Insulin-Like Growth Factor Binding Protein 7 Predicts Renal and Cardiovascular Outcomes in the Canagliflozin Cardiovascular Assessment Study

James L. Januzzi Jr.,[1] Javed Butler,[2] Naveed Sattar,[3] Jialin Xu,[4] Wayne Shaw,[5] Norman Rosenthal,[5] Michael Pfeifer,[6] Kenneth W. Mahaffey,[7] Bruce Neal,[8,9] and Michael K. Hansen[4]

Diabetes Care 2021;44:210–216 | https://doi.org/10.2337/dc20-1889

OBJECTIVE

To analyze the association between concentrations of plasma insulin-like growth factor binding protein 7 (IGFBP7) with renal and cardiac outcomes among participants with type 2 diabetes and high cardiovascular risk.

RESEARCH DESIGN AND METHODS

Associations between IGFBP7 levels and clinical outcomes were assessed among participants in the Canagliflozin Cardiovascular Assessment Study (CANVAS) with type 2 diabetes and high cardiovascular risk.

RESULTS

Among CANVAS participants, 3,577 and 2,898 had IGFBP7 measured at baseline and 1 year, respectively. Per log-unit higher concentration, baseline IGFBP7 was significantly associated with the composite renal end point of sustained 40% reduction in estimated glomerular filtration rate, need for renal replacement therapy, or renal death (hazard ratio [HR] 3.51; $P < 0.001$) and the composite renal end point plus cardiovascular death (HR 4.90; $P < 0.001$). Other outcomes, including development or progression of albuminuria, were also predicted by baseline IGFBP7. Most outcomes were improved by canagliflozin regardless of baseline IGFBP7; however, those with baseline concentrations ≥96.5 ng/mL appeared to benefit more from canagliflozin relative to the first progression of albuminuria compared with those with lower baseline IGFBP7 (HR 0.64 vs. 0.95; $P_{interaction} = 0.003$). Canagliflozin did not lower IGFBP7 concentrations by 1 year; however, at 1 year, higher IGFBP7 concentrations more strongly predicted the composite renal end point (HR 15.7; $P < 0.001$). Patients with rising IGFBP7 between baseline and 1 year had the highest number of composite renal events.

CONCLUSIONS

Plasma IGFBP7 concentrations predicted renal and cardiac events among participants with type 2 diabetes and high cardiovascular risk. More data are needed regarding circulating IGFBP7 and progression of diabetic kidney disease and its complications.

[1]*Cardiology Division, Massachusetts General Hospital and Baim Institute for Clinical Research, Boston, MA*
[2]*University of Mississippi, Jackson, MS*
[3]*Glasgow Cardiovascular Research, Glasgow, U.K.*
[4]*Janssen Research & Development, LLC, Spring House, PA*
[5]*Janssen Research & Development, LLC, Raritan, NJ*
[6]*Janssen Scientific Affairs, LLC, Titusville, NJ*
[7]*Stanford Center for Clinical Research, Department of Medicine, Stanford University School of Medicine, Stanford, CA*
[8]*The George Institute for Global Health and Charles Perkins Centre, University of Sydney, Sydney, Australia*
[9]*Imperial College London, London, U.K.*

Corresponding author: James L. Januzzi Jr., jjanuzzi@partners.org

Received 28 July 2020 and accepted 2 October 2020

Clinical trial reg. no. NCT01032629, clinicaltrials.gov

This article contains supplementary material online at https://doi.org/10.2337/figshare.13050866.

Patients with type 2 diabetes have a heightened risk for development of glomerulosclerosis, tubulointerstitial fibrosis, proteinuria, and progressive reduction in estimated glomerular filtration rate (eGFR) (1). Diabetes is a leading cause of need for renal replacement therapy (RRT), and diabetic kidney disease is accompanied by substantial risk for cardiovascular events, such as death. An unmet need is an objective means by which to predict diabetic kidney disease onset or its progression.

In the recent Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, among a population of patients with type 2 diabetes and high cardiovascular risk who are at risk for development or progression of diabetic kidney disease compared with placebo, treatment with the sodium–glucose cotransporter 2 inhibitor canagliflozin significantly reduced rates of progressive albuminuria (2,3). Furthermore, canagliflozin treatment reduced the frequency of the composite end point of sustained 40% reduction of eGFR, need for RRT, or death from cardiorenal causes (4–6). Effects of canagliflozin to improve renal outcomes and the composite of renal outcomes plus cardiovascular death were recently affirmed in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial (3).

Given the importance of diabetic kidney disease and therapies shown to mitigate its severity and associated complications, tools to predict its onset and progression would be desirable. Circulating biomarkers represent an attractive option for this application, given the potential for detecting signals of disease that might not otherwise be recognized; however, most biomarkers reported to date have underperformed for predicting onset or progression of diabetic kidney disease, and specific biomarkers identifying the benefit of therapies to reduce onset or progression of diabetic kidney disease remain elusive. Insulin-like growth factor binding protein 7 (IGFBP7) is a 29-kDa protein secreted by numerous tissues of the body. It is a member of the senescence-associated secretory phenotype with pluripotent in vivo roles, notably including induction of G1/S cell cycle arrest (7). Prior work has linked urinary concentrations of IGFBP7 (measured together with tissue inhibitor of metalloproteinase 2) for prediction of acute kidney injury (8). Whether IGFBP7 measurement provides information in diabetic kidney disease is not known, and its measurement in plasma for such evaluation has not been explored. Accordingly, circulating concentrations of IGFBP7 were measured among participants in the CANVAS trial. We hypothesized IGFBP7 concentrations would predict risk for kidney end points in the trial and evaluated for the presence of an interaction between biomarkers and effects of canagliflozin.

RESEARCH DESIGN AND METHODS

Patients

The study design, participant characteristics, and main results from the CANVAS Program have been previously published (2–6,9,10). The CANVAS Program was an integrated analysis of two similarly designed and conducted trials, CANVAS and CANVAS-Renal (CANVAS-R). Data from this analysis are solely from the CANVAS trial (see Supplementary Material for a list of sites and investigators). Participants were individuals with type 2 diabetes (glycated hemoglobin [HbA_{1c}] level $\geq$7.0% and $\leq$10.5%) and high risk for cardiovascular events. The patients were $\geq$30 years of age with a history of symptomatic atherosclerotic cardiovascular disease or were $\geq$50 years of age with two or more risk factors for cardiovascular disease. Participants were required to have an eGFR $>$30 mL/min/1.73 m^2. CANVAS participants were randomized (1:1:1) to canagliflozin 100 or 300 mg or placebo. All major cardiovascular events, kidney outcomes, and deaths were adjudicated by end point adjudication committees.

Figure 1 is a study flow diagram outlining participants in the current study. Samples for biomarker measurement in this post hoc analysis were collected from patients enrolled in the CANVAS trial who consented for the collection of samples for exploratory biomarker research. Approval was obtained from institutional review boards and independent ethics committees for each participating center.

Plasma samples were collected at baseline and year 1 and stored at −80°C. IGFBP7 was measured using a preclinical research-use only assay on an automated platform blinded to the treatment arm and visit information (Roche Diagnostics, Penzberg, Germany). The detection method for IGFBP7 was a sandwich immunoassay developed on the Elecsys platform for electrochemiluminescence detection (Roche Diagnostics). Mouse monoclonal antibodies were generated and screened for specific detection of IGFBP7. The precision within-run coefficient of variation for IGFBP7 was 2%, and the limit of detection was 0.01 ng/mL.

Outcomes

For the purposes of this analysis, we evaluated the predictive ability of IGFBP7 concentrations at baseline and 1 year for key renal outcomes of the CANVAS Program. The statistical analysis plan was assembled before IGFBP7 measurement, and analyses were performed according to intention to treat. The primary outcome measure of interest was the renal composite end point from CANVAS, comprising a 40% reduction in eGFR sustained for two or more consecutive measures, the need for RRT (dialysis or transplantation), or death from renal causes (defined as death with a proximate renal cause). Additional outcomes included progression to macroalbuminuria (among those without macroalbuminuria at baseline) and a composite progression of albuminuria (defined as $>$30% increase in albuminuria and a change from normoalbuminuria to microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria). Lastly, given that the primary end point of the CREDENCE trial was a comparable composite renal end point plus cardiovascular death (3), this end point was included in the present analysis.

Statistical Analysis

This post hoc analysis examined several questions: effects of canagliflozin on IGFBP7 concentrations from baseline to 1 year, associations between baseline IGFBP7 and outcomes, associations between IGFBP7 at 1 year and outcomes, and association between IGFBP7 categorical change at 1 year and outcomes. In each outcome analysis, canagliflozin treatment effect as a function of IGFBP7 status was examined.

To address nonnormality, IGFBP7 values were log-transformed before analysis. Clinical demographic data and cardiovascular and renal outcomes data, including off-treatment events, were merged with IGFBP7 results. Given the similar treatment effect from both canagliflozin treatment regimens (100 and 300 mg daily), data from patients receiving either of the two doses were combined in this analysis. To

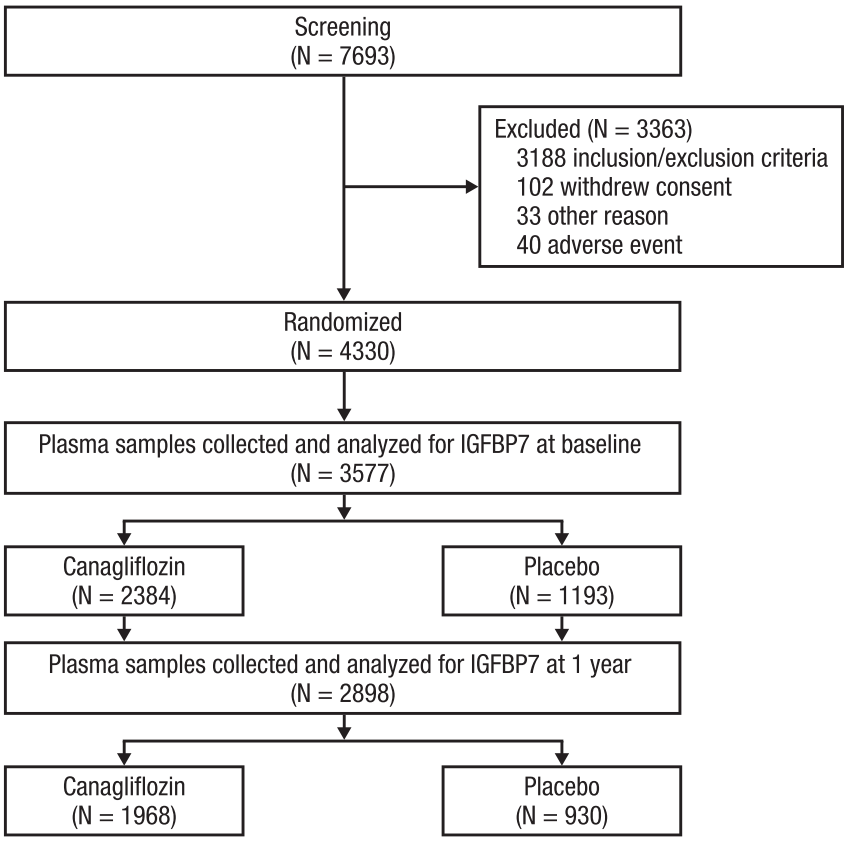

Figure 1—Study flow for CANVAS IGFBP7 analysis.

estimate the treatment effect on IGFBP7 concentrations at 1 year, a base linear model was constructed for log-transformed biomarker levels at 1 year by selecting important baseline covariates in patients randomized to placebo in the main study based on Bayesian information criterion. The candidate covariates at baseline included age, eGFR, BMI, systolic blood pressure, HbA_{1c}, duration of diabetes, urine albumin-to-creatinine ratio (UACR), history of heart failure, and history of diuretic treatment. The treatment term (canagliflozin vs. placebo) was then added to a base model to test the treatment effect on IGFBP7 concentrations at 1 year. The geometric mean ratio and 95% CI were estimated for canagliflozin compared with placebo, and the nominal *P* value was also reported.

To estimate the association between the clinical outcome end points and IGFBP7 levels, a base model was also constructed for each end point from the same candidate covariates described above (plus treatment) using Cox proportional hazards model, and proportion of hazards were checked and verified. IGFBP7 concentrations at baseline and 1 year were subsequently added to explore the association between outcome end points and IGFBP7 concentrations. The hazard ratio (HR) for a 2.72 [= exp(1)]–fold increase in IGFBP7, 95% CI, and nominal *P* value were also reported. The model C index and change in the C index with the addition of IGFBP7 results to the model were calculated.

To provide a clinical context to results from IGFBP7 between treatment arms, IGFBP7 concentrations dichotomized at a median baseline value of 96.5 ng/mL or examined across quartiles and the interaction of these values with treatment were added into the base model described previously.

All statistics were performed using R 3.6.1 software, with two-sided *P* values <0.05 considered significant.

Data Availability

Clinical data from the CANVAS Program are available in the public domain via the Yale University Open Data Access Project (https://yoda.yale.edu/).

RESULTS

Of the 4,330 participants enrolled in the CANVAS trial, plasma samples were collected and analyzed for N-terminal pro-B type natriuretic peptide (NT-proBNP) in 3,577 participants at baseline and in 2,898 participants at 1 year (Fig. 1). The baseline characteristics for participants with biomarker samples were balanced between those assigned to canagliflozin and placebo and were generally consistent with the overall CANVAS trial population (Table 1). On average, the study participants with biomarker samples were 62.5 ± 7.8 years of age, were more likely to be male and White, and had type 2 diabetes for an average of 13.5 ± 7.4 years. Overall, those in this analysis had a baseline eGFR of 77.5 ± 18.5 mL/min/1.73 m^2 and UACR of 9.5 ± 36.6 mg/g.

Effects of Canagliflozin on IGFBP7 Concentrations

Baseline geometric mean concentrations of IGFBP7 were similar between those allocated to receive canagliflozin (97.6 ng/mL) or placebo (96.7 ng/mL). During follow-up, a slight increase in IGFBP7 concentrations was seen in both treatment arms; geometric mean concentrations were again similar between those receiving canagliflozin versus placebo (99.0 vs. 98.9 ng/mL). In models adjusted for log-transformed baseline IGFBP7, age, HbA_{1c}, eGFR, UACR, and treatment assignment, the treatment effect of canagliflozin versus placebo at 1 year was not significant ($\beta = -0.0044$ [95% CI –0.0201, 0.0113]; $P = 0.58$). Findings were similar in sensitivity analyses with more parsimonious models. Supplementary Table 1 details baseline and 1-year IGFBP7 concentrations by UACR status at baseline. This demonstrates substantially higher concentrations of IGFBP7 in those with micro- and macroalbuminuria at baseline and 1 year compared with those with normoalbuminuria. Treatment effect of canagliflozin on IGFBP7 by 1 year remained nonsignificant in those with microalbuminuria (ratio of mean IGFBP7 change canagliflozin-to-placebo, 0.98; $P = 0.27$); in those with macroalbuminuria at baseline ($n = 162$), the ratio of mean IGFBP7 change (canagliflozin-to-placebo) by 1 year did not achieve statistical significance (0.89; $P = 0.11$).

Baseline IGFBP7 Concentration and Outcomes

Table 2 details the association between baseline log-transformed IGFBP7

Table 1—Baseline characteristics of CANVAS participants with samples available for IGFBP7 analysis

Characteristic	Canagliflozin (n = 2,384)	Placebo (n = 1,193)
Age, years	62.8 (7.9)	62.5 (7.8)
Female, *n* (%)	789 (33)	395 (33)
Race, *n* (%)		
White	1,941 (81)	968 (81)
Asian	233 (10)	121 (10)
Black	55 (2)	31 (3)
eGFR, mL/min/1.73 m^2	77.2 (18.7)	76.8 (19.0)
BMI, kg/m^2	32.7 (6.1)	32.6 (6.2)
SBP, mmHg	136.4 (15.9)	137.2 (15.8)
HbA_{1c}, %	8.2 (0.9)	8.2 (0.9)
HbA_{1c}, mmol/mol	66 (9.8)	66 (9.8)
Diabetes duration, years	13.6 (7.5)	13.4 (7.5)
UACR, mg/g	9.1 (35.7)	11.3 (40.4)
History of heart failure, *n* (%)	296 (12)	170 (13)
Diuretic use, *n* (%)	1,109 (47)	552 (46)
Sulfonylurea use, *n* (%)	1,043 (44)	521 (44)
GLP-1 use, *n* (%)	60 (3)	26 (2)
Statin use, *n* (%)	1,787 (75)	866 (73)
Insulin use, *n* (%)	1,258 (53)	621 (52)
Metformin use, *n* (%)	1,737 (73)	858 (72)
RAAS inhibitor use, *n* (%)	1,950 (82)	977 (82)
β-Blocker use, *n* (%)	1,210 (51)	605 (51)

Data are mean (SD) unless otherwise indicated. GLP-1, glucagon-like peptide 1; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

concentrations and outcomes of interest for this analysis among the 3,577 study participants with samples for analysis in the CANVAS study. In adjusted analyses, higher concentrations of the biomarker were associated with risk for the composite renal end point (HR 3.51; 95% CI 1.66–7.42; $P < 0.001$), the composite renal end point plus cardiovascular death (HR 4.90; 95% CI 3.16–7.60; $P < 0.001$), plus the composite renal end point plus progression to macroalbuminuria (HR 3.80; 95% CI 1.54–4.07; $P < 0.001$). Higher baseline IGFBP7 also predicted individual end points such as progression to macroalbuminuria, 40% decline in eGFR, and the composite of first progression of albuminuria. As well, addition of IGFBP7 to the best models for predicting each outcome generally increased the C index for most outcomes, although these increases were small. Supplementary Table 2 details the same analyses with baseline treatment forced into the model; this demonstrates attenuation of the HR magnitude, but nearly all remained significant. Supplementary Table 3 lists outcomes relative to the dichotomized baseline IGFBP7 concentration of 96.5 ng/mL. Larger reductions in risk were consistently seen in those with higher IGFBP7, but most outcomes did not demonstrate an interaction baseline IGFBP7 and treatment effect. One possible exception was that those with higher IGFBP7 concentrations appeared to specifically benefit from canagliflozin treatment with respect to the end point of first progression of micro- or macroalbuminuria, where an interaction between baseline IGFBP7 and canagliflozin effects was observed. For example, those with a baseline IGFBP7 ≥96.5 ng/mL demonstrated greater impact of canagliflozin versus placebo on the first progression of albuminuria (44.7% vs. 35.7%; HR 0.64) than in those with lower IGFBP7 concentrations who showed similar rates of subsequent first progression of albuminuria whether randomized to placebo or canagliflozin (30.9% vs. 32.2%; HR 0.95; $P_{interaction} = 0.003$). Examined across quartiles of IGFBP7, larger effects of canagliflozin versus placebo were confirmed above the median split ($P_{interaction} = 0.03$) (Fig. 2).

IGFBP7 Concentration and Outcomes at 1 Year

For the 2,898 study participants with a baseline and 1-year sample, we then examined predictive ability of log-transformed IGFBP7 to predict outcomes (Table 2). Associations between log-transformed IGFBP7 at 1 year and risk for end points were consistent with baseline predictive ability for some end points and even stronger than the baseline values for others. For example, higher IGFBP7 concentrations at 1 year predicted the composite renal end point substantially more strongly than the baseline value (HR 15.7; 95% CI 7.68–32.0; $P < 0.001$); plotted HRs across 1-year IGFBP7 concentrations are detailed in Supplementary Fig. 1. Much of this reflected the ability of higher IGFBP7 concentrations at 1 year to very strongly predict a subsequent 40% reduction in eGFR (HR 14.8; 95% CI 7.2–30.6; $P < 0.001$). Addition of log-transformed IGFBP7 concentrations increased the C index for best models to predict each outcome. Supplementary Table 4 demonstrates outcomes relative to the dichotomized IGFBP7 concentrations at 1 year, once again demonstrating substantial predictive ability of 1-year IGFBP7 to prognosticate subsequent cardiorenal outcomes. No interaction term was detected between 1-year IGFBP7 concentrations and treatment allocation relative to subsequent events, but the absolute reductions in outcomes associated with canagliflozin treatment were greater in those with higher IGFBP7 concentrations.

IGFBP7 Categorical Analysis From Baseline to 1 Year

Given the importance of both baseline and 1-year IGFBP7 concentrations, we then examined rates of the composite renal end point relative to the change in IGFBP7 from baseline to 1 year relative to the dichotomous cut point of 96.5 ng/mL. We further divided patients relative to treatment with placebo versus canagliflozin. As shown in Supplementary Fig. 2, rates of the renal composite end point were particularly highest in those with elevated IGFBP7 concentrations at baseline and 1 year, where the impact of canagliflozin treatment was most obvious. Notably, the outcomes in those starting the trial with elevated values but with lower concentrations at 1 year were similar to those with low concentrations at both time points, while those with rising concentrations had worse outcomes than would have been predicted by the baseline sample alone.

Table 2—Log-transformed IGFBP7 at baseline and 1 year relative to subsequent outcomes in CANVAS

	Baseline IGFBP7					Baseline and 1-year IGFBP7			
Events	HR_{adj} (95% CI)*	*P*	C index with clinical covariates only	C index with baseline IGFBP7 only	C index with both (improvement from clinical covariates only)	HR_{adj} (95% CI)*	*P*	C index with clinical covariates only	C index with both (improvement from clinical covariates only)
Sustained decline in eGFR by 40%†	2.27 (1.05–4.93)	0.038	0.73	0.69	0.73 (0)	14.8 (7.2–30.6)	<0.001	0.77	0.79 (+0.04)
Progression to macroalbuminuria	2.50 (1.54–4.07)	<0.001	0.81	0.63	0.81 (0)	3.80 (1.80–7.80)	<0.001	0.66	0.81 (0.01)
First progression of albuminuria	1.80 (1.36–2.38)	<0.001	0.56	0.56	0.58 (+0.01)	1.76 (1.16–2.65)	0.007	0.56	0.57 (+0.01)
Cardiovascular death	6.55 (3.93–10.9)	<0.001	0.66	0.67	0.69 (+0.03)	2.69 (0.86–8.35)	0.09	0.65	0.68 (0)
Renal composite‡	3.51 (1.66–7.42)	0.001	0.73	0.70	0.74 (+0.01)	15.7 (7.68–32.0)	<0.001	0.77	0.80 (+0.04)
Renal composite plus cardiovascular death	4.90 (3.16–7.60)	<0.001	0.67	0.67	0.70 (+0.03)	6.90 (4.10–11.7)	<0.001	0.68	0.71 (+0.01)
Renal composite plus progression to macroalbuminuria	3.80 (2.50–4.07)	<0.001	0.63	0.64	0.66 (+0.03)	7.40 (4.50–12.2)	<0.001	0.68	0.69 (+0.02)

HR_{adj}, adjusted HR. *Covariates for adjustment were selected using the Bayesian information criterion in patients randomized to placebo in the main study along with baseline IGFBP7 and treatment allocation. Improvement in the C index was changed above a base model of covariates excluding biomarker concentrations. †A 40% decrease in eGFR was sustained for two or more consecutive measures. ‡The renal composite end point from CANVAS comprised a 40% decrease in eGFR (sustained for two or more consecutive measures), the need for RRT (dialysis or transplantation), or renal death.

CONCLUSIONS

In this post hoc analysis of patients with available blood samples in CANVAS, baseline concentrations of IGFBP7 were strongly prognostic for a wide range of kidney end points, notably predicting progression of chronic kidney disease, albuminuria, and composite end points, including major renal outcomes. In addition, IGFBP7 concentrations also independently predicted the renal composite end point plus cardiovascular death (the primary end point of the recent CREDENCE trial). An elevated baseline IGFBP7 also appeared to specifically identify those likely to benefit from canagliflozin relative to first progression of albuminuria; however, this observation should be approached with caution given the post hoc nature of the analysis. While baseline concentrations of the biomarker were prognostic, in some circumstances, a second IGFBP7 measurement at 1 year added potentially even stronger predictive value, particularly for a subsequent decline in eGFR. Lastly, those patients with elevated IGFBP7 at baseline or 1 year seemed to have the worst outcomes and possibly greatest absolute gains from being treated with canagliflozin compared with placebo. As far as we are aware, these data are the first to link circulating IGFBP7 concentrations to major kidney end points in patients with type 2 diabetes.

IGFBP7 is a member of a large family of insulin growth factor–binding peptides with pluripotent effects in vivo. Among the identified roles of IGFBP7 is participation in the senescence-associated secretory phenotype (7), wherein cell cycle arrest is induced in damaged tissue; this process is associated with tissue aging, cell death, and fibrosis. Recent work regarding IGFBP7 has mainly focused on the biomarker in patients with heart failure (11–16), where concentrations of IGFBP7 are higher in those with more severe disease and are associated with structural abnormalities of the heart (15,16). Although urinary IGFBP7 has been associated with acute kidney injury (8), no data exist regarding the role of urinary or circulating IGFBP7 to predict chronic kidney outcomes in patients with type 2 diabetes. Our results are thus highly novel and considerably extend results for blood-based measurement of IGFBP7 for renal and cardiorenal outcomes.

Prior data are limited regarding the meaning of IGFBP7 concentration in type 2 diabetes, although an association between circulating IGFBP7 concentrations and insulin resistance has been reported (17). Notably, using proteomic screening, Watanabe et al. (18) reported induction of IGFBP7 in an in vitro model of tubulointerstitial damage after exposure to transforming growth factor-β1, a key mediator of diabetic kidney disease. In immunohistochemical analyses, IGFBP7 was found to be localized in tubular cell cytoplasm, and its knockdown was associated with less cellular death. Furthermore, in the report by Watanabe et al. (18), elevated urinary IGFBP7 concentrations were found in clinical samples from patients with type 2 diabetes with proteinuria. Because tubular injury is a critical determinant of development and manifestation of diabetic kidney disease, it is tempting to speculate whether circulating IGFBP7 concentrations in CANVAS patients reflect risk for tubular fibrosis and proteinuria. More studies are planned. Our data suggest circulating IGFBP7 concentrations are promising as an early marker of renal tubular cell fibrosis and predictor of progressive kidney dysfunction with proteinuria among patients with type 2 diabetes.

In the CANVAS Program, canagliflozin reduced rates of major cardiac and renal events compared with placebo (2,3). In the present analysis, we found consistent

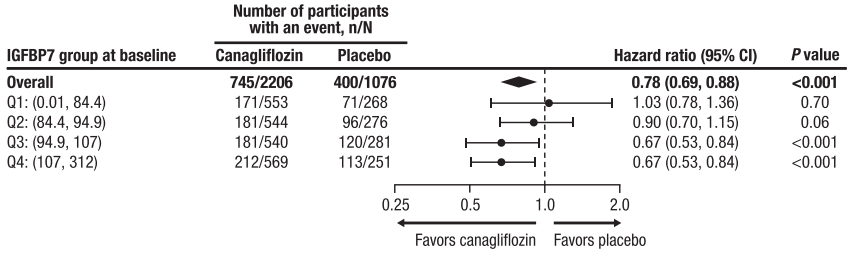

Figure 2—Reduction of first progression of micro- or macroalbuminuria as a function of treatment assignment (canagliflozin or placebo) across baseline IGFBP7 concentrations. Specific benefit from canagliflozin vs. placebo appeared present in those patients with higher IGFBP7 values ($P_{interaction} = 0.03$). Q, quartile.

relative benefit of canagliflozin regardless of IGFBP7 concentration, such that with most end points, no interaction between the drug and biomarker was present; however, rates of each complication studied were substantially higher among those with elevated IGFBP7 concentrations, so absolute reductions in risk associated with canagliflozin were greater in such patients. Notably, interaction between IGFBP7 and benefit from canagliflozin was found relative to first progression of albuminuria; this finding is curious given aforementioned links between IGFBP7 and tubulointerstitial fibrosis. Lastly, patients with elevated IGFBP7 at both baseline and 1 year had the highest rates of worsening eGFR, and in these patients, reduction of events in those taking canagliflozin was particularly noteworthy. Prospective studies would be needed to confirm any potential role of IGFBP7 measurement to identify those at risk for diabetic kidney disease most likely to benefit from treatment with sodium–glucose cotransporter 2 inhibitors.

This study is limited in that it was a retrospective post hoc study performed only in patients from the CANVAS study with available samples. While consistent across numerous kidney end points, these results are therefore hypothesis-generating and need confirmation. This is particularly so for the results suggesting an interaction between baseline IGFBP7 concentrations and subsequent benefits from canagliflozin on progression of albuminuria; this finding may be the result of chance and requires validation. Further analyses of IGFBP7 concentrations in patients with established diabetic kidney disease are planned, and these results will be useful to prepare the analytic approach. Potential for incomplete adjustment for confounding variables is another limitation, especially considering the substantial variation that can occur between measurements of certain variables such as eGFR and albuminuria. Lastly, multiple comparisons were made without adjustment for multiplicity, although for a post hoc exploratory analysis such as this, the need for such correction is debated.

In conclusion, among patients randomized to treatment with canagliflozin or placebo in CANVAS, elevated or rising concentrations of the tissue senescence biomarker IGFBP7 were associated strongly with subsequent risk for a wide range of renal complications and the composite of renal events and cardiovascular death. An elevated baseline IGFBP7 appeared to associate with specific benefit from canagliflozin treatment with regard to reduction of albuminuria progression. Development and progression of kidney disease is a pivotal moment in the course of type 2 diabetes, but a major obstacle to preventing or treating diabetic kidney disease is a lack of reliable tools for its prognostication. The results of this study extend basic science data regarding IGFBP7 in diabetic kidney disease and suggest a potential clinical role for blood measurement of IGFBP7 to predict diabetic kidney disease complications and possibly for selecting its treatment. Further studies of IGFBP7 in patients with diabetic kidney disease are planned.

Acknowledgments. Technical editorial assistance was provided by Alanna Kahhan of MedErgy and was funded by Janssen Research & Development, LLC. J.L.J. is supported by the Hutter Family Professorship.

Duality of Interest. The CANVAS trial was sponsored by Janssen Research & Development, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation. J.L.J. is a Trustee of the American College of Cardiology; has received grant support from Novartis and Abbott; has received consulting income from Abbott, Janssen, Novartis, Pfizer, Merck, and Roche Diagnostics; and participates in clinical end point committees/data safety monitoring boards for Abbott, AbbVie, Amgen, Bayer, CVRx, Janssen, and Takeda. J.B. reports relationships with Abbott, Adrenomed, Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, G3 Pharmaceuticals, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, Novo Nordisk, Relypsa, Roche, Sanofi, V-Wave Ltd., and Vifor. N.S. has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Napp, Novo Nordisk, and Sanofi and has received grant support from Boehringer Ingelheim. J.X., W.S., N.R., M.P., and M.K.H. are full-time employees of Janssen Pharmaceuticals, Inc. Financial disclosures for K.W.M. can be viewed at https://med.stanford.edu/profiles/kenneth-mahaffey. B.N. has received research support and has served as a consultant and speaker for Janssen, with all fees paid to his employer, and interacts regularly on a nonfinancial basis with multiple large corporations in the pharmaceutical industry, the food processing industry, and the quick service restaurant industry in Australia and overseas. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. J.L.J. wrote the paper, had full access to the study design information, and had final responsibility for the decision to submit for publication. J.L.J., J.B., N.S., J.X., W.S., N.R., M.P., K.W.M., B.N., and M.K.H. contributed to the design and conduct of the study and interpretation of the data. All authors provided input into subsequent drafts and approved the final version for submission. J.L.J. and M.K.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Thomas MC, Brownlee M, Susztak K, et al. Diabetic kidney disease. Nat Rev Dis Primers 2015;1:15018
2. Perkovic V, de Zeeuw D, Mahaffey KW, et al. Canagliflozin and renal outcomes in type 2 diabetes: results from the CANVAS Program randomised clinical trials. Lancet Diabetes Endocrinol 2018;6:691–704
3. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
4. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–657
5. Neuen BL, Ohkuma T, Neal B, et al. Cardiovascular and renal outcomes with canagliflozin according to baseline kidney function. Circulation 2018;138:1537–1550
6. Neuen BL, Ohkuma T, Neal B, et al. Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria:

data from the CANVAS Program. J Am Soc Nephrol 2019;30:2229–2242
7. Severino V, Alessio N, Farina A, et al. Insulin-like growth factor binding proteins 4 and 7 released by senescent cells promote premature senescence in mesenchymal stem cells. Cell Death Dis 2013;4:e911
8. Zhang D, Yuan Y, Guo L, Wang Q. Comparison of urinary TIMP-2 and IGFBP7 cut-offs to predict acute kidney injury in critically ill patients: a PRISMA-compliant systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e16232
9. Neal B, Perkovic V, de Zeeuw D, et al. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)–a randomized placebo-controlled trial. Am Heart J 2013;166:217–223.e11
10. Neal B, Perkovic V, Matthews DR, et al.; CANVAS-R Trial Collaborative Group. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): a randomized, placebo-controlled trial. Diabetes Obes Metab 2017;19:387–393
11. Gandhi PU, Chow SL, Rector TS, et al. Prognostic value of insulin-like growth factor-binding protein 7 in patients with heart failure and preserved ejection fraction. J Card Fail 2017;23:20–28
12. Gandhi PU, Gaggin HK, Redfield MM, et al. Insulin-like growth factor-binding protein-7 as a biomarker of diastolic dysfunction and functional capacity in heart failure with preserved ejection fraction: results from the RELAX trial. JACC Heart Fail 2016;4:860–869
13. Gandhi PU, Gaggin HK, Sheftel AD, et al. Prognostic usefulness of insulin-like growth factor-binding protein 7 in heart failure with reduced ejection fraction: a novel biomarker of myocardial diastolic function? Am J Cardiol 2014;114:1543–1549
14. Januzzi JL Jr, Packer M, Claggett B, et al. IGFBP7 (insulin-like growth factor-binding protein-7) and neprilysin inhibition in patients with heart failure. Circ Heart Fail 2018;11:e005133
15. Ibrahim NE, Afilalo M, Chen-Tournoux A, et al. Diagnostic and prognostic utilities of insulin-like growth factor binding protein-7 in patients with dyspnea. JACC Heart Fail 2020;8:415–422
16. Kalayci A, Peacock WF, Nagurney JT, et al. Echocardiographic assessment of insulin-like growth factor binding protein-7 and early identification of acute heart failure. ESC Heart Fail 2020;7:1664–1675
17. Liu Y, Wu M, Ling J, et al. Serum IGFBP7 levels associate with insulin resistance and the risk of metabolic syndrome in a Chinese population. Sci Rep 2015;5:10227
18. Watanabe J, Takiyama Y, Honjyo J, et al. Role of IGFBP7 in diabetic nephropathy: TGF-β1 induces IGFBP7 via Smad2/4 in human renal proximal tubular epithelial cells. PLoS One 2016;11:e0150897