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ORIGINAL ARTICLE

Individualized prediction of the effect of angiotensin receptor blockade on renal and cardiovascular outcomes in patients with diabetic nephropathy

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Aims: To predict individualized treatment effects of angiotensin receptor blockers (ARBs) on cardiovascular and renal complications in order to help clinicians and patients assess the benefit of treatment (or adherence) and estimate remaining disease risk.

Materials and methods: In patients with diabetic nephropathy, the 3-year treatment effect of ARBs was predicted in terms of absolute risk reduction (ARR) for end-stage renal disease (ESRD) and cardiovascular disease (CVD; i.e. myocardial infarction, stroke, hospitalization for heart failure) and all-cause mortality. Competing-risk-adjusted proportional hazard models were developed based on the Irbesartan Diabetic Nephropathy Trial (IDNT) and externally validated in the Reduction of Endpoints NIDDM with Angiotensin II Antagonist Losartan (RENAAL) trial.

Results: Predictors included in the model were age, sex, smoking sex, systolic blood pressure, urinary albumin/creatinine ratio, estimated glomerular filtration rate, albumin and phosphorus. The median predicted 3-year risk without treatment was 6.0% for ESRD and 28.0% for CVD and mortality. The median [interquartile range (IQR)] predicted 3-year ARR was 1.2 (0.4-3.1)% for ESRD and 2.2 (1.8-2.6)% for CVD and mortality, resulting in a combined ARR of 3.4 (2.4-5.5)%. The remaining disease risk was 4.7 (IQR 1.7-12.8)% for ESRD and 25.8% (IQR 20.3-31.9)% for CVD and mortality.

Conclusions: The combined effects of ARBs on ESRD and CVD and mortality in patients with diabetic nephropathy vary considerably between patients. A substantial proportion of patients remain at high risk for both outcomes despite ARB treatment.

KEYWORDS

cardiovascular disease, end-stage renal disease, nephropathy, predictors, type 2 diabetes

1 | INTRODUCTION

Patients with type 2 diabetes and nephropathy are at risk of end-stage renal disease (ESRD) and cardiovascular disease (CVD). To delay progression of renal disease and reduce cardiovascular risk, optimum patient management is required. Angiotensin receptor blockers (ARBs) are recommended because they reduce the relative 3-year risk of progression of nephropathy on average by 33% [95% confidence interval (CI) 13 to 48] and the risk of cardiovascular mortality by 4% (95% CI −1 to 10) in patients with and without type 2 diabetes.[1,2] However, the average treatment effect reported by trials does not directly translate to the individual patient because treatment effect may vary across patients. Predicting individualized treatment effects can inform clinicians about treatment benefit and residual risk.[3–5] This may help clinicians and patients to assess the benefit of treatment (or adherence) and to estimate remaining disease risk. Estimating residual disease risk helps to identify "high-risk" patients in whom additional treatment targets need to be considered in order to reduce renal and cardiovascular risk.

Previous prediction models in patients with chronic kidney disease have mainly focused on predicting absolute risk for renal adverse outcomes;[6–8] however, morbidity and mortality in patients with diabetic nephropathy frequently have cardiovascular causes,

which need to be addressed when assessing future risk. Moreover, reducing cardiovascular risk is an important treatment target when starting ARB treatment.

The aim of the present study was to develop a multivariable risk model to predict clinically relevant renal and cardiovascular outcomes and determine absolute treatment effect of ARBs in individual patients with type 2 diabetes and nephropathy.

2 | MATERIALS AND METHODS

Data from the Irbesartan Diabetic Nephropathy Trial (IDNT) and the Reduction of Endpoints NIDDM with Angiotensin II Antagonist Losartan (RENAAL) trial were used. Both trials showed the renoprotective effects of ARB treatment in participants with type 2 diabetes and nephropathy. The design, rationale and outcomes of the IDNT and RENAAL study have been described elsewhere.[1,9]

Briefly, both trials studied the renal protective effect of ARBs (irbesartan 300 mg daily in the IDNT and losartan 50-100 mg daily in the RENAAL study) on the composite endpoint of doubling of serum creatinine, ESRD and death in participants aged between 30 and 70 years with type 2 diabetes and nephropathy. ESRD was defined as the initiation of dialysis or renal transplantation. The IDNT also included serum creatinine >530 μmol/L in this definition. The IDNT included 1715 participants who were randomized to receive either irbesartan, amlodipine or placebo. For the purpose of the present study the amlodipine arm was excluded. Eligible participants needed to have serum creatinine levels of 106-265 μmol/L (≥88 μmol/L for women), proteinuria (24-hour protein excretion ≥900 mg) and a history of hypertension (≥135/85 mm Hg untreated or receiving antihypertensive treatment). After a mean follow-up of 2.6 years the hazard ratio for the occurrence of the primary composite endpoint was 0.81 (95% CI 0.67-0.99) favouring irbesartan. The RENAAL study enrolled 1513 participants randomized to receive either losartan or placebo. Inclusion criteria were serum creatinine levels of ≥133-265 μmol/L (≥115 μmol/L for women) and proteinuria (urinary albumin:creatinine ratio ≥300 mg/g or 24-hour urine protein >500 mg). Participants could either be hypertensive or normotensive. After a mean follow-up time of 3.4 years the hazard ratio for the occurrence of the composite endpoint was 0.84 (95% CI 0.72-0.98) favouring losartan.

2.1 | Model derivation

Cox proportional hazard models were developed in the IDNT for the following outcomes of interest: (1) ESRD (need for long-term dialysis or renal replacement therapy); (2) CVD (non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure or death from CVD) and non-cardiovascular mortality. The outcomes were modelled in a competing risk framework as the time to first event, to enable additivity of the predicted absolute risks.[10] Competing risk analysis prevents overestimation of predicted risk by mutually accounting for the events of interest, as well as events preventing them from happening (i.e. fatal myocardial infarction preventing ESRD occurring), but can also be used to estimate time to first event. Three participants who developed a renal and a cardiovascular outcome on the same day were assumed to have the latter occurring first (i.e. occurrence of a myocardial infarction preceding ESRD). Models were developed for the risk and treatment effect prediction at 3 years. To minimize over-fitting, only well-known risk factors for ESRD and CVD were considered candidate predictors.[6,8,11–13] Candidate predictors included age, sex, smoking within the previous year, systolic blood pressure, urinary albumin/creatinine ratio (ACR), estimated glomerular filtration rate (eGFR) using the CKD-EPI equation, glycated haemoglobin (HbA1c), albumin, haemoglobin, phosphorus and calcium. These measures are usually available in patients with chronic kidney disease or can easily be obtained. Heterogeneity of treatment effect across baseline risk for disease was assessed by incorporating an interaction term between baseline risk and treatment in the renal and cardiovascular model separately.[14] Since effect modification of treatment by specific risk factors has not been demonstrated, further interaction terms were not evaluated.[15] Thus, a constant relative treatment effect was used for further analyses.

Data on one or more covariates were missing in 163 participants (14.2%) in the IDNT and were imputed using bootstrapping and predictive mean matching (aregImpute-algorithm in R, Hmisc-package),[16] assuming that these values were missing at random: ACR (n = 60), eGFR (n = 7), HbA1c (n = 107), albumin (n = 3), haemoglobin (n = 6), phosphorus (n = 4) and calcium (n = 3). To reduce the effect of outliers, continuous predictors were truncated at the 1st and 99th percentile. Continuous predictors that were not linearly related to the outcome were transformed if necessary to optimize model fit. The increase in model likelihood ratio after transformation, while taking the extra degrees of freedom into account, was evaluated by Akaike's Information Criterion (AIC).[17] This resulted in log-transformation of ACR.

To develop a risk score that adequately predicted renal and cardiovascular outcomes, selection of predictors was based on stepwise backward selection on the basis of AIC for the combined outcome. The final model was then fitted to predict the 3-year risks for each outcome separately. To reduce optimism, coefficients were penalized by a bootstrap-based uniform shrinkage factor.[17] Proportional hazard assumptions were evaluated using Schoenfeld residuals. Visual inspection showed no non-proportionality.

2.2 | Model validation

The final models were validated using data from the RENAAL trial by applying the fixed baseline hazard and coefficients. Missing data on covariates of 70 participants (4.6%) were single-imputed as described above. The discriminative ability, the extent to which a model can correctly distinguish between those who had the event and those who did not have the event, was quantified by the C-statistic adapted for competing risks.[18] Calibration, which describes the agreement of predicted probabilities and the observed outcomes, was demonstrated by calibration plots. The calibration plots were based on sextiles of predicted risk to provide a sufficient number of patients in each group.

2.3 | Risk stratification

The individualized absolute risk reductions (iARRs) were calculated for all patients in the combined data from the IDNT and the RENAAL study by calculating the difference between baseline risk for both outcomes and residual risk after ARB treatment. The predicted risks for the separate outcomes were summed and truncated at 100% to provide a total individual absolute risk. The individual number needed to treat (iNNT) was calculated as: 1/iARR.

A calculation sheet was developed for graphical presentation of the predicted iARR and iNNT for individual patients.

2.4 | Sensitivity analyses

A separate model was developed including only ARB treatment and ACR, a known strong predictor for ESRD.[13] The C-statistic of this simpler model was compared with the full model to evaluate if addition of the predictors in the final model improved model performance.[19]

Finally, another model was developed in which heart failure was excluded from the CVD and mortality outcome to evaluate if this would improve model performance. Hospitalization for heart failure occurred in 132 participants in the RENAAL trial and in 215 participants in the IDNT.

3 | RESULTS

3.1 | Baseline characteristics

Participants in the IDNT and RENAAL trial had a median age of 60 and 61 years, respectively (Table 1). For participants in the IDNT the median (IQR) ACR was 173 (90-317) mg/mmol eGFR was 44 (32-58) mL/min/1.73 m^2 and HbA1c was 7.9 (6.9-9.1)%. In the RENAAL study, the median (IQR) ACR was 141 (63-288) mg/mmol eGFR was 38 (29-47) mL/min/1.73 m^2 and HbA1c was 8.2 (7.4-9.5)%. During the 2468 person-years of follow-up in the IDNT, 182 renal events and 294 cardiovascular events occurred, including 98 cardiovascular deaths; 180 participants died from any cause. In the RENAAL study, during 3550 person-years of follow-up, 341 renal events and 436 cardiovascular events occurred, including 169 cardiovascular deaths; 313 participants died from any cause.

TABLE 1 Baseline characteristics of participants in the IDNT and RENAAL study

	IDNT *n* = 1147	RENAAL *n* = 1513
Age, years	60 (54-65)	61 (55-66)
Male	781 (68)	956 (63)
Race		
White	852 (74)	735 (49)
Black	141 (12)	230 (15)
Hispanic	54 (5)	277 (18)
Asian	51 (4)	252 (17)
Other	49 (4)	19 (1)
Smoking	201 (18)	273 (18)
Medication use		
α-blocker	103 (9)	364 (24)
β-blocker	215 (19)	277 (18)
Angiotensin-converting enzyme	512 (45)	737 (49)
Angiotensin II antagonist	33 (3)	49 (3)
Diuretic	546 (48)	878 (58)
Calcium-channel antagonist	450 (39)	1078 (71)
Body mass index, kg/m^2	30 (27-34)	29 (25-33)
Systolic blood pressure, mm Hg	159 (144-171)	151 (140-165)
Diastolic blood pressure, mm Hg	87 (80-94)	82 (75-90)
ACR, mg/g	1527 (800-2807)	1246 (558-2545)
Creatinine, mg/dL	1.6 (1.3-2.0)	1.8 (1.5-2.2)
eGFR, mL/min/1.73 m^2)	44 (32-58)	38 (29-47)
Albumin, g/dL	3.9 (3.6-4.1)	3.8 (3.5-4.1)
Phosphorus, mg/mL	9.2 (8.8-9.5)	9.4 (9.1-9.7)
Calcium, mg/dL	3.8 (3.4-4.2)	3.9 (3.5-4.3)
Total cholesterol, mg/dL	220 (188-259)	220 (189-260)
Low density lipoprotein, mg/dL	139 (112-170)	137 (111-167)
High density lipoprotein, mg/dL	40 (33-49)	42 (35-53)
Haemoglobin, mg/dL	13.1 (11.7-14.4)	12.4 (11.2-13.8)
HbA1c, %	7.9 (6.9-9.1)	8.2 (7.4-9.5)

Values are presented as median (interquartile range) or count (percentage).

3.2 | Model derivation and validation

During backward selection of all potential predictors, smoking, HbA1c, haemoglobin and calcium were removed from the model. The final model included age, sex, systolic blood pressure, ACR, eGFR, albumin and phosphorus. No heterogeneity of treatment effect was found (interaction term baseline risk × treatment $p > .05$), indicating that the relative treatment effect was not different for participants with low or high predicted risk.

Discrimination of the final model for predicting 3-year ESRD risk was excellent (C-statistic external validation 0.80 (95% CI 0.78-0.83; Table 2). The discriminative ability for predicting CVD and mortality was moderate (C-statistic external validation 0.61, 95% CI 0.59-0.64). Calibration was well balanced for the observed and predicted 3-year risks of both outcomes combined but underestimated participants with high predicted risks for renal complications (Figure 1).

3.3 | Risk prediction and absolute risk reduction of renal and cardiovascular events

The computational formulae for calculating predicted absolute risks and risk reductions are provided in Table S1, Supporting Information. The participants in the IDNT and the RENAAL study had a high median (IQR) predicted 3-year risk of 34.5 (26.1-49.6)% for the adverse outcomes combined, including 6.0 (2.1-15.9)% for ESRD and 28.0 (22.1-34.5)% for CVD and mortality. There was a wide distribution for the predicted risk of ESRD, with 19.7% of the participants having a predicted 3-year risk higher than 20% (Figure 2). The predicted 3-year risk for CVD and mortality was high (>20%) for 82.7% of the participants.

TABLE 2 Hazard ratios and C-index of prediction models

	Model for ESRD		Model for CVD and mortality	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Log urinary albumin/creatinine, mg/g	3.34 (2.66-4.18)	2.04 (1.50-278)	1.38 (1.20-1.58)	1.12 (0.95-1.32)
Age, per year		0.98 (0.96-1.01)		1.04 (1.02-1.05)
Male gender		1.58 (1.07-2.34)		1.14 (0.92-1.42)
Systolic blood pressure, per 10 mm Hg		1.01 (0.92-1.11)		1.04 (0.98-1.09)
eGFR, per mL/min/1.73m^2		0.93 (0.92-0.95)		1.00 (0.99-1.00)
Albumin, per g/dL		0.64 (0.38-1.06)		0.62 (0.46-0.83)
Phosphorus, per mg/mL		1.01 (0.77-1.33)		1.18 (1.00-1.41)
Irbesartan treatment	0.72 (0.50-1.02)	0.79 (0.56-1.12)	0.95 (0.76-1.18)	0.91 (0.75-1.11)
C-statistic (internal validation)	0.77 (0.73-0.81)	0.85 (0.83-0.88)	0.60 (0.57-0.63)	0.64 (0.61-0.67)
C-statistic (external validation)	0.76 (0.73-0.79)	0.80 (0.78-0.83)	0.56 (0.53-0.59)	0.61 (0.59-0.64)

HR, hazard ratio.

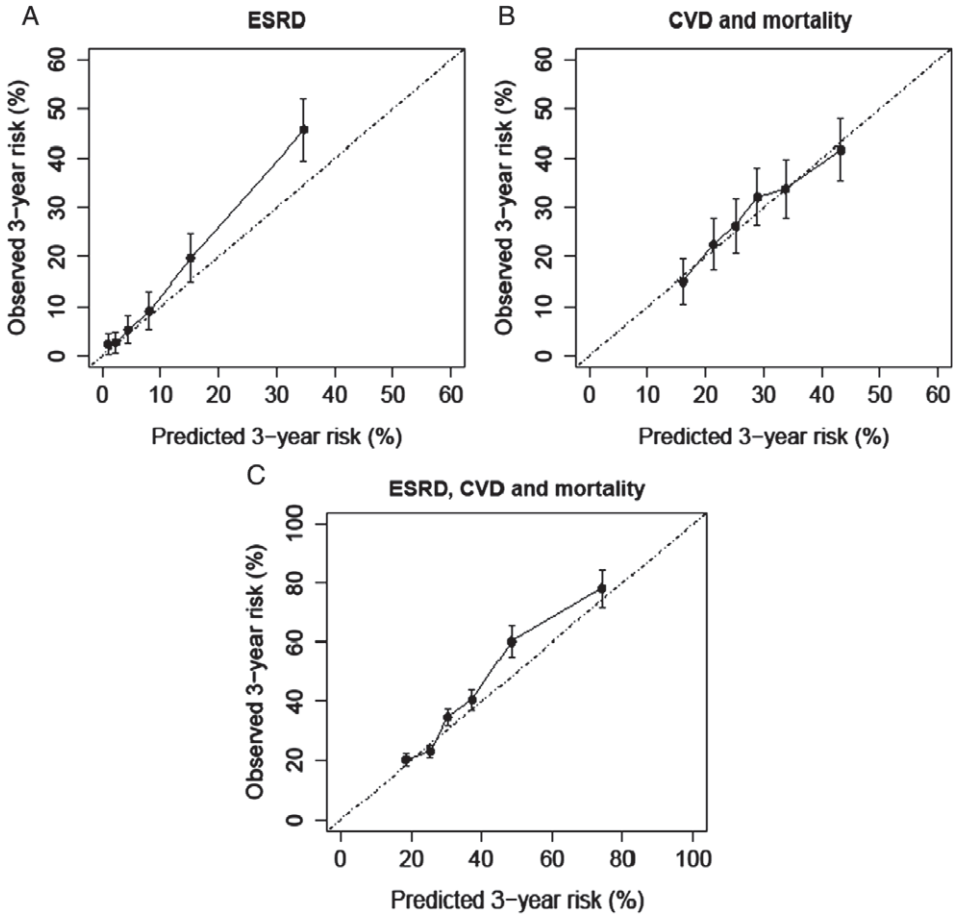

FIGURE 1 Calibration plots of predicted and observed risk for ESRD (A), CVD and mortality (B) and combined (C) in sextiles of predicted risk in the RENAAL study population.

The predicted 3-year treatment effect for ESRD was small on average but with a wide range, with some patients having a much larger treatment effect than others [median (IQR) ARR 1.2%; 0.4-3.1)%]. The absolute treatment effect for CVD and mortality on the other hand was almost twice as large on average, but varied much less across participants [median (IQR) ARR 2.2 (1.8-2.6)%]. The median (IQR) combined treatment effect was 3.4 (2.4-5.5)%, resulting in a residual risk of 4.7 (1.7-12.8)% for ESRD and 25.8 (20.3-31.9)% for CVD and mortality.

Participants with a 3-year iARR >8% were older, had higher systolic blood pressure, higher albuminuria levels and lower eGFR levels compared with participants with a iARR <2% (Table S2, Supporting Information).

To enhance the applicability of the prediction model in practice, an interactive calculation spreadsheet was developed, demonstrating a patient at high risk and a patient at low risk (Figure 3). As illustrated, in a 65-year-old man with an ACR of 450 mg/mmol treatment with ARB resulted in a predicted 3-year ARR for ESRD of 4% and a risk reduction of 2% for CVD and mortality, resulting in a 3-year iNNT of 17 for this patient (Figure 3A). This patient's predicted 3-year residual risk was 15% for ESRD and 27% for CVD and mortality. In a 45-year-old woman with an ACR of 150 mg/mmol the

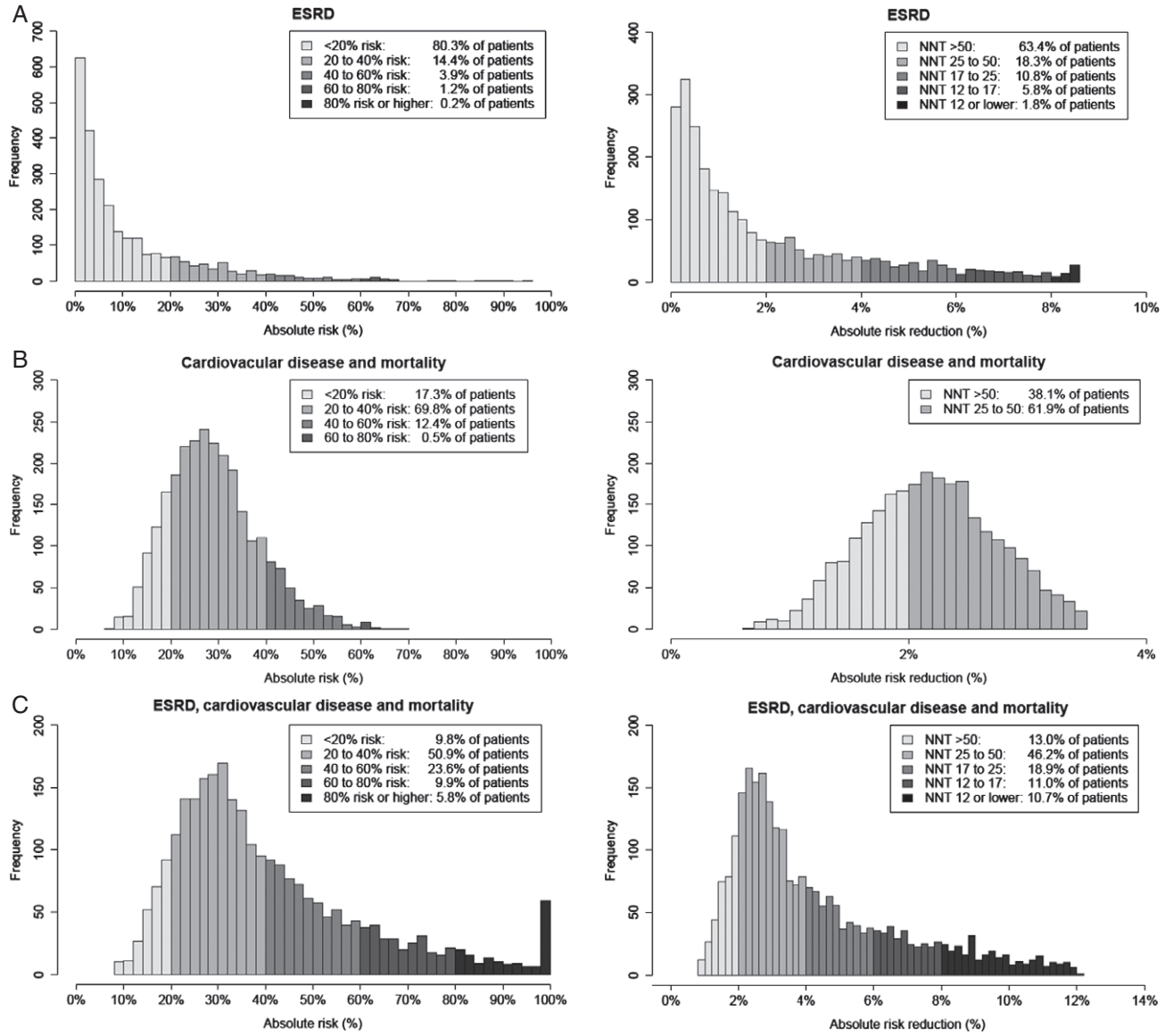

FIGURE 2 Distribution of the predicted 3-year absolute risk and absolute risk reduction for (A) ESRD, (B) CVD and mortality and (C) combined among all participants in the IDNT and RENAAL trials.

predicted 3-year ARR with ARB was 2% for the adverse events combined, resulting in residual risk of 4% for ESRD and 10% for CVD and mortality (Figure 3B).

3.4 | Sensitivity analyses

A separate model was developed including only ACR and ARB treatment to evaluate if addition of the predictors in the full model improved model performance. This model showed good discriminative ability for ESRD (C-statistic external validation 0.76, 95% CI 0.73-0.79), but the C-statistic was significantly lower than the C-statistic of the full model ($p < .01$; Table 2).

In an attempt to explain the moderate discrimination for prediction of CVD and mortality, heart failure was removed from the outcome, but this did not improve the discriminative ability (C-statistic external validation 0.59, 95% CI 0.57-0.63; $p = 1.00$).

4 | DISCUSSION

Patients with type 2 diabetes and nephropathy are on average at high predicted 3-year risk for ESRD, CVD and mortality but individual risk predictions range from low to very high risk. The predicted 3-year ARB treatment effect for ESRD varies considerably across patients. Patients with diabetic nephropathy remain at high risk for ESRD and CVD mortality despite ARB treatment.

With this model, doctors can inform their patient about future risk and benefit from treatment. This could potentially lead to better drug adherence because lack of belief in benefit of treatment is an important predictor of poor adherence.[20] The IDNT and RENAAL study reported a relative risk reduction for ESRD and mortality of 19% (95% CI 1-33) and 16% (95% CI 2-28) on average.[1,9] This study, however, shows that the absolute treatment effect in individual patients varies considerably. Moreover, most patients with type 2 diabetes and nephropathy remain at high residual risk for ESRD, CVD

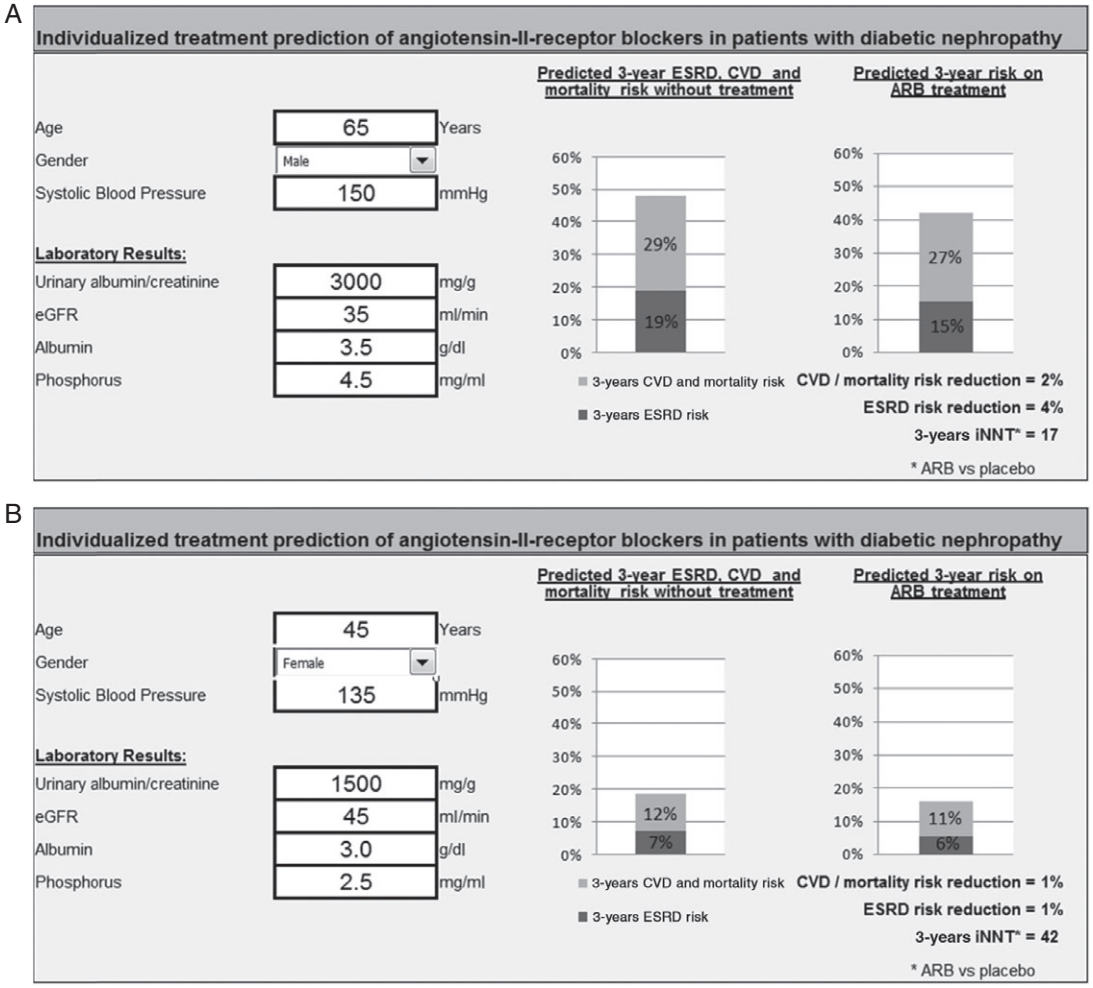

FIGURE 3 Calculation sheet examples of individualized prediction of treatment effect of ARB versus placebo in (A) a high-risk and (B) a low-risk patient with diabetic nephropathy. Predicted 3-year risk with and without treatment for (1) ESRD and (2) CVD and mortality is calculated with an interactive calculation sheet. Treatment with ARB could decrease the risk of adverse events by 6%, resulting in a iNNT of 17 similar patients to prevent one event from occurring (A). Treatment with ARB could decrease the risk of adverse events by 2%, resulting in a iNNT of 42 (B).

and mortality, despite ARB treatment. Identifying patients with a high residual risk may trigger clinicians to attain other treatment targets in patients with diabetic nephropathy such as hyperlipidemia (e.g. serum LDL cholesterol <2.5 mmol/L in people with diabetes without CVD and serum LDL cholesterol <1.8 mmol/L for people with diabetes with CVD).[21,22] Prediction of residual risk can also be valuable in patients who are adequately treated with an ARB. It gives clinicians the opportunity to discuss lifestyle changes (i.e. weight loss or smoking cessation) that could contribute to a further reduction of the disease risk.

Our prediction model showed that there was a large benefit on renal and cardiovascular complications as a majority of the patients had high predicted risk reductions. This supports the current guideline recommendation that all patients with diabetic nephropathy receive renin-angiotensin-aldosterone system inhibition although for individual patients ARB treatment benefits vary.[23] For 347 patients (13.0%) the predicted 3-year combined treatment effect for ESRD, CVD and mortality was <2% (iNNT > 50), raising the question of whether additional treatment might be more beneficial. It is probably inappropriate to conclude that these patients do not benefit from ARB treatment. Table S2, Supporting Information showed that these patients were younger and had less severe kidney disease, indicating that ARB treatment was initiated at an earlier stage of disease. A recent lifetime analysis of the IDNT and RENAAL trials showed that ARB treatment benefit, in terms of delay in ESRD, was attributed to a large extent to an initial albuminuria-lowering response and was more beneficial early in the course of diabetic kidney disease.[24] This indicates that the beneficial effects from ARB treatment may just not yet become apparent during the 3 years of follow-up. Thus, a low predicted 3-year treatment benefit in low-risk patients does not imply that they do not have considerable potential treatment benefit in the long term. The model should therefore not be used to withhold ARB treatment in patients with a low predicted treatment benefit. Whether additional treatment going beyond renin-angiotensin system inhibition further reduces ESRD risk is currently under investigation in various large outcome trials.[25–27]

Other ESRD risk scores could also be used to estimate individual residual ESRD risk. We showed that the relative effect of ARB treatment is equal to patients with low or high predicted ESRD risk. Moreover, we found that the combined effect of ARBs on ESRD, CVD and mortality was almost exclusively effected by reduction of ESRD risk. This study confirms, therefore, that absolute ARB treatment effect in

this population is proportional to ESRD risk. A recent externally validated model for predicting ESRD showed good model performance in various chronic kidney disease populations including that in the RENAAL trial.[28] However, our developed risk model is also externally validated and in addition takes competing risk by mortality into account.

Previously developed models predicting the risk of developing ESRD had a similar discriminative ability when externally validated.[6,8,28] In line with our results ACR was the strongest predictor for ESRD, emphasizing the importance as a prognostic factor for renal adverse outcomes; however, the present analyses show that prediction of the effect of ARB treatment and residual risk can still be significantly improved by the addition of other readily available clinical and laboratory variables.

The strength of the present study lies in the development of a well performing and externally validated risk model based on randomized trial data with accurate measurement of clinical variables and outcome. This model facilitates prediction of the effect of ARB treatment on ESRD and CVD and mortality combined, enabling residual risk prediction of the most prevalent adverse events that are related to high morbidity and mortality in patients with diabetic nephropathy. The model consists of clinical variables that are easily available in daily practice which enhances the clinical applicability.

Some limitations must also be taken into consideration. First, calibration showed that the model slightly underestimated the predicted ESRD risk in the high-risk patients. In clinical practice this would have little consequence because there is no debate on whether or not these patients should start treatment. Discrimination for CVD and mortality was moderate, indicating that it is difficult to distinguish between low- and high-risk patients with diabetic nephropathy. Second, as a result of statistical imprecision in patients with extreme risk factor levels, 52 patients (2.0%) had a combined predicted risk above 100%, which we truncated at this level. This means that the prediction model should be used with caution for patients with very high values of predictors. Third, CVD risk, and thereby treatment effect, could be overestimated by a maximum of 2% because of higher rates of statin prescription in current practice. In the RENAAL trial the proportion of patients with statin therapy was 26.8% while in more recent trials >65% of patients with diabetic nephropathy used statin therapy.[29,30] In patients with chronic kidney disease the lipid-lowering drug combination of simvastatin 20 mg plus ezetimibe 10 mg resulted in an ARR of 2.1% for major atherosclerotic events in 4.9 years compared with placebo, demonstrating the maximum CVD risk reduction achieved by lipid-lowering therapy in current practice.[31] The effect of improved statin therapy on predicted variation in treatment benefit and residual risk is most likely limited; however, validation of the model in a contemporary cohort is necessary to confirm this. Lastly, in the competing risk analysis, only first events were used while in reality ARB treatment may also help to prevent subsequent events. Thus, disregarding subsequent events in the present analyses may have led to an underestimation of the effect of ARB treatment; however, predicting the first events resembles clinical practice, where new treatment strategies are considered after the occurrence of any adverse event. Yet this limitation further supports that treatment effect prediction should not be used for withholding or discontinuing ARB treatment in patients with diabetic nephropathy.

In conclusion, patients with type 2 diabetes and nephropathy largely benefit from ARB treatment by reduction of renal and cardiovascular complications but treatment effect varies considerably across patients. These patients remain at high residual risk for both ESRD and cardiovascular morbidity and mortality, emphasizing the need to develop additional treatments for these patients.

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Author contributions

N.S., J.D., F.V., P.B., Y.G. and H.H. contributed substantially to the design of the study. All authors contributed to the interpretation of the data and writing the manuscript. All authors approved the final version of the manuscript.

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