Chapter 5

The Importance of Short-term Off-target Effects in Estimating the Long-term Renal and Cardiovascular Protection of Antihypertensive drugs

Paul A. Smink
Yan Miao
Marinus J.C. Eijkemans,
Stephan J.L. Bakker
Itamar Raz
Hans-Henrik Parving
Diederick E. Grobbee
Dick de Zeeuw
Hiddo J. Lambers Heerspink

JAMA Internal Medicine, submitted
Abstract

**Background:** Antihypertensive drugs are developed and registered on the basis of blood pressure lowering efficacy combined with safety. However, their long term use aims at preventing cardiovascular morbidity and mortality. It becomes increasingly clear that antihypertensive drugs have multiple off-target effects that may contribute to its efficacy on cardiovascular outcomes. The aim of the present analysis was to assess whether a multiple risk parameter response outcome (PRE)score, incorporating the drug’s short-term on-target and off-target effects, better predicts the ultimate renal/cardiovascular protection than changes in single on-target or off-target effects.

**Methods:** Data were used from individuals with type 2 diabetes and nephropathy participating in the RENAAL or IDNT trials. A PRE score was developed by multivariable Cox regression analysis in the placebo arm of RENAAL and was then applied to the baseline and month-6 measurements of the ARB treatment arm of RENAAL to predict renal or cardiovascular risk. The net risk difference at these time-points after correction for placebo effects indicated the estimated long-term drug effect. Subsequently, the obtained PRE score was validated in the IDNT trial.

**Findings:** Changes in systolic blood pressure predicted relative risk reductions significantly different from the actual observed risk reduction in RENAAL, both for renal (5.7%, vs 21.8%, respectively), and cardiovascular outcomes (3.0%, vs 9.2%, respectively). However, drug efficacy estimation with the PRE score, that incorporated many off-target effects, did not statistically significantly differ from the actual risk reduction both for renal (30.1% (95% CI 10.8-49.5) vs 21.8% [6.5-34.5]; \( P = 0.44 \)) and cardiovascular outcomes (9.4% [1.9-17.0] vs 9.2% [-7.6-23.6], \( P = 0.98 \)). Validation of the PRE score in IDNT also accurately predicted the renal (26.6% [14.3 - 38.9] vs 26.0% [6.4 - 41.5] \( P = 0.95 \)) and cardiovascular treatment effect (7.9% [1.3 - 14.5] vs 11.9% [-8.4 - 28.5] \( P = 0.67 \)).

**Interpretation:** A PRE score based on month-6 changes in on-target and off-target risk markers performs better in estimating effects of antihypertensive drugs on hard renal and cardiovascular outcomes than any change in single on-target or off-target risk markers.
The ultimate public health goal of antihypertensive therapy is to reduce the risk of cardiovascular morbidity and mortality.\textsuperscript{1} Antihypertensive drugs are, however, not registered based on their efficacy to reduce the risk of renal or cardiovascular events, but are developed and registered based on their blood pressure lowering capacity. To this end, the effect of the drug on blood pressure is established in short-term studies and is subsequently used to estimate the potential long-term renal or cardiovascular protective effect using external data. This process assumes firstly that the drug effect on blood pressure (the on-target risk factor) is directly associated with a reduction in the risk of renal or cardiovascular complications, and secondly, that the drug does not influence other risk factors (off-target risk factors) that influence renal or cardiovascular events either positively or adversely. The latter assumption has however been challenged by several studies and reviews.\textsuperscript{2-4}

The Losartan Intervention For Endpoint reduction (LIFE) trial showed that the Angiotensin Receptor Blocker (ARB) losartan exerted equal blood pressure lowering effects as the β-blocker atenolol but conferred superior cardiovascular protective effects.\textsuperscript{2} The Irbesartan Diabetic Nephropathy Trial (IDNT) showed that the ARB irbesartan conferred additional renal protective effects compared to the Calcium Channel Blocker amlodipine at equal blood pressure control.\textsuperscript{3} The Renoprotection of Optimal Anti-proteinuric Dose (ROAD) trial showed that a supramaximal dose of losartan improves the anti-albuminuric response and conferred markedly more renoprotection at similar blood pressure control compared with losartan at the maximally recommended blood pressure dose.\textsuperscript{5} These studies suggest that antihypertensive drugs, in these examples ARBs, exert additional beneficial effects on renal or cardiovascular risk factors, so called off-target effects, which contribute to the ultimate long-term effect of the drug. It has, however, also been shown that administration of antihypertensive drugs can induce changes in risk factors, such as increasing serum potassium, which in fact may increase the risk for renal/cardiovascular outcome, thus counteracting the beneficial effects of these drugs.\textsuperscript{6-8} This implies that only focusing on blood pressure, the on-target risk factor, may result in a misleading impression of the drug’s protective efficacy. We
hypothesize that knowing the short term effect of an antihypertensive on all renal/cardiovascular risk markers would allow the composition of a response score that better predicts the long term effect of such a drug on the ultimate renal/cardiovascular outcome. This may have major consequences for drug development, drug registration, and individual patient care and highlights the necessity to identify those off-target effects.

The aim of the present analysis was firstly to identify off-target effects of an ARB and assess the impact of the off-target effect on the ARB’s renal/cardiovascular efficacy. Secondly, we aimed to construct a multiple risk parameter response outcome (PRE) score based on the short-term (6 months) on-target and off-target effects of ARBs in order to estimate the effect of the drug on long term renal/cardiovascular morbidity and mortality. Thirdly, we compared the accuracy of ARB efficacy estimates based on the multiple PRE score with scores based on single on-target or off-target risk markers. Finally, we validated the accuracy of the PRE score in a separate different trial dataset and in a different antihypertensive drug class.

Methods

Study Design

Data were used from the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and IDNT trials. The rationale, study design and outcomes for these trials have been previously published and were almost similar. In brief, the overall aim of the trials was to assess the impact of an ARB on hard renal (primary endpoint) and cardiovascular outcomes (secondary endpoint) by testing losartan 100 mg/day vs placebo in the RENAAL trial and irbesartan 300 mg/day vs placebo in the IDNT trial. Individuals in the IDNT trial could also be randomly assigned to the calcium channel blocker (CCB) amlodipine 10 mg/day. Inclusion criteria for both trials were presence of type 2 diabetes, nephropathy, 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 the guidelines of the declaration of Helsinki.

Measurements
In both RENAAL and IDNT, a range of renal and cardiovascular biomarkers were measured at baseline and at 6 months intervals thereafter. We designate the term biomarker throughout this article for parameters like blood pressure, cholesterol, calcium, and phosphate, irrespective whether they are causally related to cardiovascular morbidity or mortality. All biomarkers collected at baseline and month 6 were used to create the PRE score. All measured biomarkers at month 6 were selected because we did not know a priori which biomarkers would change during ARB therapy and secondly to exclude any potential bias as a result of biomarker selection. Changes in on-target and off-target biomarkers after ARB treatment were calculated as the difference between the baseline and the 6-month value. 6-month values were chosen because most parameters were available at 6-month and ARB treatment effects were considered fully present. Because total cholesterol, hemoglobin, serum albumin, calcium, and phosphate were not measured at month 6 in the RENAAL trial, 12-month values were used.

Renal and Cardiovascular Outcomes
The primary outcome for the present analysis was defined as a composite of a confirmed doubling of serum creatinine from baseline (DSCR), serum creatinine > 6.0 mg/dL (in the IDNT trial), or end-stage renal disease (ESRD). The latter was defined as chronic dialysis or renal transplantation. The secondary cardiovascular outcome was another endpoint for the present study which was defined in both trials as the composite of myocardial infarction, stroke, hospitalization for heart failure, revascularization procedures or death related to cardiovascular disease. All renal and cardiovascular events were adjudicated by an independent blinded committee using rigorous definitions.
Model Development

A risk score was developed by estimating the relation between single or multiple biomarkers and renal or cardiovascular outcomes in the placebo group of the RENAAL trial. The single and multiple risk estimates were subsequently applied to the baseline and 6-month measurements of the ARB treatment arm to predict renal or cardiovascular risk at both time points. The difference in the estimated risk at these time-points in the placebo arm was subtracted from the difference in estimated risk in the ARB arm. In doing so we obtained single or multiple PRE scores that indicate the long-term renal or cardiovascular risk change conferred by ARB treatment, based on either changes in single or multiple biomarkers. To test the validity of this approach, the obtained single or multiple PRE scores were compared with the actual observed renal or cardiovascular outcomes of the trials. Any model shows too optimistic performance from the dataset from which it is developed. The risk response scores were therefore externally validated by developing the scores in the RENAAL trial and testing them in the IDNT trial. To further establish the external validity, the PRE score, developed in the RENAAL trial, was used to estimate the renal and cardiovascular effect of the CCB amlodipine in the IDNT trial.

Model Evaluation

The methodology to develop the PRE score assumes that the association between biomarkers at baseline and renal or cardiovascular events in the placebo group is similar as the association between single or multiple risk markers at 6-month and renal or cardiovascular events during ARB therapy. To verify the validity of this assumption, we determined whether 6 months ARB treatment modified the association between biomarkers and renal or cardiovascular events. We did not detect an interaction between the biomarkers and ARB treatment for the renal or cardiovascular outcome as tabulated in Table 1. This indicates that ARB treatment did not modify the association between single or multiple biomarkers and renal or cardiovascular events. Imputation of missing data yielded essentially similar results as the main analyses.
Statistical Analysis

Mean and standard deviation were provided for 6-month changes in biomarkers and statistical significance for the between group difference was determined based on a two-sided t-test. Univariable and multivariable Cox proportional hazard regressions were used to determine the relationship between baseline biomarkers in the placebo treatment arm and renal or cardiovascular outcome. For individuals who experienced more than one renal or cardiovascular event during follow-up, survival time to the first relevant endpoint was used in each analysis. Participants were censored at their date of death or, for those still alive at the end of follow-up, the date of their last clinic visit before the termination of the trials. The multivariable Cox analysis included the following biomarkers, systolic blood pressure, urine albumin-to-creatinine ratio (UACR), potassium, hemoglobin, uric acid, HbA1c, total cholesterol, Body Mass Index, calcium, phosphate, and albumin.

Table 1: ARB therapy during 6 months did not modify the association between biomarker and renal or CV outcome in the RENAAL trial. Similar results were obtained in the IDNT trial (data not shown).

<table>
<thead>
<tr>
<th>biomarker</th>
<th>Renal outcomes</th>
<th>CV outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-coefficient</td>
<td>P value</td>
</tr>
<tr>
<td>Systolic BP*</td>
<td>0.01</td>
<td>0.54</td>
</tr>
<tr>
<td>Log UACR*</td>
<td>0.10</td>
<td>0.74</td>
</tr>
<tr>
<td>Potassium*</td>
<td>0.43</td>
<td>0.30</td>
</tr>
<tr>
<td>Hemoglobin*</td>
<td>-0.13</td>
<td>0.35</td>
</tr>
<tr>
<td>Uric acid*</td>
<td>0.12</td>
<td>0.42</td>
</tr>
<tr>
<td>HbA1c*</td>
<td>0.30</td>
<td>0.09</td>
</tr>
<tr>
<td>Cholesterol*</td>
<td>-0.01</td>
<td>0.24</td>
</tr>
<tr>
<td>BMI*</td>
<td>0.02</td>
<td>0.63</td>
</tr>
<tr>
<td>Albumin*</td>
<td>-0.73</td>
<td>0.28</td>
</tr>
<tr>
<td>Calcium*</td>
<td>0.10</td>
<td>0.84</td>
</tr>
<tr>
<td>Phosphate*</td>
<td>0.85</td>
<td>0.03</td>
</tr>
<tr>
<td>Multiple*</td>
<td>-0.71</td>
<td>0.51</td>
</tr>
</tbody>
</table>

†Treatment variable indicates whether patients received losartan or placebo
Abbreviations: BP, blood pressure; CV, cardiovascular; UACR, urine albumin-to-creatinine ratio

Bootstrap methods were applied, repeating the entire modeling with 1000 independent random samples with replacement, to take into account the variability of the point estimates of the regression coefficients of the components of the single
and multiple risk scores. To determine the actual observed effect of losartan or irbesartan on renal/cardiovascular outcomes, the dichotomous treatment variable was used in a Cox regression model and the relative risk reduction was calculated as (1 - hazard ratio) multiplied by 100%. Bootstrap methods, based on 1000 replications, were also used to derive the 95% confidence interval of the difference between the actual observed and predicted treatment effect. The difference between the predicted and observed treatment effect was tested by means of two-sided t-tests. We verified normal distribution of the predicted treatment effect and performed log-transformation if required. Time-dependent Cox regression analysis was used to assess the interaction between treatment and biomarkers at baseline in the placebo group or 6-month biomarkers in the ARB treatment group with renal/cardiovascular outcomes. A two-sided P value of 0.05 indicated statistical significance. Analyses were conducted with R 2.14.1 (R Project for Statistical Computing www.r-project.org).

Results

Baseline characteristics between the ARB and placebo groups in the RENAAL trial were well balanced.\textsuperscript{11} Losartan significantly changed multiple off-target renal or cardiovascular biomarkers beyond blood pressure. Relative to placebo, losartan decreased UACR, total cholesterol, hemoglobin, and uric acid, it increased potassium, calcium, albumin, and body mass index, while it had no effect on Hba1C and phosphate (Figure 1).

Estimated renal and cardiovascular treatment effect by single and multiple PRE scores

During 3.4 years of follow-up 489 renal and 515 cardiovascular events were recorded in the RENAAL trial. Treatment with losartan resulted in a relative renal risk reduction of 21.8% (95% CI, 6.5 - 34.5%; \( P = 0.007 \)) and a relative cardiovascular risk reduction of 9.2% (95% CI -7.9 - 23.6%; \( P = 0.27 \)), as represented by the horizontal line in Figure 2\textsuperscript{A} and 2\textsuperscript{B}. Single biomarkers either
The Importance of Short-Term Off-Target Effects in Estimating Renal and Cardiovascular Protection

Figure 1: Change in biomarkers after 6 months placebo, ARB, or CCB treatment in the RENAAL and IDNT trials.
* $P < 0.05$  ** $P < 0.001$
significantly underestimated or overestimated the actual observed drug effect on renal and cardiovascular outcomes (Figure 2A and 2B). In particular, the 6-month change in blood pressure, induced by the antihypertensive ARB, significantly underestimated the renal and cardiovascular outcome (difference between estimated and actual risk reduction was 16.0% for renal and 6.2% for cardiovascular outcome). The multiple PRE score (using all biomarker changes at 6-month) predicted a 3.4 years renal risk reduction of 30.1% (95% CI, 10.8 - 49.5%). This came close to the observed risk reduction ($P = 0.44$ for the difference in the estimate). The PRE score predicted a 9.4% (95% CI, 1.9 - 17.0%) cardiovascular risk reduction which was again nearly equal to the observed cardiovascular risk reduction ($P = 0.98$ for the difference in the estimate; Figure 2A and 2B).

External Validation of the PRE score in a separate trial database

To test the validity of the PRE score we applied it to an external separate trial database, the IDNT trial, to estimate the treatment effect of the ARB irbesartan on renal and cardiovascular outcomes. Irbesartan caused similar directional changes in renal or cardiovascular biomarkers as losartan although the magnitude of these changes varied compared with losartan (Figure 1). When we entered the irbesartan induced changes in multiple renal or cardiovascular biomarkers in the PRE score, developed in RENAAL, the PRE score estimated a 26.6% (95% CI 14.3 - 38.9%) relative renal risk reduction which was nearly equal to the observed relative renal risk reduction of 26.0% (6.4 - 41.5%; $P = 0.95$ vs predicted drug effect; Figure 3A). The PRE score estimated a relative cardiovascular risk reduction with irbesartan of 7.9% (1.3 - 14.5%) which did not significantly differ from the observed cardiovascular risk reduction of 11.9% (-8.4 +28.5 %; $P = 0.67$; Figure 3B).

Development of the PRE score in the IDNT trial and application to the irbesartan arm of IDNT or losartan arm of the RENAAL trial yielded essentially similar results in that the estimation of the observed treatment effect based on the multiple risk response score outperformed scores based on single biomarkers (Supplemental
Figure 2. Observed and predicted long-term relative renal and cardiovascular risk change (%) based on single and multiple PRE scores. Figure A displays the results for renal outcome and Figure B displays the results for cardiovascular outcome. The actual observed treatment effect is indicated by the solid line. The predicted treatment effect based on single and multiple PRE scores are shown by the vertical bars. The PRE score was developed in the RENAAL trial and applied to the baseline and month-6 values of the placebo and losartan treatment arm of the RENAAL trial.
Figures 1 and 2). A sensitivity analysis using changes in biomarkers at month 12 provided similar results.

External Validation of the PRE score to Another Antihypertensive Drug Class
To further establish the external validity of the PRE score, we assessed whether the PRE score accurately predicted the treatment effect of the CCB amlodipine on renal and cardiovascular outcomes in the IDNT trial. Amlodipine decreased blood pressure and potassium compared to placebo at month 6, but did not change other biomarkers (Figure 1). Based on the 6-month change in blood pressure alone (the on-target parameter) a renal risk reduction was predicted whereas the observed renal risk tended to increase with amlodipine (Figure 4A). The PRE score estimated a 5.0% (95% CI, -6.6 - 16.6%) relative renal risk increase which did not differ from the observed renal risk increase of 11.3% (-10.3 - 38.0%; \( P = 0.56 \) vs predicted drug effect; Figure 4A). The PRE score estimated a relative cardiovascular risk reduction with amlodipine of -1.3% (-4.5 - +1.8%) which did not significantly differ from the actual observed cardiovascular risk reduction of -14.6% (-30.9 - 5.5%); \( P = 0.14 \); Figure 4B).

Discussion
We confirmed that the ARB losartan exerts multiple off-target effects in individuals with type 2 diabetes and nephropathy. These off-target effects are either positively or negatively associated with renal/cardiovascular morbidity or mortality. In addition, we showed that only using the short-term change in blood pressure, the on-target effect of this antihypertensive agent, cannot capture the ultimate effect of losartan on renal/cardiovascular morbidity or mortality. In contrast, the PRE score, based on short-term drug responses of all (available) on-target and multiple off-target biomarkers, is accurate in predicting the ultimate long-term drug effect on renal or cardiovascular outcomes and performs significantly better than any single on-target or off-target biomarker, also in external datasets.

Often drugs change other biomarkers than the one they are targeted to, so called off-target effects. We demonstrated that the antihypertensive agent losartan
Figure 3 Validation of the PRE score in the IDNT trial. Figure A displays the results for renal outcome and figure B the results for cardiovascular outcome. The PRE score is developed in the RENAAL trial and applied to the baseline and month 6 measurements of the irbesartan and placebo arm of the IDNT trial. The renal and cardiovascular protective effect based on the short-term change in systolic blood pressure (the on-target parameter) is indicated by the light grey bar left. The PRE score based drug effect on renal and cardiovascular outcomes is shown by the grey bar in the middle. The actual observed drug effect on renal and cardiovascular outcomes in the IDNT trial is indicated by the dark grey bar on the right.

The Importance of Short-Term Off-Target Effects in Estimating Renal and Cardiovascular Protection
does not only lower blood pressure, but also reduces urine albumin excretion, hemoglobin, uric acid, and cholesterol, and increases serum potassium, calcium, and albumin. Importantly, these different biomarkers vary in their response to the drug: blood pressure may decrease whereas potassium does not change or the other way around, and each of these different drug responses are associated with renal or cardiovascular morbidity or mortality change. It is therefore not surprising that a combination of changes in on-target and off-target multiple biomarkers more accurately captures the long-term drug effect than changes in single on-target or off-target biomarkers.

The blood pressure lowering effect of losartan markedly underestimated the renal/cardiovascular protective effects of these drugs despite the fact that these drugs are developed and registered as antihypertensive drugs. Recent trials have shown that this phenomenon is not limited to ARBs, but is applicable to other antihypertensive drugs or drug-combinations, and even extends to other drugs used in cardiovascular risk management as well, as recently reviewed. Taken together, these trials exemplify that the magnitude of renal or cardiovascular protection conferred with antihypertensive agents, or other drugs used to decrease cardiovascular risk, cannot always be determined from their on-target drug effect but depends on the composite effect on all on-target and off-target biomarkers. Of note, while in the ARB example the observed renoprotective effect is larger than estimated from blood pressure alone, in the CCB example the actual renoprotective effect is less than estimated from blood pressure alone. The latter situation has been observed for other drugs as well. For example, in the case of rosiglitazone, the actual long-term cardiovascular drug effect is less than estimated from the reduction in HbA1c.

The PRE score uses multiple risk parameters as is done in many other risk estimation engines like the Framingham, UKPDS, or more recent ADVANCE risk engine. What is the advantage of the PRE score? Traditional risk engines in patients with diabetes such as the UKPDS or the more recent ADVANCE risk engine only include traditional cardiovascular risk factors and are based on a minimal number of readily available clinical lab parameters to predict individual prognosis. The PRE score is based on many other biomarkers that are
The Importance of Short-Term Off-Target Effects in Estimating Renal and Cardiovascular Protection

**Figure 4:** Validation of the PRE score in the IDNT trial for the CCB amlodipine. Figure A displays the results for renal outcome and figure B the results for cardiovascular outcome. The PRE score is developed in the RENAAL trial and applied to the baseline and month 6 measurements of the amlodipine and placebo arm of the IDNT trial. The renal and cardiovascular protective effect based on the short-term change in systolic blood pressure (the on-target parameter) is indicated by the light grey bar left. The PRE score based drug effect on renal and cardiovascular outcomes is shown by the grey bar in the middle. The actual observed drug effect of amlodipine on renal and cardiovascular outcomes in the IDNT trial is indicated by the dark grey bar on the right.

The Importance of Short-Term Off-Target Effects in Estimating Renal and Cardiovascular Protection
influenced by drug therapy and determine the outcome of the individual, thus increasing the accuracy of the estimates. Indeed, models based on blood pressure, Hba1c and cholesterol alone only predicted ~10% renal and ~2% relative cardiovascular risk reductions in the RENAAL trial. In addition, the PRE score does not include age and sex as they are non-modifiable.

The present study may have implications for drug development, drug registration and individual patient care. As far as drug development is concerned, a multiple on-target and off-target PRE score enables more accurate drug efficacy assessment on renal/cardiovascular morbidity and mortality by evaluating the short-term effect of the drug on a prefixed set of biomarkers. This will then help to determine which drugs have the potential to reach the market in early stages of drug development, even before long-term trials are conducted. Novel tools to better estimate drug efficacy is highly needed because attrition rates in late phase drug-development are still approximately 50% and are mostly attributable to drug inefficacy (66%).

As far as drug registration is concerned, drugs are registered based on the target of interest. The on-target effects are well measured, recorded and evaluated, whereas the off-target drug effects are usually measured as safety biomarkers in trials, meaning less rigorous measurements. The PRE score requires that all biomarker effects are measured rigorously. A multiple PRE score including on-target and off-target drug effects will have the advantage to enable more accurate drug efficacy assessment, which can guide the drug regulator to make well informed decisions about drug marketing authorization. Finally, the PRE score may offer the physician and the patient a better tool to estimate the overall prescribed drug effect on long-term outcomes. In case the PRE score has not changed sufficiently after starting medication, decisions can be made to increase the dose or change the drugs guided by the single components of the PRE score. This could make the PRE score particularly relevant for the patient-clinician dialogue.

Several aspects of the model should be considered. As with many prediction analyses, the model depends on the biomarkers measured in the trials. A PRE score consisting of multiple laboratory parameters accurately predicted long-term renal and cardiovascular drug effects. Nevertheless, we cannot exclude
that additional biomarkers that offset each other were not incorporated in the model and we have only used all biomarkers that were measured in these trials. Secondly, the underlying assumption of the model is that the relation between a biomarker and renal or cardiovascular outcome is not modified by drug treatment. In other words, the relation between a cardiovascular and outcome in the placebo group is similar to the relation between a cardiovascular and outcome after 6 months ARB treatment. We verified the correctness of this assumption in our analyses. Thirdly, the accuracy of the PRE score depends on the background database such as its size, event rate, its accuracy, and the variation in the levels of multiple biomarkers. The current analyses were derived from the placebo arm of the RENAAL trial. This can be improved by increasing the placebo treated background database. The PRE score is applied to ARB and CCB treatment in patients with diabetes and nephropathy. No inferences can be made about the performance of the score to predict long-term effects of other drugs in other disease areas. Fourthly, the trials were not sufficiently powered to detect statistically significant treatment effects on cardiovascular outcomes, compromising the precision of the observed and predicted cardiovascular treatment effects. In particular, the amlodipine arm in the IDNT trial was merely used to ascertain blood pressure independent effects of irbesartan. The trial was not powered to detect significant treatment effects of amlodipine, which may explain the lack of precision in the effect size. Yet, the PRE score estimates of amlodipine showed no effect on the renal or cardiovascular outcomes which were in line with the observed treatment effects. Strengths of this study are the large size of the trials, the availability of many biomarkers at baseline and after 6 months follow-up, the validation of the score in a separate independent population, and the similarity of the predicted and observed effect sizes.

In conclusion, measuring only the short-term blood pressure effect of ARB treatment, the on-target parameter, may result in misinterpretations in estimating the long-term renal and cardiovascular protective effect. This can have major impact on drug registration, individual patients, and society. The PRE score based on multiple on-target and off-target biomarkers is accurate in predicting the long-term outcome of ARB in patients with diabetes and nephropathy. This may not only
apply for the studied drugs. Future studies should be directed towards other drugs and indications with known off-target effects.

Acknowledgements

We acknowledge the supportive role of all RENAAL and IDNT investigators, support staff, and participating patients.
This work was performed as part of the Escher project (project nr. T6-202) within the framework of the Dutch Top Institute Pharma.
Supplemental Figure 1A and 1B: PRE score development in the IDNT trial and application to the baseline and month 6 measurements of the placebo and irbesartan treatment arm of the IDNT trial (figure A renal outcomes; figure B cardiovascular outcomes).
Supplemental Figure 2A and 2B: Validation of the PRE score in the RENAAL trial by applying the IDNT developed PRE score to the baseline and month 6 measurements of the placebo and losartan treatment arm of the RENAAL trial (figure C renal outcomes; figure D cardiovascular outcomes).
References


