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Introduction

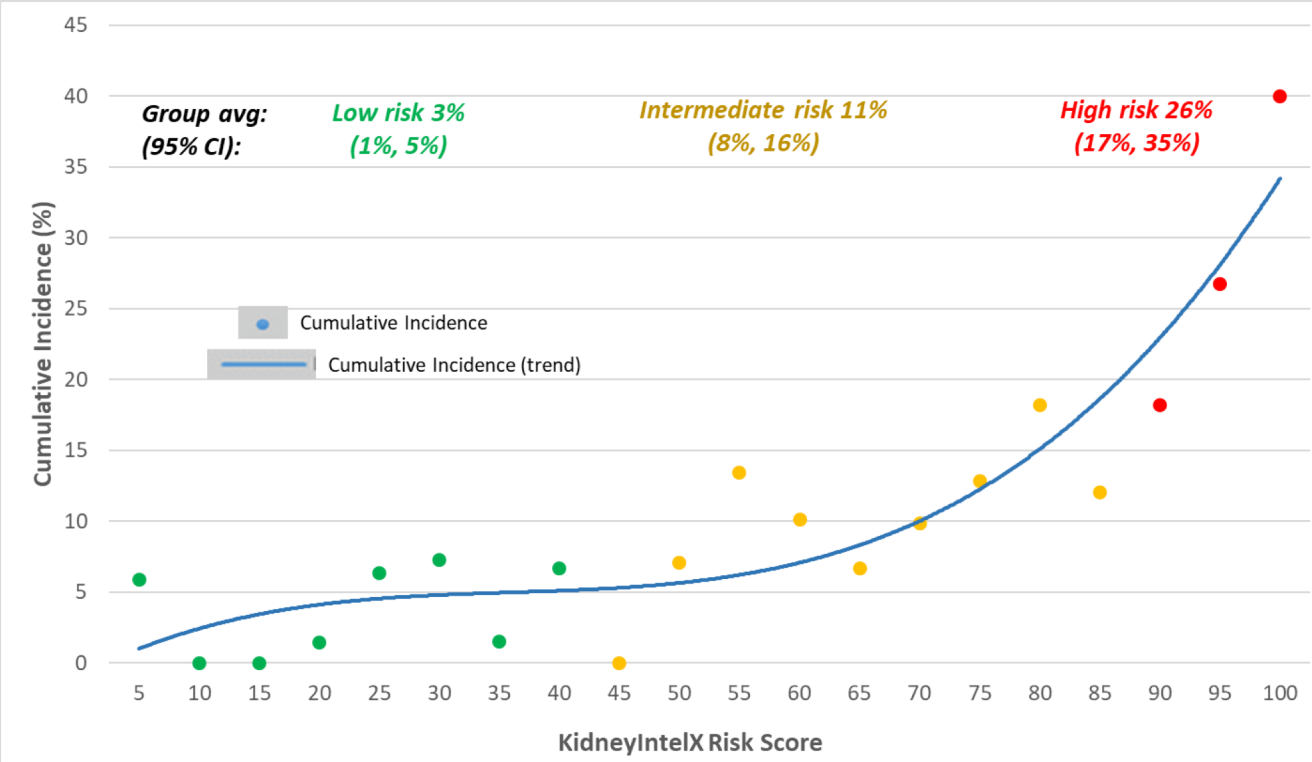
- Prediction of progression during early stages of DKD and determination of those most likely to derive benefit from novel therapies is challenging
- KidneyIntelX is a new test that incorporates clinical data and three plasma biomarkers using machine learning into a composite risk score for DKD progression that has yet to be applied to a clinical trial cohort

Methods

- Post-hoc analysis of CANVAS participants (n=1325) with prevalent DKD (estimated glomerular filtration rate (eGFR) <60 ml/min or UACR > 30 mg/g at enrollment)
- Plasma soluble Tumor Necrosis Factor Receptor 1 (sTNFR-1), sTNFR-2, and Kidney Injury Molecule-1 (KIM-1), were measured with proprietary multiplex assays
- KidneyIntelX risk scores between 5 and 45 were considered “low risk”, between 50 and 85 were “intermediate risk”, and those with KidneyIntelX scores of 90, 95 and 100 were classified as “high risk”, as per previous validation studies.
- We calculated chronic eGFR slope from 6 weeks in the canagliflozin arm and from baseline in the placebo arm and compared the proportion of individuals experiencing the composite kidney outcome of eGFR decline of ≥5 ml/min/year, ≥40% sustained decline in eGFR, or kidney failure within 5 years in CANVAS participants stratified by KidneyIntelX risk categories vs. the KDIGO risk strata
- We also assessed clinical response to canagliflozin vs. placebo within KidneyIntelX and KDIGO risk strata

Results

Cumulative Incidence of the Composite Kidney Outcome by KidneyIntelX Risk Scores



Characteristics

Table 1. Baseline characteristics of CANVAS Participants with DKD and with baseline samples analyzed (n=1325)

Age, in years, Median [Q1 - Q3]	64 [58 - 70]
Female, n (%)	444 (31.8)
White Race, n (%)	1127 (81.3)
Follow Up Time, In Years, Median [Q1 - Q3]	6.2 [5.8 - 7.3]
Laboratory Characteristics	
Baseline eGFR in ml/min, Median [Q1 - Q3]	65 [54 - 81.7]
eGFR Strata	
30 - 44.9, n (%)	138 (9.8)
45 - 59.9, n (%)	466 (33.3)
60 - 89.9, n (%)	576 (41.2)
≥ 90, n (%)	216 (15.4)
Baseline UACR (mg/g), Median [Q1 - Q3]	56.1 [25.3 - 158.8]
UACR < 30, n (%)	373 (26.7)
UACR 30-299, n (%)	809 (57.9)
UACR ≥ 300, n (%)	210 (15)
Baseline HbA1c in %, Median [Q1 - Q3]	8.2 [7.5 - 8.9]
Plasma Biomarkers, pg/ml- Median [Q1 - Q3]	
TNFR1, Median [Q1 - Q3]	3010 [2461 - 3748]
TNFR2, Median [Q1 - Q3]	11320 [9030 - 14077]
KIM-1, Median [Q1 - Q3]	149 [98 - 249]
Cumulative Incidence of Events (%)	
eGFR slope ≥ 5 ml/min/1.73 m ² /year, n (%)	82 (5.9)
Sustained 40% Decline in eGFR or Kidney failure, n(%)	95 (6.8)
Composite Endpoint, n (%)	134 (9.6)

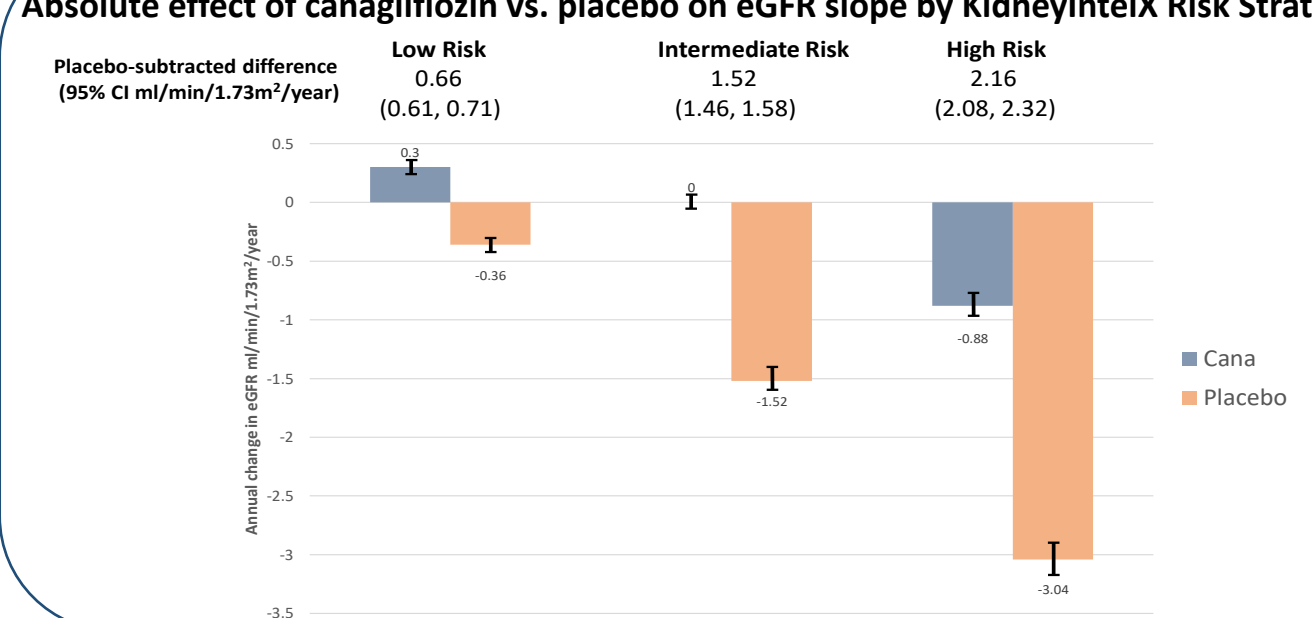
Absolute & Relative Risks for Kidney Outcomes by KidneyIntelX vs. KDIGO Risk Strata

	Participants with an event (n/N)		Relative Risk for the Kidney Outcome	RR (95%CI)	P heterogeneity
	Low Risk	Highest Risk			
Overall					< 0.001
KidneyIntelX	17/552	50/193		8.4 (5.0, 14.2)	
KDIGO	61/914	19/108		2.5 (1.8, 3.6)	
Placebo					<0.01
KidneyIntelX	4/193	23/71		15.6 (5.6, 43.6)	
KDIGO	19/324	7/35		3.4 (1.5, 7.5)	
Canagliflozin					< 0.05
KidneyIntelX	13/342	28/122		6.0 (3.2, 11.3)	
KDIGO	42/590	12/73		2.3 (1.3, 4.2)	

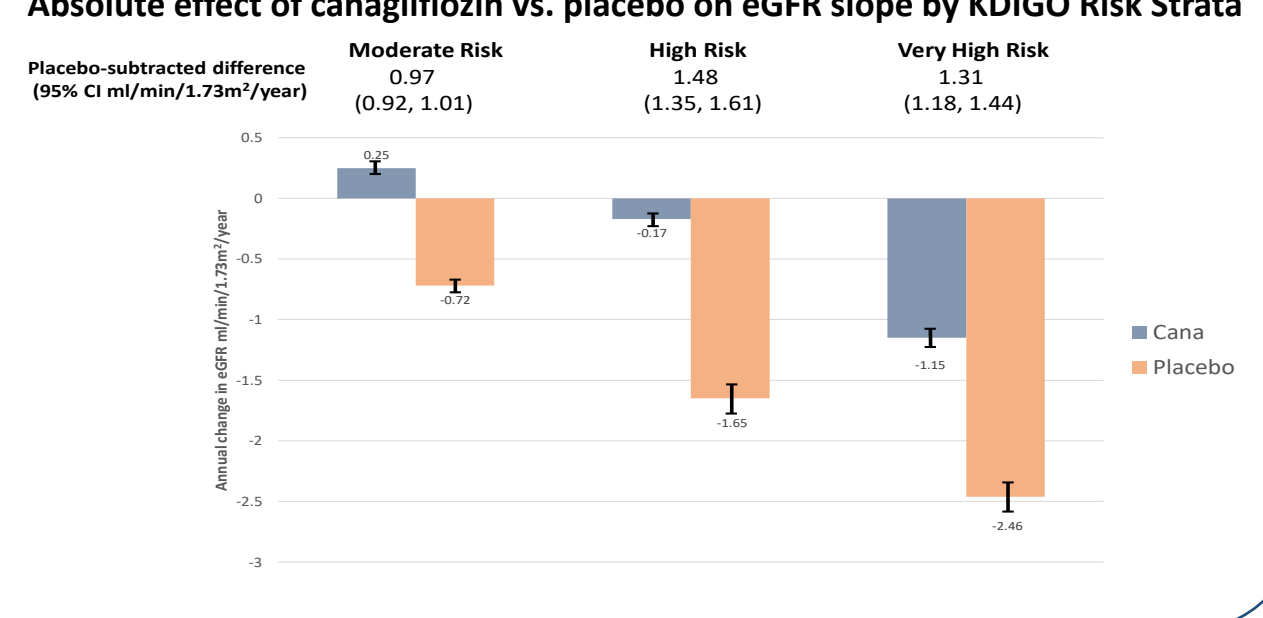
Associations of baseline KidneyIntelX and KDIGO Risk Strata with the composite kidney outcome

Baseline Risk	Risk Category	Incidence and Risk Ratio for Composite Kidney Outcome					
		Overall		Canagliflozin		Placebo	
		Cumulative Incidence	Risk Ratio* (95% CI)	Cumulative Incidence	Risk Ratio* (95% CI)	Cumulative Incidence	Risk Ratio* (95% CI)
KidneyIntelX	Low Risk	17/552 (3.1%)	Ref	13/342 (3.8%)	Ref	4/193 (2.1%)	Ref
	Intermediate Risk	63/580 (10.9%)	3.5 (2.1, 5.9)	30/377 (9.5%)	2.1 (1.1, 3.9)	27/203 (13.3%)	6.4 (2.3, 18.0)
	High Risk	50/193 (26.4%)	8.4 (5.0, 14.2)	28/122 (22.9%)	6.0 (3.2, 11.3)	23/71 (32.4%)	15.6 (5.6, 43.6)
KDIGO	Moderate Risk	61/914 (6.7%)	Ref	42/590 (7.1%)	Ref	19/324 (5.8%)	Ref
	High Risk	51/303 (16.8%)	2.5 (1.8, 3.6)	23/195 (12.0%)	1.7 (1.0, 2.7)	28/108 (25.9%)	4.4 (2.6, 7.6)
	Very High Risk	19/108 (17.6%)	2.6 (1.6, 4.2)	12/73 (16.4%)	2.3 (1.3, 4.2)	7/35 (20.0%)	3.4 (1.5, 7.5)

Absolute effect of canagliflozin vs. placebo on eGFR slope by KidneyIntelX Risk Strata



Absolute effect of canagliflozin vs. placebo on eGFR slope by KDIGO Risk Strata



Conclusions

KidneyIntelX successfully risk-stratified a large multi-national external cohort for risk of progression of DKD, with larger gradients of risk compared to KDIGO risk strata. In addition, there were greater differences in eGFR slope for canagliflozin vs. placebo in those with higher vs. lower baseline KidneyIntelX scores, as well as compared to KDIGO risk strata.