changes in eGFR over time. This latter group has also been shown to be associated with poor outcomes, perhaps related to changes in muscle mass in patients with chronic illness; or it may represent those whose trajectory is recovering from an episode of acute kidney injury, which is itself has been shown to be an independent risk factor for CKD progression [36]. Changes in muscle mass over time may also be responsible for inaccurate ΔeGFR calculations in older patients, which could not be accounted for in this study. Secondly, our work will be affected by limitations attributed to retrospective observational studies including an inability to confirm causal association or to account for unmeasured confounders. Thirdly, our disease-specific analysis had small numbers of patients and may not be sufficiently powered to define specific predictive associations. We were unable to evaluate risk factors specific to ADPKD for this reason due to there being only 2 patients with stable disease and 52 with rapid progression. Fourthly, it is a single-centre study with a largely Caucasian population and thus the results may not be generalisable to other ethnic patient cohorts in other geographical locations.

## 4.6 CONCLUSIONS

Rapid linear CKD progression represents a confluence of several risk factors, which act heterogeneously depending on the underlying aetiology of CKD. Patients with rapid linear progression are at high risk for adverse clinical outcomes and therefore warrant frequent specialist monitoring. Further refining of current risk prediction tools in CKD will hopefully help optimise care for such high-risk patients.

## 4.7 REFERENCES


1. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011;80:17–28.
2. Echouffo-Tcheugui JB, Kengne AP. Risk models to predict chronic kidney disease and its progression: a systematic review. PLOS Medicine. 2012;9:e1001344.
3. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure. a meta-analysis. JAMA. 2016;315:164–174.
4. Grams ME, Sang Y, Ballew SH, et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int. 2018;93:1442–1451.
5. Ali I, Kalra P. Risk prediction in chronic kidney disease. Curr Opin Nephrol Hypertens. 2019;28:513–518.
6. Rosanksy SJ. Renal function trajectory is more important than chronic kidney disease stage for managing patients with chronic kidney disease. Am J Nephrol. 2012;36:1-10.
7. Sumida K, Kovesdy CP. Disease trajectories before ESRD: implications for clinical management. Sem Nephrol. 2017;37:132–143.
8. Vigil A, Condés E, Camacho R, et al. Predictors of a rapid decline of renal function in patients with chronic kidney disease referred to a nephrology outpatient clinic: a longitudinal study. Adv Nephrol. 2015:657624.
9. Sukmark T, Sukmark S. Predictors of faster progression in chronic kidney disease. J Med Assoc Thai. 2014;97:812-819.
10. Go AS, Yang J, Tan TC, et al. Contemporary rates and predictors of fast progression of chronic kidney disease in adults with and without diabetes mellitus. BMC Nephrol. 2018;19:146.
11. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3:i-150.
12. Levey AS, Greene T, Schluchter MD, et al. Glomerular filtration rate measurements in clinical trials. Modification of Diet in Renal Disease Study

Group and the Diabetes Control and Complications Trial Research Group. J Am Soc Nephrol. 1993;4:1159–1171.

13. Stringer S, Sharma P, Dutton M, et al. The natural history of, and risk factors for, progressive Chronic Kidney Disease (CKD): the Renal Impairment in Secondary care (RIISC) study; rationale and protocol. BMC Nephrol. 2013;14:95.
14. Li L, Astor BC, Lewis J, Hu B, Appel LJ, Lipkowitz MS, et al. Longitudinal progression trajectory of GFR among patients with CKD. Am J Kidney Dis. 2012;59:504-512.
15. Agarwal R, Duffin K, Laska DA, et al. A prospective study of multiple protein biomarkers to predict progression in diabetic chronic kidney disease. Nephrol Dial Transplant. 2014;29:2293-2302.
16. Noordzij M, Leffondré K, Van Stralen KJ, et al. When do we need competing risks methods for survival analysis in nephrology? Nephrol Dial Transplant. 2013;28:2670–2677.
17. Levin A, Djurdjev O, Beaulieu M, et al. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. Am J Kidney Dis. 2008;52:661-671.
18. Kawachi K, Kataoka H, Manabe S, et al. Low HDL cholesterol as a predictor of chronic kidney disease progression: a cross-classification approach and matched cohort analysis. Heart Vessels. 2019;34:1440-1455.
19. Zhang J, Zhang R, Wang Y, et al. The level of serum albumin is associated with renal prognosis in patients with diabetic nephropathy. J Diabetes Res. 2019;17:e7825804.
20. Keane WF, Zhang Z, Lyle PA, et al. Risk scores for predicting outcomes in patients with type 2 diabetes and nephropathy: the RENAAL study. Clin J Am Soc Nephrol. 2006;1:761–767.
21. Jafar TH, Stark PC, Schmid CH, et al. Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. Kidney Int. 2001;60:1131–1140.
22. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. J Am Soc Nephrol. 2007;18:2758-2765.
23. Evans M, Grams ME, Sang Y, et al. Risk factors for prognosis in patients with severely decreased GFR. Kidney Int Rep. 2018;3:625-637.
24. Rebholz CM, Coresh J, Ballew SH, et al. Kidney failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: comparing ascertainment of

treated and untreated kidney failure in a cohort study. Am J Kidney Dis. 2015;66:231-239.

25. Imai E, Horio M, Yamagata K, et al. Slower decline of glomerular filtration rate in the Japanese general population: a longitudinal 10-year follow-up study. Hypertens Res. 2008;31:433-441.
26. Chang PY, Chien LN, Lin YF, et al. Risk factors of gender for renal progression in patients with early chronic kidney disease. Medicine (Baltimore). 2016; 95:e4203.
27. Brancati FL, Whelton PK, Randall BL, et al. Risk of end-stage renal disease in diabetes mellitus: a prospective cohort study of men screened for MRFIT. Multiple Risk Factor Intervention Trial. JAMA. 1997;278:2069-2074.
28. Cheung AK, Chang TI, Cushman WC, et al. Blood pressure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2019;95:1027-1036.
29. Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease study. Kidney Int. 1997;51:1908-1919.
30. Molnar MZ, Kalantar-Zadeh K, Lott EH, et al. ACE inhibitor and angiotensin receptor blocker use and mortality in patients with chronic kidney disease. J Am Coll Cardiol. 2014;63:650-658.
31. Ku E, McCulloch CE, Vittinghoff E, et al. Use of antihypertensive agents and association with risk of adverse outcomes in chronic kidney disease: focus on angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. JAHA. 2018 ;7:e009992.
32. Sutton MG, Sharpe N. Left ventricular remodeling after myocardial infarction: pathophysiology and therapy. Circulation. 2000;101:2981–2988.
33. Manabe S, Okura T, Watanabe S, et al. Effects of angiotensin II receptor blockade with valsartan on pro-inflammatory cytokines in patients with essential hypertension. J Cardiovasc Pharmacol. 2005;46:735–739.
34. Kovesdy CP, Coresh J, Ballew SH, et al. Past decline versus current eGFR and subsequent ESRD risk. J Am Soc Nephrol. 2016;27:2447-2455.
35. Keith DS, Nichols GA, Gullion CM, et al. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organisation. Arch Intern Med. 2004;164:659-663.

36. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81:442-448.

# CHAPTER 5

## ADVERSE OUTCOMES ASSOCIATED WITH RAPID LINEAR AND NON-LINEAR PATTERNS OF CHRONIC KIDNEY DISEASE PROGRESSION

Ibrahim Ali, Rajkumar Chinnadurai, Sara T. Ibrahim, Philip A. Kalra

BMC Nephrol. 2021;22:82.
DOI: https://doi.org/10.1186/s12882-021-02282-5

## 5.1 ABSTRACT


**Background**

Patients with rapidly declining renal function face the dual threat of end-stage renal disease (ESRD) and mortality prior to ESRD. What is less well characterised is whether the pattern of the renal trajectory, linear or non-linear, unmasks subgroups of rapidly progressing patients that face adverse outcomes in a differential manner.

**Methods**

An individual eGFR slope was applied to all outpatient estimated glomerular filtration rate (eGFR) values for each patient in the Salford Kidney Study from 2002 to 2018 who had at least 2 years follow-up, ≥4 eGFR values and baseline eGFR 15 to <60ml/min/1.73m$^2$. Rapid progression was defined as an annual eGFR slope of ≤-3ml/min/1.73m$^2$/yr and patients were categorised as linear or non-linear progressors based on the nature of their eGFR-time graphs. A Fine-Gray competing risk hazard model was used to determine factors associated with progression to ESRD and with mortality prior to ESRD. Cumulative incidence function curves highlighted differences in outcomes between linear and non-linear patients.

**Results**

There were 211 rapidly deteriorating patients with linear eGFR trajectories and 61 rapid non-linear patients in the study cohort. Factors associated with ESRD included younger age, male gender, lower baseline eGFR and higher serum phosphate, whilst older age, history of myocardial infarction and anaemia predicted mortality prior to ESRD. Over a median follow-up of 3.7 years, linear progressors reached ESRD sooner whilst those with non-linear progression faced significantly higher rates of mortality prior to ESRD.

**Conclusions**

Patients with rapid eGFR decline have high rates of adverse outcomes that are differentially expressed in those progressing linearly and non-linearly as a result of differing phenotypic profiles. Consequently, addressing individual risk factor profiles is important to deliver optimal personalised patient care.

## 5.2 BACKGROUND

Patients with chronic kidney disease (CKD) that experience rapidly declining renal function are at increased risk of adverse outcomes, including increased risk of end-stage renal disease (ESRD) as well as increased risk of mortality prior to ESRD [1]. Over the past decade, there has been growing attention to not only considering the slope of renal function change, as defined by annual changes in estimated glomerular filtration rate (eGFR) [2], but also the pattern of the eGFR trajectory on patient outcomes [3,4], especially given that patients with CKD progress in ways other than in a simply linear manner [5].

Extending our understanding of how the eGFR slope and trajectory impacts patient outcomes could help to refine current risk prediction tools to stratify high-risk patients more accurately. This would help improve the communication of risk to patients and help shape management strategies, including earlier targeted treatment in an attempt to assuage future harm [6].

Whilst several studies have recognised the determinants of rapid progression, what is less well known is whether the pattern of rapid CKD progression, be it linear or non-linear, has an impact on patient outcomes. We therefore undertook this study to 1) identify the predictive factors of rapid progression in a cohort of patients progressing in a linear and non-linear pattern; 2) to examine how the pattern of rapid progression affects outcomes of ESRD and mortality prior to ESRD, and in doing so, 3) identify whether there are subgroups and phenotypic differences between linear and non-linear progressors that could enlighten specific approaches to patient management.

## 5.3 METHODS

### 5.3.1 Patient population

Patients were drawn from the Salford Kidney Study (SKS), an ongoing observational cohort study, which since 2002 has been recruiting patients aged ≥18 years old with non-dialysis CKD who have been referred to the renal services at Salford Royal NHS Foundation Trust in the United Kingdom. The SKS received ethical approval from the

North West Greater Manchester South Research Ethics Committee (REC15/NW/0818). Written informed consent was obtained from all patients. The methods described herein were carried out in accordance with relevant guidelines and regulations of the SKS.

### 5.3.2 Baseline characteristics

Patient characteristics were measured at the point of recruitment into the SKS. They include patient demographics (age, gender, ethnicity, history of past or current smoking); past medical history (primary renal disease, history of hypertension (HTN), diabetes mellitus (DM), myocardial infarction (MI), peripheral vascular disease (PVD), stroke and heart failure (HF)); medication history (use of angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blockers (ARB) and statins); and laboratory measurements (serum creatinine, eGFR calculated using the CKD epidemiology collaboration (CKD-EPI) equation, bicarbonate, urea, calcium, phosphate, albumin, haemoglobin and urine protein:creatinine ratio (uPCR), which was categorised into albuminuria grades of A1, A2 and A3 based on values of <15g/mol, 15-50g/mol and >50g/mol respectively) [7].

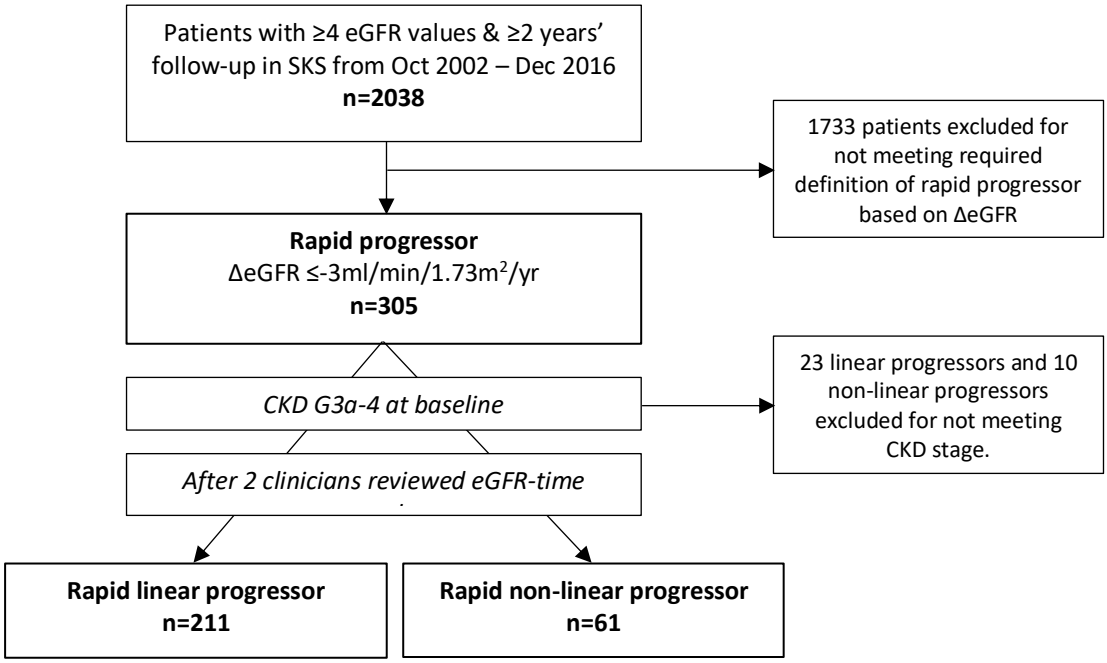
### 5.3.3 Assembling the study cohort

Patient selection into this study is shown in Figure 5.1. All the outpatient eGFR values, performed as part of routine renal care and accessed via the hospital's electronic patient record, were used to calculate the delta (Δ) eGFR slope for each patient using linear regression. As a minimum, we required at least 4 eGFR values over 2 years follow-up for the ΔeGFR to be ascertained for each patient. Patients with a ΔeGFR≤-3ml/min/1.73m$^2$/yr (i.e., losing more than 3ml/min/1.73m$^2$/yr), a threshold associated with worse outcomes [2], were defined as a rapid progressor, and they had to have baseline CKD G3a-4 (eGFR 15 to <60ml/min/1.73m$^2$) for study inclusion. To differentiate linear versus non-linear progression, the eGFR-time graphs were visually inspected independently by two clinicians, an approach that has been successfully utilised in previous studies [1, 8], and also quantitively assessed with the coefficient of determination ($R^2$).

### 5.3.4 Study outcomes

Patient outcomes included ESRD (haemodialysis, peritoneal dialysis, conservative care or pre-emptive transplantation) or mortality prior to ESRD. Outcome events were reviewed until 1st January 2020.

**Figure 5.1** Assembling the study cohort




### 5.3.5 Statistical analysis

Continuous data is presented as median (± interquartile range) and categorical data as number (percentage). To compare variables between rapid linear and rapid non-linear progressors, Mann-Whitney U test was used for continuous data and chi-squared test for categorical covariates. The Fine-Gray competing risk hazard model [9] was employed to determine the subdistribution hazard ratios of the factors associated with ESRD or mortality prior to ESRD within the study cohort. The following 20 variables were included in the model: age, gender, SBP, DBP, HTN, DM, smoking, MI, PVD, stroke, HF, ACEi/ARB use, statin use, eGFR, bicarbonate, calcium, phosphate, albumin, Hb

and A3 proteinuria. The proportional hazards assumption for each model was assessed by the non-significance of each time-by-variable interaction.

Cumulative incidence function curves were produced comparing the outcomes of ESRD and mortality between linear and non-linear progressors, for which a modified Chi-squared test was used for significance testing [10]. A comparison between linear and non-linear progressors on a composite outcome of either ESRD or mortality was also assessed and visualised as a 1-Kaplan-Meier curve, which used log-rank significance testing. Statistical significance was defined as a p-value of <0.05. Analyses were performed using SPSS (Version 25.0) (IBM SPSS, Chicago, IL) licensed to the University of Manchester and R version 4.0.2 (The R Foundation for Statistical Computing Platform).

## 5.4 RESULTS

### 5.4.1 Baseline characteristics

A total of 272 patients met the inclusion criteria of which 211 patients had linear progression and 61 patients had non-linear progression (Table 5.1). Categorisation as a linear or non-linear progressor was achieved with unanimous agreement between the two clinicians independently reviewing patients' eGFR-time graphs, illustrative examples of which are shown in Figure 5.2. Quantitatively, linear patients had a significantly higher median $R^2$ value of 0.91 (0.81-0.95) compared with 0.58 (0.36-0.60) in non-linear progressors, p-value <0.01.

There were no significant differences in laboratory measures between the two patient groups. Of note, both groups demonstrated poor baseline renal function with a median eGFR of 34ml/min/1.73m$^2$ (26-41ml/min/1.73m$^2$) and 31ml/min/1.73m$^2$ (23-41ml/min/1.73m$^2$) in linear and non-linear progressors respectively. Both groups also had high degrees of proteinuria, which was reflected in the majority of patients classified with A3 proteinuria.

**Table 5.1** Baseline characteristics of the study cohort

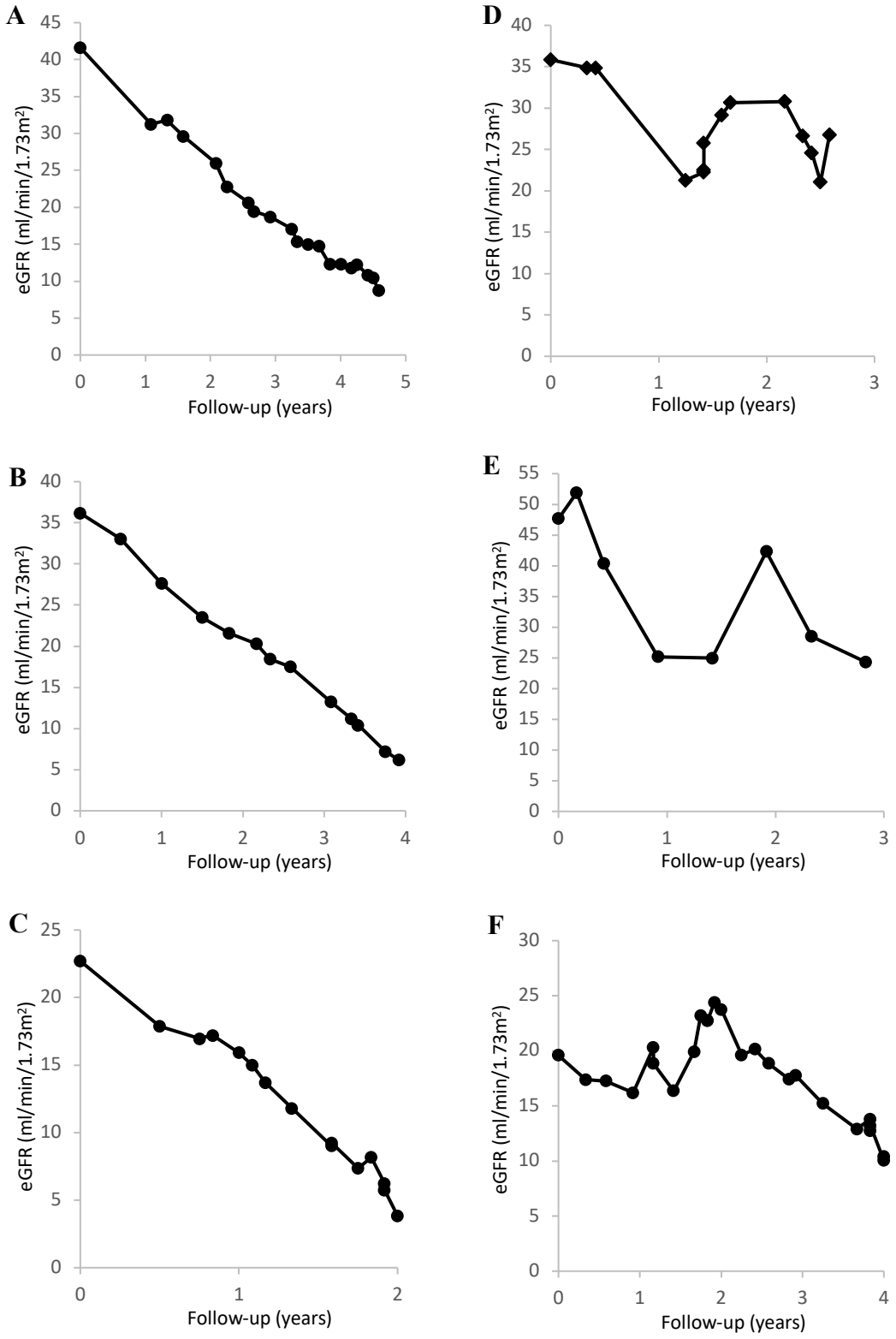
| Variable | All patients (n=272) | Rapid linear progressor (n=211) | Rapid non-linear progressor (n=61) | p-value |
|---|---|---|---|---|
| Age (years) | 58.0 (46.0-70.0) | 54.8 (44.9-67.2) | 67.4 (58.9-74.5) | **<0.01** |
| Men, *n* (%) | 134 (49) | 104 (49) | 30 (49) | 0.99 |
| Caucasian, *n* (%) | 231 (85) | 171 (81) | 60 (98) | **<0.01** |
| Systolic blood pressure (mmHg) | 140 (128-155) | 140 (128-154) | 140 (129-156) | 0.75 |
| Diastolic blood pressure (mmHg) | 78 (70-84) | 79 (70-84) | 76 (70-81) | 0.17 |
| Hypertension, *n* (%) | 254 (93) | 197 (93) | 57 (93) | 0.98 |
| Diabetes, *n* (%) | 90 (33) | 59 (28) | 31 (51) | **<0.01** |
| Past/current smoking history, *n* (%) | 174 (64) | 132 (63) | 42 (69) | 0.37 |
| Myocardial infarction, *n* (%) | 26 (10) | 12 (6) | 14 (23) | **<0.01** |
| Peripheral vascular disease, *n* (%) | 33 (12) | 20 (10) | 13 (21) | **0.01** |
| Stroke, *n* (%) | 20 (7) | 12 (6) | 8 (13) | 0.05 |
| Heart failure, *n* (%) | 27 (10) | 13 (6) | 14 (23) | **<0.01** |
| ACEi/ARB, *n* (%) | 197 (72) | 158 (75) | 39 (64) | 0.09 |
| Statin, *n* (%) | 158 (58) | 120 (57) | 38 (62) | 0.45 |
| Years follow-up | 3.7 (2.8-4.9) | 3.9 (2.9-5.0) | 3.2 (2.6-4.0) | **<0.01** |
| **Primary renal disease** | | | | |
| Diabetic nephropathy, *n* (%) | 67 (25) | 46 (22) | 21 (34) | **0.04** |
| ADPKD, *n* (%) | 55 (20) | 55 (26) | 0 (0) | **<0.01** |
| Hypertensive nephropathy, *n* (%) | 26 (10) | 15 (7) | 11 (18) | **0.01** |
| Glomerulonephritis, *n* (%) | 34 (13) | 32 (15) | 2 (3) | **0.01** |
| Other causes, *n* (%) | 66 (24) | 45 (21) | 21 (23) | **0.04** |
| Unknown, *n* (%) | 24 (9) | 18 (9) | 6 (10) | 0.75 |
| **Laboratory results** | | | | |

| | | | | |
|---|---|---|---|---|
| eGFR-EPI (ml/min/1.73m$^2$) | 34 (26-41) | 34 (26-41) | 32 (23-41) | 0.36 |
| eGFR measurements per patient, *n* | 24 (15-37) | 24 (16-36) | 21 (11-37) | 0.19 |
| ΔGFR (±ml/min/1.73m$^2$/yr) | -5.23 (-6.72 to -3.98) | -5.28 (-6.75 to -4.11) | -4.57 (-6.46 to -3.46) | 0.06 |
| Bicarbonate (mmol/L) | 22.6 (20.4-25.0) | 22.5 (20.4-25.0) | 23.0 (20.6-25.2) | 0.43 |
| Urea (mmol/L) | 12.2 (9.8-15.7) | 12.0 (9.9-15.4) | 13.9 (10.1-17.2) | 0.24 |
| Calcium (mmol/L) | 2.31 (2.23-2.39) | 2.30 (2.22-2.34) | 2.32 (2.27-2.40) | 0.15 |
| Phosphate (mmol/L) | 1.13 (1.02-1.27) | 1.15 (1.02-1.28) | 1.11 (1.03-1.25) | 0.74 |
| Albumin (g/L) | 42 (39-44) | 41 (39-44) | 42 (39-44) | 0.99 |
| Total cholesterol/HDL ratio | 3.4 (2.7-4.3) | 3.5 (2.7-4.5) | 3.2 (2.6-4.1) | 0.16 |
| Haemoglobin (g/L) | 122 (113-133) | 123 (114-133) | 121 (110-132) | 0.57 |
| Urine protein:creatinine ratio (g/mol) | 77 (24-244) | 87 (26-272) | 52 (24-171) | 0.16 |
| A1 proteinuria (<15g/mol), *n* (%) | 33 (12) | 26 (12) | 7 (12) | 0.86 |
| A2 proteinuria (15-50g/mol), *n* (%) | 82 (30) | 59 (28) | 23 (38) | 0.14 |
| A3 proteinuria (>50g/mol), *n* (%) | 157 (58) | 126 (60) | 31 (51) | 0.22 |

Continuous data are presented as median (interquartile range) and categorical variables presented as number (percentage).

P-values, comparing linear and non-linear groups, were calculated by Mann-Whitney test and Chi-squared test for continuous and categorical data respectively.

**Figure 5.2** Examples of eGFR-time graphs of linear and non-linear patients in the study cohort




Graphs A to C highlight examples of rapid linear progression, whilst graphs D to F show rapid non-linear eGFR trajectory.

The categorisation of the nature of the ΔeGFR slope in each patient group was strengthened by a large number of eGFR measurements per patient during the follow-up period with a median of 24 (16-36) in the linear group and 21 (11-37) in the non-linear group. The ΔeGFR itself met the *a priori* definition of rapid renal decline in both patient groups, and were statistically similar: in linear progressors, the median ΔeGFR was -5.28ml/min/1.73m$^2$/yr (-6.75 to -4.11ml/min/1.73m$^2$/yr) and in non-linear progressors the ΔeGFR was -4.57ml/min/1.73m$^2$/yr (-6.46 to -3.46ml/min/1.73m$^2$/yr); p-value of 0.06.

There were however significant differences between the progressor groups with respect to demographic characteristics and co-morbidities. Non-linear patients were typically older and had a higher burden of co-morbidities including diabetes, myocardial infarction, peripheral vascular disease and heart failure. There was also contrasting frequencies of the underlying disease aetiology, most notably seen for autosomal dominant polycystic kidney disease (ADPKD), which was exclusively associated with linear progressors and was the commonest primary renal disease in this group, affecting a quarter of all linear progressor patients.

### 5.4.2 Factors associated with ESRD and mortality prior to ESRD

Univariate analyses of the factors associated with ESRD and mortality prior to ESRD is presented in Tables 5.2 and 5.3. In multivariate analysis, younger age, male gender, lack of diabetes, lower eGFR and higher phosphate were significantly associated with progression to ESRD (Table 5.4).

Three clinical factors were shown to be significantly predictive for mortality prior to ESRD, including older age, history of MI and anaemia (Table 5.4). Of note, in univariate analyses (Table 5.3), higher SBP, history of diabetes, MI, PVD, HF and lack of ACEi/ARB use were associated with mortality prior to ESRD but these were found to not be significant once adjusted for other variables.

**Table 5.2** Univariate analysis using Fine-Gray hazards model to investigate factors associated with ESRD

| Variable | Univariate model HR (95% CI) | p-value |
|---|---|---|
| Age (per year) | 0.97 (0.96-0.98) | **<0.01** |
| Male | 0.93 (0.69-1.24) | 0.61 |
| Systolic blood pressure (per 1mmHg) | 0.99 (0.99-1.00) | 0.10 |
| Diastolic blood pressure (per 1mmHg) | 1.02 (1.01-1.04) | **<0.01** |
| Hypertension | 0.60 (0.35-1.01) | 0.05 |
| Diabetes mellitus | 0.60 (0.43-0.85) | **<0.01** |
| Past/current smoking history | 0.80 (0.60-1.07) | 0.14 |
| Myocardial infarction | 0.22 (0.08-0.61) | **<0.01** |
| Peripheral vascular disease | 0.59 (0.34-1.03) | 0.06 |
| Stroke | 0.72 (0.37-1.39) | 0.33 |
| Heart failure | 0.40 (0.19-0.82) | **0.01** |
| ACEi/ARB | 1.17 (0.82-1.67) | 0.39 |
| Statin | 0.81 (0.61-1.09) | 0.17 |
| eGFR (per 1ml/min/1.73m$^2$) | 0.98 (0.96-0.99) | **<0.01** |
| Bicarbonate (per 1mmol/L) | 0.96 (0.92-1.01) | 0.13 |
| Calcium (per 0.1mmol/L) | 0.55 (0.20-1.51) | 0.25 |
| Phosphate (per 0.1mmol/L) | 3.57 (1.64-7.78) | **<0.01** |
| Albumin (per 1g/L) | 1.00 (0.96-1.04) | 0.98 |
| Haemoglobin (per 1g/L) | 0.99 (0.98-1.01) | 0.78 |
| A3 proteinuria | 1.36 (1.01-1.83) | **0.04** |

**Table 5.3** Univariate analysis using Fine-Gray hazard model to investigate factors associated with mortality prior to ESRD

| Variable | Univariate model HR (95% CI) | p-value |
|---|---|---|
| Age (per year) | 1.07 (1.05-1.09) | **<0.01** |
| Male | 1.32 (0.86-2.03) | 0.21 |
| Systolic blood pressure (per 1mmHg) | 1.02 (1.01-1.03) | **<0.01** |
| Diastolic blood pressure (per 1mmHg) | 0.98 (0.97-0.99) | **0.03** |
| Hypertension | 3.04 (0.33-0.76) | 0.12 |
| Diabetes mellitus | 2.32 (1.51-3.57) | **<0.01** |
| Past/current smoking history | 1.59 (0.99-2.55) | 0.05 |
| Myocardial infarction | 3.70 (1.96-6.99) | **<0.01** |
| Peripheral vascular disease | 2.69 (1.57-4.61) | **<0.01** |
| Stroke | 1.93 (0.93-3.98) | 0.08 |
| Heart failure | 3.56 (2.13-5.96) | **<0.01** |
| ACEi/ARB | 0.61 (0.39-0.97) | **0.04** |
| Statin | 1.53 (0.97-2.42) | 0.07 |
| eGFR-EPI (per 1ml/min/1.73m$^2$) | 0.99 (0.98-1.02) | 0.65 |
| Bicarbonate (per 1mmol/L) | 1.02 (0.96-1.08) | 0.58 |
| Calcium (per 0.1mmol/L) | 1.56 (0.36-6.67) | 0.55 |
| Phosphate (per 0.1mmol/L) | 0.43 (0.16-1.14) | 0.09 |
| Albumin (per 1g/L) | 0.98 (0.95-1.01) | 0.25 |
| Haemoglobin (per 1g/L) | 0.98 (0.97-0.99) | 0.02 |
| A3 proteinuria | 0.75 (0.48-1.15) | 0.18 |

**Table 5.4** Subdistribution hazard ratios for the competing risks of ESRD and mortality based on a Fine-Gray model

| | **Mortality prior to ESRD** | | | **ESRD** | | |
|---|---|---|---|---|---|---|
| | Sub-HR | 95% CI | p-value | Sub-HR | 95% CI | p-value |
| Age | 1.06 | 1.04-1.08 | **<0.01** | 0.97 | 0.95-0.98 | **<0.01** |
| Male | 1.23 | 0.72-2.14 | 0.46 | 1.49 | 1.03-2.16 | **0.03** |
| SBP | 1.01 | 0.99-1.02 | 0.43 | 1.01 | 1.00-1.02 | 0.09 |
| DBP | 0.99 | 0.96-1.01 | 0.30 | 1.01 | 0.99-1.02 | 0.43 |
| Hypertension | 1.27 | 0.30-5.45 | 0.75 | 0.68 | 0.36-1.30 | 0.24 |
| Diabetes | 1.36 | 0.78-2.36 | 0.28 | 0.63 | 0.41-0.98 | **0.04** |
| Smoking | 1.46 | 0.82-2.59 | 0.20 | 0.89 | 0.62-1.29 | 0.55 |
| MI | 2.49 | 1.35-4.61 | **0.04** | 0.36 | 0.11-1.15 | 0.08 |
| CCF | 1.08 | 0.58-2.00 | 0.81 | 0.80 | 0.35-1.83 | 0.60 |
| Stroke | 1.00 | 0.38-2.64 | 0.99 | 0.67 | 0.30-1.52 | 0.34 |
| PVD | 1.22 | 0.63-2.33 | 0.56 | 0.98 | 0.53-1.83 | 0.95 |
| ACEi/ARB | 0.63 | 0.39-1.01 | 0.06 | 1.06 | 0.71-1.58 | 0.77 |
| Statin | 0.79 | 0.45-1.37 | 0.40 | 1.32 | 0.92-1.91 | 0.13 |
| eGFR | 1.01 | 0.98-1.03 | 0.48 | 0.96 | 0.94-0.97 | **<0.01** |
| Bicarbonate | 1.00 | 0.94-1.07 | 0.89 | 1.02 | 0.97-1.08 | 0.49 |
| Calcium | 0.92 | 0.22-3.87 | 0.91 | 0.48 | 0.15-1.48 | 0.20 |
| Phosphate | 0.38 | 0.10-1.42 | 0.15 | 3.15 | 1.29-7.67 | **0.01** |
| Albumin | 1.00 | 0.95-1.05 | 0.83 | 0.99 | 0.95-1.02 | 0.43 |
| Haemoglobin | 0.97 | 0.95-0.99 | **0.02** | 1.00 | 0.99-1.01 | 0.86 |
| A3 proteinuria | 0.58 | 0.34-1.00 | 0.05 | 1.00 | 0.71-1.42 | 0.99 |

### 5.4.3 Survival analysis comparing linear and non-linear progressors

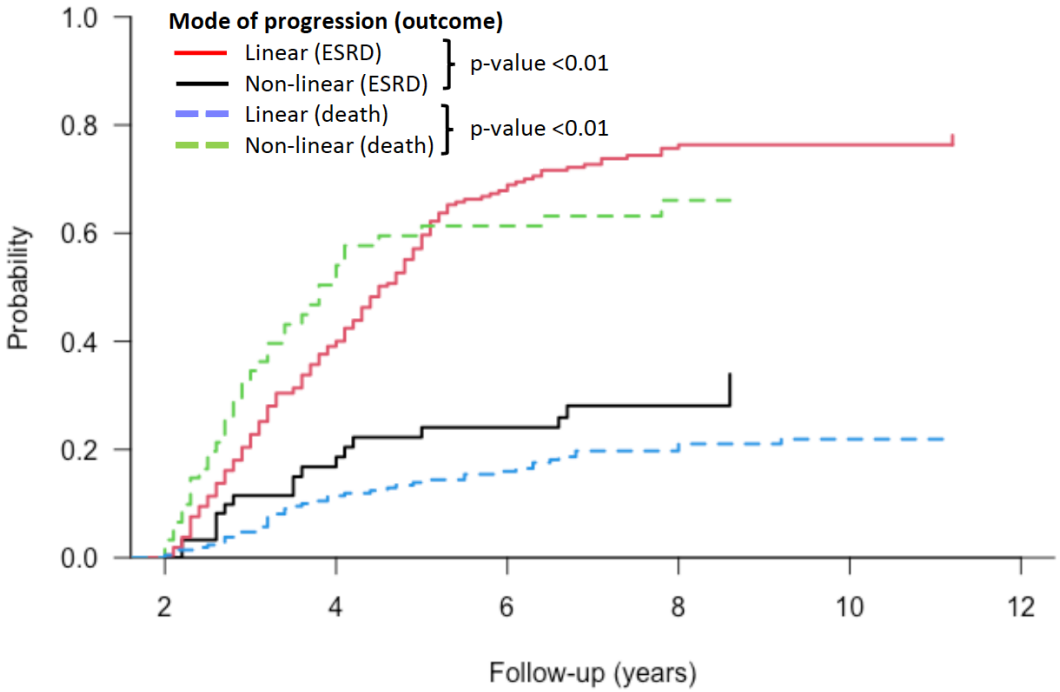
The study cohort had a median follow-up of 3.7 years (2.8-4.9 years), during which time there were 173 patients who reached ESRD and 81 patients who died prior to ESRD (Table 5.5).

**Table 5.5** Outcome data

| | **Rapid linear progressor (n=211)** | **Rapid non-linear progressor (n=61)** |
|---|---|---|
| ESRD, *n* (%) | 156 (76) | 17 (28) |
| Death prior to ESRD, *n* (%) | 43 (20) | 38 (62) |
| Under follow-up, *n* (%) | 9 (4) | 5 (8) |
| Care transferred to another hospital, *n* (%) | 3 (1) | 1 (2) |

Cumulative incidence function curves (Figure 5.3) revealed that rapid linear patients were more likely to develop ESRD compared to their non-linear counterparts (p-value<0.01), but that non-linear progressors suffered higher rates of death prior to ESRD (p-value<0.01). However, when the outcomes were combined as a single endpoint of either ESRD or mortality prior to ESRD (Figure 5.4), there was no statistical difference between rapid linear or non-linear progressors (p-value=0.08).

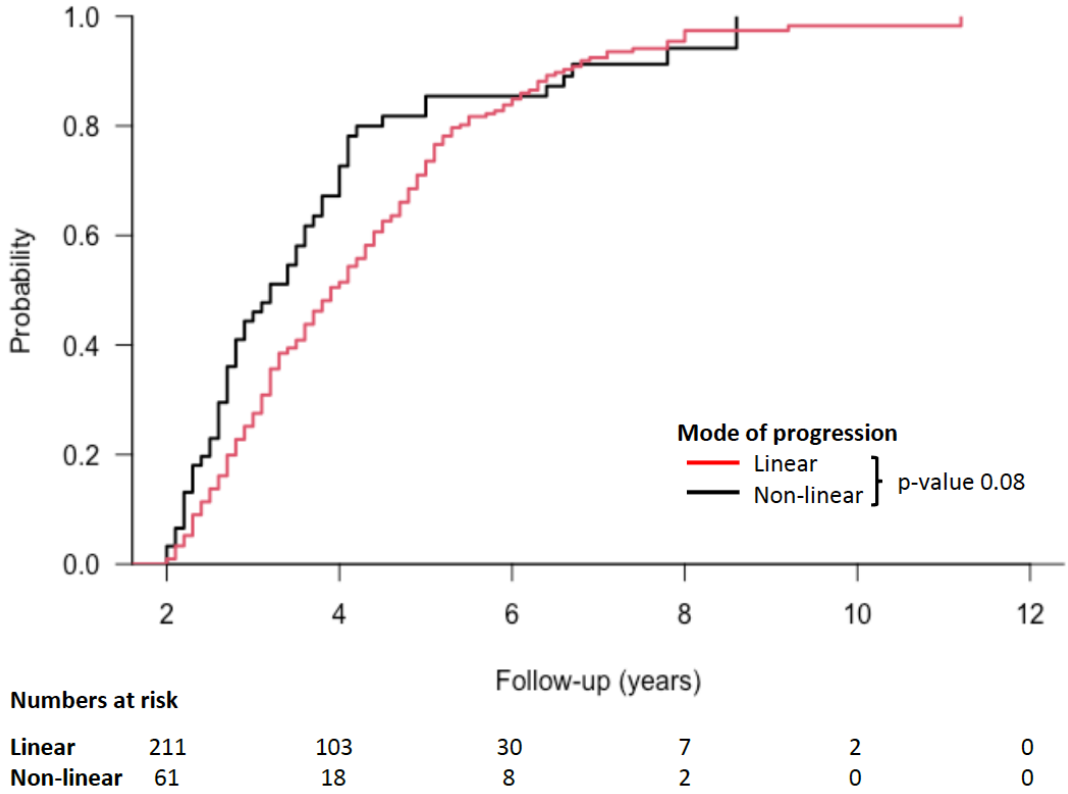
**Figure 5.3** Cumulative incidence functions for ESRD and death prior to ESRD compared between linear and non-linear progressors




**Numbers at risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Linear** | 211 | 103 | 30 | 7 | 2 | 0 |
| **Non-linear** | 61 | 18 | 8 | 2 | 0 | 0 |

**Figure 5.4** 1-Kaplan-Meier curves for probability of survival from the composite outcome of either ESRD or death prior to ESRD compared between linear and non-linear progressors




## 5.5 DISCUSSION

This study highlights the differential impact of the pattern of renal trajectory on adverse outcomes in patients with rapidly deteriorating renal function. Patients with rapid linear progression face higher rates of ESRD sooner whilst those with non-linear progression experience higher rates of mortality prior to ESRD.

### 5.5.1 Patterns of progression and determinants of adverse outcomes

Our cohort of rapid progressors was predominantly comprised of patients with linear progression, with only 22% of patients deemed to have non-linear progression. This corroborates with work by Weldegiorgis et al [11], who showed that the majority of the 3523 pooled patients with CKD from six randomised trials demonstrated linear eGFR decline. For instance, they reported a >50% probability of non-linear progression in

15.1% to 21.2% of patients from non-diabetic kidney trials and 19.3% to 31.7% in diabetic kidney trials.

With respect to the determinants of adverse outcomes, previous work has shown that younger age [12], male gender [13,14], lower eGFR [7] and higher phosphate [15] are all independently associated with ESRD, and this was borne out in our analysis. In addition, we found that older age [12], a history of MI [16-18], and anaemia [19] are significant determinants of mortality prior to ESRD, and these findings again align with the reported literature. Thus, in our cohort of clearly characterised linear and non-linear progressors, we show the expected overlap of predictive factors important to those who rapidly progress. However, we notably found a lack of diabetes to be predictive for ESRD and also found that A3 proteinuria was not predictive of worse outcomes in our analysis. These findings may likely be attributed to the specific disease characteristics in our population. Indeed, 20% of the entire cohort had ADPKD, of whom 87% reached ESRD. Of the 55 patients with ADPKD only 1 (2%) had diabetes and 8 (15%) were classed as having A3 proteinuria (data not shown), and this may have affected the impact of diabetes and A3 proteinuria on our outcomes in this cohort.

What is less well known is the association of the pattern of rapid CKD progression, either linear or non-linear, on outcomes such as ESRD and mortality. We hypothesised that rapid linear progressors would fare significantly worse than non-linear progressors, largely as a result of the inevitable culmination of ESRD in linear progressors, whereas potential fluctuating phases of stability may offer a degree of protection to those with non-linear renal decline. We discovered that whilst linear progressors do indeed reach ESRD sooner, non-linear patients were at a significantly greater risk of the competing event of death prior to ESRD.

Phenotypic differences between the two patient groups can help to unravel these findings. For instance, the primary renal disease in 26% of the rapid linear progressors was ADPKD, a condition typically characterised by a linear trajectory to ESRD [20], as a result of the unremitting enlargement of renal cysts that eventually destroy the normal renal architecture.

Furthermore, we found non-linear patients were significantly older, suffered from diabetes and cardiovascular co-morbidities, including MI, PVD and HF. It is conceivable that such patients experience non-linear fluctuations in renal function, including acute kidney injury (AKI), due to uncorrected alterations in their fluid status, as is seen in decompensated heart failure [21]. Additional adjustments to their medications with up-titration of diuretics or with ACEi and ARBs may also cause transient and abrupt eGFR decline. It is clear that the greater burden of cardiovascular disease and the propensity for outpatient AKI-on-CKD events [22] explains the increased mortality experienced by non-linear progressors observed in our cohort.

### 5.5.2 Clinical implications

In considering the pattern of CKD progression, we show how two distinct subtypes of rapid progression, linear and non-linear, affect outcomes differentially, which can be explained by differences in patient characteristics. This provides the basis for delivering personalised care to patients, dictated by their disease aetiology, risk factor profile and pattern of CKD progression, and highlights how in some patients the risk of death supersedes the need to prepare for ESRD [6]. This will no doubt influence the communication of risk imparted to patients and help direct the shape of future treatment. Further research in this area is of importance not least because patient heterogeneity for future adverse outcomes is not adequately captured within the current KDIGO staging for CKD, which is based on eGFR and urine albumin:creatinine ratio alone [7]. The future of precision medicine, therefore, relies upon the establishment of improved and refined models that can accurately risk stratify specific CKD patient subgroups.

However, whilst there are specific differences between linear and non-linear progressors with respect to outcomes, there was no survival difference in our analysis between the patients when combining the outcomes as a composite endpoint. Based on this, it is important to emphasise the risk conferred to patients from rapid renal decline *per se,* irrespective of the underlying pattern of progression. In effect, therefore, early identification of rapid progression should prompt close monitoring and aggressive risk factor modification to stabilise and curb a falling eGFR trajectory as best as possible.

Furthermore, this study highlights the significance of estimating ΔeGFR for predicting future outcomes. Indeed, in addition to the last eGFR level, the past eGFR trend has been shown to predict a patient's future risk of ESRD, especially those with advanced CKD in whom the absolute risk of ESRD is higher [23]. This raises the question as to whether ΔeGFR can be incorporated into current risk prediction tools such as the well-validated Kidney Failure Risk Equation (KFRE), which predicts the 2- and 5-year risk of ESRD in patients with CKD stage 3-5 [15]. However, given that it is equally relevant to reconcile whether death may be more likely than ESRD, the CKD Prognosis Consortium risk calculator provides the 2- and 4-year risk of ESRD as well as the risk of non-fatal cardiovascular events and death prior to ESRD in patients with CKD stage 4, and provides an estimation of the timing of these events in relation to ESRD [24]. Again, whether quantification of the ΔeGFR could improve the risk score in this prediction tool is an area for future research. Further work is also required to determine what time period the ΔeGFR should be assessed over. For instance, does inclusion of a patient's ΔeGFR calculated over the last year, last 2-years or over a longer time period improve predictive utility over current risk prediction models?

### 5.5.3 Strengths and limitations

This study extends our understanding of CKD progression by providing a closer examination of linear and non-linear patterns of rapid progression on future clinical endpoints. It is strengthened by a systematic approach to patient selection that characterises the CKD pattern robustly.

There are also limitations to our work. By its nature of being an observational study, we could not confirm causal association or fully account for unmeasured confounders. In addition, it is a single-centre study with a predominantly Caucasian population and thus the findings may not be generalisable to other patient populations.

## 5.6 CONCLUSIONS

Patients who progress rapidly are exposed to the dual threat of ESRD or mortality prior to ESRD. However, differences in patient characteristics exist between those who progress rapidly in a linear or non-linear fashion, and this has a significant bearing on observed future outcomes. Thus, the phenotypic risk factor profile and individual eGFR trajectory should provide the substrate for personalised therapeutic interventions in this highly vulnerable group of patients in order to deliver optimal CKD care.

## 5.7 REFERENCES


1. Ali I, Chinnadurai R, Ibrahim ST, et al. Predictive factors of rapid linear renal progression and mortality in patients with chronic kidney disease. BMC Nephrol. 2020;21:345.
2. Rosanksy SJ. Renal function trajectory is more important than chronic kidney disease stage for managing patients with chronic kidney disease. Am J Nephrol. 2012;36:1-10.
3. Collister D, Ferguson T, Komenda P, et al. The patterns, risk factors, and prediction of progression in chronic kidney disease: a narrative review. Semin Nephrol. 2016;36:273-282.
4. Caravaca-Fontán F, Azevedo L, Luna E, et al. Patterns of progression of chronic kidney disease at later stages. Clin Kidney J. 2018;11:246-253.
5. Li L, Astor BC, Lewis J, et al. Longitudinal progression trajectory of GFR among patients with CKD. Am J Kidney Dis. 2012;59:504-512.
6. Sumida K, Kovesdy CP. Disease trajectories before ESRD: implications for clinical management. Semin Nephrol. 2017;37:132-143.
7. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011;80:17–28.
8. Agarwal R, Duffin K, Laska DA, et al. A prospective study of multiple protein biomarkers to predict progression in diabetic chronic kidney disease. Nephrol Dial Transplant. 2014;29:2293-2302.
9. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. J. Am. Stat. Assoc. 1999;94:496-509.
10. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat. 1988;16:1141-1154.
11. Weldegiorgis M, de Zeeuw D, Li L, et al: Longitudinal estimated GFR trajectories in patients with and without type 2 diabetes and nephropathy. Am J Kidney Dis. 2018;71:91-101.
12. Levin A, Djurdjev O, Beaulieu M, et al. Variability and risk factors for kidney disease progression and death following attainment of stage 4 CKD in a referred cohort. Am J Kidney Dis. 2008;52:661-671.

13. Eriksen BO, Ingrebetsen OC. The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int. 2006;69:375-382.
14. Rebholz CM, Coresh J, Ballew SH, et al. Kidney failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: comparing ascertainment of treated and untreated kidney failure in a cohort study. Am J Kidney Dis. 2015;66:231-239.
15. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure. a meta-analysis. JAMA. 2016;315:164–174.
16. Potier L, Roussel R, Zeller M, et al. Chronic kidney disease, diabetes, and risk of mortality after acute myocardial infarction: insight from the FAST-MI program. Diabetes Care. 2020;43:e43-e44.
17. Shilpak MG, Heidenreich PA, Noguchi H, et al. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med. 2002;137:555-562.
18. Margolis G, Vig S, Flint N, et al. Prognostic implications of chronic kidney disease on patients presenting with ST-segment elevation myocardial infarction with versus without stent thrombosis. Cardiorenal Med. 2017;7:150-157.
19. Toft G, Heide-Jørgensen U, van Haalen H, et al. Anemia and clinical outcomes in patients with non-dialysis dependent or dialysis dependent severe chronic kidney disease: a Danish population-based study. J Nephrol. 2020;33:147–156.
20. Hunsicker LG, Adler S, Caggiula A, et al. Predictors of the progression of renal disease in the Modification of Diet in Renal Disease study. Kidney Int. 1997;51:1908-1919.
21. Rangaswami J, Bhalla V, Blair JEA, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment Strategies: a scientific statement from the American Heart Association. Circulation. 2019;139:e840-e878.
22. Yeh HC, Ting IW, Huang HC, et al. Acute kidney injury in the outpatient setting associates with risk of end-stage renal disease and death in patients with CKD. Sci Rep. 2019;9:17658.
23. Kovesdy CP, Coresh J, Ballew SH, et al. Past decline versus current eGFR and subsequent ESRD risk. J Am Soc Nephrol. 2016;27:2447-2455.

24. Grams ME, Sang Y, Ballew SH, et al. Predicting timing of clinical outcomes in patients with chronic kidney disease and severely decreased glomerular filtration rate. Kidney Int. 2018;93:1442–1451.

# CHAPTER 6

---

# A PARADIGM TO DISCOVER BIOMARKERS ASSOCIATED WITH CHRONIC KIDNEY DISEASE PROGRESSION

---

Ibrahim Ali, Sara T. Ibrahim, Rajkumar Chinnadurai, Darren Green, Maarten Taal, Tony D. Whetton, Philip A. Kalra

Biomarker Insights. 2020;15:1-5.

DOI: https://doi.org/10.1177/1177271920976146

## 6.1 ABSTRACT

Biomarker discovery in the field of risk prediction in chronic kidney disease (CKD) embraces the prospect of improving our ability to risk stratify future adverse outcomes and thereby guide patient care in a new era of personalised medicine. However, many studies that report biomarkers predictive of CKD progression share a key methodological limitation: failure to characterise patients' renal progression precisely. This weakens any observable association between a biomarker and an outcome poorly defined by a patient's change in renal function over time. In this commentary, we discuss the need for a better approach in this research arena and describe a compelling strategy that has the advantage of offering robust and meaningful biomarker exploration relevant to CKD progression.

## 6.2 INTRODUCTION

Chronic kidney disease (CKD) is a global health problem given that reduced glomerular filtration rate (eGFR) increases the risk of progressive renal decline, multi-organ complications, major cardiovascular events and all-cause mortality [1].

Accurately predicting which patients will experience deteriorating renal function is an important tenet to CKD care. Being able to determine the likely future eGFR trajectory would help to instigate timely treatment, potentially reduce the burden of adverse outcomes and optimise provision and planning for renal replacement therapy in patients at high-risk of progression. To meet the clinical need of better risk prediction tools, there has been significant interest in discovering novel biomarkers that could aid risk stratification, as well as provide new insights into unravelling CKD pathophysiology [2].

A plethora of studies have investigated a wide range of biomarkers, including those derived from proteomics [3-5], metabolomics [6] and genomics [7] that may help identify patients at risk of CKD progression. These studies, however, are heterogeneous in their study population, follow-up time and their definition of progression. Some define progression based on clinical endpoints such as progression to end-stage renal

disease, whilst others characterise patients based on an eGFR trajectory: either stable non-progressors or those with varying rates of progression determined by the change in eGFR over time. Different biomarkers have been shown to be associated with different endpoints [8] and so it is important to make this distinction clear.

In studies where CKD progression is defined by a change in eGFR over time, efforts to accurately define rates of progression face a number of challenges. For instance, changes in renal function may reflect episodes of acute kidney injury as opposed to true progression, and it is recognised that deterioration can be non-linear and episodic, with phases of stability interrupted by periods of eGFR decline. In addition, various interventions such as initiation or up-titration of prognostically beneficial reno-protective agents that block the renin-angiotensin system can cause the eGFR to reduce acutely but this may equate to slower renal decline in the long-term.

Recognising these limitations, guidelines from Kidney Disease Improving Global Outcomes (KDIGO) suggest two strategies to define a rate of CKD progression based on clinical utility [9]. The first is to assess the absolute change in renal function, requiring a change in GFR category with at least a 25% drop in eGFR from baseline. Alternative endpoints of doubling of creatinine or ≥30% decline in eGFR have also been proposed [10]. The second approach is to calculate the rate of eGFR change per year with a slope analysis. Both these methods, however, are still beset by two limiting factors: the number of available eGFR readings and the duration of a patient's follow-up. Indeed, some biomarker studies are prone to significant limitation by defining CKD progression based on only two eGFR measurements – one at baseline and one at follow-up [11,12]. This approach is limited by the problem of regression to the mean and raises two additional concerns: one, it assumes linear progression has occurred between two time points and, secondly, that if an acute change in eGFR has occurred, that it is non-reversible. It is conceivable that a biomarker discovered in this methodological construct may simply reflect an acute injury as opposed to being associated with genuine, long-term progressive decline (Figure 6.1).

**Figure 6.1** The limitation of biomarker testing to predict CKD progression using 2 eGFR samples (points A and B)

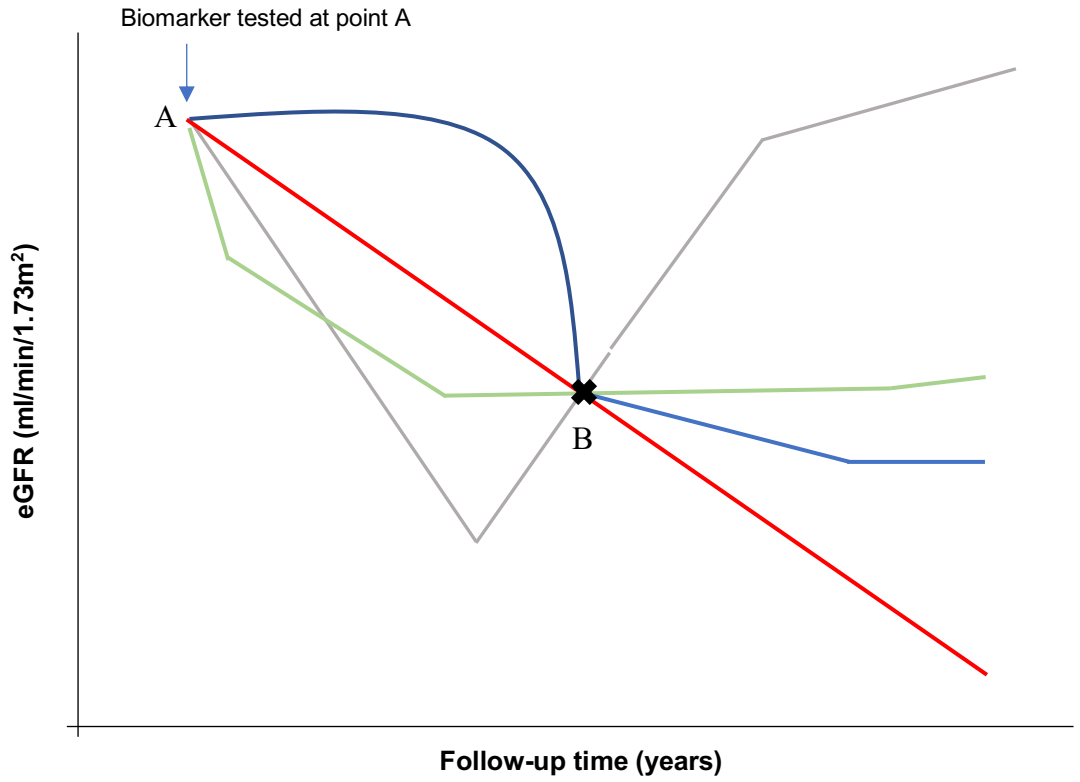
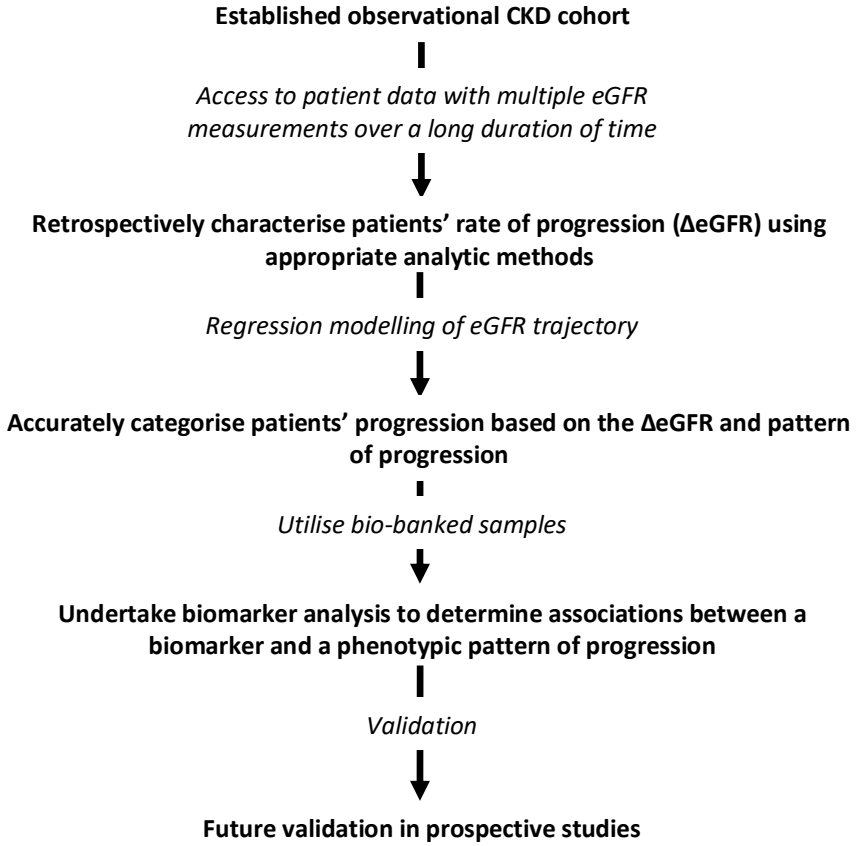



Figure 6.1 illustrates four different patients' modes of progression from point A to point B and beyond. The red line is indicative of progressive linear decline. The blue line highlights that point B was reached following an acute decline and thereafter the renal trajectory is one of a slower rate of decline. The green line shows different rates of decline between point A and B, followed by a phase of stability. The grey line shows an initial acute decline, but renal function is recovering when point B is reached and continues to do so beyond this point.

If a biomarker is tested at point A for all four patients and repeat eGFR was performed at point B, the biomarker signal at point A may be perceived to be associated with true CKD progression. However, it cannot accurately characterise changes in renal trajectory between point A and B and equally fails to take account of future CKD progression, limiting its clinical utility.

It is therefore important that efforts invested in biomarker profiling are matched equally by a rigorous approach to determining patients' phenotypic pattern of progression beforehand. Herein, we propose a new paradigm that overcomes methodological limitations in biomarker studies concerned with CKD progression (Figure 6.2). This paradigm relies upon harnessing data from established CKD cohorts, which provide an invaluable resource to identify patients in whom the pattern and rate of CKD progression can be accurately characterised using validated techniques, and which provides the means to undertake biomarker analysis in bio-banked samples during the course of patients' CKD progression.

**Figure 6.2** A paradigm for discovering biomarkers associated with CKD progression



## 6.3 TOWARDS A BETTER PARADIGM

### 6.3.1 Rates and patterns of CKD progression

Large, prospective CKD cohorts around the world (such as the Salford Kidney Study [13], the German CKD Study [14] or the Chronic Renal Insufficiency Cohort Study [15]) afford access to patients who have already undergone multiple eGFR measurements over many years of follow-up. This permits a retrospective assessment of detecting true CKD progression: the greater the number of measurements over a longer period of time, the greater the ability to define patients' eGFR trajectories. Although current recommendations suggest acquiring 4 eGFR measurements over 2 years [16], our own experience would advocate for a greater number of measurements over a longer period of time. Quantifying the rate of progression accurately is then achieved by applying validated analytic methods to define the rate of eGFR change over time ($\Delta$eGFR, ml/min/1.73m$^2$/yr). Some studies have relied upon an absolute change in eGFR or the percentage change in eGFR over time [5], but these methods assume linearity in kidney function. Indeed, previous studies have highlighted that patients progress in a variety of different patterns and trajectories [17-19]. For instance, O'Hare et a [19] showed 4 unique patterns of CKD progression in 5606 patients in the 2 years prior to initiation of dialysis, including slowly progressive patients with persistently low eGFR of <30ml/min/1.73m$^2$, progressive loss of eGFR from approximately 30-59ml/min/1.73m$^2$, accelerated eGFR decline in those with eGFR >60ml/min/1.73m$^2$ and those with catastrophic loss in function ≤6 months from eGFR levels >60ml/min/1.73m$^2$. Given renal trajectory can be heterogeneous, more sophisticated methods of characterising CKD trajectory ought to be employed including generalised estimation equations or linear mixed regression models, which can better handle non-linear trajectories, by taking account of the variability in the eGFR values, and the variable number of eGFR measurements and follow-up duration patients have [20,21].

Nonetheless, work by Weldegiorgis et al [22], who analysed data from 6 randomised controlled trials that included diabetic and non-diabetic patients with CKD, showed that the majority of the 3523 pooled patients in fact followed a linear pattern of eGFR decline. If patients with a linear pattern of progression are the focus of interest, especially given biomarker signals in these patients may have a stronger and more

accurate association with progression than in patients with non-linear progression, then a more systematic approach to determine eGFR trajectory may be required. In such cases, ordinary least squares linear regression can be first applied to all measured eGFR values for a patient to quantify the ΔeGFR. This should then be allied with a visual inspection of the eGFR-time graphs to help unmask those with non-linear progression. This latter step can be supplemented further by determining the 95% confidence interval (CI) of the ΔeGFR calculation, which can help indicate linearity – the smaller the CI, by definition, the greater the degree of linearity [23].

Fundamentally, having the ΔeGFR calculated using a robust methodological approach provides the foundations to meaningfully evaluate whether or not a distinct biomarker pattern exists in specific forms of CKD progression, and such information may provide insight into pathophysiological mechanisms driving progression. Patterns of progression could be defined by a combination of descriptive terms such as linear or non-linear, slow progressively or exponential decline (in parallel with patterns described by O'Hare et al) or simply rapid progressors, stable non-progressors or those with positively improving eGFR [24]. Categorisation of patients as a rapid progressor or a stable patient is based on pre-defined ΔeGFR cut-off values. KDIGO recommend defining rapid progression as those with a ΔeGFR of <-5ml/min/1.73m$^2$/yr (i.e., losing more than 5ml/min/1.73m$^2$/yr) [9], but adverse clinical outcomes have been shown to be associated with rates of <-3ml/min/1.73m$^2$/yr [25,26] and this ought to be the lowest threshold for ΔeGFR to define rapid progression. A ΔeGFR of -0.5 to +0.5ml/min/1.73m$^2$/yr can define stable patients, where stability is reflected in a ΔeGFR that centres on zero (i.e., no change in eGFR over time). More positive ΔeGFR values (for instance, a ΔeGFR >+0.5ml/min/1.73m$^2$/yr) could define those with improving renal function.

### 6.3.2 Existing cohorts offer a potential treasure trove for biomarker discovery

The paradigm relies on a retrospective method to select patients for future biomarker work, which specifically has two key advantages. Firstly, biomarkers can be tested in bio-banked samples in appropriately selected patients whose functional outcome is already known, enabling the question of whether the biomarker is associated with a specific pattern of CKD progression to be answered more confidently. Secondly, bio-banked samples also create enhanced opportunities for biomarker research, such as the

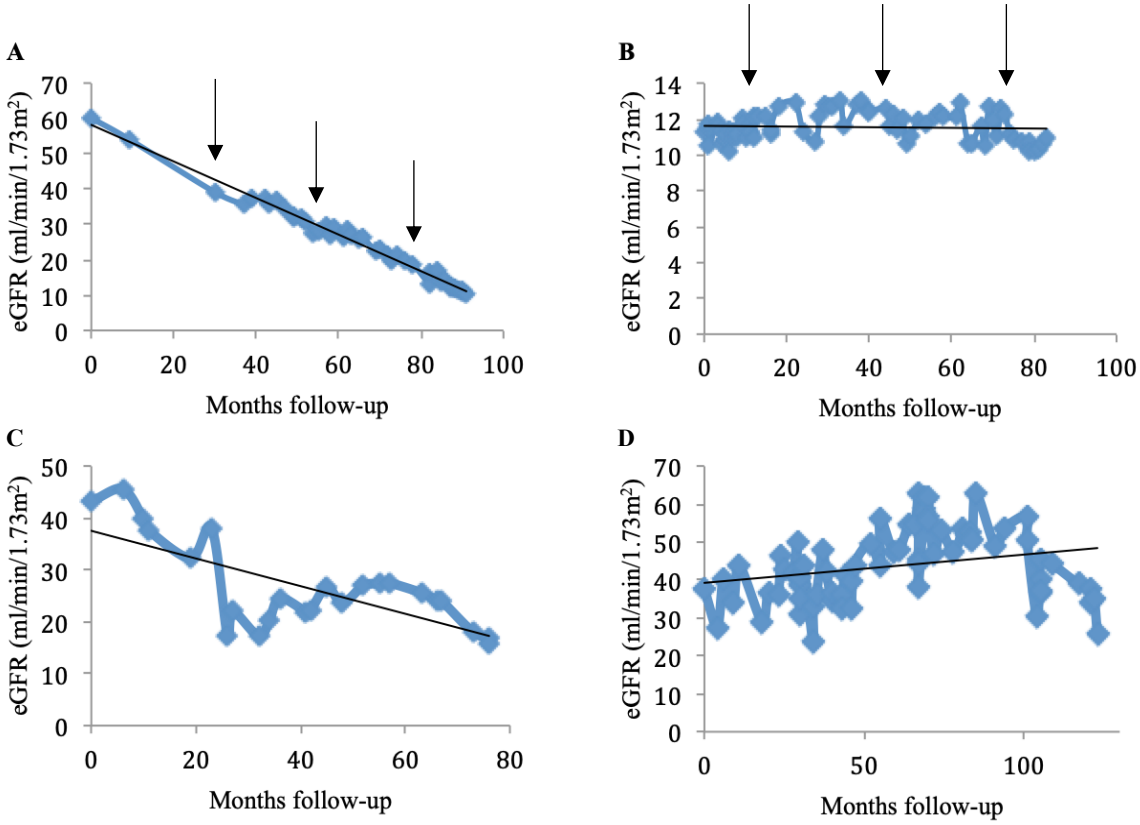
serial testing of a biomarker, especially at points of renal decline, where possible. This would overcome the limitation of attempting to attribute significance to biomarkers measured at baseline being associated with patients who have variable, non-linear progression. This approach therefore provides the means for further exploratory research: firstly, in assessing whether repeated biomarker measurements remain consistently present in those with linear forms of progression; secondly, whether a biomarker quantitatively changes with worsening renal function in those with rapid progression; and thirdly, in assessing if biomarker signals change when a patient experiences a change in renal trajectory. Biomarkers discovered in this retrospective manner would then ideally be validated by examining them in patients in future prospective studies to ascertain whether they are able to predict different rates of CKD progression.

Whilst there may be specific biomarkers that cannot be measured in this retrospective manner, and which may require evaluation with new studies, we would advocate for collaborative efforts to harness and uncover the potential treasure trove of biomarker discovery from the analysis of stored samples in existing cohorts. As a corollary, we would recommend for the routine ongoing collection and storage of bio-banked samples in ongoing studies to afford the means to accomplish future research using this paradigm.

We illustrate aspects of the paradigm concepts using illustrative examples of eGFR-time graphs in Figure 6.3. Each eGFR-time graph shows the changes in renal function over time for an individual patient within the Salford Kidney Study (SKS). The SKS is a prospective observational cohort study that has been recruiting non-dialysis dependent CKD patients since 2002. Any patient referred to the renal services at Salford Royal NHS Foundation Trust (a tertiary renal centre in the United Kingdom with a catchment population of 1.55 million) and is over 18 years old with an eGFR of <60ml/min/1.73m$^2$ is eligible for recruitment. Blood and urine sampling for routine clinical tests is performed at baseline and at subsequent clinic visits and is available throughout the patient journey via laboratory linkage to the electronic patient record. Further samples including EDTA whole blood, serum and citrate plasma are collected, centrifuged and bio-banked at -80$^o$C for future research. We present cases in Figure 6.3 where a consistent linear pattern of progression is sought in patients and how bio-banked

samples at various time-points in these patients' follow-up allow important biomarker evaluation to be undertaken.

**Figure 6.3** Illustrative eGFR-time graphs of individual patients to demonstrate the selection of patients with linear CKD progression into biomarker studies




Panels A to D highlight the eGFR-time graphs for 4 individual patients in the Salford Kidney Study.

In each case, the ΔeGFR has been calculated with linear regression with the specific aim of identifying patients with a linear, consistent pattern of progression, be it either stable or rapid (defined in this instance as a ΔeGFR of <-4ml ml/min/1.73m$^2$/yr) in nature. A linear regression line has been applied to all graphs. **A.** The linear ΔeGFR is -6.5ml/min/1.73m$^2$/yr (95% CI -6.7 to -6.2). Linear progression is clearly seen on the eGFR-time graph. Note also the small CI of 0.5ml/min/1.73m$^2$/yr, reflecting a strong degree of linearity of the eGFR values. **B.** The linear ΔeGFR is -0.2ml/min/1.73m$^2$/yr (95% CI -0.3 to -0.1) and stability is seen throughout follow-up. This patient could be defined as a 'stable patient'. Bio-banked samples in both patients A and patient B at

various times (highlighted by arrows) would provide the means to evaluate the differences in biomarkers between these two patients. Additionally, the opportunity to undertake longitudinal assessment of biomarkers within each patient (at each arrow) would provide valuable insight into whether changes occur to biomarkers over time. **C.** The linear ΔeGFR for this patient was -3.2ml/min/1.73m$^2$/yr (95% CI -4.6 to -1.8) but the graph reveals a fluctuating course in renal function. This patient would not be suitable for a study focused on linear progression specifically. **D.** The ΔeGFR is +0.15ml/min/1.72m$^2$/yr (95% CI -1.2 to +1.5), but similar to graph C, the eGFR varies widely over the follow-up period. Thus, the panels show how eGFR-time graphs can help visually substantiate the linear ΔeGFR or unmask non-linear progression.

## 6.4 CONCLUSION

Studies involved in CKD progression that define their outcome based on a change in renal function share a number of important limitations, especially a weak and imprecise characterisation of eGFR trajectory. There is a pressing need for more robust work with improved patient phenotype identification to help determine whether biomarkers offer clinical value. To that end, we recommend utilisation of currently established CKD cohorts that not only provides a means to accurately characterise a patient's eGFR trajectory but also offer new avenues in biomarker research using bio-banked samples at different points in a patient's CKD progression timeline.

## 6.5 REFERENCES


1. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011;80:17-28.
2. Ali I, Kalra P. Risk prediction in chronic kidney disease. Curr Opin Nephrol Hypertens. 2019;28:513–518.
3. Bolignano D, Lacquaniti A, Coppolino G, et al. Neutrophil gelatinase-associated lipocalin (NGAL) and progression of chronic kidney disease. Clin J Am Soc Nephrol. 2009;4:337–344.
4. Peralta CA, Katz R, Bonventre JV, et al. Associations of urinary levels of kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) with kidney function decline in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis. 2012;60:904–911.
5. Rodríguez-Ortiz ME, Pontillo C, Rodríguez M, et al. Novel urinary biomarkers for improved prediction of progressive eGFR loss in early chronic kidney disease stages and in high risk individuals without chronic kidney disease. Nature Scientific Reports. 2018;8:15980.
6. Zacharias HU, Altenbuchinger M, Schultheiss UT, et al. A novel metabolic signature to predict the requirement of dialysis or renal transplantation in patients with chronic kidney disease. J Proteome Res. 2019;18:1796–1805.
7. Lin BM, Nadkarni GN, Tao R, et al. Genetics of chronic kidney disease stages across ancestries: the PAGE study. Front Genet. 2019;10:494.
8. Agarwal R, Duffin K, Laska DA, et al. A prospective study of multiple protein biomarkers to predict progression in diabetic chronic kidney disease. Nephrol Dial Transplant. 2014;29:2293-2302.
9. KDIGO. Chapter 2: Definition, identification, and prediction of CKD progression. Kidney Int. 2013;3:63–72.
10. Levey AS, Inker LA, Matsushita K, et al. GFR Decline as an end point for clinical trials in CKD: A scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014;64:821-835.

11. Carlsson AC, Ingelsson E, Sundstrom J, et al. Use of proteomics to investigate kidney function decline over 5 years. Clin J Am Soc Nephrol. 2017;12:1226–1235.
12. Nkuipou-Kenfack E, Duranton F, Gayrard N, et al. Assessment of metabolomic and proteomic biomarkers in detection and prognosis of progression of renal function in chronic kidney disease. PLoS ONE. 2014;9:e96955.
13. NHS Health Research Authority. Salford Kidney Study. Available at: https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/salford-kidney-study/. [Accessed 4 August 2020].
14. German Chronic Kidney Disease. Available at: https://www.gckd.org. [Accessed 4 August 2020].
15. Chronic Renal Insufficiency Cohort Study. Available at: http://www.cristudy.org/Chronic-Kidney-Disease/Chronic-Renal-Insufficiency-Cohort-Study/. [Accessed 4 August 2020].
16. Levey AS, Inker LA, Matsushita K, et al. GFR Decline as an end point for clinical trials in CKD: A scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014;64:821-835.
17. Li L, Astor BC, Lewis L, et al. Longitudinal progression trajectory of GFR among patients with CKD. Am J Kidney Dis. 2012;59:504-512.
18. Caravaca-Fontán F, Azevedo L, Luna E, et al. Patterns of progression of chronic kidney disease at later stages. Clin Kidney J. 2018;11:246-253
19. O'Hare AM, Batten A, Burrows NR, et al. Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. Am J Kidney Dis. 2012;59:513-522.
20. Boucquemont J, Heinze G, Jager KJ, et al. Regression methods for investigating risk factors of chronic kidney disease outcomes: the state of the art. BMC Nephrol. 2014;14:45.
21. Sumida K, Kovesdy CB. Disease trajectories before ESRD: implications for clinical management. Semin Nephrol. 2017;37:132-143.
22. Weldegiorgis M, de Zeeuw D, Li L et al. Longitudinal Estimated GFR Trajectories in Patients With and Without Type 2 Diabetes and Nephropathy. Am J Kidney Dis. 2018;71:91-101.

23. Ali I, Chinnadurai R, Ibrahim ST et al. Predictive factors of rapid linear renal progression and mortality in patients with chronic kidney disease. BMC Nephrol. 2020;21:345.
24. Collister D, Ferguson T, Komenda P, et al. The patterns, risk factors, and prediction of progression in chronic kidney disease: a narrative review. Semin Nephrol. 2016;36:273-282.
25. Shlipak MG, Katz R, Kestenbaum B, et al. Rapid decline of kidney function increases cardiovascular risk in the elderly. J Am Soc Nephrol. 2009;20:2625-2630.
26. Matsushita K, Selvin E, Bash LD, et al. Change in estimated GFR associates with coronary heart disease and mortality. Clin J Am Soc Nephrol. 2009;20:2617-2624.

## CHAPTER 7

# A VALIDATION STUDY OF THE 4-VARIABLE AND 8-VARIABLE KIDNEY FAILURE RISK EQUATION IN TRANSPLANT RECIPIENTS IN THE UNITED KINGDOM

Ibrahim Ali, Philip A. Kalra

BMC Nephrol. 2021;22:57.
DOI: https://doi.org/10.1186/s12882-021-02259-4

## 7.1 ABSTRACT


### Background

There is emerging evidence that the 4-variable Kidney Failure Risk Equation (KFRE) can be used for risk prediction of graft failure in transplant recipients. However, geographical validation of the 4-variable KFRE in transplant patients is lacking, as is whether the more extensive 8-variable KFRE improves predictive accuracy. This study aimed to validate the 4- and 8-variable KFRE predictions of the 5-year death-censored risk of graft failure in patients in the United Kingdom.

### Methods

A retrospective cohort study involved 415 transplant recipients who had their first renal transplant between 2003 and 2015 and were under follow-up at Salford Royal NHS Foundation Trust. The KFRE risk scores were calculated on variables taken 1-year post-transplant. The area under the receiver operating characteristic curves (AUC) and calibration plots were evaluated to determine discrimination and calibration of the 4- and 8-variable KFREs in the whole cohort as well as in a subgroup analysis of living and deceased donor recipients and in patients with an eGFR <45ml/min/1.73m$^2$.

### Results

There were 16 graft failure events (4%) in the whole cohort. The 4- and 8-variable KFREs showed good discrimination with AUC of 0.743 (95% confidence interval [CI] 0.610-0.876) and 0.751 (95% CI 0.629-0.872) respectively. In patients with an eGFR <45ml/min/1.73m$^2$, the 8-variable KFRE had good discrimination with an AUC of 0.785 (95% CI 0.558-0.982) but the 4-variable provided excellent discrimination in this group with an AUC of 0.817 (0.646-0.988). Calibration plots however showed poor calibration with risk scores tending to underestimate risk of graft failure in low-risk patients and overestimate risk in high-risk patients, which was seen in the primary and subgroup analyses.

**Conclusions**

Despite adequate discrimination, the 4- and 8-variable KFREs are imprecise in predicting graft failure in transplant recipients using data 1-year post-transplant. Larger, international studies involving diverse patient populations should be considered to corroborate these findings.

## 7.2 BACKGROUND

Renal transplantation offers the best long-term outcomes for patients with end-stage renal disease (ESRD) [1-2]. However, despite advances in treatment to counter short-term transplant complications, many patients still experience late transplant decline and progression to graft failure [3]. In patients with a failing transplant, accurate risk stratification is important to prepare and inform the potential need for renal replacement therapy in a timely manner.

The Kidney Failure Risk Equation (KFRE) is the most extensively validated risk prediction tool for estimating the 2- and 5-year risk of ESRD in patients with chronic kidney disease (CKD) stages 3-5 [4]. The validation of this tool in transplant recipients has been undertaken in 3 studies to date. Two have assessed the 4-variable KFRE, which relies on age, gender, estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (uACR), in North American populations and has shown it can adequately prognosticate graft failure in patients surviving the first-year post-transplant [5,6]. Most recently, validation of the 4-variable KFRE has also been undertaken in a post-hoc analysis of the Folic Acid for Vascular Outcomes Reduction in Transplantation trial (FAVORIT) and comprised 2889 patients from cohorts in North America and one from Brazil [7]. This analysis also found that the 2- and 5-year risk of graft failure estimated by the 4-variable KFRE can provide adequate risk prediction, but the investigators raised concerns that the risk calculation was imprecise if it was undertaken using data within 2-years post-transplantation.

To date, what is not known is whether the 8-variable KFRE, which in addition to the 4-variable parameters comprises serum calcium, phosphate, bicarbonate and albumin, provides any further improvement to risk prediction in transplant recipients. In addition, further exploration on the accuracy of the KFRE at 1-year post-transplantation is

required. In this study, we sought to validate both the 4- and 8-variable KFREs for predicting the 5-year risk of graft failure in transplant recipients. In doing so, we aimed to 1) evaluate the KFREs for the first time, to the best of our knowledge, in a transplant population in the United Kingdom (UK); and 2) provide novel insight of the validity of the 8-variable KFRE in transplant recipients.

## 7.3 METHODS

### 7.3.1 Patient population

A single-centre retrospective cohort study was undertaken. All patients aged 18 years or more who had 1) received a renal transplant between 1st January 2003 and 31st July 2015 and were under follow-up at Salford Royal NHS Foundation Trust, and 2) had all measurements available for analysis approximately 1-year post-transplant (and limited up to 18 months post-transplant) were extracted from the hospital's electronic patient record. Patients who died or reached graft failure (defined as initiating haemodialysis, peritoneal dialysis or receiving another renal transplant) within 1-year of their first transplant were excluded.

### 7.3.2 Data variables

All variables for calculating the KFRE measured at least 1-year post-transplant were extracted from the hospital's electronic record for each patient. These variables enabled the 5-year risk of graft failure to be calculated using the published non-North American 4- and 8-variable KFREs (Appendix A1).

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Serum calcium and phosphate, both measured in mmol/L were converted to mg/dL by multiplying values by 4 and 3.1 respectively. Albumin, measured in g/L, was converted to g/dL by dividing values by 10. uACR was estimated from urine protein:creatinine ratio (uPCR) for all patients using a conversion calculation available online, which has been shown to provide good discrimination for use with the KFRE [8]. The uACR units of mg/mmol were switched to mg/g by multiplying values by 8.84. These conversions ensured the unit measurements aligned with the units used in the original development KFRE study [9].

### 7.3.3 Study outcome

Death-censored graft failure at 5 years from the point of the 1-year post-transplant measurements was the primary outcome. Outcome data was determined until 31st July 2020 to enable 5-year risk calculations for all patients.

### 7.3.4 Subgroup analyses

Given that the KFRE was originally developed to predict risk of ESRD in those with CKD stages 3a-5, a subgroup analysis was performed for patients with an eGFR <45ml/min/1.73m$^2$, a cut-off value shown to improve prediction performance [6]. The KFRE was also assessed separately in patients with living and deceased donors in the whole cohort and in those with an eGFR <45ml/min/1.73m$^2$.

### 7.3.5 Statistical analysis

For baseline characteristics, continuous data is presented as median (interquartile range) and categorical data as number (percentage). To compare the baseline characteristics between living and deceased donor recipients, p-values were calculated by Mann-Whitney test for continuous data and Chi-squared test for categorical data.

To assess the KFRE performance, the discrimination and calibration properties of the 4- and 8-variable KFRE risk scores were evaluated. Discrimination refers to the ability of a model to differentiate high-risk patients from low-risk patients. Receiver-operator characteristic (ROC) curves were created, and discrimination was defined by the area under the curve (AUC) along with 95% confidence intervals (CI). An AUC of 1.0 represents perfect discrimination whereas 0.5 means the model's ability to discriminate cases is no better than chance [10]. Good discrimination is characterised by an AUC of between 0.7-0.8 and excellent discrimination at values >0.8. Calibration refers to the extent the predicted scores agree with the actual observed data. This was assessed visually by a calibration plot, comparing the predicted risk on the x-axis (split into decile risk groups) with the observed proportion of events in each risk group on the y-axis [10]. Perfect calibration, whereby the predicted probabilities match the observed events, is characterised by an ideal line of 45°.

Statistical analyses were conducted using SPSS (Version 25.0) (IBM SPSS, Chicago, IL), licensed to the University of Manchester. A p-value of <0.05 was considered statistically significant.

### 7.3.6 Ethical approval

The study complies with the declaration of Helsinki and was registered with the Research and Innovation department of the Northern Care Alliance NHS Group (Ref: S20HIP57) who approved the methodological protocol as outlined above. As this was a retrospective observational study using measurements routinely collected and using fully anonymised data, the need for individual patient consent was waived by the Research and Innovation review committee, who granted study approval. The study was performed in accordance with the regulations outlined by the review committee.

The reporting of this validation study adheres to recommendations of the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement [11].

## 7.4 RESULTS

### 7.4.1 Patient characteristics

The inclusion criteria were met by 415 patients (Figure 7.1), for whom demographic and laboratory measures are provided in Table 7.1. The 1-year post-transplant laboratory measurements were taken at a median time-point of 1.07 years (1.03-1.19 years). The median age was 49.8 years (38.9-59.6 years) in the study cohort, which was predominantly Caucasian (88% of patients). The most common underlying disease aetiology was glomerulonephritis. The median eGFR was 54.1ml/min/1.73m$^2$ (41.6-70.5ml/min/1.73m$^2$) and 30% of patients with an eGFR <45ml/min/1.73m$^2$ comprised part of the subgroup analysis. Of the 415 patients, 97 (24%) were living donor recipients, who were younger in comparison to deceased donor recipients and had a statistically higher level of albumin, although the levels were within normal limits in both groups.

Within 5-years of follow-up, 16 patients reached the primary outcome of graft failure. A total of 35 patients died prior to graft failure and these patients were censored for the analysis. Table 7.2 compares the baseline characteristics of our cohort with the original KFRE development cohort.

**Figure 7.1** Assembling the study cohort

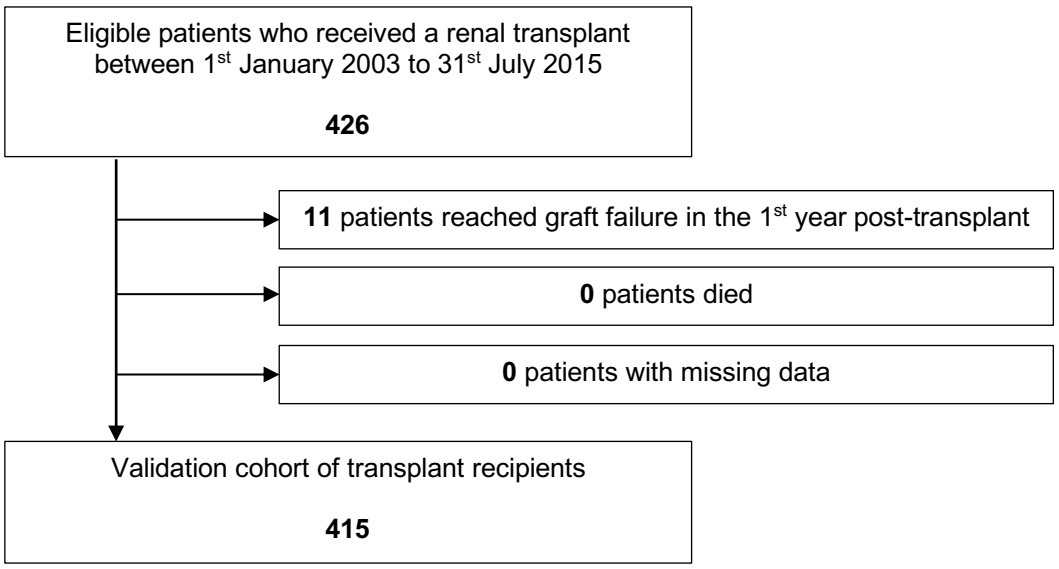


**Table 7.1** Characteristics of the study cohort 1-year post-transplant

| Variable | All patients (n=415) | Living donor recipient (n=97) | Deceased donor recipient (n=318) | p-value^ |
|---|---|---|---|---|
| Age, years | 49.8 (38.9-59.6) | 40.0 (30.7-53.3) | 51.2 (41.5-62.4) | **<0.001** |
| Male, *n* (%) | 244 (59) | 51 (53) | 174 (61) | 0.155 |
| Caucasian, *n* (%) | 352 (88) | 97 (100) | 311 (98) | 0.141 |
| Hypertension, *n* (%) | 383 (92) | 90 (93) | 293 (92) | 0.835 |
| Diabetes mellitus, *n* (%) | 48 (12) | 6 (6) | 42 (13) | 0.058 |
| | | | | |
| **Primary renal disease** | | | | |
| Glomerulonephritis, *n* (%) | 120 (29) | 35 (36) | 85 (27) | 0.075 |
| ADPKD, *n* (%) | 55 (13) | 14 (14) | 41 (13) | 0.695 |
| Diabetic nephropathy, *n* (%) | 44 (11) | 6 (6) | 38 (12) | 0.106 |
| Hypertensive nephropathy, *n* (%) | 21 (5) | 5 (5) | 16 (5) | 0.961 |
| | | | | |
| **Laboratory values** | | | | |
| *eGFR, ml/min/1.73m$^2$ | 54.1 (41.6-70.5) | 58 (46-75) | 53 (40-70) | 0.114 |
| eGFR<45ml/min/1.73m$^2$, *n* (%) | 125 (30) | 24 (25) | 104 (33) | 0.137 |
| †uACR, mg/g | 22.1 (11.5-65.4) | 23.9 (12.4-68.1) | 21.2 (12.4-64.5) | 0.473 |
| ‡Calcium, mg/dL | 9.44 (9.1-9.9) | 9.40 (9.08-9.80) | 9.48 (9.12-9.96) | 0.151 |
| ‡Phosphate, mg/dL | 2.88 (2.43-3.31) | 2.88 (2.45-3.38) | 2.85 (2.42-3.31) | 0.917 |
| Bicarbonate, mEq/L | 22.8 (21.2-25.0) | 22.6 (21.3-23.8) | 23.0 (21.2-25.4) | 0.185 |
| ¶Albumin, g/dL | 4.4 (4.2-4.6) | 4.5 (4.4-4.7) | 4.4 (4.2-4.6) | **0.004** |
| | | | | |
| **Outcome** | | | | |
| Graft failure within 5 years, *n* (%) | 16 (4) | 6 (6) | 10 (3) | 0.173 |
| Time to graft failure, years | 3.51 (2.87-4.19) | 3.14 (2.86-3.94) | 3.62 (3.02-4.14) | 0.588 |

Continuous data are presented as median (interquartile range) and categorical as number (percentage).

^P-values calculated by Mann-Whitney test for continuous data and Chi-squared test for categorical data, comparing living with deceased donor recipients. A p-value of <0.05 was considered statistically significant. *eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. †urine albumin:creatinine ratios were acquired by converting urine protein:creatinine ratios using an online calculator [5] and thereafter switching units from mg/mmol to mg/g by multiplying values by 8.84. ‡Calcium and phosphate were measured in mmol/L and converted to mg/dL by multiplying values by 4 and 3.1 respectively. ¶Albumin was measured in g/L and converted to g/dL by dividing by 10.

**Table 7.2** Comparison of the study cohort to the KFRE development cohort

| | **Validation cohort in transplant recipients (n = 415)** | **Original KFRE development cohort (n = 3449)** |
|---|---|---|
| **Age, years** | 49 (14) | 70 (14) |
| **Female, *n* (%)** | 171 (41) | 1503 (44) |
| **eGFR, ml/min/1.73m$^2$** | 57 (22) | 36 (13) |
| **Serum bicarbonate, mEq/L** | 23 (3) | 26 (4) |
| **Serum calcium, mg/dL** | 9.5 (0.7) | 9.4 (0.6) |
| **Serum phosphate, mg/dL** | 2.9 (0.7) | 4.0 (0.9) |
| **Serum albumin, mg/dL** | 4.4 (0.3) | 4.0 (0.5) |
| **Urine albumin:creatinine ratio, mg/g** | 102 (264) | 93 (378) |
| **Outcome events of graft failure, *n* (%)** | 16 (4) | 386 (11) |

Continuous data is presented as mean (standard deviation) except for urine albumin:creatinine ratio, which is shown as median (interquartile range).

### 7.4.2 KFRE performance: discrimination

A summary of the AUCs for the 4- and 8-variable KFREs is shown in Table 7.3. The 4- and 8-variable KFREs showed good discrimination with AUC values of 0.743 (95% CI 0.610-0.876) and 0.751 (95% CI 0.629-0.872) respectively. In patients with an eGFR <45ml/min/1.73m$^2$, the 4-varible KFRE had excellent discrimination (AUC 0.817, 95% CI 0.646-0.988) whilst the 8-variable KFRE also demonstrated good discriminatory ability in these patients and had a slightly better AUC of 0.785 (95% CI 0.558-0.982) compared with the 8-variable KFRE in the entire cohort of 0.751 (95% CI 0.629-0.872).

**Table 7.3** Summary of discrimination statistics for the 4- and 8-variable KFREs

| | Number in group | Graft failure, *n* (%) | 4-variable KFRE AUC (95% CI) | 8-variable KFRE AUC (95% CI) |
|---|---|---|---|---|
| **All patients** | 415 | 16 (4) | 0.743 (0.610-0.876) | 0.751 (0.629-0.872) |
| **Patients with eGFR<45ml/min/1.73m$^2$** | 128 | 9 (7) | 0.817 (0.646-0.988) | 0.785 (0.558-0.982) |
| **Deceased donor recipient** | 318 | 10 (3) | 0.685 (0.503-0.868) | 0.707 (0.544-0.870) |
| **Living donor recipient** | 97 | 6 (6) | 0.846 (0.683-1.000) | 0.841 (0.684-0.997) |
| **Deceased donor recipient eGFR <45ml/min/1.73m$^2$** | 104 | 5 (5) | 0.846 (0.663-1.000) | 0.800 (0.558-1.000) |
| **Living donor recipient eGFR <45ml/min/1.73m$^2$** | 24 | 4 (17) | 0.787 (0.471-1.000) | 0.762 (0.453-1.000) |

### 7.4.3 KFRE performance: calibration

The calibration plots shown in Figure 7.2 reveal inadequate calibration for the 4- and 8-variable KFREs in the transplant cohort: compared with the perfect calibration slope of 45°, there was a tendency for both the 4- and 8-variable KFREs to underestimate the risk scores at lower risk scores and over-estimate risk in higher risk patients, which was seen within the whole cohort and in those with an eGFR <45ml/min/1.73m$^2$.

### 7.4.4 Donor type subgroup analysis

For the subgroup analysis of living and deceased donor recipients there were 6 outcome events in those with living donors and 10 events in those with deceased donors. The 4- and 8-variable KFREs demonstrated poorer discriminative ability in deceased donor recipients compared to living donor recipients in the whole cohort, but this was improved in those with an eGFR <45ml/min/1.73m$^2$ (Table 7.3). Calibration plots, however, revealed that the 4- and 8-varibale KFREs were imperfect in both living and deceased donor groups (Figure 7.3) and remained so when further stratified to those with an eGFR<45ml/min/1.73m$^2$ (Figure 7.4).

**Figure 7.2** Calibration plots for the 4- and 8-variable KFREs in transplant recipients

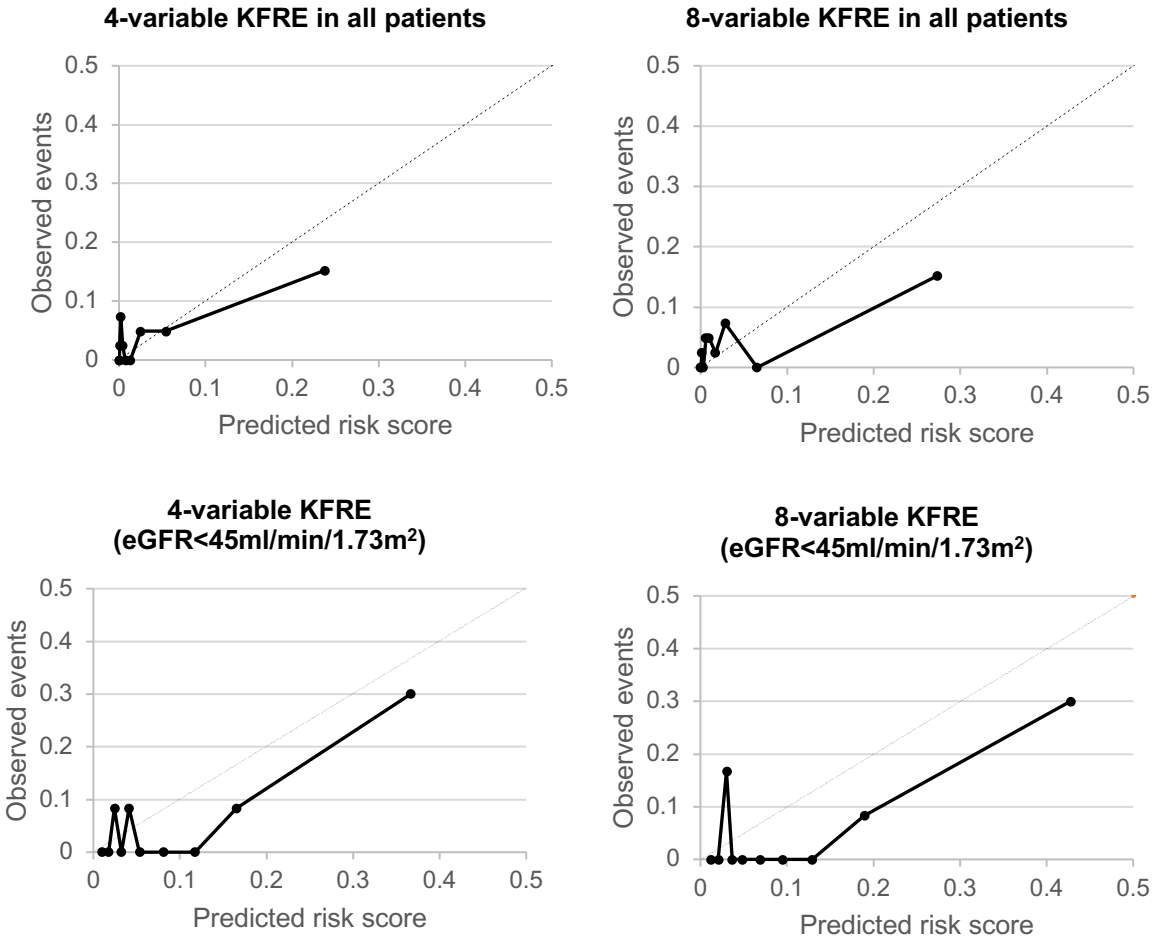


**Figure 7.3** Calibration plots for the 4- and 8-variable KFREs in living and deceased donor recipients

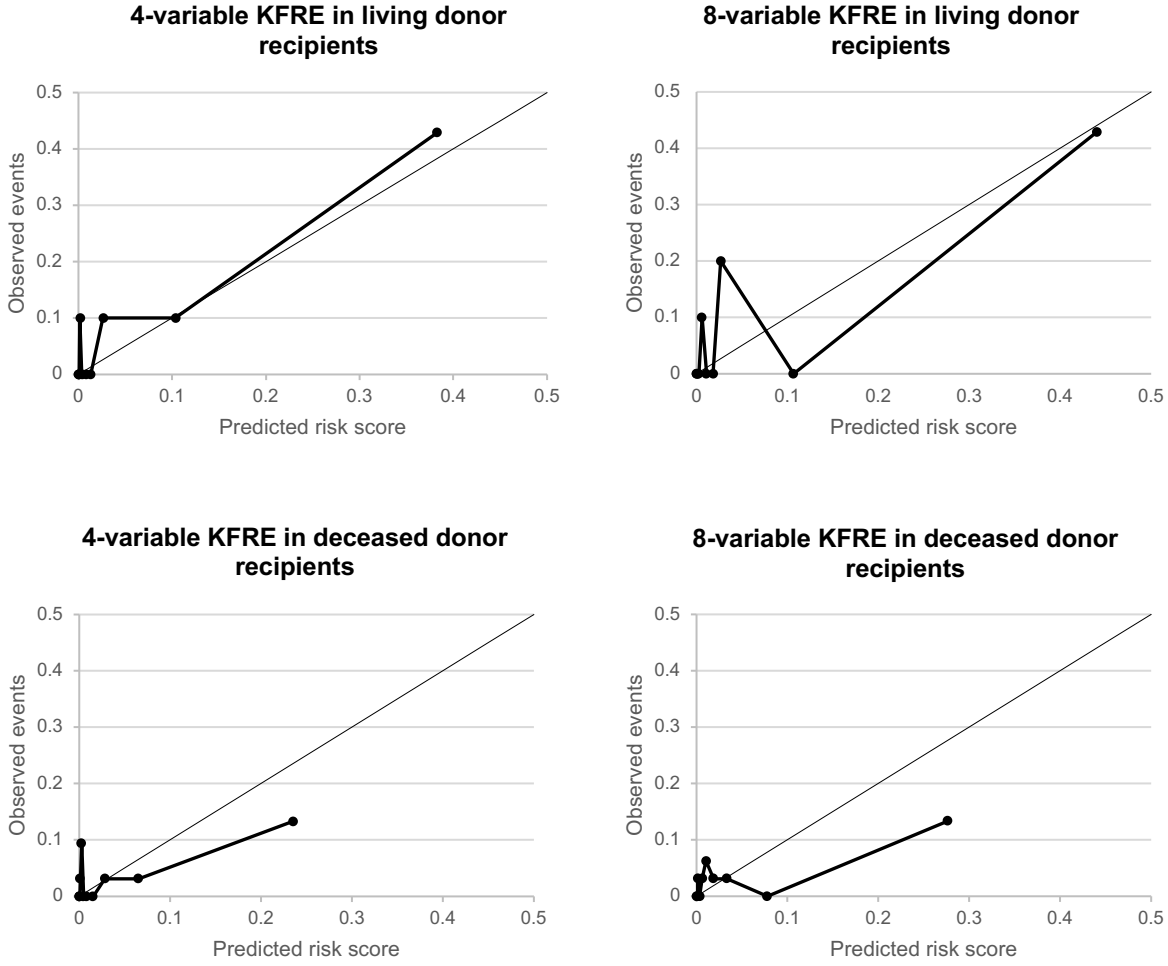
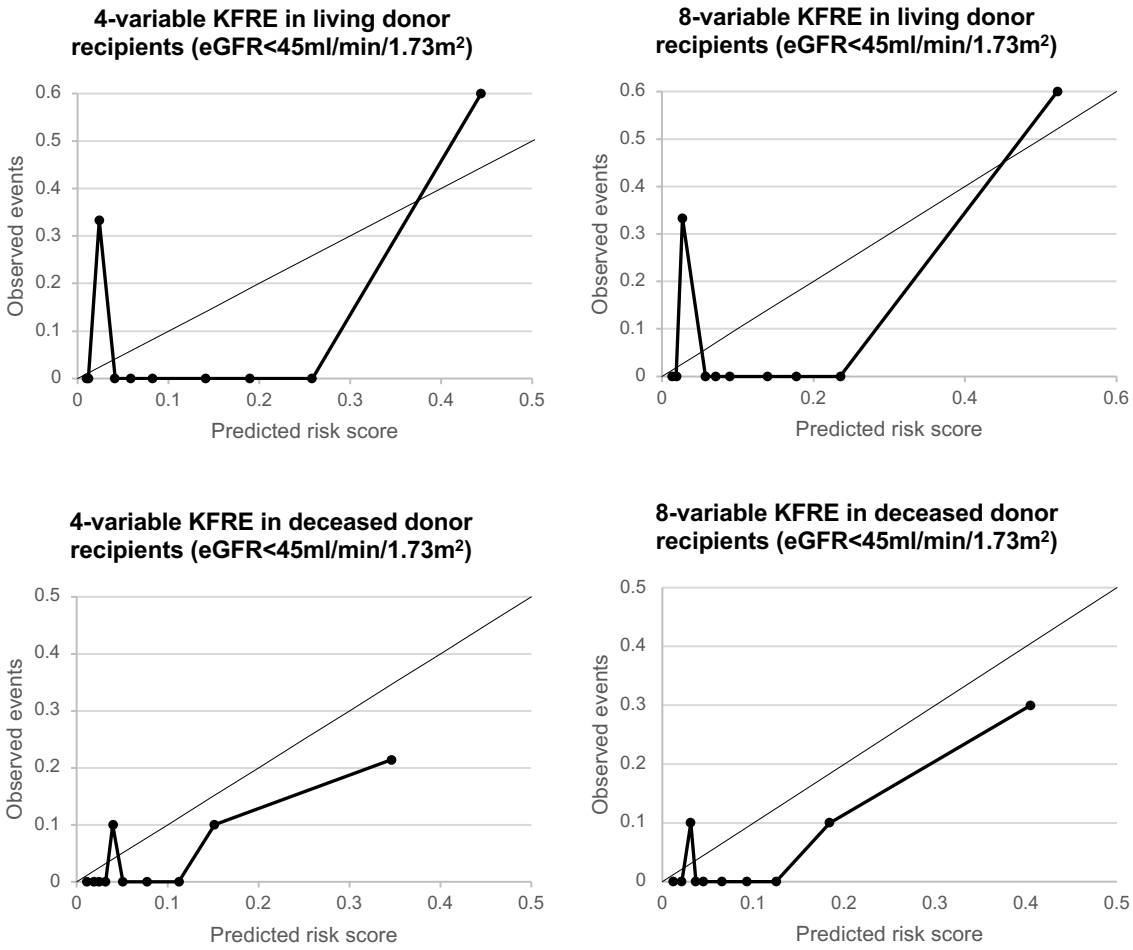


**Figure 7.4** Calibration plots for the 4- and 8-variable KFREs in living and deceased donor recipients (eGFR <45ml/min/1.73m$^2$)



## 7.5 DISCUSSION

This validation study highlights that the 4- and 8-variable KFREs have adequate discriminative ability in predicting the 5-year risk of graft failure in transplant recipients surviving 1-year post-transplant but that they were imprecise with respect to calibration and had a tendency to underestimate risk in low-risk patients and overestimate risk in high-risk patients.

### 7.5.1 Comparison with other validation studies using the KFRE

The discriminatory ability of the 4-variable KFRE in our study is in keeping with recently published studies. For instance, Akbari et al [5] validated the 4-variable KFRE in 877 transplant patients and found the AUC of the 5-year risk of graft failure (based on values taken 1-year post-transplant) to be 0.72 (95% CI 0.69-0.79) in the whole cohort. Similarly, Tangri et al [6] reported a pooled C-statistic (a measure identical to the AUC for a binary outcome) of 0.73 (95% CI 0.67-0.80) based on data from four different patient cohorts in Canada. These figures align closely with our finding of an AUC of 0.743 (95% CI 0.610-0.876) for the 4-variable KFRE. In addition, Tangri et al [6] also showed that the pooled C-statistic increased to 0.83 (95% CI 0.74-0.91) when the KFRE was applied to transplant patients with an eGFR <45ml/min/1.73m$^2$, and this excellent discrimination is reproduced in our cohort with an AUC of 0.817 (95% CI 0.646-0.988) for the 4-variable KFRE. Similarly, in the recent post-hoc analysis of the FAVORIT trial [7] (in which only patients with eGFR <60ml/min/1.73m$^2$ were included), Chu et al found an overall C-statistic of 0.81 (95% CI 0.78-0.84). Whilst they did not undertake a subgroup analysis in patients with an eGFR <45ml/min/1.73m$^2$, 60.7% of their cohort fell into this eGFR category, highlighting the KFRE demonstrates improved discrimination in patients with more advanced transplant dysfunction.

We show for the first time that the 8-variable KFRE also demonstrated good discrimination in the whole cohort, and although this improved in patients with an eGFR <45ml/min/1.73m$^2$, it was outperformed by the 4-variable KFRE in this latter group of patients. These differences are likely explained from the incorporation of extra variables in the 8-variable KFRE, such as calcium, phosphate and bicarbonate, which may not offer significant prognostic utility in transplant recipients. In contrast, lower

albumin levels at 1-year post-transplant, perhaps reflective of underlying inflammation, have been shown to prognosticate transplant failure [12,13], and the inclusion of this parameter may explain the slightly better discrimination seen with the 8-variable equation within the whole cohort as compared with the 4-variable KFRE.

However, with respect to calibration, we found the 4- and 8-variable KFREs did not accurately predict observed events. Importantly, miscalibration was demonstrated in the studies by Tangri et al [3] and Chu et al [7]. In the latter study, the calibration plots for the 5-year 4-variable KFRE consistently showed an underestimation of risk scores in lower risk patients and overestimation of risk in higher risk patients. This effect was particularly noticeable in patients who had been transplanted for less than 2-years and was the rationale behind the authors' recommendation to use measurements taken 2-years post-transplant as opposed to 1-year post-transplant when making KFRE calculations. It is also interesting that Akbari et al [5] found the highest AUC of 0.87 (95% CI 0.83-0.90) when 2-year post-transplant measurements were taken to calculate the KFRE in patients with an eGFR <60ml/min/1.73m$^2$, compared to 0.76 (95% CI 0.72-0.80) when utilising 1-year post-transplant variables. However, the authors did not report calibration of the KFRE in their study so further work will be necessary to resolve the matter of what time-point post-transplant the KFRE can offer its best predictive performance.

In our subgroup analysis of patients receiving transplants from living and deceased donors, we show the AUC of both the 4- and 8-variable KFREs was higher in living donor recipients compared with deceased donor recipients in the whole cohort. Our findings suggest that donor type affects the ability of the KFRE to risk predict, in contrast to work by Akbari et al [5] and Chu et al [7], who both found performance of the KFRE to be similar between living and deceased donor recipients. Phenotypically, the living donor recipients were significantly younger and had higher levels of albumin compared to their deceased donor counterparts, but these variables alone are not sufficient to explain the differential performance of the KFRE. Certainly, living donor recipients are known to have better graft outcomes compared to deceased donor recipients [14] and therefore it is conceivable that transplant-specific differences in our cohort could account for this discrepancy. The weaker discriminative ability in deceased donor recipients was reversed when our analysis focussed on those with an eGFR

<45ml/min/1.73m$^2$ in this group, further highlighting the dependency on eGFR levels on the KFRE risk performance. The favourable discrimination performance, however, was countered by imprecise calibration in this subgroup analysis, likely attributed to the small number of events in the donor groups.

### 7.5.2 Clinical implications

The discrimination performance of the KFRE in our study cohort aligns with other transplant-specific calculators developed to predict graft failure [15], especially for patients with an eGFR <45ml/min/1.73m$^2$. For instance, Shabir et al [13] developed a model predicting the 5-year risk of death-censored graft failure and overall graft failure including death, and this comprised sex, ethnicity, and the 1-year post-transplant variables of age, eGFR, uACR, serum albumin and a prior episode of acute rejection. The model validated well in 4 external cohorts with C-statistics for death-censored graft failure ranging from 0.78 to 0.90. A more recent and promising model that has surfaced is the iBox prediction score [16]. This comprises eight functional, histological and immunological variables to predict the 3-, 5- and 7-year risk of graft failure in transplant recipients. A key strength of this model is the extent of external, geographical validation involving 3557 transplant patients across Europe and America and has shown excellent discrimination with a C-statistic of 0.81 (95% CI 0.78 – 0.84) in Europe and 0.80 (95% CI 0.76 – 0.84) in America.

Factors such as eGFR and uACR are clearly important predictors of graft failure and thus the KFRE offers an attractive tool for risk prediction given it is an easy-to-use tool, utilises accessible measures, negates the need for histological data and can be incorporated into electronic health systems to provide rapid risk estimation. However, calibration performance cannot be ignored and is often considered the more essential element of a risk prediction tool [10]. Reasons for miscalibration are typically due to differences in the predictor variables between the validation and development cohort as well as differences in the incidence of the outcome event [17]. Our cohort had a low event rate of 16 patients with graft failure and this likely contributed to miscalibration. Nonetheless, the KFRE is clearly limited in precision given that it was originally developed for use in non-transplant patients with CKD stages 3a-5, and hence ignores other factors known to drive transplant deterioration such as human leucocyte antigen mismatching, delayed graft function, episodes of rejection, development of donor

specific antibodies, recurrence of primary disease and transplant glomerulopathy [14]. Interestingly, Chu et al [7] show that the KFRE performance improves in patients 2-years post-transplant, suggesting that early complications such as delayed graft function or rejection predisposing to graft failure may impact the KFRE predictive performance. For now, we would argue that pending further studies on the role that the KFRE offers to transplant risk prediction, clinicians should rely on well-validated transplant-specific algorithms to guide personalised management, such as the iBox tool, which is not limited in performance by eGFR level and can be used for risk evaluation at any point 10 years post-transplant [16].

### 7.5.3 Strengths and limitations

We show for the first time the predictive performance of the 8-variable KFRE in transplant recipients, which had been previously postulated as offering better risk prediction than the 4-variable KFRE [5]. We show that whilst the 8-variable KFRE offers good overall discrimination, it is not as strong as the 4-variable KFRE in patients with an eGFR <45ml/min/1.73m$^2$, likely as a result of lack of predictor power offered by variables such as calcium, phosphate or bicarbonate. This study also delivers for the first time an independent, geographical validation of the KFRE in transplant patients in a UK-based cohort, and corroborates findings previously shown in other cohorts, namely that whilst discrimination is adequate, calibration is imprecise when using 1-year post-transplant variables.

Our study also has important limitations. Firstly, our cohort was small and the event rate low and this likely affected calibration of the KFREs in the whole cohort and subgroup analyses. The sample size in a validation study is determined by the outcome event rate but the adequate number of events to permit analysis remains unclear and there is no universally agreed approach in this regard [18]. What is perhaps relevant for validation studies involved with transplant patients is the recognition that the 5-year rates of graft failure would be expected to be generally low. In the UK, the national average for the 5-year graft failure rate combining both deceased and living donor recipients is approximately 11% based on the 2019 report by the National Health Service Blood and Transport health authority [19]. From the studies in the literature that report the proportion of 5-year events in patients with 1-year post-transplant KFRE calculations, rates are typically less than 10%: Akbari et al [5] reported 37 events in their single-

centre study, which was 4.2% of the whole cohort; Tangri et al [6] evaluated 4 separate cohorts consisting of 19 (4.1%), 36 (3.8%), 52 (5.2%) and 116 (9.2%) events; and Chu et al [7] reported a total of 49 (6.0%) events. Thus, whilst our sample size is small, our event rate of 4% is nonetheless similar to previously published studies. Secondly, we were unable to provide the 2-year KFRE risk scores of graft failure as there were no outcome events in this time period. Thirdly, we were required to convert the uPCR to uACR for all the study patients and this may have had an effect on the predicted risk scores. However, many institutions continue to rely on uPCR measurements, and a validated conversion tool now exists as an online calculator [8] to provide a means to obtain reliably converted albuminuria values. Finally, our patient population was derived from a single centre and were largely Caucasian, which limits the generalisability of our findings to other ethnically diverse populations.

## 7.6 CONCLUSIONS

At 1-year post-transplant, the 4- and 8-variable KFREs provide adequate discrimination for predicting graft failure in transplant recipients, especially in those with an eGFR <45ml/min/1.73m$^2$. However, due to imprecise calibration, their overall predictive performance is limited, and it is likely relevant that these equations do not take transplant-specific variables, such as rejection episodes, into consideration. Additional validation studies of the KFRE using larger, international transplant cohorts would be desirable to corroborate our findings. Future studies should also consider exploring the time-point post-transplant the KFRE offers optimal risk prediction as this would help gauge the potential role the KFRE could play in future transplant care.

## 7.7 REFERENCES


1. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first deceased-donor transplant. N Engl J Med. 1999;341:1725–1730.
2. Kaballo MA, Canney M, O'Kelly P, et al. A comparative analysis of survival of patients on dialysis and after kidney transplantation. Clin Kidney J. 2018;11:389-393.
3. Raynaud M, Aubert O, Reese PP, et al. Trajectories of glomerular filtration rate and progression to end stage kidney disease after kidney transplantation. Kidney Int. 2021;99:186-197.
4. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure: A Meta-analysis. JAMA. 2016;315:164-174.
5. Akbari S, Knoll G, White CA, et al. Accuracy of Kidney Failure Risk Equation in transplant recipients. Kidney Int Rep. 2019;4:1334-1337.
6. Tangri N, Ferguson TW, Wiebe C, et al. Validation of the Kidney Failure Risk Equation in kidney transplant recipients. Can J Kidney Health Dis. 2020;7:1-9.
7. Chu CD, Ku E, Fallahzadeh MK, et al. The Kidney Failure Risk Equation for prediction of allograft loss in kidney transplant recipients. Kidney Med. 2020;28:753-761.
8. Sumida K, Nadkarni GN, Grams ME, et al. Urine protein-creatinine conversion calculator. John Hopkins University. Available at: http://ckdpcrisk.org/pcr2acr/. [Accessed 24 September 2020].
9. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305:1553-1559.
10. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and calibration of clinical prediction models. Users' guides to the medical literature. JAMA. 2017;318:1377-1384.
11. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med. 2015;162:55-63.

12. Jeon H, Rhee S, Shin D, et al. Serum albumin level has association with both graft failure and mortality in kidney transplant recipients. Am J Transplant. 2016;16 (suppl 3).
13. Shabir S, Halimi J-M, Cherukuri A, et al. Predicting 5-year risk of kidney transplant failure: a prediction instrument using data available at 1 year post-transplantation. Am J Kidney Dis. 2014;63:643-651.
14. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2018 Annual Data Report: kidney. Am J Transplant. 2020;20(suppl 1):20-130.
15. Kaboré R, Haller MC, Harambat J, et al. Risk prediction models for graft failure in kidney transplantation: a systematic review. Nephrol Dial Transplant. 2017;32(suppl 2:ii68-ii76.
16. Loupy A, Aubert O, Orandi BJ, et al. Prediction system for risk of allograft loss in patients receiving kidney transplants: international derivation and validation study. BMJ. 2019;366:l4923.
17. Van Calster B, McLernon DJ, Smeden MV, et al. Calibration: the Achilles heel of predictive analytics. BMC Medicine. 2019;17:230.
18. Moons KGM, Altman DG, Reitsma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015;162:W1-W73.
19. NHS Blood and Transplant. Annual report on kidney transplantation. Report for 2018/2019. 2019. Available at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16778/nhsbt-kidney-transplantation-annual-report-2018-19.pdf. [Accessed 7 Dec 2020].

## CHAPTER 8

# A VALIDATION STUDY OF THE KIDNEY FAILURE RISK EQUATION IN ADVANCED CHRONIC KIDNEY DISEASE ACCORDING TO DISEASE AETIOLOGY WITH EVALUATION OF DISCRIMINATION, CALIBRATION AND CLINICAL UTILITY

Ibrahim Ali, Rosemary L. Donne, Philip A. Kalra

BMC Nephrol. 2021;22:194.
DOI: https://doi.org/10.1186/s12882-021-02402-1

## 8.1 ABSTRACT


### Background

The Kidney Failure Risk Equation (KFRE) predicts the 2- and 5-year risk of end-stage renal disease (ESRD) in patients with chronic kidney disease (CKD) stages 3a-5. Its predictive performance in advanced CKD and in specific disease aetiologies requires further exploration. This study validates the 4- and 8-variable KFREs in an advanced CKD population in the United Kingdom by evaluating discrimination, calibration and clinical utility.

### Methods

Patients enrolled in the Salford Kidney Study who were referred to the Advanced Kidney Care Service (AKCS) clinic at Salford Royal Hospital NHS Foundation Trust between 2011 and 2018 were included. The 4- and 8-variable KFREs were calculated on the first AKCS visit and the observed events of ESRD (dialysis or pre-emptive transplantation) within 2- and 5-years were the primary outcome. The area under the receiver operator characteristic curve (AUC) and calibration plots were used to evaluate discrimination and calibration respectively in the whole cohort and in specific disease aetiologies: diabetic nephropathy, hypertensive nephropathy, glomerulonephritis, autosomal dominant polycystic kidney disease (ADPKD) and other diseases. Clinical utility was assessed with decision curve analyses, comparing the net benefit of using the KFREs against estimated glomerular filtration rate (eGFR) cut-offs of $<20ml/min/1.73m^2$ and $<15ml/min/1.73m^2$ to guide further treatment.

### Results

A total of 743 patients comprised the 2-year analysis and 613 patients were in the 5-year analysis. Discrimination was good in the whole cohort: the 4-variable KFRE had an AUC of 0.796 (95% confidence interval [CI] 0.762-0.831) for predicting ESRD at 2-years and 0.773 (95% CI 0.736-0.810) at 5-years, and there was good-to-excellent discrimination across disease aetiologies. Calibration plots revealed underestimation of risk at 2-years and overestimation of risk at 5-years, especially in high-risk patients. There was, however, underestimation of risk in patients with ADPKD for all KFRE calculations. The predictive accuracy was similar between the 4- and 8-variable KFREs.

Finally, compared to eGFR-based thresholds, the KFRE was the optimal tool to guide further care based on decision curve analyses.

**Conclusions**

The 4- and 8-variable KFREs demonstrate adequate discrimination and calibration for predicting ESRD in an advanced CKD population and, importantly, can provide better clinical utility than using an eGFR-based strategy to inform decision-making.

## 8.2 INTRODUCTION

Chronic kidney disease (CKD) is not a benign condition given worsening kidney function is an independent risk factor for progression to end-stage renal disease (ESRD), cardiovascular events and all-cause mortality [1]. Accurately predicting ESRD is a cornerstone of optimal CKD care as it enables targeted treatment in high-risk patients, including supporting better risk communication with patients and appropriate prioritisation of treatment pathways that include education regarding renal replacement therapies (RRT), especially the benefits of pre-emptive living donor kidney transplantation [2-4].

To date, the Kidney Failure Risk Equation (KFRE) remains the most well-validated risk prediction tool, predicting the 2- and 5-year risk of progression to ESRD in patients with CKD stages 3a-5 [5]. The 4-variable KFRE requires age, sex, estimated glomerular filtration rate (eGFR) and albuminuria, whilst the 8-variable KFRE incorporates the additional parameters of serum calcium, phosphate, albumin and bicarbonate. Not only has the KFRE been shown to be accurate for risk prediction, but absolute risk thresholds have been implemented into clinical care systems, such as a 2-year ESRD risk of ≥40% to guide dialysis access planning in patients who have chosen future dialysis [6].

Whilst the KFRE appears a promising aid to decision-making, there is a lack of evidence regarding its ability to risk predict in more advanced CKD and in specific disease aetiologies, which are known to progress at different trajectories. Thus far, the only study to have explored this was by Hundemer at el [7], who validated the 4-variable KFRE in a Canadian cohort of patients referred to a multi-disciplinary pre-

dialysis clinic. They showed the KFRE adequately predicted ESRD in this cohort with a median eGFR of 15ml/min/1.73m$^2$ (interquartile range: 12-19ml/min/1.73m$^2$), irrespective of whether patients had diabetic nephropathy, hypertensive nephropathy, glomerulonephritis, autosomal dominant polycystic kidney disease (ADPKD) or other conditions. However, the authors did not validate the predictive performance of the 8-variable KFRE, which may be of particular relevance in advanced CKD given the potential prognostic importance for mineral-bone disease, acidosis and inflammation at CKD stages 4-5, and which are captured by the extra parameters of the 8-variable KFRE. Furthermore, whilst statistical measures of model performance were reported, such as discrimination and calibration, the clinical utility of the KFRE was not evaluated. However, measures of utility are recognised as a useful marker of prediction model performance [8].

In light of the work by Hundemer et al [7], and to address gaps in the literature, we undertook a validation study of the KFRE in order to 1) provide insight, to the best of our knowledge for the first time, on the predictive accuracy of both the 4- and 8-variable KFREs in an advanced CKD cohort, stratified to disease aetiology, in the United Kingdom (UK); and 2) determine whether the KFREs could offer clinical utility, and thus provide evidence to develop a risk-based strategy to deliver care as opposed to one that relies on eGFR thresholds.

## 8.3 METHODS

### 8.3.1 Study population and setting

A retrospective analysis was undertaken in patients in the Salford Kidney Study (SKS). The SKS is an ongoing observational study, which since 2002 has focused on recruiting patients with non-dialysis CKD. Patients referred to the renal services at Salford Royal NHS Foundation Trust (SRFT), a tertiary renal centre in the UK, who are aged 18 years or older with an eGFR <60ml/min/1.73m$^2$ are eligible for enrolment. This study focused on patients in the SKS who were referred to the advanced kidney care service (AKCS) clinic in SRFT, a multidisciplinary clinic comprising doctors, specialist nurses and dieticians that provides holistic care for patients with advanced CKD. Patients are typically referred to the AKCS clinic once they reach an eGFR of <20ml/min/1.73m$^2$ or

if they have an eGFR of 20-30ml/min/1.73m$^2$ but are deemed to be rapidly progressing by the referring clinician. Emphasis in the AKCS clinic is placed on treating complications of CKD (such as anaemia, fluid retention and mineral bone disease) and educating patients about potential future treatment options. Opportunities for pre-emptive transplant are optimised by early discussion about living kidney donation, assessment of suitability for transplant at the first clinic visit and prompt referral to a dedicated one-stop transplant work-up clinic. The frequency of clinic visits and monitoring is largely guided by changes in patients' symptoms and eGFR values and is at the discretion of the clinician in clinic.

### 8.3.2 Data variables

The 4-variable KFRE requires age, sex, eGFR and uACR, whilst the 8-variable KFRE comprises these four variables along with serum calcium, phosphate, albumin and bicarbonate [4]. The eGFR was determined using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The following unit conversions were made to align measurements in the SKS to the original KFRE study: calcium, measured in mmol/L, was converted to mg/dL by multiplying values by 4; phosphate, measured in mmol/L, was converted to mg/dL by multiplying by 3.1; albumin, measured in g/L, was converted to g/dL by dividing values by 10. The urine protein:creatinine ratio (uPCR) units of mg/mmol were converted to mg/g by multiplying values by 8.84. The uACR was then derived from the uPCR for all patients using a validated conversion formula that has been shown to provide good discrimination when used with the KFRE (Appendix A2) [9]. All variables used in this present analysis were taken on each patient's first attendance in the AKCS clinic.

### 8.3.3 Cohort assembly

Patients with an eGFR <30ml/min/1.73m$^2$ who attended their first AKCS clinic from 1$^{st}$ September 2011 to 31$^{st}$ October 2018 were included in order to enable a minimum 2-year follow-up in all subjects, and this comprised the whole study cohort. To permit calculation of the 5-year risk of ESRD, only patients from within the whole cohort who had their first AKCS clinic visit from 1$^{st}$ September 2011 up until 31$^{st}$ October 2015 were included in the 5-year analysis. Patients were excluded if they were referred out of the AKCS clinic or transferred to other hospitals for ongoing care as the primary ESRD

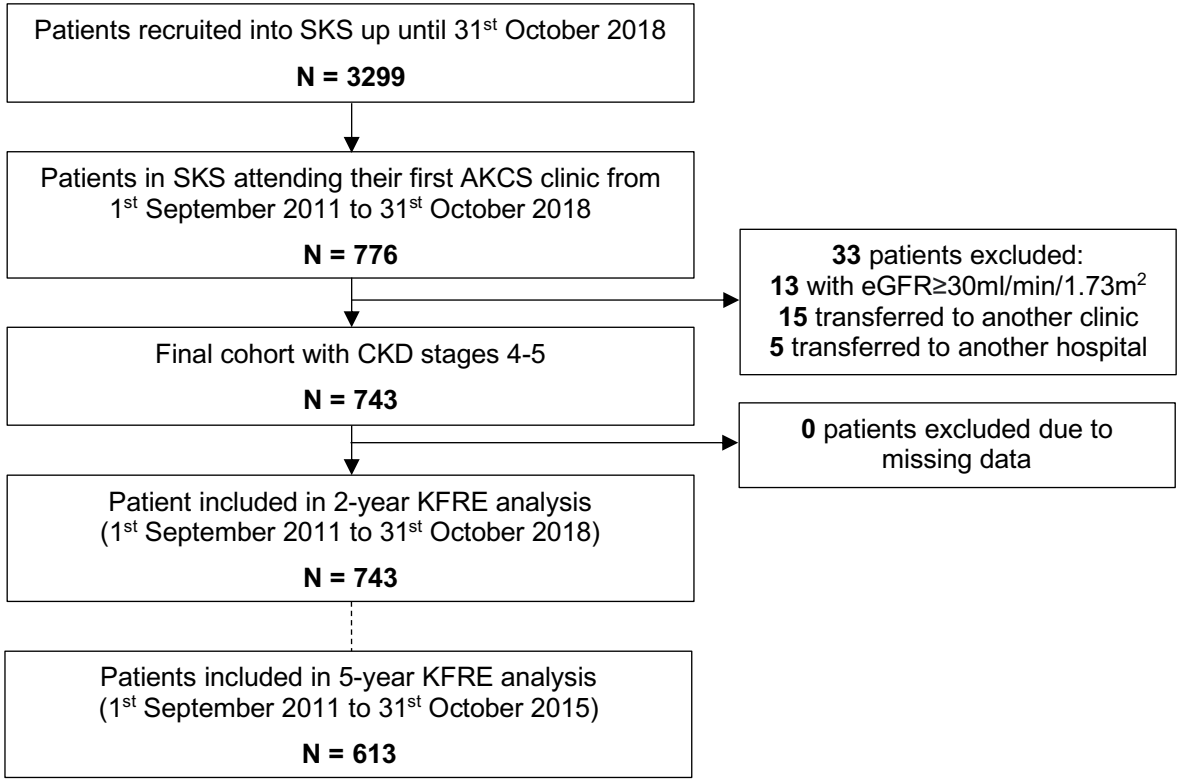
outcomes for these patients could not be determined. No patients were excluded due to missing data in our cohort (Figure 8.1).

Patients were subdivided into five disease categories: diabetic nephropathy, hypertensive nephropathy, glomerulonephritis, autosomal dominant adult polycystic kidney disease (ADPKD), and all other causes. The diagnosis of diabetic or hypertensive nephropathy was based on either histological data or clinical judgement by the patient's lead clinician. Patients were diagnosed with glomerulonephritis based on histology and those with ADPKD met international diagnostic guidelines.

### 8.3.4 Study outcomes

The death-censored events of ESRD at 2- and 5-years, calculated using the calibrated non-North American 4- and 8-variable KFREs (Appendix A1), were the primary outcomes. ESRD was defined as initiation of haemodialysis, peritoneal dialysis, conservative care or receiving a pre-emptive renal transplant. A death-censored analysis was undertaken as this is in keeping with the original KFRE development study [4] but a sensitivity analysis that considered death prior to ESRD as a competing event was undertaken. Outcome data was evaluated until 1st November 2020.

**Figure 8.1** Study cohort assembly



### 8.3.5 Statistical analysis

For baseline characteristics, continuous data is presented as median with interquartile ranges and categorical data as absolute numbers with percentages. The predictive performance of the 4- and 8-variable KFREs at 2- and 5-years were evaluated using discrimination and calibration metrics for the whole cohort and for patients in the five disease categories.

Discrimination, which is the extent a model can differentiate patients with or without the study outcome based on the risk score, was defined by the area under the curve (AUC) of a receiver operator characteristic curve (ROC), along with 95% confidence intervals [CI] [10]. Perfect discrimination amounts to an AUC of 1.0. We defined acceptable discrimination by an AUC of 0.6-0.7, good discrimination as an AUC of 0.7-0.8, whilst values >0.8 represented excellent discrimination [11]. Pairwise comparisons of the AUCs were undertaken using DeLong's method [12] to assess for differences in discrimination performance between the 4- and 8-variable KFREs in the whole cohort and between each disease group separately.

Calibration, the extent the predicted risk scores accurately estimate the observed values, was visually assessed by a calibration plot. Here, the predicted risk scores are plotted against the observed outcome of ESRD, which is treated as a binary outcome, and a smoothing function is then applied [13]. Perfect agreement between the predicted risks and observed events produces a calibration line of 45°.

Whilst discrimination and calibration provide statistical measures of performance, both fail to adequately describe the clinical utility of a model. To address this, a decision curve analysis can be undertaken that illustrates the impact of a risk model in supporting decision-making at various threshold probabilities [8,14]. The threshold probabilities, plotted on the x-axis, represent the range of appropriate risk probabilities (identified beforehand) at which a model could guide treatment when compared to the default strategies of 'treatment for all' and 'treatment for no-one'. For our study, the upper risk limit for the 2-year KFRE analysis was set at 40%, a criterion proposed as a suitable cut-off for deciding upon planning for dialysis access and transplantation [5,6]. For the 5-year KFRE analysis, the upper limit was set at 50% [5]. A treatment can refer to a variety of measures including further investigations or initiation of a therapy. In our

study, we denote treatment as increased frequency of monitoring and prioritisation of referral for kidney transplant or timely dialysis access planning. The net benefit, plotted on the y-axis of a decision curve analysis, takes account of the relationship between the number of true positive and false positive cases within the sample population across the pre-defined range of threshold probabilities and is given by the following equation:

$$\text{Net benefit} = \left(\frac{\text{True positive}}{\text{Total sample size}}\right) - \left[\left(\frac{\text{False positive}}{\text{Total sample size}}\right) \times \left(\frac{\text{Threshold probability}}{1 - \text{threshold probability}}\right)\right]$$

Net benefit, represented as true positive cases, can also be expressed as the number of unnecessary interventions avoided in a population by simply focusing on true negative cases. For our study, unnecessary interventions translate as identifying patients who would suit less intensive monitoring and for whom referral for transplantation or dialysis access planning could be delayed.

When comparing different prediction methods, the model with the highest net benefit on the y-axis across the range of threshold probabilities would be deemed to be of optimal value [14]. In this study, the utility of the 4- and 8-variable KFREs for risk prediction at 2- and 5-years was compared against an eGFR-based strategy to guide further treatment using cut-off values of an eGFR <20ml/min/1.73m$^2$ and <15ml/min/1.73m$^2$. In addition, the median time-to-ESRD was calculated for the optimal model to provide information on the appropriate timeframe for when dialysis access formation should be undertaken.

### 8.3.6 Sensitivity analysis

Survival curves for the 4-variable KFREs were produced to compare the differences in outcome between a death-censored analysis and an analysis in which death prior to ESRD is handled as a competing event.

All statistical analyses were conducted using R, version 4.0.2 (The R Foundation for Statistical Computing Platform). A p-value of <0.05 was considered statistically significant.

### 8.3.7 Ethical approval

The SKS received ethical approval from the North West Greater Manchester South Research Ethics Committee (REC15/NW/0818). Written informed consent was obtained from all patients. The methods described herein were carried out in accordance with relevant guidelines and regulations of the SKS.

The reporting of this validation study complies with the TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) statement [15].

## 8.4 RESULTS

### 8.4.1 Baseline characteristics

A total of 743 patients were included in the 2-year analysis of the 4- and 8-variable KFREs (Table 8.1). In this cohort, the median age was 68.5 years (56.9-77.2 years), and the majority of patients were male (62%) and was almost exclusively Caucasian (94%). The vast majority had a co-morbid diagnosis of hypertension (97%) and 40% of patients had diabetes. The most common disease-specific aetiology was diabetic nephropathy (24%). The median eGFR was 16m/min/1.73m$^2$ (13-18ml/min/1.73m$^2$), which was similar across the disease categories, and the median uACR was 409mg/g (85-1356mg/g), which was comparatively higher in patients with glomerulonephritis and diabetic nephropathy than in patients with hypertensive nephropathy and ADPKD. All these characteristics were similar in the cohort of 613 patients, which comprised the 5-year analysis of the 4- and 8-variable KFREs (Table 8.2). A comparison of the baseline characteristics of the 2-year cohort with the original KFRE development cohort [4] is provided in Table 8.3.

**Table 8.1** Baseline characteristics according to disease aetiology for all patients attending the AKCS clinic from 2011-2018

| Variable | Whole cohort | Diabetic nephropathy | Hypertensive nephropathy | GN | ADPKD | Other diseases |
|---|---|---|---|---|---|---|
| Patient numbers | 743 | 178 | 125 | 86 | 64 | 290 |
| Age, years | 68.5 (56.9-77.1) | 66.1 (57.4-74.9) | 76.3 (69.0-81.5) | 62.6 (47.1-72.5) | 54.3 (46.4-63.3) | 71.2 (61.3-78.5) |
| Male, *n* (%) | 462 (62) | 118 (66) | 83 (66) | 55 (64) | 38 (59) | 165 (57) |
| Caucasian, *n* (%) | 695 (94) | 163 (92) | 121 (97) | 79 (92) | 63 (98) | 275 (95) |
| Hypertension, *n* (%) | 723 (97) | 176 (99) | 125 (100) | 85 (99) | 61 (95) | 276 (95) |
| Diabetes mellitus, *n* (%) | 296 (40) | 178 (100) | 33 (26) | 17 (20) | 2 (3) | 66 (23) |
| | | | | | | |
| **Laboratory values** | | | | | | |
| *eGFR, ml/min/1.73m$^2$ | 16 (13-18) | 16 (13-19) | 15 (13-18) | 16 (12-18) | 16 (13-18) | 15 (13-18) |
| †urine albumin:creatinine ratio, mg/g | 409 (85-1356) | 896 (245-2304) | 172 (43-621) | 1345 (496-2520) | 130 (45-332) | 362 (80-996) |
| ‡Calcium, mg/dL | 9.32 (8.96-9.72) | 9.36 (9.04-9.75) | 9.20 (8.76-9.56) | 9.28 (8.96-9.76) | 9.32 (8.91-9.56) | 9.40 (8.96-9.76) |
| ‡Phosphate, mg/dL | 3.91 (3.41-4.53) | 4.00 (3.44-4.62) | 3.81 (3.32-4.50) | 4.31 (3.60-4.86) | 4.03 (3.57-4.35) | 3.84 (3.32-4.37) |
| Bicarbonate, mEq/L | 21.8 (19.6-24.4) | 22.4 (20.3-25.5) | 21.6 (19.7-23.8) | 20.8 (19.2-23.5) | 22.2 (19.1-23.8) | 21.7 (19.4-24.4) |
| ¶Albumin, g/dL | 4.2 (3.9-4.4) | 4.0 (3.7-4.2) | 4.2 (4.0-4.4) | 4.0 (3.7-4.3) | 4.4 (4.2-4.6) | 4.2 (3.9-4.4) |
| | | | | | | |
| **KFRE scores** | | | | | | |
| 4-variable 2-year score, % | 24 (11-42) | 31 (13-53) | 15 (7-30) | 39 (23-66) | 19 (11-33) | 22 (10-36) |
| 4-variable 5-year score, % | 65 (36-88) | 76 (43-95) | 47 (24-75) | 85 (63-98) | 56 (36-79) | 61 (33-83) |
| 8-variable 2-year score, % | 20 (10-39) | 23 (12-46) | 15 (7-28) | 31 (18-67) | 18 (9-28) | 19 (9-32) |
| 8-variable 5-year score, % | 64 (37-89) | 68 (45-94) | 53 (27-77) | 81 (59-99) | 60 (34-78) | 61 (35-82) |

Continuous data expressed as median (interquartile range) and categorical data as number (percentage). *eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. †urine albumin:creatinine ratios were acquired by converting urine protein:creatinine ratios using a validated formula [9]. ‡Calcium and phosphate were measured in mmol/L and converted to mg/dL by multiplying values by 4 and 3.1 respectively. ¶Albumin was measured in g/L and converted to g/dL by dividing by 10.

**Table 8.2** Baseline characteristics of patients within the 5-year KFRE analysis

| Variable | Whole cohort | Diabetic nephropathy | Hypertensive nephropathy | GN | ADPKD | Other diseases |
|---|---|---|---|---|---|---|
| Patient numbers | 613 | 140 | 115 | 75 | 49 | 234 |
| Age, years | 68.7 (56.6-77.4) | 66.2 (56.4-74.7) | 76.3 (69.3-81.4) | 59.4 (45.3-72.0) | 54.2 (46.4-64.4) | 71.3 (61.7-79.2) |
| Male, *n* (%) | 386 (63) | 95 (68) | 74 (64) | 49 (65) | 30 (61) | 138 (59) |
| Caucasian, *n* (%) | 578 (94) | 130 (93) | 111 (97) | 69 (92) | 49 (80) | 220 (94) |
| Hypertension, *n* (%) | 595 (97) | 138 (99) | 115 (100) | 75 (100) | 46 (94) | 221 (94) |
| Diabetes mellitus, *n* (%) | 246 (40) | 140 (100) | 32 (28) | 15 (20) | 2 (4) | 57 (24) |
| | | | | | | |
| **Laboratory values** | | | | | | |
| [1]eGFR, ml/min/1.73m$^2$ | 15 (12-18) | 16 (13-19) | 15 (12-18) | 16 (12-19) | 16 (12-18) | 15 (13-18) |
| [†]urine albumin:creatinine ratio, mg/g | 386 (81-1263) | 734 (144-2220) | 166 (42-596) | 1166 (424-2517) | 143 (47-328) | 357 (81-914) |
| [‡]Calcium, mg/dL | 9.32 (8.92-9.72) | 9.40 (9.00-9.76) | 9.24 (8.76-9.68) | 9.28 (8.96-9.76) | 9.32 (8.88-9.56) | 9.34 (8.96-9.72) |
| [‡]Phosphate, mg/dL | 3.91 (3.35-4.50) | 4.00 (3.43-4.62) | 3.78 (3.29-4.34) | 4.22 (3.46-4.84) | 4.03 (3.57-4.34) | 3.81 (3.29-4.37) |
| Bicarbonate, mEq/L | 21.3 (19.3-23.7) | 22.0 (20.2-24.4) | 21.5 (19.7-23.6) | 20.7 (19.0-22.9) | 20.7 (18.8-23.5) | 21.3 (19.1-23.7) |
| [¶]Albumin, g/dL | 4.2 (3.9-4.4) | 4.0 (3.7-4.2) | 4.2 (4.0-4.4) | 4.0 (3.7-4.4) | 4.4 (4.2-4.6) | 4.2 (4.0-4.4) |
| | | | | | | |
| **KFRE scores** | | | | | | |
| 4-variable 2-year score, % | 24 (11-42) | 31 (13-52) | 15 (7-30) | 38 (22-65) | 20 (12-36) | 22 (9-37) |
| 4-variable 5-year score, % | 65 (36-88) | 76 (41-94) | 46 (24-74) | 85 (62-98) | 59 (39-83) | 62 (33-83) |
| 8-variable 2-year score, % | 21 (10-40) | 23 (12-50) | 13 (7-28) | 30 (18-66) | 22 (13-31) | 19 (10-34) |
| 8-variable 5-year score, % | 65 (38-90) | 69 (45-96) | 47 (27-77) | 79 (59-99) | 66 (46-81) | 62 (37-84) |

Continuous data expressed as median (interquartile range) and categorical data as number (percentage). [*]eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. [†]urine albumin:creatinine ratios were acquired by converting urine protein:creatinine ratios using an online calculator [9] and thereafter switching units from mg/mmol to mg/g by multiplying values by 8.84. [‡]Calcium and phosphate were measured in mmol/L and converted to mg/dL by multiplying values by 4 and 3.1 respectively. [¶]Albumin was measured in g/L and converted to g/dL by dividing by 10.

**Table 8.3** Comparison of the SKS study cohort to the KFRE development cohort

| | **2-year validation cohort in SKS (n = 743)** | **Original KFRE development cohort (n = 3449)** |
|---|---|---|
| **Age, years** | 66 (15) | 70 (14) |
| **Male, *n* (%)** | 462 (62) | 1946 (56) |
| **eGFR, ml/min/1.73m$^2$** | 16 (4) | 36 (13) |
| **Serum bicarbonate, mEq/L** | 22 (4) | 26 (4) |
| **Serum calcium, mg/dL** | 9.3 (0.6) | 9.4 (0.6) |
| **Serum phosphate, mg/dL** | 4.0 (1.0) | 4.0 (0.9) |
| **Serum albumin, mg/dL** | 4.0 (0.4) | 4.0 (0.5) |
| **Urine albumin:creatinine ratio, mg/g** | 409 (1271) | 93 (378) |
| **2-year events of ESRD, *n* (%)** | 257 (35) | 386 (11) |

All continuous variables are presented as means (standard deviation) except for urine albumin:creatinine ratio, which is shown as median (interquartile range).

### 8.4.2 KFRE risk scores and outcome data

In the 2-year analysis, the median 2-year risk score for the 4- and 8-variable KFREs were similar at 24% (95% CI 11-42%) and 20% (95% CI 10-39%) respectively (Table 8.1), with the highest risk scores seen in patients with glomerulonephritis, followed by those with diabetic nephropathy. In the 5-year analysis cohort (Table 8.2), the median 4- and 8-variable 5-year risk scores were both 65% (95% CI of 36-88% for the 4-variable KFRE and 36-83% for the 8-variable KFRE). As per the 2-year analysis, the highest disease-specific 5-year risks for both the 4- and 8-variable KFREs were produced in those with glomerulonephritis followed by those with diabetic nephropathy.

Table 8.4 provides the outcome data for ESRD and death prior to ESRD in the whole cohort and across disease categories. For the 2-year analysis, 257 patients (35%) reached ESRD within 2-years, whilst 101 patients (14%) died prior to ESRD. In the 5-year analysis, 331 patients (54%) reached ERSD within 5-years and there were 164 deaths (27%) prior to ESRD.

**Table 8.4** Outcome data for the analyses at 2-years and 5-years

| | Whole cohort | Diabetic nephropathy | Hypertensive nephropathy | GN | ADPKD | Other diseases |
|---|---|---|---|---|---|---|
| **2-year outcomes** | | | | | | |
| Patient numbers | 743 | 178 | 125 | 86 | 64 | 290 |
| ESRD, *n* (%) | 257 (35) | 65 (37) | 32 (26) | 40 (47) | 40 (63) | 80 (28) |
| Deaths prior to ESRD, *n* (%) | 101 (14) | 29 (16) | 26 (21) | 9 (10) | 0 (0) | 36 (12) |
| **5-year outcomes** | | | | | | |
| Patient numbers | 613 | 140 | 115 | 75 | 49 | 234 |
| ESRD, *n* (%) | 331 (54) | 78 (56) | 45 (39) | 51 (68) | 44 (90) | 113 (48) |
| Deaths prior to ESRD, *n* (%) | 164 (27) | 47 (34) | 42 (37) | 13 (17) | 3 (6) | 59 (25) |

### 8.4.3 KFRE discrimination performance

Figure 8.2 shows the ROC curves for the 4- and 8-variable KFREs predicting risk at 2- and 5-years for the whole cohort and in each of the disease groups. A summary of the AUC values is provided in Table 8.5 for the 2-year analysis and in Table 8.6 for the 5-year analysis. In the 2-year analysis, the 4-variable KFRE had good discrimination in the whole cohort with an AUC of 0.796 (95% CI 0.762-0.831). It showed excellent discrimination for diabetic nephropathy at 0.850 (95% CI 0.789-0.910), hypertensive nephropathy at 0.841 (95% CI 0.744-0.938) and glomerulonephritis at 0.842 (95% CI 0.757-0.926), with good discrimination for ADPKD at 0.713 (95% CI 0.584-0.841) and for other diseases at 0.777 (95% CI 0.716-0.838). The 8-variable KFRE produced statistically similar AUC readings compared with the 4-variable KFRE at 2- and 5-years (Tables 8.5 and 8.6).

**Figure 8.2** ROC curves for the 4- and 8-variable KFREs at 2- and 5-years according to disease aetiology

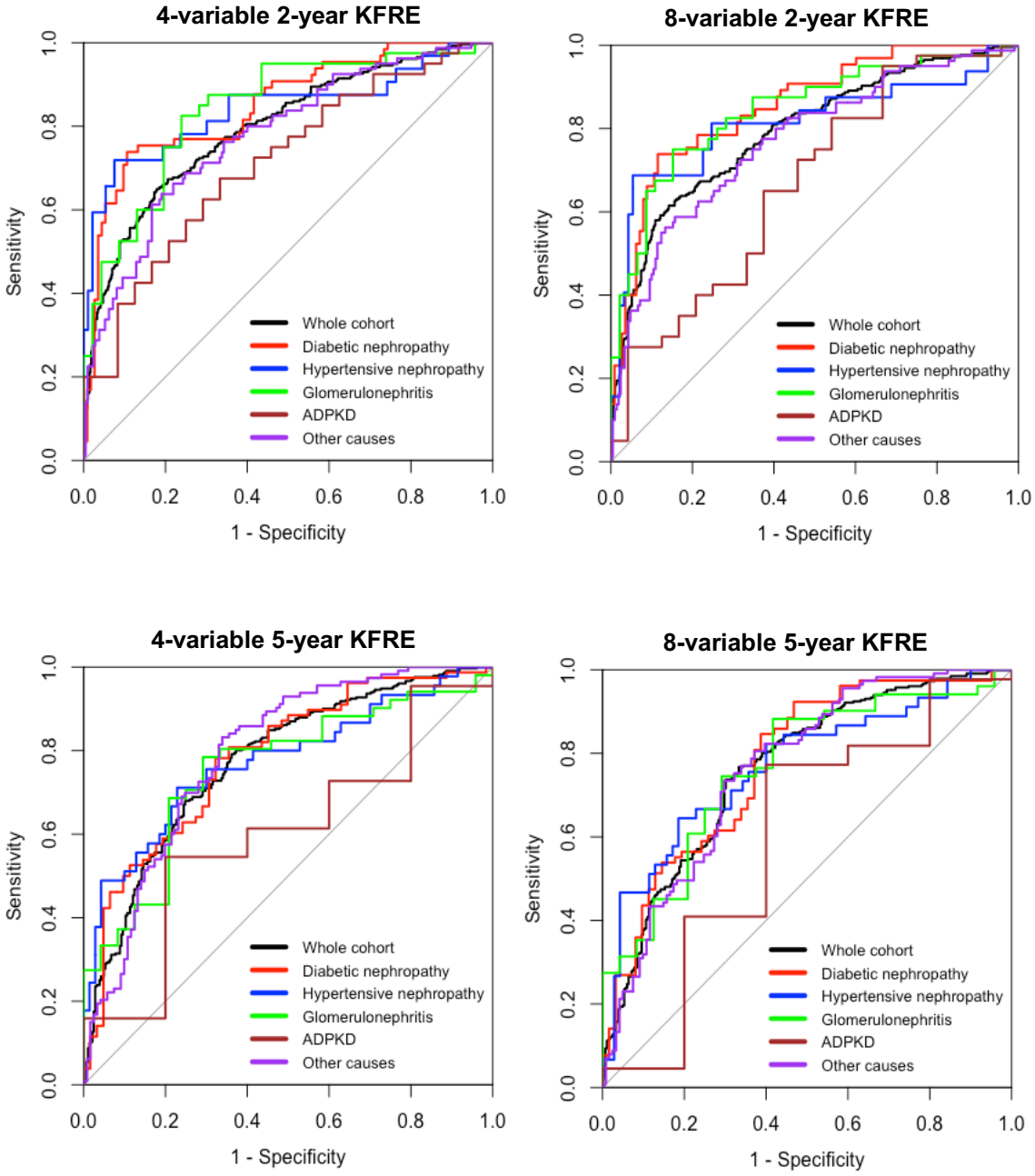


**Table 8.5** AUCs for the 2-year analysis of the 4- and 8-variable KFREs

| Patients | 4-variable 2-year risk AUC (95% CI) | 8-variable 2-year risk AUC (95% CI) | p-value |
|---|---|---|---|
| Whole cohort | 0.796 (0.762-0.831) | 0.793 (0.758-0.828) | 0.66 |
| Diabetic nephropathy | 0.850 (0.789-0.910) | 0.856 (0.798-0.912) | 0.72 |
| Hypertensive nephropathy | 0.841 (0.744-0.938) | 0.814 (0.710-0.919) | 0.07 |
| Glomerulonephritis | 0.842 (0.757-0.926) | 0.843 (0.757-0.929) | 0.96 |
| ADPKD | 0.713 (0.584-0.841) | 0.668 (0.527-0.808) | 0.18 |
| Other diseases | 0.777 (0.716-0.838) | 0.770 (0.707-0.833) | 0.73 |

Comparison between AUCs undertaken by DeLong's method [12].

**Table 8.6** AUCs for the 5-year analysis of the 4- and 8-variable KFREs

| Patients | 4-variable 5-year risk AUC (95% CI) | 8-variable 5-year risk AUC (95% CI) | p-value |
|---|---|---|---|
| Whole cohort | 0.773 (0.736-0.810) | 0.763 (0.725-0.800) | 0.22 |
| Diabetic nephropathy | 0.783 (0.706-0.859) | 0.776 (0.698-0.854) | 0.71 |
| Hypertensive nephropathy | 0.774 (0.682-0.866) | 0.769 (0.677-0.861) | 0.76 |
| Glomerulonephritis | 0.755 (0.640-0.870) | 0.764 (0.649-0.879) | 0.70 |
| ADPKD | 0.600 (0.328-0.872) | 0.605 (0.268-0.941) | 0.95 |
| Other diseases | 0.790 (0.732-0.848) | 0.763 (0.702-0.823) | 0.09 |

Comparison between AUCs undertaken by Delong's method [12].

For the 5-year analysis (Table 8.6), the 4-variable KFRE showed good discrimination in the whole cohort with an AUC of 0.773 (95% CI 0.736-0.810) and good discrimination was seen in the other disease categories except for ADPKD, which showed a much lower AUC of 0.600 (95% CI 0.328-0.872). These findings were similarly reproduced with the 8-variable 5-year calculations.

Pairwise comparisons of all the ROC curves between each of the disease categories (Tables 8.7 and 8.8) did not show any statistically significant differences except between patients with ADPKD compared with those with diabetic nephropathy and glomerulonephritis, but this only applied to the 8-variable 2-year KFRE (Table 8.7).

**Table 8.7** AUC comparison between disease aetiologies for the 4-variable KFRE

| | 4-variable 2-year risk | | 4-variable 5-year risk | |
|---|---|---|---|---|
| | **Difference in AUC** | **p-value** | **Difference in AUC** | **p-value** |
| **Diabetes vs. HTN** | 0.009 | 0.88 | 0.009 | 0.89 |
| **Diabetes vs. GN** | 0.008 | 0.88 | 0.028 | 0.70 |
| **Diabetes vs. ADPKD** | 0.137 | 0.06 | 0.183 | 0.21 |
| **Diabetes vs. Other** | 0.073 | 0.10 | 0.007 | 0.88 |
| **HTN vs. GN** | 0.001 | 0.99 | 0.019 | 0.80 |
| **HTN vs. ADPKD** | 0.128 | 0.12 | 0.174 | 0.24 |
| **HTN vs. Other** | 0.064 | 0.27 | 0.016 | 0.77 |
| **GN vs. ADPKD** | 0.129 | 0.10 | 0.155 | 0.31 |
| **GN vs. Other** | 0.065 | 0.22 | 0.035 | 0.59 |
| **ADPKD vs. Other** | 0.064 | 0.38 | 0.190 | 0.19 |

Pairwise comparisons of the AUCs were undertaken using DeLong's method [12].

**Table 8.8** AUC comparison between disease aetiologies for the 8-variable KFRE

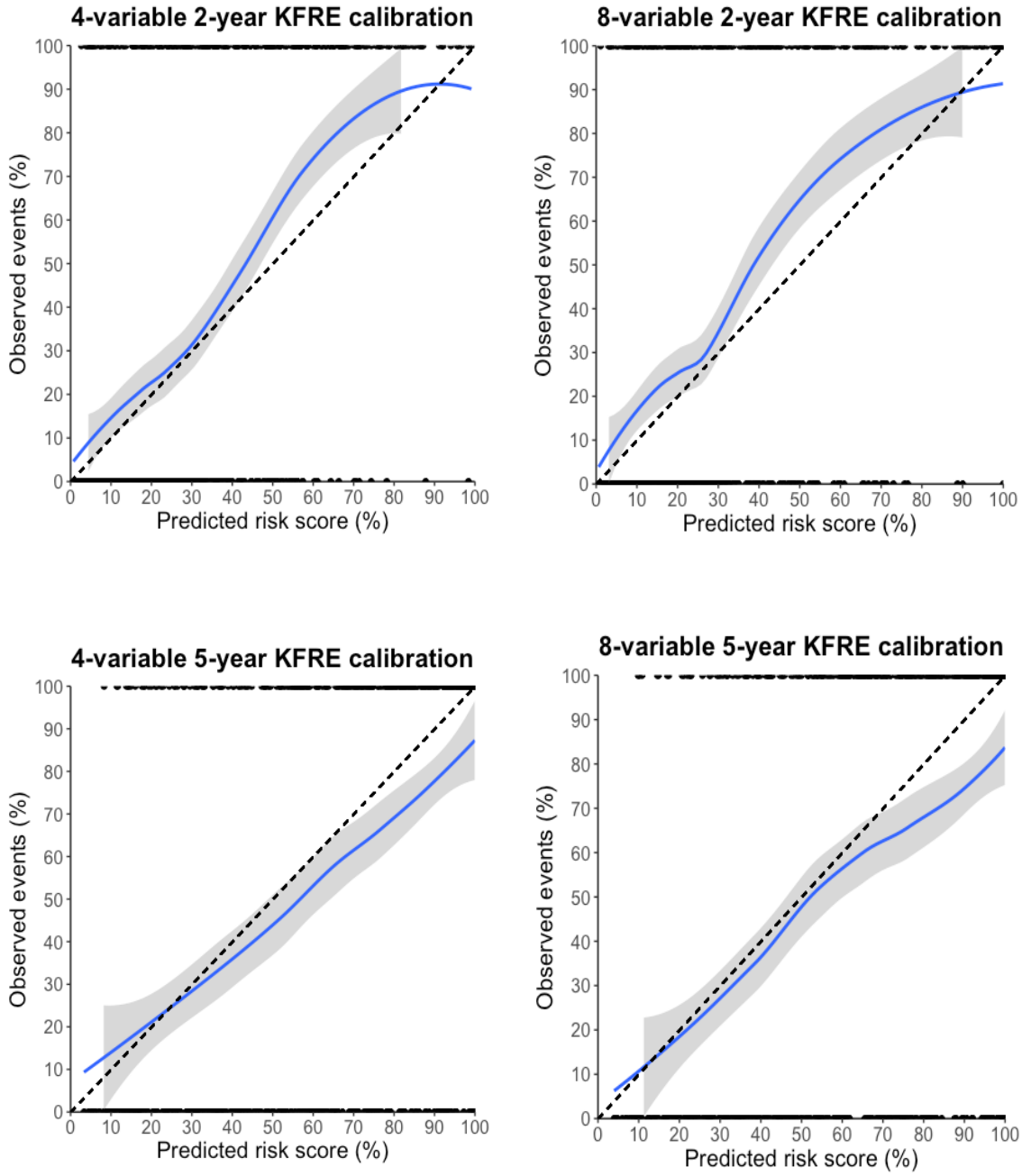
| | 8-variable 2-year risk | | 8-variable 5-year risk | |
|---|---|---|---|---|
| | **Difference in AUC** | **p-value** | **Difference in AUC** | **p-value** |
| **Diabetes vs. HTN** | 0.042 | 0.50 | 0.007 | 0.91 |
| **Diabetes vs. GN** | 0.013 | 0.82 | 0.012 | 0.87 |
| **Diabetes vs. ADPKD** | 0.188 | 0.02 | 0.171 | 0.34 |
| **Diabetes vs. Other** | 0.079 | 0.05 | 0.013 | 0.80 |
| **HTN vs. GN** | 0.029 | 0.68 | 0.005 | 0.95 |
| **HTN vs. ADPKD** | 0.146 | 0.10 | 0.164 | 0.36 |
| **HTN vs. Other** | 0.044 | 0.48 | 0.006 | 0.92 |
| **GN vs. ADPKD** | 0.175 | 0.04 | 0.159 | 0.38 |
| **GN vs. Other** | 0.073 | 0.18 | 0.001 | 0.99 |
| **ADPKD vs. Other** | 0.102 | 0.20 | 0.158 | 0.37 |

Pairwise comparisons of the AUCs were undertaken using DeLong's method [12].

### 8.4.4 KFRE calibration performance

The calibration plots in Figure 8.3 show adequate calibration for the 4- and 8-variable KFREs at 2- and 5-years but there was a tendency for underestimation of risk scores in the 2-year analysis, whereas overestimation of risk was more notably seen in the 5-year calibration plots for both the 4- and 8-variable KFREs. These differences in risk prediction were also borne out in the tabulated calibration data across disease aetiologies shown in Table 8.9, with the exception being patients with ADPKD, for whom the KFRE consistently underestimated the observed events in all calculations in the 2- and 5-year analyses.

**Figure 8.3** Calibration plots for the 4- and 8-variable KFREs at 2- and 5-years




A smoothing loess line has been applied to each graph. Grey shaded area represents 95% confidence intervals of the observed frequency of events. The black dots at 0% represent patients who did not develop ESRD and those at 100% represent patients who did develop ESRD.

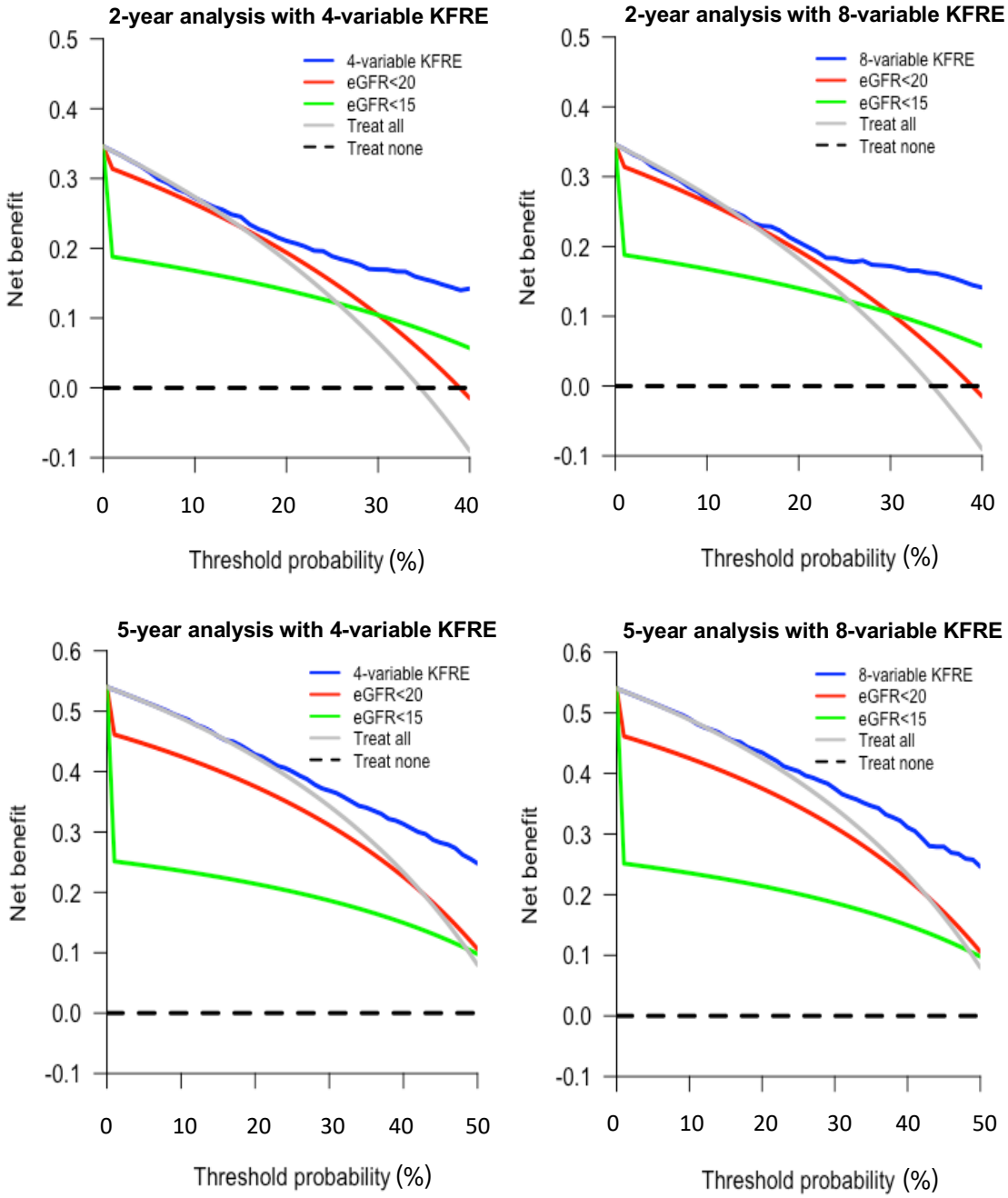
**Table 8.9** Tabulated overall calibration for 4- and 8-variable KFRE according to disease aetiology

| **4-variable 2-year KFRE risk prediction** | | |
|---|---|---|
| **Disease** | **Average predicted score, %** | **2-year observed events, %** |
| Whole cohort | 29 | 35 |
| Diabetic nephropathy | 35 | 37 |
| Hypertensive nephropathy | 21 | 26 |
| Glomerulonephritis | 43 | 47 |
| ADPKD | 21 | 63 |
| Other diseases | 26 | 28 |
| **8-variable 2-year KFRE risk prediction** | | |
| **Disease** | **Average predicted score, %** | **2-year observed events, %** |
| Whole cohort | 24 | 35 |
| Diabetic nephropathy | 32 | 37 |
| Hypertensive nephropathy | 22 | 26 |
| Glomerulonephritis | 44 | 47 |
| ADPKD | 22 | 63 |
| Other diseases | 25 | 28 |
| **4-variable 5-year KFRE risk prediction** | | |
| **Disease** | **Average predicted score, %** | **5-year observed events, %** |
| Whole cohort | 61 | 54 |
| Diabetic nephropathy | 67 | 56 |
| Hypertensive nephropathy | 49 | 39 |
| Glomerulonephritis | 77 | 68 |
| ADPKD | 58 | 90 |
| Other diseases | 59 | 48 |
| **8-variable 5-year KFRE risk prediction** | | |
| **Disease** | **Average predicted score, %** | **5-year observed events, %** |
| Whole cohort | 62 | 54 |
| Diabetic nephropathy | 67 | 56 |
| Hypertensive nephropathy | 52 | 39 |
| Glomerulonephritis | 77 | 68 |
| ADPKD | 62 | 90 |
| Other diseases | 60 | 48 |

### 8.4.5 Clinical utility

The decision analysis curves in Figure 8.4 show the 4- and 8-variable KFREs are better for guiding further intervention at relevant threshold probabilities compared to using eGFR cut-offs at <20ml/min/1.73m$^2$ and <15ml/min/1.73m$^2$.

**Figure 8.4** Decision curves analyses for the 4- and 8-variable KFREs at 2- and 5-years




The decision curves show that the both the 4- and 8-variable KFREs produced the highest net benefit for patients at 40% ESRD risk at 2-years and 50% ESRD risk at 5-years when compared to using eGFR thresholds of <20ml/min/1.73m$^2$ and <15ml/min/1.73m$^2$.

When compared with an eGFR cut-off of <15ml/min/1.73m$^2$ at a 40% threshold probability, the 4-variable 2-year KFRE was able to identify an extra 8 patients per 100 that would progress to ESRD and identify 13 more patients per 100 for whom intervention could be delayed. The median time-to-ESRD for patients with a 2-year KFRE risk of ≥40% was approximately 11 months (6-19 months).

At a 50% risk threshold, the 4-variable 5-year KFRE identified 14 extra patients per 100 who would progress to ESRD and could identify delaying intervention in 14 more patients per 100 when compared with using an eGFR <20ml/min/1.73m$^2$. In addition, it was able to identify 15 more true positive cases per 100 patients and 15 extra true negative cases compared with using an eGFR of <15ml/min/1.73m$^2$ to guide further treatment. The median time-to-ESRD for patients with a 5-year KFRE risk of ≥50% was approximately 20 months (10-37 months).

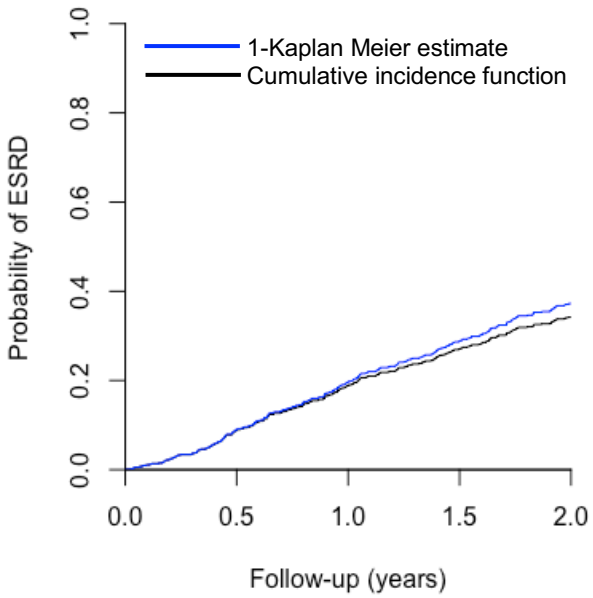
The net benefit results of the 4-variable KFRE were similarly seen when using the 8-variable KFRE for 2- and 5-year risk prediction.

### 8.4.6 Sensitivity analysis

The cumulative incidence of ESRD using the Kaplan-Meier survival curve, in which death prior to ESRD was censored, was compared to the cumulative incidence of ESRD when adjusted for death as a competing event. Using the 4-variable KFRE as the main example, Figure 8.5 shows that the death-censored approach overestimates the probability of ESRD, which was especially apparent at 5-years follow-up.

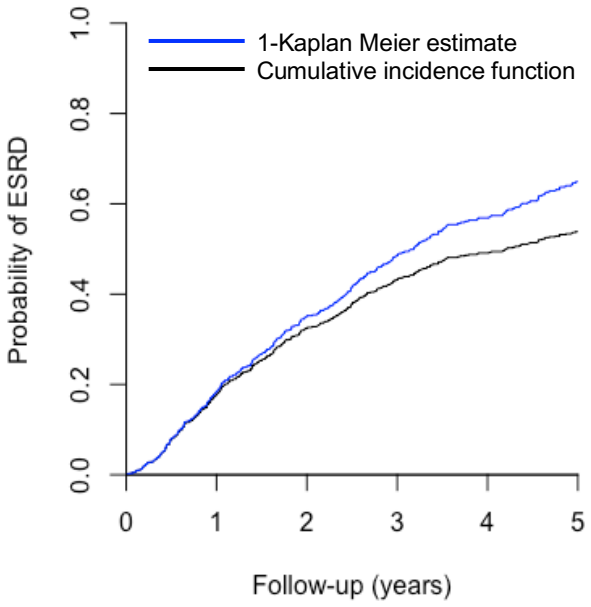
**Figure 8.5** Sensitivity analysis to show probability of events with 1-Kaplan Meier estimate (death as a censored event) compared with cumulative incidence function (death as a competing event)

**4-variable 2-year KFRE**




| | | | |
|---|---|---|---|
| Number at risk | 743 | 535 | 360 |
| Cumulative events | 0 | 150 | 257 |

**4-variable 5-year KFRE**




| | | | | | | |
|---|---|---|---|---|---|---|
| Number at risk | 613 | 455 | 335 | 232 | 166 | 111 |
| Cumulative events | 0 | 117 | 200 | 267 | 303 | 331 |

## 8.5 DISCUSSION

This validation study shows that the use of the 4- and 8-variable KFREs can be of clinical utility in an advanced CKD population and offers evidence for switching towards a risk-based model of care above one that relies solely on eGFR thresholds to trigger intervention in high-risk patients.

We undertook a similar study to the one reported by Hundemer et al [7], who recently provided a closer evaluation of the 4-variable KFRE in patients with advanced CKD and in specific disease categories, which had hitherto been lacking. The median eGFR of 15ml/min/1.73m$^2$ (12-19ml/min/1.73m$^2$) in their work closely matches the 16ml/min/1.73m$^2$ (13-18ml/min/1.73m$^2$) in ours and we share similar baseline patient characteristics of age and sex. The rates of ESRD were higher in their study compared to ours (42% and 64% reached ESRD at 2- and 5-years compared to 35% and 54% in our study), and this was reflected in higher KFRE risk scores. Nonetheless, we similarly found that patients with glomerulonephritis and diabetic nephropathy had the highest disease-specific risk scores whereas those with hypertensive nephropathy and ADPKD had the lowest. Our work extends upon the study by Hundemer et al [7] with a geographical validation of the KFREs in a UK cohort and we provide the following four main contributions:

### 8.5.1 The 4-variable KFRE is sufficient for risk prediction in advanced CKD

We show for the first time that the 8-variable KFRE performs on par with its 4-variable counterpart for patients in the whole cohort and across disease aetiologies. The 8-variable KFRE has previously been shown to have a slightly better risk prediction compared to the 4-variable KFRE [4] and we hypothesised that the 8-variable KFRE may have a better performance given its extended parameters captures abnormalities more prevalent in advanced CKD. However, our finding suggests the 4-variable KFRE is more than adequate for risk prediction in this patient group, likely due to the important predictive power of eGFR and albuminuria at later stages of CKD. In this regard, by using less variables, the 4-variable KFRE presents an attractively accessible tool for estimating future risk of ESRD across CKD stages 3a-5.

### 8.5.2 The KFRE has good discrimination for 2- and 5-year risk prediction

We show that the 4-variable KFRE had good discrimination in the whole cohort for prediction of ESRD at 2- and 5-years with AUCs of 0.796 (95% CI 0.762-0.831) and 0.773 (95% CI 0.736-0.810) respectively. These were slightly lower than the AUC of 0.83 (95% CI 0.81-0.85) at 2-years and 0.81 (95% CI 0.77-0.84) at 5-years in the report by Hundemer et al [7] but the studies share similarly excellent discrimination for certain disease aetiologies such as diabetic nephropathy, hypertensive nephropathy and glomerulonephritis at the 2-year time-point.

### 8.5.3 Calibration showed an overestimation of risk at 5-years in the whole cohort but there was consistent underestimation of risk in patients with ADPKD at 2- and 5-years

With respect to calibration, we found the KFREs underestimated risk at 2-years and overestimated risk at 5-years, especially in patients with higher predicted risk scores. The overestimation of risk at 5-years is likely explained by the death-censored analysis, which was undertaken as per the original KFRE development study [4]. We show in our sensitivity analysis that this approach does lead to an overestimation of the observed events of ESRD over time as compared to an analysis that treats death as a competing event, which has been shown to be the case in a recent analysis [16].

In contrast to the findings by Hundemer et al [7], we highlight that the KFRE had a poorer performance in patients with ADPKD in our cohort. For instance, ADPKD demonstrated the lowest AUC values amongst the disease categories across the 4- and 8-variable KFREs. Interestingly, this underperformance was statistically significant when compared with the discriminative ability of the 8-variable KFRE in patients with diabetic nephropathy and glomerulonephritis within the 2-year analysis. This latter finding provides further compelling weight towards reliance on the 4-variable KFRE, especially in those with ADPKD. However, with respect to calibration, all the KFREs consistently underestimated the risk of ESRD in this patient group, which is of particular relevance given that patients with ADPKD had the highest proportion of ESRD at 2- and 5-years (Table 8.4). Renal progression in ADPKD is notably different to other disease aetiologies in that it can be characterised by rapid rates of decline, often in a linear fashion [17], and this reflects the genetically pre-determined expansion of

renal cysts that destroy healthy parenchyma over time, and which is not influenced by modification of risk factors such as uACR. This disease mechanism is evidently not well predicted through the variables within the KFRE alone. Interestingly, there is emerging evidence that suggests that total kidney volume, calculated on ultrasonographic parameters, can be combined with the KFRE to afford better risk prediction performance in ADPKD [18] but further work will be required to corroborate these findings. For now, based on our findings, we would argue using the KFREs with caution in patients with ADPKD.

### 8.5.4 Overall, the KFREs demonstrate better clinical utility than relying on eGFR to guide further management

Our validation study offers novel insight into the clinical impact of the 4- and 8-variable KFREs in an advanced CKD population by assessing clinical utility through decision curve analyses, which incorporates the measures of discrimination and calibration [14]. We show that intervening on patients on the basis of a KFRE assessment was the optimal model of choice compared to using eGFR cut-offs of <20ml/min/1.73m$^2$ and <15ml/min/1.73m$^2$ over a range of appropriate threshold probabilities. Specifically, the 2-year KFREs were superior at the 40% ESRD threshold and the 5-year KFREs were superior at the 50% ESRD threshold, both thresholds identified in the literature as being relevant to guiding further care [5,6]. This provides evidence for the overall accuracy of the KFREs in advanced CKD and suggests they can be relied upon more than eGFR alone to support clinical decisions.

### 8.5.5 Clinical implications and future perspectives

We consider that there are two important roles in the application of the KFREs in multidisciplinary advanced care clinics: risk communication and planning for RRT. Communicating risk to patients is important as it provides an avenue to engage, counsel and potentially modify behaviour for patients at high-risk. Using the KFRE has been shown to be far more accurate than subjectively determining patients' risk: in a prospective study of 257 patients with CKD stages 3-5, the KFRE better matched 2-year outcomes of ESRD than the predicted estimates from nephrologists and patients, who both tended to overestimate risk [19].

With accurate risk prediction comes the corollary of using thresholds to plan for RRT in a timely manner. Our AKCS clinic prioritises pre-emptive transplantation given that this affords the best long-term outcomes [20]. Recognising that it is important to factor in time for medical optimisation and thereafter the time waiting for a transplant, especially from a deceased donor, the risk threshold for referral for transplant work-up becomes automatically lower. Arguably, a 'treatment-for-all' strategy (i.e., immediate referral for transplant work-up in a suitable patient) is best for patients upon arrival in the AKCS clinic. However, there is potential to refine the approach to planning for arteriovenous (AV) fistula formation, which guidelines recommend should be undertaken around 6 months prior to dialysis initiation [21]. Our work highlights that the KFRE could be employed in those with ≥40% ESRD risk over 2-years to help prioritise patients appropriately, especially given the median time-to-ESRD was 11 months (6-19 months) in this subset of patients. This could help reduce the uncertainty of the optimal time to refer patients for AV fistula formation, whist reducing the morbidity associated with AV fistula creation in patients for whom it is not yet needed [22].

In addition, appropriately timing the initial referral and triage into the AKCS clinic would also be valuable to maximise this treatment opportunity. Indeed, a proposed KFRE cut-off of ≥10% at 2-years has been reported to select patients into multidisciplinary advanced care clinics, a strategy that has captured high-risk patients with an eGFR >30ml/min/1.73m$^2$. This approach has provided significant cost-savings through the reallocation of resources to those most likely to progress to ESRD [6] and was valued to be of benefit from a qualitative analysis of clinicians and patients' perspectives [23]. Further prospective work with quality improvement initiatives or cluster randomised trials would be helpful to gauge how successful the KFRE is at achieving higher rates of pre-emptive transplantation or mature AV fistula formation in those who progress to ESRD.

A limiting step in the routine use of the KFRE at our institution is the need for conversion of uPCR to uACR and a change in practice would ideally be needed to help integrate an immediate and accessible risk score into our electronic patient record. It is also important to acknowledge that risk scores obtained by the KFRE should only be used along with clinical judgement given the complexities of care in advanced CKD, where shared decision-making regarding future RRT needs to take account of patients'

preferences, their comorbidities, symptoms and the competing risk of death prior to ESRD.

### 8.5.6 Strengths and limitations

Our study provides for the first time a comprehensive, independent, geographical validation of both the 4- and 8-variable KFREs in advanced CKD in a UK-based cohort with specific evaluation of discrimination, calibration and clinical utility. We also provide insight into the applicability of the KFRE in an advanced kidney care clinic setting by focussing attention on the importance of communicating risk to patients, facilitating pre-emptive transplant and planning for AV fistula formation. This will be of significance to institutions who are considering the merits of using the KFRE in their practices.

There are important limitations to our work. Firstly, there may have been misclassification of patients with diabetic or hypertensive nephropathy as the majority of these patients had not undergone a renal biopsy. This, however, is reflective of routine practice where the clinical probability of these particular diseases typically outweighs the risk of undergoing a biopsy for diagnostic confirmation. Nonetheless, our patient characteristics are in keeping with what we would expect in specific disease aetiologies, notably with higher levels of albuminuria in diabetic nephropathy compared with hypertensive nephropathy. Secondly, we were dependent on converting uPCR to uACR for all our patients, which may have impacted the predicted risk scores, but the online conversion tool we used has been shown to be effective with KFRE calculations. Finally, our study cohort originated from a single-centre and was largely Caucasian, which limits the generalisability of our results to other diverse clinical settings.

## 8.7 CONCLUSIONS

The KFRE is an accessible and useful tool for risk prediction in patients with advanced CKD and in different disease aetiologies. Based on its beneficial clinical utility, the KFRE could be used in multidisciplinary advanced kidney care clinics to help deliver personalised and accurate care. The communication of risk scores can help facilitate early discussion to optimise living donor pre-emptive transplant and assist in decisions on the timing for dialysis access formation. Its use is also likely to be beneficial when managing patients at earlier stages of CKD to identify those at risk of rapid progression. Prospective data would be welcome to highlight the effectiveness of the KFRE in these patient groups, which would help herald a paradigm shift towards the routine use of objective risk-based assessments in delivering optimal CKD care.

## 8.8 REFERENCES


1. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011;80:17–28.
2. Ali I, Kalra P. Risk prediction in chronic kidney disease. Curr Opin Nephrol Hypertens. 2019;28:513–518.
3. Grams ME, Coresh J. Predicting risk of RRT in patients with CKD. Clin J Am Soc Nephrol. 2017;12:3-4.
4. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305:1553-1559.
5. Tangri N, Grams ME, Levey AS, et al. Multinational assessment of accuracy of equations for predicting risk of kidney failure. a meta-analysis. JAMA. 2016;315:164–174.
6. Tangri N, Ferguson T, Komenda P. Pro: risk scores for chronic kidney disease progression are robust, powerful and ready for implementation. Nephrol Dial Transplant. 2017;32:751.
7. Hundemer GL, Tangri N, Sood MM, et al. Performance of the Kidney Failure Risk Equation by disease etiology in advanced CKD. Clin J Am Soc Nephrol. 2020;15:1424-1432.
8. Vickers AJ, Calster BV, Steyerberg EW. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. BMJ. 2016;352:i6.
9. Sumida K, Nadkarni GN, Grams ME, et al. Conversion of urine protein-creatinine ratio or urine dipstick protein to urine albumin-creatinine ratio for use in chronic kidney disease screening and prognosis. Ann Intern Med. 2020;173:426-435.
10. Alba AC, Agoritsas T, Walsh M, et al. Discrimination and calibration of clinical prediction models. Users' guides to the medical literature. JAMA. 2017;318:1377-1384.
11. Rigatto C, Sood MM, Tangri N. Risk prediction in chronic kidney disease: pitfalls and caveats. Curr Opin Nephrol Hypertens. 2012;21:612-618.
12. DeLong ER, Delong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-845.

13. Au EH, Francis A, Bernier-Jean A, et al. Prediction modelling – part 1: regression modelling. Kidney Int. 2020;97:877-884.
14. Vickers AJ, Calster BV, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. Diagn Progn Res. 2019;3:18.
15. Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med. 2015;162:55-63.
16. Ravani P, Fiocco M, Liu P, et al. Influence of mortality on estimating the risk of kidney failure in people with stage 4 CKD. J Am Soc Nephrol. 2019; 30: 2219–2227.
17. Ali I, Chinnadurai R, Ibrahim ST, et al. Predictive factors of rapid linear renal progression and mortality in patients with chronic kidney disease. BMC Nephrol. 2020;21:345.
18. Akbari A, Tangri N, Brown PA, et al. Prediction of progression in polycystic kidney disease using the kidney failure risk equation and ultrasound parameters. Can J Kidney Health Dis. 2020;7:2054358120911274.
19. Potok OA, Nguyen HA, Abdelmalek JA, et al. Patients', nephrologists', and predicted estimations of ESKD risk compared with 2-year incidence of ESKD. Clin J Am Soc Nephrol. 2019;14:206-212.
20. KDIGO. Clinical practice guideline on the evaluation and management of candidates for kidney transplantation. Transplantation. 2020;104:4S.
21. NICE. Renal replacement therapy and conservative management. NICE guideline [NG107]. 2018. Available at: https://www.nice.org.uk/guidance/ng107/chapter/Recommendations#preparing-for-renal-replacement-therapy-or-conservative-management. [Accessed 28 December 2020].
22. Kaushal A, Naimark D, Tangri N. Use of the Kidney Failure Risk Equation to reduce uncertainty in predicting time to ESRD. Am J Kidney Dis. 2015;65:369-371.
23. Smekal MD, Tam-Tham H, Finlay J, et al. Patient and provider experience and perspectives of a risk-based approach to multidisciplinary chronic kidney disease care: a mixed methods study. BMC Nephrol. 2019;20:110.

## CHAPTER 9

# THE ROLE OF PATIROMER: COMPARING OPAL-HK DATA WITH UNTREATED REAL-WORLD PATIENTS IN THE UNITED KINGDOM – A RETROSPECTIVE, PROPENSITY-MATCHED ANALYSIS

Ibrahim Ali, Rajkumar Chinnadurai, Georgiana Cornea, Michele Intorcia, Philip A. Kalra

PLoS ONE 15(8): e0237467.
DOI: https://doi.org/10.1371/journal.pone.0237467

## 9.1 ABSTRACT


**Background**

The first phase of the published OPAL-HK study was a single-group treatment phase, which showed that patiromer normalised serum potassium at 4 weeks in patients with chronic kidney disease stages 3-4 who were receiving renin-angiotensin-aldosterone inhibitors. We utilised real-world data to provide a control comparison to evaluate patiromer's efficacy in lowering serum potassium.

**Methods**

The Salford Kidney Study (SKS) in the United Kingdom provided a matched cohort. After applying OPAL-HK inclusion and exclusion criteria, patients with an outpatient potassium level between 5.1mmol/L to <6.5mmol/L and whose next outpatient level was checked 24-42 days later were selected. Patients underwent 1:1 matching with the 243 OPAL-HK patients using propensity matching based on 6 variables: age, gender, estimated glomerular filtration rate, diabetes, heart failure and potassium level. The study outcomes aligned with the OPAL-HK treatment phase: mean change in baseline potassium, and the proportion of patients with a potassium of 3.8 to <5.1mmol/L at follow-up.

**Results**

The study comprised 87 precisely matched patients. The mean follow-up in the 87 SKS patients was 31±5 days. At baseline, matched patients had a mean potassium of 5.5±0.3mmol/L. At follow-up, the mean level was unchanged in SKS patients but was 4.5±0.5mmol/L in the OPAL-HK group ($p<0.001$), a mean (±SE) change of -1.00±0.06mmol/L. The target range of 3.8 to <5.1mmol/L was reached in 80% of OPAL-HK patients compared with 0% in the SKS cohort. There were very few interventions undertaken to reduce hyperkalaemia in SKS patients.

**Conclusions**

Using real-world data as a matched control arm for the first phase of the OPAL-HK study, we highlight a potential role for patiromer in lowering potassium levels in patients with CKD 3-4 receiving renin-angiotensin-aldosterone inhibitors.

## 9.2 INTRODUCTION

Hyperkalaemia is an important electrolyte disturbance that most commonly occurs in patients with advanced chronic kidney disease (CKD) [1]. Notwithstanding the potentially life-threatening cardiac arrhythmias that can arise with hyperkalaemia, patients also face the potential undesirable consequence of reducing or indefinitely discontinuing renin-angiotensin-aldosterone system inhibitors (RAASi), which are known to provide long-term reno- and cardioprotection [2]. Therefore, efforts to maintain normokalaemia and permit continuation of RAASi is a well-established tenet for optimal CKD management [3]. Achieving normokalaemia in the outpatient setting whilst maintaining RAASi may be achieved through a combination of measures including low-potassium dietary advice, addition of a loop or thiazide diuretic, correction of acidosis with sodium bicarbonate and with potassium binders such as sodium polystyrene sulfonate (SPS). This latter intervention, beset by a lack of evidence for long-term use and the significant risk of gastrointestinal side effects [4], has been transformed thanks to the introduction of new oral potassium-binding agents such as patiromer. Patiromer is a non-absorbed, sodium-free potassium-binding polymer that non-specifically binds potassium for calcium along the gastrointestinal tract, facilitating potassium excretion.

OPAL-HK is a major multicentre prospective trial that investigated the efficacy and safety of patiromer at lowering potassium levels in CKD patients [5]. The study recruited 243 patients with CKD stages 3-4 who were receiving RAASi and whose baseline serum potassium was 5.1 to <6.5mmol/L. The initial part of the study was a single-group, single-blinded treatment phase with patiromer over 4 weeks, followed by a placebo-controlled withdrawal phase over 8 weeks. In the treatment phase, patiromer was shown to reduce serum potassium by a mean ± standard error (SE) of -1.01±0.03mmol/L, and 76% of patients reached a target potassium range of 3.8 to <5.1mmol/L at the end of the 4-week follow-up. In this phase, serum potassium levels were measured at baseline and on day 3 and weekly thereafter. In the withdrawal phase, discontinuation of patiromer resulted in a statistically higher serum potassium and a higher proportion of patients with levels >5.5mmol/L at the end of follow-up compared to the group that continued to take patiromer.

Given the lack of a control arm for the first phase of the OPAL-HK trial, we undertook a study to provide further insight into the efficacy of patiromer. The aims were to (1) utilise real-world data from an observational CKD cohort in the United Kingdom (UK) to provide a control, untreated, comparison group to the first phase of OPAL-HK and evaluate patiromer's efficacy in lowering serum potassium; and (2) demonstrate the feasibility of comparing real-world patient data with clinical trial data, which is particularly pertinent to hyperkalaemia trials where placebo interventions would be deemed unethical.

## 9.3 METHODS

### 9.3.1 Patient population

Patients for the matched cohort were selected from the Salford Kidney Study (SKS). This is an ongoing prospective observational study in the UK that has been recruiting patients aged ≥18 years with CKD stage 3-5 since 2002. Demographic data is collected at entry into SKS. Blood and urine sampling for routine clinical tests is performed at baseline and at subsequent clinic visits and results are readily available on the hospital's electronic patient record. Patients are followed in SKS until endpoints are reached, which include death, initiation of renal replacement therapy (chronic dialysis or transplantation), loss to follow-up, discharge from renal clinic or withdrawal of consent. The study complies with the declaration of Helsinki and ethical approval has been obtained from the regional ethical committee (current REC reference 15/NW/0818). All participants provided written informed consent.

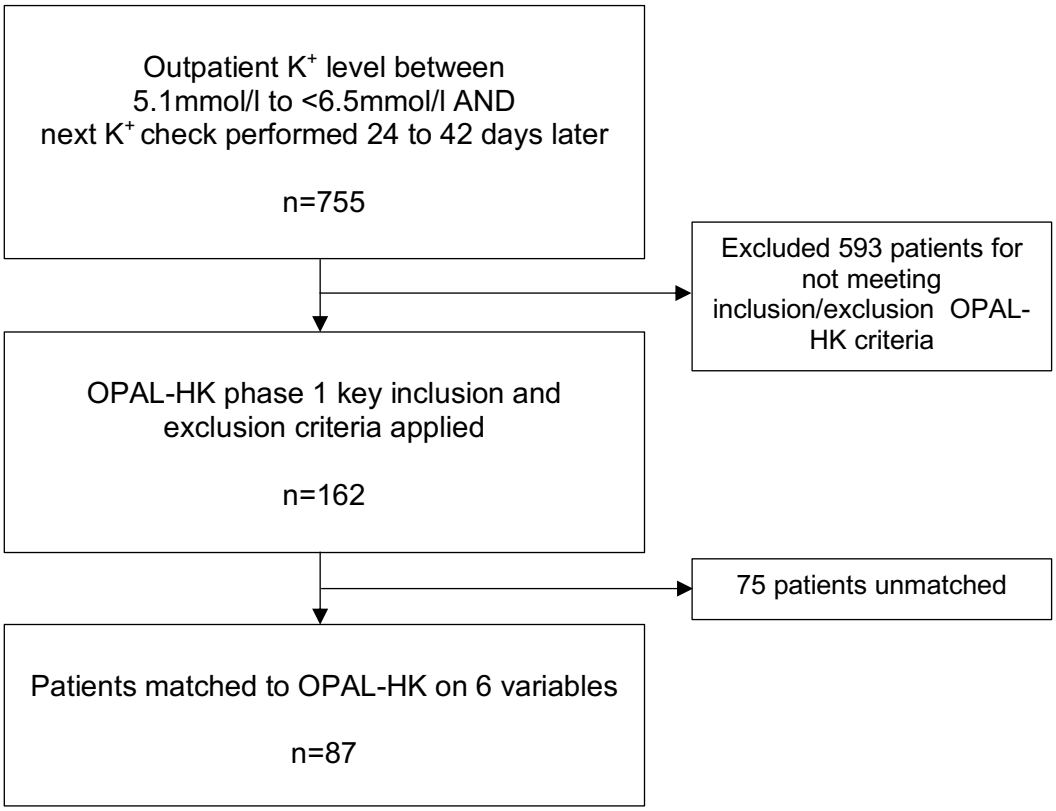
### 9.3.2 Creating a matched cohort

The first phase of OPAL-HK enrolled 243 patients aged 18-80 years with CKD stages 3-4, (corresponding to an estimated glomerular filtration rate (eGFR) of 15 to <60ml/min/1.73m$^2$, calculated by either CKD-EPI or MDRD equation [5]), and whose baseline potassium was between 5.1 to <6.5mmol/L. All patients were receiving stable doses of RAASi for at least 28 days. Exclusion criteria in the OPAL-HK study included a high potassium requiring emergency treatment at baseline, type 1 diabetes, systolic blood pressure ≥180mmHg or <110mmHg or a diastolic blood pressure of ≥110mmHg or <60mmHg, use of potassium-altering chronic medications if doses not stable 28 days

prior to selection (loop and thiazide diuretics, non-selective beta blockers, amiloride, triamterene, drospirenone, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, digoxin, bronchodilators, theophylline, heparin, synthetic thyroid hormone) and current use of sodium bicarbonate, sodium polystyrene sulfonate, calcium polystyrene sulfonate and potassium supplements. Patients were followed-up for 4 weeks.

To acquire a matched cohort to the 243 OPAL-HK patients, a three-step process was applied to patient selection in SKS (Figure 9.1). First, patients were chosen if they had an outpatient potassium level at any point after recruitment into SKS between 5.1mmol/L and <6.5mmol/L and whose next outpatient potassium level was obtained 24 to 42 days (3.5 to 6 weeks) later. This follow-up timeframe was chosen, as opposed to a precise 28 days, to account for the spread of clinic availability in real-world practice. Secondly, key OPAL-HK inclusion and exclusion criteria as listed above were applied. All criteria were cross-checked by reviewing patient's clinic letters and drug prescriptions from the hospital electronic health record. This provided a patient cohort of 162 patients. Baseline demographic data for these patients were updated to reflect the time-point of entry into this analysis. The final stage involved 1:1 matching of 162 SKS patients with 243 OPAL-HK patients using propensity scores based on 6 baseline variables: age, gender, eGFR, diabetes, heart failure and potassium level. This step resulted in a final cohort of 87 SKS patients matched to 87 partner patients in OPAL-HK. All 87 patients in the OPAL-HK cohort had completed the full 4 weeks of patiromer treatment.

**Figure 9.1** Patient selection from the Salford Kidney Study




### 9.3.3 Study endpoints in the matched analysis

The study endpoints for this analysis were aligned to those in the first phase of the OPAL-HK study: the primary endpoint was the mean change in serum potassium from baseline to follow-up, and the secondary endpoint was the proportion of patients who had a serum potassium in the range of 3.8 to <5.1mmol/L at follow-up.

### 9.3.4 Statistical analysis

Propensity scores were generated using binary logistic regression that utilised six baseline variables described above. Patients were matched in a 1:1 ratio using the nearest neighbour method with the same propensity score.

Continuous data is presented as means ± standard deviation (SD) and categorical data expressed as total numbers with percentages. Baseline differences between SKS and OPAL-HK groups were analysed with independent Student's t-test for continuous data and Chi-squared tests for categorical data. Comparison between eGFR and potassium results in SKS patients at baseline and follow-up were analysed using paired t-test. A p-value of <0.05 was considered significant. All analyses including propensity score

matching was performed using IBM SPSS (Version 22), licensed to University of Manchester.

## 9.4 RESULTS

### 9.4.1 Baseline characteristics

Table 9.1 highlights the baseline characteristics of the SKS cohort that met the inclusion and exclusion criteria of the first phase of the OPAL-HK study. There were similarities between the two groups with respect to age and gender, but they were statistically dissimilar with respect to baseline potassium level, eGFR and the presence of diabetes and heart failure. A precisely matched cohort of 87 patients in each patient group was subsequently created based on 6 variables (Table 9.2). The matched cohorts were used for analysis of study endpoints.

**Table 9.1** Comparison of baseline characteristics between patients in the first phase of the OPAL-HK study and SKS patients meeting the inclusion and exclusion criteria of the study

| Baseline characteristic | OPAL-HK (n=243) | SKS (n=162) | P-value |
|---|---|---|---|
| Male sex – no. (%) | 140 (58) | 90 (56) | 0.709 |
| Age – years | 64.2 ± 10.5 | 63.2 ± 13.4 | 0.423 |
| White race – no. (%) | 239 (98) | 159 (98) | 0.876 |
| Type 2 diabetes – no. (%) | 139 (57) | 67 (41) | 0.002 |
| Heart failure – no. (%) | 104 (42) | 40 (25) | <0.001 |
| Myocardial infarction – no. (%) | 60 (25) | 8 (5) | <0.001 |
| Hypertension – no. (%) | 236 (97) | 162 (100) | 0.029 |
| Serum [$K^+$] (mmol/L) | 5.6 ± 0.5 | 5.4 ± 0.3 | 0.002 |
| eGFR (ml/min/1.73m$^2$) | 35.4 ± 16.2 | 29.8 ± 10.7 | <0.001 |
| RAASi use | | | |
| - ACEi – no. (%) | 170 (70) | 108 (67) | 0.569 |
| - ARB – no. (%) | 92 (38) | 70 (43) | 0.231 |
| - Aldosterone antagonist – no. (%) | 22 (9) | 8 (5) | 0.122 |
| - Renin inhibitor – no. (%) | 2 (1) | 2 (1) | 0.682 |
| - Dual-blockade* – no. (%) | 41 (17) | 32 (20) | 0.373 |
| Diuretic use – no. (%) | 132 (54) | 85 (52) | 0.807 |

Continuous data is presented as means (±SD). P value by Student's t test for continuous data and chi-squared test for categorial data. *Dual RAAS blockade indicates any combination of ≥2 the following: ACEi, ARB, aldosterone antagonist, or renin inhibitor.

**Table 9.2** Comparison of baseline characteristics in the matched cohorts

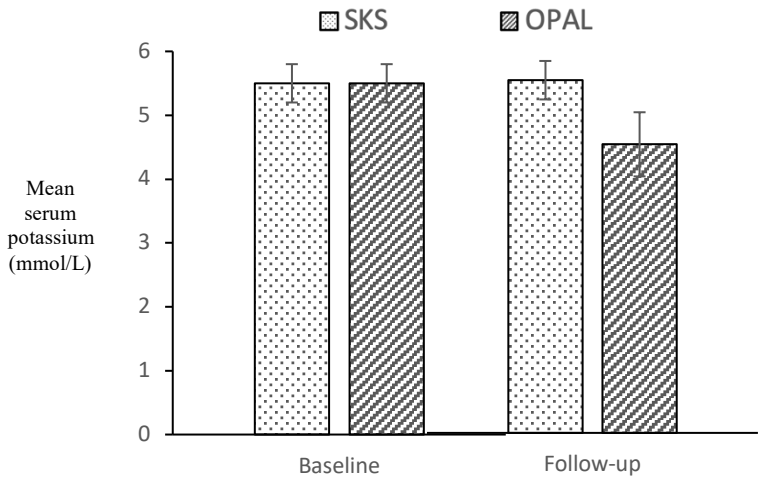
| Baseline characteristic | OPAL-HK (n=87) | SKS (n=87) | P-value |
|---|---|---|---|
| Male sex – no. (%) | 47 (54) | 52 (60) | 0.445 |
| Age – years | 63.7 ± 9.5 | 63.9 ± 13.3 | 0.934 |
| Type 2 diabetes – no. (%) | 46 (53) | 45 (52) | 0.880 |
| Heart failure – no. (%) | 24 (28) | 29 (33) | 0.412 |
| Serum [$K^+$], (mmol/L) | 5.5 ± 0.3 | 5.5 ± 0.3 | 0.678 |
| eGFR (ml/min/1.73m$^2$) | 31.2 ± 11.7 | 30.9 ± 11.9 | 0.873 |

P-value by Student's t test and chi-squared test for categorical data.

### 9.4.2 Study endpoints in the matched analysis

The mean follow-up in the matched SKS cohort was 31±5 days. In both SKS and OPAL-HK patients, the mean baseline potassium level was identical at 5.5±0.3mmol/L. At the end of follow-up, the mean potassium level was unchanged in SKS patients but had significantly reduced to 4.5±0.5mmol/L in the OPAL-HK group ($p<0.001$) (Figure 9.2). This represented a mean (±SE) change of -1.00±0.06mmol/L, in line with the results of 243 patients within the OPAL-HK trial, which reported a mean (±SE) change of -1.01±0.03mmol/L. This change in potassium in OPAL-HK patients was a consistent feature observed in patients in different stages of CKD with or without diabetes and heart failure (Table 9.3).

**Figure 9.2** Change in mean potassium level from baseline to follow-up




Follow-up was at 4 weeks in OPAL-HK. In SKS, mean follow-up time was 31±5 days.

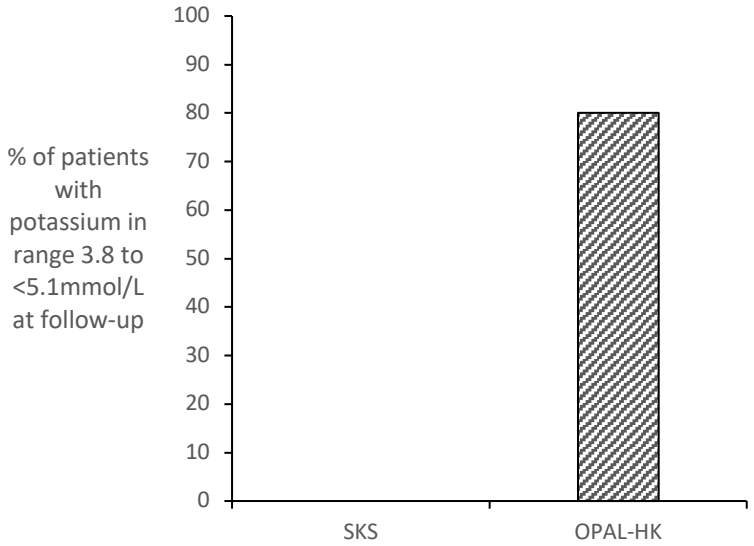
**Table 9.3** Changes in mean potassium from baseline to follow-up according to CKD stage, and presence of diabetes or heart failure

| | SKS | | | OPAL-HK | | |
|---|---|---|---|---|---|---|
| | Patient numbers | Mean [$K^+$] (mmol/L) | | Patient numbers | Mean [$K^+$] (mmol/L) | |
| | | Baseline | Follow-up | | Baseline | Follow-up |
| CKD stage 3 | 39 | 5.4 ± 0.3 | 5.4 ± 0.3 | 36 | 5.5 ± 0.3 | 4.5 ± 0.5 |
| CKD stage 4 | 48 | 5.5 ± 0.3 | 5.5 ± 0.3 | 51 | 5.5 ± 0.3 | 4.5 ± 0.5 |
| CKD 3 or 4 + diabetes only | 29 | 5.6 ± 0.4 | 5.5 ± 0.4 | 33 | 5.5 ± 0.3 | 4.5 ± 0.4 |
| CKD 3 or 4 + heart failure only | 13 | 5.5 ± 0.3 | 5.3 ± 0.2 | 11 | 5.5 ± 0.2 | 4.5 ± 0.7 |
| CKD 3 or 4 + diabetes + heart failure | 16 | 5.5 ± 0.3 | 5.3 ± 0.2 | 13 | 5.5 ± 0.2 | 4.5 ± 0.7 |

[$K^+$] values expressed as mean ± SD.

For the secondary endpoint, 80% of patients in OPAL-HK (70 of 87 patients) reached the target potassium range of 3.8 to <5.1mmol/L at the end of follow-up compared with 0% from the comparator SKS cohort (Figure 9.3). This is similar to the 76% of patients quoted to reach this target range in the published OPAL-HK study.

**Figure 9.3** Proportion of patients in potassium range 3.8 to <5.1mmol/L at follow-up



Just as in the OPAL-HK study, there was no clinically significant change in renal function from baseline to follow-up in the 87 matched SKS patients: mean baseline eGFR was 30.9±11.9ml/min/1.73m$^2$ and 31.9±12.6ml/min/1.73m$^2$ at follow-up (p=0.144).

The number of patients that switched from one potassium range to another, from baseline to follow-up, are shown in Table 9.4, stratified across CKD stages. The majority of patients in OPAL-HK reached a potassium level of <5.1mmol/L irrespective of their baseline potassium range and CKD stage. In contrast, SKS patients were spread more heterogeneously across the range values at follow-up. For instance, 52 patients had a baseline potassium of 5.1-5.5mmol/L but only 39 patients remained in this range at follow-up; 13 patients had results in higher potassium ranges. At follow-up in the group of 29 patients with baseline potassium between 5.6-6.0mmol/L, 16 patients had a lower potassium, 9 remained in the same range and 4 had a higher potassium level.

**Table 9.4** Baseline and follow-up potassium in SKS and OPAL-HK patients stratified to CKD stage

| | | | **Follow-up [$K^+$] range (mmol/L)** | | | |
|---|---|---|---|---|---|---|
| | | | **<5.1** | **5.1-5.5** | **5.6-6.0** | **>6.0** |
| | | **Baseline [$K^+$] range (mmol/L)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| **SKS** | **CKD 3 at baseline (n=39)** | **5.1-5.5 (n=28)** | 0 (0) | 21 (75) | 4 (14) | 3 (11) |
| | | **5.6-6.0 (n=10)** | 0 (0) | 8 (80) | 1 (10) | 1 (10) |
| | | **>6.0 (n=1)** | 0 (0) | 0 (0) | 1 (100) | 0 (0) |
| | **CKD 4 at baseline (n=48)** | **5.1-5.5 (n=24)** | 0 (0) | 18 (75) | 6 (25) | 0 (0) |
| | | **5.6-6.0 (n=19)** | 0 (0) | 8 (42) | 8 (42) | 3 (16) |
| | | **>6.0 (n=5)** | 0 (0) | 2 (40) | 2 (40) | 1 (20) |
| **OPAL-HK** | **CKD 3 at baseline (n=36)** | **5.1-5.5 (n=23)** | 20 (87) | 3 (13) | 0 (0) | 0 (0) |
| | | **5.6-6.0 (n=12)** | 11 (92) | 1 (8) | 0 (0) | 0 (0) |
| | | **>6.0 (n=1)** | 1 (100) | 0 (0) | 0 (0) | 0 (0) |
| | **CKD 4 at baseline (n=51)** | **5.1-5.5 (n=26)** | 19 (73) | 4 (15) | 3 (12) | 0 (0) |
| | | **5.6-6.0 (n=23)** | 22 (96) | 1 (4) | 0 (0) | 0 (0) |
| | | **>6.0 (n=2)** | 2 (100) | 0 (0) | 0 (0) | 0 (0) |

### 9.4.3 Interventions in SKS

There were no interventions for patients with a baseline potassium of <6.0mmol/L. Amongst the 9 patients with a potassium of 6.0mmol/L or more, only 5 patients received an outpatient intervention as determined from a clinic letter or clinical note found in the patient's electronic health record. Each of these patients received care from a different physician and interventions were not consistent at specific potassium values (Table 9.5).

**Table 9.5** Interventions for SKS patients with baseline $[K^+] \geq 6.0$mmol/L

| | **Baseline $[K^+]$/mmol/L** | **Intervention** | **Follow-up $[K^+]$/mmol/L** |
|---|---|---|---|
| **Patient 1** | 6.0 | No action | 6.1 |
| **Patient 2** | 6.0 | Dietary advice | 6.3 |
| **Patient 3** | 6.0 | ACEi stopped | 5.6 |
| **Patient 4** | 6.1 | Dietary advice | 5.7 |
| **Patient 5** | 6.1 | No action | 6.1 |
| **Patient 6** | 6.2 | Furosemide added | 5.8 |
| **Patient 7** | 6.2 | Dietary advice. ACEi halved | 5.6 |
| **Patient 8** | 6.2 | No action | 5.4 |
| **Patient 9** | 6.4 | No action | 5.4 |

Amongst the 5 patients who had an intervention, there was a mean change in potassium of -0.3±0.4mmol/L, with 4 out of the 5 patients reaching a potassium level of <6.0mmol/L, and this included 2 patients who had a change in their RAASi therapy. There were 4 patients, however, without any documented action, in whom the mean potassium change was -0.4±0.5mmol/L at follow-up.

### 9.4.4 Unmatched analysis

A separate analysis was undertaken for the original unmatched 162 SKS patients that met the inclusion and exclusion criteria of the OPAL-HK study. Similar changes in potassium were found: the baseline mean potassium level was 5.4±0.3mmol/L, which remained unchanged at follow-up, and 0% achieved a potassium in the range 3.8 to <5.1mmol/L.

## 9.5 DISCUSSION

Comparing a real-world CKD cohort precisely matched to the first phase of the OPAL-HK study, we have shown that patiromer plays a role in lowering potassium levels in patients who have CKD stages 3 or 4 and who are taking RAASi treatment.

Undertaking placebo-controlled trials in hyperkalaemic patients would be considered unethical given the potential for harm to patients with uncorrected elevations in potassium [6]. We believe our study is the first to provide a real-world comparison arm to overcome this challenge faced by trials studying interventions for hyperkalaemia.

In our analysis, patiromer reduced potassium levels by -1.01±0.03mmol/L, and 80% of patients were in a target range of 3.8 to <5.1mmol/L at week 4. This was in sharp contrast to the SKS cohort, in which some patients developed potassium levels of >6.0mmol/L at follow-up even when their baseline potassium was between 5.1-5.5mmol/L (Table 9.3). No patient, however, had a follow-up potassium of >6.0mmol/L in the OPAL-HK cohort.

It is important to note that the SKS cohort is based in the UK, where national guidelines advise altering or discontinuing RAASi in patients with CKD only when the potassium is >6.0mmol/L [6]. This is clearly reflected in the small number of patients who underwent an alteration in their RAASi (Table 9.5) and also explains why the majority of SKS patients in this analysis did not experience an overall mean change in potassium. In effect, therefore, the SKS cohort was akin to a placebo group in which the vast majority of patients received no discernible action to lower potassium, which is an accurate reflection of the standard care for managing ambulatory hyperkalaemia in CKD patients in the UK.

Typical interventions for hyperkalaemia management include reducing or stopping RAASi, promoting a low-potassium diet (usually with input from a dietician), initiating or up-titrating sodium bicarbonate to correct acidosis and initiating or up-titrating diuretics in the presence of fluid overload [7]. Some of these actions were only implemented in the small group of SKS patients with a baseline potassium ≥6.0mmol/L,

but there was significant variation in the care afforded by different clinicians (Table 9.5).

A significant weight of evidence exists from several studies highlighting the clinical efficacy of patiromer at permitting use of RAASi by preventing hyperkalaemia. In PEARL-HF [8], 105 patients with either chronic heart failure and a history of hyperkalaemia resulting in discontinuation of a RAASi and/or beta-adrenergic blocking agent, or CKD (defined as an eGFR <60ml/min/1.72m$^2$) were initiated on spironolactone 25mg/day and were randomised to a double-blind treatment with either patiromer 25.2g/day or placebo for 4 weeks. Spironolactone, initiated at 25mg/day, was increased to 50mg/day on day 15 if potassium was ≤5.1mmol/L. Patiromer was shown to reduce serum potassium levels with a difference between groups of -0.45mmol/L ($p<0.001$), reduce the incidence of patients reaching a potassium of >5.5mmol/L (7.3% patiromer vs. 24.5% placebo; $p=0.015$), and allow a higher proportion of patients to up-titrate spironolactone to 50mg/day (91% patiromer vs. 74% placebo; $p=0.019$). However, only 50% of patients had CKD in this study and this was reflected in the high mean (±SD) baseline eGFR of 84±35ml/min/1.73m$^2$ in the treatment group.

In contrast, the AMETHYST-DN [9] study focused on 306 diabetic patients with more advanced CKD (65% had CKD stage 3; 22% had stage 4) and who were all receiving RAASi. Patients were stratified to either having mild (>5.0-5.5mmol/L) or moderate (>5.5 to <6.0mmol/L) hyperkalaemia and then randomised to different doses of patiromer. The study showed that patiromer was effective at lowering potassium after 4 weeks of treatment, and this effect was sustained for up to 1 year. However, it was an unblinded study without a control arm.

The AMBER trial [10], in contrast, was a double-blind, placebo-controlled trial, although it did not focus on patients with baseline hyperkalaemia. This study enrolled 295 patients aged ≥18 years, with an eGFR of 25-45ml/min/1.73m$^2$, a baseline potassium between 4.3 and 5.1mmol/L and resistant hypertension. The main endpoint showed a statistically higher proportion of patients who were receiving patiromer remained on spironolactone compared with those receiving placebo (86% versus 66% respectively) at 12 weeks follow-up.

In addition to its efficacy at achieving and maintaining normokalaemia, patiromer has been consistently shown to be well tolerated with a very good safety profile. The majority of adverse effects reported from trials are gastrointestinal-related, including constipation (6.2%), diarrhoea (3.0%), abdominal pain (2.9%) and flatulence (1.8%). These adverse reactions are typically only mild-to-moderate in nature [11]. Hypomagnesaemia (5.3%) is also a recognised complication [11], and although there is no evidence of an increased risk of cardiac arrhythmias associated with patiromer-related hypomagnesaemia, monitoring of levels is advised and consideration given to magnesium replacement if it arises.

### 9.5.1 Strengths and limitations

Our work has a number of limitations. Firstly, although diet was not controlled, patients in the OPAL-HK study received counselling on maintaining a low-potassium diet at each visit during the trial regardless of their baseline potassium level. This was not the case in the real-world SKS cohort, in which dietetic input was routinely sought only when patients developed potassium levels of ≥6.0mmol/L. Amongst the 87 matched SKS patients, 13 had received dietetic review for low-potassium guidance in the past. During the study period, only 3 patients received dietetic advice (Table 9.5), all in instances where the potassium level was ≥6.0mmol/L. As the two cohorts differed in dietary potassium intervention, changes in potassium in the first phase of the OPAL-HK can only therefore partly be attributed to patiromer use. Secondly, OPAL-HK patients had a blood test at day 3 and then weekly thereafter for 4 weeks. In contrast, the SKS cohort had a blood test at baseline and then at follow-up, which was 3.5 to 6 weeks between the two potassium readings. The difference in intensive monitoring and follow-up is, however, only significant in that it permitted patients in OPAL-HK to receive dietary counselling at each visit. The less intensive and wider follow-up timeframe in the SKS cohort is a reflection of real-world practice, dependent upon clinical need as adjudged by the managing clinician. Thirdly, use of retrospective real-world data can be affected by a lack of quality in data recording. We attempted to overcome this by cross-checking the data to ensure all patients' parameters were accurate at the point of entry into the analysis. We could not, however, account for changes in patient care beyond what had been recorded in clinic letters between the baseline and follow-up potassium measurement. Some SKS patients appeared to not receive any intervention despite their potassium being >6.0mmol/L but they may have received undocumented intervention.

Given SKS patient selection in this study spanned the timeframe from the cohort's inception in 2002, different patients may have been exposed to a differential degree of care. However, routine interventions for hyperkalaemia management have remained unchanged since 2002, and the 87 SKS patients in our analysis represent standards of care which is characteristic of current UK guidance and practice. Fourthly, given this work only focuses on UK patients, the results may not be generalisable to other patient populations. Finally, the total number of SKS patients that underwent analysis was much smaller than the 243 patients initially enrolled into OPAL-HK. The final groups, however, were precisely matched, and this is arguably a strength of the study as it permitted more robust analysis. Regardless, similar findings were reached in the unmatched cohort of 162 patients. In addition, given there was little difference in the results of the primary and secondary endpoints in our work compared to the OPAL-HK study, our 87 OPAL-HK patients were representative of the overall 243 patients in the OPAL-HK trial.

Notwithstanding the discrepancy in dietary intervention, the routine, real-world care in the SKS cohort still affords a valuable control arm in this specific study because (1) all patients met the inclusion and exclusion criteria of the OPAL-HK study, which excluded patients taking sodium bicarbonate or other potassium binders; (2) patients were closely matched based on propensity-matched scores; (3) there was no significant difference between baseline and follow-up eGFR and thus changes in renal function were unlikely to affect potassium levels; and (4) there were a minimal number of interventions in the SKS cohort, and thus the RAASi doses were unchanged in the vast majority of patients at follow-up.

## 9.6 CONCLUSION

Achieving normokalaemia to permit continuation of prognostically beneficial RAASi remains a primary concern for optimal CKD care and for patients with heart failure. We provide evidence using a comparative UK-based CKD cohort that emphasises the potential benefit of patiromer in lowering potassium levels in patients with CKD stages 3-4 after 4 weeks of follow-up, whereas there was no change in potassium concentration in their real-world matched comparators, reflecting a minimal degree of potassium

lowering interventions in regular clinical practice, especially in patients with levels above the normal range but less than 6mmol/L. Further longer-term prospective data evaluating patiromer against standard care in managing hyperkalaemia, especially in patients with potassium levels >6.0mmol/L, and ideally enabling access to major clinical outcome data, would be desirable.

## 9.7 REFERENCES


1. Sarafidis PA, Blacklock R, Wood E, et al. Prevalence and factors associated with hyperkalaemia in predialysis patients followed in a low-clearance clinic. Clin J Am Soc Nephrol. 2012;7:1234-1241.
2. Hou FF, Xie D, Zhang X, et al. Renoprotection of optimal antiproteinuric doses (ROAD) study: a randomised controlled study of benazepril and losartan in chronic renal insufficiency. J Am Soc Nephrol. 2007;18:1889-1898.
3. KDIGO: Clinical practice guideline for the evaluation and management of chronic Kidney disease. Kidney Int. 2013;3:i-150.
4. Georgianos PI, Agarwal R. Revisting RAAS-blockade in CKD with newer potassium binding drugs. Kidney Int. 2018;93:325-334.
5. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372:211–221.
6. NICE: Chronic kidney disease in adults: assessment and management. 2015. Available at: https://www.nice.org.uk/guidance/cg182. [Accessed 3 Feb 2020].
7. Kovesdy CP: Management of hyperkalaemia in chronic kidney disease. Nat. Rev. Nephrol. 2014;10:653-662.
8. Pitt B, Anker SD, Bushinsky DA, et al; PEARL-HG Investigators: Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. European Heart Journal. 2011;32:820-828.
9. Bakris GL, Pitt B, Weir MR, et al. AMETHYST-DN Investigators: Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. JAMA. 2015;314:151–161.
10. Agarwal R, Rossignol P, Romero A, et al. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet. 2019;394:1540-1550.

11. Electronic Medicine Compendium. Veltassa (Patiromer) 8.4g powder for oral suspension. Available at: https://www.medicines.org.uk/emc/product/779/. [Accessed 27 June 2020].

## CHAPTER 10

---

# EXPERIENCE OF A BESPOKE HYPERKALAEMIA CLINIC TO FACILITATE PRESCRIBING OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITORS IN PATIENTS WITH HEART FAILURE WITH REDUCED EJECTION FRACTION

---

Ibrahim Ali, Darren Green, Paul Kalra, Philip A. Kalra

*Planned for submission*

## 10.1 ABSTRACT


### Background

Evidence-based practice recommends prescribing renin-angiotensin-aldosterone system inhibitors (RAASi) at maximally tolerated doses to improve prognosis in patients with heart failure with reduced ejection fraction (HFrEF), but suboptimal dosing or discontinuation of these medications often occurs due to RAASi-associated hyperkalaemia, the incidence of which is increased in those with concomitant diabetes and chronic kidney disease (CKD). We established a nephrology-led hyperkalaemia clinic to oversee prescribing of patiromer, an oral potassium-binder, to facilitate RAASi optimisation.

### Methods

The hyperkalaemia clinic was established in July 2019 at a nephrology tertiary centre in the United Kingdom. Patients with HFrEF, under cardiology services at district hospitals, who were unable to increase RAASi dosage due to hyperkalaemia were referred to the clinic to initiate patiromer. Patients were all commenced on patiromer 8.4g daily. Adjustments to RAASi and electrolyte monitoring were deferred to the referring cardiology teams. Study outcomes included the percentage of patients who achieved an increase in RAASi dosage and the proportion of patients with serum potassium level in the normal range at follow-up. Outcome data were evaluated until 1st May 2021.

### Results

A total of 34 patients were reviewed in the clinic between July 2019 and December 2020. Mean age was 71.6 years (±10.6 years), 56% had diabetes and 71% had CKD stages 3a-5; mean eGFR was 56ml/min/1.73m$^2$ (±21ml/min/1.73m$^2$). The majority of patients (88%) were receiving RAASi at referral. During follow-up, 12 patients discontinued patiromer (6 of whom did so due to gastrointestinal side effects) and were discharged; two patients died from non-hyperkalaemia related illness, and one switched to an alternative potassium-binder. Over a mean follow-up of 13.4 months (±5.8 months), 17 of the 20 patients (85%) who continued with a potassium-binder achieved an increase in RAASi dosage, with 4 patients (21%) receiving maximal dosing of at

least one RAASi. This was attained by controlling serum potassium levels during follow-up. No patients required magnesium supplementation. Of the 19 patients on patiromer, 12 (63%) continued this therapy for more than 12 months and 4 (21%) had received it safely for 20 months.

**Conclusions**

The prescribing of patiromer in a nephrology-led hyperkalaemia clinic successfully facilitated RAASi up-titration in patients with HFrEF by controlling potassium levels. Our real-world clinic experience highlights the encouraging safety and efficacy profile of patiromer, and its use should be strongly considered to improve optimal RAASi prescribing in this high-risk patient cohort.

## 10.2 INTRODUCTION

Renin-angiotensin-aldosterone system inhibitors (RAASi) represent a key group of pharmacological therapies for patients with heart failure with reduced ejection fraction (HFrEF) [1] given angiotensin converting enzyme inhibitors (ACEi) [2], angiotensin receptor blockers (ARB) [3], mineralocorticoid antagonists (MRA) [4] and angiotensin receptor-neprilysin inhibitors [5] improve patient survival. Achieving maximal dosing of RAASi is therefore recommended in international guidelines [1] but is often hindered by the occurrence of hyperkalaemia (typically defined as potassium >5.0mmol/L), which results in either submaximal RAASi dosing or RAASi discontinuation, actions which consequently contribute to poorer long-term prognosis [6]. The risk of hyperkalaemia in heart failure is further increased in those with diabetes and chronic kidney disease (CKD) [7-9], and episodes of hyperkalaemia can often be recurrent in these high-risk patients [10].

The advent of novel oral potassium binders, patiromer (Veltassa®) and sodium zirconium cyclosilicate, (SZC; Lokelma®) have heralded a promising ability to overcome the challenges of hyperkalaemia management in patients with heart failure receiving RAASi [11-15]. For instance, the 4-week PEARL-HF [11] trial recruited 105 patients with heart failure, of whom 41% had experienced RAASi discontinuation due to hyperkalaemia. Compared with placebo, patiromer significantly reduced potassium

levels and increased the proportion of patients who could safely tolerate a dose increase of spironolactone (91% versus 74%). Furthermore, 105 patients with heart failure in a subgroup of the AMETHYST-DN trial [12] also maintained normokalaemia with patiromer for up to 52 weeks. A 12-month study of SZC [15] in 758 patients showed that after initial normalisation of potassium with SZC, a mean serum potassium of ≤5.1mmol/L was achieved in 88% of patients, and amongst the patients taking RAASi, 87% continued them or had a dose increase. There were however only 15% with heart failure in the maintenance phase of this study and thus further data are awaited to extend the evidence base for using SZC in patients with heart failure [16].

However, whilst guidance now supports the use of potassium binders [17], there is a lack of real-world experience of how potassium binders change RAASi prescribing in patients with heart failure. Encouraged by the evidence and appeal of the new potassium binders, especially with patiromer, we established a hyperkalaemia clinic within the renal services at our centre for the purpose of prescribing patiromer to facilitate RAASi optimisation in symptomatic patients with HFrEF. This current work reports on the outcomes of the first 21 months since inception of this clinic with specific focus placed on changes to RAASi prescribing, serum potassium levels and estimated glomerular filtration rate (eGFR) in our patient cohort during follow-up.

## 10.3 METHODS

### 10.3.1 Study population

The study population comprised patients with HFrEF who were referred from local district general hospital heart failure services to a bespoke hyperkalaemia clinic at Salford Royal NHS Foundation Trust between July 2019 and December 2020. Patients with symptomatic heart failure for whom initiation or up-titration of RAASi were limited by the occurrence of hyperkalaemia were the targets for referral. These primarily included patients whose potassium had climbed >5.3mmol/L whilst receiving a RAASi and where the clinical team overseeing heart failure care felt further dose increases were felt not possible or had led to RAASi reduction or discontinuation.

### 10.3.2 Hyperkalaemia clinic service

Since its inception in July 2019, the clinic has run on a monthly basis led by a consultant nephrologist. The main intervention has been to oversee the initial and continued prescribing of patiromer, but it has also simultaneously provided specialist renal care to those with advanced CKD. Prior to commencing patiromer, patients are educated on the importance of achieving normokalaemia, provided with low-potassium dietary information if they had not already received this from the referring team, and given information about patiromer including directions for administration, common side effects and the importance of taking the drug three hours before, or after, other prescribed medications [18]. Upon commencing patiromer, recommendations for early checking of potassium and magnesium levels after patiromer initiation and during follow-up is provided to the referring team with subsequent monitoring taking place every 3-4 months in the bespoke hyperkalaemia clinic. RAASi up-titration is also deferred to the referring heart failure teams and is recommended when repeat potassium monitoring demonstrates values to be in the normal laboratory range (3.5-5.3mmol/L). The referring team also has responsibility for electrolyte monitoring upon any RAASi dose titration. SZC is chosen at the discretion of the consultant nephrologist if patiromer is not tolerated. Patients are reviewed in the hyperkalaemia clinic every 3-4 months at the discretion of the consultant nephrologist for assessment of i) tolerance to therapy, ii) the need to continue a potassium binder, and iii) patient's potassium control. Patients are discharged from clinic if they discontinue patiromer due to drug intolerance or if patiromer is judged to be no longer indicated.

### 10.3.3 Baseline clinic variables

Demographic data included age, gender, ethnicity, systolic and diastolic blood pressure. Co-morbidities, in addition to heart failure, included diabetes mellitus, hypertension and CKD. Medications included ACEi, ARB, MRA, angiotensin receptor-neprilysin inhibitor, diuretics, beta-blockers, sodium bicarbonate and insulin. Laboratory measurements included estimated glomerular filtration rate (eGFR), calculated using the CKD-EPI equation, serum bicarbonate (in mmol/L) and serum potassium (in mmol/L).

### 10.3.4 Study outcomes

The primary outcome was the percentage of patients receiving a potassium binder for whom RAASi prescribing was increased. An increase in RAASi was defined as

initiating a RAASi, an increase in the dose of a prescribed RAASi or the initiation of an additional RAASi agent, either prescribed alone or as part of a combination therapy. Secondary outcomes included the proportion of patients with a serum potassium in the normal laboratory range change and change in eGFR from the point of referral to patients' last clinic visit. Outcome data were evaluated until 1st May 2021.

### 10.3.5 Statistical analysis

Continuous variables are presented as mean and standard deviation and categorical data as absolute numbers with percentages. The paired Student's t-test was used to analyse changes to patients' potassium and eGFR levels during follow-up. A p-value of $<0.05$ was considered statistically significant. Statistical analyses were conducted using R, version 4.0.2 (The R Foundation for Statistical Computing Platform).

### 10.3.6 Ethical approval

All patients referred to the hyperkalaemic clinic were enrolled into the Salford Kidney Study (SKS) [19], an ongoing prospective epidemiological study, which since 2002 has been recruiting patients with non-dialysis dependent chronic kidney disease. The SKS gained ethical approval from the North West Greater Manchester South Research Ethics Committee (REC15/NW/0818). Written informed consent was obtained from all patients.

## 10.4 RESULTS

### 10.4.1 Baseline characteristics

A total of 34 patients with HFrEF were referred to the hyperkalaemia clinic from July 2019 until December 2020. In this cohort, the mean age was 71.6 years (±10.6 years), and patients were predominantly female (71%), and almost exclusively Caucasian (94%), as shown in Table 10.1. There was a high prevalence of significant co-morbidities, including hypertension (53%), diabetes mellitus (56%) and CKD stages 3a-5 (71%); the mean eGFR was 56ml/min/1.73m$^2$ (±21ml/min/1.73m$^2$). Most patients were already established on a RAASi (88%) at the first clinic visit with 76% receiving an ACEi or ARB, either alone or in combination with an MRA. Two patients were receiving an angiotensin receptor-neprilysin inhibitor. The mean potassium at first clinic

visit was 4.9mmol/L (±0.5mmol/L). At review in clinic, most patients (68%) had a potassium in the normal range whilst 9 patients (26%) had a value between 5.3-6.0mmol/L. The serum bicarbonate was normal in all patients with a mean of 27.2mmol/L (±2.2mmol/L).

**Table 10.1** Clinic baseline characteristics

| Variable | Patients (n=34) |
|---|---|
| Age, years | 71.6 (±10.6) |
| Male, *n* (%) | 10 (29) |
| Caucasian, *n* (%) | 32 (94) |
| Hypertension, *n* (%) | 18 (53) |
| Diabetes mellitus, *n* (%) | 19 (56) |
| Chronic kidney disease, *n* (%) | |
| - G1 (eGFR>90 ml/min/1.73m$^2$) | 4 (12) |
| - G2 (eGFR 60-89 ml/min/1.73m$^2$) | 7 (21) |
| - G3a (eGFR 45-59 ml/min/1.73m$^2$) | 15 (44) |
| - G3b (eGFR 30-44 ml/min/1.73m$^2$) | 7 (21) |
| - G4 (eGFR 15-29 ml/min/1.73m$^2$) | 2 (6) |
| - G5 (eGFR <15 ml/min/1.73m$^2$) | 0 (0) |
| *Systolic blood pressure, mmHg | 129 (±18) |
| *Diastolic blood pressure, mmHg | 74 (±13) |
| **Medications** | |
| No RAASi | 4 (12) |
| ACEi alone, *n* (%) | 12 (35) |
| ARB alone, *n* (%) | 3 (9) |
| MRA alone, *n* (%) | 2 (6) |
| ACEi + MRA, *n* (%) | 8 (24) |
| ARB + MRA, *n* (%) | 3 (9) |
| Angiotensin receptor-neprilysin inhibitor alone, *n* (%) | 2 (6) |
| Diuretic, *n* (%) | 18 (53) |
| Beta-blocker, *n* (%) | 31 (91) |
| Sodium bicarbonate, *n* (%) | 3 (9) |
| Insulin, *n* (%) | 3 (9) |
| **Laboratory values** | |
| eGFR, ml/min/1.73m$^2$ | 56 (±21) |
| ^Serum potassium, mmol/L | 4.9 (±0.5) |
| - Serum potassium ≤5.3, *n* (%) | 25 (74) |
| - Serum potassium 5.4-6.0, *n* (%) | 7 (21) |
| - Serum potassium >6.0, *n* (%) | 0 (0) |
| #Serum bicarbonate, mmol/L | 27.2 (±2.20) |

*Blood pressure measurements not available in 6 patients.

^Serum potassium haemolysed in 2 patients.

#Serum bicarbonate not available in 9 patients.

### 10.4.2 Follow-up

All 34 patents were initiated on a starting dose of patiromer 8.4g once daily. Over a follow-up of 10.5 months (±6.4 months), 13 patients (38%) discontinued patiromer (Figure 10.1). Of this latter group, 6 did so due to gastrointestinal side effects. Other reasons for discontinuation included patient reluctance to increase RAASi; a concern for patient compliance in the setting of vascular dementia and improved echocardiographic findings of heart function that led to patient discharge from the heart failure services (Table 10.2). From those that discontinued patiromer, one patient was successfully switched to SZC and remained under follow-up, whilst the remaining 12 patients were discharged. Two patients died having had only one clinic visit (1 died from sepsis and the other from an intracerebral haemorrhage).

**Figure 10.1** Patient follow-up outcomes

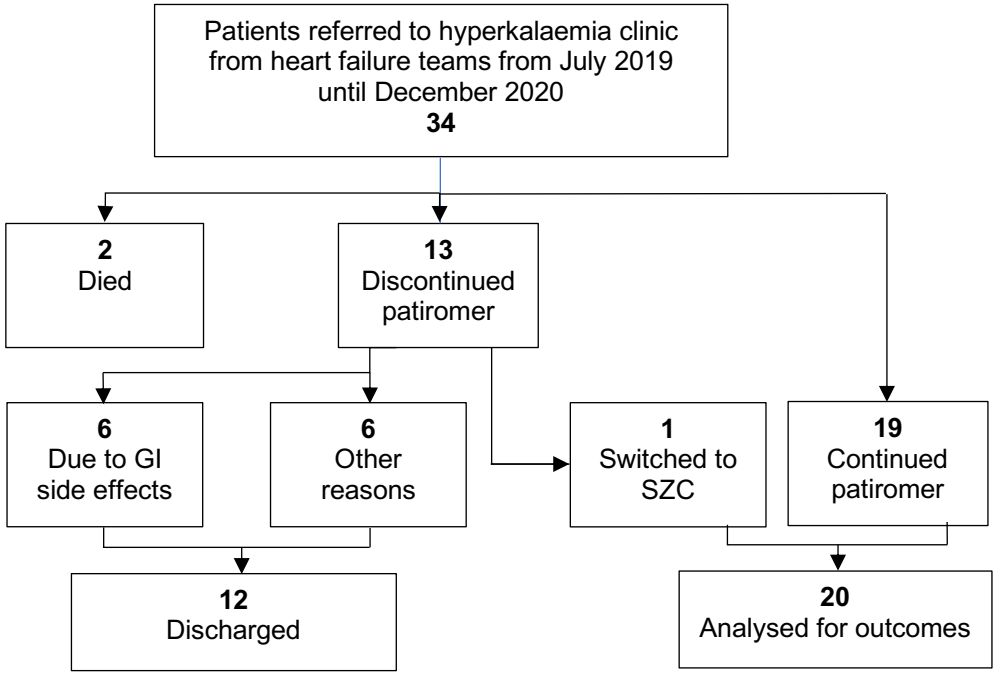


**Table 10.2** Reasons for patiromer discontinuation

| | Reason for patiromer discontinuation |
|---|---|
| 1 | Nausea and vomiting |
| 2 | Abdominal cramps |
| 3 | Unpalatable |
| 4 | Nausea |
| 5 | Diarrhoea |
| 6 | Abdominal pain and diarrhoea |
| 7 | Abdominal pain |
| 8 | Non-specific intolerance |
| 9 | Non-specific intolerance |
| 10 | Decision made to trial SZC when potassium 5.8mmol/L despite being on 16.8g patiromer |
| 11 | Patient not keen to up-titrate RAASi so patiromer no longer required |
| 12 | Subsequently felt not suitable for patiromer due to vascular dementia |
| 13 | Discharged from heart failure services due to improved ejection fraction; patiromer no longer indicated |

### 10.4.3 Changes to RAASi prescribing

A total of 20 patients were analysed for the study outcomes: 19 patients were receiving patiromer 8.4g daily and 1 patient received SZC 5g daily. The mean follow-up time in this patient group was 13.4 months (±5.8 months). All patients had had at least 2 hyperkalaemia clinic visits. The minimum time that a patient received patiromer was for at least 3 months, with 12 (63%) receiving it for more than 12 months and 4 patients (21%) receiving it for 20 months. The patient receiving SZC received it for 7 months up until their last clinic visit. Seventeen of the 20 patients (85%) receiving a potassium binder were able to have an increase in their RAASi medication by the end of the study follow-up (Table 10.3): 3 patients were initiated on a RAASi, 8 had their RAASi dose increased, 4 had an additional agent added and 2 had both an increase in their RAASi and an addition of another agent. RAASi dose increases ranged from 50% to 700% of patients' original clinic dose; median increase of 200% (interquartile range: 112-200%). Four patients (21%) attained maximal dosing of a RAASi by the end of the study follow-up.

**Table 10.3** RAASi modifications before and after initiation of a potassium binder

| Patient | At first visit | Dose (mg) | Frequency | At last visit | Dose (mg) | Frequency |
|---|---|---|---|---|---|---|
| 1 | No RAASi | - | - | Irbesartan | 150 | Once daily |
| 2 | No RAASi | - | - | Lisinopril | 10 | Once daily |
| 3 | No RAASi | - | - | Lisinopril | 12.5 | Once daily |
| 4 | Ramipril | 1.25 | Thrice weekly | Ramipril<br>**Eplerenone** | 2.5<br>**50** | Once daily<br>**Once daily** |
| 5 | Ramipril | 1.25 | Once daily | **Ramipril**<br>Spironolactone | **10**<br>25 | **Once daily**<br>Once daily |
| 6 | Ramipril | 1.25 | Once daily | Ramipril<br>Spironolactone | 1.25<br>12.5 | Once daily<br>Alternate days |
| 7 | Ramipril | 2.5 | Once daily | Ramipril | 2.5 | Once daily |
| 8 | Ramipril | 2.5 | Once daily | Ramipril | 5 | Once daily |
| 9 | Candesartan | 6 | Once daily | Candesartan<br>Eplerenone | 6<br>25 | Once daily<br>Once daily |
| 10 | Candesartan | 8 | Once daily | Candesartan<br>Spironolactone | 4<br>25 | Once daily<br>Once daily |
| 11 | Valsartan | 240 | Once daily | Valsartan<br>Eplerenone | 240<br>12.5 | Once daily<br>Once daily |
| 12 | Spironolactone | 25 | Twice weekly | Spironolactone | 25 | Thrice weekly |
| ^13 | Sacubitril/ valsartan | 49/51 | Once daily | **Sacubitril/ valsartan** | **97/103** | **Twice daily** |
| 14 | Ramipril<br>Spironolactone | 1.25<br>12.5 | Once daily<br>Once daily | Ramipril<br>Spironolactone | 3.75<br>12.5 | Once daily<br>Once daily |
| 15 | Ramipril<br>Spironolactone | 2.5<br>25 | Once daily<br>Once daily | Sacubritil/ valsartan<br>Spironolactone | 97/103<br>25 | Once daily<br>Once daily |
| 16 | Ramipril<br>Eplerenone | 2.5<br>25 | Once daily<br>Once daily | Ramipril<br>Eplerenone | 6.25<br>25 | Once daily<br>Once daily |
| 17 | Ramipril<br>Eplerenone | 5<br>50 | Once daily<br>Once daily | Sacubitril/ valsartan<br>Eplerenone | 49/51<br>50 | Once daily<br>Once daily |
| 18 | Ramipril<br>Spironolactone | 10<br>12.5 | Once daily<br>Alternate days | Sacubitril/ valsartan<br>Spironolactone | 24/26<br>12.5 | Once daily<br>Alternate days |
| 19 | Candesartan<br>Spironolactone | 12<br>12.5 | Once daily<br>Thrice weekly | Candesartan<br>**Eplerenone** | 20<br>**50** | Once daily<br>**Once daily** |
| 20 | Losartan<br>Spironolactone | 25<br>25 | Once daily<br>Once daily | Losartan<br>Spironolactone | 25<br>25<br>alternating with 50 | Once daily<br>Alternate days |

^This patient received SZC 5g daily. All other patients were taking patiromer 8.4g once daily.

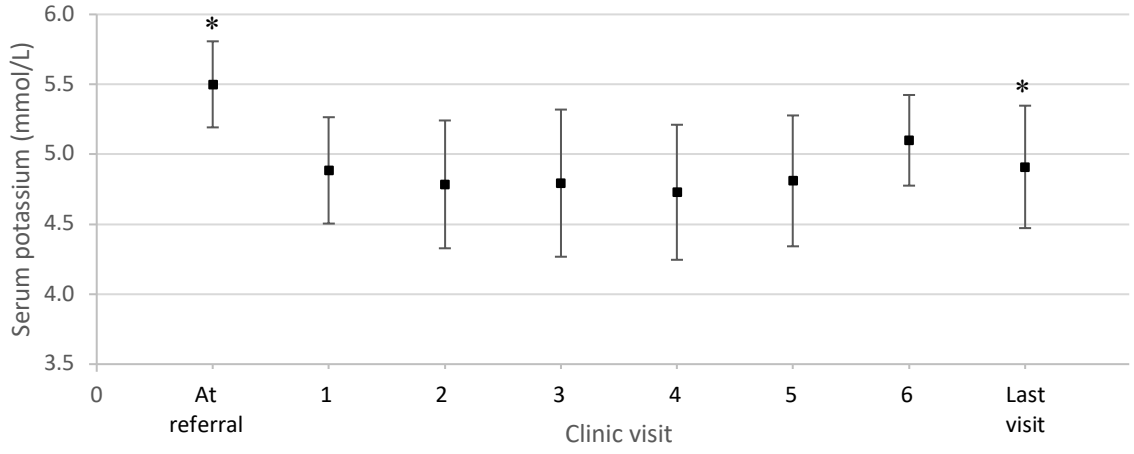
Maximal doses of a RAASi at the last clinic visit are highlighted in blue.

### 10.4.4 Changes to potassium, magnesium and eGFR levels

With respect to potassium control in the 20 patients who remained under follow-up, 45% of patients (9/20) had a potassium in the normal range at the time of referral to the clinic, 85% (17/20) at their first clinic visit and 75% (15/20) at their last clinic visit. The mean serum potassium was 5.5mmol/L (±0.3mmol/L) at the point of referral to the clinic, 4.9mmoL/L (±0.4mmol/L) at the first clinic visit (approximately 6 weeks on average after referral) and 4.9mmol/L (±0.4mmol/L) at patients' last clinic visit (Figure 10.2); $p<0.001$ for the difference between the patients' potassium at the time of referral and at their last clinic visit. No patient experienced hyperkalaemia of >6.0mmol/L or hypokalaemia of <3.5mmol/L at any point during follow-up. Furthermore, no patients received magnesium supplementation during the follow-up period; patients' mean magnesium was 0.76mmol/L (±0.08mmol/L) at the last clinic visit.

With respect to changes in eGFR during follow-up, 8 patients (40%) experienced a decline in eGFR. The mean eGFR at the time of referral was 57ml/min/1.73m$^2$ (±22ml/min/1.73m$^2$), 60ml/min/1.73m$^2$ (±22ml/min/1.73m$^2$) at the first clinic visit and 55ml/min/1.73m$^2$ (±25ml/min/1.73m$^2$) at the last clinic visit; $p=0.37$ comparing patients' eGFR at time of referral and at their last clinic visit.

**Figure 10.2** Patients' mean potassium at referral and at clinic visits during follow-up




The error bars represent standard deviation. At referral, n=20; clinic visit 1, n=20; clinic visit 2, n=20; clinic visit 3, n=16; clinic visit 4, n=14; clinic visit 5, n=10; clinic visit 6, n=5. The last visit represents the mean potassium of all patients at their last clinic visit. *$p<0.001$ for the difference in patients' potassium at referral and at patients' last clinic visit analysed using paired Student's t-test.

## 10.5 DISCUSSION

This study provides for the first time, to the best of our knowledge, a real-world experience of prescribing potassium binders in a nephrology-led hyperkalaemia clinic. Whilst patiromer was not tolerated in a quarter of patients, we show that for those who continued treatment, and SZC in one case, RAASi optimisation was facilitated in patients with HFrEF by controlling potassium. We also highlight the safe continuation of patiromer beyond 12 months in clinical practice.

### 10.5.1 Optimisation of RAASi

Born out of our enthusiasm for the potential of patiromer in managing hyperkalaemia, we established an outpatient service to support our local heart failure services in coordinating and overseeing the prescribing of patiromer. This role was suited to nephrology given our experiences of managing ambulatory hyperkalaemia in patients with CKD, in particular ensuring acidosis is corrected and patients receive information to maintain a low-potassium diet.

Whilst there was a lack of treatment algorithms in the literature for managing hyperkalaemia in heart failure at the time of establishing our clinic, we devised a relatively simple management approach based on a central tenet: if the serum potassium is in the normal range whilst on patiromer, up-titration of RAASi should be undertaken for improved heart failure symptom control and maximum prognostic benefit. This proved to be achievable through the collaborative efforts of the referring heart failure teams as 85% of patients taking a potassium binder long-term experienced an increase in RAASi prescription. The majority of patients experienced an increase in their RAASi dose (e.g., from ramipril 2.5mg daily to 5mg daily or sacubitril/valsartan 49/51mg daily, increased to 97/103mg twice daily; Table 10.3, patients 8 and 13 respectively) but some experienced both an up-titration of their initial RAASi and an additional agent (e.g., ramipril 1.25mg daily increased to ramipril 10mg with the addition of spironolactone 25mg daily; Table 10.3, patient 5). Importantly, 4 patients (21%) reached maximal doses of at least one RAASi by the end of the study follow-up.

### 10.5.2 Potassium control

Current guidance from the National Institute for Health and Care Excellence (NICE) recommends that patiromer or SZC be prescribed for outpatients with heart failure who are taking a suboptimal dose of RAASi if they have had a serum potassium of ≥6.0mmol/L [20]. We employed a modified approach in the hyperkalaemia clinic: all our patients received patiromer at 8.4g once daily even where the potassium was in the normal range. This is because patients had been specifically referred since the heart failure teams had encountered elevated potassium levels when RAASi doses had been previously increased, and which had hindered further RAASi increases or had led to its discontinuation. Whilst the confidence to continue RAASi will vary between healthcare professionals, there was a reluctance to initiate or up-titrate RAASi when serum potassium was in the range 5.3-6.0mmol/L. This is most likely due to concerns for the potential for levels to rise beyond 6.0mmol/L, which is a level that often necessitates hospitalisation for acute potassium-lowering management due to the risk of life-threatening cardiac arrhythmias. Our strategy enabled patients to maintain better potassium control throughout their follow-up, and no patient experienced potassium levels of ≥6.0mmol/L.

We now welcome the recent publication of a proposed treatment algorithm based on expert consensus for managing RAASi-associated hyperkalaemia in patients with heart failure [21]. The algorithm details a methodology for prescribing patiromer, importantly recommending its use when potassium levels are ≥5.1mmol/L. It also provides advice on the frequency of electrolyte monitoring whilst a patient is receiving a potassium binder and after RAASi doses are adjusted. We envisage this will support the development of clinical practice guidelines for our local heart failure services and may permit them to execute both patiromer prescribing and RAASi titration under a single service framework as opposed to our current model. This will be an important step to help increase the accessibility of patiromer and afford prompt RAASi titration for patients under the care of single specialist team.

### 10.5.3 Safety

A quarter of patients discontinued patiromer due to an intolerance, the most common cause being gastrointestinal side-effects. This is a well-recognised issue and occurred in

18% of our cohort, similar to figures observed in trial data: 17% of patients in the OPAL-HK trial [12] and 21% of patients in the PEARL-HF trial [11].

Hypomagnesaemia can also arise with patiromer treatment, but mean serum magnesium levels were within normal limits at follow-up in our cohort and no patients required supplementation. In the patient taking SZC, peripheral swelling or oedema did not arise. Whilst the eGFR did fall in 8 patients (40%) who continued with a potassium binder, these patients all experienced an increase in their RAASi prescription during follow-up and there was no statistical difference between the eGFR at referral and at patients' last clinic visit.

### 10.5.4 Strengths and limitations

A key limitation of the hyperkalaemia clinic is the dependence on the referring team to make the necessary RAASi adjustments and ensure appropriate blood monitoring is undertaken. Whilst the majority of patients did receive an increase in RAASi dosage, we question whether more rapid titration of RAASi could have occurred, and a greater proportion of patients could have been in receipt of maximal RAASi doses during the follow-up period. A closer and more direct multidisciplinary collaboration could improve this critical aspect of patient care. In the long-term, we may foresee the service being entirely delivered by the cardiology teams with support from ourselves if concerns regarding CKD arose. Secondly, we lacked baseline serum magnesium levels, but follow-up magnesium levels showed no patient required supplementation. Thirdly, the early blood monitoring undertaken by the district hospitals upon initiation of a potassium binder was not collected in this study. However, no issues regarding these tests were directly raised by the referring teams and follow-up results in the clinic highlighted the efficacy of patiromer in maintaining potassium levels <6.0mmol/L. Fourthly, not all patients who discontinued patiromer were directly offered SZC, which may have been a suitable and effective alternative. However, during the early phase of the clinic's operation, there was little familiarity with its use in heart failure and so it was not prescribed. We have subsequently communicated with the referring heart failure teams to raise the question as to whether they may wish to trial SZC in patients who are intolerant to patiromer. Finally, we report on the experience of a small cohort of patients from a single-centre and lack long-term data on patients' symptoms or major clinical endpoints. The ongoing DIAMOND trial [22], seeking to recruit over 2000

patients, will hopefully provide evidence on the effectiveness of patiromer to facilitate continuation of RAASi and to positively affect endpoints of cardiovascular hospitalisation events and cardiovascular death compared with placebo.

Our work also has strengths. We highlight, through the delivery of a bespoke hyperkalaemia clinic, that the use of patiromer was efficacious at controlling potassium and facilitating RAASi administration over an extended period of time. We show that patiromer can be used safely for more than 12 months, extending the evidence base for its safe use beyond that reported in clinical trials [13]. Despite our cohort being small, it was characterised by a high-risk patient group that was most likely to benefit from RAASi therapy. Our work also has the advantage of providing a granular inspection of RAASi prescribing and we suggest there is scope for this to be improved to align more closely with international guidelines [17].

Ultimately, we hope our real-world clinic experience, in tandem with the recently published treatment algorithm for managing hyperkalaemia in heart failure, will provide confidence to multidisciplinary specialists to consider incorporating potassium binders more readily into routine clinical care to negate the impact of RAASi-associated hyperkalaemia in patients with HFrEF.

## 10.6 CONCLUSIONS

In the setting of a nephrology-led hyperkalaemia clinic, patients with HFrEF who tolerated novel potassium binders, largely patiromer, benefited from potassium control that subsequently facilitated RAASi optimisation. Whilst RAASi doses were increased for the majority of patients, we await larger clinical studies to evaluate the impact of potassium binders on major outcomes such as cardiovascular and all-cause mortality.

## 10.7 REFERENCES


1. Ponikowski P, Voors AA, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–2200.
2. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA. 1995;273:1450-1456.
3. Granger CB, McMurray JJV, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362:772–776.
4. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med. 1999;341:709-717.
5. McMurray JJ, Packer M, Desai AS, et al. PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
6. Epstein M, Reaven NL, Funk SE, et al. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care. 2015;21:S212-220.
7. Michel A, Martin-Pérez M, Ruigómez A, et al. Risk factors for hyperkalaemia in a cohort of patients with newly diagnosed heart failure: a nested case-control study in UK general practice. Eur. J. Heart Fail. 2015;17:205-213.
8. Desai AS, Swedberg K, McMurray JJV, et al. Incidence and predictors of hyperkalaemia in patients with heart failure. An analysis of the CHARM program. J Am Coll Cardiol. 2007;50:1959-1966.
9. KDIGO: Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3:i-150.
10. Rosano GMC, Tamargo J, Kjeldsen KP, et al. Expert consensus document on the management of hyperkalaemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working

Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. Eur Heart J Cardiovasc Pharmacother. 2018;4:180-188.

11. Pitt B, Anker SD, Bushinsky DA, et al. PEARL-HG Investigators: Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. European Heart Journal. 2011;32:820-828.
12. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372:211–221.
13. Bakris GL, Pitt B, Weir MR, et al. AMETHYST-DN Investigators: Effect of Patiromer on Serum Potassium Level in Patients With Hyperkalemia and Diabetic Kidney Disease: The AMETHYST-DN Randomized Clinical Trial. JAMA. 2015;314:151–161.
14. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalaemia. The HARMONIZE randomised controlled trial. JAMA. 2014;312:2223-2233.
15. Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalaemia. A 12-months phase 3 study. Clin J Am Soc Nephro. 2019;14:798-809.
16. Kiran S, Rohan S, Shelley Z. Hyperkalaemia in heart failure. Current Opinion in Cardiology. 2020;35:150-155.
17. Seferovic PM, Ponikowski P, Anker SD, et al. Clinical practice update on heart failure 2019: Pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21:1169–1186.
18. National Institute of Health and Clinical Excellence. Patiromer calcium. British National Formulary. Available at: https://bnf.nice.org.uk/drug/patiromer-calcium.html. [Accessed 5 May 2021].
19. NHS Health Research Authority. Salford Kidney Study. Available at :https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/salford-kidney-study/. [Accessed 5 May 2021].

20. National Institute of Health and Clinical Excellence. Patiromer for treating hyperkalaemia. Available at: https://www.nice.org.uk/guidance/ta623/chapter/1-Recommendations. [Accessed 5 May 2021].
21. Silva-Cardoso J, Brito D, Frazão JM, et al. Management of RAASi-associated hyperkalaemia in patients with cardiovascular disease. Heart Fail Rev. 2021;doi.org/10.1007/s10741-020-10069-3.
22. National Institute of Health. Patiromer for the management of hyperkalaemia in subjects receiving RAASi medications for the treatment of heart failure (DIAMOND). ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT03888066. [Accessed 5 May 2021].

# CHAPTER 11

# DISCUSSION

## 11.1 Preface

This chapter discusses the key findings from this thesis and outlines a number of avenues for future research in the areas of risk prediction and hyperkalaemia management.

## 11.2 THEME 1: RISK PREDICTION IN CKD

The interplay of risk factors implicated in CKD progression, the scope for improved CKD biomarker research, and the validation of risk prediction tools were all studied in the research theme of risk prediction in CKD. A number of contributions have been made from these studies, which are summarised below.

**Chapter 4**

**Predictive factors for rapid linear progression and mortality in patients with chronic kidney disease**

This chapter undertook an evaluation of the risk factor profile in patients progressing rapidly in a linear fashion. It highlights that there is a differential weighting of predictor variables for rapid progression between those with diabetic nephropathy, hypertensive nephropathy and glomerulonephritis, shedding light on how a risk assessment may vary in different patient groups. In addition to the heterogeneous interplay of risk determinants, the study aptly demonstrated the significantly increased risk of ESRD and mortality in patients with rapidly declining eGFR compared to those with a stable trajectory. This emphasises the need to consider the rate of eGFR change over time when risk stratifying patients for future adverse outcomes.

**Chapter 5**

**Adverse outcomes associated with rapid linear and non-linear patterns of chronic kidney progression**

This chapter extends the analysis of the preceding study by further highlighting the importance of characterising eGFR trajectory accurately with respect to risk prediction in CKD. Patients rapidly progressing in a linear pattern experience significantly higher rates of ESRD compared to patients progressing in a non-linear manner, who instead face higher rates of mortality. The existence of such patient subgroups advocates the need for better recognition, assessment and personalised care for those facing the competing risks of ESRD and mortality.

**Chapter 6**

**A paradigm to discover biomarkers associated with chronic kidney disease progression**

Conducting robust research in unravelling the association of potential biomarkers with progressive kidney disease and subsequently validating the results is a key priority, not just to help better understand the pathophysiology of CKD progression but also to improve our ability to risk stratify patients. For the purposes of identifying biomarker signals that associate with changes in eGFR over time, this chapter describes a paradigm to help improve our practice in CKD biomarker discovery. It recommends that researchers use currently available observational CKD cohorts as the starting point to gather data given the availability of large patient numbers with many years of follow-up. The necessary objective thereafter is appropriate patient selection through the accurate characterisation of patients' rate and pattern of CKD progression. This would enable discovered biomarkers to be clearly associated with a defined eGFR trajectory and increase the confidence to undertake subsequent validation research.

**Chapter 7**

**A validation study of the 4-variable and 8-variable kidney failure risk equation in transplant recipients in the United Kingdom**

In the wake of emerging evidence of the ability of the 4-variable KFRE to risk predict graft failure in transplant recipients, this chapter provided the first evaluation of both the 4- and 8-variable KFREs in a UK-based transplant cohort using parameters available 1-year post-transplant. In keeping with the reported literature, the discrimination of the KFRE was adequate, especially in patients with an eGFR <45ml/min/1.73m$^2$, but predictive accuracy was undermined by poor calibration. Whether utilisation of alternative time-points post-transplant improves upon the KFRE's accuracy remains to be seen.

## Chapter 8

## A validation study of the kidney failure risk equation in advanced chronic kidney disease according to disease aetiology with evaluation of discrimination, calibration and clinical utility

This chapter provided, for the first time, an assessment of the 4- and 8-variable KFREs within an advanced CKD population in the UK. It showed that the 4-variable KFRE was sufficiently accurate at risk prediction compared to the 8-variable KFRE. In addition, the KFREs performed well according to disease aetiology except in patients with ADPKD, in whom there was a significant underestimation of risk. Despite this, the KFREs demonstrated superior clinical utility in decision curve analyses to guide patient care compared with utilising eGFR-based thresholds. This provides clear evidence to change from the current dependence on non-personalised eGFR thresholds to the objective, validated KFRE scores to improve risk communication and prioritisation of resources to high-risk individuals.

## 11.3 THEME 2: HYPERKALAEMIA MANAGEMENT

Alongside the ability to better risk predict future outcomes, CKD management hinges on the capacity to stabilise progressive disease. Novel oral potassium binders potentially offer significant clinical value for clinicians in managing CKD by permitting the continuation and up-titration of prognostically beneficial RAASi agents.

**Chapter 9**

**The role of patiromer: comparing OPAL-HK data with untreated real-world patients in the United Kingdom – a retrospective, propensity-matched analysis**

This chapter provides evidence using real-world data from the SKS that patiromer can effectively reduce serum potassium levels in patients with CKD stages 3a-4 who, without therapy, are at risk of hyperkalaemic episodes. The methodology also demonstrated the potential feasibility of using real-world patient data as control arms for trials involved in investigating hyperkalaemia management.

**Chapter 10**

**Management of hyperkalaemia to facilitate renal-angiotensin-aldosterone blockade therapy in patients with heart failure – experience in a bespoke clinic in the United Kingdom**

This chapter shows that in patients with HFrEF who tolerate oral potassium binders, RAASi therapy can be successfully initiated and up-titrated in patients who had previously had evidence of hyperkalaemia. Indeed, some patients were able to reach maximal doses without concern for the development of hyperkalaemia, which had previously affected RAASi prescribing. This real-world experience provides significant appeal for oral potassium binders in optimising reno- and cardioprotection in high-risk patients.

## 11.4 FUTURE WORK

The scope and output of this thesis provides several avenues for further research in the field of risk prediction and hyperkalaemia management.

### 11.4.1 Enriching the phenotypic analysis of the SKS

There is an important limitation of the SKS: the predominantly Caucasian cohort is not truly representative of the population within the surrounding boroughs of the North West region of Greater Manchester that are served by the renal services at Salford Royal NHS Foundation Trust. Notably, there is higher proportion of South Asians and other non-white residents in the areas of Oldham, Rochdale and Bolton [1,2]. Given that ethnicity has been shown to be implicated in CKD progression, efforts to recruit patients from ethnic minorities into SKS is important to help characterise the risk factor phenotype of these patients and to enable better targeted treatment.

In addition, based on the 2019 Index of Multiple Deprivation scores, Salford, Rochdale and Oldham were placed amongst the top 20 local authorities with the highest proportion of its neighbourhoods within the most deprived 10% areas nationally [3]. The SKS therefore is well-suited to dedicate research to explore how deprivation impacts on major adverse outcomes such as CKD progression, ESRD, CVE and mortality. Whilst there is some indication that deprivation does associate with poor CKD outcomes [4], further work is needed to explore whether confounding factors and comorbidities explain this association. Shining a research spotlight on the wider determinants of health such as socioeconomic status, educational attainment and health literacy may help to enrich our ability to further differentiate individuals at risk of poor outcomes.

### 11.4.2 Proteomic biomarker discovery

NURTuRE (National Unified Renal Translational Research Enterprise) has been established to provide a national renal biorepository of samples to facilitate translational research in CKD, and forms part of the Medical Research Council's Precision Medicine Initiative to accelerate research into biomarker discovery and improved risk stratification [5]. As part of the latter, in a research strand focusing on CKD, 419

patients with rapid progression and stable disease, as defined by their ΔeGFR, were selected from the SKS and underwent proteomic analysis using SWATH-MS (Sequential Window Acquisition of all Theoretical fragment ion Mass Spectra) technology at the Stoller Biomarker Discovery Centre at the University of Manchester. This project occurred concurrently with the undertaking of this thesis. Preliminary proteomic signals have now been discovered from this analysis that have the potential to distinguish rapid and stable CKD phenotypes, and it is intended that future validation of these biomarkers will be undertaken within the NURTuRE cohort. This research harbours exciting prospects into establishing mechanistic pathways responsible for CKD progression, which will hopefully provide substrates for the development of specific therapeutic interventions.

### 11.4.3 Assessing the performance of the KFRE with additional parameters

The KFRE is a well-validated tool for risk prediction but there may be scope to improve its precision with additional clinical parameters. Given chapters 4 to 6 highlighted the importance of the ΔeGFR in characterising progression and given the volume of longitudinal data within the SKS, it would be interesting to evaluate how patients' preceding eGFR slopes, calculated using values over a defined number of years, could affect the 4-variable KFRE performance at 2- and 5-years. Similarly, exploring whether time-averaged values of albuminuria improve risk prediction may also prove fruitful. In both these instances, the KFRE scores using these new parameters would be compared with the original KFRE by way of discrimination, calibration and decision curve analyses. Additional factors that may be worthy of inclusion in an adjusted KFRE model include a history of cardiovascular events, hospitalisation or AKI, graded by severity, in the preceding year to the index point of the KFRE calculation.

### 11.4.4 Quality improvement project to implement the KFRE in advanced CKD

Whilst undertaking the analyses above may illuminate the possibilities for improving the KFRE, it is necessary to assess its performance in current clinical practice, not least because the decade that has passed since its original publication has led to a wealth of validation work, including analyses developed in this thesis, that highlight the KFRE can be an effective tool at forecasting the future risk of ESRD.

The published work in Chapter 8 has therefore been a catalyst to launch a quality improvement project (QIP) to utilise the KFRE within the multidisciplinary setting of the AKCS clinic at Salford Royal NHS Foundation Trust. The implementation of this project will be strengthened by the current integration of the KFRE into the hospital's electronic health record, which will produce automated real-time risk scores for patients in the renal clinic. The experience of using the KFRE from this QIP will hopefully lead to its routine adoption across the renal department with the aim being that by prioritising patient referral based on risk scores, higher rates of pre-emptive transplantation and planned dialysis initiation with established access can be achieved. Figure 11.1 illustrates the driver diagram to achieve the first aim of the project using the KFRE in 80% of face-to-face AKCS clinic reviews at Salford Royal NHS Foundation Trust.

### 11.4.5 Utilisation of the KFRE in primary care

As work continues in the arena of secondary care to evaluate the impact of the KFRE on patient outcomes, the implementation of the KFRE in primary care has been endorsed by NICE, which have recommended that patients be referred for specialist assessment if their 5-year KFRE is >5% [6]. This updated guidance considers work by Majors et al [7] who validated the KFRE in 35,539 patients in primary care in the UK. The researchers showed that a hybrid approach of using a re-calibrated KFRE of 5% over 5 years and/or an ACR≥70g/mol reduced overall patient referrals to secondary care but maintained better sensitivity and specificity in identifying patients who develop ESRD compared to the original NICE referral criteria.

In light of the NICE recommendations, efforts to engage, promote and educate general practitioners in applying the KFRE in clinical care is urgently needed. It is also important to simultaneously ensure the KFRE is rapidly incorporated into primary care electronic health care systems, without which its implementation will be significantly hampered [8].

The adoption of the KFRE into national guidelines represents the first step towards recognising the importance of communicating patients' care centred on risk assessment and in using risk-based tools in referral pathways at critical time points in patients' CKD management – be it referral into secondary care, entry into MDT-based pre-dialysis clinics and referral towards timely transplant work-up or fistula formation.

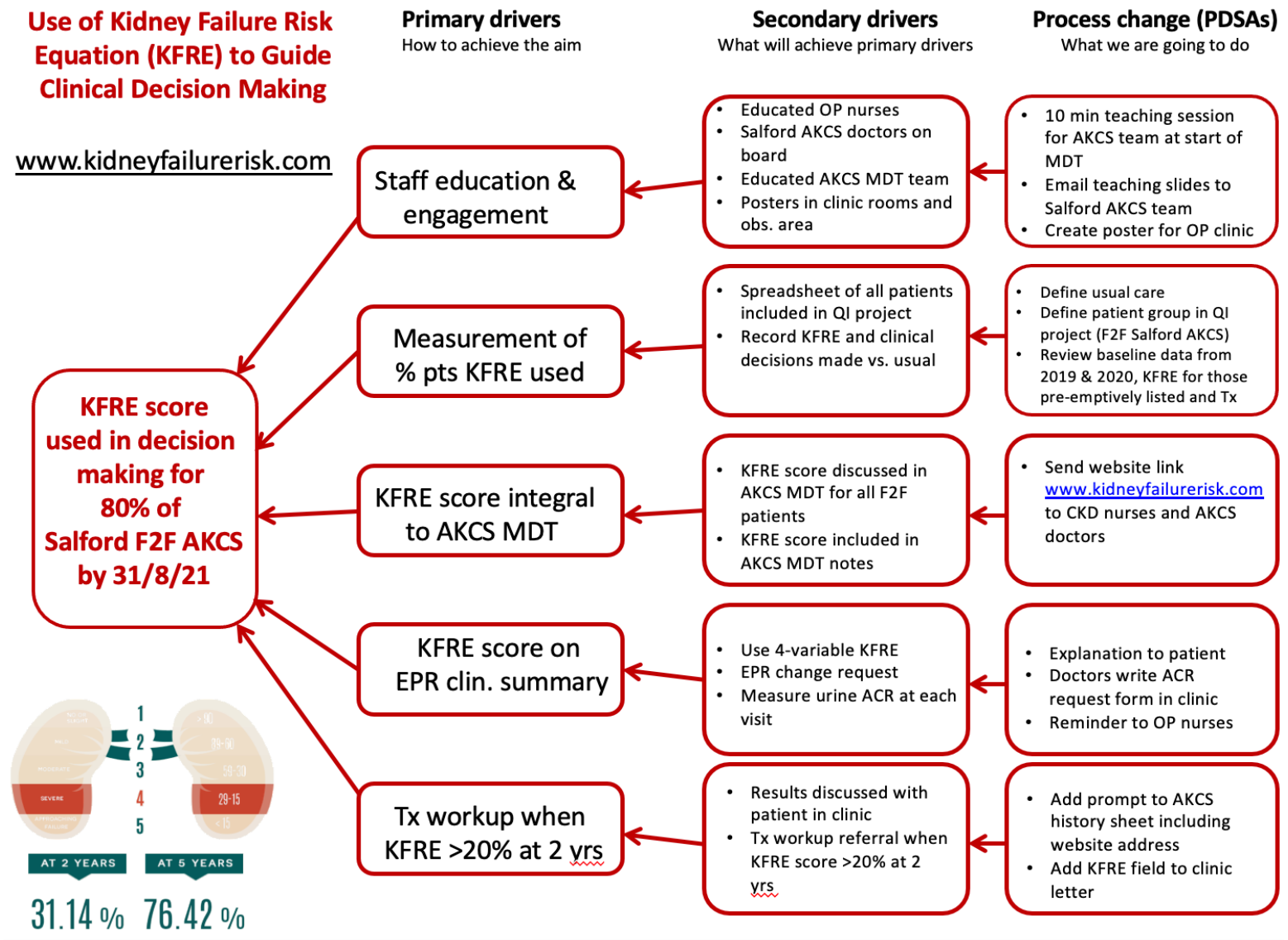
### 11.4.6 Guidance for managing hyperkalaemia

Based on the hyperkalaemia clinic experience in chapter 10, there is ongoing work in developing detailed Trust-wide guidelines for managing ambulatory hyperkalaemia that incorporates both patiromer and SZC within the protocol. Supported by updated guidance issued by the Renal Association [9], the new protocol will hopefully result in increased prescribing of these novel oral potassium binders in patients with CKD who would benefit from RAASi continuation.

### 11.4.7 Impact on RAASi discontinuation

Finally, the impact of RAASi discontinuation or down-titration due to hyperkalaemia and its consequences on the long-term risk of ESRD, CVE, hospitalisation and mortality in those with CKD stages 4-5 has not been previously investigated. A prospective research study with SKS participants could help explore this unanswered question and provide insight into the importance of potassium control and RAASi prescribing in later stages of CKD.

**Figure 11.1** Driver diagram for the initial implementation of the KFRE in the AKCS clinic



## 11.5 TAKE-HOME MESSAGES

- Patients with rapid linear CKD progression face a significantly increased risk of ESRD and mortality compared with patients who have stable CKD.

- There are subgroups of patients progressing in a linear and non-linear manner who experience adverse outcomes of ESRD and mortality in a differential manner.

- A key aspect of biomarker research in the field of CKD progression is to accurately characterise the rate and pattern of patients' eGFR trajectory to ensure discovered biomarkers can be more precisely aligned to specific forms of CKD progression.

- The overall accuracy of the 4- and 8-variable KFREs is limited by poor calibration in predicting graft failure in transplant recipients.

- The 4- and 8-variable KFREs offers clinical utility to inform decision making in patients with advanced CKD and is superior to an eGFR-based strategy of patient care.

- The efficacy for patiromer is further shown through the use of a real-world control arm matched to patients in the OPAL-HK trial.

- Patients with heart failure who tolerate oral potassium binders can successfully experience an increase in RAASi therapy by controlling potassium levels.

## 11.6 CONCLUSION

Progressive CKD and its sequalae remains a major global health problem. In order to provide optimal CKD care, there continues to be growing interest in the multifaceted dimensions of risk prediction and hyperkalaemia management, both of which have been explored in this thesis. Specifically, the potential of the KFRE to deliver accurate risk stratification and the utilisation of oral potassium binders to permit RAASi continuation in high-risk patients highlights the significant optimism that clinicians and patients can have in the future of nephrology care. Further research in these areas to refine risk prediction tools and protocolise effective prescribing of potassium binders would help make CKD, despite its heterogeneity and complexity, an exemplar condition that sets standards in the delivery of personalised care.

## 11.7 REFERENCES


1. UK Census Data. Rochdale ethnic group quick stats. Available at: https://www.ukcensusdata.com/rochdale-e08000005#sthash.p9mTgu5R.dpbs. [Accessed 12 June 2021].
2. NHS Oldham Clinical Commissioning Group. Population statistics. Available at: http://www.oldhamccg.nhs.uk/About-Us/Our-Population. [Accessed 12 June 2021].
3. Ministry of Housing, Communities and Local Government. The English Indices of Deprivation 2019 (IoD 2019). Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/835115/IoD2019_Statistical_Release.pdf. [Accessed 12 June 2021].
4. Guthrie GD, Bell S. Deprivation and kidney disease—a predictor of poor outcomes. Clin. Kidney J. 2020;13:128–132.
5. Medical Research Council. Precision Medicine. Available at: https://mrc.ukri.org/research/initiatives/precision-medicine/research/. [Accessed 12 June 2021].
6. NICE. Chronic kidney disease in adults: assessment and management. 2015. Available at: https://www.nice.org.uk/guidance/cg182, [Accessed 14 Aug 2018].
7. Majors RW, Shepherd D, Medcalf JF, et al. The kidney failure risk equation for prediction of end stage renal disease in UK primary care: an external validation and clinical impact projection cohort study. PLoS Med. 2019;16e1002955
8. Sharma V, Ali I, Veer SVD, et al. Adoption of clinical risk prediction tools is limited by a lack of integration with electronic health records. BMJ Health Care Inform. 2021;28:e100253.
9. The Renal Association. Management of hyperkalaemia in the community. Available at: https://renal.org/sites/renal.org/files/APPENDIX%205%20-%20HYPERKALAEMIA%20ALGORITHM%20IN%20COMMUNITY.pdf. [Accessed 12 June 2021].

**(A1)**

**The 4- and 8-variable Kidney Failure Risk Equation calculations for the 2- and 5-year predicted risk of ESRD**

**4-variable 2-year calibrated non-North American equation:**

1 - 0.9832^exp(-0.2201 x (age/10 – 7.036) + 0.2467 x (male – 0.5642) – 0.5567 x (eGFR/5 – 7.222) + 0.4510 x (logACR – 5.137))

**8-variable 2-year calibrated non-North American equation:**

1 - 0.9827 ^ exp(-0.1992 x (age/10 – 7.036) + 0.1602 (male – 0.5642) – 0.4919 x (eGFR/5 – 7.222) + 0.3364 x (logACR – 5.137) – 0.3441 x (albumin – 3.997) + 0.2604 x (phosphate – 3.916) – 0.07354 x (bicarbonate – 25.57) – 0.2228 x (calcium – 9.355))

**4-variable 5-year calibrated non-North American equation:**

1 - 0.9365^exp(-0.2201 x (age/10 – 7.036) + 0.2467 x (male – 0.5642) – 0.5567 x (eGFR/5 – 7.222) + 0.4510 x (logACR – 5.137))

**8-variable 5-year calibrated non-North American equation:**

1 - 0.9245 ^ exp(-0.1992 x (age/10 – 7.036) + 0.1602 (male – 0.5642) – 0.4919 x (eGFR/5 – 7.222) + 0.3364 x (logACR – 5.137) – 0.3441 x (albumin – 3.997) + 0.2604 x (phosphate – 3.916) – 0.07354 x (bicarbonate – 25.57) – 0.2228 x (calcium – 9.355))

In the above equations,

Age is the patient's age in years, at the time of the laboratory measurements.

Male is equal to 1, otherwise 0.

eGFR is the estimated glomerular filtration rate in ml/min/1.73m$^2$, calculated using the CKD-EPI equation.

LogACR is the natural logarithm of the urine albumin:creatinine ratio, measured in mg/g.

Albumin is serum albumin measured in mg/dl.

Phosphate is serum phosphate is measured in mg/dl.

Bicarbonate is serum bicarbonate measured in mEq/L

Calcium is serum calcium measured in mg/dl.

**(A2)**
**Formula to convert uPCR to uACR**

exp(5.2659+0.2934*LN(MIN(uPCR/50,1))+1.5643*LN(MAX(MIN(uPCR/500,1),0.1))
)+1.1109*LN(MAX(uPCR/500,1)))-
0.0773*(female)+0.0797*(diabetic)+0.1265*(hypertensive))

In the above equation,
uPCR is measured in mg/g.
Female=1
Diabetic=1
Hypertensive=1

**(A3)**

**Contributions to other publications related to this thesis**

Ibrahim ST, Chinnadurai R, **Ali I**, et al. Genetic polymorphism in C3 is associated with progression in chronic kidney disease (CKD) patients with IgA nephropathy but not in other causes of CKD. PLoS ONE. 2020;15:e0228101.

**(A4)**

**International abstract presentations related to this thesis**

**Ali I**, Ibrahim S, Chinnadurai R, Green D, Whetton T, Taal M, Kalra PA. Biomarkers and CKD progression – avoiding pitfalls in methodology. ASN. 2019, Washington D.C, USA.

**Ali, I,** Chinnadurai R, Cornea G, Intorcia M, Kalra PA. Comparing OPAL-HK data to real-world data from the United Kingdom: how effective is patiromer at achieving normokalaemia? ERA-EDTA. 2020, Milan, Italy.

**Ali I,** Donne R. A single-centre audit to evaluate the pathway towards pre-emptive transplantation – is there scope for improvement? ISN World Congress of Nephrology. 2020, Abu Dhabi.

**Ali I**, Kalra PA. Management of hyperkalaemia to facilitate RAASi therapy in patients with heart failure in a bespoke UK clinic. ERA-EDTA. 2021, Berlin, Germany.