Control Number: 18612

Should Cardiologists Risk-Stratify Patients With Atherosclerotic Cardiovascular Disease by Kidney Function?

Results From the VERTIS CV Trial Evaluating Efficacy of Ertugliflozin on Cardiovascular and Kidney Outcomes by Baseline Kidney Function

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eValuation of ERTugliflozin effIcacy and Safety

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Presented at the Scientific Sessions of the American Heart Association, November 13, 2020

Disclosures and funding

- **David Z.I. Cherney, MD, PhD**
  - Received Merck honorarium for SAC participation, Pfizer-non-financial support and consulting fees or speaking honorarium, or both, from Bristol Myers Squibb, Novo Nordisk, Mitsubishis-Tanabe, MAZE, Janssen, Bayer, Boehringer Ingelheim-Eli Lilly, AstraZeneca, Merck & Co. Inc. a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, Prometic, and Sanofi, and has received operating funds from Janssen, Boehringer Ingelheim-Eli Lilly, Sanofi, AstraZeneca, and Merck & Co. Inc
- The VERTIS CV study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, in collaboration with Pfizer Inc, New York, NY, USA

SAC=scientific advisory committee.

Background

- Studies with SGLT2 inhibitors have show reduction in the risk of adverse CV and kidney outcomes in people with T2DM[1]
- Identifying clinical factors that predict clinical outcomes benefit from SGLT2 inhibition is of clinical importance
- Kidney disease, as defined by eGFR and/or the presence of albuminuria, is an important risk factor for CV disease[2]
- Patients with T2DM are rarely risk-stratified by kidney parameters in cardiology practice
- Here we present prespecified exploratory analyses from VERTIS CV,[3] assessing effects of ertugliflozin on CV events by baseline:
  - eGFR (CKD stage)
  - baseline UACR
  - baseline KDIGO CKD

[1]Neuen et al. *Lancet Diabetes Endocrinol*. 2019;7:845–854. [2]Fox et al. *Lancet*. 2012;380(9854):1662–73. [3]Cannon et al. *N Eng J Med*. 2020 Sep 23. doi: 10.1056/NEJMoa2004967. CKD=chronic kidney disease. CV=cardiovascular. eGFR=estimated glomerular filtration rate. KDIGO CKD=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. SGLT2=sodium-glucose cotransporter 2. T2DM=type 2 diabetes mellitus. UACR=urinary albumin-to-creatinine ratio.

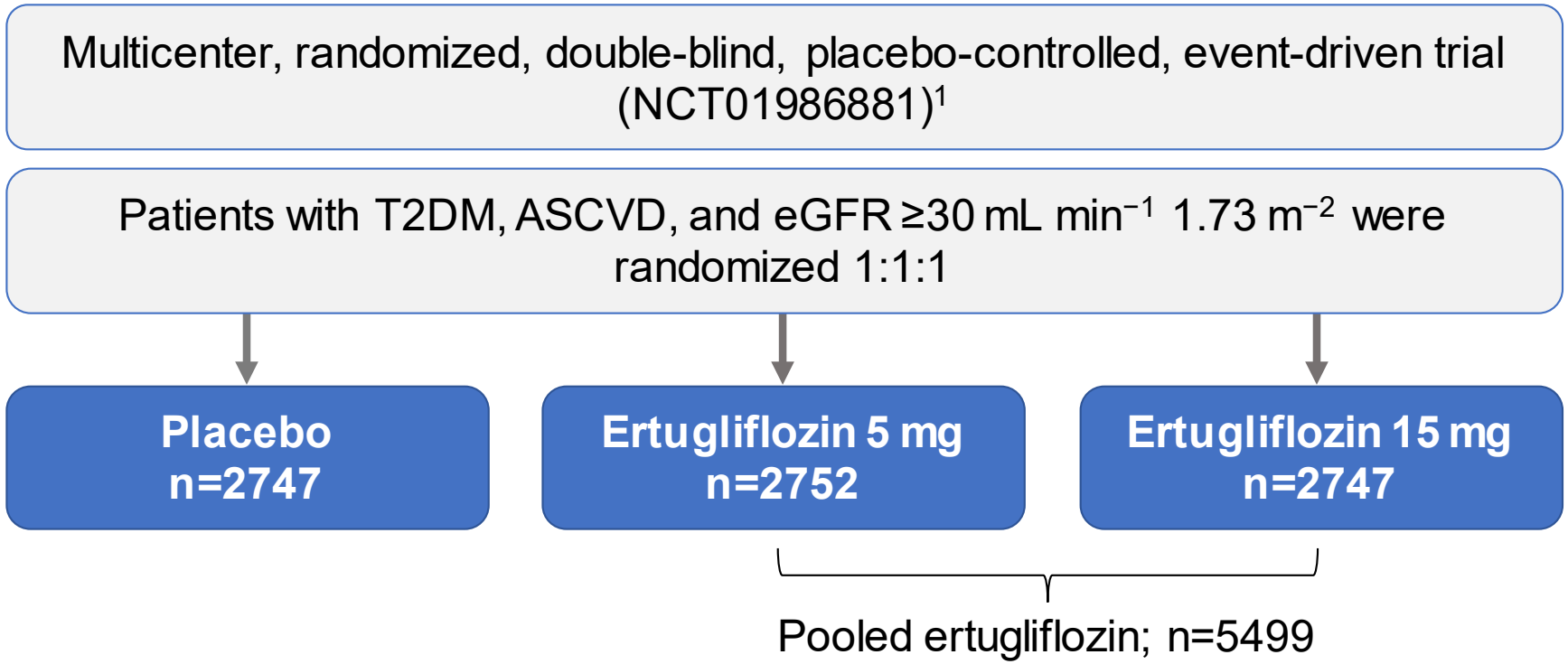
Classification by baseline kidney categories

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR, mL min^{-1} 1.73 m^{-2} Description and range				Persistent albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90	Low risk	Moderate Risk	High risk
	G2	Mildly decreased	60–89	Low risk	Moderate risk	High risk
	G3a	Mildly to moderately decreased	45–59	Moderate risk	High risk	Very high risk
	G3b	Moderately to severely decreased	30–44	High risk	Very high risk	Very high risk
	G4	Severely decreased	15–29	Patients with eGFR <30 mL min^{-1} 1.73 m^{-2} excluded from VERTIS CV		
	G5	Kidney failure	<15			

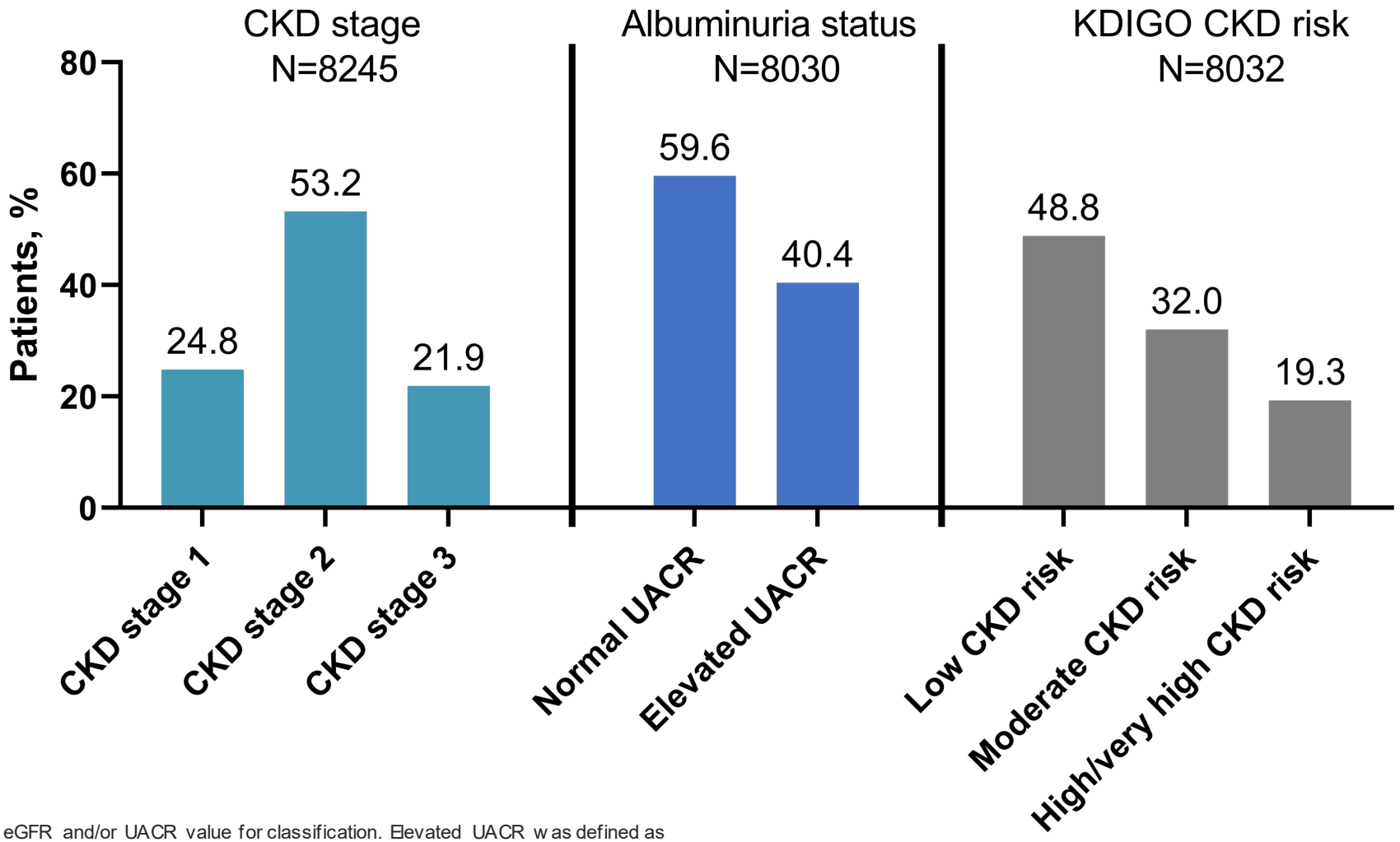
CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. KDIGO=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. Reprinted from *Kidney International,* 80(1), Andrew S. Levey, Paul E. de Jong, Josef Coresh, Meguid E.l. Nahas, Brad C. Astor, Kunihiro Matsushita, Ron T. Gansevoort, Bertram L. Kasiske, Kai-Uwe Eckardt. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report, 17–28, Copyright (2011), with permission from Elsevier.

VERTIS CV study design



[1]Cannon CP et al. *N Eng J Med*. 2020 Sep 23. doi: 10.1056/NEJMoa2004967.
ASCVD=atherosclerotic cardiovascular disease. eGFR=estimated glomerular filtration rate. T2DM=type 2 diabetes mellitus.

VERTIS CV: Distribution by baseline kidney categories (overall population)



Patients required a baseline eGFR and/or UACR value for classification. Elevated UACR was defined as UACR ≥30mg/g. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. KDIGO CKD=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. UACR=urinary albumin-to-creatinine ratio.

Baseline characteristics by CKD stage

	CKD stage 1 n=2048	CKD stage 2 n=4390	CKD stage 3 n=1807
Male, n (%)	1549 (75.6)	3064 (69.8)	1156 (64.0)
Age, years (SD)	60.3 (7.7)	64.7 (7.5)	68.2 (7.6)
Duration of T2DM, years (SD)	10.6 (6.9)	12.9 (8.3)	15.7 (9.0)
HbA1c, % (SD)	8.3 (1.0)	8.2 (1.0)	8.2 (0.9)
RAS blocker use, n (%)	1597 (78.0)	3585 (81.7)	1503 (83.2)
Diuretic use, n (%)	646 (31.5)	1876 (42.7)	1020 (56.4)

Characteristics for patients with a baseline eGFR value included. CKD=chronic kidney disease. HbA1c=glycated hemoglobin. RAS=renin–angiotensin system. SD=standard deviation. T2DM=type 2 diabetes mellitus.

Baseline characteristics by albuminuria category and KDIGO CKD risk

	Normal UACR n=4783	Elevated albuminuria n=3247
Male, n (%)	3209 (67.1)	2418 (74.5)
Age, years (SD)	64.3 (8.1)	64.4 (8.0)
Duration of T2DM, years (SD)	12.4 (8.2)	13.8 (8.4)
HbA1c, % (SD)	8.1 (0.9)	8.4 (1.0)
RAS blocker use, n (%)	3838 (80.2)	2678 (82.5)
Diuretic use, n (%)	2006 (41.9)	1454 (44.8)

	KDIGO CKD Low risk n=3916	KDIGO CKD Moderate risk n=2568	KDIGO CKD High/very high risk n=1548
Male, n (%)	2705 (69.1)	1824 (71.0)	1099 (71.0)
Age, years (SD)	63.4 (7.9)	64.7 (7.9)	66.4 (8.1)
Duration of T2DM, years (SD)	11.8 (7.8)	13.4 (8.4)	15.5 (8.8)
HbA1c, % (SD)	8.1 (0.9)	8.3 (1.0)	8.4 (1.0)
RAS blocker use, n (%)	3129 (79.9)	2100 (81.8)	1291 (83.4)
Diuretic use, n (%)	1517 (38.7)	1096 (42.7)	849 (54.8)

Characteristics for patients with a baseline eGFR and/or UACR value included. HbA1c=glycated hemoglobin. KDIGO CKD=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. RAS=renin–angiotensin system. SD=standard deviation. T2DM=Type 2 diabetes mellitus. UACR=urinary albumin-to-creatinine ratio.

Time to first MACE by baseline kidney function category

	Ertugliflozin		Placebo				
	Patients with events	Rate per 1000 patient-years	Patients with events	Rate per 1000 patient-years	AERR	Hazard ratio (95% CI)	*P* value for interaction
All patients	735	40.0	368	40.3	−0.3	0.99 (0.88, 1.12)	
CKD stage 1	135	28.7	72	31.2	−2.5	0.92 (0.69, 1.22)	
CKD stage 2	380	38.5	193	39.7	−1.2	0.97 (0.82, 1.16)	0.58
CKD stage 3	220	58.0	103	52.8	5.2	1.10 (0.87, 1.39)	
Normal UACR	344	31.8	169	31.1	0.7	1.02 (0.85, 1.23)	0.66
Elevated UACR	375	53.6	193	55.6	−2.0	0.96 (0.81, 1.15)	
KDIGO low risk	254	28.4	130	29.0	−0.6	0.98 (0.79, 1.21)	
KDIGO moderate risk	256	44.7	125	44.7	0.0	1.00 (0.81, 1.24)	0.99
KDIGO high/very high risk	208	65.4	107	66.0	−0.6	0.99 (0.79, 1.25)	

All analyses were performed on the intention-to-treat population. AERR=absolute event rate reduction. CI=confidence interval. CKD=chronic kidney disease. CV=cardiovascular. KDIGO CKD=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. MACE=major adverse cardiovascular event. UACR=urinary albumin-to-creatinine ratio.

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CV death events by baseline kidney function category

	Ertugliflozin		Placebo				
	Patients with events	Rate per 1000 patient-years	Patients with events	Rate per 1000 patient-years	AERR	Hazard ratio (95% CI)	*P* value for interaction
All patients	341	17.6	184	19.0	−1.4	0.92 (0.77, 1.11)	
CKD stage 1	68	13.9	26	10.7	3.2	1.30 (0.83, 2.05)	
CKD stage 2	162	15.5	94	18.2	−2.7	0.85 (0.66, 1.10)	0.26
CKD stage 3	111	27.1	64	30.8	−3.7	0.88 (0.64, 1.19)	
Normal UACR	155	13.7	72	12.6	1.1	1.08 (0.82, 1.43)	0.13
Elevated UACR	180	24.0	110	29.4	−5.4	0.81 (0.64, 1.03)	
KDIGO low risk	109	11.7	50	10.6	1.1	1.10 (0.79, 1.54)	
KDIGO moderate risk	113	18.5	63	21.0	−2.5	0.88 (0.65, 1.20)	0.44
KDIGO high/very high risk	111	32.2	68	38.8	−6.6	0.83 (0.61, 1.12)	

All analyses were performed on the intention-to-treat population. AERR=absolute event rate reduction. CI=confidence interval. CKD=chronic kidney disease. CV=cardiovascular. KDIGO CKD=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. UACR=urinary albumin-to-creatinine ratio.

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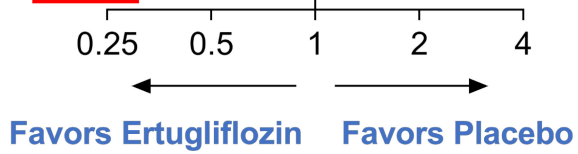
Time to first HHF event by baseline kidney function category

	Ertugliflozin		Placebo				
	Patients with events	Rate per 1000 patient-years	Patients with events	Rate per 1000 patient-years	AERR	Hazard ratio (95% CI)	*P* value for interaction
All patients	139	7.3	99	10.5	−3.2	0.70 (0.54. 0.90)	
CKD stage 1	19	4.0	7	2.9	1.1	1.36 (0.57, 3.23)	
CKD stage 2	75	7.4	47	9.4	−2.0	0.79 (0.55, 1.13)	0.08
CKD stage 3	45	11.4	45	22.7	−11.3	0.50 (0.33, 0.76)	
Normal UACR	51	4.6	23	4.1	0.5	1.12 (0.69, 1.83)	0.02
Elevated UACR	83	11.4	74	20.8	−9.4	0.55 (0.40, 0.75)	
KDIGO low risk	38	4.2	14	3.0	1.2	1.38 (0.75, 2.54)	
KDIGO moderate risk	34	5.7	33	11.3	−5.6	0.50 (0.31, 0.81)	0.03
KDIGO high/very high risk	62	18.8	50	30.6	−11.8	0.61 (0.42, 0.89)	



All analyses were performed on the intention-to-treat population. AERR=absolute event rate reduction. CI=confidence interval. CKD=chronic kidney disease. HHF=hospitalization for heart failure. KDIGO CKD=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. UACR=urinary albumin-to-creatinine ratio.

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Composite of time to first event of HHF or CV death events by baseline kidney function category

	Ertugliflozin		Placebo				
	Patients with events	Rate per 1000 patient-years	Patients with events	Rate per 1000 patient-years	AERR	Hazard ratio (95% CI)	*P* value for interaction
All patients	444	23.4	250	26.6	−3.2	0.88 (0.75, 1.03)	
CKD stage 1	81	16.9	32	13.3	3.6	1.27 (0.84, 1.91)	
CKD stage 2	222	21.8	126	25.0	−3.2	0.87 (0.70, 1.08)	0.13
CKD stage 3	141	35.6	92	46.5	−10.9	0.76 (0.59, 0.995)	
Normal UACR	190	17.1	83	14.8	2.3	1.16 (0.89, 1.50)	0.01
Elevated UACR	244	33.5	163	45.8	−12.3	0.73 (0.60, 0.89)	
KDIGO low risk	139	15.2	57	12.3	2.9	1.24 (0.91, 1.68)	
KDIGO moderate risk	138	23.1	88	30.3	−7.2	0.76 (0.58, 0.99)	0.03
KDIGO high/very high risk	155	47.0	100	61.1	−14.1	0.77 (0.60, 0.99)	

All analyses were performed on the intention-to-treat population. AERR=absolute event rate reduction. CI=confidence interval. CKD=chronic kidney disease. CV=cardiovascular. HHF=hospitalization for heart failure. KDIGO CKD=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. UACR=urinary albumin-to-creatinine ratio.

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Conclusions

- Event rates were higher for all reported CV outcomes with worsening CKD stage, albuminuria and KDIGO CKD risk category
- The impact of ertugliflozin on HHF and the composite of HHF/CV death was larger, with absolute event rate reductions of 5–14/1000 patient-years in patients with:
  - CKD stage 3
  - elevated UACR
  - moderate and high/very high KDIGO CKD risk
- 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:
  - CV risk
  - Response to SGLT2 inhibition

CKD=chronic kidney disease. CV=cardiovascular. HHF=hospitalization for heart failure. KDIGO CKD=Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease. SGLT2=Sodium-glucose cotransporter-2. T2DM=type 2 diabetes mellitus. UACR=urinary albumin-to-creatinine ratio.

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