# PromarkerD Predicts Late-Stage Renal Function Decline in Type 2 Diabetes in the Canagliflozin Cardiovascular Assessment Study (CANVAS)

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## Background & Aim

- A third of people with type 2 diabetes (T2D) have chronic kidney disease (CKD), the leading cause of end-stage renal disease (ESRD).
- Current standard of care tests (urinary albumin-to-creatinine ratio (uACR), and estimated glomerular filtration rate (eGFR)) have limited ability to predict CKD progression.
- PromarkerD is a novel blood test that has been shown to predict early-stage renal function decline (incident CKD or eGFR <60 mL/min/1.73m$^2$) in T2D[1,2,3]
- The aim of this study was to assess the ability of PromarkerD to predict later-stage renal decline in participants with T2D from CANVAS, a randomized controlled trial of canagliflozin vs. placebo (NCT01032629)[4].

## Methods

- PromarkerD scores were measured at baseline in 3,525 CANVAS participants (mean age 62.7 years, 67% males, median diabetes duration 12.5 years, mean eGFR 77 mL/min/1.73m$^2$ and median uACR 11.6 mg/g).
- PromarkerD is a biomarker-based test that combines the concentration of three proteins (CD5L, ApoA4, IGFBP3) measured by immuno-affinity mass spectrometry, with clinical data (age, serum HDL-cholesterol, eGFR) to provide test scores categorized as low-, moderate- or high-risk for adverse renal outcomes.
- The ability of PromarkerD (modeled as both risk categories and a continuous risk score) to predict three composite cardio-renal outcomes was assessed using Cox proportional hazards (time-to-event) modeling:
  - **Outcome 1)** ≥40% eGFR decline, ESRD, or renal death
  - **Outcome 2)** cardiovascular disease (CVD) death or outcome 1
  - **Outcome 3)** progression to macroalbuminuria (uACR >300 mg/g) or outcome 1
- Adjustment for canagliflozin treatment, as well as a range of clinically relevant risk factors was performed.
- Follow-up was from baseline to date of first outcome or censoring due to exit from study.

## Participant Characteristics

- During 5.4-5.7 years (mean range) of follow-up, 138 (3.9%), 380 (10.8%) and 427 (12.1%) participants experienced outcomes 1 to 3, respectively. Total follow-up time for all participants ranged from 19.1 thousand person years for outcome 3 to 19.9 thousand person years for outcome 1.
- With the exception of gender, significant baseline differences were observed for all demographic characteristics when comparing participants with at least 1 outcome to those without (Table 1).

| Table 1. Participant characteristics at baseline | Total cohort N=3,525 | No cardio-renal outcome N=2,873 | ≥1 cardio-renal outcome N=652 | P-value |
|---|---|---|---|---|
| Participants in treatment arm (N, %) | 2,346 (66.6) | 1,947 (67.8) | 399 (61.2) | 0.001 |
| Age (years) | 62.7±7.8 | 62.4±7.8 | 64.0±7.9 | <0.001 |
| Male gender (N, %) | 2,364 (67.1) | 1,909 (66.4) | 455 (69.8) | 0.10 |
| Diabetes duration (years) | 12.5 [8.0-18.0] | 12.0 [8.0-17.2] | 13.0 [9.7-19.0] | <0.001 |
| $HbA_{1C}$ (%) | 8.0 [7.5-8.7] | 8.0 [7.4-8.7] | 8.2 [7.6-8.9] | <0.001 |
| Supine systolic blood pressure (mm Hg) | 137±16 | 136±16 | 139±16 | 0.001 |
| Urinary ACR (mg/g)* | 11.6 [6.4-35.2] | 10.0 [6.0-23.2] | 43.6 [12.4-159.0] | <0.001 |
| eGFR (mL/min/1.73m$^2$) | 77.0±18.7 | 77.9±18.3 | 72.9±19.9 | <0.001 |

All values are mean±standard deviation, proportions or median [interquartile range]; *17 participants excluded as missing baseline uACR values.

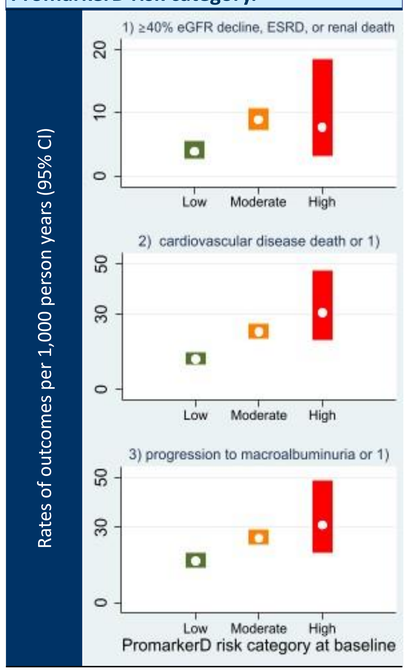
| Table 2. Outcomes experienced by baseline PromarkerD risk category (N, %) | Total cohort N=3,525 | Outcome 1 N=138 | Outcome 2 N=380 | Outcome 3 N=427 |
|---|---|---|---|---|
| Low (<30%) | 1,336 (37.9) | 30 (21.7) | 93 (24.5) | 123 (28.8) |
| Moderate (30% - <60%) | 2,067 (58.6) | 103 (74.6) | 276 (70.3) | 285 (66.7) |
| High (≥60%) | 122 (3.5) | 5 (3.6) | 20 (5.3) | 19 (4.5) |

## Results – PromarkerD Predicts Late-Stage Renal Outcomes

***PromarkerD Risk Categories:***

- Participants with PromarkerD moderate- or high-risk scores were more likely to experience cardio-renal outcomes than low-risk participants (Table 2).
- Significantly higher rates of cardio-renal outcomes were experienced in participants with PromarkerD moderate-risk scores compared to those classified as low-risk (unadjusted, p<0.001) (Figure 1, Table 3). A similar trend was observed for high-risk versus low-risk, but likely due to small numbers, this result was not statistically significant.
- The hazard rates for experiencing any of the cardio-renal outcomes remained significantly elevated (p≤0.001) for participants with moderate-risk compared to low-risk scores after adjustment for canagliflozin treatment, baseline eGFR and uACR (Table 3), as well as further adjustment for other baseline confounders including age, diabetes duration, $HbA_{1c}$ and systolic blood pressure (p≤0.003, data not shown).

**Figure 1. Cardio-renal outcomes by baseline PromarkerD risk category.**




| Table 3. Association of baseline PromarkerD risk categories with cardio-renal outcomes. | unadjusted | adjusted for treatment with Canagliflozin, eGFR and uACR |
|---|---|---|
| Outcome | PromarkerD moderate- vs low-risk [HR (95%CI), *P*) | |
| 1) ≥40% eGFR decline, ESRD, or renal death | 2.30 (1.53-3.45), <0.001 | 2.08 (1.38-3.14), 0.001 |
| 2) CVD death or (1) | 1.91 (1.51-2.42), <0.001 | 1.71 (1.34-2.17), <0.001 |
| 3) progression to macroalbuminuria or (1) | 1.56 (1.26-1.92), <0.001 | 1.43 (1.15-1.77), 0.001 |
| Outcome | PromarkerD high- vs low-risk [HR (95%CI), *P*) | |
| 1) ≥40% eGFR decline, ESRD, or renal death | 2.01 (0.78-5.19), 0.15 | 1.67 (0.64-4.36), 0.30 |
| 2) CVD death or (1) | 2.56 (1.58-4.15), <0.001 | 1.80 (1.08-2.97), 0.02 |
| 3) progression to macroalbuminuria or (1) | 1.88 (1.16-3.04), 0.01 | 1.55 (0.95-2.53), 0.082 |

***PromarkerD Risk Scores:***

- When PromarkerD score was assessed as a continuous variable, it was observed that for each 10% increase in PromarkerD score, there was an average increase in the hazard rate of developing cardio-renal outcomes of between 12% (Outcome 3) and 27% (Outcome 2). These results were attenuated after adjustment, but remained consistent with unadjusted analyses (Table 4) (P≤0.041).

| Table 4. Association of baseline PromarkerD score with cardio-renal outcomes. | unadjusted | adjusted for treatment with Canagliflozin, eGFR and uACR |
|---|---|---|
| Outcome | Per 10 point increase in PromarkerD [HR (95%CI), *P*) | |
| 1) ≥40% eGFR decline, ESRD, or renal death | 1.22 (1.08-1.38), 0.001 | 1.17 (1.03-1.33), 0.015 |
| 2) CVD death or (1) | 1.27 (1.18-1.37), <0.001 | 1.20 (1.11-1.29), <0.001 |
| 3) progression to macroalbuminuria or (1) | 1.12 (1.05-1.20), 0.001 | 1.08 (1.00-1.16), 0.041 |

## Conclusions

- This post-hoc analysis of data from 3,525 CANVAS participants with T2D showed that PromarkerD can predict late-stage renal function decline:
  - Moderate- and high-risk scores were increasingly prognostic for outcomes versus low-risk scores by risk category;
  - Higher PromarkerD scores were significantly predictive of outcomes by continuous risk score; and
  - Following adjustment for canagliflozin treatment, eGFR and uACR, as well as other known conventional clinical risk factors including age, diabetes duration, $HbA_{1c}$, and systolic blood pressure, PromarkerD remained a significant independent predictor of outcomes.
- This study extends the clinical utility of PromarkerD from predicting not only early-stage kidney disease (incident CKD or eGFR <60 mL/min/1.73m$^2$) in people with T2D, but also later-stage outcomes (40% decline in eGFR or progression to macroalbuminuria) in people with and without existing kidney damage.
- Given the significant findings for the composite outcomes including cardiovascular death and progression to macroalbuminuria, further studies are warranted to explore the prognostic utility of PromarkerD for additional cardiovascular-specific outcomes.

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