Proteomics International

CANVAS Program

Validation of the PromarkerD Test for Predicting Renal Decline in Type 2 Diabetes in the CANagliflozin cardioVascular Assessment Study (CANVAS)

Kirsten E. Peters[1,2], Jialin Xu[3], Scott D. Bringans[1], Wendy A. Davis[2], Timothy M.E. Davis[2], Michael K. Hansen[3], Richard J. Lipscombe[1]

[1] Proteomics International, Perth, Western Australia, Australia.
[2] Medical School, University of Western Australia, Crawley, Western Australia, Australia.
[3] Janssen Research & Development, LLC, Spring House, PA, USA.

PromarkerD

CHANGING LIVES

A new blood test for predicting diabetic kidney disease

Poster 1118-P presented in category 12-G Clinical Therapeutics/New Technology – SGLT Inhibitors
American Diabetes Association 80th Scientific Sessions
June 12-16th, 2020

Disclosures

- The PromarkerD biomarker concentrations were measured by Proteomics International, and the PromarkerD scores were calculated using a proprietary algorithm
- This analysis used archived samples from the CANVAS study and was funded by Proteomics International
- The CANVAS study was funded by Janssen Research & Development, LLC. Canagliflozin has been developed by Janssen Research & Development, LLC, in collaboration with Mitsubishi Tanabe Pharma Corporation
- Presenter disclosures: K. Peters is an employee and shareholder of Proteomics International Laboratories Ltd, which is the owner of a patent covering the use of the PromarkerD test. Consequently, K. Peters may receive financial benefit from the commercial use of the PromarkerD test
- Technical editorial support was provided by Alaina Mitsch, PhD, of MedErgy, and was funded by Janssen Research & Development, LLC

PromarkerD
CHANGING LIVES

Introduction

- Diabetes is the leading cause of end-stage renal disease (ESRD)[1]
- Chronic kidney disease (CKD) develops in 1 in 3 people with type 2 diabetes (T2D)[2]
- The ability of baseline urinary albumin:creatinine ratio (uACR) or estimated glomerular filtration rate (eGFR) to predict onset and progression of CKD complicating diabetes is limited[3]
- PromarkerD is a novel blood test that can predict future renal function decline in people with T2D[4,5]
- This study sought to validate the prognostic utility of PromarkerD in individuals with T2D from CANVAS, a randomized controlled trial of canagliflozin vs. placebo (NCT01032629)[6]

[1] https://www.cdc.gov/kidneydisease/pdf/2019_National-Chronic-Kidney-Disease-Fact-Sheet.pdf, [2] https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf,
[3] Dunkler et al., JASN. 2015;10:1371-1379, [4] Peters et al., Diab Care. 2017;40:1548-1555, [5] Peters et al., J Diab Comp. 2019;33:107406, [6] Neal et al., N Eng J Med. 2017;377(7):644-657.

PromarkerD Test System

- The PromarkerD test system was developed and validated in community-based adults with T2D from the Fremantle Diabetes Study Phase II (FDS2) in Australia[4,5,7]
- PromarkerD is a simple blood test that combines the concentration of three plasma biomarkers (CD5L, ApoA4 and IGFBP3) with clinical factors (age, serum HDL-cholesterol, eGFR) to provide prognostic and diagnostic test scores
- In FDS2, PromarkerD predicted 86% of people with diabetes who developed CKD (eGFR <60 mL/min/1.73m^2) within four years (sensitivity 86%, specificity 78%, ROC-AUC=0.88)[4]
- PromarkerD also has excellent negative predictive value, or "rule-out" capability, of 98% for four-year risk of developing CKD[4]

[4] Peters et al., Diab Care. 2017;40:1548-1555, [5] Peters et al., J Diab Comp. 2019;33:107406, [7] Davis et al. Int J Epid. 2013;42(2):412-421.

PromarkerD Score x Outcome

- Baseline PromarkerD scores were measured prior to randomization in 2,976 CANVAS participants all with baseline eGFR ≥60 mL/min/1.73m^2 (n=982 placebo arm, n=1,994 canagliflozin arm)
- Biomarker concentrations (CD5L, ApoA4, IGFBP3) measured by immunoaffinity targeted mass spectrometry were combined with the age, serum HDL-cholesterol and eGFR of each subject at the baseline trial visit using a previously defined algorithm to provide prognostic test scores
- The prognostic test score predicts incident CKD (defined as an eGFR drop <60 mL/min/1.73m^2) during the four years from randomization
- During the follow-up period, 926 (31.1%) individuals developed CKD, 274 (27.9%) of the subjects on placebo and 652 (32.7%) of those on canagliflozin

Statistical Analyses

- The test score (predicted probability) ranges from 0% to 100% and is categorized as low-, moderate- or high-risk as determined by pre-specified cut-offs for optimal sensitivity and specificity

Prognostic

- A logistic regression model was used to fit incident CKD against PromarkerD score and treatment with canagliflozin, with odds ratios presented for PromarkerD scores adjusted for treatment
- PromarkerD scores were modeled as both continuous scores (from 0% to 100%) and as risk categories (moderate- or high-risk compared to the low-risk category as reference)
- Prognostic performance was assessed by ROC-AUC analysis using the test scores

PromarkerD
CHANGING LIVES

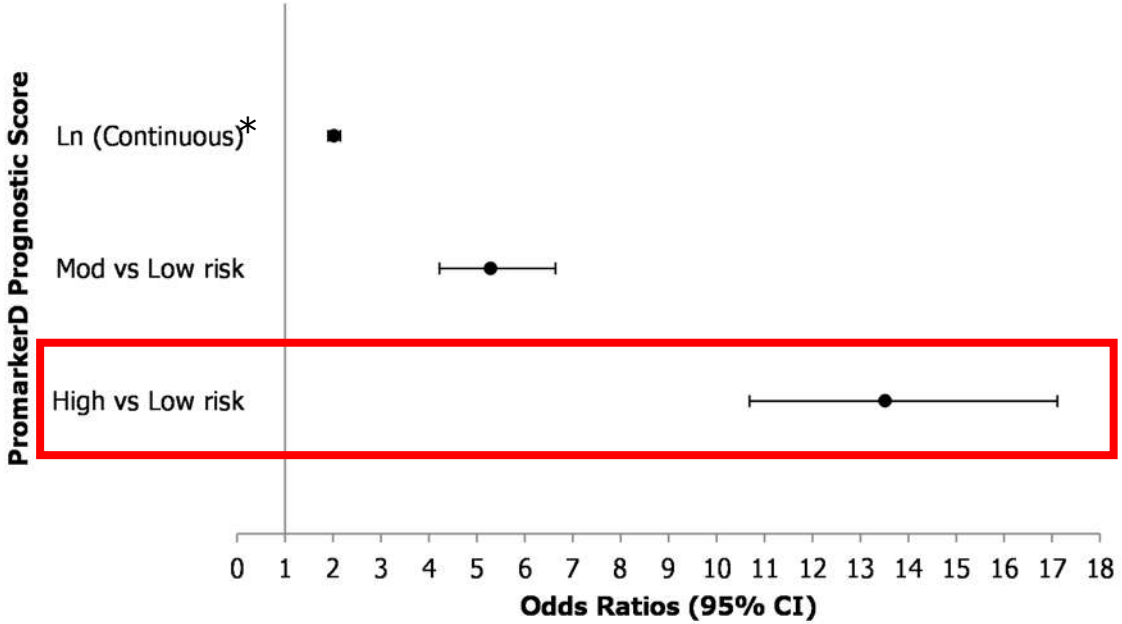
Baseline Characteristics

Characteristic	Canagliflozin (n = 1,994)	Placebo (n = 982)	Total (n = 2,976)
Age (years)	62.0±7.7	61.6±7.6	61.9±7.7
Female sex, n (%)	641 (32.1)	308 (31.4)	949 (31.9)
BMI (kg/m^2)	32.7±6.1	32.3±6.1	32.6±6.1
Diabetes duration (years)*	12.1 [8.0-17.0]	12.0 [8.0-16.8]	12.0 [8.0-17.0]
HbA_{1c} (%)*	8.0 [7.5-8.7]	8.0 [7.5-8.8]	8.0 [7.5-8.7]
Serum total cholesterol (mmol/L)	4.3±1.1	4.4±1.2	4.3±1.2
Serum HDL-cholesterol (mmol/L)	1.20±0.32	1.20±0.31	1.20±0.32
Serum triglycerides (mmol/L)†	1.7 (1.0-2.8)	1.7 (1.0-2.9)	1.7 (1.0-2.8)
Systolic blood pressure (mmHg)	136±16	137±16	137±16
Diastolic blood pressure (mmHg)	78±10	79±10	78±10
eGFR (mL/min/1.73m^2)	82.3±15.3	82.4±15.7	82.3±15.5
uACR (mg/g)*	11.2 [6.4-30.6]	11.0 [6.1-32.6]	11.2 [6.3-31.6]
Microalbuminuria, n (%)	425 (21.3)	209 (21.3)	634 (21.3)
Macroalbuminuria, n (%)	76 (3.8)	56 (5.7)	132 (4.4)

All values are mean±SD (standard deviation) unless labeled otherwise; * Median [IQR – interquartile range]; † Geometric Mean (SD range). BMI, body mass index; eGFR, estimated glomerular filtration rate (CKDEPI); uACR, urine albumin to creatinine ratio; Microalbuminuria and macroalbuminuria were defined as uACR 30-300 mg/g and >300 mg/g, respectively.

- PromarkerD scores were measured in 2,976 participants at baseline
- Prognostic test score:
  - Overall median 2.9%
  - Number of subjects (%) by risk categories
    - Low-risk: 2,099 (70.5%)
    - Moderate-risk: 405 (13.6%)
    - High-risk: 472 (15.9%)
- No significant difference in test scores by allocated treatment (P=0.56)

PromarkerD Predicts Incident CKD in CANVAS



* The prognostic test score was natural logarithm (ln-transformed) due to a non-normal distribution.

- After adjustment for canagliflozin, moderate- and high-risk test scores were increasingly prognostic for incident CKD versus low-risk
  - Moderate-risk scores: OR=5.3 [95%CI 4.2, 6.6], $P=2.8x10^{-47}$
  - **High-risk scores: OR=13.5** [95%CI 10.7, 17.1], $\mathbf{P=1.3x10^{-104}}$
- The test score was also significantly associated with incident CKD when modeled as a continuous score (OR=2.0 [95%CI 1.9, 2.2], $P=2.3x10^{-109}$)

PromarkerD Test Performance in CANVAS

Participants	Placebo	Placebo+Canagliflozin
Number with outcome/total (%)	274/982 (27.9%)	926/2,976 (31.1%)
ROC-AUC (95%CI)	0.79 (0.76, 0.82)	0.81 (0.80, 0.83)
At optimal cut-off*:	(7.1%)	(5.9%)
Sensitivity (%)	69.3	73.2
Specificity (%)	76.7	76.8
PPV (%)	53.5	58.8
NPV (%)	86.6	86.4
At moderate-risk cut-off:		
Sensitivity (%)	59.1	60.6
Specificity (%)	81.8	84.6
PPV (%)	55.7	64.0
NPV (%)	83.8	82.6
At high-risk cut-off:		
Sensitivity (%)	35.8	37.7
Specificity (%)	93.4	94.0
PPV (%)	67.6	73.9
NPV (%)	79.0	77.0

Performance measures are given for moderate (10%), and high (20%) risk cut-offs for incident CKD, as well as for the * optimal cut-off (shown in parentheses) defined by maximum Youden Index (YI). ROC-AUC = receiver operating curve - area under the curve; PPV = positive predictive value; NPV = negative predictive value.

- PromarkerD provided good discrimination for incident CKD in both placebo- and canagliflozin-treated participants
  - AUC = 0.81 (95% CI 0.80, 0.83)
  - Test sensitivity = 73.2%
  - Test specificity = 76.8%
- Demographic and clinical differences with FDS2 may explain the lower test performance
  (FDS2: AUC=0.88, Sn=86%, Sp=78%)
- Further work is needed to explore these differences

Conclusions

- Analysis of the PromarkerD test system in CANVAS shows the test predicted clinically significant incident CKD over 4 years in this multi-center clinical study of 2,976 individuals with type 2 diabetes
- These data provide further validation of the prognostic utility of PromarkerD and thus its potential to facilitate preventive management strategies by enabling earlier intervention of at-risk individuals
- PromarkerD shows potential for monitoring disease progression, improvement in patient outcomes and risk stratification in future clinical trials. Future studies are needed to investigate the role of PromarkerD in these areas