Long-term monitoring in primary care for chronic kidney disease and chronic heart failure: a multi-method research programme

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Scientific summary

Long-term monitoring for kidney disease and heart failure

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Scientific summary

Background

As life expectancy improves, more people are living with chronic conditions, many of which are managed in primary care. Earlier diagnoses also shift the burden of disease management towards primary care. Monitoring is an established, and often incentivised, component of the management of long-term conditions, but the evidence base for monitoring, and details of a monitoring strategy (e.g. frequency), is sparse. It has been shown previously that more frequent monitoring is not necessarily better for health.

Objectives

We aimed to improve understanding, methods, the evidence base and the practice of clinical monitoring in UK primary care, using two exemplar chronic diseases managed in primary care: chronic kidney disease and chronic heart failure.

For chronic kidney disease, the aims were to describe current monitoring practice, including national variations and time trends; summarise evidence comparing different equations for deriving estimated glomerular filtration rate from serum creatinine; study the accuracy of diagnosed chronic kidney disease stages based on estimated glomerular filtration rate; identify pharmacological interventions that delay progression of chronic kidney disease; assess how outcomes vary with frequency of monitoring; compare the predictive power of current (serum creatinine) and novel (cystatin C) biomarkers for calculating estimated glomerular filtration rate; investigate patients' and health professionals' attitudes to and experiences of monitoring; and estimate the cost-effectiveness of monitoring more or less frequently.

For chronic heart failure, the aims were to assess whether or not natriuretic peptide-guided treatment improves outcomes; identify individual components of the interventions that lead to these improvements; evaluate the effectiveness of remote monitoring from home; review evidence of the diagnostic accuracy of point-of-care devices in primary care; estimate the variability of natriuretic peptide and weight measurement; investigate the feasibility of using point-of-care natriuretic peptide testing devices in the monitoring of chronic heart failure; understand patient and health professional views and experiences of monitoring chronic heart failure; and investigate the health economic issues of chronic heart failure monitoring.

Methods and results

Chronic kidney disease

We used a database of laboratory tests in Oxfordshire and a national database (the Clinical Practice Research Datalink) to study trends and variation in monitoring of kidney disease with blood and urine tests. The local data allowed us to study long-term trends over two decades across primary and secondary care. The Clinical Practice Research Datalink data allowed us to focus on primary care testing and to observe national variations in practice. In Oxfordshire, we found a steady increase from 1997 in serum creatinine testing, with the proportion of these corresponding to normal kidney function increasing from 59% to 83% between 1993 and 2013. Nationally, rates of kidney function testing increased over time in all age groups. Testing of serum creatinine levels increased rapidly between 2006 and 2007,

and testing of proteinuria increased rapidly between 2009 and 2010, dates that correspond to the introduction of relevant indicators to the Quality and Outcomes Framework.

We systematically searched literature databases for studies comparing estimated glomerular filtration rates calculated from serum creatinine using equations from the Modification of Diet in Renal Disease study or the Chronic Kidney Disease Epidemiology Collaboration with measured glomerular filtration rates in adult populations, and pooled data from 48 studies of 26,875 patients. The mean accuracy (i.e. the percentage of observations with an estimated glomerular filtration rate within 30% of the measured glomerular filtration rate) for the Chronic Kidney Disease Epidemiology Collaboration equation was 2.7% higher (95% confidence interval 1.6% to 3.8%) than for the Modification of Diet in Renal Disease equation, but with medium/large heterogeneity ($I^2 = 56\%$).

We used data from 1,973,068 adults in 643 general practices between 2005 and 2014 to fit a hidden Markov model for chronic kidney disease stage stratified by proteinuria status. This approach distinguishes true change in disease from apparent changes due to measurement error. The rate per year of true transition from one chronic kidney disease stage to the next was approximately 2% for people with normal urine albumin levels, between 3% and 5% for people with microalbuminuria (3–30 mg/mmol) and between 3% and 12% for people with macroalbuminuria (> 30 mg/mmol). We estimate misclassification of chronic kidney disease stage due to measurement variability in estimated glomerular filtration rate to occur in between 12% and 15% of all tests in primary care.

We systematically searched literature databases for randomised controlled trials of sodium bicarbonate or antihypertensive, lipid-modifying or glycaemic-control drugs in adults with chronic kidney disease followed up for at least 2 years. The primary outcome was renal function measured by measured glomerular filtration rate, estimated glomerular filtration rate, creatinine clearance or estimated creatinine clearance. In 35 studies of > 51,000 patients, we found that lipid-modifying drugs and (in diabetes) glycaemic-control drugs were associated with better renal function. No evidence of benefit of sodium bicarbonate (only two trials) or antihypertensive drugs was found.

We recruited 750 adults with chronic kidney disease in 14 general practices in the Thames Valley, to investigate whether baseline renal function measured by cystatin C or measured by serum creatinine is better at predicting change in renal function. Blood samples were taken at baseline (0, 2 and 12 weeks), at 6 months and at 6-monthly intervals for a further 18 months. The estimated glomerular filtration rate was calculated for all time points using these two biomarkers. For this report, we include 745 participants in a complete-case analysis, including patients with at least one baseline result for both creatinine and cystatin C, and at least two results for both creatinine and cystatin C from visits between 6 and 24 months. The *c*-statistic for baseline estimated glomerular filtration rate using creatinine as a predictor of future change in estimated glomerular filtration rate using creatinine was 0.495 (95% confidence interval 0.471 to 0.521). The *c*-statistic for baseline estimated glomerular filtration rate using cystatin C as a predictor of future change in estimated glomerular filtration rate using cystatin C was 0.500 (95% confidence interval 0.474 to 0.525).

Forty-five people with chronic kidney disease were interviewed, and 16 health professionals participated in four focus groups. Patient interviews revealed that phrases such as ‘kidney damage’ or ‘kidney failure’ could be frightening, and the term ‘chronic’ was sometimes misinterpreted as meaning ‘serious’. The diagnosis of an asymptomatic condition such as chronic kidney disease was reported as difficult to understand. To avoid unnecessary anxiety, primary care professionals often did not use the term ‘chronic kidney disease’ when talking to patients with early-stage kidney impairment. Patients could be concerned and wanted to know more about possible causes, the meaning of test results and preventative actions to reduce further decline.

The general practitioners relied on Clinical Commissioning Group or Quality and Outcomes Framework alerts for patient management recommendations, rather than National Institute for Health Care and

Excellence guidance. Regarding current chronic kidney disease guidelines specifically, there was confusion about when and how albumin–creatinine ratio tests should be used.

We incorporated our findings into a model of the cost-effectiveness of frequencies of monitoring chronic kidney disease in primary care. We assessed 'no monitoring', monitoring every 5, 4, 3 and 2 years and annual monitoring. Clinicians and stakeholders advised that a key objective of estimated glomerular filtration rate monitoring in primary care is guiding treatments to reduce cardiovascular risk among people with reduced kidney function. Based on the review of interventions and current guidelines, we assumed that monitoring would guide treatment with 20 mg of atorvastatin (Lipitor®, Pfizer Inc., New York, NY, USA) daily for people without prior cardiovascular disease and/or chronic kidney disease and 80 mg of atorvastatin daily for all others, with treatment with 10 mg ramipril (Tritace®, Sanofi, Paris, France) daily for people with chronic kidney disease. Under these assumptions, monitoring had little or no effect on predicted health outcomes for people with chronic kidney disease because the majority of people indicated for statin and blood pressure-lowering treatments as a result of progression of chronic kidney disease would already be indicated for the same treatment because of cardiovascular risk.

Chronic heart failure

We updated a systematic review to assess whether or not treatment guided by serial B-type natriuretic peptide or N-terminal prohormone of B-type natriuretic peptide (collectively called 'natriuretic peptide') monitoring improves outcomes, compared with treatment guided by clinical assessment alone. The updated evidence, from 19 trials, indicates that natriuretic peptide-guided treatment can reduce all-cause mortality by 13% and heart failure admission by 20%.

We identified common features of the most successful of these trials: predefined treatment protocols, setting stringent natriuretic peptide targets, incorporating relative targets and location in specialist heart failure settings. We recommend that future reviews should combine individual participant data to control for patient-level differences.

We conducted a systematic review of the clinical effectiveness of remote monitoring (telemonitoring and/or structured telephone support) for adults with heart failure. A meta-analysis of 53 studies showed statistically significant reductions in some (all-cause mortality, heart failure hospital admission), but not all, outcomes with either telemonitoring or structured telephone support.

We conducted a systematic review of point-of-care natriuretic peptide diagnostic accuracy studies. Of 37 eligible studies, five were conducted solely in primary care. The types of patients, the health-care settings and the thresholds used varied across studies. For the B-type natriuretic peptide test, in populations with low chronic heart failure prevalence, pooled sensitivity and specificity were 0.95 (95% confidence interval 0.91 to 0.97) and 0.57 (95% confidence interval 0.43 to 0.70), respectively, whereas, for N-terminal prohormone of B-type natriuretic peptide, pooled sensitivity and specificity were 0.99 (95% confidence interval 0.57 to 1.00) and 0.60 (95% confidence interval 0.44 to 0.74), respectively. Note that sensitivity varies in the primary care studies.

We estimated variability in B-type natriuretic peptide concentrations and weight in patients with heart failure in the control arm ($n = 30$) of a 13-week randomised controlled trial among patients with stable New York Heart Association class II to III chronic heart failure. The between-person coefficient of variation of weight was 26% and of B-type natriuretic peptide was 137%. Between-person variation in B-type natriuretic peptide varied with age (coefficient of variation: 170% for those aged < 55 years, 88% for those aged ≥ 55 years), but not obesity. Within-person variation was substantial, but smaller than between-person variation (coefficient of variation: 46% for B-type natriuretic peptide, 1.2% for weight). This suggests that monitoring over 3 months is unlikely to detect true B-type natriuretic peptide change against background noise in this small, stable heart failure, sample.

To assess the feasibility of point-of-care natriuretic peptide measurement in primary care, we recruited 27 adults with a confirmed heart failure. Participants attended visits at 0, 6 and 12 months. At each visit, venous blood samples were taken for point-of-care N-terminal prohormone of B-type natriuretic peptide measurement, laboratory N-terminal prohormone of B-type natriuretic peptide and renal function testing. Testing was successfully carried out at 100% of planned study visits. Within-person variability in point-of-care N-terminal prohormone of B-type natriuretic peptide over 12 months was 881 pg/ml (95% confidence interval 380 to 1382 pg/ml). Between-person variability in point-of-care N-terminal prohormone of B-type natriuretic peptide over 12 months was 1972 pg/ml (95% confidence interval 1525 to 2791 pg/ml). Between-person variability in point-of-care N-terminal prohormone of B-type natriuretic peptide was around twice as large as within-person variability over 12 months, indicating that deviations from individual set points for N-terminal prohormone of B-type natriuretic peptide are likely to be more helpful than population-level thresholds.

To understand the acceptability and impact of monitoring regimes among individuals with chronic heart failure, we analysed 59 patient interviews and conducted focus groups with 16 health professionals. Current practice varies, in both primary and secondary care, including some measurement of weight and blood pressure at home, and some use of telemonitoring. Monitoring by specialist nurses was particularly valued. Monitoring provided reassurance, although guidance about when to seek help did not seem to have been given, other than for emergencies. Patients found hypothetical future changes acceptable (e.g. increased reliance on blood testing) or welcome (point-of-care testing in general practice surgeries).

Community heart failure nurses were fully informed of relevant National Institute for Health and Care Excellence guidelines and used them daily, with adjustment for patient complexity (comorbidities). General practitioners and practice nurses expressed unfamiliarity with the latest National Institute for Health and Care Excellence guidelines. Therefore, community heart failure nurses usually lead on treatment plans. General practitioners and community heart failure nurses recognise natriuretic peptide as a useful diagnostic test for chronic heart failure, but community heart failure nurses could see no benefit of measuring natriuretic peptide as part of routine monitoring, instead suggesting that changes in chronic heart failure severity would be reflected in patients' symptoms. Health-care professionals believed that financial and time costs of the test would outweigh any potential benefits.

In a systematic review, we found 40 previous health economic models addressing heart failure monitoring, management strategies and treatments in primary care. Three studied diagnosis, 11 studied management strategies and 26 studied drug interventions. Data to inform parameters in the models (disease risks, quality of life and costs) were sourced predominantly from randomised controlled trials in chronic heart failure patients in secondary care (39 out of 40 models). Therefore, the models are unlikely to be representative of the chronic heart failure population seen in contemporary primary care.

Conclusions

Laboratory monitoring of chronic kidney disease has grown dramatically over the years, but it is not obvious what treatment can be taken in response to a decline in estimated glomerular filtration rate. The treatments with proven renoprotective properties are often already indicated for other reasons, for example statins and antihypertensives for cardiovascular prevention or glucose-lowering therapies in people with diabetes. Meanwhile, the terminology of 'chronic kidney disease' can be misunderstood by patients. Hence, it is difficult to ascribe quantifiable benefits to annual monitoring of chronic kidney disease. For chronic heart failure, treatment regimens are well established, but monitoring methods less so. Natriuretic peptide testing at the point of care may be feasible in general practice, but for both natriuretic peptide testing and weight measurement, there is high measurement variability to overcome, making it premature to recommend home or point-of-care monitoring for chronic heart failure.

Research recommendations

- Determining, with high precision, the bias, and accuracy, of estimated glomerular filtration rate equations would be of high value for the NHS, to determine when (in what settings) and how (with what protocol) these equations should be used.
- Protocols to determine best practice for combining estimated glomerular filtration rate measurements might help reduce individual measurement error.
- The possible advantages of cystatin C over serum creatinine in our cohort study need to be confirmed.
- At least one alternative to the term 'chronic kidney disease' has been proposed; its potential to improve communications should be investigated.
- Closing the gap (identified in the systematic review of interventions) of evidenced interventions that specifically protect renal function would have the greatest potential to improve the cost-effectiveness of chronic kidney disease monitoring.
- Further studies of natriuretic peptide-guided treatment for chronic heart failure are needed, especially in primary care.
- New studies of remote monitoring need to be incorporated promptly into systematic reviews and should reflect any technological changes.
- A setting-appropriate threshold must be determined if point-of-care natriuretic peptide monitoring is to be incorporated into primary care pathways.

Implications for practice

Chronic kidney disease

- Laboratories could improve the accuracy of estimated glomerular filtration rate by switching to the Chronic Kidney Disease Epidemiology Collaboration equation for its calculation.
- Potential treatments that might positively affect kidney function are lipid-modifying treatment and glycaemic-control medication.
- The rate of change of kidney function in a primary care population is slow, and most apparent changes will be due to measurement noise (error) and not real change.
- The terms 'chronic' and 'disease' act as barriers in the communication between health practitioners and patients. A potential solution is the use of alternative terms such as 'kidney age'.
- Monitoring individuals with chronic kidney disease is, at present, difficult to justify by usual rationales such as treatment initiation or titration.

Chronic heart failure

- No evidence was found of natriuretic peptide use as part of a diagnostic pathway in primary care, which goes against the National Institute for Health and Care Excellence's recommendation; its use could be incentivised.
- Both natriuretic peptide and weight are highly variable measures; therefore, any change observed should be interpreted with caution.
- The use of point-of-care tests to measure natriuretic peptide in general practice is feasible, but does not lead to reductions in observed variability.
- There are substantial barriers to the implementation of natriuretic peptide-guided treatment in primary care. In particular, the perception of health practitioners, both nurses and clinicians, is that the use of natriuretic peptide measures may not be beneficial.

Study registration

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