Accuracy of glomerular filtration rate estimation using creatinine and cystatin C for identifying and monitoring moderate chronic kidney disease: the eGFR-C study

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Scientific summary

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Scientific summary

Background

Chronic kidney disease (CKD) is commonly identified using estimation of glomerular filtration rate (GFR) and/or detection of albuminuria [urinary albumin-to-creatinine ratio (ACR)]. Ideally, GFR is measured using reference procedures, but these are cumbersome and impractical for clinical practice. Estimation of GFR using equations based on serum creatinine with adjustments for age, gender and black ethnicity has been widely used. In the UK, the Modification of Diet in Renal Disease (MDRD) study equation and more recently the Chronic Kidney Disease Epidemiology Collaboration creatinine (CKD-EPI$_{creatinine}$) equation have been recommended. Other more recently published equations, including CKD-EPI cystatin C-containing equations (CKD-EPI$_{cystatin}$, CKD-EPI$_{creatinine\text{-}cystatin}$), the Berlin Initiative Study equations, the Caucasian, Asian, Pediatric and Adult equation, the Lund–Malmö revised equation, the full age spectrum equation, the European Kidney Function Consortium equation and the 2021 revisions of the CKD-EPI equations, have not yet gained widespread acceptance in clinical practice.

In addition to the accurate identification of CKD, the ability of tests to identify which individuals with CKD have higher risk of progressive or mortal disease is a crucial issue. Many people with stage 3 CKD are not at increased risk of CKD progression and there are concerns that CKD detection using creatinine-based approaches may identify some individuals who are at low risk and unlikely to benefit from active management. Equations utilising serum cystatin C, an alternative marker of GFR, instead of, or in addition to, creatinine have been proposed. Given the higher unit cost of cystatin C compared to creatinine, its diagnostic accuracy and clinical utility should be validated ahead of widespread introduction into the NHS.

Objectives

Primary objectives

The comparative performance of GFR-estimating equations in assessing and monitoring measured glomerular filtration rate (mGFR) in people with stage 3 CKD (GFR 30–59 ml/minute/1.73 m^2) was evaluated. The aims of the study were to:

1. estimate and compare the accuracy of the MDRD and three CKD-EPI equations
2. estimate the accuracy of the GFR-estimating equations according to ethnic group (particularly Caucasian, South Asian and African-Caribbean), baseline diabetes, albuminuria and other characteristics
3. evaluate and compare how accurately these GFR-estimating equations track and detect change in mGFR over 3 years
4. establish the biological variability of mGFR and estimated glomerular filtration rate (eGFR)
5. estimate which GFR-estimating equation, together with ACR, or ACR alone, most accurately predicts mortality and CKD progression
6. estimate and model disease progression (decline in GFR or increase in ACR) and differences in progression between ethnic groups (Caucasian, South Asian and African-Caribbean), baseline diabetes and albuminuria status and other potential risk factors
7. explore the comparative cost-effectiveness of monitoring strategies for identifying people who have CKD progression utilising different GFR-estimating equations.

Secondary objectives

1. Estimate and compare the accuracy of more recently published GFR-estimating equations.
2. Evaluate and compare how accurately these newer equations reflect and detect change in GFR over 3 years.

3. Estimate and compare the performance of the MDRD and CKD-EPI equations using the Haycock instead of the Du Bois equation for body surface area (BSA) adjustment.
4. Assess the impact of cystatin C calibration on the performance of the CKD-EPI equations.
5. Assess the impact of creatinine methodology [enzymatic vs. isotope-dilution mass spectrometry (ID-MS)] on the performance of the MDRD and creatinine-based CKD-EPI equations.

Methods

1. Main study. A 3-year prospective longitudinal cohort study using 6-monthly GFR estimates and baseline and final mGFR values was undertaken to assess and compare the accuracy of each estimate of GFR and change in GFR.
2. Substudy of disease progression. Predictors of progression of GFR in a subset of the cohort who received annual GFR measurements were modelled.
3. Substudy of biological variation. Components of variability in mGFR and eGFR were quantified.
4. An economic evaluation tested the consequences of implementing creatinine- and/or cystatin C-based eGFR for monitoring subjects who are initially stage 3 CKD.

Glomerular filtration rate was measured using iohexol clearance. Iohexol was measured by ID-MS. Creatinine was measured by a commercial enzymatic assay and by ID-MS. Cystatin C was measured by a commercial immunoassay. Both creatinine and cystatin C methods were internationally standardised.

Setting

Primary, secondary and tertiary care. Recruitment occurred across six centres in England.

Participants

Adults (≥ 18 years) with stage 3 CKD proportionally enriched to include people more likely to have progressive kidney disease (i.e. those with proteinuria and/or diabetes) and including South Asian and African-Caribbean people.

Interventions

Estimated GFR using the MDRD and three CKD-EPI equations, using either creatinine or cystatin C or a combination of both, in addition to urinary ACR. Other GFR-estimating equations were also studied.

Main outcome measures

Measured GFR was the reference test against which GFR-estimating equations were compared. Accuracy of GFR-estimating equations was expressed as P30, the percentage of estimated values within 30% of mGFR, with P30 ≥ 90% considered acceptable. P30 incorporates elements of bias and imprecision. The ability of eGFR equations to both track and detect change in mGFR over time gave an estimate of temporal error. For each individual, the average change per year in eGFR and mGFR was derived and error, the difference between the annual change in mGFR and eGFR, calculated. Large error was accepted as ≥ 3 ml/minute/1.73 m^2/year, or > 5%/year difference between mGFR and eGFR. Ability of equations to detect change was studied based on whether or not eGFR detected overall change, or decline only, in mGFR over 3 years against threshold changes variously defined as (1) > 10 ml/minute/1.73 m^2; (2) > reference change value (RCV) (a > 21.5% increase or a > 17.7%

decrease); (3) > 25% change; and (4) > 25% change and a change in disease stage. Sensitivity and specificity of eGFRs to identify progressive disease were evaluated. Estimated GFRs, in addition to urinary ACR, were also tested as predictors of progression and mortality.

In the substudy of disease progression the change in mGFR, and the difference between mGFRs and eGFRs (bias), assessed every 12 months, were modelled over time using a longitudinal linear random coefficients regression model, to estimate average and variability in disease progression and bias. A model of disease progression based on mGFR was developed and differences in progression for risk factors estimated.

In the biological variation substudy, analytical (CV_A) and individual (CV_I) components of variation were calculated and used to derive the RCV for significant changes in serial results for both mGFR and eGFR.

Results from the main study informed a measurement model analysis. The trajectory of participants mGFR and eGFR over 10 years was used to estimate the proportion meeting the National Institute for Health and Care Excellence (NICE) definition of accelerated progression or of progression to CKD stage G4, assuming an annual testing schedule, and the number of participants expected to be incorrectly managed at each of the evaluated monitoring time points using different estimating equations. Based on the findings, the comparative costs of monitoring with GFR-estimating equations were calculated.

Sample size

1. Main study. Complete baseline data *n* = 1167. Three-year follow-up GFR data *n* = 875.
2. Disease progression substudy. *n* = 278.
3. Biological variation substudy. *n* = 20.

Results

All estimates of GFR relating to the primary study objectives were negatively biased compared to mGFR. There was no difference in median bias (ml/minute/1.73 m^2) against mGFR between the MDRD (−3.7), CKD-$EPI_{creatinine}$ (−2.8), CKD-$EPI_{cystatin}$ (−4.1) and CKD-$EPI_{creatinine\text{-}cystatin}$ (−3.9) equations. Accuracy (P30) of the CKD-$EPI_{cystatin}$ equation (89.5%) did not differ from that of the MDRD (89.5%) and CKD-$EPI_{creatinine}$ (90.2%) equations: accuracy of the CKD-$EPI_{creatinine\text{-}cystatin}$ equation (94.9%) was superior ($p < 0.001$) to these equations. Similar performance characteristics were observed for more recently described GFR-estimating equations. Accuracy of cystatin C-containing equations was critically influenced by the commercial assay used, for example median bias of CKD-$EPI_{cystatin}$ equation changed from −9.8 to −4.1 when Siemens as opposed to Abbott assay was used, with a corresponding increase in P30 from 72.5% to 89.5%. To a lesser extent, a consistent positive bias (4.7 µmol/l) in the creatinine assay compared to the ID-MS reference method also increased the negative bias of GFR estimates.

P30 of eGFR equations was unaffected by whether mGFR was adjusted for BSA using the Du Bois or the Haycock equation. Nevertheless, use of Haycock-adjusted mGFR reduced negative bias of all GFR-estimating equations by approximately 1.4 ml/minute/1.73 m^2.

P30 of the main study GFR-estimating equations was examined by categories of age, gender, diabetes, albuminuria, body mass index (BMI), level of GFR and ethnic group: no significant differences were seen across any of these categories for any of the study equations. Interpretation of accuracy data across ethnic groups was limited by the small sample size of South Asian (*n* = 66) and African-Caribbean (*n* = 60) groups. However, removal of the African-Caribbean adjustment factor from the MDRD and CKD-$EPI_{creatinine}$ equations led to reduced point estimates of accuracy amongst African-Caribbean individuals (e.g. P30 for the CKD-$EPI_{creatinine}$ equation decreased from 81.7% to 70.0%).

When monitoring changes in GFR over time, all GFR equations tended to underestimate GFR decline. In relation to the tolerance limits (± 3 ml/minute/1.73 m^2/years or ± 5%/years) of the slope of change for mGFR, equations achieved > 70% concordance. The CKD-EPI$_{creatinine-cystatin}$ equation had better concordance than the other three primary study equations ($p < 0.05$ for ± 3 ml/minute/1.73 m^2/years), although confidence intervals overlapped in all cases. All newer equations that incorporated both creatinine and cystatin C also achieved higher point estimates of agreement than their corresponding creatinine-only equations.

In relation to detection of decline in mGFR, irrespective of which threshold change was studied, while the specificity of GFR-estimating equations was reasonable (> 83% in all cases), sensitivity for detecting change was < 63% in all cases. There was no clear difference in sensitivity or specificity between the four main study equations. For all equations and all thresholds, there was no clear evidence of improved performance of cystatin-containing equations compared to their matched creatinine-only equation.

In the substudy of disease progression, modelling data showed a strong association between albuminuria status and rate of progression in mGFR and CKD-EPI$_{creatinine}$ eGFR, with those with albuminuria having faster progression (steeper decline). Higher baseline mGFR values were associated with faster progression rate for mGFR. African-Caribbean ethnicity increased (slower decline) and South Asian ethnicity decreased (faster decline) the estimate of progression slope for mGFR and CKD-EPI$_{creatinine}$ GFR. However, recruitment of ethnic minority participants in particular to the substudy fell short of target, limiting the strength of any conclusions.

Within-subject biological variation of mGFR was 6.7%, with similar, although in some cases significantly lower, biological variation of eGFR (5.0, 5.3, 5.3 and 5.0% for MDRD, CKD-EPI$_{creatinine}$, CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine-cystatin}$ equations, respectively). Derived RCVs (%, positive/negative) were 21.5/−17.7 (mGFR), 15.1/−13.1 (MDRD), 15.9/−13.7 (CKD-EPI$_{creatinine}$), 15.9/−13.8 (CKD-EPI$_{cystatin}$) and 15.1/−13.1 (CKD-EPI$_{creatinine-cystatin}$).

We observed 62 deaths during the 3-year follow-up period. The study was not powered for hard end points. However, in agreement with earlier studies, regression models including each GFR-estimating equation separately demonstrated mortality was associated with lower eGFR, increasing age and male gender. An association with categorical albuminuria was not observed. There was no evidence of superiority of CKD-EPI equations, including the cystatin C-containing equations, as predictors of death compared to the MDRD equation.

A measurement model analysis found no evidence to suggest that any of the estimating equations were superior for identifying CKD progression based on NICE-defined clinical end points. The average incremental per patient costs (compared to MDRD) of monitoring over a 10-year period using the cystatin C-based equations were estimated (CKD-EPI$_{cystatin}$ £42.20; CKD-EPI$_{creatinine-cystatin}$ £43.32).

Conclusions

Most GFR equations achieved acceptable accuracy as judged by P30. There was little difference between the equations in accuracy, with evidence of superior accuracy for the CKD-EPI$_{creatinine-cystatin}$ equation. Across several important characteristics (age, gender, diabetes, albuminuria, BMI, GFR level) we found no difference in accuracy of GFR-estimating equations. In relation to GFR estimation in African-Caribbean individuals, there was evidence to suggest caution should be exercised before advocating simple removal of the black race factor from the original CKD-EPI equations.

In the longitudinal study, the CKD-EPI$_{creatinine-cystatin}$ displayed slightly better concordance with mGFR than the other main study equations when tracking patients, but all study equations underestimated the mGFR decline. The sensitivity of GFR equations to detect clinically relevant threshold changes in mGFR,

either overall or when considering decline in GFR only, was ≤ 63% for all equations. This is of concern given that such thresholds, including the NICE definition of accelerated progression and the change recognised as being true as determined by biological variation (RCV), were studied.

Overall, data comparing the accuracy of different GFR-estimating equations demonstrated no notable benefit of using a cystatin C-containing equation in detecting GFR change. The measurement model underpinning the health economic analysis focused on the comparative accuracy of the estimating equations to detect accelerated progression. The analysis estimated accuracy over a longer trajectory than the main study and factored in measurement error, but found no clear benefit of using a cystatin C-based estimating equation. There was therefore no evidence to suggest that adding cystatin C measurement to current GFR monitoring protocols would be cost-effective.

The disease progression modelling of the substudy data noted faster progression associated with higher baseline GFR and albuminuria; the latter consistent with other studies. Any conclusions relating to the influence of ethnicity were tempered by poor recruitment of ethnic minority individuals.

The biological variability data have implications for monitoring of patients with CKD and clinical ability to understand CKD progression, both in clinical practice and research. The information presented provides an evidence base allowing clinicians to have meaningful discussions with their patients about the implications of changes in their GFR results.

Inclusion of cystatin C in GFR-estimating equations was associated with marginal improvements in accuracy, but no clear advantages in terms of detecting GFR change over time. Problems of standardisation of cystatin C assays remain, despite the introduction of an international standard. The use of cystatin C increases the economic cost of CKD monitoring with little apparent gain. These data do not support the use of cystatin C for the routine monitoring of GFR in people with stage 3 CKD. Further research is warranted to investigate specific patient groups that may benefit from cystatin C use.

Trial registration

This trial is registered as ISRCTN42955626 www.controlled-trials.com/ISRCTN42955626 (accessed 26 July 2023).

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