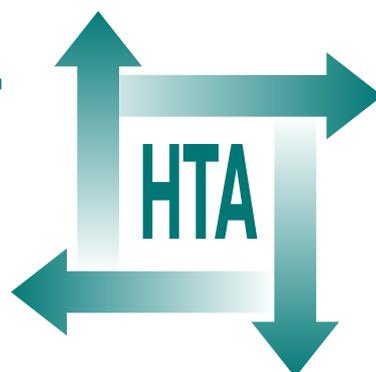# Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis

C Black, P Sharma, G Scotland, K McCullough,
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HTA

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Declared competing interests of authors: none

This report should be referenced as follows:

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

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Abstract

Early referral strategies for management of people with markers of renal disease: a systematic review of the evidence of clinical effectiveness, cost-effectiveness and economic analysis

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Background: Chronic kidney disease (CKD) is a long-term condition and has been described as the gradual loss of kidney function over time. Early in the disease process, people with CKD often experience no symptoms. For a long time, CKD has been an underdiagnosed condition. Even in the absence of symptoms, CKD appears to add significantly to the burden of cardiovascular disease and death and, for an important minority, can progress to kidney failure.

Objective: To systematically review the evidence of the clinical effectiveness and cost-effectiveness of early referral strategies for management of people with markers of renal disease.

Data sources: Electronic searches of 12 major databases (such as MEDLINE, EMBASE, CINAHL, etc.) were conducted for the time period of 1990 to April 2008 to identify studies comparing early referral to other care options for people with CKD. Additional searching was performed in the NHS Economic Evaluation Database to support the cost-effectiveness literature review.

Review methods: Two authors reviewed all titles, abstracts and full papers to select relevant literature. A Markov model was constructed to represent the natural history of CKD. The model allowed cohorts to be tracked according to estimated glomerular filtration rate (eGFR) status and the presence of other complications known to influence CKD progression and the incidence of cardiovascular events.

Results: From 36 relevant natural history studies, CKD was found to be, despite marked heterogeneity between studies, a marker of increased risk of mortality, renal progression and end-stage renal disease. Mortality was generally high and increased with stage of CKD. After adjustment for comorbidities, the relative risk of mortality among those with CKD identified from the general population increased with stage. For clinical populations, the relative risk was higher. All three outcomes increased as eGFR fell. Only seven studies, and no randomised controlled trials, were identified as relevant to assessing the clinical effectiveness of early referral strategies for CKD. In the five retrospective studies constructed from cohorts starting on renal replacement therapy (RRT), mortality was reduced in the early referral group (more than 12 months prior to RRT) even as late as 5 years after initiation of RRT. Only two studies included predialysis participants. One study, in people screened for diabetic nephropathy, reported a reduction in the decline in renal function associated with early referral to nephrology specialists (eGFR decline 3.4 ml/min/1.73 m^2) when compared with a similar group that had no access to nephrology services until dialysis was required (eGFR decline 12.0 ml/min/1.73 m^2). The second study, among a group of veterans with two creatinine levels of at least 140 mg/dl, reported that a composite end point of death or progression was lower in the group receiving nephrology follow-up than in those receiving only primary care follow-up. The greatest effect was observed in those with stage 3 or worse disease after adjustment for comorbidities, age, race, smoking

and proteinuria {stage 3: hazard ratio (HR) 0.8 [95% confidence interval (CI) 0.61 to 0.9)]; stage 4: HR 0.75 (95% CI 0.45 to 0.89)}. In the base-case analysis, all early referral strategies produced more quality-adjusted life-years (QALYs) than referral upon transit to stage 5 CKD (eGFR 15 ml/min/1.73 m²). Referral for everyone with an eGFR below 60 ml/min/1.73 m² (stage 3a CKD) generated the most QALYs and, compared with referral for stage 4 CKD (eGFR < 30 ml/min/1.73 m²), had an incremental cost-effectiveness ratio of approximately £3806 per QALY.

Limitations: Because of a lack of data on the natural history of CKD in individuals without diabetes, and a lack of evidence on the costs and effects of early referral, the Markov model relied on many assumptions. The findings were particularly sensitive to changes in eGFR decline rates and the relative effect of early referral on CKD progression and cardiovascular events; the latter parameter being derived from a single non-randomised study.

Conclusions: Despite substantial focus on the early identification and proactive management of CKD in the last few years, we have identified significant evidence gaps about how best to manage people with CKD. There was some evidence to suggest that the care of people with CKD could be improved and, because these people are at risk from both renal and cardiovascular outcomes, strategies to improve the management of people with CKD have the potential to offer an efficient use of health service resources. Given the number of people now being recognised as having markers of kidney impairment, there is an urgent need for further research to support service change.

Contents

List of abbreviations

ACE I	angiotensin converting enzyme inhibitor
ACM	all-cause mortality
ACR	albumin–creatinine ratio
ARB	angiotensin receptor blocker
ARIC	Atherosclerosis Risk in Communities
BMJ	*British Medical Journal*
BP	blood pressure
CG	Cockcroft–Gault
CHS	Cardiovascular Heart Study
CI	confidence interval
CKD	chronic kidney disease
CVD	cardiovascular disease
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FHS	Framingham Heart Study
GFR	glomerular filtration rate
GP	general practitioner
HBP	high blood pressure
HR	hazard ratio
HUI	Health Utilities Index
HLOC	health-specific locus of control
ICER	incremental cost-effectiveness ratio
IT	information technology
KDOQI	Kidney Disease Outcomes Quality Initiative
KDQOL-36	Kidney Disease Quality of Life short form-36
MDC	multidisciplinary care
MDRD	Modification of Diet in Renal Disease
MI	myocardial infarction
NHANES	National Health and Nutritional Examination Survey
NICE	National Institute for Health and Clinical Excellence
NKF	National Kidney Foundation
OR	odds ratio
QALY	quality-adjusted life-year
QOF	Quality and Outcomes Framework
RAAS	renin–angiotensin aldosterone system
RCT	randomised controlled trial
RR	relative risk
RRT	renal replacement therapy
SCS	shared care scheme
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SIMON	Southampton Integrated Monitoring of Nephrology
SMR	standardised mortality rate
TTO	time trade-off

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Chronic kidney disease (CKD) is a long-term condition and has been described as the gradual loss of kidney function over time. Early in the disease process, people with CKD often experience no symptoms. For a long time, CKD has been an underdiagnosed condition. Even in the absence of symptoms, CKD appears to add significantly to the burden of cardiovascular disease and death and, for an important minority, can progress to kidney failure. In the last 10 years, the focus on mild to moderate, or 'early', CKD has grown, and an internationally adopted definition of CKD was introduced in 2002. Large population health surveys in the USA have estimated that 11% of the population have CKD.

Objectives

To systematically review the evidence of the clinical effectiveness and cost-effectiveness of early referral strategies for management of people with markers of renal disease. There were three phases of research:

1. Systematic review of the evidence of clinical effectiveness – to assess and synthesise the evidence for early referral strategies. In addition, we sought to explore the natural progression of patients identified as having CKD and the characteristics for an effective early referral programme.
2. Systematic review of the evidence of cost effectiveness – to assess and synthesise the evidence of cost-effectiveness of early referral strategies.
3. Economic analysis – informed by the findings of phase 1 and 2, to model the economic implications of different early referral strategies to assess the cost-effectiveness.

Methods

Systematic literature reviews of the clinical effectiveness of early referral and the natural history of CKD were undertaken. Electronic searches of MEDLINE, EMBASE, CINAHL, Science Citation Index, ISI Proceedings, British Nursing Index, Health Management Information Consortium, Social Science Citation Index, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, National Research Register and the UK Clinical Research Network (updated to February 2009 for main search) were conducted for the time period of 1990 to April 2008 to identify studies comparing early referral to other care options for people with CKD. Search terms did not restrict based on timing of referral; studies of early or late referral were identified. Additional searching was performed in NHS Economic Evaluation Database to support the cost-effectiveness literature review.

We considered evidence from any study design that compared a strategy for early referral with a relevant comparator group and any intervention that aimed to achieve the early referral of those with markers of renal disease to specialist nephrology care.

To identify the relevant literature on the natural history of CKD we searched MEDLINE (1950 to week 2 March 2008) and EMBASE (1996 to week 4 March 2008). Searches were restricted to English and were from 1998 to 2008.

Two authors reviewed all titles, abstracts and full papers to select relevant literature. Data extraction, including quality assessment, was undertaken by two reviewers. Data were summarised in tabular form and reported narratively. A supplementary chapter on models of care for CKD was undertaken to support the development of the economics model and to supplement the limited evidence identified from the clinical effectiveness review.

A Markov model was constructed to represent the natural history of CKD. The model allowed cohorts to be tracked according to estimated glomerular filtration rate (eGFR) status and the presence of other complications known to influence CKD progression and the incidence of cardiovascular events. Within each cycle of the model, individuals could progress to more severe CKD states, experience fatal and non-fatal cardiovascular events, or die from other causes. The cost-effectiveness of various early referral strategies was

assessed by superimposing additional costs and anticipated effects on top of the natural history model.

Results

From 36 relevant natural history studies, CKD was found to be, despite marked heterogeneity between studies, a marker of increased risk of mortality, renal progression and end-stage renal disease (ESRD). For many patients, other comorbidities associated with CKD contribute to this increased risk. Mortality was generally high (24–39% at 5 years, 20–52% at 10.0–12.6 years) and increased with stage of CKD. After adjustment for comorbidities, the relative risk of mortality among those with CKD identified from the general population ranged from 1.12 to 1.78 and increased with stage (from 1.2 in stage 3a to 1.8 in stage 3b). For clinical populations, the relative risk was higher. ESRD was not a common outcome for people with mild to moderate CKD, particularly when identified through population screening (1.3–4.0% at 8 and 10 years for stage 3 CKD). All three outcomes increased as eGFR fell. There appeared to be a substantial subgroup (for stage 3: from 41% to as high as 96%) for whom an eGFR lower than 60 ml/min/1.73 m² did not mark the start of declining kidney function after 2–4 years' follow-up. There was little reported about the impact on quality of life.

Only seven studies, and no randomised controlled trials, were identified as relevant to assessing the clinical effectiveness of early referral strategies for CKD. In the five retrospective studies constructed from cohorts starting on renal replacement therapy (RRT), mortality was reduced in the early referral group (more than 12 months prior to RRT) even as late as 5 years after initiation of RRT. Only two studies included predialysis participants. One study, in people screened for diabetic nephropathy, reported a reduction in the decline in renal function associated with early referral to nephrology specialists (eGFR decline 3.4 ml/min/1.73 m²) when compared with a similar group that had no access to nephrology services until dialysis was required (eGFR decline 12.0 ml/min/1.73 m²). The second study, among a group of veterans with two creatinine levels of at least 140 mg/dl, reported that a composite end point of death or progression was lower in the group receiving nephrology follow-up than in those receiving only primary care follow-up. The greatest effect was observed in those with stage 3 or worse disease after adjustment for comorbidities, age, race, smoking and proteinuria {stage 3: hazard ratio (HR) 0.8 [95% confidence interval (CI) 0.61 to 0.9)]; stage 4: HR 0.75 (95% CI 0.45 to 0.89)}. Those cared for by specialists tended to have lower blood pressure and receive more aggressive antihypertensive therapy. Quality of life was not reported.

Cost-effectiveness modelling suggested that early referral strategies may have the potential to offer an efficient use of resources. In the base-case analysis, all early referral strategies produced more quality-adjusted life-years (QALYs) than referral upon transit to stage 5 CKD (eGFR 15 ml/min/1.73 m²). Referral for everyone with an eGFR below 60 ml/min/1.73 m² (stage 3a CKD) generated the most QALYs and, compared with referral for stage 4 CKD (eGFR < 30 ml/min/1.73 m²), had an incremental cost-effectiveness ratio (ICER) of approximately £3806 per QALY. However, because of a lack of data on the natural history of CKD in individuals without diabetes, and a lack of evidence on the costs and effects of early referral, our model relied on many assumptions. The findings were particularly sensitive to changes in eGFR decline rates and the relative effect of early referral on CKD progression and cardiovascular events; the latter parameter being derived from a single non-randomised study. Moreover, the costs of implementing the modelled referral strategy will likely prove prohibitive. There is clear need for prospective cohort studies to assess CKD progression and the incidence of cardiovascular events in individuals identified in primary care as having an eGFR less than 60 ml/min/1.73 m², with and without other complications/comorbidities such as microalbuminuria, proteinuria, diabetes and pre-existing cardiovascular disease. Once these data are available they will allow more accurate modelling of the cost-effectiveness of referral based on different eGFR cut-offs and other comorbidities. Future economic modelling should focus on assessing the cost-effectiveness of improving the management of individuals with early CKD in primary care.

Discussion

We have reported evidence of the potential for improvements in the care of people with CKD. While an early referral model, combining some form of shared care between primary and secondary care has the potential to be cost-effective, it is unlikely that such a model is affordable or feasible. Key areas of uncertainty were

identified around the natural history of people with CKD, in particular stage 1–3 CKD identified by the current 'opportunistic screening' approach, and whether subgroups can be identified where the risk of progression is low.

Priorities for further research include:

- Cohort studies of the natural history of stage 1–3 CKD.
- Review of the clinical effectiveness and cost-effectiveness of the main pharmacological interventions in people with stage 1–3 CKD.
- Randomised controlled trials of models of care for people with CKD. As a priority, shared care (with proactive involvement of primary care with delivery of more than simply a phlebotomy service) should be compared with standard specialist nephrology and primary care. Any trials should include prospective economic evaluations.

Conclusions

Despite substantial focus on the early identification and proactive management of CKD in the last

few years, we have identified significant evidence gaps about how best to manage people with CKD. There was some evidence to suggest that the care of people with CKD could be improved and, because these people are at risk from both renal and cardiovascular outcomes, strategies to improve the management of people with CKD have the potential to offer an efficient use of health service resources. However, given the great uncertainty surrounding many parameter estimates, the effectiveness and cost-effectiveness of care strategies needs to be demonstrated in prospective randomised studies prior to implementation. Given the number of people now being recognised as having markers of kidney impairment, there is an urgent need for further research to support service change. The natural history of CKD in this new population identified as having kidney impairment needs to be better understood. For many, CKD occurs as part of a complex comorbidity cluster, with hypertension, diabetes mellitus and cardiovascular disease. In focusing on developing and evaluating approaches to provide care for people with CKD, it will be important to keep sight of opportunities to avoid developing silos of care and to balance with the need to identify those who have the most to gain from early specialist intervention.

Chapter 1

Background

Introduction

Chronic kidney disease (CKD) is a long-term condition and has been described as the gradual, and usually permanent, loss of kidney function over time.[1] Early in the disease process, people with CKD often experience no symptoms and CKD has, for a long time, been an underdiagnosed condition. Even in the absence of symptoms, CKD appears to add significantly to the burden of cardiovascular disease (CVD) and death and, for an important minority, can progress to severe kidney function impairment and kidney failure (end-stage renal disease; ESRD).[2]

In the last 10 years the focus on mild to moderate or 'early' CKD has grown. Its recognition as a major public health issue was highlighted by large population health surveys in the USA reporting an estimated 11% of the population as having evidence of renal impairment.[3] A number of authors have written of the 'exploding' CKD burden and have called for screening, early intervention and prevention as key steps in managing the individual and societal impact of the rising rates of disease.

End-stage renal disease

End-stage renal disease, severe renal function impairment or established renal failure is associated with high morbidity and mortality, poor quality of life, and high health service and societal costs. As the kidneys fail, the body becomes unable to excrete waste products, excess fluids and salts, or to control acidity. Haemoglobin production, blood pressure (BP) control and bone metabolism are also affected.

Since the first successful dialysis treatment in 1960, the nephrology community has focused much attention on the management of ESRD.[4] Data from 122 countries (representing 92% of the total world population) on treatment for ESRD identified that 1,783,000 people were receiving renal replacement therapy (RRT) by the end of 2004; 77% on dialysis and 23% with functioning renal transplants. Half of the dialysis patients, and more than 70% of

transplant patients were from North America and Europe.[5] With an annual growth of approximately 6% compared with 2003, the number of people on RRT was rising globally.[5]

In the UK in 2007, the UK Renal Registry reported an acceptance rate for new RRT patients of 109 patients per 1,000,000.[6] The point prevalence of RRT at the end of 2007 was 45,484, an annual population prevalence of 0.075% and a 5% increase on the previous year. The acceptance rate has been relatively stable over recent years, thus the rising prevalence is being driven largely by improvements in survival on RRT (*Figure 1*). The 1-year survival on RRT for patients starting RRT in 2006 was 94.8% [95% confidence interval (CI) 93.4 to 95.8] for all primary renal disease excluding diabetic nephropathy. Survival was reduced by age at onset of RRT.[7]

While survival on RRT has improved, more than 30% of 18–64 year olds die within 5 years of developing ESRD, and patients' quality of life is impaired.[6,8,9]

The number of people requiring RRT is expected to continue to increase as a result of population ageing, the increase in type 2 diabetes mellitus, improved technology facilitating access to RRT for patients with comorbidities and improved survival of people with ESRD. This has important resource implications for the NHS, which is estimated to spend 2% of the total annual NHS budget on delivering RRT, although this group comprises only 0.05% of the total population.[10] In 2002, the National Institute for Health and Clinical Excellence (NICE) estimated that the average annual cost of haemodialysis in a satellite renal unit was £21,000 per patient.[11]

Definition of chronic kidney disease

Until recently, no agreed definition of CKD existed. Serum creatinine was commonly reported as a surrogate marker of filtration. The absolute upper limit of 'normal' serum creatinine value varied between laboratories and was vulnerable to patient
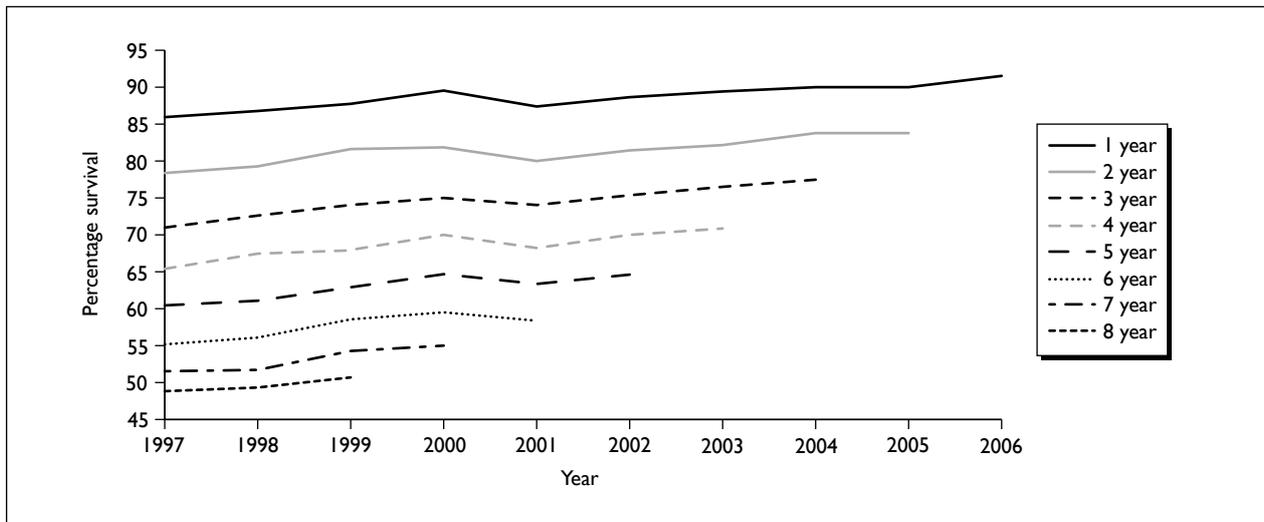
FIGURE 1 *Change in Kaplan–Meier long-term survival by year of starting RRT; for incident patients aged 18–64 years. Reproduced from the UK Renal Registry Report (2008);[7] UK Renal Registry, Bristol, UK; editors: David Ansell, Terry Feest, Andrew Williams and Chris Winearls. The data reported here have been supplied by the UK Renal Registry of the Renal Association. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy or interpretation of the UK Renal Registry or the Renal Association.*

characteristics such as age, sex, race, size, muscle bulk, diet, etc.,[12,13] and various cut-off thresholds to define CKD had been reported.[14,15]

The glomerular filtration rate (GFR) has become the most accepted test to assess filtration.[12] GFR defined as 'the volume of plasma from which a given substance is completely cleared by glomerular filtration per unit time', can be measured by assessing the clearance of exogenous or endogenous markers.[16] Commonly used exogenous markers include radioisotopic and non-radioisotopic substances such as inulin (gold standard), I-iothalamate, Cr-ethylenediaminetetraacetic acid (EDTA) and iohexol, but these are expensive and complex procedures for routine clinical use.[12,16]

Creatinine is the principal endogenous marker that is used to measure GFR. Creatinine clearance measurement, calculated from timed urine collection (24-hour urine) and serum creatinine, can result in overestimation of GFR due to tubular secretion of creatinine and problems of accurate urine collection.[17,18] Estimating GFR based on serum creatinine and additionally correcting for variables such as age, gender, racial origin and body weight can be more reliable than 24-hour urinary creatinine clearance.[16] Two validated equations are commonly used to estimate GFR based on serum creatinine: the Modification of Diet in Renal Disease (MDRD) formula and the Cockcroft–Gault (CG) equation to estimate

creatinine clearance. MDRD has been adopted by laboratories reporting estimated GFR (eGFR) in the UK, but modifications to the equation are being developed with an aim to improving accuracy.[19]

Normal GFR in young adults is approximately 120–130 ml/min/1.73 m^2, but varies with sex, ethnicity and body size, and declines with increasing age. In February 2002, with the aim of providing a uniform definition of CKD, the Kidney Disease Outcomes Quality Initiative (KDOQI) of the US National Kidney Foundation (NKF) introduced the following definition of CKD and stages of CKD:

> Kidney damage (with or without decreased GFR) or decreased kidney function (GFR < 60 ml/min/1.73 m^2) for 3 or more months where kidney damage is defined as pathological abnormalities or markers of damage including abnormalities in blood or urine tests or in imaging studies.[20]

A threshold of GFR less than 60 ml/min/1.73 m^2 was selected because it is less than half the level of normal adult GFR.[21] Additionally, this threshold (which is substantially above the level related to kidney failure) is detectable with current estimating equations for GFR based on serum creatinine, and there is evidence that GFR of 60 ml/min/1.73 m^2 and lower is associated with an increased risk of complications of CKD and other adverse outcomes.[21]

TABLE 1 *Kidney Disease Outcomes Quality Initiative: CKD Stages*

CKD stages	Definition
Stage 1	Kidney damage with normal or raised GFR (≥ 90 ml/min/1.73 m²)
Stage 2	Kidney damage with mildly impaired GFR (60–89 ml/min/1.73 m²)
Stage 3	Moderately impaired GFR (30–59 ml/min/1.73 m²)
Stage 4	Severely impaired GFR (15–29 ml/min/1.73 m²)
Stage 5	End-stage renal failure or GFR (< 15 ml/min/1.73 m²)
GFR, glomerular filtration rate.	

To avoid the misclassification of acute renal failure as CKD, the KDOQI required that reduced GFR and/or kidney damage must be present for at least 3 months. Further, the KDOQI classified CKD into five stages based on level of kidney function (*Table 1*).[20] The potential markers of kidney damage included proteinuria, haematuria, microalbuminuria in people with diabetes mellitus and abnormal imaging studies. Stage 3 CKD was regarded as the earliest stage of CKD for which GFR alone was a sufficient indicator of kidney disease.

Prior to 2002, the lack of common definition and terminology made the study of CKD difficult; prevalence estimates varied widely and the translation of research findings into clinical practice or policy was challenging. The KDOQI classification of CKD has been adopted internationally and has raised the profile of CKD, facilitating research and identifying people with evidence of kidney function impairment that had previously gone undetected.

The UK Renal Association proposed modifications to stage 3, dividing it into 3A (eGFR 45–59 ml/min/1.73 m²) and 3B (30–44 ml/min/1.73 m²).[22] Recent NICE guidelines on the management of CKD proposed further modification of the staging system to include an indication of the presence of proteinuria.[23]

Emerging 'epidemic': epidemiology of chronic kidney disease

With the introduction of the KDOQI definition for CKD, and analysis from large population-based US health surveys (Nutrition Health and Nutrition Examination Survey II; NHANES II) estimating that 11% of the over 20-year-old population may have evidence of CKD, a number of commentators described CKD as a major public health issue.[3,24–26] Analysis of repeated NHANES surveys suggested that the prevalence of CKD, as defined by the KDOQI (albeit reliant on a single measure of kidney function and therefore likely to over estimate the true prevalence of CKD), was increasing.[27,28] This is a finding in keeping with an ageing population and the rise in obesity, diabetes and hypertension.[29]

Internationally, prevalence studies have been published from a wide range of countries across Europe, Asia, Central America and Australia. Methodologically they rely on two main approaches: population surveys or routine clinical laboratory data. In studies of stage 3–5 CKD, and therefore relying only on eGFR, estimates of prevalence have varied from 3.8%[30] to 42.6%.[31] The reason for such heterogeneity may be contributed to by methodological differences (definition of chronicity, denominator used, sampling strategy, approach to minimisation of assay bias) as well as differences in the study population (age, sex, race, comorbidities). In Europe, Hallan and colleagues[32] (2006) reported an adult population prevalence of 4.7% for CKD based on a single eGFR estimate, and a similar prevalence has been reported in Italy, Switzerland, Spain and Iceland.[33–36]

In the UK, the only population-based survey estimate of CKD prevalence comes from a cohort of men aged 60–79 years and tested in 1998–2000. Wannamethee and colleagues[37] estimated the prevalence of CKD to be 15.7%. In 2004–5, two studies, using routine laboratory data from the UK to estimate the prevalence of CKD based on eGFR, reported a prevalence of stage 3–5 CKD of 4.9%[38] and 4.3% respectively.[39]

Management of chronic kidney disease: a UK perspective

The international adoption of the KDOQI definition for CKD initiated the epidemiological recognition that a far greater proportion of the population than previously recognised had evidence of kidney function impairment.

In England, the National Service Framework for Renal Services set out a vision for renal services. In 2004, the first part of the framework focused on dialysis and transplantation, providing recommendations for a pathway of care and emphasising the place of planned identification and referral of patients who are progressing towards ESRD.[10] The second part delivered a framework for CKD as well as covering acute renal failure and end of life care.[2] The framework set out the expectation that people considered to be at risk of developing or having undetected CKD should be identified, assessed and managed proactively with a focus on interventions to preserve kidney function, and minimise disease progression and complications. It also acknowledged the cardiovascular burden in patients with CKD. The framework targeted, in particular, those with diabetes mellitus and hypertension, and supported the proactive monitoring for CKD in such high risk patient groups.[2]

Chronic kidney disease guidelines first published by the UK Renal Association in 2005 sought to provide clarity on how people with CKD should be identified and optimally managed.[40] The National Service Framework set out the need for development of protocols around measuring kidney function and the estimation of eGFR. The UK Renal Association guidelines recommended the adoption of the simplified MDRD equation.[41]

In 2006, the Quality and Outcomes Framework (QOF) incentive-based scheme supporting the General Medical Services contracts with primary care included a renal domain and set four renal criteria for primary care:

1. to establish a register of all patients with CKD (defined as an eGFR lower than 60 ml/min/1.73 m^2)
2. for those on the register to have had a recorded BP in the previous 15 months
3. for the BP to be below 140/85 mmHg
4. for treatment with renin–angiotensin system blocking medicines.

The need, nationally, for access to consistent eGFR reporting was therefore critical to support the development of registers without introducing geographical inequalities. The UK National External Quality Assessment Scheme was charged with harmonising laboratory methodology in order to minimise variability between laboratories, and, in 2006, the routine laboratory reporting of eGFR was rolled out across the UK.[41]

The introduction of eGFR reporting and in particular the decision to report values for eGFR only if lower than 60 ml/min/1.73 m^2, treating all values higher than 60ml/min/1.73 m^2 as 'normal', has made it very straightforward for clinicians to identify patients meeting the KDOQI definition of CKD.

Implications for health

Chronic kidney disease has the potential to affect a number of health areas:

- progressive renal function loss and ultimately ESRD and the need for RRT
- CKD-associated complications (anaemia, bone mineral metabolism disorders, hypertension)
- CVD
- survival
- quality of life
- anxiety.

These are considered in more depth in Chapter 3.

The treatment of CKD has focused the management of complications and preparation for ESRD and RRT. The introduction of medicines that inhibit the renin–angiotensin–aldosterone axis brought evidence of benefit in slowing the progression of kidney function decline and proteinuria. Recognition of the high cardiovascular morbidity and mortality among those with CKD of all stages suggests that there is also the potential to modify other risk factors for CVD.

Preventing progression and cardiovascular disease

In recent years there have been numerous trials of pharmacological interventions aimed at modifying the risk of renal disease progression and CVD. In 2008, NICE[23] and the Scottish Intercollegiate Guidelines Network (SIGN)[42] both published guidelines for the management of CKD. The management strategies for the prevention of

progression of renal disease and reduction of cardiovascular risk have hinged largely on three areas:

- BP control
- lipid profile modification using statins
- lifestyle risk factor modification.

Blood pressure control

NICE and SIGN guidelines note several systematic reviews and meta-analyses that support the important role of BP management in the prevention of progression of CKD. NICE recommended a target systolic BP below 140 mmHg and diastolic below 90 mmHg. SIGN recommended a target of below 130 mmHg for systolic BP. The guidelines also presented evidence for the role of reduction of proteinuria in reducing the risk of renal disease progression.

The role of two groups of antihypertensive agents, angiotensin converting enzyme inhibitors (ACE Is) and angiotensin receptor blockers (ARBs), has received particular attention in the management of CKD.

Angiotensin converting enzyme inhibitors

In people with non-diabetic CKD, ACE Is have little benefit over placebo or other antihypertensive treatments in reducing all-cause mortality (ACM).[43] A statistically significant reduction in the risk of developing ESRD alone, or doubling of serum creatinine and ESRD [relative risk (RR) reduction of 40% and 30% respectively] was observed from a meta-analysis of 11 trials and after adjustment for difference in study baseline characteristics.[43] The risk reduction was modified by, but independent of, change in BP and proteinuria. A benefit on renal outcomes from ACE Is was observed for those with proteinuria above 0.5 g/day. Below 0.5 g/day, a benefit could not be excluded but the findings were less robust.

Even in diabetics with CKD, ACE Is had no benefit on ACM[44] unless patients were treated at maximum tolerable dose (RR 0.78, 95% CI 0.61 to 0.98),[44] ACE Is reduced the risk of ESRD by 31% in diabetics when compared with placebo.[44] ACE Is can prevent the progression of micro- to macroalbuminuria (reported RR reduction of 55–65% versus placebo) in diabetic renal patients.[44,45] Regression from micro- to normoalbuminuria was also increased (RR 3.06, 95% CI 1.76 to 5.35).[44] When analysis was restricted

to those with proteinuria, the findings were similar, with no evidence of benefit from ACE Is (as compared with placebo) on mortality, but a statistically significant effect on reduction of ESRD or doubling of serum creatinine (RR 0.60, 95% CI 0.49 to 0.73).[45]

Angiotensin receptor blockers

Similar to ACE Is, ARBs have no significant impact on ACM in diabetics with CKD when compared with placebo or standard antihypertensive agents,[44,46] or CVD morbidity and mortality.[46] However, there was evidence of a reduction in progression of CKD,[44] with statistically significant risk reductions for ESRD (22%) and doubling of serum creatinine (21%). ARBs reduced progression from micro- to macroalbuminuria by more than 50% as well as significantly increasing the numbers returning from micro- to normoalbuminuria. Regarding adverse effects, the only significant increase observed was in hyperkalaemia.

Strippoli and colleagues[44] identified three studies that compared ACE Is with ARBs. They found no evidence of a difference in effect on mortality or renal outcomes.

A systematic review by Casas and colleagues[47] reported on effects of ACE Is or ARBs on renal outcomes, compared with placebo or other active interventions. Evidence of statistically significant risk reductions for ESRD was observed (RR 0.87, 95% CI 0.75 to 0.99). Small reductions in creatinine concentration (mean difference −7.07 μmol/l, 95% CI −13.26 to −0.88) and urinary albumin excretion (mean difference −15.7 mg/day, 95% CI −24.73 to −6.74) were reported, but significant heterogeneity among studies was noted. No significant difference was observed in change of GFR or on the composite end point of doubling of creatinine and ESRD. ACE Is/ARBs had no significant effects on GFR, ESRD or doubling of creatinine in diabetics. However, small reduction in urinary albumin excretion was observed in those with diabetic kidney disease (mean difference −12.21 mg/day, 95% CI −21.68 to −2.74). Casas and colleagues[47] noted that larger studies were more likely to report smaller benefits, suggesting publication or other source of small study bias.

In people with CKD and diabetes with microalbuminuria, NICE and SIGN recommend treatment with ACE Is or ARBs regardless of BP. In non-diabetics with CKD, hypertension should be controlled using the range of available

5

antihypertensives. However, both guidelines recommend that in the presence of proteinuria and CKD, hypertension should be managed first line with ACE Is/ARBs.[23,42]

Anticholesteraemic agents

In a systematic review and meta-analysis of six trials, Strippoli and colleagues[48] reported that statins had no significant benefits on mortality risk reduction in CKD when compared with placebo or other antilipaemic agents, although some benefit (19% reduction in ACM) in the predialysis group was observed. The same study reported a significant risk reduction in CVD morbidity (RR 0.75, 95% CI 0.66 to 0.85) and mortality (RR 0.81, 95% CI 0.73 to 0.90). The impact of statins on the rate of change in eGFR and proteinuria was variable between trials and between reviews.[48–50]

NICE and SIGN guidelines recommend that statin therapy should be considered in all patients with stage 1–3 CKD with a predicted 10-year cardiovascular risk of at least 20%.

Lifestyle intervention

Both guidelines recommend that healthy lifestyle advice should be offered to people with CKD, supporting an active lifestyle, a healthy diet, maintenance of a healthy weight and stopping smoking. However, evidence to support how best to deliver these interventions to people with CKD was lacking, as were trials of intervention to estimate the potential effect size.

NICE and SIGN noted the place of protein restriction in certain clinical circumstances and the need for this to be carefully assessed and supported. Systematic review of protein restriction diets has reported evidence of reducing risk of ESRD and/or ACM by 31–77% (from only one study with 82 participants) as compared with usual protein diet.[51,52] Protein restricted diet in type 1 and type 2 diabetes mellitus had little impact on the decline of GFR.[52,53]

The evidence base around treatments for CKD focuses on CKD as a single group and does not specifically identify the effectiveness of treatments for different stages of CKD. The benefits, and potential harms, to those with mild to moderate CKD have not been well reported.

When to refer to a specialist

Over the last two decades, commentators have noted the high proportion, 30–50% in some reports, of patients who are referred late to specialist nephrology care.[54–56] Late referral has been variously defined as the first referral to specialist nephrology care occurring between less than 1 month and 6 months prior to the patient requiring the initiation of RRT. Retrospective studies have demonstrated an association between late referral and poor outcomes on RRT when compared with those referred earlier.[57]

In 2008, NICE and SIGN issued guidelines for the management of people with CKD.[23,42] Like the UK Renal Association guidelines, guidance was given about the clinical features that may make referral to a specialist appropriate. The guidelines aimed to strike a balance between early referral and service capacity, and identified uncertainties around the potential benefits (and harms) of early referral.

NICE recommended the following groups to be considered for referral to a specialist:

- those with stage 4 and 5 CKD (with or without diabetes)
- those with higher levels of proteinuria [albumin–creatinine ratio (ACR) of at least 70 mg/mmol] unless known to be due to diabetes and already appropriately treated proteinuria (ACR of at least 30 mg/mmol) together with haematuria and rapidly declining eGFR (more than 5 ml/min/1.73 m^2 in 1 year, or more than 10 ml/min/1.73 m^2 within 5 years)
- those with hypertension that remains poorly controlled despite the use of at least four antihypertensive drugs at therapeutic doses
- those with, or suspected of having, rare or genetic causes of CKD
- those with suspected renal artery stenosis
- those with CKD and renal outflow obstruction should normally be referred to urological services, unless urgent medical intervention is required.

SIGN guidelines noted the lack of evidence about when to refer individuals to a specialist, and provided an algorithm (*Figure 2*) to aid decision-making which recognised that patients may seek medical attention for a number of different reasons.
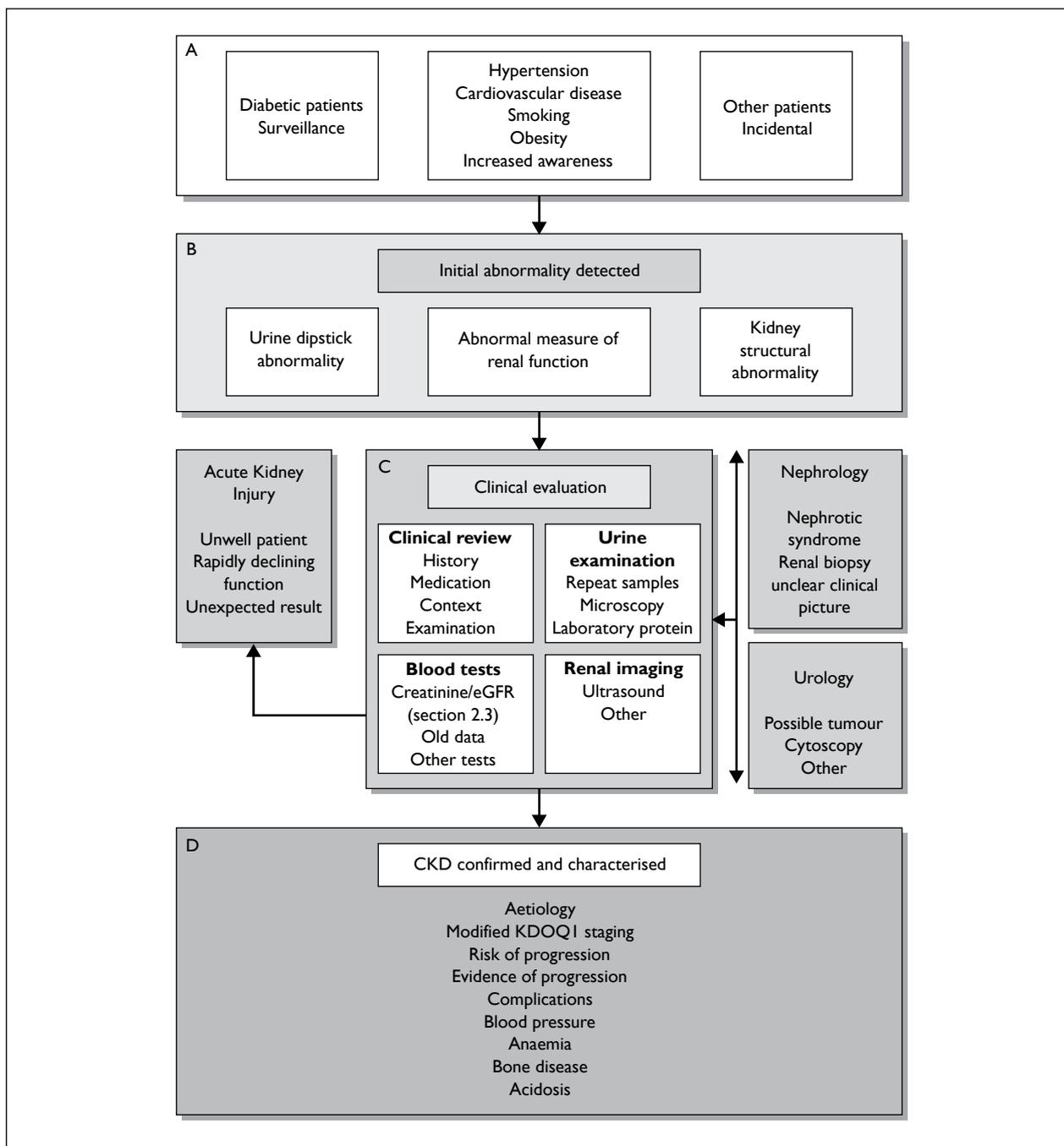
FIGURE 2 *Algorithm to support decision-making for referral of patients with evidence of renal impairment. Reproduced with permission from SIGN guidelines 2008.[41]*

Attention has turned to earlier referral for CKD and the opportunity to intervene not only to delay progression of renal disease and treat its complications at this early stage, but also to prevent CVD. Early referral to specialist nephrology care might provide a patient with access to an array of investigations, preventative treatments, education, dietary advice, etc., with an aim of:

- diagnosis of cause of renal disease – particularly to identify any causes that may be amenable to specific therapy
- appropriate use of renoprotective interventions – diet, cessation of smoking and pharmacotherapy to delay/prevent the progression of the renal disease (antihypertensive and specific antiproteinuric agents)

- appropriate use of cardioprotective interventions – pharmacotherapy to prevent/delay or minimise the impact of CVD (diet, exercise, smoking, lipid lowering therapy, smoking cessation and antiplatelet therapy)
- control of other metabolic and endocrine complications such as anaemia and renal bone disease
- preparation for a planned start to RRT – early intervention with all the above measures allows potential for a patient to reach RRT later and with fewer comorbidities, better nutrition and better psychological adjustment.

Aims and objectives

The aim of this report was to systematically review the evidence of the clinical effectiveness and cost-effectiveness of early referral strategies for management of people with markers of renal disease. There were three phases of research:

1. Systematic review of the evidence of clinical effectiveness – to assess and synthesise the evidence for early referral strategies. In addition, we sought to explore the natural progression of patients identified as having CKD and the characteristics for an effective early referral programme including:

   – Which patient groups were likely to benefit most?
   – What interventions were effective?
   – How were those interventions delivered most effectively?
   – At what stage in disease progression was the greatest benefit achieved?
   – What were the barriers to early referral?
2. Systematic review of the evidence of cost-effectiveness – to assess and synthesise the evidence of cost-effectiveness of early referral strategies.
3. Economic analysis – informed by the findings of phases 1 and 2, to model the economic implications of different early referral strategies to assess the cost-effectiveness.

In Chapter 2 we set out the methods used for the literature reviews. The natural history of CKD is reported in Chapter 3. The impact of late referral is considered in Chapter 4. Chapter 5 reports the findings of the review of clinical effectiveness of early referral strategies, and Chapter 6 considers other models of care for people with CKD. Chapter 7 reports the findings from the review of evidence of cost-effectiveness and describes the economic modelling to assess the potential cost-effectiveness of different early referral strategies. Finally, Chapter 8 provides a discussion, implications for the health service and research recommendations.

Chapter 2

Methods

In this chapter we detail the methods used for the systematic review of the clinical effectiveness of early referral for CKD and for the review of the natural history of CKD. We also set out the methods for the supplementary chapter on models of care for CKD undertaken to support the development of the economics model and to supplement the limited evidence identified for clinical effectiveness. The methods for the economic modelling are described later, in Chapter 7.

Clinical effectiveness and cost-effectiveness literature reviews

Clinical effectiveness review method

Data sources and search strategy

Sensitive electronic searches were undertaken to identify studies comparing early referral to other care options for people with CKD. Initial searching was undertaken between January and April 2008, with the main search updated in February 2009. Electronic searches were restricted to reports published in the English language since 1990. We searched for meeting abstracts from January 2006 only. In addition, reference lists of all included studies were scanned to identify additional potentially relevant studies. The search strategy is summarised in Appendix 1 and included clinical and cost effectiveness studies. Search terms did not restrict based on timing of referral; studies of early or late referral were identified.

The following databases were searched:

- Ovid MEDLINE, 1950 to 4 February 2009
- Ovid MEDLINE In-Process and Non-Indexed Citations
- EMBASE, 1988 to week 5 2008
- Science Citation Index, 4 February 2008
- ISI Proceedings, 4 February 2008
- British Nursing Index, 1994 to January 2008
- British Nursing Index Archive, 1985–96
- Health Management Information Consortium, January 2008

- Cumulative Index to Nursing & Allied Health Literature, 1982 to week 1 December 2007
- Social Science Citation Index, 4 February 2008
- Cochrane Central Register of Controlled Trials: Cochrane Library Issue 1 2008
- Cochrane Database of Systematic Reviews: Cochrane Library Issue 1 2008
- National Research Register Archive (up to October 2007), 19 March 2008
- The UK Clinical Research Network, 19 March 2008
- The European Dialysis and Transplant Nurses Association/European Renal Care Association 35th International Conference 2006 and 36th International Conference 2007 Final Programmes.

Additional searching was performed in NHS Economic Evaluation Database to support the cost-effectiveness literature review.

Study selection

Initial searching indicated that we would find very few randomised controlled trials (RCTs) of early referral strategies versus standard care. We therefore considered evidence from any study design that compared a strategy for early referral with a relevant comparator group. We included prospective and retrospective study designs. The research focused on adults with markers for early renal disease in either primary or secondary care. We included any intervention that aimed to achieve the early referral of people with markers of renal disease to specialist nephrology care. For retrospective studies, the definition of early referral was taken as referral at least 12 months before RRT. For prospective study designs, referral prior to reaching stage 5 CKD was required but other definitions of early referral were accepted (e.g. based on proteinuria thresholds in diabetic nephropathy). In the absence of a 'gold standard' for care, acceptable comparators included usual care, later referral (defined as less than 12 months prior to RRT for retrospective studies) or primary care. Outcomes of interest included:

- renal function
- onset of RRT
- quality of life

- ACM
- CVD mortality
- hospitalisations
- emergency dialysis
- survival on dialysis.

Details of the care package were also sought.

Titles, abstracts and keywords were reviewed by two systematic reviewers, independently, to identify studies that met the inclusion criteria outlined above. Full papers were then considered for inclusion. Discrepancies were resolved by discussion, with involvement of a third reviewer if necessary.

The search identified that there was a substantial evidence base on the effect of late referral (defined as less than 12 months prior to RRT) and, where studies included mortality as an outcome, this has been included in Appendix 5. A supplementary search for literature about potential barriers to early referral was conducted using MEDLINE (1996 to week 2 April 2008) and EMBASE (1996 to week 15 2008).

Quality assessment of included studies
Two systematic reviewers independently assessed the methodological quality of the included studies. The quality of included studies was assessed using the criteria outlined in the Centre for Reviews and Dissemination Report 4.[58] Checklists were adapted from those developed by NICE.[59]

Data extraction
Data extraction from the included studies was carried out independently by two systematic reviewers. Study characteristics, outcome results and aspects of study quality were collected using a standardised form (see Appendix 2). Any discrepancies were resolved by discussion and, where necessary, by involvement of a third reviewer (two occasions relating to terminology).

Data synthesis
Study characteristics and results were tabulated; analysis was qualitative. It was not possible to pool results for quantitative analysis because of the heterogeneity of study characteristics and the diversity in reporting of outcomes.

Economics review methods

The literature searches focused on identifying studies that assessed the cost-effectiveness of nephrology referral strategies for individuals with stage 3 CKD. In addition to the databases mentioned above, the reference lists of relevant studies were hand-searched. All abstracts were reviewed and the full article was obtained for any studies that were potentially relevant. Articles cited by other relevant studies were also retrieved for review. The review focused primarily on studies relating to individuals without diabetes, as more formal care pathways were already in place for individuals with diabetes and diabetic nephropathy.[60]

Study selection
Our inclusion criteria for formal appraisal were studies assessing the costs and consequences (long- or short-term) of early referral strategies for individuals with markers of renal disease. Early referral was defined as referral to a specialist prior to stage 4 CKD (i.e. eGFR higher than $30\,\text{ml/min}/1.73\,\text{m}^2$). We were not explicitly interested in extracting data from studies assessing the cost-effectiveness of population screening for proteinuria, but studies that looked at screening in non-diabetic populations were obtained to help inform the development of the economic model. Finally, studies assessing the cost-effectiveness of single interventions in individuals with CKD, such as the use of ACE Is to slow progression, were excluded from formal appraisal.

Quality assessment of included studies
Studies meeting our inclusion criteria were appraised using the *British Medical Journal* guidelines for reviewers of economic evaluations.[61] The quality of included decision models was also assessed against a published checklist for good practice in decision analytic modelling in health technology assessment.[62]

Data extraction
Plans were made to formally extract data from studies directly assessing the cost-effectiveness of nephrology referral for individuals with stage 3 disease compared with referral at stage 4 or 5 (current practice).

Other literature reviews

Separate systematic reviews were undertaken to support the following areas of the report: natural history of CKD and models of care for CKD.

Search strategies

Natural history
A systematic literature review was conducted to identify relevant literature on the natural history

of CKD. MEDLINE (1950 to March week 2 2008) and EMBASE (1996 to March week 4 2008) were searched. An internet search (Google scholar; http://scholar.google.co.uk/) was performed and potentially relevant studies were identified from clinical experts. Searches were restricted to the English language and were from 1998. Bibliographic searching of any included study was also undertaken (see Appendix 1 for the search strategy).

Systematic reviews, meta-analyses, observational cohorts and follow-up studies (prospective or retrospective) of adult populations with at least 2 years' of follow-up were considered. RCTs were excluded owing to the highly selected nature of their participants. Those studies where the main study populations were defined as having CKD were included. However, studies with broader participant inclusion criteria (diabetes, CVD or hypertension) were considered for inclusion when participants with CKD accounted for a substantial number of the total study population. Studies with less than 100 subjects were excluded. While a definition of CKD based on the KDOQI classification was considered to be optimal, the definition of CKD used by the authors was accepted.

Included studies were quality assessed. Systematic reviews and meta-analyses were evaluated based on a methodology checklist outlined by NICE.[63] Other study designs were evaluated based on a quality assessment tool adapted from various methodological criteria.[39,64–67]

Care model

Database searching was carried out in MEDLINE (1950 to present) and EMBASE (1996 to 2008 week 25) combining keywords and medical subject heading (see Appendix 1). Internet and bibliographic searches of included studies were performed. No relevant studies were identified from the Cochrane review database and *Health Technology Assessment* (HTA) journal database of published reports. Any full papers or abstracts published in English (evaluation, audit, description of care) that reported a model of care for the management of CKD patients were included. Care models of management of RRT patients were excluded.

Data extraction

Data extraction was undertaken by one author and checked by a second author. A specifically designed and piloted data extraction form was used for each component. Information about study design, participants, definition and measure of CKD and relevant outcomes of the study were extracted. The data were extracted for all participants and for relevant clinical subpopulation including stages of CKD, diabetes mellitus, CVD, high blood pressure (HBP), sex, age group and race.

In the review of reports of care models, additional data were extracted about: setting (primary, secondary or other); model of care or intervention provided or proposed; description of participants or staff involved; and relevant outcomes/outcomes foreseen including, primarily, clinical outcomes and attitudes of patient or health-care provider towards service and, secondarily, improvements or changes in care/service and barriers to implementation of services.

Data synthesis

For all reviews, the study characteristics and results were tabulated and analysed qualitatively. A thematic approach was adopted for analysis of the barriers to early referral and care models.

Chapter 3
Natural history

Introduction

Understanding the natural history of CKD is critical to understanding the effectiveness of interventions involving the 'early' referral of patients with CKD to specialists.

This review of the natural history of CKD focused on renal impairment defined by GFR. GFR was chosen because in the UK, since 2006, there has been universal reporting of eGFR from laboratories. In addition, general practitioners (GPs) in the UK have been asked to record all patients with an eGFR of less than 60 ml/min/1.73 m^2 (stage 3 or higher) on a practice register. This cohort, therefore, makes up a critical and substantial component of the people increasingly labelled with CKD in the UK and for whom the appropriateness and timing of referral to a specialist is uncertain. The key outcomes of interest were ACM, cardiovascular mortality and morbidity, renal progression and ESRD, and quality of life.

Results

Description of included studies

The process of study identification and the number of relevant published papers are given in *Figure 3*. Thirty-six studies were data extracted and appraised (42 published papers; five studies with more than one publication). Details of the excluded studies are given in Appendix 3.

A summary of the characteristics of the included studies is given in *Table 2*.

We did not identify any systematic reviews of the natural history of CKD that considered all of the outcomes of interest, but we did identify three systematic reviews that presented information about some aspects of natural history.

One review compared the risk of ACM and cardiovascular mortality in those with CKD as compared with non-CKD populations where studies included a range of study participants from healthy adults to those with comorbidities.[68] We identified a second review comparing the risk of non-fatal myocardial infarction (MI) and cardiovascular mortality between those with evidence of CKD and no CKD in seven population studies of apparently healthy adults.[69] These two reviews overlapped in one study (NHANES II 2002),[70] and Tonelli and colleagues[68] reported data from three primary cohort studies [ARIC (Atherosclerosis Risk in Communities) 2003,[71] CHS (Cardiovascular Heart Study) 2003,[72] FHS (Framingham Heart Study) 1999[73]] which were included by Di and colleagues[69] as a single study that pooled individual patient data from the original studies.[74]

These were good quality reviews (see Appendix 4) and we therefore focused our further searches on studies quantifying the extent of progression and mortality in CKD populations. We limited our included studies to only those defining their study populations as having CKD, rather than further comparing risk to the general population. We did include comparative studies if they had not been included in the above reviews or where additional information of interest in our review was available in the original study. One study[75] from Tonelli and colleagues[68] and two studies[74,76] from Di and colleagues[69] were identified in our searches and included as primary studies because they presented additional information pertinent to this review.

Finally, Dale and colleagues[77] reviewed studies of health utility in people with CKD and ESRD. Only one study[78] included this review met our inclusion criteria and was thus data extracted separately.

All other studies included were prospective (21) or retrospective cohorts (13). Two included studies, defining their study population based on the presence of diabetes only, were retained because participants with CKD accounted for a substantial number of the total study population.[79,80] Irie and colleagues[81] reported on a subgroup of the participants included in the study by Imai and colleagues[82] but reported on different outcomes and their work was, therefore, included as a separate study.
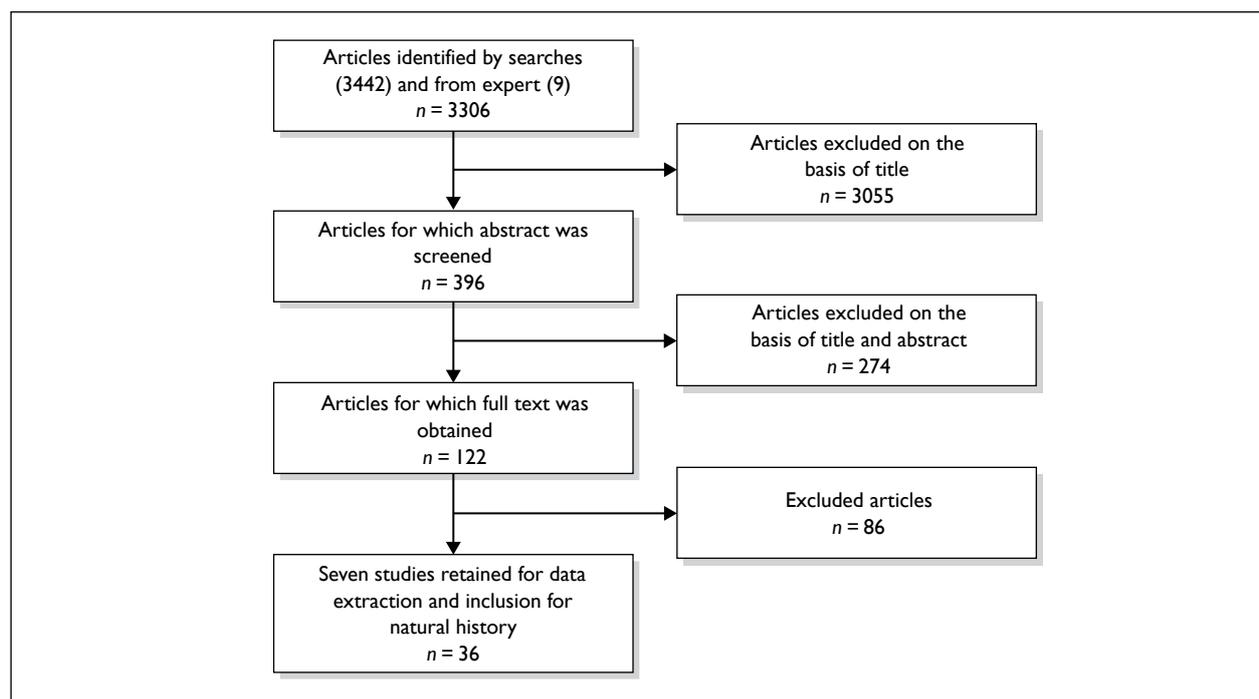
FIGURE 3 *Representation of the flow of studies through the natural history review process.*

Definition of chronic kidney disease

Among the included studies, various definitions of renal impairment were reported. Definitions based on the KDOQI were the most widely used to describe CKD and classify stages, with an eGFR of less than 60 ml/min/1.73 m² (stage 3 or worse) being the most commonly reported threshold (see *Table 2*). Others defined impaired renal function based on serum creatinine, creatinine clearance, microalbuminuria or some combination of measures. Several studies did not clearly define what they considered to be CKD, but they presented data for subgroups that met the inclusion criteria of our review and were therefore reported.

Where GFR was reported, most studies used the MDRD equation to estimate GFR; two studies used the CG equation.[83,84] The re-expressed, ID-MS (isotope dilution-mass spectrometry) traceable MDRD formula was used in two studies.[32,85] One compared the MDRD equation, the CG equation and the Mayo Clinic equations for estimating GFR.[86] Three studies used the Cr-EDTA injection[87–89] while another study used the iohexol clearance technique[90] to measure kidney function. Five studies did not specify which measure was used to assess renal function.[78,91–94] The systematic

reviews included a variety of measures for assessing kidney function.[68,69]

We were able to define two categories of study based on the populations they included:

- Screened population – drawing from people in the community and using a population screening approach.
- Clinical population – drawing from clinical record databases, laboratories, primary care or clinical settings and the blood sample taken for a clinical indication.

Methodological quality of included studies

The quality of cohort or follow-up studies was assessed based on the following four criteria:

- sample selection
- follow-up
- determination of chronicity
- measure of renal impairment.

A summary of the quality assessment is presented in *Table 3*. Only 13 studies adequately defined CKD to be chronic. Assay calibration for the measurement of serum creatinine is a major

determinant of the accuracy of GFR,[112] and differences between clinical laboratories in calibration of serum creatinine or assays could be a source of error.[113] Among the included studies, only 12 accounted for differences in assays over time or between labs. More than half of the studies had either complete follow-up or reported loss to follow-up of less than 10%. Most of the studies (27) fulfilled all or 85% of the criteria for study design and sample selection (see Appendix 4 for the quality assessment for systematic reviews).

Outcomes

The outcomes reported by included studies are summarised in *Table 4*. ACM was the most commonly reported outcome, with few studies reporting aspects of quality of life. Thirteen studies presented the outcomes by CKD stages as per the KDOQI.[32,75,78–80,82,83,85,94,101,106,110,111]

In the following section, we present a summary of the results of studies of general CKD populations not restricted to specific subgroups. We then present data for the following pre-specified subgroups: diabetes mellitus, hypertension (HBP), CVD, gender, race and age.

All-cause mortality: general chronic kidney disease population

ACM risk in those with CKD compared with no CKD

Eriksen and Ingebretsen[96] reported a hazard ratio (HR) of 1.25 (95% CI 1.14 to 1.37) for each 10-ml/min/1.73 m² decrease in eGFR. Five primary studies reported a small increased risk of mortality (risk ratios ranged from 1.12 to 1.78) for people with CKD as compared with those without CKD (*Figure 4*).[74,76,81,85,92] These studies were based on general populations undergoing health screening[76,81,85] or clinical record database review,[92] and all but one[92] adjusted for comorbidities, age and sex. Herzog and colleagues[92] adjusted for comorbidities only. A further two population health screening studies, comparing ACM in CKD cohorts with the population as standardised mortality rates (SMRs), noted higher risks of mortality with SMR 2.2 (95% CI 2.1 to 2.4)[96] and SMR 8.3 (95% CI 7.5 to 9.2),[98] but did not adjust for comorbidity (*Figure 4*). Evans and colleagues[98] included a cohort of participants with marked renal impairment with a serum creatinine level of at least 250 µmol/l. John and colleagues[104] reported age and sex-adjusted

SMRs for a CKD cohort compared with the general population, based on laboratory data (SMR 1.53, 95% CI 1.44 to 1.62).

Tonelli and colleagues[68] reported an unadjusted increased risk of death among those with CKD compared with no CKD in 93% of the 37 studies included in their meta-analysis (RR range 0.94–5.00); however, significant heterogeneity was noted. From a series of meta-regression analyses, authors reported that a greater risk associated with CKD was observed in younger patients, women and studies in 'general populations'. In nine studies classed as including a 'general population', the risk for mortality in the CKD group was threefold higher (RR 3.0, 95% CI 2.18 to 4.11), but again substantial heterogeneity was observed. Studies based on population health survey data (NHANES I[114] and II,[70] FHS[73]) reported lower HR/RR of 1.38–2.26. One population-based heart risk factor study in North America (ARIC[71]) reported higher risk estimates (3.54); three studies included populations known to be at high risk of mortality and CKD (people over 65 years, aboriginal Australians, clinical records based cohort). Adjusted analysis for general population studies (possible for three studies) was also presented by Tonelli and colleagues[68] and this reduced heterogeneity as well as reducing the risk estimate to close to 1 for all but one of the studies. Further details are given in Appendix 5.

Two studies reported adjusted risk of ACM by CKD stage (*Table 5*).[75,85] Go and colleagues,[75] studying a clinical population, reported an increasing risk with stage from HR 1.2 for stage 3a to 5.9 for stage 5 (compared with no CKD). Astor and colleagues,[85] studying a general population, also reported an increase in risk with stage.

ACM rate in populations with CKD

Four studies reported ACM per 10,000 person-years.[74–76,85] All reported death rates among those with CKD that were greater than for those with no CKD (definitions varied) (*Table 6*). Death rate varied substantially between studies; Wiener and colleagues[74] reported the highest rate of 3080 deaths per 10,000 person-years, considerably more than any of the other studies. This study also reported a high death rate (980 per 10,000 person-years) in the population with no CKD. There was evidence that death rate increased with the degree of proteinuria[85] and stage,[75] and was higher in men than in women.[76]

TABLE 2 *Characteristics of the included studies*

Author/year/country	Study design	Total number of participants	% with CKD (of total participants)	DM (% of total participants unless specified)	CVD	HBP	Median follow-up (years)	Mean age (years)	Definition of CKD used in the study[a]
Astor 2008,[85] USA	PC, Screened population, NHANES III	14,586	Stage 3 and 4: 5.8	4.8	7.6	47.1	8.7	44.2	eGFR 15–59 and microA and macroA
Bruno 2007,[79] Italy	PC, clinical population, (clinics, GP and clinical records) Casale Monferrato study	1539	Stage 1: 7.3, Stage 2: 58.3, Stage 3a: 26.0, Stage 3b: 6.9, Stage 4: 1.4	All	–	–	10[b]	–	eGFR <60 and microA
Cvengros 2005,[91] USA	PC, clinical population (hospital, renal clinic)	207	100[c]	47.8	–	–	1.3[d]	59.77	SCr ≥3 (unit not given)
Di 2007,[69] Iceland (various)	SR[e], includes PC, screened population	2007, seven studies	Lowest quintile: 38.6[c], varied by study	–	–	–	3–20[f]	–	eGFR <67.6 (lowest quintile)
Djamali 2003,[83] USA	RC, clinical population (hospital, renal clinic)	CKD: 872; RRT: 890	Stage 1: 8, Stage 2: 28, Stage 3: 46, Stage 4: 16, Stage 5: 2	Stage 1: 10, Stage 2: 36, Stage 3: 43, Stage 4: 10, Stage 5: 1	–	–	4.6[f]	54	SCr >115 µmol/l
Drey 2003,[95] UK	PC, clinical population. (laboratory database)	1076	Stage 3: 52, Stage 4 and 5: 48	–	–	–	5.5[f]	≥70[g]: 74%	SCr ≥150 µmol/l
Eriksen 2006,[96,97] Norway	PC, clinical population (laboratory database)	3047	Stage 3: 100	–	–	–	3.7	75	eGFR 30–59

Author/year/country	Study design	Total number of participants	% with CKD (of total participants)	DM	CVD	HBP	Median follow-up (years)	Mean age (years)	Definition of CKD used in the study[a]
				(% of total participants unless specified)					
Evans 2005,[98] Sweden	PC, clinical population (68 medical laboratories across Sweden)	920	Stage 4 and 5: 100	31	–	–	5	<45[g]: 18.2%; 45–64: 40.9%;≥65: 41.0%	M: SCr>300 µmol/l; F: SCr>250 µmol/l
Go 2004,[75] USA	RC, clinical population (laboratory and clinical database)	1,120,295	Stage 3a: 13.7 Stage 3b: 3.0 Stage 4: 0.6 Stage 5: 0.1	9.6	6.3	19.1	2.8	52.2	eGFR<60
Gorodetskaya 2005,[78] USA	PC, clinical population	205	Stage 3: 24.9 Stage 4: 32.2 Stage 5: 13.6	Stage 3: 43 Stage 4: 44 Stage 5: 68 Dialysis: 40 GFR≥60ml/min/1.73m²: 18	Stage 3: 12 Stage 4: 42 Stage 5: 36 Dialysis: 18 eGFR≥60ml/min/1.73m²: 5		10 months[d,f]	62.8	eGFR<70 (eGFR 60–70: 10.8%); dialysis: 18.5%
Hallan 2006,[32,99,100] Norway	PC, general population (community health screening), HUNT II	65,604	4.7[c]	3	7.9	11.1	8	49	eGFR<60
Hemmelgarn 2006,[101] Canada	RC, clinical population (laboratory service computerised database)	10,184	Stage 3: 31.3 Stage 4 and worse: 4.1	Stage 2: 14.2 Stage 3: 19.8 Stage 4 and worse: 31	–	–	2	75.1–77.8	eGFR<60
Herzog 2004,[92] USA	RC, clinical population (Medicare database)	1,136,201	3.2[c]	39.60[h]	53.60[h]	79.8[h]	1.9	76.5[g]≥80: 40%	CKD defined based on ICD-9 codes

TABLE 2 Characteristics of the included studies (continued)

Author/year/ country	Study design	Total number of participants	% with CKD (of total participants)	DM	CVD	HBP	Median follow-up (years)	Mean age (years)	Definition of CKD used in the study[a]
				(% of total participants unless specified)					
Hovind 2001,[93,102] Denmark	PC, clinical population (Steno Diabetes Center, diabetic nephropathy registry)	301	100[c]	All	–	–	6.7	36	Diabetic nephropathy (persistent microalbuminuria > 200 mcg/ min + retinopathy)
Hsu 2003,[103] USA	RC, screened population (national data set on health and nutrition of the non-institutionalised US population), NHANES II & III, and USRDS	B: 4112 W: 9238	B: 2.7[c] W: 3.1[c]	B: 30[h] W: 71.81[h]	–	–	3–8 years[b]	B: 61 W: 62	eGFR 15–59
Imai 2008,[82] Japan	PC, screened population (community health survey)	120,727	Stage 3: 21.3 Stage 4 and worse: 0.01	–	–	M: 17.8 F: 11.9	10[b]	Range 40–79	eGFR < 60
Irie 2006,[81] Japan	PC, Screened population (community health survey)	M: 30,764 F: 60,668	M: 3.0[c] F: 3.0[c]	–	–	–	10.1[f]	Range 40–79	Data presented for eGFR < 60 and eGFR ≥ 60
John 2004,[104] UK	PC, clinical population (laboratory database)	3822 (referred and unreferred)	100[c]	–	–	–	2.6	82[g,i] ≥ 80: 66.4%	M: SCr ≥ 180 µmol/l; F: SCr ≥ 135 µmol/l
Jones 2006,[105] UK	RC, clinical population (renal unit database)	726	Stage 3: 46 Stage 4: 35 Stage 5: 19	DN:17	–	HN: 10	2.9	72	eGFR < 15 to 59

Author/year/ country	Study design	Total number of participants	% with CKD (of total participants)	DM	CVD	HBP	Median follow-up (years)	Mean age (years)	Definition of CKD used in the study[a]
				(% of total participants unless specified)					
Keith 2004,[106,107] USA	PC, clinical population (clinical database of HMO)	27,998	Stage 2 (with proteinuria): 6.2 Stage 3: 40.3 Stage 4: 2.8	15.8	13.1	37.4	5.5	60.8	eGFR<90 (with proteinuria)
Khatami 2007,[108] UK	RC, clinical population (hospital database)	8160	24[c]	5.5[h]	1.6[h]	–	4[b]	M: 63.5[i] F: 67[i]	GFR<60
Kollerits 2007,[90] Austria	PC, clinical population (nephrology department in various countries)	177	100[c]	None	–	–	3.9[f]	46.4	CKD estimated based on SCr
Leehey 2005,[109] USA	RC, clinical population (VA medical centre database)	343	100[b]	All	–	–	3a	69[g] ≥65: 73%	SCr>124 µmol/l and microA
Levin 2001,[84] Canada	PC, clinical population (seven Nephrology units)	313	CrCl 10–49: 80.2 CrCl 50–75: 19.8	29.1	45.7	72.2	1.9	56.3	CrCl 10–75 ml/min
Maaravi 2007,[86] Israel	PC, screened population (sampled from community)	441	34.2[c]	16.1	26.1		12[b]	All 70 years at initial examination	eGFR<60
Meisinger 2006,[76] Germany	PC, screened population (community health survey), MONICA	M: 3860 F: 3674	M: 12.4[c] F: 20.5[c]	M: 9.4[h] F: 6.9[h]	M: 11.5[h] F:4.1[h]	M: 62.3[h] F:55.5[h]	12.5	M: 62.4 F: 61.5	eGFR 15–59

TABLE 2 Characteristics of the included studies (continued)

Author/year/country	Study design	Total number of participants	% with CKD (of total participants)	DM	CVD	HBP	Median follow-up (years)	Mean age (years)	Definition of CKD used in the study[a]
				(% of total participants unless specified)					
Mulec 1998,[87] Sweden	RC, clinical population (database of type I DM patients)	158	100[c]	All	–	–	8[f]	35.5	Nephropathy (persistent macroA >300 mg/24 hours)
O'Hare 2006,[110] USA	RC, clinical population (VA Medicare database and USRDS)	2,583,911	Stage 3: 18.4 Stage 4 and 5: 1.5	–	–	–	3.17[f]	63.6	eGFR <60
Orlando 2007,[111] USA	RC, clinical population (VA laboratory database)	1553	100[c]	52	49	92	3.6[f]	70	SCr ≥123.8 μmol/l
Patel 2005,[80] USA	RC, clinical population (VA medical database)	12,570	Stage 1 and 2: 18.0 Stage 3a: 18.0 Stage 3b: 8.0 Stage 4: 3.0 Stage 5: 1.0	All	52	47	3[b]	66	eGFR <60 (or proteinuria)
Rossing 2004,[89] Denmark	PC, clinical population (registry of Steno Diabetes Center)	227	100[c]	All type 2 DM	10	–	6.5	57	Nephropathy (persistent macroA >300 mg/24 hours) and retinopathy
Tarnow 2005,[90] Denmark	PC, clinical population (sampled from Steno Diabetes Center)	198	100[c]	All type 1 DM	5.1		9[b]	41	Nephropathy (persistent macroA >300 mg/24 hours) and retinopathy
Tonelli 2006,[68] Canada	SR, both general and clinical population	1,371,990 from 39 studies	100[c]	Range: 0–100	Range: 0–100	Range: 0–100	4.5	34–79	Estimated CrCl or GFR: 60ml/min (with or without standardisation to body surface area), SCr >120 μmol/l

continued

Author/year/ country	Study design	Total number of participants	% with CKD (of total participants)	DM	CVD	HBP	Median follow-up (years)	Mean age (years)	Definition of CKD used in the study[a]
				(% of total participants unless specified)					
Tseng 2008,[94] USA	RC, clinical population (national database of VHA diabetic patients)	39,031	Stage 3: 92.4 Stage 4: 7.6	All	67.1	–	1.6	70	eGFR between 15 and 60
Wannamethee 2006,[37] UK	PC, general population (age and sex registers of GP)	4029	15.6[c]	15.5[h]	27.1[h]	38.8[h]	6[f]	67.7	eGFR between 15 and <60
Weiner 2004,[74] USA	PC, general population (community-based data sets) ARIC, CHS, FHS, FOS	22,634	7.4[c]	9.5	–	39.7	10[b]	57.1	eGFR 15 to <60 ml/ min/1.73 m²

A, albuminuria; ARIC, Atherosclerosis Risk in Communities; B, Black people; BRHS, British Regional Heart Study; CHS, Cardiovascular Heart Study; CKD, chronic kidney disease; Cr, creatinine; CrCl, creatinine clearance; CVD, cardiovascular disease; DM, diabetes mellitus; DN, diabetic nephropathy; eGFR: estimated glomerular filtration rate; F, female; FHS, Framingham Heart Study; FOS, Framingham Offspring Study; HBP, high blood pressure; HMO, health maintenance organisation; HUNT, The Nord-Trøndelag Health Study; ICD-9-CM, *International Classification of Diseases*, Ninth Edition, Clinical Modification; M, male; macroA, macroalbuminuria; microA, microalbuminuria; MONICA, MONItoring trends and determinants in CArdiovascular diseases; NHANES, National Health and Nutritional Examination Survey (NHANES II 1976–80, NHANES III 1988–94); P: Proteinuria; PC, prospective cohort; PY, person-year; RC, retrospective cohort; RCT, randomised controlled trial; SCr, serum creatinine; SR, systematic review; USRDS, United States Renal Data System; VA, veterans affairs; VHA, veterans health affairs; W, White people.

a eGFR measured in ml/min/1.73 m² unless stated.
b Fixed time of follow-up.
c Proportion of CKD as defined in the study.
d Study on quality of life and was not restricted to criteria of at least 2 years' follow-up.
e Prospective cohort study (Reykjavik study) included within the meta-analysis.
f Mean follow-up.
g Age groups in years.
h Comorbidities in participants with CKD.
i Median age in years.
j Irie 2006[81] included one of the subgroup analysed in Imai 2008[82] which consisted of participants from five communities of Japan.

TABLE 3 *Quality assessment of included primary studies*

Study ID	Hypothesis/ aim clearly described	Complete capture of study population	Clear inclusion and exclusion criteria	Clinical and demographic characteristics detailed	Information recorded prospectively (minimal recall bias)	Ascertainment of sample described
Astor 2008[85]	Yes	Yes	Yes	Yes	Yes	Yes
Bruno 2007[79]	Yes	Yes	Yes	Yes	Yes	Yes
Cvengros 2005[91]	Yes	Yes	Yes	Yes	Yes	Yes
Djamali 2003[83]	Yes	Unclear	Yes	Yes	Yes	No
Drey 2003[95]	Yes	Yes	Yes	Yes	Yes	Yes
Eriksen 2006[96]	Yes	Yes	Yes	Yes	Yes	Yes
Evans 2005[98]	Yes	Yes	Yes	Yes	Yes	Yes
Go 2004[75]	Yes	Yes	Yes	Yes	Yes	Yes
Gorodetskaya 2005[78]	Yes	No	Yes	Yes	Yes	Yes
Hallan 2006[32]	Yes	Yes	Yes	Yes	Yes	Yes
Hemmelgarn 2006[101]	Yes	Yes	Yes	Yes	Yes	Yes
Herzog 2004[92]	Yes	Yes	Yes	Yes	Yes	Yes
Hovind 2001[93]	Yes	Unclear	Yes	Yes	Yes	Yes
Hsu 2003[103]	Yes	Yes	Yes	Yes	Yes	Yes
Imai 2008[82]	Yes	Yes	Yes	Yes	Yes	Yes
Irie 2006[81]	Yes	Yes	Yes	Yes	Yes	Yes
John 2004[104]	Yes	Yes	Yes	Yes	Yes	Yes
Jones 2006[105]	Yes	No	Unclear	Yes	Yes	Yes
Keith 2004[106]	Yes	Yes	Yes	Yes	Yes	Yes
Khatami 2007[108]	Yes	Unclear	Yes	Unclear	Yes	Yes
Kollerits 2007[90]	Yes	Unclear	Yes	Yes	Yes	Unclear
Leehey 2005[109]	Yes	Unclear	Yes	Yes	Yes	Yes
Levin 2001[84]	Yes	Unclear	Yes	Yes	Yes	Yes
Maaravi 2007[86]	Yes	Yes	Yes	Yes	Yes	Unclear
Meisienger 2006[76]	Yes	Yes	Yes	Yes	Yes	Yes
Mulec 1998[87]	Yes	Unclear	Yes	Yes	Yes	Yes
O'Hare 2006[110]	Yes	Yes	Yes	Yes	Yes	Yes
Orlando 2007[111]	Yes	Unclear	Yes	Yes	Yes	Yes
Patel 2005[80]	Yes	Unclear	Yes	Yes	Yes	Yes
Rossing 2004[88]	Yes	Unclear	Yes	Yes	Yes	Yes
Tarnow 2005[89]	Yes	Unclear	Yes	Yes	Yes	Yes
Tseng 2008[94]	Yes	Yes	Yes	Yes	Yes	Yes
Wannamethee 2006[37]	Yes	Yes	Yes	Yes	Yes	Yes
Weiner 2004[74]	Yes	Yes	Yes	Yes	Yes	Yes

a CKD is defined to be chronic if decreased eGFR persisted for more than 3 months.
Quality assessment of two systematic reviews (Di 2007[68] and Tonelli 2006[67]) is not presented here, but is given in Appendix 4.

Assessment of outcome described	Number lost to follow-up reported	Loss to follow-up <10%	Reason for loss to follow-up given	Characteristics of patients loss to follow-up described	Design specific sources of bias mentioned	Appropriate methods to deal with bias/ confounding	Chronicity: adequately defined[a]	Accounted for differences in assays
Yes	Complete	–	–	–	Yes	Yes	Unclear	Yes
Yes	Yes	Yes	No	No	Yes	Unclear	No	No
Yes	Yes	No	No	No	Yes	Yes	No	No
No	Yes	No	Yes	No	Yes	No	Yes	No
Yes	Yes	Yes	No	No	Yes	No	No	Yes
Yes	Complete	–	–	–	Yes	Yes	Yes	Unclear
Yes	Complete	–	–	–	Yes	Yes	Yes	No
Yes	Yes	No	Yes	Yes	No	No	Yes	Yes
Yes	Yes	No	Yes	No	Yes	No	No	No
Yes	Complete	–	–	–	Yes	Yes	No	Yes
Yes	Complete	–	–	–	Yes	Yes	No	Yes
Unclear	Complete	–	–	–	Yes	Yes	No	No
Unclear	No	–	–	–	Yes	Yes	Yes	No
Yes	Complete	–	–	–	Yes	Yes	No	Yes
Yes	Complete	–	–	–	Yes	Yes	No	Yes
Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Yes	Complete	–	–	–	No	No	Yes	Yes
Yes	Complete	–	–	–	Yes	Yes	Yes	Yes
Yes	Complete	–	–	–	Yes	Yes	Yes	Unclear
Yes	Complete	–	–	–	No	No	Unclear	Yes
No	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Yes	Complete	–	–	–	Yes	Yes	Yes	No
Unclear	Yes	Yes	No	No	Yes	No	No	No
Unclear	Complete	–	–	–	Yes	Yes	Unclear	Unclear
Yes	Yes	Yes	Yes	No	Yes	Yes	No	Unclear
Unclear	Complete	–	–	–	No	No	Unclear	No
Yes	Unclear	–	–	–	Yes	Yes	No	No
Yes	Yes	Yes	No	No	Yes	Yes	Yes	No
Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	No
Yes	Unclear	–	–	–	Yes	Yes	Yes	Unclear
Yes	Yes	Yes	Yes	No	No	No	No	Unclear
Yes	Complete	–	–	–	Yes	Yes	Yes	No
Yes	Yes	Yes	No	No	Yes	Yes	No	No
Unclear	Yes	Yes	No	No	Yes	Yes	No	Yes

TABLE 4 *Outcomes reported in included studies*

Study ID	ACM	CVD M&M	RRT	ESRD	CKDP	QoL
Astor 2008[85]	×	×				
Bruno 2007[79]	×	×				
Cvengros 2005[91]						×
Di 2007[69]		×				
Djamali 2003[83]	×				×	
Drey 2003[95]	×	×	×	×		
Eriksen 2006[96]	×			×	×	
Evans 2005[98]	×	×	×		×	
Go 2004[75]	×	×	×			
Gorodetskaya 2005[78]			×		×	×
Hallan 2006[32]		×		×		
Hemmelgarn 2006[101]	×		×		×	
Herzog 2004[92]	×					
Hovind 2001[93]					×	
Hsu 2003[103]				×	×	
Imai 2008[82]					×	
Irie 2006[81]	×	×				
John 2004[104]	×	×			×	
Jones 2006[105]	×		×		×	
Keith 2004[106]	×	×	×			
Khatami 2007[108]					×	
Kollerits 2007[90]			×		×	
Leehey 2005[109]					×	
Levin 2001[84]	×	×	×	×		
Maaravi 2007[86]	×					
Meisienger 2006[76]	×	×				
Mulec 1998[87]					×	
O'Hare 2006[110]	×					
Orlando 2007[111]	×				×	
Patel 2005[80]	×			×	×	
Rossing 2004[88]	×	×		×	×	
Tarnow 2005[89]	×	×				
Tonelli 2006[68]	×	×				
Tseng 2008[94]	×		×			
Wannamethee 2006[37]		×				
Weiner 2004[74]	×	×				

ACM, all-cause mortality; CKDP, chronic kidney disease progression; CVD M&M, cardiovascular disease morbidity and mortality; ESRD, end-stage renal disease; RRT, renal replacement therapy; QoL, quality of life.
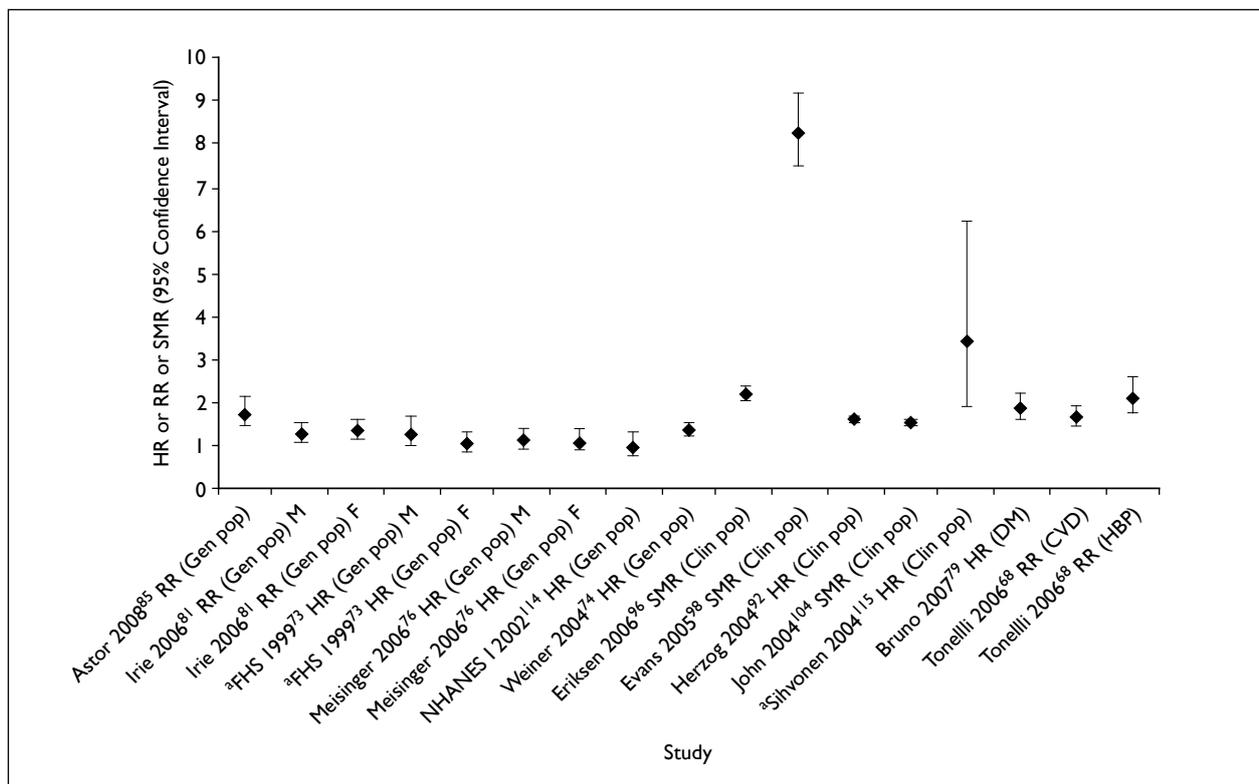
FIGURE 4 *Risk of all-cause mortality. Comparing those with CKD with those without CKD. ªThree studies reported by Tonelli 2006[68] as 'general populations' with adjusted analysis; Sihvonen 2004[115] included only people with rheumatoid arthritis so recoded as 'clinical population' in this review. Clin, clinical; CVD, cardiovascular diseases; DM, diabetes mellitus; F, female; FHS, Framingham Heart Study; Gen, general; HBP, high blood pressure; HR, hazard ratio; M, male; NHANES I, National Health and Nutritional Survey I; Pop, population; RR, relative risk; SMR, standardised mortality rate.*

TABLE 5 *Risk of all-cause mortality by CKD stage*

Study ID	Measures	Values (variance)	Reference group	Adjusted analysis
Astor 2008[84]	RR (95% CI)	Stage 2: 1.05 (0.89 to 1.25) Stage 3–5: 1.77 (1.47 to 2.13)	eGFR ≥ 90 ml/min/1.73 m²	Age, sex, race/ethnicity, previous CVD, BP, use of antihypertensive medication, DM, smoking, BMI, physical activity, cholesterol and C-reactive protein
Go 2004[74]	HR (95% CI)	Stage 3a: 1.2 (1.1 to 1.2) Stage 3b: 1.8 (1.7 to 1.9) Stage 4: 3.2 (3.1 to 3.4) Stage 5: 5.9 (5.4 to 6.5)	eGFR ≥ 60 ml/min/1.73 m²	Age, sex, income, education, dialysis, prior CVD, DM, HBP, dyslipidaemia, cancer, serum albumin < 3.5 g/dl, dementia, cirrhosis, chronic lung disease, proteinuria, prior hospitalisation
BP, blood pressure; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HBP, high blood pressure; HR, hazard ratio; RR, relative risk.				

Seven primary studies presented cumulative mortality for a specified time period.[81,83,86,92,96,98,105] At 1 year, mortality varied from only 3%[98] to 15%.[105] At 5 years, 31–39% died.[96,98] For studies reporting 9.0–12.5 years' follow-up, cumulative mortality ranged from 19.7% to 52.0%.[81,83,86,96] Five other studies presented the proportion of deaths in a given mean follow-up time and thus were not directly comparable.[68,76,84,101,104] Drey and colleagues[95] reported an exceptionally high proportion of deaths (69%) in mean 5.5 years. The results of these are summarised in *Table 6*.

Four primary studies reported the proportion of deaths for different stages of CKD.[75,83,106,111] The proportion of people dying was observed to increase with declining eGFR.

Cardiovascular disease morbidity and mortality: chronic kidney disease population

Studies did not report a consistent definition of CVD morbidity and mortality, and reporting was often lacking in detail so caution should be used when drawing comparisons across studies.

CVD risk in those with CKD compared with no CKD

As for ACM, most studies observed a higher risk of CVD deaths or events in those with CKD as compared with people without CKD. As shown in *Figure 5*, the adjusted risk estimates for general population studies were reasonably consistent

TABLE 6 *Summarised result of all-cause mortality for general CKD population (eGFR < 60 ml/min/1.73 m2 unless stated)*

Study ID	Measures	Values (variance)	Follow-up	Comparators/ CKD other stages	Comments
Deaths per person-years					
Astor 2008[85]	Events/10,000 person-years (read from graph)	Stage 3–5 no A: 290 Stage 3–5 microA: 510 Stage 3–5 macroA: 880	13 years	eGFR > 90 ml/min/1.73 m² no A: 180	
Go 2004[75]	Events/10,000 person-years	Stage 3a: 108 Stage 3b: 476 Stage 4: 1136 Stage 5: 1414	Median 2.84 years	eGFR ≥ 60 ml/min/1.73 m²: 76	
Meisinger 2006[76]	Events/10,000 person-years	M: 329.3 F: 154.8	Median 12.5 years	eGFR ≥ 60 ml/min/1.73 m²: M: 194.7; F: 90	
Weiner 2004[74]	Events/10,000 person-years	3080	Mean 8.3 years	eGFR ≥ 60 ml/min/1.73 m²: 980	
Cumulative mortality within follow-up period					
Djamali 2003[83]	Deaths in 12.6 years[a]	19.7%	12.6 years		CKD defined as SCr > 115 µmol/l; presented as survival analysis in paper
Eriksen 2006[96]	Deaths in 5 years (95% CI) Deaths in 10 years (95% CI)	32% (30 to 34) 52% (48 to 55)	10 years		Presented as cumulative incidence of death in paper
Evans 2005[98]	Deaths in 1 year Deaths in 5 years	3% 39%	5 years		Presented as survival rate in paper
Herzog 2004[92]	Deaths in 1 year CKD only Deaths in 1 year CKD + CHF + anaemia	8.2% 22.9%	1 year		CKD defined based on ICD-9-CM codes

TABLE 6 Summarised result of all-cause mortality for general CKD population (eGFR < 60 ml/min/1.73 m2 unless stated) (continued)

Study ID	Measures	Values (variance)	Follow-up	Comparators/ CKD other stages	Comments
Irie 2006[81]	Deaths in 10 years	20.7%	10 years		
Jones 2006[105]	Deaths in 1 year	15%	3 years		
	Deaths in 3 years	25%			
Keith 2004[106]	Deaths in 5 years	Stage 3: 24.3%	5 years	eGFR 60–89 ml/ min/1.73 m² no P: 10.2%	
		Stage 4: 45.7%		Stage 2: 19.5%	
Maaravi 2007[86]	Deaths in 12 years	MDRD equation 36.4%	12 years		Presented as survival rate in paper
		CG equation 35.4%			
Mortality (%)					
Drey 2003[95]	Deaths	SCr > 1.7 mg/dl: 69%	Mean 5.5 years		Median survival 35 months
		SCr 1.7–3.3 mg/dl: 69%			
		SCr 3.4–5.7 mg/dl: 77%			
		SCr > 5.7 mg/dl: 59%			
Go 2004[75]		Stage 3a: 7.54%	Median 2.8 years	eGFR ≥ 60 ml/ min/1.73 m²: 2.79%	
		Stage 3b: 22.7%			
		Stage 4: 62.2%			
Hemmelgarn 2006[101]	Deaths	eGFR < 30 ml/ min/1.73 m²: 6%	Median 2 years		
John 2004[104]	Deaths	38.6%	Median 2.6 years		Median survival 28.1 months CKD: SCr ≥ 135 μmol/l
Levin 2001[84]	Deaths	2.6%	Median 1.9 years (462 patient years)		Selected by physicians to be expected to be alive at 12 months CKD: CrCl 10–75 ml/min
Meisinger 2006[76]	Deaths	M: 30%; F: 17%	Median 12.5 years	eGFR ≥ 60 ml/ min/1.73 m²: M: 22%; F: 10.7%	
Orlando 2007[111]	Deaths	Stage 3: 49%	Mean 3.6 years	Stage 1: 21%	
		Stage 4: 52%		Stage 2: 31%	
		Stage 5: 27%			
Tonelli 2006[68]	Deaths	12.4%	Median 4.5 years	eGFR ≥ 60 ml/ min/1.73 m²: 3.1%	

A, albuminuria; CG, Cockcroft–Gault; CHF, congestive heart failure; CKD, chronic kidney disease; CPT, physicians' current procedural terminology; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; F, female; ICD-9-CM, *International Classification of Diseases*, Ninth Edition, Clinical Modification; macroA, macroalbuminuria; M, male; MDRD, Modification of Diet in Renal Disease; microA, microalbuminuria; P, proteinuria; SCr, serum creatinine.
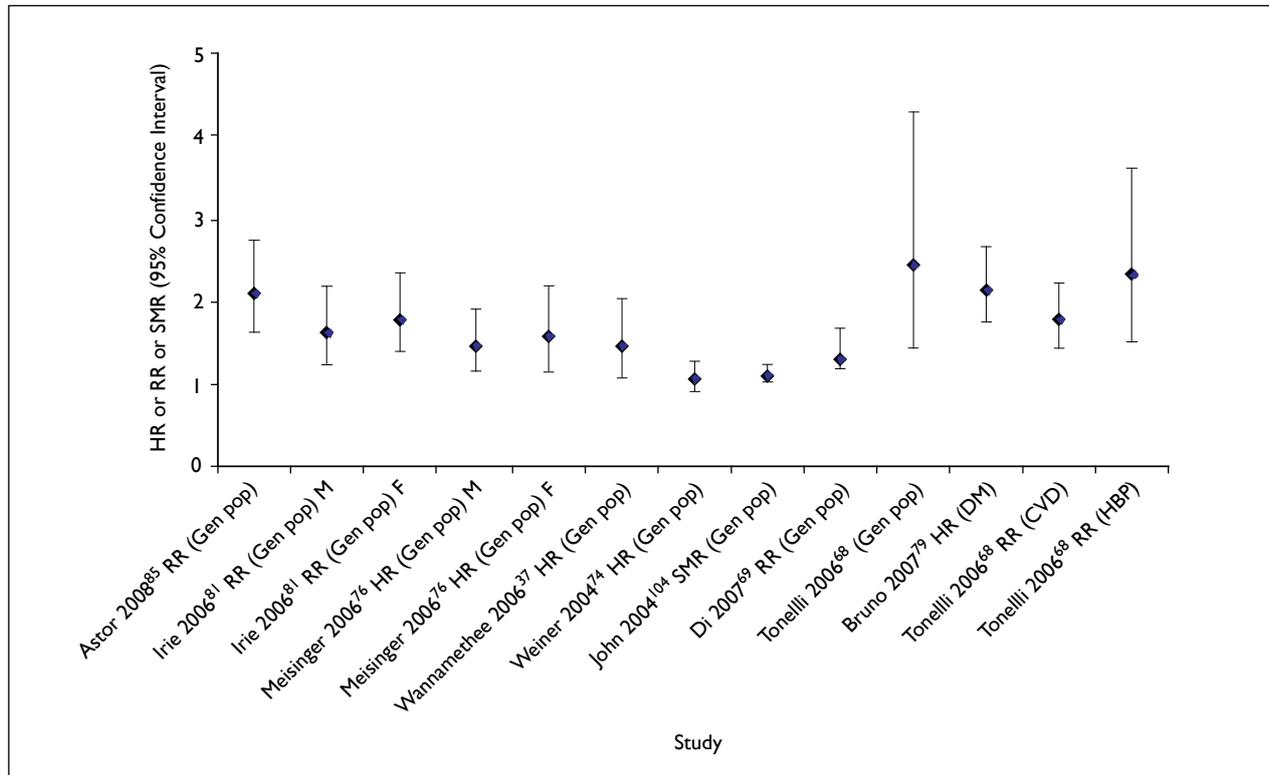
FIGURE 5 *Risk of cardiovascular morbidity and mortality. Comparing those with CKD with those without CKD. CVD, cardiovascular diseases; DM, diabetes mellitus; F, female; Gen, general; HBP, high blood pressure; HR, hazard ratio; M, male; Pop, population; RR, relative risk; SMR, standardised mortality rate.*

(RR 1.14–1.81) with the exception of studies by Astor and colleagues[85] (RR 2.12, 95% CI 1.65 to 2.73), Weiner and colleagues[74] (HR 1.09, 95% CI 0.91 to 1.29) (pooled analysis of four population-based health studies in the USA), and Tonelli and colleagues.[68] Across the 14 studies included in a review by Tonelli and colleagues[68] that reported on CVD mortality and morbidity, the unadjusted RRs ranged from 1.43 to 3.73. The risk for CVD mortality was 2.47 (95% CI 1.42 to 4.30) in the CKD group as compared with the non-CKD population for three general population studies, but substantial heterogeneity was observed.[68] The authors described adjusted analysis for all 14 studies being particularly sensitive to age, with a greater risk associated with CKD in younger people (no details in paper). Di and colleagues[69] also reported an increased risk of CVD morbidity and mortality (RR 1.41, 95% CI 1.19 to 1.68) from the meta-analysis of seven general population studies, with statistically significant heterogeneity observed ($p = 0.045$).

Two studies, reporting the risk of CVD events associated with different stages of CKD, reported an increase with decreasing eGFR (*Table 7*).

CVD rate in populations with CKD

The rate of CVD deaths or events was reported in five studies and varied between studies by population, age, sex and CKD stage.[32,74–76,85] Rates of CVD events and deaths more than doubled from stage 3a to stage 3b.

Cardiovascular disease morbidity and mortality was reported for follow-up periods that ranged from a median of 23 months[84] to 12.5 years.[76] Frequency of CVD death was low in the study by Levin and colleagues,[84] where study participants were selected because they were thought to be clinically healthier. Proportions experiencing CVD death or a CVD event increased with CKD stage and were higher in men than in women.[32,75] Summarised results of the CVD rates and proportions experiencing CVD morbidity and mortality are presented in *Table 8*.

Renal outcome: chronic kidney disease population

Nineteen studies reported renal outcomes and included ESRD, RRT and/or CKD progression. The results are summarised in *Table 9*.

TABLE 7 *Risk of CVD morbidity and mortality during different stages of CKD*

Study ID	Measures	Values (variance)	Reference group	Adjusted analysis
Astor 2008[85]	CVD deaths, RR (95% CI)	Stage 2: 1.37 (1.07 to 1.75) Stage 3–5: 2.12 (1.65 to 2.73)	eGFR ≥ 90 ml/min/1.73 m²	Age, sex, race/ethnicity, previous CVD, BP, use of antihypertensive medication, DM, smoking, BMI, physical activity, cholesterol and C-reactive protein
Go 2004[75]	CVD events, HR (95% CI)	Stage 3a: 1.4 (1.4 to 1.5) Stage 3b: 2.0 (1.9 to 2.1) Stage 4: 2.8 (2.6 to 2.9) Stage 5: 3.4 (3.1 to 3.8)	eGFR ≥ 60 ml/min/1.73 m²	Age, sex, income, education, dialysis, prior CVD, DM, HBP, dyslipidaemia, cancer, serum albumin < 3.5g/dl; dementia, cirrhosis, chronic lung disease, proteinuria, prior hospitalisation

BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HBP, high blood pressure; HR, hazard ratio; RR, relative risk.

TABLE 8 *Summarised result of cardiovascular morbidity/mortality for general CKD population (eGFR < 60 ml/min/1.73 m² unless stated)*

Study ID	Measures	Values (variances)	Follow-up	Comparators/ other CKD stages	Comments
Deaths per person-years					
Astor 2008[85]	CVD deaths rate/10,000 person-years (read from graph)	Stage 3–5 no A: 120 Stage 3–5 microA: 240 Stage 3–5 macroA: 410	13 years	eGFR ≥ 60 ml/min/1.73 m²: 50	Adjusted to the incidence rates of a 60-year-old non-Hispanic white male
Go 2004[75]	CVD events rate/10,000 person-years	Stage 3a: 365 Stage 3b: 1129 Stage 4: 2180 Stage 5: 3660	Median 2.8 years	eGFR ≥ 60 ml/min/1.73 m²: 211	Rates standardised to age
Hallan 2006[32]	CVD deaths rate/10,000 person-years	Stage 3a: 350 Stage 3b: 740 eGFR < 30 ml/min/1.73 m²: 1010	Median 8 years	eGFR ≥ 60 ml/min/1.73 m²: 40	
Meisinger 2006[76]	CVD deaths rate/10,000 person-years	M: 189.8 F: 87.1	Median 12.5 years	eGFR ≥ 60 ml/min/1.73 m²: M: 82.7; F: 33	
Meisinger 2006[76]	Incident rates of MI/10,000 person-years	M: 146.5 F: 48.2	Median 12.5 years	eGFR ≥ 60 ml/min/1.73 m²: M: 84.1; F: 22.9	
Weiner 2004[74]	Incident rates of MI or fatal CHD/10,000 person-years	1390	Mean 8.3 years	eGFR ≥ 60 ml/min/1.73 m²: 650	
Cumulative CVD mortality/morbidity					
Irie 2006[81]	Number of CVD deaths	M: 82/824 (10.0%) F: 150/2073 (7.2%)	10 fixed years		
Keith 2004[106]	Number of CHD	3435/13,796 (24.9%)	5.5 fixed years		

continued

TABLE 8 *Summarised result of cardiovascular morbidity/mortality for general CKD population (eGFR < 60 ml/min/1.73 m² unless stated) (continued)*

Study ID	Measures	Values (variances)	Follow-up	Comparators/ other CKD stages	Comments
Events (%) during follow-up					
Drey 2003[95]	Number of CVD deaths	339/1071 (31.7%)	Mean 5.5 years		CKD: SCr ≥ 150.3 μmol/l
Evans 2005[98]	Number of CVD deaths	146/920 (15.9%)	Mean 4.4 years		CKD: stage 4 and 5 only
Go 2004[75]	Number of CVD events	Stage 3a: 34,690/153,426 (22.6%) Stage 3b: 18,580/34,275 (54.2%) Stage 4: 8809/7085 Stage 5: 3824/1373	Median 2.8 years	eGFR ≥ 60 ml/min/1.73 m²: 73,108/924,136 (7.9%)	An individual could experience more than one event – number of events presented
Hallan 2006[32]	Number of CVD deaths	Total: 691/3057 (22.6%) Stage 3a: 456/2389 (19.1%) Stage 3b: 185/548 (33.8%) eGFR < 30 ml/min/1.73 m²: 50/120 (41.7%)	Median 8 years	eGFR ≥ 60 ml/min/1.73 m²: 1913/62,099 (3.1%)	
John 2004[104]	Number of CVD deaths or events	497/3240 (15.3%)	Median 2.6 years		CKD: M: SCr ≥ 180 μmol/l F: SCr ≥ 135 μmol/l
Levin 2001[84]	Number of CVD events	New or worsening symptoms: 48/244 (19.7%)	Median 23 months (462 patient years)		CKD: CrCl 10–75 ml/min
Meisinger 2006[76]	Number of CVD events	M: 83/480 (17.3%) F: 72/753 (9.6%)	Median 12.5 years	eGFR ≥ 60 ml/min/1.73 m²: M: 317/3380 (9.4%); F: 115/2921 (3.9%)	
Meisinger 2006[76]	Number of incident MI	M: 46/441 (10.4%) F: 31/737 (4.2%)	Median 12.5 years	eGFR ≥ 60 ml/min/1.73 m²: M: 275/3221 (8.5%) F: 71/2894 (2.5%)	
Tonelli 2006[68]	Number of CVD events	182/750 (24.3%)	Median 4.5 years		
Weiner 2004[74]	Number of MI or fatal CHD events	168/1664 (10.1%)	Mean 8.3 years	eGFR ≥ 60 ml/min/1.73 m²: 1111/20,970 (5.3%)	

A, albuminuria; CHD, coronary heart disease; CKD, chronic kidney disease; CrCl, creatinine clearance; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; F, female; M, male; MI, myocardial infarction; SCr, serum creatinine.

Eriksen and Ingebretsen[96] reported a 2.5 times increase in the risk of developing ESRD for every 10-ml/min/1.73 m²/year decline in renal function, and the incidence of developing ESRD for those with an eGFR of less than 60 ml/min/1.73 m²/year was five times greater than for the general population.[96] Hallan and colleagues[32] presented the adjusted risk of ESRD in different stages of CKD and noted a fourfold increase from stage 3a to stage 3b. From stage 4, the risk of ESRD was substantially increased (HR 68.5, 95% CI 30 to 156) and an incidence rate of 260 per 10,000 person-years was reported.

The rate of CKD progression was measured in terms of mean rate of decline of creatinine

TABLE 9 *Summarised result of renal outcomes for general CKD population (eGFR < 60 ml/min/1.73 m2 unless stated)*

Study ID	Measures	Values (variance)	Follow-up	Definitions of renal outcomes	Comments
ESRD					
Risk and rates					
Eriksen 2006[96]	HR (95% CI) of renal failure	2.5 (1.89 to 3.31)	10 years	Renal failure defined as irreversible stage 5 CKD or initiation of RRT	For each eGFR decrease of 10 ml/min/1.73 m²; adjusted for age and sex
Eriksen 2006[96]	Incidence rate ratio (95% CI) of renal failure	5.3 (3.9 to 7.3)	10 years	Renal failure defined as irreversible stage 5 CKD or initiation of RRT	Standardised to Tromsø general population
Hallan 2006[32]	HR (95% CI) of ESRD	Stage 3a: 1.0 (reference) Stage 3b: 4.2 (1.5 to 11) eGFR < 30: 68.5 (30 to 156)	Median 8 years	ESRD not defined	Adjusted for sex, age, diabetes, and hypertension (smoking, BMI and CVD at baseline were not significant)
Hallan 2006[32]	Incidence rate of ESRD/100 person-years	Stage 3a: 0.04 Stage 3b: 0.2 eGFR < 30: 2.6	Median 8 years	ESRD not defined	
Cumulative ESRD and ESRD during follow-up duration					
Eriksen 2006[96]	Renal failure		10 years	Renal failure defined as irreversible stage 5 CKD or initiation of RRT	
	5 years cumulative incidence (95% CI)	0.02 (0.01 to 0.02)			
	10 years cumulative incidence (95% CI)	0.04 (0.03 to 0.06)			
Hallan 2006[32]	Number reaching ESRD	Total: 38/3057 (1.2%) Stage 3a: 9/2389 (0.4%) Stage 3b: 7/548 (1.3%) eGFR < 30: 22/120 (18.3%)	Median 8 years	ESRD not defined	eGFR ≥ 60 ml/min/1.73 m²: 13/62066 (0.02%)
Djamali 2003[83]	Kidney deaths (presented as kidney survival in the study)	Stage 3: 13.5 years 12.9% Stage 4: 11.2 years 4.9%	Mean 4.6 years	Kidney survival defined as time from first visit to time of last visit or incidence of ESRD or patient death with functional kidney	Stage 1: 12.7 years 38.1% Stage 2: 12.1 years 26.8% Adjusted for age and sex
RRT					
Levin 2001[84]	Number reaching RRT	Dialysis: 24/313 (7.7%) Transplant: 1/313 (0.3%)	Median 1.9 years (462 patient years' follow-up)	RRT was defined as need for either dialysis or transplantation	CKD: CrCl 10–75 ml/min
	Incidence of RRT at 6 months	10/268 (3.7%)			
	Incidence of RRT at 12 months	7/218 (3.2%)			

TABLE 9 *Summarised result of renal outcomes for general CKD population (eGFR < 60 ml/min/1.73 m2 unless stated) (continued)*

Study ID	Measures	Values (variance)	Follow-up	Definitions of renal outcomes	Comments
					continued
	Incidence of RRT at 24 months	18/94 (19.1%)			
Kollerits 2007[90]	Number reaching RRT	29/177 (16.4%)	Mean 3.9 years		
Drey 2003[95]	Number reaching RRT	4%	Mean 5.5 years	RRT: either dialysis or transplantation	SCr ≥ 150.3 μmol/l
Hemmelgarn 2006[101]	Number reaching dialysis	eGFR < 30: 81/87 dialysis (93.1%)	Median 2 years		eGFR < 90 ml/min/1.73 m²
Keith 2004[106]	Number reaching RRT	Stage 3: transplant 0.2%; dialysis 1.1%	5.5 years	RRT defined as initiation of dialysis or renal transplantation	Stage 2 no protein: transplant 0.01%; dialysis 0.06%
		Stage 4: transplant 2.3%; dialysis 17.6%			Stage 2 + protein: transplant 0.2%; dialysis 0.9%
Evans 2005[98]	Number reaching dialysis	739 (80.3%)	Median 4.4 years		Mean observation time in the RRT analysis was 2.0 (SD 1.8) years
	Number of transplantation	248 (34%)			
Gorodetskaya 2005[78]	Number starting dialysis	Stage 4 +: 31/115 (27.0%)	Mean 10 (range 6–24) months		
Jones 2006[105]	Number starting RRT	73 (10%)	Median 2.9 years		

CKD progression

Rate of CKD progression

Study ID	Measures	Values (variance)	Follow-up	Definitions of renal outcomes	Comments
Djamali 2003[83]	Mean rate of CrCl decline (SD) ml/min/year	Stage 3: 5.4 (7.4) Stage 4: 5.7 (5.6) Stage 5: 1.5 (8.5)	Mean 4.6 years		Stage 1: 11 (12) Stage 2: 8.4 (10) CKD: SCr > 115 μmol/l
Hemmelgarn 2006[101]	Mean rate of eGFR decline (95% CI) ml/min/year	Stage 3–5 *Male:* No DM: 3.5 (2.7 to 4.3) DM: 7.2 (5.9 to 8.6) *Female:* No DM: 2.0 (1.4 to 2.6) DM: 5.1 (3.8 to 6.3)	Median 2 years		
Gorodetskaya 2005[78]	Mean rate of decline in eGFR (IQR) ml/min/1.73 m²/year	Stage 4 +: 1.3 (2.4 to 0.4)	Mean 10 (range 6–24) months		
Imai 2008[82]	Mean rate of decline in eGFR	Presented graphically only			
Jones 2006[105]	Mean rate of decline in eGFR (IQR) ml/min/1.73 m²/year	Pre referral 5.4 (2 to 13) Post referral 0.34 (−3 to 3)	Median 2.9 years		

TABLE 9 Summarised result of renal outcomes for general CKD population (eGFR<60 ml/min/1.73 m2 unless stated) (continued)

Study ID	Measures	Values (variance)	Follow-up	Definitions of renal outcomes	Comments
Proportion experiencing CKD progression during follow-up					
Kollerits 2007[90]	Proportion progressed to renal end point	65/177 (36.7%)	Mean 3.9 years	Renal end point defined as RRT or doubling of baseline SCr	CKD estimated based on SCr
	Doubling of baseline SCr without reaching ESRD	36/177 (20.3%)			
John 2004[104]	Proportion as per various rate of eGFR (ml/min/1.73 m²) decline per year	eGFR decline: <2: 79.3% 2–3.9: 8.7% ≥4: 12.4%	Median 2.6 years		CKD: M: SCr ≥ 180 μmol/l F: SCr ≥ 135 μmol/l
Jones 2006[105]	Declining GFR (slopes more negative than 1 ml/min/1.73 m²)	*Post referral:* Decline: 314/726 (43.3%) No decline: 412 (56.7%) *Pre referral:* Decline: 607 (83.6%) No decline: 119 (16%)	Median 2.9 years		
Khatami 2007[108]	Proportion progressing to stages 4 and 5	22/520 (4.2%)	4 years		eGFR<60 ml/min/1.73 m² at baseline
	Proportion regressed to stage 2	'Approx 20%'			
	Proportion stable	'Approx 76%'			
Orlando 2007[111]	Proportion of progressors	Stage 3: 70 (17%) Stage 4: 21 (24%) Stage 5: 6 (23%)	Mean 3.6 years	Progression defined as from one stage to other	Stage 1: 583 (48%) Stage 2: 276(31%)

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; F, female; HR, hazard ratio; IQR, interquartile range; M, male; SCr, serum creatinine; SD, standard deviation; RR, relative risk ratio; RRT, renal replacement therapy.

clearance by Djamali and colleagues,[83] and they reported a mean 6.6-ml/min/year decline. Normal GFR decline was defined, by the KDOQI, as a reduction in eGFR by approximately 1 ml/min/1.73 m²/year from a normal level of 125 ml/min/1.73 m². Jones and colleagues[105] defined CKD progression as any slope more negative than a decline of 1 ml/min/1.73 m²/year. The study found that 84% of study participants had evidence of progression (slope decline of more than 1 ml/min/1.73 m²/year) with 52% of these experiencing fast progression (slope decline of at least 5 ml/min/1.73 m²/year). As they followed the cohort over time (and following referral to a specialist service) the mean rate of decline was noted to reduce. This may be the result of interventions, referral or stage of disease. John and colleagues[104] also reported CKD progression according to rates of decline in GFR; 8.3% showed a decline of at least 5 ml/min/1.73 m²/year, 12.4% had decline rates between 2.0 and 4.9 ml/min/1.73 m²/year, with the remaining 79.3% having little evidence of renal function decline. Gorodetskaya and colleagues[78]

reported an estimated mean rate of decline in eGFR as 1.3 ml/min/1.73 m²/year [standard deviation (SD) 0.4–2.4] for those with an initial eGFR lower than 30 ml/min/1.73 m². Djamali and colleagues[83] reported that the absolute rate of CKD progression was fastest during stages 1 and 2. By contrast Hemmelgarn and colleagues[101] reported the absolute rate of progression increased as eGFR declined.

Eriksen and Ingebretsen[96] presented cumulative incidence of ESRD, reporting 2% and 4% at 5 and 10 years respectively. Another study reported incidence of RRT in 6 months (3.7%), 12 months (3.2%) and 24 months (19.1%).[84] The other studies presented the number starting dialysis or receiving a renal transplant as a proportion in a given follow-up time and, therefore, could not be compared directly. An exceptionally high proportion of RRT (80.3%) during 4.4 years' follow-up was observed by Evans and colleagues.[98]

One study presented the progression and regression of CKD (eGFR lower than 60 ml/min/1.73 m²) over 4 years of follow-up[108] for a subset of 522 patients with a repeat creatinine. Around 4% progressed to stages 4 and 5, 20% improved to stage 2 or better, and most (76%) were stable during the 4 years of follow-up. Hemmelgarn and colleagues[101] reported that 41% of study participants with stage 3 disease and approximately 25% (from graph) of those with eGFR lower than 30 ml/min/1.73 m² had stable, or an increase in, eGFR during the 2-year study period. Orlando and colleagues[111] reported that in stages 1 and 2, the highest proportion of people showed evidence of progression (48% and 31% respectively). In stage 3–5, 17–24% progressed. Of note, in each stage the proportion not progressing because of death increased (from 21% in stage 1 to 52% in stage 4). Nonetheless, 22–38% of the study population neither progressed nor died.

Quality of life

Two papers describe aspects of quality of life in patients with CKD.[78,91] One prospectively analysed the association between kidney function, health-related quality of life and estimates of utility in 205 people.[78] This was based on the data obtained from three measures of quality of life, i.e. Kidney Disease Quality of Life short form-36 (KDQOL-36™), Health Utilities Index (HUI) and time trade-off (TTO). KDQOL-36 is a specific measure of health-related quality of life for CKD that

includes effects and burden of kidney disease and physical and mental health score while HUI-3 is a generic instrument that measures the population preference or utility function such as vision, pain, hearing or cognitive function. TTO measures the health preferences of patients. Health-related quality of life according to the KDQOL-36™ and HUI-3 was found to decrease significantly across the stages of CKD, but only once eGFR had fallen below 30 ml/min/1.73 m² (with the exception of the mental health score which was unchanged with stage). For example, HUI-3 (ranges from 1 to –0.36 where 1 represents perfect health and 0 death, negative scores represent states considered worse than death) reported estimates of 0.67 (SD 0.31) for eGFR > 60 ml/min/1.73 m², 0.67 (SD 0.31) at stage 3, 0.55 (SD 0.34) at stage 4 and 0.54 (SD 0.36) at stage 5. For TTO there was a small but statistically insignificant decline in quality of life from stage 3 to stage 5.

The other study prospectively investigated the effect of the internal health-specific locus of control (HLOC) on changes in depression state in patients with progressive CKD.[91] The study mostly described the psychological measure and predictors of chronic disease. Internal HLOC measures patients' belief in personal control over their health outcomes. The study found that internal HLOC score change from baseline was a significant predictor for changes in depression from baseline to follow-up, with increased internal control on one's health predicting lower depression. Further, Cvengros and colleagues[91] identified that this association was restricted to those progressing to receive dialysis. The CKD patients who did not progress to end stage seemed to have no relation between changes in internal HLOC to follow-up depression.

Subgroup analysis

CKD with diabetes

The results from cohorts that included only people with diabetes mellitus are summarised in Appendix 6. In studies with at least 6–10 years' follow-up, mortality was reported as ranging from 19.7%[79] to 35.0%[88] with cardiovascular deaths accounting for a substantial proportion of this. GFR declined at between 3.8 and 4.5 ml/min/1.73 m²/year and, after 6.5 years, 7% of the study population was reported to have ESRD.[88] Three studies presented data that compared diabetics with non-diabetics.[101,105,111] Jones and colleagues[105] observed that diabetic nephropathy was a predictor for

having 'fast progressive' disease (eGFR decline of > 5 ml/min/year). Hemmelgarn and colleagues[101] showed that CKD progression increased as the stages increased, with higher progression in late stages (CKD stages 3 and 4). Relative to the non-diabetic population, Orlando and colleagues[111] found a higher risk of progression among those with diabetes in stage 1–2 (RR versus no diabetes mellitus 1.32, 95% CI 1.13 to 1.55), but no difference in progression in higher stages.

CKD with cardiovascular disease and hypertension (HBP)

While many studies included people with CVD and hypertension (HBP), few presented data on outcomes stratified by these subgroups. One study compared the risk of CKD progression for different CKD stages for those with CVD at baseline with those without CVD.[111] Compared with no CVD at baseline, people with CVD in CKD stage 1–3 were at a 35–52% increased risk of progression; in stage 4–5 there was no difference in the risk of progression.[111] Others presented the number accepted onto RRT as a proportion in a given follow-up time (see Appendix 6). Tonelli and colleagues[68] analysed ACM and CVD mortality for studies recruiting only patients with CVD or patients with HBP at baseline, comparing CKD with no CKD. For those with CVD and CKD at baseline, the RR of ACM compared with no CKD was 1.71 (95% CI 1.49 to 1.96), substantially lower than that reported in the studies in general populations summarised in the section All-cause mortality: general CKD population (RR 3.0), and possibly reflecting the nature of the 'general population' studies that included known high risk groups. The RR for CVD mortality was 1.8 (95% CI 1.45 to 2.24), again lower than the studies of general populations. For studies of populations with hypertension, Tonelli and colleagues[68] reported an ACM RR of 2.15 (95% CI 1.17 to 2.61) and a CVD mortality RR of 2.35 (95% CI 1.52 to 3.64). See Appendix 6 for detailed results.

Gender, race and age in CKD

The age standardised risk of mortality was reported by Evans and colleagues[98] to be higher in females with CKD (SMR 12.3, 95% CI 10.3 to 14.5) than in males (SMR 7.2, 95% CI 6.3 to 8.1), as compared with the general population. Males had higher cumulative mortality and cumulative incidence of ESRD after 10 years than females.[96] Drey and colleagues[95] found a similar proportion of deaths in males (69.34%) as in females (67.76%) during 5.5 years of mean follow-up. Meisinger and

colleagues[76] and Irie and colleagues[81] reported a higher risk of CVD mortality in females than in males (see *Table 44*, Appendix 6), while risk of ACM was similar in both genders. The rate of decline in GFR was found to be higher in males than in females.[82,101] See Appendix 6 for detailed results.

Chronic kidney disease seemed to have a greater impact on ACM risk (HR 1.83, 95% CI 1.33 to 2.52) for African-Americans than for white people (1.31, 95% CI 1.16 to 1.49) (ACM in those with CKD versus no CKD).[74] Similarly, risk of cardiovascular morbidity increased more in African-Americans with CKD (2.09, 95% CI 1.33 to 2.52) than in white people with CKD (1.01, 95% CI 0.84 to 1.21).[74] Additionally, Hsu and colleagues[103] reported the 5-year incidence rate of ESRD cases was higher among African-Americans (5.4%) than among white people (1.1%).

The mortality and incidence rate ratios for ESRD were significantly higher in younger groups (less than 69 years old) than in older patients when comparing CKD with no CKD.[96] Hsu and colleagues[103] also presented incident ESRD rates that were greater among younger patients (20–60 years old) than among older ones (61–74 years old). The mortality rate ranged from 0.4% per year for 18- to 44-year-old patients with an eGFR $\geq$ 60 ml/min/1.73 m^2 to 36.0% per year for the most elderly patients (85–100 years old) with an eGFR $\leq$ 15 ml/min/1.73 m^2.[110] The RR of mortality increased with decreasing eGFR, but the relative impact was less as age increased.[110] For example, risk of ACM for those with an eGFR of 40–49 ml/min/1.73 m^2 decreased from HR 1.90 (95% CI 1.35 to 2.67) in 18–44 year olds to HR 1.35 (95% CI 1.32 to 1.39) in 65–74 year olds. Similarly, for those with eGFR of 30–39 ml/min/1.73 m^2, the HR decreased from 3.58 (95% CI 2.54 to 5.05) in 18–44 year olds to HR 1.81 (95% CI 1.75 to 1.87) in 65–74 year olds.[110] Imai and colleagues[82] reported that the mean rate of decline of GFR from an initial GFR of 30–39 ml/min/1.73 m^2 was higher (3.28, SD 0.72 ml/min/year) in younger males (40–49 years old) than in those in older age groups, with mean rate of decline 0.91 (SD 3.28) in 50–59 year olds, 0.98 (SD 0.18) in 60–69 year olds and 1.24 (SD 0.25) in 70–79 year olds. No difference in progression rate across age groups in male participants with a starting GFR of 60–69 ml/min/1.73 m^2 was observed, although the progression rate was much lower (0.31–0.36, SD 0.01–0.03 ml/min/year).[82] Among female

participants, the mean rate of decline of GFR from an initial GFR of 60–69 ml/min/1.73 m² was higher for ages 40–49 years (0.45, SD 0.01) ml/min/year than for 50–79 year olds (range 0.24–0.29, SD 0.01–0.02 ml/min/year). See Appendix 6 for detailed results.

Discussion

We identified 36 studies describing the natural history of CKD.

Studies could be broadly defined into two categories based on the types of study participants:

- 'Screened population' studies where researchers drew participants from the general population through some type of health survey process. This group included a mix of population surveys using robust methods to minimise participant selection bias and others relying on volunteers responding to calls to participate in health screening.
- 'Clinical population' studies where studies were based on the identification of people with evidence of CKD from clinical settings including laboratory data, hospital clinics and general practice registers. In common, these participants had all had a blood test for a clinical indication that identified them as having CKD. While some may have had blood tests as part of a general health check, the majority would have had a medical condition or symptoms that led to testing.

The significance of these differences in study design is that the age and comorbid profiles of the two groups differed, with those in clinical populations tending to be older and to have a greater burden of comorbidity.

While the studies were generally large, with adequate follow-up and minimal losses to follow-up, there were a number of limitations. The definition of CKD was not standard across all studies, and less than half were able to define chronicity (i.e. had more than one abnormal test result at least 3 months apart). This means that such studies will have overestimated the 'CKD' population and this may affect the associations observed between CKD and outcomes. In addition, the use of different definitions for clinical outcomes (and in some cases, the lack of clarity about the definition) made comparison between studies difficult. In particular,

cardiovascular morbidity and mortality included a number of definitions and this is likely to account for at least some of the heterogeneity in results observed. Few studies reported their outcomes by race. While the studies covered a range of geographical areas, the heterogeneity in methods makes it difficult to determine if differences in outcomes were related to race. Finally, none of the studies described in any detail the health care available to their study populations. Differences in management between study populations may also be contributing to the heterogeneity in outcomes observed.

All-cause mortality rate was generally high in the studies included in this review; 24.3–39.0% at 5 years and 19.7–52% at 10–12.6 years. ACM rate was higher in males than females and increased with stage of CKD. Populations defined by having an eGFR < 60 ml/min/1.73 m² were consistently found to have a higher mortality than comparator groups where there was no evidence of CKD.

In studies comparing risk in those with CKD with those without CKD, there was evidence that an eGFR < 60 ml/min/1.73 m² was a predictor of ACM in some but not all of the studies. Adjustment for comorbidities, age and sex reduced the RR. We observed that in studies constructed from the general population, the risk of ACM associated with CKD, after adjustment, was small. Many of the cohort studies included people with a range of comorbidities and often reported a higher risk of ACM. CKD commonly occurs in association with comorbidities known to increase the risk of cardiovascular mortality (HBP, diabetes mellitus, CVD, increased age), and adjustment for comorbidities consistently reduced ACM risk ratios.[76,79] We made a decision to exclude data from the control arms of RCTs. While such studies do provide a view of the natural history of the condition, the strict selection of patients to participate in RCTs means that their outcomes are very different. For example, Jafar and colleagues[43] reported a meta-analysis of RCTs for ACE Is in non-diabetic renal disease. From pooled RCT data, they reported a low ACM (1.2% in a mean follow-up of 2.2 years) and a relatively high progression to ESRD (11.6%), reflecting the selection of trial participants and the difficulty in generalising such findings.

However, in studies constructed from populations with high levels of comorbidity (diabetes, hypertension, CVD), the risk of ACM associated

with CKD, compared with no CKD, was somewhat higher. The reverse was observed in the review by Tonelli and colleagues,[68] but for only the unadjusted analysis. This is an oversimplification of the true impact of CKD on mortality. Analyses by stage demonstrated a substantially increased risk associated with increasing stage. Indeed, stage 3b carried a markedly increased risk as compared with 3a.

Some of the variation in ACM between studies may have been as a result of methodological issues: definition of CKD, duration of follow-up and composition of the cohort. However, this does not appear to account for all the heterogeneity. For example, Eriksen and Ingebretsen[96] and Djamali and colleagues[83] both reported clinical cohorts defined based on more than one measure of eGFR < 60 ml/min/1.73 m², one study was from the USA[82] and one from Norway.[96] Despite both studies considering people with mild to moderate CKD, Djamali and colleagues[83] reported a substantially lower death rate over the 12.6 years of follow-up than that reported by Eriksen and Ingebretsen[96] (19.7% versus 52%).

With the exception of study by Weiner and colleagues,[74] the risk of CVD morbidity and mortality was reported to be greater in those with CKD than those with no CKD, and again this risk increased as the CKD stage increased, even after adjustment for comorbidities. Reported rates of CVD morbidity and mortality varied between studies, reflecting definitions used for CVD and the other methodological issues outlined above.

Attention in the renal community has focused on early recognition of CKD with the aim of prevention of progression to ESRD. As for ACM, there was substantial heterogeneity in the reported proportion of patients progressing to ESRD and in the definitions used for renal progression. These differences related in part to methodological issues, but were substantially influenced by the study population characteristics and how the cohort was constructed. Clinical cohorts had higher progression rates even where patients were in 'early' stages of CKD at baseline, reflecting some selection bias when compared with the general population.

We found that frequency of ESRD as an outcome was variable and appeared to relate to patient characteristics. In studies of people identified as having a low eGFR as a result of population health screening, the risk of ESRD was low, even after 8 years of follow-up. Where patients were recruited from clinics into follow-up studies, the risk of ESRD was substantially greater, reflecting a selection bias that partly represents clinical practice. Those with lower eGFR, diabetes and HBP experienced a greater risk of progression to ESRD. While few studies reported the proportion of patients who did not show a change in renal function, where it was reported, stable or even improvements in eGFR were common place. Where progression in eGFR was observed, many participants had not progressed to ESRD during the course of follow-up (up to 8 years). For an individual with CKD, the most common outcome during study follow-up was death, not progression to ESRD.[32,95,104]

CKD stage was associated with an increase in mortality and renal progression, with a substantially greater risk observed for those in stage 3b than those in stage 3a. The rate of renal progression also appeared to be variable and influenced by age, stage and comorbidities.

The impact of CKD on quality of life was rarely reported in the natural history literature. Cross-sectional analysis of the short form 36-item questionnaire results from a large population study in Australia[116] which has noted significant impairment of quality of life for those with an eGFR < 60 ml/min/1.73 m², even after adjustment for comorbidities. Mental health was affected the most in younger people and physical function in the older group.

In this chapter we focused on eGFR as a measure of renal function impairment, reflecting current clinical practice with the creation of CKD registers in primary care based on eGFR < 60 ml/min/1.73 m². Proteinuria and, in diabetes, microalbuminuria have been widely accepted as independent markers of kidney damage. While all people with diabetes are screened for microalbuminuria, there is not yet a consensus on screening for microalbuminuria or proteinuria in adults without diabetes. Recent analysis of the Prevention of Renal and Vascular Endstage Disease cohort study in the Netherlands demonstrated the potential predictive value of testing for microalbuminuria in the general population. Microalbuminuria was associated with an increased risk of needing RRT over 9 years' follow-up (20–100 mg/l, HR 3.0; 100–200 mg/l, HR 47).[117] However, a large number of people with microalbuminuria (and often no other renal risk

factors) were identified from which only a small number required RRT. As with low eGFR, people with evidence of microalbuminuria or proteinuria were at increased risk of CVD. Intervention with ACE Is or statins in groups with microalbuminuria or proteinuria and other CVD risk factors has shown benefit in reducing progression, but it is unknown whether such benefits can be attained for those without other CVD risk factors, and at what cost.[118] Hallan and colleagues[32] recently reported on the benefits of screening all people with reduced eGFR for microalbuminuria or proteinuria. This method improved the specificity of detecting people with significant kidney function impairment (1.4% of the population had both reduced eGFR and microalbuminuria or proteinuria as compared with 4.9% with reduced eGFR alone) without losing detection power for ESRD (identified 65.6% of people who developed ESRD versus 69.4% using eGFR alone).[100]

Conclusion

Chronic kidney disease is an important marker of increased risk of ACM and ESRD. For many, other comorbidities, associated with CKD, contribute to this increased risk. However, there appears to be a substantial subgroup for whom an eGFR $< 60\,\mathrm{ml/min/1.73\,m^2}$ does not mark the start of declining kidney function. In the UK, there has been a change in approach to indentifying CKD in the population, utilising GPs to establish clinical registers of all patients with an eGFR $< 60\,\mathrm{ml/min/1.73\,m^2}$ from blood tests undertaken for a clinical indication. This opportunistic screening has identified large numbers of people with evidence of kidney function impairment that had previously gone unrecognised. The outcomes in people with CKD identified through such an approach remain uncertain, but as described here, there was evidence that the risk of renal progression and mortality were influenced by the approach adopted to identify people with CKD.

Chapter 4
Clinical effectiveness

Introduction

Late referral to specialist nephrology care is an important problem and numerous potential barriers have been identified. Evidence-based guidelines have recognised the need for earlier referral and, in particular, to allow for preparation for transplant or dialysis. In Appendix 7, the literature about the impact of 'very' late referral has been summarised. In these studies, very late referral was compared, in most cases, with referral that was 1–6 months before the initiation of dialysis or RRT. Thus patients included in these studies were in an advanced stage of CKD and might all now be considered to have been referred late to specialists.

In this chapter we consider whether there is evidence that early referral for CKD is clinically effective.

Definition

A definition for 'early referral' was not specified in the original commissioning brief. There are two elements to 'early referral': timing and the intervention. 'Early' can be defined in three ways:

1. Time in relation to another event such as starting RRT.
2. Severity or stage of disease.
3. Duration from the onset of the condition.

While duration from onset might be considered to be the gold standard definition, it is almost impossible to determine onset in the absence of regular population screening for a condition. For the purposes of our review, we accepted definitions of early based on time from dialysis (> 12 months) or severity (stage 3–4 disease).

'Referral' was defined as an appointment with a specialist in nephrology care (medical, nursing or other allied health-care professional).

Results

Study characteristics

The number of published papers identified at each stage of the systematic review is shown in *Figure 6*. There were 3306 articles identified by searches. The full text of 63 articles were retrieved for scrutiny against the inclusion and exclusion criteria. A total of 56 full text articles were excluded. Excluded studies, together with the reason for exclusion are listed in Appendix 3.

No systematic reviews were identified in the search. Seven studies[56,111,119–123] met the inclusion and exclusion criteria, and were included in the review; their characteristics are summarised in *Table 10*. We did not find any randomised or controlled trials. All seven included studies were cohort designs. The key feature of these cohorts was how they were constructed in relation to the timing of the 'intervention' of interest to us – predialysis care. Five of the cohorts recruited people who were starting on dialysis for the first time and reviewed their records to define the timing of their first referral to nephrology care.[56,119,121–123] These cohorts, therefore, included only those people surviving and progressing to require dialysis and did not include people with CKD who died before reaching dialysis or who did not have a progressive deterioration in their renal function within the study period. We have called these 'retrospective cohorts' in terms of the timing of the cohort construction in relation to specialist referral. The remaining two cohorts identified people with CKD and followed them prospectively, comparing those who were referred to specialist care and those who were cared for only by a primary care physician.[111,120] We have called these 'prospective cohorts'.

Three studies originated in the USA,[111,122,123] two in France,[119,121] one in Mexico[120] and one in the UK.[56] A total of 114,073 people were reported in the included studies, but study size varied considerably,
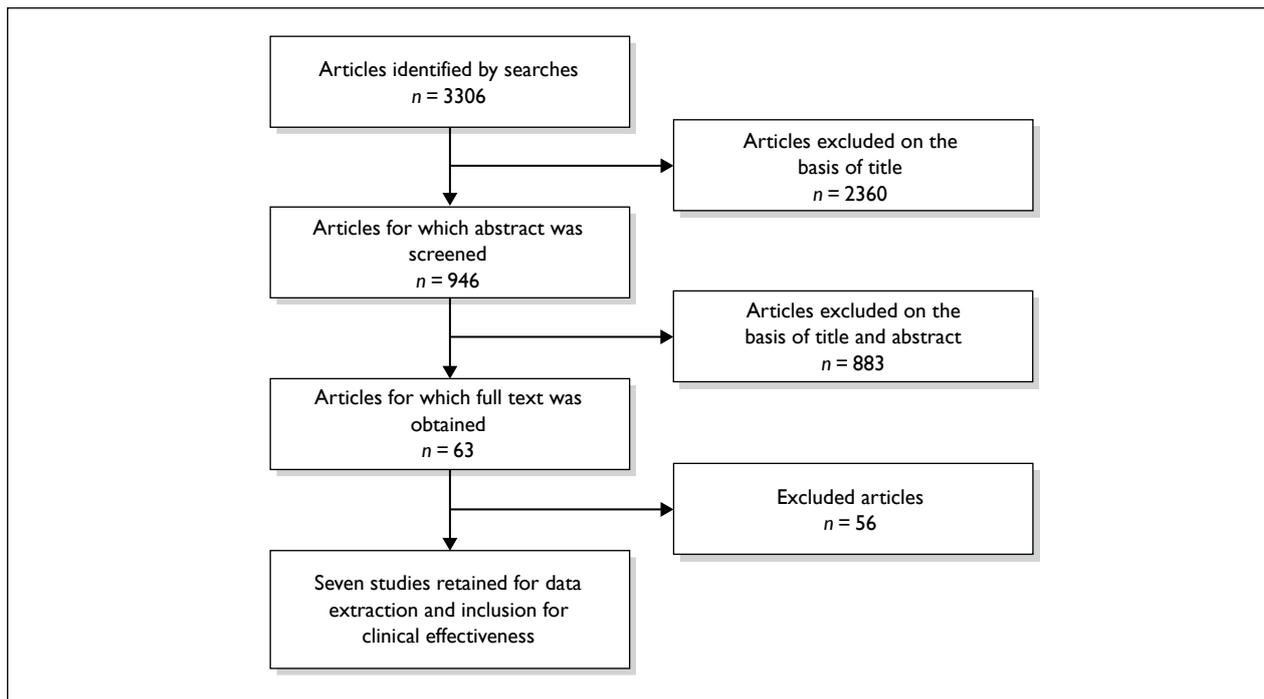
FIGURE 6 *Flowchart of identification of studies for inclusion in the systematic review of clinical effectiveness.*

ranging from 117 to 109,321 people. One thousand six hundred and seventy participants had pre-ESRD at the time of inclusion in the cohort (i.e. participated in a 'prospective cohort' study).

One study was restricted to patients with diabetes mellitus and renal impairment.[120] The other six studies did not restrict their cohorts by the underlying cause of renal impairment; nonetheless, diabetes mellitus was commonly reported among participants, ranging from 13.2% to 52.4%. Males exceeded females in all of the studies, ranging from 51% to 100%.

Few of the studies reported information about the stage of CKD at key time points, i.e. first diagnosis or first referral to a specialist. Kessler and colleagues[119] noted the time since first creatinine level > 177 μmol/l (2 mg/dl). Martínez-Ramírez and colleagues[120] diagnosed renal impairment based on micro- (30–300 mg/dl) and macroalbuminuria (> 300 mg/dl). They reported that 40% had CKD stage 1, 35% stage 2 and 25% stage 3 at the start of their study period with a mean eGFR of 78.6–83.8 ml/min/1.73 m². Orlando and colleagues[111] defined CKD as a creatinine level ≥ 1.4 mg/dl and noted at baseline that 89% of study participants had evidence of proteinuria.

Quality of included studies

Each included study was quality assessed and the results are summarised in *Table 11*. While all the retrospective studies suffered from differences in the groups at baseline, attempts were made to adjust for these differences in the analysis. There were five main problems with the included studies in determining effectiveness of early referral:

- None of the studies randomly allocated participants to the intervention groups. While attempts were made to adjust for differences in the analysis, unknown confounders could not be addressed. In particular, complex confounders such as confounding by indication could not be accounted for.
- There were significant differences in the baseline characteristics of the comparison groups in all studies, with the exception of the study reported by Martínez-Ramírez and colleagues.[120]
- None of the studies adequately described the 'intervention' in terms of the type of care delivered to enable comparisons between studies.
- Only two studies defined their cohorts prospectively in relation to the intervention.[111,120] Studies designed around

TABLE 10 Summary of included clinical effectiveness studies

Study	Jungers 2001[121]	Kessler 2003[119]	Khan 2005[122]	Kinchen 2002[123]	Martínez-Ramírez 2006[120]	Orlando 2007[111]	Roderick 2002[56]
Setting							
Country	France	France	USA	USA	Mexico	USA	UK
Clinical Setting	Single hospital dialysis unit	13 nephrology units (11 not for profit) in region (100%)	Centres for Medicare and Medicaid Services database	From 81 dialysis clinics in 19 states	Two diabetes clinics	North Caroline Veterans Administration laboratory database	Six nephrology units in one region of UK
Study design							
Type of study	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort	Cohort
Recruitment	Incident dialysis	Incident RRT (including pre-emptive transplant)	Incident dialysis	Incident dialysis	Randomly selected patients with type 2 diabetes and evaluated for nephropathy (proportion of total clinic not stated)	Selected all patients with two serum creatinine measurements at least 3 months ≥ 1.4mg/dl	Incident RRT
Recruitment period	1989–98	1997–9	1995–8	1995–8	Not stated	1998–9	1996–7
Retrospective or prospective	Retrospective in relation to 'intervention' of pre-dialysis care	Retrospective in relation to 'intervention' of pre-dialysis care	Retrospective in relation to 'intervention' of pre-dialysis care	Retrospective in relation to 'intervention' of pre-dialysis care	Prospective in relation to 'intervention' of pre-dialysis care	Prospective in relation to 'intervention' of pre-dialysis care	Retrospective in relation to 'intervention' of pre-dialysis care
Follow-up	Up to 5 years post RRT	Up to 2 years post RRT Median follow-up for survival was 22.2 months (range, 1 day to 46.3 months)	Up to 1 year post RRT	Post RRT follow-up median 2.2 years	1 year	3.5 years	6 months post RRT
Participants							
Total number	1152	502	109,321	1041	117	1553	361 (only 353 reported in data tables)

continued

TABLE 10 Summary of included clinical effectiveness studies (continued)

Study	Jungers 2001[121]	Kessler 2003[119]	Khan 2005[122]	Kinchen 2002[123]	Martinez-Ramirez 2006[120]	Orlando 2007[111]	Roderick 2002[56]
Characteristics							
Age	53.8 (SD 17.2) years	62.8 (SD 16) years	75.5 (SD 5.8) years	Age <65 years = 64.9%	Study = 62.5 (SD 9.3) years; Comparator = 62.8 (SD 9.9) years	Median 70 (range 26–98) years	Median 64 (range 15–69) years
Sex %	1.74 male/female ratio	59.4% male; 40.6% female	51% male; 49% female	55.2% male; 44.8% female	Study = 27 female (51%); Comparator = 25 female (38%)	100% male	60% male; 40% female
Diabetes %	13.2%	31.9%	53%	52.4%	100%	52%	Diabetic nephropathy 11–19%
CVD %	15.1%	57.2%	59%	Not specified	Study = 13%; Comparator = 15%	49%	Not specified
Hypertension %	Not specified	Not specified	82%	95.3%	Study = 60%; Control = 60%	92%	Not specified
CKD stage % (at first referral/start of prospective study)	Not specified	Not specified	Not specified	Not specified	Study: stage 1 = 42%; stage 2 = 37%; stage 3 = 21% Comparator: stage 1 = 39%; stage 2 = 34%; stage 3 = 27%	NR	Not specified
Inclusion criteria	Consecutive patients with ESRD	Consecutive patients with ESRD	≥67 years at initiation of dialysis Medicare as their primary payer with coverage for both institutional (part A) and physician (part B) supplier services 24 months before initiation of dialysis	Incident dialysis at one of the recruiting clinics No details of proportion agreeing to participate	Diabetic nephropathy diagnosed by 24-hour urine protein/microalbuminuria	All patients with two creatinine values ≥1.4mg/dl, at least 3 months apart	All patients with ESRD accepted onto the renal replacement programme of the six established units in the south and western region between 1 June 1996 and 31 May 1997

Study	Jungers 2001[121]	Kessler 2003[119]	Khan 2005[122]	Kinchen 2002[123]	Martinez-Ramirez 2006[120]	Orlando 2007[111]	Roderick 2002[56]
Exclusion criteria	Patients with acute renal failure (*n*=60) or advanced malignancy (*n*=35)	Individuals with acute, reversible renal failure, those returning to dialysis following kidney graft failure	26,769 were excluded because of the absence of Medicare part A claims or because Medicare was not the primary payer during the 24 months before initiation of dialysis	Patients were excluded if they were younger than 18 years of age or did not speak English or Spanish	Transient cause of proteinuria <18 years old	Patients were excluded if: not followed in health-care organisation, primary care or nephrology clinics if RRT was initiated within 90 days of the abnormal creatinine measurement	Patients with acute renal failure, those transferred in from other units already on dialysis and returns to dialysis from failed transplants were excluded
Comparator groups	Duration of predialysis nephrological care: <6 months=258 6–35 months=267 36–71 months=225 ≥72 months=307	Group 1=261 (patients referred to a nephrologist more than 12 months before initiation of RRT) Group 2=85 (patients referred 12 months or less but more than 4 months before first RRT) Group 3=42 (referred 4 months or less but more than 1 month before RRT) Group 4 (late referral)=60 (CRF for more than 1 month but referred≤1 month before RRT) Group 5=54 ('acute disease' with both CRF diagnosis and nephrology referral no more than 1 month before first RRT)	Group 1 (no nephrology care in 24 months prior to dialysis)=55,087 Group 2 (MNC during 24 months prior to dialysis but 0 visits in last 6 months)=5820 Group 3 (MNC during 24 months prior to dialysis and 1–2 visits in last 6 months)=24943 Group 4 (MNC during 24 months prior to dialysis and ≥3 visits in last 6 months)=23,471	Group 1=399 (referral>12months before dialysis) Group 2=184 (referral 4–12 months before dialysis) Group 3=245 (referral<4 months before dialysis)	Study (referred to nephrologists)=52 Comparator (no access to nephrologists)=65	Primary care physicians only=1097 Nephrology (primary care physicians plus nephrology clinics)=456	Time from referral to dialysis: Less than 1 month=84 1–4 months=40 (all less than 4 months=124) 4–12 months=52 >12 months=177

CKD, chronic kidney disease; CRF, chronic renal failure; CVD, cardiovascular disease; ESRD, end-stage renal disease; MNC, months of nephrology care, RRT, renal replacement therapy; SD, standard deviation.

TABLE 11 *Summary of quality assessment of included studies*

Study	Jungers 2001[121]	Kessler 2003[119]	Khan 2005[122]	Kinchen 2002[123]	Martinez-Ramirez 2006[120]	Orlando 2007[111]	Roderick 2002[56]
Groups similar at baseline	No. Baseline characteristics significantly differed between the four quartiles in terms of gender and comorbidity (diabetic, vascular disease)	No. Baseline characteristics significantly differed between the referral groups in terms of age and comorbidity	No. Baseline characteristics significantly differed between the referral groups in terms of sex, cause of renal disease and visits to other health-care professionals	No. There were significant differences in baseline characteristics of patients between early, intermediate and late evaluation	Yes	No. Baseline characteristics significantly differed between the referral groups in terms of age, comorbidities, proteinuria, CKD stage	No. Baseline characteristics significantly differed between the referral groups in terms of age, comorbidities, cause of CKD and type of referring physician
Outcomes measured in a standard, valid and reliable way	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dropouts/ Withdrawals	95 excluded (60 had acute or rapid progressive renal failure, 35 had advanced malignancy); 86 were lost to follow-up after moving out of the Paris area	Not stated	26,769 were excluded because of the absence of Medicare part A claims or because Medicare was not the primary payer during the 24 months before initiation of dialysis	213 did not have information about first referral to nephrologist	Seven (five withdrew; two lost to follow-up)	133 (8%) lost to follow-up although no details provided	50 (12%) had incomplete records and were excluded; 361 included but only 353 reported in analysis – not explained
Intention to treat analysis	Not applicable	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable
Diagnosis based on more than one blood test	Criteria for referral not stated	Criteria for referral not stated	Criteria for referral not stated	Criteria for referral not stated	Diagnosis based on confirmed urinary protein	Yes (two creatinines, 3 months apart)	Criteria for referral not stated
Blinding	No	No	No	No	No	No	No
Did the study minimise the risk of bias	Adjusted for age, diabetes mellitus, hypertensive nephropathy and CVD	Statistically significant associated factors were adjusted for in final risk model	Statistically significant associated factors were adjusted for in final risk model	Statistically significant associated factors were adjusted for in final risk model	Statistically significant associated factors were adjusted for in final risk model	Range of factors considered to be of relevance were adjusted for in final risk model	Factors considered to be of relevance were adjusted for in risk model (no details given)

CKD, chronic kidney disease; CVD, cardiovascular disease.

cohorts of people starting dialysis miss all the people with CKD who have not yet progressed to end-stage disease or who die before they reach that point.

- Only the two prospective studies reported the criteria they used to define CKD.[111,120] None of the studies defined the criteria for triggering referral to a specialist.

Does early referral improve outcomes?

Renal function: progression and onset of RRT

Five studies reported creatinine clearance or eGFR at the start of RRT but did not report renal function at the time of referral, at first diagnosis or during follow-up.[56,119,121–123] Only two studies reported renal function over time as an outcome.[111,120]

Renal function at the onset of RRT was not substantially or consistently altered by referral to the specialist team at least 12 months prior to requiring RRT.[56,119,121–123]

Orlando and colleagues[111] retrospectively compared those receiving care by primary care physicians alone with those receiving specialist nephrology input to assess progression (defined by change of stage or death). More progressed to a more advanced stage of CKD in the nephrology referral group at each stage of disease than the primary care only group, but fewer died. There was little difference in time spent in follow-up between groups in stages 1 and 2. For stage 3, 316 more days were spent in follow-up in the nephrology group than the primary care only group. The difference in deaths was particularly marked for those with stage 3 or worse CKD. Cox HRs for the risk of progression, adjusting for age, race, medication use, comorbidities and risk factors showed no statistically significant difference between nephrology referral and primary care only for those with stage 1 or 2 disease. For those with stage 3 or worse, nephrology care reduced progression or death (after adjustment) with an HR of 0.8 (95% CI 0.61 to 0.90) for stage 3 disease and 0.75 (95% CI 0.45 to 0.89) for stage 4. Of the 1553 participants, 26 progressed to ESRD during the 5-year follow-up with six (0.4%) in the primary care only group and 20 (1.29%) in the specialist care group. The higher progression in the referred group reflects, at least in part, that fewer people died during stages 3–5 and thus survived to require dialysis.[111]

Martínez-Ramírez and colleagues[120] reported that during the 1-year prospective follow-up of diabetic patients with evidence of early or overt nephropathy, only one patient deteriorated to requiring RRT (in the unreferred group). Among the group where no referral to a specialist service was available, mean (SD) eGFR deteriorated from 78.6 (28.1) ml/min/1.73 m^2 to 66.6 (29.9) ml/min/1.73 m^2, a statistically significant fall of 12.0 ml/min/1.73 m^2 ($p < 0.05$). In the cohort referred early to specialist nephrology care, mean (SD) eGFR was 83.8 (26.1) ml/min/1.73 m^2 at baseline and was not statistically significantly altered after 12 months [80.4 (35.5) ml/min/1.73 m^2]. A similar pattern was observed regardless of whether the patient had early or overt diabetic nephropathy (defined by the presence of microalbuminuria with eGFR > 60 ml/min/1.73 m^2 versus proteinuria or eGFR < 60 ml/min/1.73 m^2).[120]

Table 12 summarises the data from these studies.

Mortality

All seven studies reported mortality as an outcome.[56,111,119–123] Roderick and colleagues,[56] however, did not report it by the referral groups of interest here. Martínez-Ramírez and colleagues[120] reported three deaths during the 1-year follow-up, all in the group who were not referred to specialist care, and all cardiovascular deaths. Orlando and colleagues[111] reported higher numbers of deaths among those cared for in primary care than among those referred to a specialist. This pattern held at all stages of CKD.

In all of the retrospective studies, starting their cohorts from the initiation of dialysis, better dialysis survival was associated with early referral. This improvement was observed from 90 days[119] to 5 years[121] after initiation of dialysis. Jungers and colleagues[121] reported survival was highest in the group referred more than 72 months prior to dialysis. The difference in survival could be observed from 3 months after starting dialysis and was marked by 5 years (77.3% in those referred > 72 months prior to dialysis versus 57.8% in those referred less than 6 months prior to dialysis; $p < 0.001$). CVD accounted for more than 50% of the deaths. The earlier referral groups (> 36 months and > 72 months) experienced fewer CVD deaths than those referred later. Adjusting for age, sex and comorbidities (diabetes mellitus, HBP, CVD), the RR of death for those with referral > 72 months prior to dialysis, as compared with < 6 months, was 0.24 (95% CI 0.10 to 0.59) at 1 year and 0.53 (95% CI 0.35 to 0.79) at 5 years.

TABLE 12 *Summary of effect of early referral on renal progression*

Study	Referral pattern	Change in kidney function			
		GFR baseline [mean (SD) ml/ min/1.73 m²]	GFR final [mean (SD)]	Change from baseline (*p*-value)	Difference at final (*p*-value)
Martínez-Ramírez 2006[120]	Referral to specialist (SR)	83.8 (26.1)	80.4 (35.5)	−3.4 (NS)	13.8 (*p* < 0.05)
	No specialist referral (no SR)	78.6 (28.1)	66.6 (29.9)	−12.0 (*p* < 0.05)	
	SR (early nephropathy)	95.6 (20.9)	98.8 (36.4)	3.2 (NS)	13.1 (NS)
	No SR (early nephropathy)	99.0 (21.6)	85.7 (27.3)	−13.3 (*p* < 0.05)	
	SR (overt nephropathy)	71.1 (25.4)	61.3 (22.2)	−9.8 (*p* < 0.05)	10.5 (NS)
	No SR (overt nephropathy)	61.7 (24.6)	50.8 (21.3)	−10.9 (*p* < 0.05)	

Study	Number transitioning through each stage and outcomes						
Orlando 2007[111]		Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	Pre-ACKD to ACKD
	PCP-only	**995**	**624**	**209**	**28**	**6**	**1090**
	CKD progression	445 (45%)	156 (25%)	14 (7%)	4 (14%)	1 (17%)	27 (2%)
	Died	231 (23%)	217 (35%)	131 (63%)	20 (71%)	2 (33%)	509 (47%)
	Composite end point[a]	676 (68%)	376 (60%)	145 (69%)	24 (86%)	3 (50%)	536 (49%)
	Median days spent in stage	1168	1247	895	558	655	1936
	Nephrology group	**222**	**263**	**207**	**58**	**20**	**440**
	CKD progression	138 (62%)	120 (46%)	56 (27%)	17 (29%)	5 (25%)	67 (15%)
	Died	24 (11%)	53 (20%)	74 (36%)	25 (43%)	5 (25%)	147 (33%)
	Composite end point[a]	162 (73%)	173 (66%)	130 (63%)	42 (72%)	10 (50%)	214 (49%)
	Median days spent in stage	1127	1100	1211	834	776	1991
	[a]PCP-only vs nephrology *p*-value	0.41	0.32	< 0.001	0.03	NA	< 0.001
	[b]Adjusted HR (95% CI)	1.08 (0.91 to 1.29)	1.20 (0.99 to 1.45)	0.80 (0.61 to 0.90)	0.75 (0.45 to 0.89)	NA	0.91 (0.76 to 0.99)

ACE I, angiotensin converting enzyme inhibitor; ACKD, advanced chronic kidney disease (stage 4 or 5); CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; NA, not applicable; NS, not significant; PCP, primary care physicians; SD, standard deviation; SR, specialist referral.
a Death or CKD progression.
b Adjusted for age, race, ACE I use, statin use, comorbidities, smoking and proteinuria.

Kessler and colleagues[119] reported an association between timing of referral and survival in the first 90 days after initiating dialysis, with an almost threefold increase in risk (HR 2.7, 95% CI 1.2 to 6.3) once referral was less than 12 months prior to dialysis, and as great as five times higher (HR 5.2, 95% CI 2.2 to 12.3) if referral was less than 1 month prior to dialysis after adjustment for age, sex and systolic BP. For survival over 3 months, the only independently associated factor relating

to referral timing was for those referred between 1 and 4 months prior to dialysis, where a HR of 2.2 (95% CI 1.4 to 3.5) was observed compared with referral < 1 month. Khan and colleagues[121] reported lower 1-year mortality on dialysis in those referred during the 24 months prior to dialysis (25–35%) as compared with those with no pre-dialysis referrals (51%) [HR 1.5 (95% CI 1.44 to 1.55) after adjustment for age, sex, race, erythropoietin injections, non-nephrology care and comorbidities]. There was evidence of a 'dose-response' gradient, with those receiving the most nephrology visits having the lowest mortality. Kinchen and colleagues[123] reported lower mortality on dialysis in those referred more than 12 months, as compared to those referred less than 4 months, prior to dialysis. The differential in survival was observed to at least 3 years. An HR of 1.6 (95% CI 1.11 to 2.24) for later referral, as compared to referral > 12 months prior to dialysis, was observed after adjustment for type of dialysis, demographic characteristics, socioeconomic status, years of smoking, exercise status and Index of Coexistent Disease score. *Table 13* provides a more detailed summary of the mortality data reported.

Hospitalisations

Three studies reported hospitalisations as an outcome.[56,111,121]

Orlando and colleagues[111] compared hospitalisations in the group referred to nephrology specialists with those with renal disease managed only in primary care. The number of hospitalisation days differed little between the two groups (mean 2.8 versus 2.5 days respectively; $p = 0.03$).

One study reported on the impact of early referral on hospitalisation in the first 6 months after dialysis was initiated.[56] Roderick and colleagues[56] observed that those in the group with referral < 1 month prior to dialysis had more hospitalisation episodes within the first 6 months of dialysis than all others (1–4 months, 4–12 months and > 12 months) (mean 2.6 versus 1.7, $p = 0.001$). The median length of stay was shorter in those referred more than 1 month prior to dialysis (10 versus 18 days in the < 1-month group). Lengthening referral time to greater than 1 month prior to dialysis did not have any substantial effect on this outcome.

Jungers and colleagues[121] reported the impact of referral on the duration of initial hospitalisation at the time of starting dialysis. They found a

statistically significantly lower duration of initial hospitalisation in those referred at least 6 months prior to dialysis [mean 23.8 (SD 17.1) days] versus those referred 6 to 35 months prior to dialysis [mean of 7.5 (SD 8.9) days; $p < 0.001$] and some evidence of a dose response with improvements out to referral > 72 months prior to dialysis.

Emergency dialysis

Kessler and colleagues[119] reported statistically significantly higher emergency dialysis among those referred late than those referred more than 12 months prior to dialysis (83.3% versus 29.1%; $p < 0.001$).

Quality of life

None of the included studies reported quality of life as an outcome.

Barriers to early referral

None of these studies reported barriers as an outcome. In discussion, Khan and colleagues[122] noted the challenge of identifying patients with CKD early enough so that early referral intervention could be undertaken. Kinchen and colleagues[123] noted that the reasons for late referral were numerous and included a lack of symptoms, non-compliance, lack of access to care, and primary care physicians' attitudes and knowledge. Orlando and colleagues[111] acknowledges that specialist nephrology referral for all patients with CKD, even if restricted to all with stage 3 disease or worse, was beyond the capacity of existing nephrology services.

What elements of early referral design and delivery are important?

Because of the nature of the studies identified (largely retrospective with regards to the 'intervention' of early referral), the characteristics of the intervention were poorly reported. In the study by Martínez-Ramírez and colleagues,[120] the referred cohort received a total of three visits in 12 months to see a single nephrologist along with standard care of monthly visits to a primary care physician who was instructed not to modify the prescriptions of the nephrologist.

A number of studies did, however, describe aspects of management and how they differed between early referral to a specialist as compared with remaining in generalist care.

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TABLE 13 *Summary of effect of early referral on all-cause mortality*

All-cause mortality					
		Predialysis nephrological care duration (months)			
Jungers 2001[121]		**<6**	**6–35**	**36–71**	**≥72**
	n	86	67	40	54
	3 months' mortality (SD)	7.3%±1.7[a]	4.2%±1.2	1.8%±0.9	0.7%±0.6
	1-year mortality (SD)	13.6%±2.2[b]	7.4%±1.6	7.2%±1.8	2.5%±0.9
	5 years' mortality (SD)	42.2%±4.2[c]	34.7%±3.9	22.9%±3.7	22.8%±3.6
	Cardiovascular mortality				
		<6	**6–35**	**36–71**	**≥72**
	At 5 years *n* (%)	53 (62%)	41 (61%)	21 (52%)	29 (52%)
	Duration of specialist care pre-dialysis (months)				
Kinchen 2002[123]		**<4 months**	**4–12 months**	**>12 months**	
	n	245	184	399	
	1-year mortality	13.3%	9.5%	4.3%	
	2 years' mortality	27.6%	22.4%	14.6%	
	3 years' mortality	37.0%	32.7%	26.3%	
Martínez-Ramírez 2006[120]		**Primary care**	**Nephrology care**		
	n	65	52		
	1-year mortality	3 (5%)	0		
Khan 2005[122]		**Frequency of specialist care pre-dialysis**			
		0 MNC in 24 months before dialysis	0 MNC in 6 months before dialysis	1–2 MNC in 6 months before dialysis	≥3 MNC in 6 months before dialysis
	n	55,087	5820	24,943	23,471
	1-year mortality	51%	35%	33%	25%

Orlando 2007[111]		**Primary care**		**Nephrology care**	
		Proportion	**Median days spent in each stage**	**Proportion**	**Median days spent in each stage**
	Stage 1	231 (23%)	1168	24 (11%)	1127
	Stage 2	217 (35%)	1247	53 (20%)	1100
	Stage 3	131 (63%)	895	74 (36%)	1211
	Stage 4	20 (71%)	558	25 (43%)	834
	Stage 5	2 (33%)	655	5 (25%)	776

Jungers 2001[121]	**RR for death for PDNC ≥72 months**	**RR**[d]	**95% CI**	
	At 3 months	0.13	0.03 to 0.58	Adjusted for age, diabetes, hypertension, cardiovascular diseases and nephropathy.
	At 1 year	0.24	0.10 to 0.59	
	At 2 years	0.44	0.25 to 0.81	
	At 3 years	0.45	0.28 to 0.74	
	At 5 years	0.53	0.35 to 0.79	

CI, confidence interval; MNC, months of nephrological care; PDNC, predialysis nephrology care; RR, relative risk; SD, standard deviation
a <6 months vs 36–71 months: *p*<0.01; vs ≥72 months: *p*<0.001.
b <6 months vs 36–71 months or ≥72 months: *p*<0.001.
c <6 months vs 36–71 months: *p*<0.01; vs ≥72 months: *p*<0.001.

Blood pressure control

In the two prospective studies of early referral for CKD, improvements in BP control were observed. Martínez-Ramírez and colleagues[120] reported statistically significant improvements in systolic BP in the referred cohort [140 (SD 30) mmHg to 130 (SD 21) mmHg] while BP control deteriorated in the unreferred group [140 (SD 19) mmHg to 145 (SD 23) mmHg] ($p < 0.05$). Orlando and colleagues[111] reported that a higher proportion of patients in the nephrology care group had good BP control (41% versus 36%; $p = 0.06$).

At the initiation of dialysis, Jungers and colleagues[121] reported BP was lower in all the group referred more than 6 months prior to dialysis and lowest in the group referred more than 72 months prior to dialysis [systolic BP mean 171 (SD 23) mmHg in the < 6-month group versus 148 (SD 17) mmHg in the 6- to 35-month group and 141 (SD 12) mmHg in the ≥ 72 months group; $p < 0.001$]. However, Kessler and colleagues[119] and Kinchen and colleagues[123] did not observe statistically significant differences in BP control at the start of dialysis. Khan and colleagues[122] and Roderick and colleagues[56] did not report BP control.

Other clinical markers

Four studies[56,111,121,123] reported serum albumin was statistically significantly higher if referred early, but none presented information about the underlying diagnoses. Those with nephrotic syndrome may have presented earlier, but have relatively preserved renal function despite their apparently poor clinical markers, e.g. low albumin

as a result of heavy proteinuria. Kinchen and colleagues[123] described statistically significant differences in serum albumin < 36 g/l at the time of initiation of dialysis (60.5% versus 77.9%; $p < 0.001$), when comparing early and late referral. Orlando and colleagues[111] reported albumin levels < 40 g/l in 59% versus 49% ($p < 0.001$) (early versus late respectively). Roderick and colleagues[56] noted albumin was lower in those referred less than 1 month prior to dialysis [mean 32 g/l (SD 0.83)] than for those with referral > 12 months [mean 37 g/l (SD 0.56)] ($p < 0.001$). Khan and colleagues[122] found no statistically significant difference in albumin. Kinchen and colleagues[123] also described statistically significant differences in haematocrit < 0.3% (56% versus 68.1%; $p < 0.001$). Khan and colleagues,[122] Roderick and colleagues[56] and Orlando and colleagues[111] did not observe substantial differences in haematocrit between early and late referral groups.

Treatments

Martínez-Ramírez and colleagues[120] reported statistically significant improvements in systolic BP in the referred cohort. In terms of treatments, the use of ACE Is increased more in the referred group and there was substantially higher use of ARBs and statins. Non-steroidal anti-inflammatory drug use fell in the referred group, but increased in the unreferred group (*Table 14*). Orlando and colleagues,[111] however, reported no statistically significant differences between the groups for lipid lowering agent or ACE I use.

Roderick and colleagues[56] reported that vitamin D supplementation (late 20% versus early 40%),

TABLE 14 Comparison of treatments in the referred and unreferred groups[120]

Comparisons of baseline and final treatments between cohorts, number (%)						
	Referred			**Unreferred**		
Treatment	**Baseline**	**Final**	**Change**	**Baseline**	**Final**	**Change**
ACE I	25 (48)	44 (90)[a,b]	19 (42)	35 (53)	37 (70)[b]	2 (17)
ARBs	1 (2)	22 (45)[a,b]	21 (43)	0 (0)	2 (4)	2 (4)
Statins	2 (4)	21 (43)[a,b]	19 (39)	10 (16)	5 (9)	−5 (−7)
Aspirin	11 (21)	12 (24)	1 (3)	8 (15)	4 (7)	−4 (−8)
Other NSAID	6 (11)	0 (0)[a,b]	−6 (−11)	3 (5)	17 (32)[b]	14 (27)

ACE I, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; NSAID, non-steroidal anti-inflammatory drugs.
a $p < 0.05$ vs control cohort in the same evaluation.
b $p < 0.05$ vs baseline of the same cohort.

phosphate binders (late 29% versus early 44%), sodium bicarbonate (late 10% versus early 28%), lipid lowering agents (late 6% versus early 11%) and erythropoietin (late 5% versus early 23%) were all prescribed more frequently in those referred more than 12 months before starting dialysis.

Kinchen and colleagues[123] described statistically significant differences in the following factors when comparing early and late referral: exercise one or more times per week (26.3% versus 14.9% respectively; $p < 0.001$); and erythropoietin treatment (25.3% versus 12.7%; $p < 0.001$).

Which patient groups benefit the most from referral and at what stage of disease?

Kinchen and colleagues[122] reported that late referral was associated with a greater hazard of death on dialysis in diabetic subgroups (HR 2.4, 95% CI 1.28 to 4.47); in black ethnic subgroups (HR 6.9, 95% CI 1.07 to 44.71); and if the cause of the ESRD is attributed to diabetes or hypertension (HR 2.0, 95% CI 1.14 to 3.46) (*Table 15*). Martínez-Ramírez and colleagues[120] noted a more marked effect of nephrology referral on those with early diabetic nephropathy (microalbuminuria) compared with those with overt proteinuria (*Table 15*).

Orlando and colleagues[111] observed that the impact of nephrology care on the composite end point of renal progression and death was only observed for stages 3–5. In stages 1–2 there was no statistically significant difference between nephrology care and primary care alone and, if anything, survival/renal progression were better in the primary care alone group.

Discussion

In comparison to the considerable literature base about the effect of late referral (see Appendix 7), we identified only seven studies that considered the impact of early referral on outcomes in people with evidence of renal impairment.[56,111,119–123] This was despite adopting a wide definition of 'early' and 'referral'.

Five of the studies were retrospective, based on cohorts established at the time of starting RRT and then looking back to identify the timing and format of care in the months and years prior to RRT.[56,119,121–123] Two studies compared management

solely by primary care physicians to referral to specialist nephrology services for patients with evidence of CKD.[111,120]

No clinical trials were identified. No studies randomised patients to specialist care versus primary care or current practice. Few studies reported the stage of CKD, or other markers of renal impairment, at the time of referral to specialist services.

As a result it is difficult to draw conclusions about the clinical effectiveness of early referral strategies or indeed, what aspects of the strategies are driving the effect on outcomes.

Referral strategies

The limitations of the studies are discussed below, but one of the major difficulties was reporting of what the referral strategy encompassed. The limited details have been summarised in *Table 16*. Most studies based referral on 'clinical indication' that was not further specified. One screened all patients with diabetes mellitus as a high-risk group for renal disease. Management appeared to focus on pharmacotherapy for management of complications of CKD or for modification of cardiovascular risk and renal progression. None of the studies considered whether cardiovascular risk reduction could be delivered through optimisation of the management of the other comorbidities. eGFR, proteinuria, albuminuria and serum creatinine were all described as screening tests.

Evidence of clinical effectiveness of early referral

Despite the difficulties around the definition of CKD and referral, we sought to report what evidence was available about the effect of early referral on clinical outcomes.

Progression

One of the key aims of referral to specialist nephrology services is to initiate interventions to stop or slow progression towards ESRD. Many studies have demonstrated the effectiveness of ACE Is and ARBs in reducing the progressive decline in eGFR in trials.[42–46] BP control is also important.[42] The comparison of nephrology referral for all those with diabetic nephropathy versus those with no access to nephrologists in Mexico[120] demonstrated better preservation in function in those referred to a specialist. The comparator group, with no access to specialist services, experienced a mean decline in renal function of

TABLE 15 Summary of impact of early referral for subgroups: renal progression and mortality

	Progression	GFR baseline [mean (SD)]	GFR final [mean (SD)]	Change from baseline (*p*-value)	Difference between groups (*p*-value)
Martinez-Ramírez 2006[120]	Referral to specialist	83.8 (26.1)	80.4 (35.5)	–3.4 (NS)	13.8 ($p<0.05$)
	No referral to specialist	78.6 (28.1)	66.6 (29.9)	–12.0 ($p<0.05$)	
	ER (early diabetic nephropathy)	95.6 (20.9)	98.8 (36.4)	3.2 (NS)	13.1 (NS)
	LR (early diabetic nephropathy)	99.0 (21.6)	85.7 (27.3)	–13.3 ($p<0.05$)	
	ER (overt diabetic nephropathy)	71.1 (25.4)	61.3 (22.2)	–9.8 ($p<0.05$)	10.5 (NS)
	LR (overt diabetic nephropathy)	61.7 (24.6)	50.8 (21.3)	–10.9 ($p<0.05$)	
Kinchen 2002[123]	**Mortality [HR (95% CI)] for different durations of specialist care pre-dialysis**				
		>12 months	4–12 months	<4 months	
	All patients	1.0 (reference group)	1.4 (0.92 to 1.99)	1.6 (1.11 to 2.24)	Adjusted for type of dialysis, demographic characteristics, socioeconomic status, years of smoking, exercise status and Index of Coexistent Disease score. Sensitivity analyses: redefinition of late referral, time of evaluation missing
	DM – yes	1.0	1.6 (0.84 to 2.94)	2.4 (1.28 to 4.47)	
	DM – no	1.0	0.6 (0.23 to 1.61)	0.9 (0.42 to 1.97)	
	Ethnicity – white	1.0	1.0 (0.60 to 1.73)	1.5 (0.92 to 2.37)	
	Ethnicity – black	1.0	1.8 (0.26 to 12.30)	6.9 (1.07 to 44.71)	
	Attributed cause of ESRD – hypertension or DM	1.0	1.1 (0.59 to 1.93)	1.99 (1.14 to 3.46)	
	Attributed cause of ESRD – glomerulonephritis or other	1.0	1.0 (0.35 to 2.63)	0.6 (0.22 to 1.51)	
	Age <65 years	1.0	1.4 (0.68 to 2.91)	1.5 (0.82 to 2.87)	
	Age ≥65 years	1.0	1.0 (0.46 to 1.99)	1.7 (0.86 to 3.22)	

CI, confidence interval; DM, diabetes mellitus; ER, early referral; ESRD, end-stage renal disease; HR, hazard ratio; LR, late referral; NS, not significant; SD, standard deviation.

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TABLE 16 *Summary of the characteristics of the early referral strategies: population selection, testing methods, sampling and management*

	Population selection			
	Screening	**High risk groups**	**Opportunistic**	**Clinical indication**
Testing				
Albuminuria	Martínez-Ramírez 2006[120]	Martínez-Ramírez 2006[120]		
Creatinine		Orlando 2007[111]		
eGFR				
Not described				Jungers 2001;[121] Kessler 2003;[119] Khan 2005;[122] Kinchen 2002;[123] Roderick 2002[56]

eGFR, estimated glomerular filtration rate.

	Testing			
	Albuminuria	**Creatinine**	**eGFR**	**Not described**
Sampling				
Single sample				
Two samples, 3 months apart		Orlando 2007[111]		
Repeat sampling and exclusion of reversible causes	Martínez-Ramírez 2006[120]			
Not described				Jungers 2001;[121] Kessler 2003;[119] Khan 2005;[122] Kinchen 2002;[123] Roderick 2002[56]
Cut-off level to define referral	Martínez-Ramírez 2006[120] Albumin > 30 mg/dl	Orlando 2007[111] Creatinine > 140 mg/dl		
Not described				Jungers 2001;[121] Kessler 2003;[119] Khan 2005;[122] Kinchen 2002;[123] Roderick 2002[56]

eGFR, estimated glomerular filtration rate.

Management						
	Medicine interventions					
Management of reversible causes of impaired renal function	**Management of complications of CKD**	**Cardio-protection**	**Lifestyle modification**	**Preparation for RRT**	**Not described**	
Population selection						
Screening	Martínez-Ramírez 2006[120]		Martínez-Ramírez 2006[120]			
High risk groups	Martínez-Ramírez 2006[120]		Martínez-Ramírez 2006[120]		Orlando 2007[111]	
Opportunistic						
Clinical indication	Roderick 2002[56]		Roderick 2002[56]	Roderick 2002[56]	Jungers 2001;[121] Kessler 2003;[119] Khan 2005;[122] Kinchen 2002[123]	

CKD, chronic kidney disease; RRT, renal replacement therapy.

12 ml/min/1.73 m², which is approximately three times higher than we found described in the natural history review.[88] This pattern was observed regardless of degree of baseline microalbuminuria. There was a high proportion of stage 1 and 2 CKD patients in this study and, as described by Djamali and colleagues,[83] the absolute rate of decline may be at its fastest during these stages. Orlando and colleagues[111] reported a higher risk (RR 1.32, 95% CI 1.13 to 1.55) of progression in stage 1–2, but not stage 3–5 for people with diabetes than those with no diabetes. The high rate of decline in function in the primary care only group may, therefore, be generalisable to a wider clinical setting.

Similarly, Orlando and colleagues[111] reported better outcomes for a composite end point of death or progression in those referred to specialists with stage 3 disease or worse. However, looking at renal progression alone, the crude data suggest more people in specialist care experienced progression. This may be as a result of differences in case-mix, survival and referral bias (where the sick or low risks are not referred by GPs) rather than due to differences in care. Predialysis survival was noted to be better in the group referred to specialists.[111] This finding may reflect a selection bias where people considered to have other serious comorbidities were less likely to be referred. However, a composite end point of death and renal progression was found to be significantly reduced by referral to a specialist for people with stage 3–5 CKD, even after adjustment for comorbidities and age.

Mortality
If patients progress to ESRD and survive to dialysis then there was evidence that post-dialysis survival was improved by early referral, even for referral more than 72 months prior to dialysis. Improved survival was sustained beyond that relating to initial establishment on RRT. This suggests that the survival advantage was not simply explained by technical preparation for dialysis and nutritional status. The differential effect of early referral to a specialist (> 72 months) on survival post dialysis lasted for at least 5 years.

The clinical difference at initiation of dialysis may reflect differences in care that are markers for overall care, or may in part reflect an improvement in clinical status of the patient at the time he or she starts dialysis that is causally linked to survival. Some hypothesise that they are markers for improved cardiovascular risk modification that then manifest in improved survival long after

the early dialysis phase.[121] However, in the types of studies presented, the differences in clinical markers may also reflect selection bias, where clinical staffs are selecting the healthiest and fittest to refer for dialysis.[123,124]

Kessler and colleagues[119] noted those referred late had low contact with primary care compared with those referred early. If CKD was diagnosed only within 1 month of requiring dialysis, then 43.4% of patients received no regular primary care input.

There was little evidence that hospitalisations were affected in the pre- or post-dialysis phase by early specialist referral beyond 1 month prior to starting dialysis.

Other measures of effectiveness
Given the chronic nature of this condition and the important potential to effect quality of life it was perhaps surprising that no studies reported aspects of quality of life.

The nature of what early referral meant in terms of clinical care was essentially not described. The limited detail available has been summarised above. Looking at the impact of different care on aspects of management (of risk factors) and prescribing identified inconsistencies between studies. However, BP control and/or ACE I/ARB prescribing were the most consistently identified differences between referral and standard non-specialist care. The use of CVD risk modifiers such as statins was also reported to be higher in specialist care by some authors.[111,120]

Which groups likely to benefit most

There was very limited information about subgroups that may have the most to benefit. Referral less than 12 months prior to starting dialysis was associated with poorer outcomes in certain groups: African-Americans, those with diabetes and those with hypertension;[123] a finding consistent with other studies of late referral (see Appendix 7). The authors did not report whether certain groups benefited more from early referral. Orlando and colleagues[111] reported that the benefit of referral to a specialist was not observed until stage 3 or worse. In contrast, in patients with diabetes, the greatest gains were reported when referral was made at the earliest stage (microalbuminuria).[120] It is important to note that studies defined their cohorts based on meeting criteria for chronic CKD. In clinical practice,

when a patient first presents with a reduced eGFR or evidence of renal damage, it is often not immediately possible to determine the chronicity or otherwise of their condition. A proportion of patients presenting with apparently 'early' features of CKD will in fact have an acute renal problem that requires rapid referral to a nephrologist or, in some cases, urologist.[23,41]

Limitations of the evidence base

The major limitations of the evidence base have been alluded to already. The lack of studies and in particular RCTs made assessment of effectiveness of strategies for early referral difficult. The Cochrane Renal Group noted, in 2002, that there was a paucity of RCT data for interventions in renal disease, lower than all other internal medicine specialties. Furthermore, patients with renal disease are under-represented in many large intervention trials. For example, an analysis of 86 intervention trials for CVD between 1998 and 2005 noted that 80% excluded ESRD and 75% excluded patients with known CKD.[125] Indeed much of the evidence base around the management of patients with renal disease has relied on observational studies, extrapolation of RCT findings from other clinical groups and expert opinion.

Our review included all study designs, and has found evidence that there are some differences in the outcomes experienced after referral to a specialist compared with remaining in primary care. Some of those differences may be explained by the complex decision-making process around selecting which patients to refer. Adjustment for confounding in the analysis corrects for some of the differences in case-mix but not all. There are, however, differences in the care received by people in specialist care when compared with primary care. Differences in the medicines prescribed and markers of their general clinical condition support the hypothesis that care differs.

The evidence base reviewed here was not helpful in unpacking which components of a model of care are important. Orlando and colleagues[111] provided the only estimate of the RR of ACM and progression comparing referral to a nephrologist with primary care alone. This study relied on routine health-care data and the two groups were significantly different at baseline. Observed differences were adjusted for in the analysis, but this adjustment could not account for unmeasured differences between the two groups. The generalisability of this study was also limited; the data were based on a veterans' health-care organisation (participants were all male) and the study took place in the USA, where non-specialist health care is very different from the primary care provision in the UK.

Conclusions

The studies identified provide some evidence to support the role of 'early' referral for CKD, identifying benefits in terms of BP control and renal progression among those referred earlier to specialist services. Very early referral benefits may be greater for certain clinical groups (those with diabetes) while others may show little gain until at least stage 3 disease. The evidence reviewed in this chapter does support the need for further good quality RCTs of methods of care delivery and timing of intervention. While referral to a specialist might be one approach to achieving optimal care, other care models exist. Given the large proportion of the population with stage 1–3 CKD and, from the review of natural history, the low progression to ESRD but significant cardiovascular morbidity and mortality once population screening is adopted, there may be appropriate and alternative ways of delivering care to such patients. The next chapter considers the other models of care delivery for CKD and the evidence of effectiveness.

Chapter 5
Models of care

Introduction

Two decades of rapid expansion in services for people with kidney disease have focused largely on delivery of care for people with severe impairment of kidney function and those requiring RRT. In 2002, the UK Renal Association[126] supported the early detection and referral of people with evidence of CKD to enable early treatment with the aim of halting disease progression in those with CKD and preventing kidney function impairment in those who were at high risk of developing CKD. The need for involvement of primary care in early identification was highlighted along with the need for access to expert nephrology assessment in order to reduce complications, including ESRD.[126]

The shift in focus to active early recognition and management of chronic conditions has been a growing focus for health services in recent years. Along with growing demand and changing population demographics, important drivers for change included the recognition that people with chronic diseases frequently did not receive advice about modifying risk factors and did not feel included in the treatment decision-making process.[127] Various chronic care models have been proposed but the essence is consistent, with a focus on self-care and including recognition of the importance of community services, informal support networks, multidisciplinary support and primary care in delivering care alongside specialist services. Chronic care models have now been adopted within the World Health Organization in recognition of the global nature of the challenge to support and manage people with chronic illnesses.[128]

In the management of diabetes mellitus, the chronic care model has been widely adopted and well studied. Care often includes a combination of self-management using various interventions along with management in partnership with primary and secondary care; a model with demonstrable clinical effectiveness and cost-effectiveness. Improvements in health outcomes including glycosylated haemoglobin, fasting blood glucose levels and diabetes knowledge were observed when patients were provided with group-based diabetes education programmes.[129] There was evidence to support disease management (an organised, practical, integrated and population-based approach of management to health-care services that focused on particular disease and aspects of delivery services) and case management (an intervention to manage patients at high risk of poor outcomes and includes identification of an individual, assessment, development of a care plan, implementation and monitoring of outcomes).[130] Similarly, multifaceted, professional intervention and enhancing the role of nurses in diabetes care have shown improvements in patients' health outcomes and process of care.[131]

A similar kind of care including educational interventions, involvement of multiskilled professionals and enhancing the role of professionals may prove advantageous in CKD management. Here we report evidence about the types of care models that have been adopted for the management of CKD patients. The methods used to identify these studies were outlined in Chapter 2.

Result

Initially, 40 studies were identified, of which three were excluded as they described only the components of care that should be considered[132,133] or evaluated the care received before and after a clinical trial [RENAAL: The Reduction in Endpoint Study in NIDDM (non-insulin dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan Study].[134] They did not describe or evaluate a model of care. Thus a total of 37 studies were included and categorised into four groups:

- surveys/audits ($n = 4$) surveys/audits of current care provision[135–138]
- evaluation studies ($n = 13$) evaluating single services or comparing different services[139–151]
- descriptive studies ($n = 7$) describing single services, groups of services, individual specialties within services or an intervention for care[152–158]

- aspirational studies (*n* = 14) reporting proposals for how the services/model of care for CKD management could be in future.[159–172]

The findings from these papers are presented below. Firstly, using the survey data, we provide an overview of the types of models of care delivery in the UK. We then present details of the types of models of care described in the literature, picking out commonality in the facets of the care programmes. The evidence of effectiveness for the models of care is summarised and, finally, the substantial literature describing aspirations for renal services is considered with regards to potential key components of care models.

Overview of existing models of care delivery

Chronic kidney disease management in the UK has been reported in the two surveys.[135,136] A questionnaire by Ahmad and colleagues[135] surveyed all 72 renal units in the UK and focused on the management of CKD patients with stages 4 and 5. Similarly, Jones and colleagues[136] surveyed all 71 renal units and 11 district general hospital nephrology units, asking about systems of care for stable uncomplicated CKD patients that did not rely on direct contact with nephrologists. Five basic types of management pattern for CKD patients were reported: multidisciplinary renal teams, low clearance clinics, predialysis education,[135] nurse-led clinics and shared care scheme (SCS)[136] (*Table 17*).

Multidisciplinary renal teams were reported by 97% of the renal units and comprised different skilled professionals who, along with nephrologists, managed CKD patients. Regular meetings brought the team together.[135] Dieticians and dialysis education providers were common, attending CKD clinics in more than 95% of the renal units.[135] Additionally, 70% of units ran satellite clinics for CKD patients in a general district hospital from where patients could access the full team services.[135] Only two units reported to have shared primary and secondary care schemes.[136] A further six centres were developing SCSs; three were developing nurse-led services where nurse specialists would manage stable patients and/or the initial assessment of new referrals.[136] Low clearance clinics were run by 71% of units to manage patients approaching RRT, while 10 units were planning to set up such clinics. Most of the low clearance clinics were run by specialist renal nurses who had various roles including communicating with the staff

involved in CKD management, patient education, counselling, transplant assessments, prescribing under medical supervision and reviewing patients.[135] Pre-dialysis education was noted in 16% of the units[136] where dialysis nurses, transplant co-ordinators, dieticians and pharmacists provided dialysis education to CKD patients.[135]

A survey of the organisation of care provided to CKD stage 3–5 patients by nephrology clinics in Italy[139] highlighted important and frequent deviations from guidelines in the centres' policies for caring for CKD patients including: the definition of low eGFR, management of anaemia and bone mineral metabolism, and preparation for dialysis. A report of a local CKD network established in the UK (membership included: local GPs, consultant nephrologists, consultant nurses, commissioners, a patient representative and representatives from the primary care trusts) described a network approach with supporting referral guidelines and an education programme that had been introduced to support increasing local demand on nephrology services.[140]

Models of care observed (from evaluative/descriptive studies)

From the 19 evaluation and descriptive papers, three broad models of care were identified: multidisciplinary care (MDC), structured care by an individual specialty, and educational interventions. Among the MDCs, two were SCSs. Structured care by an individual specialty included studies reporting on a single clinical specialty (e.g. nurses, pharmacists) operating a service in isolation or as part of a multidisciplinary group (*Table 18*). The models of care are described in more detail below. Some of the papers described more than one model of care.[153,154,157,158]

Multidisciplinary care
Multidisciplinary care was the most commonly described approach to the management of CKD populations. *Table 19* details the services and settings. MDC models were described in primary care[150] and hospital-based clinics.[142,143,145,146,151,152,154] The MDC disease management programmes based in primary care involved community-based teams of nurses, dieticians, social workers and GPs with a wide scope including a named nurse available to each patient.[150] Hospital care-based MDC nephrology clinics comprised nurses, nurse-educators, social workers, dieticians, nephrologists and academics. Joint diabetics and renal clinics

TABLE 17 *Types of management pattern for CKD patients*

Type of care	Number of units providing care	Detail of care		
Multidisciplinary renal team services (MSRT)[135]	70/72 units (97%)	Multidisciplinary teams consisted of dietician, dialysis education provider, anaemia co-ordinator, pharmacist, social worker, access co-ordinator, counsellor, diabetic nurse, occupational therapist, psychologist, physiotherapist and blood pressure nurse	Regular MSRT meeting	47/70 units (67%)
			Monthly meeting	36%
			Weekly meeting	49%
		Regular multidisciplinary teams meetings held as a part of this service		
Shared care (SC) scheme[136]	2/76 units (3%)	Stable uncomplicated CKD patients referred to SC where they are under the care of a GP but supervised by nephrologists based on clinical information and regular review. Patients attended the clinic every 6–12 months (as per the letter and blood form sent to them) and GP gathered clinical information (BP, urinanalysis, etc.) according to the SC form. Most of the time the practice nurse completed these forms. The patients examination result was reviewed by nephrologists and referred to hospital clinic or retained in SC as needed	Developing SC	6/76 (8%) units
			Planning nurse management	2/76 (3%) units
			Developing initial assessment by nurse for new referrals	1/76 units (1%)
Low clearance clinics[135]	50/70 units (71%)	These clinics were run for managing patients approaching RRT. Services carried out by renal nurse included delivery of CKD education, counselling, transplant education, prescribing and altering prescription under medical supervision, and communication with other personnel involved in the CKD patient care. Nephrologists and renal nurse reviewed patient on alternate basis	Renal nurse involvement in 84% of units	
Predialysis education[135]	13/76 units (17%)	The education was about types of dialysis, dietary restrictions, fluid balance, CKD-related anaemia, and renal bone disease, which were all well covered. Less commonly included were aspects of cardiovascular risk factors, sexual health and psychological support. Education materials were available in audio and Braille or translated in other languages. Specific dialysis education provider, dialysis nurses, transplant co-ordinators, dieticians and pharmacists were involved		

CKD, chronic kidney disease; RRT, renal replacement therapy.

included MDC teams with specialists from clinical specialties.[152] Some described a case management approach with a named team for individual patients.[145]

Shared care scheme

The Southampton Integrated Monitoring of Nephrology (SIMON) programme was the only structured SCS reported in detail in the literature that formally spanned secondary and primary care.[147] It included an intensive hospital nephrology clinic and shared primary and nephrology care scheme. All patients were initially seen at the hospital nephrology clinic and while patients with stable CKD were monitored regularly through the shared primary and nephrology care

TABLE 18 *Models of care reported in the included studies*

Study ID	Description of care	MDC	SCIS	EI
Bending 2007[152]	Joint diabetes and renal clinic at Eastbourne, UK	✕		
Compton 2002[153]	The Healthy Start Program at Ochsner Clinic in New Orleans, LA, USA	✕		
	A renal disease management programme within a managed care setting – Boston, MA, USA			
	CKD programme at Western New England Renal and Transplant Associates	✕		
	The division of Nephrology at Virginia Commonwealth University/ Medical College of Virginia, VA, USA			✕
Cortes-Sanabria 2008[141]	Primary care led by family physician with educative intervention [IMSS Primary Health-Care Units (Unidad de Medicina Familiar)] in Guadalajara City, Mexico			✕
Curtis 2005[142]	Multidisciplinary clinic of hospitals in Canada and Italy	✕		
Ghossein 2002[154]	Comprehensive renal care clinic called Healthy Living at Northwestern Memorial Hospital in Chicago, IL, USA	✕		✕
Hardy 2007[143]	Redesigned service for the management of diabetic nephropathy and diabetics with microalbuminuria at Whiston Diabetes Centre, Mersyside, UK (SCS)	✕		
Harnett 2008[144]	Primary care service and virtual care service		✕	
Harris 1998[145]	Multidisciplinary case management clinic (general practice medicine of Regenstrief Health Center, IN, USA, affiliated with multispecialty outpatient facility)	✕		
Hemmelgarn 2007[146]	Multidisciplinary clinic of Canada (Southern Alberta Renal program)	✕		
Hostetter 2003[155]	National Kidney Disease Education Program, MD, USA			✕
Jones 2006[147]	SIMON programme of Southampton, UK, that includes intensive hospital nephrology clinic (HC) and shared primary and nephrology care scheme (SCS)	✕		
Joy 2005[156]	Physicians–pharmacist collaborative practice model		✕	
Kelly 2008[148]	Pharmacist-led structured care (a protocol driven clinic)		✕	
Leung 2005[149]	Pharmacist and diabetes specialist-led structured care at hospital		✕	
Minutolo 2005[137]	Physician-led primary care service and nephrologist-led secondary care service		✕	
Minutolo 2006[138]	Physician-led primary care service and specialist (nephrologists or diabetologists)-led secondary care service		✕	
Richards 2008[150]	Disease management programme of West Lincolnshire Primary Care Trust, UK	✕		
Thanamayooran 2005[151]	Multidisciplinary nephrology clinic of Halifax, Canada (tertiary care hospital)	✕		
Thomas 2004[157]	Patient-centred management and education at South-west Thames, UK (Primary care)		✕	✕
Thomas 2005[158]	A patient-centred education programme at local family doctor surgeries (primary care)		✕	✕

EI, educational interventions; IMSS, Mexican Institute of Social Security; MDC, multidisciplinary care; SCIS, structured care by individual specialty; SCS, shared care scheme; SIMON, Southampton Integrated Monitoring of Nephrology.

TABLE 19 *Description of multidisciplinary care (MDC) for CKD settings and services*

Reference	Study type	Type of CKD patients	Multidisciplinary clinic	Facets of MDC programme	Staff delivering the programme	Comparator group
Bending 2007[152]	Descriptive	Established diabetes kidney disease	Joint diabetes and renal clinic at Eastbourne, UK	Referral through diabetes specialist service for initial diagnosis and then for follow-up depending upon the level of SCr in order to provide renal support therapy. The service includes a prior routine structured screening for microalbuminuria and clinical proteinuria and early intervention (ACE I/ARB) to control BP and glycaemia in all patients to halt the development of incipient diabetic nephropathy		NA
Compton 2002[153]	Descriptive review paper	CKD at early stages	The Healthy Start program at Ochsner Clinic in New Orleans	Multidisciplinary programme, aimed to intervene in CKD at early stage, thus slowing progression of the disease and improving patient outcomes	NR	NA
Compton 2002[153]	Descriptive review paper	CKD patients, stage not specified	A renal disease management programme within a managed care setting, Boston, MA, USA	Multidisciplinary programme promoting early referral where interventions to slow the progression of the disease could have impact on the morbidity and mortality associated with CKD. Educational opportunities provided to patients and family members	Primary care physicians, nephrologists, nephrology nurses, nutritionists	NA
Curtis 2005[142]	Cohort study, those exposed to MDC vs standard nephrology care	Incident dialysis patients	Multidisciplinary clinic of hospitals in Canada and Italy	MDC included educational programmes as well as regular, protocolised clinic and laboratory follow-up of patients with CKD. The frequency of both visits and laboratory tests was predetermined, based on the level of kidney function with reminder system to facilitate follow-up. Regularly scheduled blood work and clinical examination and pre-specified educational topics were reviewed with each patient	Canada – nurse, educator, physician, social worker, nutritionist, and pharmacist Italy – programme dedicated nephrologists and multidisciplinary nurses who took responsibility for implementing recommended diagnostic and intervention strategies	Standard nephrology care Nephrologists with access to facilities and staff of multidisciplinary clinic for their patients. Care was standardised and managed according to standard unit practices

continued

TABLE 19 Description of multidisciplinary care (MDC) for CKD settings and services (continued)

Reference	Study type	Type of CKD patients	Multidisciplinary clinic	Facets of MDC programme	Staff delivering the programme	Comparator group
Ghossein 2002[154]	Evaluation of comprehensive renal care	CKD stage 3–5	Comprehensive renal care clinic called 'Healthy Living' at Northwestern Memorial Hospital, Chicago, IL, USA	Main aspects of programme were treating the complications of CKD (anaemia, renal osteodystrophy), providing nutritional support, identifying and managing comorbidities, preparing for transplantation and dialysis. The main aim of the service was to slow or stabilise the progression of CKD. The referring primary care physicians were given educational sessions including lectures and discussions (one-to-one or small group). Clinical parameters and medication of the patients were monitored and were screened to check for comorbid conditions. Education on dialysis provided to patients	Nephrologists, physician assistant, nurses, nutritionist, having an access to renal social workers, patient educator, renal dietician, separate transplant team	NA
Hardy 2007[143]	Evaluation of redesigned service	Type 2 diabetic patients with microalbuminuria and diabetic nephropathy	Redesigned service for the management of diabetic nephropathy and diabetics with microalbuminuria at a single diabetes clinic	Uncomplicated patients were discharged to primary care, while complicated problems were followed in dedicated hospital-based clinics. A specialist nephropathy clinic was established to focus on multifactorial interventions. Patients with diabetic kidney disease referred from primary care (or within hospital) were sent to 'new patient clinic' for assessment, consultation, education and optimisation of treatment with subsequent visits at one of the other dedicated 'nephropathy' clinics. 6–8 patients visited each clinic for approximately 35 minutes per patient. Following each of these nephropathy clinics, all patients were discussed in detail in a multidisciplinary team meeting	Diabetologists, diabetes nurse, consultant and a senior clinical fellow having access to nephrologists. Three nephropathy clinics: one led by consultant, two led by diabetes nurse specialist	Before redesigning of the service, patients with diabetic kidney disease were cared for within a 'general' diabetic outpatient clinic in secondary care which included new referrals, follow-ups and patients with a wide range of complications

Reference	Study type	Type of CKD patients	Multidisciplinary clinic	Facets of MDC programme	Staff delivering the programme	Comparator group
Harris 1998[145]	Randomised controlled clinical trial of an intensive multidisciplinary case management programme	Chronic renal insufficiency (SCr > 1.4 mg/dl)	Multidisciplinary case management clinic (general practice medicine of Regenstrief Health Center, affiliated with multispecialty outpatient facility)	The frequency of this case management clinic was every 6 months, 4 months or 3 months depending on SCr level. Intervention patient received a comprehensive programme that included medication review, compliance assessment, education, surveillance of patients, dietary counselling, social service interview and communication with primary care provider where appropriate. The use of ACE I was increased, BP control improved; use of nephrotoxic drugs and protein intake decreased, barriers to care decreased	Nephrologists, nephrology fellow, a renal nurse, a renal dietician and a social worker	Usual care Patients got usual primary care from physicians with access to nephrologists if referred to the standard renal service
Hemmelgarn 2007[146]	Retrospective cohort study, compared MDC with non-MDC	CKD stage 3 and greater	Multidisciplinary clinic in Canada (hospital based)	Programme included patient education, laboratory and clinical examinations (every 1–3 months and every 3–6 months respectively). Education session included discussion about CKD, fluid and dietary restrictions, monitoring BP, medicine management, and lifestyle modification to reduce CVD risk and delay CKD progression. Patients were provided with a booklet produced by the Kidney Foundation	Primary nephrologists (referred their patients to MDC), specialised clinic nurse, registered dietician and social worker	Non-MDC Description not reported
Jones 2006[147]	Retrospective review of SIMON programme	CKD stage 3–5	SIMON programme of Southampton, UK, that includes intensive hospital nephrology clinic (HC) and shared primary and nephrology care scheme	Initially all patients were reviewed in hospital renal clinic. Those requiring continued care were retained in HC. Stable and uncomplicated patients were enrolled in shared primary and nephrology care scheme by nephrologists, and monitored by using clinical and laboratory reviews recorded in primary care without attending renal unit. Blood and urine tests and clinical examination (BP, weight, medications, etc.) carried out every 6–12 months if necessary. Data recorded in SIMON database which was reviewed by nephrologists electronically. Nephrologists and primary care physicians communicated between each other regarding patients recall to the HC or any changes in medication. SIMON programme used a computerised graphing system that allowed visual analysis of changes in GFR and other blood test	Nephrologists, primary care physicians, nurses	NA

TABLE 19 Description of multidisciplinary care (MDC) for CKD settings and services (continued)

Reference	Study type	Type of CKD patients	Multidisciplinary clinic	Facets of MDC programme	Staff delivering the programme	Comparator group
Richards 2008[150]	Evaluation of disease management programme	CKD stages 4 and 5, and those at borderline of CKD 3/4	Disease management program of West Lincolnshire Primary Care Trust, UK	Patient education (encouraged to engage in their own care and to raise awareness of cardiovascular risk factors), medicine management, dietetic advice and optimisation of clinical management to achieve clinical targets. The programme had same the fundamentals as the multidisciplinary renal clinic but had wider scope and was proactive. There was a named nurse for each patient who could be accessed directly by telephone or face-to-face without needing an appointment. Patients received proactive intervention from the clinical team at a frequency dictated by the patient's risk assessment and/or by the patients themselves	Delivered by a community-based team of nurses, dietician and social worker	NA
Thanamayooran 2005[151]	Review of a prospective cohort	CKD patients with CrCl <60 ml/min	Multidisciplinary nephrology clinic of Halifax, Canada (tertiary care hospital)	Patients were seen annually, every 6 months or every 3 months according to the level of GFR. The service was free of charge to the patient including medical, surgical and ancillary cost. Although there was no protocol for care, consensus was set for some of the clinical parameters like BP control, using ACE Is and ARBs, metabolic control of calcium, phosphate, parathyroid hormone and control of anaemia. A large peritoneal dialysis and haemodialysis programme was maintained at this centre	Nurses, nurse-educators, social workers, dieticians and full time academic nephrologists	NA

ACE I, angiotensin converting enzyme inhibitor, ARB, angiotensin receptor blocker; BP, blood pressure; CKD, chronic kidney disease; CrCl, creatinine clearance; CVD, cardiovascular disease; GFR, glomerular filtration rate; NA, not applicable, NR, not reported; SCr, serum creatinine; SIMON, Southampton Integrated Monitoring of Nephrology.

scheme, complicated patients and those requiring continued care were retained in the hospital nephrology clinic.

The other described MDC involved referral from primary care to hospital care, or between two specialist clinics, in the usual way.[143,145,146,151,152,154]

Structured care by an individual specialty

Apart from nephrologists, CKD management has been influenced by the involvement of other health-care professionals. Pharmacy programmes included structured clinics solely led by pharmacists using protocols to manage the medication of patients with microalbuminuria and nephropathy.[148] Pharmacists also operated within structured disease management programmes implemented by pharmacists and diabetes specialists managing diabetic nephropathy patients together.[149] Joy and colleagues[156] described the support of pharmacists as part of a multidisciplinary team for the management of CKD patients. Some care programmes were run by renal specialist nurses, or renal specialists working closely with general nurses.[157,158] Two studies compared the care given in primary care with that of specialists (nephrology and diabetology) in Italy.[137,138] Care by GPs was also compared with virtual clinic management (*Table 20*).[144]

Educational intervention

Educational interventions for care in CKD were described by some of the studies. Generally, two types of educational programme were observed: education of general staff and patient education.[141,142,146,150,153–158] The education programmes varied in content and delivery style and are detailed further in *Table 21*.

Description of the key facets of the care programmes

Various facets of programmes for CKD management have been reported within the three types of care model identified. See *Table 22* for a summary of the different elements of the programmes.

Patients surveillance

Patient surveillance, including regular clinical and laboratory examinations (e.g. BP, weight, haemoglobin, calcium, phosphate, other metabolic parameters) along with medical review, was the most commonly reported element of care within all models of care. Patient clinic visits or follow-

up varied from monthly to annually depending on the level of kidney function and clinical need.[142,146,147,151,152] Appointments lasted for 30–35 minutes[143,148] and some included discussion of a patient in a multidisciplinary team meeting. Harnett and colleagues[144] reported so-called 'virtual methods' to conduct this surveillance with a patient attending a practice nurse for examinations and the results being logged for a remote specialist team to review them in the context of that patient's clinical record.[147] None of the studies described in any detail how patients were selected for inclusion in the CKD care model. Most appeared to rely on measures of eGFR (or creatinine thresholds), but there was rarely a description of why patients were originally tested (i.e. clinical need versus screening) or whether other factors were used to influence selection for further management.

Patient education

Patient education included reviewing pre-specified educational topics with patients,[142] discussion about CKD, dietary restriction, monitoring BP, medicine management, lifestyle modification,[146,150] education on dialysis[154] and discussion about clinical parameters.[153] Some CKD management programmes developed a guideline, self-care manual or performance-based programme for patient education with education classes held prior to clinics.[153] A patient-centred education and management approach was reported where renal nurses were working along with other specialists and primary care teams.[157,158]

Health-care professional education

Only three papers reported education provided to health-care professionals.[141,154,156] In two studies, primary family physicians were provided with educational sessions.[141,154] The educational intervention to physicians included lectures based on interactive theory–practice models and discussions (one-to-one or small group discussion of real cases led by investigators). Lectures included a theory course covering various aspects such as basic anatomy and physiology of kidney, epidemiology and clinical measures and advanced topics such as associated comorbidities, prevention and management.

Medicine management

With the aim of optimisation of treatment, most of the CKD programmes considered medicine management; in particular the use of ACE Is and ARBs.[145,149] Pharmacist-led structured care models included medicine management and optimisation of treatment which were based on prescribing

TABLE 20 *Description of structured care by individual specialty (SCIS)*

Reference	Study type	Type of CKD patients	SCIS	Detail of care	Comparator group
Harnett 2008[144]	Evaluation study of patients monitored in primary care compared with virtual clinic	CKD patients, all stages	Virtual care as per CKD management guidelines	Virtual care: CKD patients were monitored remotely by regular blood tests followed by sending regular reports based on their blood and urine tests (haemoglobin, urine protein:creatinine ratio, cholesterol and estimated GFR)	GPs led primary care
Joy 2005[156]	Descriptive, editorial	CKD patients, stage not specified	Physician–pharmacist collaborative practice model	Pharmacists as a part of multidisciplinary health-care team involved in CKD management. Those with specialised training in nephrology were members of national nephrology organisations (USA) and involved in following activities: • designing of CKD guidelines and practice documents • analysing and interpreting US Renal Data System data • providing continuing educational programmes to CKD patients/family member/other health-care professionals within multidisciplinary clinics • advising pharmaceutical industry or other professionals regarding use of medication in CKD population • planning of identification and management of CKD patients	NA
Kelly 2008[148]	Evaluation study of a structured care programme to manage patients with microalbuminuria and nephropathy	Patients with microalbuminuria and nephropathy	Pharmacist-led structured care (clinic)	Patients were referred to this clinic by a physician based on referral and diagnostic criteria. Patients attended the clinic four to six weekly until optimisation of their treatment (using pharmacists prescribing recommendations and clinic standards), allocated appointment time being 30 minutes. Clinical examination included checking BP, pulse, weight, lipids, renal function, liver function, HbA$_{1c}$ and early morning ACR, FBC, calcium and phosphate were also measured. A medical history and full drug history using two or more sources were completed. Knowledge of their drug treatments and smoking status were ascertained with patients. Smoking cessation services provided	NA
Leung 2005[49]	Prospective cohort study of a diabetes management programme	Type 2 diabetic nephropathy	Pharmacist and diabetes specialist-led structured care at hospital	Pharmacist, diabetes specialist implemented this disease management programme that included periodic laboratory assessments, patient adherence, risk factors control, and use of renin–angiotensin system inhibitor	Usual care Description not reported

Reference	Study type	Type of CKD patients	SCIS	Detail of care	Comparator group
Minutolo 2005[137]	Evaluation study of primary care compared with nephrology care	Hypertensive CKD patients (excluding patients with eGFR < 15 ml/min/1.73 m^2)	Primary care: led by physician	Laboratory tests within 1 week after enrolment, and clinical examination of renal disease of patient were carried out followed by a medical visit (height, weight and BP measured and recorded). Preliminary laboratory tests record and structured anonymous form provided by co-ordinator centre to physician. Physicians aware of BP targets in CKD patients	Nephrology care: nephrologists led
Minutolo 2006[138]	Cross-sectional study comparing primary care with nephrology care and diabetology care	Diabetic CKD (eGFR between 15 and 60 ml/min/1.73 m^2)	Primary care: led by physician	Medical history (including cardiovascular events), demographic data, laboratory data and current therapy data recorded at each medical visit of patient as per structured anonymous form provided by the co-ordinating centre. Physicians were aware of BP, HbA$_{1c}$ and LDL targets in CKD patients	Nephrology care: led by nephrologists; Diabetology care: led by diabetologists
Thomas 2004[157]	4-year evaluation study (ongoing study); result presented for first phase of the study	Diabetic renal disease	Nurses led management in collaboration with GP	Patient-centred management and education at south-west Thames (primary care). Diabetes care and education during GP visit and practice nurse consultations in each practice	NA
Thomas 2005[158]	A 4-year prospective study; only first year findings presented	Diabetic renal disease	Renal specialist nurse working closely with local community nurses and doctors	A patient-centred education programme at local family doctor surgeries (primary care). A renal specialist nurse working closely with local community nurses and doctors. Education provided to patient	NA

ACR, albumin–creatinine ratio; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FBC, full blood count; HbA$_{1c}$, glycosylated haemoglobin; LDL, low-density lipoprotein; NA, not applicable; SCIS, structured care by individual speciality.

TABLE 21 *Description of educational interventions*

Reference	Study type	Type of CKD patients	Setting	Detail of care	Staff involved	Comparator
Compton 2002[153]	Descriptive paper	CKD patients, stage not specified	CKD programme at Western New England Renal and Transplant Associates	Guidelines, a charting format and a self-care manual were developed. Education classes for patients and family members held twice a month. Clinical parameters (bone disease, anaemia, blood pressure, hypercholesterolemia, nutrition, acidosis and palliative care issues) addressed. CKD patients followed by nephrology team	Nephrologists and nurse practitioners	NA
Compton 2002[153]	Descriptive paper	CKD patients, stage not specified	Division of Nephrology at Virginia Commonwealth University/Medical College of Virginia, VA, USA	Development of a CKD patient education. Performance-based programme was designed that included 1-hour class every week prior to clinic for patient and family member	Nephrologists, a nurse practitioner, transplant co-ordinator, clinical social worker, nutritionist and a pharmacist. An instructional designer (pursuing her doctorate in education)	NA
Cortes-Sanabria 2008[141]	A pilot study for cluster-randomised trial	Patients with diabetes mellitus and CKD	Primary care led by family physician with educative intervention IMSS Primary Health-Care Units (Unidad de Medicina Familiar, UMF) in Guadalajara City, Mexico	An educative intervention included theory course, analytical literature review and discussion of real clinical cases led by two investigators. Clinical and biochemical examination performed at baseline, at the end of educative intervention and 6 months after intervention. All patients had routine monthly visits and management according to their primary care physician's clinical criteria	Physicians	Family physician without educative intervention
Hostetter 2003[155]	Descriptive	CKD patients, all stages	US national kidney disease education programme	Resource for patients, carers and primary care physicians. Provides information about testing, treatment and risk factors via a website. Supporting work to ensure clear targets are embedded in health-care system to support the management of CKD	Health-care professionals representing organisations involved in CKD under the umbrella of the National Institute for Health	NA

CKD, chronic kidney disease; IMSS, Mexican Institute of Social Security; NA, not applicable.

recommendations and clinical standards.[148] Medicine management included a full drug history and ascertaining patients' knowledge of their medicine treatments.[148]

Managing/preventing complications

Some of the MDC clinics focused on the management and prevention of complications associated with CKD.[146,149,150,152,154] Education on lifestyle and cardiovascular risk factors was provided to reduce CVD risk and to delay CKD progression.[146,149,150] To prevent the development of diabetic nephropathy, some care focused on screening for microalbuminuria and clinical proteinuria.[152] Ghossein and colleagues[154] mentioned that a comprehensive renal care programme included screening for, and treating, the complications of CKD such as anaemia and renal osteodystrophy. Additionally, some MDCs endeavoured to run structured screening programmes (screening for comorbid conditions, microalbuminuria or proteinuria, or to identify those to prepare for dialysis and transplant).[152,154] The separation of 'new referral' assessment from follow-up was reported to enable more focused clinics and to identify patients where no follow-up was required.[143]

Nutritional advice

Nutritional advice was provided as a part of education programmes[146,153] or as a separate element of more comprehensive care models.[145,150,154]

Social care

A few models of care included a component related to social care services.[142,145,146,151] Social care workers were involved to decrease barriers to care by interviewing patients and by direct intervention if needed.[145] Others stated that social workers were also involved in providing education to patients.[146]

Assessment of effectiveness

Clinical markers

Patients under the care of a MDC were consistently reported to have improved clinical surrogates such as BP, glycosylated haemoglobin and cholesterol when compared with before the start of treatment in the MDC (*Table 23*). Patients under the care of the SIMON programme had a significant reduction in mean BP after referral.[147] Likewise BP was improved when patients attended multidisciplinary nephrology clinics and redesigned services.[143,151] It was observed that in the redesigned service for

diabetic nephropathy patients, the mean fall in BP was −11/7 mmHg (148/80 mmHg at baseline to 137/73 mmHg at follow-up, $p < 0.001$) and 33% achieved a BP target of 125/75 mmHg.[143] Moreover, patients' glycosylated haemoglobin and low density lipoprotein cholesterol improved and there was minimal progression of microalbuminuria to diabetic nephropathy, and the proportion of patients with proteinuria fell. Similarly, in a multidisciplinary nephrology clinic, mean BP fell from $151 \pm 27/80 \pm 13$ mmHg at the initial visit to $135 \pm 18/75 \pm 11$ mmHg at follow-up of 4 years.[151]

Structured care programmes run by pharmacists resulted in clinically and statistically significant improvements in mean BP (from $150.5 \pm 19.3/79.7 \pm 10.2$ mmHg to $132.6 \pm 15.2/67.8 \pm 10.5$ mmHg, $p < 0.001$). Similar trends of significant results were observed for cholesterol and glycosylated haemoglobin in CKD patients.[148] Likewise, CKD management by collaborative approach between pharmacists and diabetes specialists proved to be beneficial with improvements in clinical surrogates (BP and low density lipoprotein cholesterol) and risk reduction of end points compared with those receiving usual care.[149] Those using educative intervention among family physicians have shown clinical improvements in BP and kidney function.[141]

Where comparator groups of patients were available, the findings were less consistent.

Curtis and colleagues[142] reported patients exposed to MDC had clinical benefits including higher levels of haemoglobin, albumin and calcium at dialysis start than those receiving standard care. Minutolo and colleagues[137] reported that hypertensive patients with CKD under nephrology care seemed to have improved BP (21.5% patients reached BP target of 130/80 mmHg, 95% CI 15.6 to 27.4, $p < 0.0001$) compared with primary care (5.8%, 95% CI 2.9 to 8.6). Patients were 2.6 times less likely to have reached their target BP in primary care versus nephrology care (after adjustment for age, diabetes and eGFR). However, in patients with diabetic renal disease, there was little difference in the proportions achieving target BP (10–14%), with similarly low levels in nephrology, diabetology and primary care.[137]

Harris and colleagues,[145] reporting the only RCT, showed no difference in weight, BP or creatinine clearance when they compared people managed in an intensive MDC management programme with those receiving standard care.

TABLE 22 *Description of key facets of care models*

References	Patient education	Health-care professional education	Medicine management	Nutritional advice	Patients surveillance	Social care service	Managing/ preventing complication	Dialysis and transplant management	Structured screening programme
Bending 2007[152]					x		x		x
[a]Compton 2002[153]	x			x	x		x		
Cortes-Sanabria 2008[141]		x			x				
Curtis 2005[142]	x			x	x	x			
Ghossein 2002[154]	x	x	x	x	x		x	x	x
Hardy 2007[143]	x		x		x				
Harnett 2008[144]					x				
Harris 1998[145]	x		x	x	x	x			
Hemmelgarn 2007[146]	x			x	x	x	x		
Jones 2006[147]			x		x				
Joy 2005[156]	x	x	x						
Kelly 2008[148]			x		x				
Leung 2005[149]			x		x		x		
Minutolo 2005[137]					x		x		
Minutolo 2006[138]					x		x		
Richards 2008[150]	x		x	x	x		x		
Thanamayooran 2005[151]	x			x	x	x	x		
Thomas 2004[157]	x								
Thomas 2005[158]	x								

a Compton includes more than one model of care.

Prescription changes

Statistically significantly higher prescriptions of renin–angiotensin aldosterone system (RAAS) inhibitor agents were noted.[143,147] Prescription rates were found to be significantly higher in specialist care than in primary care, and the choice of medicines differed.[137,138] Nephrologists were more likely to use dual blockade of RAAS using ACE Is and ARBs and were more likely to prescribe loop diuretics than either primary care physicians or diabeteologists.[138] These differences existed after accounting for clear differences in case-mix. Use of antihypertensives (including RAAS inhibitor agents) and cholesterol reducing drugs (statins) appeared to increase with the involvement of pharmacists and diabetes specialists in CKD care.[148,149] Prescription of ACE I, in those without contradictions, increased from 66% to 100%, while that of ARBs (single or in combination) increased by 29%.[148] Prescriptions for antihypertensive agents by physicians who underwent an educative intervention were higher than those by physicians without educative intervention.[141] Harris and colleagues,[145] however, reported little difference in prescribing behaviour between those cared for in intensive multidisciplinary case management and those receiving standard care.

Long-term outcomes

Long-term outcomes have been reported only for MDC models. See *Table 24* for outcomes reflecting mortality and CKD progression.

Survival or mortality

Hemmelgarn and colleagues[146] and Curtis and colleagues[142] compared MDC with standard care, reporting a significant survival advantage for those CKD patients attending MDC clinics. A significant reduction in the risk of death (adjusted) (HR 0.50, 95% CI 0.35 to 0.71) was observed in MDC patients compared with non-MDC patients by Hemmelgarn and colleagues,[146] but no difference in hospitalisation rates were reported. Similarly, Leung and colleagues[149] reported on adjusted risk reduction for mortality and ESRD (HR 0.40, 95% CI 0.23 to 0.68) for MDC compared with usual care.

Curtis and colleagues[142] noted that incident dialysis patients who had received MDC had better survival on dialysis than those in standard care. In addition, the redesigned nephropathy clinic reported lower rates of mortality than two major renal studies: RENAAL (Reduction in End points in NIDDM with the Angiotensin II Antagonist Losartan) trial and IDNT (Irbesartan in Diabetic Nephropathy Trial)

trial (2.2/100 person-years versus 6.8/100 person-years and 5.8/100 person-years respectively).[143] However, an RCT of MDC management found no significant survival advantage of CKD patients within MDC compared with usual care, despite heavy costs for various aspects of the MDC intervention group.[145]

CKD progression

Most authors reported that MDC had a positive impact on slowing CKD progression (see *Table 24*). In an MDC clinic with an SCS, the median decline in GFR slowed significantly from –5.2 (–12.8 to –1.9) ml/min/1.73 m^2/year before referral to –0.5 (–3.3 to 2.5) ml/min/1.73 m^2/year after referral ($p < 0.001$).[147] Others reported that in patients with CKD stage 3, GFR decreased at a slower rate and those with CKD stages 4 and 5 had stable eGFR throughout the 15-month follow-up while receiving care within a comprehensive renal clinic involving a multidisciplinary team.[154] The diabetes clinic taking care of diabetic nephropathy patients reported lower event rates such as doubling of serum creatinine (1.4/100 person-years) and ESRD (1.1/100 person-years) after the service was redesigned compared with previous trials on management of diabetic nephropathy: REENAL trial and IDNT trial.[143] Leung and colleagues,[149] reported that the rate of renal decline slowed in patients with diabetic nephropathy where pharmacist and diabetes specialist worked together.

Attitudes of patients/health-care providers

The service delivered by joint diabetes and renal clinics for the patients with established diabetic kidney disease at Eastbourne, UK, has been appreciated by patients and was considered to be a level of care expected by GPs.[152] Joint clinics have also been supported by NICE.[173]

The perception of Canadian nephrologists towards MDC-based CKD clinics has been presented in one survey.[159] More than 90% of nephrologists reported that MDC-based CKD clinics were easily accessible to them. Regarding decision-making on referral to MDC clinics, most (more than 80%) of the nephrologists found calculated creatinine clearance the most useful method rather than depending on estimated months before ESRD. Fifty-seven per cent of nephrologists reported that they referred patients with a creatinine clearance of 20–29 ml/min, while around 30% reported earlier referral with creatinine clearance between 30 and 59 ml/min as the best time for referral. Others referred at lower creatinine clearance

TABLE 23 Short-term outcomes

Reference	Clinical parameters	Outcomes/values [mean (SD)]				Duration of follow-up	Type of care
Cortes-Sanabria 2008[141]	BP [(systolic/diastolic) mmHg]	Physician with educative intervention: −22.0 (20.2)/−9.8 (11.3)	Physician without educative intervention: 10.8 (24.3)/2.7 (11.6)		$p<0.05$	1 year	Primary care with physician getting educative intervention
Curtis 2005[142]	Haemoglobin (g/l)	At dialysis start Standard nephrologists' care: 90 (14) MDC and nephrologists' care: 102 (18)	After 12 months post dialysis Standard nephrologists' care: 110 (17) MDC and nephrologists' care: 120 (16)		$p<0.0001$	1 year	MDC as an addition to standard nephrology care
Hardy 2007[143]	BP [(systolic/diastolic) mmHg]	At baseline: 148/80	After follow-up: 137/73	Mean fall in BP −11/7 mmHg, 33% achieved BP target of 125/75 mmHg	$p<0.001$	Mean 26 (SD 10) months	Redesigned diabetic nephropathy clinic
	HbA$_{1c}$ %	At baseline: 7.7(1.7%)	After follow-up: 7.4 (1.3%)	44% (56/127) achieved the 7% HbA$_{1c}$ target	$p=0.03$		
	LDL-C (mmol/l)	At baseline: 2.8 (1)	After follow-up: 2.1 (0.8)	81% (103/127) achieved the LDL-C target of <2.6mmol/l	$p<0.001$		
Harris 1998[145]	BP [(systolic/diastolic) mmHg]	At enrolment MDC: 143 (23)/83 (13) Usual care: 145 (26)/82 (12)	3rd through 5th year after enrolment MDC: 142 (17)/79 (8) Usual care: 145 (17)/78 (9)		Non-significant both at baseline and after 5 years	5 years	MDC vs usual care

Reference	Clinical parameters	Outcomes/values [mean (SD)]		p-value	Duration of follow-up	Type of care
Jones 2006[147]	BP [(systolic/ diastolic) mmHg]	Before referral	After referral	p < 0.001	3 years from the first referral	MDC, shared care scheme (SIMON programme)
		SC: 152/82 (read from graph)	SC: 148/80 (read from graph)			
		HC: mean 156 (29)/84 (14)	HC: 150 (21)/81 (11)			
Kelly 2008[148]	BP [(systolic/ diastolic) mmHg]	At entry to the clinic: 150.5 (19.3)/79.7 (10.2)	At exit: 132.6 (15.2)/67.8 (10.5)	p < 0.001	18 months from the entry	Pharmacist-led structured care
	Cholesterol (mmol/l)	At entry: 4.56 (1.06)	At exit: 4.03 (1.07)	p < 0.001	18 months from the entry	
	HbA$_{1c}$ (%)	At entry: 8.5 (1.7)	At exit: 8.2 (1.7)	p < 0.05	18 months from the entry	
Leung 2005[149]	Greater reductions in BP and LDL-C reported	Values not reported in abstract			2 years	Pharmacist and diabetes specialist led structured care
Minutolo 2005[137]	BP [% (95% CI)]	Nephrology care: 21.5 (15.6 to 27.4)	Primary care: 5.8 (2.9 to 8.6)	p < 0.0001	1 year	Nephrology care vs primary care
Minutolo 2006[138]	BP	Nephrology care assessment 100%, patients at goal 14.2%	Primary care assessment 100%, patients at goal 10.3%	p = 0.421	6 months	Nephrology care vs primary care vs diabetology care
			Diabetology care assessment 100%, patients at goal 13.4%			
	HbA$_{1c}$	Assessment 87.6%, patients at goal 60.5%	Assessment 45.6%, patients at goal 46.4%	p < 0.0001	6 months	
	Haemoglobin	Assessment 98.1%, patients at goal 70.9%	Assessment 81%, patients at goal 72.8%	p < 0.0001	6 months	

TABLE 23 Short-term outcomes (continued)

Reference	Clinical parameters	Outcomes/values [mean (SD)]			Duration of follow-up	Type of care
Richards 2008[150]	BP (median, IQR) [systolic/diastolic) mmHg]	Before enrolment: 139 (124–154)/76 (69–84)	After enrolment: 130 (125–145)/71 (65–79)	Target <130/<80 mmHg — Systolic: *p*=0.05; Diastolic: *p*=0.002	9 months from the enrolment	Primary care-based disease management programme
	Cholesterol (median, IQR) mmol/l	Before enrolment: 4.6 (3.9–5.4)	After enrolment: 4.2 (3.5–5.0)	Target <5 mmol	9 months from the enrolment	
Thanamayooran 2005[151]	BP[a] [(systolic/diastolic) mmHg]	Initial visit: 151 (27)/80 (13)	After 4 years of follow-up: 135 (18)/75 (11)	Initial visit *p*<0.0001 vs all subsequent years	4 years of follow-up from initial visit	Multidisciplinary nephrology clinic
	Haemoglobin (g/l)	Initial visit — Stage 3, 124 (17); Stage 4, 117 (18); Stage 5, 100 (18)	Follow-up visits — Stage 3, 123 (16); Stage 4, 116 (18); Stage 5, 107 (13)		4 years of follow-up from initial visit	

BP, blood pressure; CI, confidence interval; HbA$_{ic}$, glycosylated haemoglobin; HC, hospital care; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; MDC, multidisciplinary care; SC, shared care; SD, standard deviation.

a Reports BP during different stages of chronic kidney disease at initial visit and at follow-up. Improvement in BP decreases as the stages increases.

TABLE 24 *Long-term outcomes*

Survival/mortality

Reference	Outcomes/measure	Values	*p*-value	Comparator	Duration of follow-up	Type of care
Curtis 2005[142]	Survival advantage (Kaplan–Meier survival)	MDC Statistically significant survival	*p* = 0.01	Compared with standard nephrology care	Mean 41 (SD = 34) months	MDC vs standard nephrology care
Hardy 2007[143]	Mortality rate	2.2/100 py		REENAL trial 6.8/100 py; IDNT trial 5.8/100 py	Mean 26 (SD = 10) months	Redesigned diabetic nephropathy clinic
Harris 1998[145]	Cumulative mortality after 5 years	Intervention group: 59 (29%)	*p* = 0.29	Control group: 77 (33%)	5 years	Multidisciplinary case management clinic
	Survival advantage	HR[a] 0.90, 95% CI 0.71 to 1.14	*p* = 0.36	Compared with control group		
Hemmelgarn 2007[146]	Death	MDC: 61 (32.6%)		Non-MDC: 77 (41.2%)	3 years	MDC compared with non-MDC
	Reduction in the risk of death	HR[b] 0.50, 95% CI 0.35 to 0.71		Compared with non-MDC	3 years	
	Hospitalisation	123 (65.8%) at least one hospitalisation		131(70.1%) at least one hospitalisation	3 years	
	Reduction in the risk of hospitalisation	HR[b] 0.83, 95% CI 0.64 to 1.06	*p* = 0.18	Compared with non-MDC	3 years	
CKD progression						
Ghossein 2002[154]	GFR decline	CKD stage 3: calculated GFR decreased during the first 7.5 months and then continued to decrease albeit at a reduced rate. CKD stages 4 and 5: stabilised throughout the 15 months of follow-up. Presented in a graph. No values given				Comprehensive renal care clinic called Healthy Living
Hardy 2007[143]	Rate of doubling of serum creatinine	1.4/100 py		REENAL trial 7.9/100 py; IDNT trial 3.9/100 py	Mean 26 (SD = 10) months	Redesigned diabetic nephropathy clinic
	Rate of ESRD	1.1/100 py		REENAL trial 6.8/100 py; IDNT trial 5.4/100 py	Mean 26 (SD = 10) months	

TABLE 24 Long-term outcomes *(continued)*

Survival/mortality

Reference	Outcomes/measure	Values		p-value	Comparator	Duration of follow-up	Type of care
Jones 2006[147]	Decline in eGFR, ml/min/1.73 m² (median, IQR)	Before referral: −5.2 (−12.8 to −1.9) SCS<6 months: −2.7 (−9.4 to −1.3) SCS>6 months: −4.1 (−11.3 to −1.4) HC: −6.2 (−13.9 to −2.4)	After referral: −0.5 (−3.3 to 2.5) SCS<6 months: −0.3 (−2.7 to 1.4) SCS>6 months: 0.1 (−1.2 to 1.7) HC: −0.9 (−5.2 to 3.4)	p<0.001		5 years	MDC, shared care scheme (SIMON programme)
Richards 2008[150]	Decline in eGFR, ml/min/1.73 m² (median, IQR)	Before enrolment (preceding 9 months) −3.69 (−7.46 to −1.49)	After enrolment (subsequent 12 months) 0.32 (−2.61 to 3.12)	p<0.001		12 months from the enrolment	Primary care based disease management programme
	Patients with decline of eGFR ≥5 ml/min/1.73 m² (median, IQR)	Before enrolment −9.90 (−12.36 to −6.55)	After enrolment −1.70 (−6.41 to 1.64)	p<0.001		12 months from the enrolment	
	Preservation of renal function (as per CKD stages)	Stage 3 to stage 2 = 3 patients; stage 3 to stage 3 = 103 patients; stage 4 to stage 3 = 1 patient; stage 5 to stage 4 = 4 patients; stage 5 to dialysis = 8 patients	Stage 3 to stage 4 = 15 patients; stage 4 to stage 5 = 1 patient;			12 months from the enrolment	

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HC, hospital care; HR, hazard ratio; IDNT, Irbesartan in Diabetic Nephropathy trial; IQR, interquartile range; MDC, multidisciplinary care; py, person-years; REENAL, the Reduction in End points in NIDDM with the Angiotensin II Antagonist Losartan; SCS, shared care scheme; SD, standard deviation; SIMON, Southampton Integrated Monitoring of Nephrology.
a Adjusted for age, sex, race, enrolment at serum creatinine level, plus height and pulse at the enrolment visit, assignment to the intervention group.
b Adjusted for age, gender, baseline GFR, diabetes, and comorbidity.

(10–19 ml/min). The survey also presented information about perceptions of the availability of multidisciplinary staff. More than 90% of nephrologists reported that they had excellent access to nurses, dieticians and social workers. Around 64% believed that pharmacists were comparatively less commonly available. According to nephrologists' opinion, nurses provided more information about dialysis to patients than about palliative care, prognosis or pre-emptive transplant.

Overall, nephrologists (94.5%) believed that MDC-based clinics were superior to conventional clinics. Most of them (83%) also thought that this kind of clinic could be managed by nurses using algorithms, thus helping to reduce the burden on nephrologists. They were supportive of the value of MDC clinics for those with stable and slowly progressing CKD but reported that the clinics were not sufficiently funded.

Aspirational model of care

Fourteen papers describing aspirations for the care of patients with CKD were reviewed.[159–172]

Two broad categories of aspirations for care were described:

- optimal management of CKD patients
- integrated approach for CKD management.

Optimal management

Four papers proposed similar ranges of strategies of care for the management of early CKD patients that they hoped would lead to improved outcomes.[160–163] The emphasis was on early detection of CKD and associated comorbid conditions. The proposals focused mainly on the need for delaying CKD progression, and preventing or treating complications by using timely intervention. Importantly, these papers identified the need for precise measures to stratify CKD patients into groups that may help to predict future risks. Patient education, to increase awareness of CKD and risk of comorbidities in CKD, was recommended as a part of optimal management. Moreover, two papers highlighted the importance of having co-ordinated care for the management of early CKD.[162,164]

Authors proposed that implementing the strategy of optimal management and early detection of the disease may help reduce hospitalisation, morbidity and mortality, and eventually help to reduce cost.

For example, identifying comorbid conditions like anaemia and CVD at earlier states, and treating them, may reduce the risk of future morbidity and mortality. Controlling BP, proteinuria and other metabolic parameters may reduce the risk of CKD-related comorbidities. Authors were proponents of the use of ACE Is and ARBs, identifying CKD at earlier stages and referring patients to the nephrologists to slow CKD progression. The use of existing data from patient database systems to develop an intervention programme to optimally managed CKD patients was suggested.[160]

Integrated approach for management

Seven papers proposed the advantages of collaborative approaches in CKD management.[164,165,167–172] Involvement of multidisciplinary staff (GPs with specialist interest, specialist nurses, pharmacists, nutritionists, etc.) and co-operation between these staff may aid early referral and management. The key role of nurses was highlighted as: patient educators, care managers communicating between care providers and support staff, and following up patients to monitor their progression.[166–168] Four of the papers suggested that patients should be managed and evaluated in primary care by skilled support staff, with only complex or severe cases referred to specialists or nephrologists in secondary care.[166,168,171,172] Furthermore, they noted the importance of care plans being developed based on evidence-based practice guidelines. Recognition that CKD was a chronic and complex condition was found to be useful in supporting collaboration and education needs.[164] The proponents of an integrated approach for management also hoped that it would contribute to reducing mortality and hospitalisation and delaying progression. Moreover, this co-operative care potentially provided a mechanism to deliver optimal management of CKD at early stages and thus increase quality of care and improve quality of life of patients while reducing cost.

Similar to the above proposals, *A vision for the future of renal services*, 2002[126] also focused on prioritising early diagnosis and treatment of those with CKD and those who were at risk of developing CKD. The authors recommended the need for clinical networks as a model of future services provision. Details of the network focused on preparation for end-stage disease and those with progressive renal disease, but did note the need to integrate services across disciplines and to deliver a flexible and appropriate care for the individual patient's needs. They also noted the need to tackle inequalities,

giving attention to the elderly, children, socially disadvantaged, ethnic minorities and those with comorbidity.[126]

Key themes from aspirational proposals

Thematic review of the aspiration studies identified the following key elements to care:

Strategy for early detection

Early identification of CKD and those who are at risk of CKD was seen as critical. Screening was discussed in the context of using eGFR and albuminuria in diabetes. Screening of higher risk group patients (> 65 years of age, any form of CVD, diabetes, a family history of CKD, hypertension) was noted and development of new screening strategies focused on the link between CKD and CVD.

Measures for defining at risk groups

Although CKD could be defined in terms of serum creatinine or urinary albumin levels, GFR estimation was proposed as the most precise measure to stratify CKD risk. High risk patients such as those with CVD, hypertension and diabetes were recognised. Urinary albumin was noted to be an important, and independent, risk factor.

Strategies for delaying progression

There was a focus of attention on development and implementation of strategies to delay progression. The need to determine individualised information about a patient's probability of progression to renal end points was a priority. Identifying comorbid conditions, with timely intervention to prevent and manage these complications, was also considered crucial. Authors cited various examples of 'effective drug therapy': some antihypertensives agents (ACE Is or ARBs), antilipaemic agents (statins) to halt disease progression, and treating anaemia.

Co-ordinated care

The need for co-ordinated care tailored to the patients needs was recognised. Delivery was dichotomised between the need for nephrology specialist input versus primary care. Vision of shared care models utilising multidisciplinary skill sets needed high levels of co-ordination, but offered a potential way to reduce the burden on secondary care while ensuring high-quality patient care.

Patient education

It was highlighted that patient participation in his or her own care was essential for optimal management of chronic diseases. Increasing patient awareness of CKD and associated risk factors may help reduce the development of irreversible renal damages and other complications.

Discussion

Currently, specialist renal care is widely delivered through multidisciplinary teams in secondary care, and while attention is shifting towards how to care for the many people with evidence of CKD, the focus remains on the more intensive care needs of those with advanced CKD. Integration of specialist renal care with primary care was not a major feature in the UK, beyond that of referral; although at the time of the surveys there was evidence that some shared care practices were being developed. Since the last survey, CKD was introduced into primary care QOF targets and CKD care in the UK has been undergoing a period of substantial change. In this chapter we sought to explore the literature for evidence of other models for delivering care to people with CKD who did not rely solely on early referral to a specialist nephrologist. While a number of models of care were described in the literature, disappointingly, only one RCT evaluating the effectiveness of different care models was identified.[145]

Three principal models of care were reported:

1. Multidisciplinary clinics – very much developed along the lines of those for dialysis patients, but generally restricted to secondary care. Only two studies reported a primary care-based MDC where specialists and primary care practitioners worked together to deliver care to people with CKD.[147,150] These adopted a secondary care-led approach, using primary care only as a vehicle to obtain routine monitoring and referral but with most decision-making driven by specialists. In some, the wider determinants of health were addressed through support from social workers facilitating access to care and financial services, and from a range of professionals providing health lifestyle advice.
2. Structured care delivered by individual specialties – a number of papers reported the often protocol driven utilisation of particular clinical specialists to deliver components of care for people with CKD. The roles of pharmacists, nurses, nutritionalists and other medical specialists (diabetologists) were all described.
3. Educational initiatives – either directed at health-care professionals or for the patients

and carers. Education was recognised as being key in underpinning the delivery of a service, although some of the MDCs reported little about the value of working together across specialties as a method for education of health-care practitioners.

However, the division, while assisting in classification and description of the types of intervention, was somewhat artificial in practice with an overlap in approaches reported for the more comprehensive care packages. Nonetheless, a substantial number of the reports described services that appeared to adopt a single model operating in isolation.

Many of the MDC reports described the separation of CKD clinics from other renal services including, in some cases, from new referrals. Where reported, clinics offered high intensity of care but with low throughput of patients; a challenge when trying to deliver care for large numbers of patients.

While information technology (IT) systems would undoubtedly have supported many of the clinics described, the innovative use of IT and virtual follow-up through the review of clinical data by a specialist, remote from the patient, was also reported. The time taken to review these 'virtual' records was not described and, in the absence of an RCT and long-term follow-up, the potential safety and effectiveness of this approach could not be assessed. Others utilised multidisciplinary meetings to discuss patients' care and management, remote from the patient. Again, the time taken to undertake this work was not described.

Regardless of the care model adopted or the attributes of the model, there was evidence of positive effects with regard to clinical markers and long-term outcomes from observational studies reliant on 'before and after' study designs. One cohort study comparing MDC to standard care did report benefit[142] but the only RCT[145] found no evidence of improvements in clinical parameters, long-term survival or renal progression; a lack of benefit despite substantial additional cost. In other clinical settings, however, intensive and aggressive risk factor management has been demonstrated to be of clinical benefit in RCTs. The Steno-2 study,[174] in people with diabetes and microalbuminuria, randomised people to intensive management of their diabetes and cardiovascular risk factors versus standard best practice. The clinical setting was the same, only the interventions differed between groups. Here, patients receiving intensive diabetes

management had better cardiovascular (HR 0.47 for CVD, 95% CI 0.24 to 0.73) and renal outcomes (HR 0.39 for nephropathy, 95% CI 0.17 to 0.87) after follow-up of 7.8 years.

So, despite universally promising results from observational data and evaluations, the only clinical trial has failed to demonstrate clinical benefit.

All of the models that provided some level of evaluation had methodological issues. Many of the studies were descriptive, relying on individual patient clinical findings at referral versus after care for a given period. If referral reflected the first recognition and proactive management of the person's CKD, then improvements in various clinical parameters might be expected regardless of where or how that care was given. Where evaluations of a new service were conducted, most relied on evidence of change in care or clinical parameters compared with before entry into the care programme. Without a comparator group, it is difficult to interpret the changes observed in both these study designs. Regression to the mean may account for some of the changes observed. The effect of the model of care on health outcomes is difficult to assess.

Evaluations against a control group provided this comparison but, where made retrospectively, were vulnerable to bias and gave little detail of the care received by patients. Harris and colleagues[145] reported the only RCT of a nephrology case management intervention compared with standard care (general practice plus referral to specialist standard renal care as per normal) and, unlike the positive findings of other studies, they found no difference in the outcomes of patients receiving MDC care versus standard care. Despite being a reasonable quality RCT, with very similar groups at baseline, the two care models ran in the same hospital outpatient unit. Staff were independent but the opportunity for 'contamination' between the two groups was high. Indeed, the number of visits to the unit was similar in the intervention and standard care arms.

The review of aspirational literature identified a dichotomy in thinking about CKD management perhaps not truly reflected in the evaluation studies to date. Like the evaluation literature, there was a strong sense from many authors describing a vision for future services of the need for specialist nephrology input at the earliest opportunity in order to minimise the risk of renal disease progression. Others, however, described

an approach more consistent with chronic disease management and the recognition of the need for a collaborative approach across disciplines; utilising the skills to deliver enhanced care to large numbers of people with the intensity and skill mix tailored to suit the individual patient's clinical requirements. Notably, this literature rarely identified the uncertainty regarding what interventions work, or the lack of good quality evaluations or trials. The authors consistently reiterated beliefs and assumptions.

In this chapter we have drawn together a body of literature describing a range of potential models of care for people with CKD, beyond that of early referral to nephrologists. We have noted a number of limitations. The diversity makes this literature difficult to identify when searching both in finding search terms sufficiently broad as to find the range of care models but also when seeking publications. We have restricted searches to published literature. Additional descriptive literature is likely to exist in grey literature sources and this will have been omitted here. We are, however, confident that any trials would have appeared in published form. Data extraction was undertaken by a single reviewer using a piloted template and checked by a second reviewer. The themes reported here were developed iteratively by one reviewer as the data were analysed and checked by a second reviewer.

Conclusions

A range of different models or components of care were reported in the literature and there was some evidence of an impact on surrogate end points such as BP control and renal progression. Authors reported aspects of care that fitted well within the chronic disease care model: the need for multidisciplinary teams; good communication between clinical staff involved in care and with patients; the role of self-care and education; and the utilisation of other allied health-care professionals to deliver aspects of care. However, the literature also identified the challenge of polarisation of attitudes towards care: specialist care delivered by early referral to specialists in kidney disease versus a shared care and collaboration approach based on increasing the skills of a wider pool of health-care professionals. While tackling CKD in the context of diabetes and diabetes services was discussed, we did not identify literature reporting on approaches to tackle CKD as part of a group of conditions that increase the risk of CVD. There was once again a striking lack of high-quality trials of effectiveness. The components of the models of care reported here provide a useful source of information about the feasibility of delivering aspects of care; pilots of potential models. The only controlled trial reported compared an MDC clinic with standard
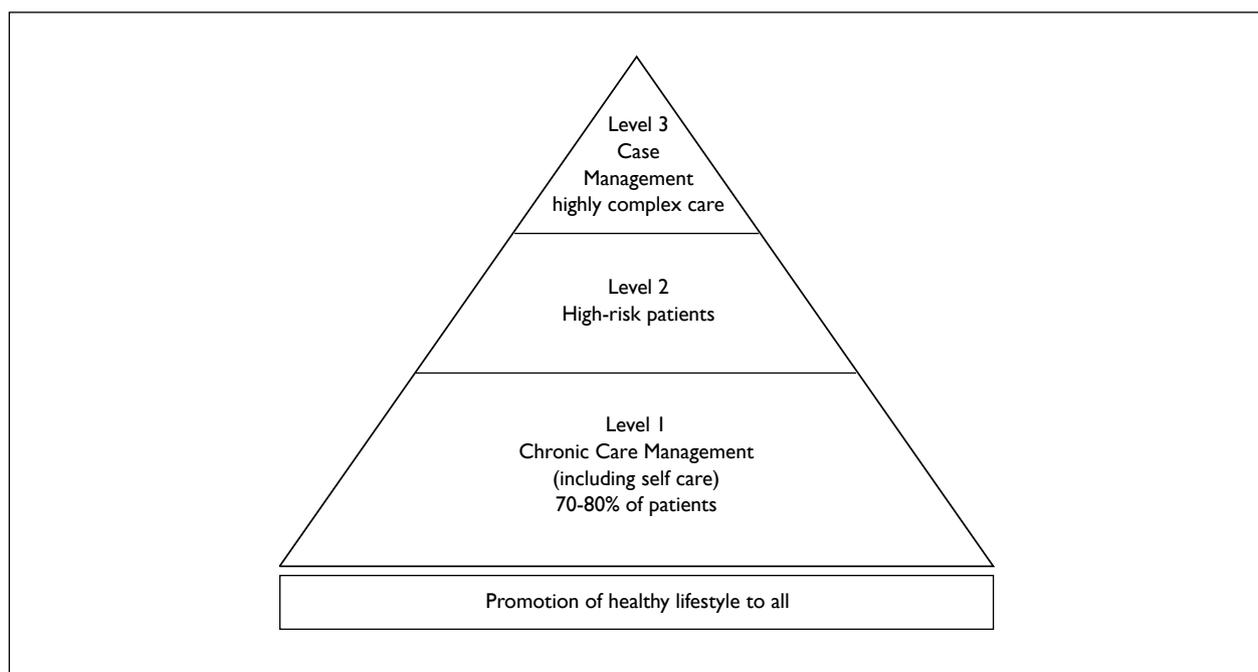
FIGURE 7 *Pyramid model of population health management for long-term conditions. [Adapted from Department of Health (2004)* Improving Chronic Disease Management.*]*[177]

case management care and found little evidence of improvements in patient care.[145] This perhaps reflects the fact that only a minority of patients have highly complex needs that gain substantial benefits from the very structured input of formal case management from an MDC (*Figure 7*). For many, a more straightforward care package may be optimal and, for most, education and supported self-care may be all that is required. Indeed, much of this care and education would be generic to a number of chronic conditions (diabetes, CVD and hypertension), and a combined approach that acknowledges this overlap could be trialled. Such an approach could then dovetail with screening programmes that seek to identify people at increased cardiovascular risk.[175,176] The challenge, then, is to be able to identify who requires which

level of care and to ensure that people can move between levels to access the most appropriate care for them at the appropriate time. The identification of the relatively small, but important, group of people with rapidly worsening kidney function, acute kidney injury and specific renal diagnoses that are both treatable and reversible will also be critical to the success of any intervention.

The literature described here could be viewed as feasibility studies, and any future trial of models for the management of CKD should draw on these approaches. It seems likely that a successful model of care will draw on a range of health-care skills and disciplines. High-quality RCTs are needed to assess the effectiveness of any such intervention.

Chapter 6
Cost-effectiveness and economic modelling

The aim of this chapter is to assess the existing evidence relating to the long-term cost-effectiveness of early referral strategies for patients with markers of renal disease, and to develop a new economic model to assess the cost-effectiveness of early referral strategies from the perspective of the NHS. The chapter focuses on the cost-effectiveness of interventions in individuals with non-diabetic CKD, as formal care pathways are already established for individuals with diabetes and diabetic nephropathy.

Review cost-effectiveness studies

Systematic searches of the literature revealed no studies that directly matched our inclusion criteria. Two studies were identified that assessed the cost-effectiveness of screening for proteinuria[178,179] and one study assessed the cost-effectiveness of nephrology referral for patients with late stage 4 CKD.[180] The findings of these studies are summarised briefly below.

McLaughlin and colleagues[180] developed a Markov model assessing the cost per life-year of nephrology referral for patients with a creatinine clearance rate of 20 ml/min (equivalent to late stage 4 CKD) compared with nephrology referral upon development of uraemia. The analysis was conducted from the perspective of the Canadian health-care provider, over a 5-year time horizon. Applying rates of renal function decline of 5.6 ml/min/year and 7.7 ml/min/year in the referral and control arms respectively (using data obtained from Canadian cohort studies), the model predicted that earlier referral would increase survival and life-years free of dialysis, and be cost saving from a health service provider's perspective. This was based on an effect estimate obtained from a prospective study that showed education could increase dialysis free survival by an average of 4.6 months in patients with deteriorating renal function.[181] The model took into consideration ACM and total costs of care, but it is unclear whether the model captured potential differences in costs associated with cardiovascular morbidity between the two groups.

Boulware and colleagues[179] conducted a modelling study to assess the cost-effectiveness of screening for proteinuria using dipstick urinalysis in adults with neither hypertension nor diabetes, and in adults with hypertension. The authors developed a Markov model that tracked renal function decline in individuals with proteinuria identified through screening, compared with renal function decline in individuals with undetected proteinuria. Those identified through screening were assumed to be treated with ACE Is which slowed progression of renal insufficiency by 30% and reduced ACM by 23%; the RR reductions were taken from a systematic review of RCTs. The study concluded that screening for proteinuria would not be cost-effective in individuals with neither hypertension nor diabetes, but would be cost-effective in individuals with hypertension [incremental cost-effectiveness ratio (ICER): US$18,621 per quality-adjusted life-year (QALY) (£11,232/QALY)]. However, the model did not appear to consider cost savings or utility gains associated with the prevention of cardiovascular morbidity.

Atthobari and colleagues[178] subsequently conducted a cost-effectiveness analysis of screening for albuminuria that did take into consideration the effects of ACE Is on cardiovascular events. The economic evaluation was based on data from the Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT); a study that assessed the effect of fosinopril (an ACE I) on the incidence of cardiovascular events in individuals with albuminuria (> 15 mg/day), normal BP ($< 160/100$ mmHg) and normal cholesterol.[182] The study considered the costs of screening for albuminuria and treating identified cases with fosinopril, and the hospital costs associated with CVD events over a follow-up period of 46 months. Based on a non-significant risk reduction for CVD events associated with fosinopril (HR 0.87, 95% CI 0.49 to 1.57), the authors estimated that screening for albuminuria would cost €16,700 (£14,671) per life-year gained. Using bootstrap resampling to assess uncertainty, the authors estimated a 59% chance of the ICER falling below a willingness-to-pay threshold of €20,000 (£17,570) per life-year gained.

In addition to the above studies assessing cost-effectiveness of screening for proteinuria, a number of studies have assessed the cost-effectiveness of using ACE Is and ARBs in individuals with renal insufficiency. Most of these studies have been carried out for individuals with diabetes, and have found the use of these medications to be cost saving or highly cost-effective.[183–187] However, a few studies have also looked at the cost-effectiveness of ACE Is in individuals with non-diabetic nephropathies and have reported similar findings.[188,189] These studies demonstrate the potential for non-diabetic CKD management to be improved.

A report to Kidney Health Australia, identified through searches of grey literature, also suggests that improved treatment for individuals with hypertension, proteinuria, and or diabetes may offer a cost-effective option for preventing the incidence of CKD and ESRD.[190] This study made use of Markov models to assess the cost-effectiveness of various improved treatment and screening strategies for hypertension, proteinuria and diabetes. The authors concluded that intensive treatment for individuals with hypertension (without diabetes) would cost ~A\$15,589 (£8247) per QALY gained, compared with standard management. They also suggest that screening for hypertension, proteinuria and diabetes would offer a cost-effective approach to reducing morbidity and mortality associated with CKD. These cost-effectiveness estimates were modelled using data from trials of individual clinical interventions (addition of ACE Is for diabetics, intensive glycaemic control for diabetics, intensive management for individuals with hypertension, and ACE Is for those with proteinuria) and do not explicitly imply the involvement of early referral to a nephrologist.

In addition to the above economic evaluations, a number of costs of illness studies were identified through our literature searches. These studies have been reviewed by Khan and Amedia.[191] Most were based on the retrospective analysis of insurance claims of individuals with CKD in the USA. A consistent finding was that health-care expenditures increase markedly through the stages of CKD to ESRD – mainly as a result of higher rates of hospitalisations due to comorbidities. The costs peak upon transition to ESRD requiring the initiation of RRT. This pattern of expenditure demonstrates the potential for early interventions that slow CKD progression and reduce the incidence of cardiovascular events.

Economic modelling

Model structure

A Markov cohort model was developed to represent the natural history of CKD using TREEAGE PRO 2008 (*Figure 8*). Direct health service costs under current practice were then incorporated into the model. Following this, alternative early referral strategies were superimposed on top of the baseline model, and relative costs and consequences were assessed.

The states of the model are based on the stages of CKD as defined by the KDOQI,[20] although stages 1 and 2 were combined to form a single state (eGFR $\geq$ 60 ml/min/1.73 m^2) with microalbuminuria or overt proteinuria used as the defining marker of kidney damage, and stage 3 was separated into two states: CKD 3a (eGFR 45–59 ml/min/1.73 m^2) and CKD 3b (eGFR 30–44 ml/min/1.73 m^2).

In addition to the core CKD states described above, further states were defined to keep track of comorbidities known to influence CKD progression and/or the incidence of cardiovascular events; ACR 30–299 mg/g, ACR $\geq$ 300 mg/g and prevalent CVD. States were also defined to keep track of cardiovascular mortality and mortality from other causes.

Cohort simulation was used to analyse the model, based on annual transition and event probabilities estimated from the literature. Within each cycle of the model, proportions could die from other causes, experience fatal cardiovascular events, experience non-fatal cardiovascular events and develop ACR 30–299 mg/g and ACR $\geq$ 300 mg/g. A representation of the model structure is presented in *Figure 8*. Details of the model cohort, transition probabilities, and incorporated costs are described below. In developing the natural history model we selected the most appropriate studies from the natural history review (see Chapter 3), where quality was deemed to be adequate and reporting allowed the relevant variables to be extracted.

Cohort details

The starting point for the analysis was taken as a cohort of individuals identified as having CKD in a primary care setting, but as yet unknown to nephrology services. People with diabetes were excluded from the analysis, as in the UK they already receive annual checks for kidney disease, have a structured care programme and are more likely to be on appropriate treatments than individuals with CKD without diabetes.
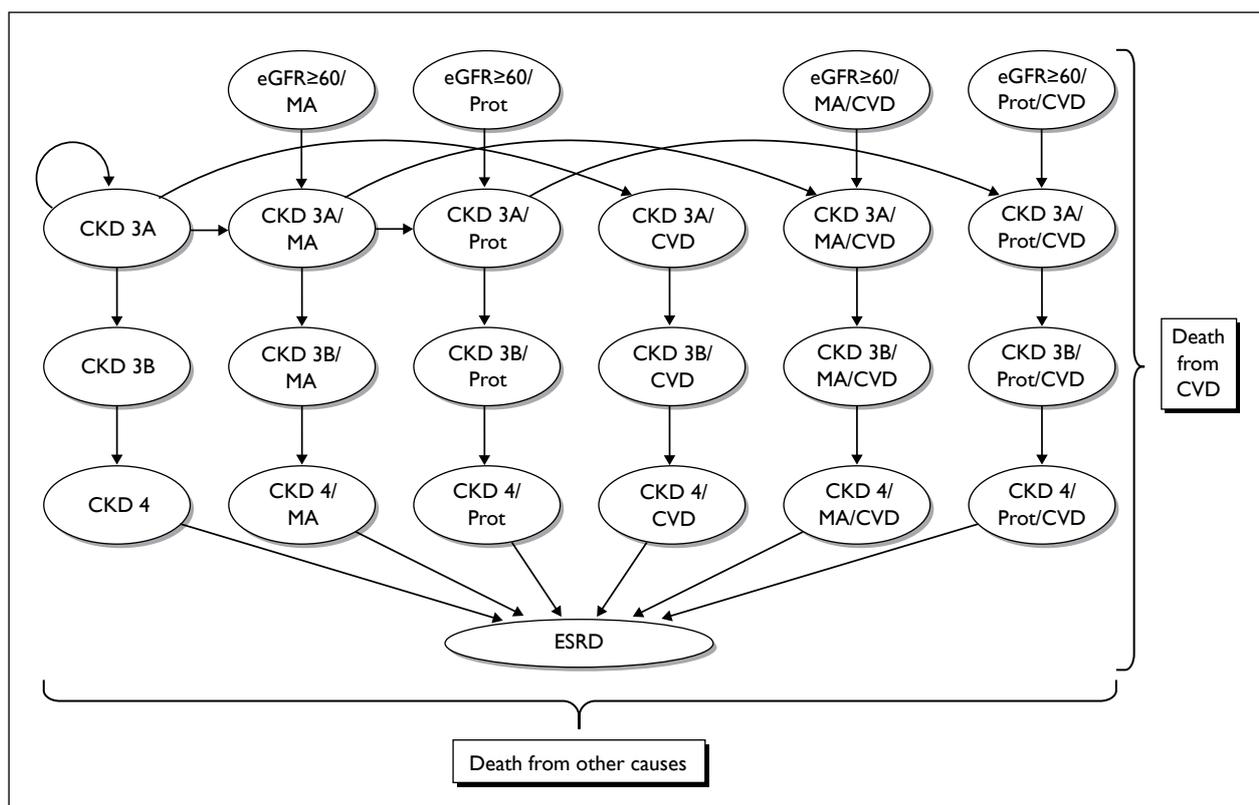
FIGURE 8 *Representation of the Markov model structure. As well as transiting down through the CKD stages, individuals can transit across the comorbidity states as they develop microalbuminuria, proteinuria and CVD. Individuals in all states can die from CVD or other causes in any cycle of the model. Not all of the possible transitions are marked on the diagram (individuals with stage 3b and stage 4 CKD can also transit to microalbuminuria, proteinuria and CVD states).*

As we wanted to model cardiovascular events and CKD progression according to patient history, i.e. levels of urine albumin/protein and CVD status, we attempted to identify demographic and CVD risk profile data for cohorts stratified by these variables.

In order to build up a picture of the demographic/risk characteristics for the cohort strata of interest, we used a UK study reporting demographic information and cardiovascular risk factors for 11,731 individuals with reduced eGFR, collected as part of routine practice from 17 primary care practices across Kent, Surrey and Greater Manchester (*Table 25*) in the UK.[192] This study also reported proportions with diabetes and pre-existing CVD. In addition we assumed that 32% of the cohort would have an ACR ≥ 30 mg/g, as reported for a US cohort identified through population screening,[193] and that the mean cholesterol–high-density lipoprotein ratio would be 5.1.[194]

We then stratified the original cohort by ACR level (< 30 mg/g; ≥ 30 mg/g), pre-existing CVD (yes; no) and diabetes status (yes; no) using

adjustment factors estimated from a number of studies where individuals with CKD had been cross-classified by these variables (*Table 26*). For example, when stratifying the cohort by ACR level, the proportion of people with hypertension was calibrated to be 1.34 times higher in the 31.8% with an ACR ≥ 30 mg/g than in the 68.2% with an ACR < 30 mg/g.

Further to the adjustments outlined in *Table 26*, it was assumed that systolic BP would be 5 mmHg higher, and the total cholesterol/high density lipoprotein ratio 0.2 units higher in individuals with an ACR ≥ 30 mg/g, CVD or both.[195,196] Finally, in removing people with diabetes from each of the strata, adjustments were made to reflect the fact that BMI tends to be higher in these individuals.[197] The estimated cohort profiles for the four strata of interest are presented in *Table 27*.

Transition probabilities

CVD risk estimation
Annual cardiovascular event risks for the different disease states were built up through a staged

TABLE 25 *Demographics, cardiovascular risk factors, and comorbidities in a cohort with eGFR 15–59 ml/min/1.73m²*

	n = 11,731	Proportion
Demographics		
Male	3949	0.337
Female	7782	0.663
Characteristics		
Age (mean) years	72	
BMI (mean) kg/m²	27.48	
SBP (mean) mmHg	139.71	
Comorbidities		
Diabetes	1568	0.134
Hypertension	8839	0.753
Treated hypertension	5739	0.649
All CVD (IHD, PVD, HF, cerebrovascular disease)	3691	0.315

BMI, body mass index; CVD, cardiovascular disease; HF, heart failure; IHD, ischaemic heart disease; PVD, peripheral vascular disease; SBP, systolic blood pressure.

TABLE 26 *Factors used to adjust cohort characteristics based on reported differences between subgroups defined by the presence/absence of comorbidities in people with eGFR 15–59 ml/min/1.73 m²*

Comorbidity	With comorbidity	Without comorbidity	RR ratio	Source
ACR ≥ 30 mg/g				
Hypertension (%)	78.3	58.3	1.343	Foster 2007[195]
Diabetes (%)	34.9	9.9	3.525	Foster 2007[195]
CVD (%)	38.6	16	2.413	Foster 2007[195]
% male	63.9	47.2	1.354	Foster 2007[195]
Prevalent CVD				
Hypertension (%)	84.3	62.1	1.357	Weiner 2006[196]
Diabetes	24.2	13.9	1.741	Weiner 2006[196]
% male	49.9	33	1.512	Weiner 2006[196]
Diabetes				
Mean systolic BP (mmHg)	146	144	1.014	Gerstein 2000[198]
Hypertension (%)	91.5	89.3	1.025	Lorber 2006[197]
Mean BMI	31.2	27.6	1.130	Lorber 2006[197]

ACR, albumin–creatinine ratio; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; RR, relative risk.

TABLE 27 *Estimated demographic and risk profiles for people with reduced eGFR stratified by albuminuria status and prevalent CVD*

	eGFR 15–59 ml/min/1.73 m²			
	ACR < 30 mg/g with no CVD	**ACR < 30 mg/g with CVD**	**ACR ≥ 30 mg/g with no CVD**	**ACR ≥ 30 mg/g with CVD**
Demographics				
Male (%)	0.272	0.412	0.323	0.489
Female (%)	0.728	0.588	0.677	0.511
Age (mean) years	72	72	72	72
Risk characteristics				
BMI (mean) kg/m²	27.0	27.0	27.0	27.0
SBP (mean) mmHg	137.4	142.4	142.4	142.4
Cholesterol–HDL ratio	5.0	5.2	5.2	5.2
Comorbidities (%)				
Hypertension	62.9	85.5	81.5	100.
Treated hypertension	40.8	55.5	52.9	64.9
Annual CVD event risk from QRISK2	3.0	3.5	3.3	3.6

ACR, albumin–creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; SBP, systolic blood pressure.

approach. Annual base risks were first estimated for each cohort stratum using the demographic/ risk profiles in *Table 27* and the QRISK2 (ClinRisk Ltd, University of Nottingham, UK) web-based risk calculator.[199] This is based on a CVD risk algorithm which has been developed and validated for the general population of England and Wales.[200] Adjustments were made for gender and the proportion of people with hypertension within each stratum. These risk estimates reflect the average annual probabilities of cardiovascular events in cohorts with these risk profiles, without CKD or pre-existing CVD. Included in the definition of CVD events are coronary heart disease (angina and myocardial infarction), stroke and transient ischaemic attacks. Although there is likely to be a tendency for those with an ACR ≥ 30 mg/g or with CVD to be older than those with CKD alone, we assumed a constant age of 72 years across the strata when calculating base risks for incorporation in the model. This is because Markov models have to be analysed for cohorts of a single age. In addition, the effect of increasing age on cardiovascular events was incorporated in the model using an HR for increasing age (see below).

Following estimation of the base risks, we estimated annual probabilities of CVD events for each disease

state by multiplying the base risks by RRs and/ or HRs for CVD events associated with reduced eGFR, ACR 30–299 mg/g, ACR ≥ 300 mg/g and pre-existing CVD (*Table 28*). The RRs associated with reduced eGFR, ACR 30–299 mg/g and ACR ≥ 300 mg/g were obtained from a study based on data from NHANES III.[84] This study reported RRs for cardiovascular mortality by eGFR category (15–59 ml/min/1.73 m², 60–89 ml/min/1.73 m² and ≥ 90 ml/min/1.73 m²) and ACR levels (< 30 mg/g, 30–299 mg/g and ≥ 300 mg/g). We assume that the RRs for any CVD event (fatal and non-fatal) would be similar. The RRs were adjusted for all the factors in *Table 27* used to generate the base risks.

To estimate the increased risk of cardiovascular events in people with pre-existing CVD, we used an adjusted HR associated with prevalent CVD based on data reported by Parikh and colleagues.[194] We estimated the HR inferred by existing CVD in people with CKD by dividing the HR associated with having CKD and CVD by the HR associated with having CKD without CVD.

In order to incorporate the increased probability of cardiovascular events with increasing age, we incorporated an HR for CVD events associated with a 10-year increase in age.[196] The HR was adjusted

TABLE 28 *Adjusted HRs and RRs used to estimate risks of cardiovascular events for each discrete morbidity state in the model*

Morbidity/comorbidity	HR or RR	95% CI	Source
CKD 1 and 2 (ACR 30–299 mg/g)	2.19	1.45 to 3.29	Astor 2008[84]
CKD 1 and 2 (ACR ≥ 300 mg/g)	3.40	0.99 to 8.28	Astor 2008[84]
CKD 3–4 (ACR < 30 mg/g)	2.36	1.67 to 3.34	Astor 2008[84]
CKD 3–4 (ACR 30–299 mg/g)	3.01	2.04 to 4.42	Astor 2008[84]
CKD 3–4 (ACR ≥ 300 mg/g)	4.35	2.39 to 7.90	Astor 2008[84]
Pre-existing CVD (HR)	1.38		Parikh 2008[194]
HR for 10-year increase in age	1.57	1.46 to 1.69	Weiner 2006[196]

ACR, albumin–creatinine ratio; CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; RR, relative risk.

for pre-existing CVD and CKD and other classical risk factors.

When using HRs to estimate annual event probabilities, base risks were converted to average rates before being multiplied by HRs, and then converted back into risks (probabilities). The resultant annual CVD event risks for each disease state in the model are reported in *Table 29*.

The risk estimates reported in *Table 29* represent approximations of the annual risk of experiencing any CVD event (fatal and non-fatal myocardial infarction, angina, fatal and non-fatal stroke, and transient ischaemic attacks). We assume that fixed proportions of people experiencing CVD events would die as a result within the year of the event. Proportions of 25% and 50% were selected for CVD events occurring in those with CKD stage 3a, and CKD stages 3b and 4 respectively in order that the model predicted cumulative cardiovascular mortality in line with the different CVD mortality rates observed for these subgroups in similar cohorts[32,194,196] (see Model validation). Given the great uncertainty surrounding these assumptions,

we subjected them to extensive sensitivity analysis. For purposes of costing, 33.5% of non-fatal events were assumed to be major (myocardial infarction or stroke) and 66.5% of non-fatal events were assumed to be non-major (angina, transient ischaemic attacks) – based loosely on numbers of non-fatal major and other CVD events reported in the Heart Protection Study.[201] Again, these assumptions were subjected to sensitivity analysis.

Chronic kidney disease progression
In order to generate annual transition probabilities for CKD stage progression, we used a data set of all individuals with a recorded eGFR (calculated from recorded serum creatinine results) extracted from the Primary Care Clinical Informatics Unit (PCCIU) research database for another study.[39] The PCCIU research database comprises patient data from 320 Scottish primary care practices (~1.8 million patients). This represents 38% of Scottish practices and has been shown to be representative of the Scottish population. We simulated CKD progression over a 5-year period using reported rates of eGFR decline by level of urine albumin/protein at baseline, and calculated the average

TABLE 29 *Annual CVD event risk by CKD stage and comorbidity*

CKD stage		Annual CVD event risks					
	CKD	CKD with ACR 30–299 mg/g	CKD with ACR ≥ 300 mg/g	CKD with CVD	CKD with ACR 30–299 mg/g and CVD	CKD with ACR ≥ 300 mg/g and CVD
Stage 1 and 2		0.073	0.113		0.109	0.169
Stage 3a	0.071	0.100	0.145	0.112	0.150	0.216
Stage 3b	0.071	0.100	0.145	0.112	0.150	0.216
Stage 4	0.071	0.100	0.145	0.112	0.150	0.216

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease.

proportion of individuals that would be expected to transit annually from each CKD state to the next state. In the first instance we applied annual rates of eGFR decline of –2.5 ml/min/year for people with a normal ACR, –3.5 ml/min/year for people with microalbuminuria and –5.5 ml/min/year for people with proteinuria as reported in the MDRD study.[202] However, application of the resultant CKD transition probabilities resulted in estimates of cumulative ESRD incidence significantly higher than the rates reported for general CKD cohorts in the literature. We therefore proportionally reduced these rates until they gave estimates of ESRD close to the cumulative 10-year incidence of ESRD observed in the study by Eriksen and Ingebretsen.[96] This study consisted mainly of individuals with early stage 3 disease (eGFR 45–59 ml/min/1.73 m²) and so probably underestimated the incidence of CKD in our cohort. The resultant transition probabilities are displayed in *Table 30*. We assumed that individuals in the cohort had established CKD and so, by definition, could not regress to less severe CKD states. It was also assumed that individuals could progress a maximum of one CKD stage per year.

Albumin–creatinine ratio

Individuals in the cohort were allowed to develop ACR 30–299 mg/g or ACR ≥ 300 mg/g over the course of the simulation. As we could find no evidence on the rate at which people with a low eGFR develop these complications, we used the rates reported for people with diabetes in the base-case analysis; 2% (95% CI 1.9 to 2.2) per year for development of ACR 30–299 mg/g, and 2.8% (95% CI 2.5 to 3.2) per year for development of ACR ≥ 300 mg/g from ACR 30–299 mg/g.[203]

Mortality from other cause

In each cycle of the model, individuals experience an age- and sex-adjusted probability of dying from causes other than CVD or ESRD. These probabilities were estimated by removing deaths due to CVD and renal disease from the data used to derive the interim life-tables published by the UK Office for National Statistics.[204,205]

Utilities

A recent review of the literature[77] identified only one study reporting utility values (based on community preferences) for the full range of CKD

TABLE 30 *CKD state transition probabilities by level of urine albumin/protein*

	Reduced eGFR alone				
	CKD 1 and 2	CKD 3a	CKD 3b	CKD 4	CKD 5
CKD 1 and 2					
CKD 3a	0	0.927	0.073	0	0
CKD 3b	0	0	0.952	0.048	0
CKD 4	0	0	0	0.966	0.034
	Reduced eGFR with ACR 30–299 mg/g				
	CKD 1 and 2	CKD 3a	CKD 3b	CKD 4	CKD 5
CKD 1 and 2	0.930	0.070	0	0	0
CKD 3a	0	0.895	0.105	0	0
CKD 3b	0	0	0.931	0.069	
CKD 4	0	0	0	0.950	0.050
	Reduced eGFR with ACR ≥ 300 mg/g				
	CKD 1 and 2	CKD 3a	CKD 3b	CKD 4	CKD 5
CKD 1 and 2	0.880	0.120	0	0	0
CKD 3a	0	0.833	0.167	0	0
CKD 3b	0	0	0.882	0.118	0
CKD 4	0	0	0	0.911	0.089

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

states (stages 1 and 2 through to ESRD pre and post dialysis). This US study used HUI-3 to assign utility scores to 269 patients spread across the CKD stages.[78] Unfortunately this study did not report utility scores by cohort strata (microalbuminuria, proteinuria and CVD), so we had to apply the same utility scores to CKD stages regardless of complication/comorbidity status. As a result our model may underestimate QALY gains attributable to the prevention of non-fatal CVD events.

Resource use and costs

Prior to assessing the incremental cost of early referral strategies, it was first important to establish the level of care that people with reduced eGFR, identifiable through primary care registers, currently receive in primary care. Following the development of standard resource use profiles, we estimated the incremental cost of implementing formal referral strategies, at various eGFR and ACR cut-offs, to an SCS described by Jones and colleagues[147] and described in Models of care.

Patients referred to a specialist either received care from nephrology outpatient clinics, or if considered stable, were referred back to primary care where they received regular clinical reviews from their GP, which were then appraised remotely by nephrologists. This intervention was selected for the model as it was the best described intervention identified in Models of care which incorporates some element of 'early referral'. There was also some evidence that can deliver a change in outcomes.

The baseline scenario against which all referral strategies are assessed is formal referral to, and hospital-based care under, a nephrologist upon transit to stage 5 CKD (referred to as standard practice from here on). All unit costs used in the analysis are presented in *Table 31*. *Table 32* presents estimated resource use and total costs by CKD stage and comorbidity status, pre referral.

Table 33 shows estimated resource use and costs by CKD stage and comorbidity status, after implementation of the referral intervention. All costs are presented in 2006–7 prices.

Standard practice
In order to come up with estimates of annual resource use and costs of referral by stage of CKD and level of comorbidity (CVD and ACR > 30 mg/g), we used a combination of published data and assumptions based on expert opinion.

One of the main sources of current resource use data for unreferred CKD was the study by Stevens and colleagues,[192] which reported hypertension rates and antihypertensive medication use by stage of CKD for a retrospective sample of 11,731 patients with an eGFR below 60 ml/min/1.73 m². The cohort was identified, using computerised records, from patients across 17 primary practices in England, who had a valid serum creatinine test between 1998 and 2003. The cohort was largely unknown to nephrology services.

Primary care resource use and medication costs were estimated by CKD stage for the four cohort strata described in *Table 27*. We based our costing, as far as possible, on resource use data reported by Stevens and colleagues.[192] However, as this study relied on data collected between 1998 and 2003, we also attempted to update the initial costing to reflect possible increases in the use of resources for these individuals in recent years. The initial estimates were used in the base-case analysis.

Consultation costs
Stevens and colleagues[192] reported the proportion of people by reduced eGFR categories (stage 3a, stage 3b and stage 4 ml/min/1.73 m²) on hypertensive medication. We assumed all people on hypertensive medication[192] would undergo on average four primary care consultations per year – the mean number of primary care visits reported for people with hypertension enrolled in an RCT of hypertension self-monitoring.[206] Three of these visits were costed as consultations with a practice nurse, and one was costed as a consultation with a GP. For those people without hypertension, or with untreated hypertension, we assumed one routine visit to the GP per year, unless they had comorbid CVD, in which case we assumed four GP visits per year.

Medication costs
The following data, reported by Stevens and colleagues,[192] were used to build up a picture of annual medication consumption and costs by CKD stage and comorbidity status: the proportion of people with hypertension receiving any hypertensive medication; the proportion of people on hypertensive medication receiving ACE Is or ARBs; the mean number of hypertensive medications prescribed per patient with treated hypertension; and the proportion of patients with comorbid CVD receiving ACE Is or ARBs, antiplatelet agents, and lipid lowering agents. We also assumed that the level of hypertensive medication use would be 10 percentage points higher in those with comorbid CVD. As Stevens

and colleagues[192] did not report the proportion of people without CVD on statins and antiplatelet agents, we assumed that 50% of people without CVD receiving hypertensive treatment would also receive these medications (based on expert opinion of individuals within the research team).

For medication use under nephrology care, we assumed that 90% of all people with hypertension, an ACR > 30 mg/g or comorbid CVD would receive an ACE I.

The annual cost of being on different types of medication was estimated using unit prices from the *British National Formulary*, for a range of generic and non-generic drugs in each drug category (ACE Is/ARBs, other antihypertensive medications, statins, antiplatelet agents). The unit costs presented in *Table 7* represent the average annual costs of being on any drug within each of the specific categories.

Total health service costs
The unit cost information in *Table 31* was applied to the resource use information in *Table 32* (proportions using medications and mean numbers of consultation for the different subgroups) to derive total health service costs by CKD stage and comorbidity status (see *Table 32*). For CKD stages 1 and 2, we assumed the same level of resource use as for people with stage 3 CKD with an ACR > 30 mg/g. We assumed that upon transit to stage 5 CKD, prior to initiation of dialysis, individuals incur the average cost of those with stage 4 CKD under hospital nephrology care. For those with stage 5 CKD on dialysis, we applied published UK estimates of the annual cost of different modes of dialysis,[207] weighted according to the proportions of people on these different modes as detailed in the Renal Registry Report (2008).[7] Data from the Aberdeen nephrology clinic suggest that 40% of surviving patients will commence dialysis within a year of transiting to stage 5. For subsequent years, we assumed the percentage of surviving patients on dialysis increased to 80%, with the remaining 20% managed conservatively. Costs associated with transplantation were not factored in as it was assumed that transplant rates would be low in the aging cohort considered in the model.

In attempting to update the health service costs under current practice, to reflect possible increases in certain types of recourse use, we increased the proportion of individuals on hypertensive medications, ACE Is and statins by 10%.

Early referral strategy
In estimating the costs of a formal referral strategy for people with reduced eGFR on GP registers, we followed the description of the SIMON programme, as reported by Jones and colleagues.[147]

In this shared primary and secondary care nephrology scheme, people with reduced eGFR were first referred to nephrologist for assessment. Those considered to be stable and uncomplicated were then managed under an SCS where they were monitored by nephrologists through clinical and biochemical reviews recorded in primary care. Those considered to be unstable and/ or complicated were managed under hospital outpatient care, but could be referred to shared care at a later date should their condition stabilise.

The scheme required an administrative system where patient records and reviews were stored on a central database. For those under shared care, administrators sent out blood and urine test forms every 6–12 months, depending on clinical condition, and asked that the patient attend their primary care practice to have the tests performed. The patient's BP, weight, medications and urinalysis (ACR) results were recorded by practice nurses and then sent back to the administrative staff. Results were entered into the database and nephrologists reviewed the results via an electronic system, which used specialist software to chart trends in eGFR and other blood tests. If a patient's renal function deteriorates significantly, or there is concern about BP control, the patient can be recalled for hospital care. Through this system, nephrologists can also advise on medication use.

We used the above description along with available unit cost data and several assumptions to estimate the average annual cost of implementing this system for cohorts of patients with varying levels of renal insufficiency and comorbidity.

Consultation costs
Upon referral to nephrology services, all patients incur the cost of an initial face-to-face consultation with a nephrologist (see *Table 31*). Then, by CKD stage and level of comorbidity, we assume that certain proportions of patients will be considered stable enough to be managed under shared care (see below). For these people, we assume an average time to enrolment in shared care of 3.6 months, as reported by Jones and colleagues,[147] and assume that on average two follow-up nephrology outpatient visits are required during

TABLE 31 *Unit costs used in the model*

	Average	Lower	Upper	Source of uncertainty	Source
Clinical inputs					
Consultant-led face-to-face outpatient (first visit)	£200.00	£101.00	£243.00	Quartiles	*NHS reference costs (2006–7)*[208]
Consultant-led face-to-face outpatient (follow-up visits)	£114.68	£59.24	£129.73	Quartiles	*NHS reference costs (2006–7)*[208]
GP consultation	£30.00	£24.00	£34.00	With and without qualification and direct care staff costs	*Unit costs of health and social care (2007)*[209]
Practice nurse consultation	£8.00				*Unit costs of health and social care (2007)*[209]
Consultant result reviews (assume 10 minutes per review)	£12.17	£5.17	£19.17	Lower limit assumes a registrar, upper assumes consultant carrying out reviews	*Unit costs of health and social care (2007)*[209]
Drug costs (per year on treatment)					
ACE I or ARB	£98.04	£49.59	£146.49	Lower limit (generic); upper limit (non-generic)	*British National Formulary (2008)*[210]
Other antihypertensive drug	£103.12	£58.32	£96.36	Lower limit (generic); upper limit (non-generic)	*British National Formulary (2008)*[210]
Statins	£100.08	£17.04	£183.12	Lower limit (generic); upper limit (non-generic)	*British National Formulary (2008)*[210]
Antiplatelet agents (aspirin)	£3.36				*British National Formulary (2008)*[210]
Blood and urinalysis					
ACR test	£2.16	£1.04	£5.93	Range from survey of providers	NICE clinical guideline (2008)[211]
Blood tests (plasma/serum creatinine)	£3.00			No uncertainty reported	*NHS reference costs (2007)*[208]
Annual hospitalisation costs associated with CVD events					
CVD death	£3012.67	£2751.30	£3270.30	2.5th and 97.5th percentile of gamma distribution fitted using reported mean and standard error	Heart Protection Study Collaborative (2006)[201]
Major non-fatal CVD event (MI or stroke)	£8044.84	£7806.70	£8294.10	2.5th and 97.5th percentile of gamma distribution fitted using reported mean and standard error	Heart Protection Study Collaborative (2006)[201]
Other CVD event (angina or transient ischaemic attack)	£3944.85	£3810.00	£4091.50	2.5th and 97.5th percentile of gamma distribution fitted using reported mean and standard error	Heart Protection Study Collaborative (2006)[201]
History of CVD event (but no event current year)	£247.96	£211.40	£291.20	2.5th and 97.5th percentile of gamma distribution fitted using reported mean and standard error	Heart Protection Study Collaborative (2006)[201]

ACE I, angiotensin converting enzyme inhibitor; ACR, albumin–creatinine ratio; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; MI, myocardial infarction.

TABLE 32 Annual costs by CKD stage and comorbidity status, without referral

Co-morbidity status	CKD only			CKD with ACR>30mg			CKD with CVD			CKD with ACR>30mg & CVD		
CKD stage	3a	3b	4	3a	3b	4	3a	3b	4	3a	3b	4
Proportion with hypertension	0.629	0.629	0.629	0.815	0.815	0.815	0.855	0.855	0.855	1.000	1.000	1.000
Proportion of those with hypertension on hypertensive medication	0.622	0.721	0.746	0.622	0.721	0.746	0.722	0.821	0.846	0.722	0.821	0.846
Mean number of hypertensive medications per treated individual	1.66	1.76	1.84	1.66	1.76	1.84	1.66	1.76	1.84	1.66	1.76	1.84
Proportion of those on hypertensive medication on ACE I/ARB	0.43	0.375	0.325	0.43	0.375	0.325						
Proportion of all those with CVD on ACE I/ARB												
Proportion of total cohort on ACE I/ARB	0.168	0.170	0.153	0.218	0.220	0.198	0.411	0.411	0.411	0.411	0.411	0.411
Proportion of total cohort on a statin	0.196	0.227	0.235	0.253	0.294	0.304	0.507	0.507	0.507	0.507	0.507	0.507
Proportion of total cohort on antiplatelet agents (aspirin)	0.196	0.227	0.235	0.253	0.294	0.304	0.514	0.514	0.514	0.514	0.514	0.514
Consultations												
Primary care consultations in those with treated hypertension	4	4	4	4	4	4	4	4	4	4	4	4
Primary care consultations in those without treated hypertension	1	1	1	1	1	1	4	4	4	4	4	4
Costs (£)												
Average annual cost of consultations	65.21	70.82	72.23	75.62	82.89	84.72	120.00	120.00	120.00	120.00	120.00	120.00
Average annual medication costs	86.35	104.90	112.53	111.89	135.92	145.80	198.43	220.16	230.01	216.35	241.77	253.28
Average annual health service costs for CKD and CVD management	151.56	175.72	184.76	187.51	218.80	230.52	318.43	340.16	350.01	336.35	361.77	373.28

ACE I, angiotensin converting enzyme inhibitor; ACR, albumin–creatinine ratio; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CVD, cardiovascular disease.

this period. Once patients are enrolled in the SCS, we assume that they incur the cost of one primary care review within the year.

Those who remain under hospital care from initial referral onward incur the cost of the initial consultation followed by the cost of three follow-up outpatient visits within the year of referral.

For consultation costs in subsequent years we assume a mean number of 1.5 primary care reviews per year for those managed under shared care, and four outpatient follow-up visits per year for those managed under hospital care. Those under hospital care are assumed to also require four visits to their GP each year. The cost of a shared care review was taken as the cost of a practice nurse consultation, the cost of an ACR and serum creatinine test, plus the cost for 10 minutes of a nephrologist's time (consultant or registrar) to review results.

Unit costs for nephrology outpatient visits were taken from the Department of Health's *NHS reference costs* (2006–7)[208] and the unit cost for consultations with nurse practitioners and GPs were taken from the *Unit costs of health and social care 2007*.[209]

In addition, we applied an annual cost per patient of £5.22 to cover administrative costs for the formal referral strategy, maintenance of the database, operation of the call–recall system, and purchasing and updating of any software required for reviewing results. This is based on a previous estimation carried out by the authors (GS and PM) of the administrative costs per patient of operating a systematic screening programme for diabetic retinopathy (unpublished data). It includes the cost of running a call–recall system, of storing and maintaining patient's data electronically on a central server, and of purchasing specialist software to aid the grading process.

Proportions under shared care and hospital care

Assumptions were made regarding the proportions of people who would be managed under shared care and hospital care by CKD stage and level of comorbidity. We assumed that 50% of those with stage 3b or stage 4 CKD (ACR < 300 mg/g) would be managed under shared care, and that 100% of patients with an ACR > 300 mg/g would be retained for management under hospital care. For those with stage 3a CKD, we assumed that 75% of those with an ACR < 300 mg/g would be managed under

shared care, and that 100% of patients with an ACR > 300 mg/g would be managed under hospital care.

Medication costs

We assumed that under the formal referral strategy, the proportion of people with hypertension on any hypertensive medication would increase by 10 percentage points compared with standard practice (lower resource use scenario).

For those under hospital care after initial referral, we assumed that 90% of all people with hypertension, an ACR > 30 mg/g or comorbid CVD would receive an ACE I or ARB. For those under shared care, we inflated the proportions of individuals on ACE Is or ARBs in primary care (under current practice) using multipliers estimated from the study by Jones and colleagues;[148] the proportion using ACE Is or ARBs increased by 58% for those managed under shared care after referral to the SIMON programme. We also applied proportional increases in the use of lipid lowering agents and aspirin, as reported for all patients enrolled in the SIMON programme, to estimate the levels of use of these medications under the formal referral strategy.

Total health service costs

Using the above assumptions, we estimated average annual costs of care by CKD stage and level of comorbidity, under a formal early referral programme (see *Table 35*). In addition, we assumed that people with stages 1 and 2 CKD would incur the same costs as those with stage 3a CKD with an ACR > 30 mg/g. For those with stage 5 CKD, prior to initiation of dialysis, we assumed the average annual cost across comorbidity groups in those with stage 4 CKD. The same assumptions were applied, as described above, for individuals on dialysis.

Additional hospital costs associated with CVD events

Costs associated with CVD events were taken from a published cost-effectiveness study which assessed patient level hospitalisation costs associated with major cardiovascular events (myocardial infarction, stroke), other CVD events (angina, transient ischaemic attacks, etc.) and CVD deaths.[201] This study also reported hospitalisation costs in the years following CVD events, when no other CVD events occurred (see *Table 7*). These costs were applied in the model as transition costs. Given the high CVD mortality risk in people with ESRD (~0.125 per year), we assumed that 50% of these people would experience a CVD event each year;

TABLE 33 *Estimated annual costs (£) of consultations and medications under a formal referral strategy, by CKD stage and level of comorbidity*

	CKD alone	ACR > 30 mg/g	ACR > 300 mg/g	CKD with CVD	CKD with ACR > 30 mg/g and CVD	CKD with ACR > 300 mg/g and CVD
CKD stages 1 and 2		£376.56	£780.60		£583.96	£839.70
CKD stage 3a	£344.37	£376.56	£780.60	£572.07	£583.96	£839.70
CKD stage 3b	£475.15	£532.86	£796.10	£584.95	£599.02	£850.02
CKD stage 4	£492.00	£542.34	£804.61	£593.03	£608.48	£858.27

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease.

with a CVD event fatality rate of 25%, this results in an annual risk of CVD mortality of 0.125. Those experiencing non-fatal CVD events incur the associated hospitalisation costs.

Effectiveness

In the absence of robust effectiveness evidence for the shared care strategy reported by Jones and colleagues,[148] we applied a relative effect estimate obtained from a cohort study assessing the impact of nephrology referral on CKD progression and ACM, assuming that the shared care strategy might have a similar effect on CKD progression and CVD. Orlando and colleagues[111] reported HRs associated with early referral for a composite end point of progression to the next stage of CKD or death. These HRs were reported for each CKD stage and were similar for CKD stages 3 and 4 (0.80, 95% CI 0.61 to 0.90 and 0.75, 95% CI 0.45 to 0.89 respectively). Given the lack of statistically significant difference between these estimates we assumed a constant HR of 0.8 associated with early referral across stages 3 and 4. Although Orlando and colleagues[111] did not report the impact of early referral on CVD events separately, many of the deaths occurring in the cohort were due to CVD causes. We therefore applied the HR directly to the CKD transition probabilities and CVD event risks used in the natural history model. Given the large uncertainty surrounding the relative effectiveness of early referral, we varied this parameter substantially in the sensitivity analysis.

Cost-effectiveness analysis

In the first instance we assessed the incremental cost-effectiveness of early referral for everyone with an eGFR below 60 ml/min/1.73 m² (CKD 3a) compared with referral upon transit to stage 5 CKD (from here on referred to as standard practice). Although this may no longer represent current practice in the UK, we decided to use this as the base comparator as it provides a useful reference point against which to compare all referral cut-offs incrementally. We then assessed the incremental cost-effectiveness of scenarios where referral occurs only for those with an eGFR below 45 ml/min/1.73 m² (CKD 3b), or below 30 ml/min/1.73 m² (CKD 4). Under these scenarios we assumed that those above the thresholds would experience the same CVD event risks and transition probabilities as those under standard care, but that they would incur an eGFR and ACR monitoring cost; these individuals would have to be monitored in primary care in order to be picked up and appropriately referred upon falling below the thresholds. The cost of monitoring was taken as the cost of two consultations per year with a practice nurse for urinalysis and a plasma creatinine test. We also assumed that monitoring in primary care, under this referral strategy, would incur the same administrative costs as referral to the nephrology SCS (£5.22).

We then assessed the cost-effectiveness of referring only those people with ACRs over 30 mg/g or 300 mg/g (microalbuminuria or proteinuria respectively). Finally, we assessed the cost-effectiveness of referring anyone with stage 3b CKD and an ACR > 30 mg/g, and anyone with stage 3b or an ACR > 300 mg/g. The latter strategy is similar to referral criteria recommended in recent clinical guidelines on the management of CKD.[212] The model was run over a 35-year time horizon using a discount rate of 3.5% for future costs and consequences. Discounting was applied to adjust for positive time preference: the observation that society prefers to receive benefits in the present and incur costs in the future. The discount rate currently recommended by the UK Treasury (http://www.hm-treasury.gov.uk/) is 3.5%.

The cohort was initially distributed across the CKD and comorbidity states (*Table 34*) according to proportions reported by Stevens and colleagues.[192] Within each CKD category we applied proportions with microalbuminuria and proteinuria as reported for the NHANES III cohort.[193] Given that CVD prevalence is higher in those with microalbuminuria and proteinuria, we adjusted the proportions with CVD in the microalbuminuria/proteinuria states accordingly.

Sensitivity analysis

Following the base-case analysis we explored the impact of varying uncertain model parameters and assumptions. The model was rerun for the following scenarios, most of which are biased against early referral:

- Annual rates of eGFR decline were doubled.
- The risk of ACR > 30 mg/g development was set to zero.
- CVD event risks were halved.
- The effect of nephrology referral on CVD events was set to zero.
- The effect of nephrology referral on eGFR decline (CKD progression) was set to zero.
- The effect of nephrology referral on CVD events and eGFR decline was simultaneously halved.
- The effects of nephrology referral on CVD events and eGFR decline were halved and constrained to last 5 years (the median length of follow-up in the study by Orlando and colleagues).[111]
- Costs for standard care were set at their upper limit.
- Costs of care under early nephrology referral were doubled.
- Costs associated with fatal and non-fatal CVD events were varied within the 95% confidence limits of their assigned distributions (see Probabilistic sensitivity analysis).

The cost of caring for people with ESRD was also subjected to sensitivity analysis. For the lower limit we applied the lowest dialysis cost estimates reported by Baboolal and colleagues[207] and also assumed that only 70% of patients with ESRD would end up on dialysis, i.e. 30% would be managed conservatively. For the upper limit we applied high dialysis cost estimates[207] and assumed that 60% of patients would commence dialysis within a year of transiting to ESRD, and that the proportion on dialysis would subsequently increase to 90%. In addition, we explored the impact of allowing for increasing cardiovascular event rates by CKD stage, and assessed the potential impact of allowing for non-linear rates of eGFR decline (by applying higher rates of eGFR decline for people with stage 4 CKD). Finally, we considered a scenario where individuals with an ACR ≥ 30 mg/g were considered separately from the main cohort.

Probabilistic sensitivity analysis

The impact of joint uncertainty across all model parameters was assessed using probabilistic sensitivity analysis. Monte Carlo simulation was employed whereby values were simultaneously selected for each parameter from an assigned distribution and the results recorded. The process was repeated 1000 times to give an estimate of the sampling distribution of cost and effect differences between the referral strategies. These results were then used to generate cost-effectiveness acceptability curves.

Gamma distributions were fitted to all cost parameters. As we had no information on the statistical precision of our CKD cost estimates (under standard practice), base-case costs were treated as means for these parameters and variances were selected so that our feasible high cost estimates fell below the 97.5th percentiles of the resultant distributions. For CKD costs under nephrology referral, distributions were centred

TABLE 34 *Initial distribution of cohort across the disease states*

	CKD alone	ACR > 30 mg/g	ACR > 300 mg/g	CKD with CVD	CKD with ACR > 30 mg/g and CVD	CKD with ACR > 300 mg/g and CVD
Stage 3a	0.447	0.070	0.023	0.112	0.066	0.022
Stage 3b	0.108	0.009	0.003	0.051	0.030	0.010
Stage 4	0.012	0.004	0.008	0.004	0.008	0.013

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease.

on our base-case estimates and assigned variances so that feasible high estimates fell within the 95% CIs of resultant distributions. The same principals were followed when assigning distributions to costs associated with ESRD. For costs associated with cardiovascular events, we applied gamma distributions using means and reported standard errors.[201]

For probabilities of CKD stage progression we assigned beta distributions. We centred these distributions on the base-case estimates and selected variances so that high estimates fell within the 97.5th percentiles of the resultant distributions. For probabilities of developing microalbuminuria and proteinuria, we assigned beta distributions using point estimates and CIs reported for individuals with diabetes.[203] For RRs of CVD events conveyed by CKD, ACR > 30 mg/g, and ACR > 300 mg/g, we assigned log normal distributions using reported point estimates and CIs.[84] The same approach was used to assign a log normal distribution to the HR associated with nephrology referral.[111] For CVD event fatality rates, and the ratio of major to minor CVD events (used in the cost calculation), we reduced and increased point estimates by 50% and assigned uniform distributions.

Given the uncertainty underlying our effectiveness estimate, we also ran a probabilistic sensitivity analysis where the distribution for this parameter

was centred on a 10% risk reduction (as opposed to a 20% risk reduction).

Model validation

The predicted survival curve for the CKD cohort (without early referral) was compared with the survival curve for an age- and sex-matched cohort of the UK general population (*Figure 9*). As anticipated, predicted life expectancy was lower for the CKD cohort than for the age- and sex-matched general population. Our model predicts a reduction in life expectancy of 2.5 years, from 13.45 years to 10.93 years.

Figure 10 shows the cumulative incidence of ESRD, cardiovascular mortality and other cause mortality predicted by the model using the base-case parameter estimates and assumptions. Values reported in the literature for these outcomes in CKD cohorts vary widely. To give some examples, Menon and colleagues[213] reported a 10-year cumulative incidence for ESRD of around 50% for those with a baseline eGFR between 24.5 and 55.5 ml/min/1.73 m² enrolled in the MDRD study. However, about 50% of individuals in this cohort had either polycystic or glomerular disease. Wakai and colleagues[214] reported a 7-year cumulative incidence for ESRD of 23.3% in a Japanese cohort with immunoglobulin A nephropathy. On the other hand, Eriksen and Ingebretsen[96] reported a cumulative 10-year incidence for ESRD of only
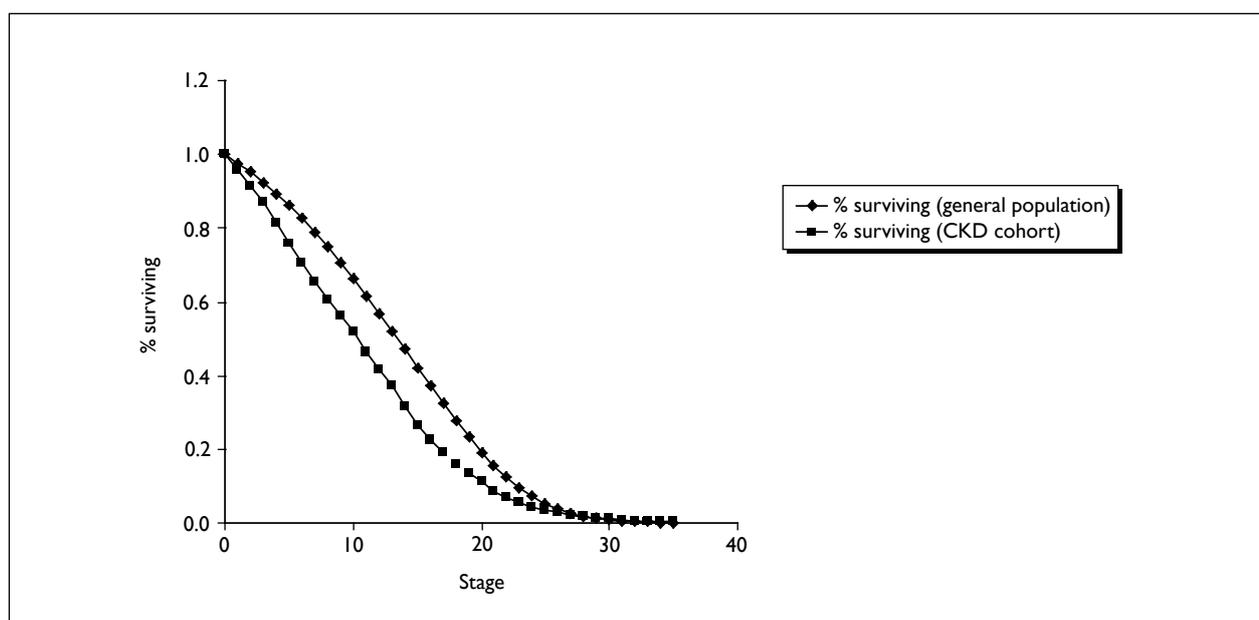
FIGURE 9 *Predicted survival curve compared with the sex- and age-matched survival curve for the UK general population. CKD, chronic kidney disease.*

4% in a cohort of individuals with stage 3 CKD (identified through routine clinical measurements).

The corresponding 10-year cumulative incidence of ESRD predicted for the cohort modelled in the current analysis is 3.5%, indicating that our estimates are on the conservative side. We assessed the impact of increasing CKD progression rates through sensitivity analysis.

The 10-year cumulative incidence of cardiovascular mortality predicted by the model is 30% (*Figure 10*). Comparisons with estimates from published cohort studies are complicated by the fact that few studies have looked at long-term cardiovascular outcomes in CKD cohorts identified through case finding in general practice. Parikh and colleagues[194] report a 10-year cumulative incidence for cardiovascular mortality of 16% and 21% for groups with stage 3a and 3b CKD respectively with no pre-existing CVD. Hallan and colleagues,[32] on the other hand, report higher 8-year cumulative incidence rates of approximately 20% and 40% for cohorts with stage 3a and 3b CKD respectively (including individuals with pre-existing CVD and diabetes). However, Weiner and colleagues[196] report a lower 10-year cumulative incidence of ~35% for a composite outcome of myocardial infarction, fatal coronary heart disease, ACM and non-fatal stroke. Although the cohort in this latter study consisted of individuals identified through screening, rather than individuals picked up as part of routine clinical practice, it raises the possibility that our model may be overestimating fatal and non-fatal CVD events. Given the variation in reported estimates, we subjected the CVD event risks and event fatality rates to extensive sensitivity analysis.

Results

The base-case results are presented in *Table 35* and *Figure 11*. The axis of *Figure 11* indicates that under baseline parameter estimates and assumptions, all strategies generate more QALYs than the practice of referral upon transit to CKD stage 5 (standard practice). Referral for everyone with an eGFR below 30 ml/min/1.73 m² (CKD 4) had an ICER of £5923 compared with standard practice.

Referral for everyone with an eGFR below 60 ml/min/1.73 m² (CKD 3a) generated the most QALYs and, compared with referral for everyone at CKD 4, had an ICER of ~£3806 per QALY. Compared with referral for everyone at CKD 3b, referral at CKD 3a had an ICER of £3751 per QALY. The referral strategy based purely on the presence of proteinuria was dominated by the strategy of referral at stage 4. Compared with strategies of referral for those with ACR > 30 mg/g only, those with CKD 3b or ACR > 30 mg/g, or those with CKD 3b or ACR > 300 mg/g, referral at stage 3a had an ICER of ~£3440 per QALY, £3573 per QALY and ~£3473 per QALY respectively.
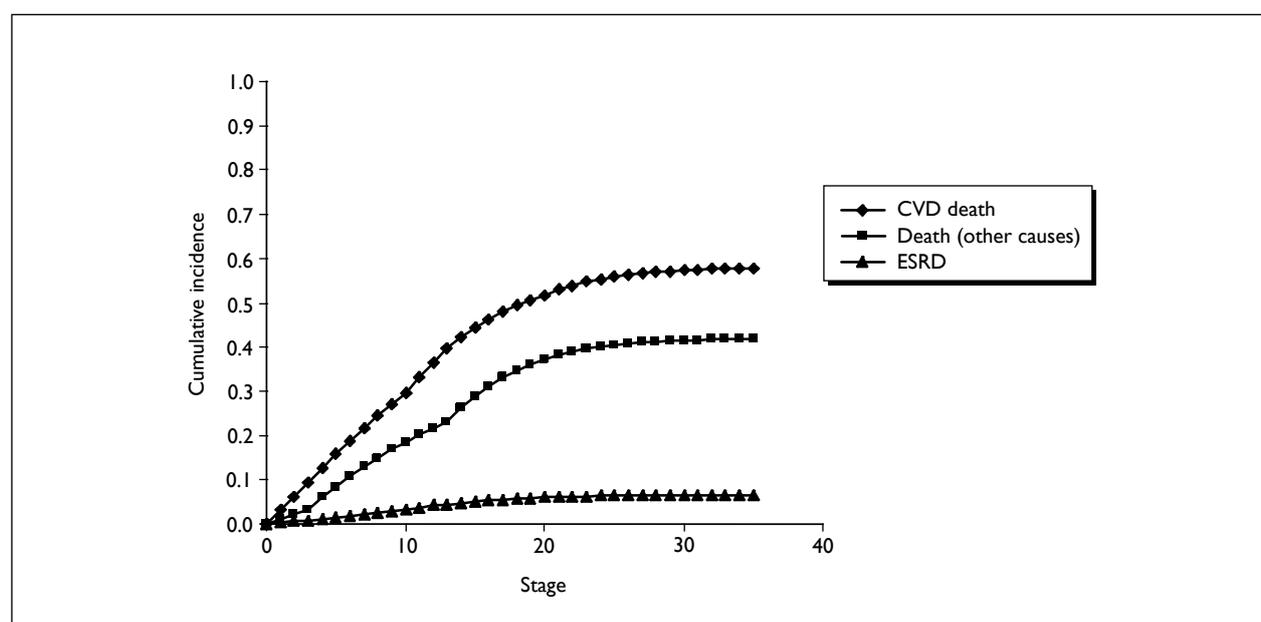
FIGURE 10 *Predicted cumulative incidence of end-stage renal disease (ESRD), cardiovascular mortality and mortality from other causes. CVD, cardiovascular disease.*

TABLE 35 *Base-case cost-effectiveness results (per individual with CKD)*

Strategy[a]	Total cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
Standard practice	£11,796		5.579		
Refer at CKD 3a	£13,487	£1691	5.992	0.413	£4091
Refer at CKD 3b	£12,808	£1012	5.811	0.232	£4352
Refer at CKD 4	£12,129	£332	5.635	0.056	£5923
Refer ACR 30–299 mg/g	£12,596	£800	5.733	0.154	£5194
Refer ACR ≥ 300 mg/g	£12,308	£512	5.628	0.049	Dominated
Refer at CKD 3b or ACR ≥ 30 mg/g	£13,051	£1255	5.870	0.291	£4313
Refer at CKD 3b or ACR ≥ 300 mg/g	£12,915	£1118	5.827	0.248	£4508

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; Dominated, the strategy is more costly and less effective than an alternative strategy; eGFR, estimated glomerular filtration rate; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.
a   All strategies compared incrementally to standard practice.

Thus CKD 3a is the preferred strategy from the base-case analysis.

The QALY gains associated with early referral are attributable to survival improvements (*Figure 12*) and a reduction progression, and in the cumulative incidence of ESRD (*Figure 13*). Compared with referral upon transit to stage 5 CKD, referral at CKD 3a is associated with an increase of 0.605 discounted life-years (0.97 undiscounted life-years)

and an 18% reduction in the cumulative incidence of ESRD.

Deterministic sensitivity analysis
The findings of various deterministic sensitivity analyses are presented in *Table 36*.

The model results were most sensitive to underlying rates of eGFR decline, the underlying risk of developing ACR > 30 mg/g, the effect of
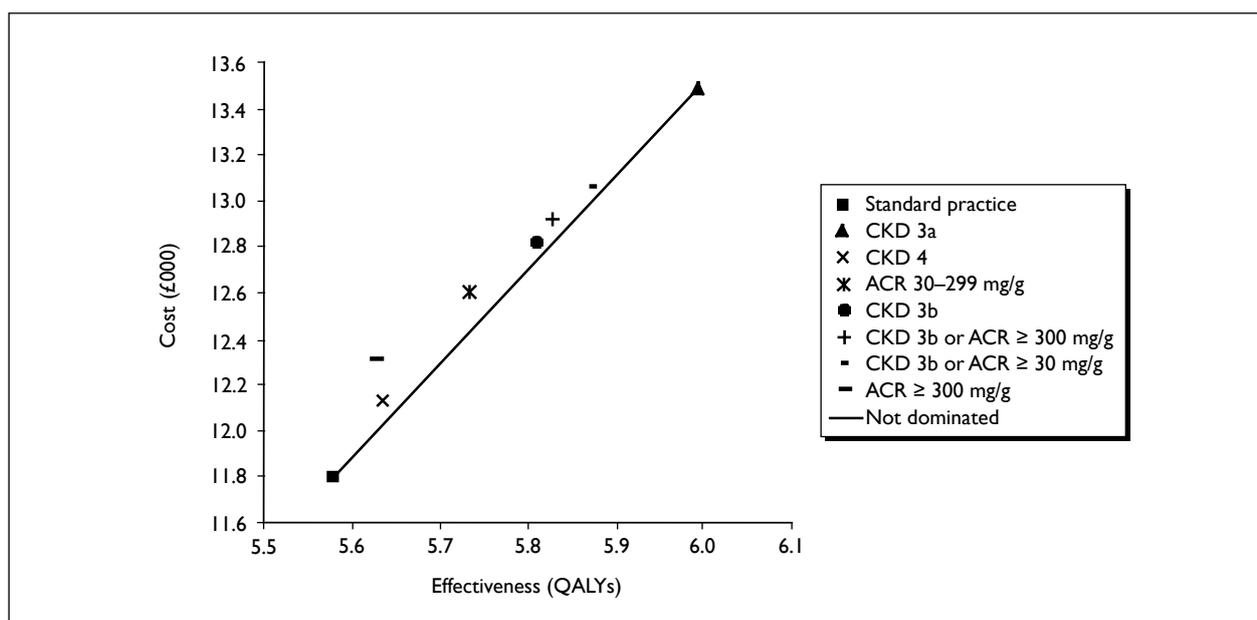
FIGURE 11 *Base-case cost-effectiveness results. ACR, albumin–creatinine ratio; CKD, chronic kidney disease; QALYs, quality-adjusted life-years.*
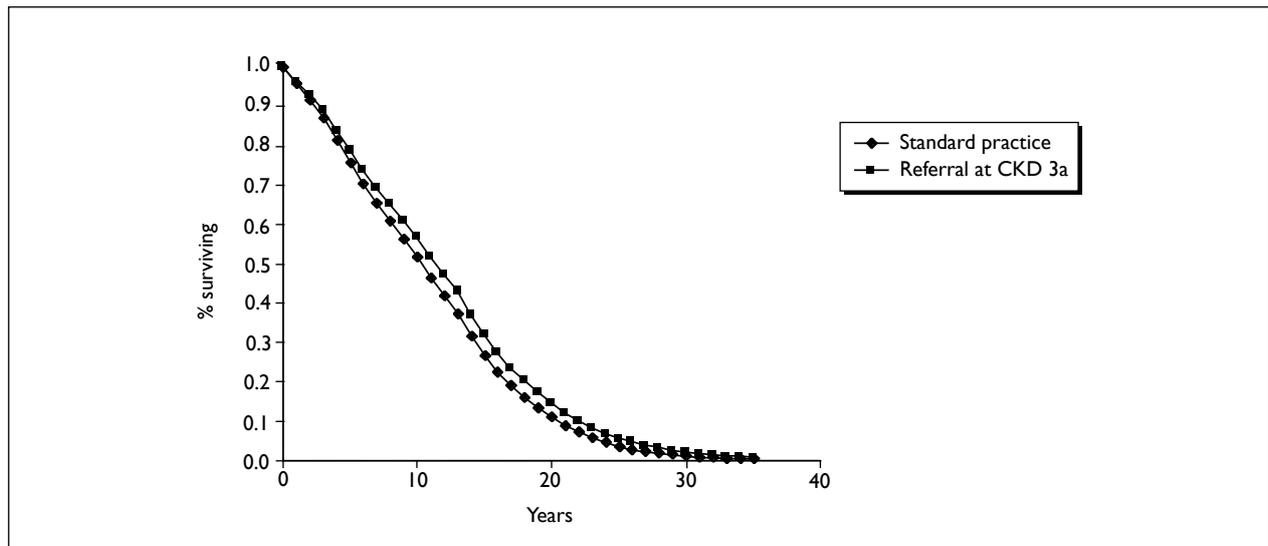
FIGURE 12 *Survival curves with and without early referral to nephrology services (referral for everyone with eGFR < 60 ml/min/1.73 m².). CKD, chronic kidney disease.*

referral on eGFR decline (CKD progression) and the costs of care under formal early nephrology referral. When we halved the rates of eGFR decline, the model predicted a cumulative 10-year incidence of ESRD below that reported by Eriksen and Ingebretsen.[96] However, early referral remained cost-effective under this specification, as it did under all other one-way sensitivity analyses presented in *Table 36*.

In addition to the scenarios presented in *Table 36*, halving and doubling CVD event fatality rates did not alter the overall findings, with referral at CKD

3a (< 60 ml/min/1.73 m²) remaining the preferred strategy across all values.

When several parameters were simultaneously weighted against early nephrology referral, the ICER for referral at CKD 3a approached a value unlikely to be considered cost-effective (final row of *Table 36*).

In order to assess the potential implications of a non-linear pattern of eGFR decline, we modelled a scenario where the rate of eGFR decline increases at stage 4 compared with stages 3a and 3b. For
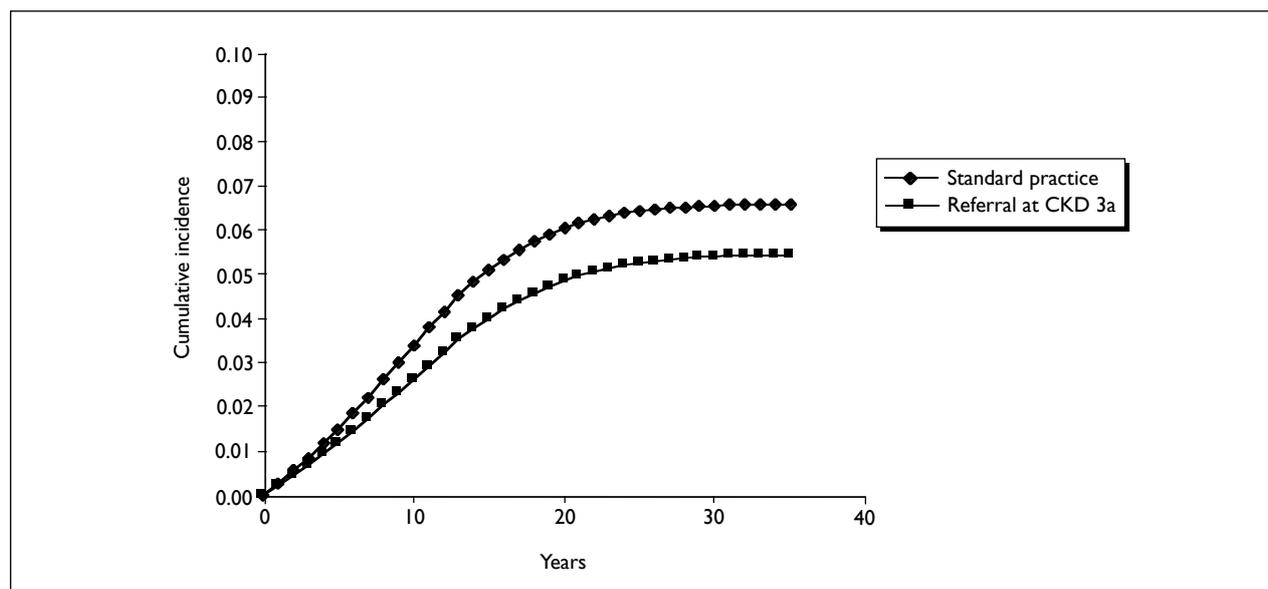
FIGURE 13 *Cumulative incidence of ESRD with and without early referral to nephrology services (referral for everyone with eGFR < 60 ml/min/1.73 m²). CKD, chronic kidney disease.*

TABLE 36 *Deterministic sensitivity analyses – referral for everyone with eGFR < 60 ml/min/1.73 m² compared with standard practice (referral around time of developing ESRD)*

Scenarios	Incremental cost	Incremental effectiveness (QALYs)	ICER
Refer CKD stage 3 (base case)	£1691	0.413	£4091
Annual rates of eGFR decline doubled	£388	0.437	£888
Risks for ACR > 30 mg/g development are zero	£2031	0.322	£6314
CVD event risks halved	£1659	0.337	£4923
No direct effect of referral on CVD events	£1730	0.087	£19,885
Zero effect of referral on CKD progression	£2631	0.230	£8218
Effect of referral on CKD progression and CVD events halved	£2118	0.199	£10,662
Effect of referral on CKD progression and CVD events halved and constrained to last 5 years	£2360	0.095	£24,908
High costs for standard practice	£1430	0.413	£3460
Costs of care under nephrology referral doubled	£6624	0.413	£16,027
Lower limit for CVD event costs	£1708	0.413	£4132
Lower limits for ESRD costs	£1830	0.413	£4428
Discount rate 6%	£1449	0.308	£4704
10-year time horizon	£1257	0.154	£8158
Costs under early nephrology referral doubled, effect sizes halved, base risk for ACR > 30 mg/g development halved	£6856	0.200	£34,323

ACR, albumin–creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

this analysis we used the rates of decline reported in the MDRD study[202] for individuals with stage 4 CKD, while maintaining the lower rates of decline for those with 3a and 3b. This improved the cost-effectiveness of all referral options. Compared with referral at stage 5, the ICERs for referral at stages 4, 3b and 3a decreased to £3103, £2817 and £2954 per QALY respectively. Compared with referral at stage 4, the ICER for referral at stage 3b was £2729 per QALY, and compared with referral at stage 3b, the ICER for referral at stage 3a dropped to £3132 per QALY.

Adjustment of cardiovascular events rates by CKD stage, to give a pattern of increasing cardiovascular mortality consistent with data reported by Go and colleagues,[75] was found to have little impact on cost-effectiveness. Referral at stage 3a remained the most cost-effective strategy under this scenario, with an ICER of £4360 per QALY versus standard practice, and an ICER of £4011 and £4133 per QALY versus referral at stage 4 and stage 3b respectively.

Finally, we explored a scenario where individuals with an ACR ≥ 30 mg/g were considered separately. Although early referral in this group saves more QALYs on average, compared with the CKD cohort as a whole, average costs are also higher owing to the higher costs of managing this group under the early referral scheme. Under this scenario the ICERs for referral at stage 3a were £4009, £3951 and £4074 compared with standard practice, referral at stage 4 and referral at stage 3b respectively.

Probabilistic sensitivity analysis
Figure 14 plots the probability of each strategy being considered the most cost-effective option for different values of societal willingness to pay for an additional QALY, using optimistic assumptions about effectiveness of early referral.

Above a willingness-to-pay threshold of ~£4100, referral for everyone with an eGFR < 60 ml/min/1.73 m² (referral at CKD 3a) has the highest probability of being the most cost-effective option.
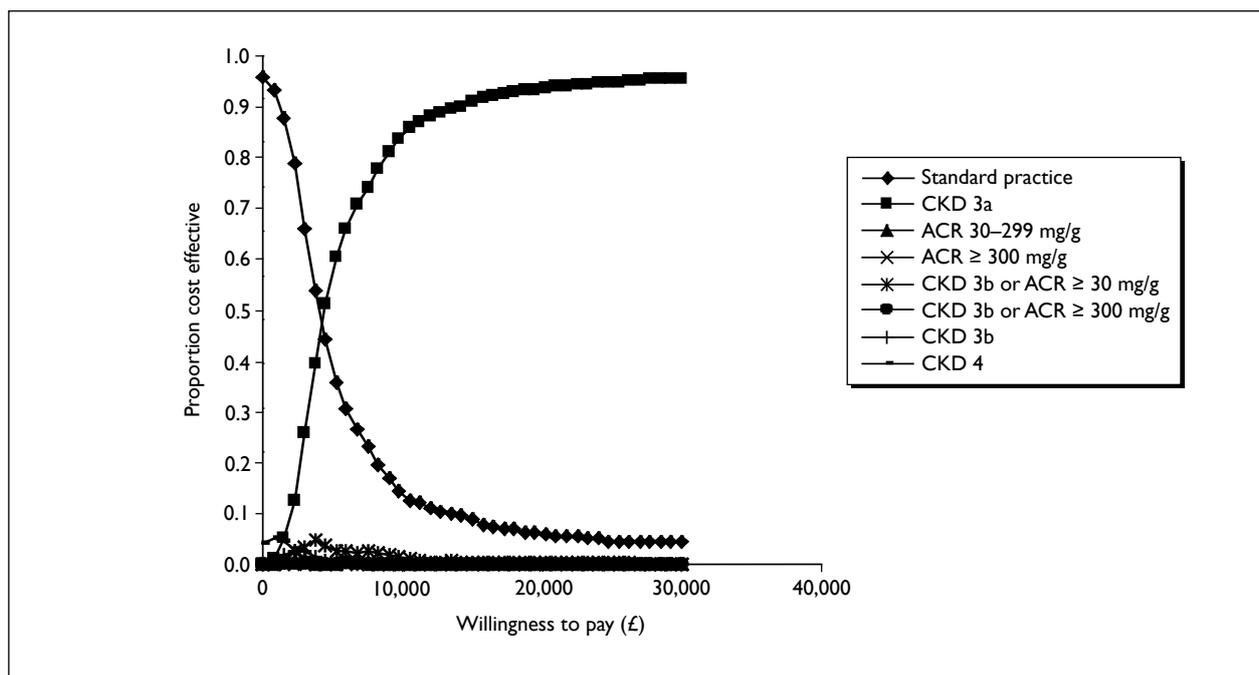
FIGURE 14 *Cost-effectiveness acceptability curves for alternative referral strategies. ACR, albumin–creatinine ratio; CKD, chronic kidney disease.*

However, when the distribution for the effectiveness of early referral is centred on a 10% risk reduction (for CKD progression and cardiovascular events) and constrained to last 5 years, the acceptability curve indicates only a 55% chance of early referral (at stage 3a) being cost-effective at a willingness-to-pay threshold of £30,000 per QALY (*Figure 15*).
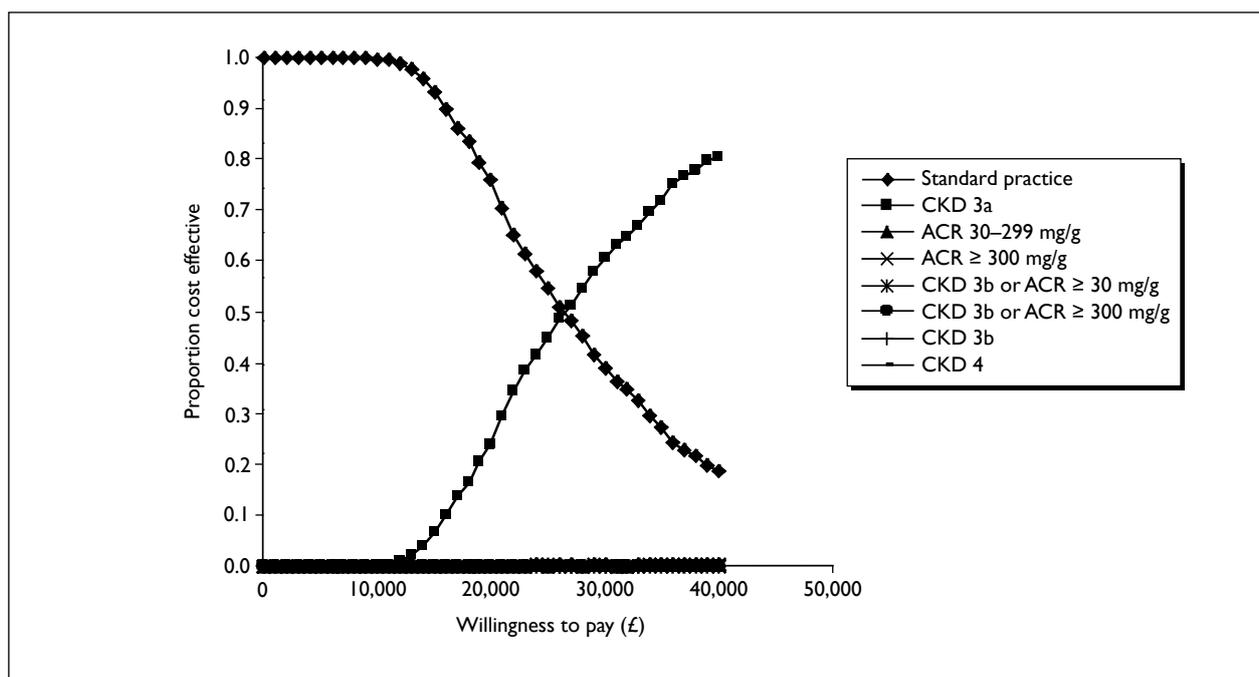
FIGURE 15 *Cost-effectiveness acceptability curves for alternative referral strategies when baseline CKD progression rates are centred on feasible low estimates. ACR, albumin–creatinine ratio; CKD, chronic kidney disease.*

Discussion

This modelling exercise has attempted to assess the cost-effectiveness of referring individuals with markers of renal disease (based on various eGFR and ACR cut-offs) to a shared care nephrology programme. The baseline strategy against which the early referral strategies are compared is referral to nephrology upon transit to stage 5 CKD. Although this may not reflect current practice, it provides a useful baseline against which to compare the alternative referral cut-offs incrementally.

Results of the base-case analysis suggest early referral may offer an efficient use of scarce health service resources. All strategies produced more QALYs than standard practice (referral upon transit to stage 5 CKD). Referral for everyone with an eGFR below 30 ml/min/1.73 m² (stage 4 CKD) produced 0.056 additional QALYs per patient at an additional cost to the NHS of £332 per patient (ICER: £5923 per QALY). Compared with referral upon transit to stage 4 CKD, referral at stage 3b increases the number of QALYs gained (0.176) for a increase in cost of £679 (ICER: ~£3857 per QALY). Referral at stage 3a again increases the number of QALYs gained (0.181) compared with referral at stage 3b, with an ICER of £3751 per QALY. Thus, under the base-case parameter values and assumptions, referral at stage 3a is the preferred option on grounds of cost-effectiveness.

Referral for everyone with stage 3b CKD, or ACR > 30 mg/g, is more effective and more costly than referral based on an eGFR < 45 ml/min alone, as these strategies reach individuals at stage 3a who have evidence of kidney damage. Compared with referral at CKD 3b, they have higher ICERs than referral for everyone with stage 3a CKD (£4119 and £6625 per QALY versus £3751 per QALY respectively), due to the fact that they result in no reduction in progression or cardiovascular event rates for the large portion of the cohort with stage 3a CKD alone. However, when the group with microalbuminuria or proteinuria is considered separately, the ICER for referral at stage 3a is slightly more favourable than the ICER for referral at stage 3a for the cohort as a whole (£4009 versus £4091 relative to standard practice respectively).

The superiority of earlier referral observed in the model is due to the fact that as patients progress to more severe disease states, they experience higher costs associated with CKD management and experience a higher risk of cardiovascular events and death. The costs incurred in preventing progression to more severe disease states are offset by the costs and life-years saved as a result. In particular, the earlier referral occurs, the lower the cumulative incidence of ESRD, which is associated with very high annual costs and mortality (~£27,000 per patient per year). Deterministic sensitivity analysis confirms this in revealing that the ICER is highly sensitive to changes in the baseline risk of CKD progression and the effect of referral on the risk of CKD progression and cardiovascular events. When we applied more conservative CKD progression rates, and reduced the effect of early referral on CKD progression and cardiovascular events, the ICER for early referral rose above £30,000 per QALY, the threshold applied by NICE to guide decisions on cost-effectiveness.

A factor that was not formally considered in the current analysis is the possibility that CKD cohorts have a higher background risk of mortality from other causes. This was because no published data were identified indicating that CKD confers an increased risk for this outcome. However, unpublished data from a cohort study in Aberdeen, UK suggest that this may be the case (Dr Keith McCullough, University of Aberdeen, personal communication, 2009). To investigate the potential impact of such an effect, we multiplied other cause mortality by 2.36; the HR for CVD mortality associated with CKD. Under this scenario, the cost-effectiveness of early referral decreased only slightly, with the ICER for referral at stage 3a increasing to £5167 compared with standard practice.

Affordability and feasibility

Although, our analysis suggests that early referral and improved management of individuals with CKD may represent a cost-effective use of health service resources, the affordability and feasibility of the intervention is questionable. To give an indication of the potential impact of moving from a strategy of referral to shared care at stage 4 to referral at stage 3a, recent QOF data suggest that there are ~1.74 million adults registered in England and Scotland as having stage 3a CKD or worse under the QOF. Assuming 74% have stage 3a CKD and 21% have stage 3b CKD,[202] the net incremental cost of moving to a shared care strategy at stage 3a would be in the region of £1.02B over 3 years (discounted at 3.5%). The corresponding cost of moving to a strategy of shared care at stage 3b would be ~£375M. These estimates are based on the modelled net

incremental cost per patient of referral at stage 3a or stage 3b versus referral at stage 4 (over a 3-year time horizon) multiplied by 1.74 million. The unit costs for referral, upon which these estimates are based, may not reflect the true cost of scaling up nephrology services to the level required to meet the extra demand (increased numbers of nephrologists, increased clinic space and increased administrative costs). Assuming that referral at stage 4 is the current practice, and that existing nephrologists are working at capacity, movement to early referral at stage 3a might require somewhere in the region of 1300 additional nephrologists, while movement to referral at stage 3b would require ~500 additional nephrologists across England and Scotland. These estimates are based on further assumptions that an individual nephrologist could manage ~1250 stage 3a patients per year under an SCS (assuming 25% would require outpatient hospital treatment while the rest could be managed in primary care) or 800 stage 3b patients per year (assuming 50% would require outpatient hospital treatment). As these numbers are unlikely to prove feasible, it is likely that alternative approaches to the management of individuals with CKD will have to be found.

Comparison with other studies

As outlined in the review section of this chapter, we were unable to identify any published studies specifically assessing the cost-effectiveness of early referral strategies (referral during stage 3a) for patients with markers of renal disease. However, our finding that referral at stage 4 CKD is highly cost-effective compared with referral upon transit to stage 5 CKD is consistent with the previously published modelling study by McLaughlin and colleagues.[180] Our findings are also generally consistent with studies showing the use of ACE Is to be cost-effective in individuals with non-diabetic nephropathies.[188,189] Improved uptake and appropriate use of ACE Is is one of the mechanisms by which early referral may reduce progression and prevent cardiovascular mortality. Our findings are also consistent with the substantial body of evidence that shows early treatment of diabetic nephropathies with ACE Is or ARBs to be highly cost-effective, owing to their preventive effect on progression to ESRD.[215,216]

Strengths and weakness of the study

Owing to a lack of data on the natural history of CKD in individuals without diabetes, and a lack of evidence on the costs and effects of early referral, our model should be seen as an exploratory piece

of research. Many assumptions had to be made regarding the transition of individuals through the CKD stages, the risk of cardiovascular events by stage, and the costs and effectiveness of early referral. In particular, more research is required to assess eGFR decline rates in individuals with early stage 3 CKD. In our base-case analysis, we estimated CKD transition rates by applying average rates of eGFR decline in line with rates reported in the literature for individuals with clinically established CKD to a cohort of individuals with an eGFR < 60 ml/min/1.73 m² identified in primary care. Although these progression rates gave a predicted cumulative incidence of ESRD in line with that observed for a similar cohort,[96] there is emerging evidence to suggest that a subset of patients identified with a low eGFR in primary care are relatively stable and do not in fact progress. Some may even regress to less severe stages of disease. Our analysis makes the assumption that everyone in the cohort has progressive renal insufficiency, and as a result may overestimate cost-effectiveness of early referral individuals with stable eGFR who do not progress, and underestimate cost-effectiveness for individuals who have more progressive disease. More detailed investigation in primary care to identify those individuals who are progressive could potentially improve cost-effectiveness and affordability of early referral strategies.

Another weakness of the study is that, due to lack of evidence, the modelling relies on an effectiveness estimate for early referral taken from the only prospective study looking at the impact of early referral on a cohort that included individuals without diabetes. Although this was one of the highest quality studies identified by the clinical effectiveness review (see Chapter 5), controlling for various patient characteristics and treatment factors expected to influence outcome (diabetes, proteinuria and hypertension), it may still be subject to bias. Moreover, the cohort was entirely male, 50% had diabetes and the vast majority had proteinuria (89%). Therefore, there is a question over whether the 20% reduction in CKD progression and cardiovascular mortality observed for early referral in this cohort can be achieved in mixed gender CKD cohorts without diabetes. Another factor that may limit the generalisability of the Orlando study[111] is that the primary care arm may not reflect current primary care standards in the UK. Primary care management for people with CKD in the UK may have substantially improved as a result of the introduction of the QOF. Thus, the

relative effect achievable through early referral may be diminished. Sensitivity analysis demonstrates that cost-effectiveness is highly sensitive to the relative effect of early referral on CKD progression and/or cardiovascular event risks (see *Table 36*).

Potential for future research and further modelling

Although we attempted to use the best available evidence on the natural history of early CKD progression and the effectiveness of early referral, data in these areas are incomplete. There is clear need for prospective cohort studies to assess CKD progression and the incidence of cardiovascular events in individuals who have been identified as having an eGFR < 60 ml/min, with and without other complications/comorbidities such as microalbuminuria, proteinuria, diabetes and pre-existing CVD. This is particularly pertinent for those with mild CKD who have been detected through opportunistic testing and who, in the past, would not have come to the attention of a renal physician. Once these data are available they will allow more accurate modelling of the cost-effectiveness of referral based on different eGFR cut-offs and other comorbidities.

In addition, there is a clear need for prospective randomised studies to assess the effect of early referral or improved management strategies on the progression of CKD and the incidence of CVD events in the different subgroups of interest. The cost-effectiveness results reported here assume that early referral is associated with a 20% reduction in the risk of progression to the next stage or CVD mortality, regardless of CKD stage or level comorbidity. This was based on a reported HR associated with referral for individuals with CKD, which was adjusted for various comorbidities known to influence outcomes; but a question remains over the generalisability of these findings, particularly to cohorts with early stage 3 CKD.

No cardiovascular risk estimating equations were available at the time of writing, which incorporated eGFR, microalbuminuria or proteinuria as risk factors for cardiovascular events. As a result, we had to apply adjusted RR estimates for CVD events (associated with specific renal disease markers) to baseline risks for the cohort based on classical CVD risk factors. This staged approach will result in imprecision in the overall estimate of CVD event risk within each stage of the model. If in the future risk estimating equations that incorporate markers of renal disease become available, we will be able to update the model accordingly.

Reducing the risk of CKD progression and CVD in primary care also presents a feasible option for improving the management of individuals with markers of renal disease. This modelling study has focused on the potential cost-effectiveness of early referral to a specialist, but it is not the act of referral itself that reduces the risk of progression. A combination of factors such as obtaining better BP control, increasing appropriate use of ACE Is and other medications, and encouraging positive lifestyle changes are the likely mechanisms by which referral to a specialist affects the progression of disease. Appropriate use of these interventions may already be improving in primary care under the QOF, and it may be the case that further improvements can be achieved in a primary care setting without the need for referral. Furthermore, if the relative benefits of nephrology care were to be limited to improving the quality of life of patients within stage (through better management of anaemia for example), rather than preventing progression and prolonging life, then this would favour referral at later stages. Given the potentially prohibitive costs of implementing the SCS we have modelled here, it is pertinent that further research explores ways of improving management and outcomes for individuals with CKD in primary care.

Conclusions

Strategies to improve the management of people with CKD may offer an efficient use of health service resources. However, given the great uncertainty surrounding many parameter estimates, the effectiveness and cost-effectiveness of early referral needs to be demonstrated in prospective randomised studies. In addition, research is required to assess whether improved outcomes can be achieved for people with early stage renal disease through improved management in the primary care setting.

Chapter 7

Discussion

Overview of findings

In the previous chapters we have presented the findings of a series of systematic reviews and the development of an economic model assessing aspects of the clinical effectiveness and cost-effectiveness of early referral for CKD.

The review of the natural history of CKD identified evidence that reduced eGFR was a predictor for mortality, CVD, renal disease progression and ESRD. In cohorts of people with CKD, death was a common outcome regardless of whether the cohort was population or clinically based. The association between CKD and these outcomes was attenuated by taking into account comorbidities and age. Increasing stage of CKD was associated with higher levels of ACM, CVD and renal outcomes. A substantial increase in the risk of ACM and renal outcomes was noted when stage 3a was compared to stage 3b.

While RR estimates for ACM and renal outcomes increased with stage, the number of people in the affected category reduced. This should be borne in mind when considering where to target care. It may be possible to identify subgroups at higher risk of poor health outcomes but, because the prevalence of CKD falls steeply with eGFR, the absolute numbers of people experiencing a negative outcome will also fall.

The concept of 'early referral' implies a stage in an inevitable pathway. Though limited, there was some evidence that there may be a subgroup of people for whom the label of CKD does not result in progressive deterioration in kidney function or an increased risk of CVD. This subgroup was rarely considered in the literature and poorly characterised, but may account for more than 50% of those with CKD defined by KDOQI. This group will have little to gain from referral and the potential for harm from investigation, anxiety and unnecessary treatment. At the current time, there is no good way to identify such individuals. Any models of care for CKD should, therefore, be evaluated in the context of an RCT to ensure the benefits sufficiently outweigh the harms for people with different stages of CKD. Indeed, even

the evidence base around the effectiveness of pharmacological treatments (ACE I/ARB, statins) have largely considered CKD as a single group and have not considered the effect size for different stages of CKD.

Literature considering the effectiveness of early referral for CKD was limited and again there was heavy reliance on a study design that recruits people at the time of initiating RRT, with retrospective consideration of the care they have received. We found evidence that referral to a nephrology specialist more than 12 months prior to starting RRT (and even as early as more than 72 months before RRT) may improve outcomes including long-term survival on RRT. This also supports the survival benefits being related to not only planning and preparation for RRT but also risk factor modification for causes of mortality (in particular CVD).

Only two studies provided information about the impact of referral on the pre-RRT phase of care (and thus also included people who did not survive to dialysis).[111,120] Here there was some evidence that early referral (defined by degree of renal impairment) could be beneficial in terms of slowing progression and reducing mortality. A conclusion that must be treated with some caution for the following reasons: patients were not randomly allocated to the treatment groups; one study included only patients with diabetes and described a care setting likely to be substantially different from that in the UK; and very little information was available about what care was received. While little information was available about the care given, those in the early referral groups were more likely to be on ACE Is or ARBs. BP control was generally tighter in the referred group and some authors reported higher prescribing of statins.

The review of models of care for people with CKD found a dichotomy in the literature between early referral to specialist teams and approaches to shared care across a range of disciplines but including the primary care team. Three models of care were described: multidisciplinary clinics (including shared care across specialties and with primary care); structured care packages led by an

individual clinical specialty (such as renal nurses or pharmacists); and educative approaches to develop skills in both patients and professionals. Where evaluations were reported, there was evidence of the potential for well-designed services to provide benefit, with improvements in markers of disease and care. However, the reliance on self-reporting and descriptive or before-and-after designs by many authors did not allow robust assessment of effectiveness. Indeed, the only RCT (of MDC delivered as a case management programme versus standard care that combined primary care plus referral to a nephrologist in the usual way) found no statistically significant benefit but substantially higher cost.

We did not find any cost-effectiveness studies of early referral for CKD. One cost-effectiveness study of referral of patients with creatinine clearance rate of 20 ml/min (equivalent to advanced stage 4 CKD) versus referral on the development of clinically significant uraemia (e.g. established ESRD) reported potential cost savings with the earlier referral approach. The model derived effect estimates of potential benefits from a prospective study of an education intervention that had demonstrated improvements in dialysis free survival. The model focused on renal outcomes.[180]

In the absence of high-quality RCT evidence of clinical effectiveness of early referral, we undertook an economic modelling exercise to assess the potential cost-effectiveness of referring individuals with markers for renal disease. This allowed us to determine what factors were driving the economic model and where uncertainty was having the greatest impact. We constructed a Markov model utilising the evidence from the review of the natural history of CKD and clinical effectiveness of early referral. Using individual patient creatinines from primary care to estimate GFR for our cohort, we applied reported eGFR decline rates to simulate how people with CKD might progress through CKD stages and the outcomes they might encounter. In order to consider the potential cost impact of an early referral strategy, we used the best described referral programme reported in the models of care review (a shared care programme described by Jones and colleagues)[147] as an example of how a service might operate. We compared this to referral to a nephrology service in stage 5 as a base case. We recognise that this may no longer reflect current practice in the UK but, as the review of models of care noted, UK practice was evolving rapidly and was not uniform across the country. We therefore felt that

this provided a simple and transparent model against which to compare our hypothetical referral strategies. Moreover, this approach still allowed us to assess the incremental costs and consequences of sequentially increasing the eGFR referral cut-off up through the disease stages. The estimates of potential health benefits from such an intervention were obtained from a study using routine health-care data to retrospectively compare early referral to a nephrology service with primary care only. All the referral strategies considered produced more QALYs than our standard care package. Referral at stage 3a was considered to be the best option with an ICER of £973 per QALY. Thus the base-case modelling suggested that a package of early referral has the potential to offer a cost-effective use of resources. The model was found to be most sensitive to changes in the baseline risk of CKD progression (including the assumption that all patients have progressive diseases) and the effect of referral on risk of CKD progression.

Implications for health-care delivery

We have reported evidence of the potential for improvements in the care of people with CKD. While an early referral model, combining some form of shared care between primary and secondary care, has the potential to be cost-effective, it is unlikely that such a model is affordable or feasible. Key areas of uncertainty were identified around the natural history of people with CKD, in particular stage 1–3 CKD identified by the current 'opportunistic screening' approach, and whether subgroups can be identified where the risk of progression is low.

Indeed, the approaches already adopted in the UK to identify people with CKD have brought to the attention of the health-care system many people who would have previously gone unrecognised.[217,218] The majority of these people have stage 3 CKD. Such people are not those previously cared for by renal services. They would also not have made up a large component of people in clinical trials for treatments for CKD. As a result, the evidence for the optimal care of such people is unclear and this review further identifies the importance of well-designed clinical trials of interventions that will address the care of people with CKD.

CVD was observed to be high among those with an eGFR < 60 ml/min/1.73 m². At the current time CKD is not included as a high risk group

in the cardiovascular risk calculators widely used to determine a person's need for CVD prevention. The National Screening Committee has been considering the place of vascular risk factor screening (including screening for CKD) for a number of years, and in England progress continues towards the introduction of an 'NHS health check' screening programme.[175] All 40–74 year olds not already known to have diabetes mellitus, CVD or CKD will be invited for a 5 yearly risk factor check. Anyone with a BP ≥ 140/90 mmHg will be assessed for CKD with a blood test to estimate GFR. This wider population screening will further identify people who would not previously have come to the attention of services. The potential health benefits and harms from early identification and intervention in such a group remain poorly understood. Population screening studies have been conducted to determine if people with previously unknown CKD can be identified effectively. Various combinations of age, comorbidity, microalbuminuria and eGFR criteria have been used. To date, we have found no evidence of evaluation of these screening approaches in combination with an intervention to assess the effectiveness in reducing morbidity and mortality in the screened population.[175,219,220]

The focus of this review was to consider the evidence of clinical effectiveness and cost-effectiveness of 'early referral' to specialist services. The model of CKD services considered in the economics analysis relied heavily on specialist referral to secondary care but recognised that it was not feasible to do this in isolation from primary care. To implement a referral programme such as the SIMON model for all patients with CKD stage 3 or worse, even if it was possible to define a subgroup for whom progression was unlikely and referral therefore unnecessary, would require nephrology specialist capacity that is currently unavailable and unlikely to be affordable or feasible. Chapter 5 identified other options, all capable of delivering changes in clinical markers of improved control of risk factors that should be considered and evaluated in RCTs to identify the most clinically effective and cost-effective way forward.

The care of people with CKD in the UK is in a state of change. In recent years, attention has become more focused on the care of people with CKD, including the 'early' recognition and management of people with mild and moderate disease. The introduction of CKD to QOF has placed primary care at the centre of this process.

The evidence from this review supports the adoption of approaches that seek to develop shared care between primary and secondary care, rather than focusing on early specialist referral. The economic modelling undertaken here suggests that interventions that can achieve the sort of health gains in reduction of progression, ESRD, CVD and mortality reported in the clinical effectiveness review have a good chance of being cost-effective and are, therefore, worthy of further evaluation.

Future research

A number of critical areas of uncertainty were highlighted in this review and economic analysis. Further research is, therefore required and the research priorities in order of need are summarised below.

1. Cohort study of the natural history of CKD stage 1–3. A number of cohort studies are underway in the UK focusing on different populations (the elderly; black and Indian-Asians; laboratory detected CKD). The current natural history literature has identified that how a population was detected has important implications in terms of comorbidities and outcomes. The challenge, therefore, has been in applying the findings from the literature to what the natural history will be for people encountered in clinical practice.
    In order to better understand the impact of the changing approaches to CKD detection we need to understand the natural history of CKD in relevant populations. People included in cohort studies should reflect the different approach being adopted to identify CKD in clinical practice: population screening; screening of high risk groups; laboratory-detected CKD; and opportunistic detection as part of routine clinical care (e.g. addition to the QOF CKD register).
    Cohorts might be constructed from existing clinical data (laboratory or QOF registers) and involve record linkage to provide long-term follow-up or will require recruitment and follow-up of people with CKD. The introduction of screening programmes that include CKD should include an element of follow-up, particularly for those who were found to have evidence of kidney impairment. Where possible such cohort studies should include measure of eGFR, creatinine, microalbuminuria and proteinuria as well as emerging prognostic markers. Details of

current care should be collected to allow a better understanding about where the opportunities are to optimise care. Measures of quality of life and the impact of diagnosis should be included along with the traditional outcomes of CVD morbidity and mortality, renal progression and ESRD.

Based on the event rates reported in the natural history literature, a cohort constructed from patients identified with CKD through opportunistic screening might anticipate observing 500 deaths for every 1000 patients followed up for 10 years with 40 people progressing to ESRD. General population screening will identify a 'healthier' population and mortality could be expected to be lower; 250 per 1000 followed for 10 years with 10 people progressing to ESRD.

2. Review of the clinical effectiveness and cost-effectiveness of the main pharmacological interventions in people with CKD stage 1–3. Secondary research reviewing published studies of ACE Is/ARBs and statins reporting for this subgroup of CKD may be sufficient. A protocol has been published on Cochrane to this end but it is likely that most trials have not reported for these subgroups of CKD.[221] Individual patient data meta-analysis from the key trials may provide sufficient data, but outcomes among such trial participants have been substantially different from population studies suggesting they are highly selected. RCTs of such interventions in patients with CKD stage 1–3 may be required.

3. An RCT of models of care for people with CKD. Management of CKD is complex and the approach needs to be tailored to fit a patient's needs. A population-based model of chronic disease management with intensive case management for those with complex needs, disease management for those with more straightforward CKD, and supported self-care for those with stable and mild CKD with few other risk factors for CVD could draw on aspects of many of the reports in Chapters 4 and 5. An intervention should consider skill mix, education and support, communication,

barriers to referral, sustainability and feasibility. RCTs will need to break down such a model to evaluate aspects of care, comparing how different levels of care are delivered and who delivers them: MDC teams, specialist nephrologist, specialist nurse, GP with special interest, GPs and practice nurses, etc. As a priority, shared care (with proactive involvement of primary care with delivery of more than simply a phlebotomy service) should be compared to standard specialist nephrology and primary care. Any trials should include prospective economic evaluations.

Conclusions

Despite substantial focus on the early identification and proactive management of CKD in the last few years, we have identified significant evidence gaps about how best to manage people with CKD. There was some evidence to suggest that the care of people with CKD could be improved and, because these people are at risk from both renal and cardiovascular outcomes, strategies to improve the management of people with CKD have the potential to offer an efficient use of health service resources. However, given the great uncertainty surrounding many parameter estimates, the effectiveness and cost-effectiveness of care strategies need to be demonstrated in prospective randomised studies prior to implementation. Given the numbers of people now being recognised as having markers of kidney impairment, there is an urgent need for further research to support service change. The natural history of CKD in this new population of people identified as having kidney impairment needs to be better understood. For many, CKD occurs as part of a complex comorbidity cluster, with hypertension, diabetes mellitus and CVD. In focusing on developing and evaluating approaches to provide care for people with CKD, it will be important to keep sight of opportunities to avoid developing silos of care and to balance with the need to identify those who have the most to gain from early specialist intervention.

Acknowledgements

Contributions of authors

Dr C. Black (Senior Clinical Lecturer, Public Health) led the review and drafted the final report; she also led the review of clinical effectiveness. Ms P. Sharma (Research Assistant, Public Health) drafted sections of the background and led the review of natural history and care models. Ms D. McGurn (Systematic reviewer) data extracted and drafted the chapter on late referral. Mr G. Scotland (Research Fellow, Health Economics) and Dr P. McNamee (Senior Research Fellow, Health Economics) undertook the cost-effectiveness analysis and drafted this section. Ms L. Robertson (Research Assistant, Public Health) and Ms P. Sharma developed the search strategy and undertook all searching. Dr N. Fluck (Consultant Nephrologist) and Dr K. McCullouch (Nephrologist) provide clinical expertise. Professors W. Cairns Smith (Professor of Public Health) and A. MacLeod (Professor of Medicine and Therapeutics) provide research methods expertise. All authors contributed to the design, the interpretation of findings and populating the economics model, and read and commented on the final draft.

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Appendix 1

Search strategy summary

Searches for clinical effectiveness
Databases searched
MEDLINE (Ovid)
MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1950 to present
1. Kidney Failure, Chronic/
2. exp "Referral and Consultation"/
3. 1 and 2
4. (renal or kidney or nephropath$or nephrolog$).tw.
5. referr$.tw.
6. (timing or timely or time or early or earlier or late or later).tw.
7. (referr$and (kidney or renal or nephrolog$)).m_titl.
8. 4 and 5 and 6
9. 3 or 7 or 8
10. limit 9 to (nglish language and yr="1990 – 2008")

EMBASE (Ovid) 1988 to 2008 Week 05
1. Kidney Failure, Chronic/
2. (renal or kidney or nephropath$or nephrolog$).tw.
3. referr$.tw.
4. (timing or timely or time or early or earlier or late or later).tw.
5. (referr$and (kidney or renal or nephropath$or nephrolog$)).m_titl.
6. 2 and 3 and 4
7. exp patient referral/
8. 1 and 7
9. 2 and 3 and 4
10. 5 or 8 or 9
11. limit 10 to (English language and yr= "1990 – 2008")

SCIENCE CITATION INDEX (SCI) searched on 4 February 2008
1. Topic=((renal or kidney or nephropath* or nephrolog*) and referr*)
2. Databases = SCI-EXPANDED; timespan = 1990–2008
3. #1 AND Language=(English) AND Document Type=(Meeting Abstract OR Meeting Summary OR Meeting-Abstract)

4. Databases = SCI-EXPANDED; timespan = 1990–2008

ISI Proceedings
1. Topic=((renal or kidney or nephropath* or nephrolog*) and referr*)
2. Timespan = All Years. Databases = STP
3. Refined by: Document Type=(PROCEEDINGS PAPER OR MEETING ABSTRACT) > Document Type=(PROCEEDINGS PAPER OR MEETING ABSTRACT)

British Nursing Index, British Nursing Index Archive, HMIC, CINAHL
1. (kidney or renal or nephrolog$or nephropath$).mp. and referr$.tw. [mp=ti, ab, hw, it, ot]

The National Research Register (NRR) archive up to October 2007
https://portal.nihr.ac.uk/Pages/NRRArchive.aspx

The UK Clinical Research Network
http://www.ukcrn.org.uk/index.html

COCHRANE LIBRARY
CDSR and CENTRAL

1. (referral to the paediatric):ti
2. (renal or kidney or nephropath* or nephrolog*) and (refer or referral):ti and (renal or kidney or nephropath* or nephrolog*) and (refer or referral):ab, from 1990 to 2008 in Cochrane Reviews and Clinical Trials

Additional searches for cost-effectiveness

NHS EED searched on 26 March 2008
1. MeSH Diabetic Nephropathies EXPLODE 1 2
2. MeSH Kidney Diseases EXPLODE 1
3. MeSH Kidney Failure, Chronic EXPLODE 1 2
4. #1 or #2 or #3
5. MeSH Referral and Consultation EXPLODE 1
6. #4 and #5
7. renal OR kidney OR Nephrolog*:tw
8. refer*
9. timing OR timely OR time OR early OR earlier OR late OR later

10. #7 and #8 and #9
11. refer*:ti
12. kidney OR ren
13. kidney OR renal OR Nephrolog*:ti
14. #11 and #12
15. #6 or #10 or #13

Searches for natural history
Databases searched
MEDLINE (Ovid) 1996 to March 2008

1. Exp *Kidney Failure, Chronic/
2. Exp *Natural History/
3. Exp Disease Progression/
4. renal or kidney or nephropath$or nephrolog$).tw.
5. CKD.tw.
6. Natural course.tw.
7. Disease course.tw.
8. (Cohort or follow up or follow-up or longitudinal or prospective or screening or cross sectional or cross-sectional).tw.
9. (renal or kidney or nephropath$or nephrolog$).ti.
10. Exp Mass Screening/
11. Exp cohort studies/or exp cross-sectional studies/
12. Exp "review"/
13. Mass screen$.tw.
14. Review.ti.
15. Population-based stud$.tw.
16. 1 or 4 or 5 or 9
17. 2 or 3 or 6 or 7
18. 8 or 10 or 11 or 12 or 13 or 14 or 15

19. (Cohort or follow up or follow-up or longitudinal or prospective or screening or cross sectional or cross-sectional).ti.
20. Population-based stud$.ti.
21. 18 or 19 or 20
22. disease course or natural course).ti.
23. 17 or 22
24. 16 and 21 and 23
25. Limit 24 to (English language and humans and yr= "1998–2008")

EMBASE (Ovid) 1996 to March 2008
Similar keywords as outlined in MEDLINE search were used with slight modification.

Searches for care model
Databases searched
MEDLINE (Ovid) 1950 to June 2008

1. exp *Kidney Failure, Chronic/
2. exp *Patient Care Management/
3. (renal or kidney or nephro$or ckd).ti
4. (manag$or service or care or practice or pathway).ti
5. 1 and 2
6. 3 and 4
7. 5 or 6
8. limit 7 to (English language and yr="2002 – 2008")
9. Animals/
10. 8 not 9

EMBASE (Ovid) 1996 to June 2008
Similar keywords as outlined in MEDLINE search were used with slight modification.

Appendix 2

Data extraction form

Clinical effectiveness
DATA EXTRACTION FORM (NICE guidelines manual)

Person extracting data:
Date:

Bibliographic reference:

Ref ID	
Authors	
Title	
Journal	
Volume (issue)	
Year	
Pages	
Reference type	Abstract Full publication
Country	
Stated aim of study	
Source of funding	

Study type:

Study type	
Prospective/retrospective	

Number of patients:

Patient selection	
How were patients identified	
Inclusion criteria	
Exclusion criteria	
Number of patients started/completed Give numbers and reasons (if reported) and indication if withdrawals were similar to those who completed study	
Classification of CKD (e.g. KDOQI) Number of patients at different stages of CKD	

Patient characteristics at baseline

Data and indication if there were any significant differences observed

Definition of early/late referral (months)	
Other definitions	

Intervention

Initiation of referral	
Intervention studied Give as much detail as possible: setting, care, treatments, staffing, number and duration of visits, education	

Comparison

Alternative treatment	

Length of follow-up

Outcome measures

Primary outcomes	
Secondary outcomes	
Safety	
Adverse effects	

Results

Renal Function	
All-cause mortality	
CVD mortality	
Onset of RRT	
Quality of life	
Barriers to early referral	
Hospitalisation	
Emergency dialysis	
Survival on dialysis	
Costs	
Treatments	
Subgroups	
Integrity/Fidelity of Intervention Was the intervention implemented as planned? Adherence Exposure Quality of delivery Participant responsiveness Programme differentiation Subgroup variation	

Additional comments:

Appendix 3

Excluded studies

Clinical effectiveness

TABLE 37 Studies excluded from the clinical effectiveness systematic review

Study	Reason for exclusion
Anees 2007[222]	Cross-sectional survey
Arora 1999[223]	ER defined as <12 months
Avorn 2002[224]	ER defined as <12 months
Baker 2003[225]	Late referral
Barril 2002[226]	Not early CKD
Brown 2003[227]	Screening
Burton 1999[228]	Too little detail
Caskey 2003[229]	ER defined as <12 months
Cass 2002[230]	ER defined as <12 months
Chan 2007[231]	Review; ER defined as <12 months
Chandna 1999[232]	Timing of referral not assessed
Curtis 2007[233]	Timing of referral not assessed
Dautlich 1999[234]	Referral patterns
Department of Health 2005[2]	Not relevant to area
Dogan 2005[235]	ER defined as <12 months
Ellis 1998[236]	ER defined as <12 months
Fan 2002[237]	ER defined as <12 months
Fox 2006[238]	Qualitative study of primary care practices and knowledge regarding CKD
Goransson 2001[239]	ER defined as <12 months
Harris 1999[240]	ER defined as <12 months
Hyder 2000[241]	Referral patterns
Innes 1992[242]	Not comparing ER with LR
Iseki 2002[243]	ER defined as <12 months
Ismail 1998[244]	Review; non-systematic
Jones 2006[147]	Evaluating the effectiveness of a shared care scheme
Jones, 2006[105]	Natural history of CKD before and after first referral to nephrologist
Jungers 1993[245]	ER defined as <12 months
Jungers 1993[246]	ER defined as <12 months
Jungers 1997[247]	Abstract 1997
Jungers 2001[121]	ER defined as <12 months
Kazmi 2002[248]	ER defined as <12 months
Kazmi 2004[249]	ER defined as <12 months
Klebe 2007[250]	Economics
	Cost of implementing CKD guidelines

continued

TABLE 37 *Studies excluded from the clinical effectiveness systematic review (continued)*

Study	Reason for exclusion
Komenda 2006[169]	Non-systematic review
Lhotta 2003[251]	ER defined as < 12 months
Lin 2003[252]	ER defined as < 12 months
Lin 2004[253]	ER defined as < 12 months
Locatelli 2002[254]	Non-systematic review
London 2003[255]	Predictors of suboptimum care
Lusenti 2006[256]	Specific RAS intervention
McLaughlin 2001[180]	Economic evaluation
Mendelssohn 1999[257]	Guidelines
Nakamura 2007[55]	ER defined as < 12 months
Ohmit 2003[258]	Screening
Paris 2002[259]	Does not report mortality
Rao 2002[260]	Patterns of referral
Rasgon 2003[261]	Insufficient detail
Ratcliffe 1984[262]	1984
Ravani 2003[263]	ER defined as < 12 months
Roderick 1999[264]	Abstract 1999
	Published in full reference ID 15
Roderick 2002[265]	Avoid ability of late referral
Roubicek 2000[266]	ER defined as < 12 months
Rutherford 1997[267]	ER defined as < 12 months
Schmidt 1998[268]	Economic evaluation
Schwenger 2006[269]	ER defined as < 12 months
Sesso 1996[270]	ER defined as < 12 months
Shin 2007[271]	ER defined as < 12 months
Stack 2003[272]	ER defined as < 12 months
Stoves 2001[273]	ER defined as < 12 months
Thanamayooran 2005[151]	Evaluation of a multidisciplinary clinic
Thomas 2007[274]	Guidelines
Tseng 2008[94]	Not comparing early with late referral
Wavamunno 2005[275]	Non-systematic review
White 2002[276]	Evaluation of pre-dialysis clinic
Winkelmayer 2003[277]	ER defined as < 12 months
Wu 2003[278]	ER defined as < 12 months
AHRQ 2002[279]	Summary of research findings
AHRQ 2005[280]	Summary of research findings
AHRQ 2002[281]	Summary of research findings

AHRQ, Agency for Healthcare Research and Quality; CKD, chronic kidney disease; ER, early referral; LR, late referral; RAS, renal artery stenosis.

Natural history

TABLE 38 *Studies excluded from systematic review of natural history of CKD*

Study	Reason for exclusion
Adler 2003[203]	RCT, do not give outcomes by CKD group
Altman 1999[282]	Less than 100 patients
Boes 2006[283]	Mainly prediction study
Bruno 2003[284]	Study of incidence
Busch 2006[285]	RCT
Chandie 2006[286]	Does not include the cohort of CKD
Chauveau 2007[287]	Less than 100 patients
Chonchol 2007[288]	Does not separate out people with CKD from people without CKD
Chow 2003[115]	Cross-sectional study
Christensen 1999[289]	Less than 100 patients
Costacou 2007[290]	Less than 100 patients
Dale 2008[77]	Reviews most of the studies including patients with ESRD
Damman 2007[291]	Cohort of patient with heart failure
Dean 2005[292]	Less than 2 years' follow-up
Drummond 2002[293]	Does not separate out people with CKD from people without CKD
Earle 2001[294]	Less than 100 patients
Edwards 2005[295]	Does not identify those with or without CKD
El Kossi 2003[296]	Cohort of transplant not CKD
Fliser 2005[297]	Study of prediction only
Fliser 2007[298]	Duplicate cohort as above so only use one with relevant information
Fouque 2006[51]	RCT
Fried 2001[50]	Does not mention the difference of declining GFR
Fried 2004[299]	Presents the data by changing eGFR not by CKD
Hadjadj 2004[300]	Less than 100 patients
Hebert 2003[301]	Does not report the progression of CKD for whole cohort or relevant subgroup
Henry 2002[302]	Does not present data by CKD group
Hovind 2003[303]	Does not separate out people with or without CKD
Hovind 2001[304]	Does not split data by CKD
Hoy 2006[305]	Includes Australian Aborigines only
Hsu 2006[306]	Includes black people only
Imbasciati 2007[307]	Less than 100 patients
Iseki 2004[308]	Does not separate patients with or without CKD
Jacobsen 1999[309]	Does not separate patients with or without CKD
Jacobsen 2003[310]	Does not separate patient with or without CKD
Jafar 2001[311]	RCT and cohort defined only by protein
Jafar 2001[43]	Duplicate of above study
Jafar 2003[312]	RCT and cohort defined by sex only
Jafar 2003[313]	Cohort defined by protein and blood pressure

TABLE 38 *Studies excluded from systematic review of natural history of CKD (continued)*

Study	Reason for exclusion
Jovanovic 1999[314]	Less than 100 patients
Jude 2002[315]	Cohort presented by protein only, not by eGFR
Kasiske 1998[316]	Does not present change in renal function
Kim 2003[317]	Less than 100 patients
Kohli 2006[318]	Less than 100 patients
Kristjansson 2001[319]	Does not define by CKD group
Kronborg 2008[320]	Do not report data for CKD subgroup
Kshirsagar 2000[45]	Study predicting risk not giving a rate of decline in GFR
Larsson 2005[321]	Does not define by CKD group
Leeder 2006[322]	Presented by haemoglobin subgroup
Lerma 2005[323]	Editorial
Locatelli 2000[324]	Comparison of two RCTs
Mann 2003[325]	Does not identify subgroups of CKD
Marcotte 2006[326]	Less than 100 patients
Massy 1999[327]	No relevant subgroups
McClellan 2004[328]	Cohort of patients with acute myocardial infarction
Menon 2008[329]	Includes patients who were initially restricted to protein diet in RCTs
Merkin 2005[330]	Cohort defined by socioeconomic status only
Middleton 2006[331]	Testing the value of different screening criteria
Morita 2006[332]	Follow-up <2 years
Muhlhauser 2000[333]	Does not separate based on creatinine values
Neild 2004[334]	Cohort of people with reflux, specific renal diagnosis
Orth 2008[335]	Not a systematic review
Perlman 2003[336]	Does not include the cohort of CKD but those with ESRD
Ruggenenti 1998[337]	Cohort analysis of RCT
Rigalleau 2007[338]	Comment
Rottey 2000[339]	Less than 100 patients
Samuelsson 2000[340]	Letter
Sesso 2008[341]	Does not separate out by CKD group
Song 2005[342]	Less than 100 patients
Stam 2006[343]	Does not separate out by CKD group
Stojceva-Taneva 2001[344]	Less than 100 patients
Thomas 2006[345]	Less than 100 patients
Ueda 2003[346]	Less than 100 patients
Wang 2005[347]	Cross-sectional study
Wasse 2006[348]	Editorial
Wright 2002[349]	Less than 100 patients

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESRD; end-stage renal disease; GFR, glomerular filtration rate; RCT(s), randomised controlled trial(s).

Appendix 4

Quality assessment

TABLE 39 *Quality assessment of systematic reviews included in Chapter 3*

	Di 2007[68]	**Tonelli 2006**[67]
Internal validity[a]		
The study addresses an appropriate and clearly focused question	Well covered	Well covered
A description of the methodology used is included	Well covered	Well covered
The literature search is sufficiently rigorous to identify all the relevant studies	Well covered	Well covered
Study quality is assessed and taken into account	Not addressed	Well covered
There are enough similarities between the studies selected to make combining them reasonable	Adequately addressed	Adequately addressed
Overall assessment of the study		
How well was the study done to minimise bias? Code ++, + or –	++	++
If coded as + or – what is the likely direction in which bias might affect the study results?	NA	NA
Description of the study		
What types of study are included in the review?[b]	Cohort	Cohort
How does this review help to answer your key question? *Summarise the main conclusion of the review and how it relates to the relevant key question. Comment on any particular strengths or weaknesses of the review*	Study found that there is a moderate association between lower than average eGFR and CHD risk in general healthy population. Inclusion of participants from community with high response and follow-up rates were the main strength of this study. Study found less evidence for heterogeneity among studies and publication bias. Measurement bias was minimised by checking for serum creatinine assay within included studies; however, study failed to check for chronicity of CKD increasing the risk of inclusion of participants with acute renal failure	This study concluded that CKD (non-dialysis dependent) is associated with an increased risk for all-cause mortality or cardiovascular death and supports intervention in patients with CKD to prevent adverse outcomes. Overall, the study was of good quality. The study did not account for the chronicity (>3 months) of CKD which may have reduced classification bias by reducing cases with acute renal failure

CHD, coronary heart disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NA, not applicable.
a   Well covered, adequately addressed, poorly addressed, not addressed, not reported or not applicable
b   RCT, controlled clinical trial, cohort, case–control or other.

Appendix 5
Summarised result of Chapter 3

TABLE 40 *Risk of all-cause mortality and cardiovascular mortality and morbidity for general CKD population (eGFR < 60 ml/min/1.73 m²) unless stated*

Study ID	Measures	Values (variance)	Adjusted for what	Comparator/reference group
ACM				
HR or RR				
Astor 2008[85]	RR (95% CI)	1.77 (1.47 to 2.13)	Age, sex, race/ethnicity, previous cardiovascular diseases, blood pressure, use of antihypertensive medication, diabetes, smoking, body mass index, physical activity, cholesterol and C-reactive protein	eGFR ≥ 90 ml/min/1.73 m²
Eriksen 2006[96,97]	HR (95% CI) (stage 3 only)	1.25 (1.14 to 1.37)	Sex and age	For each eGFR decrease of 10 ml/min/1.73 m²
Herzog 2004[92]	HR CKD only (95% CI)	1.64 (1.58 to 1.70)	Associated comorbidity	Compared to those without CKD, CHF or anaemia
	HR CKD + CHF + anaemia (95% CI)	3.63 (3.52 to 3.75)	CKD defined based on ICD-9-CM and CPT codes	
Irie 2006[81]	RR (95% CI)	M: 1.31 (1.12 to 1.52) F: 1.39 (1.20 to 1.62)	Age, high blood pressure, smoking, alcohol, diabetes, cholesterol, body mass index, urinary protein	eGFR > 100 ml/min/1.73 m²
Meisinger 2006[76]	HR (95% CI)	M: 1.17 (0.97 to 1.41) F: 1.12 (0.90 to 1.39)	Age and survey, history of diabetes, smoking, body mass index, alcohol, high blood pressure, physical activity, dyslipidaemia	eGFR ≥ 60 ml/min/1.73 m²
Tonelli 2006[68]	RR (95% CI)	3.0 (2.18 to 4.11) (NB heterogeneity reported)	Pooled estimate therefore variable with each included study (range 0.94–5.00)	eGFR ≥ 60 ml/min/1.73 m²
FHS 1999[a]	HR (95% CI)	M: 1.31 (1.02 to 1.68 F: 1.08 (0.87 to 1.34)	Adjusted	eGFR ≥ 60 ml/min/1.73 m²
NHANES I 2002[a]	HR (95% CI)	1.00 (0.76 to 1.32)	Adjusted	eGFR ≥ 60 ml/min/1.73 m²
Shivonen 2004[a]	HR (95% CI)	3.48 (1.95 to 6.21)	Adjusted	eGFR ≥ 60 ml/min/1.73 m²
Weiner 2004[74]	HR (95% CI)	1.36 (1.21 to 1.53)	Age, sex, high blood pressure, diabetes, systolic blood pressure, body mass index, cholesterol, smoking, alcohol, left ventricular hypertrophy, high school graduation and race	eGFR ≥ 60 ml/min/1.73 m²
SMR				
Eriksen 2006[96,97]	Mortality rate ratio (95% CI)	2.2 (2.1 to 2.4)	Standardised for age and sex	Tromsø general population
Evans 2005[98]	SMR (95% CI)	8.3 (7.5 to 9.2)	Standardised for age and sex	Swedish population

continued

TABLE 40 *Risk of all-cause mortality and cardiovascular mortality and morbidity for general CKD population (eGFR < 60 ml/min/1.73 m²) unless stated (continued)*

Study ID	Measures	Values (variance)	Adjusted for what	Comparator/reference group
John 2004[104]	SMR (95% CI)	1.53 (1.44 to 1.62)	Standardised for age and sex	Population of south-east England
Cardiovascular morbidity and mortality				
HR or RR				
Astor 2008[85]	RR of CVD deaths (95% CI)	2.12 (1.65 to 2.73)	Age, sex, race/ethnicity, previous cardiovascular diseases, blood pressure, use of antihypertensive medication, diabetes, smoking, body mass index, physical activity, cholesterol and C-reactive protein	eGFR ≥ 90 ml/min/1.73 m²
Irie 2006[81]	RR of CVD deaths (95% CI)	M: 1.65 (1.25 to 2.18) F: 1.81 (1.39 to 2.36)	Adjusted for age, high blood pressure, smoking, alcohol, diabetes, cholesterol, body mass index, urinary protein	eGFR > 100 ml/min/1.73 m²
Meisinger 2006[76]	HR for CVD deaths (95% CI)	M: 1.48 (1.15 to 1.92) F: 1.60 (1.17 to 2.18)	Adjusted for age and survey, history of diabetes, smoking, body mass index, alcohol, high blood pressure, physical activity, dyslipidaemia	Without CKD
Meisinger 2006[76]	HR for incident MI (95% CI)	M: 1.51 (1.09 to 2.10) F: 1.67 (1.07 to 2.61)	Adjusted for age and survey, history of diabetes, smoking, body mass index, alcohol, high blood pressure, physical activity, dyslipidaemia	Without CKD
Tonelli 2006[68]	RR of CVD mortality (95% CI)	2.47 (1.42 to 4.30) (heterogeneity reported)	Adjustment varies between the included studies	eGFR ≥ 60 ml/min/1.73 m²
Wannamethee 2006[37]	HR for CVD death (95% CI)	eGFR < 60 ml/min/1.73 m²: 1.49 (1.10 to 2.03) eGFR 60–69 ml/min/1.73 m²: 1.27 (0.95 to 1.68)	Adjusted for age, smoking, activity, alcohol, body mass index, cardiovascular diseases, diabetes, forced expiratory volume 1, albumin, systolic blood pressure, left ventricular hypertrophy, high blood pressure, high-density lipoprotein-cholesterol	eGFR > 70 ml/min/1.73 m²
Weiner 2004[74]	HR of MI/fatal CHD (95% CI)	1.09 (0.91 to 1.29)	Age, sex, high blood pressure, diabetes, systolic blood pressure, body mass index, cholesterol, smoking, alcohol, left ventricular hypertrophy, high school graduation and race	eGFR ≥ 60 ml/min/1.73 m²
Di 2007[69]	RR for CHD (95% CI)	1.32 (1.19 to 1.68)	Adjusted varies between the included studies	eGFR ≥ 60 ml/min/1.73 m²
John 2004[104]	SMR for CVD mortality (95% CI)	1.14 (1.03 to 1.25)	Standardised for age and sex	Population of south-east England

ACM, all-cause mortality; CHD, coronary heart disease; CHF, congestive heart failure; CI, confidence interval; CKD, chronic kidney disease; CPT, physicians' current procedural terminology; eGFR, estimated glomerular filtration rate; F, female; FHS, Framingham Heart Study; HR, hazard ratio; ICD-9-CM, *International Classification of Diseases*, Ninth Edition, Clinical Modification; M, male; MI, myocardial infarction; NHANES, National Health and Nutritional Examination Survey; RR, relative risk; SMR, standardised mortality rate.
a   Study within Tonelli *et al.* 2006.[68]

Appendix 6

Summarised result (subgroups) of Chapter 3

TABLE 41 All-cause mortality/cardiovascular disease morbidity and mortality/renal outcomes for diabetes mellitus in CKD

Study ID	Measures	Value (variance)		Notes
		Total CKD	**CKD stages**	
ACM				
Bruno 2007[79]	HR of mortality (95% CI)	1.92 (1.64 to 2.23)	Stage 1: reference Stage 2: 0.83 (0.58 to 1.17) Stage 3a: 1.02 (0.70 to 1.49) Stage 3b: 1.10 (0.72 to 1.68) Stage 4: 4.12 (2.36 to 7.18)	HR adjusted for age and sex. Compared with eGFR ≥ 60 ml/min/1.73 m^2
Bruno 2007[79]	Mortality rate per 10,000 person-years	953	Stage 1: 42.5 Stage 2: 49.5 Stage 3a: 85.8 Stage 3b: 108.8 Stage 4: 377.1	Compared to 487 with eGFR ≥ 60 ml/min/1.73 m^2
Patel 2005[80]	Mortality rate per 10,000 person-years		eGFR > 60 no proteinuria: 470 eGFR > 60 + proteinuria: 580 Stage 3a: 810 Stage 3b: 1500 Stage 4: 2010 Stage 5: 2980	
Cumulative mortality within follow-up period				
Bruno 2007[79]	Number of deaths	304/1539 (19.75%)	Stage 1: 37/113 (32.7%) Stage 2: 329/898 (36.6%) Stage 3a: 217/400 (54.3%) Stage 3b: 66/106 (62.3%) Stage 4: 21/21 (100%)	10 years' follow-up
Tarnow 2004[89]	Number of deaths	51 (26%)		9 years' follow-up
Rossing 2004[88]	Number of deaths	79 (35%)		Median follow-up 6.5 years
Tseng 2008[94]	Number of deaths	6934 (17.8%)	Stage 3a: 3984/27,312 (14.6%) Stage 3b: 1963/8760 (22.4%) Stage 4: 987/2959 (33.4%)	Median follow-up 19.3 (range < 0.01 to 24) months
Tseng 2008[94]	Number of dialysis-free deaths	6454 (16.5%)	Stage 3a: 3854/27,312 (14.1%) Stage 3b: 1810/8760 (20.7%) Stage 4: 790/2959 (26.7%)	

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TABLE 41 *All-cause mortality/cardiovascular disease morbidity and mortality/renal outcomes for diabetes mellitus in CKD (continued)*

Study ID	Measures	Value (variance)		Notes
		Total CKD	**CKD stages**	
				continued
CVD morbidity/mortality				
Bruno 2007[79]	HR of CVD deaths (95% CI)	2.16 (1.74 to 2.68)	Stage 1: reference Stage 2: 0.77 (0.46 to 1.29) Stage 3a: 0.96 (0.55 to 1.67) Stage 3b: 1.19 (0.65 to 2.17) Stage 4: 4.64 (2.15 to 10.01)	Adjusted for age and sex, compared with GFR ≥ 60: 1
Bruno 2007[79]	CVD deaths rate per 10,000 person-years	507	Stage 1: 19.5 Stage 2: 22.9 Stage 3a: 43.8 Stage 3b: 64.3 Stage 4: 213.6	Compared to 225 with GFR≥60
Cumulative cardiovascular mortality/events during follow-up				
Bruno 2007[79]	Number of CVD deaths	162/1539 (10.5%)	Stage 1: 17/113 (15%) Stage 2: 152/898 (16.9%) Stage 3a: 111/400 (27.8%) Stage 3b: 39/106 (36.8%) Stage 4: 12/21 (57.1%)	Mean follow-up 10 years
Tarnow 2004[89]	CVD events (95% CI)	11% (8 to 14)		9 years' follow-up
Rossing 2004[88]	Number of deaths	55/227 (24.2%)		Median follow-up 6.5 years
Rossing 2004[88]	Number of new CVD events	Range: 7–38 (3–17%)		Median follow-up 6.5 years
Renal outcomes				
Leehey 2005[109]	Mean rate of decline of GFR (range) ml/min/1.73 m²/year	4.5 (–14 to 32)		
Mulec 1998[87]	Rate of decline in GFR (SD) ml/min/1.73 m²/year	3.8 (3.7)		
Hovind 2001[93]	Mean rate of GFR decline (SD) ml/min/1.73 m²/year	4.0 (0.2)		Median follow-up 6.7 (range 3–14) years
Rossing 2004[88]	Mean rate of decline of GFR (SD) ml/min/year	5.2 (4.1)		Not standardised to body surface area
Hemmelgarn 2006[101]	Rate of decline in eGFR (95% CI) ml/min/1.73 m²/year		Stage 2: F: 1.6 (1.0 to 2.1); M: 2.1 (1.6 to 2.6) Stage 3: F: 2.8 (2.3 to 3.3); M: 3.6 (3.1 to 4.2) Stage 4: F: 2.9 (2.2 to 3.7); M: 3.2 (2.3 to 4.0)	Adjusted for age

TABLE 41 All-cause mortality/cardiovascular disease morbidity and mortality/renal outcomes for diabetes mellitus in CKD (continued)

Study ID	Measures	Value (variance)		Notes
		Total CKD	**CKD stages**	**Notes**
Patel 2005[80]	Rate of progression to ESRD as events per 100 person-years		eGFR > 60 no proteinuria: 0.0 eGFR > 60 + proteinuria: 0.2 Stage 3a: 0.3 Stage 3b: 1.7 Stage 4: 14.2 Stage 5: 0	Progression to ESRD is defined as a change to an estimated GFR less than 15 ml/min/1.73 m^2
	Rate of any progression as events per 100 person-years		eGFR > 60 no proteinuria: 3.2 eGFR > 60 + proteinuria: 7.8 Stage 3a: 10.5 Stage 3b: 11.8 Stage 4: 15.1 Stage 5: 0	Any progression of CKD is defined as a change to any disease group category with a lower GFR and/or presence of proteinuria with at least a 20 % decrease in estimated GFR (to avoid trivial changes in CKD classifications)
Orlando 2007[111]	HR of progression (95% CI)		Stage 1 to 2: 1.32 (1.13 to 1.55) Stage 2 to 3: 1.18 (0.97 to 1.43) Stage 3 to 4: 1.13 (0.86 to 1.50)	Compared to non-diabetics CKD
Rossing 2004[88]	Proportion of doubling of baseline serum creatinine	63/227 (28%)		Median follow-up 6.5 years
Khatami 2007[108]	Proportion progressed to CKD stages 4 and 5	8.6%		4 years' follow-up, eGFR < 60 ml/min/1.73 m^2 at baseline
Jones 2006[105]	Proportion of progressors	64/314 (20.4%)	≤ −5 ml/min/year: 32/145 (22%) > −5 to ≤ −1 ml/min/year: 32/169 (19%)	Non-progressors 60/412 (15%). Progression defined as ≤ −1 ml/min/year Median follow-up 2.9 years
Rossing 2004[88]	Number reaching ESRD within follow-up	15 (7%)		Median follow-up 6.5 years (range 3–17)
Tseng 2008[94]	Number of dialysis during follow-up	841 (2.2%)	Stage 3a: 203/27,312 (0.7%) Stage 3b: 251/8760 (2.9%) Stage 4: 387/2959 (13.1%)	Median 19.3 months (1.6 years)

ACM, all-cause mortality; CI, confidence interval; CKD, chronic kidney disease, CVD, cardiovascular diseases; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; F, female; HR, hazard ratio; M, male; SD, standard deviation.

TABLE 42 *All-cause mortality/cardiovascular disease morbidity and mortality/renal outcomes for those with CKD and CVD or hypertension*

Study ID	Measures	Values (variances)		Comparator	Comments
		Total CKD	**CKD stages**	**Comparator**	**Comments**
CKD with CVD					
Levin 2001[84]	Proportion of RRT	At 6 months: 4/118 (3.4%) At 12 months: 6/92 (6.5%) At 24 months: 6/31 (19.4%)		No CVD At 6 months: 10/268 (3.7%) At 12 months: 7/218 (3.2%) At 24 months: 18/94 (19.1%)	Median follow-up 23 months
Orlando 2007[111]	HR for progression (95% CI)		Stage 1 to 2: 1.35 (1.14 to 1.61) Stage 2 to 3: 1.52 (1.23 to 1.93) Stage 3 to 4: 0.86 (0.64 to 1.17)	Compared with no CVD	
Tonelli 2006[68]	RR for ACM (95% CI)	1.71 (1.49 to 1.96)		Compared with no CVD	Pooled from nine studies
Tonelli 2006[68]	RR for CVD mortality	1.8 (1.45 to 2.24)		Compared with no CVD	Pooled from seven studies
Tseng 2008[94] (diabetic population at baseline)	HR for dialysis (95% CI)	1.25 (1.17 to 1.33)			Adjusted for nephrology referrals, age, sex, race, poverty, index eGFR, life threatening disease, physical comorbid, mental morbidity, no of visits
	HR for dialysis free death (95% CI)	1.30 (1.27 to 1.32)			
	HR for ACM (95% CI)	1.29 (1.27 to 1.32)			
CKD with HBP					
Orlando 2007[111]	HR of CKD progression (95% CI)		Stage 1 to 2: 0.8 (0.66 to 1.35) Stage 2 to 3: 0.93 (0.72 to 1.57) Stage 3 to 4: 0.91 (0.77 to 1.53)	Compared with no HBP	
Tonelli 2006[68]	HR of ACM (95% CI)	2.15 (1.77 to 2.61)		Compared with no HBP	Pooled from eight studies
Tonelli 2006[68]	HR of CVD mortality (95% CI)	2.35 (1.52 to 3.64)		Compared with no HBP	Pooled from three studies

ACM, all-cause mortality; CI, confidence interval; CKD, chronic kidney disease, CVD, cardiovascular diseases; eGFR, estimated glomerular filtration rate; HBP, high blood pressure; HR, hazard ratio; RR, relative risk; RRT, renal replacement therapy.

TABLE 43 *Summarised result for different age groups in CKD*

Study ID	Measure	Age groups	Value (variance)	Comments
ACM				
Bruno 2007[79]	HR of ACM (95% CI)	<70 years	1.51 (1.07 to 2.13)	eGFR<60 vs ≥60, adjusted for age and sex (diabetics at baseline)
		≥70 years	1.09 (0.89 to 1.35)	
Evans 2005[98]	SMR for ACM (95% CI)	<69 years	20.6 (11 to 35.3)	All population CKD stages 4 and 5
Eriksen 2006[96,97]	Cumulative mortality of 10 years (95% CI)	<69 years	0.17 (0.14 to 0.21)	All population CKD stage 3
		70–79 years	0.49 (0.45 to 0.54)	
		>79 years	0.84 (0.80 to 0.89)	
Drey 2003[95]	Number of deaths in median follow-up of 5.5 years	<50 years	17/70 (24.3%)	Median survival time: 50–59 years: 55 months >80 years: 26 months
		50–59 years	27/52 (51.9%)	
		60–69 years	92/159 (57.9%)	
		70–79 years	246/379 (64.9%)	
		>80 years	354/410 (86.3%)	
Eriksen 2006[96,97]	Mortality rate ratios (95% CI)	<69 years	3.1 (2.5 to 3.9)	All population CKD stage 3
		70–79 years	2.0 (1.8 to 2.3)	
		>79 years	2.2 (2.0 to 2.3)	
Cardiovascular morbidity and mortality				
Bruno 2007[79]	HR of CVD mortality (95% CI)	<70 years	1.46 (0.85 to 2.51)	eGFR<60 vs ≥60, adjusted for age and sex (diabetics at baseline)
		≥70 years	1.07 (0.80 to 1.42)	
John 2004[104]	SMR for CVD mortality (95% CI)	<60 years	10.8 (1.28 to 20.32)	Compared to population of south-east England; standardised for age and sex
		≥80 years	0.96 (0.86 to 1.06)	
ESRD				
Eriksen 2006[96,97]	10 years' cumulative incidence of ESRD (95% CI)	<69 years	0.07 (0.05 to 0.11)	All population CKD stage 3
		70–79 years	0.04 (0.02 to 0.07)	
		>79 years	0.03 (0.01 to 0.05)	
Cumulative incidence				
Hsu 2003[103]	Incident of ESRD (4 years and 6 years)	Age 20–60 years	Black people: 14,593; white people: 20,323	Fixed 1991–6 and 1994–9
		Age 61–74 years	Black people: 6714; white people: 18,693	
Drey 2003[95]	Incident of ESRD in follow-up	<60 years	28 (21%)	Mean 5.5 years
		≥60 years	11 (1.5%)	

TABLE 43 *Summarised result for different age groups in CKD*

Study ID	Measure	Age groups	Value (variance)	Comments
Eriksen 2006[96,97]	Incidence rate ratios of ESRD (95% CI)	<69 years	36.6 (21.2 to 63.2)	All population CKD stage 3
		70–79 years	3.1 (2.3 to 7.0)	
		>79 years	3.7 (2.2 to 6.2)	
Hsu 2003[103]	New ESRD cases (1996)/CRI prevalence (1991)	Age 20–60 years	Black people: 0.099; white people: 0.017	
		Age 61–74 years	Black people: 0.027; white people: 0.008	

ACM, all-cause mortality; CI, confidence interval; CKD, chronic kidney disease, CRI; chronic renal insufficiency; CVD, cardiovascular diseases; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SD, standard deviation; SMR, standardised mortality rate.

TABLE 44 *Summarised result for gender differences in CKD*

		Value (variances)		
Study ID	Measures	Male	Female	Comments
ACM				
Evans 2005[98]	SMR of mortality (95% CI)	7.2 (6.3 to 8.1)	12.3 (10.3 to 14.5)	Compared to general Swedish population
Eriksen 2006[96,97]	10 years' cumulative mortality (95% CI)	0.61 (0.56 to 0.67)	0.47 (0.43 to 0.50)	
Eriksen 2006[96,97]	Number of deaths during follow-up	383 (41%)	576 (27%)	Median follow-up 3.6 years
Drey 2003[95]	Number of deaths during follow-up	448/646 (69.35%)	288/425 (67.76%)	Mean 5.5 years
Eriksen 2006[96,97]	Mortality rate ratios (95% CI)	2.4 (2.2 to 2.7)	2.1 (1.9 to 2.3)	
Renal outcomes				
Eriksen 2006[96,97]	10 years' cumulative incidence of ESRD (95% CI)	0.08 (0.05 to 0.11)	0.03 (0.02 to 0.04)	
Eriksen 2006[96,97]	ESRD during follow-up	Stage 5: 33 (4%) RRT: 2 (0.2%)	Stage 5: 25 (1%) RRT: 2 (0.1%)	Median follow-up 3.6 years
Hsu 2003[103]	Incidence of ESRD (4 and 6 years)	Black people: 10,555 White people: 22,001	Black people: 10,752 White people: 17,015	1991–6 and 1994–9
Eriksen 2006[96,97]	ESRD incidence rate ratios	6.5 (4.3 to 9.9)	4.3 (2.7 to 6.9)	
Hsu 2003[103]	New ESRD cases(1996)/ CRI prevalence (1991)	Black people: 0.069 White people: 0.015	Black people: 0.044 White people: 0.008	
Hovind 2001[93]	Mean rate of GFR decline (SD) ml/ min/1.73 m^2/year	4.1 (0.3)	4.0 (0.4)	Median follow-up 6.7 years

ACM, all-cause mortality; CI, confidence interval; CRI; chronic renal insufficiency; ESRD, end-stage renal disease; GFR, glomerular filtration rate; RRT renal replacement therapy; SD, standard deviation; SMR, standardised mortality rate.

Appendix 7

Late referral for CKD: evidence of the impact on health outcomes

Background

As CKD progresses towards ESRD, the patient and clinical team need to prepare. Decisions about RRT modality, preparation for transplant if appropriate, establishment of vascular access for haemodialysis, nutritional preparation, management of anaemia, and fluid and electrolyte balance are all important aspects of preparations. During this time, patients and their carers need support and also the time to plan and prepare. The 12 months prior to dialysis have been described by some as a critical time, and yet very late referral to specialist renal services remains common place. Between 20% and 50% of referrals reportedly occur within 4 months of the need to start dialysis.[54–56,350,351]

In searching for literature about the effectiveness of early referral for CKD, we identified a substantial literature evidencing the implications of late referral and this is summarised here.

Chan and colleagues[57] recently published a meta-analysis which compared the differences in mortality and duration of hospitalisation in CKD patients who were referred early to a nephrologist versus those who were referred late. They concluded that late referral of CKD patients significantly increased the risk of death (RR 1.99, 95% CI 1.66 to 2.39).

Chan and colleagues'[57] review focused on ACM and hospitalisation in dialysis patients in relation to the timing of referral to specialist nephrology care. In this appendix, we considered other outcomes, including cardiovascular mortality and morbidity and quality of life, and sought information about what criteria or factors triggered referral. We focused on studies reporting, as a minimum, mortality as an outcome and comparing referral less than 12 months before the initiation of RRT to earlier referral.

Results

Twenty-seven studies were identified from the literature search. Of these, 10 studies were excluded because they did not measure mortality, leaving 17 studies.

The studies reported findings from a wide range of countries: three studies from the UK,[236,237,273] a further four from Europe,[239,251,266,269] three from the USA,[249,277,352] five from Asia,[243,252,253,271,278] one from Australia/New Zealand[230] and one from Brazil.[270] All 17 studies were available in full publication.

All 17 of the studies were retrospective, based on recruiting participants at the initiation of RRT.

The time interval used to define 'late referral' differed among the studies. Three studies[237,243,270] considered 'late referral' as being less than 1 month between first contact with renal specialty and the commencement of dialysis. Seven studies[230,236,239,271,273,277,352] defined 'late referral' as being less than 3 months between referral and starting dialysis. A definition of less than 16 weeks/4 months was used in two studies,[249,266] while one study[251] determined 'late referral' in relation to GFR. Patients with a GFR < 20 ml/min/1.73 m² at first referral were grouped as 'late referral'. The remaining four studies[252,253,269,278] considered late referral as being referred less than 6 months prior to commencing RRT.

Six of the 17 studies included in excess of 1000 participants.[230,243,249,273,277,352] The majority of the studies included smaller patient groups, where participant numbers ranged from 52 to 270. The number of study participants across all studies totalled 16,600. Only one study reported a measure of renal function at the time of referral.[251] Four of the studies specified in their methods that people with acute renal failure were excluded.[230,239,249,266] *Table 45* summarises the included studies.

TABLE 45 Summary of included studies of late referral

Study ID	Country	Definition of late referral	Total number starting dialysis	Inclusion criteria	Total number of study participants	% late referrals
Avorn 2002[352]	USA	≤90 days	17,884	Adequate records; 'insured' patients; first diagnosis of renal disease >1 year prior to dialysis; >30 days dialysis (exclusion: second dialysis not received but survived >1 month or >2 months between dialysis)	3014	34
Cass 2002[230]	Australia and New Zealand	<3 months	5590	Patients with ESRD; started RRT in Australia (exclusion: ARF, death or transplantation within first year of dialysis)	4243	26.9
Ellis 1998[236]	UK	<12 weeks	198	Commencing RRT due to ESRD	198	32.3
Fan 2002[237]	UK	<30 days	211	Started HD for first time (exclusion: established on HD for >30 days)	98	28
Goransson 2001[239]	Norway	<3 months	242	Patients with renal failure/serum creatinine >normal for >1 year (exclusion: ARF and entering RRT due to failing kidney graft)	242	81.7
Iseki 2002[243]	Japan	<28 days	1551	Exclusion: patients who died within first month of RRT; difficulty in confirming the first start day or serum creatinine level at first visit	1162	21.4
Kazmi 2004[249]	USA	≥4 months	4024	≥18 years old; completed questionnaire; survived first 60 days dialysis (exclusion: ARF, pre-emptive or kidney transplant recipients, AIDS or cancer patients, returning to dialysis)	2195	34
Lhotta 2003[251]	Austria	GFR <20 ml/min/1.73 m²	NR	Starting RRT	75	56
Lin 2003[252]	Taiwan	<6 months	NR	Type 2 diabetic receiving HD for at least 6 months (exclusion: switching between modalities)	115	54
Lin 2004[253]	Taiwan	<6 months	NR	RRT for at least 3 months (exclusion: switching modalities)	105	57
Roubicek 2000[266]	France	<16 weeks	309	Dialysis for the first time, available medical records (exclusion: acute irreversible or rapidly progressing renal failure)	270	34
Schwenger 2006[269]	Germany	<8 weeks	280	Initiating HD	254	47
Sesso 1996[270]	Brazil	<1 month	252	Exclusion: diabetic ESRD; diagnosis made >1 and <3 months before dialysis	184	57.6
Shin 2007[271]	Korea	<90 days	119	Receiving HD for 4-hour session three times/week (exclusion: those transferred from another dialysis programme, hypersensitivity to membrane, current infection, malignancy, liver disease, autoimmune disease, receiving drugs that affect immunity)	119	43.7

TABLE 45 *Summary of included studies of late referral (continued)*

Study ID	Country	Definition of late referral	Total number starting dialysis	Inclusion criteria	Total number of study participants	% late referrals
Stoves 2008[273]	UK	<90 days	1260	(Exclusion: in receipt of transplant, transfer away from the unit)	1260	37.1
Winkelmayer 2003[277]	USA	<90 days	NR	Diagnosis of renal disease >1 year before first dialysis (exclusion: patients on single dialysis and survived >1 month or limited dialysis treatment and survived >2 months)	3014	34
Wu 2003[278]	Taiwan	<6 months	NR	Type 2 diabetic nephropathy, new onset ESRD, on PD for more than 3 months	52	69

ARF, acute renal failure; ESRD, end-stage renal disease; HD, haemodialysis; PD, peritoneal dialysis; NR, not reported; RRT, renal replacement therapy.

Mortality

1-year mortality

Five studies reported the 1-year mortality rate after initiating RRT.[236,237,243,271,277] Three studies reported the RR of death at 1 year, comparing late to early referral[249,277,352] (*Table 46*). Two further studies reported mortality at 3 and 6 months and were included in the table for completeness.[266,270]

The 1-year ACM after initiation of RRT varied substantially between studies, ranging from 2.8%[237] to 27.5%[236] in the early referral group. In late referral groups, 1-year mortality ranged from 7.4%[237] to 39.5%.[236] Studies consistently reported higher mortality in the late referral group than in the early group at 1 year. This was also found at 6 months,[270] but at 3 months a small study[266] reported no difference. The statistical significance of the differences was not reported by most authors.

Two studies provided data on the percentage of death attributable to CVD. At 3 months, CVD mortality accounted for 50% of deaths in the early referral group and 67% in the late referral group.[266] At 6 months, 40% of deaths and 35% respectively were reported.[270]

Three studies reported risk of death associated with late as compared to early referral at 1 year.[249,277,352] Avorn and colleagues[352] and Kazmi and colleagues[249] found a statistically significant increase in risk among those referred late (37–42% greater risk than early referral) after adjustment for social demographics, insurance cover, comorbidity and aetiology of kidney disease. Winkelmayer and

colleagues[277] reported a non-significant difference [odds ratio (OR) 1.03, 95% CI 0.84 to 1.25] between the groups at 1 year after adjusting for social demographics and comorbidity.

5-year mortality

Mortality rates at 5 years after initial referral were reported in five studies.[239,243,252,266,273] In the early referral groups, mortality ranged from 27.6%[252] to 51.5%[239] at 5 years, and in the late referral groups this ranged from 36.1%[266] to 83.3%.[278] The 5-year mortality rate was higher in the late referral group in all but two studies where there was little difference.[243,266]

Iseki[243] reported no difference in risk of mortality with referral timing after adjustment (factors adjusted for were not reported) (HR 1.02, 95% CI 0.77 to 1.35). Roubicek and colleagues[266] did not report details, but also found no statistically significant difference after adjustment. Lin and colleagues[252] reported a lower RR of death in those referred early as compared to late (RR 0.45, 95% CI 0.25 to 0.81).

A further six studies reported follow-up for greater than 1 year (summarised in *Table 47*). The longest follow-up was reported by Shin and colleagues[271] at 6.7 years and 23% (early referral) versus 42% (late referral) died. Of the five studies where RR was estimated, only one reported no statistically significant difference in mortality comparing early and late referral.[251] Schwenger and colleagues[269] calculated the RR of death in the late referral group at 1.7 years after initiation of dialysis. The RR of late referral for patients under the age

TABLE 46 *Mortality at up to 1 year*

Study ID	ER		LR		Risk ratio[a] late vs early (95% CI) unadjusted	Risk ratio[a] late vs early (95% CI) adjusted	Adjusted for
	% deaths	% of ER deaths due to CVD	% deaths	% of LR deaths due to CVD			
Avorn 2002[352]	NR	NR	NR	NR	NR	RR 1.37 (1.22 to 1.52)	Age, race, socioeconomic status, presence of any renal diagnosis in year before dialysis
Ellis 1998[236]	27.5	NR	39.5	NR	NR	NR	
Fan 2002[237]	2.8	NR	7.4	NR	NR	NR	'No significant difference between ER and LR groups'
Iseki 2002[243]	10.9	NR	15.1	NR	NR	NR	
Kazmi 2004[249]	NR	NR	NR	NR	HR 1.44 (1.15 to 1.80)	HR 1.42 (1.12 to 1.80)	Social demographics, insurance cover, comorbidities, cause of kidney disease
Roubicek 2000[266]	4.2 (3 months)	50	4.2	67			
Sesso 1996[270]	12.9 (6 months)	40	29.2	35	HR 2.77 (1.36 to 5.55)	HR 2.05 (0.93 to 4.54)	Adjustment NR
Stoves 2008[273]	13.0	NR	26.0	NR	NR	NR	
Winkelmayer 2003[277]	25.2	NR	32.2	NR		HR 1.36 (1.22 to 1.51)	Age, gender, race, socioeconomic status, comorbidities

CI, confidence interval; CVD, cardiovascular disease; ER, early referral; HR, hazard ratio (reported for LR vs ER unless otherwise stated); LR, late referral; NS, not significant; NR, not reported; RR, risk ratio.

of 75 years was 2.32 (95% CI 1.48 to 3.64). For patients over 75 years, the RR was 1.8 (95% CI 0.97 to 3.34). Lin and colleagues[252] reported risk of death for patients receiving haemodialysis and peritoneal dialysis separately. The greatest impact from early referral on survival after dialysis was observed in the peritoneal dialysis group (RR 0.29, 95% CI 0.07 to 0.48).

Death due to CVD was reported in four studies.[252,266,271,273] CVD accounted for similar proportions of deaths in the early and late referral groups, with the exception of Shin and colleagues[271] who reported substantially lower proportion of deaths due to CVD in the early versus late referral groups (9% versus 30.8%; $p = 0.04$).

Specialist visits

Two studies provided a breakdown on the number of visits to a nephrology specialist by the early and late referral group.[277,352] Avorn and colleagues[352]

TABLE 47 *Summary of mortality results of studies with follow-up of > 1 year*

| | | ER | | LR | | Risk ratio (95% CI) | | |
Study ID	Follow-up	Deaths (% unless otherwise stated)	% of ER deaths due to CVD	Deaths (% unless otherwise stated)	% of LR deaths due to CVD	Late vs early unadjusted	Late vs early adjusted	Adjusted for
Cass 2002[230]	5 years	15 deaths/100 patient-years	NR	20 deaths/100 patient-years	NR	HR 1.3 (1.14 to 1.48)	HR 1.19 (1.05 to 1.35)	Age, sex, number of comorbidities, presence of primary renal disease and indigenous status
Goransson 2001[239]	5 years	51.5	NR	73.2; $p=0.018$	NR	NR	NR	
Iseki 2002[243]	5 years	33.8	NR	35.1	NR	NR	HR 1.02 (0.77 to 1.35)	Age, sex, comorbidities, diabetes
Kazmi 2004[249]	Mean 2 years	NR	NR	NR	NR	NR	HR 1.21 (1.02 to 1.43)	Insurance status, angina, education level, employment, treatment modality, ESRD network
Lhotta 2003[251]	4 years	24.2	NR	45.2	NR	HR 2.12 (0.92 to 4.85)	Referral NS	Only higher comorbidity score was associated with mortality and retained in the model
Lin 2003[252]	5 years	27.6	42	64.8	47	RR for ER 0.42 (0.25 to 0.87)	RR for ER 0.45 (0.25 to 0.81)	Glycaemic control, age, haemoglobin, albumin, cholesterol, residual renal function
Lin 2004[253]	5 years	NR	NR	NR	NR	NR	HR for ER (haemodialysis) 0.45 (0.25 to 0.81) HR for ER (peritoneal dialysis) 0.29 (0.07 to 0.48)	Age, haemoglobin, albumin, cholesterol

TABLE 47 Summary of mortality results of studies with follow-up of > 1 year (continued)

Study ID	Follow-up	ER			LR			Risk ratio (95% CI)		Adjusted for
		Deaths (% unless otherwise stated)	% of ER deaths due to CVD		Deaths (% unless otherwise stated)	% of LR deaths due to CVD		Late vs early unadjusted	Late vs early adjusted	
Roubicek 2000[266]	5 years	48	61.4		44	60.9		NR	NR	
Schwenger 2006[269]	1.7 years	NR	NR		NR	NR		NR	RR <75 years 2.32 (1.48 to 3.64) RR ≥75 years 1.8 (0.97 to 3.34)	Factors not reported
Shin 2007[271]	6.7 years	23	37.5		42	69.6 ($p<0.05$)		NR	NR	
Stoves 2008[273]	5 years	45	39		69	30		NR	HR 1.43 (0.115); $p<0.001$	Age, diabetes, albumin, 'transplantability'
Wu 2003[278]	Mean 3.3 years	43.8	43		83.3 ($p<0.05$)	47		RR for ER 0.42 (0.15 to 0.67)	RR for ER 0.41 (0.19 to 0.90)	Glycaemic control, creatinine clearance, age

continued

CI, confidence interval; CVD, cardiovascular disease; ER, early referral; ESRD, end-stage renal disease; HR, hazard ratio (reported for LR vs ER unless otherwise stated); LR, late referral; NR, not reported; RR, risk ratio; SD, standard deviation.

reported 67.9% of the early referral group receive more than five specialist visits compared to 14.5% in the late referral group and also reported an increased RR of death at 1 year in those receiving fewer than five specialist visits prior to initiation on dialysis (RR 1.15, 95% CI 1.03 to 1.28). Again, a greater percentage of specialists visits was recorded in the early than in the late referral group in the study by Winkelmayer and colleagues.[277] In the early group, 17.6% of participants received more than 10 specialist visits versus 11.2% in the late group.

The remainder of the studies failed to comment on specialist visits. Fan and colleagues[237] was the only study that described pre-dialysis education by a nurse team. Both referral groups were noted to have had pre-dialysis education. None of the studies reported details of dietician input.

Preparing for dialysis

The choice of peritoneal dialysis was reported in two studies.[237,253] Both reported that choice was available of both early and late referral, although Fan and colleagues[237] noted that in the late referral group some participants were initiated on haemodialysis initially as an emergency. Final modality decisions were made at a later date.

The percentage of haemodialysis patients with functioning permanent vascular access at the initiation of dialysis was reported in three studies.[239,266,270] Goransson and Bergrem[239] reported 43% of the early referral group versus 0% in the late referral group had functioning permanent vascular access. Sesso and Belasco[270] and Roubicek and colleagues[266] reported similarly low proportions with permanent access in the late referral group (53.1% versus 0%, early versus late and 70.7% versus 26.9%, early versus late, respectively).

Hospitalisation

There were more days spent in hospital, around the time of commencing RRT, in the late referral group than in the early group.[236,239,251,266] Ellis and colleagues[236] reported a median of 9.7 days of hospitalisation in the early group and a median of 25 days in the late group (no *p*-value given). Lhotta and colleagues[251] observed a mean initial hospital duration of 13 ± 12.5 days for early referral patients and 19.5 ± 14.1 days for late referral patients ($p = 0.04$). Length of initial hospitalisation

reported by Roubicek and colleagues[266] was 20 ± 21.5 days for the early referral group compared to 33.3 ± 21.8 days for late referral patients ($p < 0.001$). Lastly, Goransson and Bergrem[238] showed the duration of hospital stay around the commencement of dialysis to be more than four times longer for late referral patients than early referral patients – median of 31 (7–73) versus 7 (1–59) days (late versus early respectively). Again the difference between the groups was found to be statistically significant with $p < 0.0001$.

Treatments

Three studies reported on antihypertensive medication use among those referred late as compared to early.[239,251,271] Goransson and Bergrem[239] reported a median of two antihypertensive medications per person in both the late and early referral groups. Lhotta and colleagues[251] also noticed no significant difference in ACE I use between referral groups (early 90.9% versus late 88.1%; $p = 0.92$). Shin and colleagues,[271] however, found substantial differences in antihypertensive medication use with higher prescribing in the early referral group (early versus late: ACE I 81% versus 11%; ARB 43% versus 6%; β-blocker: 72% versus 15%; calcium channel blockers 42% versus 8%).

Goransson and Bergrem[239] reported oral calcitrol was more likely to be prescribed to those referred early than late (89% versus 8%), but other authors found little difference.

Predialysis erythropoietin was prescribed more in those who were referred early.[239,251]

Quality of life

Quality of life was not reported by any of the studies.

Triggers for referral

None of the studies reported the triggers or criteria used to determine when to refer. None reported on the characteristics of the patients at the time of referral.

Barriers to early referral

None of our included studies of late referral reported data on barriers to referral. A supplementary search was undertaken to identify

barriers to referral. The findings are summarised thematically below.

A recent systematic review by Navaneethan and colleagues[353] reviewed the evidence on patient and health system characteristics associated with late referral. The review included prospective and retrospective observational studies, and physician surveys in which adult patients were referred within 6 months before initiation of dialysis, or referred to nephrologists in stage 5 CKD. The authors concluded that a combination of patient and health system characteristics were associated with late referral of patients with CKD. Overall, being older, belonging to a minority group, being uninsured, suffering from multiple comorbidities, and the lack of communication between primary care physicians and nephrologists contributed to late referral of patients with CKD. Factors associated with late referral identified from this review and from other studies are discussed below, categorised as follows: disease related, patient related, health-care system related and physician related.

Disease related

In some cases, late referral may be inevitable owing to the pathogenesis and mode of onset of the kidney disease, such as irreversible acute renal failure. De novo acute diseases may lead to referral that is unavoidably late and at the stage of irreversible kidney damage. On the other hand, some kidney diseases may progress so slowly that the development of symptoms goes almost unnoticed. Overall, such disease-related causes do not account for more than 15–20% of the presently observed late referral cases.[354]

Patient related

Age
The increasing age of patients was associated with late referral in several studies conducted in North America. Winkelmayer and colleagues[355] showed that patients aged between 75 and 84 years were 73% more likely to be referred late than 65- to 74-year-olds (OR 1.73, 95% CI 1.44 to 2.08; $p < 0.001$). This association was more significant in patients over 85 years (OR 2.66, 95% CI 1.87 to 3.79; $p < 0.001$). Ifudu and colleagues[356] concluded that even patients aged > 55 years were referred late (OR 4.7, 95% CI 1.37 to 16.0) when compared to patients aged < 55 years. Navaneethan and colleagues[357] found that age > 75 years was significantly associated with late

referral among patients in a community in New York in comparison to patients aged < 75 years ($p = 0.03$). A physician survey conducted in Canada concluded that primary care physicians are less likely to refer older patients to nephrologists than younger patients.[358]

In contrast, studies from France,[246] Europe,[359] the UK[360] and Ireland[361] did not find any age differences in patients with CKD who were referred early compared to those who were referred late.

Gender
Winkelmayer and colleagues[355] found that sex was not associated with late referral (OR 1.16, 95% CI 0.99, 1.37; $p = 0.068$). Several other studies reported no gender differences in the referral of patients with CKD including one from France[246] and one European.[359]

Race
Winkelmayer and colleagues[355] identified a significant association between race other than black or white and late referral (OR 1.68, 95% CI 1.21 to 2.32). Kinchen and colleagues[123] and Ifudu and colleagues[356] showed that black and Hispanic patients were referred late. In contrast, Steel and Ellis,[360] from the UK, concluded that white people might be referred later to nephrologists than black people, although the results were non-significant ($p = 0.08$). Two studies from the USA[223,357] and one from France[246] did not identify any association between race and late referral of patients with CKD.

Social disadvantage
In an Australian study, the proportion of patients referred late varied between areas and was higher in areas of greater social disadvantage. Patients from densely populated areas with a predominantly indigenous population experienced more late referrals to nephrologists than other populations.[362]

A study from the USA[363] reported that the homeless and unemployed were more likely to present as ultra late referral (< 1 month) (OR 6.0, $p = 0.004$) and concluded that poor socioeconomic status was a major contributor to delayed referral. There was no significant association, however, between education and referral pattern.[363]

In contrast, a study from Northern Ireland showed that less affluent populations are generally referred earlier to specialists than the more affluent.[364]

Comorbidity

The presence of comorbid illness was associated with late referral in most studies. Kinchen and colleagues[123] found that patients with higher index of coexistent disease score (combination of index of physical impairment and index of disease severity) were nearly twice as likely to be referred late than their counterparts with lower scores (OR 1.8, 95% CI 1.16 to 2.84). Similar results were seen in two European studies.[124,358] Wauters and colleagues[359] concluded that the presence of an active cancer would delay the referral of patients with CKD to nephrologists. In a Scottish study, Khan and colleagues[124] allocated CKD patients to low, intermediate, and high risk groups based on their age and the presence of other comorbidities (heart disease, diabetes and pulmonary disease). The presence of these coexisting illness resulted in late referral. A physician survey by Mendelssohn and colleagues[358] identified that the presence of comorbidity would result in late or non-referral by physicians. Navaneethan and colleagues[357] determined that patients referred late had a higher Charlson Comorbidity Index (calculated with 17 comorbidities) than patients referred earlier (OR 1.17, 95% CI 1.04 to 1.32, $p = 0.009$).

In contrast, Winkelmayer and colleagues[355] determined that the presence of hypertension (OR 0.47, 95% CI 0.40 to 0.56), malignancy (OR 0.73, 95% CI 0.59 to 0.91), coronary artery disease (OR 0.69, 95% CI 0.58 to 0.82) and diabetes (OR 0.82, 95% CI 0.69 to 0.97) resulted in earlier referral to nephrologists than for patients with no comorbidities. Patients with CKD and other coexisting illness may have their renal function monitored more frequently as part of routine chemistry panels. Early referral may reflect enhanced physician awareness of the relationship between these diseases and CKD progression, or increased physician attentiveness to management of patients with CKD, because of an increased frequency of patient–physician interaction. These seemingly contradictory results could be attributed to geographic variations, type of patients included and provider misconceptions about the outcome of patients with multiple comorbidities on dialysis.[353]

Other studies have not demonstrated an association between the presence of comorbidity and late referral.[223,361]

Aetiology of renal disease

Patients with non-diabetic kidney disease were 1.4 times (95% CI 1.15 to 5.26) more likely to be referred later to nephrologists than patients with diabetic kidney disease.[357] Patients with congenital kidney disease were referred earlier than patients with hypertensive renal disease. Patients with rapidly progressing kidney disease were referred earlier than patients who had gradual worsening of renal function (OR 7.1, 95% CI 2.9 to 16.7).[246]

Patient non-compliance

Patient compliance with appointments was identified as a major issue in two studies and accounted for ~40% of late referrals. Jungers and colleagues[246] and Sprangers and colleagues[365] reported that 42% of late referrals could be attributed to patient non-compliance. Patients may be reluctant to visit a nephrologist because of lack of disease awareness and/or understanding, denial, fear of the unknown, fear of loss of independence and economic difficulties.[365]

Health-care system related

Type and location of referral and dialysis centre

In a survey of a cohort of incident dialysis patients in three European regions, Wauters and colleagues[359] identified that late referral was more frequent in large city centres than in the private or regional structures (OR 7.3, 95% CI 1.8 to 30).

The distance to the centre might also be a reason for late referral, but in one study concerning a rural population in the USA,[268] the distance to the dialysis centre was not a determining factor. In contrast, for patients of lower socioeconomic classes, an Australian study showed a correlation between higher rates of late referrals and the distance to dialysis centres.[366] In Northern Ireland, Kee and colleagues[364] also reported that increasing distance to the nearest renal centre was associated with later referral.

Physician factors

Winkelmayer and colleagues[355] found that hospital physicians (not renal specialists), rather than GPs, were more likely to refer patients with CKD later to nephrologists. A finding repeated in several studies.[54,359]

In a study by Boulware and colleagues,[367] hypothetical clinical vignettes were used to assess physician evaluation of the severity of CKD, recommendations for referral, and awareness of current guideline recommendations. The participants were randomly selected from a nationally representative sample of physicians

(family medicine and internal medicine physicians) and nephrologists. Compared to the nephrologists, both physician groups were worse at identifying patients with stage 3 (GFR 30–59 ml/min/1.73 m^2) or stage 4 (GFR 15–29 ml/min/1.73 m^2) CKD. Physicians were less likely to recommend referral for the patient scenarios and requested input from the referring nephrologist at a less frequent rate than recommended. Physicians were less likely than nephrologists to be aware of existing practice guidelines, and awareness of the guidelines did increase the likelihood of referral by the primary care physician.[367]

In a study from Ireland,[361] which also used clinical scenarios to evaluate referral behaviour, it was demonstrated that fewer than half of the patients were referred after the first encounter, whereas nearly all patients were referred as the renal function worsened and the patients became symptomatic. As the scenarios increased in complexity, the likelihood of referral decreased.[361]

Mendelssohn and colleagues[358] concluded that 'rationing by physicians about the need for dialysis' was a major factor in late referral. This non-referral was influenced by age and coexisting disease, and physicians evaluated the distance of dialysis centres and overcrowding of the nearest dialysis centres before referring a patient with CKD.[358] Similar rationing by physicians was not, however, demonstrated in a survey conducted in England.[368] Specialists (other than nephrologists) were likely to recommend referral for patients with CKD later than primary care physicians.[368]

In a survey of referring physicians, Campbell[369] documented the reasons for late referral. These included perception by the referring physicians of being evaluated negatively by nephrologists in 43% of cases, lack of communication or faulty communication between primary care physicians and nephrologists (37%), and lack of specific referral criteria for patients with ESRD (31%). It was also reported that more than 90% of referring primary care physicians felt that they had inadequate training regarding timing or indications for referral of patients with CKD.[369]

Discussion

We identified a substantial number of reports about the impact of late referral on outcomes after the initiation of dialysis. All studies recruited patients to their study at the time of initiation of dialysis. Thus all these studies focus on reporting outcomes among those who survive to dialysis. Those dying prior to dialysis were excluded. Notably, ACM on dialysis was high, though variable across studies. Variability between studies may be explained by differences in baseline characteristics, the health care received and the small size of some of the studies.

At 1 year, mortality was consistently higher in the late versus early referral group regardless of the definition of early referral. At longer follow-up, the majority of studies reported higher mortality in the late referral group but Iseki (Japan)[243] and Roubicek and colleagues (France)[266] found little difference. While absolute differences in mortality were observed, the relative difference, once adjusted for comorbidities, was less. In those reaching dialysis, CVD accounted for a substantial proportion of deaths. Other outcomes were less well reported but there was evidence that late referral impacted on the number of clinic appointments with specialists, access to choice about dialysis modality and preparation for dialysis with permanent vascular access established before dialysis started. In addition, there was evidence of an increased requirement for hospitalisation around the start of dialysis in those referred late to specialist services.

None of the studies reported eGFR at the time of referral, so the definition relied on a retrospective consideration of time prior to dialysis. One study defined 'late referral' as referral once the eGFR was < 20 ml/min. Here, authors reported mortality to be higher in the late referral group in the first year of dialysis. The difference was, however, accounted for by difference in comorbidity and age. The difference in care received was also poorly described. It was, therefore, difficult to determine whether timing of referral was mainly a surrogate for severity at the time referred, degree of comorbidity or the care delivered. The triggers for referral were not reported and data on barriers to early referral were not collected. Very late presentation to nephrology services can occur as a result of an acute and aggressive deterioration in renal function. The studies were generally poor at explicitly excluding people with an acute renal event from their analysis.

A review of additional literature seeking to identify potential barriers to early referral found a range of potential patient, health-care system and physician related factors described. Reporting of the variability of the importance of different factors suggested that individual health-care systems would have to consider local issues when designing or

modifying services to optimise referral timing. Good communication between primary care and hospital physicians, and nephrology specialists was important in ensuring timely and appropriate referral.

Conclusions

The impact of late referral on predialysis survival and outcomes has not been studied. There was evidence that late referral impacts negatively on survival on dialysis particularly in the first year. The implications for care delivery and preparation for RRT were significant but the impact on patient quality of life was not reported. Many potential barriers to earlier referral have been described in the literature and by health-care system and local setting as well as by patient- and physician-related factors. Communication between aspects of the health-care system was important to ensure appropriate referral.

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