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Tirzepatide Versus Dulaglutide Reduced Major Kidney Events in Patients With Type 2 Diabetes With Established Cardiovascular Disease and Very High-Risk Kidney Disease

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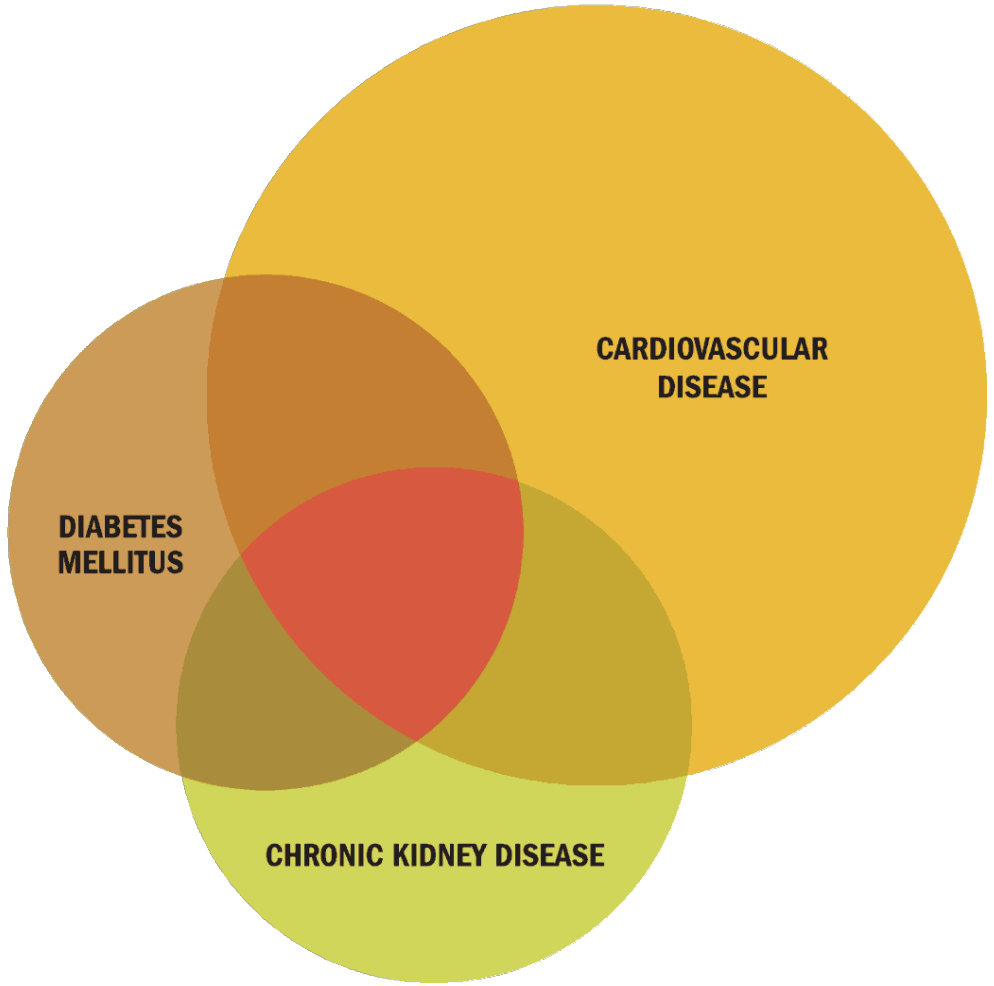
Diabetes and Chronic Kidney Disease

- Diabetes is the leading cause of chronic kidney disease (CKD) globally and estimated to develop in approximately 40% of people living with diabetes
- While lifestyle interventions, glycemic control, blood pressure management, and lipid regulation remain foundational in the prevention and management of CKD, these are now complemented by therapies with established kidney protective effects



Background: SURPASS-CVOT Trial

- Tirzepatide, a dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, has been shown to improve glycemic control and promote weight loss when compared with selective GLP-1 receptor agonists
- Benefits of tirzepatide have also been observed for atherogenic lipoproteins, blood pressure, high sensitivity C-reactive protein, albuminuria, and kidney function in comparison with selective GLP-1 receptor agonists or basal insulins
- The SURPASS-CVOT trial used an active comparator (dulaglutide) known to reduce cardiovascular (CV) events to determine the CV outcomes for tirzepatide compared with dulaglutide, a selective GLP-1 receptor agonist, in a high-risk population with type 2 diabetes (T2D)
- The SURPASS-CVOT trial offered the opportunity to directly compare the effect of tirzepatide and dulaglutide on clinically meaningful kidney outcomes

SURPASS-CVOT: Primary Objective

- To assess the efficacy of tirzepatide compared with dulaglutide on time to first occurrence of the composite endpoint of death from CV causes, myocardial infarction, or stroke when added to standard of care in participants with T2D and established atherosclerotic CV disease
- The primary objective was to initially determine non-inferiority of tirzepatide compared with dulaglutide on the primary end point and then to determine potential superiority of tirzepatide compared with dulaglutide

SURPASS-CVOT: Key Secondary Objectives

To assess the superiority of tirzepatide compared with dulaglutide for:

- Time to first occurrence of the expanded composite outcome of CV death, myocardial infarction, stroke, or coronary revascularisation
- Time to first occurrence of CV death or heart failure event requiring hospitalization and/or urgent heart failure visit
- Time to CV death
- Time to all-cause death
- Change from baseline to 36 months in estimated glomerular filtration rate (eGFR) (CKD-EPI Creatinine-Cystatin Equation 2021) in participants with high-risk chronic kidney disease

SURPASS-CVOT: Eligibility Criteria

Key Inclusion Criteria

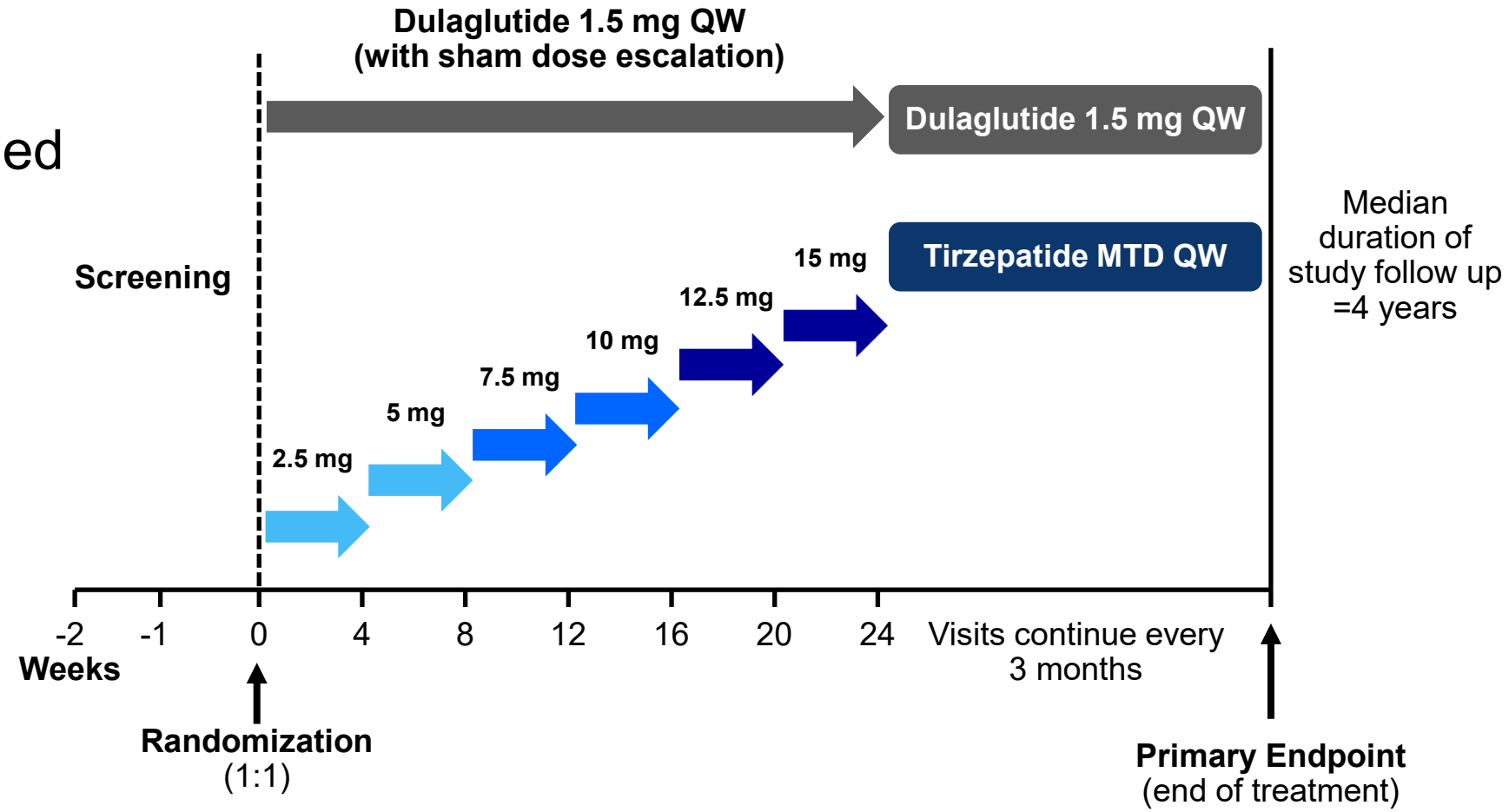
- ≥40 years with diagnosis of T2D
- Established atherosclerotic CV disease, including ≥1 of the following: coronary artery disease, cerebrovascular disease, peripheral artery disease (each as defined per protocol)
- HbA1c ≥7% and ≤10.5% at screening
- BMI ≥25 kg/m^2

Key Exclusion Criteria

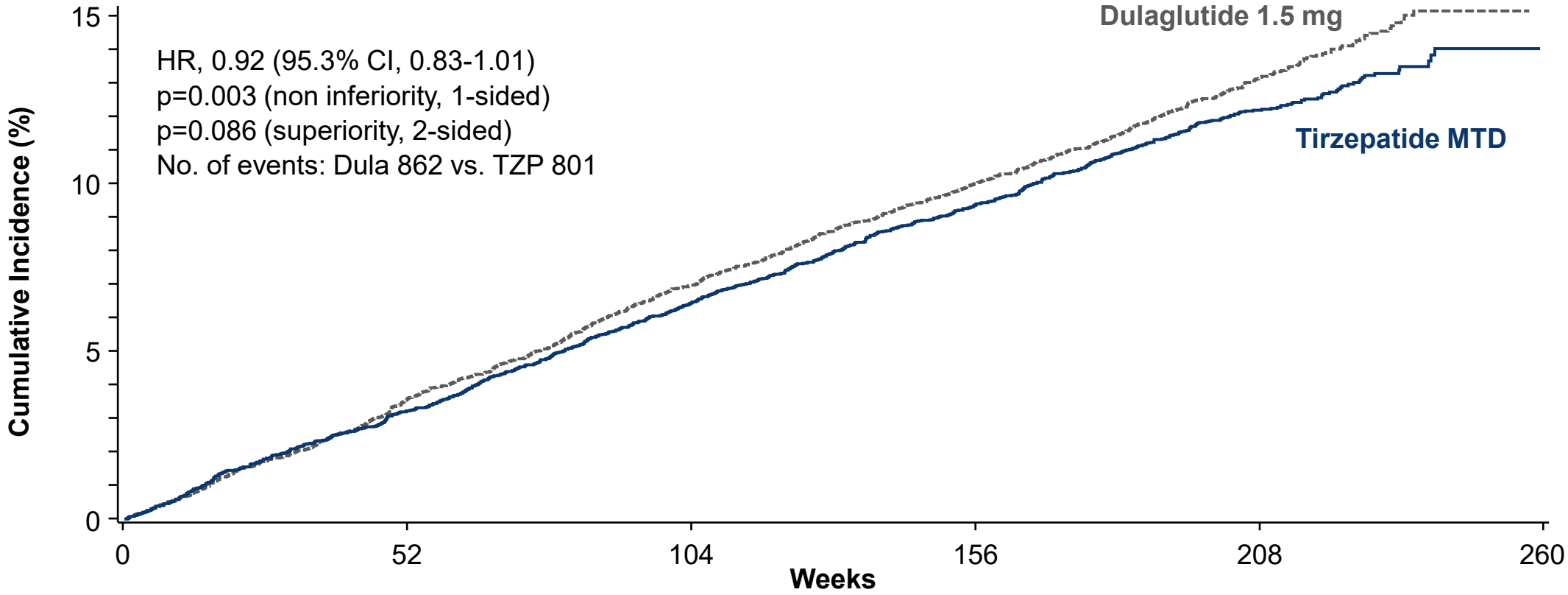
- Type 1 diabetes or uncontrolled diabetes requiring immediate therapy
- ≥1 episode of severe hypoglycemia and/or hypoglycemia unawareness within 6 months prior to screening
- Hospitalized for congestive heart failure within the prior 2 months
- Chronic New York Heart Association Functional Classification IV congestive heart failure
- Family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma (MTC) or personal history of nonfamilial MTC
- Treatment with GLP-1 receptor agonist or pramlintide within 3 months prior to Visit 1

Study Design

- Adults ≥40 years with diagnosis of T2D and established ASCVD
- HbA1c ≥7% and ≤10.5%
- BMI ≥25 kg/m^2
- N=13,165



Primary Endpoint: CV Death, MI or Stroke



No. at Risk						
TZP MTD	6586	6309	6029	5703	3305	0
Dula 1.5 mg	6579	6267	5954	5618	3226	0

Key Secondary Efficacy Endpoints

Outcome	TZP MTD (N=6586)	Dula 1.5 mg (N=6579)	HR (95% CI)
Key Secondary Efficacy Endpoints, % of Participants With Event			
MI	4.7	5.4	0.86 (0.74-1.00)
Stroke	3.5	3.8	0.91 (0.76-1.09)
CV death	5.6	6.2	0.89 (0.77-1.02)
CV death, MI, stroke, coronary revascularisation	16.5	18.5	0.88 (0.81-0.96)
CV death or hospitalization or urgent visits for HF	7.8	8.5	0.91 (0.81-1.03)
All-cause death	8.6	10.2	0.84 (0.75-0.94)

SURPASS-CVOT Prespecified Kidney Outcomes: Objective

- To assess the efficacy of tirzepatide compared with dulaglutide on kidney outcomes and safety in participants with T2D and established CV disease and in participants with high- and very high-risk CKD in the SURPASS-CVOT

Definition of CKD

- Defined according to KDIGO guideline
- eGFR was calculated using the CKD-EPI serum creatinine-cystatin C equation

KDIGO: Prognosis of CKD by GFR and Albuminuria Categories			Persistent Albuminuria Categories Description and Range		
			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
GFR Categories (mL/min/1.73 m²) Description and Range	Normal or high	≥90			
	Mildly decreased	60-89			
	Mildly to moderately decreased	45-59			
	Moderately to severely decreased	30-44			
	Severely decreased	15-29			
	Kidney failure	<15			

Low-risk (if no other markers of kidney disease, no CKD) Moderately increased risk High-risk Very high-risk

Composite and Other Kidney Outcomes

Primary endpoint

- Time to first occurrence of the 4-component primary composite kidney endpoint

Secondary endpoints

- Time to first occurrence of composite kidney endpoints 2-4
- Change in eGFR from baseline to 36 months
- Percent change in UACR from baseline to 36 months

Components of Composite Kidney Outcomes

First occurrence of:	Primary Composite Kidney Endpoint	Composite kidney outcome 2	Composite kidney outcome 3	Composite kidney outcome 4
Persistent macroalbuminuria	✓	✓		
Persistent ≥50% reduction in eGFR	✓			✓
Persistent eGFR <15 mL/min/1.73 m^2 or initiation of chronic kidney replacement therapy (dialysis/kidney transplantation)	✓		✓	✓
Death from kidney disease	✓	✓	✓	
Persistent doubling of serum creatinine level and eGFR <45 mL/min/1.73 m^2		✓		
Initiation of chronic kidney replacement therapy		✓		
Persistent ≥40% reduction in eGFR			✓	
Death from kidney or CV disease				✓

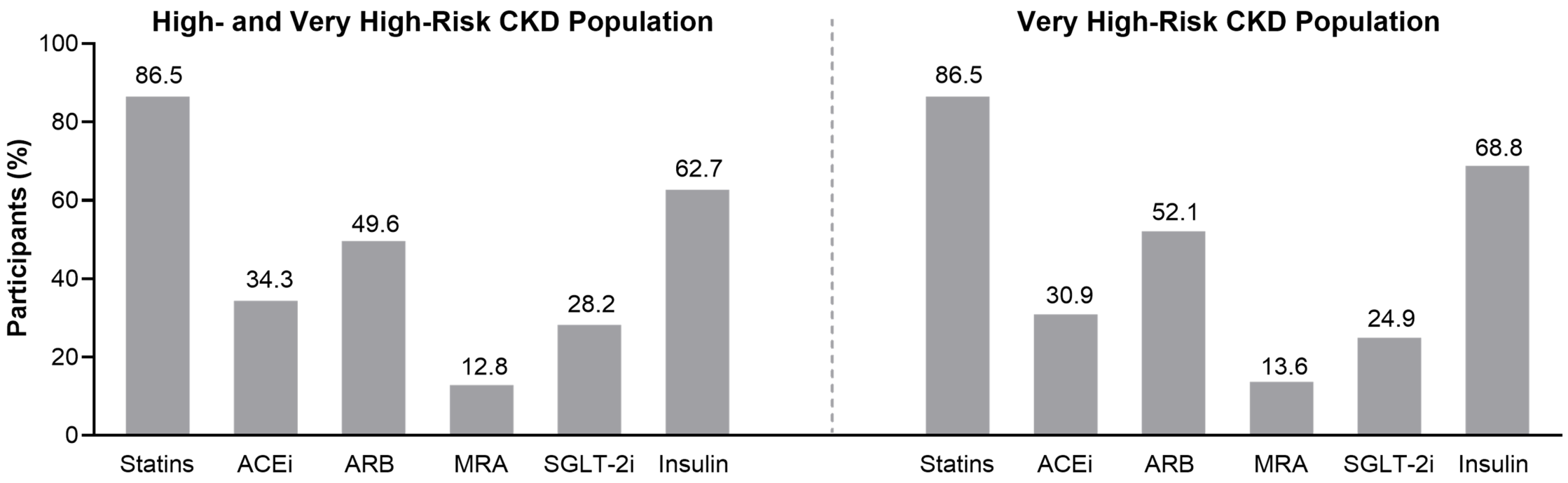
Statistical Analysis

- All analyses were based on data from all randomized participants
- The primary and secondary composite kidney outcomes were analyzed using Cox proportional hazards models with treatment (tirzepatide vs. dulaglutide) as a fixed effect, stratified by SGLT-2i use at baseline
- Change from baseline to 36 months in eGFR (creatinine-cystatin C) and percent change in UACR were assessed using analysis of covariance models treating missing values with a multiple imputation manner
- eGFR and percent change in UACR per treatment arm at each assessment (‘visit’) were estimated using mixed model for repeated measures
- All safety events were investigator reported, except for deaths due to kidney and CV disease, which were independently adjudicated

Baseline Characteristics of CKD Populations

Parameter	High- and Very High-Risk CKD Population (N=2923)	Very High-Risk CKD Population (N=1241)
Age, years	67.2	68.5
Female, %	28.1	28.2
HbA1c, %	8.5	8.5
Weight, kg	93.1	92.4
BMI, kg/m^2	33.1	33.0
T2D duration, years	17.7	19.2
eGFR, mL/min/1.73 m^2, mean	53.3	38.1
<60 mL/min/1.73 m^2, %	73.8	100
≥60 mL/min/1.73 m^2, %	26.2	0
UACR, g/kg, median	310.0	424.5
Normoalbuminuria (UACR <30 g/kg), %	12.2	4.9
Microalbuminuria (UACR 30-300 g/kg), %	36.6	36.7
Macroalbuminuria (UACR >300 g/kg), %	51.2	58.3
SGLT2i use	28.2	24.9

Baseline Medication and Study Drug Use

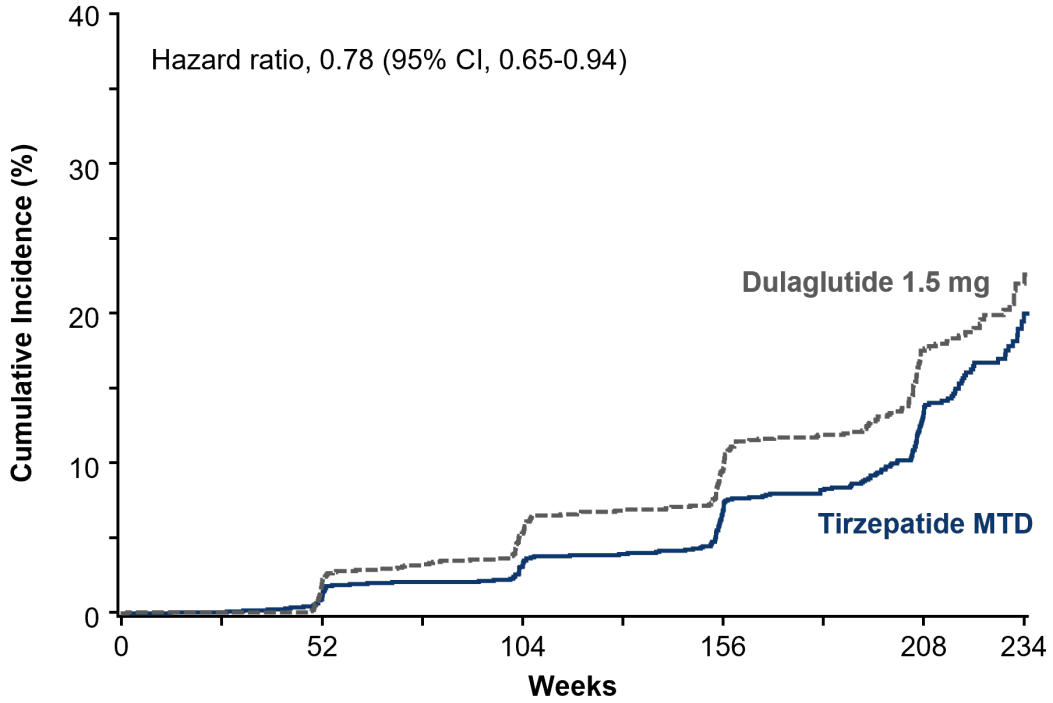


Study Drug Use

- In the high- and very high-risk, or very high-risk CKD populations, premature study drug discontinuation occurred in 26.2%, and 30.0% on tirzepatide treatment, and 25.5%, and 28.2% on dulaglutide treatment, respectively

Primary Composite Kidney Endpoint

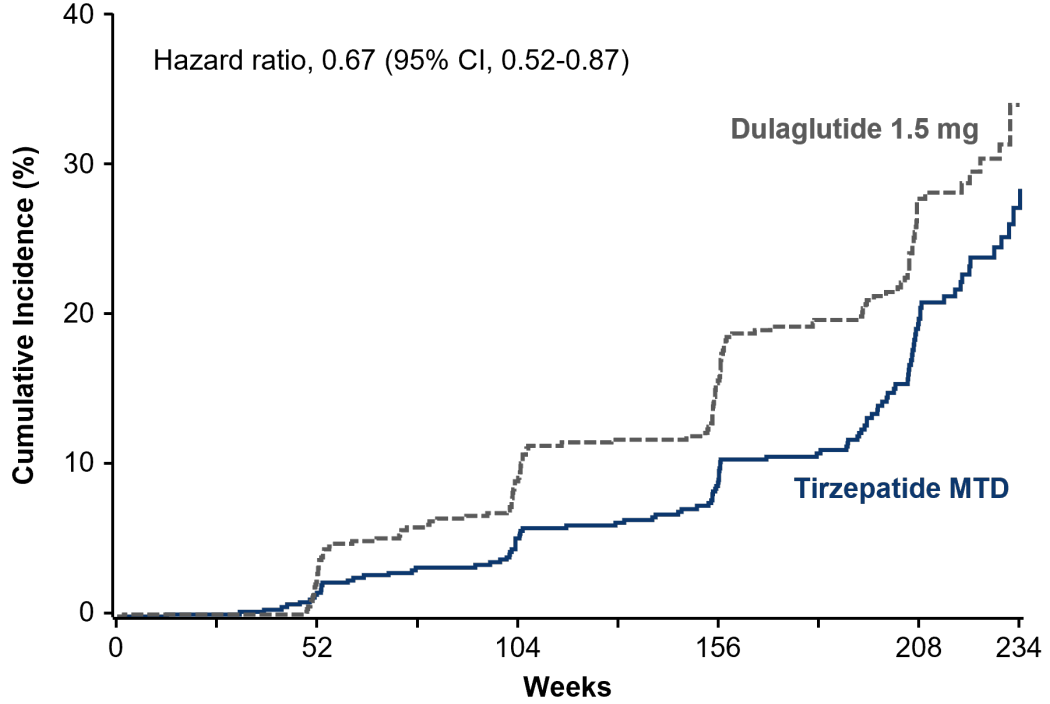
High- and Very High-Risk CKD Population



No. at Risk

TZP MTD	1520	1457	1343	1211	654	148
Dula 1.5 mg	1403	1312	1182	1048	550	129

Very High-Risk CKD Population

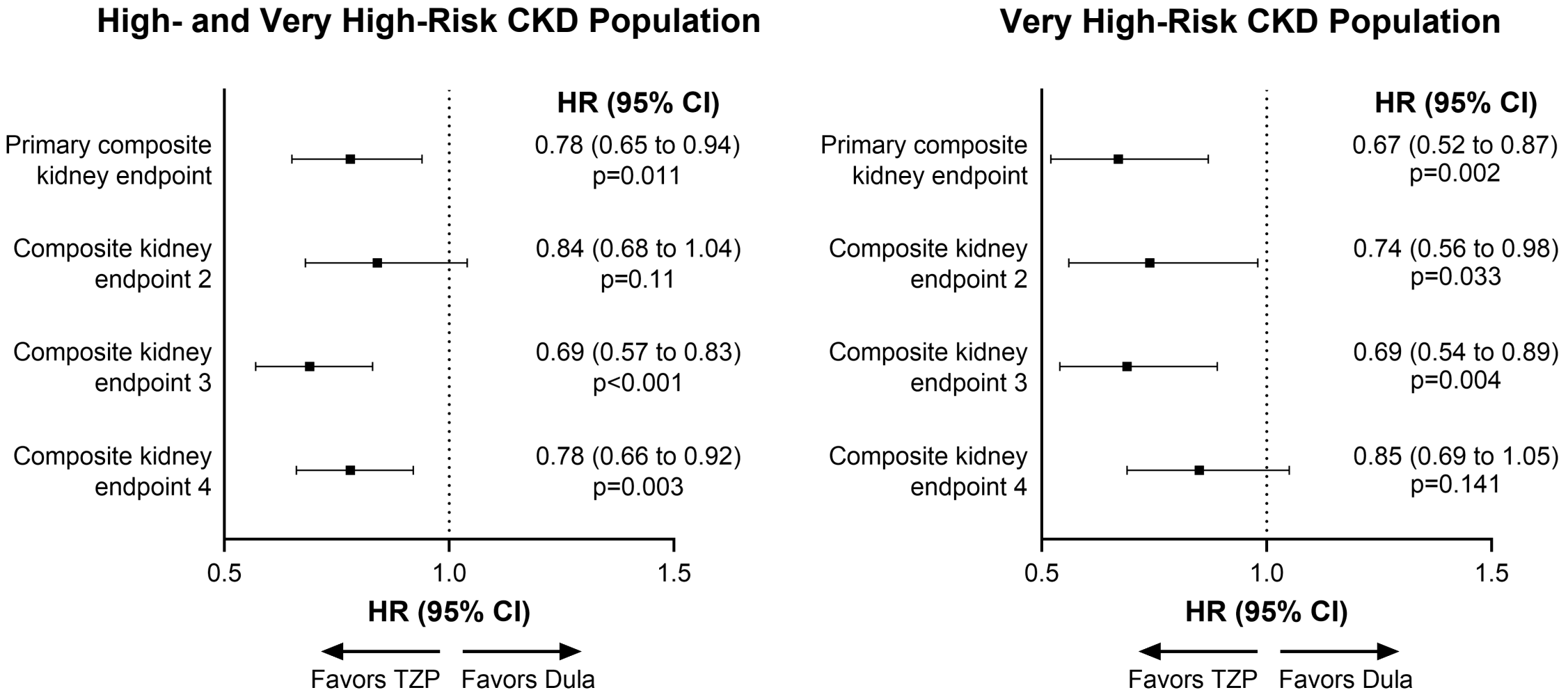


TZP MTD	646	608	540	469	222	56
Dula 1.5 mg	595	541	467	385	187	41

Primary Composite Kidney Endpoint and Components

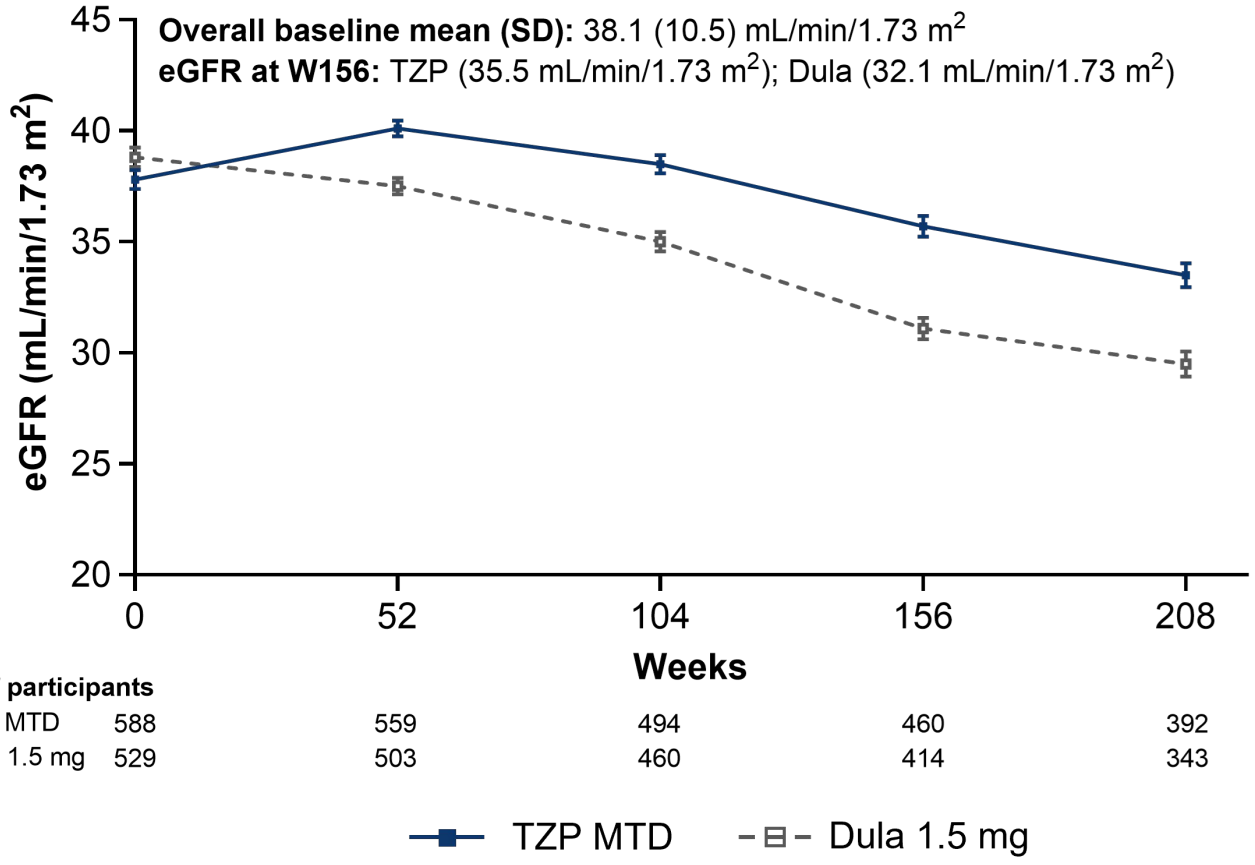
Parameter	High- and Very-High Risk CKD Population			Very High-Risk CKD Population			
	TZP MTD (N=1520)	Dula 1.5 mg (N=1403)	Hazard Ratio (95% CI)	TZP MTD (N=646)	Dula 1.5 mg (N=595)	Hazard Ratio (95% CI)	P-value
Primary composite kidney endpoint	203 (13.4)	224 (16.0)	0.78 (0.65 to 0.94)	108 (16.7)	137 (23.0)	0.67 (0.52 to 0.87)	**0.002**
Components							
Persistent macroalbuminuria	85 (5.6)	89 (6.3)	0.83 (0.62 to 1.12)	34 (5.3)	51 (8.6)	0.60 (0.39 to 0.93)	**0.021**
Persistent ≥50% reduction in eGFR	93 (6.1)	111 (7.9)	0.73 (0.55 to 0.96)	54 (8.4)	70 (11.8)	0.66 (0.46 to 0.95)	**0.023**
ESKD	73 (4.8)	73 (5.2)	0.88 (0.64 to 1.22)	59 (9.1)	56 (9.4)	0.93 (0.64 to 1.34)	0.682
Death from kidney disease	4 (0.3)	5 (0.4)	N/A	3 (0.5)	4 (0.7)	N/A	N/A

Composite Kidney Endpoints and Components

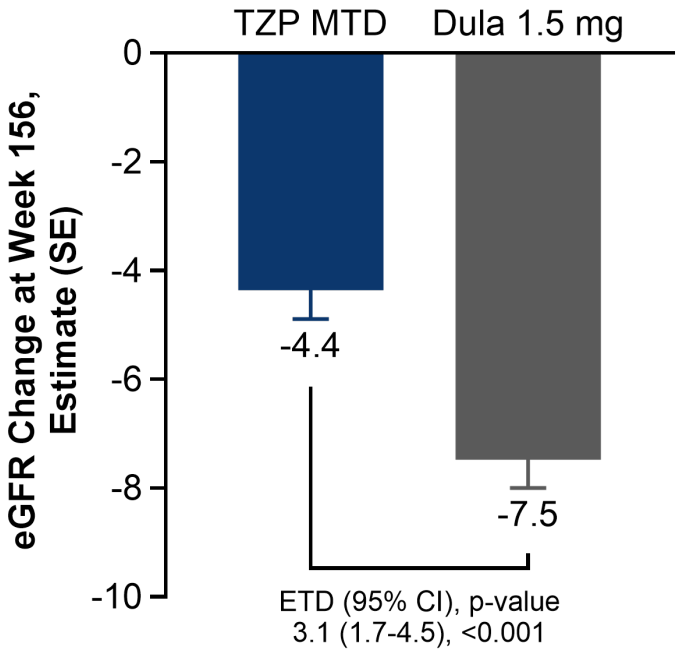


Change in eGFR: Very High-Risk CKD Population

eGFR Over Time

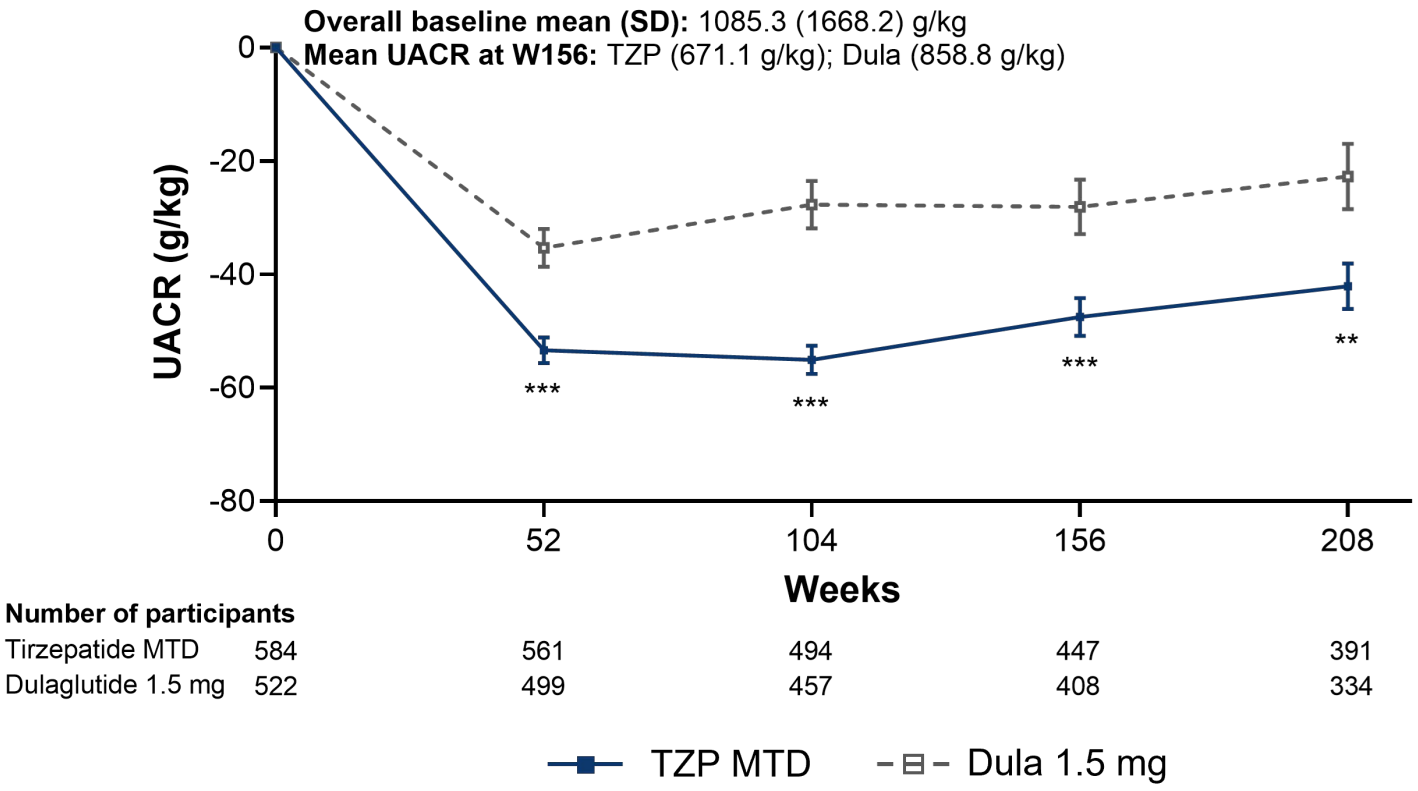


Change From Baseline

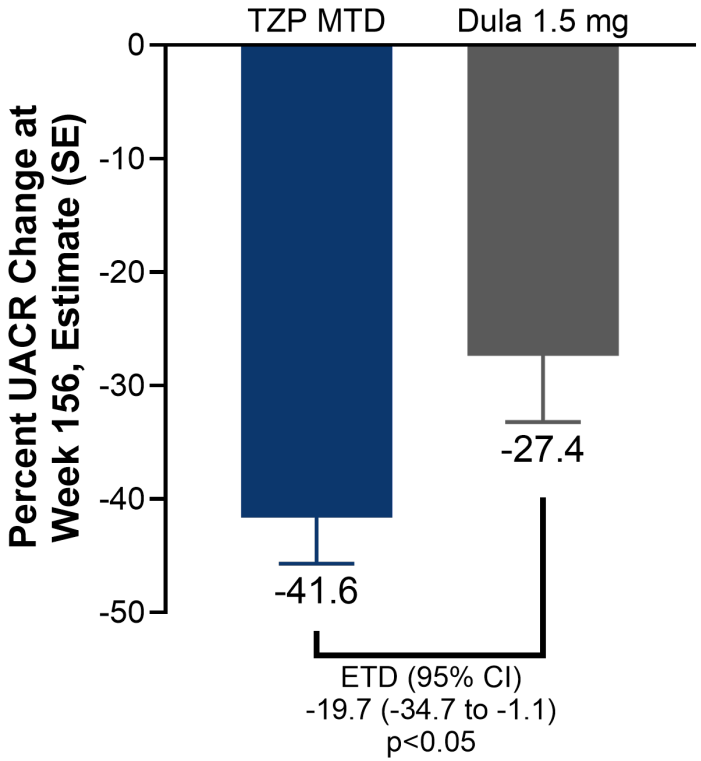


Change in UACR: Very High-Risk CKD Population

UACR Over Time

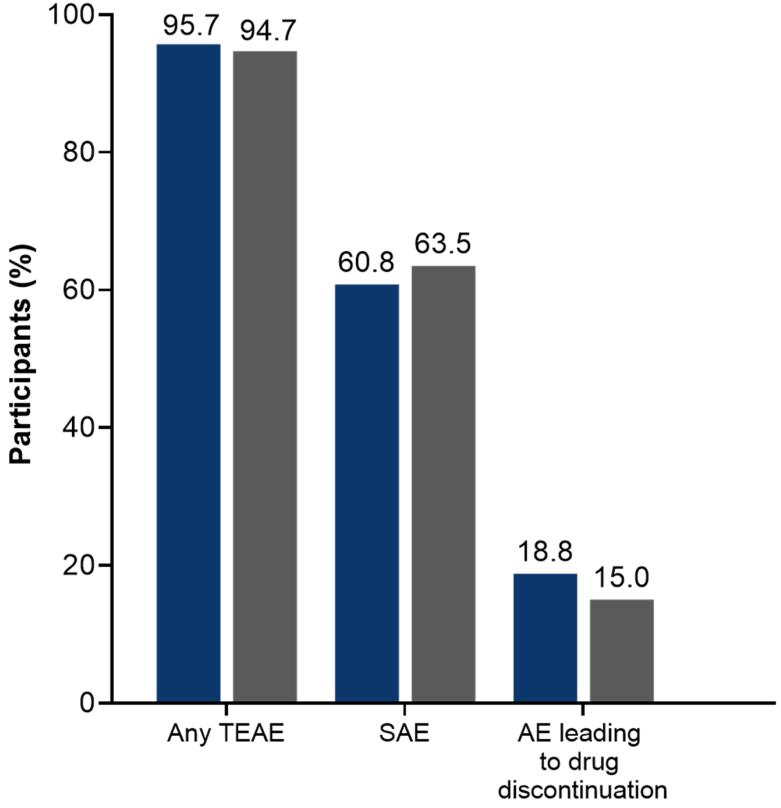


Percent Change From Baseline

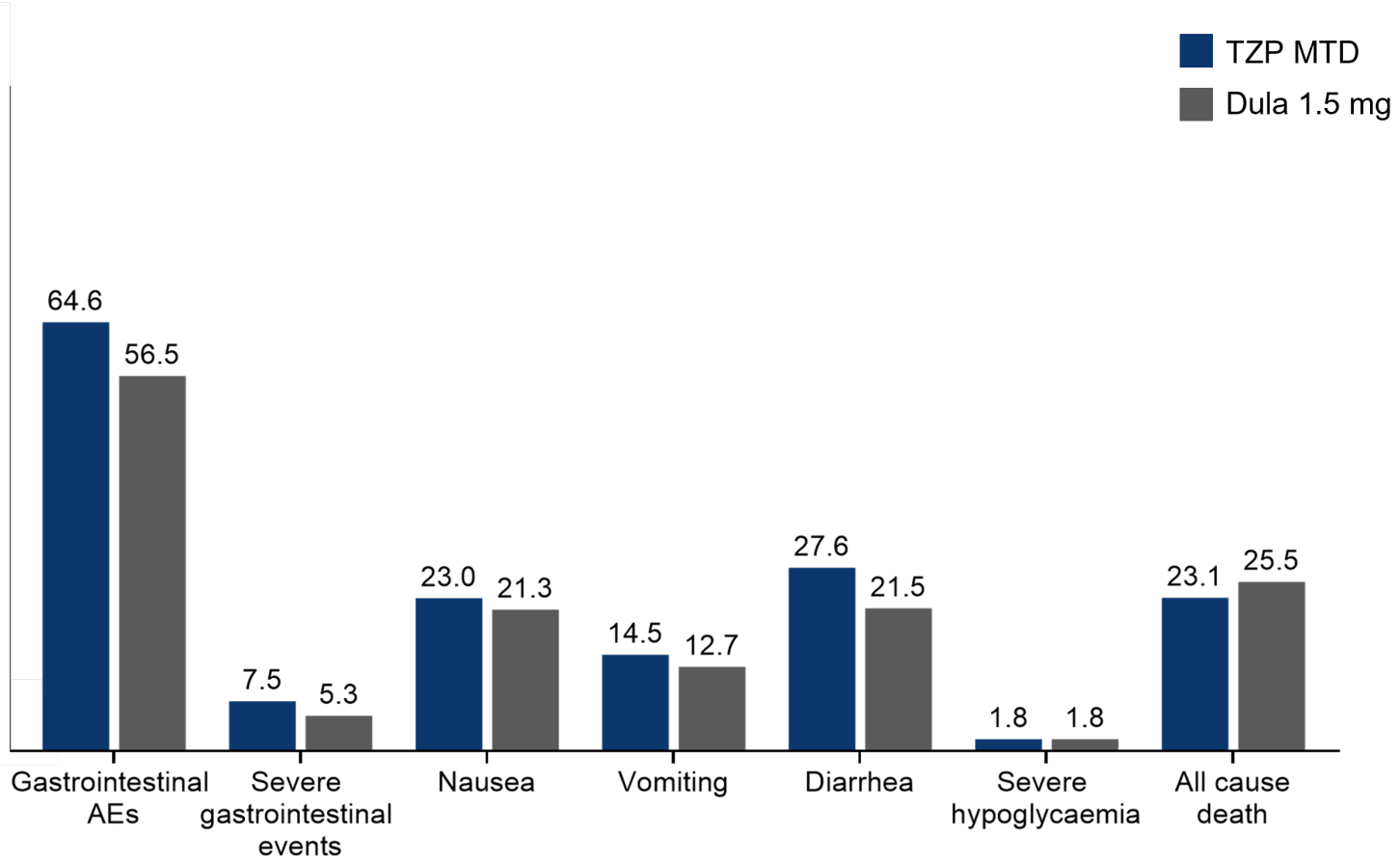


Safety: Very High-Risk CKD Population

Overall Safety



AEs of Special Interest



Summary

- In the SURPASS-CVOT trial:
  - Treatment with tirzepatide met the pre-specified criteria for non-inferiority compared with dulaglutide on the rate of the primary composite endpoint of CV death, myocardial infarction or stroke
  - Tirzepatide met the criteria for superiority compared with a putative placebo on the rate of the primary composite endpoint of CV death, myocardial infarction or stroke

Summary

- In this pre-specified analysis of kidney outcomes among participants with very high-risk CKD, tirzepatide compared with dulaglutide:
  - Reduced the risk of the major kidney composite outcomes (most apparent for eGFR decline)
  - Slowed the decline in kidney function
  - Reduced the progression of albuminuria
- Serious safety events and AEs leading to study medication discontinuation were reported in similar proportions receiving tirzepatide and dulaglutide
- Gastrointestinal adverse events were reported by more participants receiving tirzepatide than dulaglutide

Final Comment

- The SURPASS-CVOT findings add to the growing body of evidence of the kidney protective effects of tirzepatide in comparison to placebo or other glucose-lowering strategies

Acknowledgements

- The Speaker wishes to thank the investigators and participants of the SURPASS-CVOT study