The eGFR-C Study

Accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease: a prospective longitudinal study in a multiethnic population

Dr Edmund Lamb
Research Nurse Meeting - Birmingham
6th March 2014
### Agenda

- **11.00** Welcomes  
  - EJL  
- **11.05** Overview of study and aims  
  - EJL  
- **11.20** Updates  
  - RO  
- **11.30** Screening procedures  
  - GE/RO  
- **11.45** Consent procedures  
  - EJL/GE  
- **12.00** Online registration / data entry system  
  - RO  
- **12.15** Lunch  
- **1.00** Baseline assessment visits  
  - GE  
- **1.15** Subsequent assessment visits  
  - GE  
- **1.30** Sub-study  
  - EJL/GE  
- **1.45** Iohexol procedure  
  - GE  
- **2.00** Sample preparation, storage and transport  
  - GE/EJL  
- **2.30** Recruitment targets  
  - RO  
- **2.45** Adverse events  
  - RO  
- **3.00** AOB  
- **3.30** Finish
What is GFR and why does it matter?
Filtration takes place at the glomerulus.

100 uL/day/nephron → 200 L UF/day

200 L/day = 140 mL/min

17 mm Hg
Why GFR?

- Best overall index of kidney function
- Total kidney GFR = sum individual nephron GFR
- Normal GFR approx. 90 to 120 mL/min/1.73 m²
- Easily understood that kidney acts as a ‘filter’
- Decreasing GFR seen in all forms of progressive kidney disease
- Continuous scale, ‘Know your number!’
- CKD, and stages of CKD, defined in terms of GFR
KDIGO (2012): definition of CKD

Abnormalities of kidney structure or function, present for ≥3 months, with implications for health

Either of the following for >3 months:

1. Decreased GFR (<60 mL/min/1.73 m²)

2. Markers of kidney damage:
   - Albuminuria >30 mg/day
   - Urine sediment abnormalities (e.g. haematuria, red cell casts etc)
   - Electrolyte and other abnormalities due to tubular disorders
   - Abnormalities detected by histology
   - Structural abnormalities detected by imaging
   - History of kidney transplantation
KDIGO (2012): definition of CKD

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   • Structural abnormalities detected by imaging
   • History of kidney transplantation
### Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

<table>
<thead>
<tr>
<th>GFR Categories, Description and Range (mL/min/1.73 m²)</th>
<th>Albuminuria Categories, Description and Range</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 normal or high &gt;90</td>
<td>normal to mildly increased</td>
<td>54.0%</td>
<td>3.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>G2 mildly decreased 60-89</td>
<td>moderately increased</td>
<td>32.3%</td>
<td>2.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>G3a mildly to moderately decreased 45-59</td>
<td>severely increased</td>
<td>3.6%</td>
<td>0.8%</td>
<td>0.2%</td>
</tr>
<tr>
<td>G3b moderately to severely decreased 30-44</td>
<td></td>
<td>1.0%</td>
<td>0.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>G4 severely decreased 15-29</td>
<td></td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>G5 kidney failure &lt;15</td>
<td></td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

% of US adults by eGFR and ACR (KDIGO and NHANES)
How do we assess GFR?
Clearance

Traditionally, GFR assessed using concept of ‘clearance’

\[ \text{Clearance} = \frac{U_S V}{P_S T} \]

When substance \( S \) has: stable concentration in plasma, physiologically inert, freely filtered, not secreted, synthesised, reabsorbed nor metabolised by kidney

then clearance = GFR
Exogenous GFR markers

- Inulin
- $^{51}$Cr-ethylenediaminetetraacetic acid (EDTA)
- $^{99m}$Tc-diethylenetriaminepentaacetic acid (DTPA)
- $^{125}$I-iothalamate
- Iohexol

- All have relative advantages and disadvantages
- All give reasonable agreement with gold standard (inulin)
- $^{51}$Cr-EDTA preferred ‘silver standard’ method
- We favour iohexol - nonradioisotopic
Single bolus technique

GFR = \( k \times C_o \)

- Log conc.
- \( C_o \)
- Time after injection
- Distribution phase

\( k \)
Iohexol procedure

- Patients attend in morning having avoided meat/fish
- (study bloods and urine collected)
- 5 mL iohexol injected into antecubital vein.
- Blood samples collected 5, 120, 180 and 240 minutes after injection
- Iohexol measured in blood at St Thomas’s laboratory and GFR calculated based on disappearance
Endogenous markers

No need for injection
Single blood sample required

• Serum creatinine
• Estimated GFR using creatinine
• Estimated GFR using cystatin C
• Estimated GFR using cystatin C and creatinine
Serum creatinine (or cystatin C) is inversely related to GFR.

\[ \text{GFR} = \frac{k}{\text{serum creatinine}} \]

But relationship is affected also by age, gender, race (and other non-renal determinants). eGFR equations can take this into account.
GFR equations

• In the NHS GFR is currently estimated from serum creatinine using the MDRD equation
• Recent guidelines have suggested that the CKD-EPI equation is better
• There are also equations incorporating cystatin C which have advantages
• But cystatin C is more expensive to measure
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Equation</th>
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<tbody>
<tr>
<td>MDRD (ID-MS traceable)</td>
<td>$175 \times \text{Scr}^{-1.154} \times \text{age}^{-2.03} \times 0.75 \ [\text{if female}] \times 1.210 \ [\text{if black}]$</td>
</tr>
<tr>
<td>CKD-EPI(_{\text{creat}})</td>
<td>$141 \times \min(\text{Scr/κ, 1})^{\alpha} \times \max(\text{Scr/κ, 1})^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \ [\text{if female}] \times 1.159 \ [\text{if black}]$</td>
</tr>
<tr>
<td>CKD-EPI(_{\text{cys}})</td>
<td>$133 \times \min(\text{Scys/0.8, 1})^{-0.499} \times \max(\text{Scys/0.8, 1})^{-1.328} \times 0.996^{\text{Age}} \times 0.932 \ [\text{if female}]$</td>
</tr>
<tr>
<td>CKD-EPI(_{\text{creat-cys}})</td>
<td>$135 \times \min(\text{Scr/κ, 1})^{\alpha} \times \max(\text{Scr/κ, 1})^{-0.601} \times \min(\text{Scys/0.8, 1})^{-0.375} \times \max(\text{Scys/0.8, 1})^{-0.711} \times 0.995^{\text{Age}} \times 0.969 \ [\text{if female}] \times 1.08 \ [\text{if black}]$</td>
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Why does it matter to DH?

**Test costs**
- Creatinine costs approx £0.10
- Cystatin C costs approx £2.50
- Approx 50 million creatinine measurements in UK/year (£5 million)

**Earlier identification of disease/progression**
- Dialysis costs approx. £30,000 K/patient/year
Evidence gaps

- Cystatin C containing equations
- Use to monitor (and predict) progression
- British ethnic minority groups
- Background biological variability versus progressional (disease-related) change
eGFR-C: aims and objectives

1. estimate and compare the accuracy and precision of GFR-estimating equations based on the MDRD CKD-EPI equations using either creatinine or cystatin C or a combination of both in people with stage 3 CKD.

2. estimate the accuracy and precision of the GFR-estimating equations according to ethnic group (particularly Caucasians, African-Caribbean and South-Asian), and baseline diabetes and proteinuria.

3. evaluate and compare how accurately these GFR-estimating equations reflect change in GFR over three years

4. establish which GFR-estimating equation, together with ACR, or ACR alone, most accurately predicts those people that have progressive loss of kidney function (CKD progression)?

5. estimate and model disease progression (decline in GFR or increase in ACR) according to ethnic group (particularly Caucasians, African-Caribbean and South-Asian), and baseline diabetes and proteinuria.

6. compare the effectiveness and costs of monitoring strategies for identifying people that have progressive loss of kidney function (CKD progression) utilising different GFR-estimating equations and test schedules, accounting for differences in risk of progression.
**Recruitment:** adult patients (n=1300) with CKD stage 3 (GFR 30-59 mL/min/1.73 m²) recruited from secondary care clinics and primary care at 6 centres. Given study information and consented. Asked to complete clinical history questionnaire.

**Baseline visit:** Consenting participants attend hospital in the morning. Research nurse collects/verifies clinical and family history. Height, weight, waist circumference, blood pressure recorded. Reference (iohexol) GFR plus blood for creatinine, cystatin C and urinary ACR.

**Every 6 months:** repeat blood for creatinine, cystatin C, urinary ACR.

**Disease progression substudy:** n=375 at three centres (125 each of Caucasian, African-Caribbean and Asian) undergo additional reference (iohexol) GFR at 12 and 24 months.

**Biological variation substudy:** n=20 at one centre undergo four reference (iohexol) GFR and blood tests over four weeks.

**36 months visit:** All baseline measures repeated.

**Exit from study**
Initial call for commissioned research autumn 2011

Outline proposal submitted 9th Feb 2012

Full proposal submitted 19th July 2012

Provisional funding decision 7th December 2012

Final funding decision 25th February 2013

Contracts signed by DH 6th June 2013

Study start date 1st August 2013

Ethical approval October 2013

Commence recruitment 1st February 2014
eGFR-C collaborators

**Chief Investigator**
- Dr Edmund Lamb

**Co-Investigators**
- Dr Paul Cockwell (PI)
- Professor R Neil Dalton
- Professor Jon Deeks
- Dr Kevin Harris
- Ms Tracy Higgins
- Professor Phil Kalra (PI)
- Professor Kamlesh Khunti (PI)
- Mrs Fiona Loud
- Dr Paul Stevens (PI)
- Dr Claire Sharpe (PI)
- Dr Andrew Sutton
- Dr Maarten Taal (PI)

**Clinical Trials Unit (BCTU)**
- **Study Management** - Elizabeth Brettell
- Study Co-ordinator - Ryan Ottridge
- **Statistician**
- Ms Alice Sitch
<table>
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<tr>
<th>Task</th>
<th>Months</th>
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<td>Regulatory approvals</td>
<td>0-6</td>
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<tr>
<td>Staff appointments/training</td>
<td>7-12, 13-18</td>
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<tr>
<td>Main study patient recruitment/baseline tests</td>
<td>19-24, 25-30</td>
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<tr>
<td>6 monthly blood and urine tests</td>
<td>31-36, 37-42</td>
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<tr>
<td>36 month/final follow-up tests</td>
<td>43-48, 49-54</td>
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<tr>
<td>Sub-study of biological variation</td>
<td>55-60, 61-66</td>
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<tr>
<td>Sub-study of modelled disease progression</td>
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<tr>
<td>Statistical analysis and modelling</td>
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<tr>
<td>Health economic model building</td>
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<tr>
<td>Detailed health economic analysis</td>
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<td>Study closure, report writing, dissemination</td>
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