

PromarkerD

CHANGING LIVES

A new blood test for predicting diabetic kidney disease



Canagliflozin attenuates PromarkerD diabetic kidney disease risk prediction scores

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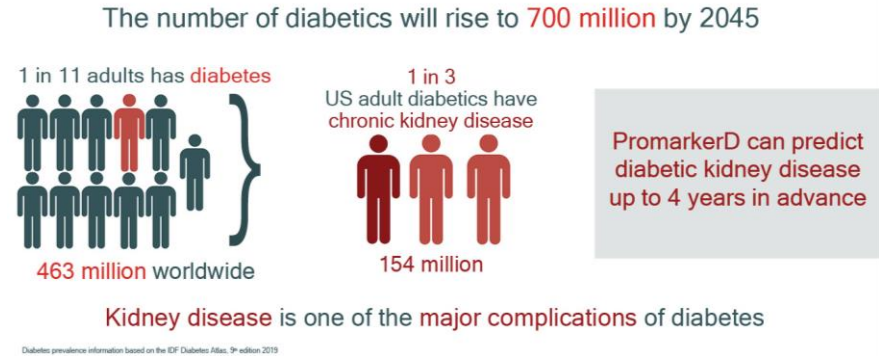

**AUSTRALASIAN
DIABETES CONGRESS 2021**

Poster 27
August 11-13th, 2021

Disclosures: This study was funded by Proteomics International. PromarkerD biomarker concentrations and risk scores were measured using archived samples from the CANVAS study by Proteomics International using a patented test owned by the company. 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.

Background & Aim

- Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease.¹
- PromarkerD is a simple biomarker-based blood test that can predict future renal function decline in individuals with T2D and no existing DKD (eGFR ≥ 60 mL/min/1.73m²).^{2,3}
- Canagliflozin (CANA), a sodium glucose transporter subtype 2 (SGLT-2) inhibitor, is approved for blood glucose lowering in T2D, and for risk reduction of renal and cardiovascular outcomes.⁴
- The effect of CANA on PromarkerD scores is unknown.



- The aim of this study was to examine the association between CANA and change in PromarkerD risk score over a three-year follow-up period in patients with T2D participating in the CANagliflozin cardioVascular Assessment Study (CANVAS).

Methods

- PromarkerD scores were measured at baseline (Yr0) and Yr3 in 2,008 T2D participants without DKD# (n=629 placebo/n=1,379 CANA, mean age 62 years, 69% males, median diabetes duration 12 years).¹
- PromarkerD scores combine 3 protein biomarker concentrations (CD5L, ApoA4, IGFBP3) with clinical data (age, serum HDL-cholesterol, eGFR*), and are categorised as low-, moderate- or high-risk for renal outcomes.
- Generalized estimating equations were used to assess the effect of canagliflozin versus placebo on PromarkerD scores, with effects assessed by baseline PromarkerD risk category.

Samples (Yr0+Yr3)

Biomarkers by IVD

Clinical Factors

PromarkerD Hub

PromarkerD Result

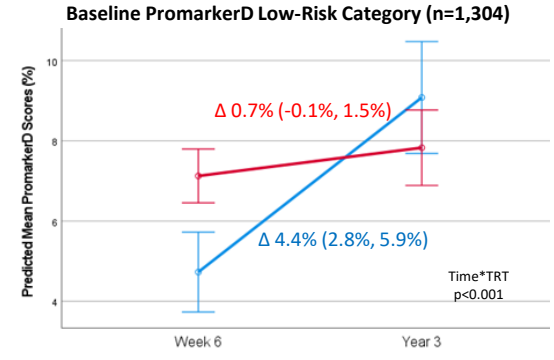
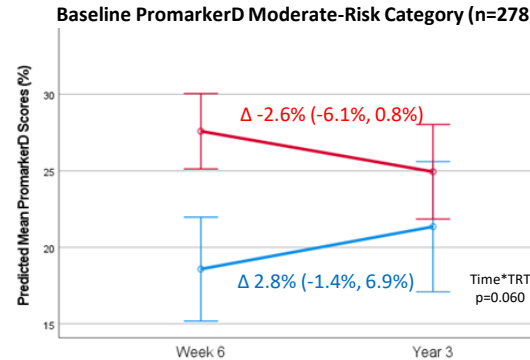
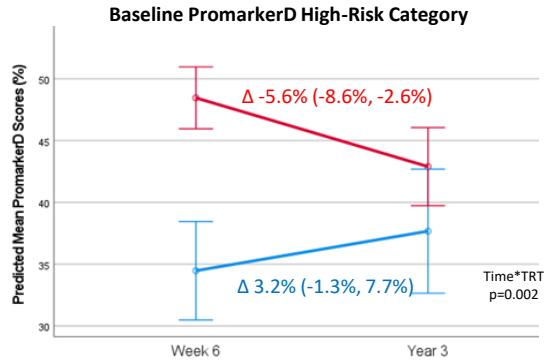


¹ Peters et al., J Clin Med. 2020;9(10):3212, # DKD defined as eGFR<60mL/min/1.73m², * Week 6 eGFR was used in Yr0 PromarkerD scores to account for the known acute drop in eGFR following CANA initiation (Oshima et al., JASN. 2020;31(10):2446); 52 individuals were missing a week 6 eGFR and were excluded.

ΔPromarkerD Scores by PromarkerD Risk Category

— Placebo
— Cana 100+300 mg

- Across all participants, those on **canagliflozin** had **decreased mean PromarkerD scores** (Δ score: -1.0% (-1.9%, -0.1%); p=0.038), while those on **placebo** **increased** over the three-year period (Δ score: 3.9% (2.5%, 5.3%); p<0.001). The effect was greatest for participants in the PromarkerD high-risk category:



PromarkerD High-Risk (Time*TRT p=0.002)	N	Mean	95%CI	Difference in the means		
				Δ ProD	95%CI	p-value
Difference in ProD scores between treatment arms						
<u>Week 6</u>						
Placebo	106	34.5	30.9, 38.0	ref		
Canagliflozin	268	48.5	45.8, 51.1	14.0	9.3, 18.7	<0.001
<u>Year 3</u>						
Placebo	106	37.7	33.2, 42.1	ref		
Canagliflozin	268	42.9	39.6, 46.2	5.2	-0.7, 11.2	0.084
Difference in ProD scores between Week 6 and Year 3 for						
<u>Placebo</u>						
Week 6	106	34.5	30.9, 38.0	ref		
Year 3	106	37.7	33.2, 42.1	3.2	-1.4, 7.8	0.17
<u>Canagliflozin</u>						
Week 6	268	48.5	45.8, 51.1	ref		
Year 3	268	42.9	39.6, 46.2	-5.6	-8.6, -2.5	<0.001

PromarkerD Moderate-Risk (Time*TRT p=0.060)	N	Mean	95%CI	Differences in the means		
				Δ ProD	95%CI	p-value
Difference in ProD scores between treatment arms						
<u>Week 6</u>						
Placebo	96	18.6	15.3, 21.9	ref		
Canagliflozin	182	27.6	25.1, 30.1	9.0	4.8, 13.2	<0.001
<u>Year 3</u>						
Placebo	96	21.3	17.0, 25.7	ref		
Canagliflozin	182	24.9	21.9, 28.0	3.6	-1.7, 8.9	0.18
Difference in ProD scores between Week 6 and Year 3 for						
<u>Placebo</u>						
Week 6	96	18.6	15.3, 21.9	ref		
Year 3	96	21.3	17.0, 25.7	2.8	-1.4, 6.9	0.19
<u>Canagliflozin</u>						
Week 6	182	27.6	25.1, 30.1	ref		
Year 3	182	24.9	21.9, 28.0	-2.6	-6.1, 0.8	0.14

PromarkerD Low-Risk (Time*TRT p<0.001)	N	Mean	95%CI	Differences in the means		
				Δ ProD	95%CI	p-value
Difference in ProD scores between treatment arms						
<u>Week 6</u>						
Placebo	408	4.7	4.0, 5.5	ref		
Canagliflozin	896	7.1	6.4, 7.9	2.4	1.2, 3.6	<0.001
<u>Year 3</u>						
Placebo	408	9.1	7.4, 10.7	ref		
Canagliflozin	896	7.8	7.0, 8.7	-1.3	-2.9, 0.4	0.15
Difference in ProD scores between Week 6 and Year 3 for						
<u>Placebo</u>						
Week 6	408	4.7	4.0, 5.5	ref		
Year 3	408	9.1	7.4, 10.7	4.4	2.8, 5.9	<0.001
<u>Canagliflozin</u>						
Week 6	896	7.1	6.4, 7.9	ref		
Year 3	896	7.8	7.0, 8.7	0.7	-0.1, 1.5	0.091

Conclusions

- This post-hoc analysis of data from 2,008 CANVAS participants with T2D and no DKD showed:
 - Canagliflozin significantly lowered mean PromarkerD scores compared to placebo over 3 years.
 - The greatest effect of canagliflozin was in those classified by PromarkerD as at high-risk of a subsequent decline in renal function.
 - PromarkerD can identify patients who are asymptomatic for DKD, and canagliflozin improves the associated PromarkerD renal risk profiles.
 - Follow-up PromarkerD testing would support cost effective individualised treatment via
 - Early introduction of preventative medications in high-risk patients, and
 - Rationalised treatment options in low-risk patients.
- Additional analyses are underway to:
 - Develop adjusted models for patients already on an SGLT2i, given the known transient acute drop in eGFR following treatment initiation. This will allow patients already on an SGLT2i to have the PromarkerD test and understand future risk of renal outcomes.
 - Assess the prognostic utility of change in PromarkerD scores over time for predicting future renal outcomes.