Definitions of progression in chronic kidney disease – predictors and relationship to renal replacement therapy in a population cohort with six years follow-up

Running title
Progression and RRT in CKD

Authors
Angharad Marks, MBBCh[1,2]
Nicholas Fluck, DPhil[2]
Gordon J. Prescott, PhD[1]
Lynn M. Robertson, MSc[1]
William G. Simpson, MBChB[2]
William Cairns S. Smith, PhD[1]
Corri Black, MBChB[1,2]

[1]University of Aberdeen, Aberdeen, UK, [2]NHS Grampian, Aberdeen, UK,

Corresponding author: Angharad Marks, Division of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill AB25 2ZD; E-mail a.marks@abdn.ac.uk

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Abstract

Background: Chronic kidney disease (CKD) is common, important and associated with increased healthcare needs due to CKD progression. Definitions of renal disease progression are multiple, and not always comparable. A measure of 'progression' directly comparable to RRT initiation would identify 'progressors' in research and for healthcare planning.

Methods: GLOMMS-I is a community cohort with CKD from 2003, followed up to June 2009 for (i) RRT initiation and (ii) 'progression': sustained reduction in eGFR by 15ml/min/1.73m^2 (equivalent to CKD stage change), or to less than 10ml/min/1.73m^2, whichever occurs first. Predictors were baseline demographics and comorbidity. The use of the KDIGO-2012 progression definition was also explored.

Results: 2289 and 1044 had stage 3 and 4 CKD, 44% male. Overall, RRT initiation and progression rates were 0.97 and 3.50 per 100 patient-years. Females had significantly lower progression and RRT initiation rates. Progression rate was not dependent on CKD stage (incidence-rate-ratio (IRR) for stage 4 (versus stage 3) 0.9 (95% CI 0.8–1.2)), whereas RRT initiation rate was (IRR 5.6 (95% CI 3.8–8.2)). Increased proteinuria was associated with both greater RRT initiation and progression rates.

Conclusion: Progression and RRT initiation rate ratios allow comparison of predictors of these outcomes. Higher rates of both in males suggest that greater RRT initiation rate is biological rather than due to preferential treatment. Similar progression but very different RRT initiation rates in stage 3 and 4 CKD, suggest that CKD stage effect on RRT initiation is a function of endpoint proximity rather than faster renal function deterioration.

Keywords: chronic kidney disease; cohort; progression; renal replacement therapy.

Chronic kidney disease (CKD) is common and important due to progression of renal disease, eventually to renal replacement therapy (RRT) initiation. Comparison of predictors of progression and RRT initiation suggest that the preferential initiation of RRT in males is the result of faster progression. The same for stage 3 and 4 CKD suggests that preferential RRT initiation in stage 4 versus 3 CKD is a result of proximity to the RRT initiation endpoint rather than faster progression.

Introduction

Chronic kidney disease (CKD) is common, and an important health issue because of its association with increased risk for end-stage renal disease (ESRD), renal replacement therapy (RRT) and mortality[1]. In 2002, KDOQI[1] defined five stages of CKD, subsequent divisions to stage 3 (3a and 3b) grouped renal function into 15ml/min/1.73m^2 glomerular filtration rate (GFR) bands. Historically it was believed that once CKD was established, there was progressive decline of GFR[1,2] linearly over time[2,3]. This is now less clear, as a growing number of studies report that not all people with CKD initiate RRT or die during follow-up[4-6]. The health impacts of CKD are not restricted to ESRD. Before reaching ESRD, there is an increase in the risk of clinically important complications, including anaemia[7], acidosis[8,9], bone disease[7] and cardiovascular events, all having their own complications and costs[10,11]. It is therefore important to be able to define kidney function deterioration as a potential predictor for future outcomes such as initiation of RRT and poorer health outcomes requiring clinical intervention.

KDOQI 2002 guidelines[1] defined progression as *"either (1) decline in the level of kidney function, … in a patient who has been followed longitudinally … , or (2) onset of kidney failure, defined by initiation of kidney replacement therapy, either for symptoms or complications of decreased kidney function".* Whilst this clinical concept of progression is clear, operationalisation of the definition for research and clinical practice use is more complex, and reflected by the large number of published approaches. Clinical trials have used doubling of creatinine[12]; 50% and 25% reductions in GFR[13]. Some report the mean annual change of eGFR over follow-up time, often using just the first and last eGFR measurement. The time spent moving from one stage to the next has been also been reported[14]. The National Institute for Health and Clinical

Excellence[15] suggested progression be identified by obtaining at least three GFRs over a period of not less than 90 days, and defined progression as a decline in eGFR of more than 5ml/min/1.73m^2 within one year, or more than 10ml/min/1.73m^2 within five years. In January 2013, KDIGO released new 2012 CKD guidelines[16]. One definition of progression outlined was *"a certain drop in eGFR … a drop in GFR category accompanied by a 25% or greater drop in eGFR from baseline"*.

The relationship between these operational definitions of progression and the initiation of RRT is difficult to understand, both in terms of research endpoints and in translating evidence into clinical practice. They highlight the need for a definition of progression that is consistent in terms of the size of the function loss, is associated with an increased risk of developing RRT, specifies a chronic change in function and can be translated simply into clinical and epidemiological practice.

In this paper, we propose a definition of increased risk to be the time to achieve a reduction in the eGFR equivalent of dropping a full CKD stage, 15ml/min/1.73m^2, and that the deterioration is sustained. We test the application of this novel definition of progression as a marker of significant renal function decline, comparing it to RRT initiation rate. We report the predictors of progression in a large, well characterised, population based cohort[6].

Subjects and Methods

The first Grampian Laboratory Outcomes Morbidity and Mortality Study (GLOMMS-I) cohort has been described elsewhere[6]. Adults (aged over 15 years) resident in Grampian (a single health authority region with single biochemistry service, in the North East of Scotland, UK), with abnormal renal function tests (an "index" creatinine above 150µmol/l for men and 130µmol/l for women measured from January to June 2003)

were identified (n=5538). Those on RRT at index were excluded. Results of those with AKI are reported elsewhere[17]. Individuals with CKD were identified and included in GLOMMS-I if they had at least three depressed eGFR values (median eGFR below 60ml/min/1.73m^2) documented over at least three months either before or after the index creatinine (3426 individuals). Casenote review provided baseline comorbidity. Regional health administration systems recorded all RRT provision, admissions, discharges, outpatient attendances and death registrations. Data linkage between these systems and the cohort took place to allow follow-up to the 30th June 2009.

GLOMMS-I was approved by the University of Aberdeen Research Ethics Committee, the NHS Grampian Caldicott Guardian and discussed with the North of Scotland NHS Research Ethics Committee.

Inclusions and exclusions

Individuals with stage 3 or 4 CKD were included in this analysis (an eGFR <15ml/min/1.73m^2 was considered too low to assess progression). Those who died on the index date were excluded.

Definition of "progression"

The sustained reduction in eGFR of 15ml/min/1.73m^2 is the equivalent of a change in CKD stage. An eGFR of <10ml/min/1.73m^2 equates to a need to initiate RRT for many, therefore a relevant end-point for those with more advanced CKD. Progression was therefore defined as having achieved either a <u>sustained</u> reduction in eGFR by 15ml/min/1.73m^2 (Figure 1) or to less than 10ml/min/1.73m^2, whichever occurred first. The reduction in eGFR was deemed sustained if the median eGFR afterwards (for all

eGFRs until RRT initiation, death, or end of follow-up) was also below this value. The KDIGO-2012 definition of progression (a 25% reduction in eGFR and change in CKD stage from baseline) was also applied, again this change needed to be sustained.

Outcomes and follow-up

Outcomes of interest were times to "progression" and initiation of RRT. All creatinine measurements in Grampian and thus eGFR values for an individual from index to end of follow-up were available. Follow-up was truncated at midnight 30th June 2009, six years from the end of the index period. Vital status at this point was noted as was the last eGFR in those still alive not on RRT. Date of last use of NHS Grampian services was checked to ensure full follow-up.

Covariates

The potential predictors of interest were baseline age, sex, CKD stage, proteinuria status, comorbidities and smoking status. Age and sex were derived from the data at the index creatinine. Baseline CKD stage was assigned based on the index eGFR: stage 3 (30-59 [3a (45-59), 3b (30-44)]ml/min/1.73m^2); and stage 4 (15-29ml/min/1.73m^2). Proteinuria status was categorised based on the last available albumin or protein creatinine ratio (ACR or PCR) up to and including the index creatinine date. Microalbuminuria was considered present if ACR was ≥2.5mg/mmol for men, ≥3.5mg/mmol for women; macroalbuminuria if ACR ≥30mg/mmol or PCR ≥50mg/mmol; and normoalbuminuria where either ACR or PCR were measured and the definitions of micro or macroalbuminuria not met. If there were no measurements of ACR or PCR prior to index, these variables were categorised as untested. Comorbidities (Table 1 and Table 2) were recorded as absent or present from casenote review.

Data linkage and assumptions

Each individual had a basic record of demographics, and a Community Health Index (CHI) and hospital number. CHI is a unique identifier assigned to all residents of Scotland registered with a General Practitioner and used at almost every healthcare facility and interaction. Mortality data were obtained by deterministic linkage to health board data using CHI number. RRT data were obtained by linkage to the local renal management system. All biochemistry samples were linked on a minimum of three identifiers to known individuals. Longitudinal records for each individual were created and CHI deterministic linkage used to link to the basic record for a given individual. The use of CHI for linkage minimises the risk of incorrectly linking two individuals who have the same gender, name and date of birth.

Analysis

For ease of understanding of overall outcome, the first outcome by the end of follow-up was checked, including death and RRT initiation. If these end points were not reached then the final eGFR measurement was used as a basic check to determine whether there had been a change in eGFR stage during follow-up. To allow assessment of whether the new sustained progression definition might be a valid, early marker of renal function deterioration, (and thus the need for RRT initiation) with similar predictors, the times to both progression and RRT initiation were calculated for each individual who reached these outcomes. The follow-up, with censoring at either death, end of follow-up or the end-point of progression or RRT initiation was calculated separately for the two outcomes. The progression rate, per 100 patient-years (py) follow-up, was calculated from the numbers achieving progression (sustained eGFR drop) and the follow-up time

for this outcome. KDIGO-2012 defined progression rate was also calculated in this way. The rate of RRT initiation per 100py was calculated from the numbers initiating RRT and the follow-up time for this outcome. The characteristics of those who progressed and those who did not were compared with Chi squared and Mann-Whitney tests as appropriate. The association between having initiated RRT and having progressed by the end of follow-up was expressed with risk ratios (RR). Kaplan-Meier survival plots were created. Stratification (with Mantel-Haenszel summary rate ratios) and Poisson models were used to explore the effect of baseline characteristics on progression (both 15ml/min/1.73m^2 drop and KDIGO-2012 defined) and RRT initiation outcomes separately. The effects of comorbidities on these outcomes were expressed as rate ratios.

Results

Of 3426 in the cohort, 12 individuals who died on index date and 92 who had stage 5 CKD were excluded. There were 3322 individuals (2289 stage 3 and 1044 stage 4) at baseline, 44% were male. Most (3102) individuals had a further eGFR after the index, the median number of further eGFR values prior to RRT initiation, death or end of follow-up was 18 (range zero to 525). The majority had died by the end of six years follow-up (Figure 2), 124 had initiated RRT. The final eGFR CKD stage was no worse for 30% of those with stage 3 at index, and 23% of those with stage 4 at index.

Progression

Overall, 1027 (31%) had a 15ml/min/1.73m^2 and 1481 (45%) a 25% drop in eGFR and CKD stage change. However most changes were not sustained, only 13.1% met our new definition of progression (characteristics in Table 1), and 13.0% the KDIGO-2012

definition. The majority of the cohort was female; however the majority of progressors were male. More progressors had macroalbuminuria at baseline.

The rates of initiating RRT and progression are shown by baseline characteristics in Table 2. The incidence rate ratios (IRRs) for progression by baseline characteristics are also shown in Table 2, as are IRRs for RRT, for comparison. The overall rates for initiating RRT and progressing (our definition) were 0.97 and 3.50 per 100py respectively. The higher rate of RRT initiation in males was supported by a higher rate of progression also, with a statistically significant low IRR for females versus males of 0.61 (95% CI 0.50-0.74) reflecting a similar IRR for RRT initiation. Macroalbuminuria was associated with higher rates of RRT initiation and also higher rates of progression with an IRR of 3.20 (95% CI 2.25-4.55) even after adjustment for other factors. Smokers had a statistically significant increase in rates of progression compared to non-smokers. Those with a haematological malignancy had a significantly higher rate of progression than those without; although there was no difference in RRT initiation rates.

Outcome by progression status is shown in Table 3. Of those who progressed, 21.4% (13.1% and 44.7% of stage 3 and 4 respectively) initiated RRT, compared to 1.1% of those who had not progressed. Progressors had an unadjusted RR for RRT initiation of 19.9 (95% CI 13.4-29.5) compared to non-progressors (RR using the KDIGO-2012 definition was 9.6 (95% CI 6.8-13.5)). 1145 (34.4%) individuals were still alive at the end of follow-up and did not meet this definition of progression (similar to that identified by the last CKD stage).

For KDIGO-2012 defined progression, the baseline characteristics of the 432 who met the definition (not published here) were almost identical to those above except only 70 (16.2%) of KDIGO progressors had CKD stage 4 disease at baseline compared to 114 (26.2%) of progression defined by a 15ml/min/1.73m^2 drop in eGFR. Also less individuals identified as progressors initiated RRT (73 vs 93). Rates of progression based on the KDIGO definition were similar to those identified by our definition (Table 2), as were the IRRs for each exposure. Exceptions to this were that stage 4 CKD appeared to become protective from progression as defined by KDIGO, ex-smokers had more progression and low levels of urinary protein were not predictive of KDIGO defined progression. Kaplan-Meier progression survival plots (adjusted for age sex and proteinuria status) by CKD stage show little difference between CKD stages based on our definition, however for the KDIGO-based definition those with stage 3 CKD had a worse progression prognosis than those with stage 4 (Figure 3).

Discussion

In this article, we propose a definition of renal disease progression which, to our knowledge, has not been used before. We have demonstrated that it can be used to describe individuals who have worsening renal function prior to the initiation of RRT, thus allowing assessment of the predictors of worsening renal function rather than the current reliance on initiation of RRT as a late outcome. The definition is based on a sustained drop in eGFR of 15ml/min/1.73m^2, equivalent of a stage change. The use of a lower threshold of 10ml/min/1.73m^2 acknowledges that at lower levels of function the amount of further loss possible is less. The association between our novel definition and the risk of future RRT supports its value as a potential early predictor of those at risk of RRT. It may also mark a need for increased healthcare support.

The majority of individuals with stage 3 and 4 CKD died. A small minority went on to initiate RRT. Of the 36.6% with stage 3 and 4 disease that neither died nor started RRT, the majority did not progress during the six years of follow-up.

Progression, defined by the sustained loss of eGFR of either 15ml/min/1.73m^2 or to 10ml/min/1.73m^2 whichever occurs first, was associated with subsequent need to initiate RRT (20-fold increase in risk), compared to non-progression. We found that males had a higher rate of progression than females. There has long been a suggestion that males initiate RRT at a greater rate than females. If males progress at a faster rate, as evidenced here, then it would seem appropriate that they initiate RRT faster also. A different pathological process or risk profile may be involved.

The finding that macroalbuminuria is a predictor of faster progression as well as the initiation of RRT is reassuring, reflecting the findings of others[18,19]. It also supports the use of treatments aimed at reducing proteinuria to reduce the initiation of RRT and progression.

Using our definition, the progression rates for CKD stage 3 and 4 are very similar despite very different RRT initiation rates. This suggests that the differential in RRT initiation rates for CKD stage reflects lead-time bias with more advanced CKD having less far to go before requiring RRT rather than inherently worse progression rates. This should encourage the initiation of management at this earlier stage to halt that progression. The KDIGO-2012-based definition[16] identified more with stage 3 CKD as having progressed (at twice the rate of those with CKD stage 4). Because of the need for

both a percentage change and a stage change, the number of people identified follows a step distribution around the stage boundaries. The KDIGO definition preferentially identifies those with CKD stage 3 since a 25% reduction and stage change are more achievable in stage 3, thus favouring those with CKD stage 3 to have progressed. This should be borne in mind by others using this KDIGO suggested definition. Otherwise the predictors are similar to our definition.

Others have explored different definitions of renal disease progression and support our finding that not all individuals end up on RRT or die. Hoefield *et al*.[20] showed that at one year of follow-up over 50% of their stage 3a, 3b, 4 and 5 patients were still alive with the same or better stage of CKD. Baek *et al*.[21] reported that at 10 years follow-up, 64.3% of referred stage 3a and 27.2% of stage 3b remained at stage 3 or better (mortality only 2.3%). Several authors[22 23] have reported that the decline in renal function over time is non-linear[18], sometimes with prolonged episodes of slower decline in renal function[18], but sometimes accelerated loss as eGFR declines[23]. Where reported, less proteinuria, higher eGFR, higher age, female sex, high serum albumin, lower BP and the use of ACE-inhibitors were associated with episodes of slower decline and the opposite for faster decline[18 19 23 24]. Some report that those with less proteinuria, eGFR $\geq$40ml/min/1.73m^2, $\leq$55 years of age, males, and with higher BP have a greater chance of having non-linear decline[18]. The use of linear regression for eGFR slope over time may not necessarily be a valid definition of progression.

Death is a competing risk for both progression and RRT initiation (as previously demonstrated[6, 25]), with many people dying prior to reaching these end-points. However,

as illustrated by Grams *et al.*[25], the use of competing risks analysis requires a good understanding of what you wish to demonstrate. In terms of demonstrating aetiological factors in an outcome of interest the cause-specific hazard ratio (or IRR used here) is the appropriate measure, subhazards (as calculated in competing risk analysis) might be more appropriate for estimating absolute risk[25,26]. Since we wished to explore whether the same aetiological factors had the same effect on progression and RRT outcomes, non-competing risks analysis was considered most appropriate.

We have demonstrated a potentially useful definition of progression, where individuals who reached a predetermined reduction in eGFR during the six year follow-up displayed similar characteristics as those who initiated RRT. The advantage of this definition of progression over RRT is that it could identify "high risk" people at a much earlier stage in their disease trajectory; a potential surrogate marker for the end outcome, RRT. This study was based on a prevalence cohort and the numbers advancing to RRT were too small to consider whether the time to achieve the new definition was associated with increased risk of RRT and over what timeframe would such a drop in function indicate a poorer prognosis. Also the minimal numbers with stage 3a CKD in this cohort limit the generalisability for those with less advanced CKD. Therefore, the use of this definition of progression as a potential surrogate marker for future RRT requirements needs to be explored in other datasets.

This study used a well-described cohort with six years of follow-up. Access to all creatinine values within the region allowed an accurate reflection of the degree of progression that is measureable in a cohort with CKD identified opportunistically. There are issues that should be borne in mind when drawing conclusions from the

results of this study. Given the longitudinal capture of the data, there is a risk of confounding associated with increasing age, although this is likely to be small over a six year period. Ill-health, might lead to weight loss and therefore a reduction in the creatinine for an individual such that there appears to be no progression of disease using eGFR, whereas measured GFR might reveal otherwise; this effect also is likely to be small. The use of routine health care data, and both in-patient and out-patient bloods, although giving a realistic picture of the information available in routine clinical practice and on which treatment decisions are made, may not offer a complete picture. Data-linkage has limitations in that individuals may be misidentified, however the use of CHI plus other identifiers should minimise this. There will be relative over-sampling at times of ill health or acute illness and under-sampling at times when the individual is well and has more normal renal function. The way the cohort was created with a creatinine threshold of greater than 150μmol/L and 130μmol/L for males and females respectively means that for many the baseline eGFR slope up to the time of index was quite steeply negative. However, for the majority, this became much less steep or even improved after the index. All these limitations, however, would reduce the incidence of this form of progression but we feel that the overall performance and associations found are valid despite these limitations.

Conclusion

In this article, we propose a novel definition of renal disease progression - a sustained reduction in eGFR by 15ml/min/1.73m^2 (equivalent to a CKD stage transition) or to 10ml/min/1.73m^2, whichever occurs first. It is simpler and performs better at identifying those who will initiate RRT than the KDIGO-2012 definition. It allows direct comparison of this definition of progression to the traditional definition - RRT initiation. This facilitates comparison of the effect of the various predictors of

progression. We found that the association of greater RRT initiation rates amongst males and those with macroalbuminuria is mirrored in higher rates of progression. However CKD stage did not affect progression rates, despite being associated with RRT initiation rates. This suggests that interventions aimed at limiting progression (rather than preparation for RRT) might be better targeted if lead by these risk factors rather than CKD stage alone.

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Conflict of interest statement. None to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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Table 1: Characteristics of the whole cohort (stage 3 and 4) and those who "progress", P-values for "progressors" versus non-progressors

		Non-progressors		Progressors		P value
	n	2887		435		
Age at baseline						
Age (years)	median (range)	79.1	(18-103)	74.9	(16-97)	<0.001
15-44	n (%)	53	(1.8)	26	(6.0)	<0.001
45-54	n (%)	79	(2.7)	28	(6.4)	
55-64	n (%)	226	(7.8)	46	(10.6)	
65-74	n (%)	614	(21.3)	119	(27.4)	
75-84	n (%)	1219	(42.2)	164	(37.7)	
85+	n (%)	696	(24.1)	52	(12.0)	
Sex						
Male	n (%)	1223	(42.4)	250	(57.5)	<0.001
Female	n (%)	1664	(57.6)	185	(42.5)	
Excretory renal function at baseline						
eGFR (ml/min/1.73m^2)	median (range)	33.4	(15-50)	35.1	(15-49)	<0.001
CKD stage 3	n (%)	1965	(68.1)	321	(73.8)	0.016
CKD stage 4	n (%)	922	(31.9)	114	(26.2)	
Albuminuria status at baseline						
ACR (mg/mmol) **if measured*	median (range)	3	(0.9-858)	15	(0.9-669)	<0.001
PCR (mg/mmol) **if measured*	median (range)	38	(1-1432)	75.5	(4-1432)	<0.001
Not measured	n (%)	2101	(72.8)	272	(62.5)	<0.001
Normoalbuminuria	n (%)	443	(15.3)	55	(12.6)	
Low albuminuria	n (%)	150	(5.2)	28	(6.4)	
High albuminuria	n (%)	193	(6.7)	80	(18.4)	
Comorbidity at baseline						
Comorbidity Count (exclude hypertension)	mean (95%CI)	1.46	(1.42, 1.50)	1.35	(1.24, 1.46)	
Ischaemic heart disease	n (%)	1175	(40.7)	159	(36.6)	0.100
Congestive cardiac failure	n (%)	515	(17.8)	58	(13.3)	0.020
Peripheral vascular disease	n (%)	339	(11.7)	48	(11.0)	0.668
Cerebrovascular disease	n (%)	436	(15.1)	62	(14.3)	0.644
Hypertension	n (%)	1507	(52.2)	245	(56.3)	0.108
Haematological malignancy	n (%)	58	(2.0)	20	(4.6)	0.001
Non haematological malignancy	n (%)	421	(14.6)	55	(12.6)	0.282
Dementia	n (%)	183	(6.3)	10	(2.3)	0.001
Chronic obstructive pulmonary disease	n (%)	258	(8.9)	27	(6.2)	0.058
Connective tissue disease	n (%)	141	(4.9)	21	(4.8)	0.959
Type 1 diabetes	n (%)	40	(1.4)	16	(3.7)	0.001
Type 2 diabetes	n (%)	659	(22.8)	106	(24.4)	0.477
Chronic liver disease	n (%)	30	(1.0)	5	(1.1)	0.834
No comorbidity at baseline	n (%)	55	(1.9)	0	(0.0)	0.004
Smoking status at baseline						
Current smoker	n (%)	277	(9.6)	59	(13.6)	<0.001
Ex-smoker	n (%)	1106	(38.3)	173	(39.8)	
Non-smoker	n (%)	1286	(44.5)	154	(35.4)	
Unknown	n (%)	218	(7.6)	49	(11.3)	

Table 2: Rates of initiating RRT and "progression" by baseline characteristics; progression and RRT incidence rate ratios

		Sustained drop of eGFR by 15 or to 10 ml/min /1.73m²	Sustained (25% reduction in eGFR and CKD stage change)	Initiation of RRT	"Progression" Sustained drop of eGFR by 15 or to 10 ml/min/1.73m2 (which ever greater)				Sustained "KDIGO progression" (25% reduction in eGFR and CKD stage change)				Initiation of RRT	
					Crude		Adjusted as appropriate for sex, age, CKD and proteinuria status at baseline		Crude		Adjusted as appropriate for sex, age, CKD and proteinuria status at baseline		Adjusted as appropriate for sex, age, CKD and proteinuria status at baseline	
		Rate /100 patient years follow-up			IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI	IRR	95%CI
		3.50	3.55	0.97										
Gender	Males	4.62	4.63	1.56	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Females	2.63	2.73	0.50	0.57	(0.47 - 0.69)	0.61	(0.50 - 0.74)	0.59	(0.49 - 0.71)	0.66	(0.54 - 0.80)	0.40	(0.27 - 0.60)
Excretory renal function at baseline														
CKD stage	Stage 3	3.55	4.13	0.46	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Stage 4	3.35	2.06	2.33	0.94	(0.76 - 1.17)	0.96	(0.78 - 1.20)	0.50	(0.39 - 0.65)	0.47	(0.36 - 0.61)	5.60	(3.84 - 8.15)
Proteinuria at baseline														
Not measured		3.10	3.16	0.53	1.21	(0.91 - 1.62)	1.27	(0.95 - 1.71)	1.14	(0.86 - 1.52)	1.14	(0.85 - 1.53)	1.27	(0.68 - 2.35)
Normoalbuminuric		2.63	2.77	0.61	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Low levels urinary protein		4.15	3.96	1.01	1.61	(1.02 - 2.54)	1.70	(1.07 - 2.68)	1.43	(0.90 - 2.28)	1.51	(0.95 - 2.40)	2.07	(0.82 - 5.21)
Higher levels urinary protein		8.96	9.36	5.73	3.48	(2.46 - 4.91)	3.14	(2.21 - 4.45)	3.38	(2.40 - 4.76)	3.59	(2.54 - 5.09)	5.31	(2.86 - 9.88)
Age (years)														
15-24		11.62	6.32	12.73	2.05	(0.72 - 5.84)	1.56	(0.55 - 4.47)	1.02	(0.24 - 4.27)	0.94	(0.54 - 0.80)	2.08	(0.78 - 5.56)
25-34		8.94	6.81	5.78	1.58	(0.78 - 3.17)	1.32	(0.65 - 2.66)	1.10	(0.50 - 2.40)	0.81	(0.22 - 3.94)	1.19	(0.52 - 2.71)
35-44		5.01	4.15	3.85	0.88	(0.44 - 1.77)	0.79	(0.39 - 1.59)	0.67	(0.32 - 1.41)	0.57	(0.37 - 1.79)	0.87	(0.39 - 1.91)
45-54		5.67	6.20	3.60	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
55-64		3.49	3.17	1.68	0.62	(0.39 - 0.99)	0.62	(0.38 - 0.99)	0.51	(0.32 - 0.82)	0.50	(0.27 - 1.20)	0.47	(0.26 - 0.86)
65-74		3.68	3.30	1.17	0.64	(0.43 - 0.97)	0.77	(0.51 - 1.16)	0.53	(0.35 - 0.80)	0.62	(0.31 - 0.81)	0.49	(0.28 - 0.84)
75-84		3.22	3.39	0.39	0.58	(0.39 - 0.86)	0.73	(0.48 - 1.09)	0.55	(0.37 - 0.81)	0.71	(0.41 - 0.94)	0.17	(0.09 - 0.31)
85-94		2.72	3.50	0.00	0.48	(0.30 - 0.76)	0.66	(0.41 - 1.05)	0.56	(0.36 - 0.88)	0.83	(0.47 - 1.06)	No events	
95-104		2.13	7.45	0.00	0.38	(0.09 - 1.58)	0.56	(0.13 - 2.38)	1.20	(0.53 - 2.74)	2.09	(0.53 - 1.30)	No events	
Comorbidity at baseline (presence vs absence)														
Ischaemic heart disease		3.38	3.56	0.69	0.95	(0.79 - 1.16)	0.97	(0.80 - 1.19)	1.00	(0.83 - 1.22)	1.01	(0.83 - 1.23)	0.88	(0.57 - 1.34)
Congestive cardiac failure		3.47	4.09	0.41	0.99	(0.75 - 1.31)	1.00	(0.76 - 1.32)	1.18	(0.91 - 1.53)	1.18	(0.91 - 1.54)	0.51	(0.24 - 1.12)
Peripheral vascular disease		3.81	3.71	1.08	1.10	(0.81 - 1.48)	1.08	(0.79 - 1.46)	1.05	(0.77 - 1.42)	1.04	(0.76 - 1.42)	1.34	(0.75 - 2.40)
Cerebrovascular disease		3.98	4.61	0.74	1.16	(0.89 - 1.52)	1.21	(0.92 - 1.59)	1.33	(1.03 - 1.72)	1.33	(1.03 - 1.73)	1.12	(0.61 - 2.05)
Hypertension		3.49	3.60	1.28	0.99	(0.82 - 1.20)	0.93	(0.77 - 1.12)	1.04	(0.86 - 1.25)	1.02	(0.84 - 1.24)	1.44	(0.94 - 2.18)
Haematological malignancy		9.44	9.25	1.81	2.78	(1.77 - 4.35)	2.42	(1.54 - 3.80)	2.66	(1.68 - 4.21)	2.23	(1.40 - 3.55)	1.48	(0.54 - 4.05)
Non haematological malignancy		3.61	3.37	0.32	1.03	(0.78 - 1.37)	1.09	(0.82 - 1.45)	0.94	(0.70 - 1.25)	0.91	(0.68 - 1.23)	0.58	(0.23 - 1.44)
Dementia		2.70	3.79	0.00	0.76	(0.41 - 1.43)	0.97	(0.51 - 1.83)	1.06	(0.62 - 1.81)	1.14	(0.66 - 1.98)	No events	
Chronic obstructive pulmonary disease		3.13	3.80	0.34	0.89	(0.60 - 1.31)	0.91	(0.61 - 1.34)	1.06	(0.74 - 1.52)	1.03	(0.72 - 1.48)	0.53	(0.17 - 1.68)
Connective tissue disease		3.65	2.08	1.02	1.04	(0.67 - 1.62)	1.19	(0.77 - 1.86)	0.57	(0.32 - 1.02)	0.64	(0.36 - 1.13)	1.59	(0.69 - 3.66)
Type 1 diabetes		7.19	8.05	5.56	2.09	(1.27 - 3.44)	1.26	(0.73 - 2.18)	2.33	(1.44 - 3.79)	1.53	(0.91 - 2.60)	2.00	(1.03 - 3.88)
Type 2 diabetes		3.72	3.79	1.29	1.07	(0.86 - 1.33)	1.00	(0.77 - 1.30)	1.10	(0.88 - 1.36)	0.99	(0.76 - 1.29)	1.44	(0.92 - 2.25)
Chronic liver disease		4.78	4.83	0.89	1.37	(0.57 - 3.30)	1.10	(0.45 - 2.68)	1.36	(0.56 - 3.28)	1.48	(0.61 - 3.61)	0.24	(0.03 - 1.75)
No comorbidity at baseline		0.00	0.00	0.00	No events		No events		No events		No events		No events	
Smoking status at baseline														
Current smoker		4.75	4.29	1.32	1.69	(1.25 - 2.28)	1.43	(1.05 - 1.94)	1.53	(1.12 - 2.10)	1.37	(0.99 - 1.90)	1.61	(0.89 - 2.93)
Ex-smoker		3.71	3.97	0.84	1.32	(1.06 - 1.63)	1.22	(0.97 - 1.53)	1.43	(1.15 - 1.77)	1.31	(1.04 - 1.64)	1.60	(0.98 - 2.61)
Non-smoker		2.82	2.78	0.61	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Unknown		4.52	4.87	2.91	1.60	(1.16 - 2.21)	1.46	(1.06 - 2.02)	1.75	(1.27 - 2.41)	1.79	(1.29 - 2.47)	2.98	(1.82 - 4.87)

Table 3: Outcome by 30th June 2009 (6 years follow-up) for cohort as a whole (stage 3 and 4 CKD) non-progressors and progressors, by our definition and KDIGO 2012

Progression measure	Our definition		KDIGO 2012 definition	
	Non-progressors	Progressors	Non-progressors	Progressors
All, n (% of whole cohort)	2887	435	2890	432
Stage 3 & 4 at baseline				
Died without starting RRT	1711 (59.3)	270 (62.1)	1723 (89.6)	258 (71.3)
Started RRT	31 (1.1)	93 (21.4)	51 (2.7)	73 (20.2)
Alive	1145 (39.7)	72 (16.6)	1116 (58.0)	101 (27.9)
Stage 3 at baseline				
Died without starting RRT	1078 (54.9)	214 (66.7)	1064 (55.3)	228 (63.0)
Started RRT	1 (0.1)	42 (13.1)	6 (0.3)	37 (10.2)
Alive	886 (45.1)	65 (20.2)	854 (44.4)	97 (26.8)
Stage 4 at baseline				
Died without starting RRT	633 (68.7)	56 (49.1)	659 (68.2)	30 (42.9)
Started RRT	30 (3.3)	51 (44.7)	45 (4.7)	36 (51.4)
Alive	259 (28.1)	7 (6.1)	262 (27.1)	4 (5.7)

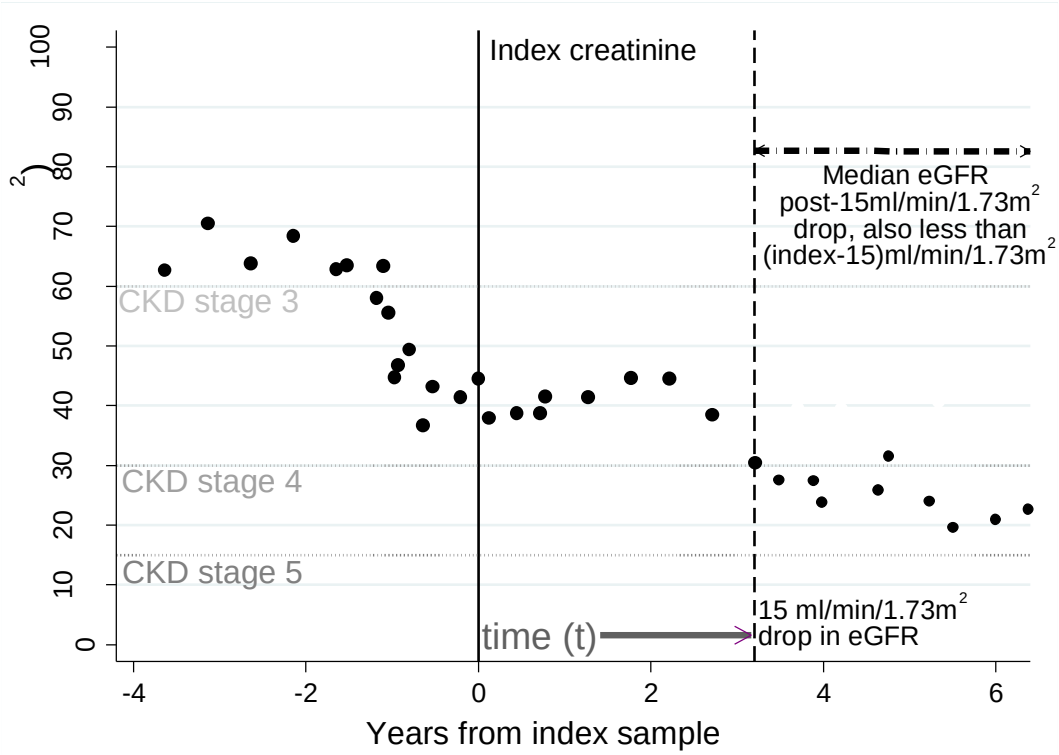


Figure 1: Illustration of "progression" defined by a sustained 15ml/min/1.73m^2 drop in eGFR. An illustrative plot for a hypothetical patient, presenting eGFR as measured over time within the study cohort.

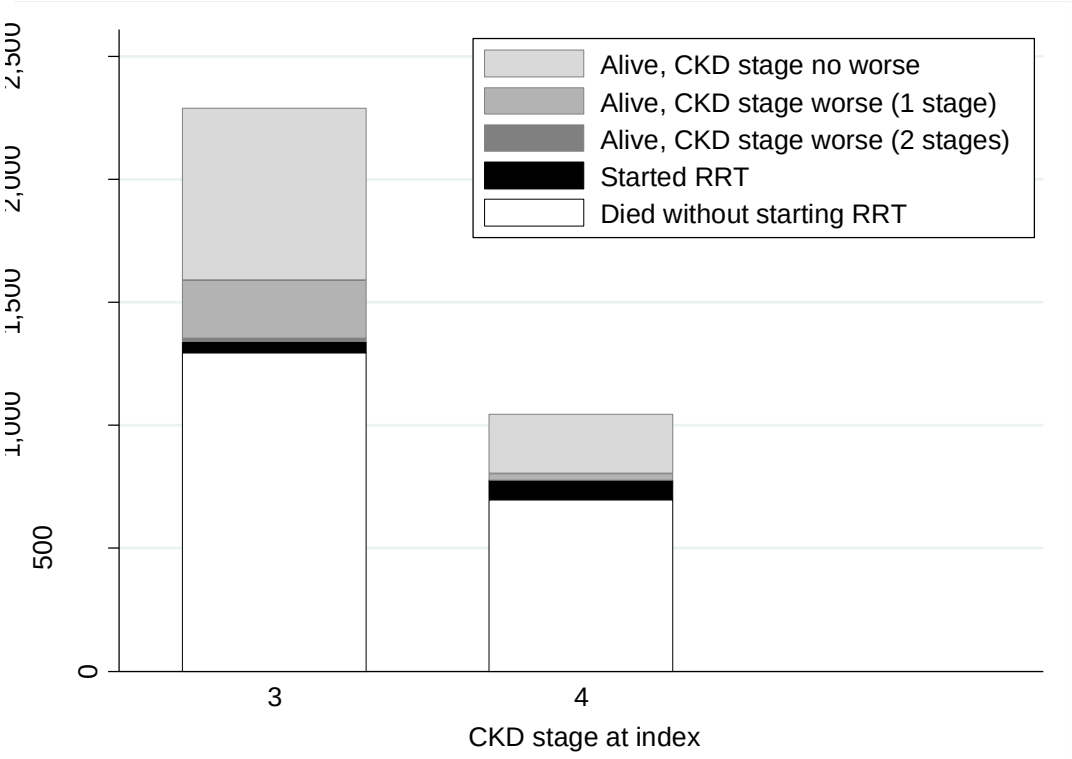


Figure 2: First outcome of death, RRT or CKD stage at end of follow-up (30th June 2009)

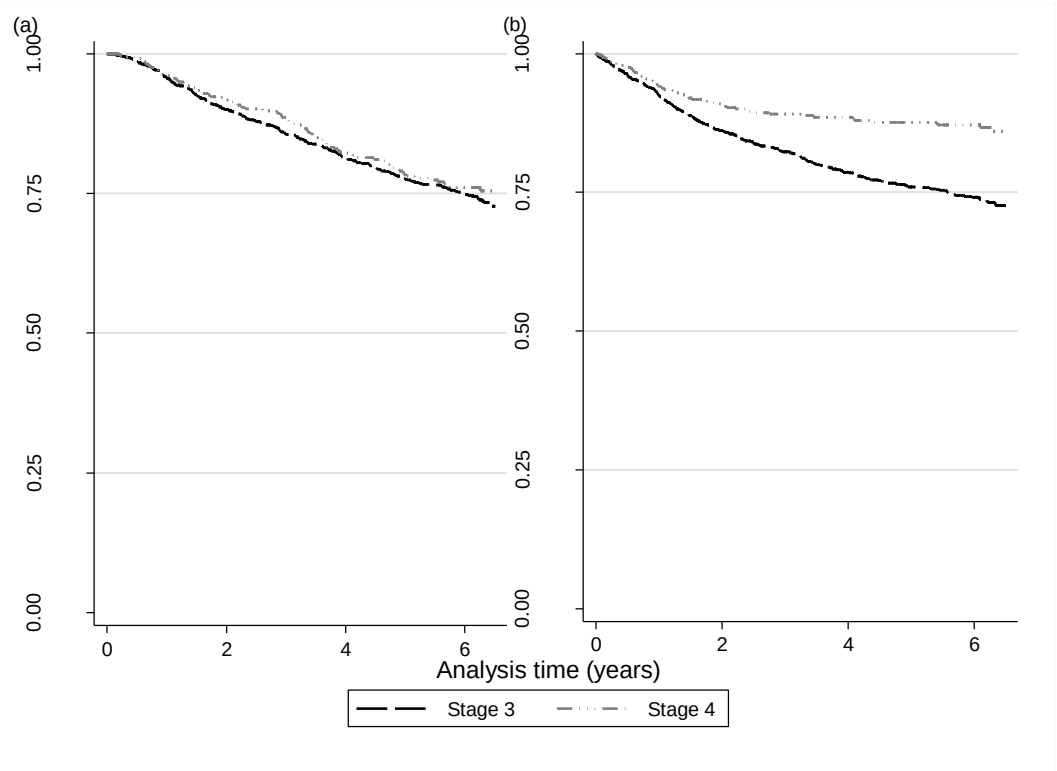
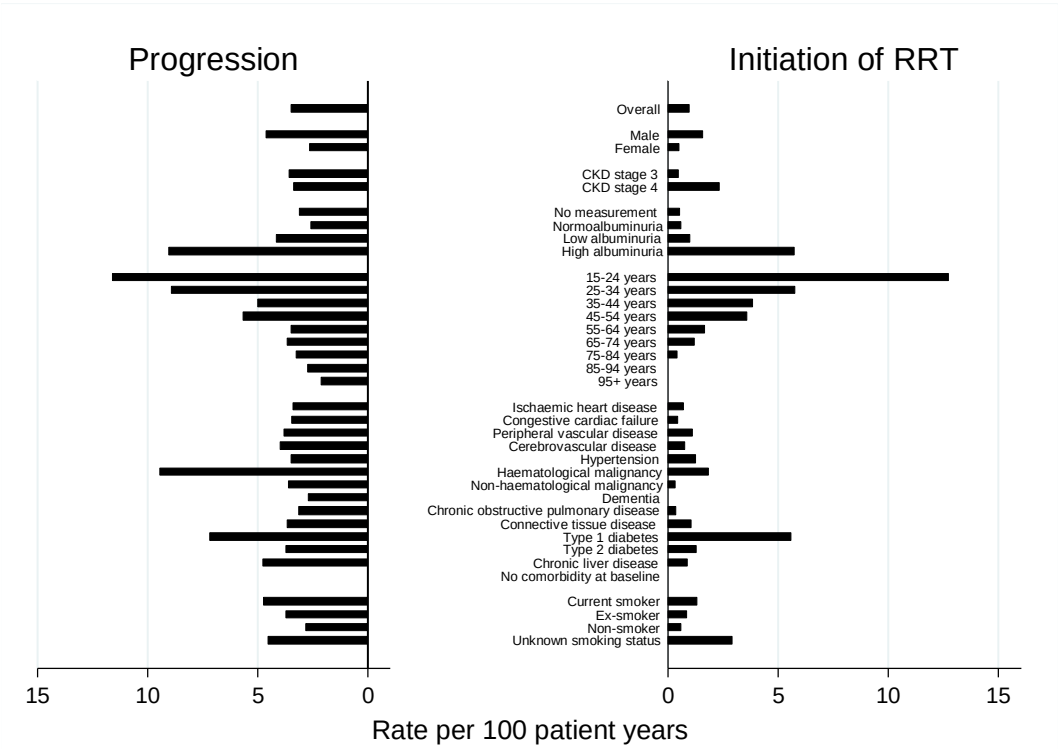


Figure 3: Kaplan-Meier sustained "progression"(a)our definition (b) KDIGO 2012 definition, survival plots by index CKD stage (adjusted for males aged 75 years with normoalbuminuria)



Supplementary figure: Rates of progression and RRT initiation by baseline characteristics