01 CV Benefit of SGLT2 inhibitor

02 Why Efficacy Matters

03 What's New in SGLT2 inhibitor Ertugliflozin

CV, cardiovascular; SGLT2, sodium–glucose cotransporter 2;

CV, cardiovascular; SGLT2, sodium–glucose cotransporter 2;

Diabetes Doubles the Risk of Vascular Disease[1]

Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies

The Emerging Risk Factors Collaboration*

Summary

Background Uncertainties persist about the magnitude of associations of diabetes mellitus and fasting glucose concentration with risk of coronary heart disease and major stroke subtypes. We aimed to quantify these associations for a wide range of circumstances.

Methods We undertook a meta-analysis of individual records of diabetes, fasting blood glucose concentration, and other risk factors in people without initial vascular disease from studies in the Emerging Risk Factors Collaboration. We combined within-study regressions that were adjusted for age, sex, smoking, systolic blood pressure, and body-mass index to calculate hazard ratios (HRs) for vascular disease.

Diabetes Doubles the Risk of Vascular Disease[1]

Outcome	Number of cases		HR (95% CI)	I² (95% CI)
Coronary heart disease	26 505		2.00 (1.83 – 2.19)	64 (54 – 71)
Coronary death	11 556		2.31 (2.05 – 2.60)	41 (24 – 54)
Non-fatal myocardial infarction	14 741		1.82 (1.64 – 2.03)	37 (19 – 51)
Cerebrovascular disease	11 176		1.82 (1.65 – 2.01)	42 (25 – 55)
Ischaemic stroke	3799		2.27 (1.95 – 2.65)	1 (0 – 20)
Haemorrhagic stroke	1183		1.56 (1.19 – 2.05)	0 (0 – 26)
Unclassified stroke	4973		1.84 (1.59 – 2.13)	33 (12 – 48)
Other vascular deaths	3826		1.73 (1.51 – 1.98)	0 (0 – 26)

Hazard Ratio (diabetes vs. no diabetes)

1. ERFC. Lancet. 2010;375:2215-22.

Dysglycaemia and CV Risk:
Impact of Glucose Perturbations in Patients Who Have Experienced MI[1]

GAMI – long-term follow-up First major event (CV mortality, MI, Stroke, or HF)

Log-rank overall: p=0.0046

- Pat + NGT
- Pat + DM
- Pat + IGT

Proportion of event-free survival

Follow-up (years)
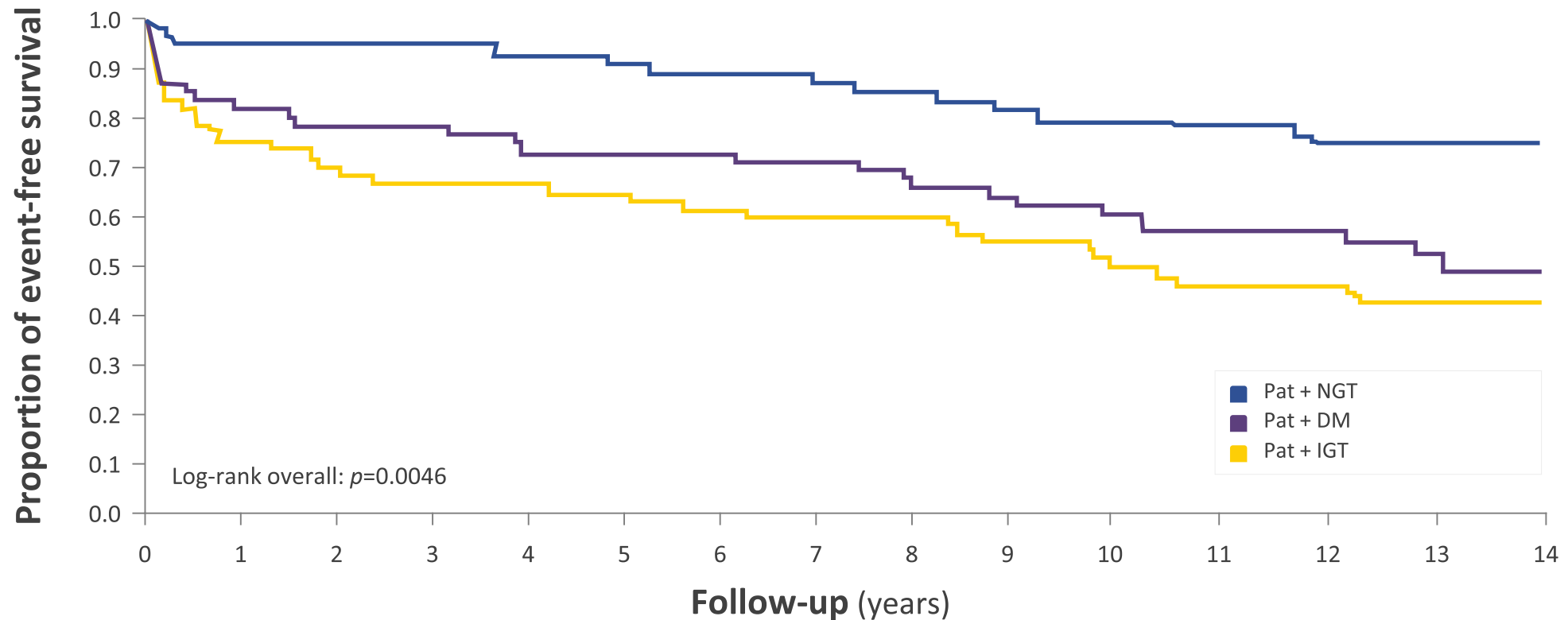
GAMI, Glucose Tolerance in Patients with Acute Myocardial Infarction; DM, diabetes mellitus; GAMI, Glucose Tolerance in Patients with Acute Myocardial Infarction; HF, heart failure; IGT, impaired glucose tolerance; MI, myocardial infarction; NGT, normal glucose tolerance; Pat, patients
Study design: During 1998–2001, consecutive patients with AMI (n = 167) and healthy controls (n = 184) with no previously known diabetes were investigated with an oral glucose tolerance test (OGTT). Patients and controls were separately followed up for cardiovascular events (first of cardiovascular ortality/AMI/stroke/heart failure) during a decade.

1. Ritsinger V *et al*, Diab Vasc Dis Res 2015;12:23–32

Higher HbA$_{1c}$ Predicts higher CV Risk[1]

Fatal & non-fatal MI

$p<0.0001$

Hazard ratio

14% decrease
per 1% reduction in HBA$_{1c}$

HbA$_{1c}$ (%)

Fatal & non-fatal stroke

$p=0.035$

12% decrease
per 1% reduction in HBA$_{1c}$

Amputation/death from PVD

$p<0.0001$

Hazard ratio

43% decrease
per 1% reduction in HBA$_{1c}$

HbA$_{1c}$ (%)

Heart failure

$p=0.021$

16% decrease
per 1% reduction in HBA$_{1c}$
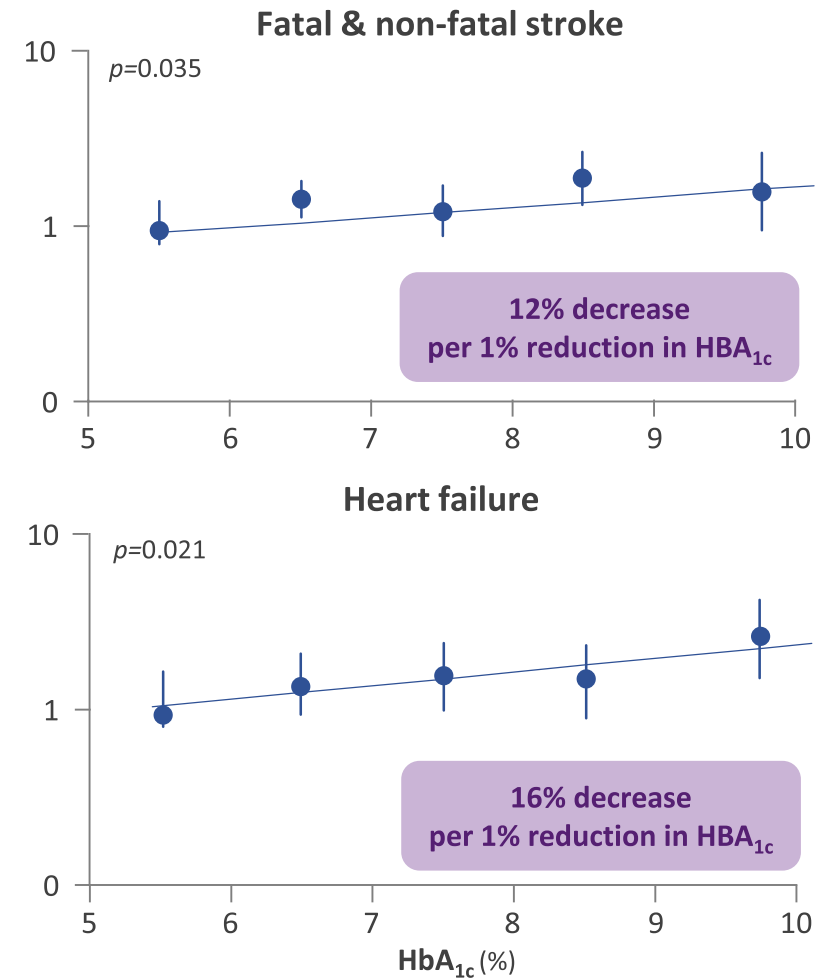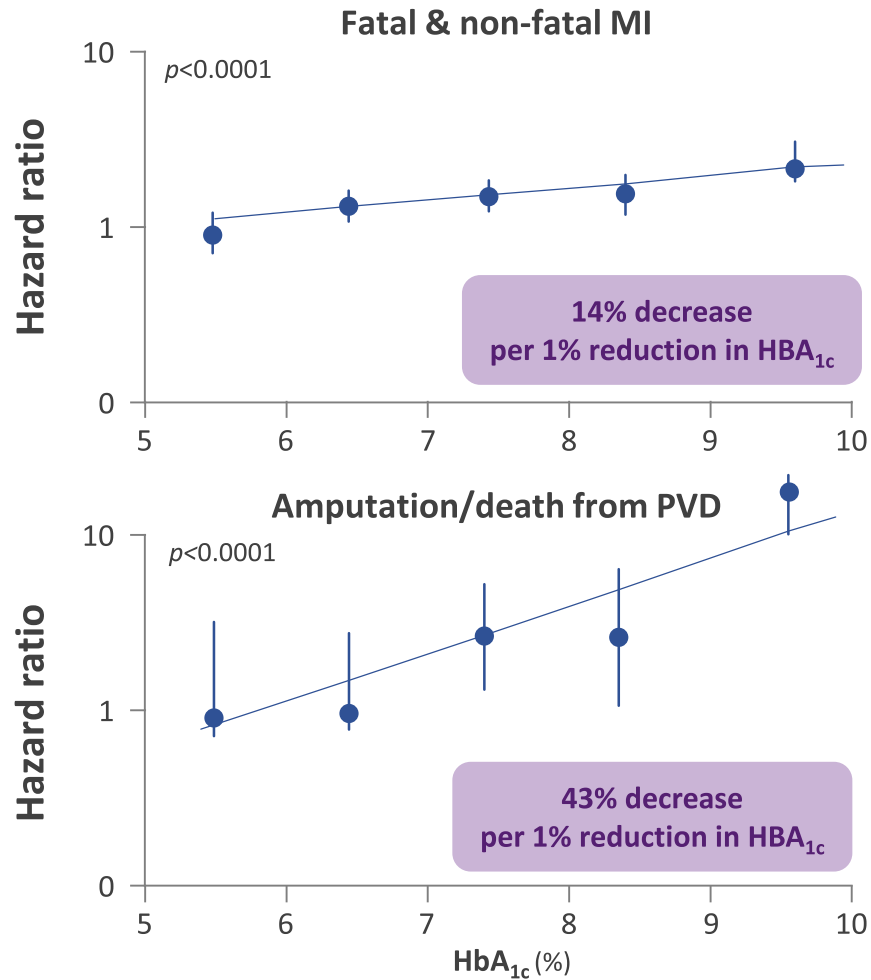
HbA$_{1c}$ (%)

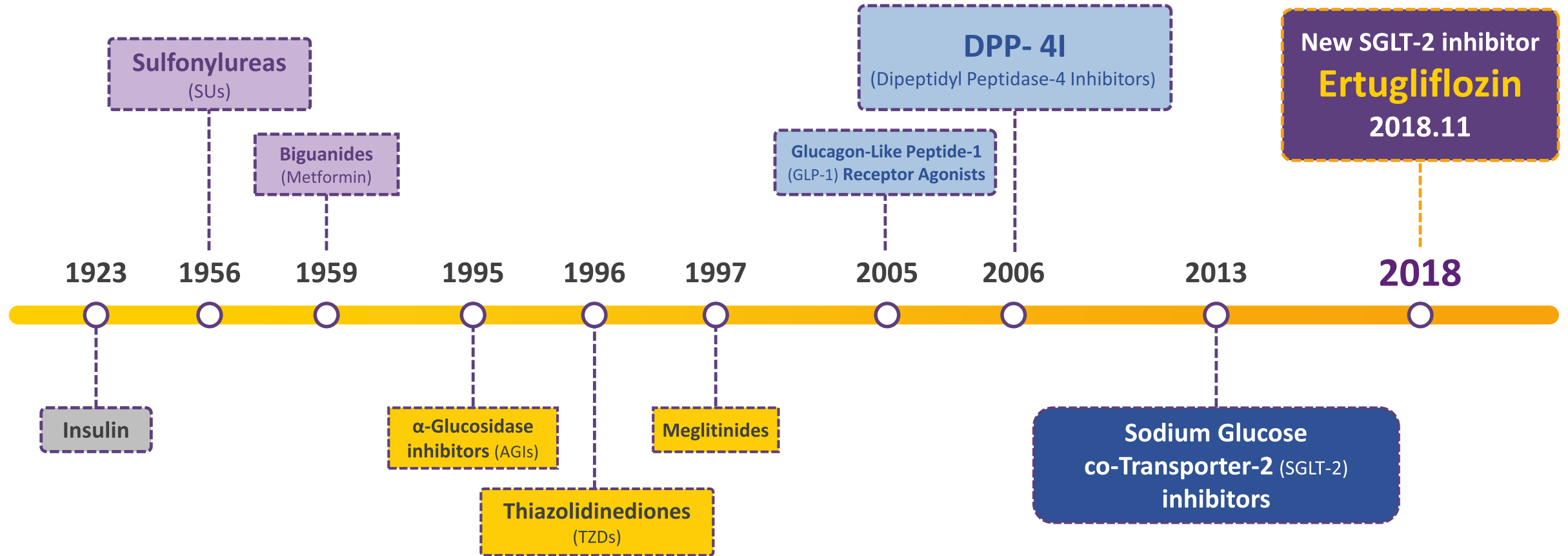Reference category (hazard ratio 1.0) is HbA1c<6% with log linear scales
CV, cardiovascular; HbA1c, glycosylated haemoglobin; MI, myocardial infarction; PVD, peripheral vascular disease
Study design: Prospective observational study including 23 hospital based clinics in England, Scotland, and Northern Ireland. Of 5102 patients, 4585 white, Asian Indian, and AfroCaribbean UKPDS patients, whether randomised or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk. Primary predefined aggregate clinical outcomes were any complications or deaths related to diabetes and all cause mortality.

1. Stratton IM *et al*. BMJ 2000;321:405–412

We need Some approaches
targeting to correct dysglycemia
to shed more light on the
link between dysglycaemia and serious outcomes.

History of the Development of Diabetes Medications[1]

Sulfonylureas (SUs)

Biguanides (Metformin)

DPP- 4I (Dipeptidyl Peptidase-4 Inhibitors)

Glucagon-Like Peptide-1 (GLP-1) **Receptor Agonists**

New SGLT-2 inhibitor Ertugliflozin 2018.11

1923 1956 1959 1995 1996 1997 2005 2006 2013 **2018**

Insulin

α-Glucosidase inhibitors (AGIs)

Meglitinides

Thiazolidinediones (TZDs)

Sodium Glucose co-Transporter-2 (SGLT-2) **inhibitors**

1. White JR, *et al*. Diabetes Spectrum 2014;27:82-86.

Cardiovascular Effects of SGLT-2 Inhibitors[1]

⚕ **Along with the primary antihyperglycemic effect, hemodynamic and metabolic effects of SGLT-2 inhibitors result in improved myocardial function and a reduced risk of heart failure.[1]**

SGLT-2 inhibitor

Kidney

Natriuresis → ↓Systolic blood pressure

Diuresis → ↓Arterial stiffness

Uricosuria → ↓Plasma volume

↓Uric acid

Glucosuria
- ↓Body weight
- ↓Hyper glycemia → ↑Glucagon, ↑Ketones
- ↓Glucose toxicity → ↓Insulin resistance

Hemodynamic effects

Metabolic effects

Heart

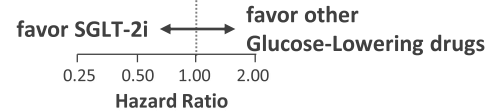1. Scheen AJ. Circ Res. 2018;122:1439-1459.
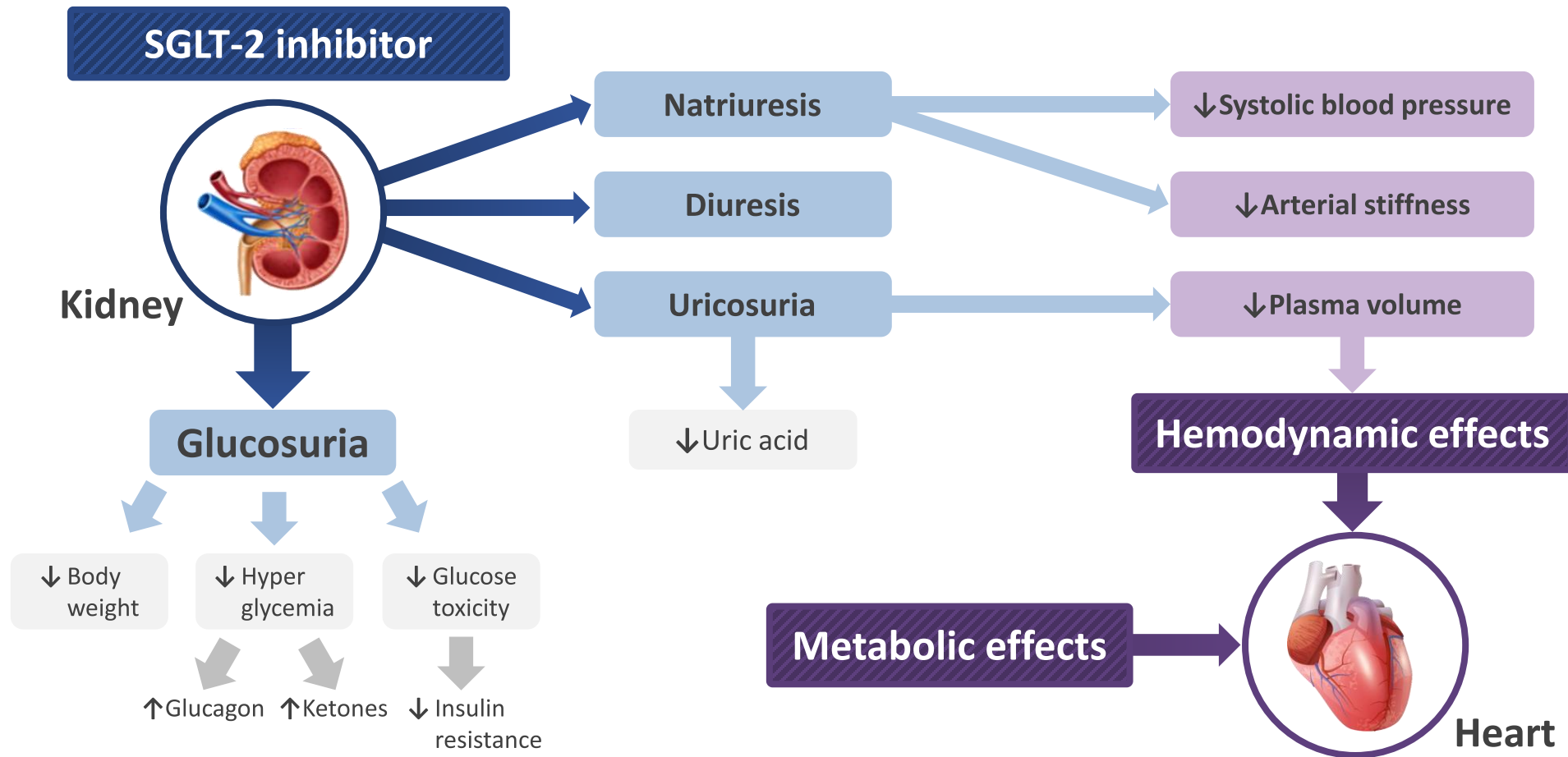
CV Benefits of SGLT-2 Inhibitors Considered as A Class Effect[1]

CVD-REAL studies suggested that SGLT-2 inhibitors' favorable results seen in CVOTs may be considered as a class effect shared by all SGLT-2 inhibitors (including dapagliflozin) **and be extrapolated to a larger population of patients with type 2 diabetes mellitus in primary prevention.**[1]

In CVD-REAL, a large multinational study conducted in 6 European countries and the U.S., **a treatment with SGLT-2 inhibitors** vs. other glucose-lowering agents was **associated with a lower risk of hospitalization for HF and all-cause death,** regardless of pre-existing CVD.[1,2]

Death	With prior cardiovascular disease*		0.56 [0.44, 0.70]
	Without prior cardiovascular disease*		0.56 [0.50, 0.63]
Heart failure	With prior cardiovascular disease*		0.72 [0.63, 082]
	Without prior cardiovascular disease*		0.61 [0.48, 0.78]
Heart failure + Death	With prior cardiovascular disease*		0.63 [0.57, 0.70]
	Without prior cardiovascular disease*		0.56 [0.50, 0.62]

favor SGLT-2i ⟷ favor other Glucose-Lowering drugs
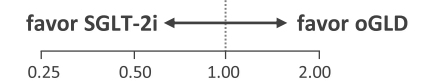
0.25   0.50   1.00   2.00
Hazard Ratio

*Diagnosis of AMI, unstable angina, stroke, heart failure, Transient ischemic attack, coronary revascularization (CABG or PCI) or occlusive peripheral artery disease prior to index drug initiation

Confirmatory findings were reported in CVD-REAL 2 study, which was conducted in South Korea, Japan, Singapore, Israel, Australia, and Canada.[3]

All-Cause Death (ACD) Number of events: 5,216		0.51 [0.37, 0.70]
Hospitalization for Heart Failure (HHF) Number of events: 5,997		0.64 [0.50, 0.82]
HHF+ACD Number of events: 9,788		0.60 [0.47, 0.76]
Myocardial Infarction Number of events: 2,249		0.81 [0.74, 0.88]
Stroke Number of events: 6,439		0.68 [5.55, 0.84]

favor SGLT-2i ⟷ favor oGLD

0.25   0.50   1.00   2.00

Study design: The CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) study was a multinational, observational study in which adults with type 2 diabetes were identified. Observational data from medical records, medical claims, electronic health and death records, and national registers collected from 5 countries (United States, United Kingdom, Sweden, Norway, and Denmark) included in CVD-REAL. Patients prescribed an SGLT-2i or other glucose-lowering drugs (GLDs) were matched based on a propensity score for initiation of an SGLT-2i. Hazard ratios (HRs) for the risk of death, HF, and HF or death in patients with and without established CVD were estimated for each country and pooled.

New users of SGLT-2i and oGLDs were identified via claims, medical records, and national registries in South Korea, Japan, Singapore, Israel, Australia, and Canada. Propensity scores for SGLT-2i initiation were developed in each country, with 1:1 matching. Hazard ratios (HRs) for death, hospitalization for heart failure (HHF), death or HHF, MI, and stroke were assessed by country and pooled using weighted meta-analysis.

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CV = cardiovascular; CVD = cardiovascular disease; CVD-REAL = Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors; with the limitation of an observational approach; CVOT = cardiovascular outcome trial; HF = heart failure; PCI = percutaneous coronary intervention; SGLT2 = sodium glucose cotransporter 2

1. Scheen AJ. Circ Res. 2018;122:1439-1459; 2. Cavender MA *et al*. JACC 2018; 71:2497-2506.; 3. Kosiborod M *et al*. JACC 2018;71:2628-2639.

CVOTs in Diabetes[1]

SAVOR-TIMI 53
n=16,492
3-P MACE

EXAMINE
n=5,380
3-P MACE

TECOS
n=14,671
4-P MACE

CARMELINA
n=7,003
3-P MACE

CAROLINA
n=6,072
3-P MACE

2013	2015	2016	2017	2018	2019	2020

EMPA-REG OUTCOME
n=7,020
3-P MACE

CANVAS Program
n=10,142
3-P MACE

PIONEER 6
n=3,176
3-P MACE

DECLARE-TIMI 58
n=17,276
3-P MACE; CV death + HF hospitalization

CREDENCE
n=4,464
ESRD, doubling of creatinine, renal/CV death

Dapa-CKD
n=4,000
≥50% sustained decline in eGFR or reaching ESRD, CV death, or renal death

ELIXA
n=6,068
4-P MACE

LEADER
n=9,340
3-P MACE

FREEDOM-CVO
n=4,156
4-P MACE

EXSCEL
n=14,752
3-P MACE

Dapa-HF
n=4,500
CV- death, HF hospitalization, Urgent HF visit

SUSTAIN-6
n=3,297
3-P MACE

REWINE
n=9,901
3-P MACE

EMPEROR-Reduced
n=2,850
CV death or HF hospitalization

DEVOTE
n=7,637
3-P MACE

ACE
n=6,522
5-P MACE
(3-P MACE + hospitalization for HF or unstable angina)

HARMONY Outcomes
n=9,400
3-P MACE

VERTIS CV
n=8,000
3-P MACE

EMPEROR-Preserved
n=4,126
CV death or HF hospitalization

IRIS
n=3,876
Fatal or nonfatal stroke or MI

Legend
- DDP-4 inhibitors
- SGLT2 inhibitors
- GLP-1 receptor agonists
- Insulin
- TZD
- α-Glucosidase inhibitors

1. Cefalu WT *et al*. Diabetes Care. 2018;41(1):14-31

SGLT-2 Inhibitors:
Large Mortality/Morbidity Trials in T2DM[1]

	VERTIS-CV	EMPA-REG OUTCOME	CANVAS	DECLARE
	Ertugliflozin	Empagliflozin	Canagliflozin	Dapagliflozin
N	8238	7034	10,142	17,160
Age (years)	64.4 ± 8.1	63.1 ± 8.6	63.3 ± 8.3	63.8 ± 6.8
Male	5764 (70)	5026 (72)	6509 (64.2)	10,738 (62.6)
Race				
White	7232 (87.8)	5089 (72)	7944 (78.3)	79.6%
Black	235 (2.9)	357 (5)	336 (3.3)	3.5%
Asian	497 (6.0)	1518 (22)	1284 (12.7)	13.4%
Other	274 (3.3)	70 (1)	578 (5.7)	3.5%
Diadetes duration (years)	12.9 ± 8.3	NA	13.5 ± 7.8	NA
HbA1c (%)	8.3 ± 0.9	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2
BMI (kg/m^2)	32.0 ± 5.4	30.6 ± 5.3	32.0 ± 5.9	32.1 ± 6.0
eGFR (mL/min per 1.73m^2)	76.0 ± 20.9	74 ± 21	76.5 ± 20.5	86.1 ± 21.8
≥90	2044 (24.8)	1534 (22)	2474 (24.4)	6855 (39.9)
60 to <90	4387 (53.3)	3671 (52)	5620 (55.5)	8739 (50.9)
30 to <60	1776 (21.6)	1796 (26)	2010 (19.8)	1565 (9.1)[†]
Established CVD (%)	99.9	>99	65.6	40.6
Myocardial infarction	3942 (47.9)	3275 (47)	2956 (29.2)	3580 (20.9)
Coronary revascularization				
CABG	1809 (22.0)	1738 (25)	1427 (14.1)	1678 (9.8)
PCI	3413 (41.4)	NA	2558 (25.3)	3655 (21.3)
Stroke	1731 (21.0)	1631 (23)	1291 (12.8)	1107 (6.5)[‡]
Peripheral arterial disease	1548 (18.8)	1449 (21)	2113 (20.8)	1025 (6.0)
History of HF	1900 (23.1)	706 (10.1)*	1461 (14.4)	1698 (9.9)

Data are n (%) or mean ± SD, unless otherwise shown. BMI, body mass index; CABG, coronary artery bypass graft; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate (calculated via Modification of Diet in Renal Disease equation); HbA1c, glycated hemoglobin; HF, heart failure; PCI, percutaneous coronary intervention.▯ Percentage based on 7020 patients. † Less than 60 mL/min per 1.73 m2.‡ Ischemic stroke..

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

CVD and Non-CVD Proportion in CVOTs of SGLT-2 Inhibitors[1-4]

(%)

Legend	
CVD	Non-CVD

VERTIS CV — 99.9 / 0.1 — CVD 8,238 pts

EMPA-REG — 99 / 1 — CVD 7,020 pts

CANVAS — 65.6 / 34.4 — CVD 6,656 pts / Non-CVD 3,486 pts / Total 10,142 pts

DECLARE — 40.6 / 59.4 — CVD 6,971 pts / Non-CVD 10,189 pts / Total 17,160 pts

1. Zinman B *et al*. Cardiovasc Diabetol 2014;13:102. 2. Neal *et al*. Am Heart J 2013;166:217–223.e11. 3. Wiviott SD *et al*. N Engl J Med 2018 4. Cannon CP *et al*. Am Heart J. 2018;206:11-23.
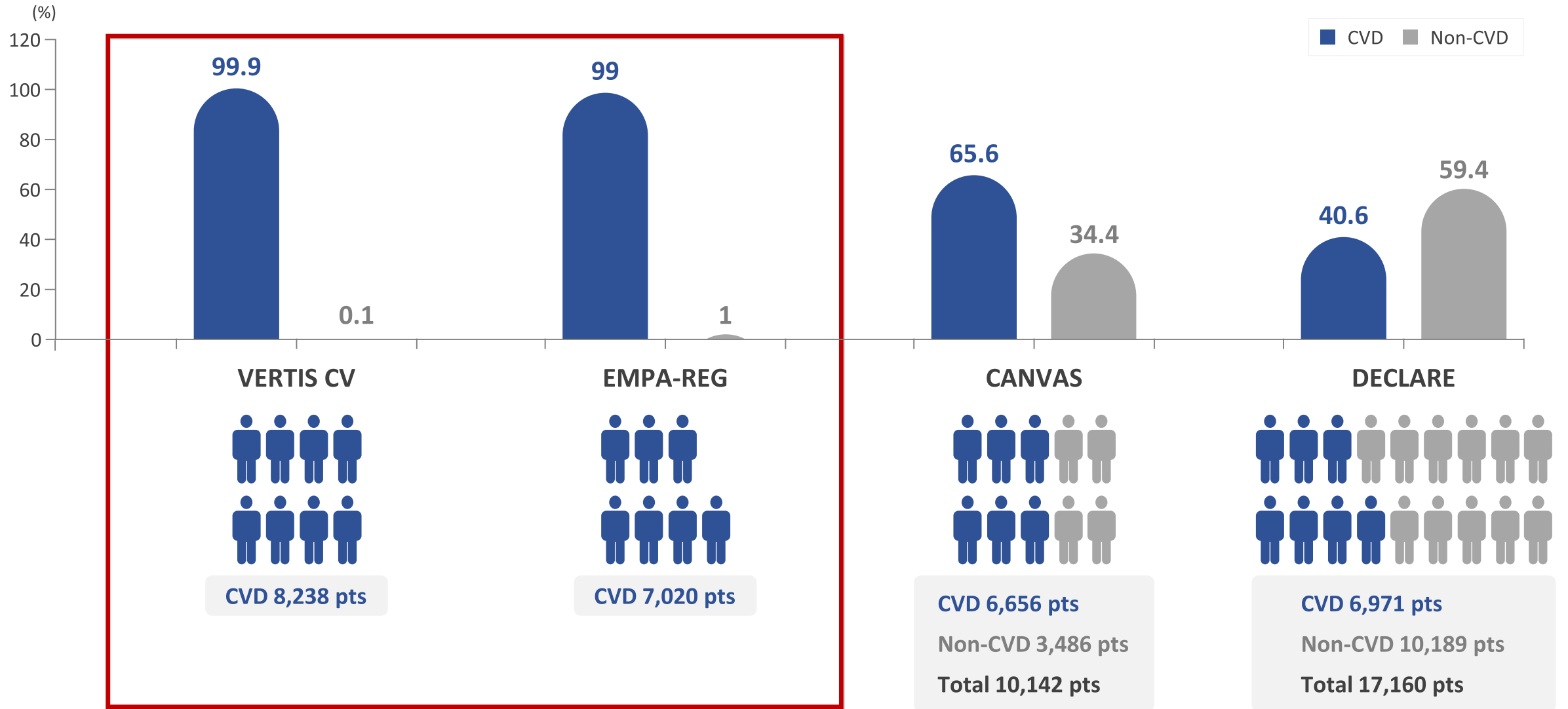
EMPA-REG OUTCOME[1]

- **Patient:**   **T2DM with established CV-disease** (n=7,020)
- **Indicator:**   **empagloflozin 10mg, 25mg** (n=4,687)
- **Comparator:**   **Placebo** (n=2,333)
- **Outcomes**   **CV death, MI, stroke** (early termination; 3.1 years)

Primary outcome :	Patients with Event/analysed Empagliflozin	Placebo	HR	(95% CI)		P-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*		0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)		< 0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.07, 1.09)		0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)		0.1638

0.25   0.50   1.00   2.00

Favors empagliflozin   Favors placebo

Empagliflozin Significantly reduced CV death
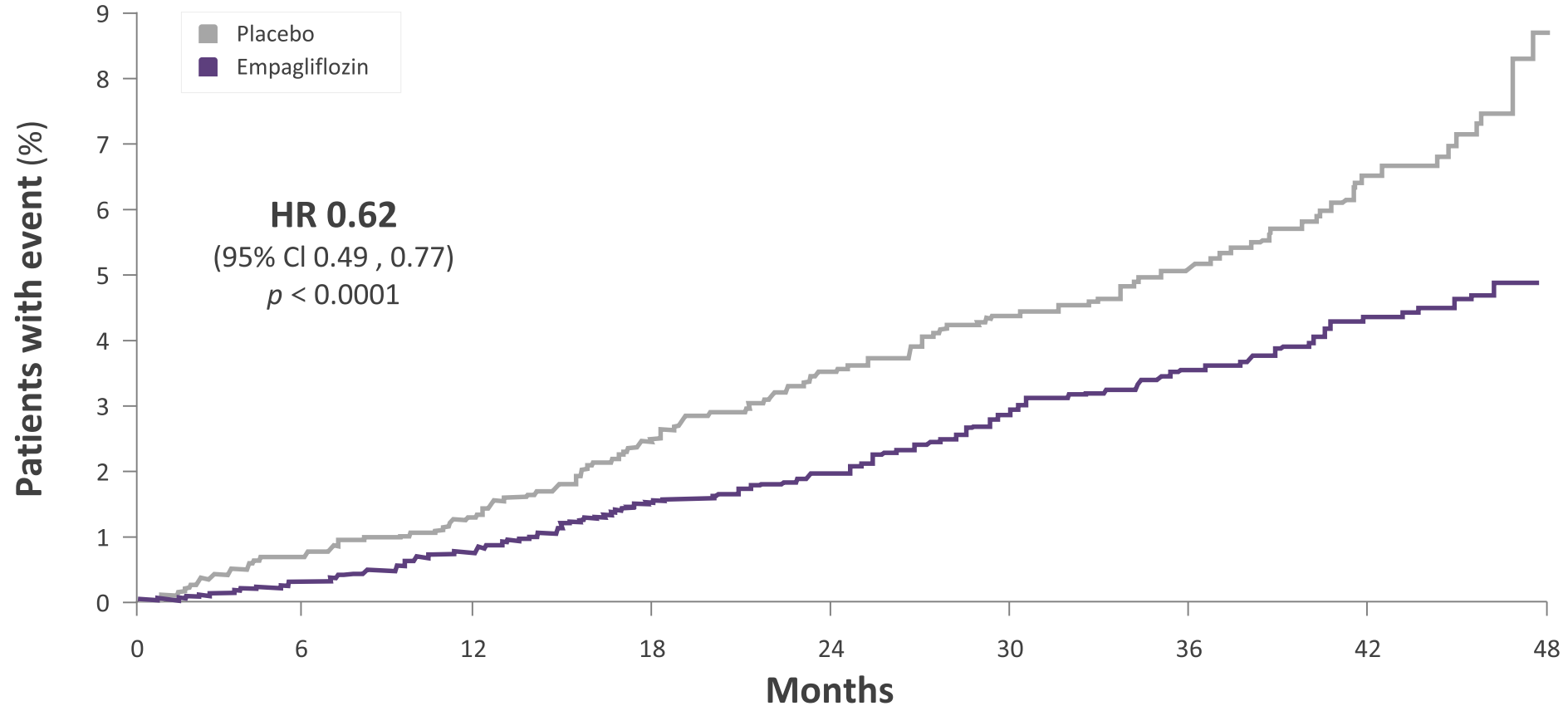
Patients with event (%) vs **Months**

Legend: Placebo, Empagliflozin

HR 0.62
(95% CI 0.49 , 0.77)
p < 0.0001

No. of patients

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

1. Zinman B *et al*. N Engl J Med 2015;373:2117-28

Empagliflozin Significantly reduced Total Mortality
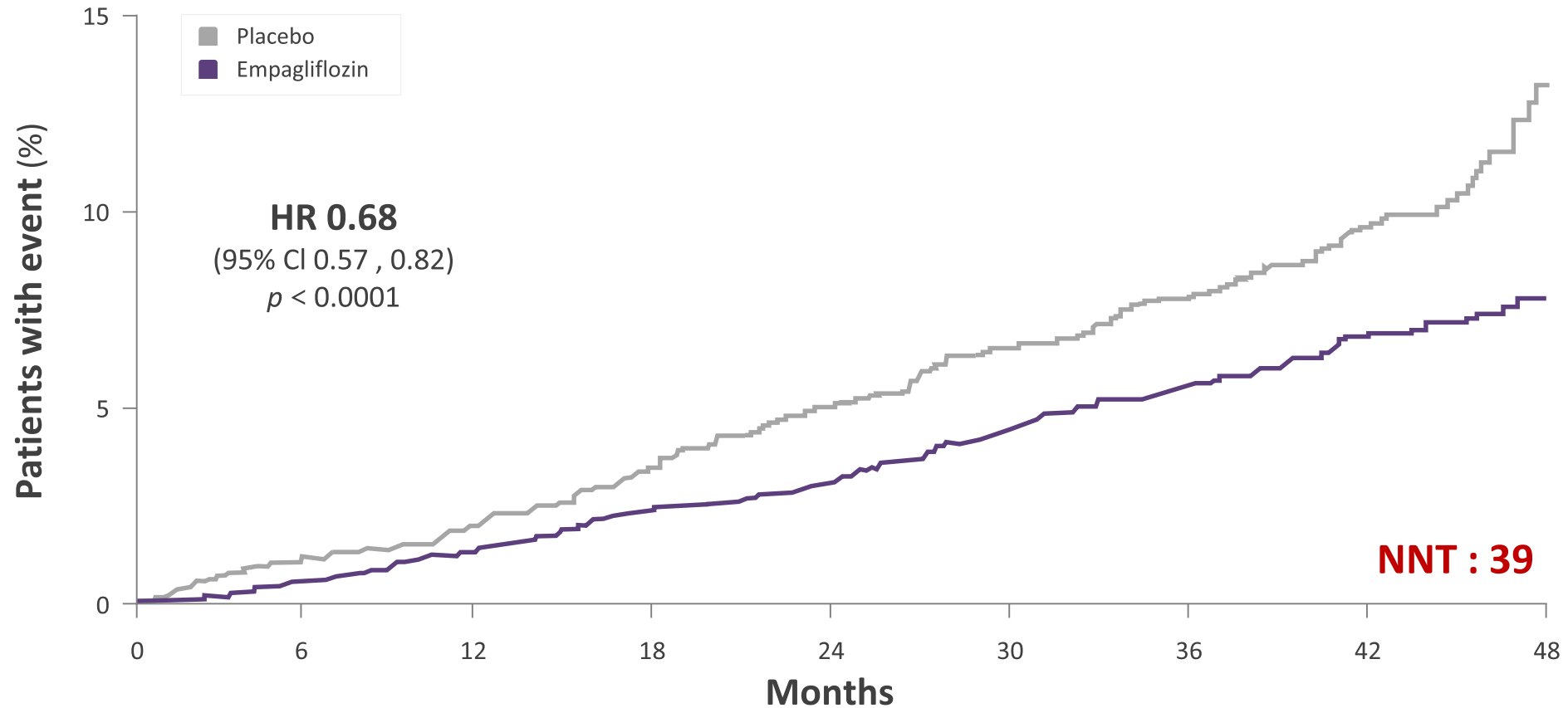
HR 0.68
(95% Cl 0.57 , 0.82)
p < 0.0001

NNT : 39

Placebo
Empagliflozin

Patients with event (%)

Months

No. of patients

Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

1. Zinman B *et al.* N Engl J Med 2015;373:2117-28

Empagliflozin Significantly reduced heart failure hospitalization

HR 0.65
(95% CI 0.50 , 0.85)
p < 0.0017

Legend: Placebo, Empagliflozin

Y-axis: Patients with event (%), 0 to 7

X-axis: Months, 0 to 48
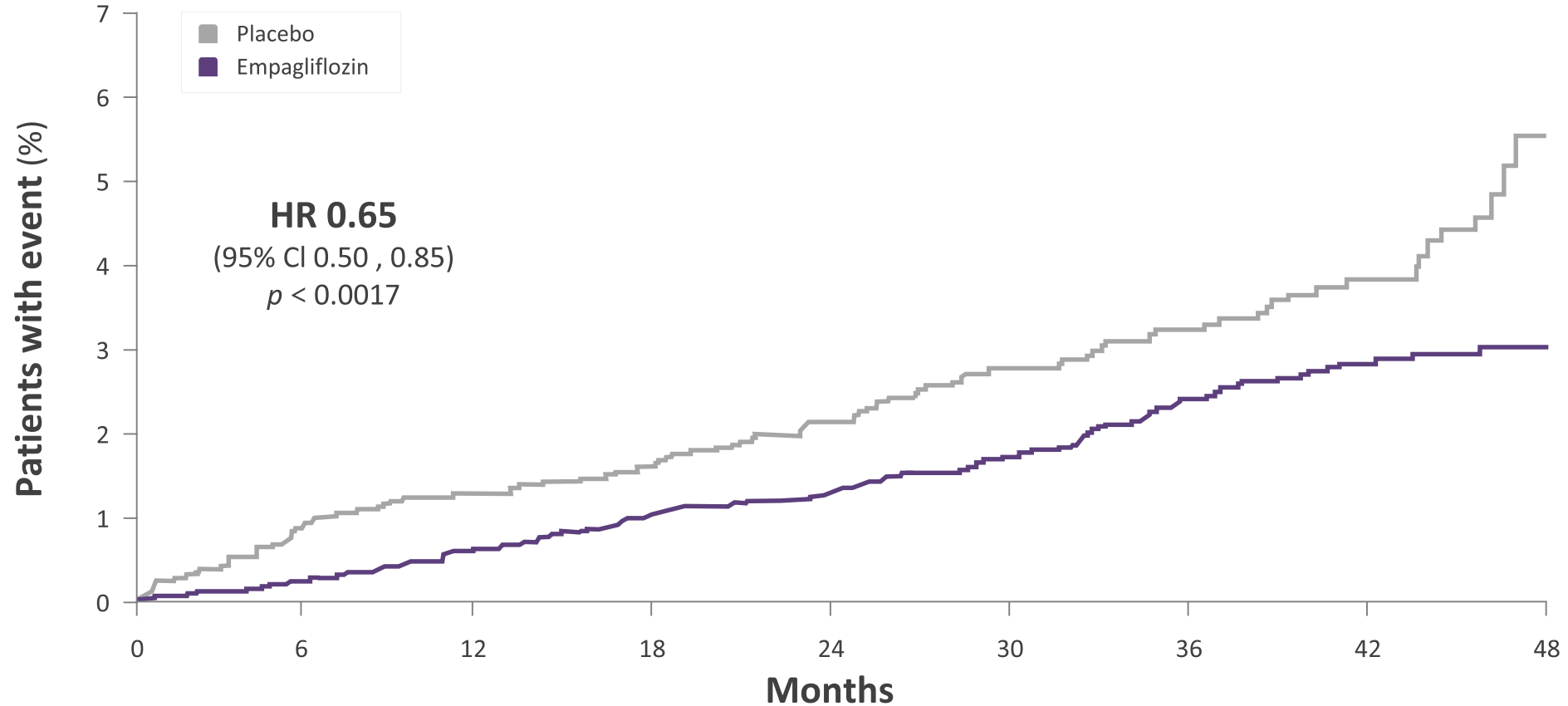
No. of patients

	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

1. Zinman B *et al*. N Engl J Med 2015;373:2117-28

After DECLARE-TIMI 58

Meta-Analysis of SGLT2i Trials on the Composite of Myocardial Infarction, Stroke, and Cardiovascular Death[1]

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

Summary

Background The magnitude of effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on specific cardiovascular and renal outcomes and whether heterogeneity is based on key baseline characteristics remains undefined.

Methods We did a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome trials of SGLT2i in patients with type 2 diabetes. We searched PubMed and Embase for trials published up to Sept 24, 2018. Data search and extraction were completed with a standardised data form and any discrepancies were resolved by consensus. Efficacy outcomes included major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death), the composite of cardiovascular death or hospitalisation for heart failure, and progression of renal disease. Hazard ratios (HRs) with 95% CIs were pooled across trials, and efficacy outcomes were stratified by baseline presence of atherosclerotic cardiovascular disease, heart failure, and degree of renal function.

Interpretation SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events that seem confined to patients with established atherosclerotic cardiovascular disease. However, they have robust benefits on reducing hospitalisation for heart failure and progression of renal disease regardless of existing atherosclerotic cardiovascular disease or a history of heart failure.
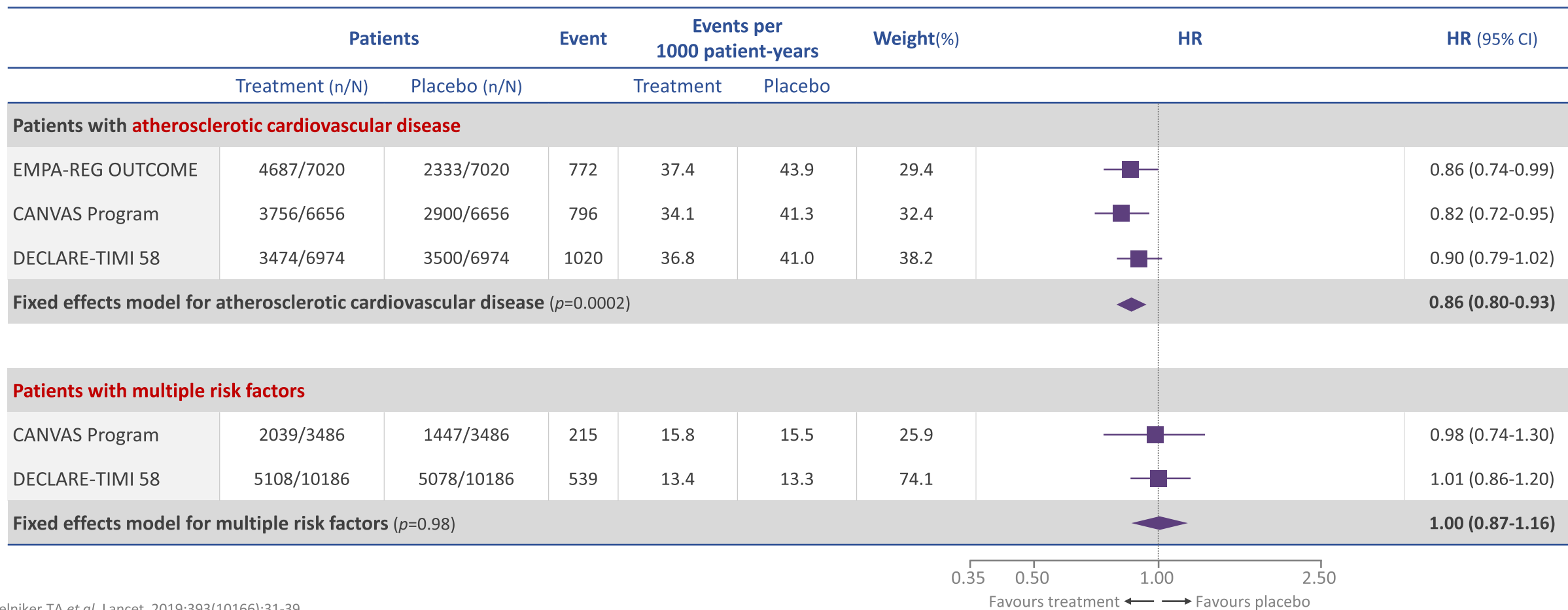
1. Zelniker TA *et al*. Lancet. 2019;393(10166):31-39.

Meta-Analysis of SGLT2i Trials on the Composite of Myocardial Infarction, Stroke, and Cardiovascular Death[1]

SGLT2i reduced the risk of a major adverse cardiac event (MI, stroke, CV death) **by 14%** in patients with atherosclerotic cardiovascular disease.[1]

	Patients		Event	Events per 1000 patient-years		Weight(%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	772	37.4	43.9	29.4		0.86 (0.74-0.99)
CANVAS Program	3756/6656	2900/6656	796	34.1	41.3	32.4		0.82 (0.72-0.95)
DECLARE-TIMI 58	3474/6974	3500/6974	1020	36.8	41.0	38.2		0.90 (0.79-1.02)
Fixed effects model for atherosclerotic cardiovascular disease (*p*=0.0002)								**0.86 (0.80-0.93)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	215	15.8	15.5	25.9		0.98 (0.74-1.30)
DECLARE-TIMI 58	5108/10186	5078/10186	539	13.4	13.3	74.1		1.01 (0.86-1.20)
Fixed effects model for multiple risk factors (*p*=0.98)								**1.00 (0.87-1.16)**

0.35   0.50   1.00   2.50

Favours treatment ⟵ ⟶ Favours placebo

1. Zelniker TA *et al*. Lancet. 2019;393(10166):31-39.

Meta-Analysis of SGLT2i Trials on Hospitalization for Heart Failure and Cardiovascular Death[1]

🦋 **In patients with atherosclerotic cardiovascular disease, the HR for the composite of cardiovascular death or hospitalization for heart failure was 0.76** (0.69–0.84) **and in patients with multiple risk factors it was 0·84** (0.69–1.01, p for interaction=0.41)**.**[1]

	Patients		Event	Events per 1000 patient-years		Weight(%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687/7020	2333/7020	463	19.7	30.1	30.9		0.66 (0.55-0.79)
CANVAS Program	3756/6656	2900/6656	524	21.0	27.4	32.8		0.77 (0.65-0.92)
DECLARE-TIMI 58	3474/6974	3500/6974	597	19.9	23.9	36.4		0.83 (0.71-0.98)
Fixed effects model for atherosclerotic cardiovascular disease (*p*=0.0001)								**0.76 (0.69-0.84)**
Patients with multiple risk factors								
CANVAS Program	2039/3486	1447/3486	128	8.9	9.8	30.2		0.83 (0.58-1.19)
DECLARE-TIMI 58	5108/10186	5078/10186	316	7.0	8.4	69.8		0.84 (0.67-1.04)
Fixed effects model for multiple risk factors (*p*=0.0634)								**0.84 (0.69-1.01)**

0.35   0.50   1.00   2.50

Favours treatment ⟵ ⟶ Favours placebo

1. Zelniker TA *et al*. Lancet. 2019;393(10166):31-39..

Meta-Analysis of SGLT2i Trials on Hospitalization for Heart Failure and Cardiovascular Death Stratified by History of Heart Failure[1]

❧ **The reduction in the composite of cardiovascular death or hospitalization for heart failure was not statistically different in patients with** (HR 0.71 [95% CI 0.61–0.84]) **or without** (0.79 [0.71–0.88]) **a history of heart failure at baseline** (*p* for interaction=0.51).[1]

	Patients		Event	Events per 1000 patient-years		Weight(%)	HR	HR (95% CI)
	Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462/706	244/706	124	63.6	85.5	23.6		0.72 (0.50-1.04)
CANVAS Program	803/1461	658/1461	203	35.4	56.8	34.1		0.61 (0.46-0.80)
DECLARE-TIMI 58	852/1724	872/1724	314	45.1	55.5	42.4		0.79 (0.63-0.99)
Fixed effects model for history of heart failure (*p*<0.0001)								**0.71 (0.61-0.84)**
Patients with multiple risk factors								
EMPA-REG OUTCOME	4225/6314	2089/6314	399	15.5	24.9	30.0		0.63 (0.51-0.78)
CANVAS Program	4992/8681	3689/8681	449	13.6	15.2	32.4		0.87 (0.72-1.06)
DECLARE-TIMI 58	7730/15436	7706/15436	599	8.9	10.5	37.6		0.84 (0.72-0.99)
Fixed effects model for no history of heart failure (*p*<0.0001)								**0.79 (0.71-0.88)**

0.35 0.50 1.00 2.50
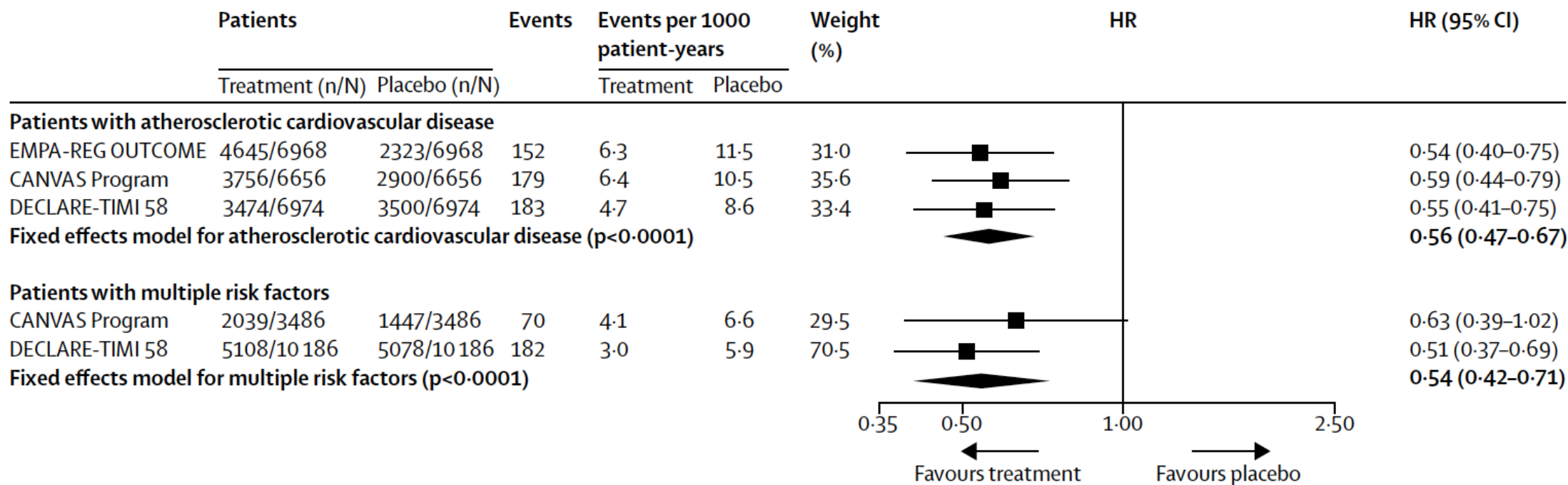
Favours treatment ⟵   ⟶ Favours placebo

1. Zelniker TA *et al*. Lancet. 2019;393(10166):31-39..

Meta-analysis of SGLT2i trials on the composite of renal worsening, end-stage renal disease, or renal death stratified

SGLT2i were renoprotective and reduced the composite of worsening of renal function, end-stage renal disease, or renal death by 45%

Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
Treatment (n/N)	Placebo (n/N)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease							
EMPA-REG OUTCOME 4645/6968	2323/6968	152	6·3	11·5	31·0		0·54 (0·40–0·75)
CANVAS Program 3756/6656	2900/6656	179	6·4	10·5	35·6		0·59 (0·44–0·79)
DECLARE-TIMI 58 3474/6974	3500/6974	183	4·7	8·6	33·4		0·55 (0·41–0·75)
Fixed effects model for atherosclerotic cardiovascular disease (p<0·0001)							**0·56 (0·47–0·67)**
Patients with multiple risk factors							
CANVAS Program 2039/3486	1447/3486	70	4·1	6·6	29·5		0·63 (0·39–1·02)
DECLARE-TIMI 58 5108/10 186	5078/10 186	182	3·0	5·9	70·5		0·51 (0·37–0·69)
Fixed effects model for multiple risk factors (p<0·0001)							**0·54 (0·42–0·71)**

0·35   0·50   1·00   2·50

← Favours treatment   Favours placebo →

1. Zelniker TA et al. Lancet. 2019;393(10166):31-39..

Research in context

Evidence before this study

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been studied in large cardiovascular outcome trials in patients with type 2 diabetes and were shown to reduce the risk of cardiovascular events. Both patients with established atherosclerotic cardiovascular disease and those with multiple risk factors but without the disease were studied in these trials. Within individual trials, the magnitude of benefit appeared to be greater on major adverse cardiovascular events in subgroups with established atherosclerotic cardiovascular disease, although formal heterogeneity was not shown. Based on these findings, American and European guidelines recommend use of SGLT2i for patients with type 2 diabetes and atherosclerotic cardiovascular disease, independent of glucose control considerations. However, no single trial has been adequately powered to test for such heterogeneity because the number of patients and events in those patients with multiple risk factors alone have been low. We prospectively planned to meta-analyse cardiovascular outcome results from the dedicated cardiovascular outcome trials stratified by presence or absence of established atherosclerotic cardiovascular disease, once data from the DECLARE-TIMI 58 trial of dapagliflozin versus placebo became available. We searched PubMed and Embase using the Medical Subject Heading terms "diabetes mellitus, type 2", "sodium-glucose-co transporter 2 inhibitor", and "clinical trial" for trials published up to Sept 24, 2018, to find all randomised cardiovascular outcome trials for SGLT2i.
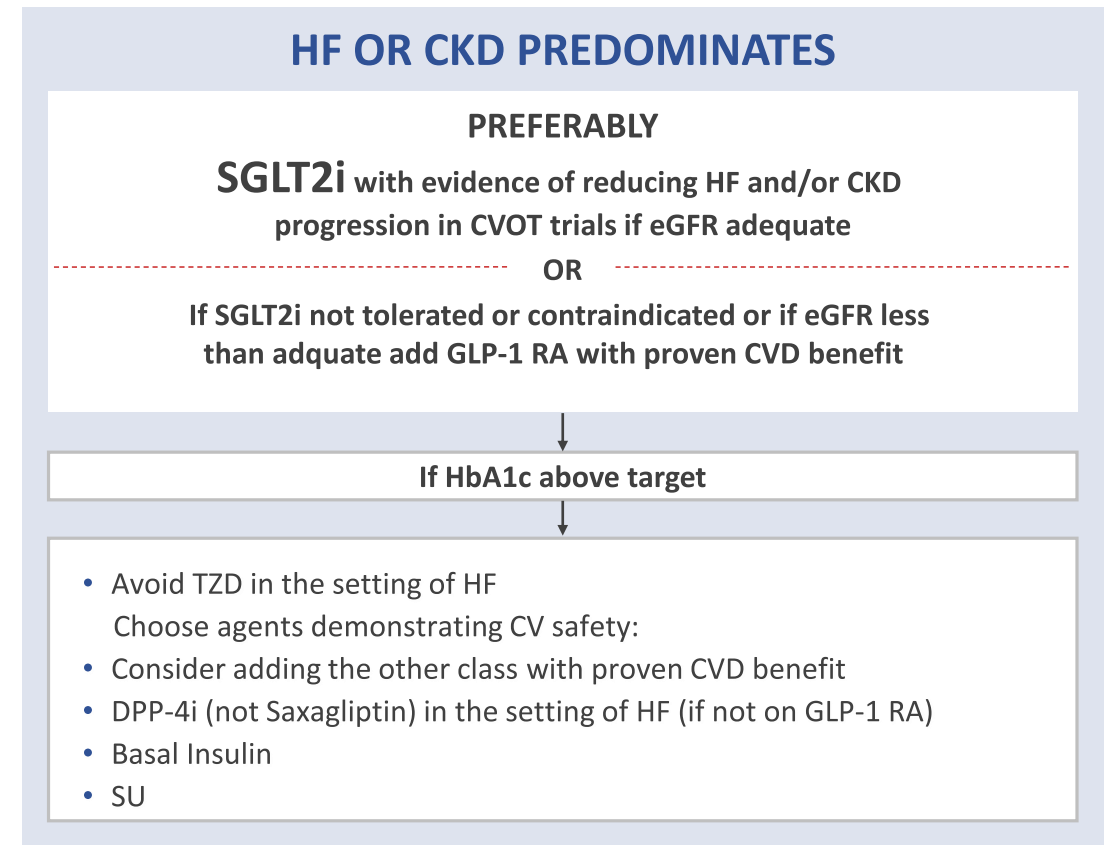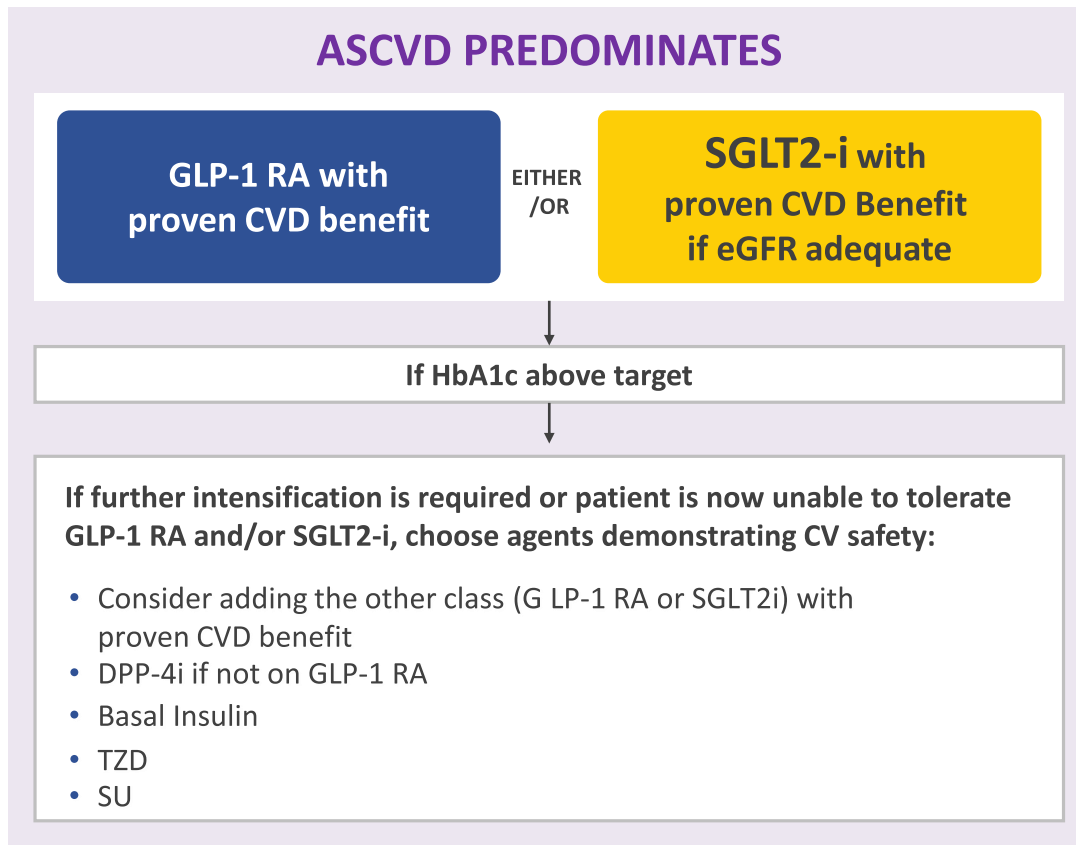
Added value of this study

Incorporating data from the trials EMPA-REG OUTCOME, the CANVAS Program, and DECLARE-TIMI 58, the present meta-analysis of SGLT2i cardiovascular outcome trials showed that the clinical benefit of SGLT2i in reducing the risk of myocardial infarction, stroke, or cardiovascular death was present only in patients with established atherosclerotic cardiovascular disease and not in those with multiple risk factors. Conversely, the reductions in risk of hospitalisation for heart failure or progression of renal disease were robust regardless of the presence of atherosclerotic cardiovascular disease or heart failure at baseline.

Implications of all the available evidence

These data suggest that SGLT2i should be considered in patients with type 2 diabetes regardless of presence of atherosclerotic cardiovascular disease or history of heart failure, given that SGLT2i safely reduce HbA$_{1c}$ and reduce the risk of hospitalisation for heart failure and progression of renal disease across a broad spectrum of patients with type 2 diabetes. Reductions in major adverse cardiovascular events can also be expected in patients with established atherosclerotic cardiovascular disease.

ADA 2019 Standards of Care in Diabetes

For patients with **ASCVD, HF or CKD** predominates, the best choice for a second agent is a GLP-1 RA or **SGLT2-I with demonstrated cardiovascular risk reduction**[1]
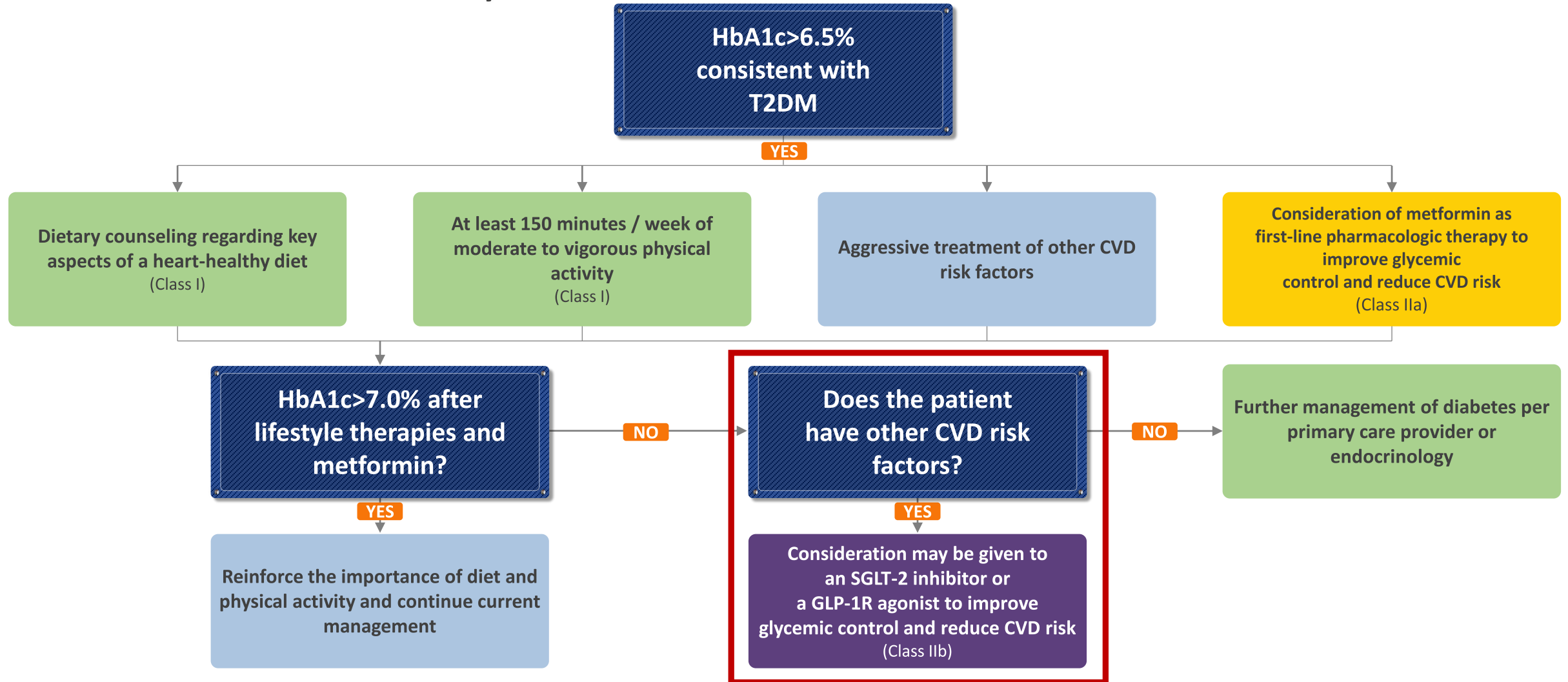
ASCVD PREDOMINATES

GLP-1 RA with proven CVD benefit	EITHER /OR	SGLT2-i with proven CVD Benefit if eGFR adequate

If HbA1c above target

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2-i, choose agents demonstrating CV safety:

- Consider adding the other class (G LP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal Insulin
- TZD
- SU

HF OR CKD PREDOMINATES

PREFERABLY

SGLT2i with evidence of reducing HF and/or CKD progression in CVOT trials if eGFR adequate

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adquate add GLP-1 RA with proven CVD benefit

If HbA1c above target

- Avoid TZD in the setting of HF
  Choose agents demonstrating CV safety:
- Consider adding the other class with proven CVD benefit
- DPP-4i (not Saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal Insulin
- SU

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione; CKD, chronic kidney disease

1. ADA Diabetes Care 2019;42(Suppl.1):S90-S102

2019 ACC/AHA Guideline
on the Primary Prevention of Cardiovascular Disease

🦋 **Treatment of T2DM for Primary Prevention of Cardiovascular Disease**

HbA1c>6.5% consistent with T2DM

YES

Dietary counseling regarding key aspects of a heart-healthy diet
(Class I)

At least 150 minutes / week of moderate to vigorous physical activity
(Class I)

Aggressive treatment of other CVD risk factors

Consideration of metformin as first-line pharmacologic therapy to improve glycemic control and reduce CVD risk
(Class IIa)

HbA1c>7.0% after lifestyle therapies and metformin?

NO

Does the patient have other CVD risk factors?

NO

Further management of diabetes per primary care provider or endocrinology

YES

Reinforce the importance of diet and physical activity and continue current management

YES

Consideration may be given to an SGLT-2 inhibitor or a GLP-1R agonist to improve glycemic control and reduce CVD risk
(Class IIb)

1. Arnett DK *et al*. Circulation 2019 Mar 17:CIR0000000000000678

CV, cardiovascular; SGLT2, sodium–glucose cotransporter 2;

Then..
Where Benefits
Fundamentally Come from ?

Sodium-Glucose Co-transporter-2 Inhibitors

- SGLT-2 - in proximal tubules reabsorbs most of filtered glucose[1]
- SGLT-1 - also in proximal tubules, normally reabsorbs remaining filtered glucose[1]

1. Jung CH *et al.* Diabetes Metab J. 2014;38(4):261-73.
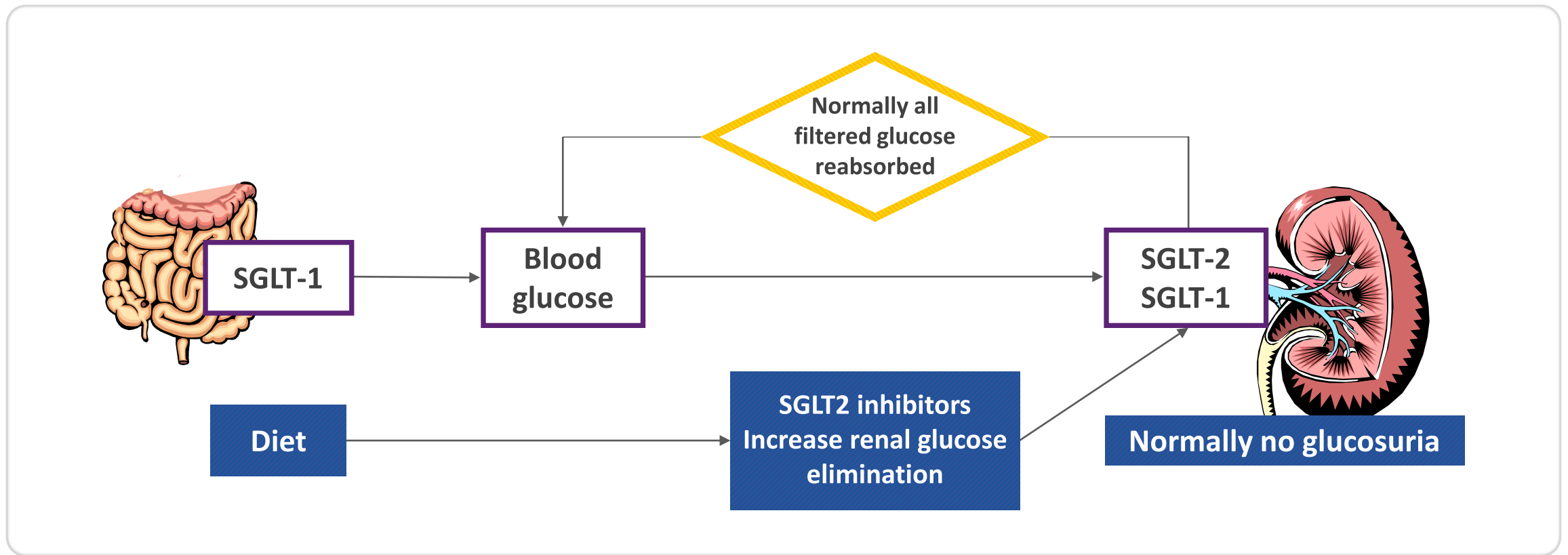
Each 1% Reduction in HbA$_{1c}$ Associated with Reduction in Risk of Diabetic Complications[1]

EVERY 1%
Reduction in HbA$_{1c}$

Decreased RISK
(*P*<.0001)

Decreased RISK
(*P*<.0001)

14% | **43%** | **1%** | **37%** | **21%**

Myocardial infarctions

Amputations or deaths from Peripheral vascular disorders

Microvascular complications

Diabetes-related deaths
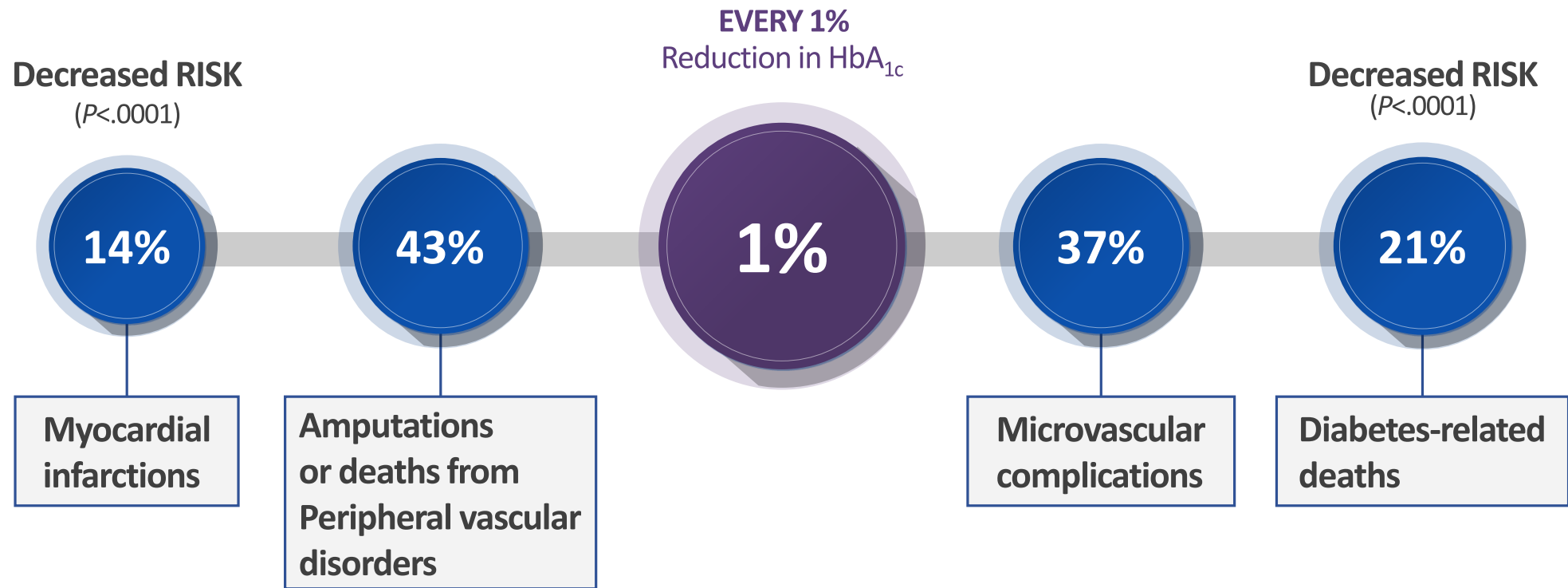
Relative risk (n=3642): Diabetes-related deaths, Microvascular complications, Myocardial infarctions, Amputations or deaths from peripheral vascular disorders

HbA1c = glycated hemoglobin

Study design: This was a prospective observational study. Setting: 23 hospital based clinics in England, Scotland, and Northern Ireland. Participants: 4585 white, Asian Indian, and Afro-Caribbean UKPDS patients, whether randomized or not to treatment, were included in analyses of incidence; of these, 3642 were included in analyses of relative risk. This study is to determine the relation between exposure to glycaemia over time and the risk of macrovascular or microvascular complications in patients with type 2 diabetes. Primary predefined aggregate clinical outcomes: any end point or deaths related to diabetes and all-cause mortality.
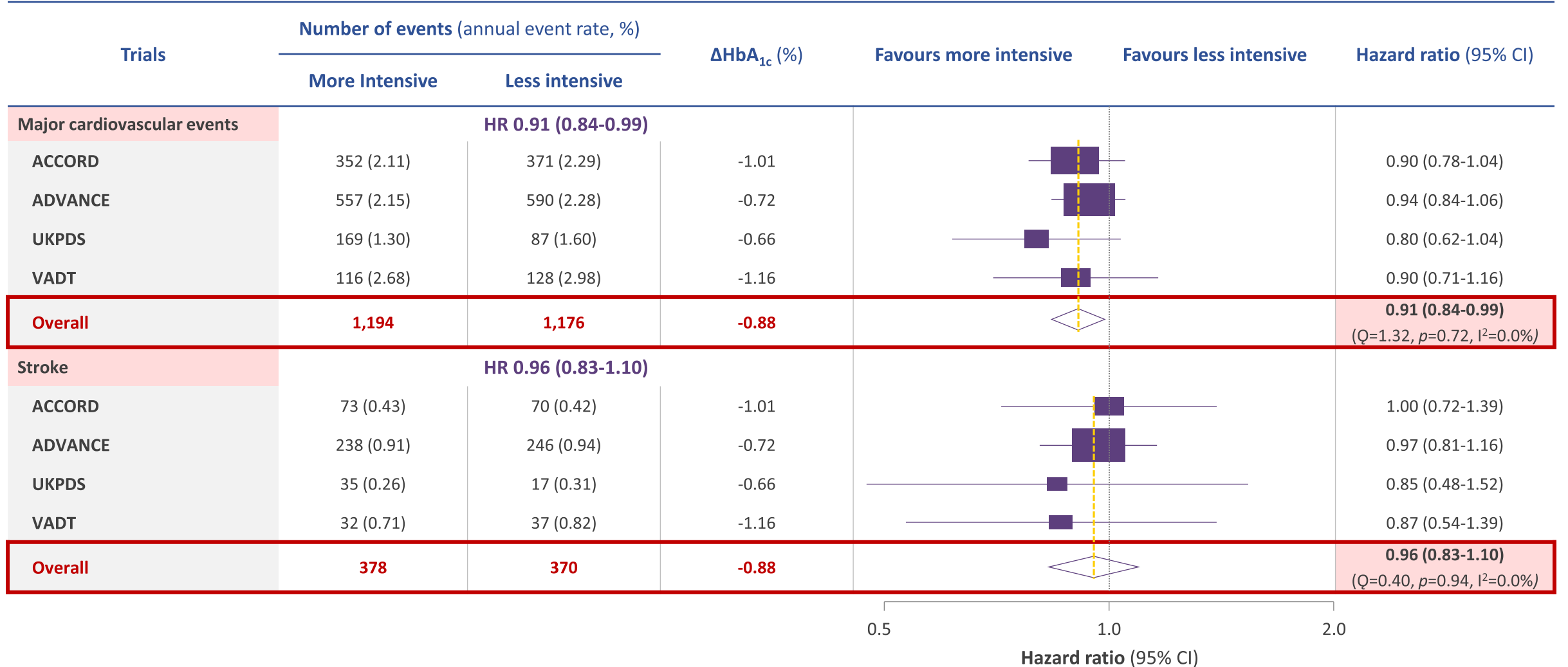
1. Stratton IM *et al.* BMJ. 2000;321:405-412

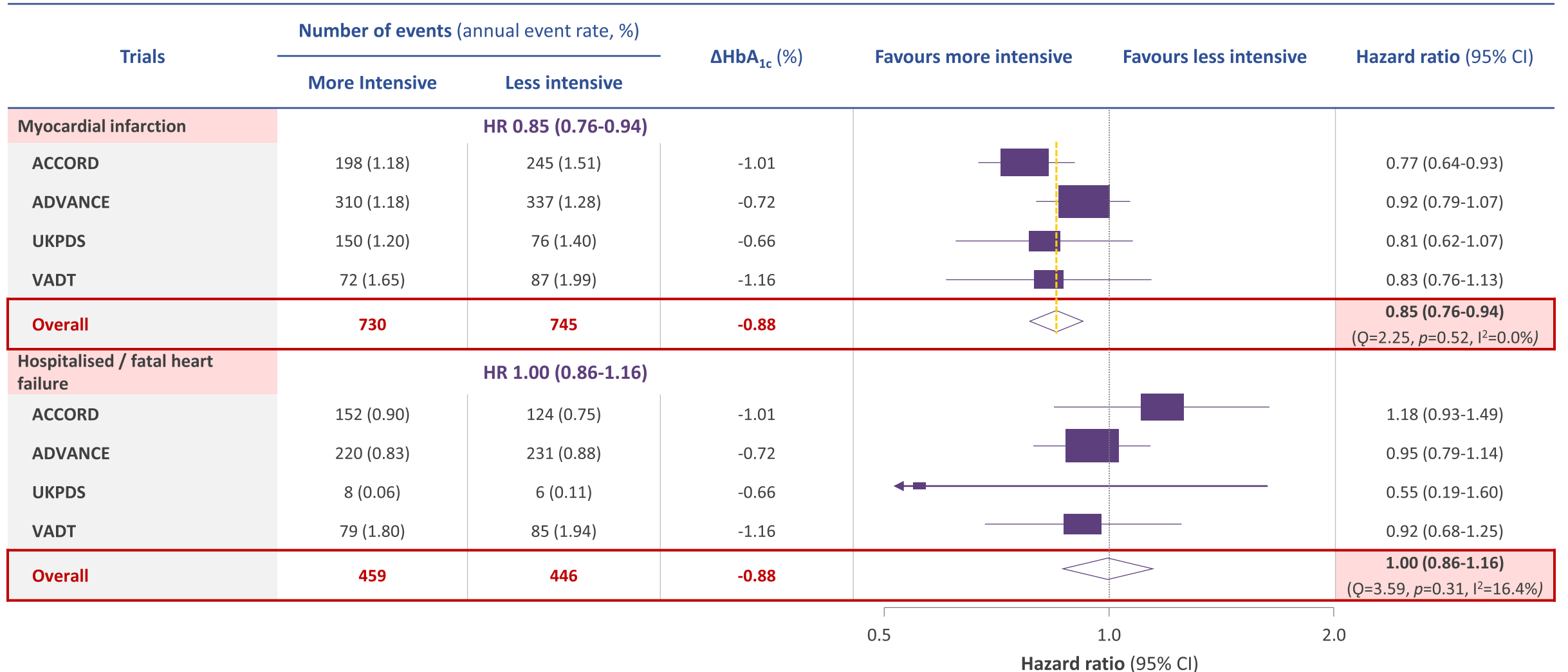# Effects of Intensive Glucose Control on Microvascular Outcomes

	More intensive glucose control	Less intensive glucose control		Hazard ratio (95% CI)
Primary kidney outcome	HR 0.80 (0.72-0.88)			
ACCORD	383/21641 (1.8%)	484/21554 (2.2%)		0.79 (0.69-0.90)
ADVANCE	233/25728 (0.9%)	301/25675 (1.2%)		0.77 (0.65-0.91)
UKPDS	127/10852 (1.2%)	54/4515 (1.2%)		0.98 (0.71-1.35)
VADT	18/3818 (0.5%)	26/3878 (0.7%)		0.70 (0.39-1.28)
Overall	**761/62039 (1.2%)**	**865/55622 (1.6%)**		**0.80 (0.72-0.88)**
I^2=0.0%; *p*=0.58				
Primary eye outcome	HR 0.80 (0.76-1.00)			
ACCORD	131/6135 (2.1%)	167/6104 (2.7%)		0.79 (0.64-0.98)
ADVANCE	35/2992 (1.2%)	49/2901 (1.7%)		0.83 (0.56-1.22)
UKPDS	200/530 (3.8%)	88/2251 (3.9%)		0.95 (0.74-1.23)
VADT	62/450 (13.8%)	63/453 (13.9%)		0.94 (0.66-1.34)
Overall	**428/14877 (2.9%)**	**367/11709 (3.1%)**		**0.87 (0.76-1.00)**
I^2=0.0%; *p*=0.69				
Primary never outcome	HR 0.98 (0.87-1.09)			
ACCORD	2055/14979 (13.7%)	2210/14923 (14.8%)		0.92 (0.87-0.98)
ADVANCE	1373/23752 (5.8%)	1299/23876 (5.4%)		1.07 (0.99-1.15)
UKPDS	453/12247 (3.7%)	208/5087 (4.1%)		0.93 (0.78-1.10)
Overall	**3881/50978 (7.6%)**	**3717/43887 (8.5%)**		**0.98 (0.87-1.09)**
I^2=78.1%; *p*=0.11				

0.25   0.50   1.00   2.00

← Favours more intensive glucose control

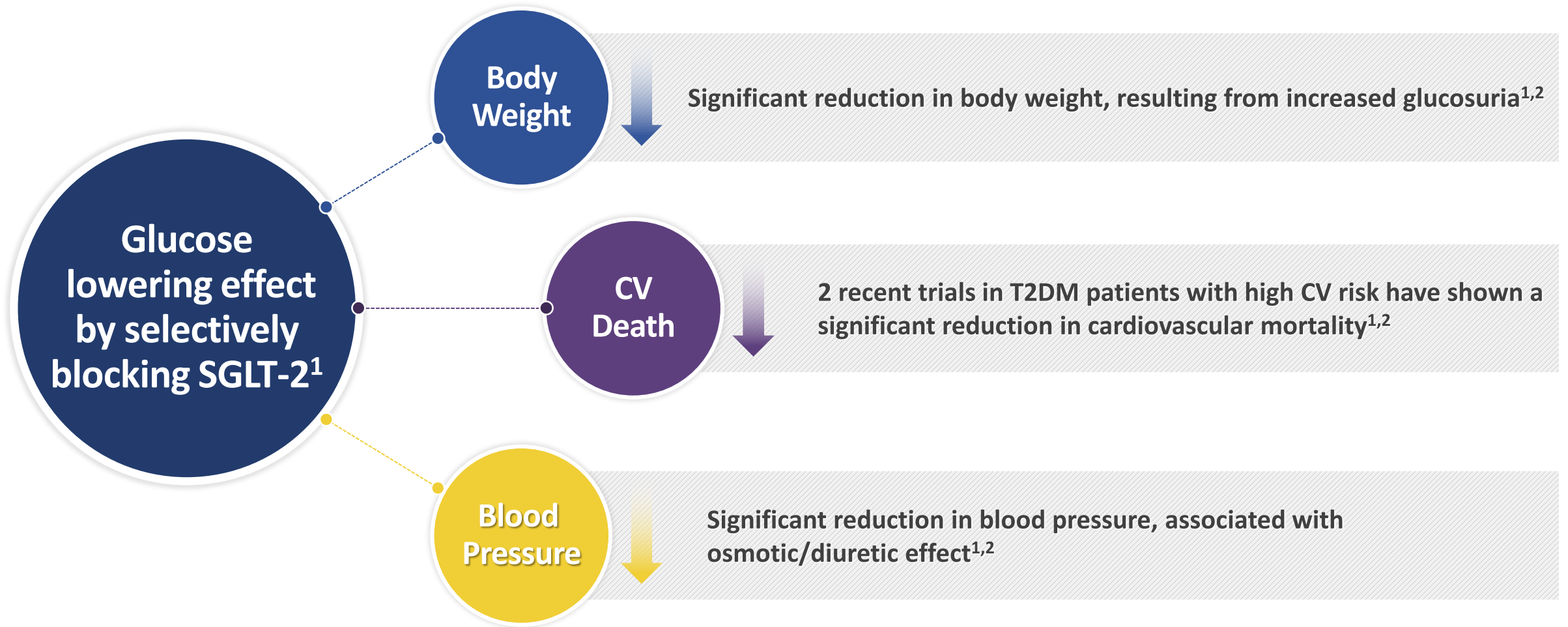Favors less intensive glucose control →

UKPDS, Uniter Kingdom Prospective Diabetes Study; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial; CI,confidence interval

1. Zoungas S *et. al* Lancet Diabetes Endocrinol 2017;5: 431–37

Intensive Glucose Control and Macrovascular Outcomes (1)

Trials	Number of events (annual event rate, %)		ΔHbA$_{1c}$ (%)	Favours more intensive	Favours less intensive	Hazard ratio (95% CI)
	More Intensive	Less intensive				
Major cardiovascular events		HR 0.91 (0.84-0.99)				
ACCORD	352 (2.11)	371 (2.29)	-1.01			0.90 (0.78-1.04)
ADVANCE	557 (2.15)	590 (2.28)	-0.72			0.94 (0.84-1.06)
UKPDS	169 (1.30)	87 (1.60)	-0.66			0.80 (0.62-1.04)
VADT	116 (2.68)	128 (2.98)	-1.16			0.90 (0.71-1.16)
Overall	**1,194**	**1,176**	**-0.88**			**0.91 (0.84-0.99)** (Q=1.32, *p*=0.72, I²=0.0%)
Stroke		HR 0.96 (0.83-1.10)				
ACCORD	73 (0.43)	70 (0.42)	-1.01			1.00 (0.72-1.39)
ADVANCE	238 (0.91)	246 (0.94)	-0.72			0.97 (0.81-1.16)
UKPDS	35 (0.26)	17 (0.31)	-0.66			0.85 (0.48-1.52)
VADT	32 (0.71)	37 (0.82)	-1.16			0.87 (0.54-1.39)
Overall	**378**	**370**	**-0.88**			**0.96 (0.83-1.10)** (Q=0.40, *p*=0.94, I²=0.0%)

0.5   1.0   2.0

Hazard ratio (95% CI)

UKPDS, Uniter Kingdom Prospective Diabetes Study; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial; CI,confidence interval

1. Control Group *et al*. Diabetologia. 2009;52:2288-2298

Intensive Glucose Control and Macrovascular Outcomes (2)

Trials	Number of events (annual event rate, %)		ΔHbA$_{1c}$ (%)	Favours more intensive	Favours less intensive	Hazard ratio (95% CI)
	More Intensive	Less intensive				
Myocardial infarction	**HR 0.85 (0.76-0.94)**					
ACCORD	198 (1.18)	245 (1.51)	-1.01			0.77 (0.64-0.93)
ADVANCE	310 (1.18)	337 (1.28)	-0.72			0.92 (0.79-1.07)
UKPDS	150 (1.20)	76 (1.40)	-0.66			0.81 (0.62-1.07)
VADT	72 (1.65)	87 (1.99)	-1.16			0.83 (0.76-1.13)
Overall	**730**	**745**	**-0.88**			**0.85 (0.76-0.94)** (Q=2.25, *p*=0.52, I^2=0.0%)
Hospitalised / fatal heart failure	**HR 1.00 (0.86-1.16)**					
ACCORD	152 (0.90)	124 (0.75)	-1.01			1.18 (0.93-1.49)
ADVANCE	220 (0.83)	231 (0.88)	-0.72			0.95 (0.79-1.14)
UKPDS	8 (0.06)	6 (0.11)	-0.66			0.55 (0.19-1.60)
VADT	79 (1.80)	85 (1.94)	-1.16			0.92 (0.68-1.25)
Overall	**459**	**446**	**-0.88**			**1.00 (0.86-1.16)** (Q=3.59, *p*=0.31, I^2=16.4%)

Hazard ratio (95% CI) axis: 0.5 — 1.0 — 2.0

UKPDS, Uniter Kingdom Prospective Diabetes Study; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; VADT, Veterans Affairs Diabetes Trial; CI,confidence interval

1. Control Group *et al*. Diabetologia. 2009;52:2288-2298

Added Benefits of SGLT-2 Inhibitors[1]

Glucose lowering effect by selectively blocking SGLT-2[1]

Body Weight

Significant reduction in body weight, resulting from increased glucosuria[1,2]

CV Death

2 recent trials in T2DM patients with high CV risk have shown a significant reduction in cardiovascular mortality[1,2]

Blood Pressure

Significant reduction in blood pressure, associated with osmotic/diuretic effect[1,2]

CV = cardiovascular; SGLT-2 = sodium-glucose cotransporter 2

1. Cinti F *et al*. Drug Des Devel Ther. 2017; 11:2905–2919.;
2. Scheen AJ. Curr Diab Rep. 2016;16(10):92

CV, cardiovascular; SGLT2, sodium–glucose cotransporter 2;

Ertugliflozin Is New Option for SGLT2Is

Dapagliflozin[4]

Empagliflozin[2]

Currently Available SGLT-2 Inhibitors*

Canagliflozin[3]

Ertugliflozin[1]

Ipragliflozin[5]

dioxa-bicyclo [3.2.1] octane
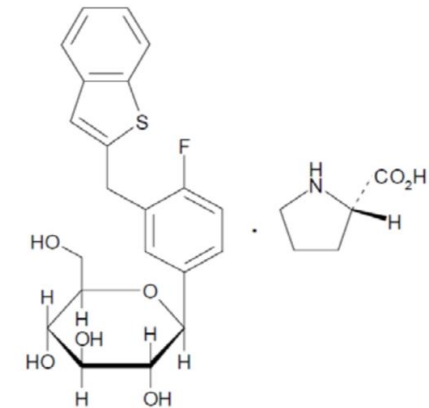
1. STEGLATRO™ (ertugliflozin) Prescribing Information. Merck & Co., Inc. 2017.; 2. INVOKANA® (canagliflozin) Prescribing Information. Janssen. 2017;
3. JARDIANCE® (empagliflozin) Prescribing Information. Boehringer Ingelheim. 2016; 4. FARXIGA® (dapagliflozin) Prescribing Information. AstraZeneca. 2017; 5. Suglat (ipragliflozin) PMDA Report on the Deliberation Results. 2013

Ertugliflozin is a new, highly selective SGLT-2 inhibitor[1]

Pharmacokinetic parameters of ertugliflozin[2]

	ERTU 5 mg	ERTU 15 mg
AUC^a, ng·hr/mL	**398**	1193
C_{max}, ng/mL	**81.3**	268
T_{max}, hr	**1**	1
$t_{1/2}^b$, hr		16.6

Ertugliflozin[1]
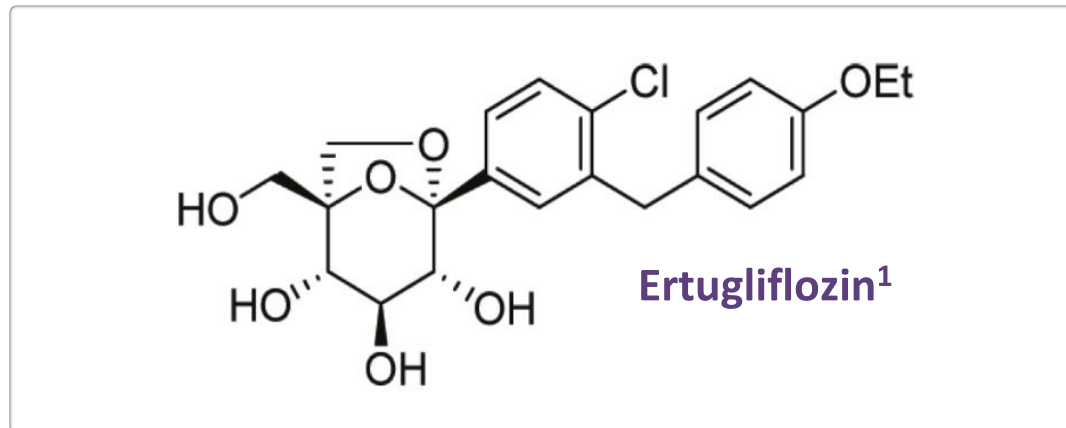
- **Proportional, dose-dependent pharmacokinetic profile[2]**

- **Rapid, complete absorption[2]**
  - Postdose peak plasma concentrations (Tmax) occur at 1 hour
  - ~100% absolute oral bioavailability following administration of a 15-mg dose

- **Metabolism and clearance[2]**
  - The primary clearance mechanism is metabolism
  - The major metabolic pathway is O-glucuronidation
  - Approximately 41% and 50% of ertugliflozin was eliminated in feces and urine, respectively

- **Ertugliflozin is supplied in 5mg dosage strengths[2]**

Adapted with permission from Mascitti V *et al*.[2]
[a]Steady-state mean plasma AUC; steady-state is reached after 4 to 6 days of once-daily dosing with ertugliflozin.
[b]Based on population pharmacokinetic analysis in patient with T2DM and normal renal function.
AUC = area under the curve; C_{max} = maximum plasma concentration; SGLT2 = sodium-glucose cotransporter 2; T_{max} = time to maximum plasma concentration; $t_{1/2}$ = half life; ERTU = ertugliflozin; T2DM = type 2 diabetes mellitus.

1. Cinti F *et al*. Drug Des Devel Ther. 2017;11:2905–2919.; 2. 스테글라트로 국내허가사항, 식품의약품안전처 2019.

In Vitro Potency and Selectivity of Various SGLT2 Inhibitors[1]

Compound	SGLT2 IC$_{50}$, nmol/L	SGLT1 IC$_{50}$, nmol/L	SGLT2/SGLT1 selectivity
Empagliflozin	3.1	8,300	2,700
Ertugliflozin	**0.9**	**1,960**	**2,200**
Dapagliflozin	1.2	1,400	1,200
Ipragliflozin	5.3	3,000	570
Canagliflozin	4.2	663	160

Adapted with permission from Mudaliar S *et al.*[1]
SGLT = sodium-glucose cotransporter; IC50 = half maximal inhibitory concentration.

1. Mudaliar S *et al*. Diabetes Care. 2015;38:2344–2353.

The pharmacokinetics and pharmacodynamics of SGLT2 inhibitors[1]

- SGLT2 inhibitors have an excellent pharmacokinetic and pharmacodynamic profile.
  The bioavailability of Ertugliflozin can rise up to 90% after oral administration and it has both renal and fecal elimination, approximately equal in percentage.[1]

Compound	Bioavailability	Time to peak action	Half-life	Excretion
Ertugliflozin	**70-90%**	**0.5-1.5 h**	**11-17 h**	**Renal (50%)** **Fecal (41%)**
Empagliflozin	~75%	1.5 h	13 h	Renal (55%) Fecal (40%)
Dapagliflozin	~78%	1-1.5 h	13 h	Renal (75%) Fecal (21%)
Ipragliflozin	~90%	1.5 h	15-16 h	Renal (~100%) Fecal (<2%)

1. Garcia-Ropero A *et al*. Expert Opin Drug Metab Toxicol 2018;14(12):1287-1302.

Ertugliflozin's Completed and Ongoing Trials

Diet and Exercise	Metformin Add-on		Add-on to Dual Combination	Special Population

VERTIS MONO[1]
Ertu vs. pbo
n=461

VERTIS SU[4]
Ertu vs. Glimepiride
n=1,325

VERTIS MET[3]
Ertu vs. pbo added to Met
n=621

VERTIS SITA2[7]
Ertu va pbo added to Met + Sita *n=462*

VERTIS CV[8]
(Outcomes Trial)
n=8,000

VERTIS SITA[2]
Ertu/Sita vs. pbo
n=291

VERTIS FACTORIAL[5]
Ertu+/-Sita
n=1,232

VERTIS ASIA[9]
Ertu vs. pbo
n=465

SU Mono Glycemic Sub-study

Insulin ± Met Glycemic Sub-study

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

Metformin + SU Glycemic Sub-study

Completed   **Ongoing**

VERTIS RENAL[6]
Ertu vs. pbo in CKD
n=467

VERTIS = eValuation of ERTugliflozin effIcacy and Safety

1. Terra SG *et al*. Diabetes Obes Metab. 2017; 19:721-728.; 2. Miller S *et al*. Diabetes Ther. 2018; 9:253-268.;3. Rosenstock J *et al*. Diabetes Obes Metab. 2018; 20:520-529.; 4. Hollander P *et al*. Diabetes Ther. 2018; 9:193-207;
5. Pratley RE *et al*. Diabetes Obes Metab. 2018;20:1111–1120.; 6. Grunberger G *et al*. Diabetes Ther. 2018; 9:49-66.; 7. Dagogo-Jack *S et al*. Diabetes Obes Metab. 2018; 20:530-540.;
8. ClinicalTrials.Gov Available at https://clinicaltrials.gov/ct2/show/NCT01986881 Accessed Aug 1, 2018; 9. Diabetes Obes Metab. 2019 Mar 4 doi: 10.1111/dom.13681

Ertugliflozin CVOT:
VERTIS CV Trial Study design (Result will be available at the end of 2019)

Patients aged ≥40 years with T2DM and established vascular disease[a] (N = ~8,000)
HbA_{1c} 7.0% – 10.5% and dose-stable on other AHA therapies
or no background AHA for ≥8 weeks

Randomized 1:1 treatment assignment

| Placebo | Ertugliflozin 5 mg | Ertugliflozin 15 mg |

Up to 6.1 years

Primary Composite Outcome
MACE (3-point): CV death, nonfatal myocardial infarction, or nonfatal stroke

Secondary Composite Outcome
CV death or hospitalization for heart failure; CV death; composite of renal death,
dialysis or transplant, doubling of serum creatinine

[a]History of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems.
T2DM = type 2 diabetes mellitus; AHA = antihyperglycemic; MACE = major adverse cardiovascular event; CV = cardiovascular.

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

Efficacy

Ertugliflozin : HbA$_{1C}$ Reduction in Various Trials

	Diet and Exercise		Metformin Add-on							Add-on to Dual Combination	
	Monotherapy VERTIS MONO[1]		**Add-on to Met** VERTIS MET[2]		**Dual Combination Add-on to Met** VERTIS FACTORIAL[3]					**Add-on to Met+Sita** VERTIS SITA2[4]	
					FDC		Ertu		Sita		
Base Line (%)	**5mg**	**15mg**	5mg	15mg	5/100mg	15/100mg	5mg	15mg	100mg	5mg	15mg
	8.16	8.35	8.1	8.1	8.6	8.6	8.6	8.6	8.5	8.1	8.0
	-0.99	-1.16	-0.7	-0.9	-1.5	-1.5	-1.0	-1.1	-1.1	-0.8	-0.9

Change vs placebo   **Change from baseline**   **Change vs placebo**
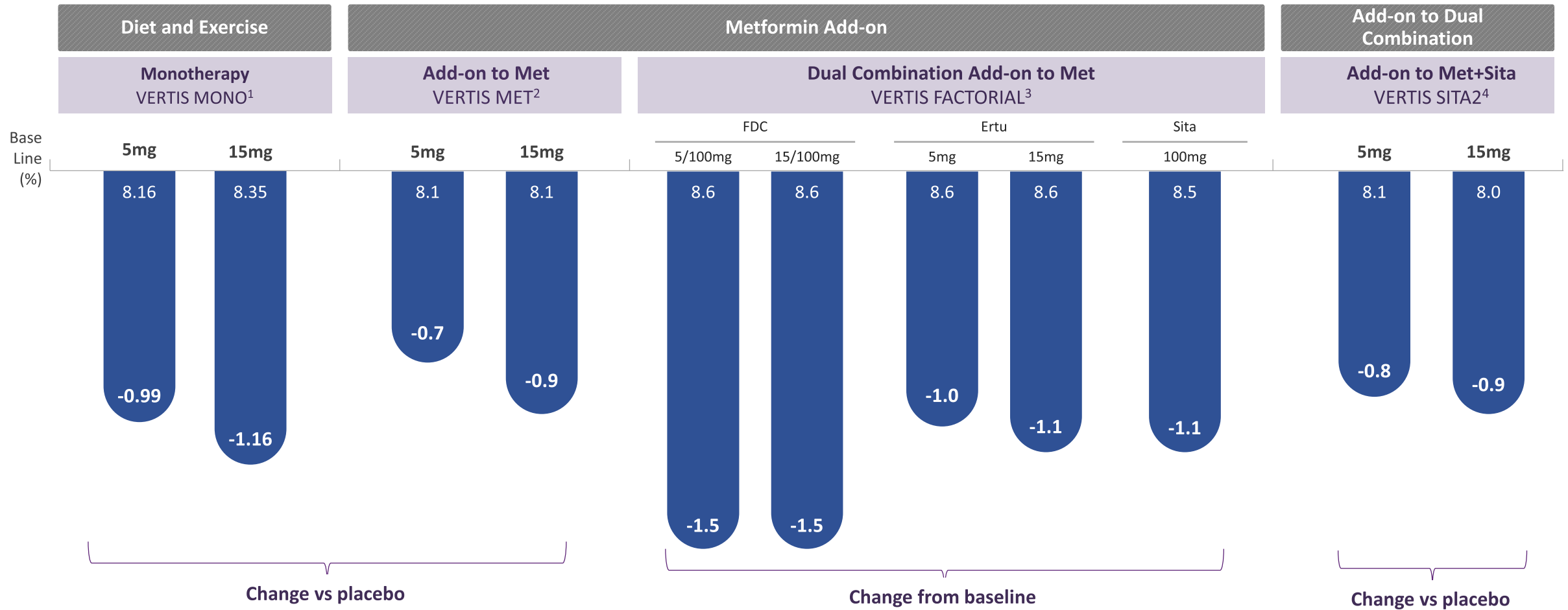
A1C Lowering (A1C (%); Placebo Adjusted, LS Mean Change from Baseline; Met, metformin; Sita, sitagliptin.

* Steglatro 5 mg and 15 mg were launched inMarch 2018 in the US

1. SG Terra *et al*. Diabetes Obes Metab 2017; 19:721. 2. J Rosenstock *et al*. Diabetes Obes Metab 2018; 20:520.
3. RE Pratley *et al*. Diabetes Obes Metab 2018;20:1111-20. 4. Dagogo-Jack S *et al*. Diabetes Obes Metab. 2018;20:530–540.

Indirect Comparison with other SGLT2-Is

Monotherapy Data

ERTU Results in the Context of other SGLT2i Phase 3 Results **Head-to-head trials were not conducted against other SGLT2 inhibitors**

ERTU[1]		EMPA[2]		DAPA[3]	
5 mg	15 mg	10 mg	25 mg	5 mg	10 mg
8.16	8.35	7.9	7.9	7.8	8.0
-0.99	-1.16	-0.7	-0.9	-0.5	-0.7

*Not head-to-head studies
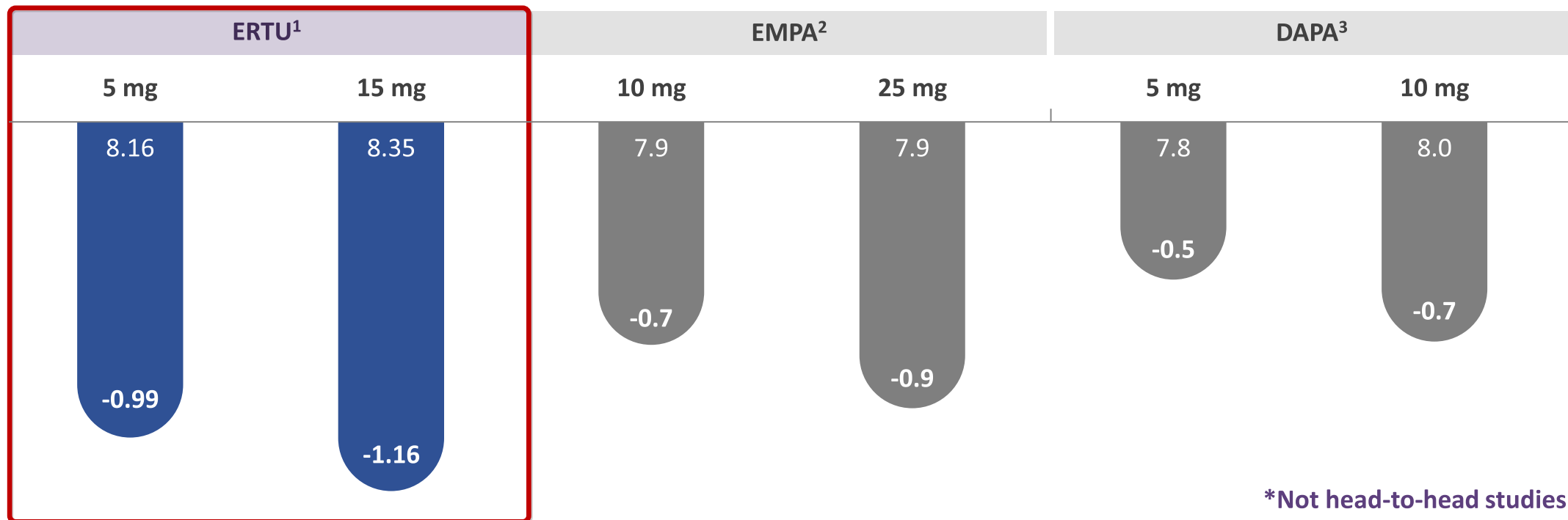
ERTU = ertugliflozin; CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; SGLT2i = sodium-glucose cotransporter 2 inhibitor
A1C Lowering (A1C (%); Placebo Adjusted, LS Mean Change from Baseline

1. Terra SG *et al*. Diabetes Obes Metab. 2017; 19:721-728.;
2. JARDIANCE® (empagliflozin) Prescribing Information. Boehringer Ingelheim. 2016;
3. FARXIGA® (dapagliflozin) Prescribing Information. AstraZeneca. 2017

Indirect Comparison with other SGLT2-Is (Network Meta-Analysis)
Monotherapy

🔹 **Both ERTU 5mg and 15mg were of comparable efficacy and safety to other SGLT2i in monotherapy in both low-dose and High-dose**
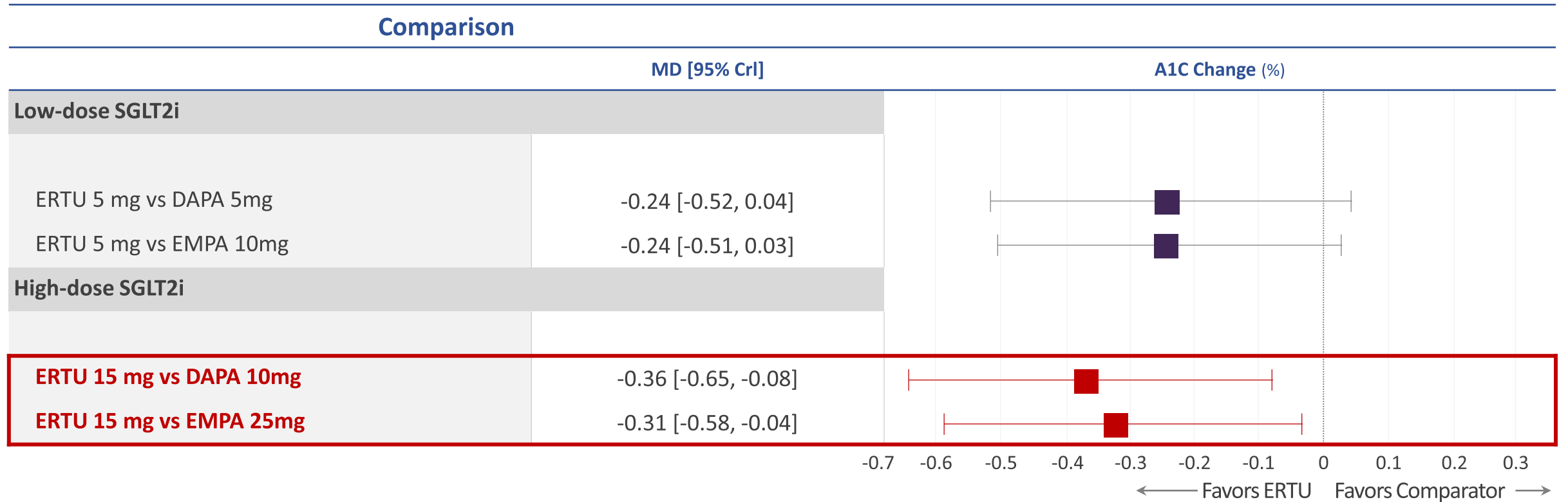
Comparison	MD [95% CrI]	A1C Change (%)
Low-dose SGLT2i		
ERTU 5 mg vs DAPA 5mg	-0.24 [-0.52, 0.04]	
ERTU 5 mg vs EMPA 10mg	-0.24 [-0.51, 0.03]	
High-dose SGLT2i		
ERTU 15 mg vs DAPA 10mg	-0.36 [-0.65, -0.08]	
ERTU 15 mg vs EMPA 25mg	-0.31 [-0.58, -0.04]	

A1C Change axis: -0.7 -0.6 -0.5 -0.4 -0.3 -0.2 -0.1 0 0.1 0.2 0.3

← Favors ERTU   Favors Comparator →

ERTU = ertugliflozin; CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; SGLT2i = sodium-glucose cotransporter 2 inhibitor; T2DM = type 2 diabetes mellitus; SBP = systolic blood pressure
Study design: A systematic literature review (SLR) identified randomized controlled trials (RCTs) reporting outcomes at 24–26 weeks of treatment. Comparators to ertugliflozin were the SGLT2is canagliflozin, dapagliflozin and empagliflozin, with non-SGLT2i comparators also evaluated third-line [insulin and glucagon-like peptide-1 receptor agonists (GLP-1 RAs)]. Outcomes were change from baseline in HbA1c, weight and systolic blood pressure (SBP) as well as HbA1c\7% and key safety events. Bayesian network meta-analysis was used to synthesize evidence. Results are presented as the median of the mean difference (MD) or as odds ratios with 95% credible intervals (CrI).

1. McNeill AM *et al*. Diabetes Ther. 2019 ;28. doi: 10.1007/s13300-019-0566-x

Indirect Comparison with other SGLT2-Is (Network Meta-Analysis)
Dual Therapy SGLT2i with Metformin

In T2DM patients inadequately controlled on metformin, significant A1C benefits were observed for ERTU 5 mg and ERTU 15 mg vs. DAPA 5 mg and DAPA 10 mg, respectively, and ERTU 15 mg vs EMPA 25 mg.
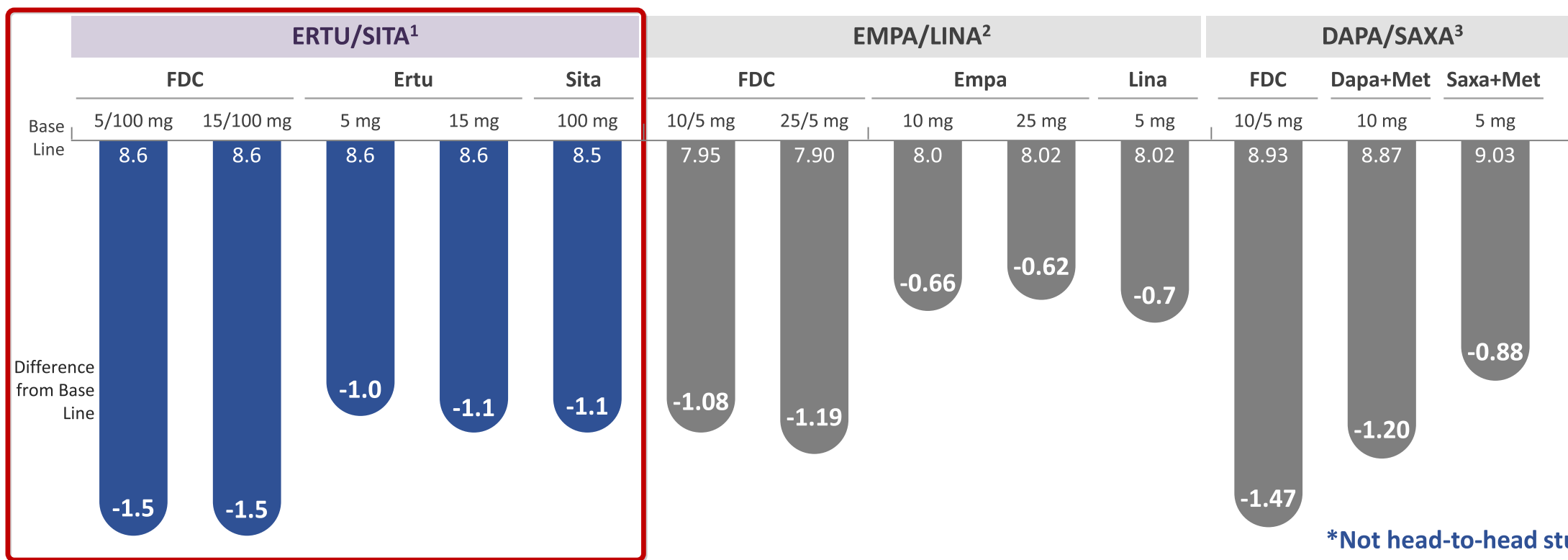
Comparison (add on to MET)	MD [95% CrI]	A1C Change (%)
Low-dose SGLT2i		
ERTU 5 mg vs DAPA 5mg	-0.22 [-0.42, -0.02]	
ERTU 5 mg vs EMPA 10mg	-0.14 [-0.34, 0.07]	
High-dose SGLT2i		
ERTU 15 mg vs DAPA 10mg	-0.26 [-0.45, -0.06]	
ERTU 15 mg vs EMPA 25mg	-0.23 [-0.44, -0.03]	

-0.5 -0.4 -0.3 -0.2 -0.1 0 0.1 0.2

← Favors ERTU   Favors Comparator →

1. McNeill AM *et al*. Diabetes Ther. 2019 ;28. doi: 10.1007/s13300-019-0566-x

Indirect Comparison of Data as Factorial
SGLT-2i + DPP-4i Add-on to Metformin Monotherapy

ERTU Results in the Context of other SGLT2i Phase 3 Results

Head-to-head trials were not conducted against other SGLT2 inhibitors

	ERTU/SITA[1]					EMPA/LINA[2]					DAPA/SAXA[3]		
	FDC		**Ertu**		**Sita**	**FDC**		**Empa**		**Lina**	**FDC**	**Dapa+Met**	**Saxa+Met**
	5/100 mg	15/100 mg	5 mg	15 mg	100 mg	10/5 mg	25/5 mg	10 mg	25 mg	5 mg	10/5 mg	10 mg	5 mg
Base Line	8.6	8.6	8.6	8.6	8.5	7.95	7.90	8.0	8.02	8.02	8.93	8.87	9.03
Difference from Base Line	-1.5	-1.5	-1.0	-1.1	-1.1	-1.08	-1.19	-0.66	-0.62	-0.7	-1.47	-1.20	-0.88

***Not head-to-head studies**

ERTU = ertugliflozin; CANA = canagliflozin; DAPA = dapagliflozin; EMPA = empagliflozin; DPP-4i = dipeptidyl peptidase 4 inhibitor; FDC = fixed dose combination; LINA = linagliptin; SAXA = saxagliptin; SITA = sitagliptin; SGLT2i = sodium-glucose cotransporter 2 inhibitor; A1C Lowering (A1C (%); Placebo Adjusted, LS Mean Change from Baseline; AE, Adverse Events; UTI, Urinary Track Infection.
Safety results: there were no other significant differences for safety outcomes (AEs, UTIs)

1. Pratley RE *et al*. Diabetes Obes Metab. 2018;20:1111–1120.; 2. DeFronzo RA *et al*. Diabetes Care 2015;38:384–393. 3. Rosenstock J *et al*. Diabetes Care. 2015;38:376–383.

Ertugliflozin Has the Most Combination Clinical Trials with Sitagliptin, which is the Most Prescribed DPP4I Worldwide
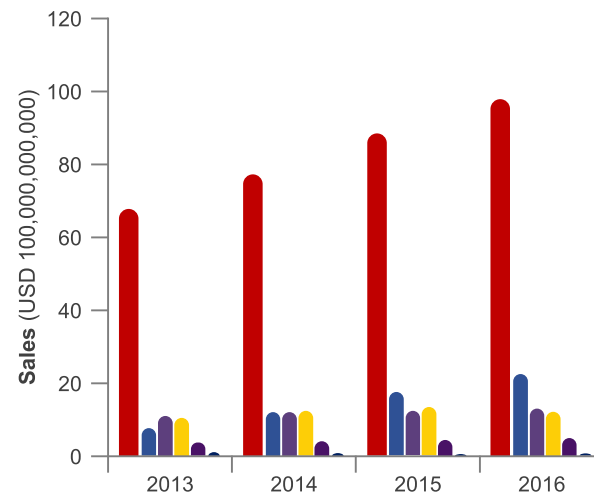
- Januvia ® is **one of the world's most prescribed DPP-4 inhibitors** with more than 10 years of experience in Korea.[1,2]

- Ertugliflozin added to sitagliptin provides clinically meaningful, **durable glycemic control and SBP reductions.**[3]

Korea DPP-4i sales (2013-2016)
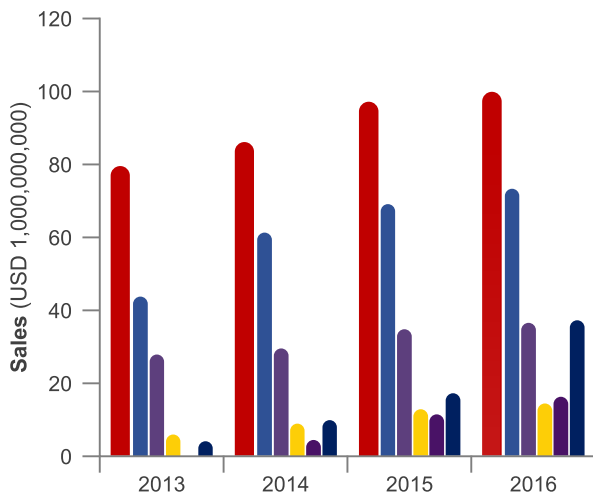
World DPP-4i sales (2013-2016)

Legend: ■ Sitagliptin ■ A ■ B ■ C ■ D ■ E

- Complementary mechanism[4]
- Additional glycemic reduction[4]
- Body weigh reduction[4]

SGLT2i, sodium-glucose cotransporter 2 inhibitor; DPP-4, dipeptidyl peptidase 4; SBP, systolic blood pressure
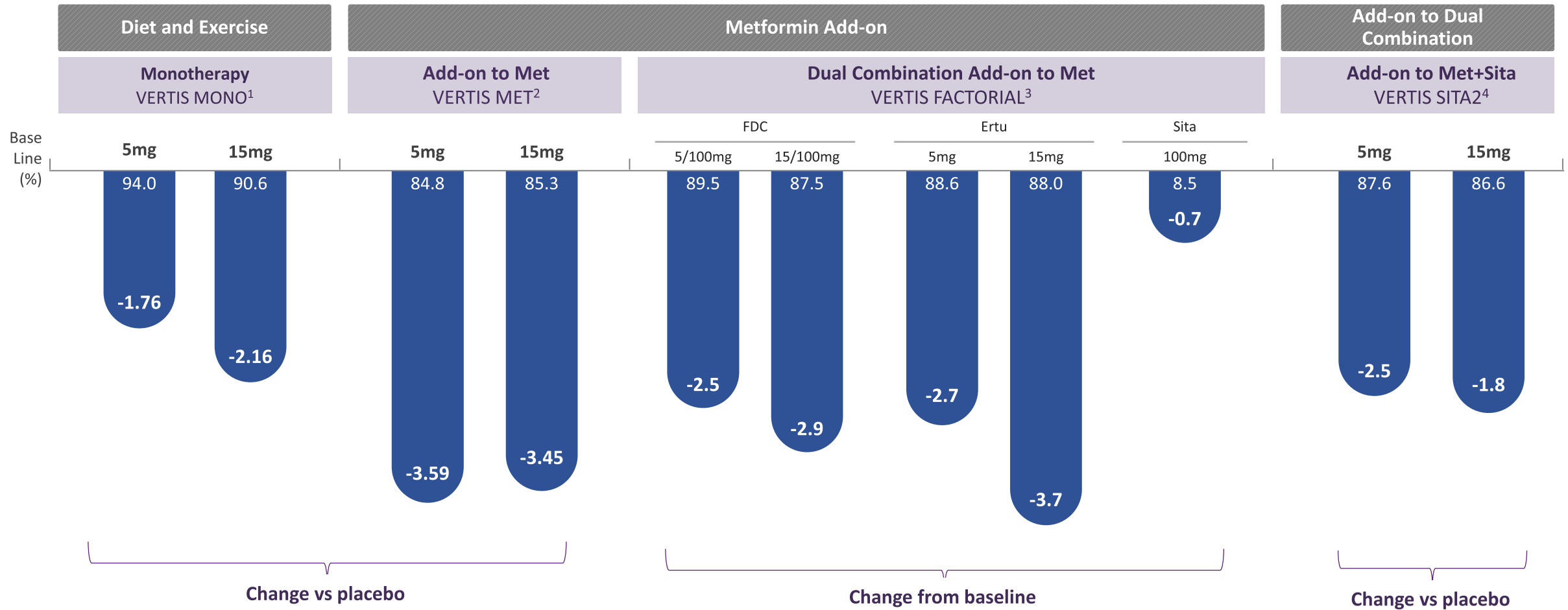
1. 식품의약품안전처. DPP-4 억제제 국내 발매 현황. 2. IMS External Sales Data (2Q2017). 3. Dagogo-Jack S, *et al*. Diabetes Obes Metab 2018;20:530–540. 4. Zou H, *et al*. Cardiovasc Diabetol 2017;16:65.

BP Reduction /Weight Loss

Ertugliflozin:
Body Weight Reduction

	Diet and Exercise		Metformin Add-on								Add-on to Dual Combination	
	Monotherapy VERTIS MONO[1]		**Add-on to Met** VERTIS MET[2]		**Dual Combination Add-on to Met** VERTIS FACTORIAL[3]						**Add-on to Met+Sita** VERTIS SITA2[4]	
					FDC		Ertu		Sita			
Base Line (%)	5mg	15mg	5mg	15mg	5/100mg	15/100mg	5mg	15mg	100mg		5mg	15mg
	94.0	90.6	84.8	85.3	89.5	87.5	88.6	88.0	8.5		87.6	86.6
	-1.76	-2.16	-3.59	-3.45	-2.5	-2.9	-2.7	-3.7	-0.7		-2.5	-1.8

Change vs placebo (Diet and Exercise)
Change from baseline (Metformin Add-on)
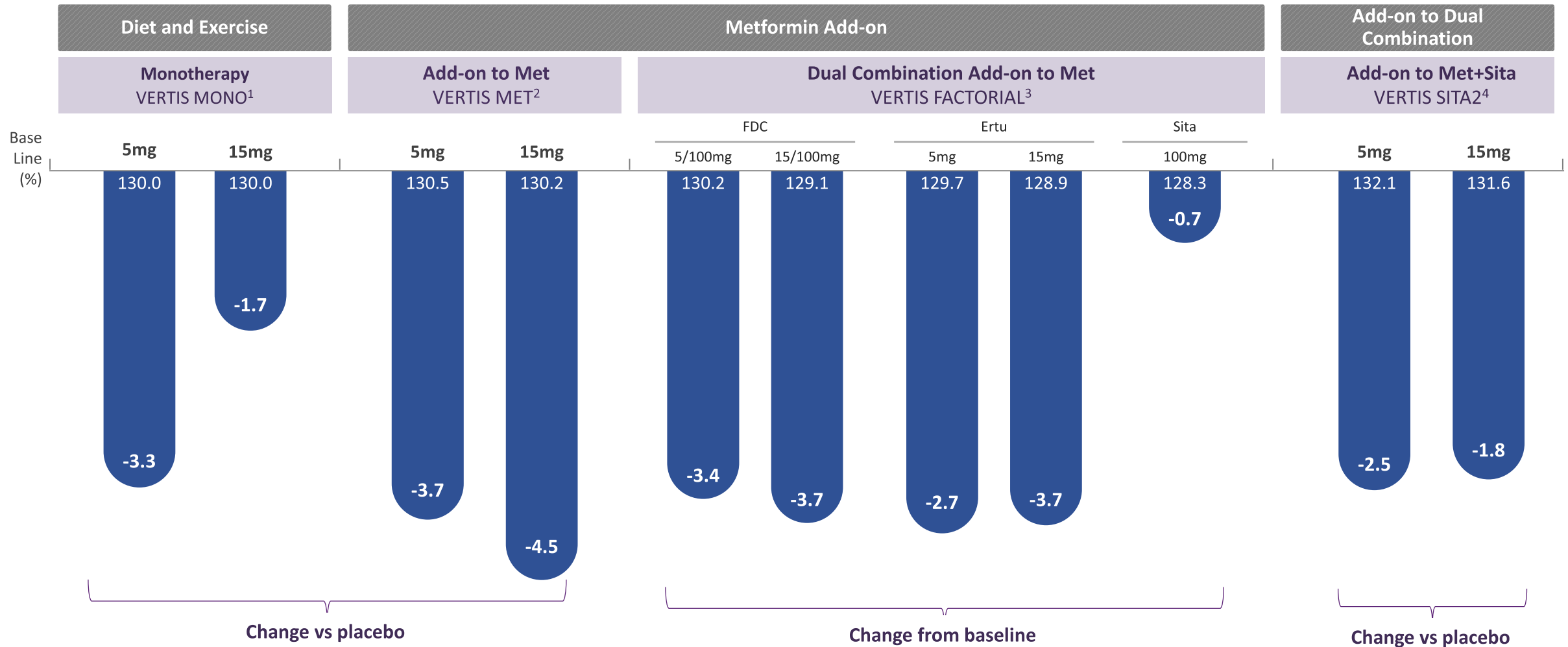**Change vs placebo** (Add-on to Dual Combination)

Met, metformin; Sita, sitagliptin.

* Steglatro 5 mg and 15 mg were launched in March 2018 in the US

1. SG Terra *et al*. Diabetes Obes Metab 2017; 19:721. 2. J Rosenstock *et al*. Diabetes Obes Metab 2018; 20:520.
3. RE Pratley *et al*. Diabetes Obes Metab 2018;20:1111-20. 4. Dagogo-Jack S *et al*. Diabetes Obes Metab. 2018;20:530–540.

Ertugliflozin:
SBP Reduction

Diet and Exercise		Metformin Add-on							Add-on to Dual Combination	
Monotherapy VERTIS MONO[1]		Add-on to Met VERTIS MET[2]		Dual Combination Add-on to Met VERTIS FACTORIAL[3]					Add-on to Met+Sita VERTIS SITA2[4]	
				FDC		Ertu		Sita		
5mg	15mg	5mg	15mg	5/100mg	15/100mg	5mg	15mg	100mg	5mg	15mg
130.0	130.0	130.5	130.2	130.2	129.1	129.7	128.9	128.3	132.1	131.6
	-1.7							-0.7		
-3.3		-3.7	-4.5	-3.4	-3.7	-2.7	-3.7		-2.5	-1.8

Base Line (%)

Change vs placebo   **Change from baseline**   **Change vs placebo**

1. SG Terra *et al*. Diabetes Obes Metab 2017; 19:721. 2. J Rosenstock *et al*. Diabetes Obes Metab 2018; 20:520.
3. RE Pratley *et al*. Diabetes Obes Metab 2018;20:1111-20. 4. Dagogo-Jack S *et al*. Diabetes Obes Metab. 2018;20:530–540.

* Steglatro 5 mg and 15 mg were launched in March 2018 in the US

Safety Profile

VERTIS MONO:
Safety Profile

	Number of Patients (%)		
	Placebo (n=153)	Ertugliflozin 5 mg (n=156)	Ertugliflozin 15 mg (n=152)
One or more AEs (ER)	80 (52.3)	82 (52.6)	85 (55.9)
AEs related to study drug (ER)[a]	19 (12.4)	32 (20.5)	28 (18.4)
One or more serious AEs (IR)	2 (1.3)	7 (4.5)	2 (1.3)
Serious AEs related to study drug (IR)[a]	0	0	0
Death (IR)	0	0	0
AE leading to discontinuation from study medication (IR)	5 (3.3)	4 (2.6)	3 (2.0)
Tier 1 AEs (ER)			
Genital mycotic infection (female)	4 (5.6)	11 (16.4)[b]	14 (22.6)[b]
Genital mycotic infection (male)[c]	1 (1.2)	3 (3.4)	5 (5.6)
Urinary tract infection	13 (8.5)	11 (7.1)	6 (3.9)
Symptomatic hypoglycemia[c]	2 (1.3)	2 (1.3)	4 (2.6)
Hypovolemia	6 (3.9)	2 (1.3)	3 (2.0)

Adapted with permission from Terra SG, et al.[1]
Data are shown as n (%).
AEs, adverse events; ER, analysis excludes events occurring after rescue medication; IR, analysis includes events occurring after rescue medication; 1 Determined by the investigator to be related to the study drug;
2 Incidence significantly higher than the placebo group; 3 Event with clinical symptoms reported by the investigator as hypoglycaemia (biochemical documentation not required).

1. Terra SG, et al. Diabetes Obes Metab 2017;19:721–728.

Safety Profile in Various Studies including Asians

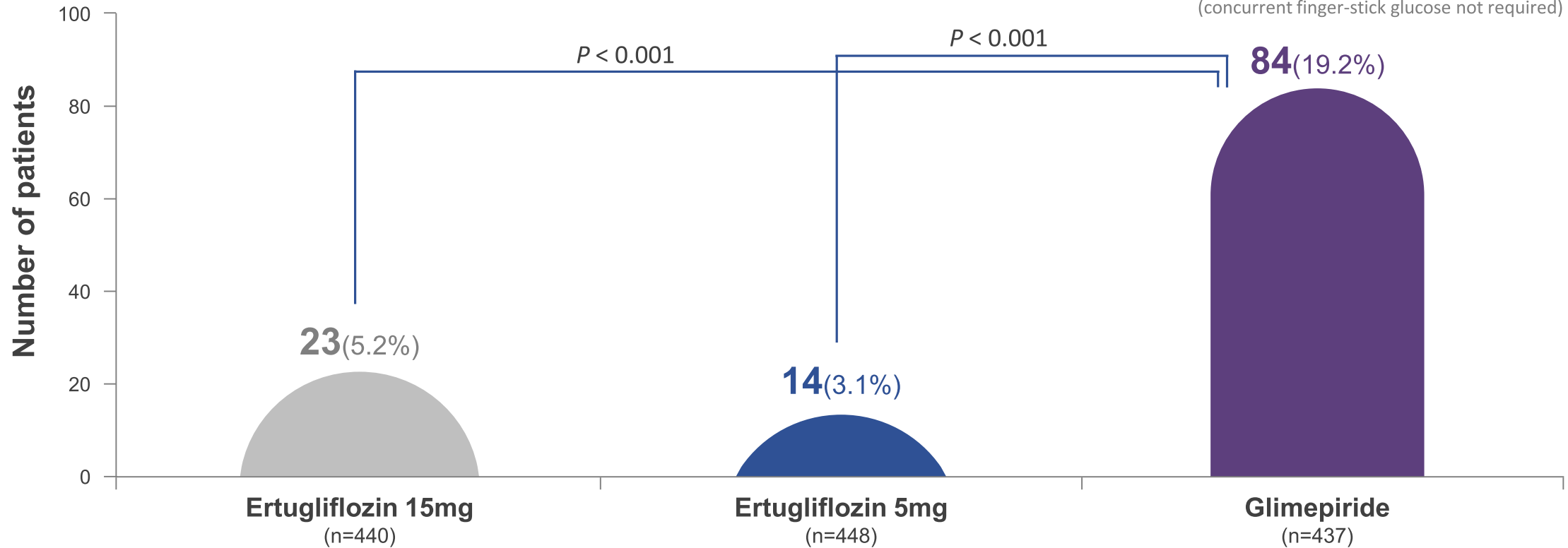| Study	Arms	Asians (%)	Adverse Events		
			GMI (women)	GMI (men)	UTI
VERTIS MONO[1] (52 weeks)	PBO/MET (n=153)	8.5	7 (9.9)	1 (1.2)	21 (13.7)
	Ertu 5mg (n=156)		18 (26.9)	3 (3.4)	17 (10.9)
	Ertu 15mg (n=152)		18 (29)	7 (7.8)	10 (6.6)
VERTIS MET[2]	PBO (n=209)	16.1	1 (0.9)	0 (0.0)	2 (1.0)
	Ertu 5mg (n=207)		6 (5.5)	3 (3.1)	6 (2.9)
	Ertu 15mg (n=205)		7 (6.3)	3 (3.2)	7 (3.4)
VERTIS SITA[3]	PBO (n=97)	NA	2 (5.0)	0 (0.0)	5 (5.2)
	Ertu 5mg + Sita 100mg (n=98)		2 (4.9)	3 (5.3)	8 (8.2)
	Ertu 15mg + sita 100mg (n=96)		3 (7.0)	1 (1.9)	3 (3.1)
VERTIS SITA 2[4] (26 weeks)	PBO (n=153)	20.3%	1/53 (1.9)	0 (0.0)	3 (2.0)
	Ertu 5mg (n=156)		6/75 (8)	4/81 (4.9)	4 (2.6)
	Ertu 15mg (n=153)		9/71 (12.7)	3/82 (3.7)	7 (4.6)
VERTIS ASIA[5]	PBO (n=167)		1 (1.3)	1 (1.1)	4 (2.4)
	Ertu 5mg (n=170)		2 (2.7)	2 (2.1)	3 (1.8)
	Ertu 15mg (n=169)		1 (1.4)	2 (2.0)	2 (1.2)

1. Aronson R *et al*. Diabetes Obes Metab. 2018;20(6):1453-1460. 2. Rosenstock J, *et al*. Diabetes Obes Metab 2018;20:520-529. 3. Miller S *et al*. Diabetes Ther. 2018; 9:253-268.
4. Dagogo-Jack S *et al*. Diabetes Obes Metab. 2018;20:530–540. 5. Ji L et al.Diabetes Obes Metab. 2019 Mar 4 doi: 10.1111/dom.13681

The incidence of symptomatic hypoglycemia was lower in the ertugliflozin groups compared with the glimepiride group[1]

VERTIS SU : Symptomatic hypoglycemia*

* Event with clinical symptoms reported by the investigator as hypoglycemia (concurrent finger-stick glucose not required)

Number of patients (y-axis: 0, 20, 40, 60, 80, 100)

P < 0.001

P < 0.001

23(5.2%) — Ertugliflozin 15mg (n=440)

14(3.1%) — Ertugliflozin 5mg (n=448)

84(19.2%) — Glimepiride (n=437)

The VERTIS SU trial evaluated the efficacy and safety of once-daily ertugliflozin 15 or 5 mg compared with glimepiride (initiated at 1 mg and uptitrated to a maximum of 6 or 8 mg/day) over 52 weeks, in patients with T2DM inadequately controlled with metformin.

1. Hollander P, *et al*. Diabetes Ther 2018;9:193-207.

Take Home Message

- ADA 2019 recommended GLP-1 RA **and SGLT2-i in patients with ASCVD.** SGLT2i have additional benefits with a **significant reduction of the major cardiovascular events** (MI, stroke, CV death)**, body weight and blood** pressure in T2DM patients with high CV risk[1]

- HbA1C reduction is related to the CV risk reduction in DM patients.
  HbA1C Reduction is fundamental for DM management[2-4]

- **Ertugliflozin is a new, highly selective and potent SGLT-2 inhibitor** with proven HbA1C Reduction in various trials including comparison studies[5]

CV, cardiovascular; SGLT2, sodium–glucose cotransporter 2; ASCVD, atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide 1 receptor agonist; T2DM = type 2 diabetes mellitus

1. ADA Diabetes Care 2019;42(Suppl.1):S90-S102. 2. . ERFC. Lancet. 2010;375:2215-22. 3. Ritsinger V *et al*, Diab Vasc Dis Res 2015;12:23–32.
4. Stratton IM *et al*. BMJ 2000;321:405–412. 5. Cinti F *et al*. Drug Des Devel Ther. 2017;11:2905–2919.