Effects of Changes in Potassium With Valsartan Use on Diabetes Risk: Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) Trial

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BACKGROUND
Low and low-normal serum potassium is associated with an increased risk of diabetes. We hypothesized that the protective effect of valsartan on diabetes risk could be mediated by its effect of raising serum potassium.

METHODS
We analyzed data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, which randomized participants at risk for diabetes to either valsartan (up to 160 mg daily) or no valsartan. Using Cox models, we evaluated the effect of valsartan on diabetes risk over a median of 4 years of follow-up and calculated the mediation effect of serum potassium as the difference in treatment hazard ratios from models excluding and including 1-year change in serum potassium. The 95% confidence interval (CI) for the difference in log hazard ratios was computed by bootstrapping.

RESULTS
The hazard ratio for developing diabetes among those on valsartan vs. no valsartan was 0.866 (95% CI = 0.795–0.943) vs. 0.868 (95% CI = 0.797–0.945), after controlling for 1-year change in potassium. The bootstrap 95% CI for a difference in these log hazard ratios was not statistically significant (−0.003 to 0.009).

CONCLUSIONS
Serum potassium does not appear to significantly mediate the protective effect of valsartan on diabetes risk.

Keywords: blood pressure; diabetes; hypertension; risk; serum potassium; valsartan.

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Although low and low-normal serum potassium has been found to be a risk factor for incident diabetes independent of diuretic use1,2 and among thiazide users,3,4 it is unknown whether interventions to raise serum potassium could reduce the risk of incident diabetes. Valsartan, an angiotensin II receptor blocker, is known to raise serum potassium and has been found to lower diabetes risk.5 We hypothesized that the protective effect of valsartan on diabetes risk could be mediated by its effect of raising serum potassium.

METHODS
We analyzed data from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, a study of participants with impaired glucose tolerance and established cardiovascular disease or cardiovascular risk factors who were randomized to lifestyle modification and either valsartan (up to 160 mg orally daily) or no valsartan.5 There were 9,306 participants randomized and followed for incident diabetes (median of 5 years of follow-up), cardiovascular events, and mortality (median of 6.5 years of follow-up). Diabetes was defined as a fasting plasma glucose level of ≥126 mg/dl or a plasma glucose level of ≥200 mg/dl at 2 hours after a 75-g oral glucose load, confirmed within 12 weeks by another glucose tolerance test.5 Because potassium handling and response to valsartan are different in those with renal disease compared with those with normal renal function, participants with renal disease were excluded from this study (defined as an estimated glomerular filtration rate of <60 ml/min/1.73m2 (n = 1,030)), leaving 8,276 subjects.6

Categorical variables are presented as percentages, continuous variables are presented as means and SDs, and they are compared according to randomized treatment by χ2 tests for categorical variables and t tests for continuous variables. Cox models were used to evaluate covariable relationships with progression to diabetes. All models included the following baseline covariables for adjustment: age, body mass index, systolic blood pressure, cardiovascular composite event (myocardial infarction, percutaneous
coronary intervention, or coronary artery bypass grafting), family history of diabetes, fasting glucose, 2-hour glucose, glycated hemoglobin, low- and high-density lipoprotein, platelet count, hemoglobin, country, and race. To provide context, we initially evaluated the association between baseline serum potassium and risk of incident diabetes. For subsequent analyses involving 1-year change in potassium (and other change measures), we excluded those who developed diabetes or died before 1 year (n = 1,548) because these events preceded the measurement of potassium at 1 year. Consequently, these analyses evaluated progression to diabetes in 6,728 patients during the 1–5 years after baseline. We then assessed the association between 1-year change in serum potassium and subsequent risk of incident diabetes after multivariable adjustment. We checked for linearity between the association of change in potassium and diabetes risk by fitting restricted cubic splines. Missing values of covariables (<3% for all covariables except glycated hemoglobin at 15%), baseline serum potassium (approximately 1%), and 1-year change in serum potassium (approximately 9%) were imputed with single imputation.

We calculated the mediation effect of the 1-year change in serum potassium on the association between valsartan use and diabetes risk as the difference in log hazard ratios for valsartan from models excluding and including 1-year change in potassium as a covariable. The 95% confidence interval (CI) for the difference in log hazard ratios was computed by bootstrapping.

We performed a sensitivity analysis on a subgroup of the participants on diuretics, assuming that this group may have greater changes in serum potassium in response to valsartan. In this group, we ran multivariable Cox models adjusted for the same variables as above in our main analysis. For this subgroup, we also calculated the mediation effect of the 1-year change in serum potassium on the association between valsartan use and diabetes risk as we did for the main analysis. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

**RESULTS**

Baseline mean serum potassium was not different between treatment groups (P = 0.25) and ranged 3.7–6.8 mEq/L. In our multivariable model, which included 8,276 participants for progression to diabetes, baseline serum potassium was not a significant predictor of diabetes risk (P = 0.22).

For our analyses with 1-year change in potassium, 6,728 participants were included; 3,380 were randomized to valsartan, and 3,348 were randomized to no valsartan. Baseline characteristics are presented in Table 1. Baseline characteristics for this subgroup were similar for both treatment arms, with a mean age of participants of 63 years and a mean body mass index of 30 kg/m². Approximately 2% of participants in each arm were black. Participants in both arms had a mean fasting glucose of 110 mg/dl, a mean 2-hour glucose of 164 mg/dl, and a mean glycated hemoglobin of 5.8%. They were also similar in terms of their prevalence of cardiovascular disease, systolic blood pressure, use of a diuretic, and serum potassium, with a mean serum potassium of 4.3 mEq/L. The only statistically significant difference between treatment groups was the number of female participants in each group, with 48.9% in the valsartan group and 51.8% in the no valsartan group. At 1 year, those taking valsartan had a significant but small increase in potassium of 0.035 mEq/L, compared with −0.029 mEq/L in the no valsartan group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Valsartan (n = 3,380)</th>
<th>No valsartan (n = 3,384)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.1 ± 6.53</td>
<td>63.4 ± 6.53</td>
<td>0.16</td>
</tr>
<tr>
<td>Female sex</td>
<td>48.9</td>
<td>51.8</td>
<td>0.02</td>
</tr>
<tr>
<td>Black</td>
<td>2.4</td>
<td>2.5</td>
<td>0.86</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30.2 ± 5.32</td>
<td>30.4 ± 5.31</td>
<td>0.09</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>100.5 ± 13.27</td>
<td>100.7 ± 13.43</td>
<td>0.45</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>110 ± 7.93</td>
<td>110 ± 7.93</td>
<td>0.94</td>
</tr>
<tr>
<td>2-hour glucose, mg/dl</td>
<td>164 ± 16.76</td>
<td>164 ± 16.58</td>
<td>0.93</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>5.8 ± 0.44</td>
<td>5.8 ± 0.43</td>
<td>0.63</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>37.8</td>
<td>38.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>139.3 ± 17.73</td>
<td>139.9 ± 17.06</td>
<td>0.12</td>
</tr>
<tr>
<td>History of cardiovascular disease (any)</td>
<td>30.1</td>
<td>29.0</td>
<td>0.30</td>
</tr>
<tr>
<td>Use of diuretic</td>
<td>29.5</td>
<td>30.5</td>
<td>0.39</td>
</tr>
<tr>
<td>Use of beta-blocker</td>
<td>39.4</td>
<td>37.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Serum potassium, mEq/L</td>
<td>4.3 ± 0.40</td>
<td>4.3 ± 0.41</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Data are mean ± SD or percentages.

* P value based on t tests for continuous variables and χ² tests for categorical variables.
Effects of Changes in Potassium With Valsartan Use on Diabetes Risk

Table 2. Summary of results evaluating the mediation effects of change in serum potassium on the association between valsartan use and risk of incident diabetes

<table>
<thead>
<tr>
<th></th>
<th>Valsartan (n = 3,380)</th>
<th>No valsartan (n = 3,348)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in serum potassium at 1 year, mEq/L, mean (SD)</td>
<td>0.035 (0.426)</td>
<td>−0.029 (0.451)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident cases of diabetes over 4 years, No. (%)</td>
<td>1016 (30)</td>
<td>1117 (33)</td>
<td>0.002</td>
</tr>
<tr>
<td>HR (95% CI) of incident diabetes in multivariable model, excluding change in serum potassium</td>
<td>0.866 (0.795–0.943)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI) of incident diabetes in full multivariate model, including 1-year change in serum potassium</td>
<td>0.868 (0.797–0.945)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

* Adjusted for the following variables: age, body mass index, systolic blood pressure, cardiovascular composite event (myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting), family history of diabetes, fasting glucose, 2-hour glucose, glycated hemoglobin, low-density lipoprotein, high-density lipoprotein, platelet count, hemoglobin, country, race, and 1-year change in serum potassium.

* The bootstrap 95% CI for a difference in the log hazard ratios for the multivariate models, excluding and including 1-year change in potassium, was not significant (−0.003 to 0.009).

(P < 0.001) (Table 2). The mean serum potassium levels at this 1-year time point were 4.36 (SD = 0.41) mEq/L and 4.31 (SD = 0.43) mEq/L for the valsartan and no valsartan groups respectively (P < 0.001). The mean fasting glucose level at 1 year was 106 (SD = 12) mg/dl for both the valsartan and no valsartan groups (P = 0.20). Two-hour postchallenge glucose levels at 1 year were 143 (SD = 37) mg/dl and 146 (SD = 39) mg/dl for the valsartan and no valsartan groups respectively (P = 0.001). In the multivariable model, 1-year change in potassium was not a significant predictor of progression to diabetes (P = 0.47). There was no evidence of nonlinearity in this relationship (P = 0.34).

In the valsartan and no valsartan groups, 30% vs. 33% of participants developed diabetes during 4 years of follow-up (P = 0.002) (Table 2). The risk of diabetes among those on valsartan compared with those not on valsartan in the model excluding 1-year change in potassium (compared with the full model controlling for change in potassium) did not change significantly (Table 2). The bootstrap 95% CI for a difference in these log hazard ratios was not significant (−0.003 to 0.009).

In our sensitivity analysis of the mediation effect of change in serum potassium on the association between valsartan use and diabetes risk among diuretic users, we included 2,065 participants that remained free of diabetes at 1 year. The mean 1-year change in potassium was −0.038 (SD = 0.50) mEq/L in the no valsartan group compared with 0.064 (SD = 0.45) mEq/L in the valsartan group (P < 0.0001). The risk of diabetes among those on valsartan compared with those not on valsartan, among diuretic users only, in the model excluding 1-year change in potassium (compared with the full model controlling for change in potassium) did not change significantly (HR = 0.82, 95% CI = 0.71–0.96; and HR = 0.83, 95% CI = 0.71–0.96, respectively). The bootstrap 95% CI for a difference in these log hazard ratios was not significant (−0.009 to 0.024).

CONCLUSIONS

In this analysis of NAVIGATOR data, we found that change in serum potassium was not a significant mediator of the association between valsartan use and diabetes risk. We did not find a significant association between either baseline serum potassium or the 1-year change in serum potassium associated with valsartan use and diabetes risk over 4 years after adjustment for covariables. However, we did find that the mean 1-year change in serum potassium associated with valsartan use was quite small.

Potassium has been found to have a significant and independent inverse association with measures of glucose and diabetes risk in previous cohort studies. Secondary analyses of antihypertensive trial data involving thiazide diuretics have also revealed an inverse association between potassium levels and diabetes risk. One quantitative review found that, in the subset of studies in which thiazide users also received potassium supplements, there were smaller declines in serum potassium as well as smaller increases in glucose. Small clinical trials performed in healthy participants found that induction of clinically significant hypokalemia, with a low-potassium diet or use of thiazide diuretics, led to impaired glucose tolerance, primarily through diminishment in insulin secretion. One of these studies examined the effects of potassium supplementation after the induction of hypokalemia and found that normal glucose tolerance was restored. In these small clinical trials, the change in potassium from a hypokalemic state, with impaired glucose tolerance, to a potassium-repleted state, with normal glucose tolerance, was at least 0.6 mEq/L.

Before NAVIGATOR, the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers was associated with decreased risk of diabetes in some studies, mostly evaluated as trial secondary outcomes. The mechanism through which these agents may affect glucose metabolism is unclear. There are several ways in which angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers have been hypothesized to affect glucose metabolism, including direct vascular effects to organs that metabolize glucose, antioxidant properties, an increasing of potassium, or effects on the production of various hormones, including bradykinin, angiotensin II, aldosterone, and nitric oxide (all of which have potential effects on insulin function). Our analysis suggests that increasing potassium
is not the mechanism of action by which valsartan reduced the risk of diabetes in this population with impaired glucose tolerance.

Limitations of this analysis include the small change in serum potassium observed with valsartan use, which may have prevented us from assessing the effect of a clinically significant change in serum potassium on diabetes risk. There were not enough data to determine potential effects of even small changes of potassium or use of valsartan on intermediate measures of glucose metabolism, such as measures of insulin resistance or insulin secretion. In this population, there is likely a different pathway through which valsartan exerts its protective effects on diabetes risk. We did not adjust or analyze other mediation effects because of limitations in the dataset as well as in our understanding of the mechanism behind this pathway. There also may be differential effects of valsartan or other such medications on patients with frank hypokalemia, which could be studied further.

This study suggests that the protective effect of valsartan on diabetes risk found in NAVIGATOR is not mediated by changes in potassium. Further study is needed to determine the mechanism through which valsartan exerts its protective effect on diabetes risk. Further study is also needed to determine if interventions that raise serum potassium more than observed in this study help to reduce diabetes risk.

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REFERENCES