

Original Article

Primary care-based disease management of chronic kidney disease (CKD), based on estimated glomerular filtration rate (eGFR) reporting, improves patient outcomes

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Abstract

Background. The majority of patients with chronic kidney disease (CKD) stages 3–5 are managed within primary care. We describe the effects, on patient outcomes, of the introduction of an algorithm-based, primary care disease management programme (DMP) for patients with CKD based on automated diagnosis using estimated glomerular filtration rate (eGFR) reporting.

Methods. Patients within West Lincolnshire Primary Care Trust, UK, population 223, 287 with CKD stage 4 or 5 were enrolled within the DMP between March 2005 and October 2006. We have analysed the performance against clinical targets looking at a change in renal function prior to and following joining the DMP and the proportion of patients achieving clinical targets for blood pressure control and lipid abnormalities.

Results. Four hundred and eighty-three patients with CKD stage 4 or 5 were enrolled in the programme. There were significant improvements in the following parameters, expressed as median values (*interquartile range*) after 9 months in the programme, compared to baseline and percentage values patients achieving target at 9 months: total cholesterol 4.2 (3.45–5.0) mmol/l versus 4.6 (3.9–5.4) mmol/l ($P < 0.01$), 75.0% versus 64.5% ($P < 0.001$); LDL 2.2 (1.6–2.8) mmol/l versus 2.5 (1.9–3.2) mmol/l ($P < 0.01$), 81.9% versus 69.2% ($P < 0.05$); systolic blood pressure 130 (125–145) mmHg versus 139 (124–154) mmHg ($P < 0.05$), 56.2% versus 37.1% ($P < 0.05$) and diastolic blood pressure 71 (65–79) mmHg versus 76 (69–84) mmHg ($P < 0.01$), 68.4% versus 90.3% ($P < 0.01$).

The median fall (*interquartile range*) in eGFR in the 9 months prior to joining the programme was 3.69 (1.49–7.46) ml/min/1.73 m² compared to 0.32 (–2.61–3.12) ml/min/1.73 m² in the 12 months after enrolment

($P < 0.001$). One hundred and twenty-two patients experienced a fall in eGFR of ≥ 5 ml/min/1.73 m², median 9.90 (6.55–12.36) ml/min/1.73 m² in the 9 months prior to joining the programme, whilst in the 12 months after enrolment, their median fall in eGFR was –1.70 (–6.41–1.64) ml/min/1.73 m² ($P < 0.001$). In the remaining patients, the median fall in eGFR was 1.92 (0.41–3.23) ml/min/1.73 m² prior to joining the programme and 0.86 (–1.03–3.53) ml/min/1.73 m² in the 12 months after enrolment ($P = 0.082$).

Conclusions. These data suggest that chronic disease management in this form is an effective method of identifying and managing patients with CKD within the UK. The improvement in cardiovascular risk factors and reduction in the rate of decline of renal function potentially have significant health benefits for the patients and should result in cost savings for the health economy.

Keywords: cardiovascular risk; CKD; disease management; eGFR; progression

Introduction

Chronic kidney disease (CKD) is a growing public health problem [1–4]. The introduction of estimated glomerular filtration rate (eGFR) reporting and the inclusion of CKD in the quality and outcomes framework (QOF) of the general practitioner contract in 2006 have highlighted the issue in the UK [5,6]. There is now good evidence that the prevalence of established CKD (stages 3–5) in the UK is similar to that described in the USA and parts of Europe [7–9]. The low acceptance rates of dialysis and high proportion of patients presenting at an advanced stage of renal failure (22–67% with <3 months predialysis care) in the UK are indicative of the historic under-diagnosis that the use of eGFR reporting should now address. It is established that only

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a small proportion of patients with CKD stages 3–5 will progress to end-stage renal failure (ESRF) and require dialysis because the majority will die of cardiovascular disease [10]. It is also established that there are simple preventative strategies aimed at reducing cardiovascular risk that will reduce the morbidity and mortality of this group of patients and delay progression towards dialysis [10]. There is a concern within both primary and secondary care that the use of eGFR reporting will dramatically increase the workload in services that are already overburdened [11,12], although data do not support this contention and this should not be a reason for denying treatment to this population of patients at risk.

Disease management programmes (DMPs) for patients with CKD have been used to address this problem within the USA for some years and have been shown to be effective [10,13–15]. The goals of such programmes are to fill the gaps in current care thereby improving patient outcomes and reducing resource utilization, *i.e.* cost.

Those patients who present late (<3 months prior to commencing dialysis) have poorer outcomes in terms of morbidity and mortality, spend significantly more time in hospital and are less likely to remain in employment [16–19]. In addition, the chance to delay the onset of dialysis has been lost and it is estimated that a reduction in the rate of decline in renal function by as little as 10% in patients with a GFR <60 ml/min would equate to saving in excess of \$9 billion over a 10-year period in the USA [20]. DMPs aim to identify patients, manage the complications of CKD and other comorbid conditions, such as cardiovascular disease, slow the progression of CKD and where appropriate enable the smooth, planned transition to dialysis.

This paper describes the results in terms of patient outcomes against defined and audited clinical targets of a primary care-based DMP introduced to West Lincolnshire Primary Care Trust (WLPCT) in April 2005.

Subjects and methods

Optimal renal care UK (ORC UK) commenced a primary care-based DMP for patients with CKD in April 2005 in WLPCT as a method of applying best practice guidance. The database was closed to new patients in November 2006. The programme was guideline and algorithm based, derived from an established DMP in the USA and the then drafted UK guidelines for the identification, management and referral of patients with CKD [21]. The programme relied on automated patient identification using eGFR derived from all serum creatinine (measured using an Olympus AU640, rate Jaffe method) values using the simplified four-variable MDRD formula [3] with results being reported to the requesting clinician and to ORC UK. Blood samples received from inpatients and patients under the age of 18 years were not considered in the analysis. The DMP did not undertake population screening and guidance as to who should be tested was not issued.

Once a patient with CKD stage 4 or 5 was identified, permission to contact the patient was sought from the referring clinician. The nature of the programme was explained to the patients and following their agreement, they

were enrolled in the programme, risk stratified and treated according to the relevant algorithms. At this stage, retrospective laboratory data were obtained where available. The DMP was delivered by a community-based team of nurses, dietician and social worker. There were four main facets to the programme: patient education, medicine management, dietetic advice and optimization of clinical management to achieve clinical targets. The programme was additional to resources previously existing within either primary or secondary care, providing a resource not previously available. Whilst the fundamentals of the programme were similar to a multidisciplinary renal clinic, the scope and the availability were different and, in addition, the programme was proactive. Each patient had a named nurse with a ready telephone and face-to-face access without the need for appointments in combination with proactive intervention from the clinical team at a frequency dictated by the patient's risk assessment and/or the patients themselves. The focus was on patient education concerning their condition and its management aiming to empower patients to become actively engaged in their own care and to raise awareness of, and so reduce, cardiovascular risk factors through lifestyle modification and appropriate medicine management.

Patients with CKD stage 3 were not routinely enrolled into the programme unless they were on the CKD 3/4 boundary. Guidance concerning management and referral was provided to the general practitioners in the form of a desktop guide containing treatment algorithms.

Differences between proportions were assessed by the chi-square test, differences between repeated measures by the Wilcoxon-signed rank sum test and differences between groups by the Mann–Whitney rank sum test with $P < 0.05$ being taken as significant. Values and regression lines were calculated using Sigma Stat 3.0 (San Jose, CA, USA). Logistic regression analysis was undertaken using SPSS version 15.0 (SPSS inc., Chicago, IL, USA, 2006).

Results

Patient characteristics

Of 40 practices within WLPCT, 34 agreed to take part in the programme. Four hundred and eighty-three patients were enrolled into the programme from a population of 185 653 aged >15 years. CKD classification of the patients at enrolment was CKD stage 3, 115; CKD stage 4, 297; CKD stage 5, 30 and on dialysis 41. The mean age was 77.1 years (males 75.9 years, females 77.9 years, $P = 0.088$); 47% were male and 29.7% were diabetic. Females were more prevalent in CKD stage 3 and CKD stage 4, 52.2% and 57.8%, respectively, but less so in CKD stage 5, 38.5%; however, these differences were not statistically significant. Patients with CKD stage 5 were younger (mean 66.9 years) than those in CKD stage 3 (mean 77.7 years) or 4 (mean 77.5 years), $P < 0.002$. At enrolment, 60.4% of patients were receiving a statin, although the proportion of patients declined with increasing CKD stages from 70.8% in CKD stage 3 compared to 50% in CKD stage 5, $P < 0.05$. At enrolment, 52.5% of patients were receiving either an ACE

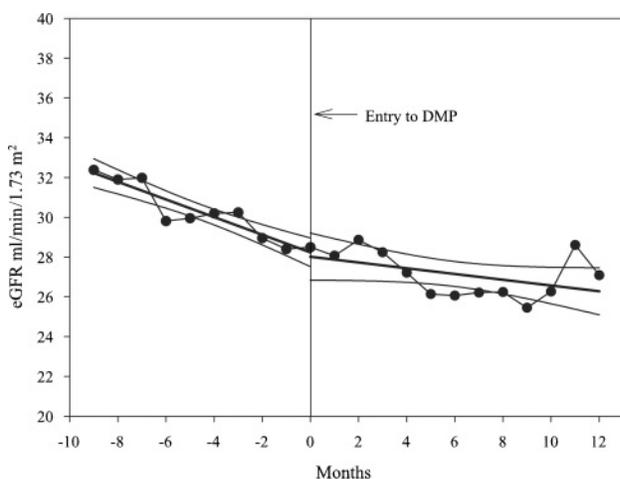


Fig. 1. Median eGFR values of patients enrolled into the DMP 9 months prior to and up to 12 months following joining the programme. Regression lines with 95% confidence intervals have been fitted to the data prior to and following entry to the DMP.

inhibitor or angiotensin receptor blocker. However, the proportion declined from 58.4% in CKD stage 3 to 19.2% in CKD stage 5, $P < 0.001$.

Achievement of clinical targets

Table 1 shows the clinical performance targets as median values and interquartile ranges and the proportion of patients achieving them at enrolment to the programme and after 9 months in the programme. There were significant improvements against the targets for total cholesterol and LDL but not HDL or triglycerides. Systolic and diastolic blood pressure improved in patients without diabetes and with a urinary protein:creatinine ratio < 100 mg/mmol. No significant changes were seen in blood pressure in diabetic patients and those with a urinary protein:creatinine ratio > 100 mg/mmol.

Preservation of renal function

Three patients with CKD 3 improved to CKD 2 whilst 15 deteriorated to CKD 4. One hundred and three patients with CKD 4 improved to CKD 3 whilst only one progressed to CKD 5. Four patients with CKD 5 improved to CKD 4 and eight progressed to dialysis.

Of the 483 patients in the DMP, a subset of 317 patients had retrospective eGFR data for the 9 months preceding their enrolment to the DMP [patients who had commenced dialysis during this time (41) were excluded from this analysis as were patients with no data post-enrolment (26)]. The median fall (a negative number implying a rise) in eGFR (interquartile range) in this group was 3.69 (1.49–7.46) ml/min/1.73 m² in the preceding 9 months compared to 0.32 (–2.61–3.12) ml/min/1.73 m² in the 12 months after enrolment ($P < 0.001$) (Figure 1). For 122 patients who experienced a fall in eGFR ≥ 5 ml/min/1.73 m², median 9.90 (6.55–12.36) ml/min/1.73 m² in that 9-month period, the median fall in eGFR in the subsequent 12 months of the DMP was –1.70 (–6.41–1.64) ml/min/1.73 m²

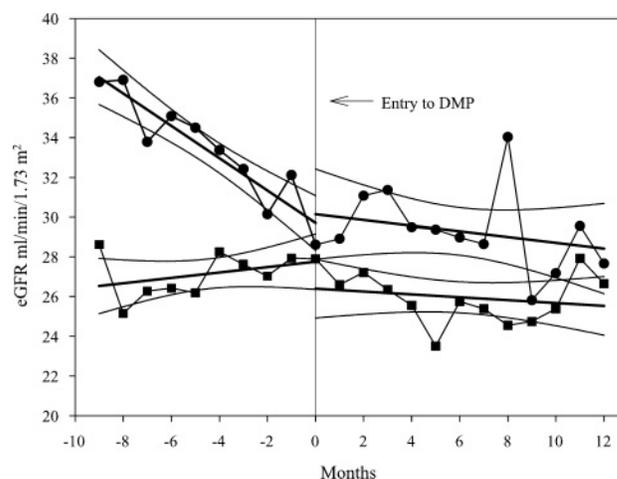


Fig. 2. Median eGFR values prior to and following joining the DMP for patients who had a fall in eGFR of ≥ 5 ml/min/1.73 m² prior to joining the DMP (circles, $n = 122$) and a fall of < 5 ml/min/1.73 m² (squares, $n = 195$). Regression lines with 95% confidence intervals have been fitted to the data prior to and following joining the programme.

($P < 0.001$). For the remaining patients, the median fall in eGFR was 1.92 (0.41–3.23) ml/min/1.73 m² prior to programme and 0.86 (–1.03–3.53) ml/min/1.73 m² in the subsequent 12 months of the DMP ($P = 0.082$) (Figure 2).

The 122 patients with a fall in eGFR ≥ 5 ml/min/1.73 m² were further divided, on the basis of their change in eGFR in the 12 months following joining the DMP, into three groups. Fourteen patients had a further fall in eGFR of ≥ 5 ml/min/1.73 m², median pre-DMP 10.63 (8.23–12.07) ml/min/1.73 m², 12 months post-DMP 8.10 (6.02–9.76) ml/min/1.73 m² ($P < 0.03$); 73 patients had a fall in eGFR of < 5 ml/min/1.73 m², median pre-DMP 8.45 (6.16–11.88) ml/min/1.73 m², 12 months post-DMP –0.36 (–2.49–1.46) ml/min/1.73 m² ($P < 0.001$) and 35 patients who had a rise in eGFR of ≥ 5 ml/min/1.73 m², median pre-DMP 11.42 (7.85–16.48) ml/min/1.73 m², median 12 months post-DMP –7.78 (–10.94–6.92) ml/min/1.73 m² ($P < 0.001$) (Figure 3).

When the 101 patients with no retrospective data are examined, their median fall in eGFR in the 12 months following joining the programme was 1.2 (–0.54–4.05) ml/min/1.73 m² compared to those with retrospective data of 0.32 (–2.61–3.12) ml/min/1.73 m² ($P < 0.01$) suggesting that the incident patients have a worse prognosis for renal function.

Median systolic blood pressure (interquartile range) in those patients whose renal function had progressed in the 9 months prior to entering the DMP was significantly lower at the time of entry, 139 (125–159) mmHg, than in those who had not progressed, 144 (130–160) mmHg, $P < 0.05$. There were no significant differences in diastolic blood pressure, 75 (68–84) mmHg and 80 (70–87) mmHg respectively, $P = 0.05$.

In an attempt to predict outcome on the basis of characteristics at presentation, a logistic regression analysis was undertaken using the following variables at enrolment to the programme: age, sex, diabetes, smoking, CKD stage,

Table 1. Performance expressed as median values and percentages of patients achieving a given target, for patients enrolled within the disease management programme. Blood pressure recordings were taken either at a routine GP visit or by one of the disease management community teams

Indicator (target)	Median values (interquartile range)		<i>P</i> (0 versus 9 months)	Percentage in range		
	Month 0	Month 9		Month 0	Month 9	<i>P</i> (0 versus 9 months)
Cholesterol (<5 mmol/l)	4.6 (3.9–5.4)	4.2 (3.5–5.0)	0.01	64.5	75.0	0.001
HDL (>1.2 mmol/l)	1.2 (1.0–1.5)	1.1 (0.9–1.4)	NS	59.4	43.8	NS
LDL (<3.0 mmol/l)	2.5 (1.9–3.2)	2.2 (1.6–2.8)	0.01	69.1	82.0	0.05
Triglycerides (<2.0 mmol/l)	1.8 (1.2–2.4)	1.8 (1.3–2.5)	NS	65.0	56.3	NS
Systolic BP ^a (<130 mmHg)	139 (124–154)	130 (125–145)	0.05	37.1	53.2	0.001
Diastolic BP ^a (<80 mmHg)	76 (69–84)	71 (65–79)	0.002	68.4	90.3	0.01
Systolic BP ^b (<120 mmHg)	140 (130–156)	135 (127–155)	NS	18.8	24.1	NS
Diastolic BP ^b (<75 mmHg)	74 (68–84)	74 (70–81)	NS	52.8	55.2	NS

^aPatients without diabetes and with a urine protein:creatinine ratio < 100.

^bPatients with diabetes or a urine protein:creatinine ratio > 100.

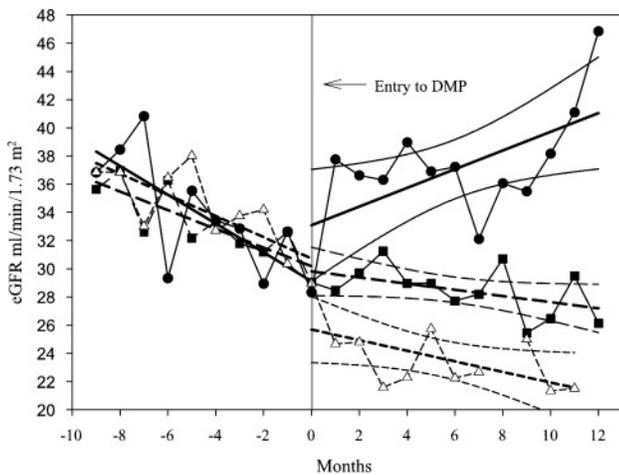


Fig. 3. Median eGFR values prior to and following joining the DMP for patients who had a fall in eGFR of ≥ 5 ml/min/1.73 m² prior to joining the DMP and who subsequently had a fall of eGFR of ≥ 5 ml/min/1.73 m² (triangles, $n = 14$); a fall of eGFR of < 5 ml/min/1.73 m² (squares, $n = 73$) and a rise in eGFR of ≥ 5 ml/min/1.73 m² (circles, $n = 35$). Regression lines with 95% confidence intervals have been fitted to the data prior to and following joining the programme; confidence limits have been left off the regression lines prior to the DMP for the sake of clarity.

blood pressure (as both a continuous and a categorical variable), cholesterol and LDL (as both continuous and categorical variables), treatment with a statin and treatment with an ACE inhibitor or angiotensin receptor blocker. The end points were progression to dialysis, decline in renal function of > 5 ml/min/1.73 m², death and a composite end point of all three. Patients on dialysis at enrolment (41) and patients with no data following enrolment (25) were excluded from this analysis. Death was significantly associated with age (RR 1.008, $P = 0.001$), CKD at presentation (RR 2.538, $P = 0.026$) and low (< 100 mmHg) systolic blood pressure (RR 6.128, $P = 0.035$). The composite

end point was related significantly to only age (RR 1.063, $P = 0.005$).

Discussion

These data suggest that reporting of eGFR derived from the four-variable MDRD equation as part of the ORC UK DMP has the potential to significantly improve health outcomes for patients with CKD thereby reducing costs to the health community from fewer cardiovascular events and delay in time to dialysis.

The chronic disease or long-term condition management model in other countries has been shown to improve clinical outcomes in a number of chronic conditions [22–24]. The experience of DMPs in the UK is limited and has not been as positive [24,25]. Patients with CKD often have several comorbidities which will increase the complexity of any DMP. DMPs for CKD (rather than dialysis patients) are relatively in their infancy and the major problem, in the USA, has been patient identification. This should not be an issue in the UK with the near national role-out of eGFR reporting. This programme is predominantly focused on patients with CKD stages 4 and 5 although there is evidence that the involvement of patients at earlier stages of CKD is also associated with improved outcomes [26–28]. However, Harris *et al.* [29] in a randomized control trial of intensive multidisciplinary case management of patients with CKD followed up for 5 years did not demonstrate any significant benefit in the intensively managed patients. There are major differences between the two groups of patients that may go some way to explaining this apparent disparity. The American patients were mainly female (68%), they were younger by some 10 years (mean), $> 80\%$ were of African-American origin, a higher proportion were diabetic (45%), $> 90\%$ suffered from urinary tract infection and $> 50\%$ were receiving nonsteroidal anti-inflammatory medication at

enrolment and after 5 years of follow-up. Surprisingly, given the above, mortality was relatively low and as a group they experienced little or no decline in renal function. This contrasts with our patients, with a 12-month mortality of 10.8% and a marked decline in renal function in 38.4% in the 9 months prior to joining the programme.

It is well established that patients with CKD are at high risk of cardiovascular disease. As GFR declines below 60 ml/min, the cardiovascular event rate rises inversely with GFR so that by the time patients reach CKD stage 5, the age-adjusted event rate has increased 18-fold [30]. This extreme cardiovascular risk accounts for much of the increased mortality of CKD and reduction of cardiovascular risk must therefore be a major aim of a DMP for CKD. The improvements in blood pressure and lipids that occurred in this programme will reduce cardiovascular morbidity and mortality rates, although the magnitude of benefit is hard to define. Event rates in CKD are underestimated by the Framingham risk score [31] and the large randomized trials that have demonstrated treatment effects for anti-hypertensive agents and statins have specifically excluded most patients with CKD. Even observational studies that relate standard risk factors to cardiovascular outcome in CKD have been confounded by the problem of 'reverse causality' [32]. Analysis of the MDRD study results, however, suggested that the adverse effect of high blood pressure in CKD patients may be powerful, with a 35% increase in hospitalization for cardiovascular and cerebrovascular disease for a 10 mmHg elevation in systolic blood pressure [33]. The improvement in median systolic and diastolic blood pressures of about 10 and 5 mmHg, respectively, obtained with the DMP have been associated with a reduction in relative risk of stroke of ~30–40% and of myocardial infarction of ~20% in the general population, and these are likely to be minimum effect sizes in patients with CKD [7]. A recently published analysis of ACE-inhibitor-based blood pressure-lowering therapy in cerebrovascular disease indicated that the effects of treatment were 1.7 times greater in patients with CKD than for those without [34]. However, neither the MDRD nor AASK studies of intensive blood pressure-lowering in CKD examined cardiovascular outcome measures [35,36]. Despite this, there is wide agreement that blood pressure control in CKD reduces both cardiovascular risk and disease progression [37, 38]; indeed with their higher absolute level of cardiovascular risk, patients with CKD may benefit more than the general population. With respect to the increased number of patients achieving target cholesterol values and the reduction in median total cholesterol and LDL of just under 0.5 mmol/l achieved by this programme, a major benefit may also accrue. Perhaps the most relevant population to our own in whom the effects of lipid lowering have been studied is that of the ASCOT study whose patients were hypertensive with other risk factors but without overt atherosclerotic disease [39]. Reductions in total cholesterol and LDL of 1.3 and 1.2 mmol/l, respectively, resulting from atorvastatin were associated with a near 30% reduction in cardiovascular event rate after only 3.3 years of treatment. This DMP appears to have resulted in only modest reductions in total cholesterol and LDL but even effects of this size are likely to reduce cardiovascular event rates substantially. The beneficial effect of cholesterol low-

ering with statins on the risk of cardiovascular end points in patients with CKD stage 3 appears to be no different from that observed in the general population [40]. Again, it should be noted that the absolute benefit seen with statins in CKD is greater than that seen in the general population because of the higher event rates. Effect sizes may be even greater with the attainment of lower LDL values that have now been shown to further reduce risk in secondary prevention trials [41]. Caution must be observed in extrapolating these results to patients with more severe CKD in light of the 4D study results that showed no benefit from statins in diabetic dialysis patients [42]. This should reinforce the need to begin cardiovascular risk reduction therapy at the earliest possible opportunity in patients with CKD.

The other main finding in this programme was the ability to reduce or even revert the decline in renal function in a high proportion of patients in a relatively short period of time. It has previously been suggested that the majority of patients with a GFR < 25 ml/min/1.73 m² will progress relentlessly to end-stage renal failure [43,44]. The data from this programme (Figure 1) suggest that there is a group of patients with poor renal function (median eGFR at presentation 27.9 ml/min/1.73 m²) at presentation whose renal function had changed little in the previous 9 months and remained stable in the subsequent 12 months. Conversely, there was a group of patients with similar levels of renal function at presentation (median eGFR at presentation 28.6 ml/min/1.73 m²) whose renal function had deteriorated significantly in the 9 months prior to presentation but in >85% of whom renal function either stabilized or actually improved in the subsequent 12 months. Such clinically important changes in renal function in patients with CKD stage 4 or 5 have been previously documented [45].

Given that mortality and morbidity of these patients is related to their level of renal function [30], the potential health benefits are large. There are a number of possible explanations for this effect. The relationship between improved blood pressure control and reduction in the rate of progression is well documented [46]. There is also good evidence for the renoprotective effects of statins [45] and blockade of the renin-angiotensin system [46, 47]. Thus it is possible that the effects seen on the rate of progression of renal impairment are related to the reductions observed in blood pressure and cholesterol. Other possibilities are the discontinuation of potentially nephrotoxic medication and the commencement of either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Whilst encouraging, the results described above need to be interpreted with caution as they were obtained from an observational study rather than a randomized controlled trial and, as such, there is the potential for bias from a number of possible sources. Patient selection may well be an issue. Only 85% of GP practices took part in the DMP and whilst they accounted for 85% of the WLCT population, a section of the population has been excluded from the programme. We cannot be certain that the outcomes of the patients in the programme apply to the excluded group and it is possible that the excluded group would have influenced the outcomes. However, the excluded group represents only a small percentage of the population that is relatively

homogeneous, with only a tiny ethnic minority population so this would seem to be unlikely. In addition, there is a possibility of Neyman [48] bias, as the risk factor (the presence of CKD) influences mortality. The likelihood of this occurring has been minimized by enrolment of both prevalent and incident patients, although it is noted above that the outcome in the incident patients may be worse. Retrospective eGFR data were not available for 28% of the patients enrolled in the programme who were necessarily excluded from the analysis in Figures 1–3 that considers the change in eGFR during the programme in relation to change in the preceding 9 months. These incident patients have been included in the logistic regression analysis that looked at characteristics on entry in relation to the outcome and it is noted that their decline in renal function during the programme is more rapid than those with retrospective data (the prevalent patients).

It is possible that the improvements in blood pressure, cholesterol and rate of decline in renal function are due to the Hawthorne effect or co-interventional bias [49]. This is an observation that merely by participating in a test, trial or study, the participants have a better experience because of the interest taken in them that is rewarding for its own sake. For this reason, better results are obtained, regardless of the change provided or treatment experienced. Whilst it is not possible to completely exclude such an effect, the programme deliberately sets out to increase patients' involvement in their own care and it is hard to see how this alone would reduce the rate of decline in eGFR or level of cholesterol in the absence of some other intervention such as a change in medication, or lifestyle or an improvement in compliance with medication. In addition, with respect to renal function, the patients appear to form two distinct groups, those with declining renal function and those with poor but stable renal function. If the effects observed were solely related to the Hawthorne effect, it is hard to understand why only those people with declining renal function were affected.

Conflict of interest statement. Dr N.T. Richards is an employee of Fresenius Medical Care Renal Services UK Ltd. Dr D. Marcelli is an employee of Fresenius Medical Care Ag and Co KaGA. All other authors declare that they have no conflict of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

(See related article by Nick Richards *et al.* The impact of population-based identification of chronic kidney disease using estimated glomerular filtration rate (eGFR) reporting. *Nephrol Dial Transplant* 2008; 23: 556–561.)

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