Appendix B3. CKD Model Technical Document

Introduction

The KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease defines CKD as "*abnormalities of kidney structure or function, present for >3 months, with implications for health*" ((1), page 19) and classifies the disease based on three parameters: cause, glomerular filtration rate (GFR) category, and albuminuria category (1).

GFR is a measure of the level of kidney function and can be estimated using equations that are based on serum creatinine or cystatin C levels (1), of which serum creatinine is routinely used in clinical practice. GFR can be estimated from serum creatinine using the Modification of Diet and Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKDEpi) equations, both of which take account of age, gender and ethnicity (2). The GFR categories in CKD can be defined as shown in Table 1 below.

Table 1 - GFR categories

GFR (ml/min/1.73 m2)	**GFR categories**
>90	Normal or high
60-89	Mildly decreased
45-59	Mildly to moderately decreased
30-44	Moderately to severely decreased
15-29	Severely decreased
<15	Kidney failure

Source: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1-150.

Albuminuria is the presence of higher than normal amounts of albumin (a type of protein) in the urine and indicates the presence of kidney damage. Albuminuria is one of a number of markers of kidney damage that includes histological and structural abnormalities (1). The presence of albumin in the urine may be measured by the albumin excretion rate (AER) or albumin-creatinine ratio (ACR) amongst other methods (2). The albuminuria categories in CKD can be defined as shown in Table 2 below.

Table 2 - Albuminuria categories

AER (mg/24 hours)	ACR (mg/mmol)	**Albuminuria categories**
<30	<3	Normal to mildly increased
30-300	3-30	Moderately increased
>300	>30	Severely increased

Source: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1-150.

The stages of CKD have been described in the Health Survey for England (HSE) 2010 report, using the Kidney Disease Outcome Quality Initiative (KDOQI) system (3). Table 3 summarises this classification system, which defines the stages of CKD based on the level of renal function (i.e. a decline in estimated GFR (eGFR)) and the presence of markers of kidney damage such as albuminuria.

Table 3 - Stages of CKD

	AER (mg/24h)		
eGFR (mL/min/1.73m²)	**<30**	**30-300**	**>300**
90+	No CKD	Stage 1	Stage 1
60-89	No CKD	Stage 2	Stage 2
45-59	Stage 3a	Stage 3a	Stage 3a
30-44	Stage 3b	Stage 3b	Stage 3b
15-29	Stage 4	Stage 4	Stage 4
<15	Stage 5	Stage 5	Stage 5

EConDA CKD Model Structure

Overview

The EConDA CKD model encompasses 2 out of the 3 categories outlined in the KDIGO guidelines, namely eGFR and albuminuria. Individuals in the model were assigned an eGFR and albuminuria percentile from each of the distributions. Based on the individual's age and sex these percentiles were used to determine their eGFR and albuminuria levels from each distribution. The GFR and albuminuria distributions were obtained from HSE data for the United Kingdom (UK). In the model albuminuria (mg./24h) was modelled in terms of three stages: 0-30; 30-300 and >300. Also, eGFR (mL/min/1.73m²) was modelled by six stages: <15; 15-30; 30-45; 45-60; 60-90 and >90.

Individuals were assigned a CKD stage based on the KDIGO guidelines (Table 3). Each person's percentiles were fixed for the entire simulation. In the baseline model the age and sex distribution of each measure dictated whether or not an individual's eGFR and/or albuminuria level changed and subsequently their CKD stage. Individuals were assigned relative risks (RRs) based on their specific eGFR and albuminuria values, and the disease outcome in question, for example cardiovascular disease (CVD) incidence.

The effect of an intervention, albumin screening, on CKD progression and therefore CVD incidence was tested by modelling its impact on the progression of both albuminuria and eGFR. It was hypothesised that albumin screening would identify individuals with albuminuria levels of >=30mg/24h and these individuals would be commenced on blood pressure-lowering medication (anti-hypertensives) to reduce their risk of CKD progression.

Scenarios

Two scenarios were modelled as part of this disease model. A baseline model and an intervention model were used to model the impact of albumin screening on CKD progression.

Baseline model

It was assumed that individuals remained on the same percentile in the GFR and albuminuria distributions over the course of the simulation. These age and sex distributions for GFR and albuminuria were also assumed to be constant overtime.

Albumin screening

Similar to the baseline model, it was assumed that individuals remained on the same percentile in the GFR and albuminuria distributions over the course of the simulation. These age and sex distributions for GFR and albuminuria were also assumed to be constant overtime. All individuals in the model went through albumin screening which was costed for each individual. Within the same year as screening if an individual was identified with an albuminuria level of ≥ 30 mg/24h they had a pre-defined probability of having their current albuminuria and/or eGFR levels set as a maximum for the remainder of the simulation. Their albuminuria and/or eGFR levels would be fixed. The probability of their current albuminuria and eGFR levels being set to a maximum were 0.55 and 0.327, respectively (4,5). If an individual was successful their albuminuria and/or GFR level would never increase past their maximum (defined at the point of screening) during the simulation. After screening all individuals who had an albuminuria level of ≥ 30 mg/24h were treated for the remaining years of the simulation.

Data inputs

Prevalence

HSE is a cross-sectional survey that is carried out annually and aims to assess the health status of children and adults living in England (6). Kidney disease and renal function have been assessed as part of the 2009 and 2010 surveys, in which GFR was estimated using the MDRD formula and albuminuria which was measured using ACR was converted to mg/24h. This conversion was done by matching the ACR boundaries with the albumin (mg/24h) boundaries. This method guaranteed that the prevalence within each albumin group remained constant across both measures. Further details are provided in appendix B4.

The HSE dataset includes a variable for CKD stage in which certain sub-categories are aggregated and therefore, to determine the prevalence of CKD by stage as presented in Table 4 below, a variable for CKD stage was created using eGFR and ACR variables available in the dataset, and categorised in keeping with the 5 stages of CKD depicted in Table 3 above.

Table 4 - Prevalence of CKD by stage in 2009/2010 (HSE)

CKD Stage	Prevalence (unweighted)
No CKD	85.96
1	2.43
2	4.41
3a	5.61
3b	1.4
4	0.16
5	0.02

Source: Derived from HSE dataset, 2009 and 2010 combined

Relative risks

A literature search was undertaken to identify published literature that quantified the association between CKD and diseases such as cardiovascular disease. Relative risk mortality datasets from a categorical meta-analysis study which analysed 1,555,332 participants from 45 cohorts and adjusted for the general population were adapted and used in the model (Table 5 and Table 6) (7). The data was used in the model to represent the RR of CHD and stroke incidence given a set of albuminuria and eGFR values.

Table 5 RR for CHD incidence given a combination of albuminuria and eGFR values. The data was adapted from RR's for all causes mortality (adapted from (7)).

	Albuminuria <30 mg/24h	Albuminuria 30-300 mg/24h	Albuminuria >300 mg/24h
eGFR > 90 mL/min per 1.73m^2	1.0	1.5	3.1
eGFR 60-90 mL/min per 1.73m^2	1.0	1.8	2.7
eGFR 45-60 mL/min per 1.73m^2	1.3	2.2	3.6
eGFR 30-45 mL/min per 1.73m^2	1.9	3.3	4.9
eGFR 15-30 mL/min per 1.73m^2	5.3	4.7	6.6
eGFR <15 mL/min per 1.73m^2	5.3	4.7	6.6

Table 6 RR for Stroke incidence given a combination of albuminuria and eGFR values. The data was adapted from RR's for all causes mortality (adapted from (7)).

	Albuminuria <30 mg/24h	Albuminuria 30-300 mg/24h	Albuminuria >300 mg/24h
eGFR > 90 mL/min per 1.73m^2	1.0	1.7	3.7
eGFR 60-90 mL/min per 1.73m^2	1.0	2.0	4.1
eGFR 45-60 mL/min per 1.73m^2	1.5	2.8	4.3
eGFR 30-45 mL/min per 1.73m^2	2.2	3.4	5.2
eGFR	14	4.8	8.1

15-30 mL/min per 1.73m^2			
eGFR <15 mL/min per 1.73m^2	14	4.8	8.1

Utility weights

Country-specific utility weights for CKD by stage were not available. Data derived from studies conducted on Japanese patients with CKD were used as a proxy measure instead. Table 7 below summarises the utility weights used to calculate CKD-related quality-adjusted life years (QALYs) in the microsimulation model.

Table 7 - Utility weights of CKD by stage

	EQ-5D	Reference
CKD	0.89	(8)
CKD (stage 1)	0.94	
CKD (stage 2)	0.92	
CKD (stage 3)	0.88	
CKD (stage 4)	0.84	
CKD (stage 5)	0.80	
ESRD	0.66	(9)

CKD model assumptions

The following assumptions were made when developing the EConDA CKD model as summarised below:

1. eGFR and albumin are independent predictors of CKD and CVD progression *(Ron Gansevoort, personal communication, 4th March 2015)*
2. Serum creatinine (and therefore eGFR) levels and AER observed at a single time point, such as at each follow-up in the PREVEND study, reflected chronic abnormalities (i.e. >3 months) in renal structure and function.
3. In the baseline model the distribution of albuminuria and GFR for each age and sex group is assumed to be independent of time.
4. In the baseline model initially individuals are randomly assigned a percentile in both the albuminuria and GFR distributions which is assumed to be fixed for the entire simulation.
5. In the baseline model individuals could only be screened once.
6. In the intervention model, it was assumed that in the same year of screening individuals who has an albuminuria level of ≥ 30 mg/24h had a probability of 0.55 and 0.327 of fixing their albuminuria and eGFR levels, respectively (4,5).

References

1. Eknoyan G, Lameire N, Eckardt K. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int [Internet]. 2013 [cited 2015 Nov 12]; Available from: http://ijpog.org/downloads/9/81_90.pdf

2. Estimating Glomerular Filtration Rate (GFR) | National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [Internet]. [cited 2015 Nov 12]. Available from: http://www.niddk.nih.gov/health-information/health-communication-programs/nkdep/lab-evaluation/gfr/estimating/Pages/estimating.aspx

3. Roth M, Roderick P, Mindell J. Kidney disease and renal function. Heal Surv Engl [Internet]. 2010 [cited 2015 Nov 12]; Available from: https://catalogue.ic.nhs.uk/publications/public-health/surveys/heal-surv-resp-heal-eng-2010/heal-surv-eng-2010-resp-heal-ch8-kidn.pdf

4. Hoerger TJ, Wittenborn JS, Segel JE, Burrows NR, Imai K, Eggers P, et al. A health policy model of CKD: 2. The cost-effectiveness of microalbuminuria screening. Am J Kidney Dis [Internet]. 2010 Mar;55(3):463–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20116910

5. Kessler R, Keusch G, Szucs TD, Wittenborn JS, Hoerger TJ, Brügger U, et al. Health economic modelling of the cost-effectiveness of microalbuminuria screening in Switzerland. Swiss Med Wkly [Internet]. 2012;142:w13508. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22307760

6. Health Survey for England (HSE) [Internet]. [cited 2015 Nov 12]. Available from: https://www.ucl.ac.uk/hssrg/studies/hse

7. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int [Internet]. 2011 Jul;80(1):17–28. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21150873

8. Tajima R, Kondo M, Kai H, Saito C, Okada M, Takahashi H, et al. Measurement of health-related quality of life in patients with chronic kidney disease in Japan with EuroQol (EQ-5D). Clin Exp Nephrol [Internet]. 2010 Aug;14(4):340–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20567874

9. Saito I, Kobayashi M, Matsushita Y, Mori A, Kawasugi K, Saruta T. Cost-utility analysis of antihypertensive combination therapy in Japan by a Monte Carlo simulation model. Hypertens Res [Internet]. 2008 Jul;31(7):1373–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18957808