The VERTIS CV Trial

Cardiovascular Outcomes Following Ertugliflozin Treatment in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

VERTIS

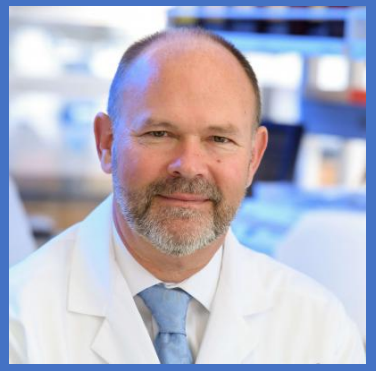
eValuation of ERTugliflozin efficacy and Safety

Presented during American Diabetes Association (ADA) Virtual 80th Scientific Sessions
June 16, 2020

Support

- 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.

Faculty



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Faculty Disclosures

- **Richard E. Pratley, MD**
  - Research grants, consulting and/or speakers fees from Hanmi Pharmaceutical Co., Janssen, Merck & Co., Inc., Novo Nordisk, Pfizer Inc, Poxel SA, Sanofi, Scohia Pharma Inc. and Sun Pharmaceutical Industries. All fees for service were paid directly to AdventHealth, a non-profit organization.
- **Sam Dagogo-Jack, MD, DSc**
  - Led clinical trials for AstraZeneca, Boehringer Ingelheim, and Novo Nordisk, Inc., has received consulting fees from AstraZeneca, Boehringer Ingelheim, Janssen, Merck & Co., Inc., and Sanofi, and has equity interests in Jana Care, Inc. and Aerami Therapeutics.
- **Christopher P. Cannon, MD**
  - Research grants from Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Merck & Co., Inc., Pfizer Inc, as well as fees from Aegerion, Alnylam, Amarin, Amgen, Applied Therapeutics, Ascendia, Boehringer Ingelheim, Bristol-Myers Squibb, Corvidia, HLS Therapeutics, Innovent, Janssen, Kowa, Merck & Co., Inc., Pfizer Inc, Sanofi.
- **Darren K. McGuire, MD, MHSC**
  - Honoraria for clinical trial leadership from AstraZeneca, Boehringer Ingelheim, Eisai, Esperion, GlaxoSmithKline, Janssen, Lexicon, Merck & Co., Inc., Novo Nordisk, Sanofi Aventis, and has received consultancy fees from Afimmune, Applied Therapeutics, AstraZeneca, Boehringer Ingelheim, Lilly, Merck & Co., Inc., Pfizer Inc, Novo Nordisk, Metavant, and Sanofi Aventis.
- **David Z.I. Cherney, MD, PhD**
  - Consulting fees or speaking honorarium or both from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Merck & Co., Inc., Prometic, and Sanofi, and has received operating funds from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck & Co., Inc., and Sanofi.

Presentation outline:

- **Introduction, Study Rationale and Design**
  Richard E. Pratley, MD
  Orlando, FL
- **Baseline Characteristics and Metabolic Results**
  Sam Dagogo-Jack, MD, DSc
  Memphis, TN
- **Cardiovascular and Renal Outcomes**
  Christopher P. Cannon, MD
  Boston, MA
- **Safety and Updated CV Meta-Analysis**
  Darren K. McGuire, MD, MHSc
  Dallas, TX
- **Overall Conclusions**
  David Z.I. Cherney, MD, PhD
  Toronto, ON

Introduction, Study Rationale and Design

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AdventHealth Translational Research Institute,
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e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety

ADA Standards of Medical Care in Diabetes - 2020

American Diabetes Association

9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes—2020*

Diabetes Care 2020;43(Suppl. 1):S98–S110 | https://doi.org/10.2337/dc20-S009

9. PHARMACOLOGIC APPROACHES TO GLYCEMIC TREATMENT

The American Diabetes Association (ADA) "Standards of Medical Care in Diabetes" includes the ADA's current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate quality of care. Members of the ADA Professional Practice Committee, a multidisciplinary expert committee (https://doi.org/10.2337/dc20-SPPC), are responsible for updating the Standards of Care annually, or more frequently as warranted. For a detailed description of ADA standards, statements, and reports, as well as the evidence-grading system for ADA's clinical practice recommendations, please refer to the Standards of Care Introduction (https://doi.org/10.2337/dc20-SINT). Readers who wish to comment on the Standards of Care are invited to do so at professional.diabetes.org/SOC.

PHARMACOLOGIC THERAPY FOR TYPE 1 DIABETES

Recommendations

9.1 Most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion. A

9.2 Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. A

9.3 Patients with type 1 diabetes should be trained to match prandial insulin doses to carbohydrate intake, premeal blood glucose, and anticipated physical activity. C

Insulin Therapy

Because the hallmark of type 1 diabetes is absent or near-absent β-cell function, insulin treatment is essential for individuals with type 1 diabetes. In addition to hyperglycemia, insulinopenia can contribute to other metabolic disturbances like hypertriglyceridemia and ketoacidosis as well as tissue catabolism that can be life threatening. Severe metabolic decompensation can be, and was, mostly prevented with once or twice daily injections for the six or seven decades after the discovery of insulin. However, over the past three decades, evidence has accumulated supporting more intensive insulin replacement, using multiple daily injections of insulin or continuous subcutaneous administration through an insulin pump, as providing the best combination of effectiveness and safety for people with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with multiple daily injections or continuous subcutaneous insulin infusion (CSII) reduced A1C and was associated with improved long-term outcomes (1–3). The study was carried out with short-acting (regular) and intermediate-acting (NPH) human insulins. In this landmark trial, lower A1C with intensive control (7%) led to ~50% reductions in microvascular complications over 6 years of treatment.

Suggested citation: American Diabetes Association. 2. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2020. Diabetes Care 2020;43(Suppl. 1):S98–S110

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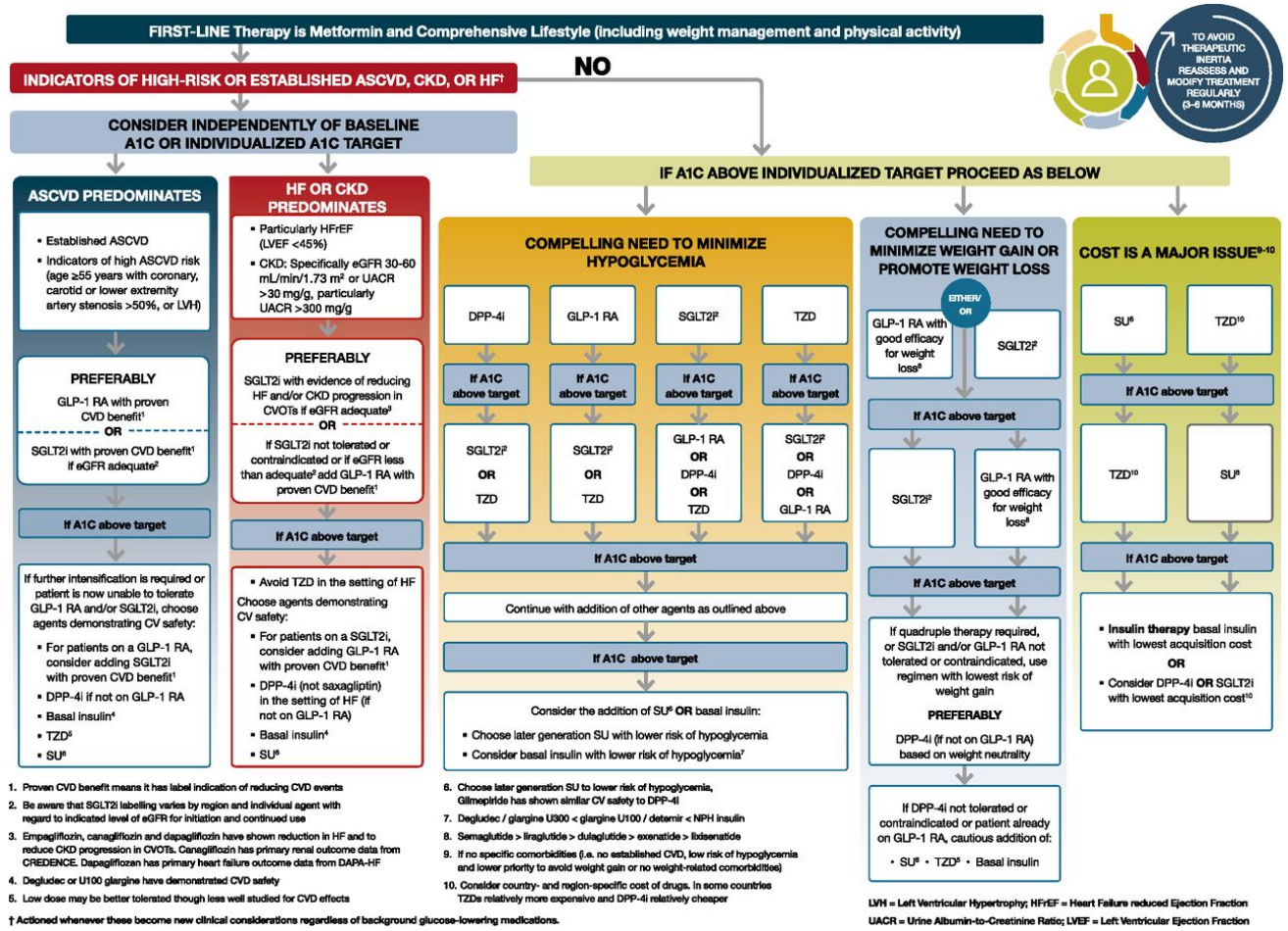
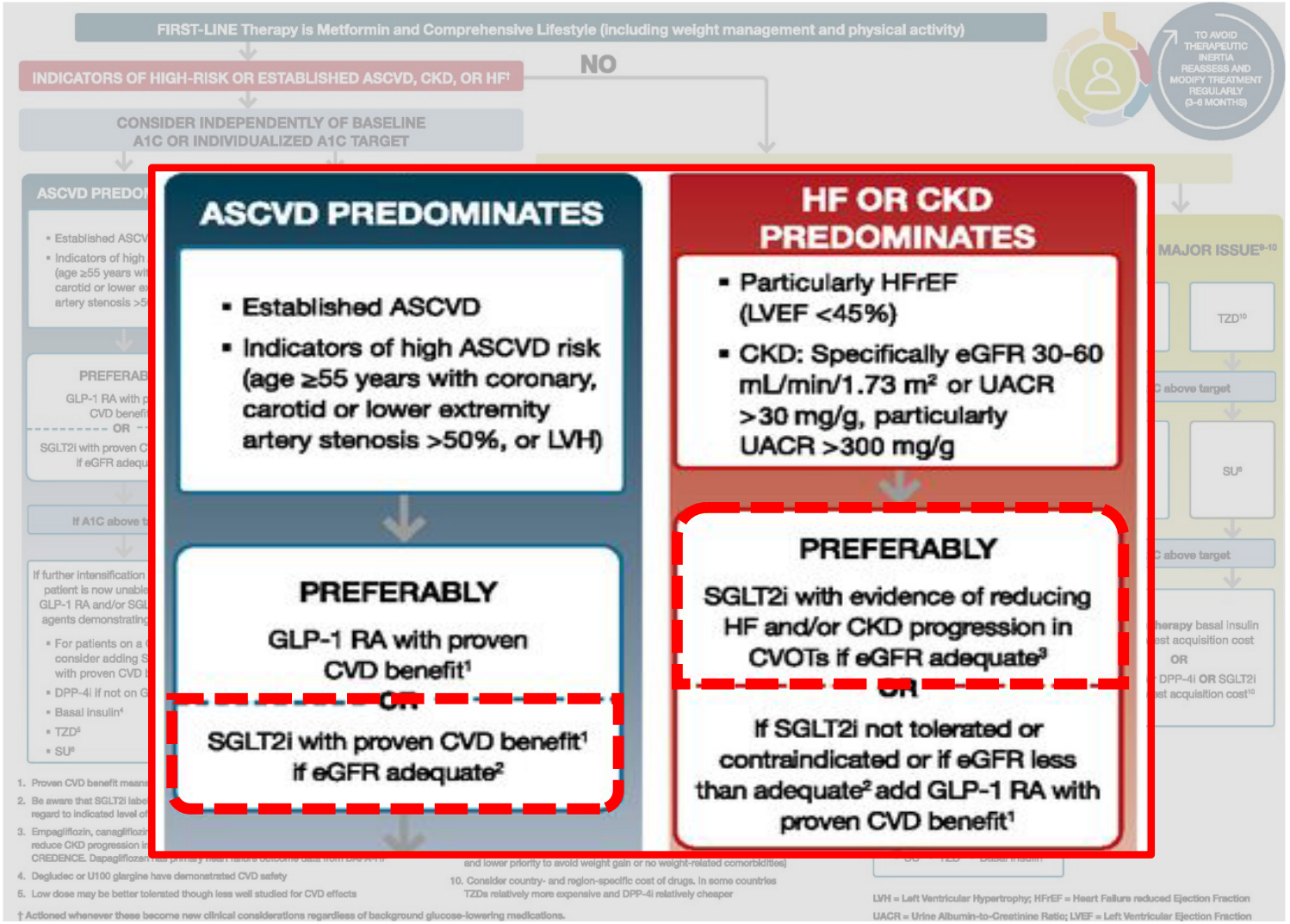


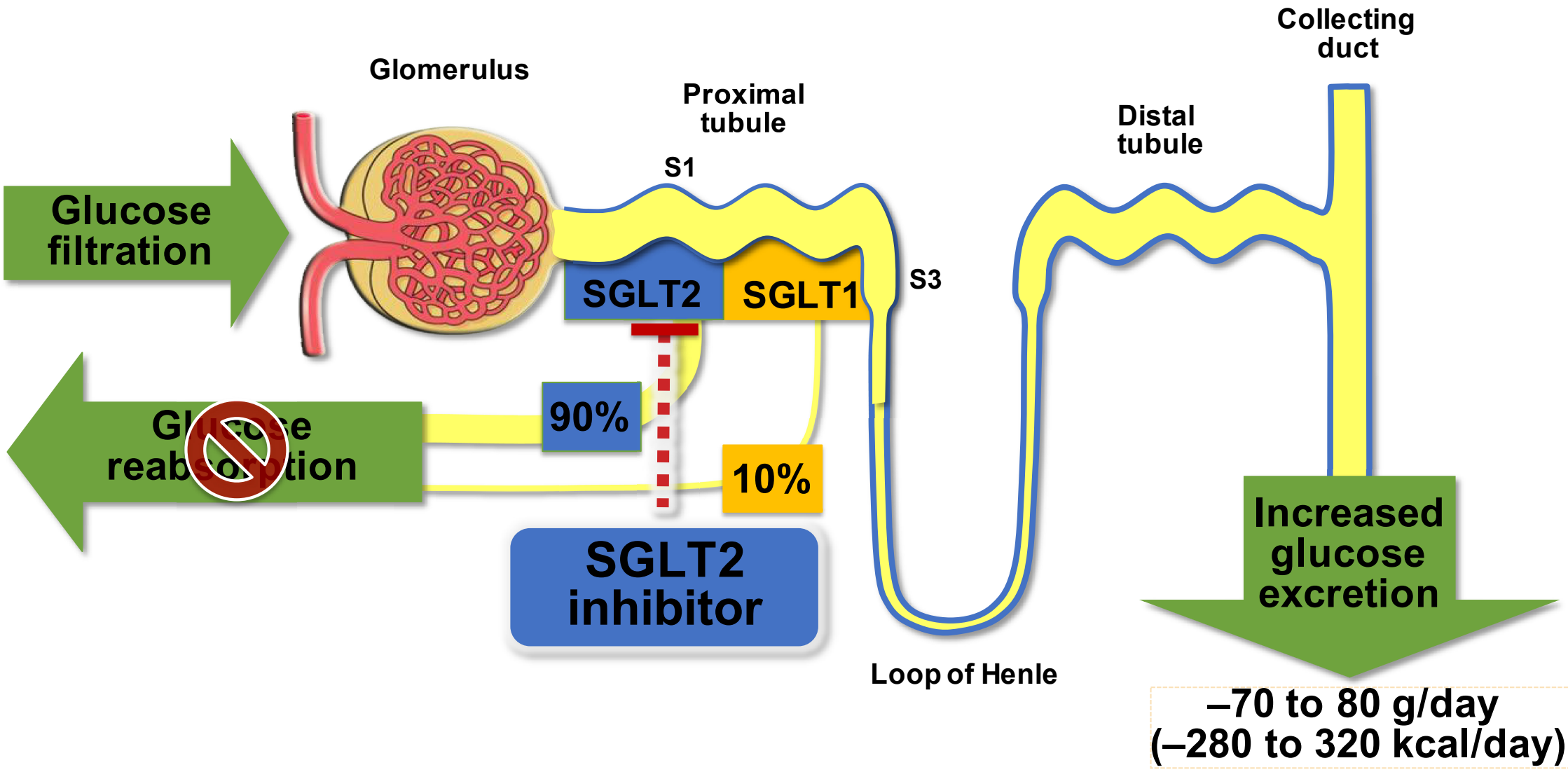
American Diabetes Association. Standards of Medical Care in Diabetes—2020. *Diabetes Care*. 202;43(Suppl 1):S98-S110.

ADA Standards of Medical Care in Diabetes - 2020



American Diabetes Association. Standards of Medical Care in Diabetes—2020. *Diabetes Care*. 202;43(Suppl 1):S98-S110.

SGLT2 inhibition reduces renal glucose reabsorption



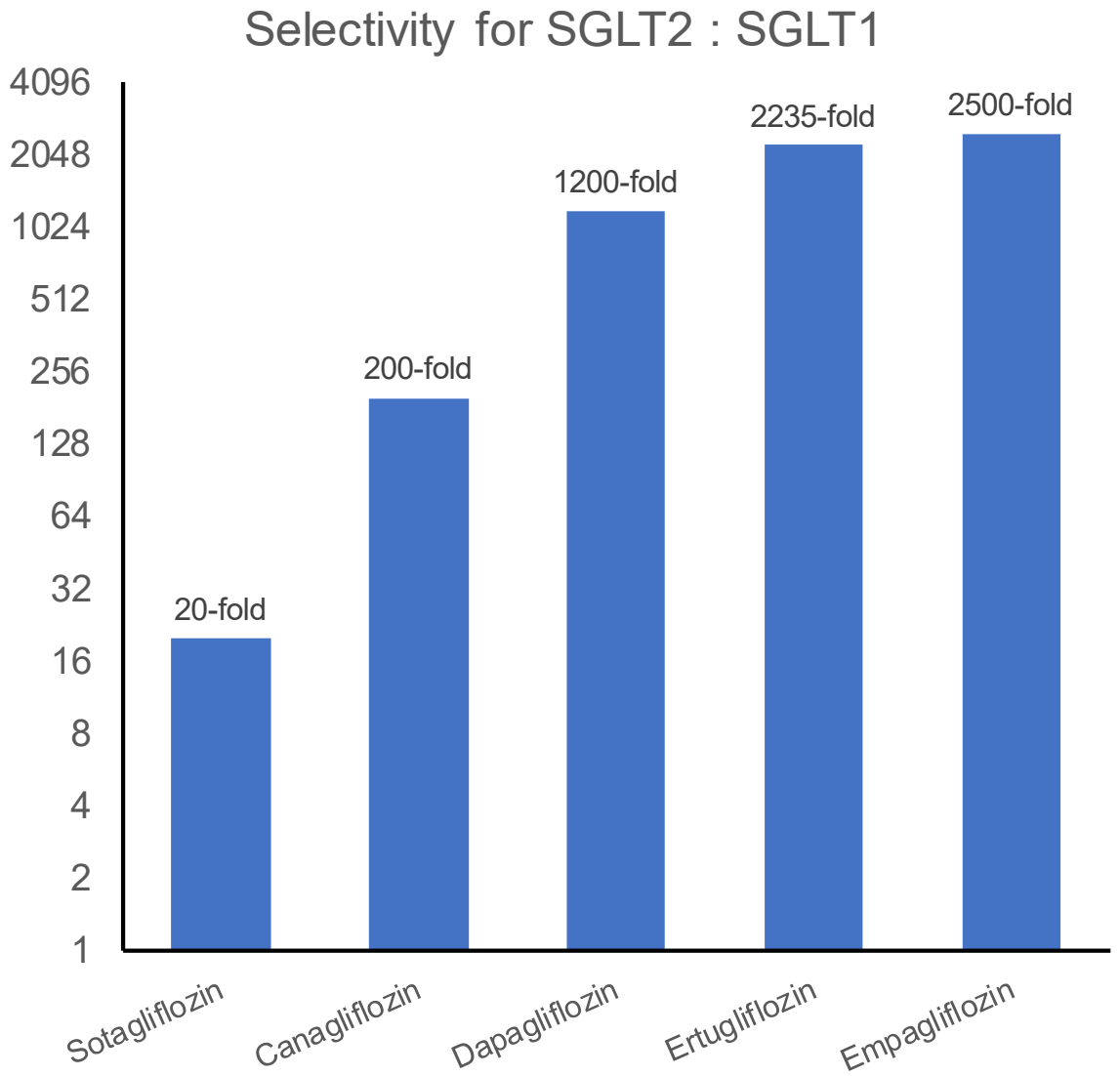
SGLT1, sodium-glucose cotransporter 1; SGLT2, sodium-glucose cotransporter 2.
Wright EM. *Am J Physiol Renal Physiol* 2001;280:F10-F18. Lee YJ et al. *Kidney Int Suppl* 2007;106:S27-S35.
Han S et al. *Diabetes* 2008;57:1723-1729. Inzucchi SE et al. *Diabetes Care* 2015;38:140-149.

VERTIS CV

Ertugliflozin is a selective SGLT2 inhibitor

In vitro potency/selectivity of ertugliflozin

- >2000-fold selectivity for SGLT2 compared with SGLT1
  - IC_{50} for SGLT2 = 0.9 nmol/L
  - IC_{50} for SGLT1 = 1960 nmol/L



SGLT1, sodium-glucose cotransporter 1; SGLT2, sodium-glucose cotransporter 2.
Mascitti V et al. *J Med Chem* 2011;54:2952-2960.

VERTIS CV

VERTIS Phase 3 clinical trial program

9 trials in ~13,000 patients in >40 countries

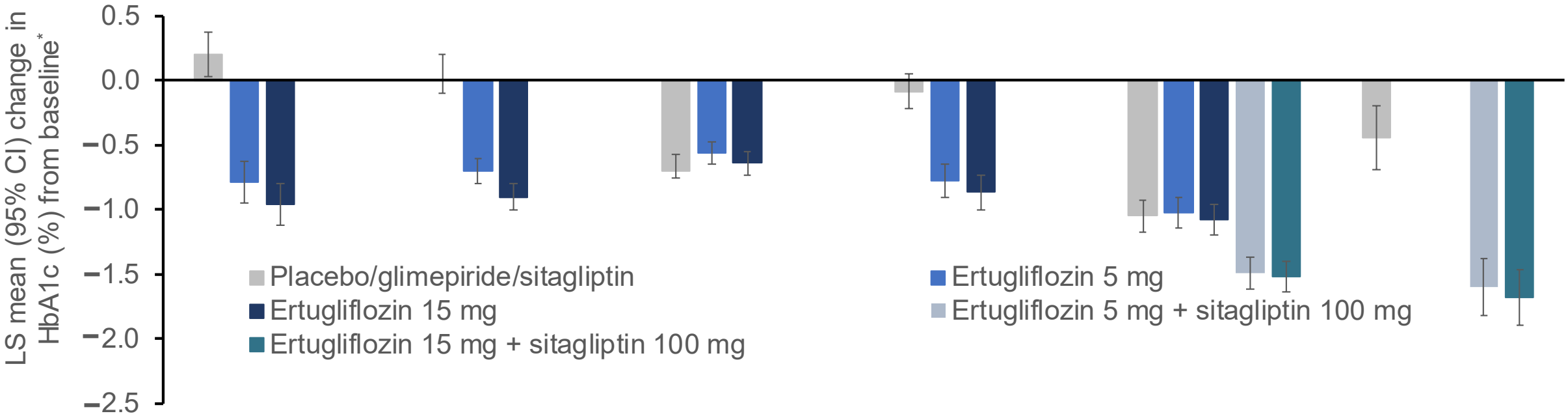
Diet and Exercise	Metformin Add-on	Add-on to Dual Combination	Special Populations
VERTIS MONO *Ertu vs Pbo* *n=461*	**VERTIS SU** *Ertu vs Glim* *n=1326*	**VERTIS SITA2** *Ertu vs Pbo added to Met + Sita* *n=464*	**VERTIS RENAL** *Ertu vs Pbo in pts with CKD* *n=468*
VERTIS SITA *Ertu/Sita vs Pbo* *n=291*	**VERTIS FACTORIAL** *Ertu +/– Sita* *n=1233*		**VERTIS CV** *Ertu vs Pbo in pts with ASCVD* *n=8246*
	VERTIS MET *Ertu vs Pbo added to Met* *n=621*		
	VERTIS ASIA *Ertu vs Pbo added to Met* *n=506*		

Ertugliflozin 5 mg and 15 mg were studied

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; Ertu, ertugliflozin; Glim, glimepiride; Met, metformin; MONO, monotherapy; Pbo, placebo; pts, patients; SITA, sitagliptin; SU, sulfonylurea; VERTIS, eValuation of ERTugliflozin efficacy and Safety.

Ertugliflozin: mean HbA1c reductions of 0.8–1.2%

	Monotherapy and add-on studies				Coadministration studies	
	VERTIS MONO[1] Ertugliflozin monotherapy	VERTIS MET[2] Ertugliflozin added on to metformin	VERTIS SU[3] Ertugliflozin vs glimepiride	VERTIS SITA2[4] Ertugliflozin added on to metformin and sitagliptin	VERTIS FACTORIAL[5] Ertugliflozin plus sitagliptin factorial	VERTIS SITA[6] Ertugliflozin plus sitagliptin
Mean baseline HbA1c (%):	8.2	8.1	7.8	8.0	8.6	8.9



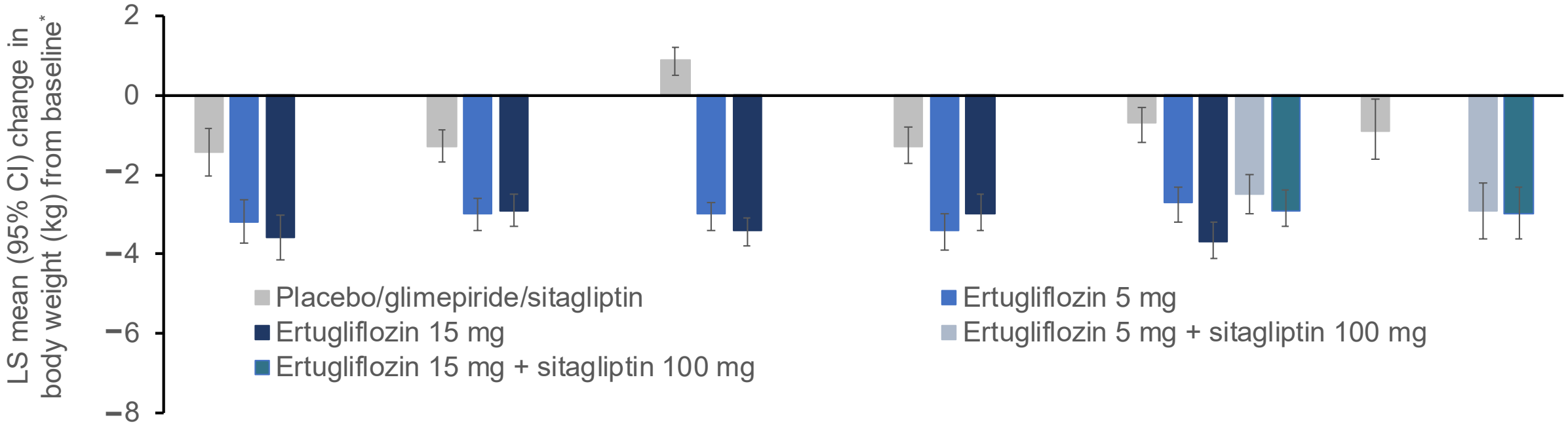
*Change from baseline at Week 26 except for VERTIS SU (Week 52).

1. Terra SG et al. *Diabetes Obes Metab* 2017;19:721-728. 2. Rosenstock J et al. *Diabetes Obes Metab* 2018;20:520-529. 3. Hollander S et al. *Diabetes Ther* 2018;9:193-207. 4. Dagogo-Jack S et al. *Diabetes Obes Metab* 2018;20:530-540. 5 Pratley RE et al. *Diabetes Obes Metab* 2018;20:1111-1120. 6. Miller S et al. *Diabetes Ther* 2018;9:253-268.

CI, confidence interval; HbA1c, glycated hemoglobin; LS, least squares.

Ertugliflozin: mean body weight reductions of ~3kg

	Monotherapy and add-on studies				Coadministration studies	
	VERTIS MONO[1] Ertugliflozin monotherapy	VERTIS MET[2] Ertugliflozin added on to metformin	VERTIS SU[3] Ertugliflozin vs glimepiride	VERTIS SITA2[4] Ertugliflozin added on to metformin and sitagliptin	VERTIS FACTORIAL[5] Ertugliflozin plus sitagliptin factorial	VERTIS SITA[6] Ertugliflozin plus sitagliptin
Mean baseline body weight (kg):	93.0	84.9	86.8	86.9	88.7	92.3



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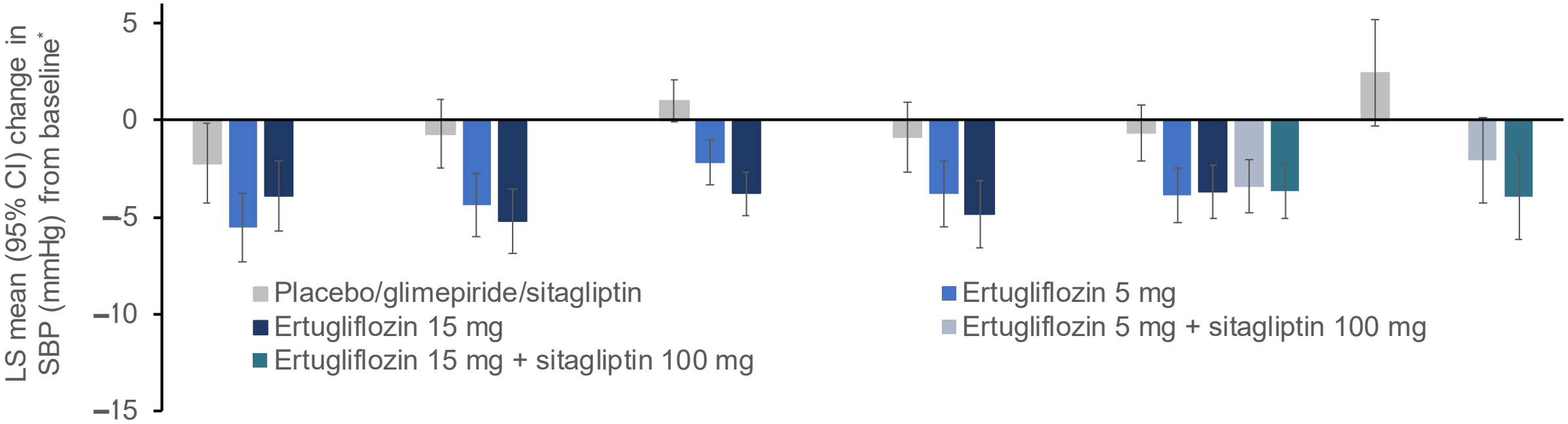
CI, confidence interval; HbA1c, glycated hemoglobin; LS, least squares.

Ertugliflozin: mean SBP reductions of ~4-6 mmHg

	Monotherapy and add-on studies				Coadministration studies	
	VERTIS MONO[1] Ertugliflozin monotherapy	VERTIS MET[2] Ertugliflozin added on to metformin	VERTIS SU[3] Ertugliflozin vs glimepiride	VERTIS SITA2[4] Ertugliflozin added on to metformin and sitagliptin	VERTIS FACTORIAL[5] Ertugliflozin plus sitagliptin factorial	VERTIS SITA[6] Ertugliflozin plus sitagliptin
Mean baseline SBP (mmHg):	130.0	130.0	130.3	131.3	129.3	129.1



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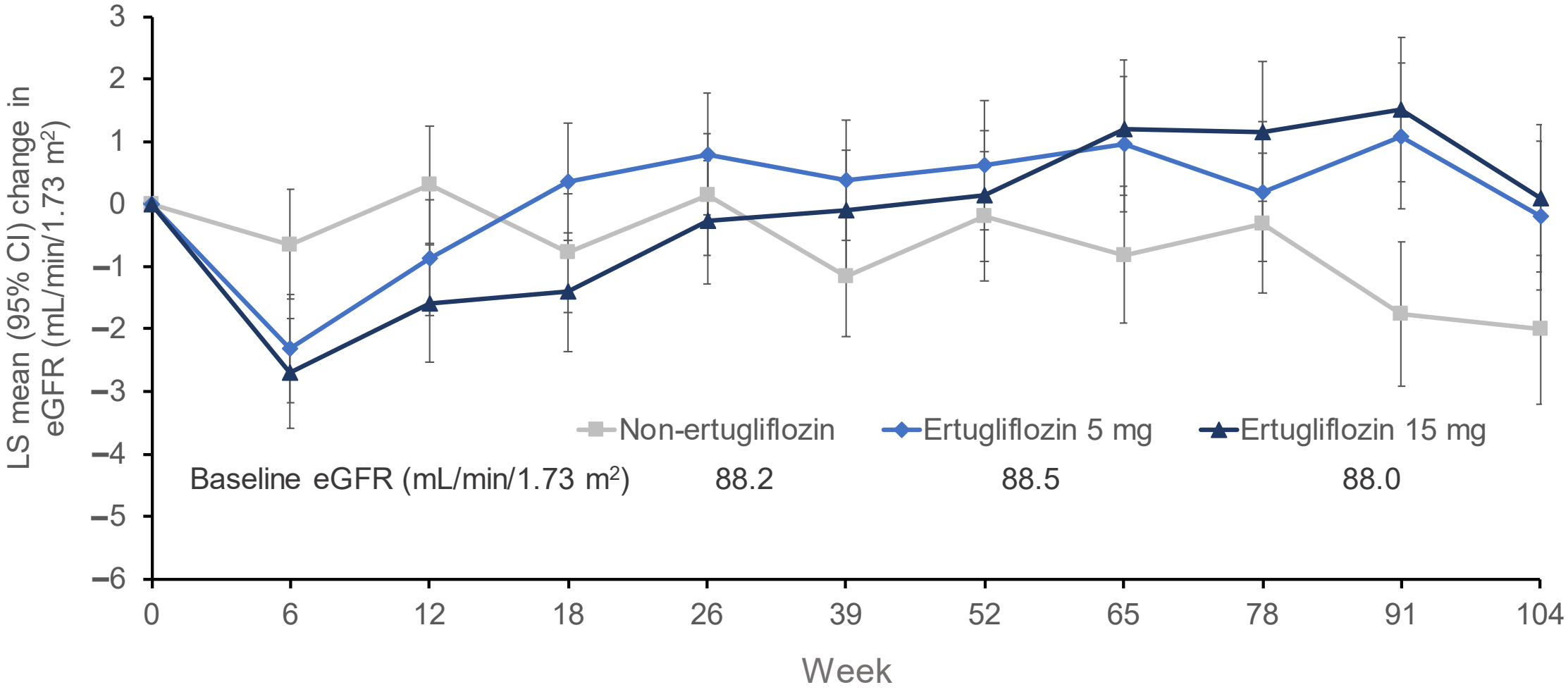
CI, confidence interval; HbA1c, glycated hemoglobin; LS, least squares.

Ertugliflozin: transient, reversible decrease in eGFR, consistent with class



Pooled analysis of two randomized controlled, active comparator studies: VERTIS SU and VERTIS MET. In the VERTIS SU study, ertugliflozin was evaluated vs glimepiride over 104 weeks. In the VERTIS MET study, ertugliflozin was evaluated vs placebo over 26 weeks.
Non-ertugliflozin refers to placebo or glimepiride.
eGFR, estimated glomerular filtration rate; LS, least squares.
Cherney D et al. *Diabetologia* 2020; doi: 10.1007/s00125-020-05133-4.

Study Design and Methodology

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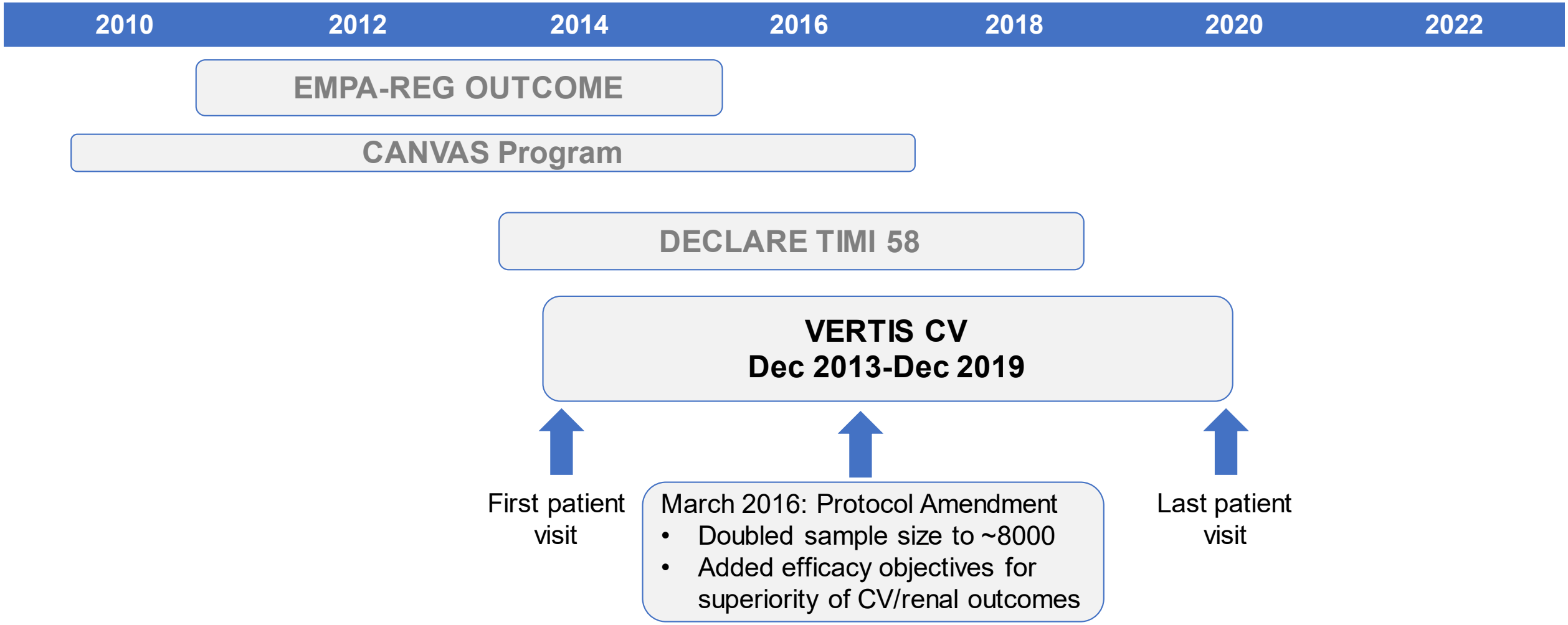
e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety

Timelines of SGLT2 inhibitor CV outcome trials designed to fulfill 2008 FDA regulatory guidance



CV, cardiovascular; FDA, Food and Drug Administration; SGLT2, sodium-glucose cotransporter 2.

VERTIS CV: global study assessing long-term effects of ertugliflozin

VERTIS CV

EVALUATION OF ERTUGLIFLOZIN EFFICACY AND SAFETY CARDIOVASCULAR OUTCOMES TRIAL

8246 randomized patients with Type 2 diabetes and ASCVD from 531 enrolling centers across 34 countries

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular.
Cannon CP et al. *Am Heart J* 2018;206:11–23.

VERTIS CV committees

Scientific Advisory Committee

- Christopher Cannon
- Bernard Charbonnel
- David Cherney
- Francesco Cosentino
- Sam Dagogo-Jack
- Darren McGuire
- Richard Pratley
- Weichung Shih

Data Monitoring Committee

- William Herman (Chair)
- Gary Cutler
- Peter McCullough
- Mark Molitch
- Giles Montelescot (until 2018)
- Michael Zile (from Oct 2018)

Cardiovascular Adjudication

- Blair O'Neill (Chair)
- Cecilia Bahit
- Sherryn Roth
- Joseph Schindler
- Isaac Silverman
- Philippe Gabriel Steg
- Tanya Turan
- James Udelson

Renal Adjudication

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- John Forman
- Emily Robinson
- Sushrut Waikar
- Daniel Weiner

Pancreatitis Adjudication

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- Ziad Gellad
- Jorge Obando (until Feb 2019)
- Keyur Patel
- Darshan Kothari (from Mar 2019)

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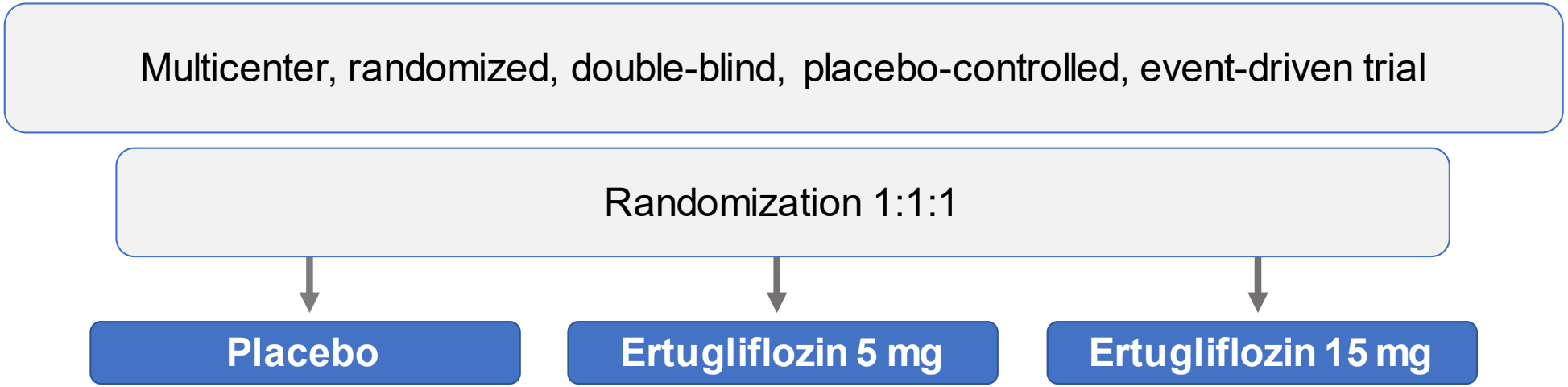
- Karin Anderson
- Frederic Gordon
- Amir Qamar
- Andrew Stolz

Fracture Adjudication

- Thomas Link (Chair)
- Andrew Haims
- Joel Newman

Study design



Primary endpoint (non-inferiority):
- Composite outcome of MACE (CV death, nonfatal MI, nonfatal stroke)

Secondary endpoints (superiority):
- Composite outcome of CV death/HHF
- CV death
- Renal composite (renal death, dialysis/transplant, doubling of serum creatinine)

Other prespecified endpoints:
- Individual components of MACE
- Composite of MACE-plus (MACE plus hospitalization for unstable angina)
- Fatal or nonfatal MI
- Fatal or nonfatal stroke
- HHF
- All-cause mortality

CV, cardiovascular; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction.
Cannon CP et al. *Am Heart J* 2018;206:11-23.

Statistical analyses

- Primary and secondary time-to-first event outcomes analyzed by Cox proportional hazards model
  - Pooled ertugliflozin dose groups vs placebo
- Noninferiority margin of 1.3 on the HR for MACE, as per regulatory guidance
- Hierarchical testing sequence across primary and key secondary superiority outcomes
- Non-inferiority analysis of MACE: analyzed by FAS
  - Includes all patients who were randomized and received at least 1 dose and included confirmed events occurring up to 365 days after the last confirmed dose for those with premature discontinuation
- Superiority analyses of secondary CV and renal outcomes: analyzed by ITT
  - Includes all randomized patients and all confirmed events with no upper limit on the event ascertainment window

CV, cardiovascular; FAS, full analysis set; HR, hazard ratio; ITT, intention-to-treat; MACE, major adverse cardiovascular events.
Cannon CP et al. *Am Heart J* 2018;206:11-23.

Study population

Selected inclusion criteria

- Aged ≥40 years
- T2DM diagnosis according to ADA guidelines – HbA1c 7.0%–10.5% (53–91 mmol/mol)
- Established ASCVD involving the coronary, cerebrovascular, and/or peripheral arterial systems
- Stable on allowable AHA or on no background AHA for ≥8 weeks prior to study participation

Selected exclusion criteria

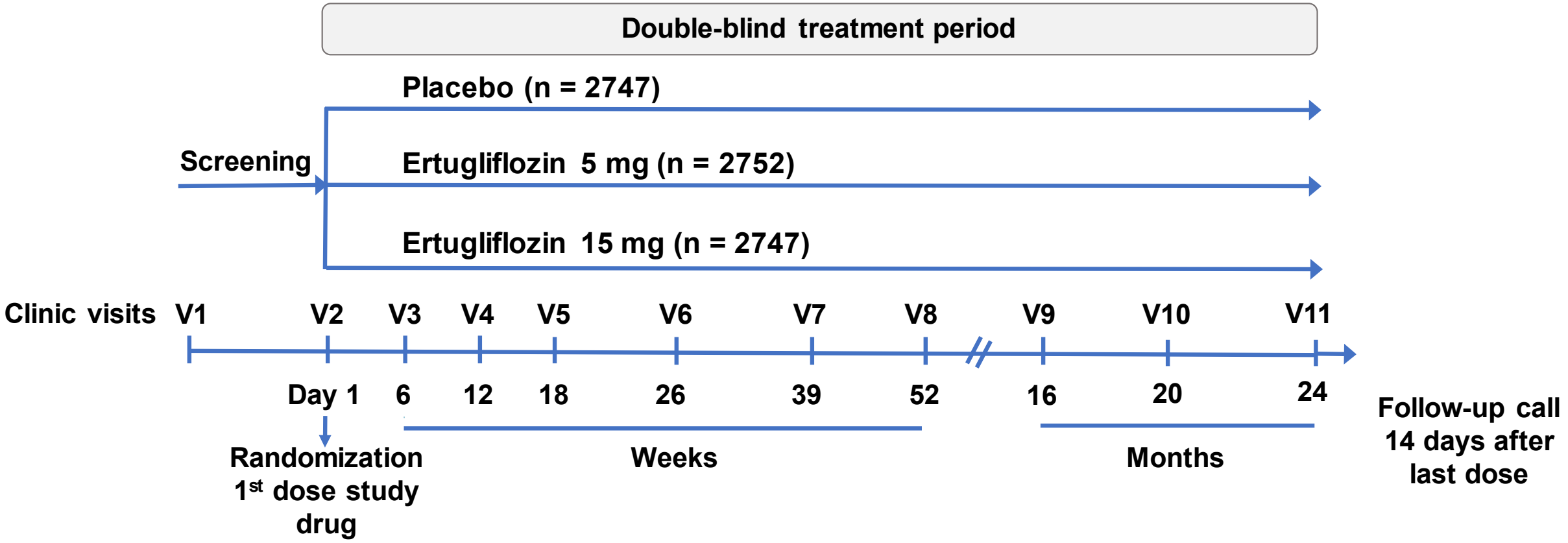
- History of T1DM or ketoacidosis
- Experiencing a CV event (e.g., myocardial infarction or stroke) or undergoing coronary or peripheral intervention procedure between the screening visit and randomization
- Undergoing any CV surgery (e.g., valvular surgery) within 3 months of the screening visit
- Planned revascularization or peripheral intervention procedure or other CV surgery
- eGFR <30 mL/min/1.73 m^2 at the screening visit
- NYHA Class IV heart failure at screening visit (Class III–IV prior to protocol amendment)

ADA, American Diabetes Association; AHA, antihyperglycemic agents; ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; NYHA, New York Heart Association; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Cannon CP et al. *Am Heart J* 2018;206:11-23.

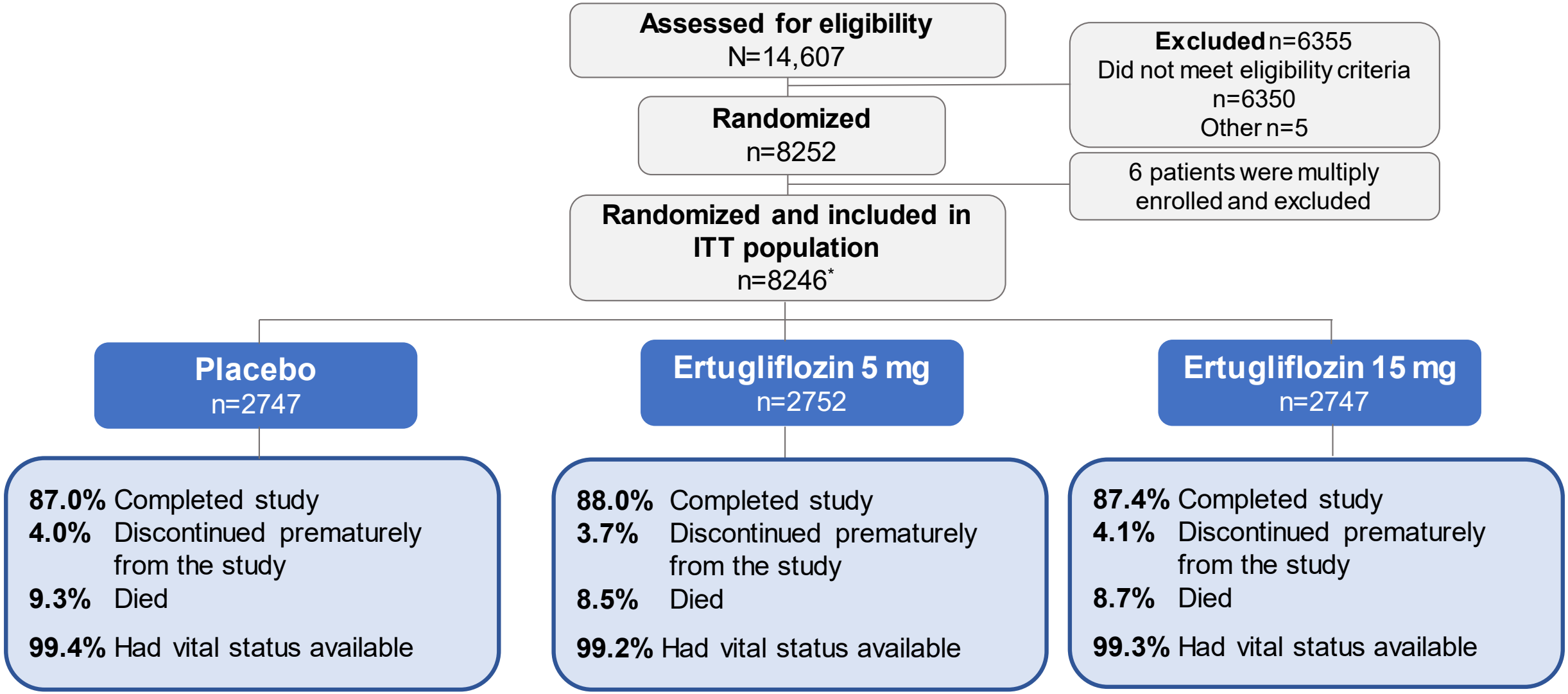
Treatment protocol

- Once-daily treatment of study medication added to background standard of care*, which was held stable during the first 18 weeks of the study†



*Excluding SGLT2 inhibitors, rosiglitazone, and chlorpropamide
†Except for patients meeting the glycemic rescue criteria or with clinically significant hypoglycemia.
V, visit.

Patient disposition



*8246 patients were randomized and constitute the ITT population for superiority testing;
8238 patients received at least one dose of investigational product and constitute the FAS for the non-inferiority analysis.
FAS, full analysis set; ITT, intention-to-treat.

Study medication disposition and overall exposure

	Placebo (n=2747)	Ertugliflozin (n=5499)
Completed the study medication	1850 (67.4)	3945 (71.7)
Died on study medication	130 (4.7)	263 (4.8)
Premature discontinuation of the study medication	767 (27.9)	1291 (23.5)
Reasons for premature discontinuation of the study medication (≥2% of patients in any group)		
Withdrawal by patient	422 (15.4)	673 (12.2)
Adverse event	184 (6.7)	403 (7.3)
Physician decision	54 (2.0)	66 (1.2)
Mean treatment exposure, years	2.8 ± 1.4	2.9 ± 1.4
Mean duration of follow-up, years	3.5 ± 1.1	3.5 ± 1.2

Summary: study design and methodology

- VERTIS CV is the latest SGLT2 inhibitor trial conducted to fulfill the 2008 regulatory guidance on new diabetes medications

- VERTIS CV: prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, event-driven trial in patients with type 2 diabetes and established atherosclerotic CV disease
  - 8246 patients were randomly assigned to receive ertugliflozin or placebo (ITT)
  - 8238 patients received ≥1 dose of study medication (FAS)
  - Mean duration of follow-up in study overall was 3.5 years
  - Rates of discontinuation from the study were low
  - Final vital status was available for >99% of patients

CV, cardiovascular; FAS, full analysis set; ITT, intention-to-treat; SGLT2, sodium-glucose cotransporter 2.

Baseline Characteristics and Metabolic Results

Sam Dagogo-Jack, MD, DSc

University of Tennessee Health Science Center, Memphis, TN

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eValuation of ERTugliflozin effIcacy and Safety

Baseline characteristics

	Placebo (n=2747)	Ertugliflozin (n=5499)
Age, years ± SD	64.4 ± 8.0	64.4 ± 8.1
Male, n (%)	1903 (69.3)	3866 (70.3)
Race, n (%)		
White	2414 (87.9)	4826 (87.8)
Black	69 (2.5)	166 (3.0)
Asian	162 (5.9)	336 (6.1)
Other	102 (3.7)	171 (3.1)
Ethnicity, n (%)		
Hispanic	343 (12.5)	700 (12.7)
Non-Hispanic	2399 (87.3)	4782 (87.0)
Region, n (%)		
North America	605 (22.0)	1208 (22.0)
South America	239 (8.7)	484 (8.8)
Europe	1546 (56.3)	3091 (56.2)
Asia	173 (6.3)	350 (6.4)
South Africa	126 (4.6)	251 (4.6)
Australia/New Zealand	58 (2.1)	115 (2.1)

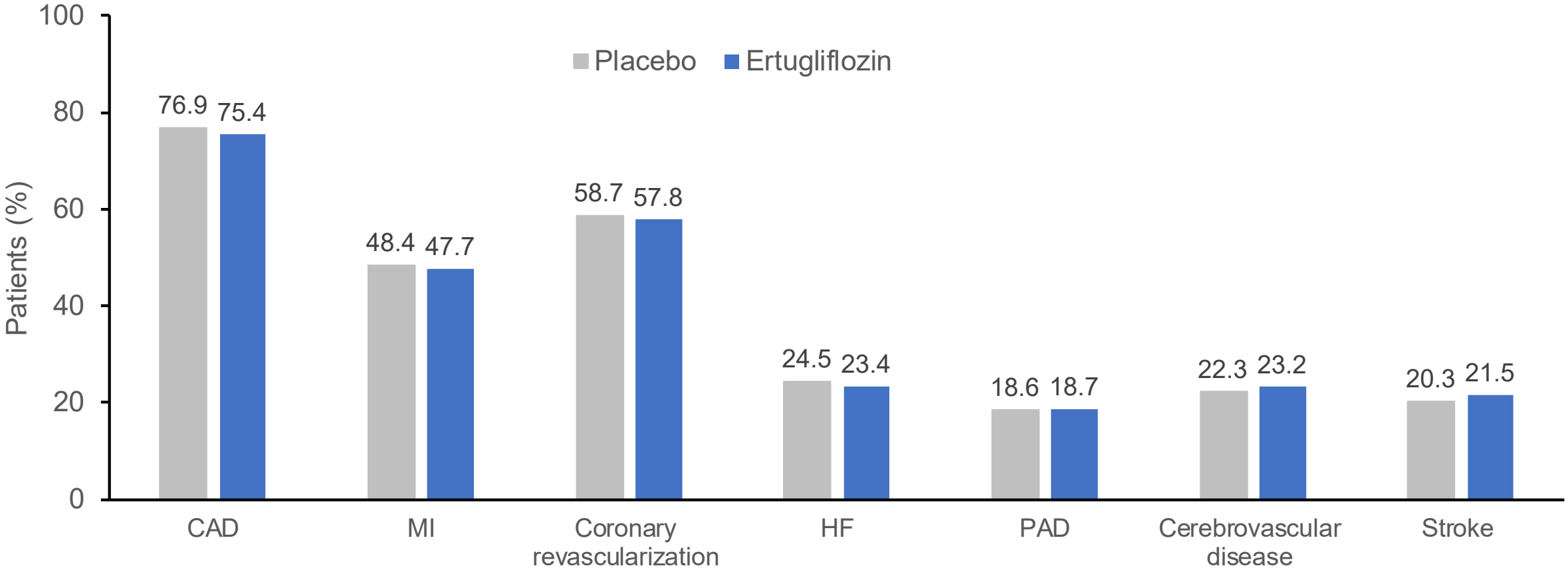
SD, standard deviation.

Baseline characteristics

	Placebo (n=2747)	Ertugliflozin (n=5499)
Duration of T2DM, years	13.1 ± 8.4	12.9 ± 8.3
HbA1c, %	8.2 ± 0.9	8.2 ± 1.0
BMI, kg/m^2	32.0 ± 5.5	31.9 ± 5.4
Total cholesterol, mg/dL	168.3 ± 45.5	168.9 ± 46.9
LDL cholesterol, mg/dL	88.8 ± 37.7	89.3 ± 38.5
HDL cholesterol, mg/dL	43.9 ± 12.3	43.7 ± 12.0
Triglycerides, mg/dL	178.9 ± 104.7	181.4 ± 119.2
SBP, mmHg	133.1 ± 13.9	133.5 ± 13.7
DBP, mmHg	76.4 ± 8.7	76.8 ± 8.3
eGFR, mL/min/1.73 m^2	75.7 ± 20.8	76.1 ± 20.9
eGFR <60 mL/min/1.73 m^2, n (%)	608 (22.1)	1199 (21.8)

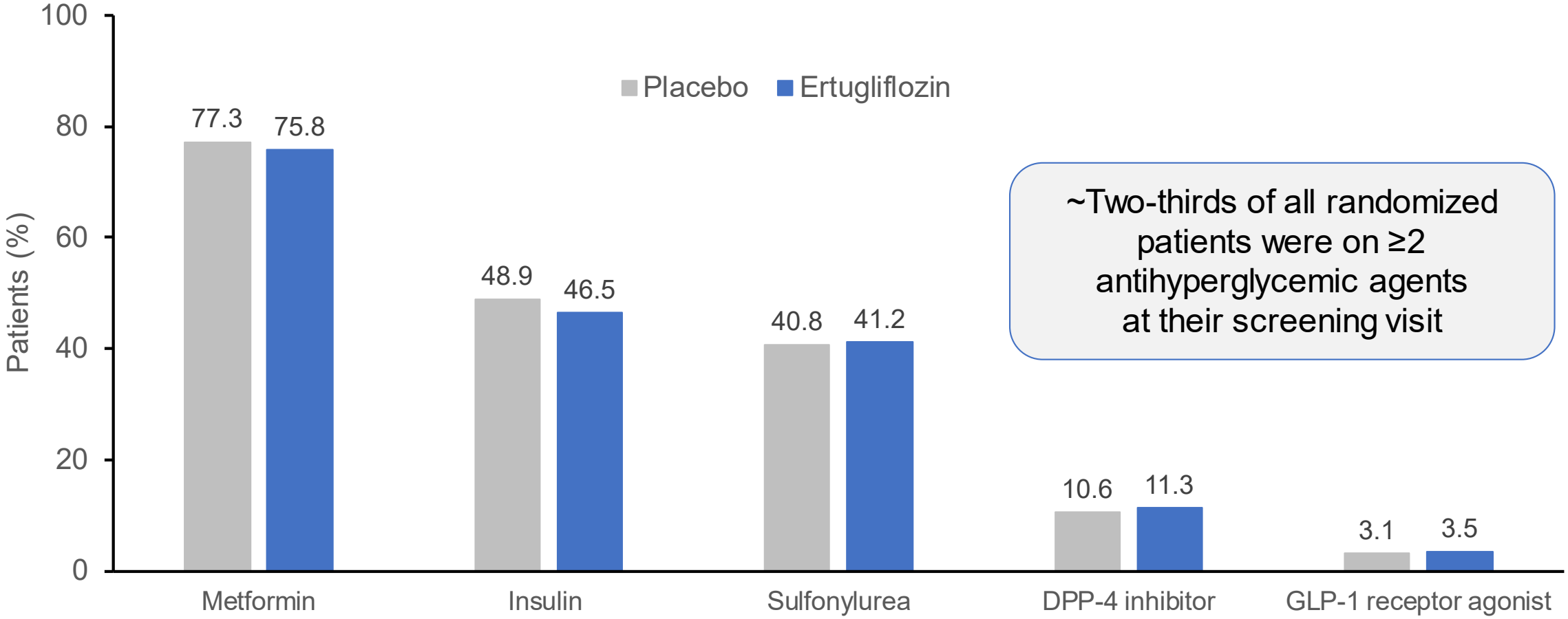
Values are means ± SD
BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

Baseline characteristics: history of CV disease



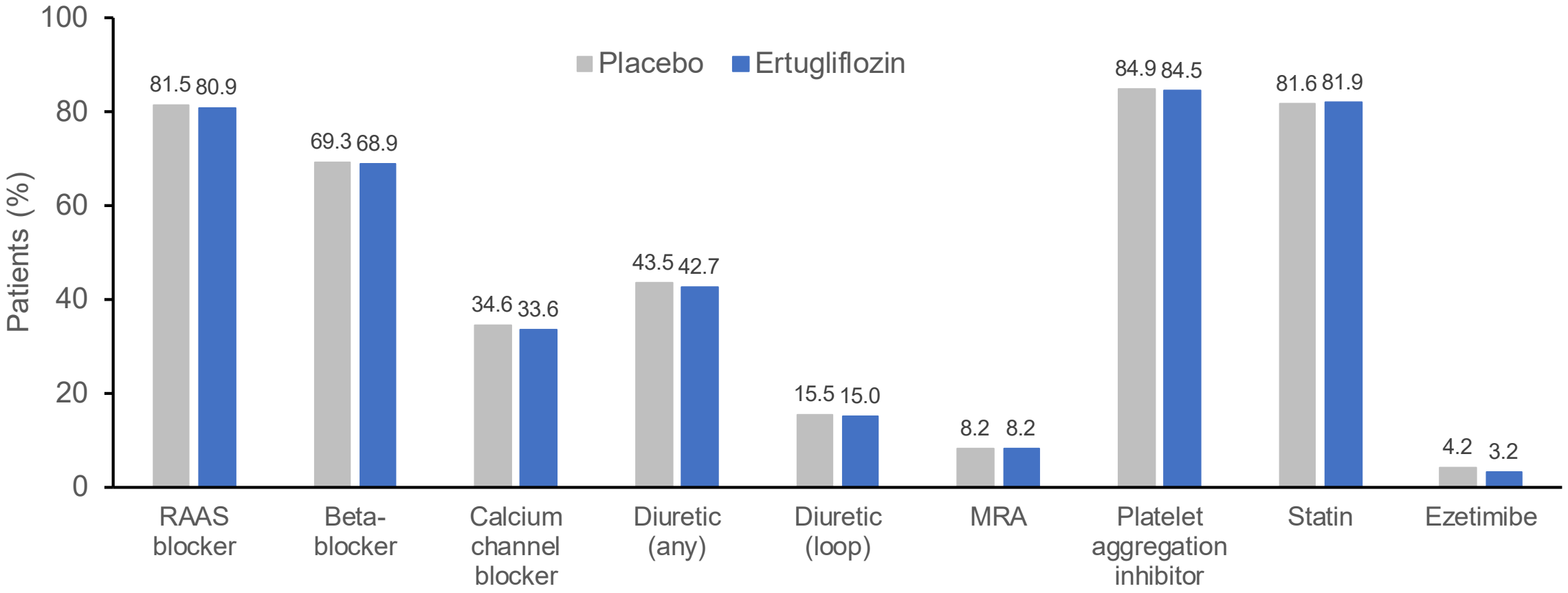
CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease.

Baseline characteristics: background antihyperglycemic medications



Medications are not mutually exclusive.
DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

Baseline characteristics: background CV medications



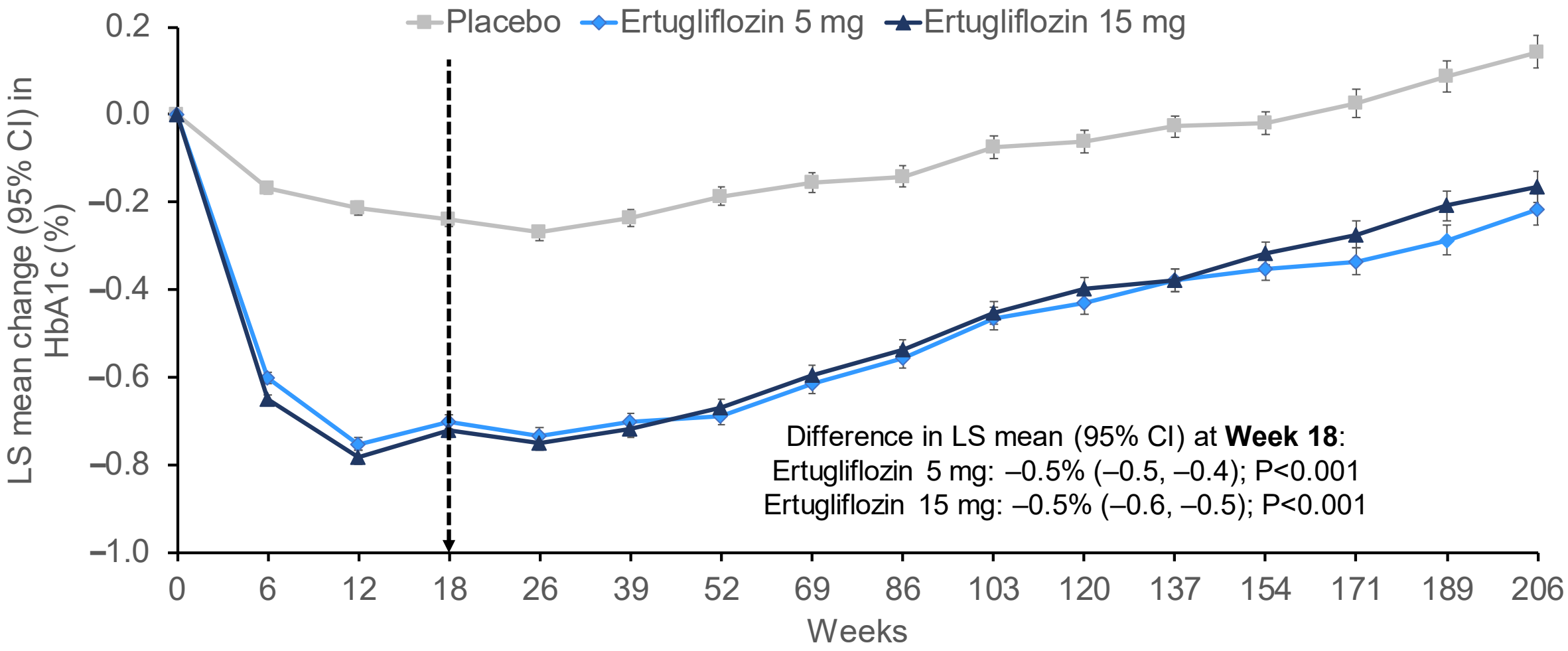
Medications are not mutually exclusive.
CV, cardiovascular; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system.

Metabolic Outcomes

VERTIS

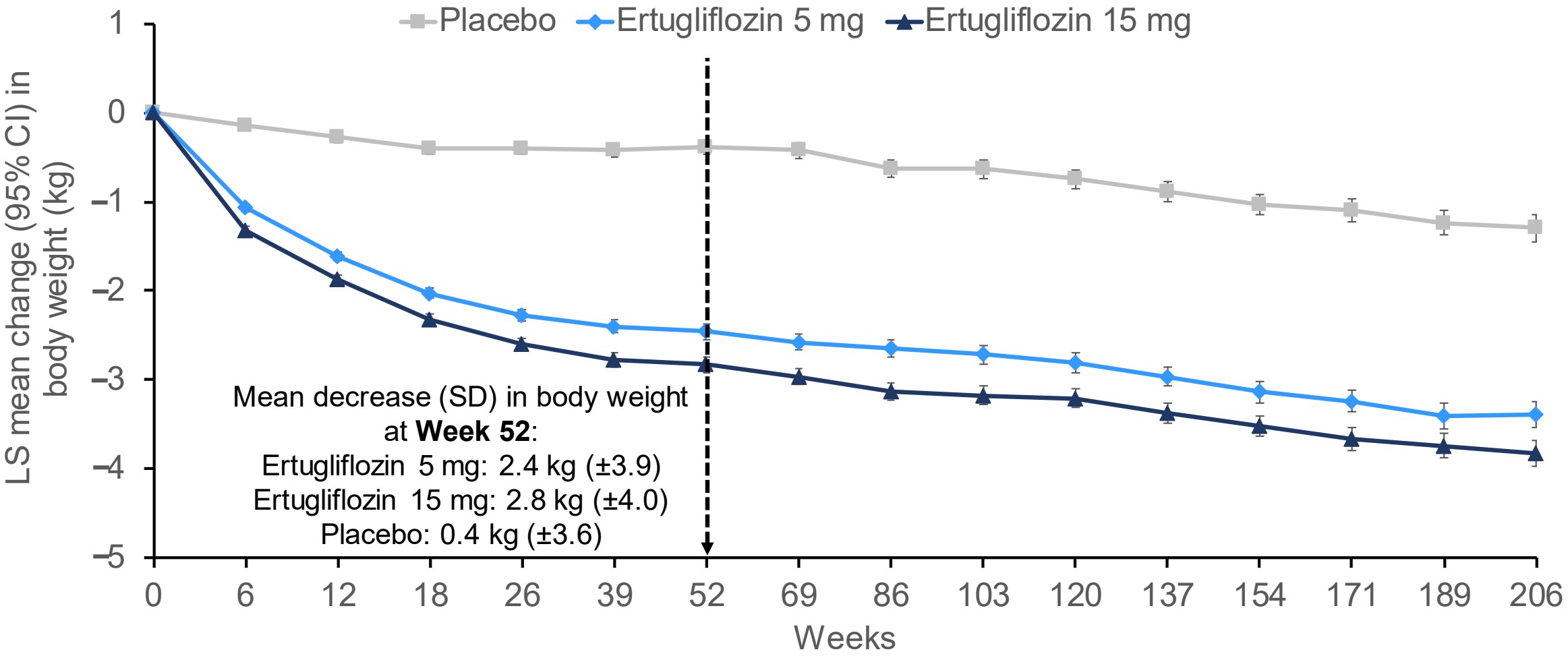
e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety

HbA1c over time



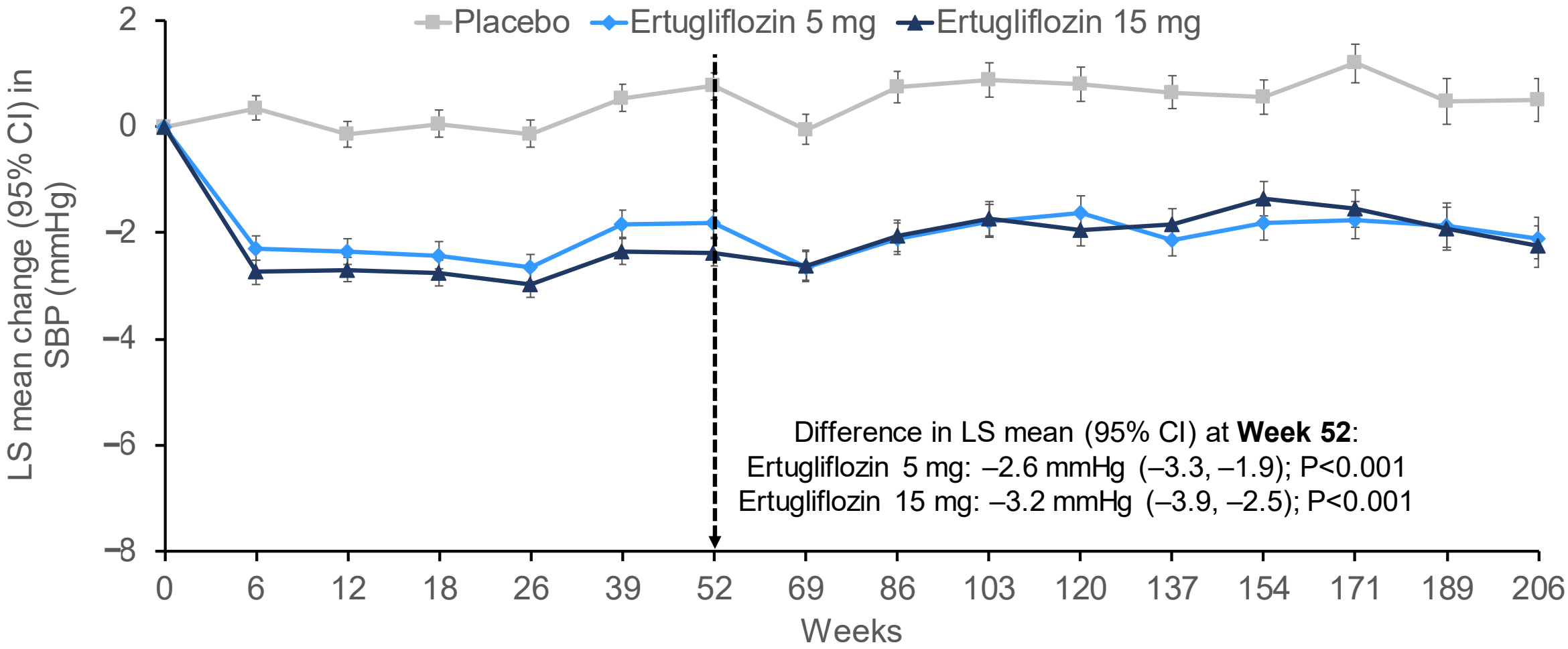
Doses of background antihyperglycemic medication were held constant for the initial 18 weeks of the study except for those patients meeting the glycemic rescue criteria or with clinically significant hypoglycemia.
CI, confidence interval; HbA1c, glycated hemoglobin; LS, least squares.

Body weight over time



CI, confidence interval; LS, least squares; SD, standard deviation.

SBP over time



CI, confidence interval; LS, least squares; SBP, systolic blood pressure.

Summary: baseline characteristics and metabolic results

- Baseline characteristics were well-balanced between treatment groups
- Patients were generally well treated with guideline-directed secondary prevention medications
- Ertugliflozin reduced HbA1c, body weight, and SBP compared with placebo and reductions were sustained over the course of the study

HbA1c, glycated hemoglobin; SBP, systolic blood pressure.

Cardiovascular and Renal Outcomes

Christopher Cannon, MD
Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA

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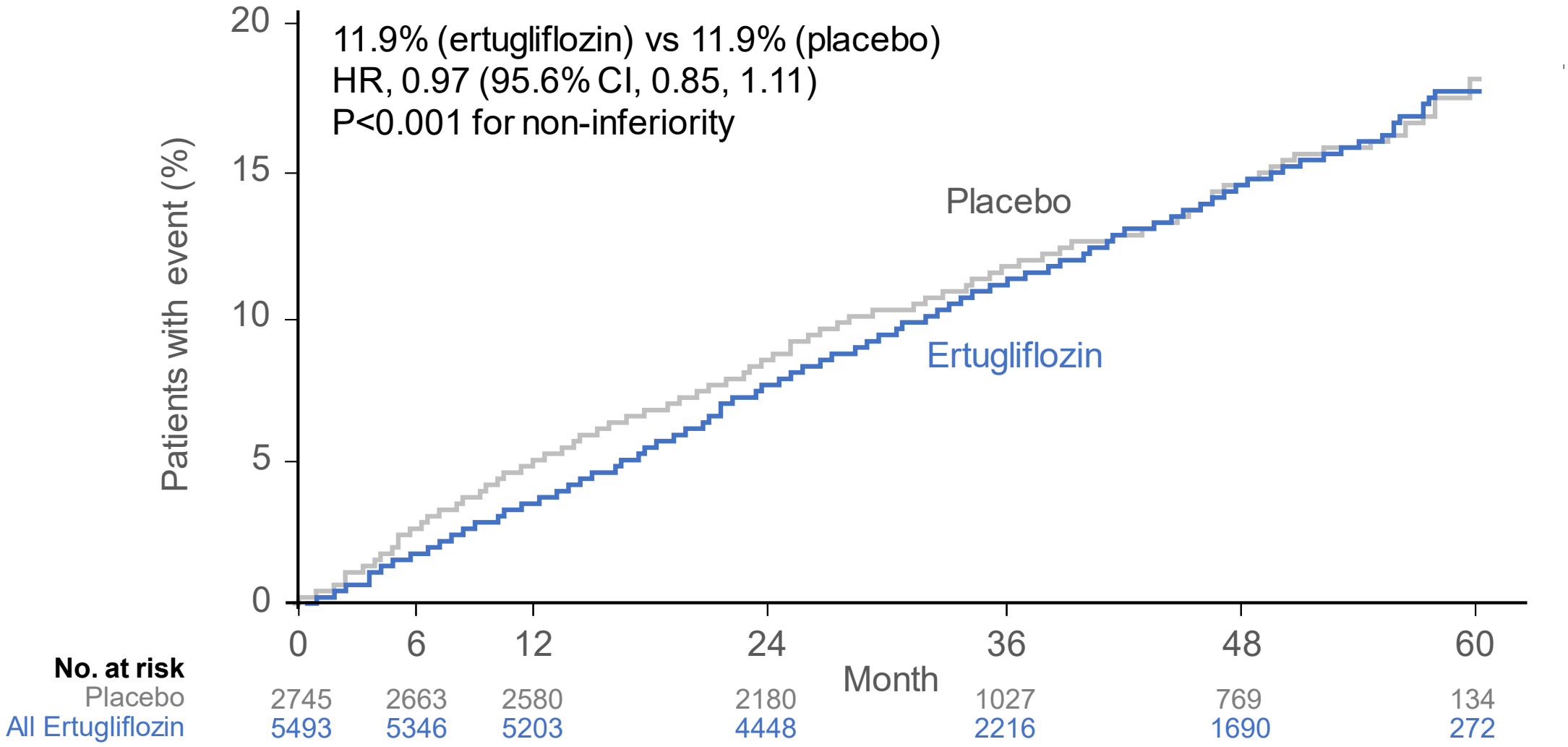
e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety

Primary outcome: MACE*

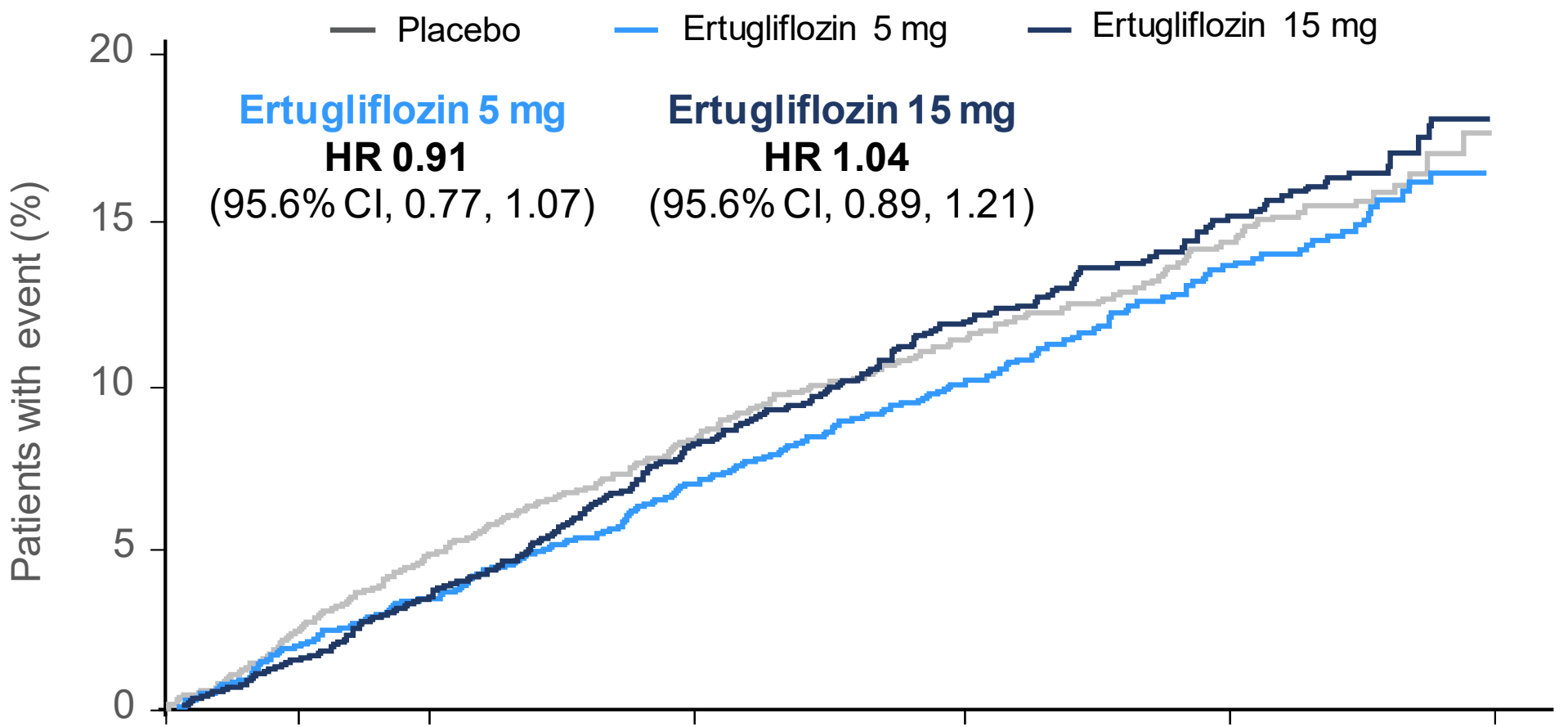
CV death, nonfatal MI, or nonfatal stroke



*Full analysis set included all randomized patients who received at least one dose of study medication (N=5493 for ertugliflozin and N=2745 for placebo). Only confirmed MACE events occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

Primary outcome: MACE*

CV death, nonfatal MI, or nonfatal stroke

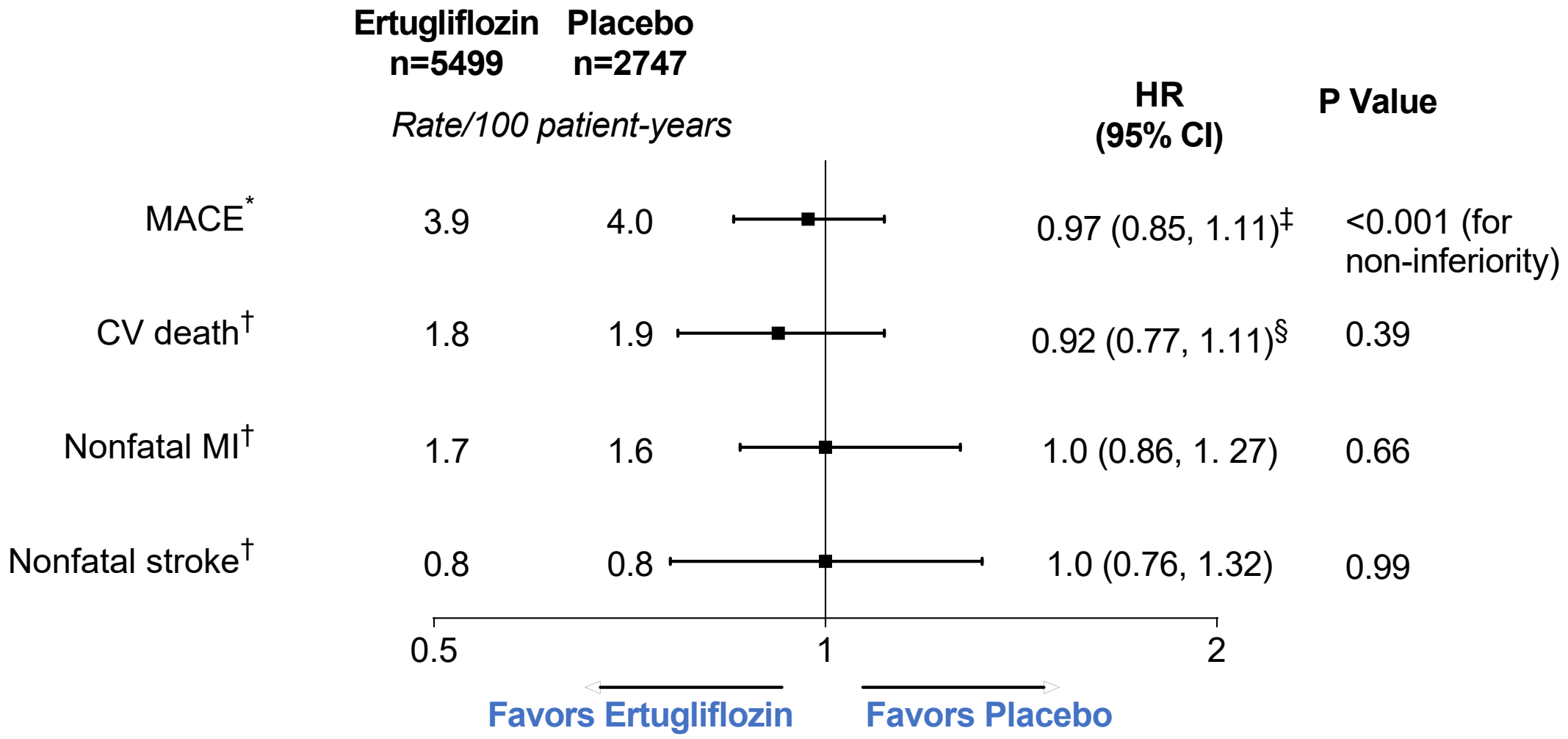


No. at risk							
Placebo	2745	2663	2580	2180	1027	769	134
Ertugliflozin 5 mg	2746	2670	2610	2247	1117	855	140
Ertugliflozin 15 mg	2747	2676	2593	2201	1099	835	132

*Full analysis set included all randomized patients who received at least one dose of study medication (N=2746 for ertugliflozin 5 mg, N=2747 for ertugliflozin 15 mg, and N=2745 for placebo). Only confirmed MACE events occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular even; MI, myocardial infarction.

MACE and individual endpoints

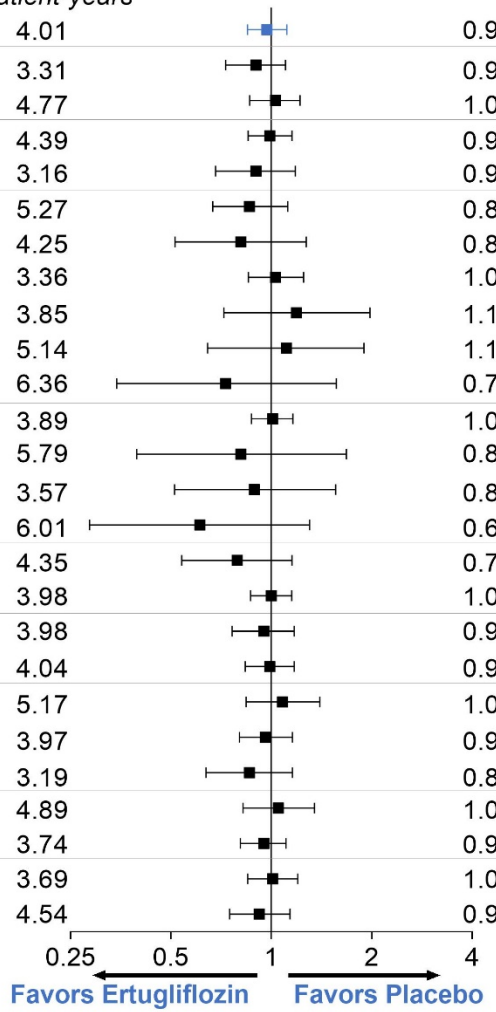
CV death, nonfatal MI, or nonfatal stroke



*Full analysis set included all randomized patients who received at least one dose of study medication (N=5493 for ertugliflozin and N=2745 for placebo). Only confirmed MACE events occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis. †Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo). ‡95.6% CI; §95.8% CI.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction.

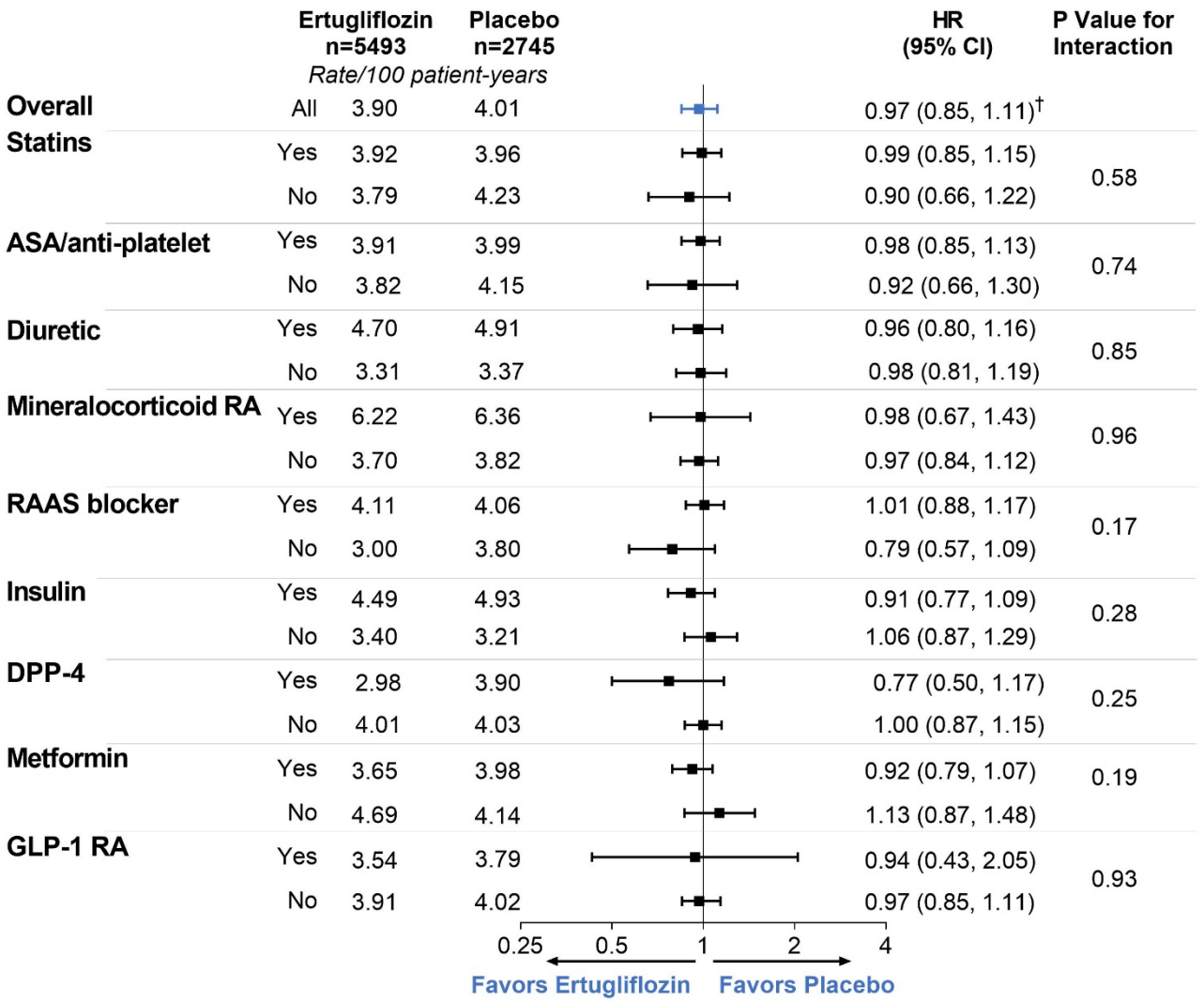
MACE: subgroup analysis (patient demographics)*

		Ertugliflozin N=5499	Placebo N=2747	HR (95% CI)	P Value for Interaction
		Rate/100 patient-years			
Overall	All	3.90	4.01	0.97 (0.85, 1.11)†	
Age	<65 years	2.96	3.31	0.90 (0.73, 1.10)	0.34
	≥65 years	4.89	4.77	1.03 (0.86, 1.22)	
Sex	Male	4.35	4.39	0.99 (0.85, 1.15)	0.53
	Female	2.83	3.16	0.90 (0.68, 1.18)	
Region	North America	4.54	5.27	0.86 (0.67, 1.12)	0.67
	South America	3.44	4.25	0.81 (0.52, 1.27)	
	Europe	3.47	3.36	1.03 (0.85. 1.25)	
	Asia	4.58	3.85	1.19 (0.72, 1.98)	
	South Africa	5.69	5.14	1.11 (0.64, 1.90)	
	Australia/New Zealand	4.70	6.36	0.73 (0.34, 1.57)	
Race	White	3.91	3.89	1.01 (0.87, 1.16)	0.58
	Black	4.72	5.79	0.81 (0.40, 1.68)	
	Asian	3.20	3.57	0.89 (0.51, 1.56)	
	Multi-Racial	3.66	6.01	0.61 (0.29, 1.30)	
Ethnicity	Hispanic/Latino	3.44	4.35	0.79 (0.54, 1.15)	0.25
	Non-Hispanic/Latino	3.97	3.98	1.00 (0.87, 1.15)	
BMI, kg/m^2	<30	3.76	3.98	0.95 (0.76, 1.17)	0.75
	≥30	3.98	4.04	0.99 (0.84, 1.17)	
eGFR, mL/min/1.73 m^2	<60	5.59	5.17	1.08 (0.84, 1.40)	0.50
	60 to <90	3.82	3.97	0.96 (0.80, 1.16)	
	≥90	2.73	3.19	0.86 (0.64, 1.16)	
History of HF	Yes	5.15	4.89	1.05 (0.82, 1.35)	0.47
	No	3.53	3.74	0.95 (0.81, 1.11)	
HbA1c	<8.5	3.72	3.69	1.01 (0.85, 1.20)	0.52
	≥8.5	4.19	4.54	0.92 (0.75, 1.14)	



*Full analysis set included all randomized patients who received at least one dose of study medication (N=5493 for ertugliflozin and N=2745 for placebo). Only confirmed MACE events occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis. †95.6% CI.
BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; HR, hazard ratio;MACE, major adverse cardiovascular event.

MACE: subgroup analysis (concomitant medication)*



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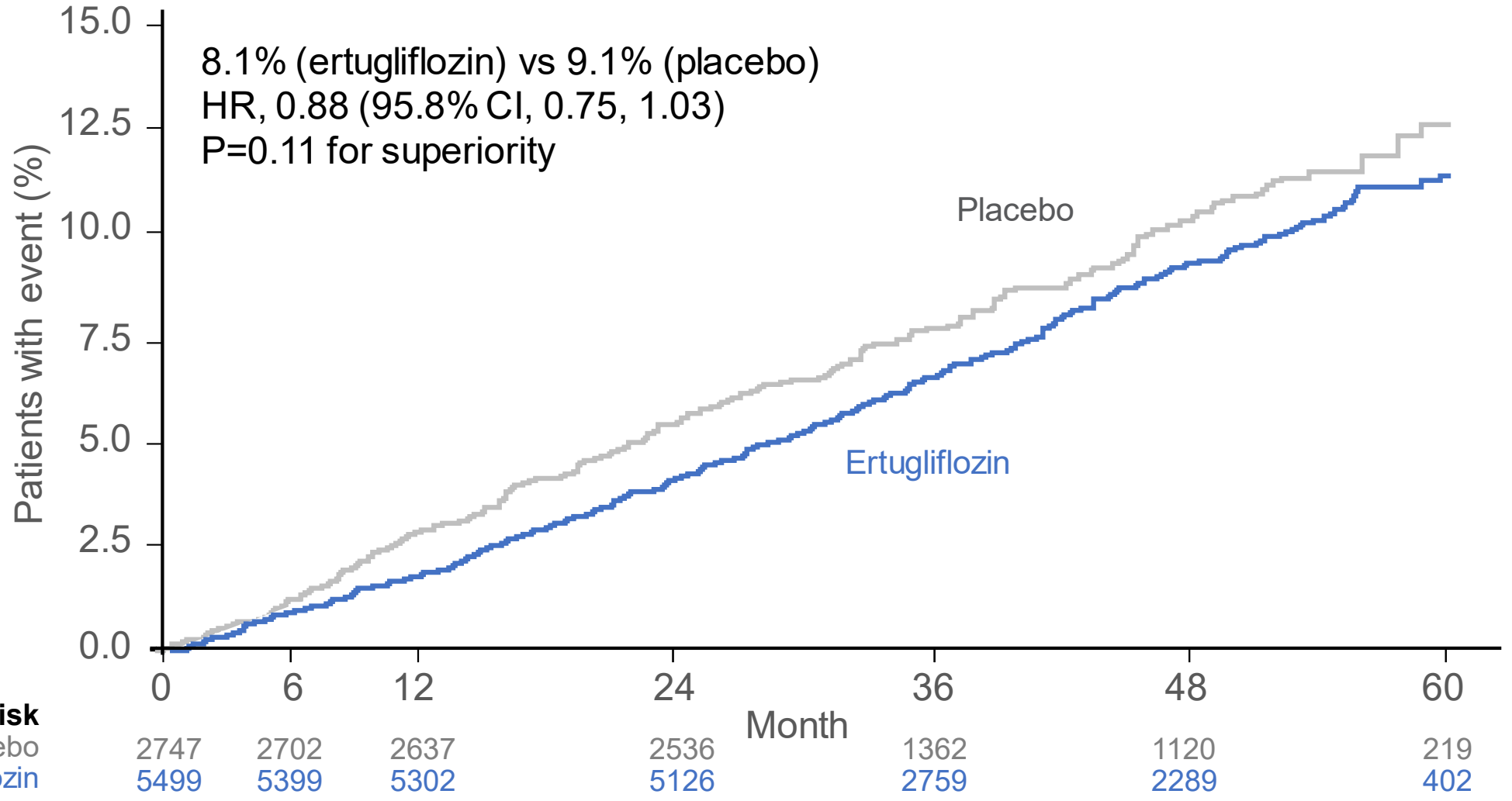
ASA, acetylsalicylic acid; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide; HR, hazard ratio; RA, receptor agonist; RAAS, renin-angiotensin-aldosterone system.

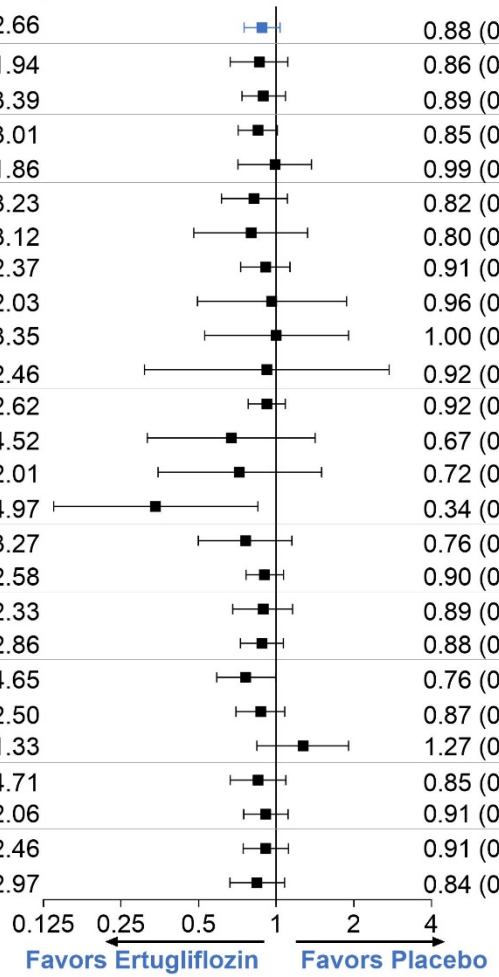
CV death or HHF*



*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI (95.8%) for the alpha-protected tests was adjusted at the final analysis to account for the interim analysis as per the protocol.
CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio.

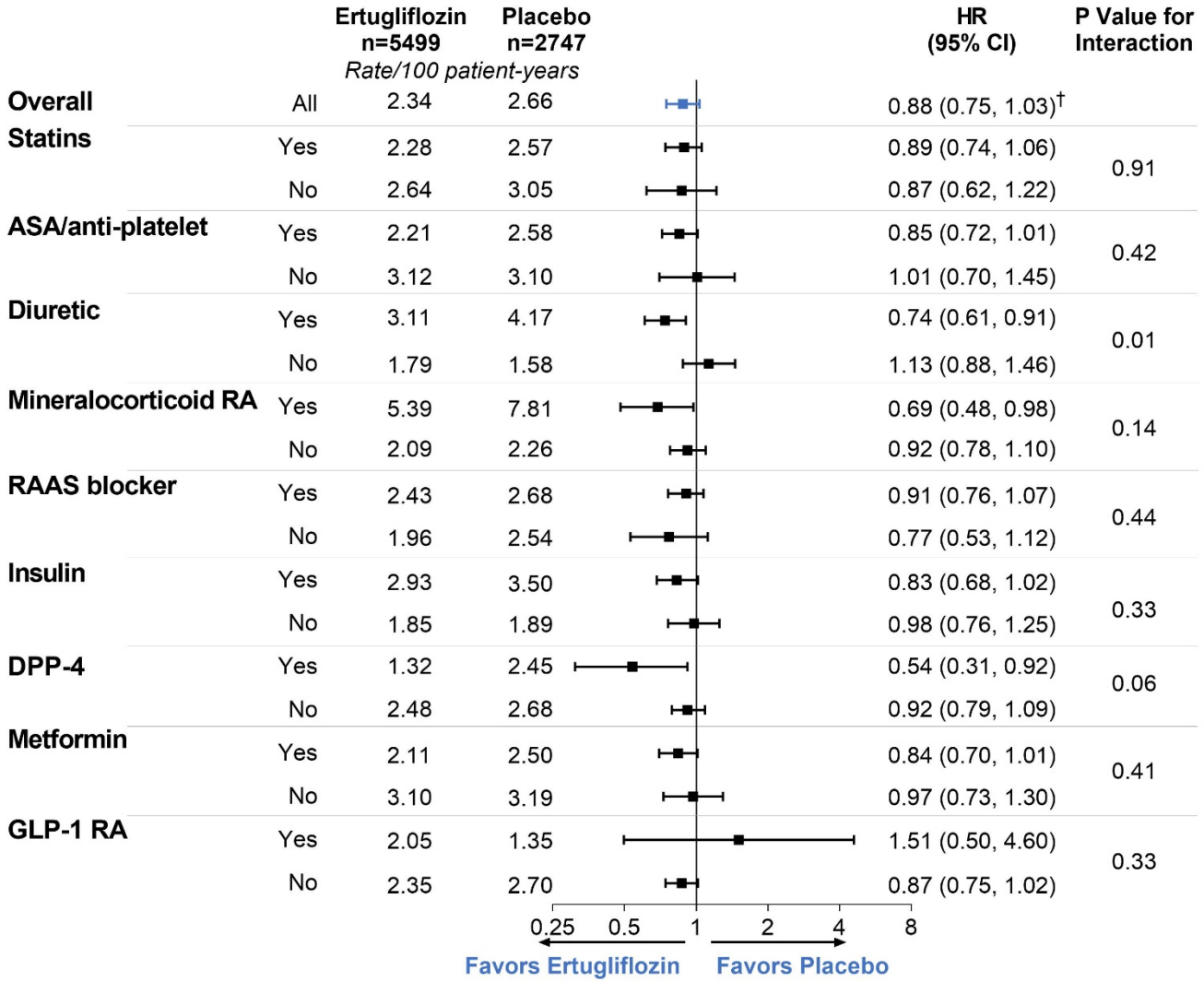
CV death or HHF: subgroup analysis (patient demographics)*

		Ertugliflozin n=5499	Placebo n=2747	HR (95% CI)	P Value for Interaction
		Rate/100 patient-years			
Overall	All	2.34	2.66	0.88 (0.75, 1.03)†	
Age	<65 years	1.66	1.94	0.86 (0.66, 1.11)	0.80
	≥65 years	3.03	3.39	0.89 (0.74, 1.09)	
Sex	Male	2.55	3.01	0.85 (0.71, 1.01)	0.42
	Female	1.83	1.86	0.99 (0.71, 1.37)	
Region	North America	2.66	3.23	0.82 (0.61, 1.10)	
	South America	2.49	3.12	0.80 (0.48, 1.32)	
	Europe	2.15	2.37	0.91 (0.73, 1.13)	0.98
	Asia	1.96	2.03	0.96 (0.50, 1.88)	
	South Africa	3.36	3.35	1.00 (0.53, 1.91)	
	Australia/New Zealand	2.26	2.46	0.92 (0.31, 2.74)	
Race	White	2.41	2.62	0.92 (0.78, 1.08)	
	Black	3.04	4.52	0.67 (0.32, 1.42)	0.16
	Asian	1.45	2.01	0.72 (0.35, 1.50)	
	Multi-Racial	1.71	4.97	0.34 (0.14, 0.85)	
Ethnicity	Hispanic/Latino	2.49	3.27	0.76 (0.50, 1.15)	0.44
	Non-Hispanic/Latino	2.33	2.58	0.90 (0.76, 1.07)	
BMI, kg/m^2	<30	2.06	2.33	0.89 (0.68, 1.16)	0.97
	≥30	2.52	2.86	0.88 (0.73, 1.06)	
eGFR, mL/min/1.73 m^2	<60	3.56	4.65	0.76 (0.59, 1.00)	
	60 to <90	2.18	2.50	0.87 (0.70, 1.08)	0.13
	≥90	1.69	1.33	1.27 (0.84, 1.91)	
History of HF	Yes	4.01	4.71	0.85 (0.66, 1.09)	0.66
	No	1.88	2.06	0.91 (0.75, 1.11)	
HbA1c	<8.5	2.25	2.46	0.91 (0.75, 1.12)	0.63
	≥8.5	2.51	2.97	0.84 (0.66, 1.08)	



*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo). †95.8% CI.
BMI, body mass index; CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HHF, hospitalization for heart failure; HF, heart failure; HR, hazard ratio.

CV death or HHF: subgroup analysis (concomitant medication)*



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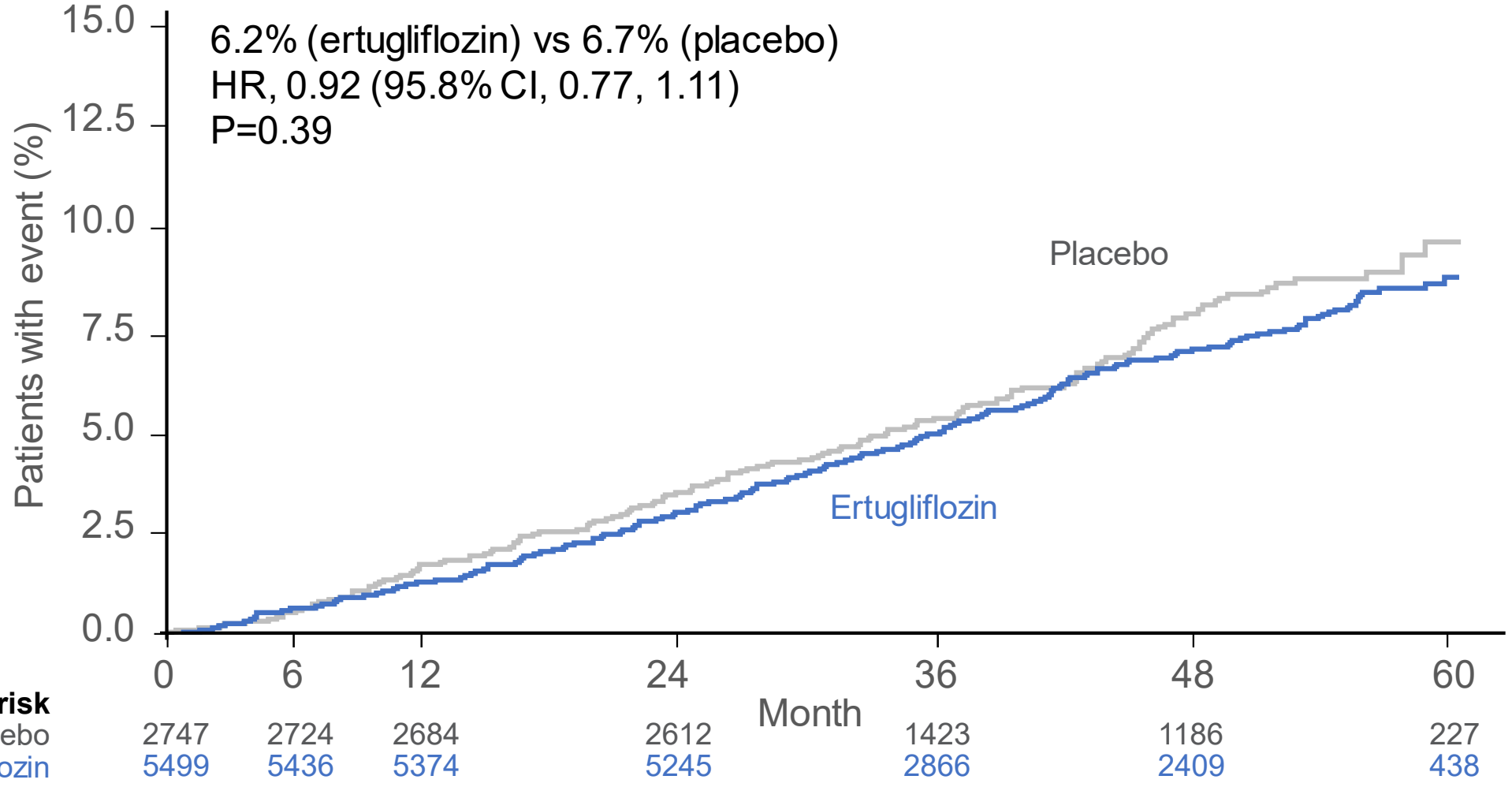
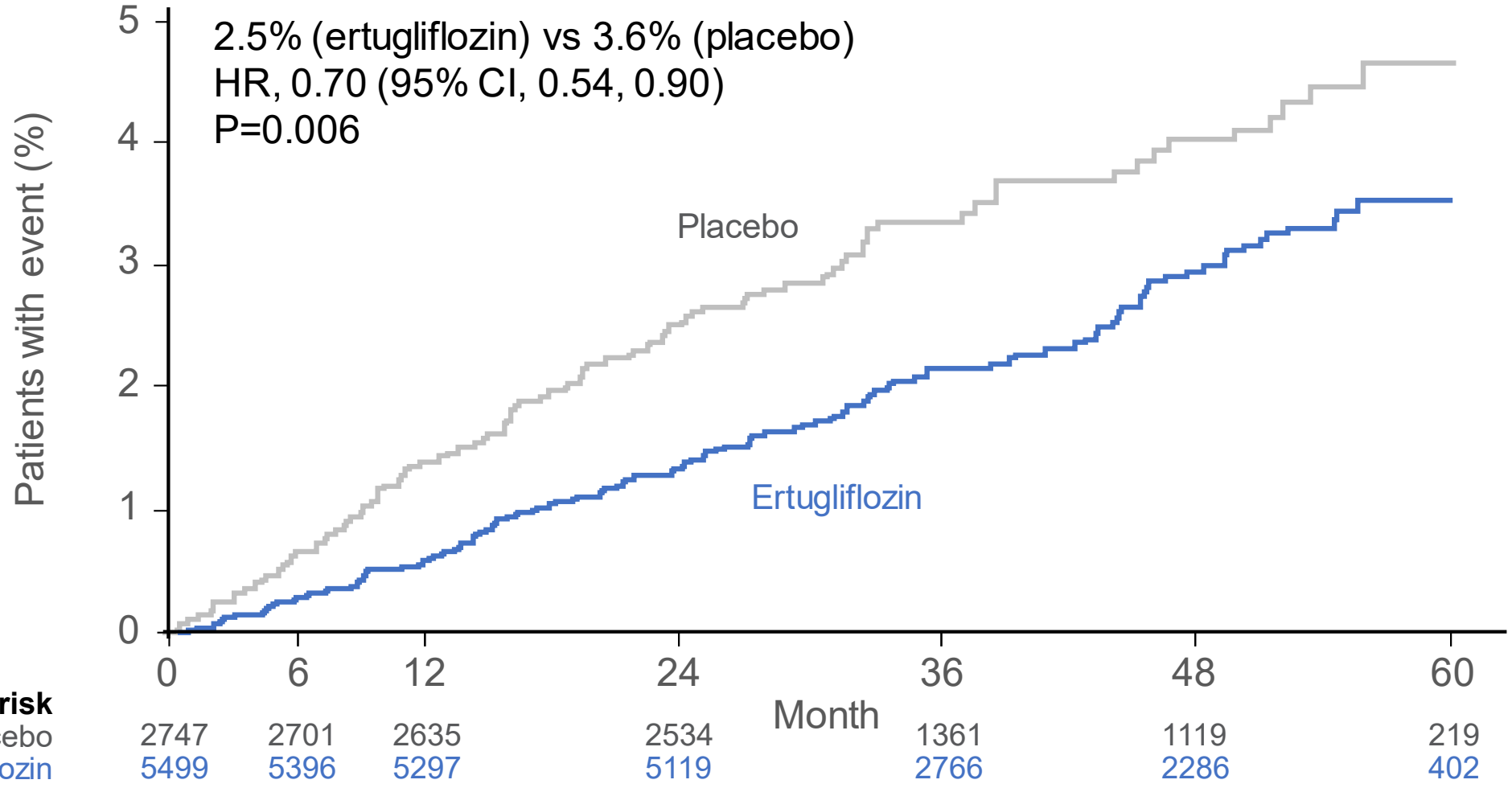
ASA, acetylsalicylic acid; HR, hazard ratio; DPP-4, dipeptidyl peptidase-4;
GLP-1, glucagon-like peptide; RA, receptor agonist; RAAS, renin-angiotensin-aldosterone system.

CV death*



*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI (95.8%) for the alpha-protected tests was adjusted at the final analysis to account for the interim analysis as per the protocol.
CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

HHF*



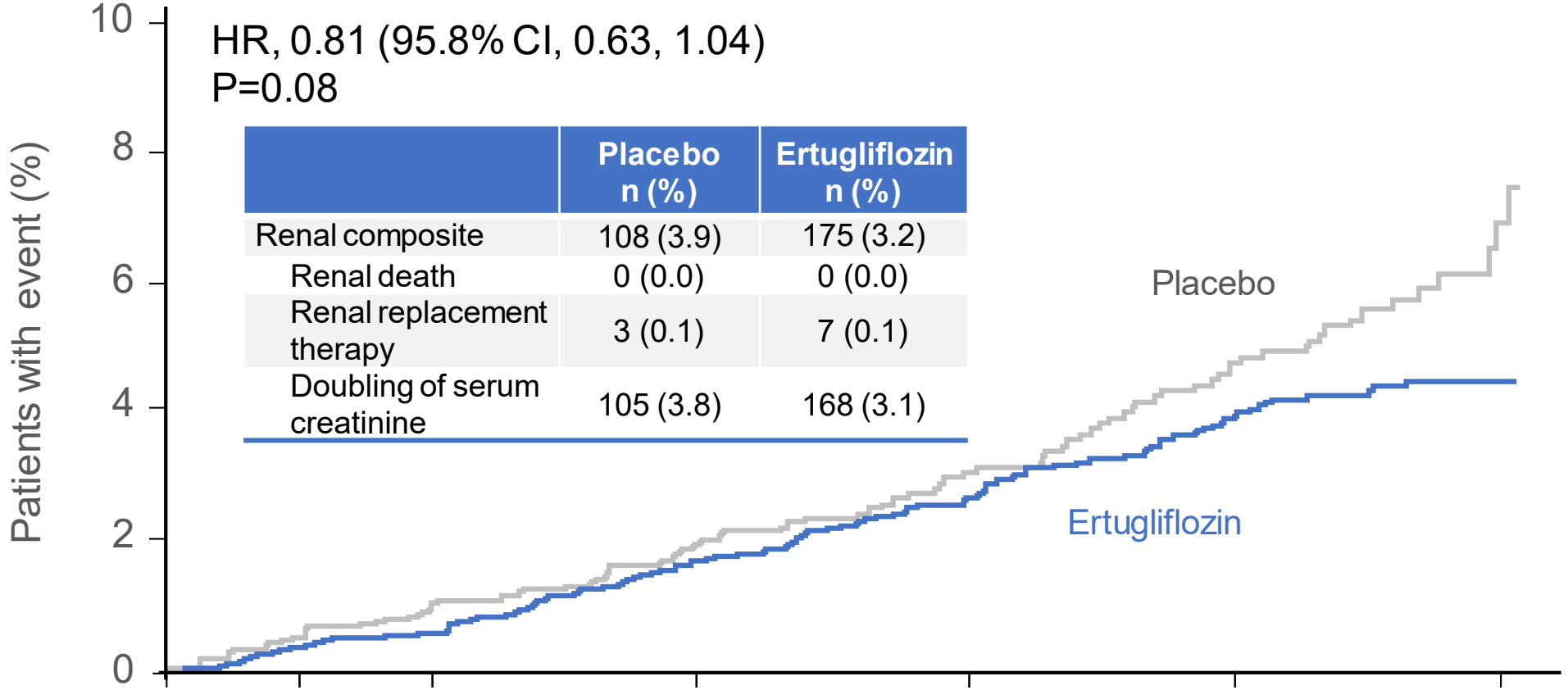
*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio.

Renal composite*

Renal death, dialysis/transplant, or doubling of serum creatinine

HR, 0.81 (95.8% CI, 0.63, 1.04)
P=0.08

	Placebo n (%)	Ertugliflozin n (%)
Renal composite	108 (3.9)	175 (3.2)
Renal death	0 (0.0)	0 (0.0)
Renal replacement therapy	3 (0.1)	7 (0.1)
Doubling of serum creatinine	105 (3.8)	168 (3.1)

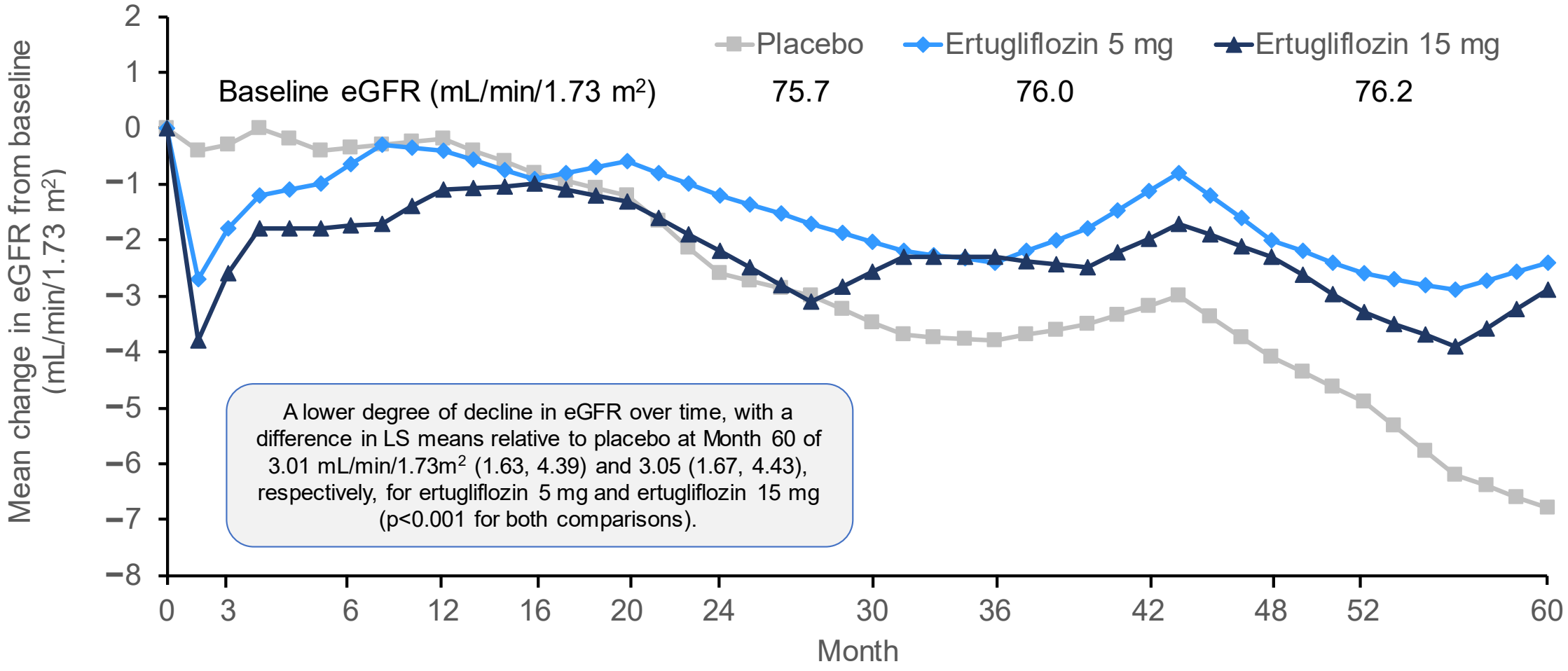


No. at risk

	0	6	12	24	36	48	60
Placebo	2747	2703	2643	2543	1371	1116	215
All Ertugliflozin	5499	5394	5299	5110	2756	2271	406

*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI (95.8%) for the alpha-protected tests was adjusted at the final analysis to account for the interim analysis as per the protocol.
CI, confidence interval; HR, hazard ratio.

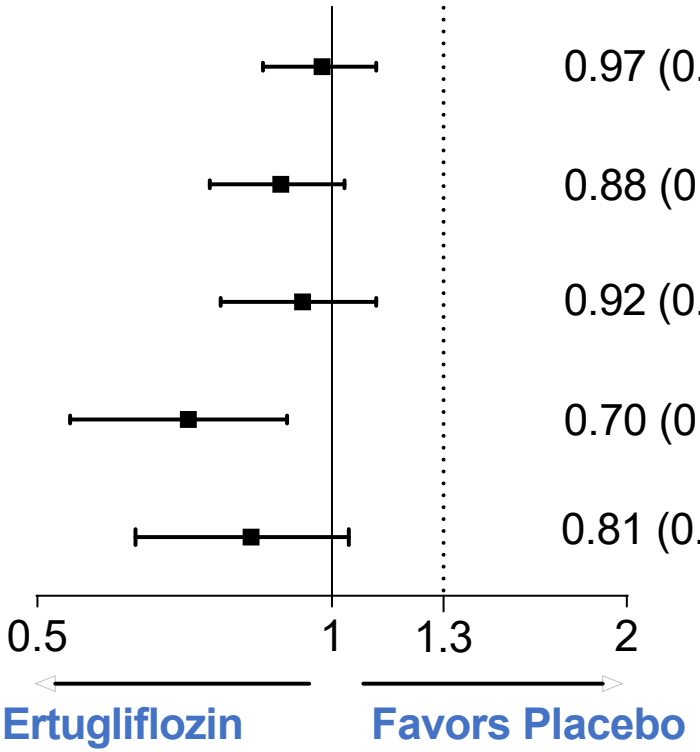
VERTIS CV: eGFR over time



eGFR, estimated glomerular filtration rate.

Primary and secondary endpoints

	Ertugliflozin n=5499	Placebo n=2747	HR (CI)	P Value
	Rate/100 patient-years			
MACE*	3.9	4.0	0.97 (0.85, 1.11)	<0.001 (for non-inferiority)
CV Death/HHF†	2.3	2.7	0.88 (0.75, 1.03)	0.11
CV Death†	1.8	1.9	0.92 (0.77, 1.11)	0.39
HHF†	0.7	1.1	0.70 (0.54, 0.90)	0.006
Renal Composite†	0.9	1.2	0.81 (0.63, 1.04)	0.08



*Full analysis set included all randomized patients who received at least one dose of study medication (N=5493 for ertugliflozin and N=2745 for placebo; 95.6% CI). Only confirmed MACE events occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis.
†Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo; 95.8% CI for CV death/HHF, CV death, and the renal composite outcome; 95% CI for HHF outcome).
CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events.

Summary: CV and renal outcomes

- In patients with type 2 diabetes and atherosclerotic CV disease, ertugliflozin added to guideline-directed secondary prevention therapies was non-inferior versus placebo for MACE
- The key secondary composite endpoint of CV death or HHF did not differ between groups, nor did CV death, but a 30% lower risk of HHF was observed with ertugliflozin
- The renal composite outcome was 19% lower, but was not statistically significant
- The overall pattern of the effects on endpoints of HHF and renal outcomes was in line with those seen in other large trials of SGLT2 inhibitors

CV, cardiovascular; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events; SGLT2, sodium-glucose cotransporter 2.

Safety and Updated CV Meta-Analysis

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University of Texas Southwestern Medical Center, Dallas, TX

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eValuation of ERTugliflozin effIcacy and Safety

Safety

VERTIS

e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety

Adverse events

	Placebo n (%) (n=2745)	Ertugliflozin 5 mg n (%) (n=2746)	Ertugliflozin 15 mg n (%) (n=2747)
≥1 AEs	2349 (85.6)	2357 (85.8)	2325 (84.6)
≥1 AEs leading to permanent study drug discontinuation	188 (6.8)	207 (7.5)	201 (7.3)
≥1 serious AEs	990 (36.1)	958 (34.9)	937 (34.1)

AEs, adverse events.

Selected adverse events

	Placebo n (%) (n=2745)	Ertugliflozin 5 mg n (%) (n=2746)	Ertugliflozin 15 mg n (%) (n=2747)
Urinary tract infection	279 (10.2)	336 (12.2)*	330 (12.0)*
Genital mycotic infection (male)	22 (1.2)	86 (4.4)†	98 (5.1)†
Genital mycotic infection (female)	20 (2.4)	48 (6.0)†	65 (7.8)†
Symptomatic hypoglycemia	790 (28.8)	768 (28.0)	728 (26.5)
Hypovolemia-related	106 (3.9)	118 (4.3)	118 (4.3)
Pancreatitis (adjudicated) Acute Chronic	 10 (0.4) 5 (0.2)	 12 (0.4) 1 (<0.1)	 5 (0.2) 2 (0.1)

*P<0.05 for the comparison with placebo.
†P<0.001 for the comparison with placebo.

Safety events of special interest

	Placebo n (%) (n=2745)	Ertugliflozin 5 mg n (%) (n=2746)	Ertugliflozin 15 mg n (%) (n=2747)
Acute kidney injury	60 (2.2)	48 (1.7)	53 (1.9)
Amputation	45 (1.6)	54 (2.0)	57 (2.1)
Diabetic ketoacidosis (adjudicated)	2 (0.1)	7 (0.3)	12 (0.4)
Fracture (adjudicated)	98 (3.6)	99 (3.6)	102 (3.7)
Fournier's gangrene	0 (0.0)	0 (0.0)	0 (0.0)

- Rates of amputations were 0.5 and 0.6 per 100 patient-years for placebo and ertugliflozin, respectively (risk difference, 0.1; 95% CI [–0.1, 0.3])

CI, confidence interval.

Summary and conclusion: safety

- Ertugliflozin was generally safe and well tolerated with a safety profile consistent with known risks of the SGLT2 inhibitor class:
  - Urinary tract infection and genital mycotic infection: frequency significantly higher with ertugliflozin versus placebo
  - Acute kidney injury: frequency did not differ with ertugliflozin versus placebo
  - Diabetic ketoacidosis: frequency low, numerically higher with ertugliflozin versus placebo
  - Amputation: frequency low, numerically higher with ertugliflozin versus placebo

SGLT2, sodium-glucose cotransporter 2.

SGLT2 Inhibitors, Cardiovascular and Renal Outcomes in Patients with Type 2 Diabetes

Systematic Review and Meta-analysis

VERTIS

e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety

Background

- SGLT2 inhibitors favorably affect a spectrum of CV and renal outcomes, with such efficacy largely independent of glycemic control[1-4]

- Accordingly, professional endocrinology and cardiology society recommendations and guidelines endorse the use of SGLT2 inhibitors to:[5-10]
  - Reduce risk for MI, stroke, and CV death in patients with T2DM with prevalent ASCVD and /or albuminuric CKD
  - Reduce risk for incident hospitalization for HF in patients with T2DM with prevalent or multiple risk factors for ASCVD and/or albuminuric CKD
  - Mitigate risk of kidney disease incidence and progression in those with or at high risk for CKD

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657. 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.
4. Perkovic V et al. *N Engl J Med* 2019. 380:2295-2306; 5. Davies MJ et al. *Diabetes Care* 2018;41:2669-2701. 6. ADA. *Diabetes Care* 2020;43(Suppl1):S98-S110.
7. Das SR et al. *J Am Coll Cardiol* 2018;72:3200-3223. 8. Arnett DK et al. *Circulation* 2019;140:e596-e646. 9. Cosentino F et al. *Eur Heart J* 2020;41:255-323.
10. Garber AJ et al. *Endocr Pract* 2020;26:107-139.
ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

Objective

- To update previous meta-analyses,[1-3] with data from VERTIS CV
- These results will further refine estimates of efficacy for CV and renal outcomes across the SGLT2 inhibitor class

SGLT2, sodium-glucose cotransporter 2.

1. Zelniker TA et al. *Lancet* 2019:393:31-39. 2. Zelniker TA et al. *Circulation* 2019;139:2022-2031. 3. Arnott C et al. *J Am Heart Assoc* 2020;9:e014908.

Studies included

- All analyses were primarily conducted on the total patient population of each of the 6 trials identified:
  - EMPA-REG OUTCOME[1]
  - CANVAS Trials Program[2]
    - CANVAS
    - CANVAS-R
  - DECLARE-TIMI 58[3]
  - CREDENCE[4]
  - VERTIS CV

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657. 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.
4. Perkovic V et al. *N Engl J Med* 2019; 380:2295-2306.

Meta-analysis methodology

- Hazard ratios and 95% confidence intervals were extracted from the literature to support a pooled meta-analysis across trials
- Fixed-effects modelling was performed with heterogeneity assessed using Cochran's Q test statistic, P value, and Higgins and Thompsons' I^2
- I^2 estimates the proportion of observed variance attributable to heterogeneity of effect beyond chance
  - Low: <25%
  - Moderate: 25%-75%
  - High: >75%

Meta-analysis methodology, cont'd

- Key outcomes:
  - Composite of MACE
  - CV death
  - Composite of HHF and CV death
  - HHF
  - Composite of renal outcomes
- Secondary analyses were performed on subgroups by presence or absence of ASCVD at baseline

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; HHF, hospitalization for heart failure.

Baseline characteristics of patient populations by trial

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]	CREDENCE[4]	VERTIS CV
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
N	7020	10,142	17,160	4401	8246
Duration of follow-up, median, years	3.1	2.4	4.2	2.6	3.0
Age, mean ± SD, years	63.1 ± 8.6	63.3 ± 8.3	63.9 ± 6.8	63.0 ± 9.2	64.4 ± 8.1
Female, %	28.5	35.8	37.4	33.9	30.0
HbA1c, mean ± SD, %	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2	8.3 ± 1.3	8.2 ± 1.0
Diabetes duration, mean ± SD, years	NA	13.5 ± 7.8	11.8 ± 7.8	15.8 ± 8.6	13.0 ± 8.3
Established CV disease, %	100	65.6	40.6	50.4	100
History of HF, %	10.1	14.4	10.0	14.8	23.7
Reduced kidney function (eGFR <60 mL/min/1.73 m^2), %	25.9	20.1	7.4	59.8	21.9

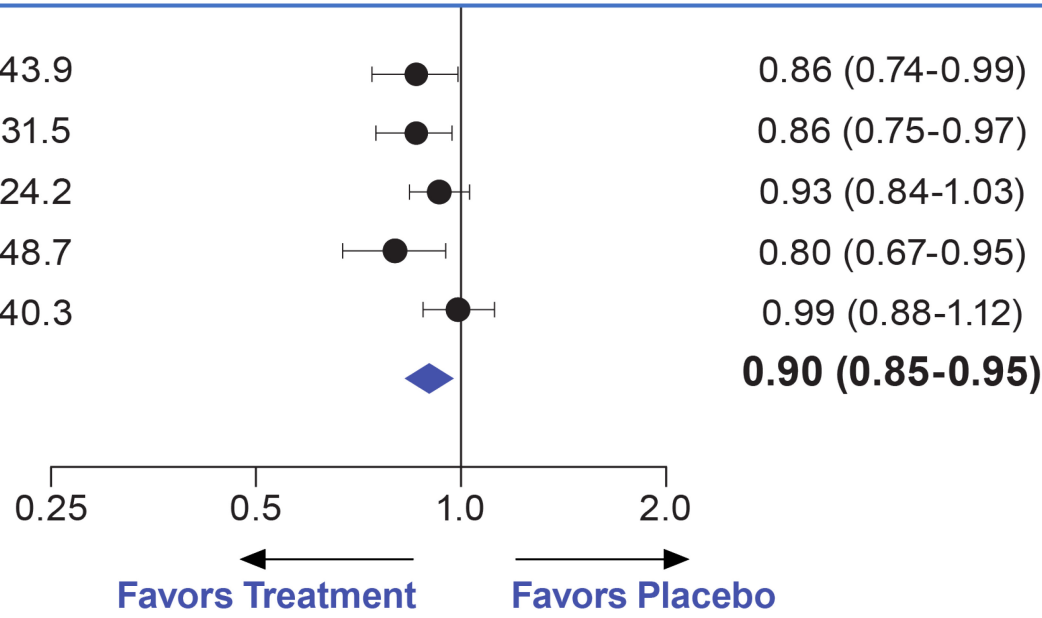
CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HF, heart failure; NA, not available; SD, standard deviation.

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657. 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.
4. Perkovic V et al. *N Engl J Med* 2019; 380:2295-306.

Time to first MACE

MACE

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	37.4	43.9	0.86 (0.74-0.99)
CANVAS Program	26.9	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	22.6	24.2	0.93 (0.84-1.03)
CREDENCE	38.7	48.7	0.80 (0.67-0.95)
VERTIS CV*	40.0	40.3	0.99 (0.88-1.12)
Pooled estimate			**0.90 (0.85-0.95)**
(Q statistic P = 0.27; I^2 = 23.4%)			

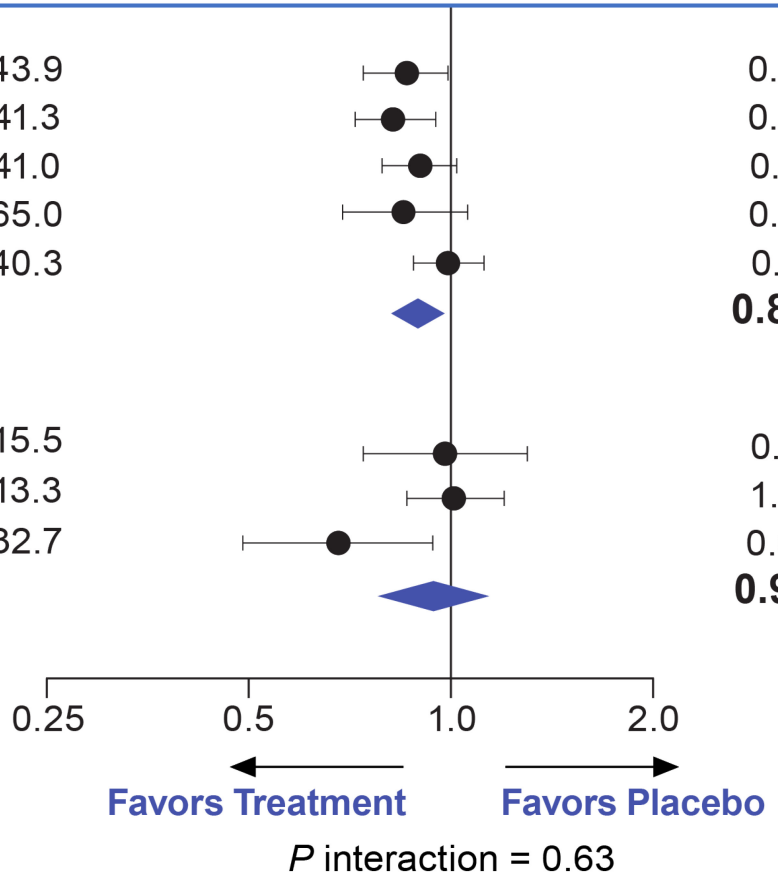


*Intention-to-treat population was used for consistency with other trials.
CI, confidence interval; MACE, major adverse cardiovascular events.

Time to first MACE – subgroup analysis by ASCVD

MACE

		Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
ASCVD	EMPA-REG OUTCOME	37.4	43.9	0.86 (0.74-0.99)
	CANVAS Program	34.1	41.3	0.82 (0.72-0.95)
	DECLARE-TIMI 58	36.8	41.0	0.90 (0.79-1.02)
	CREDENCE	55.6	65.0	0.85 (0.69-1.06)
	VERTIS CV	40.0	40.3	0.99 (0.88-1.12)
	Pooled estimate			**0.89 (0.84-0.95)**
	(Q statistic *P* = 0.34; I^2 = 11.8%)			
No ASCVD	CANVAS Program	15.8	15.5	0.98 (0.74-1.30)
	DECLARE-TIMI 58	13.4	13.3	1.01 (0.86-1.20)
	CREDENCE	22.0	32.7	0.68 (0.49-0.94)
	Pooled estimate			**0.94 (0.83-1.07)**
	(Q statistic *P* = 0.10; I^2 = 56.5%)			

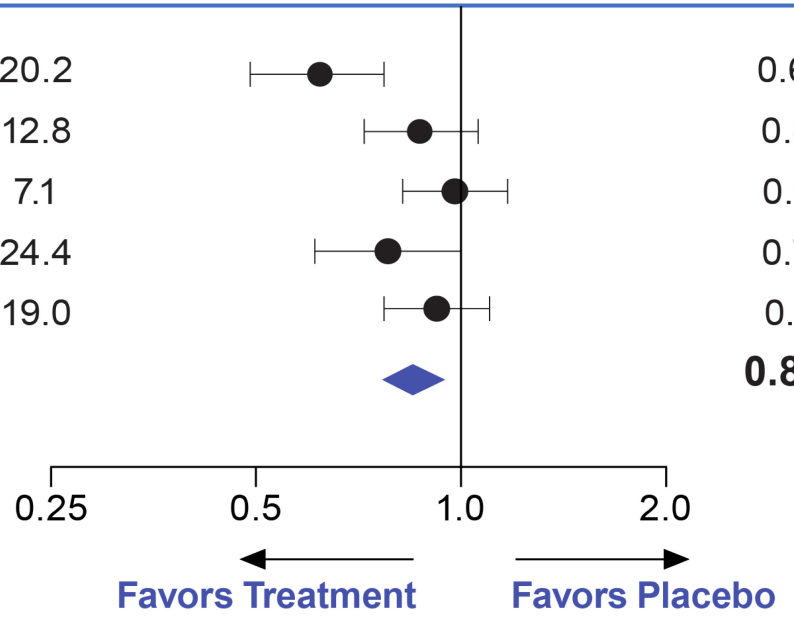


ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; MACE, major adverse cardiovascular events.

Time to CV death

CV DEATH

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	12.4	20.2	0.62 (0.49-0.77)
CANVAS Program	11.6	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	7.0	7.1	0.98 (0.82-1.17)
CREDENCE	19.0	24.4	0.78 (0.61-1.00)
VERTIS CV	17.6	19.0	0.92 (0.77-1.10)
Pooled estimate			**0.85 (0.78-0.93)**
(Q statistic P = 0.02; I^2= 64.3%)			

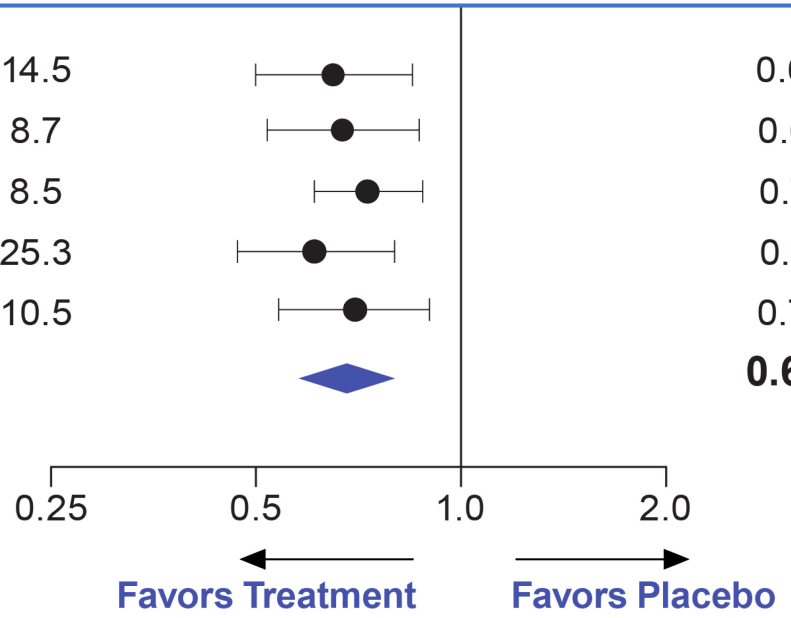


CI, confidence interval; CV, cardiovascular.

Time to first HHF

HHF

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	9.4	14.5	0.65 (0.50-0.85)
CANVAS Program	5.5	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	6.2	8.5	0.73 (0.61-0.88)
CREDENCE	15.7	25.3	0.61 (0.47-0.80)
VERTIS CV	7.3	10.5	0.70 (0.54-0.90)
Pooled estimate			**0.68 (0.61-0.76)**
(Q statistic P = 0.85; I^2= 0.0%)			

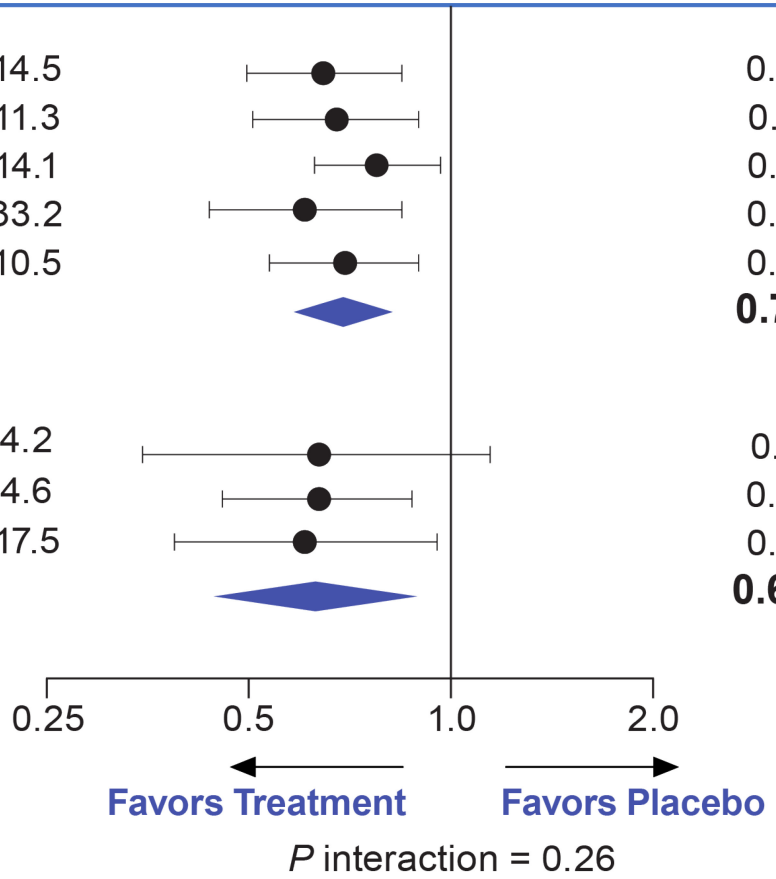


CI, confidence interval; HHF, hospitalization for heart failure.

Time to first HHF – subgroup analysis by ASCVD

HHF

		Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
ASCVD	EMPA-REG OUTCOME	9.4	14.5	0.65 (0.50-0.85)
	CANVAS Program	7.3	11.3	0.68 (0.51-0.90)
	DECLARE-TIMI 58	11.1	14.1	0.78 (0.63-0.97)
	CREDENCE	20.6	33.2	0.61 (0.44-0.85)
	VERTIS CV	7.3	10.5	0.70 (0.54-0.90)
	Pooled estimate			**0.70 (0.62-0.78)**
	(Q statistic P = 0.74; I^2 = 0.0%)			
No ASCVD	CANVAS Program	2.6	4.2	0.64 (0.35-1.15)
	DECLARE-TIMI 58	3.0	4.6	0.64 (0.46-0.88)
	CREDENCE	10.6	17.5	0.61 (0.39-0.96)
	Pooled estimate			**0.63 (0.50-0.80)**
	(Q statistic P = 0.99; I^2 = 0.0%)			

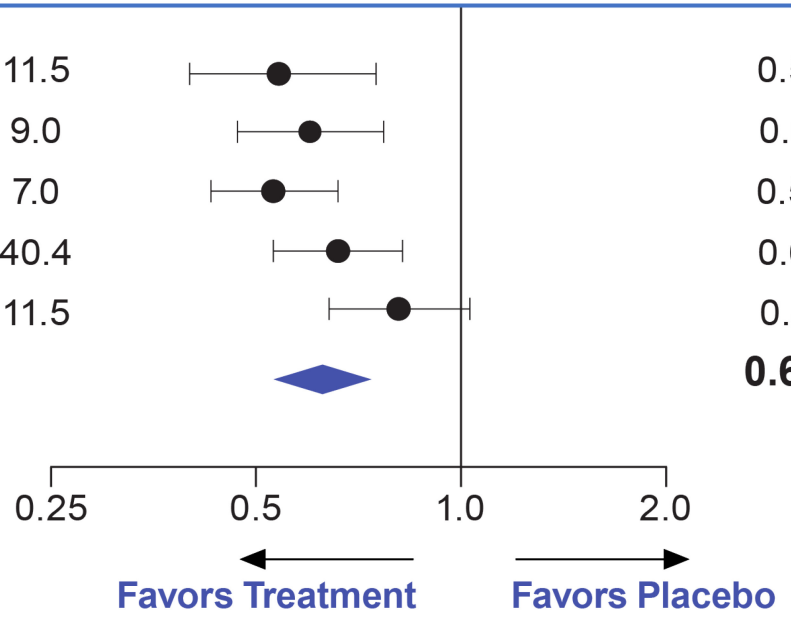


ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; HHF, hospitalization for heart failure.

Time to first renal composite outcome

RENAL COMPOSITE*

	Treatment Rate/1000 patient-years	Placebo Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	6.3	11.5	0.54 (0.40-0.75)
CANVAS Program	5.5	9.0	0.60 (0.47-0.77)
DECLARE-TIMI 58	3.7	7.0	0.53 (0.43-0.66)
CREDENCE	27.0	40.4	0.66 (0.53-0.81)
VERTIS CV	9.3	11.5	0.81 (0.64-1.03)
Pooled estimate			**0.62 (0.56-0.70)**
(Q statistic P = 0.09; I^2= 49.7%)			



*Renal composite outcome definitions varied across trials.
CI, confidence interval.

Summary: Meta-analyses

- Meta-analyses represent the totality of CV and renal outcomes data for the 4 SGLT2 inhibitors available in the US
- These results confirm that the effects of SGLT2 inhibitors on CV and renal outcomes are largely consistent across the class
  - Greatest magnitude of benefit is for reduction in risk for HHF and kidney disease progression
  - Estimates of effect on HHF risk were the most consistent across the trials
- Meta-analyses support contemporary society recommendations to prioritize the use of SGLT2 inhibitors, independent of glucose control considerations, in patients with type 2 diabetes with or at high risk for CV and renal complications

CV, cardiovascular; HHF, hospitalization for heart failure; SGLT2, sodium-glucose cotransporter 2.

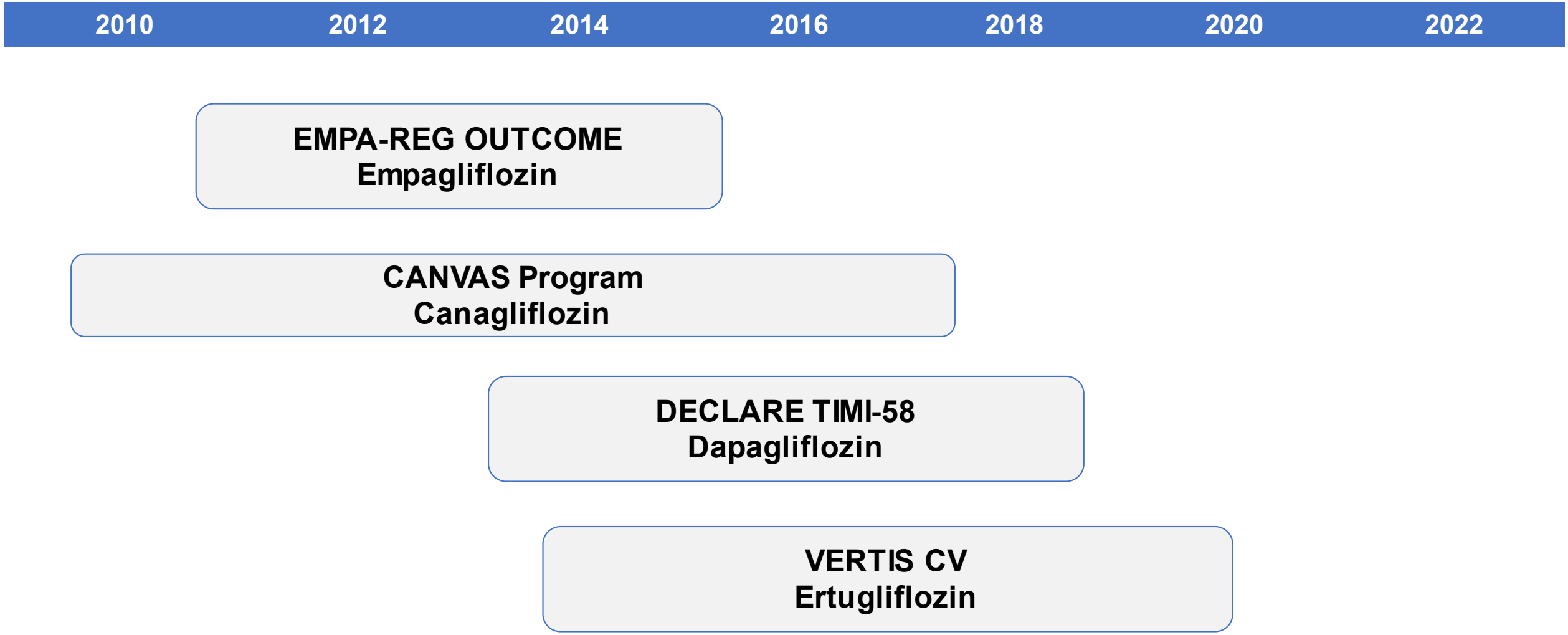
Overall Conclusions

David Cherney, MD, PhD
University of Toronto, Toronto, Ontario, Canada

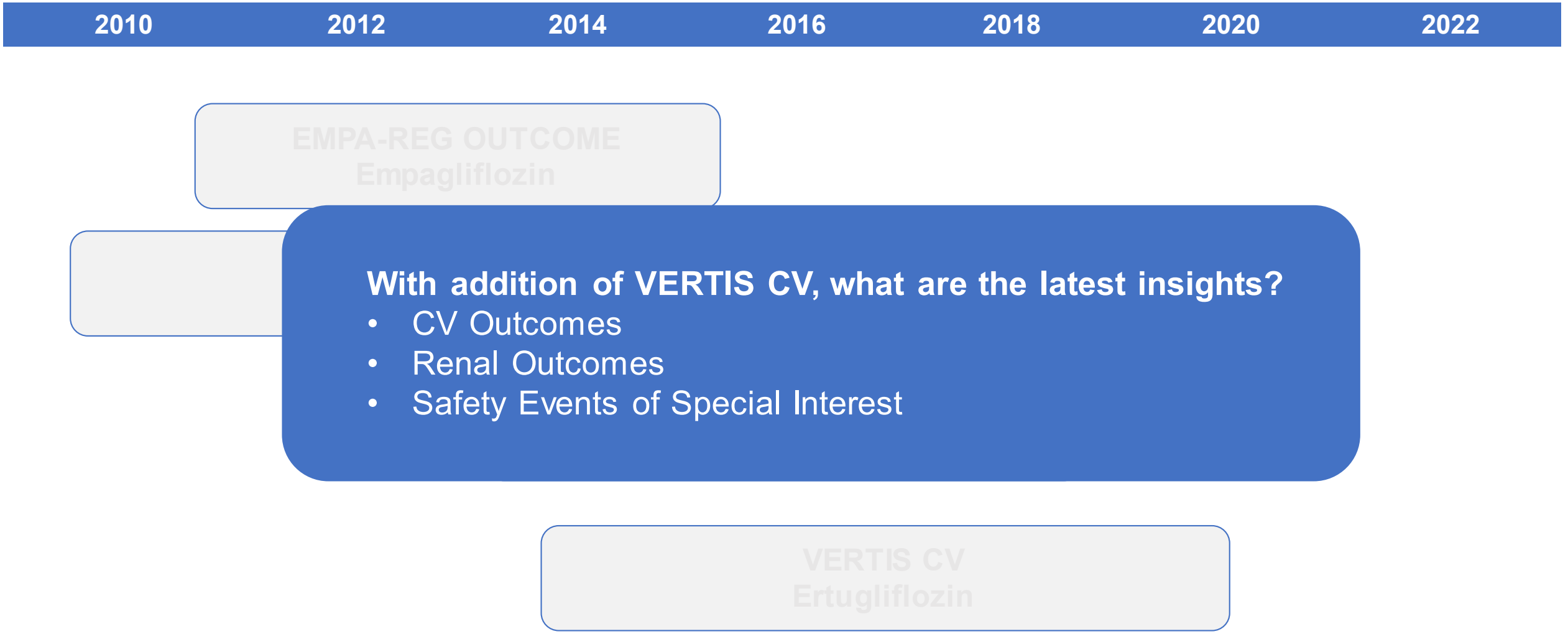
VERTIS

e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety

Timelines of SGLT2 inhibitor CV outcome trials designed to fulfill 2008 regulatory guidance



Timelines of SGLT2 inhibitor CV outcome trials designed to fulfill 2008 regulatory guidance



MACE

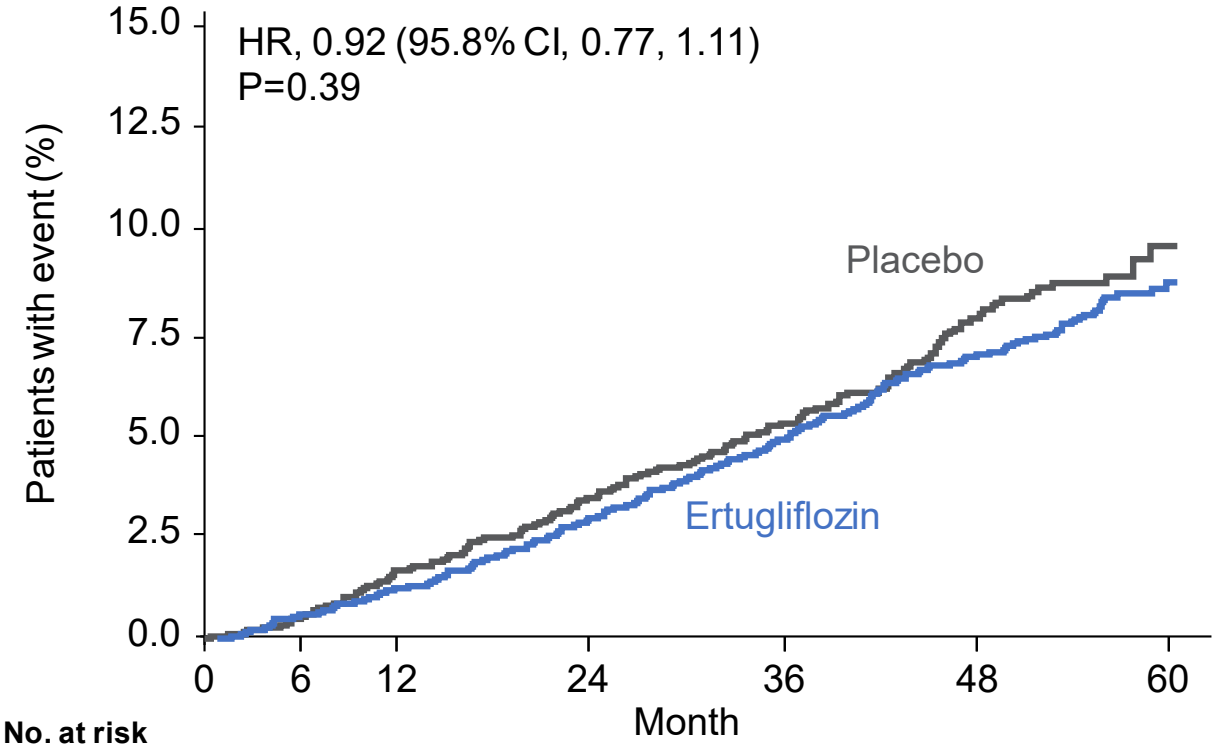
	MACE HR (95% CI)
EMPA-REG OUTCOME[1]	**0.86** (0.74, 0.99)
CANVAS Program[2]	**0.86** (0.75, 0.97)
DECLARE-TIMI 58[3]	**0.93** (0.84, 1.03)
VERTIS CV	**0.97** (0.85, 1.11)

MACE, major adverse cardiovascular events.

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

VERTIS CV: CV death and HHF*

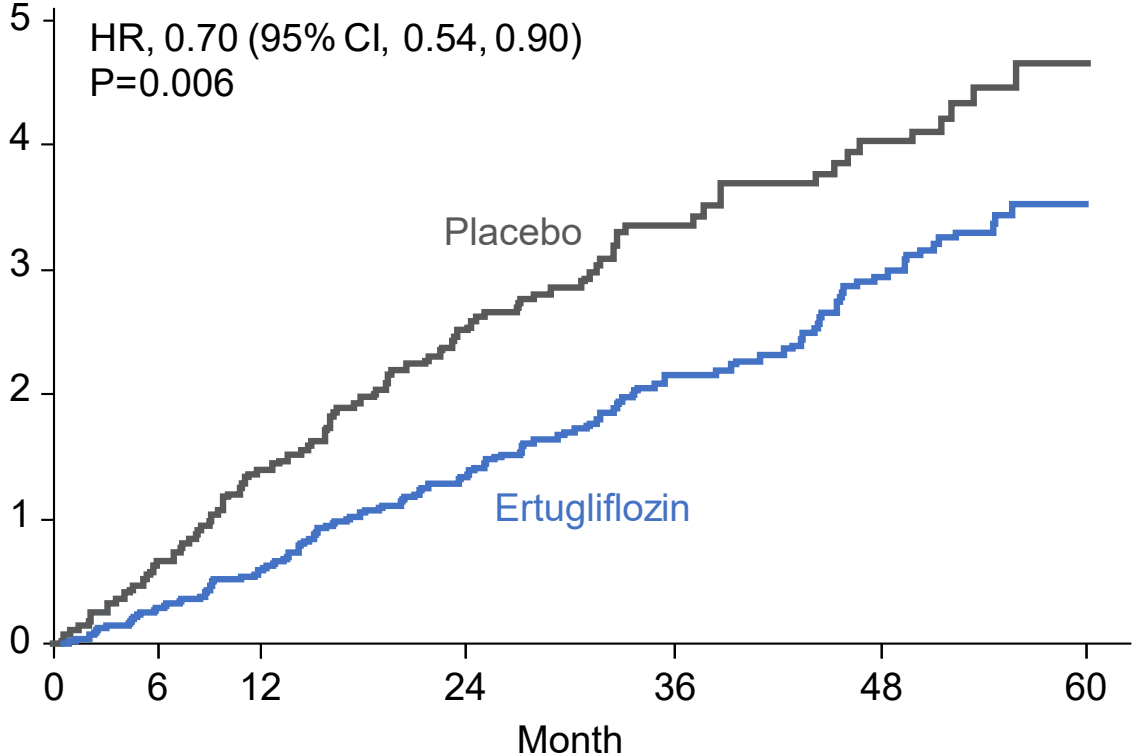
CV death



No. at risk							
Placebo	2747	2724	2684	2612	1423	1186	227
Ertugliflozin	5499	5436	5374	5245	2866	2409	438

CV death occurred in 6.2% of patients in the ertugliflozin group and 6.7% of patients in the placebo group

HHF



	2747	2701	2635	2534	1361	1119	219
	5499	5396	5297	5119	2766	2286	402

HHF occurred in 2.5% of patients in the ertugliflozin group and 3.6% of patients in the placebo group

*Intention-to-treat analysis set that included all randomized patients with no upper limit on the ascertainment window for the superiority outcomes (N=5499 for ertugliflozin and N=2747 for placebo).
CI, confidence interval; CV, cardiovascular; HFF, hospitalization for heart failure; HR, hazard ratio.

CV outcomes

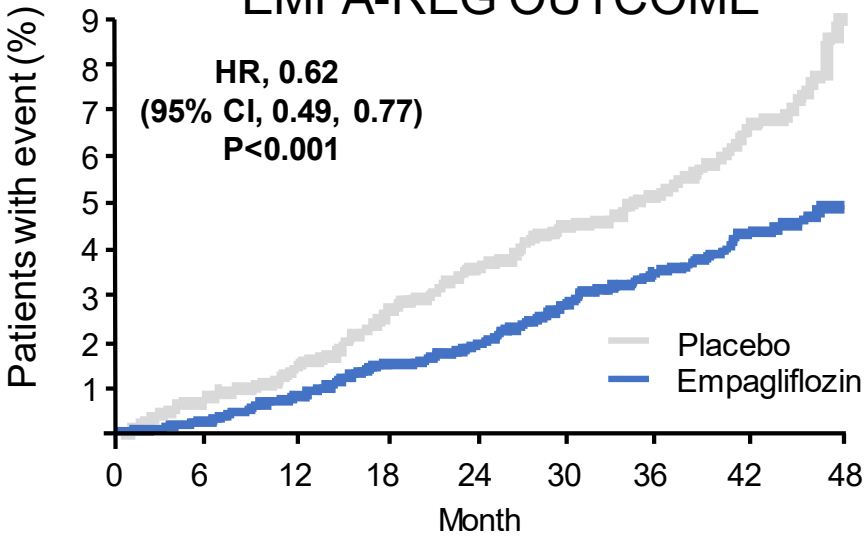
	MACE	CV Death	HHF
	HR (95% CI)	HR (95% CI)	HR (95% CI)
EMPA-REG OUTCOME[1]	**0.86** (0.74, 0.99)	**0.62** (0.49, 0.77)	**0.65** (0.50, 0.85)
CANVAS Program[2]	**0.86** (0.75, 0.97)	**0.87** (0.72, 1.06)	**0.67** (0.52, 0.87)
DECLARE-TIMI 58[3]	**0.93** (0.84, 1.03)	**0.98** (0.82 ,1.17)	**0.73** (0.61, 0.88)
VERTIS CV	**0.97** (0.85, 1.11)	**0.92** (0.77, 1.11)	**0.70** (0.54, 0.90)

CV, cardiovascular; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events.

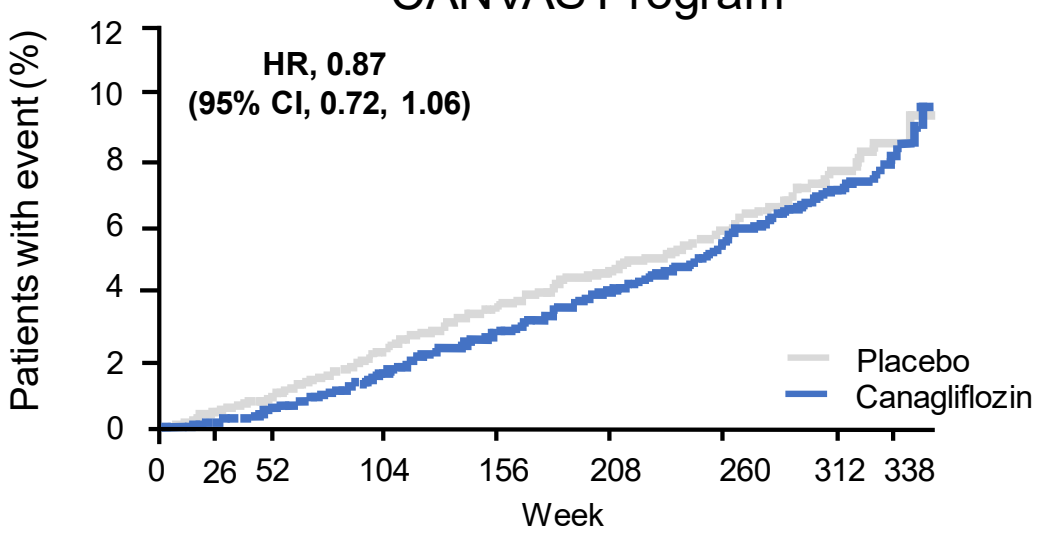
1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

CV death endpoint in SGLT2 inhibitor CV outcomes trials

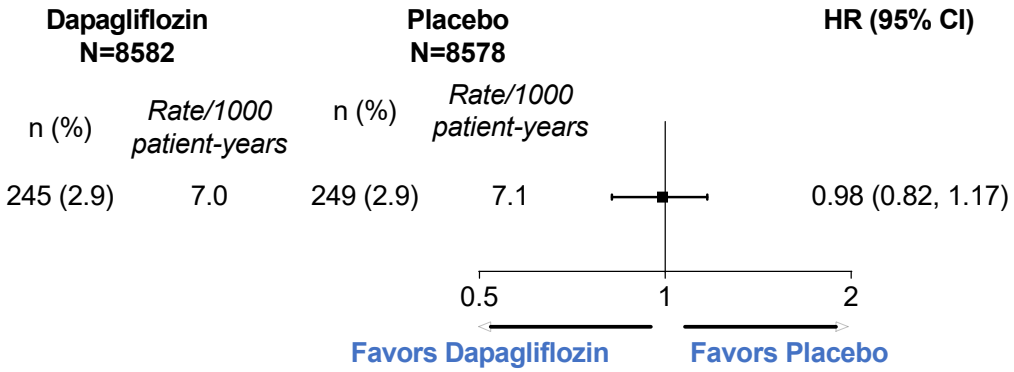
EMPA-REG OUTCOME[1]



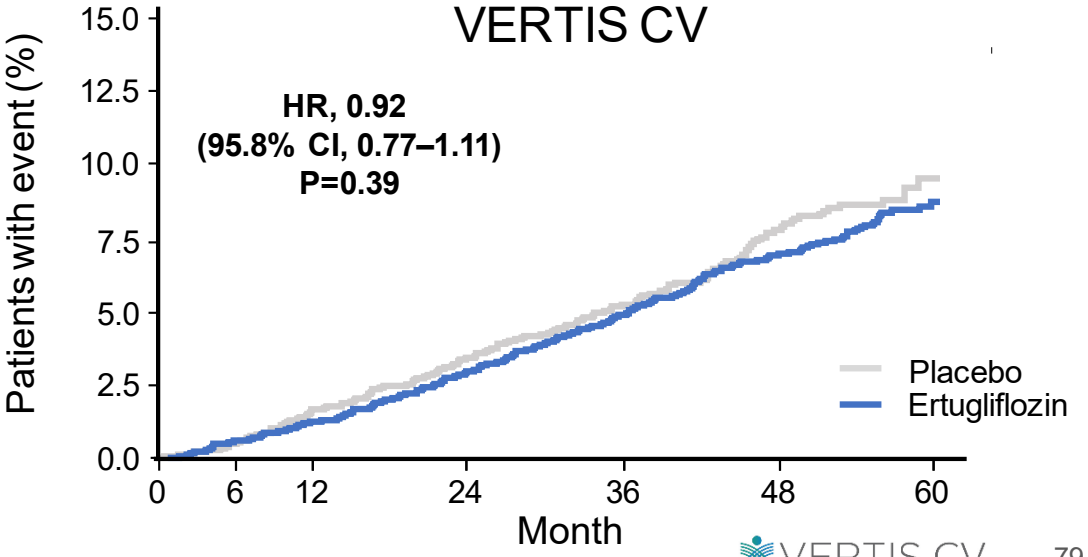
CANVAS Program[2]



DECLARE-TIMI 58[3]



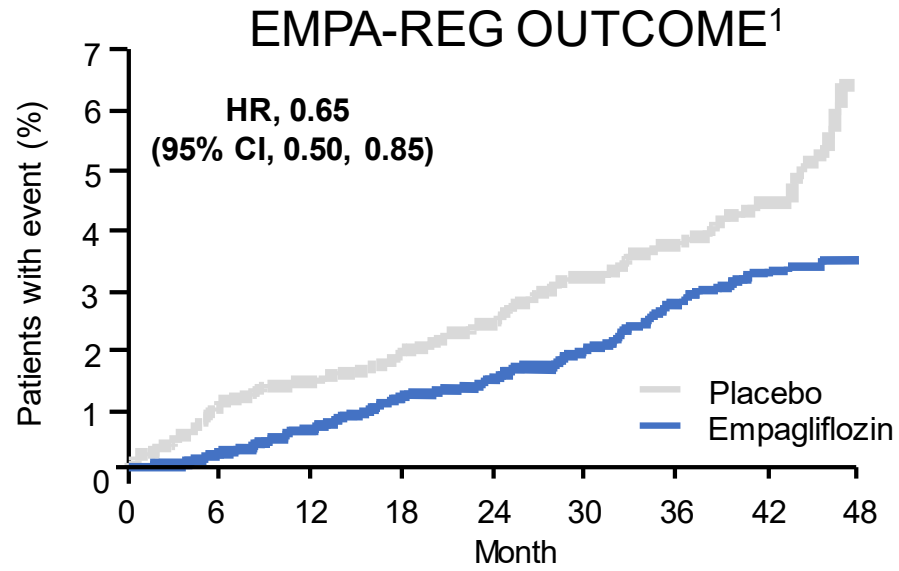
VERTIS CV

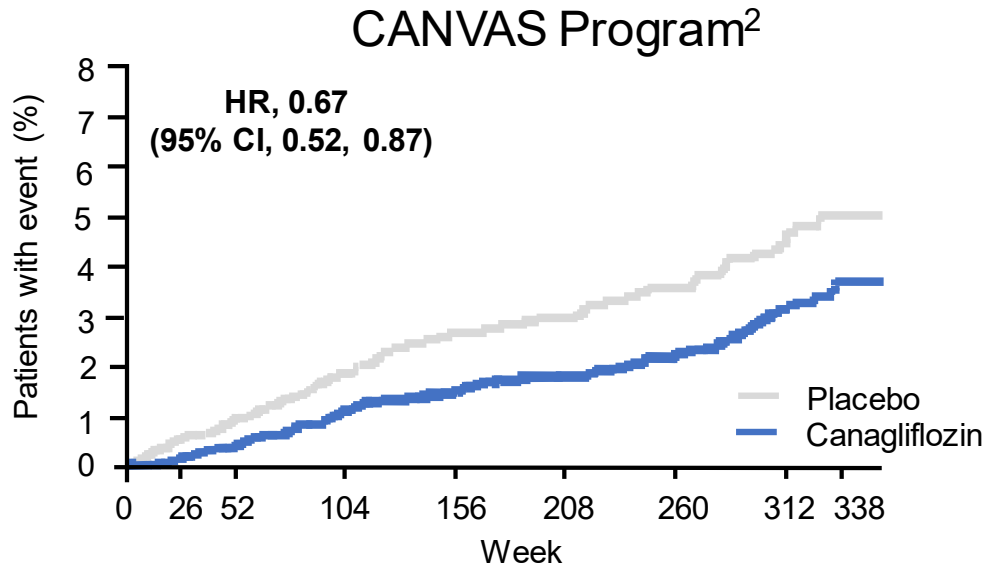


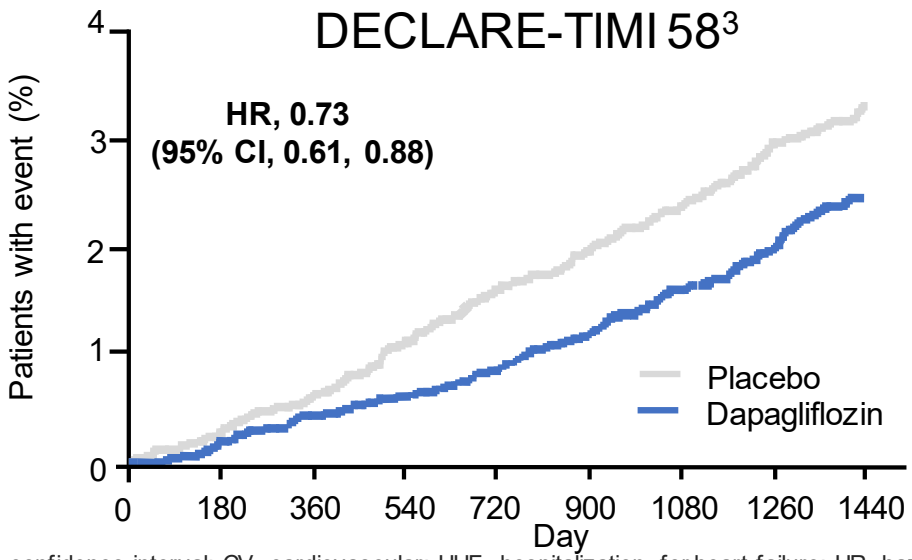
CI confidence interval; CV, cardiovascular; HR, hazard ratio

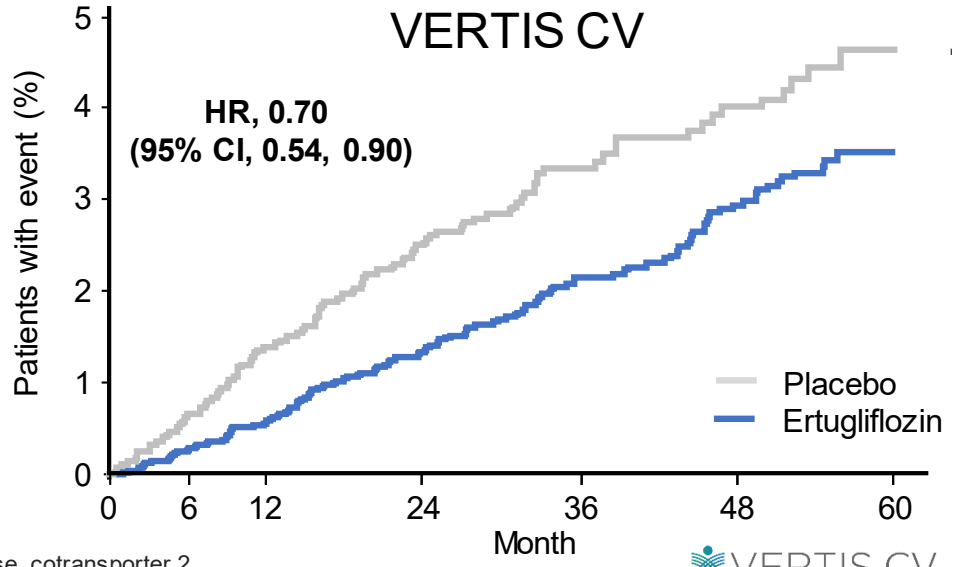
1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128; 2. Neal B et al. *N Engl J Med* 2017;377:644-657; 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

HHF outcomes in SGLT2 inhibitor CV outcomes trials









CI, confidence interval; CV, cardiovascular; HHF, hospitalization for heart failure; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357 (figure provided by D.K. McGuire, with permission).

CV outcomes

	MACE	CV Death	HHF
	HR (95% CI)	HR (95% CI)	HR (95% CI)
EMP OU			85)
CANVA			87)
DECLA			88)
VE			.90)

MACE:

- MACE efficacy across class generally modest
  - EMPA-REG OUTCOME significant on MACE due to effect on CV death and no effect on MI or stroke
  - CANVAS significant on MACE due to contribution from MI, CV death, and stroke
  - DECLARE and VERTIS CV only found trend on MACE

CV Death:

- Only EMPA-REG OUTCOME found significant reduction, driving heterogeneity in the beneficial effect for the class

HHF:

- Consistent effects across class are substantial
- Benefits are independent of baseline ASCVD, prior HF, and across spectrum of baseline eGFR

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128; 2. Neal B et al. *N Engl J Med* 2017;377:644-657;
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

Why do MACE and CV death results differ across SGLT2 inhibitor trials?

- **Differences in mechanism?**
  - SGLT2 vs SGLT1 specificity? Off-target effect?
- **Differences in patient populations studied?**
  - Secondary prevention populations studied?
    - Broadly similar with MACE event rates on par with high-risk group (~4%/year)
  - Regional differences?
- **Differences in study design?**
  - Sample size?
  - Inclusion/exclusion criteria?
  - Definition of endpoints?
  - Collection of data/endpoints?
  - Analysis of endpoints?
- **Differences in comorbidity management after 2015?**
  - More intensive BP goals after SPRINT reported and guidelines updated?
  - More intensive lipid management after PCSK9 inhibitor trials reported and guidelines updated?

Renal outcomes

	Renal-related Composite Outcomes
EMPA-REG OUTCOME[1]	Doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease
CANVAS Program[2]	Sustained 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes
DECLARE-TIMI 58[3]	Sustained ≥40% decrease in eGFR to <60 mL/min/1.73 m^2, end-stage renal disease, or death from renal causes
VERTIS CV	Renal death, dialysis/transplant, or doubling of serum creatinine from baseline

CV, cardiovascular; eGFR, estimated glomerular filtration rate.

1. Wanner C et al. *N Engl J Med* 2016;374:323-334. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

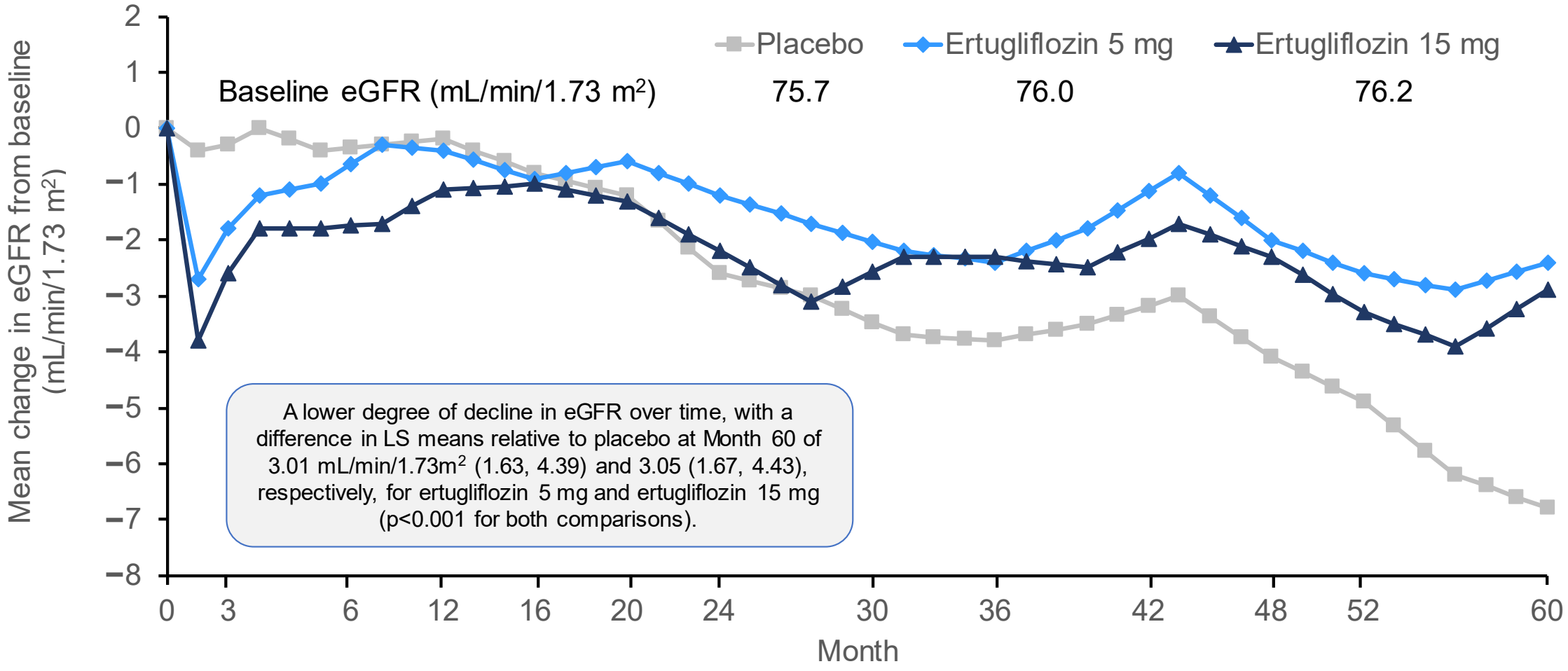
Renal outcomes

	Renal-related Composite Outcomes	HR (95% CI)
EMPA-REG OUTCOME[1]	Doubling of the serum creatinine level, initiation of renal-replacement therapy, or death from renal disease	**0.54 (0.40, 0.75)**
CANVAS Program[2]	Sustained 40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.60 (0.47, 0.77)**
DECLARE-TIMI 58[3]	Sustained ≥40% decrease in eGFR to <60 mL/min/1.73 m^2, end-stage renal disease, or death from renal causes	**0.53 (0.43, 0.66)**
VERTIS CV	Renal death, dialysis/transplant, or doubling of serum creatinine from baseline	**0.81** (0.63, 1.04)

CV, cardiovascular; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

1. Wanner C et al. *N Engl J Med* 2016;374:323-334. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

VERTIS CV: eGFR over time



eGFR, estimated glomerular filtration rate.

Renal Outcomes

Renal-related Composite Outcomes

HR (95% CI)

EMP/ OUT

CANVAS

DECLAR

VERT

Although other CV outcomes trials showed renal outcomes benefit, VERTIS CV only showed a trend in this initial renal analysis

VERTIS CV showed:

- Effect on kidney-related outcomes generally consistent with other SGLT2 inhibitor trials
- Effects on acute and chronic eGFR consistent with other SGLT2 inhibitors
- Renal AEs in line with SGLT2 inhibitor class

Definitions of renal-related composite outcomes vary across trials

AE, adverse event; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; SGLT2, sodium-glucose cotransporter 2.

1. Wanner C et al. *N Engl J Med* 2016;374:323-334. 2. Neal B et al. *N Engl J Med* 2017;377:644-657. 3. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

Safety events of special interest

Event	Empagliflozin[1]		Canagliflozin[2]		Canagliflozin[3]		Dapagliflozin[4]		Ertugliflozin	
	EMPA-REG OUTCOME		CANVAS and CANVAS-R		CREDENCE		DECLARE-TIMI 58		VERTIS CV	
	Empagliflozin N=4687	Placebo N=2333	Canagliflozin N=5790	Placebo N=4344	Canagliflozin N=2200	Placebo N=2197	Dapagliflozin N=8574	Placebo N=8569	Ertugliflozin N=5493	Placebo N=2745
	n (%)		Rate/1000 patient-years		Rate/1000 patient-years		n (%)		n (%)	
			n (%)		n (%)					
Amputation	88 (1.9)	43 (1.8)	6.3	3.4	12.3	11.2	123 (1.4)	113 (1.3)	111 (2.0)	45 (1.6)
			140 (2.4)	47 (1.1)	70 (3.2)	63 (2.9)				

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Perkovic V et al. *N Engl J Med* 2019;380:2295-2306. 4. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

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	Empagliflozin N=4687	Placebo N=2333	Canagliflozin N=5790	Placebo N=4344	Canagliflozin N=2200	Placebo N=2197	Dapagliflozin N=8574	Placebo N=8569	Ertugliflozin N=5493	Placebo N=2745
	n (%)		Rate/1000 patient-years n (%)		Rate/1000 patient-years n (%)		n (%)		n (%)	
Fracture	179 (3.8)	91 (3.9)	15.4 NA	11.9 NA	11.8 67 (3.0)	12.1 68 (3.1)	457 (5.3)	440 (5.1)	201 (3.7)	98 (3.6)
Diabetic Ketoacidosis	4 (0.1)	1 (<0.1)	0.6 NA	0.3 NA	2.2 11 (0.5)	0.2 1 (<0.1)	27 (0.3)	12 (0.1)	19 (0.3)	2 (0.1)

1. Zinman B et al. *N Engl J Med* 2015;373:2117-2128. 2. Neal B et al. *N Engl J Med* 2017;377:644-657.
3. Perkovic V et al. *N Engl J Med* 2019;380:2295-2306. 4. Wiviott SD et al. *N Engl J Med* 2019;380:347-357.
NA, not available.

Summary and conclusions

- VERTIS CV achieved its primary endpoint of non-inferiority for MACE compared with placebo in patients with T2DM and established ASCVD, demonstrating the CV safety of ertugliflozin
- VERTIS CV provides further evidence of the CV safety of SGLT2 inhibitors for the treatment of patients with T2DM and adds to the evidence of benefit on HHF consistent across the class
- VERTIS CV safety data do not alter estimates of risk for any specific safety events
- Meta-analyses support contemporary society recommendations to prioritize the use of SGLT2 inhibitors, independent of glucose control considerations, in patients with T2DM with or at high risk for CV and renal complications

CV, cardiovascular; SGLT2, sodium-glucose cotransporter 2; T2DM, type 2 diabetes mellitus.

Acknowledgments

- We thank
  - all the patients who volunteered to enroll in VERTIS CV
  - the National Retention Experts
    - Argentina (Diego Aizenberg), Australia (Anthony Roberts), Bosnia (Azra Durak-Nalbantic), Bulgaria (Dimitar Raev), Canada (Thomas Ransom), Colombia (Jose Luis Accini-Mendoza), Croatia (Silvija Canecki-Varzic), Czech Republic, Georgia (Elene Giorgadze), Greece (Konstantinos Tsioufis), Hong Kong (Katheryn Tan Choon Beng), Hungary, Israel (Basil Lewis), Italy (Piermarco Piatti), Korea (Bong Soo Cha), Latvia (Valdis Pirags), Lithuania (Vaidotas Urbanavicius), Mexico (Pedro Alberto Garcia Hernandez), Netherlands, New Zealand (Scott Russell), Philippines (Florence Santos), Poland (Monika Lukaszewicz), Romania (Noemi Pletea), Russia (Svetlana Berns), Serbia (Teodora Beljic Zivkovic), Slovakia, South Africa (Larry Distiller), Sweden, Taiwan (Dee Pei), Thailand (Clara Chow), Turkey, Ukraine (Oleksandr Parkhomenko), United Kingdom (Manish Saxena), United States (William French). Countries without an NRE listed were overseen by the Baim Institute for Clinical Research (Christopher Cannon, Julie Sutherland, Jessica Lamp, Hoey Chyi Lim)

- The representatives from the 531 enrolling centers in 34 participating countries:

Argentina: Jose Maria Pozzi, Laura Maffei, Lucrecia Nardone, Horacio Sessa, Daniela Garcia Brasca, Diego Aizenberg, Claudia Emilce Baccaro, Elizabeth Silvana Gelersztein, Fabian Calella Pedro Rosario, Ricardo Leon de la Fuente, Silvia Gorban de Lapertosa, Natacha Maldonado, Adrian Cruciani, Ines Bartolacci, Eduardo Hasbani, Gustavo Frechtel, Nelson Rodriguez Papini, Alejandro Pereyra, Oscar Montana, Cesar Zaidman, Maria Mansilla; **Australia**: Bronte Ayres, Richard Simpson, Sarah Glastras, Maged William, Timothy Davis, David Colquhoun, Joseph Proietto, Adam Roberts, Anthony Roberts, Bronwyn Stuckey, Gary Wittert, Georgia Soldatos, Parind Vora; **Bosnia and Herzegovina**: Zumreta Kusljugic, Azra Avdagic, Azra Durak-Nalbantic, Kanita Ibrahimpasic, Bosanko Horozic, Muhamed Spuzic, Valentina Soldat-Stankovic, Dragan Stevanovic, Damir Koco, Zaim Jatic, Ibrahim Terzic, Ljiljana Markovic Potkonjak, Besim Prnjavorac, Aleksandar Radanovic, Muhamed Salihbasic; **Bulgaria**: Dimitar Dimitrov, Anastas Stoikov, Velichka Damyanova, Darina Vasileva, Kiril Kirilov, Ivailo Lefterov, Lyudmila Lyubenova, Dimitar Raev, Veska Tsanova, Mitko Mitkov, Rositsa Shumkova, Kostadin Kichukov, Tatyana Simeonova-Nikolova; **Canada**: Jean-Marie Ekoe, Shekhar A. Pandey, Richard Dumas, Vincent Woo, Kevin Saunders, James Conway, Laurie Breger, Christian Constance, Michael O'Mahony, Patrice Perron, Claude Garceau, Michael Csanadi, Ronald Bourgeois, Timothy Salter, Andre Frechette, Ariel Diaz, Thomas Ransom; **Colombia**: Gregorio Sanchez-Vallejo, Sandra Isabel Barrera Silva, Jose Accini Mendoza, Luis Garcia Ortiz, Hernan Yupanqui Lozno, Dora Molina de Salazar, Julian Coronel Arroyo; **Croatia**: Pocanic Darko, Srecko Tusek, Sonja Slosic Weiss, Canecki-Varzic Silvija, Altabas Velimir, Zukanovic Sidbela, Tatjana Cikac, Jasna Vucak, Ljiljana Cenan, Zrinka Boljkovac, Srecko Margetic, Ksenija Kranjcevic; **Czech Republic**: Vera Adamkova, Kyselova Pavlina, Bedrich Wasserburger, Tomas Hrdina, Katerina Smolenakova; **Georgia**: Chagunava Ketevan, Zurab Pagava, Merab Mamatsashvili, Koba Burnadze, Vakhtang Chumburidze, Zaza Lominadze, Lali Nikoleishvili, Bondo Kobulia, Nana Koberidze, Nodar Emukhvari, Zviad Kipiani, David Metreveli, Salome Glonti, Elene Giorgadze, Tamaz Shaburishvili, Gulnara Chapidze, Julieta Gulua, Irakli Gogorishvili, Ekaterine Berukashvili, Shalva Petriashvili, Givi Kurashvili; **Greece**: Moses Elisaf, Stavros Bousboulas, Nikolaos Tentolouris, Konstantinos Tsioufis; **Hong Kong**: Andrea Luk, Kelvin Kai Hang Yiu, Chiu Chi Tsang, Vincent Tok Fai Yeung, Alex Pui-Wai Lee, Kathryn Choon Beng Tan, Ronald Ching Wan Ma; **Hungary**: Krisztina Beatrix Wudi, Zoltan Bujtor, Zsuzsanna Feher, Laszlo Koranyi, Gyorgy Paragh, Szilard Vasas, Zsolt Pauker, Nora Kesmarki, Janos Takacs, Laszlo Nagy, Csaba Salamon, Zsuzsanna Papp, Csaba Hajdu; **Israel**: Galina Abramov, Osamah Hussein, Victor Vishlitzky, Dror Dicker, Mahmud Darawsha, Baruch Itzhak, Dov Gavish, Julio Wainstein, Basil Lewis, Eliezer Klainman, Amos Katz, Mazen Elias, Rosane Ness-Abramof, Tony Hayek; **Italy**: Emanuela Orsi, Giuseppe Lembo, Piermarco Piatti, Agostino Consoli, Sergio Berti, Giuseppe Pugliese, Giuseppe Derosa; **Republic of Korea**: Hak Chul Jang, Moon-Kyu Lee, Nam Hoon Kim, Bong-Soo Cha, Kyong Soo Park, Kun Ho Yoon, Chul Woo Ahn, Kwan Woo Lee, Sei Hyun Baik; **Latvia**: Valdis Pirags, Sigita Pastare; **Lithuania**: Jurate Kavaliauskiene, Audrone Augusteniene, Antanas Navickas, Vaidotas Urbanavicius, Roma Kavaliauskiene, Ausra Sirutaviciene; **Mexico**: Guillermo Antonio Llamas Esperon, Juan Villagordoa Mesa, Pedro Alberto Garcia Hernandez, Rosa Luna Ceballos, Carlos Aguilar Salinas, Guillermo Gonzalez Galvez, Guillermo Melendez-Mier, Raul Aguilar Orozco; **Netherlands**: Harry Crijns, Klaas Hoogenberg; **New Zealand**: Helen Lunt, Russell Scott, John Baker, Michael Williams; **Philippines**: Marian Denopol, Araceli Panelo, Louie Tirador, Grace Aquitania, Gregorio Rogelio, Florence Amorado-Santos, Ramoncito Habaluyas, Allyn Sy Rosa, Ellen Palomares, Geraldine Ebo, Chela Marie Romero; **Poland**: Joanna Gladczak, Jaroslaw Hawryluk, Edward Franek, Monika Lukaszewicz, Aleksandra Madej-Dmochowska, Anna Jeznach-Steinhagen, Grzegorz Sokolowski, Jan Ruxer, Agnieszka Karczmarczyk, Ewa Krzyzagorska, Iwona Wozniak, Anna Olech-Cudzik, Marek Dwojak, Izabela Anand, Krzysztof Strojek, Ewa Czernecka, Karolina Antkowiak-Piatyszek, Aleksandra Rozanska, Waldemar Gadzinski, Piotr Mader, Monika Kuligowska-jakubowska, Malgorzata Arciszewska, Andrzej Stankiewicz, Katarzyna Cypryk, Andrzej Wittek, Joanna Sawer-Szewczyk; **Romania**: Gabriela Negrisanu, Noemi Pletea, Daniela Zaharie, Ella Pintilei, Adriana Cif, Livia Duma, Iosif Szilagyi, Ildiko Halmagyi, Magdalena Morosanu, Mircea Munteanu, Adrian Albota, Alexandrina Popescu, Dan Anton Enculescu, Nicolae Hancu, Valerica Nafornita, Lacramioara Croitoru;

Russian Federation: Elena Pavlysh, Konstantin Nikolaev, Alexandr Vishnevsky, Olga Reshetko, Liudmila Kvitkova, Olga Barbarash, Tatiana Rodionova, Oxana Shaydyuk, Olga Ershova, Petr Chizhov, Svetlana Berns, Elena Rechkova, Sergey Yakushin, Olga Zanozina, Yuri Lukyanov, Elena Vorobeva, Dmitry Zateyshchikov, Nelly Verbovaya, Olga Bolshakova, Oleg Khrustalev, Leonid Strongin, Irina Bondar, Alsu Zalevskaya, Ekaterina Filippova, Galina Chumakova, Alexey Repin, Alexey Panov; **Serbia**: Teodora Beljic Zivkovic, Milan Petakov, Mirjana Sumarac-Dumanovic, Georgina Pudar Brankovic, Aleksandra Kendereski, Stevo Stojic, Djuro Macut; **Slovakia**: Jana Babikova, Miriam Teplanova, Livia Tomasova, Emil Martinka, Beata Lachova, Gabriela Ivancova, Jana Rociakova, Zbynek Schroner, Viera Donicova, Adriana Ilavska, Katarina Raslova; **South Africa**: Lawrence Distiller, Heidi Siebert, Aysha Badat, Suzanne Blignaut, Mahomed Sarvan, Thirumani Govender, Mashra Gani, Hendrik Nortje, Mohamed Mookadam, Puvanesveri Naiker, Douwe de Jong, Louis Van Zyl, Mary Seeber, Dorothea Urbach-Bolus, Junaid Bayat, Warren Boyd, Margaretha du Toit, Zelda Punt, Susan Arnold; **Sweden**: Luts Anders, Lundvall Martin, Lindholm Carl-Johan, Tengmark Bengt-Olov, Curiac Dan, Bosson Peter, Koskinen Pekka; **Taiwan**: Chen-Ling Huang, Ju-Ying Jiang, Te-Lin Hsia, Kwo-Chang Ueng, Wei-Shiung Yang, Yung-Chuan Lu, Chwen-Yi Yang, Wayne Huey-Herng Sheu, Chern-En Chiang, Hung-I Yeh; **Thailand**: Sompongse Suwanwalaikorn, Natapong Kosachunhanun, Suchai Sritippayawan, Sirakarn Tejavanija, Songkwan Silaruks; **Turkey**: Mustafa Araz, Ramazan Sari, Dilek Sensoz Berker; **Ukraine**: Olga Godlevska, Ivan Chopey, Zinaida Teliatnikova, Petro Kuskalo, Orest Abrahamovych, Borys Mankovskyi, Ivan Fushtey, Galyna Myshanych, Susanna Tykhonova, Vira Tseluyko, Olena Koval, Oleksandr Parkhomenko, Oleksandr Prokhorov, Myroslava Vayda, Larysa Martymianova, Viktoriia Zharinova, Lyudmyla Prystupa, Larysa Pererva, Oleksandr Kovalov, Lyubov Sokolova, Volodymyr Botsyurko, Vitaliy Maslyanko, Maryna Vlasenko, Tetyana Khomazyuk, Anna Kulyk, Volodymyr Synenko, Oleksandr Karpenko, Yuriy Mostovoy, Olga Gyrina, Maryna Dolzhenko, Oleksandra Donets, Inna Sorokina, Yaroslav Malynovsky, Olena Lysunets, Roman Petrovskyy, Svitlana Panina; **United Kingdom**: Anthony Avornyo, Susannah Eyre, John Ryan, Glenn Cardwell, Anthony Robinson, Rebecca Clark, Basil Issa, Devinda Weeraratne, Rory McCrimmon, Thomas Jones, Sam Philip, Ronnie Beboso, Melanie Davies, Christina Kyriakidou, Manish Saxena, Hawys Thomas, Madhu Gowda, Imrozia Arif, Babatunde Oyesile, John Cecil; **United States**: Olakunle Akinboboye, Laura Akright, Chander Arora, Eric Ball, Sabrina Benjamin, Matthew Budoff, Harold Cathcart, Nizar Daboul, Paul Denker, Andrew Garner, Serge Jabbour, Naseem Jaffrani, Robert Jeanfreau, Thomas Knutson, Michael Lillestol, Donald McNeil, Samer Nakhle, William Randall, Jyothi Mallepalli, Jay Schmidt, Jorge Serje, James Shoemaker, Daniel Storey, Alberta Warner, Severino Pimentel, Luis Quintero, Juan Galvez, David Bernard, Humberto Cruz, Philip O'Donnell, Hemant Thawani, Ehab Sorial, Arthur Schwartzbard, John Agaiby, Bernard Garcia, Clancy Cone, Ankur Doshi, Ali Iranmanesh, Ildiko Lingvay, Kimberly Smith, Barry McLean, Joel Neutel, Adeniyi Odugbesan, Teresa Sligh, Kurt Lesh, Kathryn Rohr, Dilawar Ajani,Jerome Daniel, George Cornett, Gary Dykstra, Sharan Mahal, Michael Adams, David Ramstad, Ahmed Arif, Earl Martin, Ramon Sastre, Sunny Srivastava, Lawrence Feld, Kelvin Bush, Vinay Shah, Sarah Konigsberg, Mohammed Allaw, Richard Kelly, Brian MacGillivray, Michael McGuire, Debra Weinstein, Madhusudan Budhraja, Naeem Tahirkheli, Josefa Binker, Marc Bernstein, Nabil Andrawis, Shuaib Abdullah, Tom Christensen, Misal Khan, Mahfouz El Shahawy, Devjit Tripathy, Nandkishore Ranadive, Paul Grena, Betty Villafuerte, Charles Cook, Jose Bautista, Isam Marar, Christian Kaunzinger, Neville Bittar, Juan Frias, Rajesh Davit, Harold Bays, Robert Cohen, William Garvey, Stephen Smith, Jose-Luis Ruiz, Aaron Hartman, James Diener, Ronald Chochinov, John Hunter, Stephen Aronoff, Larry Reed, John Evans, Jeremy Ackermann, James Haaksma, Aurelio Torres-Consuegra, Jalil Khan, Kabir Yousuf, Lidia Bermudez, Benjamin Lumicao, Jorge Torres Olmeda, Evan Kessler, Michael Winnie, Robert Lending, Naveed Razzaque, Michael McCartney, Francisco Munoz, Robert Buynak, Lilia Rodriguez Ables, Sashi Makam, Josefina Lozano, Henry Paez, Ashwini Gore, Amer Al-Karadsheh, Bassem Masri, Sushma Gorrela, Jessie Louise Al-Amin, Firas Alani, Jason Haffizulla, Ron Hsieh, Luis Castillo Hernandez, Merle Turner, William French, Preetham Jetty, Mae Sheikh-Ali, Richard Leggett, Richard Perlman, Gary Goldstein.

VERTIS

e**V**aluation of **E**RTugliflozin eff**I**cacy and **S**afety