Into The Combo Era: Evolving Role Of DPP4i & SGLT2i With Complementary Effects

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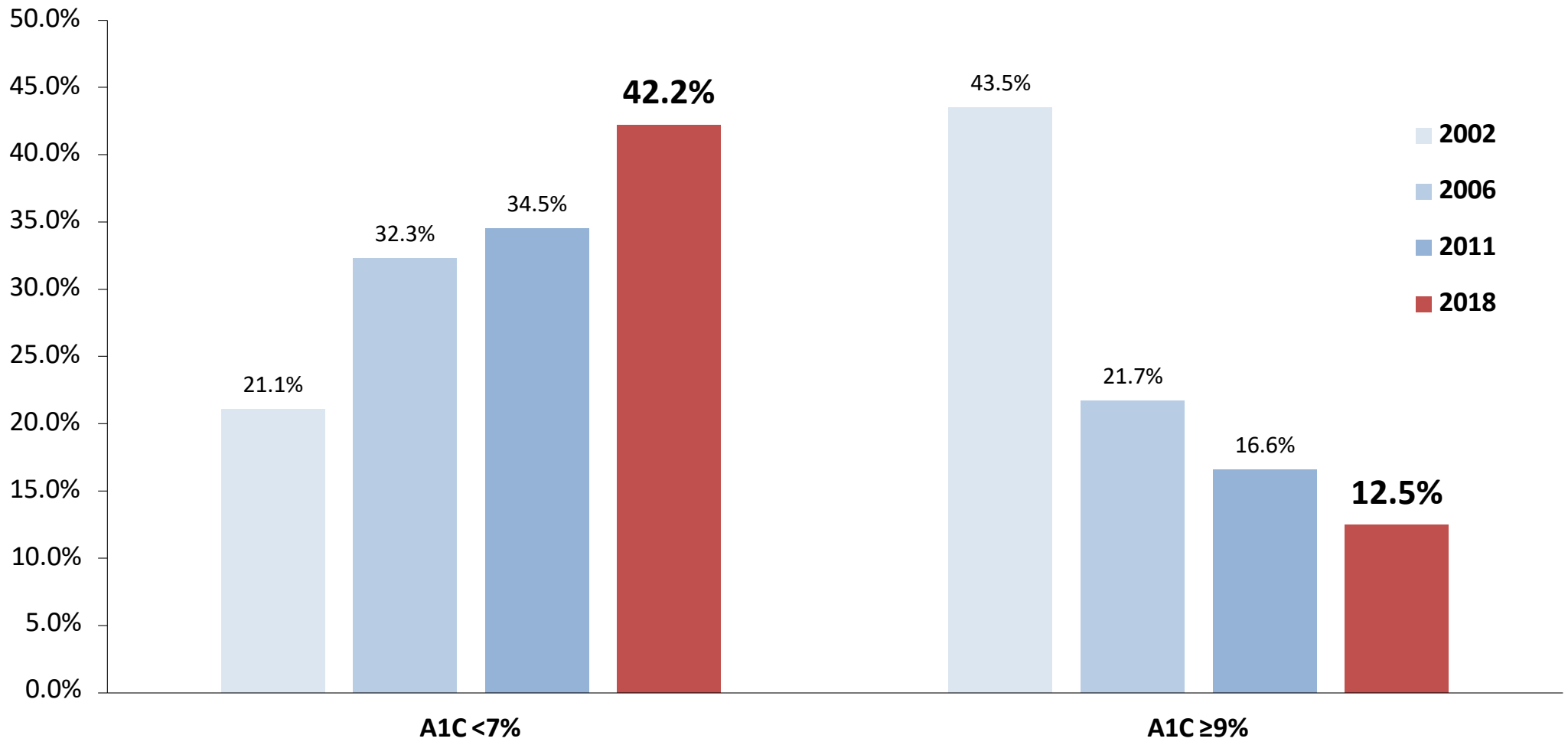
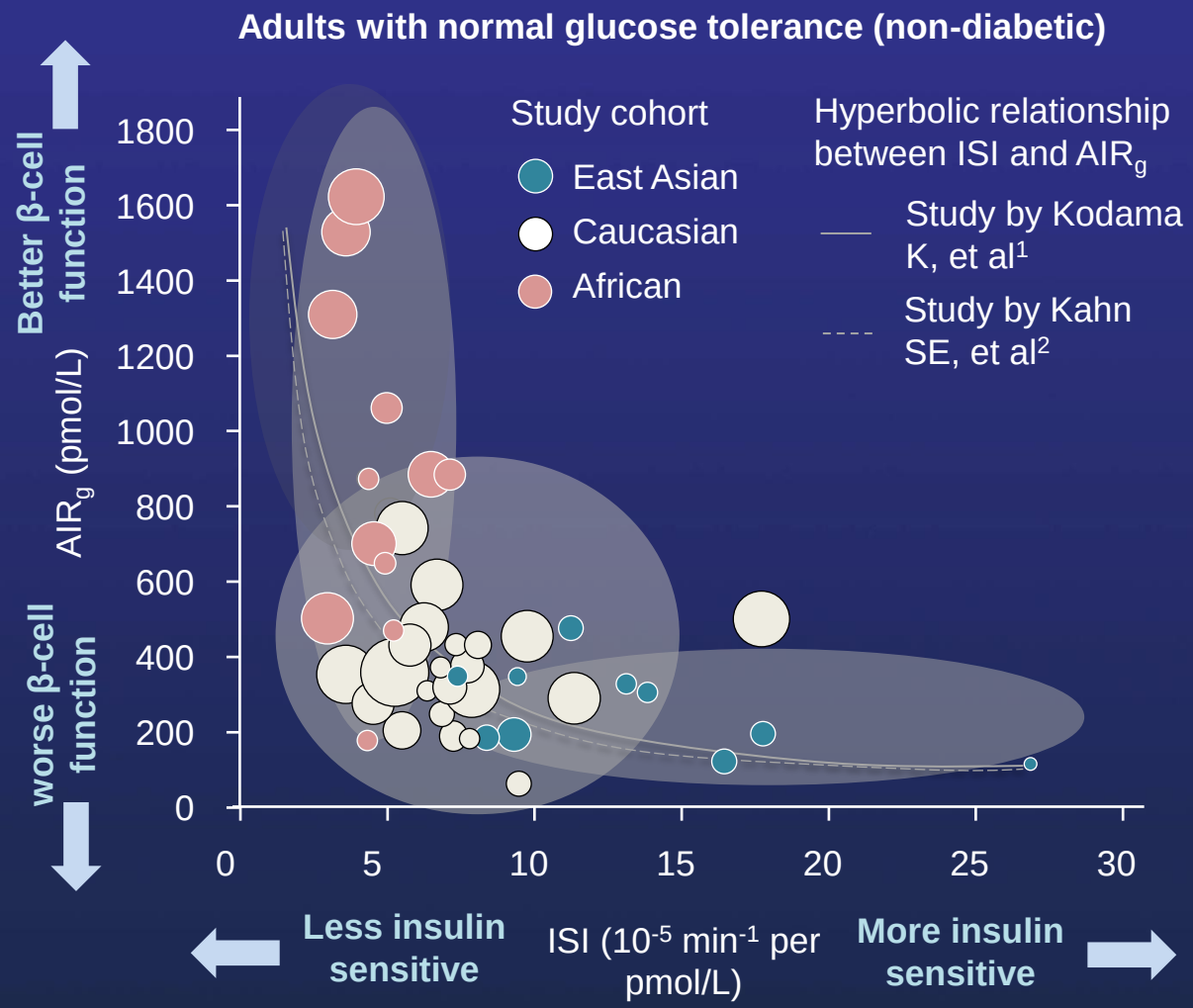
In Taiwan, nearly 60% of T2D patients remain uncontrolled HbA1c on their current therapy



1. Yu NC, et al. Diabetes Res Clin Pract 2014;106 Suppl 2:S305-8. 2. 2018 台灣糖尿病健康促進機構之品管調查研究

Ethnic differences in the mechanisms to achieve glucose homeostasis

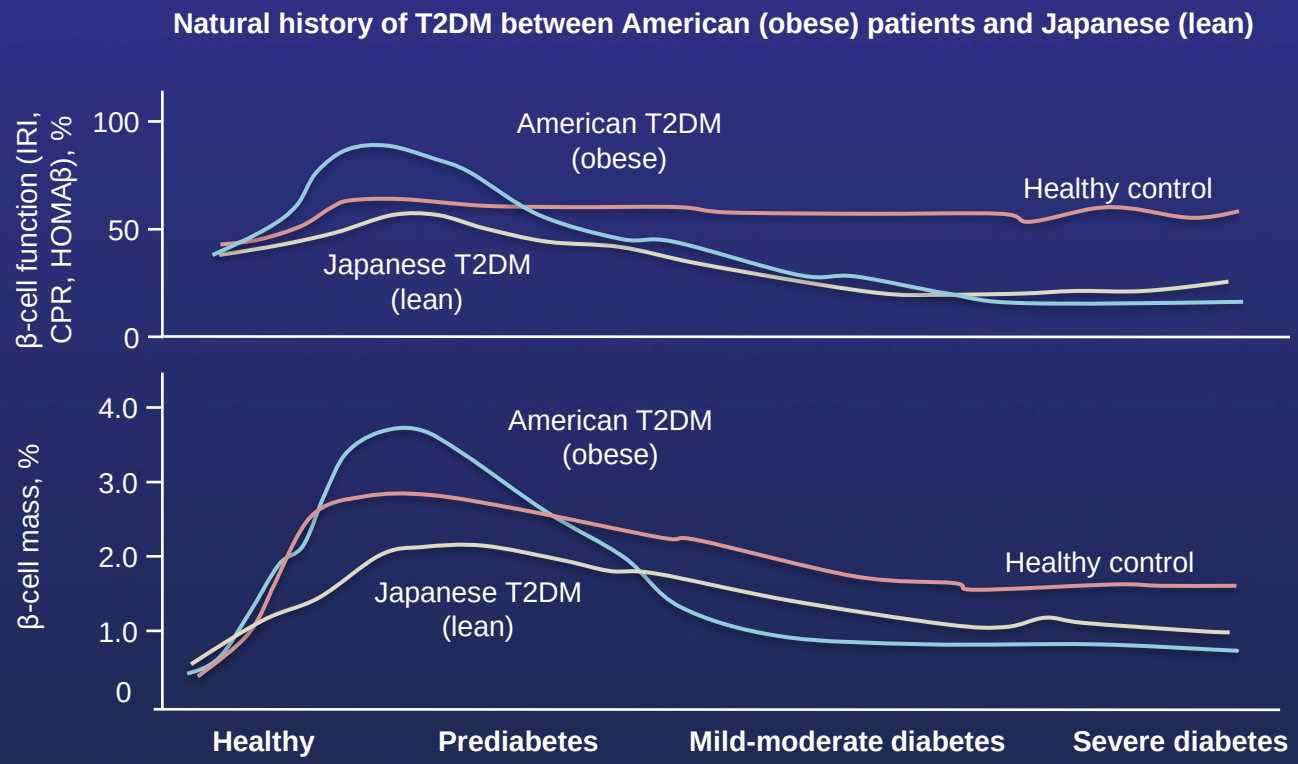
- Ethnicity has an impact on insulin sensitivity and insulin response – commonly interpreted as β-cell function
- In an analysis of 3813 individuals, healthy East Asians appeared to have lower insulin responses to glucose (AIR*) compared with Caucasian or African populations
- East Asians with T2DM had a relatively small variation in AIR, suggesting limited β-cell function or reserve
- This function worsens with age



ISI = Insulin sensitivity index; T2DM = Diabetes mellitus type 2.
*AIR (Acute Insulin Response) reflects the secretion of insulin by the pancreas and can be interpreted as β-cell function.
1.Kodama K, et al. *Diabetes Care.* 2013;36:1789-96; 2. Kahn SE, et al. *Diabetes.* 1993;42:1663-72.

β-cell mass and function in the glycemic continuum evolve differently in Caucasians and East Asians

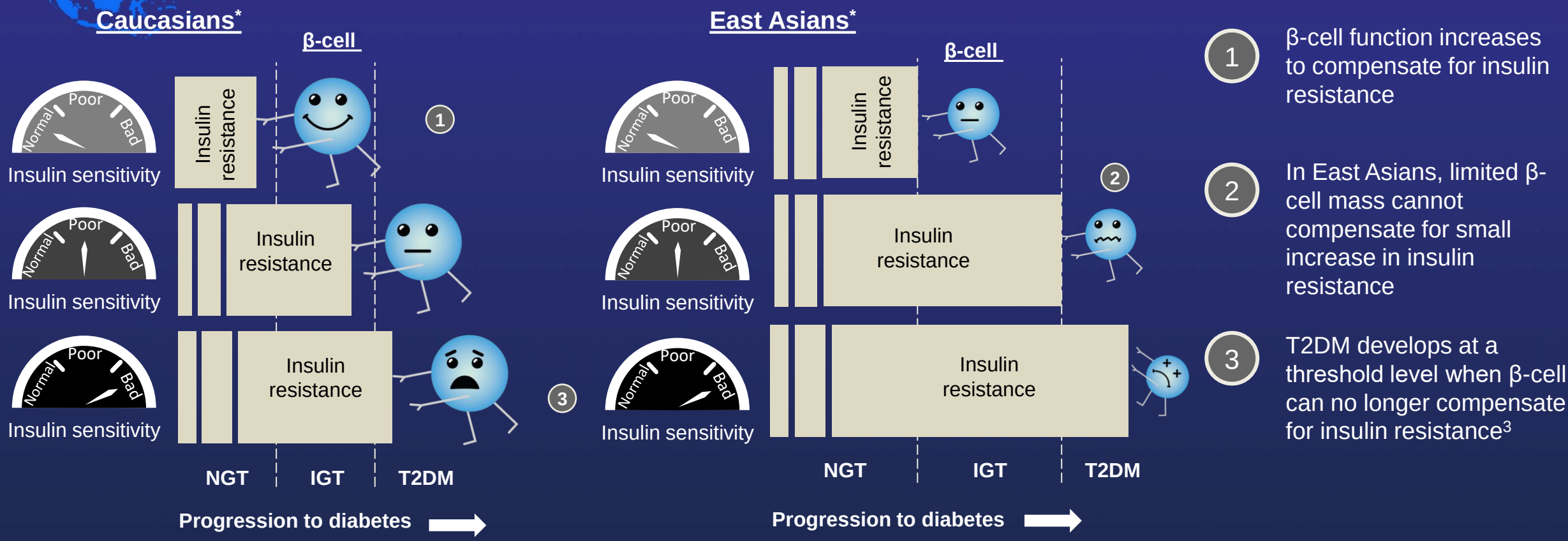
- β-cell function and mass initially increases to compensate for insulin resistance in non-Asians
- This dynamic is blunted in East Asians
- Progressive decline in β-cell function predisposes to diabetes



CPR = C-peptide immunoreactivity; HOMA-β = Homeostasis model assessment of β-cell function; IRI = Immunoreactive insulin; IGT = Impaired glucose tolerance; IFG = Impaired fasting glucose; T2DM = Type 2 Diabetes Mellitus.

1. Yagihashi S, et al. *J Diabetes Investig.* 2016;*7:155-165*

Ethnic differences in β-cell function and insulin sensitivity contribute to T2DM etiology



1. β-cell function increases to compensate for insulin resistance
2. In East Asians, limited β-cell mass cannot compensate for small increase in insulin resistance
3. T2DM develops at a threshold level when β-cell can no longer compensate for insulin resistance[3]

East Asians appear to have limited ability to compensate for insulin resistance compared with Caucasians

* = Conceptual diagrams based on referenced studies.
IGT = Impaired glucose tolerance; NGT = Normal glucose tolerance; T2DM = Diabetes mellitus type 2.
1. Ohn JH, et al. *Lancet Diabetes Endocrinol.* 2016;4:27-34; 2. Yabe D and Saino Y. *Lancet Diabetes Endocrinol.* 2016;4:2-3; 3.Kodama K, et al. *Diabetes Care.* 2013;36:1789-96.

TECOS study suggested better glucose-lowering efficacy in East Asians with a DPP-4i

- 96.4% of patients self-identified as Oriental (East) Asians were recruited in the Asia Pacific area
- East Asians showed reduction in HbA1c with sitagliptin (-0.6%) compared with other Asians and Caucasians (P=0.0006 and P=0.0002, respectively)

Placebo adjusted mean (SE) change in HbA1c from baseline to four months by race

	Placebo-adjusted ΔHbA1c		P-value for comparison vs. East Asian	P-value for comparison vs. Other Asian
	mmol/mol	%		
Caucasian	-4.3 (0.2)	-0.39 (0.02)	0.0002	0.64
Other Asian	-4.1 (0.4)	-0.37 (0.04)	0.0006	
East Asian	-6.6 (0.6)	-0.60 (0.05)		
Hispanic	-6.0 (0.6)	-0.55 (0.06)	0.52	0.014
Black	-4.9 (0.9)	-0.45 (0.08)	0.13	0.43
Indigenous	-2.7 (2.1)	-0.24 (0.19)	0.07	0.49

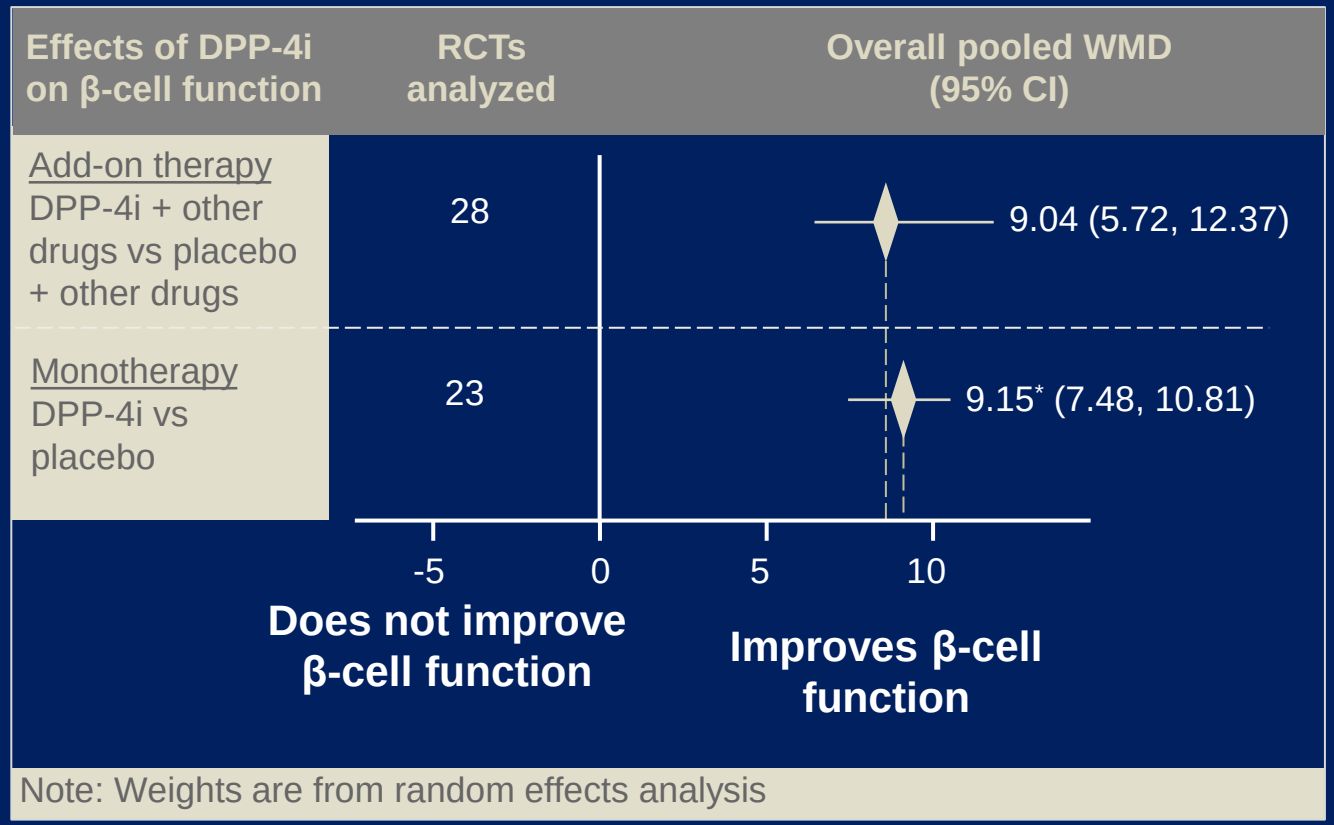
SE = Standard error; T2DM = Diabetes mellitus type 2.

1. Davis TME, et al. *Diabetes Obes Metab.* 2018;20:1427-1434.

DPP-4i enhances the ability of β-cells to produce insulin in response to glucose

- In a meta-analysis of 53 RCTs, DDP-4i add-on or monotherapy improved β-cell function by 9.04 and 9.15, respectively[1]

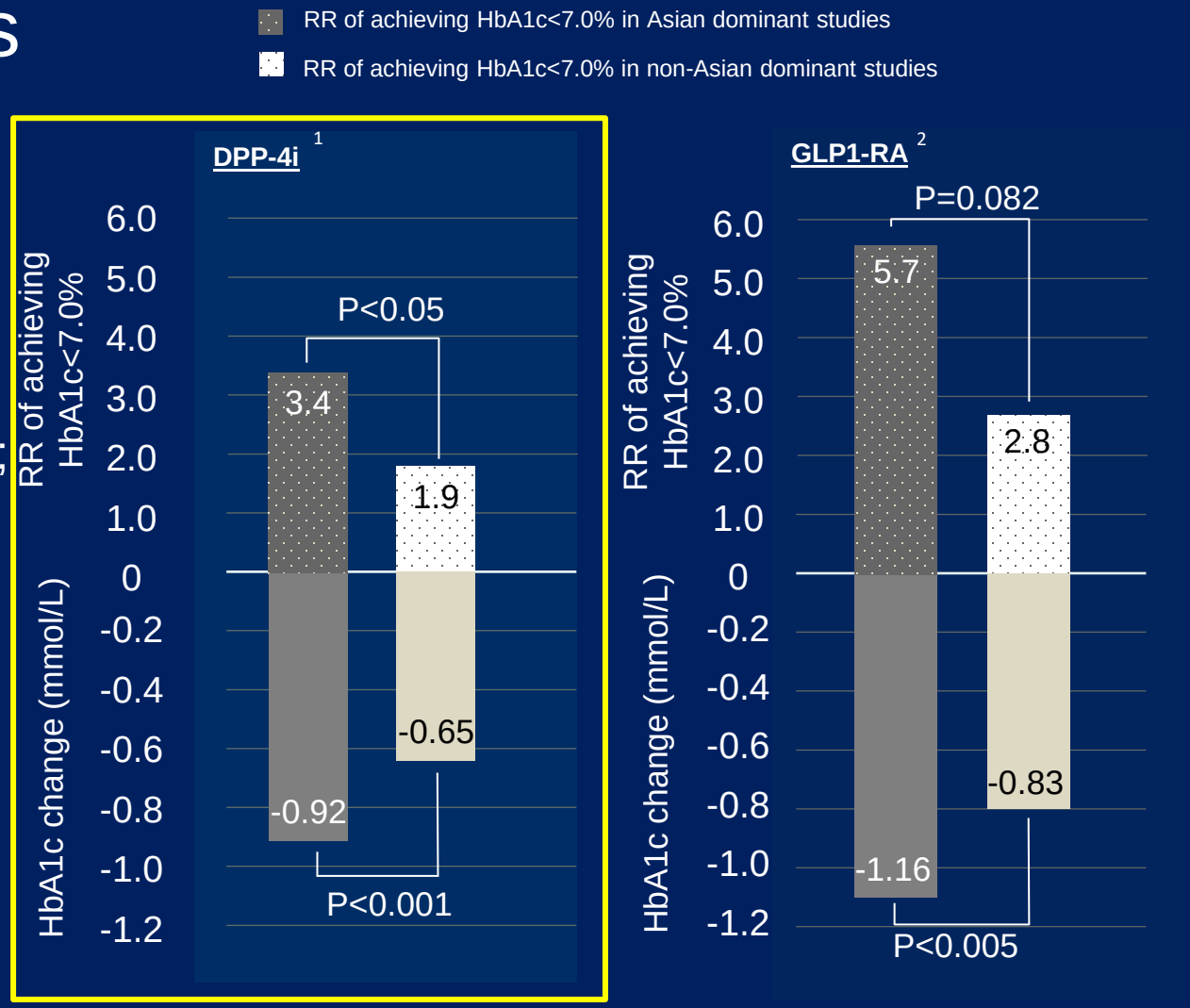
Meta-analysis of DPP-4 inhibitors on HOMA-B[1,a]



CI = Confidence interval; HOMA-B = Homoeostasis model assessment beta-cell function; GLP-1 = Glucagon-like peptide 1; RCTs = Randomized clinical trials; WMD = Weighted mean difference.
*Statistical significant; [a]surrogate marker for β-cell function.
1. Lyu X, et al. *Sci Rep.* 2017;7:44865

Better glycemic effect was observed in a meta-analysis of DPP-4i trials in Asian patients

- In a meta-analysis of 55 studies, DPP-4i showed additional reduction in HbA1c by -0.26% in Asian dominant studies than non-Asians (p<0.001)
- The RR of achieving the goal of HbA1c <7.0% was higher in Asians than non-Asians (3.4 vs 1.9; P<0.05)



GLP1-RA = Glucagon-like peptide-1 receptor agonist; RR = relative risk.

1. Kim YG, et al. *Diabetologia* 2013; 56:696-708 2. Kim YG, et al. *Diabetes Obes Metab. 2014;16:900-9*.

VERTIS ASIA:

Efficacy and Safety of Ertugliflozin in Asian Patients With T2DM Inadequately Controlled With Metformin Monotherapy

Ertugliflozin Is a Selective SGLT2 Inhibitor[1]

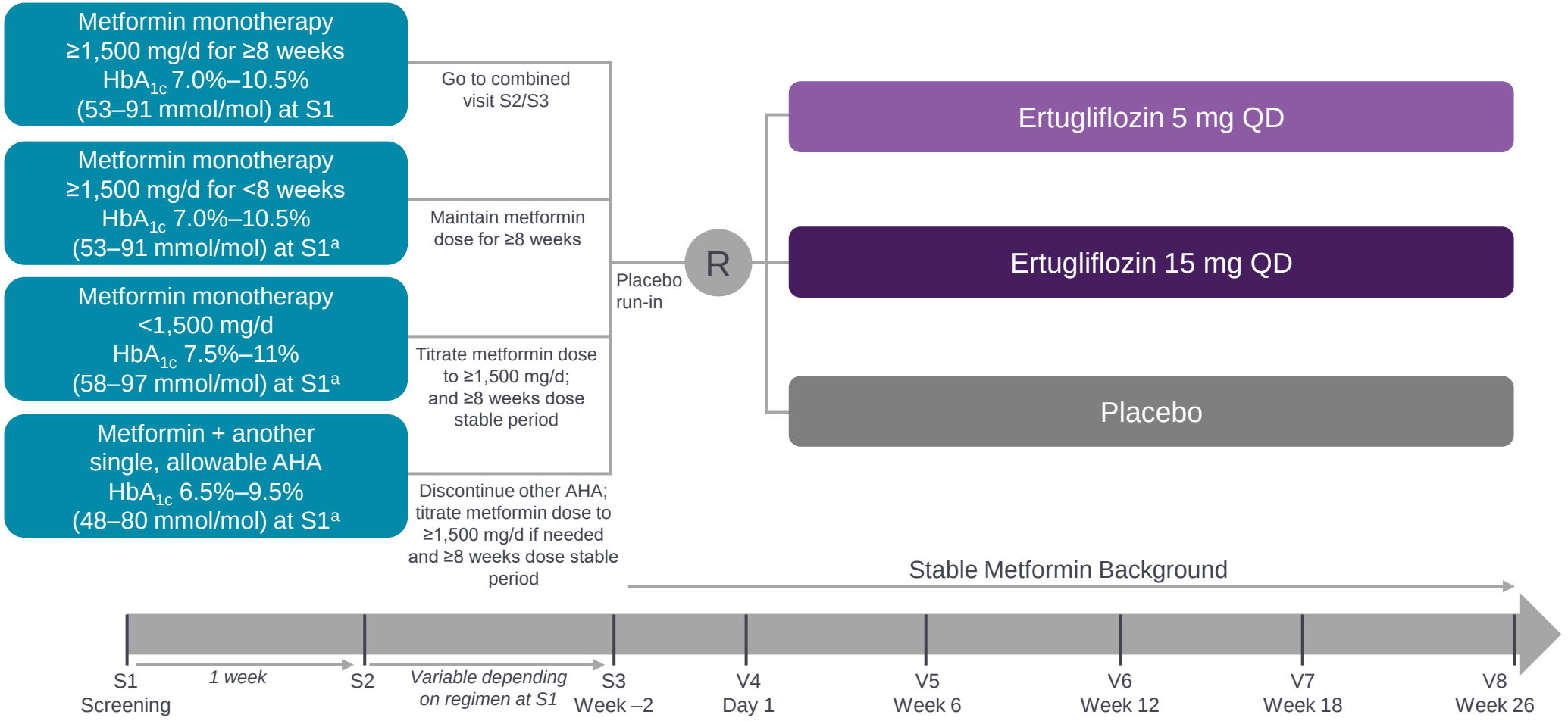
In vitro potency and selectivity of ertugliflozin[a]

- IC_{50} for SGLT2 = 0.9 nmol/L
- IC_{50} for SGLT1 = 1,960 nmol/L
- >2,000-fold selectivity for SGLT2 compared with SGLT1

[a]The potency at human SGLT was evaluated using a functional assay designed to detect the inhibition of the uptake of a glucose analog via the human SGLT expressed in CHO cells.
SGLT = sodium-glucose cotransporter; IC_{50} = half maximal inhibitory concentration; CHO = Chinese hamster ovary.

1. Mascitti V et al. *J Med Chem*. 2011;54:2952–2960.

VERTIS ASIA: Study Design[1]



Adapted with permission from Ji L et al.

[a]Patients in these groups will only be randomized if HbA_{1c} at S3 visit is between 7.0%–10.5% (inclusive).

VERTIS = eValuation of ERTugliflozin effIcacy and Safety; S = screening visit; AHA = antihyperglycemic agents; R = randomization; QD = once a day; V = visit.

1. Ji L et al. *Diabetes Obes Metab.* 2019;21:1474–1482.

VERTIS ASIA:
Patient Baseline Characteristics[1,a]

	Placebo (n=167)	ERTU 5 mg (n=170)	ERTU 15 mg (n=169)
Male, n (%)	88 (52.7)	95 (55.9)	98 (58.0)
Age, y	56.9 (9.0)	56.1 (9.0)	56.3 (9.3)
Duration of T2DM, y	6.4 (5.1)	7.0 (5.0)	7.5 (5.1)
Baseline HbA_{1c}, %	8.1 (1.0)	8.1 (0.9)	8.1 (0.9)
FPG, mg/dL	165.8 (37.6)	170.1 (36.0)	167.3 (41.1)
Body weight, kg	70.1 (12.4)	71.4 (11.1)	69.5 (10.9)
BMI, kg/m^2	26.1 (3.4)	26.0 (2.8)	25.7 (3.2)
eGFR, mL/min/1.73 m^2	99.9 (20.2)	97.9 (19.2)	100.2 (19.8)

	Placebo (n=167)	ERTU 5 mg (n=170)	ERTU 15 mg (n=169)
Territory, n (%)			
China excluding HK & Taiwan	135 (80.8)	136 (80.0)	135 (79.9)
Other	32 (19.2)	34 (20.0)	34 (20.1)
Hong Kong	7 (4.2)	10 (5.9)	10 (5.9)
Korea, Republic of	9 (5.4)	13 (7.6)	10 (5.9)
Philippines	8 (4.8)	7 (4.1)	8 (4.7)
Taiwan	8 (4.8)	4 (2.4)	6 (3.6)

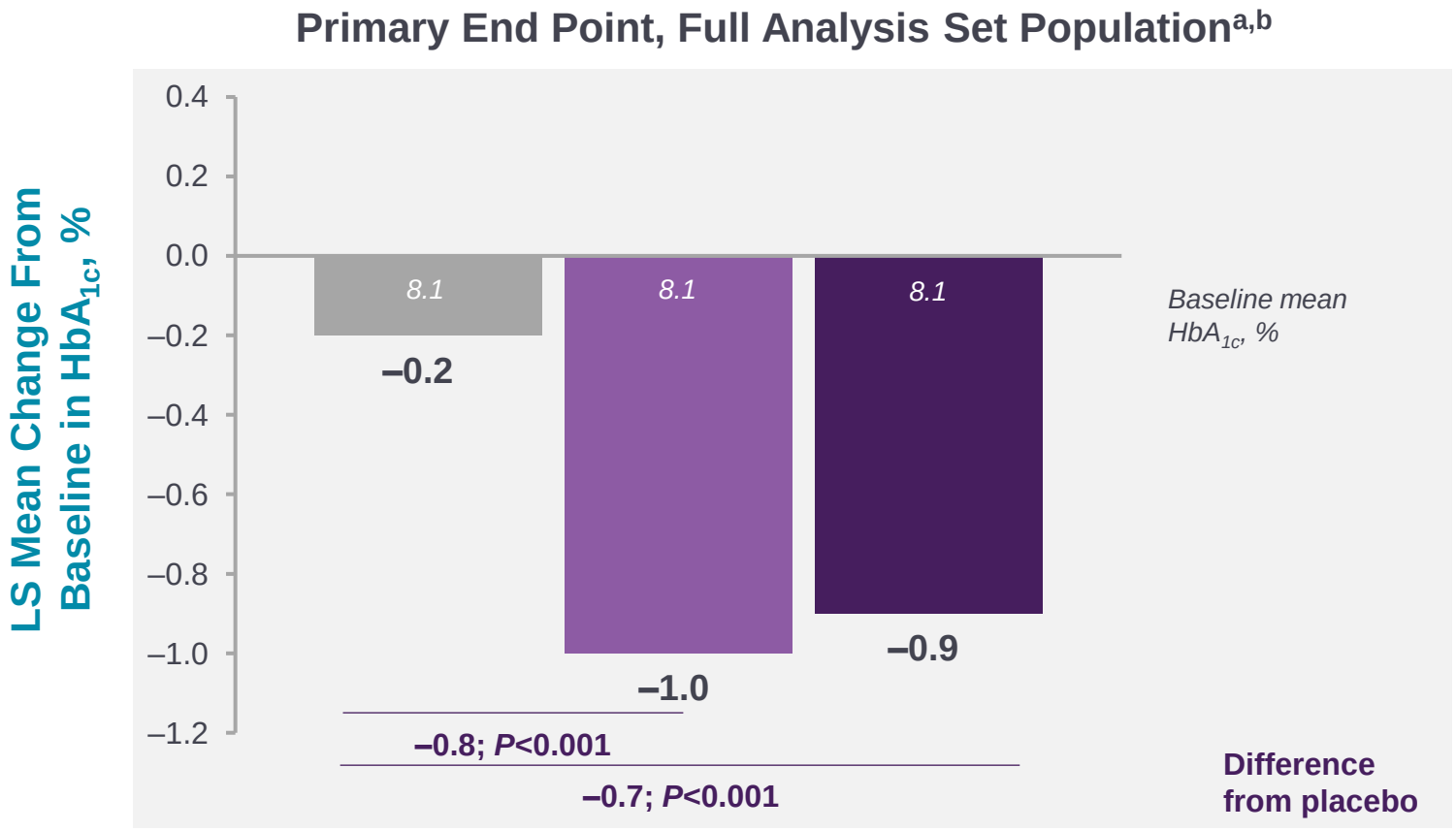
Adapted with permission from Ji L et al.

[a]Data presented are mean (SD), unless otherwise stated.

VERTIS = eValuation of ERTugliflozin effIcacy and Safety; y = years; ERTU = ertugliflozin; T2DM = type 2 diabetes mellitus; FPG = fasting plasma glucose; BMI = body mass index; eGFR = estimated glomerular filtration rate; SD = standard deviation.

1. Ji L et al. *Diabetes Obes Metab.* 2019;21:1474–1482.

VERTIS ASIA: HbA_{1c} Reductions at Week 26[1]



- More patients who received ertugliflozin 5 mg (38.2%) and 15 mg (40.8%) compared with placebo (16.2%) had HbA_{1c} <7.0% at week 26

Adapted with permission from Ji L et al.

[a]The population includes all randomized patients who received at least 1 dose of study medication and had at least 1 measurement of the analysis variable (baseline or postbaseline). The mean and SD for the change from baseline are based on nonmissing values.

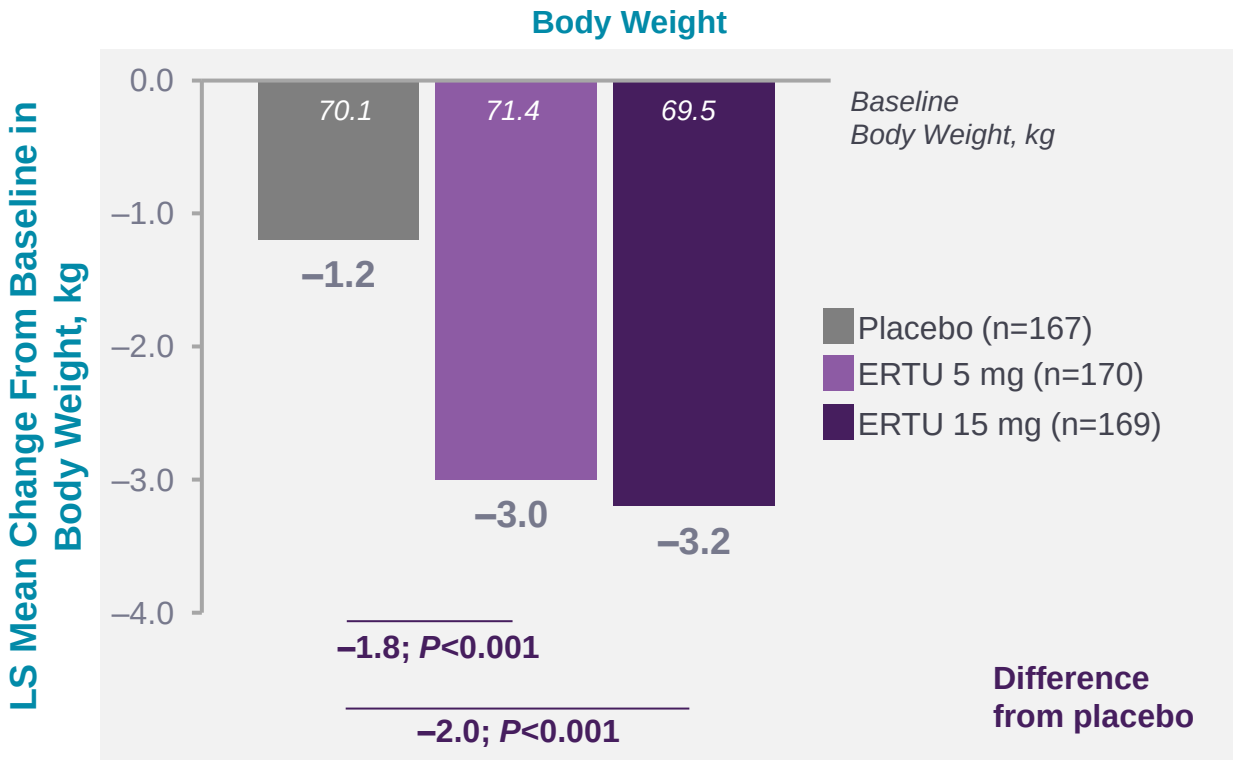
[b]Based on a cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), country (China, other), baseline eGFR (continuous), and the interaction of time by treatment. Time was treated as a categorical variable.

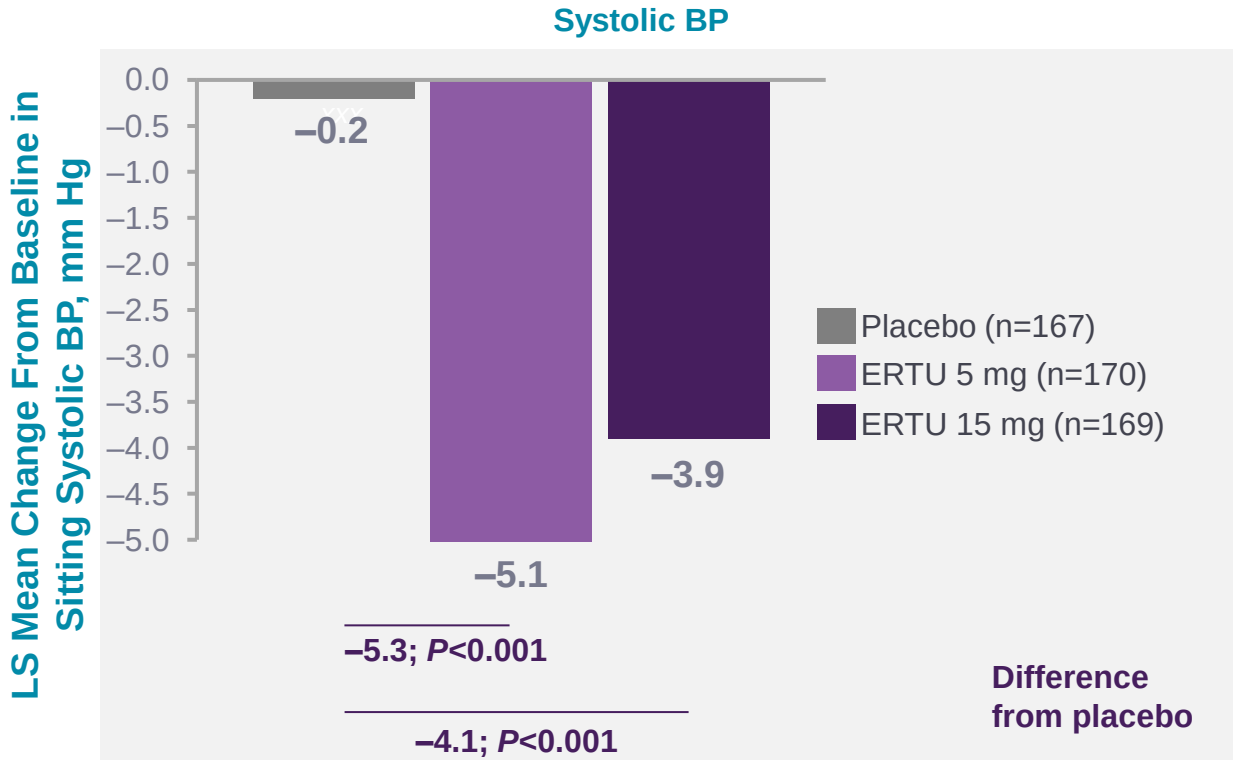
VERTIS = eValuation of ERTugliflozin effIcacy and Safety; LS = least squares; ERTU = ertugliflozin; SD = standard deviation; cLDA = constrained longitudinal data analysis; AHA = antihyperglycemic agents; eGFR = estimated glomerular filtration rate.

1. Ji L et al. *Diabetes Obes Metab.* 2019;21:1474–1482.

VERTIS ASIA:
Reductions in Body Weight and Systolic BP at Week 26[1]

Secondary End Points, Full Analysis Set Population[a,b]





ERTU is not indicated for weight loss or the treatment of hypertension.

Adapted with permission from Ji L et al.

[a]The population includes all randomized patients who received at least 1 dose of study medication and had at least 1 measurement of the analysis variable (baseline or postbaseline). The mean and SD for the change from baseline are based on nonmissing values.

[b]Based on a cLDA model with fixed effects for treatment, time, prior antihyperglycemic medication (metformin monotherapy or metformin + another AHA), country (China, other), baseline eGFR (continuous), and the interaction of time by treatment. Time was treated as a categorical variable.

VERTIS = eValuation of ERTugliflozin effIcacy and Safety; BP = blood pressure; LS = least squares; ERTU = ertugliflozin.

1. Ji L et al. *Diabetes Obes Metab.* 2019;21:1474–1482.

VERTIS ASIA: Summary of AEs Over 26 Weeks[1]

	Patients, n (%)		
	Placebo (n=167)	ERTU 5 mg (n=170)	ERTU 15 mg (n=169)
Event			
One or more AEs	99 (59.3)	96 (56.5)	90 (53.3)
AEs related to study drug[a]	23 (13.8)	29 (17.1)	24 (14.2)
One or more serious AEs	2 (1.2)	9 (5.3)	10 (5.9)
Serious AEs related to study drug[a]	1 (0.6)	0	0
Death[b]	0	0	0
AE leading to discontinuation	3 (1.8)	2 (1.2)	1 (0.6)
Prespecified AEs			
Genital mycotic infection (female)	1 (1.3)	2 (2.7)	1 (1.4)
Genital mycotic infection (male)	1 (1.1)	2 (2.1)	2 (2.0)
Urinary tract infection	4 (2.4)	3 (1.8)	2 (1.2)
Symptomatic hypoglycemia[c]	1 (0.6)	4 (2.4)	8 (4.7)
Hypovolemia	1 (0.6)	0	1 (0.6)

Adapted with permission from Ji L et al.

[a]Assessed as related to the study drug by the investigator.

[b]No deaths occurred between the first dose of treatment and 14 days after the final dose of treatment in the study; there was 1 death in the China subpopulation in the all postrandomization follow-up period (>14 days after the last dose of study medication). The patient, treated with ertugliflozin 15 mg, was diagnosed with metastatic lung cancer 20 days after the last dose of study medication and died 71 days after the last dose of study medication.

[c]The incidence of symptomatic hypoglycemia was low across the groups, but significantly higher with ertugliflozin 15 mg compared with placebo in the overall population (4.7% vs. 0.6%, *P*=0.019).

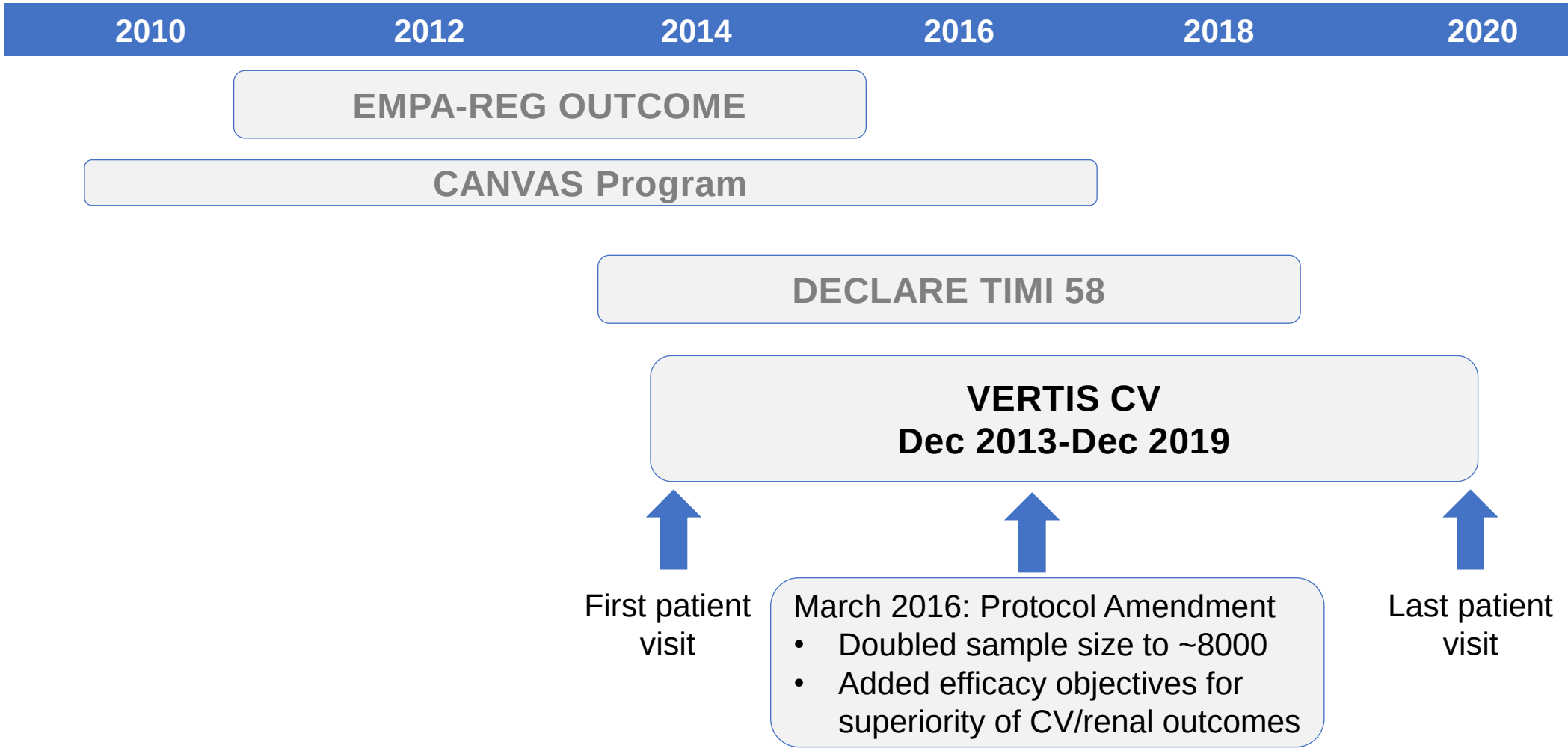
VERTIS = eValuation of ERTugliflozin effIcacy and Safety; AE = adverse event; ERTU = ertugliflozin.

1. Ji L et al. *Diabetes Obes Metab.* 2019;21:1474–1482.

The VERTIS CV Trial

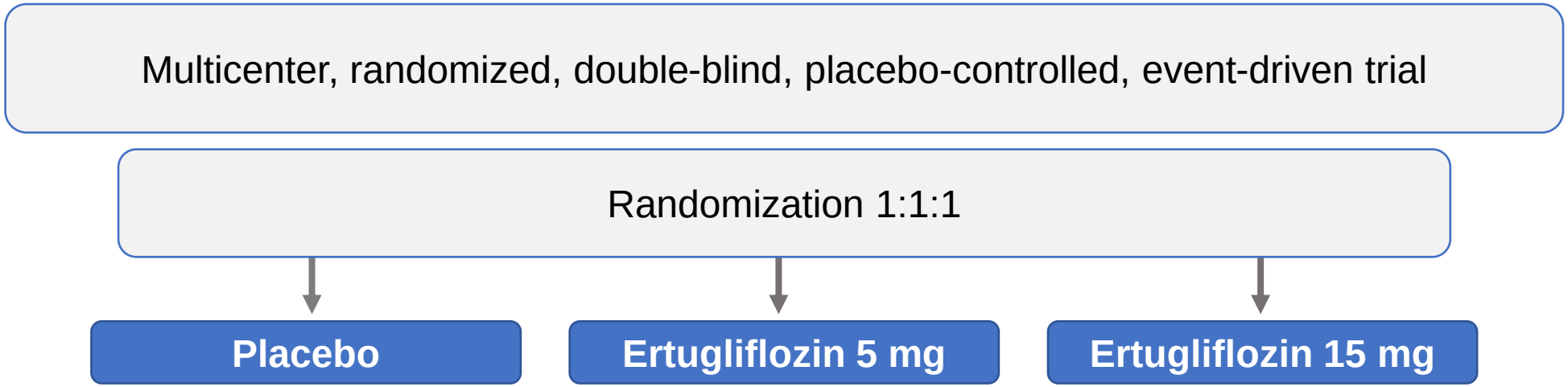
Cardiovascular Outcomes Following Ertugliflozin Treatment in Patients with Type 2 Diabetes Mellitus and Atherosclerotic Cardiovascular Disease

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.

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.

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.

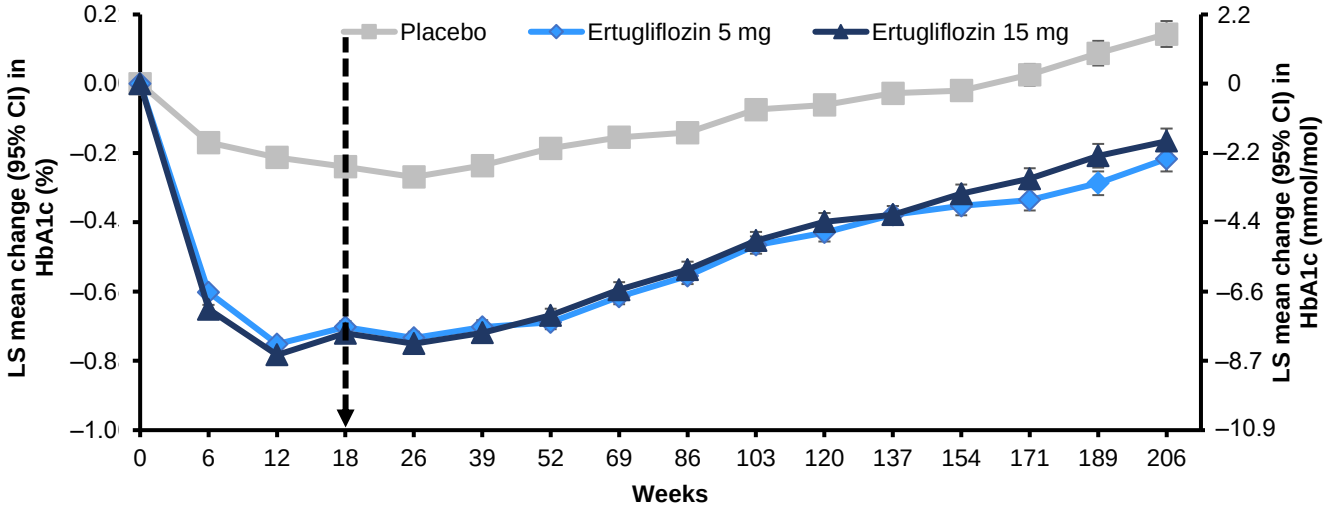
Baseline characteristics

	Placebo (n=2747)	Ertugliflozin (n=5499)
Age, years	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)
Duration of T2DM, years	13.1 (8.4)	12.9 (8.3)
BMI, kg/m^2	32.0 (5.5)	31.9 (5.4)
HbA1c, %	8.2 (0.9)	8.2 (1.0)
LDL cholesterol, mmol/L	2.3 (1.0)	2.3 (1.0)
LDL cholesterol, mg/dL	88.8 (37.7)	89.3 (38.5)
Systolic BP, mmHg	133.1 (13.9)	133.5 (13.7)
eGFR, mL min^{-1} 1.73 m^{-2}†	75.7 (20.8)	76.1 (20.9)
eGFR <60 mL min^{-1} 1.73 m^{-2}, n (%)	608 (22.1)	1199 (21.8)

Values are mean (standard deviation) unless otherwise specified

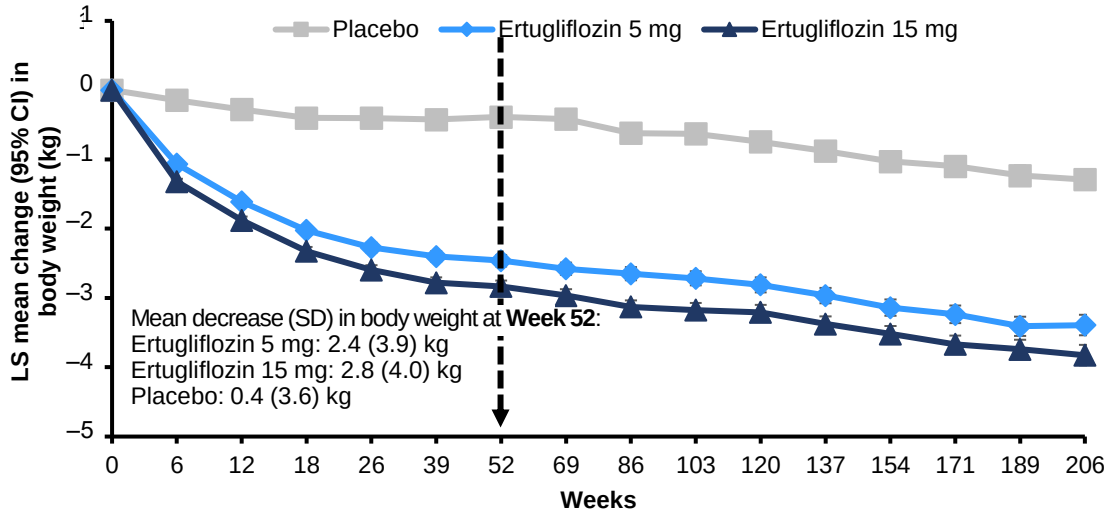
†Calculated using the Modification of Diet in Renal Disease formula. unless otherwise stated.
BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate;
HbA1c, glycated haemoglobin; LDL, low-density lipoprotein; T2DM, type 2 diabetes mellitus.

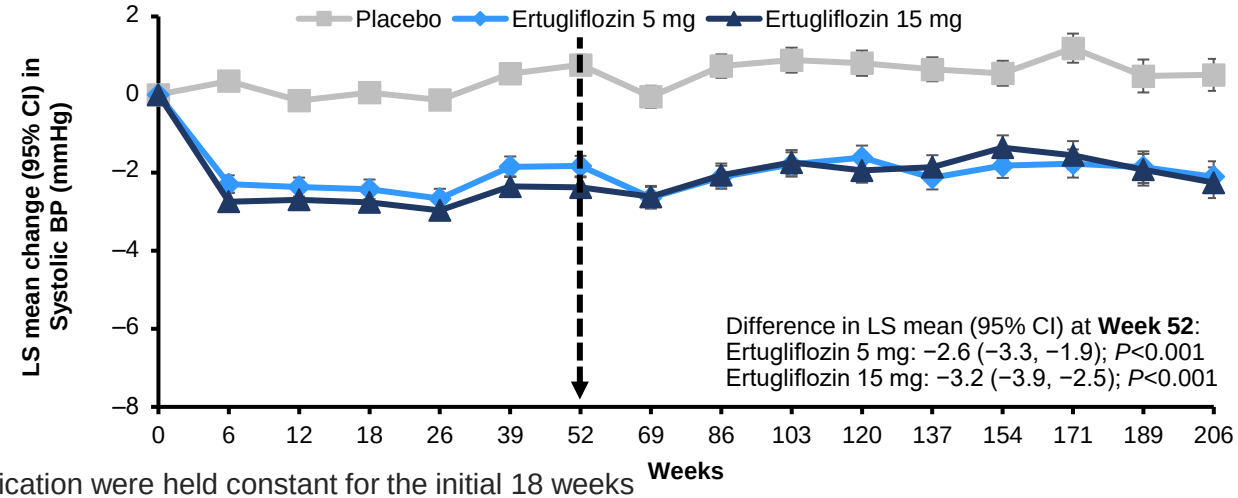
HbA1c, body weight and systolic BP over time



Difference in LS mean (% [95% CI]) at **Week 18**:
Ertugliflozin 5 mg: −0.5 (−0.5, −0.4); *P*<0.001
Ertugliflozin 15 mg: −0.5 (−0.6, −0.5); *P*<0.001

Difference in LS mean (mmol/mol [95% CI]) at **Week 18**:
Ertugliflozin 5 mg: −5.3 (−5.8, −4.8); *P*<0.001
Ertugliflozin 15 mg: −5.5 (−6.0, −5.0); *P*<0.001

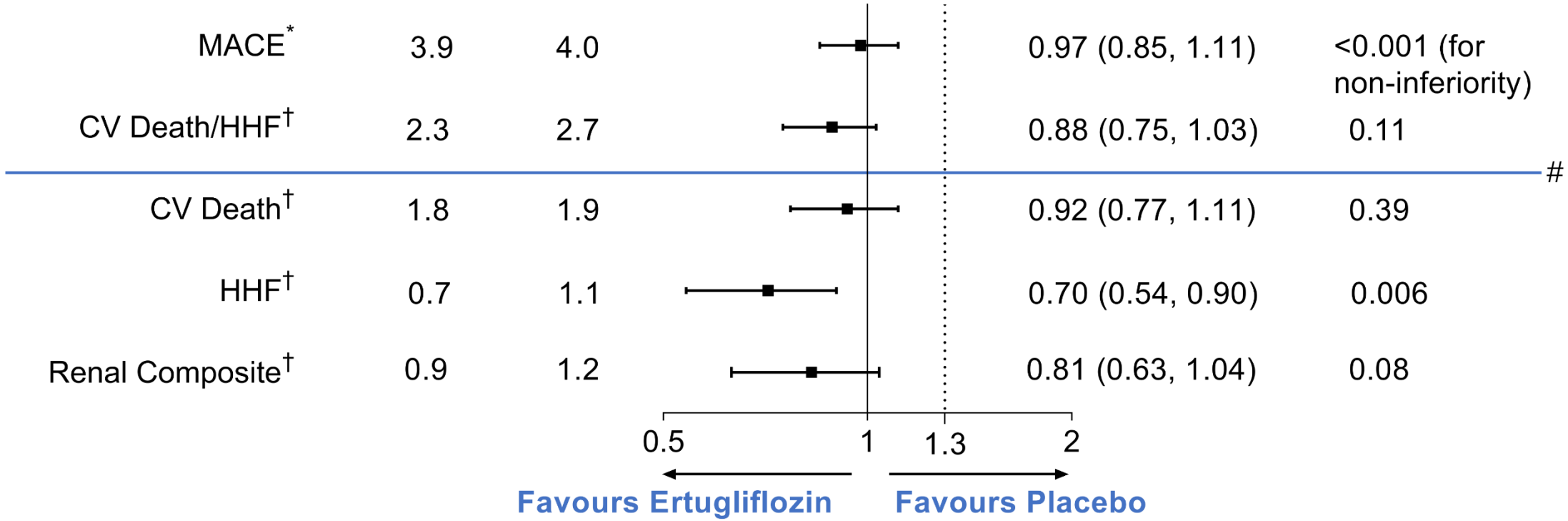




Doses of background antihyperglycaemic medication were held constant for the initial 18 weeks of the study except for those patients meeting the glycaemic rescue criteria.
BP, blood pressure; CI, confidence interval; HbA1c, glycated haemoglobin; LS, least squares; SD, standard deviation.

VERTIS CV: Primary and secondary endpoints

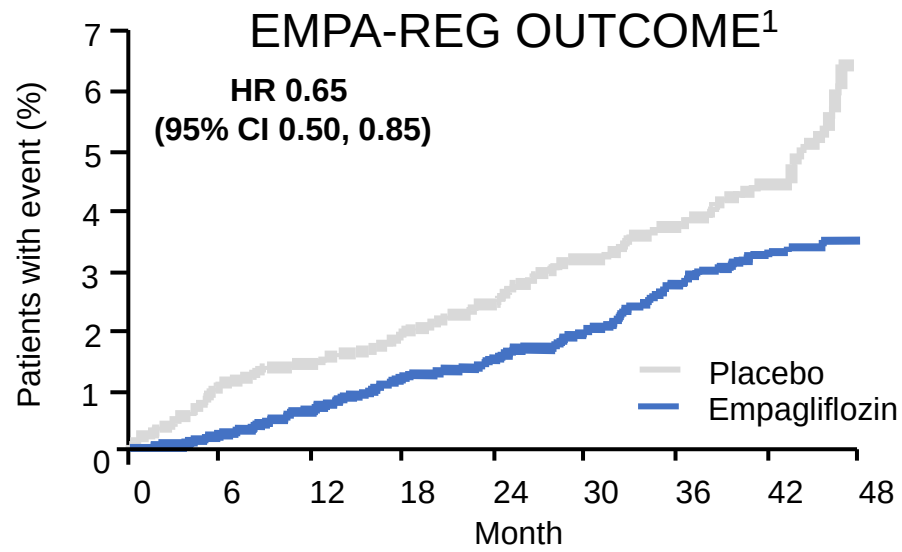
	Ertugliflozin n=5499	Placebo n=2747	HR (CI)	*P* Value
	Rate per 100 patient-years			
MACE*	3.9	4.0	0.97 (0.85, 1.11)	<0.001 (for non-inferiority)
CV Death/HHF†	2.3	2.7	0.88 (0.75, 1.03)	0.11
CV Death†	1.8	1.9	0.92 (0.77, 1.11)	0.39
HHF†	0.7	1.1	0.70 (0.54, 0.90)	0.006
Renal Composite†	0.9	1.2	0.81 (0.63,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

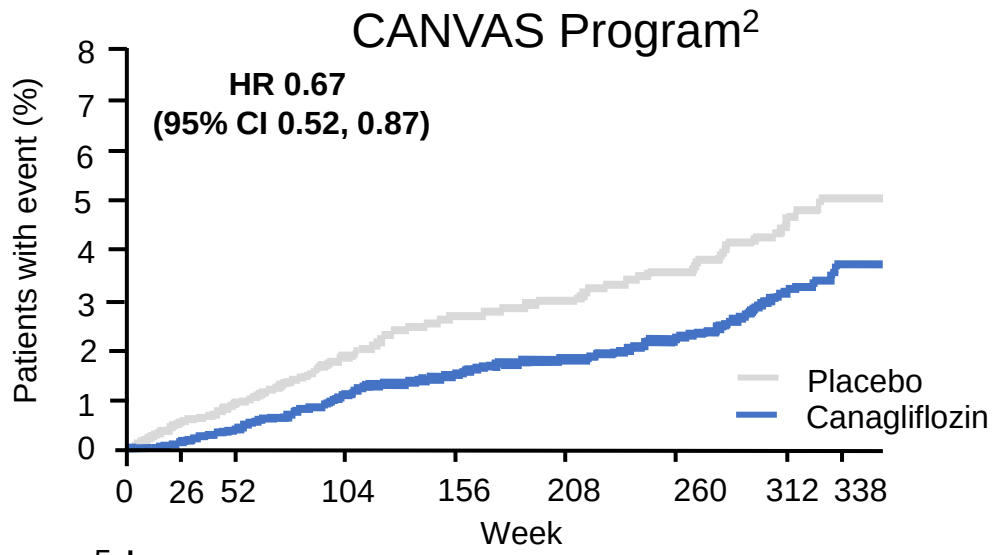


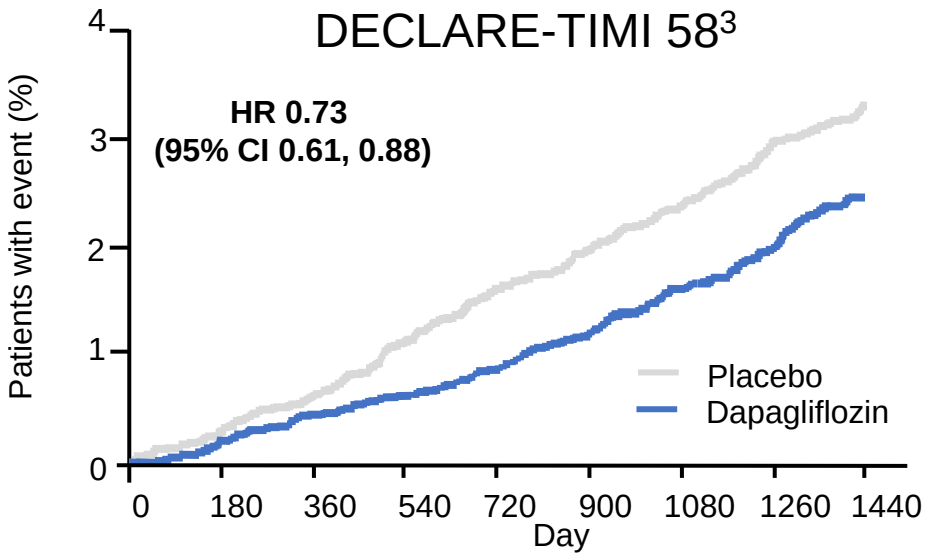
#Formal hypothesis testing sequence ended at CV death/HHF composite endpoint. Time to first HHF was a prespecified secondary endpoint, but not part of the hypothesis testing sequence. Ertugliflozin doses were pooled for analysis.

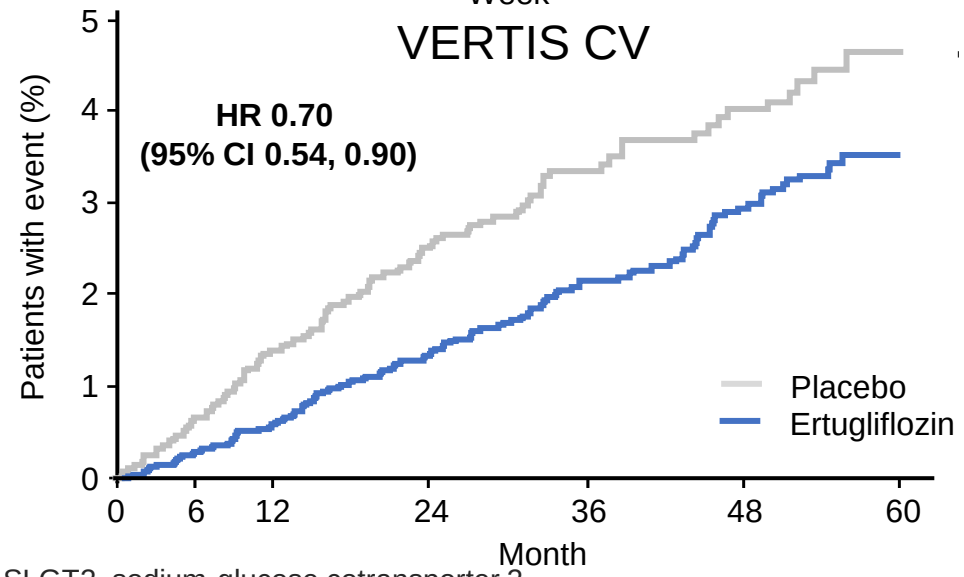
*Full analysis set included all randomised patients who received at least one dose of study medication. Only confirmed MACE events occurring up to 365 days after the last confirmed dose of study medication were included in the primary analysis.
†Intention-to-treat analysis set that included all randomised patients with no upper limit on the ascertainment window for the superiority outcomes. CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events. Adapted from Cannon CP, et al. Presented at the American Diabetes Association 80th Scientific Sessions, A Virtual Experience, Jun 16, 2020.

HHF outcomes in SGLT2 inhibitor CV outcomes trials







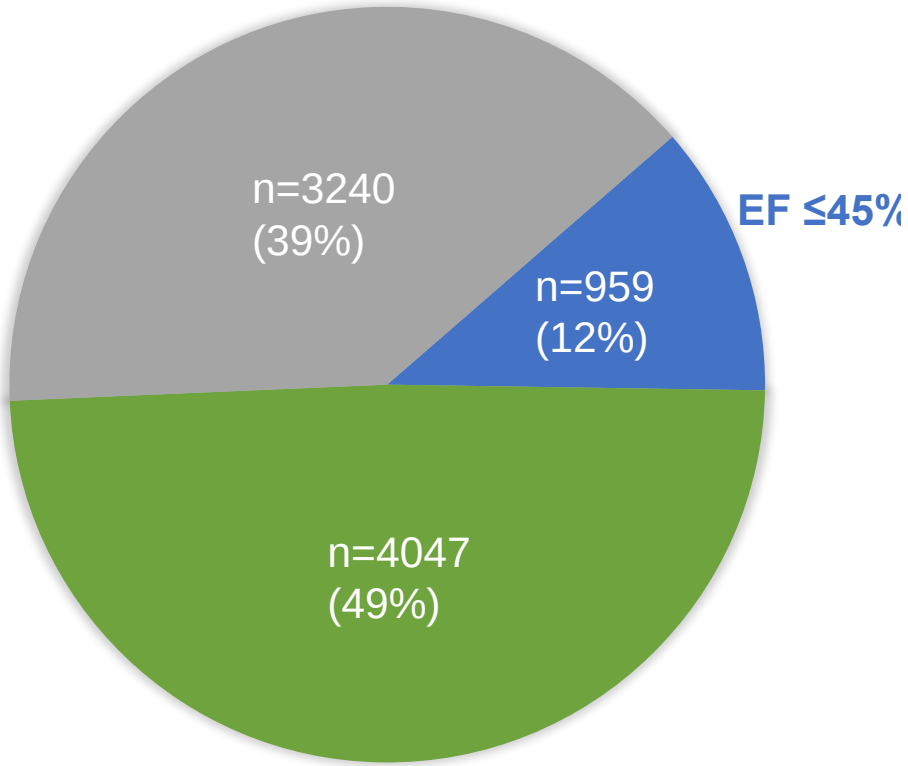


CI, confidence interval; CV, cardiovascular; HHF, hospitalisation for heart failure; HR, hazard ratio; SLGT2, sodium-glucose cotransporter 2.

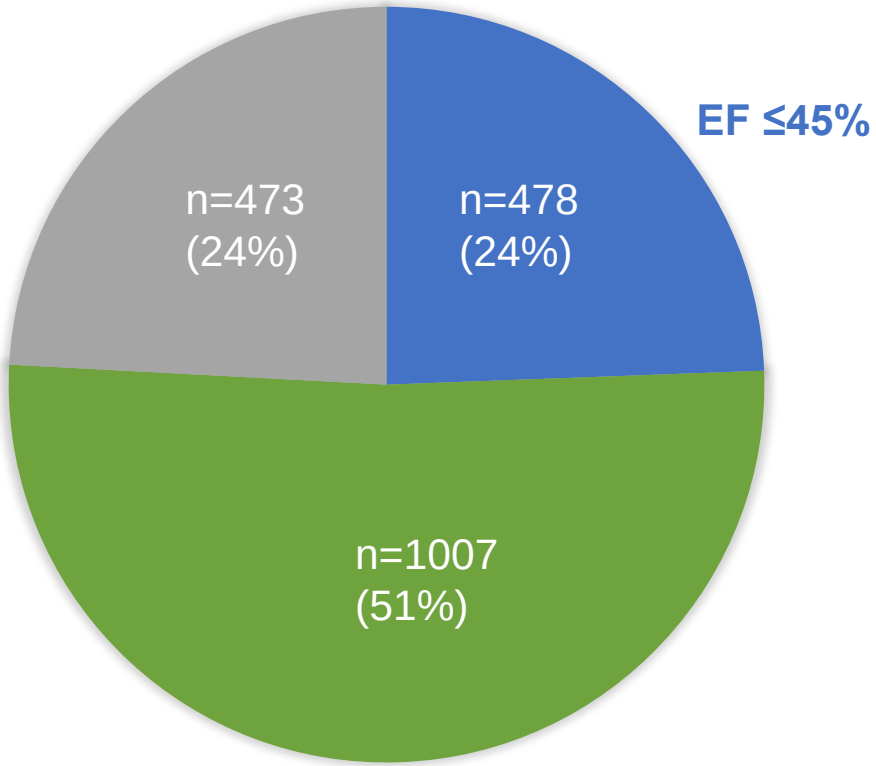
[1]Zinman B et al. *N Engl J Med.* 2015;373:2117–2128; [2]Neal B et al. *N Engl J Med.* 2017;377:644–657;
[3]Wiviott SD et al. *N Engl J Med.* 2019;380:347–357 (figure provided by D.K. McGuire, with permission).

Pre-trial EF in overall population and in those with a history of HF

ITT population (n=8246)

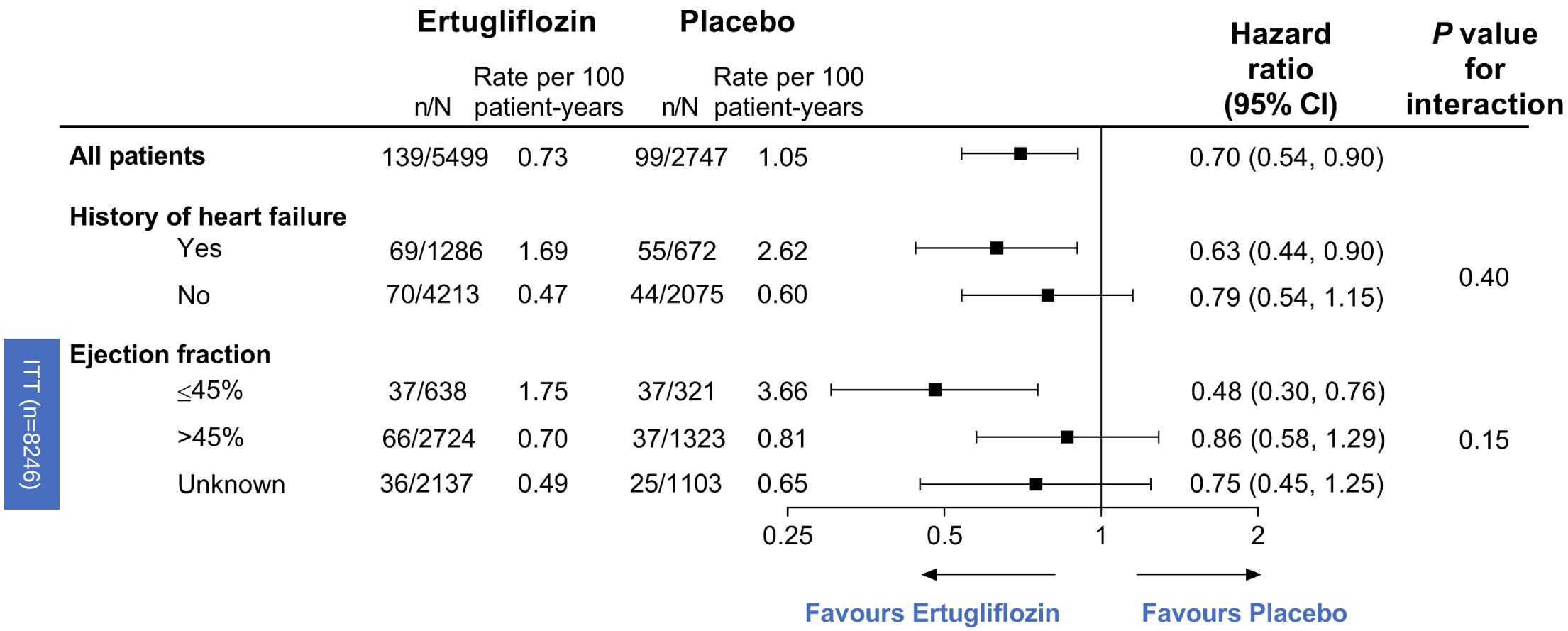


Patients with history of HF (n=1958, 24%)†



†Percentages in the pie chart do not add up to 100% due to rounding.
EF, ejection fraction; HF, heart failure; ITT, intention-to-treat.
Cosentino F et al. Presented at European Society of Cardiology Congress, 31 Aug 2020.

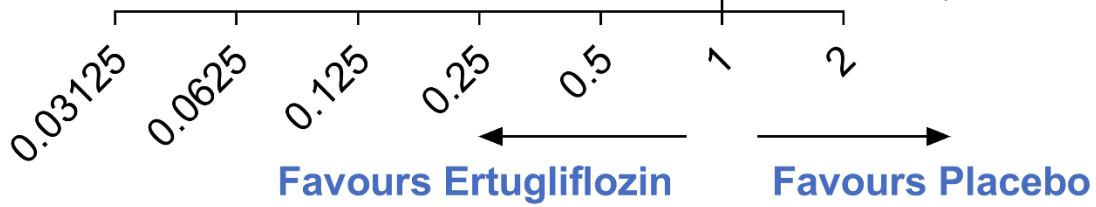
Time to first HHF by history of HF or by pre-trial EF



CI, confidence interval; EF, ejection fraction; HF, heart failure;
HHF, hospitalisation for heart failure.
Cosentino F et al. Presented at European Society of Cardiology Congress, 31 Aug 2020.

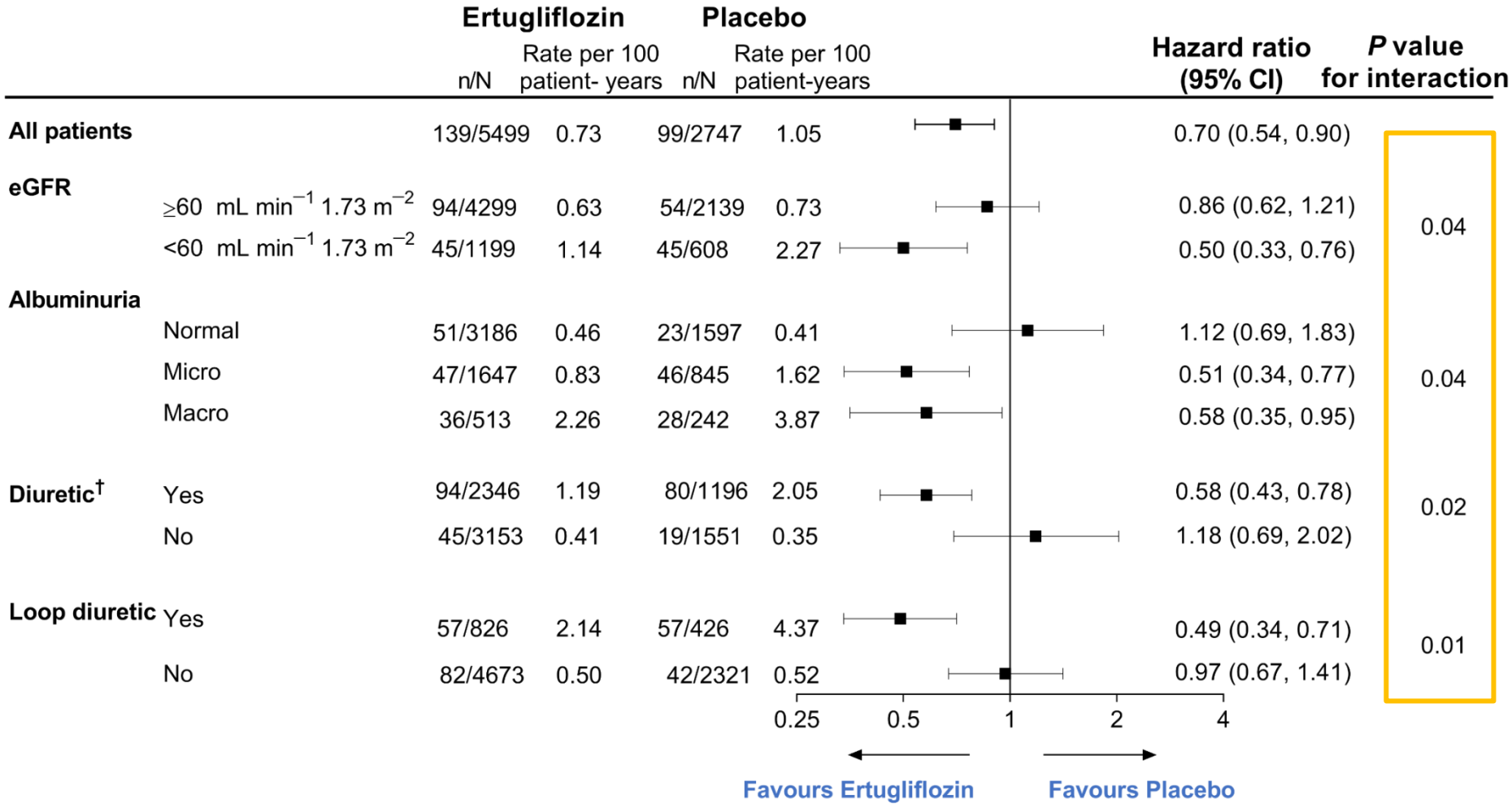
Time to first HHF by history of HF and by pre-trial EF

	Ertugliflozin n/N	Ertugliflozin Rate per 100 patient- years	Placebo n/N	Placebo Rate per 100 patient-years	Hazard Ratio (95% CI)	*P* Value
HF EF ≤45%	33/319	3.33	26/159	5.57	0.60 (0.36, 1.00)	0.11
HF EF>45%	28/680	1.29	19/327	1.84	0.70 (0.39, 1.26)	
HF EF Unknown	8/287	0.86	10/186	1.66	0.52 (0.21, 1.31)	
No HF EF≤45%	4/319	0.36	11/162	2.02	0.18 (0.06, 0.55)	
No HF EF>45%	38/2044	0.52	18/996	0.51	1.02 (0.58, 1.79)	
No HF EF Unknown	28/1850	0.43	15/917	0.46	0.94 (0.50, 1.76)	



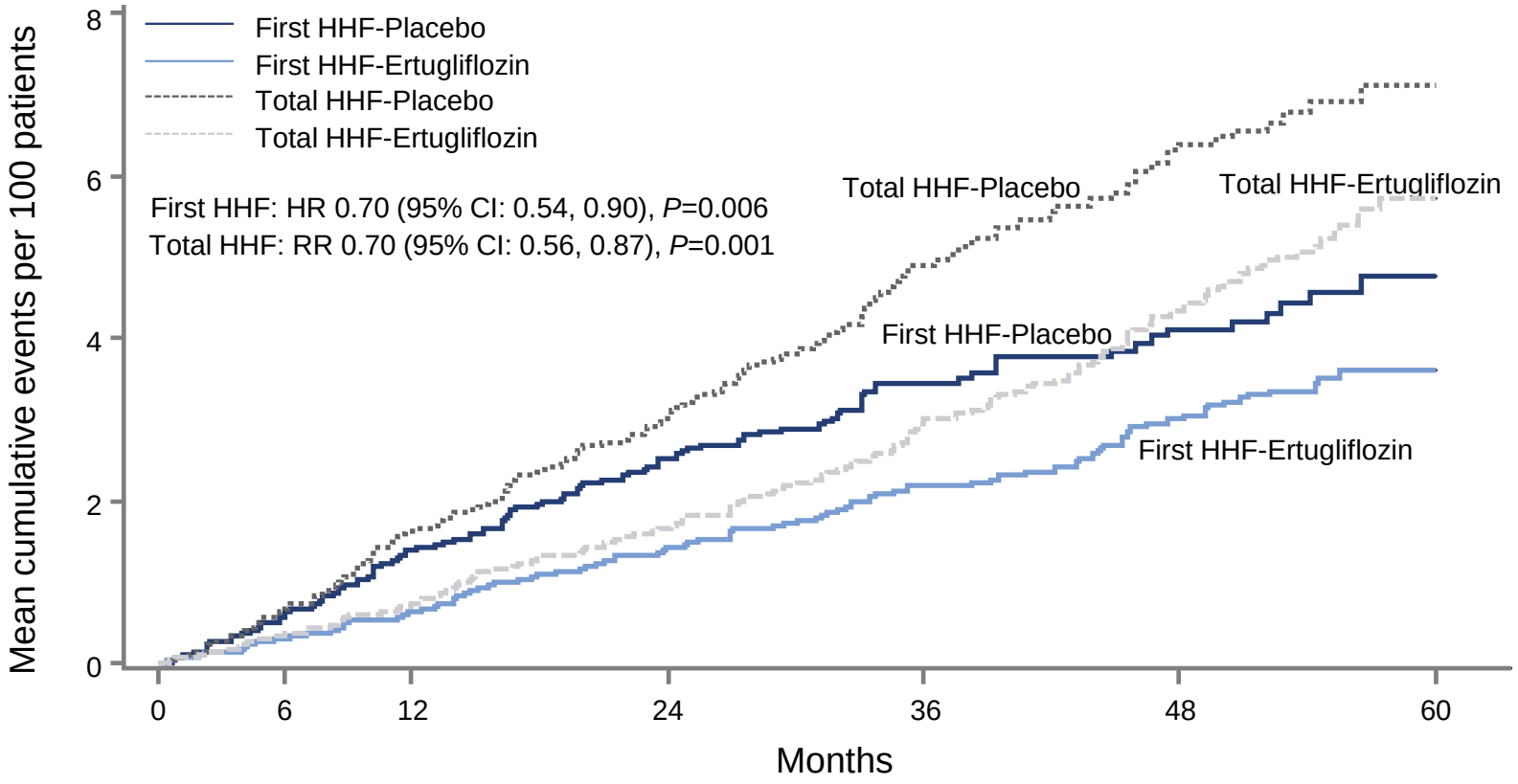
CI, confidence interval; EF, ejection fraction; HF, heart failure;
HHF, hospitalisation for heart failure.
Cosentino F et al. Presented at European Society of Cardiology Congress, 31 Aug 2020.

Time to first HHF by baseline eGFR, albuminuria and diuretics



†Includes loop and non-loop diuretics and mineralocorticoid receptor antagonists.
CI, confidence interval; eGFR, estimated glomerular filtration rate;
HHF, hospitalisation for heart failure.
Cosentino F et al. Presented at European Society of Cardiology Congress, 31 Aug 2020.

Cumulative incidence of first and total (first + recurrent) HHF events



No. at risk							
Total HHF-Placebo	2747	2715	2665	2585	1398	1151	225
Total HHF-Ertugliflozin	5499	5411	5327	5177	2806	2338	416

Ertugliflozin includes 5 mg and 15 mg doses
CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; RR, rate ratio.

Summary- CV outcomes

- In patients with T2DM and atherosclerotic CV disease, when added to guideline-directed secondary prevention therapies, ertugliflozin was **non-inferior versus placebo for MACE**

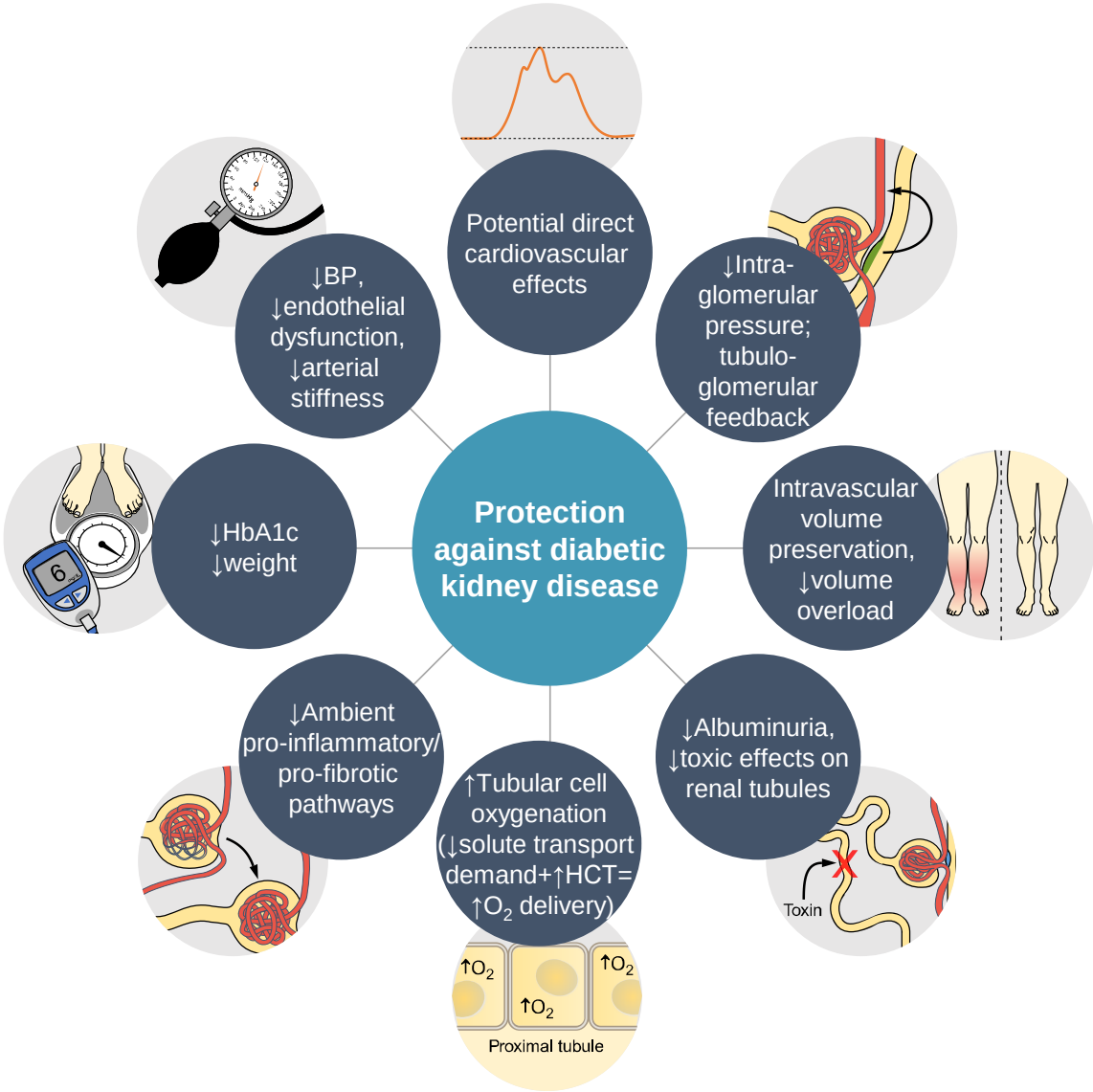
- The key secondary composite endpoint of CV death or HHF did not differ between groups, nor did CV death, but a **30% lower risk of time to first HHF** was observed with ertugliflozin
  - Effect was consistent across most subgroups, but greater benefit was observed in populations with **baseline eGFR <60 mL min^{-1} 1.73 m^{-2}, albuminuria, and diuretic use**

- VERTIS CV results provide additional evidence to support use of SGLT2 inhibitors in patients with T2DM to reduce the risk of HHF events

CV, cardiovascular; HF, heart failure; HHF, hospitalisation for heart failure;
MACE, major adverse cardiovascular events; T2DM, type 2 diabetes mellitus.

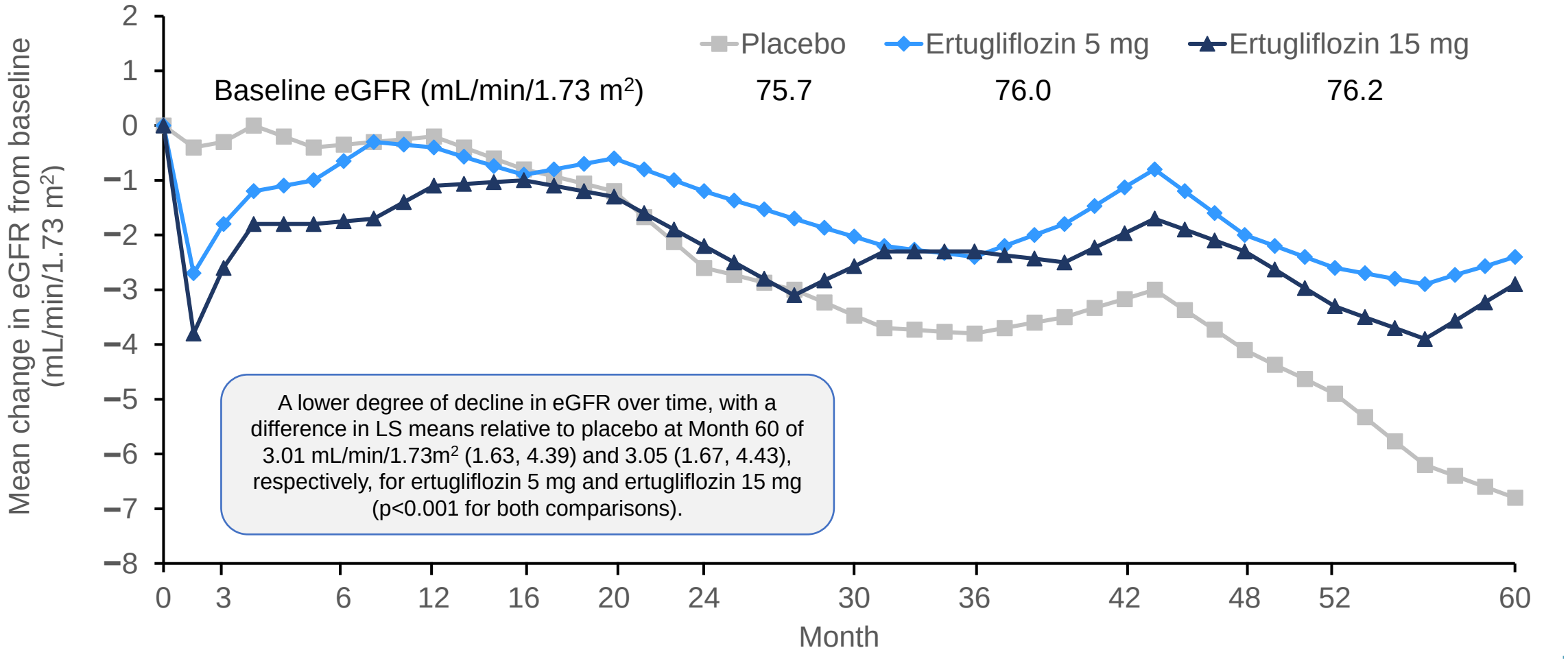
Kidney Outcomes by SGLT2i

Proposed renal protective pathways with SGLT2 inhibitors



BP, blood pressure; CKD, chronic kidney disease; HbA1c, glycated haemoglobin; HCT, haematocrit; SGLT2, sodium-glucose cotransporter 2.
Reprinted from *Kidney International*, 94(1), Hiddo J.L. Heerspink, Mikhail Kosiborod, Silvio E. Inzucchi, David Z.I. Cherney. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors, 26–39, Copyright (2018), with permission from Elsevier.

VERTIS CV: eGFR over time



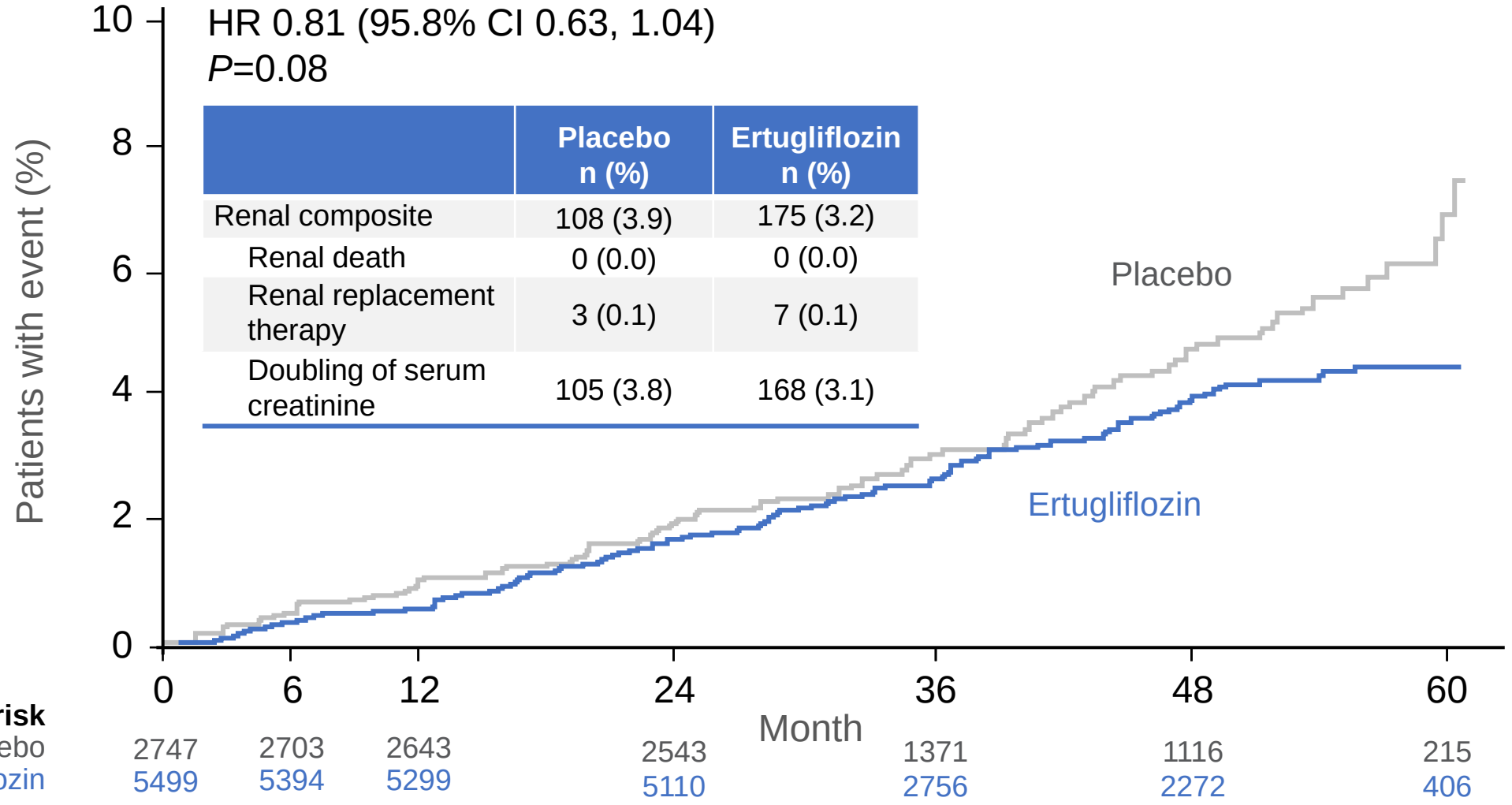
eGFR, estimated glomerular filtration rate.

Renal composite†[1]

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)



†Intention-to-treat analysis set that included all randomised 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. [1]Cannon CP. Evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial – VERTIS CV. American Diabetes Association Virtual Scientific Sessions. 2020.

Pre-specified exploratory kidney endpoints

- Cox proportional hazard of composite kidney outcomes
  - Sustained doubling of serum creatinine, chronic kidney dialysis/transplant or renal death
  - **Sustained 40% decrease in eGFR**, or chronic kidney dialysis/transplant or renal death
  - All in the overall population and by baseline kidney function categories

- Cox proportional hazard for categorical changes in albuminuria
  - **Progression** of albuminuria
  - **Regression** of albuminuria
  - In overall population and by baseline kidney function categories

- UACR over time
  - Changes over time in the geometric mean for UACR
  - In overall population and by baseline albuminuria status

- eGFR over time
  - Changes over time in eGFR calculated by the CKD-EPI formula
  - In overall population and by baseline albuminuria status

ARF, acute renal failure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio.

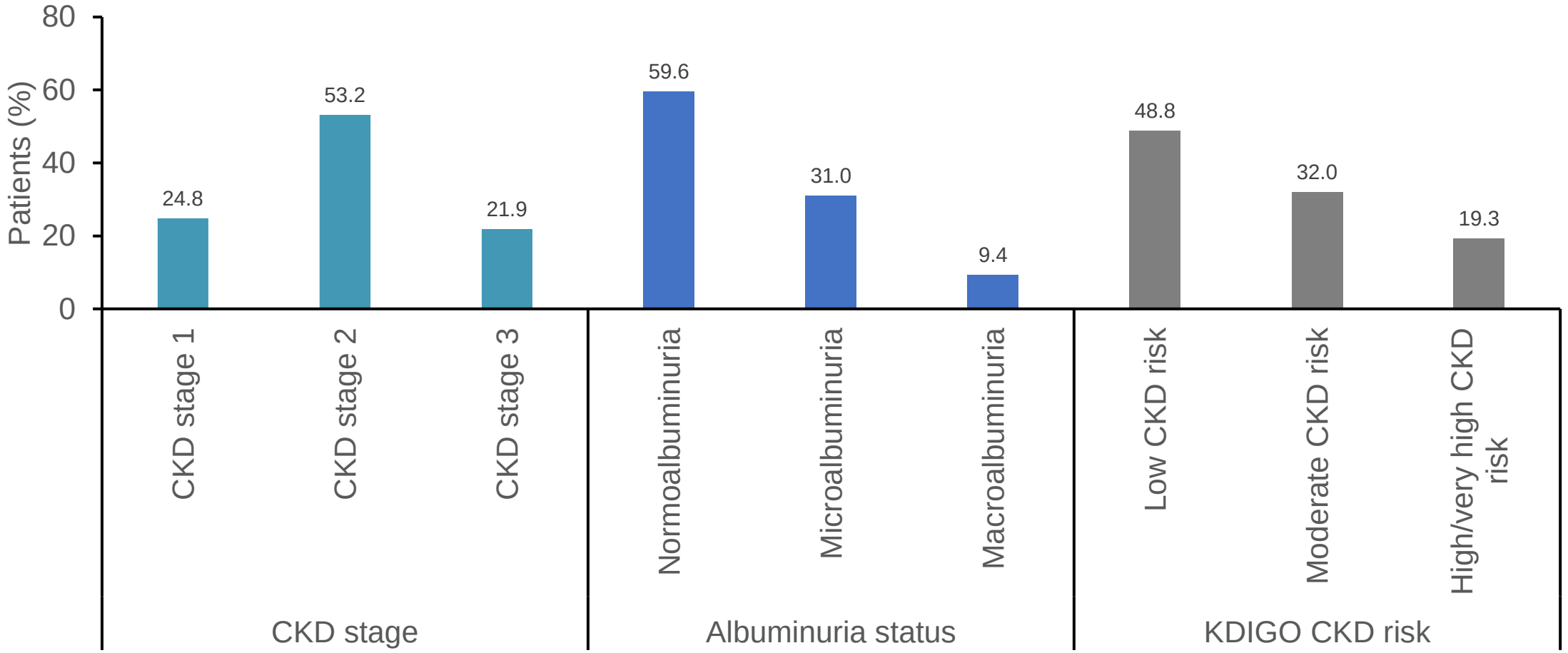
Classification by baseline kidney categories

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 decrease	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.I. 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.

Distribution by baseline kidney categories (overall population)



- Baseline kidney subgroups were generally balanced between the placebo and ertugliflozin groups

CKD, chronic kidney disease; KDIGO CKD, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease.

Pre-specified and exploratory secondary analyses

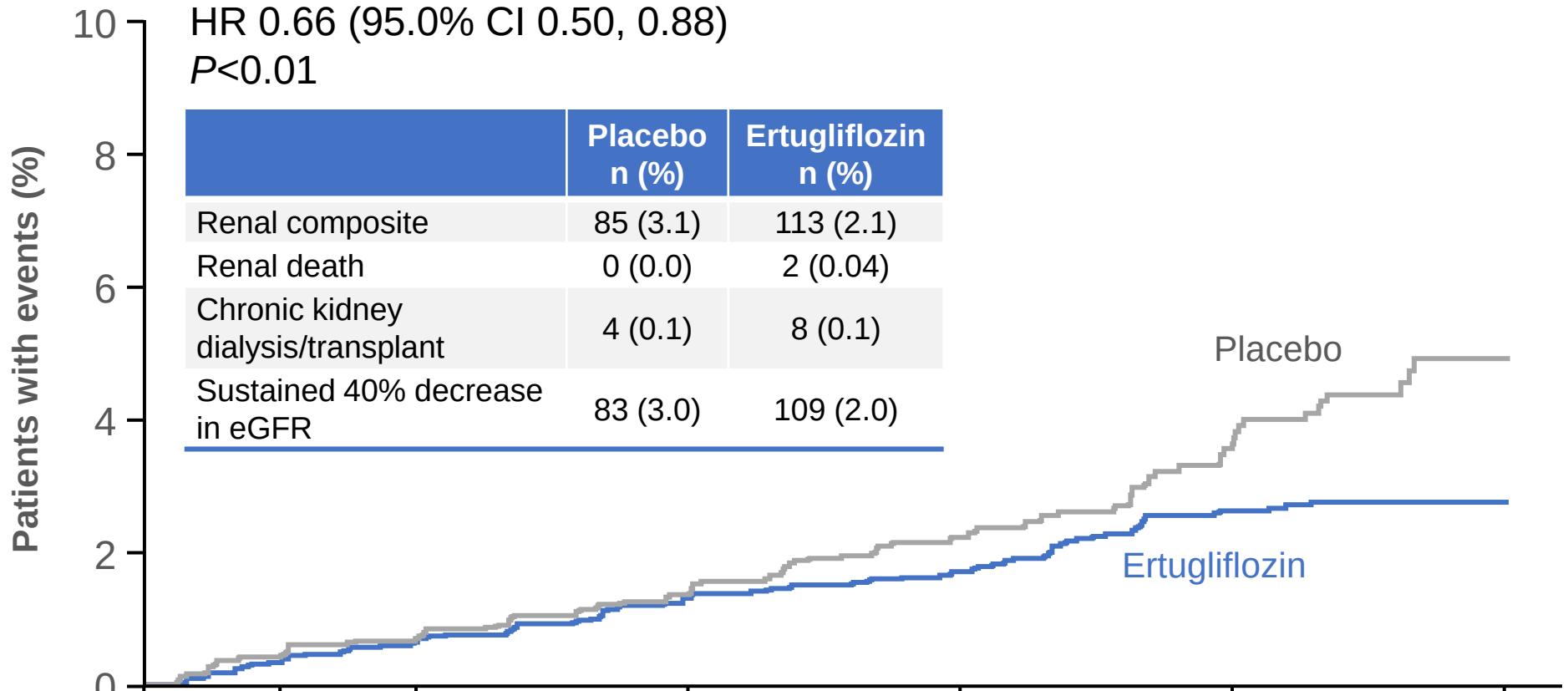
	Placebo N=2747		Ertugliflozin N=5499			
	n (%)	Event rate 100 P-Y	n (%)	Event rate 100 P-Y	HR (95% CI)	*P* value
Doubling of serum creatinine, kidney dialysis/transplant or renal death[1]	108 (3.93)	1.15	175 (3.18)	0.93	0.81 (0.63, 1.04)	0.081
Sustained doubling of serum creatinine, chronic kidney dialysis/transplant or renal death	33 (1.20)	0.35	43 (0.78)	0.23	0.65 (0.41, 1.02)	0.062
Sustained 40% reduction in eGFR, chronic kidney dialysis/transplant or renal death	85 (3.09)	0.90	113 (2.05)	0.60	0.66 (0.50, 0.88)	<0.01

eGFR calculated by the Modification of Diet in Renal Disease formula.
AERR, absolute event rate reduction; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; P-Y, person-years. [1]Cannon CP. Evaluation of ertugliflozin efficacy and safety cardiovascular outcomes trial - VERTIS CV. American Diabetes Association Virtual Scientific Sessions. 2020.

Exploratory renal composite: *Sustained 40% decrease from baseline in eGFR*, chronic kidney dialysis/transplant or renal death†

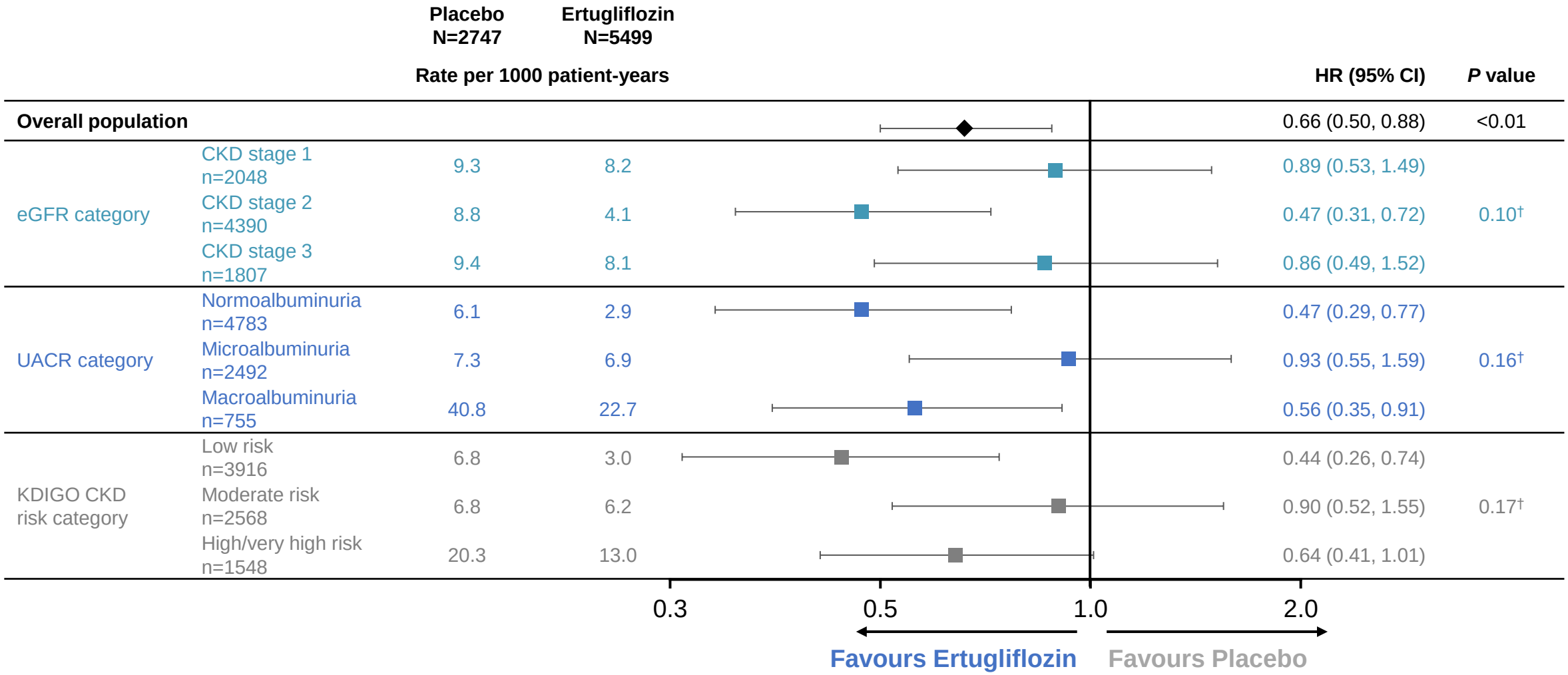
HR 0.66 (95.0% CI 0.50, 0.88)
P<0.01

	Placebo n (%)	Ertugliflozin n (%)
Renal composite	85 (3.1)	113 (2.1)
Renal death	0 (0.0)	2 (0.04)
Chronic kidney dialysis/transplant	4 (0.1)	8 (0.1)
Sustained 40% decrease in eGFR	83 (3.0)	109 (2.0)



†Intention-to-treat analysis set that included all randomised patients.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

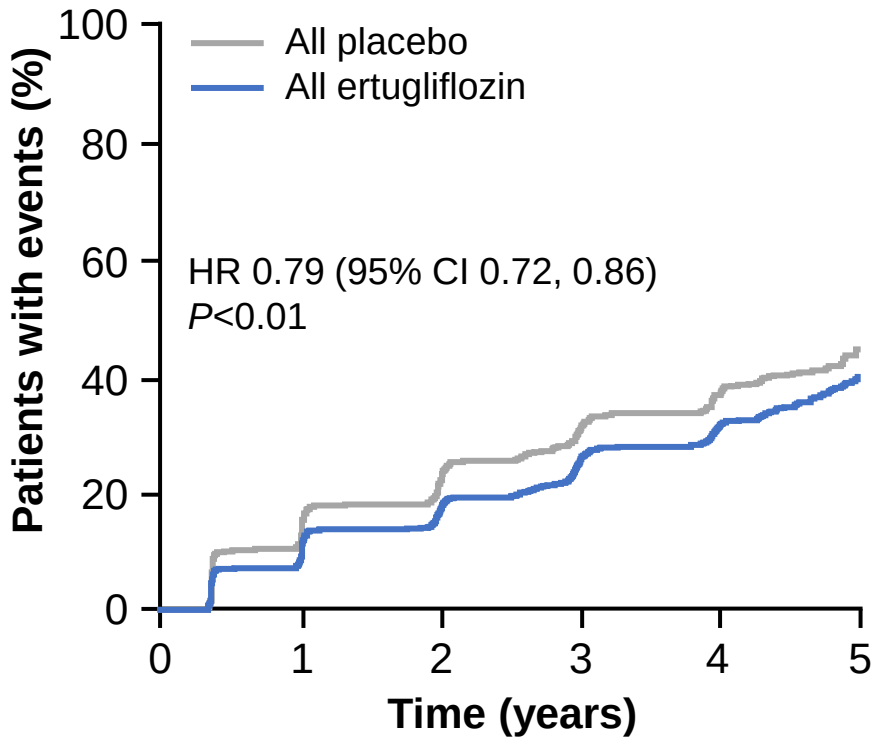
Composite of sustained 40% decrease in eGFR, or chronic kidney dialysis/transplant or renal death by baseline kidney function categories



†The interaction *P* value is for the treatment-by-subgroup interaction.
CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; KDIGO CKD, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease; UACR, urinary albumin-to-creatinine ratio

Ertugliflozin reduces the risk for progression of albuminuria in the overall cohort

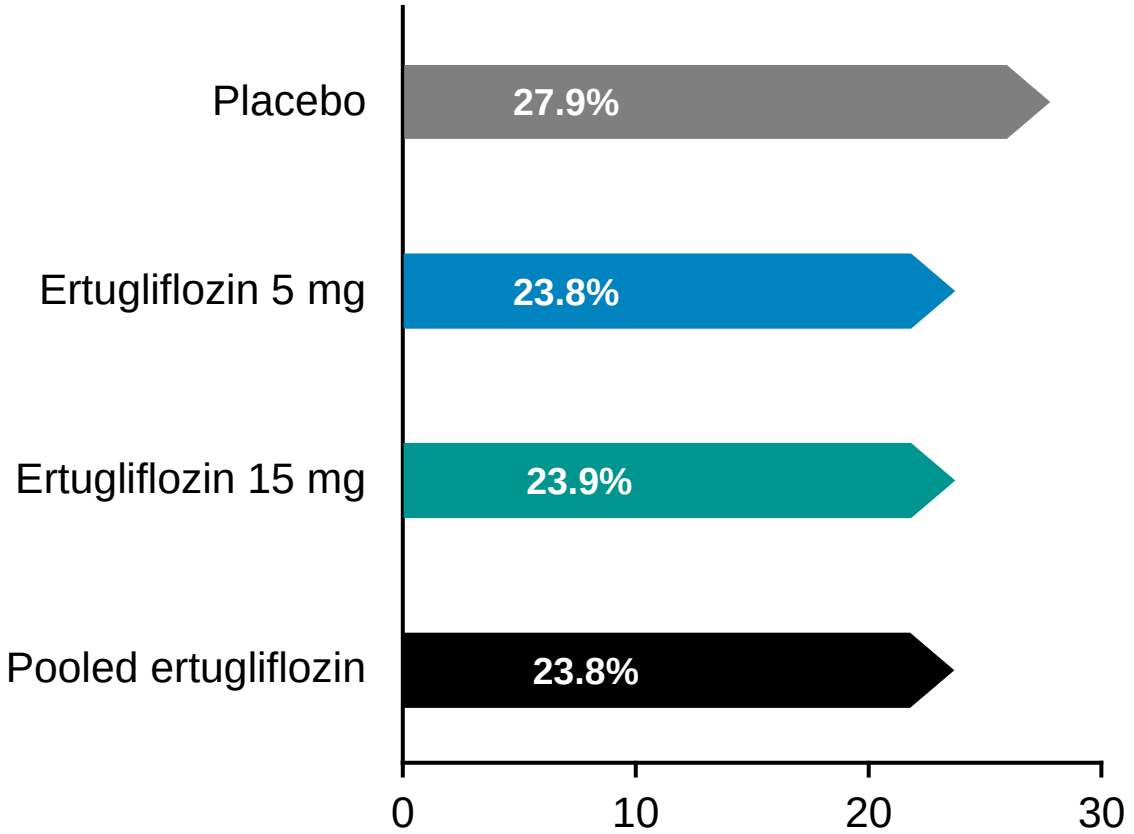
Kaplan–Meier curves of time to first progression of albuminuria†



Number of patients at risk

All placebo	2745	2006	1633	713	520	62
All ertugliflozin	5493	4245	3632	1647	1251	162

Progression to a higher albuminuric state



†Intention-to-treat analysis set that included all randomised patients.
CI, confidence interval; HR, hazard ratio.

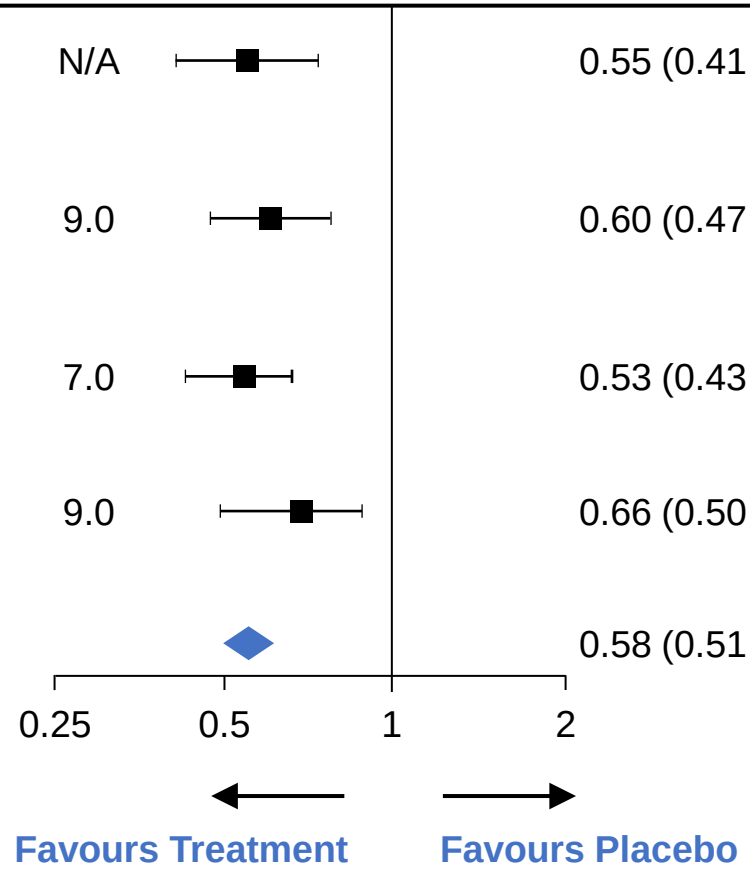
Kidney outcomes using generally consistent definitions: Sustained ≥40% decline in eGFR, ESKD or renal death

	Kidney composite outcomes	HR (95% CI)
EMPA-REG OUTCOME[1]	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.55** (0.41, 0.73)
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 and/or end-stage renal disease and/or renal death	**0.53** (0.43, 0.66)
VERTIS CV*	Sustained ≥40% reduction in eGFR, renal-replacement therapy (dialysis or transplantation), or death from renal causes	**0.66** (0.50, 0.88)

*Pre-specified exploratory, intention-to-treat analysis set, 95.0% CI.
CV, cardiovascular; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[1]Post-hoc exploratory, Perkovic V et al. *Nephrol Dial Transplant* (2019) 1–9; [2]Pre-specified exploratory, Neal B et al. *N Engl J Med* 2017;377:644-657; [3]Pre-specified secondary, Wiviott SD et al. *N Engl J Med* 2019;380:347-357.

Kidney outcomes using generally consistent definitions: Sustained ≥40% decline in eGFR, ESKD or renal death

	Treatment		Placebo		Hazard Ratio (95% CI)
	Events/N (%)	Rate per 1000 Patient-years	Events/N (%)	Rate per 1000 Patient-years	
EMPA-REG OUTCOME[1]	100/4645 (2.15)	N/A	86/2323 (3.70)	N/A	0.55 (0.41, 0.73)
CANVAS Programme[2]	124/5795 (2.14)	5.5	125/4347 (2.88)	9.0	0.60 (0.47, 0.77)
DECLARE-TIMI 58[3]	127/8582 (1.48)	3.7	238/8578 (2.77)	7.0	0.53 (0.43, 0.66)
VERTIS CV	113/5499 (2.05)	6.0	85/2747 (3.09)	9.0	0.66 (0.50, 0.88)
Pooled estimate (Q statistic *P*=0.643; I^2=0.0%)					0.58 (0.51, 0.65)



Intention-to-treat analysis set.
CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[1]Perkovic V et al. *Nephrol Dial Transplant.* 2019:1–9; [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.

Summary – renal outcome

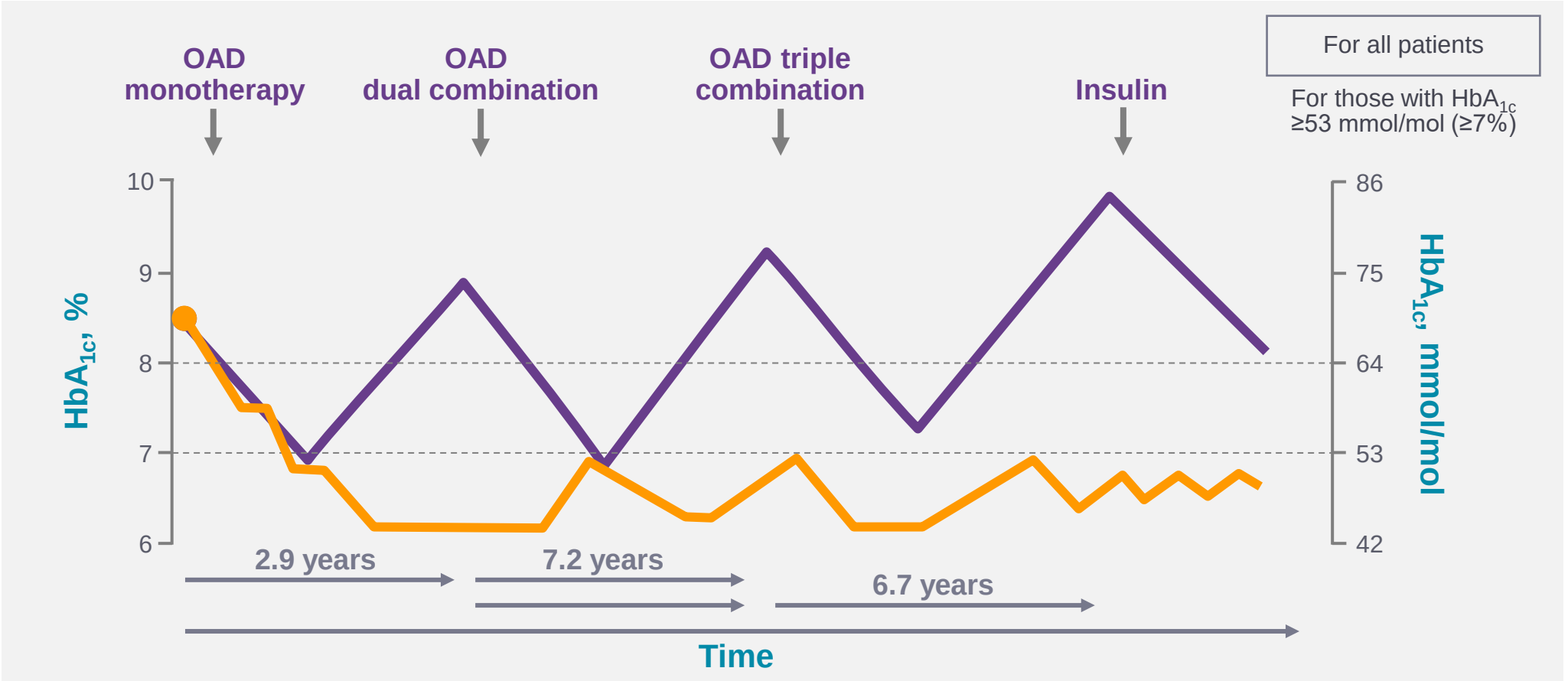
- The results of VERTIS CV provide further evidence supporting the beneficial effects of this drug class on CV and kidney outcomes:
  - Ertugliflozin reduced the risk of the pre-specified exploratory renal composite, which included a sustained 40% decline in eGFR, chronic renal replacement therapy or renal death
    - The relative risk reduction for the kidney composite was similar across CKD stage, level of UACR and KDIGO CKD risk category, demonstrating consistent kidney benefits regardless of how CKD was defined
  - Significantly reduced UACR in patients with a range of albuminuria at baseline; preserved kidney function, especially in patients with macroalbuminuria at greatest risk of DKD progression

CKD, chronic kidney disease; CV, cardiovascular; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO CKD, Kidney Disease: Improving Global Outcomes in Chronic Kidney Disease; SGLT2, sodium-glucose cotransporter 2; UACR, urinary albumin-to-creatinine ratio.

Combination of SGLT2i and DPP4i

Earlier and Appropriate Intensification May Improve Patients' Chances of Reaching HbA_{1c} Goal[1]

Published Conceptual Approach to Conventional vs Proactive Management of T2DM



Adapted with permission from Khunti et al.[1]
T2DM = type 2 diabetes mellitus; OAD = oral antidiabetic agent.

1. Khunti K et al. *Prim Care Diabetes.* 2017;11:3–12.

Complementary Actions of SGLT2 Inhibitors and DPP-4 Inhibitors[1-4]

Mechanisms of Action	SGLT2 Inhibitor	DPP-4 Inhibitor
Insulin secretion	↔	↑
Glucagon secretion	↑	↓
Glucosuria	↑	↔
β-cell sensitivity/function	↑	↑
Active incretin levels (GLP-1, GIP)	↔	↑

Physiologic Effects	SGLT2 Inhibitor	DPP-4 Inhibitor
HbA_{1c}	↓	↓
Weight	↓	↔
Blood pressure	↓	↔

Adapted with permission from Dey J et al. [1]
SGLT2 = sodium-glucose cotransporter 2; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; GIP = gastric inhibitory polypeptide.
1. Dey J et al. *Postgrad Med*. 2017;129:409–420. **2.** Ferrannini E et al. *J Clin Invest.* 2014;124:499–508. **3.** Roden M et al. *Lancet Diabetes Endocrinol.* 2013;1:208–219. **4.** Muscelli E et al. *J Clin Endocrinol Metab.* 2012;97:2818-26.

全民健康保險糖尿病用藥給付規定 (2020/5/1)

針對第二型糖尿病患，在使用metformin後合併 SGLT2i 或 DPP4i 至少六個月未能達到適當血糖控制時 (HbA1c >7.5%)

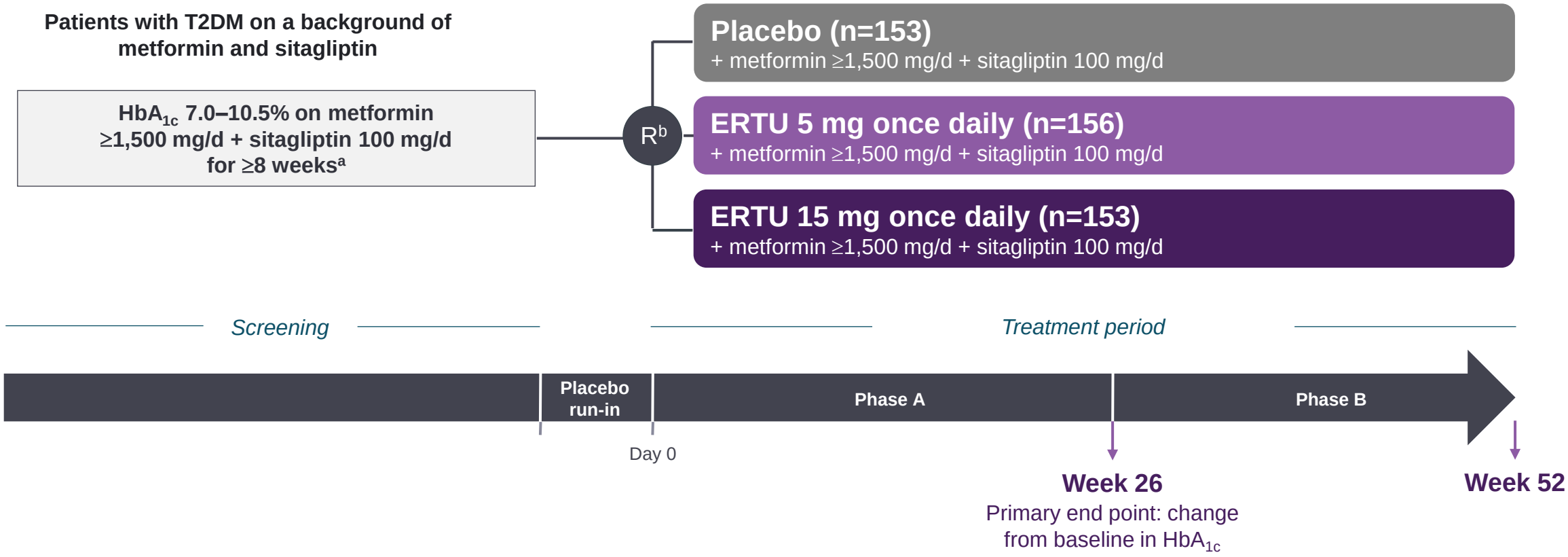
- 使用方法: 起始劑量每日早上一次每次 5mg ertugliflozin/ 100mg sitagliptin， 可與食物一起服用、亦可空腹服用
- 健保給付規範:限每日處方一粒

Reference: 衛生福利部中央健康保險署藥品給付規定 (https://www.nhi.gov.tw/Content_List.aspx?n=E70D4F1BD029DC37&topn=3FC7D09599D25979)

The Efficacy and Safety of Ertugliflozin as Combination Therapy: VERTIS SITA2

VERTIS = eValuation of ERTugliflozin effIcacy and Safety.

VERTIS SITA2: Study Design[1]



[a]Patients on the protocol regimen for <8 weeks, on metformin ≥1500 mg/day and a sulfonylurea, or on lower doses of metformin and/or another DPP-4 inhibitor at screening were eligible to enroll if they met entry criteria after the appropriate dose/medication adjustment, stabilization, or washout period.
[b]A total of 464 patients were randomized and 2 patients in the ertugliflozin 15-mg group did not receive study medication, resulting in 462 treated patients.
T2DM = type 2 diabetes mellitus; R = randomization; ERTU = ertugliflozin; DPP-4 = dipeptidyl peptidase-4.

1. Dagogo-Jack S et al. *Diabetes Obes Metab*. 2018;20:530–540.

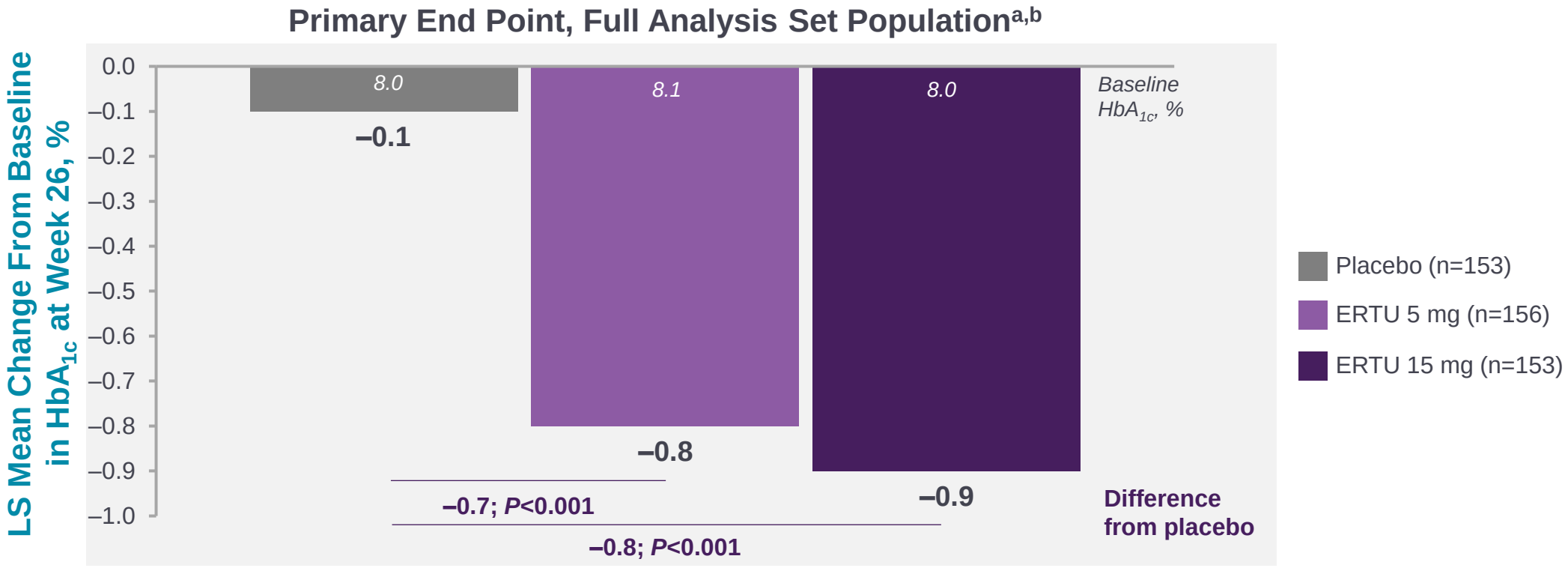
VERTIS SITA2:
Patient Baseline Characteristics[1]

	Placebo (n=153)	ERTU 5 mg (n=156)	ERTU 15 mg (n=153)
Male, n (%)	100 (65.4)	81 (51.9)	82 (53.6)
Age, y	58.3 ± 9.2	59.2 ± 9.3	59.7 ± 8.6
Duration of T2DM, y	9.4 ± 5.6	9.9 ± 6.1	9.2 ± 5.3
Baseline HbA_{1c}, %	8.0 ± 0.9	8.1 ± 0.9	8.0 ± 0.8
FPG, mg/dL	169.6 ± 37.8	167.7 ± 37.7	171.7 ± 39.1
Body weight, kg	86.4 ± 20.8	87.6 ± 18.6	86.6 ± 19.5
BMI, kg/m^2	30.3 ± 6.4	31.2 ± 5.5	30.9 ± 6.1
SBP, mmHg	130.2 ± 13.3	132.1 ± 12.5	131.6 ± 13.2
eGFR, mL/min/1.73 m^2	89.9 ± 17.5	87.0 ± 17.5	86.9 ± 15.6

Adapted with permission from Dagogo-Jack S et al.[1]
Values are mean ± standard deviation, unless otherwise indicated.
ERTU = ertugliflozin; T2DM = type 2 diabetes mellitus; FPG = fasting plasma glucose; BMI = body mass index; SBP = systolic blood pressure; eGFR = estimated glomerular filtration rate.

1. Dagogo-Jack S et al. *Diabetes Obes Metab*. 2018;20:530–540.

VERTIS SITA2: HbA_{1c} Reductions at Week 26[1]

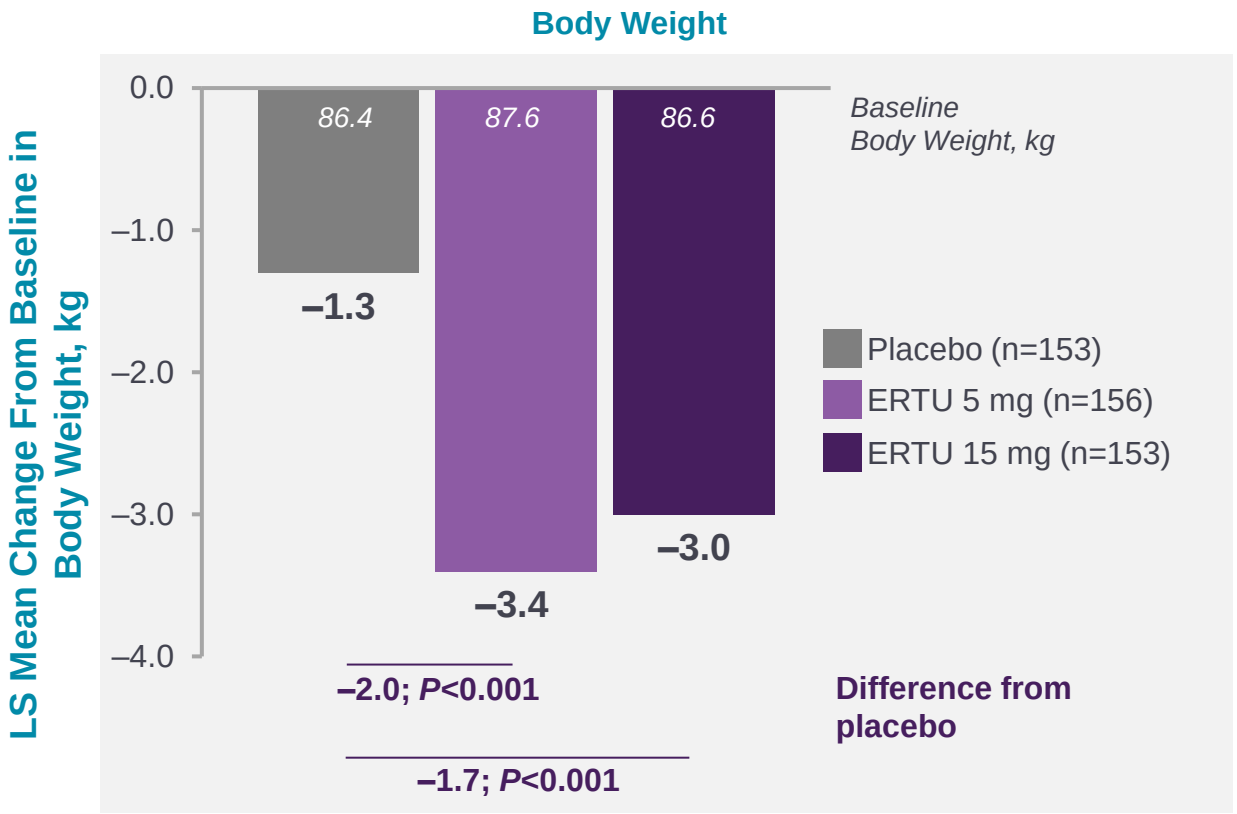


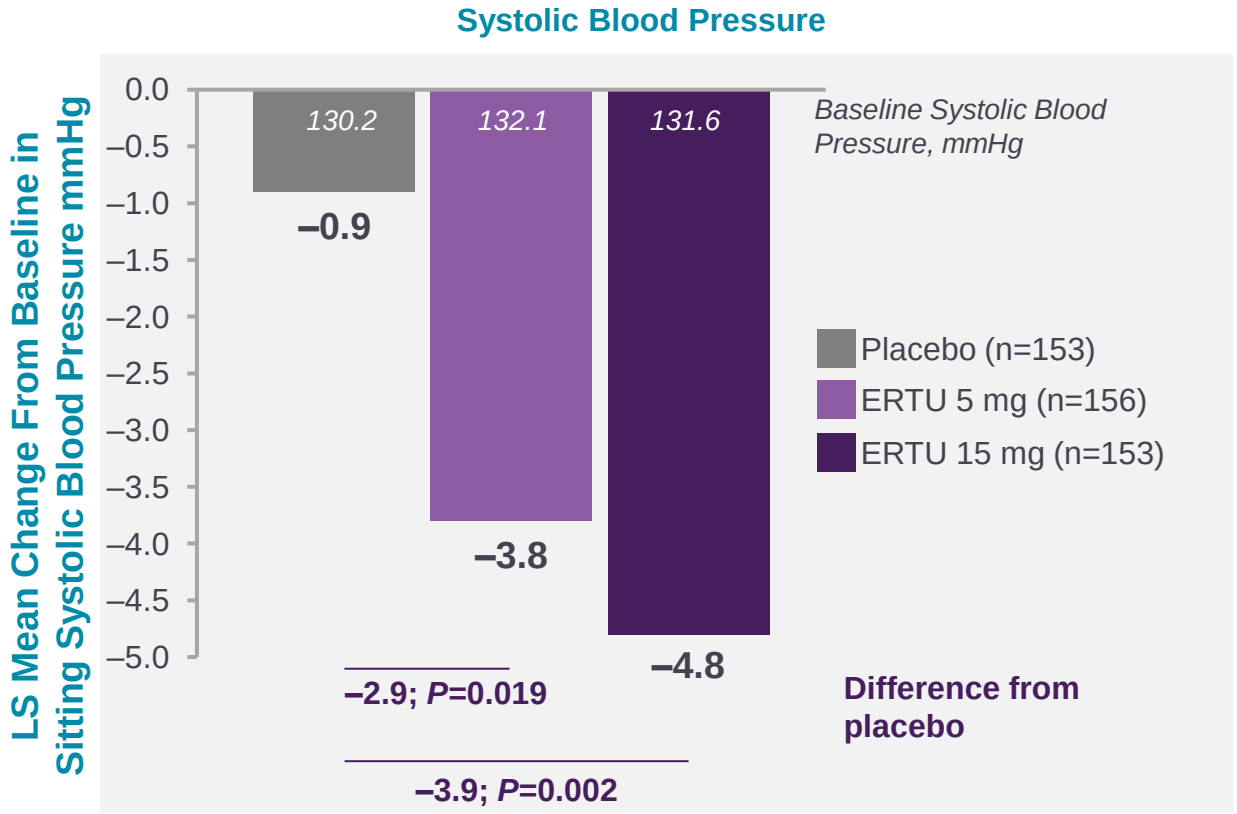
[a]The population includes all randomized patients who received at least one dose of study medication and had at least 1 measurement of the analysis variable (baseline or post-baseline). Missing data were not imputed.
[b]LS means adjusted for treatment, time, prior antihyperglycemic medication, baseline eGFR, and the interaction of time by treatment.
LS = least-squares; ERTU = ertugliflozin.

1. Dagogo-Jack S et al. *Diabetes Obes Metab*. 2018;20:530–540.

VERTIS SITA2:
Reductions in Body Weight and Systolic Blood Pressure at Week 26[1]

Secondary End Points, Full Analysis Set Population[a,b]





Ertugliflozin is not indicated for the reduction of body weight or systolic blood pressure.
[a]The population includes all randomized patients who received at least one dose of study medication and had at least 1 measurement of the analysis variable (baseline or post-baseline).
[b]LS means adjusted for treatment, time, prior antihyperglycemic medication, baseline eGFR, and the interaction of time by treatment.
LS = least squares; ERTU = ertugliflozin.

1. Dagogo-Jack S et al. *Diabetes Obes Metab*. 2018;20:530–540.

Safety

Overall and selected AEs- Vertis-CV

	Placebo n (%) (n=2745)	Ertugliflozin 5 mg n (%) (n=2746)	Ertugliflozin 15 mg n (%) (n=2747)
≥1 AE	2349 (85.6)	2357 (85.8)	2325 (84.6)
≥1 AE leading to permanent study drug discontinuation	188 (6.8)	207 (7.5)	201 (7.3)
≥1 serious AE	990 (36.1)	958 (34.9)	937 (34.1)
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 hypoglycaemia	790 (28.8)	768 (28.0)	728 (26.5)
Hypovolemia	106 (3.9)	118 (4.3)	118 (4.3)

**P*<0.05 for the comparison with placebo. ****P*<0.001 for the comparison with placebo.
AE, adverse event.

VERTIS SITA2: Prespecified Adverse Events[a] Over 26 Weeks[1]

	Number of Patients[b] (%)		
	Placebo (n=153)	ERTU 5 mg (n=156)	ERTU 15 mg (n=153)
Genital mycotic infection (female)	1 (1.9)	6 (8.0)	9 (12.7)[c]
Genital mycotic infection (male)	0	4 (4.9)[c]	3 (3.7)
Urinary tract infection	3 (2.0)	4 (2.6)	7 (4.6)
Symptomatic hypoglycemia[d]	4 (2.6)	6 (3.8)	1 (0.7)
Hypovolemia	1 (0.7)	1 (0.6)	0

Adapted with permission from Dagogo-Jack S et al.[1]

[a]AEs of special interest prespecified for inferential testing without multiplicity control.

[b]The population includes all randomized, treated patients. Data following initiation of glycemic rescue therapy were excluded.

[c]*P*<0.05 vs placebo.

[d]Symptomatic hypoglycemia based on clinical symptoms reported by investigator.

ERTU = ertugliflozin; AE = adverse events.

1. Dagogo-Jack S et al. *Diabetes Obes Metab*. 2018;20:530–540.

Summary and conclusions

- DPP4i and SGLT2i are effective for Asian T2D papulation
- VERTIS CV achieved its primary endpoint of non-inferiority for MACE compared with placebo in patients with T2DM and established ASCVD, demonstrating the safety of ertugliflozin
- Ertugliflozin was associated with a decrease in the risk of a sustained 40% decline in eGFR, with less albuminuria and with preservation of eGFR over time
- The combination of SGLT2 and DPP4 inhibitors, independent of glucose control considerations, is the trend in patients with T2DM with or at high risk for CV and kidney complications

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular;
eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure;
MACE, major adverse cardiovascular events; SGLT2, sodium-glucose cotransporter 2;
T2DM, type 2 diabetes mellitus.