Chapter 6

A Prediction of the Renal and Cardiovascular Efficacy of Aliskiren in ALTITUDE Using Short-Term Changes in Multiple Biomarkers

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Abstract

**Introduction** We recently developed and validated in existing trials a novel algorithm (PRE score) to predict long-term drug efficacy based on short term (month-6) drug-induced changes in multiple biomarkers. To show the value of the PRE score for ongoing and planned clinical trials, we here report the predicted long-term cardio-renal efficacy of aliskiren in type 2 diabetes, which was investigation in the ALTITUDE trial, but unknown at the time this study was conducted.

**Methods** We established the relation between multiple biomarkers and cardio-renal endpoints (as defined in ALTITUDE) using a background database from past clinical trials. The short-term effect of aliskiren on multiple biomarkers was taken from the AVOID trial. A PRE score was developed by multivariable Cox regression analysis in the background population and was then applied to the baseline and month-6 measurements of the aliskiren treatment arm of the AVOID trial to predict cardio-renal risk. The net risk difference at these time-points, after correction for placebo effects, was taken to indicate the estimated long-term cardio-renal risk change.

**Results** Based on the PRE score, we predicted that aliskiren treatment in ALTITUDE would confer a relative risk change of -7.9% [95% CI -2.5 - -13.4%] for the cardio-renal endpoint, a risk change of -5.1% [-1.2 - -9.0%] for the cardiovascular endpoint, and a non-significant risk change of -19.9% [-42.1 - +2.1%] for the renal endpoint.

**Conclusions** PRE score estimations suggested that aliskiren has only a marginal additive protective effect on cardio-renal endpoints in patients with type 2 diabetes. These predictions were validated by the results of the ALTITUDE trial, confirming the potential of the PRE score to prospectively predict drug efficacy on cardio-renal outcomes.
Introduction

Cardiovascular risk engines like Framingham, SCORE, and UKDPS take into account multiple biomarkers to predict cardiovascular risk. In contrast, predictions of drug efficacy are typically based on a single biomarker (e.g. blood pressure, cholesterol) to estimate the long-term cardiovascular protection afforded by the drug, although drugs are known to affect multiple biomarkers.\(^1\)

We have recently developed a novel algorithm based on short-term drug-induced changes in multiple biomarkers, so-called multiple risk Parameter Response Efficacy (PRE) score, to predict the long-term effect of a drug on cardio-renal outcomes. The score has been validated in a post-hoc environment using data from already completed clinical trials.\(^2\) To show the value of the PRE score for predicting drug efficacy of ongoing and planned clinical trials, we here report predictions of the long-term renal and cardiovascular drug efficacy of the direct renin inhibitor aliskiren on top of optimal treatment with an angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) in patients with type 2 diabetes and nephropathy. Whether this combination provides additional cardio-renal protection was investigated in the recently published ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints) trial,\(^3\) but unknown at the time this study was conducted.

Methods

General Approach

PRE score predictions of the long-term cardio-renal effect of aliskiren were made in four steps. Firstly, we established the relation between biomarkers and cardio-renal endpoints. We used the identical cardio-renal endpoints as defined and recorded in ALTITUDE.\(^3\) The relation between biomarkers and cardio-renal endpoints was established in a background population with similar patient characteristics as the ALTITUDE individuals. The background population was derived from the RENAAL (Reduction of Endpoints in NIDDM with the AII Antagonist Losartan),\(^4\) IDNT (Irbesartan Diabetic Nephropathy Trial),\(^5\) and LIFE (Losartan Intervention For
Endpoint reduction in hypertension study) trial.\textsuperscript{6} Secondly, we determined the short-term (month-6) effect of aliskiren on multiple biomarkers using data from AVOID, a clinical trial testing the effect of aliskiren on surrogate outcomes.\textsuperscript{7} We relied on data from the AVOID trial because month-6 biomarker changes in ALTITUDE were not available. Thirdly, we predicted the cardio-renal protective effect of aliskiren in ALTITUDE by estimating cardio-renal risk reductions that could be expected on the base of on observed short-term biomarker changes in AVOID. Fourthly, because short-term biomarker changes may be different between ALTITUDE and AVOID, we performed sensitivity analyses for aliskiren’s cardio-renal protective effect. More specifically, we estimated the changes in biomarkers that would be necessary to establish a 15% risk reduction for which the trial was powered, a non-significant risk reduction, and a no risk reduction at all (the null effect).

\textit{Background Database}

The background population consisted of individuals with type 2 diabetes, who had similar characteristics to the individuals participating in the ALTITUDE trial. To match the background population with the ALTITUDE population, we selected all individuals who were treated with ARBs, had an estimated glomerular filtration rate (eGFR) >25 mL/min/1.73m\textsuperscript{2}, and systolic blood pressure <160 mmHg. The background population consisted of 1,125 individuals who were followed for 48 months and experienced 282 cardio and 135 renal events. Their characteristics did not differ from the ALTITUDE baseline characteristics (\textbf{Table 1}), except that albuminuria was somewhat higher in the background population.

We constructed in the background database identical cardio-renal endpoints as defined and recorded in ALTITUDE. The primary cardio-renal endpoint in ALTITUDE was defined as the first occurrence of cardiovascular death, resuscitated death, non-fatal myocardial infarction, stroke, unplanned hospitalization for heart failure, onset of end-stage renal disease, or a doubling of serum creatinine concentration from baseline. The secondary endpoints in ALTITUDE comprised the renal and cardiovascular components of the primary composite endpoint.
Table 1: Population characteristics of the background and the ALTITUDE population.\textsuperscript{15}

<table>
<thead>
<tr>
<th></th>
<th>Background population matched with ALTITUDE</th>
<th>ALTITUDE population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LIFE (N)</td>
<td>324</td>
<td>-</td>
</tr>
<tr>
<td>RENAAL (N)</td>
<td>431</td>
<td>-</td>
</tr>
<tr>
<td>IDNT (N)</td>
<td>370</td>
<td>-</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62 (56 - 67)</td>
<td>65 (58 – 72)</td>
</tr>
<tr>
<td>Male sex</td>
<td>727 (64.6)</td>
<td>5851 (68.0)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>780 (69.3)</td>
<td>4873 (56.6)</td>
</tr>
<tr>
<td>Black</td>
<td>142 (12.6)</td>
<td>280 (3.3)</td>
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<tr>
<td>Hispanic</td>
<td>93 (8.3)</td>
<td>NA</td>
</tr>
<tr>
<td>Asian</td>
<td>87 (7.7)</td>
<td>2726 (31.7)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (2.0)</td>
<td>703 (8.2)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>140 (131 – 149)</td>
<td>135 (126 – 150)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>80 (72 – 86)</td>
<td>74 (67 – 81)</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m(^2))</td>
<td>49.8 (36.3 - 70.6)</td>
<td>51.7 (41.9 - 64.9)</td>
</tr>
<tr>
<td>eGFR ≥60 mL/min/1.73m(^2))</td>
<td>386 (34.3)</td>
<td>415 (36.0)</td>
</tr>
<tr>
<td>eGFR ≥45 to &lt;60 mL/min/1.73m(^2))</td>
<td>273 (24.3)</td>
<td>3024 (35.1)</td>
</tr>
<tr>
<td>eGFR ≥30 to &lt;45 mL/min/1.73m(^2))</td>
<td>331 (29.4)</td>
<td>2574 (29.9)</td>
</tr>
<tr>
<td>eGFR &lt;30 mL/min/1.73m(^2)</td>
<td>135 (12.0)</td>
<td>220 (2.6)</td>
</tr>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>183 (76)</td>
<td>NA</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3 (7.3 - 9.5)</td>
<td>7.5 (6.6 - 8.6)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>211 (181.2 - 243.2)</td>
<td>170 (143 – 197)</td>
</tr>
<tr>
<td>ACR (mg/g)</td>
<td>402 (53 – 1133)</td>
<td>199 (56 – 886)</td>
</tr>
<tr>
<td>ACR &lt;20 mg/g</td>
<td>183 (16.3)</td>
<td>1240 (14.4)</td>
</tr>
<tr>
<td>ACR 20-200 mg/g</td>
<td>204 (18.2)</td>
<td>2210 (25.7)</td>
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<tr>
<td>ACR &gt;200 mg/g</td>
<td>739 (65.6)</td>
<td>5012 (58.2)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>29.7 (26.4 - 33.8)</td>
<td>29.1 (25.7 - 33.2)</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.4 (1.9)</td>
<td>6.5 (0.6)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.3 (11.8 - 14.5)</td>
<td>13.0 (11.9 – 14.3)</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5 (4.2 - 4.9)</td>
<td>4.5 (4.2 - 4.8)</td>
</tr>
</tbody>
</table>

Values for continuous variables given as mean ± standard deviation or median (IQR); values for categorical variables given as number (percentage).

Abbreviations: ACR, albumin to creatinine ratio; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate IQR, inter quartile range; NA, not available.
Short-Term Effect of Aliskiren on Biomarkers

We used the AVOID trial, that included a similar population to ALTITUDE, to establish aliskiren-induced changes in multiple biomarkers. AVOID was a clinical trial designed to assess the anti-albuminuric effect of aliskiren in addition to losartan 100 mg/day. The trial enrolled individuals with type 2 diabetes, hypertension, and macroalbuminuria, who were randomly assigned to aliskiren 300 mg/day or matched placebo for 24 weeks. The primary results have been reported elsewhere.7

Biomarker Selection

To estimate drug effects of aliskiren on cardio-renal outcomes, we included all biomarkers available in AVOID at baseline and week 24. The relation between biomarkers and the cardio-renal endpoint was established in the background population. All biomarkers collected at baseline and month 6 in the background population and in the AVOID trial were used. We selected all measured biomarkers at both time-points to exclude any potential bias as a result of biomarker selection, because we did not know a priori which biomarkers would change during ARB therapy.

Statistical Analysis

Univariable and multivariable Cox proportional hazard regression models were used to determine the risk score between single or multiple biomarkers and the cardio-renal endpoints in the background population. The multivariable Cox analysis included the following biomarkers: systolic blood pressure, urine albumin-to-creatinine ratio (UACR), serum potassium, hemoglobin, serum uric acid, blood glucose, total cholesterol, and body mass index (BMI). We verified the existence of a non-linear relationship between single biomarkers and outcome based on goodness of fit using Akaike’s information criterion. Serum potassium and systolic blood pressure displayed a non-linear fit. These biomarkers were therefore modeled with Harrell’s restricted cubic spline fit in the Cox regression models for the cardio-renal endpoint and cardiovascular endpoint alone. A restricted cubic spline for both serum potassium and systolic blood pressure with three knots
produced the optimal fit and was used in all models. To take into account the variability of the point-estimates of the regression coefficients of the components of the single and multiple risk scores, a standard bootstrap procedure was applied, repeating the entire modeling with 1000 independent random samples.

To predict the treatment effect, the obtained risk score was applied to the baseline and week-24 measurements in AVOID, in order to estimate cardio-renal risk change between both time-points. The difference in the estimated risk at these time-points, adjusted for the difference in estimated risk change in the placebo arm, represented the PRE score and indicated the relative long-term cardio-renal risk change conferred by aliskiren treatment. We checked normal distribution of the predicted treatment effects and performed log-transformation if required. Some patients had missing biomarker values in AVOID. In a sensitivity analysis we imputed missing observations by multiple imputation techniques using linear regression models.

Previous studies have shown that systolic blood pressure, UACR, and potassium are significantly affected by blockade of the renin-angiotensin-aldosterone (RAAS) system. Given the importance of these biomarkers and the possibility that observations in ALTITUDE may differ from those in AVOID, we performed additional sensitivity analyses in which we estimated the changes in multiple biomarkers that would be necessary to establish a 15% risk reduction, a non-significant risk reduction, or no risk reduction (the null effect) of aliskiren on the cardio-renal endpoint (HR = 1.00). The 15% risk reduction was chosen because the ALTITUDE trial was powered to detect a 15% risk reduction. Simulations were computed by shifting the distribution of the response. A two-sided \( P \) value \( \leq 0.05 \) indicated statistical significance. Analyses were conducted with R 2.14.1 (R Project for Statistical Computing www.r-project.org).

**Results**

The effects of aliskiren on various biomarkers in AVOID after 24-weeks therapy are shown in **Figure 1**. Relative to placebo, addition of aliskiren to ARB therapy decreased systolic blood pressure, UACR, total cholesterol, and hemoglobin.
Figure 1: Change in biomarkers after 24 weeks placebo or aliskiren treatment in the AVOID trial
Aliskiren increased serum potassium, while it had no effect on BMI, blood glucose, and uric acid. These short-term biomarker effects were entered into the PRE score to predict risk changes of aliskiren on the cardio-renal endpoint. Based on the marginal reduction in systolic blood pressure, the PRE score predicted no risk change for the cardio-renal endpoint or its cardiovascular or renal component (Figure 2; left bar). Based on the decrease in UACR, the PRE score predicted substantial and significant risk reductions, while the increase in serum potassium and decrease in hemoglobin resulted in risk increases. Changes in other biomarkers resulted in marginal and statistically insignificant risk changes. Based on the multiple PRE score, which combines all biomarker effects, we predicted that aliskiren treatment in ALTITUDE would confer a relative risk change of -7.9% (95% CI, -2.5 - -13.4%) for the cardio-renal endpoint (Figure 2A), a risk change of -5.1% (95% CI, -1.2 - -9.0%) for the cardiovascular endpoint, and a non-significant risk change of -19.9% (95% CI, -42.1 - +2.1%) for the renal endpoint (Figure 2B and 2C). Imputation of missing values in AVOID yielded similar results.

Repeating the entire analysis, using simulated data, revealed that aliskiren should decrease blood pressure by at least 5 mmHg, and UACR by at least 30%, and should not increase serum potassium more than 0.2 mmol/L in order to achieve 15% cardio-renal risk reduction (Figure 3, blue line). Aliskiren shows no effect on the cardio-renal endpoint (HR = 1.00) when there is no reduction of blood pressure, <8% change in UACR and >0.85 mmol/L increase in serum potassium (Figure 3, purple line).

**Discussion**

Using the multiple risk Parameter Response Efficacy (PRE) score, we estimated that treatment with aliskiren on top of ACEi or ARB therapy will likely have a marginal additive cardio-renal protective effect in high-risk patients with type 2 diabetes. These estimations indicate that treatment with aliskiren may not be as promising as expected in this patient population.

The drug efficacy estimations on cardio-renal endpoints were computed before the results of the ALTITUDE trial were disseminated. Interestingly, the
Figure 2: Estimated relative risk change for the different endpoints based on single and multiple PRE scores.
A Prediction of the Renal and Cardiovascular Efficacy of Aliskiren in ALTITUDE

Figure 3: Simulations of biomarkers changes needed to achieve different cardio-renal risk change scenarios. Blue line: biomarker changes required to achieve a 15% cardio-renal risk reduction. Green line: biomarker changes as observed in the AVOID trial. Red line: biomarker changes resulting in a trial with a statically non-significant risk reduction. Purple line: biomarker changes resulting in no risk change (null effect).

predicted lack of cardio-renal protection with aliskiren is in line with the recently published results of the ALTITUDE trial. These results validate the PRE score drug efficacy estimations. The ALTITUDE investigators expected that treatment with aliskiren on top of conventional antihypertensive treatment would afford a 15%
relative cardio-renal risk reduction.\textsuperscript{3} This expectation was based on previous studies showing that aliskiren reduces blood pressure and albuminuria,\textsuperscript{10} and that the reduction in these parameters is an important determinant for cardio-renal protection.\textsuperscript{11} However, single drugs have multiple effects, which may be on biomarkers that also contribute to long-term cardio-renal outcome, either in a positive or negative way. In case of aliskiren, it increases serum potassium and decreases hemoglobin, and these effects may be harmful in the long-term.\textsuperscript{9,12} In the ALTITUDE trial, more cases of hyperkalemia and acute renal impairment were observed, leading to early trial termination.\textsuperscript{13}

Thus, although aliskiren caused a reduction in blood pressure and albuminuria in ALTITUDE,\textsuperscript{14} the effect of aliskiren on other biomarkers (e.g. potassium, hemoglobin) have likely offset the beneficial effect of blood pressure or albuminuria reduction. The advantage of the PRE score is that it captures the drug effect on all biomarkers and thus may provide a more accurate estimate of the long-term drug effect than estimates based on single biomarkers such as blood pressure changes with aliskiren.

What are the practical implications of our study? A PRE score, including drug induced changes in multiple biomarkers, is able to provide prospective insight into the long-term risk change that follows from treatment. Accurate PRE score based predictions may provide an early impression of the potential success or failure of costly and large-scale hard outcome trials. In doing so, the PRE score may prevent long-term exposure of many patients to ineffective or even harmful drugs. At the same time, PRE score predictions may inform pharmaceutical companies and drug regulators in early clinical development whether novel compounds have the potential to reach the market, while simultaneously facilitating clinical trial designs in late-stage clinical development.

Several aspects of our model should be considered when interpreting our findings. Firstly, the model depends on the biomarkers measured and recorded in the background population. A PRE score accurately predicted the effect of aliskiren on cardio-renal endpoints. Nevertheless, we have only used all biomarkers that were measured in these trials and we cannot exclude that additional biomarkers that offset each other were not incorporated into the model. Secondly, the
The underlying assumption of the model is that the relation between a biomarker and renal and cardiovascular outcome is not modified by drug treatment. In other words, the relation between a biomarker and outcome off-treatment is similar to the relation between biomarker and outcome on-treatment. We verified this assumption in the background population and found that the risk relation of a biomarker with outcome is similar on-treatment or off-treatment. Thirdly, we did not have information on short-term (month-6) biomarker changes in ALTITUDE. We therefore used the aliskiren-induced biomarker changes in AVOID and performed simulations to estimate changes in systolic blood pressure, UACR, and potassium, that would confer the expected 15% risk reduction, a non-significant risk reduction, or no risk reduction. As expected, the ultimate effect of aliskiren on cardio-renal outcomes changes with varying short-term drug effects on biomarkers. These analyses illustrate that the accuracy of the PRE score depends on the similarity of biomarker responses in different trials. Nevertheless, none of the observed biomarker changes in AVOID was substantial enough to reach the 15% relative risk reduction, suggesting that the expected effect size may have been too optimistic. In ALTITUDE the reduction in albuminuria at month-6 was 11%, which was markedly smaller to that observed in AVOID and came very close to the simulated null effect scenario. In all scenarios the albuminuria reduction was insufficient to overcome the harmful effects of changes in other off-target biomarkers.\(^{14}\)

We here provide the first prospective drug efficacy estimation with the PRE score. The PRE score predicted that aliskiren confers modest additional cardio-renal protective effects in high-risk patients with type 2 diabetes. These predictions are based on the expected aliskiren effect on multiple biomarkers in AVOID. The final efficacy results of the ALTITUDE trial confirm and validate the cardio-renal outcome predictions of the PRE score.
Acknowledgements

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