Early referral strategies for management of people with markers of renal disease

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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Executive summary

Health Technology Assessment 2010; Vol. 14: No. 21
DOI: 10.3310/hta14210

Health Technology Assessment
NIHR HTA programme
www.hta.ac.uk

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 m^2 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 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)}. 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 m^2). Referral for everyone with an eGFR below 60 ml/min/1.73 m^2 (stage 3a CKD) generated the most QALYs and, compared with referral for stage 4 CKD (eGFR < 30 ml/min/1.73 m^2), 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 m^2, 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.

Publication

Black C, Sharma P, Scotland G, McCullough K, McGurn D, Robertson L, *et al.* 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. *Health Technol Assess* 2010;**14**(21).

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 06/75/02. The contractual start date was in February 2008. The draft report began editorial review in July 2009 and was accepted for publication in October 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

ISSN 1366-5278

Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NETSCC, HTA.

Printed on acid-free paper in the UK by Henry Ling Ltd, The Dorset Press, Dorchester.