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RESEARCH LETTER

Gradient of Risk and Associations With Cardiovascular Efficacy of Ertugliflozin by Measures of Kidney Function

Observations From VERTIS CV

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SGLT2 (sodium-glucose cotransporter-2) inhibitors reduce the risk of cardiovascular and kidney outcomes in patients with type 2 diabetes mellitus (T2DM) with or without established cardiovascular or kidney disease.[1,2] Decreases in the urine albumin-to-creatinine ratio (UACR) after SGLT2 inhibition are associated with a lower risk of major adverse cardiovascular events and kidney outcomes.[3] Despite the prognostic importance of kidney disease for cardiovascular outcomes, patients with T2DM are rarely risk-stratified by kidney measures in cardiology practice, with these measures being absent from commonly used cardiovascular risk prediction algorithms.

We report results from prespecified exploratory analyses from the VERTIS CV study (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease; URL: https://www.clinicaltrials.gov; Unique identifier: NCT01986881), assessing effects of ertugliflozin on cardiovascular events by baseline kidney function (estimated glomerular filtration rate [eGFR] and chronic kidney disease [CKD] stage), UACR, and Kidney Disease Improving Global Outcomes CKD risk category (KDIGO CKD), which combines eGFR and UACR to assess the risk for CKD progression. Analyses include testing of treatment group-by-subgroup interactions without adjustment for multiple testing.

VERTIS CV primary results have been published.[4] The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Informed consent was obtained from all individuals. In VERTIS CV, 8246 patients were randomized to placebo (n=2747) or ertugliflozin (n=5499; 5- and 15-mg doses). In this analysis of the intention-to-treat population, cardiovascular-related outcomes included time to first major adverse cardiovascular event, hospitalization for heart failure (HHF), cardiovascular death, and a composite of HHF or cardiovascular death.

The proportions of patients with CKD stages 1, 2, and 3 at baseline were 25%, 53%, and 22%, respectively. A total of 60% and 40% of patients had normal and elevated albuminuria, respectively. A total of 49%, 32%, and 19% were classified into the KDIGO CKD low, moderate, and high/very high risk categories, respectively.

Event rates were higher for all reported cardiovascular outcomes with more advanced kidney disease (Table). Interactions were suggested for UACR and KDIGO CKD classifications by treatment for the composite of HHF/cardiovascular death and for HHF ($P<0.05$). A similar trend was observed in subgroups by CKD stage for HHF, but the interaction was not significant. Risk reductions with ertugliflozin versus placebo achieved nominal significance for HHF and the composite of HHF/cardiovascular death in the CKD stage 3 subgroup, in patients with elevated albuminuria, and in the KDIGO CKD moderate and high/very high risk categories, with the highest absolute event rate reductions in

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Table. Cox Proportional Hazards for Cardiovascular Outcomes, by Baseline Kidney Function Categories

End point	Subgroup category	Placebo, number of events (incidence)	Ertugliflozin, number of events (incidence)	Absolute event rate reduction (per 1000 p-y)	Hazard ratio (95% CI)	*P* value for interaction
MACE	All patients	368 (40.3)	735 (40.0)	−0.3	0.99 (0.88, 1.12)	—
	CKD stage 1	72 (31.2)	135 (28.7)	−2.5	0.92 (0.69, 1.22)	0.58
	CKD stage 2	193 (39.7)	380 (38.5)	−1.2	0.97 (0.82, 1.16)	
	CKD stage 3	103 (52.8)	220 (58.0)	5.2	1.10 (0.87, 1.39)	
	Normoalbuminuria	169 (31.1)	344 (31.8)	0.7	1.02 (0.85, 1.23)	0.66
	Elevated albuminuria	193 (55.6)	375 (53.6)	−2.0	0.96 (0.81, 1.15)	
	KDIGO low risk	130 (29.0)	254 (28.4)	−0.6	0.98 (0.79, 1.21)	0.99
	KDIGO moderate risk	125 (44.7)	256 (44.7)	0.0	1.00 (0.81, 1.24)	
	KDIGO high/very high risk	107 (66.0)	208 (65.4)	−0.6	0.99 (0.79, 1.25)	
Hospitalization for heart failure and cardiovascular death	All patients	250 (26.6)	444 (23.4)	−3.2	0.88 (0.75, 1.03)	—
	CKD stage 1	32 (13.3)	81 (16.9)	3.6	1.27 (0.84, 1.91)	0.13
	CKD stage 2	126 (25.0)	222 (21.8)	−3.2	0.87 (0.70, 1.08)	
	CKD stage 3	92 (46.5)	141 (35.6)	−10.9	0.76 (0.59, 1.00*)	
	Normoalbuminuria	83 (14.8)	190 (17.1)	2.3	1.16 (0.89, 1.50)	0.01
	Elevated albuminuria	163 (45.8)	244 (33.5)	−12.3	0.73 (0.60, 0.89)	
	KDIGO low risk	57 (12.3)	139 (15.2)	2.9	1.24 (0.91, 1.68)	0.03
	KDIGO moderate risk	88 (30.3)	138 (23.1)	−7.2	0.76 (0.58, 0.99)	
	KDIGO high/very high risk	100 (61.1)	155 (47.0)	−14.1	0.77 (0.60, 0.99)	
Cardiovascular death	All patients	184 (19.0)	341 (17.6)	−1.4	0.92 (0.77, 1.11)	—
	CKD stage 1	26 (10.7)	68 (13.9)	3.2	1.30 (0.83, 2.05)	0.26
	CKD stage 2	94 (18.2)	162 (15.5)	−2.7	0.85 (0.66, 1.10)	
	CKD stage 3	64 (30.8)	111 (27.1)	−3.7	0.88 (0.64, 1.19)	
	Normoalbuminuria	72 (12.6)	155 (13.7)	1.1	1.08 (0.82, 1.43)	0.13
	Elevated albuminuria	110 (29.4)	180 (24.0)	−5.4	0.81 (0.64, 1.03)	
	KDIGO low risk	50 (10.6)	109 (11.7)	1.1	1.10 (0.79, 1.54)	0.44
	KDIGO moderate risk	63 (21.0)	113 (18.5)	−2.5	0.88 (0.65, 1.20)	
	KDIGO high/very high risk	68 (38.8)	111 (32.2)	−6.6	0.83 (0.61, 1.12)	
Hospitalization for heart failure	All patients	99 (10.5)	139 (7.3)	−3.2	0.70 (0.54, 0.90)	—
	CKD stage 1	7 (2.9)	19 (4.0)	1.1	1.36 (0.57, 3.23)	0.08
	CKD stage 2	47 (9.4)	75 (7.4)	−2.0	0.79 (0.55, 1.13)	
	CKD stage 3	45 (22.7)	45 (11.4)	−11.3	0.50 (0.33, 0.76)	
	Normoalbuminuria	23 (4.1)	51 (4.6)	0.5	1.12 (0.69, 1.83)	0.02
	Elevated albuminuria	74 (20.8)	83 (11.4)	−9.4	0.55 (0.40, 0.75)	
	KDIGO low risk	14 (3.0)	38 (4.2)	1.2	1.38 (0.75, 2.54)	0.03
	KDIGO moderate risk	33 (11.3)	34 (5.7)	−5.6	0.50 (0.31, 0.81)	
	KDIGO high/very high risk	50 (30.6)	62 (18.8)	−11.8	0.61 (0.42, 0.89)	

The 3 baseline kidney function classification schemes were as follows: (1) estimated glomerular filtration rate (eGFR) categories: chronic kidney disease (CKD) stage 1 (eGFR ≥90 mL/min/1.73 m^2), CKD stage 2 (eGFR ≥60 and <90 mL/min/1.73 m^2), and CKD stage 3 (eGFR <60 mL/min/1.73 m^2); (2) Kidney Disease Improving Global Outcomes (KDIGO) CKD risk category: low risk (eGFR ≥60 mL/min/1.73 m^2 with urine albumin-to-creatinine ratio [UACR] <30 mg/g), moderate risk (eGFR 45 to <60 mL/min/1.73 m^2 with UACR <30 mg/g or eGFR ≥60 mL/min/1.73 m^2 with UACR 30 to 300 mg/g), and high/very high risk (eGFR ≥60 mL/min/1.73 m^2 and UACR >300 mg/g or eGFR 45 to 59 mL/min/1.73 m^2 and UACR >30 mg/g or eGFR <45 mL/min/1.73 m^2); (3) albuminuria category: normal (UACR <30 mg/g) or elevated (UACR ≥30 mg/g) albuminuria. MACE indicates major adverse cardiovascular events (composite of first event of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke); and p-y, patient-years.

*Upper 95% CI = 0.995. All analyses were performed on the intention-to-treat population.

these subgroups. Absolute event rate differences (per 1000 patient-years) and relative risk reductions with ertugliflozin for HHF and for a composite of HHF/cardiovascular death were highest in the CKD stage 3, KDIGO CKD moderate risk, high/very high risk, and elevated albuminuria subgroups.

Determination of cardiovascular risk is achieved using risk prediction algorithms complemented by

biomarkers. Creatinine-based estimates of glomerular filtration rate are also recognized as a cardiovascular risk factor, particularly for HHF. UACR measurements are part of guideline-based clinical practice recommendations for diabetic kidney disease screening and also a predictor of cardiorenal risk and clinical responses to treatments such as SGLT2 inhibitors.[3] The routine use of UACR testing in patients with T2DM in general practice remains low and UACR testing is not part of standard care in cardiology practice. These results support the importance of risk stratifying by both eGFR and albuminuria status, such as by the KDIGO CKD risk classification.

The effect of ertugliflozin on HHF and the composite of HHF/cardiovascular death differed on the basis of the severity of kidney disease using classifications that included UACR. The presence of significant interactions for both the KDIGO CKD and UACR classifications suggests greater benefits in patients with higher risk profiles on the basis of kidney measures for HHF and HHF/cardiovascular death. Owing to small sample sizes and low numbers of events in some subgroups, interpretability of results for these subgroups is limited, and assessment of within-subgroup statistical significance was not the aim of the analyses. The low number of events deserves emphasis, especially in lower risk subgroups, such as eGFR ≥90 mL/min/1.73 m^2, which were considered separately in this analysis, rather than being included in the eGFR ≥60 mL/min/1.73 m^2 group, which showed significant interaction for the eGFR <60 mL/min/1.73 m^2 group with respect to reduction of HHF events.[5] Further exploration of the association between cardiovascular disease, CKD, and SGLT2 inhibition is warranted in dedicated kidney disease cohorts.

In patients with T2DM and atherosclerotic cardiovascular disease, ertugliflozin reduced the risk of HHF, with greater relative risk reductions and absolute event rate reductions in patients in the KDIGO CKD moderate and high/very high risk categories and with elevated albuminuria at baseline. These results highlight the potential value of stratifying kidney disease risk by both UACR and measures of kidney function in patients with T2DM to predict cardiovascular risk and response to ertugliflozin.

ARTICLE INFORMATION

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01986881.

The sponsor's data sharing policy is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to clinical study data can be submitted through the website or by email (dataaccess@merck.com).

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REFERENCES

1. Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, Mahaffey KW, Charytan DM, Wheeler DC, Arnott C, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2019;7:845–854. doi: 10.1016/S2213-8587(19)30256-6
2. McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, Pratley R, Greenberg M, Wang S, Huyck S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol*. 2020;e204511. doi: 10.1001/jamacardio.2020.4511
3. Idzerda NMA, Stefansson BV, Pena MJ, Sjostrom DC, Wheeler DC, Heerspink HJL. Prediction of the effect of dapagliflozin on kidney and heart failure outcomes based on short-term changes in multiple risk markers. *Nephrol Dial Transplant*. 2020;35:1570–1576. doi: 10.1093/ndt/gfz064
4. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, et al; VERTIS CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med*. 2020;383:1425–1435. doi: 10.1056/NEJMoa2004967
5. Cosentino F, Cannon CP, Cherney DZI, Masiukiewicz U, Pratley R, Dagogo-Jack S, Frederich R, Charbonnel B, Mancuso J, Shih WJ, et al; VERTIS CV Investigators. Efficacy of ertugliflozin on heart failure-related events in patients with type 2 diabetes mellitus and established atherosclerotic cardiovascular disease: results of the VERTIS CV trial. *Circulation*. 2020;142:2205–2215. doi: 10.1161/CIRCULATIONAHA.120.050255