Diabetes, Obesity and Metabolism 18: 64–71, 2016.

ORIGINAL ARTICLE

Early renin–angiotensin system intervention is more beneficial than late intervention in delaying end-stage renal disease in patients with type 2 diabetes

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Aims: To develop and validate a model to simulate progression of diabetic kidney disease (DKD) from early onset until end-stage renal disease (ESRD), and to assess the effect of renin-angiotensin system (RAS) intervention in early, intermediate and advanced stages of DKD.

Methods: We used data from the BENEDICT, IRMA-2, RENAAL and IDNT trials that assessed effects of RAS intervention in patients with type 2 diabetes. We built a model with discrete disease stages based on albuminuria and estimated glomerular filtration rate (eGFR). Using survival analyses, we assessed the effect of RAS intervention on delaying ESRD in early [eGFR>60 ml/min/1.73 m^2 and albumin:creatinine ratio (ACR) <30 mg/g], intermediate (eGFR 30–60 ml/min/1.73 m^2 or ACR 30–300 mg/g) and advanced (eGFR <30 ml/min/1.73 m^2 or ACR >300 mg/g) stages of DKD for patients in different age groups.

Results: For patients at early, intermediate and advanced stage of disease, whose mean age was 60 years and who received placebo, the median time to ESRD was 21.4, 10.8 and 4.7 years, respectively. RAS intervention delayed the predicted time to ESRD by 4.2, 3.6 and 1.4 years, respectively. The benefit of early RAS intervention was more pronounced in younger patients; for example, for patients with a mean age of 45 years, RAS intervention at early, intermediate or advanced stage delayed ESRD by 5.9, 4.0 and 1.1 years versus placebo.

Conclusions: RAS intervention early in the course of proteinuric DKD is more beneficial than late intervention in delaying ESRD.

Keywords: albuminuria, kidney disease, RAS inhibitors, type 2 diabetes

Date submitted 8 July 2015; date of first decision 14 September 2015; date of final acceptance 23 September 2015

Introduction

It has been suggested that intervention in the renin-angiotensin system (RAS) early in the course of type 2 diabetic kidney disease (DKD) might be more beneficial than intervention in later stages of disease, in order to prevent progression to end-stage renal disease (ESRD) [1,2]. Unfortunately, no prospective randomized controlled trials have tested the effect of early RAS intervention on hard renal endpoints because progression of DKD to ESRD can take decades to manifest. Clinical trials would therefore require an unfeasibly long follow-up time.

Progression of DKD is characterized by several stages [3]. Initially, the harmful hyperglycaemic effects in type 2 diabetes may yield a compensatory response in the kidney by increasing glomerular pressure, leading to hyperfiltration. The hyperfiltrating nephrons cause an increase in the filtration of plasma proteins, including albumin, that leads to microalbuminuria. In later stages of the disease, the glomerular filtration rate (GFR) declines as a result of progressive kidney damage and loss of functional nephrons, often exacerbated by hypertension and increasing levels of albuminuria, ultimately culminating in ESRD.

The current classification of DKD is based on both albuminuria and GFR [4]. Previous clinical trials have been conducted at different stages of DKD [5–11]. These trials recorded transition in estimated GFR (eGFR) or albuminuria categories and determined the effect of RAS intervention using transitions in albuminuria stages (i.e. micro- or macroalbuminuria) or ESRD as endpoints. One way to determine the treatment effect of RAS intervention early in the course of DKD would be to connect data from these previous clinical trials so as to simulate the progression of DKD from early onset to ESRD and to assess the effect of RAS intervention at different stages of DKD. This would provide insight into whether treatment initiation at early stages of DKD is more beneficial in delaying ESRD than initiation at advanced stages.

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The first aim of the present study was therefore to develop and validate a statistical model to simulate progression of DKD from early onset to ESRD, by connecting data from previous clinical trials in early, intermediate and advanced disease stages. Secondly, we assessed the effect of RAS treatment on ESRD in early, intermediate and advanced stages of DKD. As the incidence of type 2 diabetes is increasing strikingly among individuals aged <40 years [12–15], we also assessed the impact of treatment initiation at different stages of disease in age-specific subgroups. Thirdly, we compared the treatment effect of RAS inhibition in patients responding to RAS treatment (based on a >30% initial decrease in albuminuria) versus patients who do not respond to RAS intervention.

Materials and Methods

Databases and Data Selection

We used data from the following completed clinical trials: the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA-2), the Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) and the Irbesartan Diabetic Nephropathy Trial (IDNT) which included patients with type 2 diabetes. The study design and results have been published elsewhere [5–8]. In all trials patients gave informed consent. The present study was conducted in accordance with the principles of the Declaration of Helsinki as revised in 2008. All trials investigated the effect of RAS inhibition [angiotensin-converting enzyme (ACE)-I/angiotensin receptor blocker (ARB)]. In BENEDICT, 1209 patients with hypertension and normoalbuminuria (<20 μg/min urinary albumin excretion) and serum creatinine levels ≤1.5 mg/dl (0.13 mmol/l) were randomly allocated to treatment with trandolapril, verapamil, their combination or placebo. The primary outcome was transition from normo- to microalbuminuria. The median follow-up time was 3.6 years. In the IRMA-2 trial, 590 patients with hypertension and microalbuminuria (20–200 μg/min urinary albumin excretion) and serum creatinine levels <1.5 mg/dl (men; 0.13 mmol/l) and <1.1 mg/dl (women; 0.097 mmol/l) were enrolled. Patients were randomly allocated to either placebo or irbesartan (150 or 300 mg) treatment. The primary outcome was the transition to macroalbuminuria. The median follow-up time was 2.0 years. The RENAAL and IDNT trials both enrolled patients (RENAAL: 1513 patients, IDNT: 1715 patients) with type 2 diabetes and macroalbuminuria [>300 mg/g albumin:creatinine ratio (ACR) in RENAAL and >900 mg/24 h proteinuria in IDNT], with serum creatinine levels between 1.0 and 3.0 mg/dl (0.27 mmol/l). Patients were randomly allocated to losartan or placebo in RENAAL, or irbesartan, amlodipine or placebo in IDNT. The primary outcome was time to first event of a composite renal endpoint including doubling of serum creatinine, ESRD or death. IDNT included serum creatinine >6 mg/dl (0.53 mmol/l) as an additional component to the primary outcome. The median follow-up time was 3.7 years for RENAAL and 3.4 years for IDNT. Albuminuria and eGFR were measured at baseline and every 3 months in RENAAL and IDNT and every 6 months in BENEDICT and IRMA-2.

Classification and Modelling of Diabetic Kidney Disease Progression

To simulate the progression of DKD we built disease stages based on albuminuria and eGFR classes [16]. To this end, we used the following albuminuria strata: ACRs of 0–15, >15–30, >30–150, >150–300, >300–1000 and >1000 mg/g. The eGFR strata were: >90, 90 to >60, 60 to >30, 30 to >15 and <15 ml/min/1.73 m^2. Because of low numbers in some strata, all patients with eGFR <15 ml/min/1.73 m^2 were merged into one group, irrespective of their albuminuria, and patients with albuminuria 0–30 mg/g and eGFR 15–30 ml/min/1.73 m^2 were also merged. These groups were combined to ensure that models could be fit for these disease stages. Occurrence of ESRD, defined as the need for renal replacement therapy (dialysis or transplantation), was recorded as the renal endpoint. All-cause mortality was used as a censoring event in the model. Albuminuria and eGFR follow-up data were used to determine the individual course of kidney disease over time. If more than two subsequent albuminuria or eGFR values were missing during follow-up, those values were imputed using a last observation carried forward approach. If there were more than two subsequent missing values, the patient was censored. Progression was defined as transition to a worse stage in renal disease (either a worsening in albuminuria, eGFR or both). A transition to the next category had to be accompanied by at least a 30% increase in albuminuria or confirmed by the next follow-up measurement.

Modelling of DKD progression was performed in two steps. Firstly, time to a transition in disease stage was estimated using survival analysis. Secondly, we used multinomial regression to calculate the patient-specific probabilities for every possible transition from each disease stage (first event of worsening in albuminuria stage, worsening of eGFR stage, worsening in both or death). The models included treatment allocation, age, gender and systolic blood pressure as covariates. These covariates were selected because they provided the best overall model fit, as determined by the Akaike information criterion. Other covariates that were tested but not included in the final model were: LDL cholesterol; HDL cholesterol; glycated haemoglobin; and serum potassium levels. The multinomial regression models contained calculated time-to-event as determined in step 1 as an additional covariate. For model building purposes, non-parametric data were log transformed and log values were used in further analyses. Statistical analyses were conducted using R version 3.1.0 (R Project for Statistical Computing, www.r-project.org), with a two sided p value <0.05 considered to indicate statistical significance.

Simulating Diabetic Kidney Disease Progression

Two steps were performed to simulate patient-specific disease progression. Firstly, actual patient-specific time to transition from the survival model was based on a random pick from the 95% confidence interval (CI) around the patient-specific point

estimate. We introduced this form of randomness to take into account patient-specific variability.

Secondly, the transition direction (i.e. progression in albuminuria, progression in eGFR, progression in both or death) was determined by a random weighted pick based on the probabilities derived from the multinomial regression model (i.e. transitions with a higher probability are more likely). After time (step 1) and direction (step 2) were calculated, the simulated patient entered a new disease stage which was used as starting point for a new simulation cycle. Calculations were repeated until the patient reaches the endpoint ESRD or death, while accumulated time (sum of all transition times) is recorded. Bootstrapping was used (100 iterations) to assess reliable point estimates.

Simulations were performed for separate patient groups by classifying patients into early, intermediate or advanced stages of DKD, and by different age categories. Our definitions of early, intermediate and advanced stage of disease were based on the Kidney Disease: Improving Global Outcomes guidelines [16] and are shown in Figure S1. Early DKD was defined as eGFR >60 ml/min/1.73 m^2 and ACR <30 mg/g, intermediate DKD as eGFR 30–60 ml/min/1.73 m^2 or ACR 30–300 mg/g, and advanced DKD as eGFR <30 ml/min/1.73 m^2 or ACR >300 mg/g. Age categories ranged from 25 to 65 years, with 5-year intervals. The age distribution for each age category was similar to the age distribution in the trials used to develop the model. Additionally, we assessed the effect of RAS intervention on delaying ESRD in patients who responded to RAS interventions (defined as a regression in albuminuria stage accompanied by a reduction in albuminuria of at least 30% after 6 months of treatment) and in non-responders. Patients with baseline albuminuria levels <15 mg/g were excluded from this analysis because they could not regress in albuminuria stage.

For simulation purposes we added an age-specific mortality probability for patients aged >65 years, on top of the mortality probabilities observed in the dataset. This takes into account that, as patients age, their probability of dying increases. These calculations were based on age- and sex-adjusted mortality rates for patients with type 2 diabetes as previously reported (Table S1) [17].

Model Validation

Internal and external validity was assessed by comparing the proportion of events derived from our model with the observed proportion of events in the trials. For internal validation, we applied the model to all patients from trials included in the training database. The time to ESRD for each individual was calculated using baseline characteristics for each individual. For external validation we applied the model to the individual patient-level data of clinical trials in diabetes not included in our training dataset: LIFE, SUN-MACRO and ALTITUDE. Their rationale, study design and results have been published elsewhere [18–20]. Additionally, we compared the proportion of ESRD events derived from our model with the observed proportion of ESRD events in trials for which no individual patient data were available. For these trials we used aggregated trial-level data, by using the published mean and standard deviation for each variable (e.g. mean age, mean blood pressure) in order to simulate patient data. We used this approach for the ADVANCE, ACCORD, TREAT, NEPHRON-D and ORIENT trials. The results and design of these trials have been published elsewhere [9,21–24], and are summarized in Table S2.

Results

Characteristics of Patients Included in the Dataset

An overview of the baseline characteristics of included trials is given in Table 1. In all included datasets, participants were diagnosed with type 2 diabetes and had a mean age of ~60 years. Albuminuria levels were in the normoalbuminuric range (n = 1209), microalbuminuric range (n = 590) and macroalbuminuric range (n = 3228). Renal function (eGFR) ranged from normal (>90 ml/min/1.73 m^2) to severely impaired (15–30 ml/min/1.73 m^2). The final dataset included 5027 patients. In this dataset, a total of 628 ESRD events and 576 death events were recorded during follow-up. The majority of deaths (357; 62%) were recorded in patients with an eGFR <45 ml/min/1.73 m^2 and an ACR >300 mg/g at baseline. For modelling purposes, we used all available transitions that patients experienced during follow-up, resulting in a median of

Table 1. Baseline characteristics of patients in the included clinical trials.

	BENEDICT N = 1209	IRMA-2 N = 590	RENAAL N = 1513	IDNT N = 1715
Age, years	61.9 (8.1)	58.0 (8.2)	60.2 (7.4)	58.9 (7.8)
Gender, % male	53%	68%	63%	66%
Systolic blood pressure, mmHg	150.8 (14.19)	153.1 (14.43)	152.5 (19.3)	159.1 (19.7)
Diastolic blood pressure, mmHg	87.5 (7.6)	90.1 (9.2)	82.4 (10.5)	86.9 (11.0)
eGFR, ml/min/1.73 m^2	81.2 (15.0)	72.2 (13.8)	39.8 (12.3)	47.3 (17.6)
Albuminuria, mg/g	5.9 (4.0–9.9)	72.55 (54.0–97.3)	1246 (558–2545)	1500 (780–2757)
HbA1c, %/mmol/mol	5.8 (1.4)/39.9	6.9 (1.7)/51.9	8.5 (1.6)/69.4	8.1 (1.7)/65.0
Potassium, mmol/l	4.3 (0.4)	4.7 (0.5)	4.6 (0.5)	4.6 (0.5)
LDL cholesterol, mmol/l	4.22 (0.93)	3.63 (1.04)	3.68 (1.19)	3.70 (1.20)
HDL cholesterol, mmol/l	1.21 (0.31)	1.13 (0.30)	1.17 (0.39)	1.10 (0.37)

Baseline characteristics of all the clinical trials that were included in the model building. Data are mean (standard deviation) except for albuminuria (albumine:creatinine ratio), which was calculated as median and interquartile range.

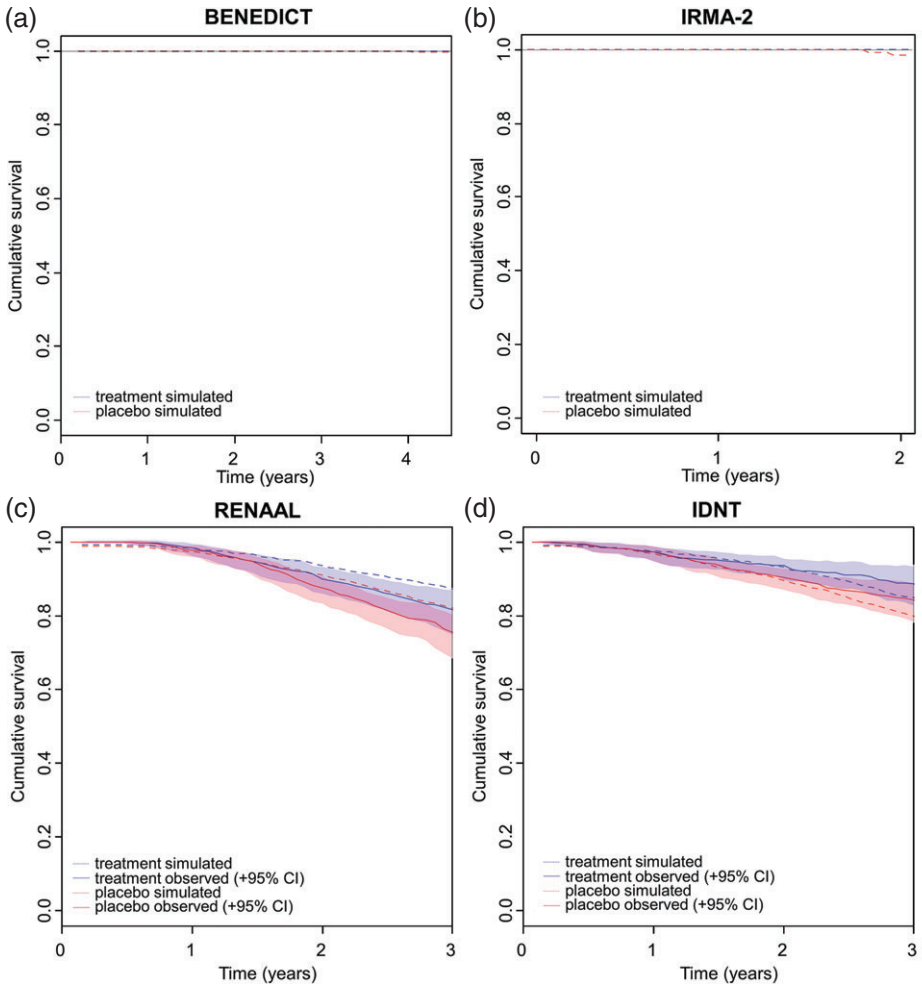

Figure 1. Kaplan–Meier plot showing the observed versus simulated renal events (with death as censoring event) over time in the (a) BENDICT, (b) IRMA-2, (c) RENAAL and (d) IDNT studies. For BENEDICT and IRMA-2 a black horizontal line is drawn because no end-stage renal disease (ESRD) events were observed in the trials. For RENAAL and IDNT the 95% confidence intervals (CIs) are the shaded areas for placebo (red) and treatment (blue).

551 transitions (interquartile range 261–1122) for each disease stage (Figure S1).

Model Validation

The predicted survival probabilities (with ESRD as the endpoint and death as the censoring event) corresponded well to the observed probabilities seen in BENEDICT, IRMA-2, RENAAL and IDNT, with predictions being within the 95% CIs of the observed probabilities for almost all years of follow-up. For the trials in which ESRD events were observed (RENAAL and IDNT), the predictions for the RENAAL trial started to fall outside of the 95% CIs after 2 years' follow-up (Figure 1). We subsequently validated our model using previous clinical trials not included in our training database. The predictions from our DKD model were in very good agreement with the observed probabilities of ESRD events in each treatment arm in each trial, with a calculated R^2 of 0.97 (Figure 2). The predicted and observed proportion of ESRD events appeared to be closer to the line of identity for trials where individual patient data were available compared with trials with aggregated trial level data.

Effect of RAS Intervention Versus Placebo in Early-, Intermediate- or Advanced-stage Disease

We subsequently assessed the effect of RAS intervention at early, intermediate or advanced stages of DKD. Figure 3 shows that the predicted time to ESRD was 21.4, 10.8 and 4.7 years for patients at early, intermediate and advanced disease stages respectively, with patients having a mean age of 60 years (the average age in most type 2 diabetes trials) and receiving placebo treatment. RAS intervention delayed the predicted time to ESRD by 4.2, 3.6 and 1.4 years, respectively (p values <0.001 for pairwise comparisons between early, intermediate and advanced). The beneficial effect of RAS intervention in the early stages of DKD became more apparent when treatment was initiated at a younger age (Table 2). For example, among patients with a mean age of 45 years, RAS intervention in early, intermediate and advanced stages of disease delayed the median time to ESRD by 5.9 years 4.0 and 1.1 years, respectively (p values <0.001 for pairwise comparisons between early, intermediate and advanced). Lastly, we assessed the differences in effects of RAS intervention between men and

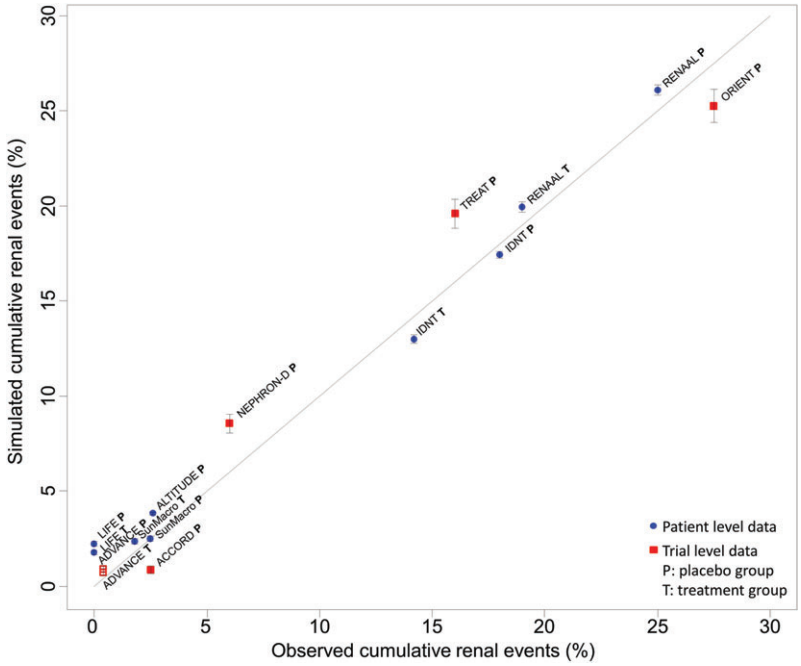

Figure 2. The agreement plot shows the observed and simulated renal events for several clinical trials in nephrology. The percentage of events based on simulated data is shown on the *y*-axis and the percentage of events derived from trials on the *x*-axis. Blue dots indicate that simulations were performed with patient-level data. Red squares indicate that simulations were performed with trial-level data. The diagonal line shows the line of exact agreement.

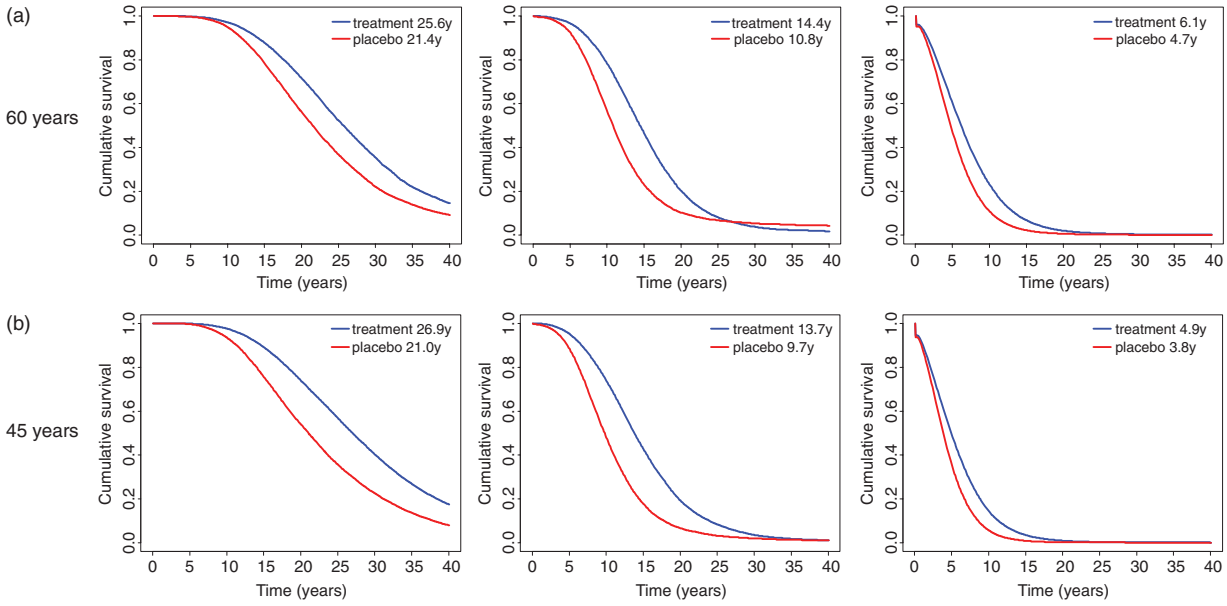

Figure 3. Difference in median time to end-stage renal disease for treatment versus placebo for intervention starting in early, intermediate or advanced stages of diabetic kidney disease. The presented patient populations have a mean age of (a) 60 and (b) 45 years. The proportion of survival is presented on the *y*-axis and the time in years is presented on the *x*-axis.

women and found that the treatment effect did not differ by gender.

Effect of Treatment Response on Time to ESRD

We finally assessed the impact of treatment response (defined as a >30% reduction in albuminuria and an improvement in albuminuria staging from baseline to 6 months of treatment) on time to ESRD. Again, analyses were performed for treatment initiated in early, intermediate or advanced stages of DKD. As expected, treatment responders benefitted more from treatment than non-responders and this effect was particularly striking when treatment was initiated at early stages of disease

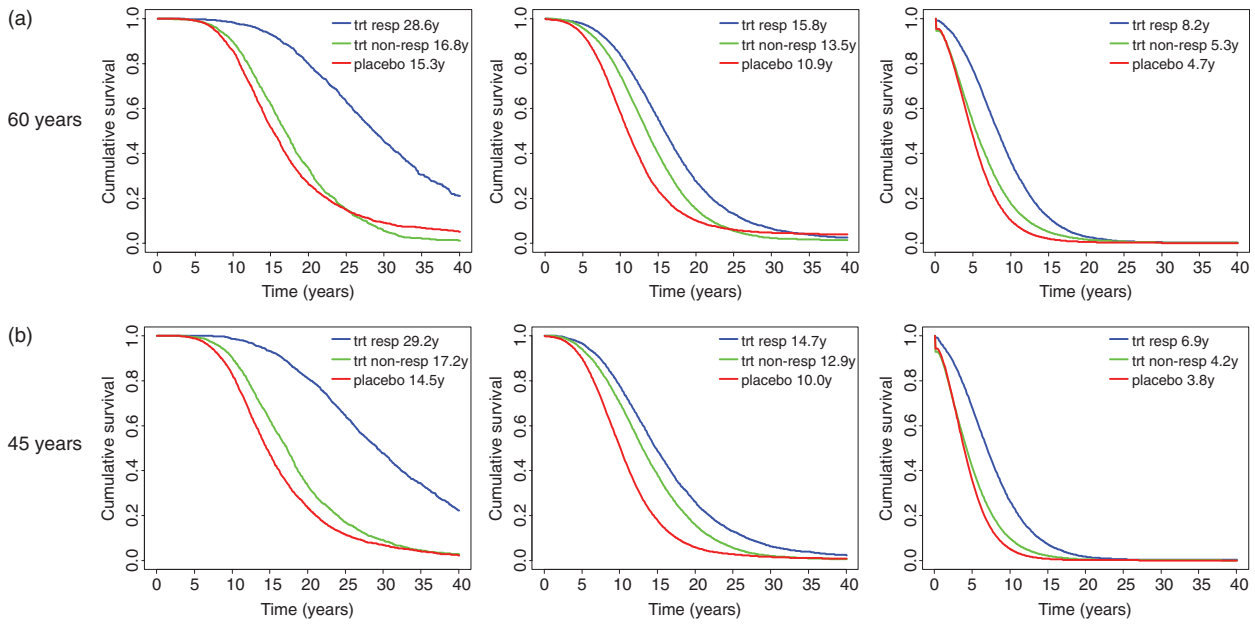

Figure 4. Analysis of the effect of treatment response (defined as a regression in albuminuria stage accompanied by a reduction in albuminuria of at least 30% after 6 months of treatment) on time to end-stage renal disease, shown for mean 60 (a) and 45 (b) years of age.

(Figure 4). For patients who responded to RAS intervention aged 60 years, treatment in the early stages of disease delayed the predicted time to ESRD by 11.8 and 13.3 years compared with the non-responder subgroup and placebo group, respectively ($p < 0.001$), while the model predicted a delay in ESRD in responders to RAS intervention in intermediate and advanced stages of 4.9 and 3.5 years compared with non-responders and placebo (both $p < 0.001$).

Discussion

We have developed and validated a model for patients with type 2 diabetes that can simulate DKD progression and assess thelong-term treatment effects of RAS inhibition from the earliest stages of disease until ESRD with reasonable accuracy. Our model showed that RAS intervention in the earliest stages of disease is most beneficial in delaying ESRD, and that this treatment effect is even more pronounced among younger patients. The beneficial treatment effect was attributed to a large extent to the initial albuminuria-lowering response. ESRD was markedly delayed among patients with an initial response in albuminuria whereas non-responders showed only little benefit compared with placebo, highlighting the importance of monitoring albuminuria during RAS intervention.

Our model predicted that half of the patients with normoalbuminuria and hypertension remain free of ESRD for ~21 years, while RAS intervention delayed this to ~26 years, confirming that progression from early stage to ESRD takes decades to manifest. This is in line with other studies that reported similar time frames. For example, the UK Prospective Diabetes Study (UKPDS) showed that patients with normoalbuminuria take a median of 19 years to develop nephropathy (defined as microalbuminuria or macroalbuminuria), and patients with macroalbuminuria take a median of 9.7 years to reach ESRD, suggesting that progression from normoalbuminuria to ESRD takes approximately three decades [25]. The longer time to reach ESRD in the UKPDS model can be attributed to the inclusion of newly diagnosed diabetes population in the UKPDS, whereas the normoalbuminuria population in the present study had hypertension and a mean diabetes duration of ~8 years. An older study conducted in the USA showed that progression of DKD from onset of type 2 diabetes to ESRD takes around two decades [26]. The finding that early intervention was particularly fruitful in younger patients raises the question as to why older patients benefit to a lesser extent. Our model showed that progression from early stage to ESRD may take several decades. Many patients have already died from advanced age or from comorbidities

Table 2. Treatment effect of renin-angiotensin system intervention on delaying end-stage renal disease.

Age at which RAS treatment is initiated (years)	Delay in ESRD (years) compared with placebo Disease stage at which RAS treatment is initiated		
	Early	Intermediate	Advanced
35	7.4	4.1	0.8
40	6.9	4.0	0.9
45	5.9	4.0	1.1
50	5.7	3.6	1.2
55	5.1	3.5	1.2
60	4.2	3.6	1.4
65	3.5	3.4	1.6

ESRD, end-stage renal disease; RAS, renin-angiotensin system.
Numbers indicate years that treatment with RAS inhibition delays ESRD compared with placebo. Results are displayed for different age groups, ranging from mean ages of 25 to 65 years, and for treatment initiation in early, intermediate or late stages of diabetic kidney disease.

by the time they would have reached ESRD, and therefore death probably obscures the beneficial effect of RAS intervention when initiated at advanced age. Large observational studies showed that patients with mild chronic kidney disease are much more likely to die before reaching ESRD [27,28], with substantially larger risks for death instead of ESRD in populations with less severe kidney disease [29,30]. Indeed, our model, which censored patients in case of death, showed that with increasing patient age at treatment initiation the death/ESRD ratio increased substantially, especially in patients with less severe kidney disease. While age modified the treatment effect of RAS intervention, we did not observe such an effect modification with gender. It is known that females have a lower risk of developing chronic kidney disease [31]. Less is known about gender differences with regard to the effects of RAS intervention on delaying ESRD. Our results showing no gender differences in the treatment effects of RAS intervention are in line with a small study with irbesartan that also reported no such differences [32].

The necessity of investigating the advantages of intervention in early versus advanced stages of DKD for different age groups is prompted by the rapid increase in type 2 diabetes in younger populations. For example, a recent study showed that the incidence of type 2 diabetes is increasing dramatically among people aged <40 years [33]. Likewise, the incidence of type 2 diabetes is markedly increasing in paediatric and adolescent populations [14,15,34]. We have shown that the benefits of RAS intervention in early DKD stages becomes more apparent at a younger age. We also showed that the ultimate treatment effect depends to a large extent on the initial albuminuria response, with more treatment benefit attributed to early intervention for patients classified as responders. Ideally, this should be confirmed in a prospective randomized clinical trial; however, given that the median time to reach ESRD is more than two decades for patients in early DKD stages, it would require unfeasibly large patient populations and follow-up times, which makes it unlikely that such a trial will ever be performed.

Although early intervention delayed progression to ESRD compared with late intervention, patients have to be treated for many years, which has obvious implications for the patient and healthcare system. Whether the benefits of early intervention to delay ESRD outweigh the medication burden and costs of treatment compared with late intervention requires further study; however, given the large burden of dialysis on individual patients, their relatives, and society coupled with the fact that ACE-Is and ARBs are generally well tolerated and cheap, it is likely that early intervention is beneficial from a pharmacoeconomic perspective as well.

The finding that RAS intervention in non-responders showed very little benefit compared with placebo raises the question of whether treatment should be discontinued in this group. We recommend that such a decision should not be made based on these data. The present study is a simulation study of multiple randomized controlled trials, and firm conclusions about treatment discontinuation require adequately designed prospective randomized controlled trials.

To our knowledge this is the first study to investigate the entire course of proteinuric DKD and compare treatment effect in early, intermediate and advanced stages of disease. A previous study by Palmer *et al.* with a Markov model compared intermediate and late intervention with data from the IRMA-2 and IDNT trials and showed that intervention in intermediate stages delays onset of ESRD compared with intervention in advanced disease stages [35]. However, the present model included more disease stages, a larger population, and covered the full range of DKD with smaller gaps between different disease stages, thereby increasing precision and power. In addition, our survival analysis enabled us to calculate patient-specific time to event, which is not possible with a Markov model, and uses individual patient characteristics, therefore providing the possibility to determine whether these characteristics modify treatment effect.

The present study has some limitations. Firstly, our resolution is limited by the number of defined disease stages used to develop the model. Larger numbers of patients, in particular those with low eGFR and low albuminuria, will increase the accuracy and precision of the model. Secondly, our model was developed for RAS intervention but is, in principle, applicable to other drug classes; however, this requires validation. Thirdly, the model does not consider improvement of disease stages during simulation. Instead of taking improvement into account, our model assumes patients remain at the same disease stage until worsening is observed; however, the model records time until worsening in albuminuria or eGFR stages occurs and takes it into account in the survival analysis. We used this approach to make sure that the model did not include unfeasibly large numbers of possible transition directions, but acknowledge that this may have led to an underestimation of the treatment effect. Only a small proportion of the patients in the observed data, however, experienced improvements without subsequently worsening beyond their starting disease stage during follow-up, suggesting that this bias probably had little impact on the main results. Fourthly, while showing good consistency with absolute event rates, the relative deviance between predicted and observed ESRD is high for trials with low event rates. The goodness-of-fit for such trials is therefore more difficult to interpret. We also acknowledge that our internal validation did not produce a perfect fit of the observed data, which may have slightly affected the accuracy of the calculated treatment effect. Lastly, our model simulates disease progression for decades in some individual patients, beyond the follow-up duration of the included trials and thereby limits the accuracy of the prediction estimates.

In conclusion, we have built a model that is capable of simulating the entire course of DKD. Using this model, we showed that early intervention with RAS inhibitors is more beneficial in delaying ESRD than intervention in later stages.

Acknowledgements

H. J. L. H. is supported by a grant from the Netherlands Organization for Scientific Research.

Conflict of Interest

D. D. Z. is a consultant for and receives honoraria (to his employer) from AbbVie, Astellas, AstraZeneca, Chemocentryx,

J&J, Hemocue, Novartis, Reata, Takeda and Vitae. H. J. L. H. is a consultant for and receives honoraria (to his employer) from AbbVie, Astellas, Astra-Zeneca, Janssen, Reata Pharmaceuticals, and ZS-Pharma. B. S., T. K., S. M., P. V., H. H. P., G. R. and J. D. have nothing to declare.

Each author contributed substantially to the design of the study, interpretation of the data, as well as drafting and revising the manuscript. All authors gave final approval to the manuscript. B. S., T. K. and S. M. performed the analysis in this study.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Definitions of early, intermediate and advanced stage of diabetic kidney disease.

Table S1. Age-adjusted mortality rates used in the model.

Table S2. Characteristics of the clinical trials used for validation.

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