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

Girish N. Nadkarni [ID],[1,2] *Dipti Takale,*[3] *Bruce Neal* [ID],[4] *Kenneth W. Mahaffey,*[5] *Yshai Yavin,*[6] *Michael K. Hansen* [ID],[6] *Fergus Fleming,*[7] *Hiddo J.L. Heerspink* [ID],[8] *and Steven G. Coca* [ID][2]

Key Points

- KidneyIntelX, a bioprognostic test for assessing risk of CKD progression, risk stratified individuals for kidney, heart failure, and death outcomes in the Canagliflozin Cardiovascular Assessment Study.
- Individuals scored as high risk seemed to derive more of benefit from treatment with canagliflozin versus placebo.
- These findings may serve to increase adoption of underutilized therapies for cardiorenal risk reduction in patients with diabetic kidney disease.

Diabetic kidney disease (DKD) is the commonest cause of CKD (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, HHF, and all-cause mortality.

The Canagliflozin Cardiovascular Assessment Study (CANVAS) trial enrolled 4330 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 $\geq$30–59.9 ml/min per 1.73 m^2 [G3a and G3b] or those with an eGFR $\geq$60 ml/min per 1.73 m^2 with a urine

albumin-creatinine ratio [uACR] $\geq$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 those, 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 end point of 57% decline in eGFR or adjudicated ESKD, HHF, or death. We measured soluble TNF receptors (sTNFR) 1 and 2, and kidney injury molecule-1 (KIM-1) *via* proprietary assays (9), and calculated KidneyIntelX scores using the existing validated algorithm (5,6). 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 (5,6). We calculated adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for high- versus low-risk strata for the composite outcome after adjusting for age, sex, race, randomization arm, baseline cardiovascular disease, and baseline measures of hemoglobin A1C, BP, low-density lipoprotein cholesterol, 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 women, the mean baseline eGFR was 65 ml/min per 1.73 m^2, the median uACR was 56 mg/g, 498 (40%)

[1]Division of Data-Driven and Digital Medicine, Icahn School of Medicine at Mount Sinai, New York, New York
[2]The Barbara T. Murphy Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, New York
[3]Persistent Systems, Pune, India
[4]The George Institute for Global Health, UNSW Sydney, Sydney, Australia
[5]Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, California
[6]Janssen Research and Development, LLC, Spring House, Pennsylvania
[7]Renalytix, New York, New York
[8]Department of Clinical Pharmacy and Pharmacology, University of Groningen, Groningen, The Netherlands

Correspondence: Drs. Girish N. Nadkarni or Steven Coca, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1243, New York, NY 10029. Email: girish.nadkarni@mountsinai.org or steven.coca@mssm.edu

Table 1. Associations with different composite outcomes for KidneyIntelX high versus low risk strata after successive adjustment for risk factors

	Adjusted HR for High versus Low Risk (95% Confidence Interval)	Adjusted HR for Intermediate versus Low Risk (95% Confidence Interval)
Time-to-event composite end point of 57% decline in eGFR or adjudicated ESKD, HHF, or death		
Model 1	3.04 (2.23 to 4.16)	1.36 (1.03 to 1.81)
Model 2	2.67 (1.9 to 3.75)	1.35 (1.01 to 1.82)
Model 3	2.10 (1.42 to 2.97)	1.40 (1.02 to 1.86)
Time-to-event composite end point of sustained 40% decline in eGFR or adjudicated ESKD, HHF, or death		
Model 1	3.25 (2.31 to 4.3)	1.47 (1.13 to 1.96)
Model 2	2.91 (1.97 to 3.85)	1.46 (1.1 to 1.97)
Model 3	2.16 (1.3 to 2.75)	1.47 (1.08 to 1.94)

Model 1 adjusted for age, sex, and randomization arm; model 2=model 1+baseline cardiovascular disease, hemoglobin A1C, systolic and diastolic BPs, low-density lipoprotein, and body mass index; model 3=model 2+baseline eGFR and baseline uACR. HR, hazard ratio; CI, confidence interval; HHF, hospitalizations for heart failure; uACR, urine albumin-creatinine ratio.

had an eGFR< 60 ml/min per 1.73 m^2, 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 was 2.1 (95% CI, 1.4 to 3) in the high- versus low-risk group, and it was 1.4 (95% CI, 1.02 to 1.9) in the intermediate- versus 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 was 2.2 (95% CI, 1.3 to 2.8)

in the high- versus low-risk group, and it was 1.5 (95% CI, 1.1 to 2) in the intermediate- versus 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 versus low risk 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 versus 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 versus 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
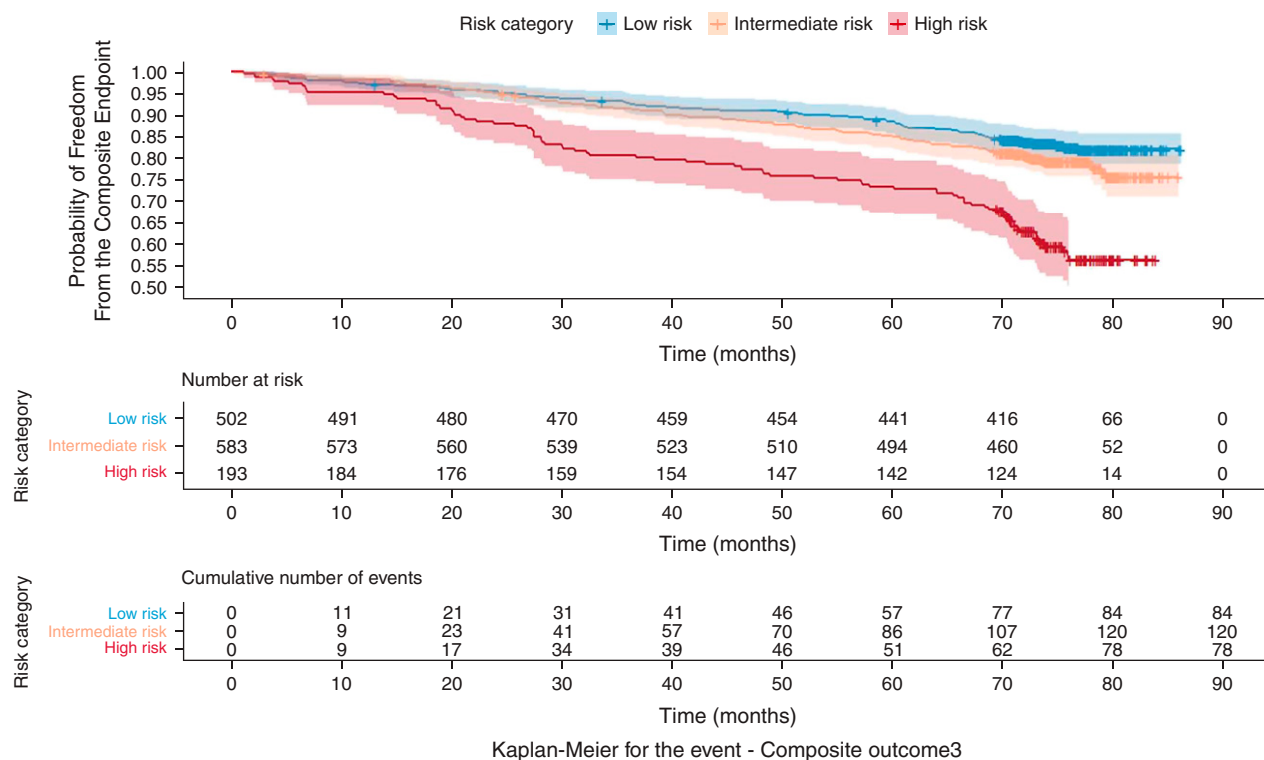

Figure 1. | **Kaplan–Meier curves for the composite event by KidneyIntelX risk strata.** The composite end point consisted of time to first occurrence of 57% decline in eGFR or adjudicated ESKD, hospitalization for heart failure, or death.

Table 2. Adjusted hazard ratios for individual components of the composite clinical outcome

Component	n/N	Adjusted Hazard Ratio for High versus Low Risk (95% Confidence Interval)
Composite outcome	282/1278	2.1 (1.4–2.9)
Kidney outcome	41/1278	20.7 (4.6–93.3)
Hospitalizations for heart failure	78/1278	1.9 (1.0–3.9)
Death	209/1278	1.3 (0.9–2.2)

Adjusted for age, sex, randomization arm, baseline cardiovascular disease, hemoglobin A1C, systolic and diastolic BPs, low-density lipoprotein, body mass index, eGFR, and urine albumin-creatinine ratio.

KidneyIntelX robustly stratified patients for a composite end point consisting of clinically relevant outcomes. KidneyIntelX combines two inflammatory markers (sTNFR1 & 2), one tubule injury marker (KIM-1), ratios of the markers, and seven clinical variables to create an individualized risk score using random forests that allows for complex nonlinear 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 full covariate adjustment (9). 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, which combines both the biomarkers and clinical features. Because the SGLT2 inhibitors, including canagliflozin which was studied in the CANVAS population, have not only beneficial effects on kidney outcomes but also robust effects on heart failure hospitalizations (10), this study has clinical implications. Indeed, although the relative risks for the composite outcome for canagliflozin versus placebo were similar across the three strata of KidneyIntelX risk, the absolute risk reductions achieved with canagliflozin compared with 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, we demonstrated that KidneyIntelX, a composite risk score trained and validated for a kidney-specific outcome, provided risk stratification for a triple composite end point 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 underutilized guideline-recommended therapies to reduce risk of kidney disease progression, HHF, and death in clinical practice.

Author Contributions
S.G. Coca was responsible for visualization; S.G. Coca, F. Fleming, M.K. Hansen, H.J.L. Heerspink, K.W. Mahaffey, G.N. Nadkarni, B. Neal, D. Takale, and Y. Yavin reviewed and edited the manuscript; S.G. Coca, F. Fleming, M.K. Hansen, H.J.L. Heerspink, G.N. Nadkarni, and B. Neal were responsible for the methodology; S.G. Coca, F. Fleming, M.K. Hansen, K.W. Mahaffey, G.N. Nadkarni, B. Neal, and Y. Yavin were responsible for the investigation; S.G. Coca, F. Fleming, M.K. Hansen, K.W. Mahaffey, D. Takale, and Y. Yavin were responsible for validation; S.G. Coca, F. Fleming, H.J.L. Heerspink, and G.N. Nadkarni were responsible for conceptualization; S.G. Coca, F. Fleming, G.N. Nadkarni, and D. Takale were responsible for formal analysis; S.G. Coca, H.J.L. Heerspink, and G.N. Nadkarni were responsible for supervision; S.G. Coca and G.N. Nadkarni wrote the original draft of the manuscript; F. Fleming, M.K. Hansen, H.J.L. Heerspink, K.W. Mahaffey, B. Neal, D. Takale, and Y. Yavin were responsible for resources; M.K. Hansen, K.W. Mahaffey, and Y. Yavin were responsible for funding acquisition; H.J.L. Heerspink and D. Takale were responsible for data curation; and G.N. Nadkarni, D. Takale, and Y. Yavin were responsible for project administration.

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