Effects of canagliflozin on cardiovascular death and hospitalization for heart failure by baseline estimated glomerular filtration rate: integrated analyses from the CANVAS Program and CREDENCE

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Background: People with type 2 diabetes mellitus (T2DM) have a greater risk of cardiovascular (CV) disease, including hospitalization for heart failure (HHF), a complication that is more common as renal function declines. The sodium glucose co-transporter 2 (SGLT2) inhibitor canagliflozin (CANA) reduced the risk of HHF in patients with T2DM and high CV risk or nephropathy in the CANVAS Program and CREDENCE trials, respectively.
Methods: This post hoc analysis included integrated, pooled data from the CANVAS Program and the CREDENCE trial. The effects of CANA compared with placebo on CV death or HHF, HHF, and CV death were assessed in subgroups defined by baseline eGFR ($<$45, 45–60, and $>$60 mL/min/1.73 m^2). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models, with subgroup by treatment interaction terms added to test for heterogeneity. Interaction P values were calculated by including treatment group and baseline eGFR in the model.
Results: A total of 14,543 participants from the CANVAS Program (N=10,142) and CREDENCE (N=4,401) were included, with mean age, 65 y; 65% male; 75% white; mean eGFR 70.3 mL/min/1.73 m^2. 1919 (13.2%) participants had baseline eGFR $<$45 mL/min/1.73 m^2 (mean, 36.7 mL/min/1.73 m^2), 2972 (20.4%) participants had eGFR 45–60 mL/min/1.73 m^2 (mean, 53.1 mL/min/1.73 m^2), and 9649 (66.3%) participants had eGFR $>$60 mL/min/1.73 m^2 (mean, 82.3 mL/min/1.73 m^2). Rates of CV death or HHF, HHF, and CV death increased as eGFR declined (Figure). CANA significantly reduced the risk of CV death or HHF and HHF compared with PBO, with consistent effects observed across subgroups.
Conclusions: CV death or HHF, HHF, and CV death event rates increased with lower baseline eGFR. CANA significantly reduced the risk of CV death or HHF, jointly and individually, in participants with T2DM and high CV risk or CKD in the CANVAS Program and the CREDENCE trial, with consistent benefits observed regardless of baseline eGFR.

Figure. Effects of CANA on CV outcomes by baseline eGFR.

	Participants with an event, n/N		Participants with an event per 1000 patient-years		Hazard ratio (95% CI)		Interaction P value
	CANA	PBO	CANA	PBO			
CV death or HHF							
Overall	543/7995	541/6545	19.4	27.9		0.70 (0.62, 0.79)	0.54
eGFR <45 mL/min/1.73 m²	109/976	146/943	40.7	62.2		0.66 (0.51, 0.84)	
eGFR 45–60 mL/min/1.73 m²	141/1559	145/1413	29.0	36.7		0.78 (0.62, 0.99)	
eGFR >60 mL/min/1.73 m²	293/5460	250/4189	14.3	19.1		0.74 (0.62, 0.87)	
HHF							
Overall	212/7995	261/6545	7.6	13.5		0.58 (0.48, 0.70)	0.84
eGFR <45 mL/min/1.73 m²	52/976	82/943	19.4	35.0		0.56 (0.39, 0.79)	
eGFR 45–60 mL/min/1.73 m²	57/1559	73/1413	11.7	18.5		0.65 (0.46, 0.92)	
eGFR >60 mL/min/1.73 m²	103/5460	106/4189	5.0	8.1		0.63 (0.48, 0.83)	
CV death							
Overall	378/7995	325/6545	13.1	16.1		0.80 (0.69, 0.93)	0.75
eGFR <45 mL/min/1.73 m²	74/976	81/943	26.6	32.8		0.81 (0.59, 1.11)	
eGFR 45–60 mL/min/1.73 m²	94/1559	82/1413	18.7	20.0		0.91 (0.67, 1.22)	
eGFR >60 mL/min/1.73 m²	210/5460	162/4189	10.0	11.9		0.81 (0.66, 1.00)	

Favors CANA   Favors PBO