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A Post Hoc Analysis of KidneyIntelX™ and Cardiorenal Outcomes in Diabetic Kidney Disease

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Girish Nadkarni, Dipti Takale, Bruce Neal, Kenneth Mahaffey, Yshai Yavin, Michael Hansen, Fergus Fleming, Hiddo Heerspink, and Steven Coca

Key Points:
*KidneyIntelX, a bioprognostic test for assessing risk of CKD progression, risk-stratified individuals for kidney, heart failure, and death outcomes in CANVAS.

*Individuals scored as high-risk seemed to derive more of benefit from treatment with canagliflozin vs. placebo.

*These findings may serve to increase adoption of under-utilized therapies for cardiorenal risk reduction in patients with diabetic kidney disease.

Abstract:

Disclosures: Mr. Fleming is the chief technology officer and co-founder of Renalytix. Drs. Nadkarni and Coca are scientific co-founders of Renalytix, have equity, royalties, and are consultants and members of the scientific advisory board. G. Nadkarni reports the following: Consultancy: Renalytix, Siemens Healthineers, Qiing Capital, GLG consulting, Daiichi Sankyo, Reata, Variant Bio; Ownership Interest: Renalytix, Verici, Dolixity, Pensieve Health, Nexus iConnect, Data2Wisdom LLC; Research Funding: Renalytix; Honoraria: Daiichi Sankyo; Patents or Royalties: Renalytix; Advisory or Leadership Role: Renalytix; and Speakers Bureau: Daiichi Sankyo. S. Coca reports the following: Consultancy: Renalytix, Takeda, CHF Solutions, Vifor, Bayer, Reprieve Cardiovascular, Axon, 3ive; Ownership Interest: Renalytix, pulseData; Research Funding: Renalytix, ProKidney, RRI, XORTX; Patents or Royalties: Renalytix; Advisory or Leadership Role: Renalytix, Reprieve Cardiovascular; and Other Interests or Relationships: Associate Editor for Kidney360, Editorial Boards of JASN, CIASN, Kidney International. F. Fleming reports the following: Employer: RenalytixAI; Ownership Interest: RenalytixAI; Verici Dx; and Advisory or Leadership Role: RenalytixAI. M. Hansen reports the following: Employer: University Medical Center Groningen; Consultancy: Ongoing consultancy agreements with AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Chinook, Dimerix, Eli-Lilly, Gilead, GoldFinch, Janssen, Merck, NovoNordisk, Traver Pharmaceuticals; Research Funding: AstraZeneca, Novo Nordisk, and Janssen research support (grant funding directed to employer); Honoraria: Lecture fees from AstraZeneca; and Speakers Bureau: AstraZeneca. K. Mahaffey reports the following: Consultancy: Amgen, Applied Therapeutics, AstraZeneca, Bayer, CSL Behring, Elsevier, Fribrogen, Invo, Johnson & Johnson, Lexicon, Myokardia, Novartis, Novo Nordisk, Otsuka, PhaseBio, Portola, Precordior, Quidel, Sanofi, Theravance; Research Funding: AHA, Apple Inc, Bayer, California Institute Regenerative Medicine, Eidos, Ferring, Gilead, Google (Verily), Idorsia, Johnson & Johnson, Lutipold, PAC-12, Precordior, Sanifit; and Honoraria: Amgen, Anthon, Applied Therapeutics, AstraZeneca, Bayer, CSL Behring, Elsevier, Inova, Intermountain Health, Johnson & Johnson, Medscape, Mount Sinai, Mundipharma, Myokardia, Novartis, Novo Nordisk, Otsuka, Portola, Sanofi, SmartMedics, Theravance. B. Neal reports the following: Consultancy: Janssen Research & Development, LLC; Research Funding: Australian National Health and Medical Research Council Principal Research Fellowship and from Janssen.; Honoraria: All paid to institution.; Janssen Research & Development, LLC.; and Advisory or Leadership Role: Serving on advisory boards and/or involvement in continuing medical education (CME) programs for Janssen, with any consultancy, honoraria, or travel support paid to his institution. D. Takale reports the following: Employer: Persistent. Y. Yavin reports the following: Employer: Janssen; and Ownership Interest: Johnson & Johnson; Bristol-Myers Squibb.

Funding: None.
Author Contributions: Girish Nadkarni: Conceptualization; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing - original draft; Writing - review and editing Dipti Takale: Data curation; Formal analysis; Project administration; Resources; Validation; Writing - review and editing Bruce Neal: Investigation; Methodology; Resources; Writing - review and editing Kenneth Mahaffey: Funding acquisition; Investigation; Resources; Validation; Writing - review and editing Yshai Yavin: Funding acquisition; Investigation; Project administration; Resources; Validation; Writing - review and editing Michael Hansen: Funding acquisition; Investigation; Methodology; Resources; Validation; Writing - review and editing Fergus Fleming: Conceptualization; Formal analysis; Investigation; Methodology; Resources; Validation; Writing - review and editing Hiddo Heerspink: Conceptualization; Data curation; Methodology; Resources; Supervision; Writing - review and editing Steven Coca: Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing - original draft; Writing - review and editing

Data Sharing Statement:

Clinical Trials Registration:

Registration Number:

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A Post Hoc Analysis of KidneyIntelX™ and Cardiorenal Outcomes in Diabetic Kidney Disease

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Diabetic kidney disease (DKD) is the commonest cause of chronic kidney disease.\(^1\) In addition to progression to kidney failure, patients with DKD are also at risk for worsening of heart function and hospitalizations for heart failure (HHF).\(^2\) Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have beneficial effects on both DKD progression and heart failure.\(^3,4\) KidneyIntelX™ is a bioprognostic test validated for assessing risk of progression of prevalent DKD, and is currently utilized in clinical practice for this indication.\(^5,6\) SGLT2i are underutilized in the United States, despite robust evidence and guideline recommendations.\(^7\) Risk stratification for clinically relevant outcomes including DKD progression and HHF can prioritize patients for intensive management and identify those with most to gain from SGLT2i treatment. Due to shared pathophysiology of DKD and heart failure, we hypothesized that KidneyIntelX would also risk stratify patients with prevalent DKD for a clinically relevant kidney outcome as well as HHF and all-cause mortality.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) trial enrolled 4,330 participants from 24 countries.\(^8\) Participants were randomly assigned using a central Web-based response system in a 1:1:1 ratio for treatment with canagliflozin 100 mg, canagliflozin 300 mg, or a matching placebo. Participants assigned to treatment with canagliflozin, or the placebo were followed for a median of 6.1 years. KidneyIntelX was evaluated in the subgroup of the CANVAS population that met the criteria for prevalent DKD (eGFR ≥ 30–59.9 mL/min/1.73 m\(^2\) [G3a and G3b] or those with an eGFR ≥60 mL/min/1.73 m\(^2\) with an UACR ≥30 mg/g) at the time of enrollment with existing biobanked blood samples.\(^6\) Thus, of the 4330 participants in the CANVAS trial, 1396 had prevalent DKD and of them 1278 had available blood samples for KidneyIntelX ascertainment and analysis. We have previously demonstrated that KidneyIntelX robustly stratified patients for risk of kidney disease progression in this subgroup of the CANVAS trial population.\(^6\) In this subsequent post-hoc analysis, we assessed the association of KidneyIntelX at baseline with the time-to-event composite endpoint of 57% decline in eGFR or adjudicated end stage kidney disease (ESKD), HHF, or death. We measured soluble tumor necrosis factor receptors (sTNFR) 1 and 2, and kidney
injury molecule-1 (KIM-1) via proprietary assays, and calculated KidneyIntelX scores using the existing validated algorithm. The model was not recalibrated, reweighted, or retrained for this new composite outcome. We divided the patient population into high (score >85), intermediate (score 50-85), and low risk (score 5-45) strata using the clinical risk score cutoffs for KidneyIntelX. We calculated adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for high vs. low-risk strata for the composite outcome after adjusting for age, sex, race, randomization arm, baseline cardiovascular disease and baseline measures of hemoglobin A1C, blood pressure, low density lipoprotein cholesterol and body mass index, baseline eGFR, and baseline UACR.

Among the 1278 CANVAS participants in this post-hoc analysis, the mean age was 64 years, 32% were female, mean baseline eGFR was 65 mL/min/1.73 m², median UACR was 56 mg/g, 498 (40%) had eGFR< 60 ml/min/1.73m² and 209 (16%) had heart failure at baseline. During a mean of 5.6 years follow-up, 282 (22%) experienced the composite outcome; 41 (3%) developed a 57% decline in eGFR or ESKD, 78 (6%) were hospitalized for heart failure, and 209 (16%) died. The proportion with events was 17, 21, and 40% for low, intermediate, and high-risk strata, respectively. The aHR for the composite outcome in high-risk was 2.1 (95% CI 1.4 to 3.0) vs. low-risk group and was 1.4 (95% CI 1.02-1.9) in the intermediate vs. low-risk group. Additionally, we conducted a sensitivity analysis using a sustained 40% decline in eGFR, rather than a doubling in serum creatinine (57% decline in eGFR) in the composite outcome. The aHR for this composite outcome in high-risk was 2.2 (95% CI 1.3-2.8) vs. low-risk group and 1.5 (95% CI 1.1-2.0) in the intermediate vs. low-risk group (Table 1). Figure 1 shows the time to the composite events stratified by KidneyIntelX risk categories (Low, Intermediate and High) and Table 2 shows the aHRs for high vs. low in each component of the composite outcome. The risk for the composite event was reduced by 22-24% across all risk strata in participants randomized to canagliflozin vs. placebo, with absolute risk reductions of 11% in the high-risk stratum, 6% in the intermediate risk stratum, and 4% in the low risk stratum; p<0.01 for high- vs. low-risk).

Although KidneyIntelX has been validated for an outcome of DKD progression, the results from this subsequent post-hoc analysis from CANVAS demonstrated that KidneyIntelX robustly stratified patients for a composite endpoint consisting of clinically relevant outcomes. KidneyIntelX combines two inflammatory (sTNFR1/2), one injury (KIM1) and 7 clinical variables to create an individualized risk score using machine learning that allows for complex non-linear interaction modeling between biomarkers and clinical variables. In prior analyses from CANVAS, each of the three biomarkers, sTNFR1, sTNFR2, and KIM-1, were associated with HHF after adjustment only for demographics and randomized treatment, but the point estimates were attenuated to null after
KidneyIntelX is a commercially available test that is in use clinically at various health systems in the United States, and is CLIA-certified as a laboratory developed test in all 50 states. Real world deployment of new risk stratification tests (including biomarkers) necessitates a comprehensible message and integration into clinical workflow to drive clinician behavior and overcome therapeutic inertia. This could be potentially done through a composite risk score, such as the KidneyIntelX bioprognostic test, that combines both the biomarkers and clinical features. Since the SGLT2 inhibitors, including canagliflozin which was studied in the CANVAS population, have beneficial effects not only on kidney outcomes but also robust effects on heart failure hospitalizations, this study has clinical implications. Indeed, while the relative risks for the composite outcome for canagliflozin vs. placebo were similar across the 3 strata of KidneyIntelX risk, the absolute risk reductions achieved with canagliflozin, compared to placebo, were greatest in the high-risk KidneyIntelX stratum, thereby potentially allowing its use to identify patients most likely to benefit from treatment. Limitations of this post-hoc analysis include the lack of an independent external validation cohort, the use of an algorithm not specifically trained for the broad clinical composite assessed herein, and although we adjusted for 11 clinical covariates, potential for residual confounding.

In conclusion, the we demonstrated that KidneyIntelX, a composite risk score trained and validated for a kidney-specific outcome, provided risk stratification for a triple composite endpoint that included not only the kidney-specific outcome of progression, but also clinically relevant outcomes of hospitalizations for heart failure and all-cause mortality, even after adjusting for several other risk factors for these outcomes. These findings suggest that KidneyIntelX may have utility as a clinical trial enrichment tool for therapies to ameliorate cardiorenal risk, and provides further impetus to increase adoption of under-utilized guideline-recommended therapies to reduce risk of kidney disease progression, HHF, and death in clinical practice.

Disclosures:
Mr. Fleming is the chief technology officer and co-founder of Renalytix. Drs. Nadkarniand Coca are scientific co-founders of Renalytix, have equity, royalties,and are consultants and members of the scientific advisory board.

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Advisory or Leadership Role: Renalytix, Reprieve Cardiovascular; and Other Interests or Relationships: Associate Editor for Kidney360, Editorial Boards of JASN, CJASN, Kidney International. F. Fleming reports the following: Employer: RenalytixAI; Ownership Interest: RenalytixAI; Verici Dx; and Advisory or Leadership Role: RenalytixAI. M. Hansen reports the following: Employer: Janssen Research & Development; and Ownership Interest: Johnson & Johnson. H. L Heerspink reports the following: Employer: University Medical Center Groningen; Consultancy: Ongoing consultancy agreements with AstraZeneca, Bayer, Boehringer Ingelheim, CSL Behring, Chinook, Dimerix, Eli-Lilly, Gilead, GoldFinch, Janssen, Merck, NovoNordisk, Traverpe Pharmaceuticals; Research Funding: AstraZeneca, NovoNordisk and Janssen research support (grant funding directed to employer); Honoraria: Lecture fees from AstraZeneca; and Speakers Bureau: AstraZeneca. K. Mahaffey reports the following: Consultancy: Amgen, Applied Therapeutics, AstraZeneca, Bayer, CSL Behring, Elsevier, Fribrogen, Invo, Johnson & Johnson, Lexicon, Myokardia, Novartis, Novo Nordisk, Otsuka, Phasebio, Portola, Precordior, Quidel, Sanofi, Theravance; Research Funding: AHA, Apple Inc, Bayer, California Institute Regenerative Medicine, Eidos, Ferring, Gilead, Google (Verily), Idorsia, Johnson & Johnson, Luitpold, PAC-12, Precordior, Sanifit; and Honoraria: Amgen, Anthos, Applied Therapeutics, AstraZeneca, Bayer, CSL Behring, Elsevier, Inova, Intermountain Health, Johnson & Johnson, Medscae, Mount Sinai, Mundi Pharma, Myokardia, Novartis, Novo Nordisk, Otsuka, Portola, Sanofi, SmartMedics, Theravance. B. Neal reports the following: Consultancy: Janssen Research & Development, LLC; Research Funding: Australian National Health and Medical Research Council Principal Research Fellowship and from Janssen,; Honoraria: All paid to institution.; Janssen Research & Development, LLC;; and Advisory or Leadership Role: Serving on advisory boards and/or involvement in continuing medical education (CME) programs for Janssen, with any consultancy, honoraria, or travel support paid to his institution. D. Takale reports the following: Employer: Persistent. Y. Yavin reports the following: Employer: Janssen; and Ownership Interest: Johnson & Johnson; Bristol-Myers Squibb.

Funding:
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Author Contributions:
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References:

Table 1. Associations with Different Composite Outcomes for KidneyIntelX High vs. Low Risk Strata after successive adjustment for risk factors

<table>
<thead>
<tr>
<th>Composite Outcome</th>
<th>Adjusted HR for High vs. Low Risk (95% CI)</th>
<th>Adjusted HR for Intermediate vs. Low Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-to-event composite endpoint of 57% decline in eGFR or adjudicated end stage kidney disease (ESKD), HHF, or death</td>
<td>Model 1 3.04 (2.23-4.16) Model 2 2.67 (1.90-3.75) Model 3 2.10 (1.42-2.97)</td>
<td>1.36 (1.03-1.81) 1.35 (1.01-1.82) 1.40 (1.02-1.86)</td>
</tr>
<tr>
<td>Time-to-event composite endpoint of sustained 40% decline in eGFR or adjudicated end stage kidney disease (ESKD), HHF, or death</td>
<td>Model 1 3.25 (2.31-4.30) Model 2 2.91 (1.97-3.85) Model 3 2.16 (1.30-2.75)</td>
<td>1.47 (1.13-1.96) 1.46 (1.10-1.97) 1.47 (1.08-1.94)</td>
</tr>
</tbody>
</table>

HR=Hazard Ratio; 95 CI=95% Confidence Interval

Model 1= Adjusted for age, sex and randomization arm; Model 2= Model 1+ Baseline cardiovascular disease, hemoglobin A1C, systolic and diastolic blood pressures, low density lipoprotein and body mass index; Model 3=Model 2+baseline eGFR and baseline UACR.

Table 2. Adjusted Hazard Ratios for Individual Components of the Composite Clinical Outcome

<table>
<thead>
<tr>
<th>Component</th>
<th>n/N</th>
<th>Adjusted Hazard Ratio for High vs. Low Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Outcome</td>
<td>282/1278</td>
<td>2.1 (1.4-2.9)</td>
</tr>
<tr>
<td>Kidney Outcome</td>
<td>41/1278</td>
<td>20.7 (4.6-93.3)</td>
</tr>
<tr>
<td>Hospitalizations for Heart Failure</td>
<td>78/1278</td>
<td>1.9 (1-3.9)</td>
</tr>
<tr>
<td>Death</td>
<td>209/1278</td>
<td>1.3 (0.9-2.2)</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, randomization arm, baseline cardiovascular disease, hemoglobin A1C, systolic and diastolic blood pressures, low density lipoprotein, body mass index, eGFR and UACR.
Figure 1. Kaplan-Meier Curves for the Composite Event by KidneyIntelX Risk Strata

Risk category: Low risk, Intermediate risk, High risk

Survival Rate vs. Time (months)

Number at risk

<table>
<thead>
<tr>
<th>Risk category</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>502</td>
<td>491</td>
<td>480</td>
<td>470</td>
<td>459</td>
<td>454</td>
<td>441</td>
<td>416</td>
<td>65</td>
<td>6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>583</td>
<td>573</td>
<td>560</td>
<td>539</td>
<td>523</td>
<td>510</td>
<td>494</td>
<td>460</td>
<td>52</td>
<td>0</td>
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<tr>
<td>High risk</td>
<td>193</td>
<td>184</td>
<td>176</td>
<td>159</td>
<td>154</td>
<td>147</td>
<td>142</td>
<td>124</td>
<td>14</td>
<td>0</td>
</tr>
</tbody>
</table>

Cumulative number of events

<table>
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<th>Risk category</th>
<th>0</th>
<th>10</th>
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<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>0</td>
<td>9</td>
<td>23</td>
<td>41</td>
<td>57</td>
<td>70</td>
<td>86</td>
<td>107</td>
<td>120</td>
<td>120</td>
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<tr>
<td>Intermediate</td>
<td>0</td>
<td>9</td>
<td>17</td>
<td>34</td>
<td>39</td>
<td>46</td>
<td>51</td>
<td>62</td>
<td>78</td>
<td>78</td>
</tr>
<tr>
<td>High risk</td>
<td>0</td>
<td>9</td>
<td>17</td>
<td>34</td>
<td>39</td>
<td>46</td>
<td>51</td>
<td>62</td>
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