Integrating biomarkers to predict renal and cardiovascular drug efficacy
Schievink, Bauke

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Chapter 2

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

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Abstract

**Aims:** Intervening in the renin-angiotensin-system (RAS) early in the course of diabetic kidney disease (DKD) may be more beneficial in delaying end-stage-renal-disease (ESRD) than late intervention. However, prospective randomized controlled trial data are lacking. We developed and validated a model to simulate progression of DKD from early onset until ESRD, and assessed the effect of RAS intervention in early, intermediate and advanced stages of DKD.

**Methods:** We used data from 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 eGFR. Using survival analyses we assessed the effect of RAS intervention on delaying ESRD in early (eGFR >60 ml/min/1.73m² and albumin:creatinine ratio (ACR) <30 mg/g), intermediate (eGFR 30-60 ml/min/1.73m² or ACR 30-300 mg/g) and advanced (eGFR <30 ml/min/1.73m² 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 being 60 years on average and receiving placebo, 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. Benefit of early RAS intervention was more pronounced in younger patients. For example for patients aged 45 years on average, 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.
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, there are no prospective randomized controlled trials that have tested the effect of early RAS intervention on hard renal endpoints, because progression of DKD to end-stage renal disease (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 hyperglycemic 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 disease glomerular filtration rate declines due to 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 glomerular filtration rate (GFR) [4]. Past clinical trials have been conducted at different stages of DKD [5-11]. These trials recorded transition in eGFR or albuminuria categories and determined the effect of RAS intervention using transitions in albuminuria stages (i.e. micro or macroalbuminuria) or ESRD as endpoint. One way to determine the treatment effect of RAS intervention early in the course of DKD would be to connect data from these past clinical trials in order 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 as to whether treatment initiation in early stages of DKD is more beneficial in delaying ESRD than initiation in advanced stages.

The first aim of our study was therefore to develop and validate a statistical model to simulate progression of DKD from early onset to ESRD, by connecting data from past 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. Since the incidence of type 2 diabetes is increasing
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strikingly among individuals aged below 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.

Methods

*Databases and data selection*

We used data from the following completed clinical trials: BErgamo NEphrologic Diabetes Complications Trial (BENEDICT), Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study (IRMA-2), Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) which included patients with type 2 diabetes. Design and results have been published elsewhere [5-8]. In all trials patients gave informed consent. Our 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 (ACE-I/ARB). In BENEDICT, 1209 hypertensive patients with normoalbuminuria (<20 μg/min urinary albumin excretion) and serum creatinine <= 1.5mg/dL were randomly allocated to treatment with trandolapril, verapamil, their combination or placebo. Primary outcome was transition from normo- to microalbuminuria. The median follow-up time was 3.6 years. In IRMA-2, 590 hypertensive patients with microalbuminuria (20 to 200 μg/min urinary albumin excretion) and serum creatinine levels <1.5 mg/dL (men) and <1.1mg/dL (women) were enrolled. Patients were randomly allocated to either placebo or irbesartan (150 or 300 mg) treatment. Primary outcome was the transition to macroalbuminuria. The median follow-up time was 2.0 years. RENAAL and IDNT both enrolled patients (RENAAL: 1513 patients, IDNT: 1715 patients) with type 2 diabetes and macroalbuminuria (>300mg/g albumin:creatinine ratio in RENAAL and >900mg/24h proteinuria in IDNT), with serum creatinine levels between 1.0 and 3.0 mg/dL. Patients were randomly allocated to losartan or placebo in RENAAL, or irbesartan, amlodipine or placebo in IDNT. Primary outcome was time to first event of a composite renal endpoint including doubling of serum creatinine, ESRD or death.
IDNT included serum creatinine >6mg/dL 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 modeling 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: 0-15, >15-30, >30-150, >300-1000 and >1000 mg/g albumin:creatinine ratio. EGFR strata were: >90, 90- >60, 60- >30, 30- >15 and <15 ml/min/1.73m². Due to low numbers in some strata, all patients with eGFR below 15ml/min/1.73m² were merged in one group irrespective of their albuminuria and patients with albuminuria 0-30mg/g and 15-30ml min/1.73m² eGFR were merged. 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 was used to determine 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 with at least a 30% increase in albuminuria or confirmed by the next follow-up measurement.

Modeling of diabetic kidney disease 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 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 AIC. The multinomial regression models contained calculated time-to-event as determined in step 1 as an additional covariate. For model building purposes nonparametric data were log transformed and log values were used in further analyses. Statistical analysis were conducted using R version
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3.1.0 (R Project for Statistical Computing, www.r-project.org) with a two sided P value <0.05 considered significant.

*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 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 definition of early, intermediate and advanced stage of disease is based on the KDIGO guidelines [16] and displayed in Supplemental Figure S1. Early DKD was defined as eGFR>60 ml/min/1.73m² and albumin:creatinine ratio (ACR) <30 mg/g, intermediate DKD defined as eGFR 30-60 ml/min/1.73m² or ACR 30-300 mg/g, and advanced DKD as eGFR <30 ml/min/1.73m² or ACR >300 mg/g. Age categories ranged from 25 to 65 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 with at least 30% reduction in albuminuria after 6 months of treatment) and 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 older than 65 years, on top of the mortality probabilities observed in the dataset. This takes into account that as patients age their probability to die increases. These calculations were based on age- and sex-adjusted mortality rates for patients with type 2 diabetes as previously reported (Supplementary Table S1) [17].

Model validation
Internal and external validity was assessed by comparing the proportion of events derived from our model with 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 of 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 of which no individual patient data was available. For these trials we used aggregated trial level data. We used this approach for ADVANCE, ACCORD, TREAT and ORIENT. The results and design of these trials have been published elsewhere [9,21-23], and are summarized in Supplementary Table S2.

Results

Characteristics of patients included in the dataset
An overview of the baseline characteristics of included trials are presented in Table 1. In all included datasets, participants were diagnosed with type 2 diabetes were and on average around 60 years of age. Albuminuria levels were in the normoalbuminuric range (N=1209), microalbuminuric range (N=590) and macroalbuminuric range (N=3228). Renal function (eGFR) ranged from normal (>90ml/min/1.73m²) to severely impaired (15-30 ml/min/1.73m²). 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 eGFR <45/ml/min/1.73m² and albumin:creatinine ratio
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>300mg/g at baseline. For modeling purposes, we used all available transitions that patients experienced during follow-up, resulting in a median of 551 transitions (interquartile range: 261-1122) for each disease stage (Supplemental Figure S1).

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

<table>
<thead>
<tr>
<th></th>
<th>BENEDICT N=1209</th>
<th>IRMA-2 N=590</th>
<th>RENAAAL N=1513</th>
<th>IDNT N=1715</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.9 (8.1)</td>
<td>58.0 (8.2)</td>
<td>60.2 (7.4)</td>
<td>58.9 (7.8)</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>53%</td>
<td>68%</td>
<td>63%</td>
<td>66%</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>150.8 (14.2)</td>
<td>153.1 (14.4)</td>
<td>152.5 (19.3)</td>
<td>159.1 (19.7)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>87.5 (7.6)</td>
<td>90.1 (9.2)</td>
<td>82.4 (10.5)</td>
<td>86.9 (11.0)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>81.2 (15.0)</td>
<td>72.2 (13.8)</td>
<td>39.8 (12.3)</td>
<td>47.3 (17.6)</td>
</tr>
<tr>
<td>Albuminuria (mg/g)</td>
<td>5.9 [4.0 – 9.9]</td>
<td>72.55 [54.0 – 97.3]</td>
<td>1246 [558 - 2545]</td>
<td>1500 [780 - 2757]</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>5.8 (1.4)</td>
<td>6.9 (1.7)</td>
<td>8.5 (1.6)</td>
<td>8.1 (1.7)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.3 (0.4)</td>
<td>4.7 (0.5)</td>
<td>4.6 (0.5)</td>
<td>4.6 (0.5)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>162.8 (36.1)</td>
<td>140.0 (40.3)</td>
<td>142.2 (45.8)</td>
<td>142.7 (46.5)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>46.9 (12.1)</td>
<td>43.6 (11.6)</td>
<td>45.1 (15.1)</td>
<td>42.4 (14.1)</td>
</tr>
</tbody>
</table>

Baseline characteristics of all the clinical trials that were included in the model building. Numbers represent mean (sd) unless otherwise indicated. Albuminuria (albumin:creatinine ratio) is calculated as median + interquartile range.

**Model validation**

The predicted survival probabilities (with ESRD as endpoint and death as censoring event) corresponded well to the observed probabilities seen in BENEDICT, IRMA-2, RENAAAL and IDNT, with predictions being within the 95% confidence intervals of the observed probabilities for almost all years of follow-up with the only exception being the RENAAAL trial after 2 years follow-up (Figure 1). We subsequently validated our model using past clinical trials not included in our training database. The predictions from our DKD model showed very good agreement with the observed probabilities of ESRD events in each treatment arm in each trial (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 was available compared to trials with aggregated trial level data.
Figure 1. Kaplan Meier plot showing the observed versus simulated renal events (with death as censoring event) over time in the BENDICT, IRMA-2, RENAAL and IDNT studies. For BENEDICT and IRMA-2 a black horizontal line is drawn because no ESRD events were observed in the trials. For RENAAL and IDNT the 95% confidence intervals are the shaded areas for placebo (red) and treatment (blue).

Effect of RAS intervention 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 stage of disease respectively, being on average 60 years of age (the average age in most type 2
Early RAS intervention is more beneficial than late intervention in delaying ESRD (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 early stages of DKD became more apparent when treatment is initiated at younger age (Table 2). For example, among patients with an average 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).

![Figure 2](image_url)

**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.
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). For patients who responded to RAS intervention aged 60 years, treatment in early stages of disease delayed the predicted time to ESRD by 11.8 years and 13.3 years compared to 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 to non-responders and placebo (both P<0.001).

Discussion

We have developed and validated a model for patients with type 2 diabetes that can accurately simulate DKD progression and assess long-term treatment effects of RAS inhibition from the earliest stages of disease until ESRD. 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 to 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 approximately 21 years, while RAS intervention delayed this to approximately 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 United Kingdom 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,
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suggesting that progression from normoalbuminuria to ESRD takes approximately three decades [24]. 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 normoalbuminuric population in our study had hypertension and a mean diabetes duration of approximately 8 years. An older, retrospective study in patients with type 1 diabetes reported that the onset of renal failure takes on average 21.6 years from diagnosis [25].

Table 2. Treatment effect of RAS intervention on delaying ESRD

<table>
<thead>
<tr>
<th>Age at which RAS treatment is initiated</th>
<th>Delay of ESRD (years) compared to placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
</tr>
<tr>
<td>35 years</td>
<td>7.4</td>
</tr>
<tr>
<td>40 years</td>
<td>6.9</td>
</tr>
<tr>
<td>45 years</td>
<td>5.9</td>
</tr>
<tr>
<td>50 years</td>
<td>5.7</td>
</tr>
<tr>
<td>55 years</td>
<td>5.1</td>
</tr>
<tr>
<td>60 years</td>
<td>4.2</td>
</tr>
<tr>
<td>65 years</td>
<td>3.5</td>
</tr>
</tbody>
</table>

Numbers indicate years that treatment with RAS inhibition delays ESRD compared to placebo. Results are displayed for different age groups, ranging from on average 35 years to 65 years, and for treatment initiation in early, intermediate or late stages of DKD.

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 by the time they would have reached ESRD, and therefore death likely 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 [26,27], with substantially larger risks for death instead of ESRD in populations with less severe kidney disease [28,29]. 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.
Figure 3. Difference in median time to ESRD for treatment versus placebo for intervention starting in early, intermediate or advanced stage of DKD. The presented patient populations are on average 60 and 45 years old. The proportion of survival is presented on the Y axis and the time in years is presented on the X axis.

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 incidence of type 2 diabetes is increasing dramatically at ages <40 years [30]. Likewise, the incidence of type 2 diabetes is markedly increasing in pediatric and adolescent populations [14,15,31]. We have shown that the benefits of RAS intervention in early DKD stages becomes more apparent at 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 takes
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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.

![Cumulative survival curves for different treatment response groups at 60 and 45 years](image)

**Figure 4.** This figure is similar to Figure 3. In this analysis we assessed the effect of treatment response (Resp; defined as a regression in albuminuria stage accompanied with at least 30% reduction in albuminuria after 6 months of treatment) on time to ESRD.

To our knowledge this is the first study that investigated the entire course of proteinuric DKD and compared 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 to intervention in advanced disease stages [32]. However, our 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.

Our study has 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. This however requires validation. Thirdly, the model does not consider improvement of disease stages during simulation. Instead of taking improvement into account, our model assumes patients stay in 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 our model does not include unfeasibly large numbers of possible transition directions.

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.
Supplement

**Supplemental Figure S1.** Overview of the different disease stages characterized in the model, including definitions for early, intermediate and advanced stages of DKD.

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

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Female</th>
<th>Mortality rate per year</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>65</td>
<td>0.93</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>0.84</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>0.71</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>0.53</td>
<td>0.42</td>
<td></td>
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<tr>
<td>85</td>
<td>0.32</td>
<td>0.22</td>
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</table>
**Supplementary Table S2.** Characteristics of the clinical trials used for validation

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Inclusion criteria</th>
<th>N patients</th>
<th>Treatment allocation</th>
<th>Primary endpoint definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>type 2 diabetes, HbA1c&gt;7.5mmol/L, cardiovascular risk factors</td>
<td>10251</td>
<td>intensive HbA1c targeting (&lt;6.0mmol/L) vs. conventional therapy</td>
<td>first occurrence of nonfatal myocardial infarction or nonfatal stroke or death from cardiovascular causes</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>type 2 diabetes, history or risk of cardiovascular disease</td>
<td>11140</td>
<td>perindopril and indapamide or matching placebo, and intensive HbA1c targeting (&lt;6.5mmol/L) vs. conventional therapy</td>
<td>composite of macrovascular events and a composite of microvascular events</td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>type 2 diabetes and chronic kidney disease or cardiovascular disease</td>
<td>8561</td>
<td>aliskiren vs. placebo on top of RAS treatment</td>
<td>first occurrence of a cardiovascular or renal event</td>
</tr>
<tr>
<td>LIFE</td>
<td>type 2 diabetes, previously untreated or treated stage II–III hypertension with ECG left ventricular hypertrophy</td>
<td>1195*</td>
<td>losartan vs. atenolol</td>
<td>cardiovascular morbidity and mortality</td>
</tr>
<tr>
<td>NEPHRON-D</td>
<td>type 2 diabetes and nephropathy</td>
<td>1448</td>
<td>losartan and lisinopril or matching placebo</td>
<td>decline in eGFR (&gt;30ml/min/1.73m² or &gt;50%), ESRD or death.</td>
</tr>
<tr>
<td>ORIENT</td>
<td>type 2 diabetes and nephropathy</td>
<td>577</td>
<td>olmesartan vs. placebo</td>
<td>first occurrence of doubling of serum creatinine, ESRD or death</td>
</tr>
<tr>
<td>TREAT</td>
<td>type 2 diabetes and chronic kidney disease</td>
<td>4038</td>
<td>darbepoetin alfa vs. placebo</td>
<td>first occurrence of cardiovascular event, ESRD or death</td>
</tr>
</tbody>
</table>

* The overall LIFE population consisted of 9194 participants of whom 1195 had diabetes. Only participants with diabetes were used for validation purposes.
Early RAS intervention is more beneficial than late intervention in delaying ESRD

References


