

## **Is chronic dialysis the right hard renal end point to evaluate reno-protective drug effects**

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## Abstract

**Background and objectives:** Renal Replacement Therapy (RRT) and doubling of serum creatinine (DScr) are considered the objective hard end points in nephrology intervention trials. Since both are assumed to reflect changes in the filtration capacity of the kidney, drug effects, if present, are attributed to kidney protection. However, decisions to start RRT are not only based on filtration capacity of the kidney but also on other factors. We therefore compared the time to RRT with the time to a fixed estimated glomerular filtration rate (eGFR) threshold and assessed the effect of the renoprotective drug irbesartan on both components.

**Design, setting, participants & measurements:** Post-hoc analysis of two clinical trials, Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of End points in Non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL), in patients with type 2 diabetes and nephropathy. The time to a predefined eGFR level of 11 mL/min/1.73m<sup>2</sup> (eGFR<sub>11</sub>), calculated by within-patient linear regression, was compared with the time to RRT or sustained serum creatinine  $\geq 6$ mg/dL.

**Results:** A large difference was observed in the median time to RRT (779 days) compared to eGFR<sub>11</sub> (~~677~~678 days; p=0.01). We also observed a large variation in the difference between the time to RRT and eGFR<sub>11</sub>. In IDNT, the hazard ratio for the effect of irbesartan on the serum creatinine  $\geq 6.0$ mg/dL end point was 0.60 (95%CI 0.39 to 0.91; p=0.02), whereas it was smaller on the RRT end point (hazard ratio: 0.78 (95%CI 0.58 to 1.07; p=0.12)).

**Conclusion:** The present study shows a difference in the time to RRT and a fixed eGFR threshold and shows that the effect of an ARB on a filtration based end point versus RRT varies. This implies that evaluating renoprotective effects of drugs with a combined RRT and DScr end point may be subject to more than testing “renoprotection”. Future trials should consider registering all parameters that lead to RRT decisions.

## **Introduction**

Trials to test the efficacy of novel drugs to slow progression of chronic kidney disease (CKD) should use well defined end points. Renal replacement therapy (RRT; chronic dialysis or kidney transplantation) and doubling of serum creatinine (DSCr) are currently considered to be the best objective renal end points and are therefore the obvious clinically relevant end point in trials on slowing CKD progression.[1, 2]

Both RRT and DSCr are assumed to measure the filtration capacity of the kidney, and thus drugs tested in trials with this combined end point are assumed to be tested for an effect on kidney function/filtration. If there is a reduction in this combined end point with the experimental drug, it can be labeled as renoprotective. This is all based on the assumption that both RRT and DSCr are indeed only reflecting changes in filtration capacity of the kidney. However, the decision for dialysis or transplantation is made not only on filtering capacity of the kidneys, but also on other parameters like judgment and decision of the physician, patient's wellbeing and co-morbidities, uremic symptoms, local habits and guidelines, and/or availability of RRT. These factors may influence the time to the RRT end point and could potentially lead to different treatment effects when considering a filtration based end point (e.g. doubling of serum creatinine or fixed serum creatinine threshold) with the RRT end point. Since drugs are usually developed based on an expectation that they will slow loss of the filtration capacity of the kidney (i.e. serum creatinine or estimated glomerular filtration rate eGFR), the result of trials that use a combined RRT/DSCr end point may result in unexpected outcomes through potential effects on other parameters than filtering capacity.

To test whether a change in the end point RRT actually reflects filtering capacity changes, we evaluated in the Irbesartan Diabetic Nephropathy Trial (IDNT) and Reduction of End points in non-insulin dependent diabetes mellitus with the Angiotensin II Antagonist

Losartan (RENAAL) trials if the initiation of RRT is based on reaching a predefined eGFR level. Secondly, we assessed and compared the treatment effect on the time to a fixed serum creatinine threshold versus RRT in the IDNT trial.

## **Material and Methods**

### *Study design*

We performed post-hoc analyses in the IDNT and RENAAL (Clinical Trials.gov identifier 00308347) trials. Both trials demonstrated that an angiotensin receptor blocker (irbesartan in IDNT and losartan in RENAAL) delays the onset of a composite end point consisting of doubling of serum creatinine, RRT, or death of any cause in patients with type 2 diabetes and nephropathy. The rationale, study design, and primary outcomes of both trials have been described in detail elsewhere.[3-6] Both trials were conducted from 1996 to 2000 and the average eGFR threshold at that time to start dialysis was 11 ml/min/1.73m<sup>2</sup>. Inclusion criteria for both trials were presence of type 2 diabetes, nephropathy, overt proteinuria, and age between 30 and 70 years. Individuals with insulin dependent diabetes or renal disease not related to diabetes were excluded in both trials. All participants gave written informed consent. Both trials were approved by local medical ethics committees and conducted according to guidelines of the Declaration of Helsinki.

### *RRT and eGFR based end points*

RRT was defined as the decision for initiation of chronic dialysis (>4 weeks) or kidney transplantation. In IDNT an additional RRT criterion for the primary analysis required a confirmed serum creatinine level equal or above 6.0 mg/dL (SCr6). For the purpose of the current analysis, the SCr6 component was excluded from the RRT definition. The effect of irbesartan on RRT and SCr6 was assessed in the IDNT trial as both components were adjudicated and pre-specified only

in the IDNT trial. SCr6 end points were not recorded in RENAAL. All RRT events were adjudicated by an independent adjudication committee using rigorous definitions and guidelines in both trials.

Serum creatinine was measured in both trials regularly at three months intervals by a central laboratory. Once a subject reached RRT, study medication was discontinued and subsequent serum creatinine measurements were not recorded. eGFR was calculated using the Modification of Diet for Renal Disease (MDRD) equation based on serum creatinine, age, race, and sex.[7]

The eGFR threshold to define kidney failure was 11 mL/min/1.73m<sup>2</sup>. Based on the eGFR slope of each individual, calculated by within-patient linear regression, we interpolated or extrapolated the time until the individual reached 11 mL/min/1.73m<sup>2</sup> (eGFR<sub>11</sub>). For illustration purposes, figure 1 displays the eGFR trajectories and time to eGFR<sub>11</sub> and RRT of two patients. The time to reach eGFR<sub>11</sub> was subsequently compared with the time to the initiation of RRT. The threshold of 11 mL/min/1.73m<sup>2</sup> was chosen since it is the average threshold that was used in clinical practice to initiate dialysis at the time the RENAAL and IDNT trials were conducted.[8] In a sensitivity analysis the eGFR based threshold for kidney failure was 15 mL/min/1.73m<sup>2</sup> as the current KDIGO guideline defines stage 5 CKD as eGFR <15 mL/min/1.73m<sup>2</sup>. [9]

The interpolation of the individual eGFR trajectory to calculate the time to RRT assumes linear eGFR trajectories in all patients. However, previous studies have shown that in a proportion of patients eGFR decline is not linear over time.[10] To account for potential non-linear eGFR trajectories, we conducted an additional analysis in which the time to the first eGFR measurement equal or below 11 mL/min/1.73m<sup>2</sup> (confirmed by the subsequent measurement) was compared with the actual time to RRT. This analysis only includes patients in whom eGFR was recorded before RRT initiation since serum creatinine was not recorded after RRT initiation. To assess internal

validity, we compared the time to the first confirmed eGFR<sub>11</sub> with the time to eGFR<sub>11</sub> calculated from the eGFR slope. To reduce the uncertainty of calculating the time to eGFR<sub>11</sub>, we analyzed a subgroup of patients in whom eGFR decline over time was optimally fitted by selecting all patients below the median residual sum of squares of the individual regression line. We subsequently compared the time to eGFR<sub>11</sub> with the time to RRT in this subgroup of patients.

### *Statistical analysis*

The time to eGFR<sub>11</sub> or SCr6 and RRT was compared by Mann-Whitney U test. The median difference between the time to eGFR<sub>11</sub> and RRT was subsequently calculated and represented the bias. Since subjects could reach eGFR<sub>11</sub> before or after RRT, the time difference was calculated separately for patients who either reached eGFR<sub>11</sub> before or after RRT. The time difference is zero if the time to eGFR<sub>11</sub> is similar as the time to RRT. Accuracy was calculated and defined as the percentage of subjects reaching eGFR<sub>11</sub> within 90 days of the actual time to RRT.

A joint model of longitudinal and survival data was used to assess the relationship between time-varying eGFR and time to RRT and time to reaching eGFR<sub>11</sub> and SCr6. The joint model links two processes by unobserved random effects through the use of a shared parameter in order to model both survival and longitudinal data simultaneously. To model the longitudinal eGFR data we used a linear mixed effects model with a random intercept and random slope. The model included an interaction term between follow-up time and treatment. To model survival data we used a Cox proportional hazard model. The model included a term for randomized treatment assignment. The joint model included both RRT and SCr6 (or eGFR<sub>11</sub>) as competing events. Patients who did not reach an event were censored at their date of death, or for those still alive at the end of the trial, the date of their last clinic visit before the termination of the study. Estimation of the joint model was based on the maximum likelihood approach. In the joint model, we assumed

that the risk for SCr6 (or eGFR<sub>11</sub>) end point at a specific time depends on features of the longitudinal trajectory at the same time point (i.e., current serum creatinine value and current slope).

The effect of irbesartan compared to placebo on the RRT end point and SCr6 end point were estimated from Cox proportional hazard models. Cox proportional hazard models were conducted based on the intention to treat principle and survival time to the first relevant end point was used in each analysis. Since RRT is a competing risk for the SCr6 end point, an additional analysis was conducted accounting for the competing event of RRT. The subhazard ratio of the treatment effect was calculated using a Fine and Gray model [11] which extends the Cox proportional hazard model to competing risk data by taking into account the sub-distribution hazard. Mean and standard deviations are provided for normally distributed data and median and 25<sup>th</sup> to 75<sup>th</sup> percentile for skewed data. Analyses were conducted with R statistical software version 2.15.3 ([www.R-project.org](http://www.R-project.org); The JM package in R was used to implement the joint model).

## Results

### *Comparison between the duration to reach RRT and eGFR<sub>11</sub>*

A total of 3055 patients with at least three eGFR measurements during follow-up were included in this analysis. Their baseline characteristics are shown in supplementary table 1. Of these 3055 patients, 448 (15%) initiated RRT during the trial period. The median time to RRT was 779 days. Median time to eGFR<sub>11</sub> was ~~677~~678 days (difference RRT ~~102~~101 days; p=0.01). A large variation was observed in the time to eGFR<sub>11</sub> and RRT (Figure 2). Among the 288 patients who reached eGFR<sub>11</sub> before RRT initiation, the median time difference between eGFR<sub>11</sub> and RRT was 150 days, whereas in the 160 subjects who reached eGFR<sub>11</sub> after initiation of RRT the median

time difference was 204 days (Table 1). The accuracy, defined as the percentage of subjects with eGFR<sub>11</sub> measurements within 90 days of the actual time to RRT, was 31% (Table 1).

To account for potential non-linear eGFR declines, we also compared the time to RRT and time to first confirmed eGFR<sub>11</sub>. Since eGFR was not recorded after a patient had reached RRT, we could only calculate the time difference if RRT was initiated after eGFR<sub>11</sub>. In the 88 patients who reached RRT after eGFR<sub>11</sub>, the median time difference between first confirmed eGFR<sub>11</sub> and RRT was 160 days, and 14% initiated RRT within 90 days of reaching eGFR<sub>11</sub> (Table 2). To assess internal validity, we compared the time to eGFR<sub>11</sub> based on the individual eGFR slope and first eGFR<sub>11</sub> measurement. The time difference was substantially smaller and accuracy higher than the comparison of either of these eGFR metrics with RRT (Table 1). We also observed a significant difference in the time to SCr6 and RRT in the IDNT trial (median time 584 [382-902] versus 688 [409 – 1011] days respectively,  $p < 0.01$ ).

A joint model analysis showed that the hazard ratio for the association between eGFR level and RRT was significantly lower compared to the association between eGFR level and time to first eGFR<sub>11</sub> or SCr6 (Table 2).

Results were similar in a sensitivity analysis of patients in whom the most optimal fit of the individual eGFR regression line could be fitted (Supplement Table S2) or when eGFR  $< 15$  mL/min/1.73m<sup>2</sup> was used to define kidney failure (Supplement Table S3).

#### *Effect of irbesartan on RRT and serum creatinine $\geq 6.0$ mg/dL*

The effects of irbesartan on a filtration based end point (time to a sustained serum creatinine of  $\geq 6.0$  mg/dL) and RRT were different. The SCr6 end point occurred in 58 patients in the placebo group and 36 patients in the irbesartan group representing a hazard ratio of 0.60 (95%CI 0.39 to 0.91;  $p = 0.01$ ). The RRT end point occurred in 90 patients in the placebo group and 74 patients in



the irbesartan group representing a non-significant hazard ratio of 0.78 (95%CI 0.58 to 1.07;  $p=0.12$ ). The effect of irbesartan on the eGFR<sub>11</sub> end point was similar to the SCr6 end point (hazard ratio 0.64 (95%CI 0.45 to 0.91;  $p=0.012$ ). Results were not different in a competing risk analysis (subhazard ratio SCr6 0.65 (95%CI 0.42 to 1.01;  $p=0.06$ ); RRT 0.86 (95%CI 0.57 to 1.29;  $p=0.46$ )). The competing risk subhazard ratio's for the treatment effect of irbesartan on the eGFR<sub>11</sub> versus RRT end point was 0.65 (95%CI 0.45 to 0.92;  $p=0.02$ ) versus 0.97 (95%CI 0.60 to 1.58;  $p=0.91$ ). In the joint model, after taking into account the patient's eGFR trajectory the treatment effect of irbesartan was 0.85 (95%CI 0.20 to 3.61).

## Discussion

In this study we found a large discrepancy between the time to reach a fixed eGFR threshold (11 ml/min/1.73m<sup>2</sup>) and the time to RRT. This suggests that, although RRT is a hard end point in trials of kidney disease progression, the decision of RRT initiation appears not only to be driven by the filtration capacity of the kidney (i.e. serum creatinine or eGFR) but also by other factors. This finding may impact the evaluation of drug efficacy in CKD trials...

How do these findings impact on the current use of doubling of serum creatinine (or predefined serum creatinine or eGFR level) and initiation of dialysis as measures for RRT? First, these data have to be substantiated by other, preferably prospective studies. More importantly, we need to understand whether we want to analyze the reno-protective potential of interventions on the basis of their ability to attenuate, halt, or even improve GFR decline, or we want to establish whether the drug postpones the need for RRT initiation. Potentially, a drug could not affect GFR change at all, but just improve the “tolerance” of the patient to withstand the sequelae of reduced kidney function and thus delay the decision of the physician to start dialysis. Although the latter is

clearly of importance (both for the patient and from a healthcare payer perspective) it may not be labeled as kidney protection. In essence, drugs that slow eGFR progression, delay overall structural kidney function loss and reduce the sequelae of reduced filtration capacity. Our data supports that reaching a predefined level of serum creatinine or eGFR should always be included as a component of a hard kidney end point, as already occurs in most kidney outcome trials.

The results of our study, based on trials which were conducted 15 to 20 years ago, are in line with recent studies, in contemporary practice, showing a wide variation as to when to initiate RRT.[12] A web-based questionnaire conducted in 11 European countries among 433 nephrologists showed that only a third of all nephrologists considered eGFR as the most important factor in the decision to initiate RRT.[13] Reasons for an earlier start of RRT included the clinical condition of the patient, such as uremic symptoms, whereas patient preference and lack of dialysis facilities delayed the start of RRT. Patients prefer initiation of dialysis over conservative treatment if they were able to dialyze during the day or evening rather than during the day only, if subsidized transport was available, and few hospital visits were required.[14] Quality of life is another important factor that is taken into account when deciding to initiate RRT.[15] A study from the United Kingdom established substantial variation among health care physicians in their likelihood to offer dialysis. The patient's mental state appeared to be the most significant factor to impact the decision to offer dialysis.[16] Taken together, the available data indicate that the decision when to start RRT is multifactorial and is unlikely to be guided by a single parameter (for example eGFR). Symptoms associated with uremia which could drive the decision to initiate dialysis are not systemically collected and analyzed in clinical trials and should be recorded in future (drug) trials to obtain more insight which factors drive RRT initiation, and examine which of these factors an investigational drug is actually working.

The variation in the time between the decision to offer dialysis and reaching a fixed serum creatinine or eGFR threshold may impact evaluation of drug efficacy. The effect of irbesartan on the RRT and serum creatinine  $\geq 6.0$  mg/dL end point seemed to differ but the confidence intervals of the effect of irbesartan on both end points were overlapping. Additionally, the joint model analysis showed that after taking into account the patient's eGFR trajectory the treatment effect of irbesartan on the RRT end point was not statistically significant. Apparently, for ARBs a large part of the protective effect is mediated by the effect on slowing eGFR decline and this may overwhelm potential effects which affect RRT decisions. Yet, as mentioned above, other interventions may influence RRT decisions through effects independent of filtration. In this respect, another trial has shown different effects of the intervention on the doubling of serum creatinine and RRT end point. In the Evaluation Prevention of Progression in CKD-2 (EPPIC-2) trial, AST-120 showed a trend towards a risk reduction for RRT of 18% whereas no effect on doubling of serum creatinine was observed. The reverse was observed in the EPPIC-1 trial. The authors suggested that regional differences in practices when to initiate dialysis could explain these different results.[17]

This study has limitations. First, the assessment of the timing between reaching eGFR<sub>11</sub> and RRT was conditional on the occurrence of RRT. A total of 228 patients reached eGFR<sub>11</sub> during the patient's follow-up but did not reach RRT. The censoring for RRT may have given a biased assessment of the time difference. However, this is probably a conservative bias since the time difference between eGFR<sub>11</sub> and RRT will likely shift upwards if the censoring of RRT is taken into account. Second, we calculated the time to eGFR<sub>11</sub> based on linear interpolation or extrapolation of the eGFR slope. Spontaneous fluctuations in eGFR decline have been demonstrated,[18] and may impact the prediction of time to eGFR<sub>11</sub>. However, to account for periods of accelerated kidney function decline we performed an additional analysis comparing the time to the first eGFR measurement of 11 ml/min/1.73m<sup>2</sup> and the time to RRT. This analysis

confirmed the results of our main analysis. Third, we recognize that estimating GFR based on creatinine level rather than relying on measured GFR can misclassify patients which would bias time to reaching of eGFR<sub>11</sub> end point.[19] Additionally, random noise in the measurement of serum creatinine may also account for the variation in timing between eGFR<sub>11</sub> and RRT rather than factors influencing the RRT decision. Fourth, the number of SCr<sub>6</sub> and RRT end points in the IDNT trial was relatively small which limited the power of analyses comparing irbesartan treatment effects. Finally, the results can only be generalized to the population who shares the characteristics of the RENAAL and IDNT population.

In conclusion, this study shows that the initiation of RRT cannot be explained by serum creatinine alone but likely also depends on other factors. If we agree that reno-protection of a drug should be expressed as the slowing, halting or improvement of filtration capacity, one should only include filtration based measures (fixed eGFR threshold of 15 ml/min/1.73m<sup>2</sup> and/or a doubling of serum creatinine) in a kidney end point. Alternatively, one could dissect the RRT decision by recording the physicians' reasons for dialysis initiation. In any case we should be clear as to which drug/intervention effect we want to detect when using the end point RRT: renal filtration, patient's wellbeing, or both.

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**Table 1:** Difference in the time to renal replacement therapy (RRT) and eGFR<sub>11</sub> in patients who either reached eGFR<sub>11</sub> before or after RRT. The left part of the table shows the number of patients who reached eGFR<sub>11</sub> before RRT was initiated and the time difference between eGFR<sub>11</sub> and RRT. The right part of the table shows the number of patients who reached eGFR<sub>11</sub> after RRT and the time difference (based on extrapolation of the eGFR slope).

	eGFR <sub>11</sub> before RRT		eGFR <sub>11</sub> after RRT		
	Patients with RRT (N)	Median (25 <sup>th</sup> – 75 <sup>th</sup> P) time difference (days)	Patients with RRT (N)	Median (25 <sup>th</sup> – 75 <sup>th</sup> P) time difference (days)	Accuracy P <sub>90</sub> (%)*
eGFR <sub>11</sub> vs. RRT	288	150 [78 – 251]	160	204 [51 – 495]	31.0
eGFR <sub>11-first</sub> vs. RRT	88	160 [115 – 266]	n/a	n/a	13.6
eGFR <sub>11</sub> vs. eGFR <sub>11-first</sub>	56	48 [26 – 66]	33	42 [20 – 81]	82.0

\* P<sub>90</sub> reflects the proportion of patients in whom RRT was initiated within 90 days of reaching eGFR<sub>11</sub>.

Abbreviations: eGFR<sub>11</sub>, time to eGFR 11 mL/min/1.73m<sup>2</sup> based on individual's eGFR slope; eGFR<sub>11-first</sub>, time to first measurement of eGFR 11 mL/min/1.73m<sup>2</sup>; P, Percentile



**Table 2:** The association between time-varying eGFR is stronger with eGFR<sub>11</sub>, eGFR<sub>15</sub>, or serum creatinine  $\geq 6.0$  mg/dL compared to the association with RRT. The hazard ratios indicate the association between the renal replacement therapy, eGFR<sub>11</sub>, eGFR<sub>15</sub>, and serum creatinine  $\geq 6$  mg/dL end points with 1 ml/min/1.73m<sup>2</sup> decline in eGFR as calculated with the joint model. The trials were jointly and separately analyzed.

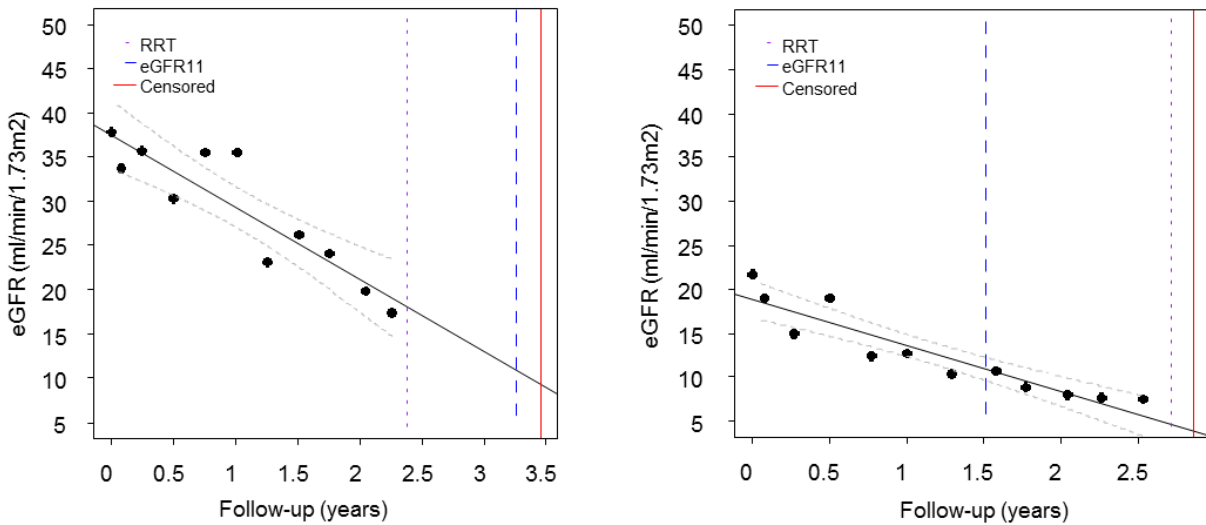
End points	N	HR (95% CI)	p-value*
<i>Combined RENAAL IDNT trials</i>			
RRT	258	1.25 [1.11 – 1.41]	<0.01
eGFR <sub>11-first</sub>	317	1.53 [1.45– 1.62]	
RRT	153	1.22 [1.12 – 1.32]	<0.01
eGFR <sub>15-first</sub>	570	1.42 [1.37 – 1.48]	
<i>IDNT</i>			
RRT	93	1.23 [1.11 – 1.69]	0.08
SCr6 ≥6.0 mg/dL	84	1.56 [1.33 – 1.82]	
RRT	64	1.18 [1.01 – 1.41]	0.01
eGFR <sub>11-first</sub>	124	1.50 [1.38 – 1.63]	
RRT	39	1.15 [1.03 – 1.37]	<0.01
eGFR <sub>15-first</sub>	216	1.49 [1.38 – 1.62]	
<i>RENAAL</i>			
RRT	194	1.29 [1.09 – 1.51]	0.03
eGFR <sub>11-first</sub>	193	1.57 [1.45 – 1.70]	
RRT	114	1.15 [1.06 – 1.24]	<0.01
eGFR <sub>15-first</sub>	354	1.30 [1.26 – 1.35]	

\*p-value, compares HR of RRT vs. SCr6/eGFR<sub>11-first</sub>/eGFR<sub>15-first</sub>

Abbreviation: N, number of events; HR, hazard ratio; CI: confidence interval ; eGFR<sub>11-first</sub>, time to first unconfirmed measurement of eGFR 11 ml/min/1.73m<sup>2</sup>; eGFR<sub>15-first</sub>, time to first unconfirmed measurement of eGFR 15 ml/min/1.73m<sup>2</sup>

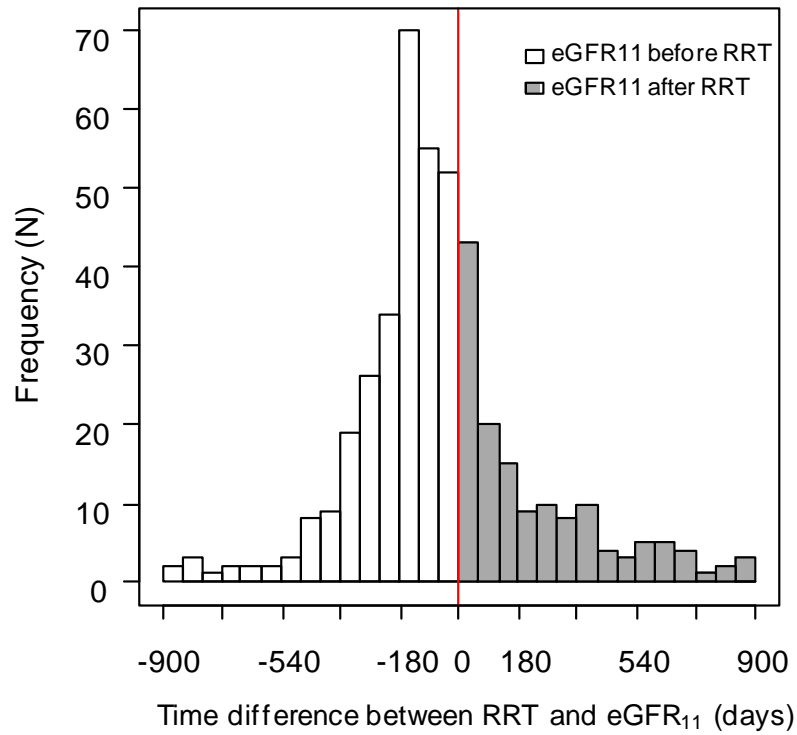
**Figure 1:** Examples of two patients who initiated renal replacement therapy (RRT)

approximately one year before reaching  $eGFR_{11}$  (panel A) or initiated RRT one year after reaching  $eGFR_{11}$  (Panel B). The purple dotted line indicates the initiation of dialysis, the vertical dotted blue line the time point when  $eGFR_{11}$  was reached, and the vertical straight red line the censor date of the individual.

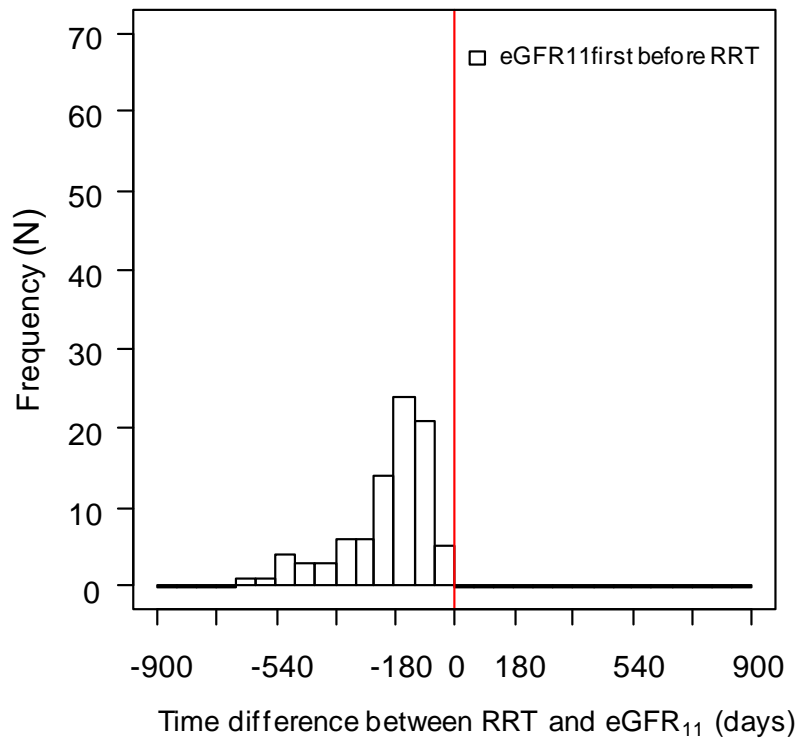


**Figure 2:** Variability between the time to reach renal replacement therapy and eGFR<sub>11</sub>. The solid vertical line at 0 represents the time to renal replacement therapy (RRT) (779 days). The white bars show patients who reach eGFR<sub>11</sub> before RRT and grey bars show patients who reach eGFR<sub>11</sub> after RRT. Panel A shows the time to eGFR<sub>11</sub> calculated based on the individual eGFR slope. Panel B shows the time to eGFR<sub>11</sub> based on the time to first confirmed eGFR measurement 11 ml/min/1.73m<sup>2</sup>. During each patient's follow-up, 228 patients reached eGFR<sub>11</sub> but not RRT. A total of 18 patients had an estimated time to eGFR<sub>11</sub> beyond the range of the histogram. In 8 patients the time interval extended to 1 year beyond the histogram, in 3 patients it extended to 1 and 2 years, in 2 patients to 2 and 4 years, and in 5 patients beyond 4 years.

**A: eGFR<sub>11</sub> vs. RRT**



**B: eGFR<sub>11-first</sub> vs. RRT**



**Table S1:** Demographic and baseline clinical characteristics

Parameters	Total N=3055	Placebo N=711	Losartan N=721	Placebo N=541	Amlodipine N=534	Irbesartan N=548
Age (yrs.)	59.4 (7.6)	60.2 (7.5)	60.0 (7.4)	58.3 (8.1)	59.1 (7.9)	59.2 (7.1)
Female Gender n, (%)	1067 (34.9)	253 (35.6)	277 (38.4)	156 (28.8)	194 (36.3)	187 (34.1)
Race, n, (%)						
Caucasian	1876 (61.4)	350 (49.2)	345 (47.9)	395 (73.0)	371 (69.5)	415 (75.7)
Black	430 (14.1)	97 (13.6)	118 (16.4)	75 (13.9)	81 (15.2)	59 (10.8)
Hispanic	336 (11.0)	131 (18.4)	132 (18.3)	22 (4.1)	26 (4.9)	25 (4.6)
Asian	319 (10.4)	125 (17.6)	115 (16.0)	26 (4.8)	30 (5.6)	23 (4.2)
Other	94 (3.1)	8 (1.1)	11 (1.5)	23 (4.3)	26 (4.9)	26 (4.7)
Serum creatinine (mg/dL)	1.8 (0.5)	1.9 (0.5)	1.9 (0.5)	1.7 (0.6)	1.7 (0.6)	1.7 (0.5)
eGFR (ml/min/1.73m <sup>2</sup> )	43.8 (15.9)	39.9 (12.7)	39.5 (11.9)	48.0 (18.4)	47.7 (17.7)	46.6 (17.0)
CER (mg/24hr)	1415 (661)	1374 (1041)	1308 (599)	1459 (585)	1446 (558)	1436 (531)
Systolic BP (mmHg)	156 (19.8)	153 (19.9)	152 (18.8)	158 (20.4)	159 (19.3)	160 (19.5)
Diastolic BP (mmHg)	84.8 (11.0)	82.4 (10.7)	82.3 (10.3)	86.8 (11.0)	87.1 (10.8)	86.9 (11.4)
Weight (kg)	84.8 (20.1)	82.1 (21.2)	82.4 (20.6)	87.2 (19.5)	86.3 (19.5)	87.8 (18.1)
UACR (mg/g)	1348 [678, 2615]	1265 [585, 2472]	1182 [545, 2620]	1526 [750, 2670]	1403 [691, 2470]	1478 [803, 2803]
Hemoglobin (mg/dL)	12.8 (1.9)	12.5 (1.8)	12.5 (1.8)	13.0 (1.9)	12.9 (1.9)	13.0 (1.9)
Urea Nitrogen (mg/dL)	31.2 (12.3)	32.3 (12.3)	32.5 (12.2)	29.7 (12.3)	29.8 (11.8)	30.8 (12.7)
Potassium (mmol/L)	4.6 (0.5)	4.6 (0.5)	4.6 (0.5)	4.6 (0.5)	4.6 (0.5)	4.6 (0.5)
Uric acid (mg/dL)	6.8 (1.8)	6.7 (1.7)	6.7 (1.7)	6.8 (1.9)	6.8 (1.8)	6.8 (1.9)
Calcium (mg/dL)	9.3 (0.5)	9.4 (0.5)	9.4 (0.5)	9.2 (0.6)	9.2 (0.5)	9.2 (0.5)
Phosphate (mg/dL)	3.8 (0.6)	3.9 (0.6)	3.9 (0.6)	3.8 (0.6)	3.8 (0.7)	3.8 (0.6)
CVD history (yes), n, (%)	1376 (45.0)	311 (43.7)	330 (45.8)	238 (44.0)	238 (44.6)	259 (47.3)

Abbreviations: BP, blood pressure; eGFR, estimated glomerular filtration rate; CER: creatinine excretion rate; UACR, urinary albumin to creatinine ratio; CVD, cardiovascular disease; Note: Values for categorical variables are reported as percentages; values for continuous variables are reported as mean  $\pm$  standard deviation or median [interquartile range]



**Table S2:** Difference in the time to RRT and eGFR<sub>11</sub> in the population with the sum of square of the residuals below the individual based eGFR regression below the median.

	eGFR <sub>11</sub> before RRT		eGFR <sub>11</sub> after RRT		
	Patients with	Median (25 <sup>th</sup> – 75 <sup>th</sup> P) time	Patients with	Median (25 <sup>th</sup> – 75 <sup>th</sup> P) time	Accuracy
	RRT (N)	difference (days)	RRT (N)	difference (days)	P <sub>90</sub> (%)
eGFR <sub>11</sub> vs. RRT	259	152 [82 – 261]	124	152 [51 – 414]	30.5
eGFR <sub>11-first</sub> vs. RRT	79	161 [115 – 276]	n/a	n/a	12.7
eGFR <sub>11</sub> vs. eGFR <sub>11-first</sub>	50	47 [27 – 64]	30	50 [21 – 82]	81.3

Abbreviations: eGFR<sub>11</sub>, time to eGFR 11 mL/min/1.73m<sup>2</sup> based on individual's eGFR slope; eGFR<sub>11-first</sub>, time to first eGFR 11 measurement confirmed by the second measurement of reaching eGFR<sub>11</sub>; P, Percentile

**Table S3:** Difference in the time to RRT and eGFR<sub>15</sub> in patients who either reached eGFR<sub>15</sub> before or after RRT

	<del>eGFR<sub>15</sub></del> -eGFR <sub>15</sub> before RRT		<del>eGFR<sub>15</sub></del> -eGFR <sub>15</sub> after RRT		Accuracy P <sub>90</sub> (%)
	Patients with RRT (N)	Median (25 <sup>th</sup> – 75 <sup>th</sup> P) time difference (days)	Patients with RRT (N)	Median (25 <sup>th</sup> – 75 <sup>th</sup> P) time difference (days)	
eGFR <sub>15</sub> vs. RRT	370	241 [140 – 364]	78	228 [100 – 436]	14.8
eGFR <sub>15-first</sub> vs. RRT	220	240 [161 – 385]	n/a	n/a	6.4
eGFR <sub>15</sub> vs. eGFR <sub>15-first</sub>	152	44 [19 – 85]	68	42 [23 – 80]	78.2

Abbreviations: eGFR<sub>15</sub>, time to eGFR 15 mL/min/1.73m<sup>2</sup> based on individual's eGFR slope; eGFR<sub>15-first</sub>, time to first eGFR 15 measurement confirmed by the second measurement of reaching eGFR<sub>15</sub>; P, Percentile