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Cardiorenal Outcomes With Ertugliflozin by Baseline Metformin Use: Post Hoc Analyses of the VERTIS CV Trial

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The universal guidance of treating patients with type 2 diabetes (T2D) with metformin first has been questioned since positive cardiovascular outcomes trials of antihyperglycemic agents were reported between 2015 and 2021, demonstrating cardiovascular efficacy of multiple glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors. This underpinned the paradigm shift in the 2019 European Society of Cardiology Guidelines on diabetes and cardiovascular diseases, from a glucose-centric to a risk-driven, evidence-based cardiocentric strategy. Recommendations include glucagon-like peptide-1 receptor agonists or SGLT2 inhibitors with proven cardiovascular benefits as first-line antihyperglycemic therapy in drug-naive patients with T2D and atherosclerotic cardiovascular disease or at high/very high cardiovascular risk.[1] The 2022 American Diabetes Association standards of medical care recommend glucagon-like peptide-1 receptor agonists and SGLT2 inhibitors, with or without metformin on the basis of glycemic needs, for those with T2D with or at high risk for atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease.[2] Whether background metformin treatment affects the cardiovascular benefits of glucagon-like peptide-1 receptor agonists and SGLT2 inhibitors remains an important question.

Prespecified unadjusted analyses from the VERTIS CV trial (Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes, NCT01986881) conducted in patients with T2D and atherosclerotic cardiovascular disease with ertugliflozin suggested no interaction of the presence or absence of baseline metformin on the composite outcome of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke), cardiovascular death, hospitalization for heart failure, the composite of cardiovascular death/hospitalization for heart failure, or 2 kidney composite end points (doubling of serum creatinine level, kidney replacement therapy, or death from kidney causes; sustained ≥40% decrease in estimated glomerular filtration rate from baseline, kidney replacement therapy, or death from kidney causes).[3] However, unadjusted analyses do not take into consideration the differences in baseline clinical characteristics between the subpopulations with and without baseline metformin use, with the corresponding biases and confounding factors that may obscure relevant interactions.

Therefore, to estimate differences in adjusted risk of cardiorenal outcomes between ertugliflozin and placebo across subgroups on the basis of baseline metformin use, we performed post hoc analyses using Cox proportional hazards modeling with propensity adjustment for metfor-

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Nonstandard Abbreviations and Acronyms

SGLT2	sodium-glucose cotransporter 2
T2D	type 2 diabetes
VERTIS CV	Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes

min use by inverse probability of treatment weighting to account for differences in baseline characteristics and risk factor profiles between patients with and without baseline metformin use. The significance level was set to 0.05 for all analyses. VERTIS CV was conducted in accordance with the principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. Informed consent was obtained from all individuals. On request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, condi-

tions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Of 8246 patients in VERTIS CV, 6286 (76%; ertugliflozin: 4164/5499 [75.7%]; placebo: 2122/2747 [77.2%]) used metformin at baseline, alone (n=1149, 18.3%) or with other antihyperglycemic agents. Of those without baseline metformin, 104 (5.4%) were not taking any antihyperglycemic agent. There were notable differences in baseline characteristics in those with, compared with those without, baseline metformin use. These differences included (in those with baseline metformin use): a higher mean estimated glomerular filtration rate (78.1 versus 69.3 mL·min^{-1}·1.73 m^{-2}), fewer patients with estimated glomerular filtration rate <60 mL·min^{-1}·1.73 m^{-2} (17.9% versus 34.8%), fewer patients on a single antihyperglycemic agent (18.3% versus 76.9%), less insulin use (40.9% versus 67.6%), higher sulfonylurea use (43.8% versus 32.2%), and shorter mean diabe-

	BL use of metformin	Ertugliflozin		Placebo		Hazard ratio (95% CI)	P$_{interaction}$
		n/N	%	n/N	%		
MACE	Yes	522/4101	12.7	273/2087	13.1	0.97 (0.914, 1.035)	0.21
	No	206/1307	15.8	87/612	14.2	1.11 (0.912, 1.347)	
HHF/CV death	Yes	299/4101	7.3	178/2087	8.5	0.95 (0.873, 1.026)	0.80
	No	140/1307	10.7	68/612	11.1	0.92 (0.736, 1.146)	
CV death	Yes	229/4101	5.6	133/2087	6.4	1.00 (0.914, 1.099)	0.90
	No	108/1307	8.3	49/612	8.0	0.98 (0.760, 1.276)	
HHF	Yes	92/4101	2.2	67/2087	3.2	0.74 (0.646, 0.855)	0.69
	No	46/1307	3.5	30/612	4.9	0.69 (0.489, 0.970)	
Kidney composite (2x serum Cr)	Yes	112/4101	2.7	66/2087	3.2	0.82 (0.726, 0.924)	0.30
	No	59/1307	4.5	41/612	6.7	0.69 (0.502, 0.939)	
Kidney composite (≥40% sustained ↓ eGFR)	Yes	77/4101	1.9	61/2087	2.9	0.71 (0.628, 0.804)	0.96
	No	33/1307	2.5	23/612	3.8	0.72 (0.466, 1.108)	

Hazard Ratio (95% CI)

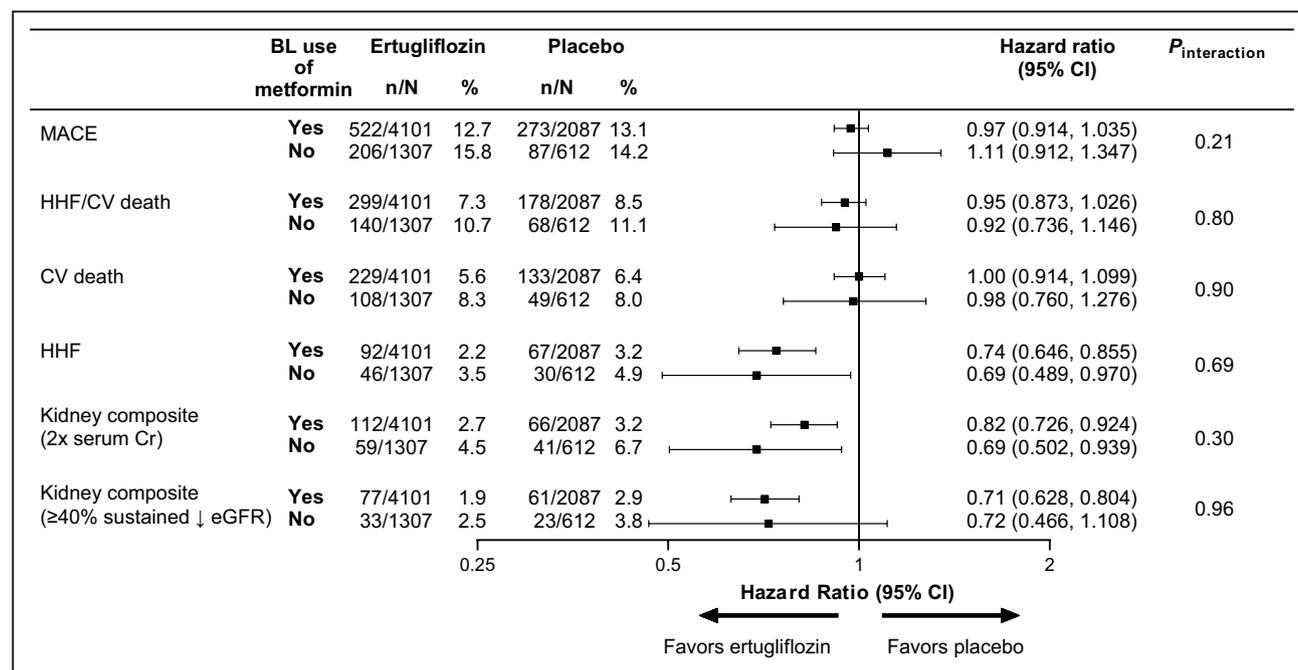← Favors ertugliflozin   Favors placebo →

Figure. Cardiovascular and kidney outcomes with ertugliflozin versus placebo by baseline metformin use after propensity adjustment for metformin use.

Differences in risk of cardiovascular and kidney outcomes between ertugliflozin and placebo across subgroups by baseline metformin use were estimated from a Cox proportional hazards model by means of propensity adjustment for metformin use by using inverse probability of treatment weighting to account for differences in baseline characteristics and risk factor profiles between patients with and without baseline metformin use. Treatment, baseline metformin use, and the interaction term between treatment and baseline metformin use were included in each model, and the enrollment cohort was included as a stratification factor. Model weights were calculated using propensity score estimates of baseline metformin use and the inverse probability of treatment weighting formula. The variables considered in propensity scoring were age, sex, race, region, body mass index, duration of type 2 diabetes, glycated hemoglobin, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, estimated glomerular filtration rate, and history of: coronary artery disease, cerebrovascular disease, peripheral arterial disease, heart failure, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, and stroke. Hazard ratios (95% CIs) are provided for ertugliflozin versus placebo by baseline metformin use. The interaction P value is shown for the 2-level treatment group (all ertugliflozin versus placebo). The kidney composite outcomes were doubling of serum creatinine level, kidney replacement therapy, or death from kidney causes and the exploratory kidney outcome of sustained ≥40% decrease in eGFR from baseline, kidney replacement therapy, or death from kidney causes. BL indicates baseline; Cr, creatinine; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; and MACE, major adverse cardiovascular events.

tes duration (12.5 versus 14.4 years). As observed in the unadjusted analyses,[3] there were no significant propensity-adjusted differences in the effects of ertugliflozin on cardiovascular or kidney outcomes by baseline metformin use (Figure; all $p_{interaction}$ values >0.2).

In VERTIS CV, 24% of patients were not on metformin at baseline. This subset of ≈2000 patients not treated with metformin is larger than that of almost every T2D metformin comparator trial before the 2008 regulatory guidance requiring cardiovascular safety assessments for all new medications developed for T2D. In the present analysis, we found no modification of ertugliflozin effect by baseline metformin use on any of the cardiorenal outcomes assessed.

The paradigm shift proposed in the 2019 European Society of Cardiology Guidelines[1] has expanded discussion regarding whether metformin should remain first line, because other antihyperglycemic medications have demonstrated cardiorenal benefits in high-risk populations. In the overall VERTIS CV trial, ertugliflozin was noninferior to placebo for major adverse cardiovascular events.[4] In addition, there was a 30% relative risk reduction with ertugliflozin in hospitalization for heart failure and a 34% relative risk reduction with ertugliflozin in the prespecified exploratory kidney composite outcome.[4,5] In the present analyses with propensity adjustment, the hospitalization for heart failure and kidney outcomes with ertugliflozin were not modified by baseline metformin status. These findings suggest that metformin is unlikely to modulate the benefits of SGLT2 inhibitors on cardiorenal outcomes and that the benefits of SGLT2 inhibitors accrue regardless of metformin use. Given the lack of robust proof of metformin efficacy for cardiovascular outcomes and a less rigorous assessment of cardiovascular safety compared with contemporary antihyperglycemic agents, the elevation of antihyperglycemic agents with proven cardiorenal efficacy and cardiovascular safety above metformin fully represents the application of evidence-based medicine.

ARTICLE INFORMATION

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

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