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

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Heart failure induced by aleglitazar treatment can be predicted based on short-term response in multiple risk markers

Bauke Schievink
Diederick Grobbee
A. Michael Lincoff
Dick de Zeeuw
Hiddo Lambers Heerspink

On behalf of the AleCardio Steering Committee

Submitted for publication
Abstract

Introduction: Hospitalization for heart failure (HF) is a common safety problem in clinical drug trials in type 2 diabetes. Novel strategies are needed to mitigate risk for HF and prevent early termination of these trials. We performed a post-hoc analysis of the AleCardio trial to assess whether the increased risk for HF associated with aleglitazar treatment could have been prevented by more stringent baseline criteria, or predicted based on short-term response in risk markers.

Methods: We calculated hazard ratios for hospitalization due to HF associated with aleglitazar treatment by restricting the baseline population in the AleCardio trial based on body weight, hemoglobin and NT pro-BNP levels. We also calculated risk for HF based on changes in these risk markers, and by integrating changes in all measured cardiovascular risk markers by using the so-called PRE score.

Results: With baseline restrictions based on body weight, hemoglobin and NT pro-BNP the hazard ratio for hospitalization due to HF associated with aleglitazar did not attenuate. For NT pro-BNP we found a strong linear relationship between short-term change and predicted risk for hospitalization due to HF. However, prediction of HF risk was more accurate with using changes in all measured risk markers (PRE score predict risk: +20.5% vs. +21.4% observed), compared to using only NT pro-BNP or any other single risk marker alone.

Discussion: Integrating short-term changes in all measured cardiovascular risk markers predicted HF risk in the AleCardio trial.
Introduction

Hospitalization for heart failure (HF) is a common safety problem in clinical drug trials in type 2 diabetes leading in some cases to early discontinuation of several clinical drug trials. Recent examples of drugs that increase risk for HF include the Nrf2 activator bardoxolone-methyl, the endothelin antagonist avosentan, the DPP-4 inhibitor saxagliptin and the PPAR agonist rosiglitazone (1-4). A common feature of these drugs is that they induce fluid retention, which increases risk of HF. In order to mitigate HF risk and early termination of future trials, it is important to exclude patients that are at risk for HF. The current inclusion/exclusion strategies are insufficient in mitigating this risk, and therefore new risk assessment strategies are needed.

Several risk markers have been proposed as proxies for HF, including body weight, hemoglobin and N-terminal pro-brain natriuretic peptide (NT pro-BNP) (5-7). However, it is unclear whether patients at risk of hospitalization for HF can reliably be identified based on baseline levels of a single or combination of these risk markers, or based on short-term treatment-induced response in these risk markers.

We performed a post-hoc analysis of the AleCardio trial in which patients with type 2 diabetes and a recent cardiovascular event were treated with the dual PPAR agonist aleglitazar. The study was terminated early due to futility and a higher incidence of hospitalization for HF in the aleglitazar treatment arm (8). We questioned whether the observed increase in HF incidence due to aleglitazar treatment could have been prevented if patient inclusion had been restricted by first excluding high risk patients on the basis of a single or combination of cardiovascular risk markers at baseline. Secondly, we questioned whether the observed HF risk could have been predicted on the basis of short-term (6 months) changes in risk markers associated with fluid retention (i.e. body weight, hemoglobin or NT pro-BNP), or by using an integrated response score with all measured cardiovascular risk markers. For the latter approach, we used the previously validated PRE score, which integrates the short-term drug effect on all measured risk markers and translates this to drug-induced risk probability of clinical outcomes (9,10).
Heart failure induced by aleglitazar can be predicted based on short-term risk marker response

Methods

*AleCardio trial design and patient population*

AleCardio (ClinicalTrials.gov identifier: NCT01042769) was a phase III trial in which 7226 patients with type 2 diabetes were randomized to treatment with either the dual PPAR agonist aleglitazar (150µg daily) or placebo, on top of conventional care. Design and outcome of the trial have been described elsewhere (8). In brief, patients were eligible if they were hospitalized for acute coronary syndrome (ACS), defined as myocardial infarction with or without ST segment elevation or biomarker-negative unstable angina. Randomization took place within 12 weeks of hospital discharge of the index ACS event, in order to allow for stabilization of the clinical condition of the patient. Exclusion criteria included hospitalization for HF currently or in the previous 12 months, peripheral edema, and chronic kidney disease, defined as an estimated glomerular filtration rate (eGFR) of less than 45ml/min/1.73m².

*Risk marker selection*

From the AleCardio dataset we selected all measured risk markers that were previously identified as predictors for cardiovascular disease. Firstly, we made subsets of the AleCardio patient population by excluding those at higher baseline risk of hospitalization for HF, based on known cardiovascular risk markers. Secondly, we assessed short-term (6-month) changes in the risk markers hemoglobin and NT pro-BNP, while body weight was assessed as a 1-month change to specifically capture fluid retention and not changes in body composition. We divided the AleCardio population in quartiles with respect to their short-term response in these risk markers. We also calculated hospitalization for HF risk based on all measured cardiovascular risk markers with the PRE score. For this analysis we included the following markers in addition to body weight, hemoglobin and NT pro-BNP: HbA1c, urinary albumin:creatinine ratio (UACR), systolic blood pressure (SBP), HDL cholesterol, LDL cholesterol, serum albumin, serum calcium and serum potassium.

*Development of the PRE score*

We predicted the effect of aleglitazar on HF risk compared to placebo by using the PRE score. The PRE score integrates the effect of short-term changes in multiple
risk markers and translates this to a probability of long term clinical outcomes in three distinct steps, and has been described and validated previously (9,10). In brief, the PRE score was first used to establish the relationship between the selected risk markers and the clinical outcome of hospitalization for HF by using baseline patient data and HF events as observed in the AleCardio trial. Secondly, the established risk marker-outcome relationships (with a median follow-up of 2 years) were applied to baseline and month 6 (exception: 1 month for body weight) risk marker levels as observed in AleCardio, in order to establish the risk difference between the two time points. PRE scores were then calculated by subtracting the baseline risk from month 6 correcting for placebo effects. The mean difference between the two time points is the relative risk change conferred by aleglitazar treatment over 2 years.

Statistical analysis
Variables were expressed as mean (SD) with log transformation for non-normal data. Statistical significance in changes in risk markers between the treatment and placebo group were calculated by ANCOVA adjusted for baseline values of each risk marker. To assess if the HF outcome could be prevented by applying a more stringent baseline selection of participations we assessed the risk of HF in subsets of patients by Cox proportional hazard models. For participants who experienced more than one HF 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 this study arm. Patients with unknown vital status were censored when they were last known to be alive. To assess whether the observed HF risk could have been predicted on the basis of single short-term risk marker responses we first established the associations between body weight, hemoglobin, and NT pro-BNP changes between baseline and 6 months and HF outcomes by Cox proportional hazard regression. Body weight, hemoglobin, and NT pro-BNP changes were divided into quartiles and entered in the Cox regression model. Each Cox regression model was adjusted for baseline values of each respective risk marker. In an additional analysis we adjusted each Cox proportional hazard model for the following covariates: age, gender, history of HF and baseline hemoglobin, body weight, NT pro-BNP, eGFR, systolic blood pressure and HbA1c.
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To assess the PRE score we established Cox proportional hazard models with all included cardiovascular risk markers at baseline. We used the coefficients for each risk marker in the model as weights for the risk equation for hospitalization for HF. These risk equations were applied to baseline and month 6 values of the selected risk markers as observed in AleCardio to establish a difference in risk for HF for each patient. The mean risk difference, after subtracting the risk difference in the placebo arm, represented the PRE score. A two-tailed p value of 0.05 was used as border for statistical significance. All statistical analyses were performed with R version 3.1.0 (R Project for Statistical Computing, www.r-project.org).

Results

Baseline characteristics
All 7226 randomized patients (n=3616 on aleglitazar, n=3610 on placebo) were included in this post-hoc analysis. Characteristics were well balanced between the aleglitazar and placebo group (Table 1). Mean baseline body weight and hemoglobin values were 83.0 kg and 13.7 g/dL respectively. Median NT pro-BNP was 382 pmol/L.

Patient selection at baseline and HF risk
We assessed whether the hazard ratio for HF associated with aleglitazar treatment could have been attenuated by restricting the patient population on baseline, prior to initiating treatment, by using a single or combination of risk markers. Restricting the baseline population based on individual risk markers or combination of risk markers did not attenuate the observed hazard ratio of 1.22 (95% confidence interval (CI) 0.94 to 1.59) for hospitalization for HF, although the confidence intervals were wide for some selections (Table 2).

Changes in body weight, hemoglobin and NT pro-BNP and HF risk
We subsequently assessed whether short-term changes in individual risk markers (i.e. body weight, hemoglobin, and NT pro-BNP) after treatment initiation (up to 6 months) could have predicted HF risk. Relative to placebo, treatment with aleglitazar significantly (P<0.001) increased body weight by 0.81 kg (95% CI: 0.70 to 0.92), NT
pro-BNP with 38.3% (95% CI: 32.8 to 44.6), and decreased hemoglobin by 0.65 g/dL (95% CI: 0.59 to 0.71; Figure 1A).

Table 1. Baseline characteristics of the patients included in the AleCardio trial. Numbers are reported in mean (SD), unless otherwise indicated.

<table>
<thead>
<tr>
<th></th>
<th>Aleglitazar (N=3616)</th>
<th>Placebo (N=3610)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>61 (10)</td>
<td>61 (10)</td>
</tr>
<tr>
<td>Sex, men (N, %)</td>
<td>2641 (73.1)</td>
<td>2619 (72.5)</td>
</tr>
<tr>
<td>Race (N, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2427 (67.2)</td>
<td>2391 (66.3)</td>
</tr>
<tr>
<td>Asian</td>
<td>942 (26.1)</td>
<td>942 (26.1)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>82.9 (18.9)</td>
<td>83.3 (19.1)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.7 (1.5)</td>
<td>13.7 (1.5)</td>
</tr>
<tr>
<td>NT pro-BNP, pmol/L (median, IQR)</td>
<td>383 [147-967]</td>
<td>378 [138-913]</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.8 (1.7)</td>
<td>7.8 (1.6)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>128 (17.4)</td>
<td>128 (17.6)</td>
</tr>
<tr>
<td>Albuminuria, mg/g (median, IQR)</td>
<td>12 [6-38]</td>
<td>12 [6-36]</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73m²</td>
<td>78 (20.3)</td>
<td>78 (20.4)</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>42 (11)</td>
<td>42 (11)</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>79 (31)</td>
<td>80 (31)</td>
</tr>
</tbody>
</table>

There was no linear relationship between the degree of body weight change and the hazard ratio for hospitalization for HF, both in the placebo and aleglitazar group (Figure 2). Only for the highest quartile in the aleglitazar group we found a significant increase in hazard ratio for HF compared to the reference category (HR: 2.22 [95% CI: 1.31 to 3.78]). For hemoglobin, we observed that a decrease after 6 months of therapy was associated with a higher hazard ratio for hospitalization due to HF, both in the placebo (HR: 4.53 [95% CI: 2.23 to 9.20, P<0.001] in first quartile compared to reference category) and aleglitazar group (HR: 2.33 [95% CI: 1.22 to 4.47, P=0.01]) group. Lastly, we observed a strong positive linear association between increases in NT pro-BNP and hazard ratio for hospitalization due to HF (P for trend <0.001; Figure 2). Multivariate adjustments of these associations did not alter the results (Supplementary Figure S1).
Heart failure induced by aleglitazar can be predicted based on short-term risk marker response

**Table 2.** Relationship between baseline levels of body weight, hemoglobin and NT pro-BNP versus hazard ratio for HF associated with aleglitazar treatment.

<table>
<thead>
<tr>
<th>Select only patients with:</th>
<th>HR for aleglitazar</th>
<th># events</th>
</tr>
</thead>
<tbody>
<tr>
<td>No restriction</td>
<td>1.22 (0.94 – 1.59)</td>
<td>222</td>
</tr>
<tr>
<td>NT pro-BNP &lt;300</td>
<td>1.22 (0.41 – 3.64)</td>
<td>13</td>
</tr>
<tr>
<td>NT pro-BNP &lt;500</td>
<td>1.46 (0.74 – 2.89)</td>
<td>34</td>
</tr>
<tr>
<td>NT pro-BNP &lt;1000</td>
<td>1.18 (0.77 – 1.81)</td>
<td>84</td>
</tr>
<tr>
<td>eGFR &gt;60</td>
<td>1.20 (0.85 – 1.68)</td>
<td>135</td>
</tr>
<tr>
<td>No CV history</td>
<td>1.21 (0.88 – 1.65)</td>
<td>159</td>
</tr>
<tr>
<td>Weight &lt;90</td>
<td>1.36 (0.98 – 1.86)</td>
<td>154</td>
</tr>
<tr>
<td>Hemoglobin &lt;12</td>
<td>1.30 (0.79 – 2.16)</td>
<td>61</td>
</tr>
</tbody>
</table>

*Combinations of risk markers*

| NT pro-BNP <500 & weight <90 | 1.16 (0.88 – 11.6) | 13 |
| NT pro-BNP <500 & eGFR >60   | 1.05 (0.45 – 2.42) | 22 |
| NT pro-BNP <500 & no CV history | 1.38 (0.63 – 3.01) | 26 |

*Changes in multiple cardiovascular risk markers and HF risk*

We finally assessed whether integrating changes in single cardiovascular risk markers into a PRE score could yield a better prediction hospitalization for HF risk due to aleglitazar treatment. In addition to body weight, hemoglobin and NT pro-BNP, treatment with aleglitazar resulted in a significant decrease in HbA1c and systolic blood pressure, and an increase in HDL cholesterol, LDL cholesterol, albumin and calcium, as shown in Figure 1B. Figure 3 shows the individual contribution of the aleglitazar-induced changes in each cardiovascular risk marker on risk change of hospitalization for HF. Changes in single risk markers underestimated the actual observed effect of aleglitazar on heart failure. However, integrating the changes in all measured risk markers with the PRE score provided the most accurate prediction of the HF risk, with a predicted risk increase of 20.5% (16.4% to 24.7%), close to the observed relative risk increase of 21.4% in the AleCardio trial. Changes in NT pro-BNP provided the largest individual contribution to the observed risk increase for HF associated with aleglitazar treatment, with a predicted risk increase of +16.6% (95% CI: +13.5% to +19.7).
Figure 1. Panel A: risk marker responses after 6 months of aleglitazar or placebo treatment (1 month for body weight) in AleCardio. All aleglitazar vs. placebo comparisons are $P<0.001$. Panel B: other risk marker responses in AleCardio. All aleglitazar vs. placebo comparisons are $P<0.001$ with the exception of potassium ($P=0.17$).

Figure 2. Relationship between response to aleglitazar or placebo on body weight, hemoglobin and NT pro-BNP versus hazard ratios for HF.
Heart failure induced by aleglitazar can be predicted based on short-term risk marker response

Discussion

The AleCardio trial revealed safety problems due to increased risk of hospitalization for HF, which was among the reasons for early termination of the trial. We found that applying more stringent inclusion criteria using available cardiovascular risk markers could not have prevented the observed outcome. However, using drug-induced changes in multiple risk markers during the first months of treatment and integrating them with the PRE score provided an accurate prediction of the effect of aleglitazar on hospitalization for HF. Use of this score may be a way forward to obtain an accurate estimate of a drug’s efficacy and safety during early stage drug development and avoid drug failures during late stage development as seen with recent clinical trials.

![Figure 3](image)

**Figure 3.** Relative risk for HF as calculated by the response in individual cardiovascular risk markers and by integrating the response into the PRE score.

Nowadays, risk assessment for identifying patients at risk for HF is performed by applying restrictions for enrolment in clinical trials such as excluding patients who have been hospitalized previously with HF or have signs of sodium/water retention.
(i.e. edema). We have tried to narrow the inclusion and exclusion criteria of the AleCardio population to ameliorate HF risk based on more stringent entry criteria using baseline single or combinations of risk markers. However, this approach did not attenuate the HF risk of aleglitazar treatment, although the confidence intervals were wide in some subpopulations. This finding is in contrast with an analysis recently performed in the BEACON trial with bardoxolone methyl. That trial was also prematurely terminated due to HF. A post-hoc analyses in BEACON revealed that using more stringent entry criteria by excluding patients with a high BNP (>200pg/mL) and a history of HF mitigated HF risk induced by bardoxolone methyl (11). The difference between our findings and those in the BEACON trial may be attributed to the different populations enrolled in the trials and the different drugs with different mechanisms of action.

Apparently, in the AleCardio trial patients first needed to be exposed to aleglitazar in order to assess who is at risk for HF. Indeed, when we tested individual risk markers associated with fluid retention, we found that a decrease in hemoglobin is associated with increased HF risk. Furthermore, there was a consistent relationship between drug-induced change in NT pro-BNP and hazard ratio for HF. NT pro-BNP is predominantly produced by cardiac myocytes in response to myocardial stretching, which is a sign of increased fluid levels and increased preload, either as a result of increased sodium/water retention or impaired functioning of the cardiac ventricles (12-14). This physiological phenomenon suggests that NT pro-BNP may indeed be used as a predictor for fluid retention and risk for HF. In support, previous studies have showed that levels of NT pro-BNP can be used in the diagnosis and prognosis for patients with HF (15). Whether treatment-induced changes in NT pro-BNP can also be used to predict the risk of hospitalization for HF is less well established. Our study adds that NT pro-BNP can also be used to monitor treatment effects, and that NT pro-BNP is a better predictor of HF risk than other individual risk markers, such as body weight and hemoglobin.

Next to its effect on fluid parameters, aleglitazar has effects on multiple other cardiovascular risk markers. Changes in these risk markers, such as albuminuria, blood pressure and HbA1c, have been associated with HF (16-18). Responses in these multiple risk markers may vary within individuals. For example, HbA1c levels may fall and NT pro-BNP levels may rise or the other way around. Integrating these short term changes in multiple risk markers in response to therapy may therefore
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provide a more accurate prediction of HF risk compared to using changes in single risk markers alone. Indeed, in the present study we showed that integrating short term risk marker changes into a PRE score provided the most accurate assessment of HF risk. These results are in line with previous analyses, which showed that the PRE score is more accurate than single risk markers alone in predicting the clinical outcomes of the direct renin inhibitor aliskiren and of the angiotensin receptor blockers losartan and irbesartan (9,10).

Identification and exclusion of patients at risk of HF before randomization into a long term trial by characterizing short-term responses in multiple risk markers during a so-called enrichment period could prevent early termination of clinical trials due to safety concerns. Consequently, it may increase the chance of finding a beneficial effect on the clinical outcome of interest. Such an approach with an enrichment design is used for the currently ongoing SONAR phase III trial (ClinicalTrials.gov identifier: NCT01858532), in which patients with type 2 diabetes and nephropathy are subjected to a six-week enrichment phase in which their response to the endothelin antagonist atrasentan is determined. In a phase II trial atrasentan treatment decreased albuminuria, but also increased body weight and decreased hemoglobin (19). Therefore in the SONAR trial only patients with a >30% decrease in the targeted parameter albuminuria and without unacceptable risk increase for HF (rise in body weight <3 kg or BNP <300 pg/ml) after the enrichment phase will proceed to randomization to either long-term treatment with atrasentan or placebo (on top of conventional care) (20).

This study has limitations. First, there was a strong initial reduction in NT pro-BNP after start of the trial. This is likely due to a high baseline level in all patients as a result of the recent ACS event prior to enrollment in the study. Secondly, the increase in HDL cholesterol seen with aleglitazar treatment increased risk for hospitalization due HF. This is somewhat surprising as an increase in HDL cholesterol is generally associated with less cardiovascular outcomes. It is unclear why the HDL component associated with increased HF risk, although our model does not assume causality and we cannot exclude the possibility of confounding. Thirdly, the limited number of HF events resulted in wide confidence intervals of the aleglitazar treatment effect on HF in some subpopulations after excluding patients at risk on the basis of baseline cardiovascular risk markers. The small number of HF events also precluded testing of all possible combinations of risk markers selections.
Finally, we acknowledge that this is a post-hoc analysis of a clinical trial with all its inherent limitations. The results can therefore only be interpreted as hypothesis generating.

In conclusion, integrating short-term changes in all known and measured cardiovascular risk markers provided the most accurate prediction of the effect of aleglitazar on HF, compared to single risk markers alone. This supports using all available risk markers to monitor the drug-induced responses in clinical trials order to predict treatment-related HF risk. A randomized controlled clinical trial design in which patients are exposed to the drug of interest before randomization in order to identify individuals at risk of HF based on changes in multiple risk markers may facilitate clinical trial conduct and may prevent early termination of clinical trials due to adverse effects.

Acknowledgements

We acknowledge the supportive role of all AleCardio investigators, support staff, and participating patients.
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Supplement

Supplemental Figure S1. Relationship between response to aleglitazar or placebo on body weight, hemoglobin and NT pro-BNP versus hazard ratios for HF, calculated by a multivariate Cox regression model.


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