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Quality of chronic kidney disease management in primary care: a retrospective study


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Quality of chronic kidney disease management in primary care: a retrospective study

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ABSTRACT

Background: Early detection and appropriate management of chronic kidney disease (CKD) in primary care are essential to reduce morbidity and mortality. Aim: To assess the quality of care (QoC) of CKD in primary healthcare in relation to patient and practice characteristics in order to tailor improvement strategies. Design and setting: Retrospective study using data between 2008 and 2011 from 47 general practices (207 469 patients of whom 162 562 were adults). Method: CKD management of patients under the care of their general practitioner (GP) was qualified using indicators derived from the Dutch interdisciplinary CKD guideline for primary care and nephrology and included (1) monitoring of renal function, albuminuria, blood pressure, and glucose, (2) monitoring of metabolic parameters, and alongside the guideline: (3) recognition of CKD. The outcome indicator was (4) achieving blood pressure targets. Multilevel logistic regression analysis was applied to identify associated patient and practice characteristics. Results: Kidney function or albuminuria data were available for 59 728 adult patients; 9288 patients had CKD, of whom 8794 were under GP care. Monitoring of disease progression was complete in 42% of CKD patients, monitoring of metabolic parameters in 2%, and blood pressure target was reached in 43.1%. GPs documented CKD in 31.4% of CKD patients. High QoC was strongly associated with diabetes, and to a lesser extent with hypertension and male sex. Conclusion: Room for improvement was found in all aspects of CKD management. As QoC was higher in patients who received structured diabetes care, future CKD care may profit from more structured primary care management, e.g. according to the chronic care model.

KEY POINTS

- Quality of care for chronic kidney disease patients in primary care can be improved.
- In comparison with guideline advice, adequate monitoring of disease progression was observed in 42%, of metabolic parameters in 2%, correct recognition of impaired renal function in 31%, and reaching blood pressure targets in 43% of chronic kidney disease patients.
- Quality of care was higher in patients with diabetes.
- Chronic kidney disease management may be improved by developing strategies similar to diabetes care.

Introduction

General practitioners (GPs) play a key role in the complex care of patients with chronic kidney disease (CKD). The K/DOQI guidelines (USA) and the National Institute for Health and Clinical Excellence (NICE) CKD guideline (UK) provide GPs with recommendations on good CKD management, including monitoring of disease progression and strictly controlling cardiovascular risk factors.[1,2] The Dutch interdisciplinary CKD guideline for primary care and nephrology is similar to these guidelines, but incorporates age in its recommendations (Web appendix Table 1).[3]

Studies have shown that high standard CKD management attenuates and delays adverse outcomes such as progression to end-stage renal failure and cardiovascular events.[4,5] However, literature also notes deficiencies in the quality of care (QoC).[6,7] The high
prevalence of comorbidity challenges the GP to balance guideline advice to the patient’s individual needs.[8]

Our study aimed to analyse QoC in routine general practice for all stages of CKD, in relation to patient and practice characteristics. We hypothesized that our study would reveal predictors of high QoC.

Material and methods

Recruitment of participants

This retrospective study used baseline patient data of general practices that participated in a cluster randomized controlled trial on the effect of web consultation between GP and nephrologist on in-person referrals: the CONTACT study (Consultation Of Nephrology by Telenephrology Allows optimal Chronic kidney disease Treatment in primary care, Netherlands Trial Registration code 2368). The CONTACT study recruited general practices during a CKD management course for GPs. Forty-seven non-academic general practices signed up for participation. Data between 2008 and 2011 were analysed from their registered populations’ electronic medical records (EMRs) (n = 207 469). We included all patients aged 18 years or older who met the CKD criteria: eGFR < 60 ml/min/1.73m² or albuminuria. Patients under secondary renal care were excluded from analysis.

Classification of patients

The interdisciplinary CKD guideline for primary care and nephrology provides guidance for the GP in selecting the best suited health care setting for patients with CKD, based on eGFR, albuminuria and age. These settings are: treatment in primary care, consultation with a nephrologist without referral, and referral to secondary care. The guideline provides specific monitoring criteria for each group. We applied this classification to our cohort, resulting in a primary care, a consultation, and a referral group (Table 1). For the primary care group this implied monitoring of disease progression, while the consultation and the referral groups additionally required monitoring of metabolic parameters (Web appendix Table 1). We used laboratory-reported MDRD calculated eGFR values and in congruence with the guideline we defined microalbuminuria as a urinary albumin to creatinine ratio (ACR) of 2.5–25mg/mmol in men and 3.5–35mg/mmol in women. Higher ratios reflected macroalbuminuria. If an ACR was unavailable, we used urine albumin concentration with cut-off values > 20–200mg/l for microalbuminuria and > 200 mg/l for macroalbuminuria. Patient age was set on the latest eGFR date.

Process and outcome indicators

We derived indicators (Table 2) from the interdisciplinary CKD guideline for primary care and nephrology.[3] Included process indicators were: (1) monitoring of disease progression (assessment of eGFR or serum creatinine, albuminuria, glucose, and blood pressure); (2) monitoring of metabolic parameters (assessment of haemoglobin, calcium, phosphate, parathyroid hormone (PTH), serum albumin, and potassium), and alongside the guideline: (3) recognition of CKD in patients with an eGFR < 60 ml/min/1.73m² (separate entity on the EMR episode list with International Classification of Primary Care (ICPC) code U99.1 for renal impairment). The outcome indicator was (4) achievement of blood pressure targets, for which the mean of the two latest measurements had to be < 140/90 mmHg. Additionally, we analysed blood pressures < 130/80 mmHg to allow comparison with existing literature.

Patient and practice characteristics

We extracted patient demographic and clinical data concerning comorbidities and medication from the EMRs (Table 3). Patient age was categorized in ranges 18–45, 45–60, 60–75, and over 75 years. Comorbidities were defined by ICPC codes as a history of diabetes (T90), hypertension (K86,K87), and cardiovascular disease (K74-K77,K89,K90,K92).[9] We selected drug prescriptions issued during 2010 for medication shown in Table 3 using Anatomical Therapeutic Chemical (ATC) codes.[10] Practice characteristics included type (solo, duo, or group practice), vocational training, location (urban or
Table 2. Performance on process and outcome indicators within 15 months prior to data extraction for patients under GP care.

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Monitoring of disease progression</th>
<th>Monitoring of metabolic parameters</th>
<th>Blood pressure targets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Renal function</td>
<td>Albuminuria</td>
<td>Fasting glucose</td>
</tr>
<tr>
<td>Primary care group:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 eGFR ≥ 60</td>
<td>892</td>
<td>817</td>
<td>763</td>
</tr>
<tr>
<td>and microalbuminuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 65 eGFR ≥ 60</td>
<td>693</td>
<td>588</td>
<td>555</td>
</tr>
<tr>
<td>and microalbuminuria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 eGFR 45–60</td>
<td>4125</td>
<td>3403</td>
<td>1686</td>
</tr>
<tr>
<td>Total primary care</td>
<td>5710</td>
<td>4808</td>
<td>3004</td>
</tr>
<tr>
<td></td>
<td>(84.2%)</td>
<td>(52.6%)</td>
<td>(68.9%)</td>
</tr>
<tr>
<td>Consultation group:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 eGFR 30–45</td>
<td>1235</td>
<td>1023</td>
<td>501</td>
</tr>
<tr>
<td>Age &lt; 65 eGFR 45–60</td>
<td>1545</td>
<td>1131</td>
<td>540</td>
</tr>
<tr>
<td>Total consultation</td>
<td>2760</td>
<td>2154</td>
<td>1041</td>
</tr>
<tr>
<td>group</td>
<td>(77.5%)</td>
<td>(37.4%)</td>
<td>(37.4%)</td>
</tr>
<tr>
<td>Referral group:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 eGFR 30–30</td>
<td>79</td>
<td>67</td>
<td>18</td>
</tr>
<tr>
<td>Age &lt; 65 eGFR 30–45</td>
<td>63</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>Age &lt; 65 eGFR &lt; 30</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>156</td>
<td>137</td>
<td>118</td>
</tr>
<tr>
<td>Total Referral group</td>
<td>304</td>
<td>256</td>
<td>156</td>
</tr>
<tr>
<td></td>
<td>(84.2%)</td>
<td>(51.3%)</td>
<td>(68.8%)</td>
</tr>
<tr>
<td>Total consultation</td>
<td>3084</td>
<td>2410</td>
<td>1197</td>
</tr>
<tr>
<td>and referral group</td>
<td>(78.1%)</td>
<td>(38.8%)</td>
<td>(56.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>8794</td>
<td>7218</td>
<td>4201</td>
</tr>
<tr>
<td></td>
<td>(82.1%)</td>
<td>(47.8%)</td>
<td>(64.7%)</td>
</tr>
</tbody>
</table>

Process- and outcome indicators are derived from the interdisciplinary CKD guideline for primary care and nephrology. For each indicator, performance in the preceding 15 months is shown. Renal function: eGFR or serum creatinine; albuminuria: albumin creatinine ratio or urine albumin. eGFR in ml/min/1.73m².

*Percentages show the achieved blood pressure targets divided by the number of blood pressure measurements.

**Percentage calculated with patients with eGFR < 60 ml/min/1.73m² as denominator (n = 69 in macroalbuminuria group).
rural based on the Statistics Netherlands’ Key figures postcode areas database of 2004), and General Practice Information System (Web appendix Table 2).

**Data analysis**

CKD stage prevalence was calculated using the registered population aged 18 years and over as denominator. We used descriptive statistics to assess adherence to process and outcome indicators and to evaluate GPs’ recognition of CKD. The guideline advises annual monitoring, but in routine general practice the monitoring could take place outside this 12-month timeframe. We took this into account and extended the period to 15 months prior to data extraction on 1 March 2011. Because of the hierarchical structure of our data (patients nested within practices) the analyses were performed with the multilevel logistic regression model (PROC GLIMMIX in SAS). To identify patient and practice characteristics associated with high-quality care, we performed a model with a random intercept and all other variables were fixed. The type of General Practice Information System was considered a confounder, since it could affect the quality of data recording. We started with a full model including all independent variables and excluded statistically non-significant variables one by one in a backward procedure. We considered a $p$-value $<0.05$ as statistically significant. Descriptive analysis was conducted using SPSS version 20.0™ (IBM PASW statistics 20, IBM, Armonk, NY, USA) and multilevel logistic regression analysis was conducted using SAS V9.2™ (SAS Institute, Cary, NC, USA).

**Results**

**Practice population**

The 47 practices served a population of 207 469 people of whom 162 562 were aged 18 or older. Data on renal function ($n = 59 728$) or albuminuria ($n = 19 217$) were present for 59 728 adult patients (31%). More data were

---

**Table 3. Patient characteristics based on data from 2008 to 2011 for patients under GP care.**

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Groups</th>
<th>Overall (n = 8794)</th>
<th>Primary care (n = 5710)</th>
<th>Consultation (n = 2780)</th>
<th>Referral (n = 304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics (SD):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years</td>
<td>71.4 (11.9)</td>
<td>73.6 (10.2)</td>
<td>66.7 (13.3)</td>
<td>72.3 (14.0)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>40.0%</td>
<td>42.7%</td>
<td>33.6%</td>
<td>47.0%</td>
<td></td>
</tr>
<tr>
<td>Comorbidity:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>32.9%</td>
<td>36.0%</td>
<td>24.5%</td>
<td>52.6%</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>56.2%</td>
<td>57.8%</td>
<td>53.5%</td>
<td>52.0%</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>35.6%</td>
<td>36.1%</td>
<td>32.4%</td>
<td>53.6%</td>
<td></td>
</tr>
<tr>
<td>Laboratory (SD), n:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, μmol/l</td>
<td>103.9 (25.9)</td>
<td>n = 8792</td>
<td>96.5 (18.5)</td>
<td>n = 5709</td>
<td>117.4 (23.7)</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>52.6 (8.1)</td>
<td>n = 8794</td>
<td>55.4 (4.9)</td>
<td>n = 5710</td>
<td>47.7 (9.0)</td>
</tr>
<tr>
<td>Fasting glucose, mmol/l</td>
<td>6.5 (1.8)</td>
<td>n = 6938</td>
<td>6.6 (1.9)</td>
<td>n = 4689</td>
<td>n = 138</td>
</tr>
<tr>
<td>Ca²⁺, mmol/l</td>
<td>2.33 (0.8)</td>
<td>n = 5022</td>
<td>3.2 (0.9)</td>
<td>n = 3357</td>
<td>0.9 (0.8)</td>
</tr>
<tr>
<td>Phosphate, mmol/l</td>
<td>1.03 (0.1)</td>
<td>n = 5022</td>
<td>1.23 (0.1)</td>
<td>n = 3357</td>
<td>0.9 (0.8)</td>
</tr>
<tr>
<td>Albumin, g/l</td>
<td>3.88 (4.4)</td>
<td>n = 271</td>
<td>3.68 (4.6)</td>
<td>n = 57</td>
<td>n = 138</td>
</tr>
<tr>
<td>Potassium, mmol/l</td>
<td>4.3 (0.45)</td>
<td>n = 2238</td>
<td>4.4 (1.56)</td>
<td>n = 6938</td>
<td>4.4 (1.56)</td>
</tr>
</tbody>
</table>

**Urine (first and third quartile), n:**

- Albumin, mg/l: 15.0 (3.4–51.0) | n = 2928 | 20.0 (5.0–53.0) | n = 2049 | 6.0 (2.9–18.0) | n = 721 | 210.6 (84.3–480.2) | n = 158 |
- Albumin/creatinine ratio: 2.5 (0.9–6.1) | n = 5022 | 3.2 (0.9–6.4) | n = 3357 | 0.9 (0.8–2.3) | n = 1254 | 37.7 (14.8-58.2) | n = 211 |

**Physical examination (SD), n:**

- SBP, mm Hg: 78.8 (9.7) | n = 7291 | 78.6 (9.5) | n = 4889 | 79.1 (9.9) | n = 2147 | 78.6 (11.3) | n = 255 |
- DBP, mm Hg: 142.7 (17.7) | n = 7290 | 143.8 (17.4) | n = 4889 | 139.8 (17.5) | n = 2146 | 145.1 (21.6) | n = 255 |

**Medication prescribed in 2010:**

- Renin angiotensin blockers: 55.9% | 56.4% | 53.7% | 67.4% |
- B-blockers: 46.3% | 46.5% | 45.4% | 52.0% |
- Diuretics: 41.4% | 40.8% | 41.8% | 49.3% |
- Calcium antagonist: 21.6% | 21.4% | 20.6% | 32.9% |
- Statins: 47.0% | 48.8% | 42.6% | 52.3% |
- Vitamin D: 3.7% | 2.2% | 6.1% | 9.5% |
- Erythropoietin: 0.3% | 0.1% | 0.5% | 1.3% |
- Blood glucose lowering drugs: 25.0% | 27.3% | 18.5% | 40.1% |
- Antithrombotics: 46.6% | 48.3% | 42.1% | 57.6% |
- NSAIDs: 21.3% | 21.1% | 22.3% | 17.8% |
available for the elderly: 71% of the population over 65 years had a renal function assessment. Diabetes was recorded in 10,623 patients (6.5% of the population), hypertension in 23,647 (14.5%), and cardiovascular disease in 12,938 (8.0%).

**Study population**
A total of 9,288 patients met the criteria for CKD, resulting in a known adult prevalence of CKD in our study of 5.7%. KDOQI stages 1–2 accounted for 1.06% (n=1,719) and stages 3–5 for 4.66% (n=7,569). Of these, 494 patients received secondary renal care and were excluded from analysis. In the cohort of 8,794 patients treated by their GP, the guideline recommended treatment in primary care in 64.9%, consultation with a nephrologist in 31.6%, and referral in 3.5% of patients. Table 3 provides detailed characteristics.

**Process and outcome indicators**
GPs completely followed the guideline in 42% (95% CI 41–43%) of their CKD patients for monitoring disease progression and in 2.4% (95% CI 1.9–2.9%) for monitoring metabolic parameters. Blood pressure was below 140/90 mmHg in 43.1% (95% CI 41.8–44.3%) and below 130/80 mmHg in 16.4% (95% CI 15.5–17.3%) of patients in whom a blood pressure measurement was available (n=6,325). All patients considered, the achievement of blood pressure targets amounted to 31.0% and 11.8% respectively. GPs recognized decreased eGFR in 31.4% (95% CI 30–32%) by using ICPC code U99.1 for impaired renal function. Table 2 provides further details on quality indicators.

**Associated patient and practice characteristics**
A history of diabetes (OR 10.97; 95% CI 9.75–12.34) or hypertension (OR 2.45; 95% CI 2.19–2.73), and male gender were associated with better monitoring of disease progression (Table 4a). A history of cardiovascular disease was negatively correlated with monitoring of disease progression. Cardiovascular disease and highest age were positively associated with monitoring of metabolic parameters (Table 4b). Factors associated with recognition of CKD were a history of cardiovascular disease, hypertension, female sex, and highest age. Blood pressure outcome target <140/90 mmHg was positively associated with a history of cardiovascular disease, and had a negative correlation with highest age.

**Discussion**

**Summary**
Our results show room for improvement in all aspects of CKD management, yet most clinical relevance lies in the achievement of blood pressure targets (43% <140/90 mmHg). A history of diabetes was strongly associated with high QoC.

**Prevalence and recognition**
In the Netherlands, the estimated community prevalence of CKD is 10.4%, with 5.1% in CKD stages 1–2, and 5.3% in stages 3–5. [11] For our data, this implies that respectively 21% and 88% of expected CKD patients could have been ascertained in primary care with the available laboratory results. However, recognized decreased eGFR was lower at only 31.4% of potentially identifiable patients. Recognition is important, as it is associated with better quality of care. [12]

**Strengths and limitations**
A key strength of our study is the utilization of routine general practice data, which provides a realistic view on quality of care. Our study represents a large proportion...
of the (potential) CKD population in primary care, as data on renal function were available for most patients over 65 years. To accurately report on QoC in routine general practice, we focused on patients under care of their GP. Several limitations should be considered. We applied the guideline classification based on single creatinine and albuminuria assessments whereas at least two or three measurements are advised. This might have led to less accurate classification, but is in line with other CKD studies. The practices' intrinsic motivation to participate in the CONTACT trial might have led to a selection bias with possible overestimation of QoC. Conversely QoC might be underestimated due to analysis of data routinely recorded in the EMR. It is not unlikely that blood pressure was measured but not registered. Furthermore, GPs had little time to implement the guideline within our studied timeframe (1 December 2009 to 1 March 2011) considering its introduction in November 2009.

Comparison with existing literature

Our results on monitoring of disease progression are in line with previous studies. Research on CKD stages 3–4 conducted within multi-specialty group practices, housing both GPs and nephrologists, found a comparable eGFR assessment rate (86%), and a slightly lower albuminuria testing rate (30%).[6] Also, impressive results are shown in the United Kingdom, where they recorded an 82% albuminuria testing rate in CKD stages 3–5.[13] Of possible influence is the pay for performance system: the Quality and Outcomes Framework (QOF). In the Netherlands, GPs are not given incentives to manage CKD, but for diabetes management local financial incentives exist.[14]

Table 4b. Significant results of multilevel logistic regression model on the association between patient and practice characteristics and QoC.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Monitoring metabolic parameters</th>
<th>Outcome variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Haemoglobin</td>
<td>Calcium</td>
</tr>
<tr>
<td>Patient characteristics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (18–45 years as reference)</td>
<td>1.00 (0.66–1.53)</td>
<td>3.10 (0.74–13.01)</td>
</tr>
<tr>
<td>45–60 years</td>
<td>1.05 (0.69–1.60)</td>
<td>5.63 (1.36–23.29)</td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>2.26 (1.47–3.49)</td>
<td>10.22 (2.48–42.14)</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.78 (0.67–0.91)</td>
<td>0.73 (0.55–0.97)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.62 (0.52–0.73)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.72 (0.62–0.84)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>1.23 (1.03–1.46)</td>
<td></td>
</tr>
</tbody>
</table>

Results are shown as odds ratios with 95% confidence intervals in parentheses. Outcome on practice location was not significant. PTH and complete monitoring of metabolic parameters yielded too few results for the model to work.

Several limitations should be considered. We applied the guideline classification based on single creatinine and albuminuria assessments whereas at least two or three measurements are advised. This might have led to less accurate classification, but is in line with other CKD studies. The practices' intrinsic motivation to participate in the CONTACT trial might have led to a selection bias with possible overestimation of QoC. Conversely QoC might be underestimated due to analysis of data routinely recorded in the EMR. It is not unlikely that blood pressure was measured but not registered. Furthermore, GPs had little time to implement the guideline within our studied timeframe (1 December 2009 to 1 March 2011) considering its introduction in November 2009.
Research shows that patient factors associated with high QoC are concurrent diabetes, hypertension, or coronary artery disease, age > 75 years, and male sex.[6,18–20] Our findings are comparable, except that cardiovascular disease was negatively associated with monitoring of disease progression. Possibly, monitoring was left to the discretion of a cardiologist.

Results derived from the QOF show that vocational training practices, group practices, and practices in less socially deprived areas were associated with a higher QoC in general.[21,22]

**Implications for research and/or practice**

In CKD stages 1 and 2 we found a high QoC for monitoring of disease progression. We hypothesize that the high prevalence of diabetes in these patients (62%), and their treatment supported by an evidence-based primary care-generated diabetes guideline, is key to their renal function and albuminuria assessments.[23,24] This guideline has been developed in, by, and for general practice, with the objective to translate disease-specific recommendations into a framework of person-centred care over time. Since its introduction in 1989, the guideline has been revised and updated in relation to scientific progress but also following practice-based experiences in its implementation.[25] Our findings suggest that embedding of CKD care in a support model and organization comparable to diabetes would stand the best chance to improve QoC in general practice.[26] This should not be a new single disease model, but should support GP-based CKD care and preferably be integrated in existing support models for chronic care to prevent fragmentation.[27]

Feedback on laboratory results and GP education to increase CKD recognition can assist GPs to better identify CKD patients.[12] Periodic reviewing of EMRs, with or without the support of nephrologists, could be a component of support models.[28] Introduction of a pay-for-performance system for CKD management has shown favourable results in the UK.[17] Quality improvement strategies should focus on better recognition, systematic monitoring of disease progression including albuminuria, and blood pressure targets.

**Acknowledgements**

The authors would like to thank the Dutch Kidney Foundation, participating practices, Lea Peters, research assistant, and Reinier Akkermans, statistician.

**Funding**

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**Ethical approval**

Ethical approval was not required according to the accredited Medical Research Ethics Committee Arnhem/Nijmegen registration number 2010/187. This study was performed according to the Code of Conduct for Health Research, which has been approved by the Data Protection Authorities for conformity with the applicable Dutch privacy legislation.

**Disclosure statement**

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**References**


