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Impact of Canagliflozin on Kidney and Cardiovascular Outcomes by Type 2 Diabetes Duration: A Pooled Analysis of the CANVAS Program and CREDENCE Trials

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Impact of Canagliflozin on Kidney, Albuminuria and Cardiovascular outcomes by Type 2 Diabetes duration: Pooled analysis of the CANVAS Program and CREDENCE trials.

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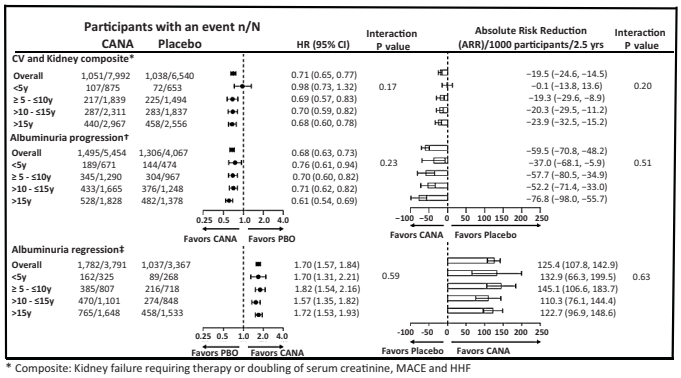
Canagliflozin consistently confers cardiorenal benefits in patients regardless of type 2 diabetes duration.

Post hoc analysis of integrated pooled, patient level data (n=14,542) — CANVAS Program (n=10,141) and CREDENCE (n=4,401)

Characteristic*	Duration of type 2 diabetes (T2D), years			
	<5 n=1,528	≥5 - ≤10 n=3,333	>10 - ≤15 n=4,148	>15 n=5,523
Age, y	59.5 (9.3)	62.0 (8.5)	62.7 (8.1)	65.3 (8.1)
Female, %	33.4	33.5	36.0	36.3
Type 2 diabetes duration, y	2.7 (1.3)	7.7 (1.7)	12.8 (1.5)	22.4 (6.1)
History Hypertension %	88.2	91.7	91.7	93.6
eGFR mL/min/1.73m²	77.0 (21.8)	73.0 (22.0)	72.7 (21.8)	65.1 (20.9)
UACR, mg/mmol	1.7 (0.8, 23.3)	2.8 (0.9, 52.0)	2.6 (0.9, 42.8)	10.6 (1.2, 84.1)

*Data are mean (SD) or median (IQR) unless otherwise noted.
ClinicalTrials.gov Identifier : NCT01032629, NCT01989754, and NCT0206579.



* Composite: Kidney failure requiring therapy or doubling of serum creatinine, MACE and HHF
† ≥ 1 step increase in ACR category along with an increase in ACR ≥ 30% from baseline; ‡ ≥ 1 step decrease in ACR category along with a decrease in ACR ≥ 30% from baseline

- Regardless of the duration of type 2 diabetes, canagliflozin demonstrated sustained reduction of CV and kidney outcomes. The total risk reduction was greater in individuals with higher cardiovascular and kidney risk.
- Within 5 years of type 2 diabetes diagnosis, canagliflozin positively impacted on albuminuria progression and regression, an important consideration in primary care

ACR, albumin-to-creatinine ratio; ARR, absolute risk reductions; CANVAS, Canagliflozin Cardiovascular Assessment Study; CREDENCE, Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy; CV, cardiovascular, eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio; IQR, interquartile range; MACE, major adverse cardiovascular event; PBO, placebo; UACR, urinary albumin-to-creatinine ratio

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  This pooled analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program and Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trials determined whether type 2 diabetes duration (by 5-year intervals) modified canagliflozin effects on cardiovascular and kidney outcomes, including progression and regression of albuminuria.

- **What is the specific question we wanted to answer?**
  This study assessed the effect of diabetes duration on the efficacy of the sodium–glucose cotransporter inhibitor canagliflozin.

- **What did we find?**
  Canagliflozin imparted benefits in participants with type 2 diabetes, across all time intervals, with no heterogeneity for cardiovascular or kidney events, including the progression and regression of albuminuria within the first 5 years of diabetes.

- **What are the implications of our findings?**
  Our findings demonstrated treating individuals with type 2 diabetes with canagliflozin confers consistent cardiorenal benefits for recent and long-standing diabetes duration.

BRIEF REPORT

Impact of Canagliflozin on Kidney and Cardiovascular Outcomes by Type 2 Diabetes Duration: A Pooled Analysis of the CANVAS Program and CREDENCE Trials

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OBJECTIVE

The study was undertaken because it was unknown whether the duration of type 2 diabetes modifies the effects of sodium–glucose cotransporter 2 inhibitor canagliflozin on cardiovascular (CV) and kidney outcomes.

RESEARCH DESIGN AND METHODS

This post hoc analysis of the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program (*N* = 10,142) and Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trial (*N* = 4,401) evaluated hazard ratios and 95% CIs using Cox proportional hazards for the effects of canagliflozin on CV and kidney outcomes, including progression and regression of albuminuria over 5-year intervals of disease duration.

RESULTS

Canagliflozin had ranges of benefit across intervals of diabetes duration, with no heterogeneity for major adverse CV events, CV death or heart failure hospitalization, and kidney failure requiring therapy or doubling serum creatinine. Furthermore, canagliflozin reduced albuminuria progression and increased albuminuria regression with no interaction across all diabetes duration subgroups.

CONCLUSIONS

Our findings suggest that earlier treatment with canagliflozin confers consistent cardiorenal benefits to individuals with type 2 diabetes.

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Type 2 diabetes remains the most common reason for kidney replacement therapy requiring dialysis. There is persistent residual kidney risk from type 2 diabetes, even after achieving blood pressure control, including the use of renin angiotensin aldosterone system inhibitors (1). To address the benefit of sodium–glucose cotransporter inhibitor (SGLT2i) on cardiovascular (CV) and kidney outcomes, we conducted a post hoc analysis to assess the effects of canagliflozin versus placebo on

CV and kidney events in participants with type 2 diabetes and high CV risk and/or CKD, according to baseline duration of diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This post hoc analysis is an integrated, pooled, patient-level data meta-analysis from the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program and the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants With Diabetic Nephropathy (CREDENCE) trials. Both were randomized, double-blinded, placebo controlled, multicenter studies. The CANVAS Program (N = 10,142) consisted of two multicenter, double-blind, placebo-controlled, randomized trials, CANVAS and Canagliflozin Cardiovascular Assessment Study–Renal (CANVAS-R). Eligible participants had type 2 diabetes (HbA_{1c} of 7.0–10.5% [53–91 mmol/mol]), an estimated glomerular filtration rate (eGFR) $>$30 mL/min/1.73 m^2, and were either aged $\geq$30 years with a history of symptomatic atherosclerotic CV disease or aged $\geq$50 years with at least two CV risk factors (2,3) The CREDENCE trial consisted of 4,401 participants with type 2 diabetes with HbA_{1c} of 6.5–12.0% (48–108 mmol/mol), eGFR of 30–89 mL/min/1.73 m^2, and albuminuria of $>$300 to $\leq$5,000 mg/g ($>$33.9–565.6 mg/mmol) (4). Participants in each study were randomized to receive canagliflozin or placebo (in addition to standard of care therapy). Although the study participants across the two treatment groups had similar characteristics, there were differences between the studies due to inclusion criteria. In CREDENCE, all participants at baseline had severely increased albuminuria. In the CANVAS Program, 18% of participants had abnormal urine albumin-to-creatinine ratio (ACR) at baseline and ~20% had an eGFR $<$60 mL/min/1.73 m^2. With respect to CV risk profile, 66% of participants in the CANVAS Program had established CV disease compared with 50% in CREDENCE. Detailed study methods, statistical analysis plan, and reporting of the CANVAS Program and CREDENCE trials have been previously published (5,6). The CREDENCE and CANVAS Program studies were approved by ethics committees at each site and registered at Clinicaltrials.gov (CREDENCE study NCT02065791, CANVAS Program studies NCT01032629 and NCT01989754).

Outcomes and Analyses

This post hoc analysis was based on the intent-to-treat analysis set of the CANVAS Program (N = 10,142) and CREDENCE trial (N = 4,401), which included participants who were randomized to canagliflozin or placebo and had values for all selected outcomes (4,7). Categorical variables are represented as counts and percentage of cohort totals, and continuous variables are represented as mean and SD or median and interquartile range. The effects of canagliflozin versus placebo were examined for CV and kidney outcomes in study participants according to baseline duration of diabetes. Diabetes duration was divided into four time periods: $<$5, $\geq$5 to $\leq$10, $>$10 to $\leq$15, and $>$15 years. This analysis pooled patient-level data from the CANVAS Program and the CREDENCE trial to determine the effect of canagliflozin versus placebo on the following outcomes:

- CV events (major adverse CV event [MACE] and the composite of CV death or hospitalization for heart failure)
- CKD progression (doubling of serum creatinine)
- The composite of kidney and CV events (kidney failure requiring therapy or doubling of serum creatinine, MACE, and hospitalization for heart failure).
- Albuminuria progression and regression (change in albuminuria class plus a change in urine ACR by at least 30% from baseline). Albuminuria was defined as normo-, micro-, or macroalbuminuria, now known as normal (stage A1; $<$30 mg/g [3.39 mg/mmol]), moderate (stage A2; 30–300 mg/g [3.39–33.9 mg/mmol]), and severe (stage A3; $>$300 mg/g [33.9 mg/mmol]) (8).

Hazard ratios (HR) and 95% CI for each outcome were estimated separately using Cox regression models, by duration of diabetes group. Interaction P values were calculated in a single model for each outcome by including treatment group by diabetes duration interaction. Absolute risk reductions per 1,000 patients over 2.5 years were calculated. A Poisson model was used to estimate the event rates per 100 patient-years of albuminuria progression or regression to compare the impact of canagliflozin on the risk of improved and worsening albuminuria.

A two-sided $P < 0.05$ for the interaction term was deemed probable to reflect a difference beyond chance. While this is a post hoc combined analysis, the analyses of these outcomes were prespecified for each of the included trials, and the results should be interpreted in this context. Analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC).

Data and Resource Availability

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access (YODA) Project site at https://yoda.yale.edu.

RESULTS

With increasing duration of diabetes, participants in these studies were older, less likely to have a history of heart failure, but more likely to have a lower eGFR and higher ACR (Table 1). There was no significant interaction between the duration of type 2 diabetes and the effect of canagliflozin on cardiovascular outcomes. The HR for MACE ranged from 1.08 to 0.77 in those with diabetes duration $<$5 to $>$15 years, and the absolute risk reduction ranged from 2.5 to $-$13.6 per 1,000 patients over 2.5 years (number needed to treat [NNT] 73) (Fig. 1). The HR for the composite outcome of CV death or hospitalization for heart failure ranged from 0.75 to 0.80 in those with diabetes duration $<$5 to $>$15 years, and the absolute risk reduction ranged from $-$8.5 to $-$7.2 per 1,000 patients over 2.5 years. Similarly, the HR for the composite CV and kidney end point ranged from 0.98 to 0.68 in those with diabetes duration $<$5 to $>$15 years, and the absolute risk reduction ranged from $-$0.1 to $-$23.9 per 1,000 patients over 2.5 years.

There was no significant interaction between the duration of type 2 diabetes and the effect of canagliflozin on the doubling of serum creatinine, on the doubling of serum creatinine or kidney failure requiring therapy, or between the

Table 1—Baseline demographic and clinical characteristics of the pooled CANVAS Program and CREDENCE trial

	<5 years			≥5 to ≤10 years			>10 years to ≤15 years			>15 years		
	CANA (*n* = 875)	PBO (*n* = 653)	Total (*N* = 1,528)	CANA (*n* = 1,839)	PBO (*n* = 1,494)	Total (*N* = 3,333)	CANA (*n* = 2,311)	PBO (*n* = 1,837)	Total (*N* = 4,148)	CANA (*n* = 2,967)	PBO (*n* = 2,556)	Total (*N* = 5,523)
Age (years)	59.4 ± 9.4	59.7 ± 9.2	59.7 ± 9.3	62.0 ± 8.5	61.9 ± 8.6	62.0 ± 8.5	62.6 ± 8.2	63.0 ± 7.9	62.7 ± 81	65.3 ± 8.0	65.4 ± 8.3	65.3 ± 8.1
Sex												
Female	277 (31.7)	233 (35.7)	510 (33.4)	611 (33.2)	506 (33.9)	1,117 (33.5)	828 (35.8)	664 (36.1)	1,492 (36.0)	1,080 (36.4)	924 (36.2)	2,004 (36.3)
Male	598 (68.3)	420 (64.3)	1,018 (66.6)	1,228 (66.8)	988 (66.1)	2,216 (66.5)	1,483 (64.2)	1,173 (63.9)	2,656 (64.0)	1,887 (63.6)	1,632 (63.8)	3,519 (63.7)
Race												
Asian	152 (17.4)	94 (14.4)	246 (16.1)	283 (15.4)	210 (14.1)	493 (14.8)	335 (14.5)	253 (13.8)	588 (14.2)	432 (14.6)	401 (15.7)	833 (15.1)
Black or African American	33 (3.8)	31 (4.7)	67 (4.2)	59 (3.2)	64 (4.3)	123 (3.7)	74 (3.2)	75 (4.1)	149 (3.6)	122 (4.1)	102 (4.0)	224 (4.1)
Other*	48 (5.5)	36 (5.5)	84 (5.5)	110 (6.0)	92 (6.2)	201 (6.1)	130 (5.6)	120 (6.5)	250 (6.0)	224 (7.5)	187 (7.3)	411 (7.4)
White	642 (73.4)	492 (75.3)	1,134 (74.2)	1,387 (75.4)	1,128 (75.5)	2,515 (75.5)	1,772 (76.7)	1,389 (75.6)	3,161 (76.2)	2,189 (73.8)	1,866 (73.0)	4,055 (73.4)
Daily cigarette smoker	199 (22.7)	183 (21.1)	382 (22.1)	358 (19.5)	276 (18.5)	634 (19.0)	419 (18.2)	346 (18.8)	765 (18.4)	385 (13.0)	323 (12.6)	708 (12.8)
History of hypertension	762 (88.1)	586 (90.7)	1,348 (89.2)	1,677 (92.2)	1,378 (93.2)	3,055 (92.7)	2,103 (91.8)	1,702 (93.4)	3,805 (92.5)	2,773 (94.2)	2,395 (94.9)	5,168 (94.5)
History of heart failure	175 (24.2)	139 (26.8)	314 (25.3)	310 (21.8)	266 (24.3)	576 (22.9)	295 (15.6)	251 (17.8)	546 (16.5)	351 (16.9)	324 (19.8)	675 (18.2)
Type 2 diabetes duration (years)	2.7 ± 1.3	2.7 ± 1.3	2.7 ± 1.3	7.7 ± 1.7	7.8 ± 1.7	7.7 ± 1.7	12.8 ± 1.5	12.8 ± 1.5	12.8 ± 1.5	22.3 ± 6.2	22.6 ± 6.1	22.4 ± 6.1
Baseline insulin use	195 (22.3)	131 (20.1)	326 (21.3)	720 (39.2)	615 (41.2)	1,335 (40.1)	1,262 (54.6)	998 (54.3)	2,260 (54.5)	2,164 (72.9)	1,889 (73.9)	4,053 (73.4)
History of CV disease	661 (75.5)	467 (71.5)	1,128 (73.8)	1,275 (69.3)	1,036 (69.3)	2,311 (69.3)	1,135 (49.1)	953 (51.9)	2,088 (50.3)	1,795 (60.5)	1,548 (60.6)	3,343 (60.5)
History of amputation	14 (2.0)	3 (0.6)	17 (1.4)	37 (2.7)	30 (2.9)	67 (2.8)	69 (3.7)	46 (3.3)	115 (3.6)	135 (6.7)	138 (8.9)	273 (7.6)
Any atherosclerotic disease (coronary, cerebrovascular, peripheral)	675 (86.5)	483 (86.3)	1,158 (86.4)	1,331 (84.8)	1,078 (86.3)	2,409 (85.5)	1,295 (63.2)	1,081 (68.0)	2,376 (65.3)	1,935 (77.2)	1,657 (80.9)	3,592 (78.9)
History-coronary vascular disease	514 (68.6)	354 (67.2)	868 (68.0)	1,004 (67.8)	812 (69.8)	1,816 (68.7)	951 (48.9)	784 (524)	1,735 (50.5)	1,414 (62.3)	1,194 (65.8)	2,608 (63.8)
History-peripheral vascular disease	191 (26.0)	129 (24.7)	320 (25.5)	370 (25.9)	319 (28.8)	689 (27.2)	417 (21.6)	349 (23.9)	766 (22.6)	728 (32.7)	653 (37.0)	1,381 (34.6)
History-cerebrovascular disease	185 (25.8)	127 (24.9)	312 (25.4)	381 (26.9)	288 (26.5)	669 (26.7)	359 (19.0)	320 (22.2)	679 (20.4)	530 (25.2)	468 (28.2)	998 (26.5)
History-coronary revascularization	286 (39.9)	196 (38.9)	482 (39.5)	576 (41.2)	472 (44.2)	1,048 (42.5)	537 (28.8)	457 (32.0)	994 (30.2)	890 (42.3)	731 (44.7)	1,621 (43.4)
History-carotid revascularization	1 (0.1)	0 (0.0)	1 (0.1)	10 (0.7)	9 (0.9)	19 (0.8)	9 (0.5)	12 (0.9)	21 (0.7)	15 (0.8)	19 (1.3)	34 (1.0)
History-peripheral revascularization	34 (4.8)	19 (3.9)	53 (4.4)	85 (6.3)	65 (6.4)	150 (6.3)	73 (4.0)	70 (5.1)	143 (4.5)	135 (6.9)	161 (10.6)	296 (8.5)
BMI (kg/m^2)	31.7 ± 6.0	32.2 ± 6.2	31.9 ± 6.1	31.9 ± 6.0	31.6 ± 5.9	31.7 ± 6.0	32.0 ± 6.0	32.0 ± 6.0	32.0 ± 6.0	31.6 ± 5.9	31.5 ± 6.1	31.5 ± 6.0

Continued on p. 504

Table 1—Continued

	<5 years			≥5 to ≤10 years			>10 years to ≤15 years			>15 years		
	CANA (*n* = 875)	PBO (*n* = 653)	Total (*N* = 1,528)	CANA (*n* = 1,839)	PBO (*n* = 1,494)	Total (*N* = 3,333)	CANA (*n* = 2,311)	PBO (*n* = 1,837)	Total (*N* = 4,148)	CANA (*n* = 2,967)	PBO (*n* = 2,556)	Total (*N* = 5,523)
SBP (mmHg)	134.7 ± 15.1	135.7 ± 15.3	135.1 ±15.2	136.2 ± 15.7	136.8 ± 15.3	136.5 ± 15.5	137.3 ± 15.4	138.6 ± 15.3	137.9 ± 15.3	138.9 ± 16.2	138.9 ± 16.4	138.9 ± 16.3
DBP (mmHg)	80.2 ± 9.3	80.7 ± 9.2	80.4 ± 9.2	78.9 ± 9.4	79.2 ± 9.5	79.0 ± 9.4	78.5 ± 9.3	78.6 ± 9.4	78.5 ± 9.4	75.9 ± 9.6	76.2 ± 9.6	76.0 ± 9.6
Hemoglobin A_{1c} (%)	8.1 ± 1.0	8.1 ± 1.1	8.1 ± 1.1	8.2 ± 1.1	8.3 ± 1.1	8.2 ± 1.1	8.3 ± 1.0	8.3 ± 1.0	8.3 ± 1.0	8.3 ± 1.0	8.3 ± 1.1	8.3 ± 1.1
eGFR (mL/min/1.73 m^2)	77.6 ± 21.8	76.3 ± 21.7	77.0 ± 21.8	73.4 ± 21. 4	72.4 ± 22.8	73.0 ± 22.0	73.6 ± 22.0	71.6 ± 21.6	72.7 ± 21.8	65.8 ± 20.5	64.4 ± 21.3	65.1 ± 20.9
eGFR group												
<60 mL/min /1.73 m^2	168 (19.2)	149 (22.9)	317 (20.8)	477 (26.0)	451 (30.2)	928 (27.9)	586 (25.4)	544 (29.6)	1,130 (27.2)	1,185 (39.9)	1,107 (43.3)	2,292 (41.5)
≥60 mL/min /1.73 m^2	707 (80.8)	503 (77.1)	1,210 (79.2)	1,361 (74.0)	1,043 (69.8)	2,404 (72.1)	1,724 (74.6)	1,293 (70.4)	3,017 (72. 8)	1,782 (60.1)	1,449 (57.7)	3,231 (58.5)
ACR (mg/mmol)	1.6 (0.8, 17.8)	1.8 (0.8, 29.7)	1.7 (0.8, 23.3)	2.3 (0.9, 44.0)	3.4 (0.9, 68.1)	2.8 (0.9, 52.0)	2.4 (0.9, 35.0)	2.9 (0.9, 50.4)	2.6 (0.9, 42.8)	7.5 (1.2, 71.9)	18.2 (1.3, 96.7)	10.6 (1.2, 84.1)
ACR groups												
30 mg/g (3.4 mg/mmol)	531 (78.6)	366 (76.1)	897 (76.5)	989 (74.7)	732 (73.8)	1,721 (74.3)	1,256 (69.9)	950 (70.6)	2,206 (70.2)	1,231 (64.0)	945 (64.4)	2,176 (64.2)
≥30 mg/g (3.4 mg/mmol)	160 (23.2)	115 (23.9)	275 (23.5)	335 (25.3)	260 (26.2)	595 (25.7)	541 (30.1)	396 (29.4)	937 (29.8)	692 (36.0)	523 (35.6)	1,215 (35.8)
Study												
28431754DIA3008	345 (39.4)	170 (26.0)	515 (33.7)	641 (34.9)	336 (22.5)	977 (29.3)	908 (39.3)	497 (27.1)	1,405 (33.9)	994 (33.5)	439 (17.2)	1,433 (25.9)
28431754DIA4003	349 (39.9)	319 (48.9)	668 (43.7)	698 (38.0)	672 (45.0)	1,370 (41.1.)	908 (39.3)	863 (47.0)	1,771 (42.7)	947 (31.9)	1,045 (40.9)	1,992 (36.1)
28431754DNE3001	81 (20.7)	164 (25.1)	345 (22.6)	500 (27.2)	386 (32.5)	986 (29.6)	495 (21.4)	477 (26.0)	972 (23.4)	1,026 (34.6)	1,072 (41.9)	2,098 (38.0)

Data are presented as mean ± SD, *n* (%), or median (interquartile range). DBP, diastolic blood pressure; PBO, placebo; SBP, systolic blood pressure. *Includes American Indian, Alaska Native, Native Hawaiian, Pacific Islander, multiple, other, and unknown.

duration of type 2 diabetes and the effect of canagliflozin on albuminuria (Fig. 1). Within the diabetes duration subgroups, for the albuminuria end points of progression and regression, canagliflozin reduced the incidence of progression, and increased the incidence of regression, across each subgroup of diabetes duration, including participants with type 2 diabetes of <5 years. In study participants with type 2 diabetes duration of <5 years, the incidence of albuminuria progression was reduced with canagliflozin compared with placebo (HR 0.76, 95% CI 0.61–0.94; absolute risk reductions for diabetes duration <5 years 37.0 per 1,000 patients over 2.5 years) and for duration >15 years (76.8 per 1,000 patients over 2.5 years; NNT 27 and 13, respectively) (Fig. 1). Similarly, albuminuria regression was more frequently observed with canagliflozin than placebo in participants with diabetes duration <5 years (HR 1.70; 95% CI 1.31–2.21; absolute risk improvement for diabetes duration <5 years 132.9 per 1,000 patients over 2.5 years, NNT 8).

Safety Outcomes

The incidence of any serious adverse event was significantly lower with canagliflozin compared with placebo in study participants with type 2 diabetes of any duration years (*P* for interaction = 0.74) (Table 2).

CONCLUSIONS

In this post hoc analysis of participants with type 2 diabetes and high CV risk or moderate to severe albuminuria, canagliflozin reduced the incidence of CV and kidney events consistently, regardless of diabetes duration. Importantly, canagliflozin reduced the incidence of albuminuria progression and increased albuminuria regression, regardless of diabetes duration, including within the first 5 years from the diagnosis of type 2 diabetes.

This analysis highlights the clinical importance of reducing kidney and CV outcomes even for people with diabetes of short duration. These findings suggest that clinicians should not wait for rising albuminuria or declining kidney function to initiate SGLT2i therapy, but rather consider earlier intervention in people at highest risk of developing CKD or CV events. This can be assessed by risk

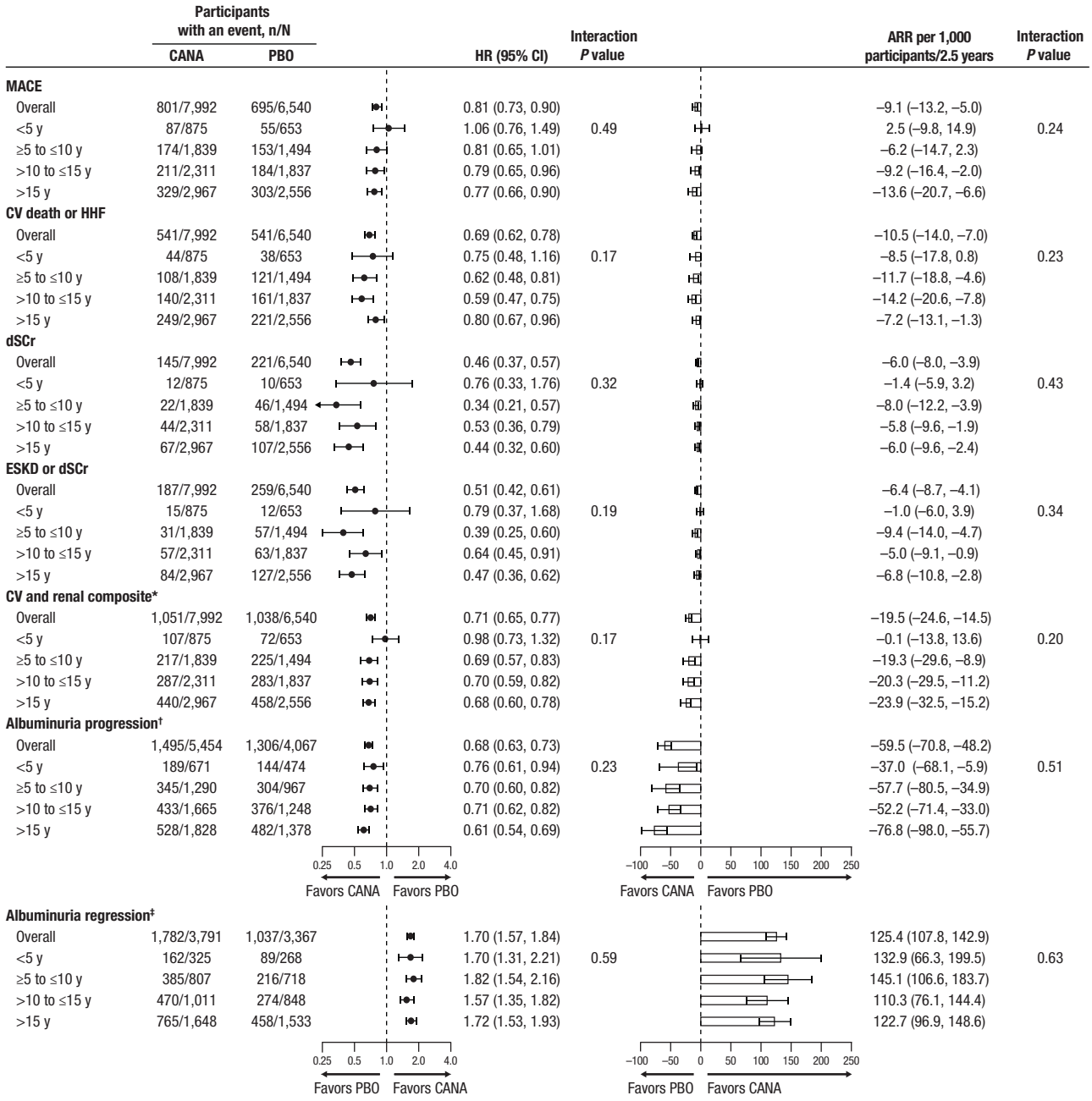

Figure 1—Effects of canagliflozin (CANA) on CV and kidney outcomes by type 2 diabetes duration. ARR, absolute risk reductions; ESKD, end-stage kidney disease; PBO, placebo. *Composite that includes MACE, hospitalization for heart failure (HHF), doubling of serum creatinine (dSCr), or kidney failure requiring therapy (KRT). †One-step or more increase in ACR category along with an increase in ACR ≥30% from baseline. ‡One-step or more decrease in ACR category along with a decrease in ACR ≥30% from baseline.

calculators (9). Indeed, SGLT2 inhibition reduces CV, kidney, and mortality outcomes irrespective of metformin use (10). The European Society of Cardiology now has SGLT2i above metformin in the treatment algorithm for drug-naive patients with type 2 diabetes at high CV risk (11).

This analysis has several limitations. It is a post hoc analysis of three randomized controlled trials. As an exploratory analysis, it was not designed with adequate statistical power to evaluate outcomes in subgroups stratified by diabetes duration. Further, the trials included moderate- to high-risk CV disease and CKD populations; hence, the findings may not be generalizable to populations with low- to moderate-risk type 2 diabetes. However, the large sample size, the inclusion of participants with different baseline CV risk, and different stages of diabetic kidney disease constitutes important strengths of our analysis.

In this analysis, earlier treatment with canagliflozin prevented albuminuria progression and promoted albuminuria regression. Canagliflozin demonstrated CV and kidney benefits, including a reduction in CKD progression regardless of diabetes duration. These findings may assist clinicians treating individuals with type 2 diabetes through shared clinical decision making to manage their disease more effectively. Treatment with canagliflozin confers meaningful and consistent

Table 2—Incidence of any serious adverse events and any kidney-related serious adverse events*

	Type 2 diabetes <5 years				Type 2 diabetes 5–10 years				Type 2 diabetes >10–15 years				Type 2 diabetes >15 years				
Adverse events	CANA	PBO	HR (95% CI)	*P* value	CANA	PBO	HR (95% CI)	*P* value	CANA	PBO	HR (95% CI)	*P* value	CANA	PBO	HR (95% CI)	*P* value	*P* interaction
Any SAE (% of subjects)	242/875 (27.7)	166/651 (25.5)	1.03 (0.85, 1.26)	0.76	558/1,838 (30.4)	472/1,493 (31.6)	0.85 (0.75, 0.97)	0.01	712/2,308 (30.8)	599/1,837 (32.6)	0.85 (0.76, 0.95)	0.01	1,144/2,964 (38.6)	923/2,554 (36.1)	0.98 (0.89, 1.07)	0.59	0.08
Any kidney-related SAE† (% of subjects)	6/875 (0.7)	5/651 (0.8)	0.89 (0.27, 2.97)	0.85	24/1,838 (1.3)	22/1,493 (1.5)	0.88 (0.49, 0.57)	0.66	23/2,308 (1.0)	31/1,837 (1.7)	0.61 (0.36, 1.05)	0.08	54/2,964 (1.8)	61/2,554 (2.4)	0.73 (0.50, 1.06)	0.09	0.74

CANA, canagliflozin; PBO, placebo; SAE, serious adverse event. *Based on the safety population (all trial participants who received the study drug). †Kidney-related SAEs based on the Medical Dictionary for Regulatory Activities (MedDRA) terminology, included kidney events (among which are AKI, blood creatinine increase, blood urea increase, eGFR decrease, dialysis, renal impairment) and were defined as life-threatening or led to unplanned hospitalization, prolonged hospitalization, or death (12).

cardiorenal benefits to individuals living with type 2 diabetes regardless of the duration of diabetes.

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