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DIABETES

Gloripa®
Empagliflozin

Synoripa®
Empagliflozin / Metformin

By
Medical Team

Objectives

- Target organs and mechanism-targeted treatments
- SGLT2 & SGLT2 inhibitors
- Efficacy Studies
- EMPA-REG OUTCOME®
- EMPA-REG RENAL®
- Cardio and Renal potential mechanisms of Empagliflozin
- EMPA REG & EMPA- RENAL summary
- Initial Combination of Empagliflozin and Metformin
- Guidelines Recommendations
- Administration, Cautions, Side effects
- Summary

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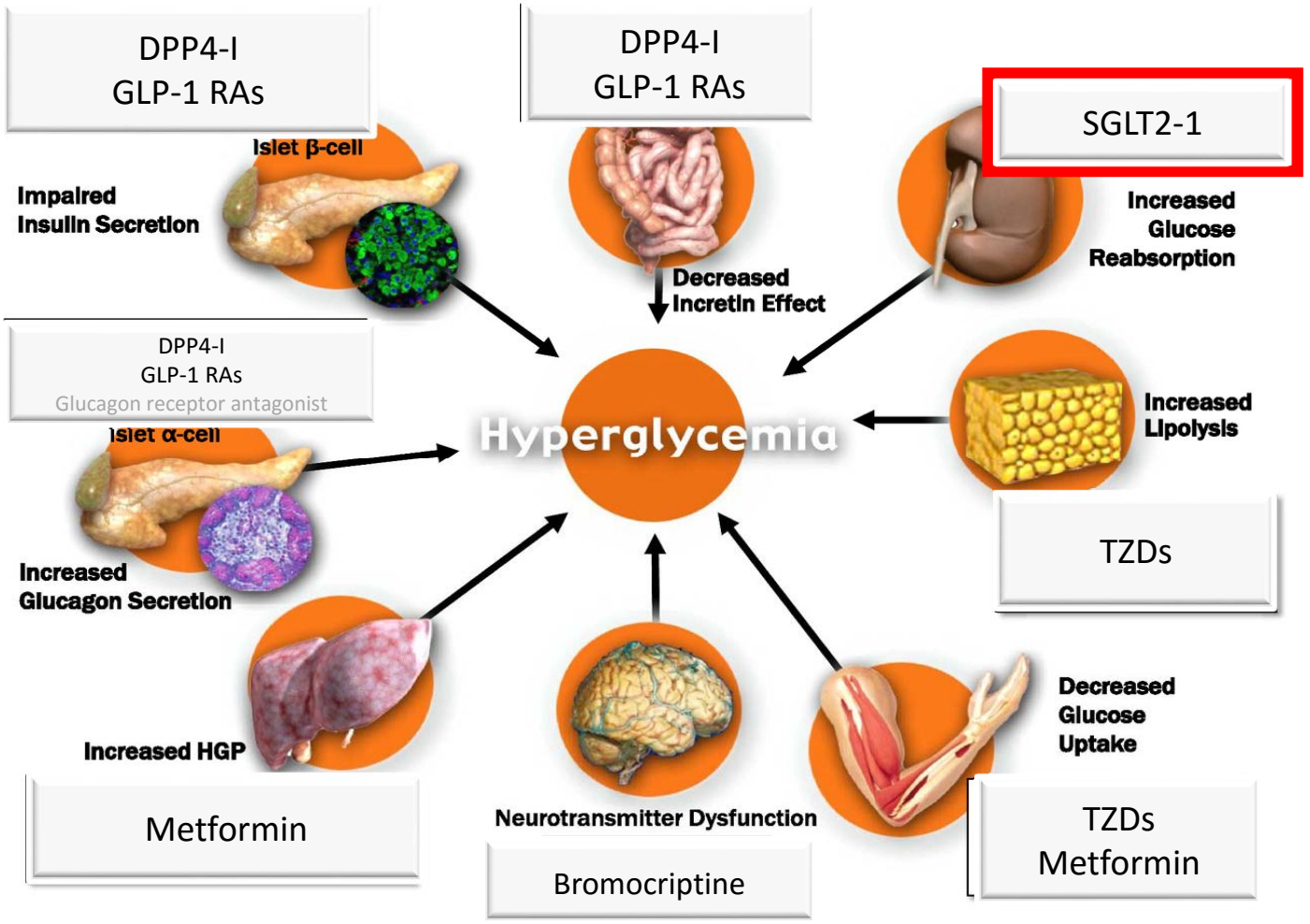
Target organs and mechanism-targeted treatments

Target Organs and action mechanism of anti-Diabetic drugs



1-Lyssenko V et al, Personalized therapy by phenotype and genotype. Diabetes care. 2016,1; 39(Supplement 2):S127-36.

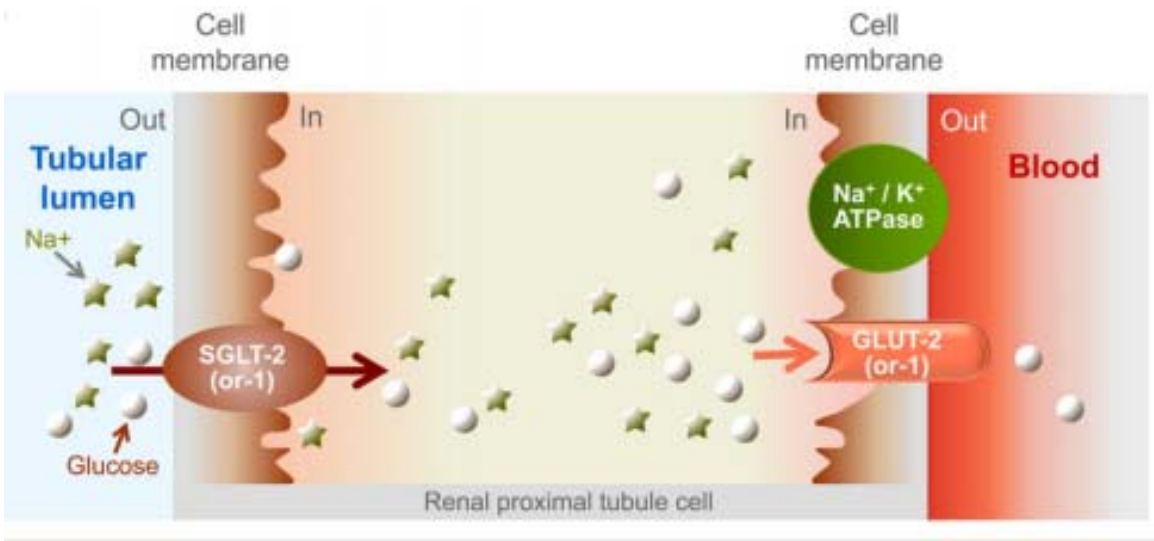
SGLT2 & SGLT2 inhibitors

Glucose Transporters

They are classified into two families[1,2]:

- *facilitative glucose transporters (GLUTs)*
- *sodium-dependent glucose transporters (SGLTs)*

- *$SGLT_1$: low capacity, high affinity, mostly in intestine*
- *$SGLT_2$: high capacity, low affinity, mostly in kidney*



1-Bays H. Sodium glucose co-transporter type 2 (SGLT2) inhibitors: targeting the kidney to improve glycemic control in diabetes mellitus. Diabetes Therapy. 2013; 4(2):195-22

2-Nair S et al,. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism. 2010; 95(1):34-42.

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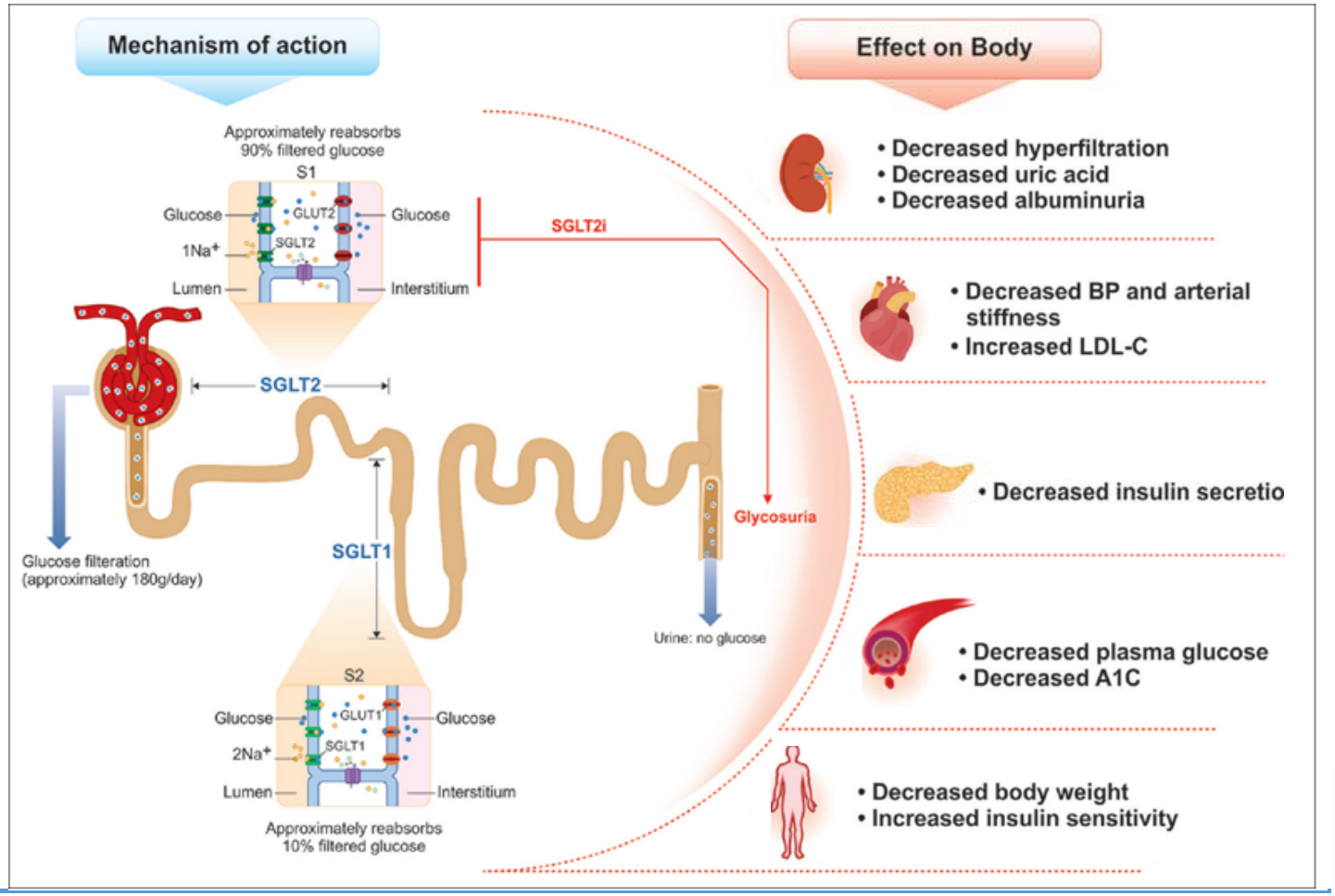
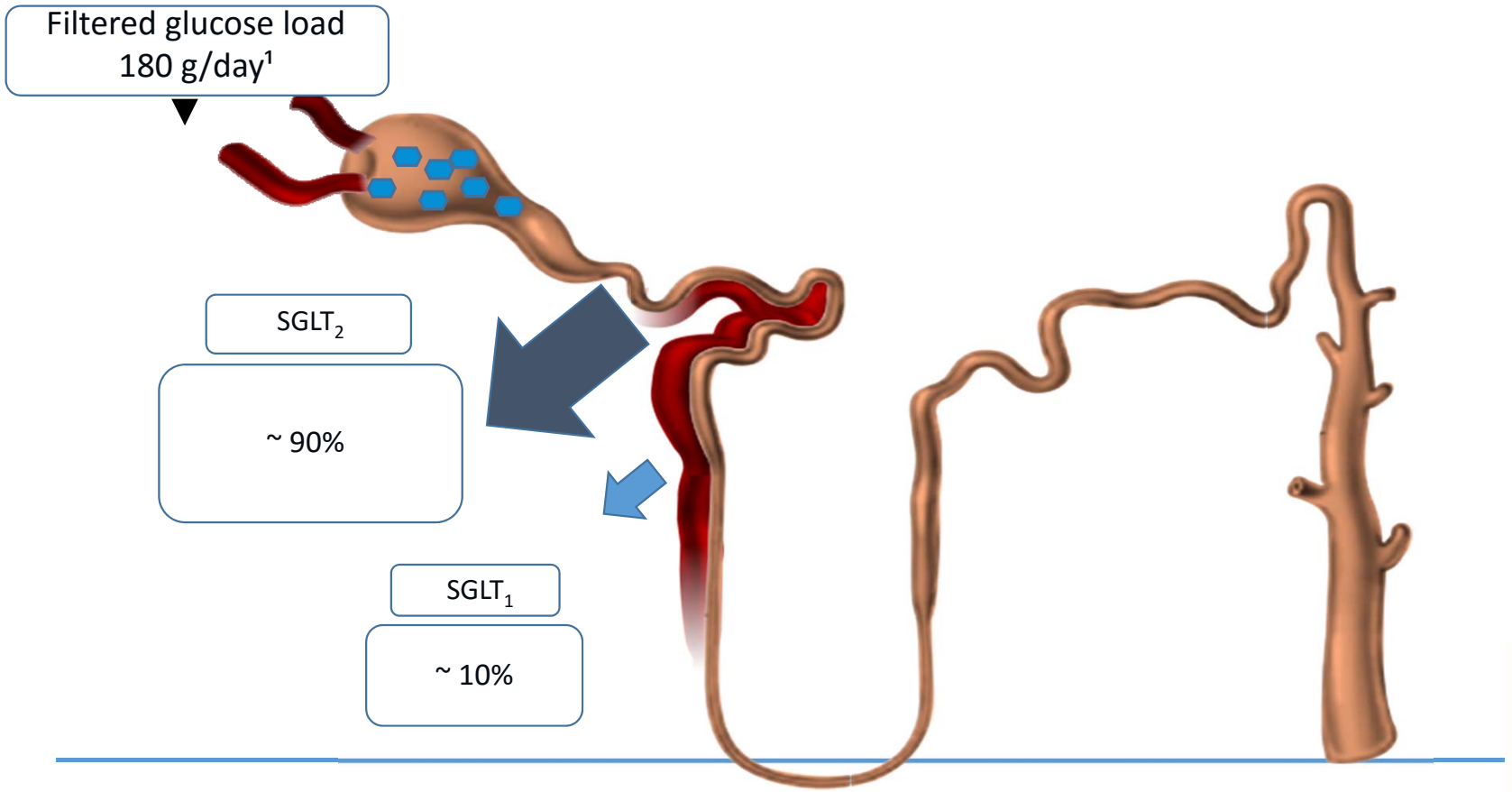
Mechanism of action and effects of SGLT-2 inhibitors on the body[1]



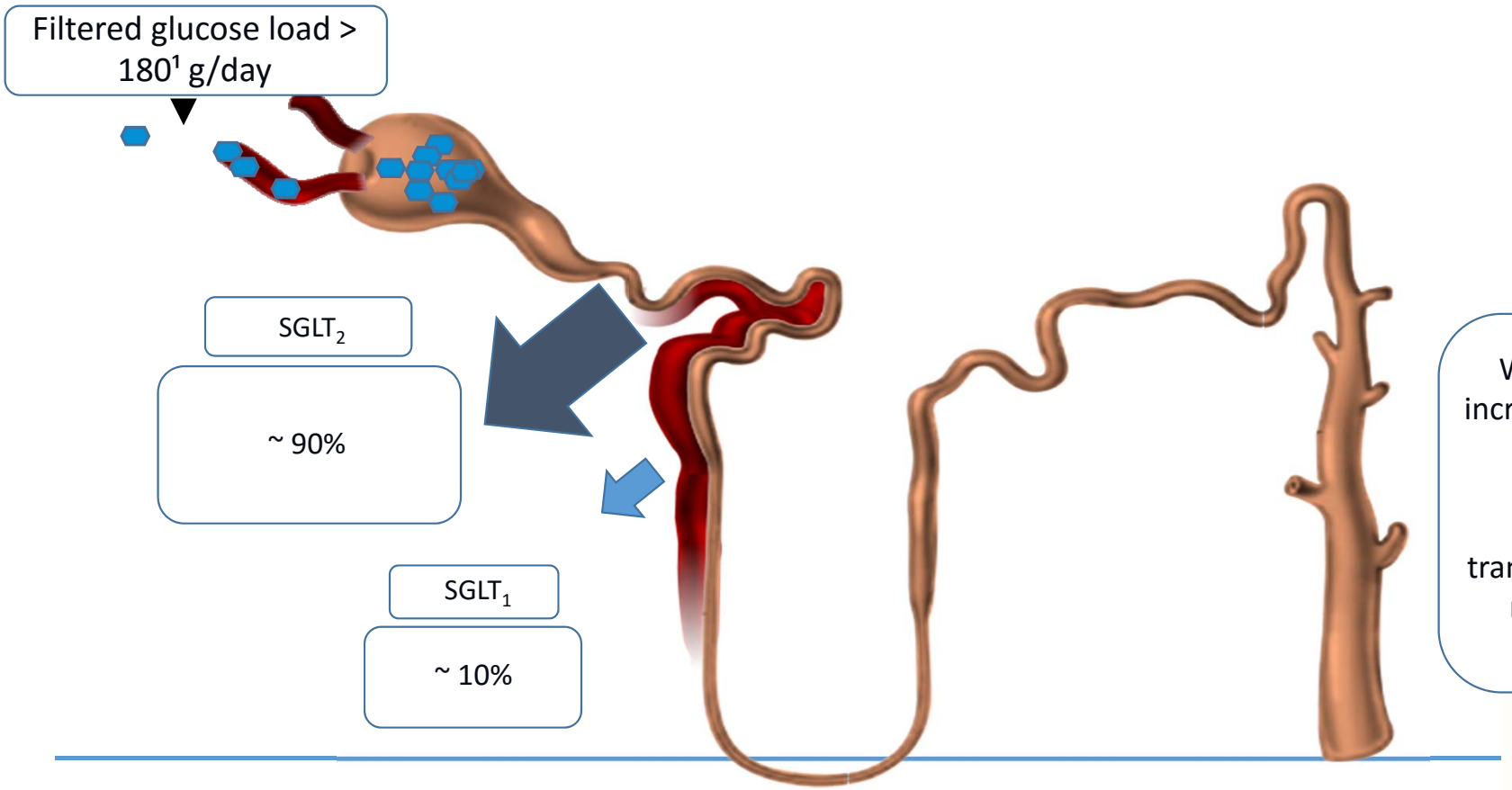
1-Birkeland Ki et.al,. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. The Lancet Diabetes & Endocrinology. 2017 Sep 1;5(9):709-17.

Renal glucose re-absorption in healthy individuals



1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2): 136-42.

Renal glucose re-absorption in patients with diabetes



When blood glucose increases above the renal threshold *(~ 180 mg/dL),* the capacity of the transporters is exceeded, resulting in urinary glucose excretion[1]

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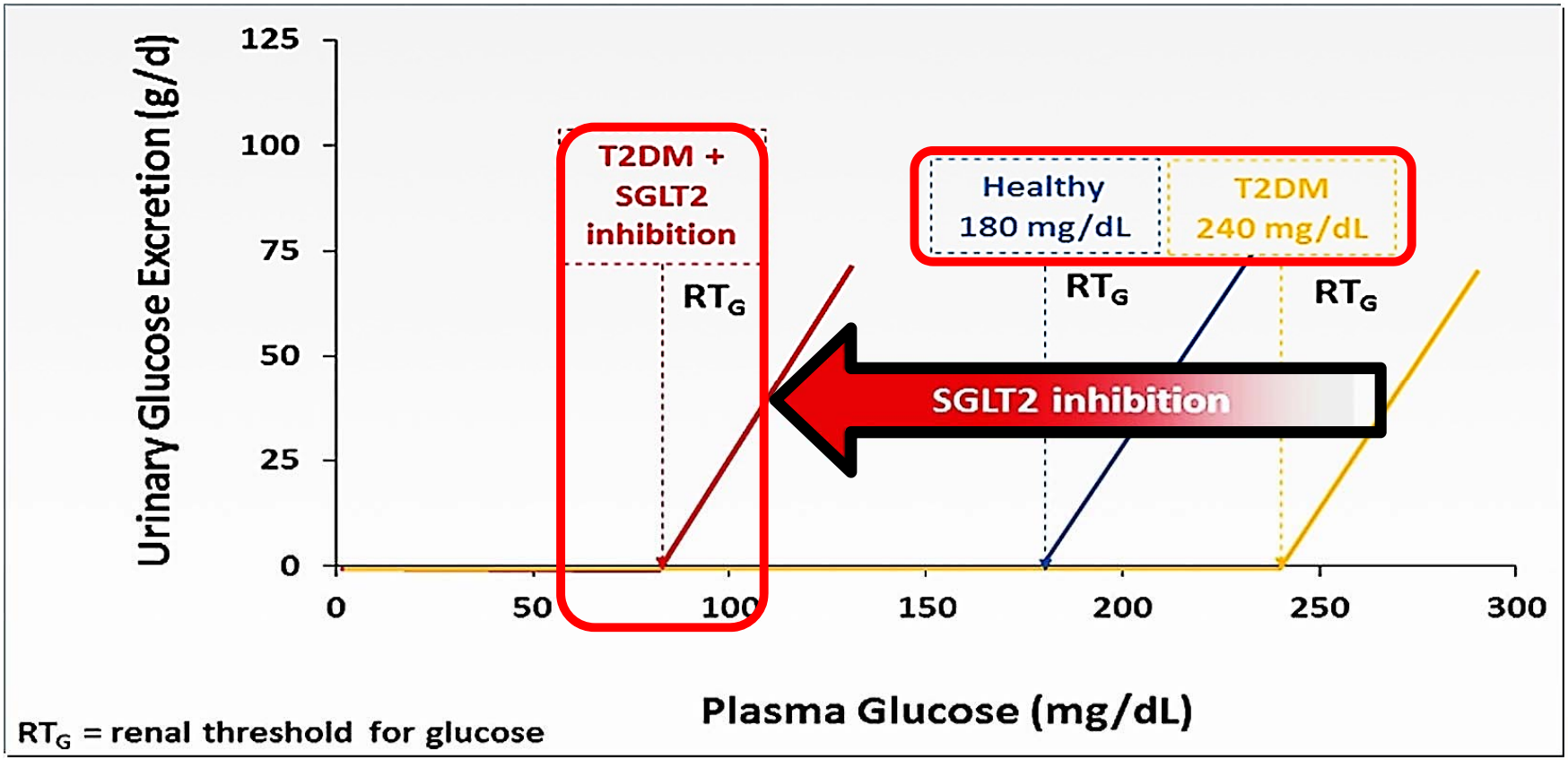
1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2): 136-42.

SGLT2i lowers renal threshold for glucose excretion[1,2]

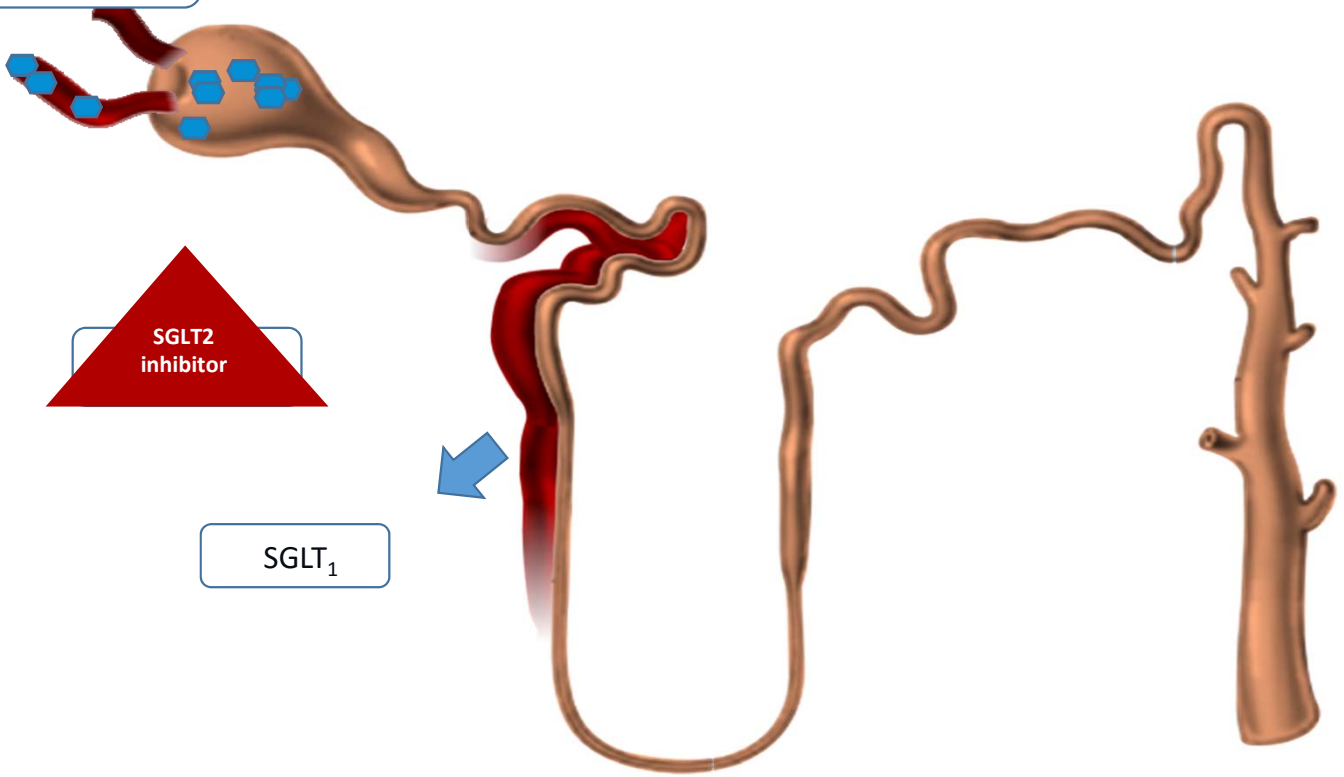


1-Abdul-Ghani M et al, Inhibition of renal glucose reabsorption: a novel strategy for achieving glucose control in type 2 diabetes mellitus. Endocrine Practice. 2008; 14(6): 782-90.

2-Nair S et al, Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism. 2010; 95(1): 34-42.

Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load
> 180 g/day

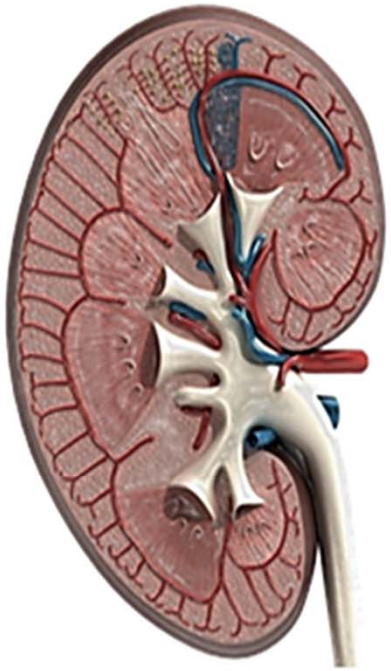


$SGLT_2$ inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis[1]

***Loss of ~ 80 g of glucose/day**

1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2):136-42.

Expected Clinical Effects of SGLT2 Inhibition[1]

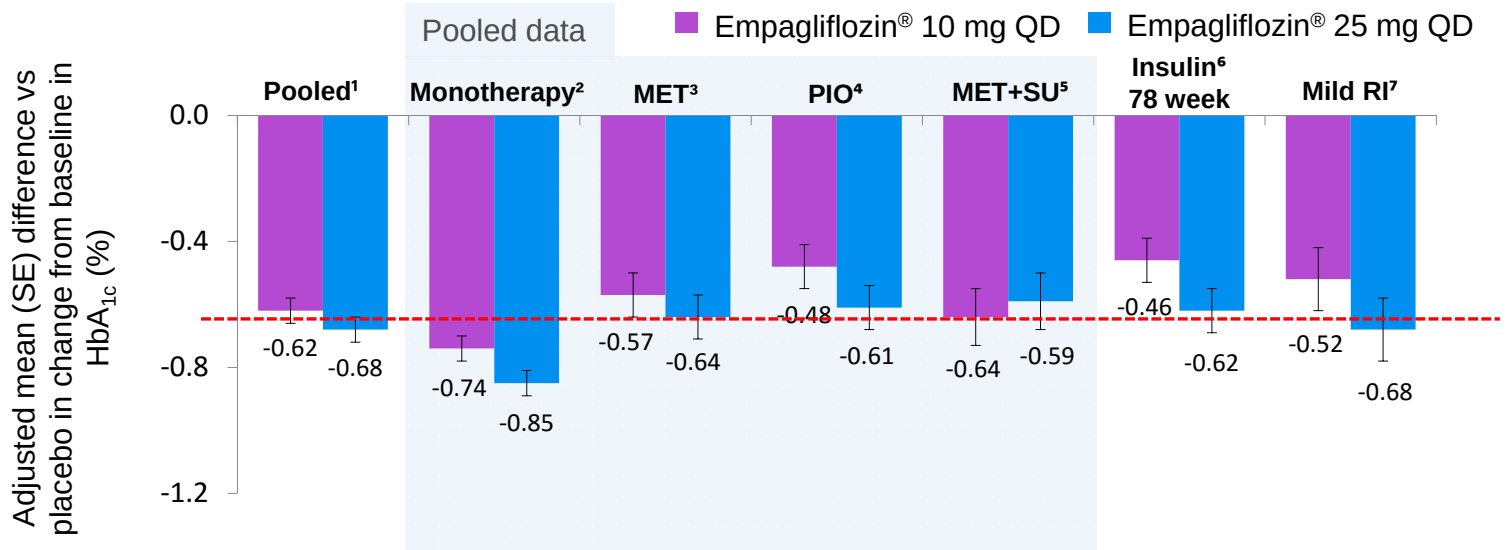


1-Abdul-Ghani M et al, Inhibition of renal glucose reabsorption: a novel strategy for achieving glucose control in type 2 diabetes mellitus. Endocrine Practice. 2008; 14(6): 782-90

Efficacy Studies

Δ HbA1c Across Different Background Therapy Empagliflozin® vs. Placebo*

Phase III pooled efficacy analysis

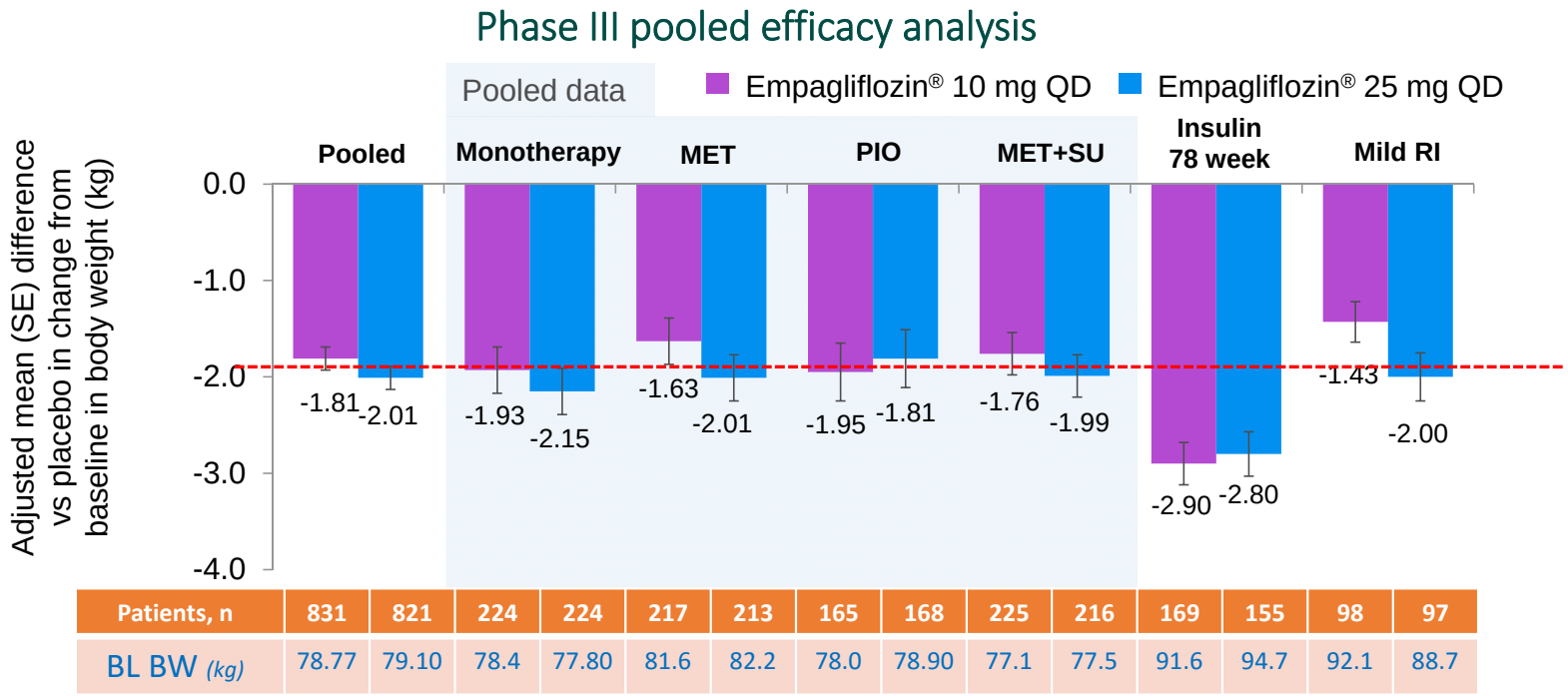


Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL HbA_{1c}, %	7.98	7.96	7.87	7.86	7.94	7.86	8.1	8.1	8.07	8.10	8.3	8.3	8.02	7.96

BL, baseline; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SE, standard error; SU, sulphonylurea.
* All data are placebo-corrected and statistically significant unless otherwise marked

1-Hach T, et al. *Diabetes*. 2013;62(suppl 1A);A21 (P69-LB); 2-Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1(3):208–219; 3- Häring H-U, et al. *Diabetes Care*. 2014 (in press);
4-Kovacs C, et al. *Diabetes Obes Metab*. 2014;16(2):147–158; 5- Häring H-U, et al. *Diabetes Care*. 2013;36(11):3396–404; 6- Rosenstock J, et al. *Diabetologia*. 2013;56(suppl 1);S372 (P931);
7-Barnett A, et al, *Lancet Diabetes Endocrinol*. 2014; doi:10.1016/S2213-8587(13)70208-0.

Δ Body Weight Across Different Background TherapyEmpagliflozin® vs. Placebo*



Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL BW *(kg)*	78.77	79.10	78.4	77.80	81.6	82.2	78.0	78.90	77.1	77.5	91.6	94.7	92.1	88.7

BL, baseline; BW, body weight; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SE, standard error; SU, sulphonylurea.
* All data are placebo-corrected and statistically significant unless otherwise marked

1-Hach T, et al. *Diabetes*. 2013;62(suppl 1A);A21 (P69-LB); 2-Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1(3):208–219; 3- Häring H-U, et al. *Diabetes Care*. 2014 (in press);
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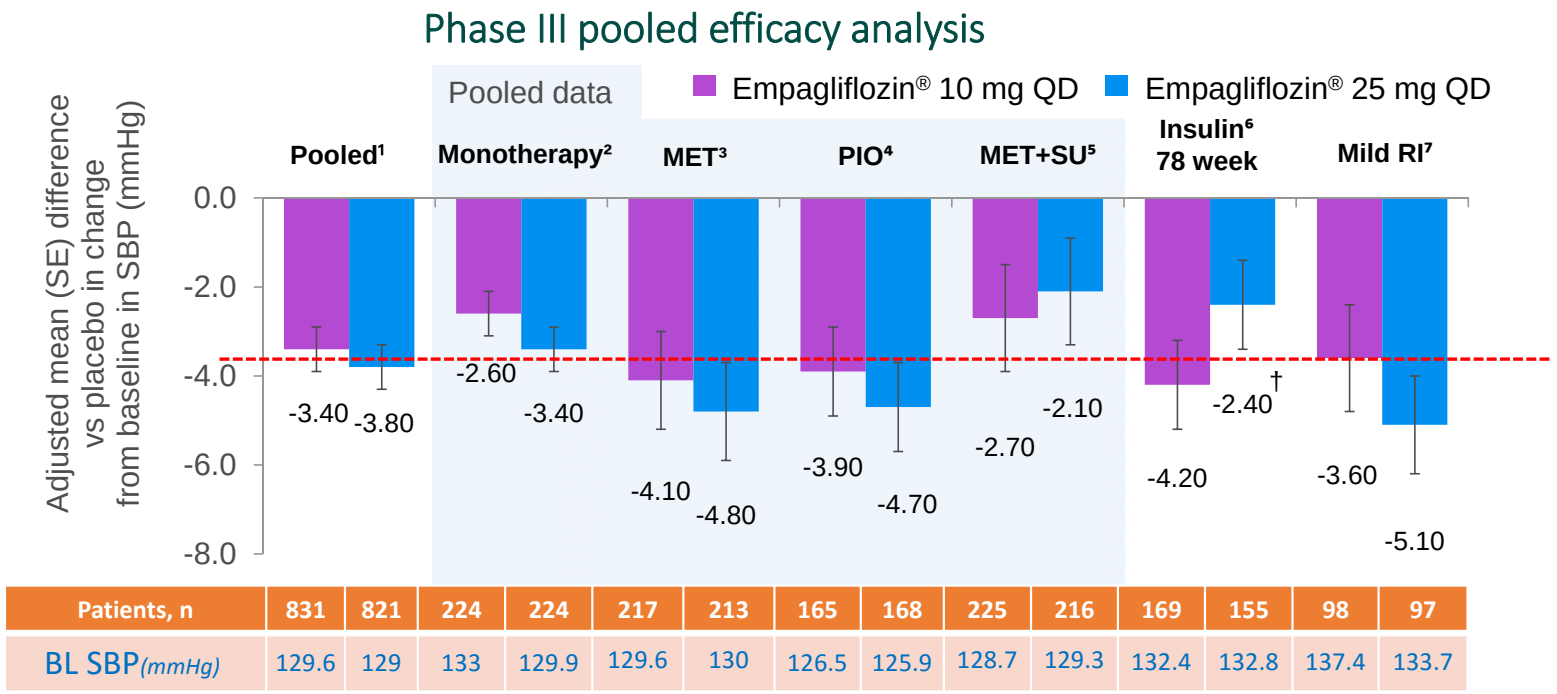
7-Barnett A, et al, *Lancet Diabetes Endocrinol*. 2014; doi:10.1016/S2213-8587(13)70208-0.

Δ SBP Across Different Background Therapy Empagliflozin® vs. Placebo*



Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL SBP *(mmHg)*	129.6	129	133	129.9	129.6	130	126.5	125.9	128.7	129.3	132.4	132.8	137.4	133.7

BL, baseline; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea.
*All statistically significant except when marked as †.

1-Hach T, et al. *Diabetes*. 2013;62(suppl 1A);A21 (P69-LB); 2-Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1(3):208–219; 3- Häring H-U, et al. *Diabetes Care*. 2014 (in press);
4-Kovacs C, et al. *Diabetes Obes Metab*. 2014;16(2):147–158; 5- Häring H-U, et al. *Diabetes Care*. 2013;36(11):3396–404; 6- Rosenstock J, et al. *Diabetologia*. 2013;56(suppl 1);S372 (P931);
7-Barnett A, et al, *Lancet Diabetes Endocrinol*. 2014; doi:10.1016/S2213-8587(13)70208-0.

EMPA-REG OUTCOME®

EMPA-REG OUTCOME

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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Objective[1]

To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events

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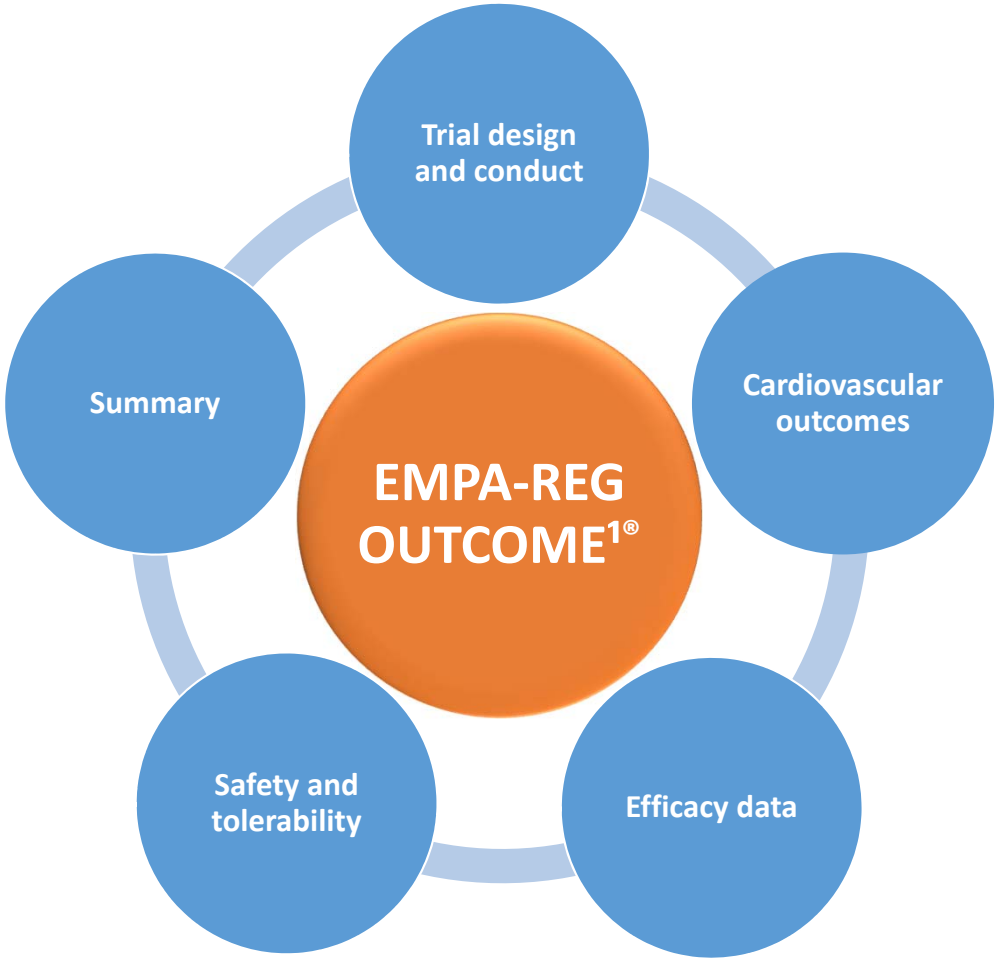
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.



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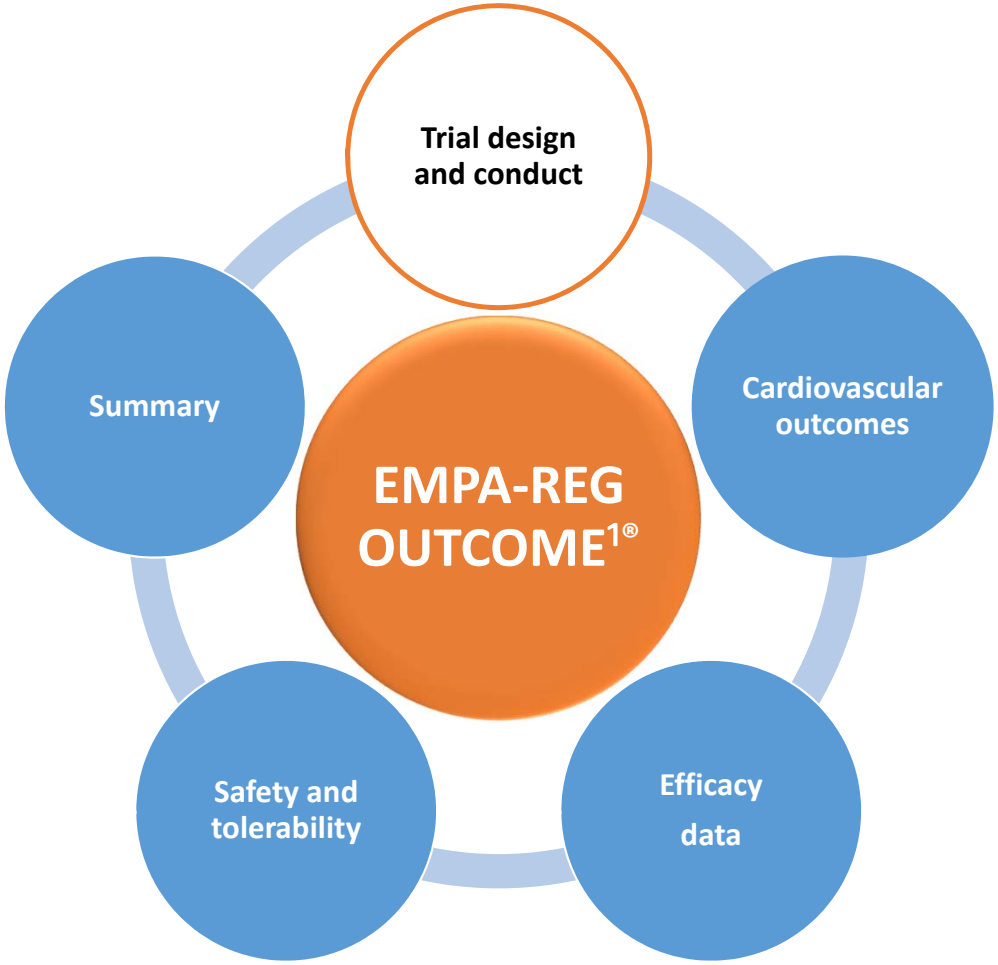

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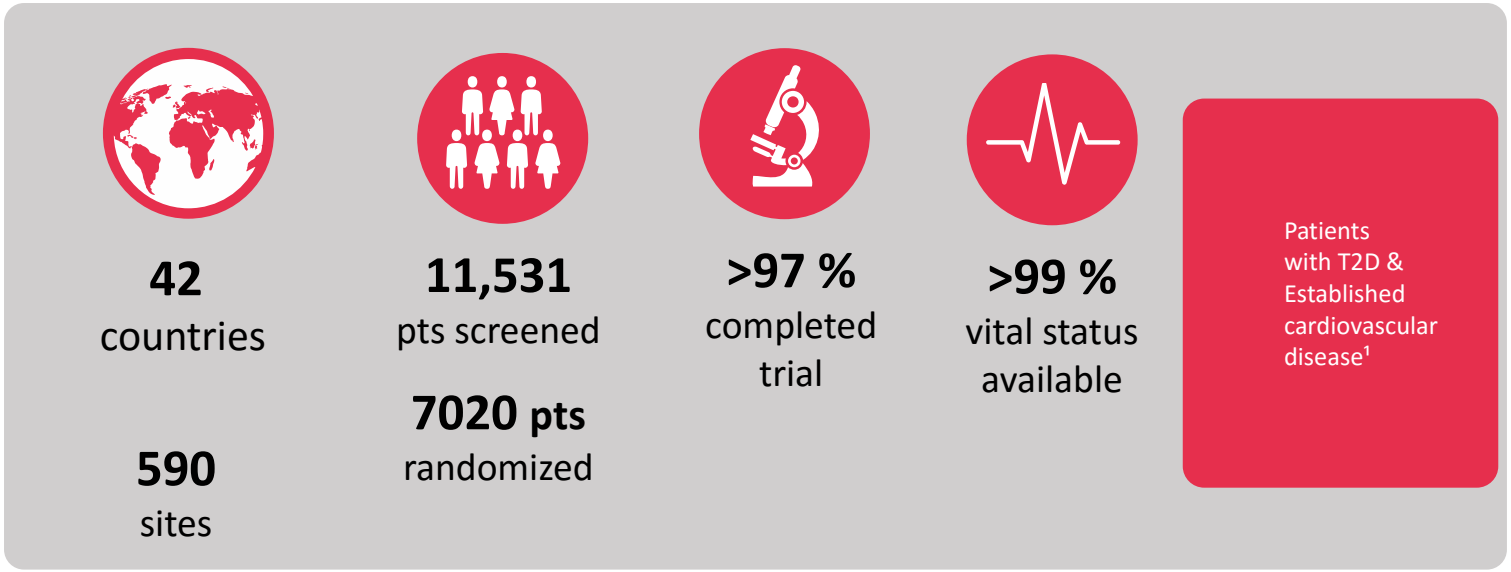
Trial Design[1]



- CV, cardiovascular.

1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28..

Trial Design[1]

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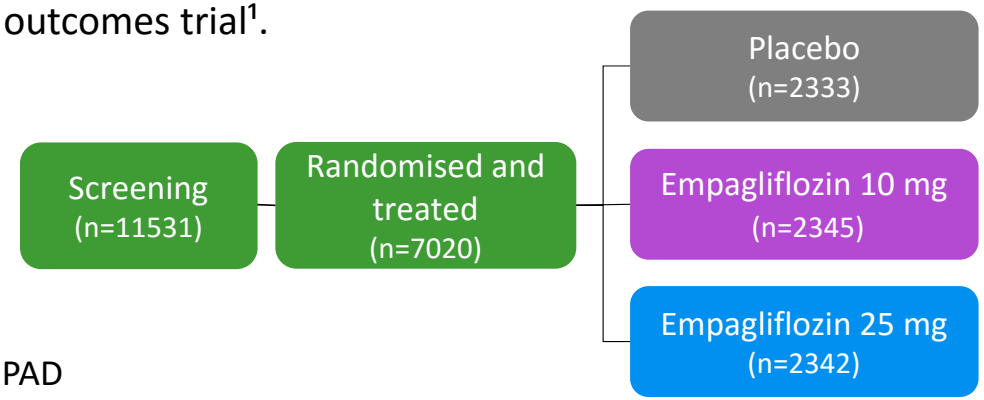
- **Design**
  - Randomized, double-blind, placebo-controlled CV outcomes trial[1].
- **Key inclusion criteria**
  - Adults with T_2DM
  - BMI ≤45 *kg/m2*
  - HbA_{1c} 7–10%*
  - Established cardiovascular disease
    - Prior MI, CAD, stroke, unstable angina or occlusive PAD
- **Key exclusion criteria**
  - eGFR <30 *mL/min/1.73m²* (MDRD)



✓ The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event.

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
*No glucose-lowering therapy for ≥12 weeks prior to randomisation or no change in dose for ≥12 weeks prior to randomisation or, in the case of insulin, unchanged by >10% compared to the dose at randomisation

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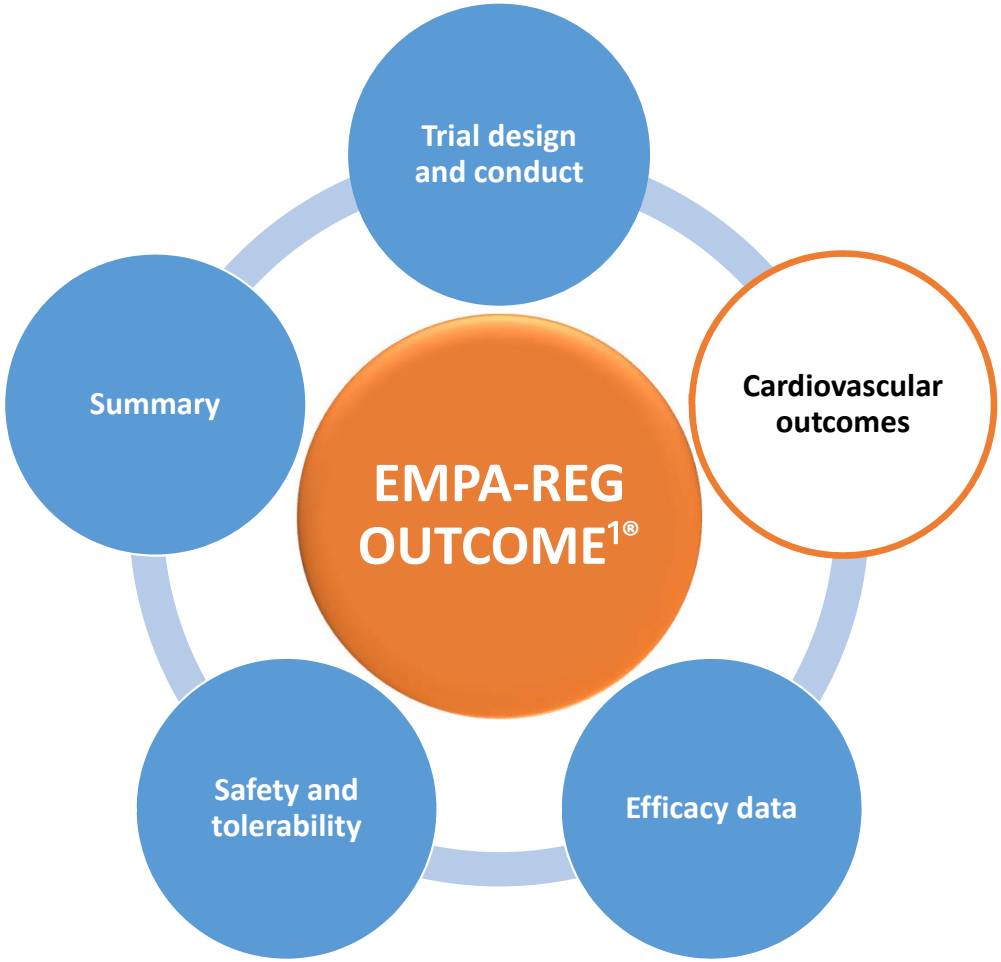
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.



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Pre-specified primary and key secondary outcomes[1]

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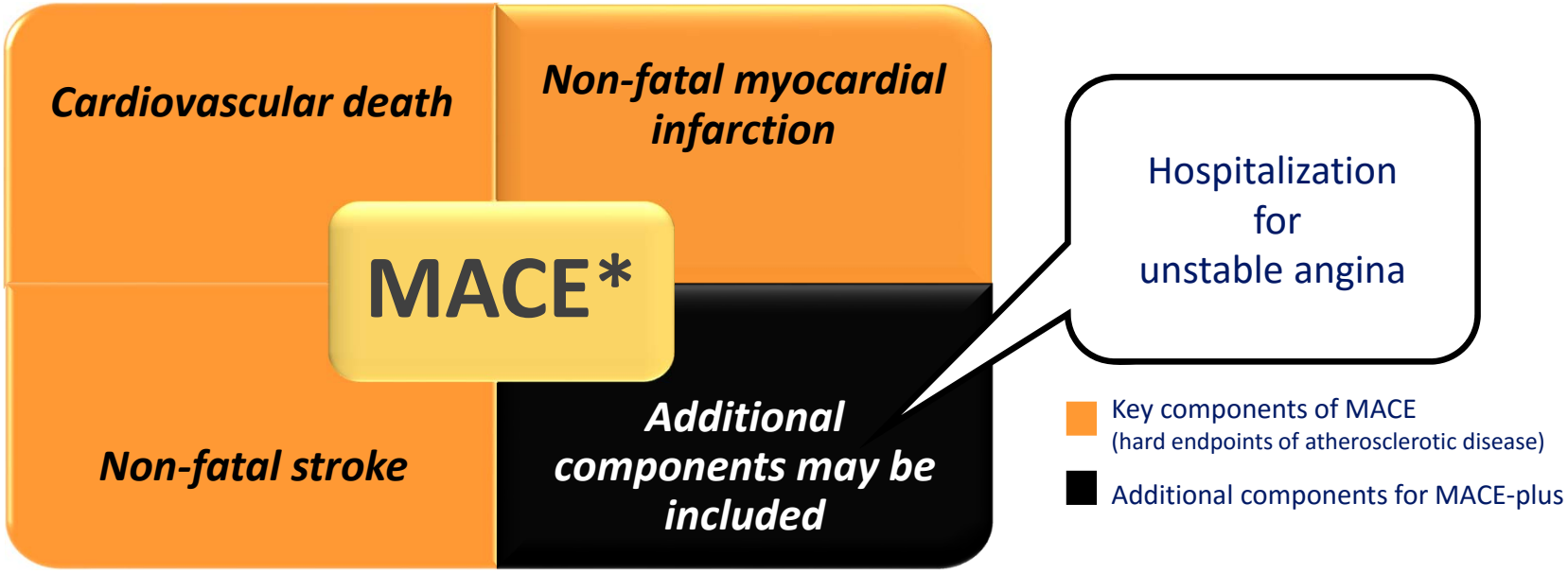

*Major Adverse Cardiovascular Events

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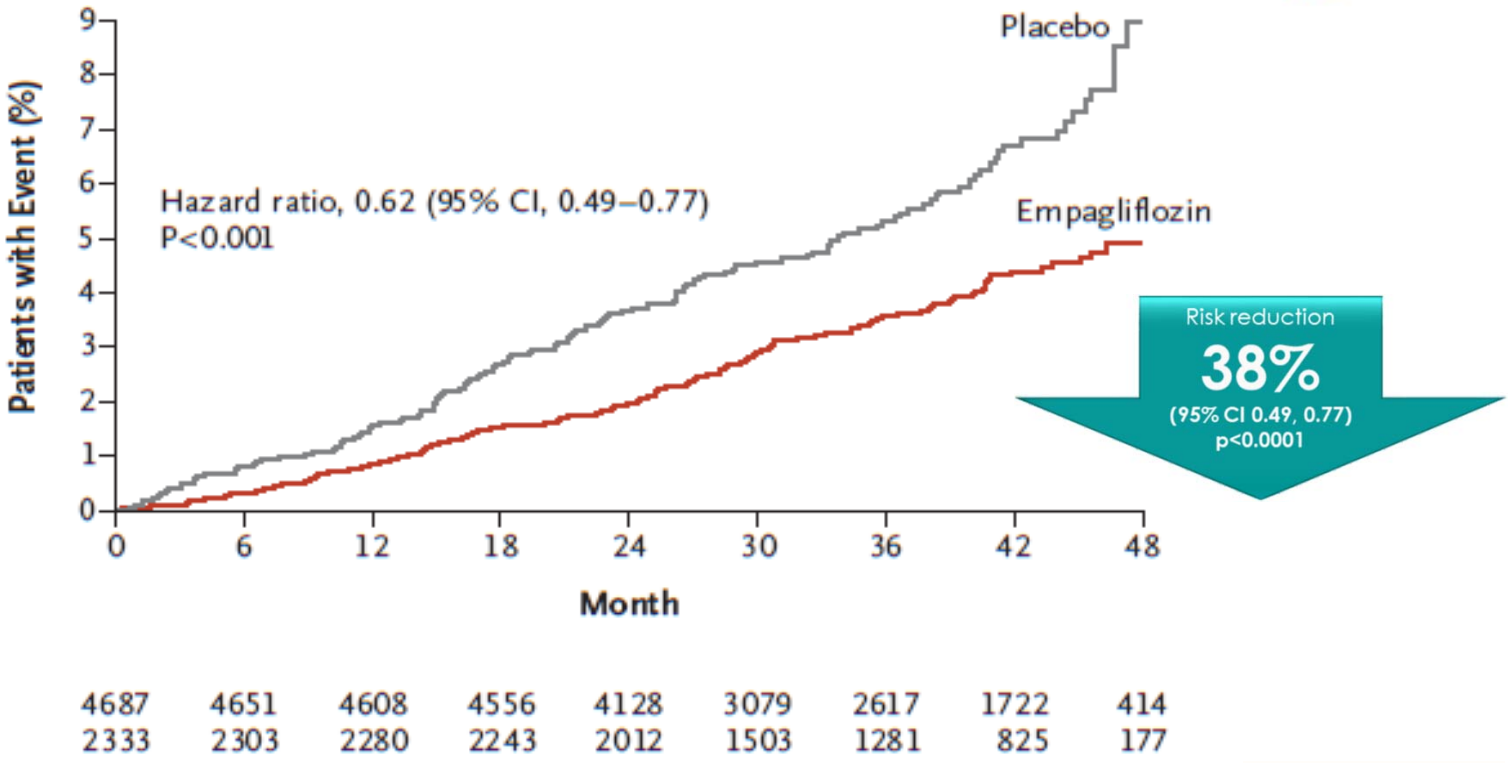
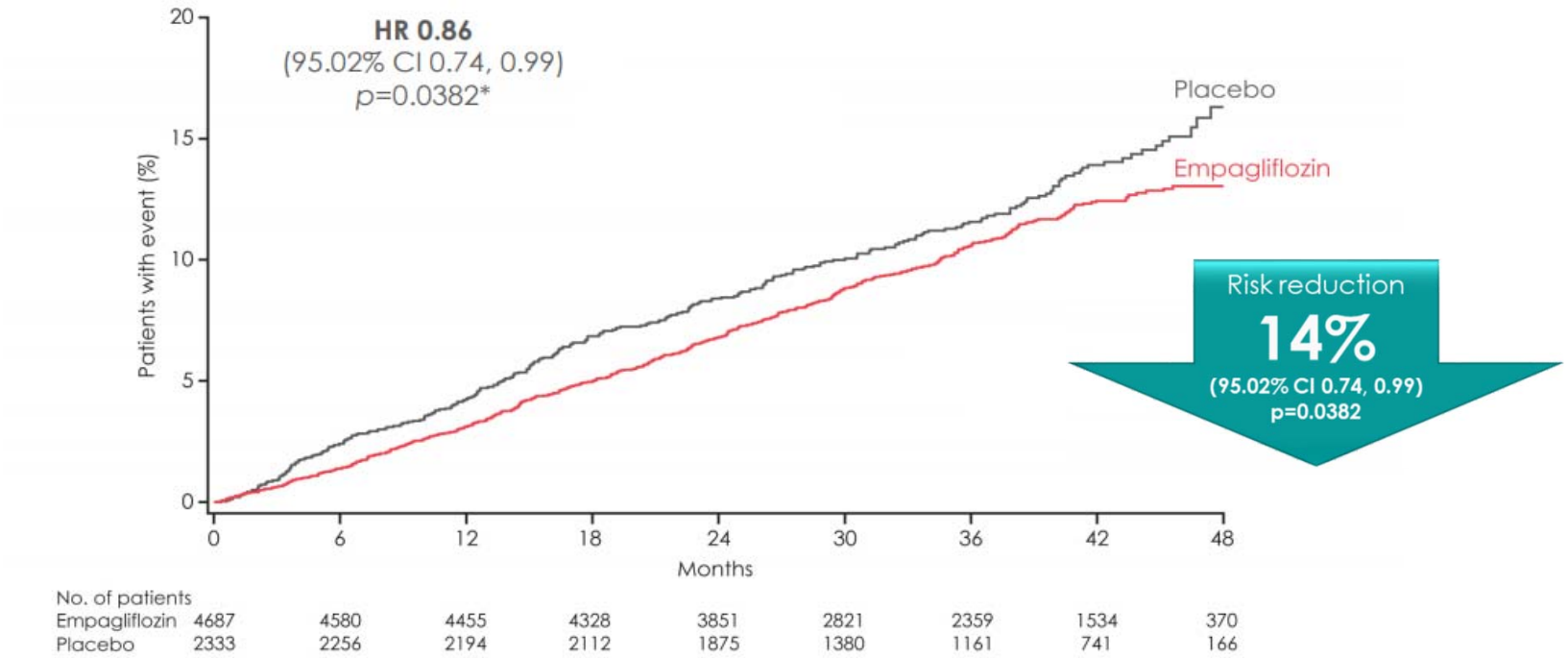
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

EMPA-REG OUTCOME®CV Death[1]



1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

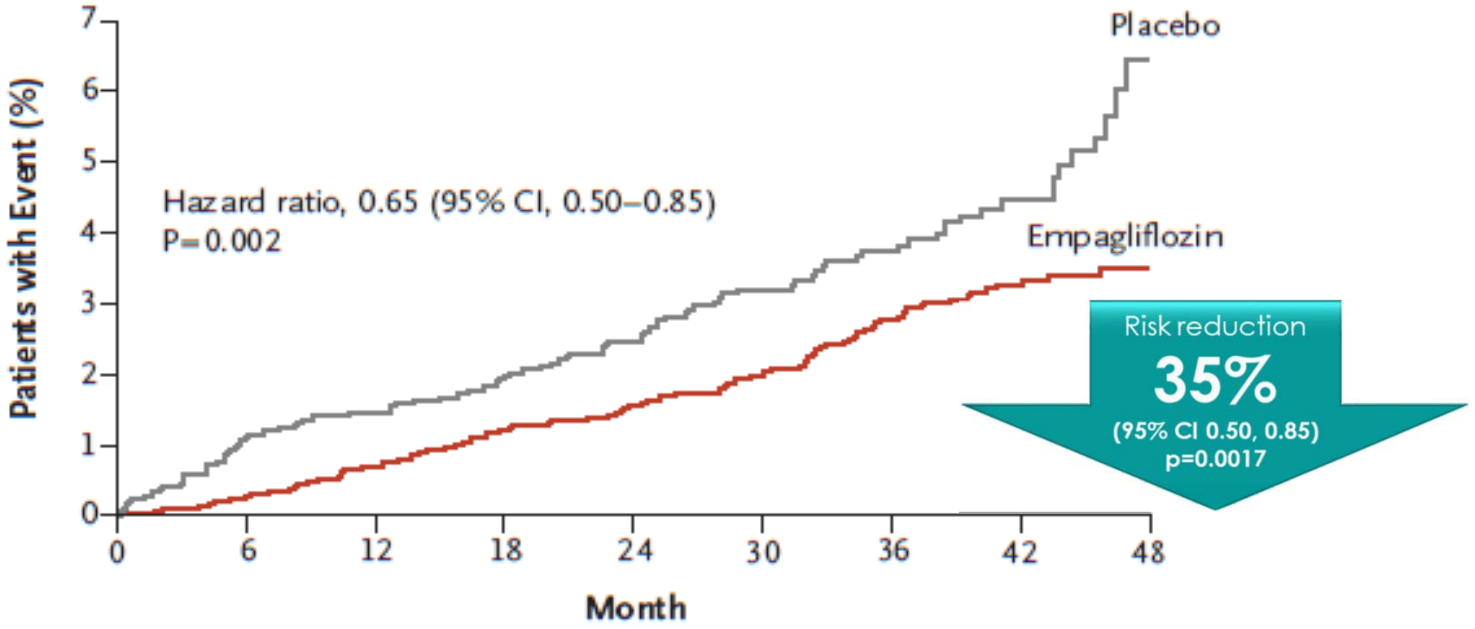
Primary Outcome: 3-point MACE (CV death, Nonfatal MI, Nonfatal stroke)[1]



Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

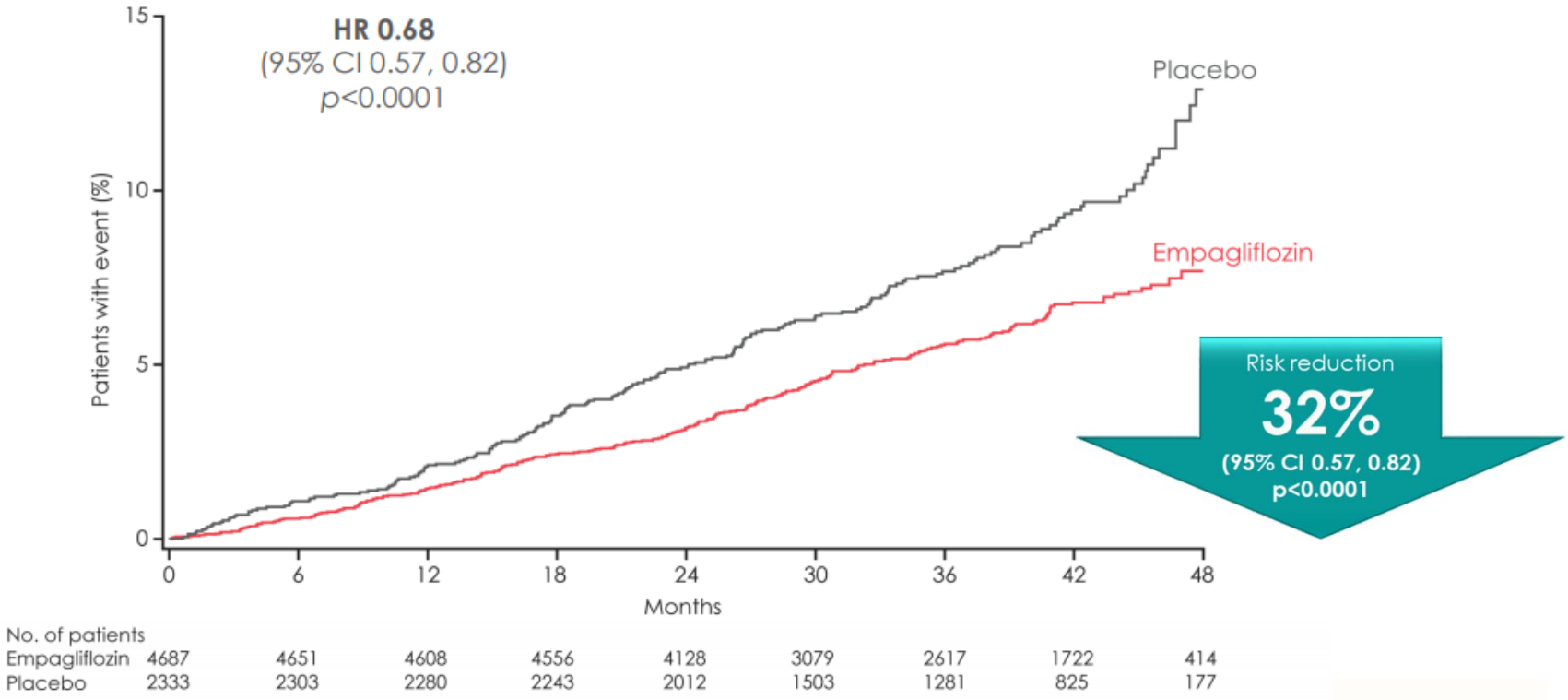
EMPA-REG OUTCOME® Hospitalization for Heart Failure[1]



No. at Risk									
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,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

EMPA-REG OUTCOME® All-cause Mortality[1]



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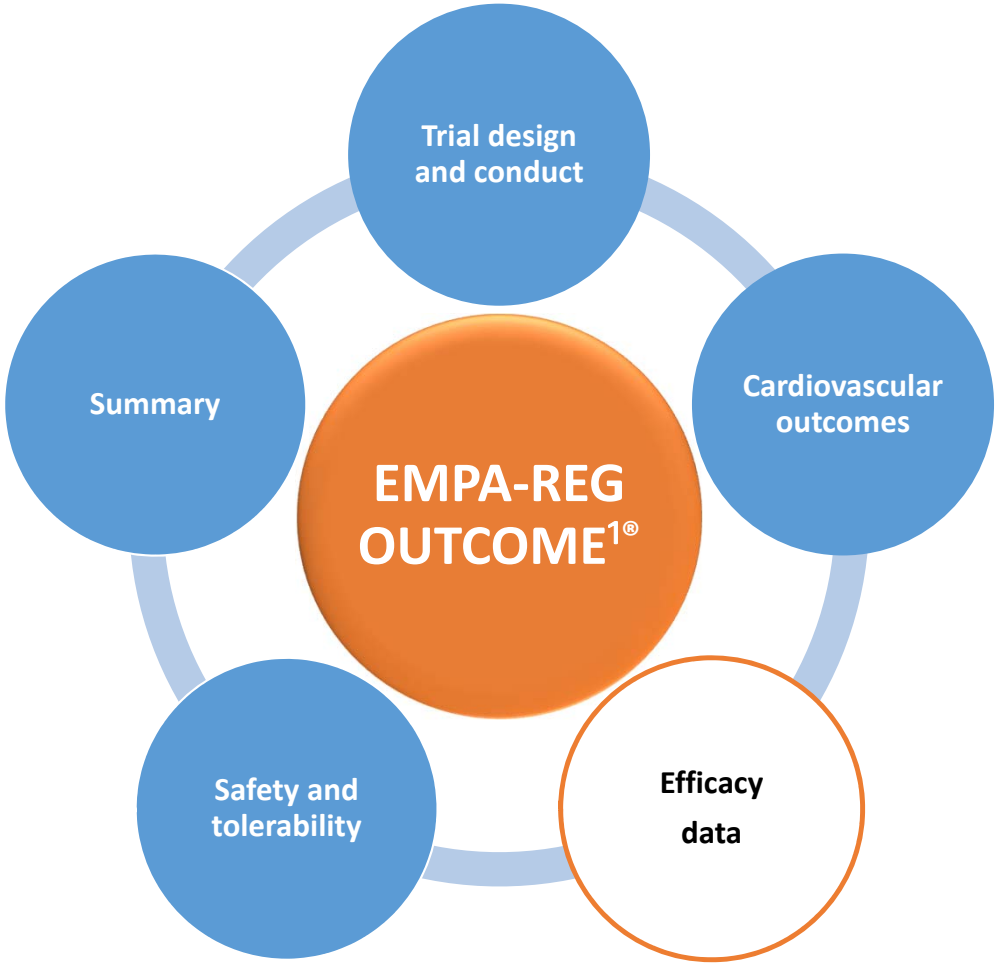
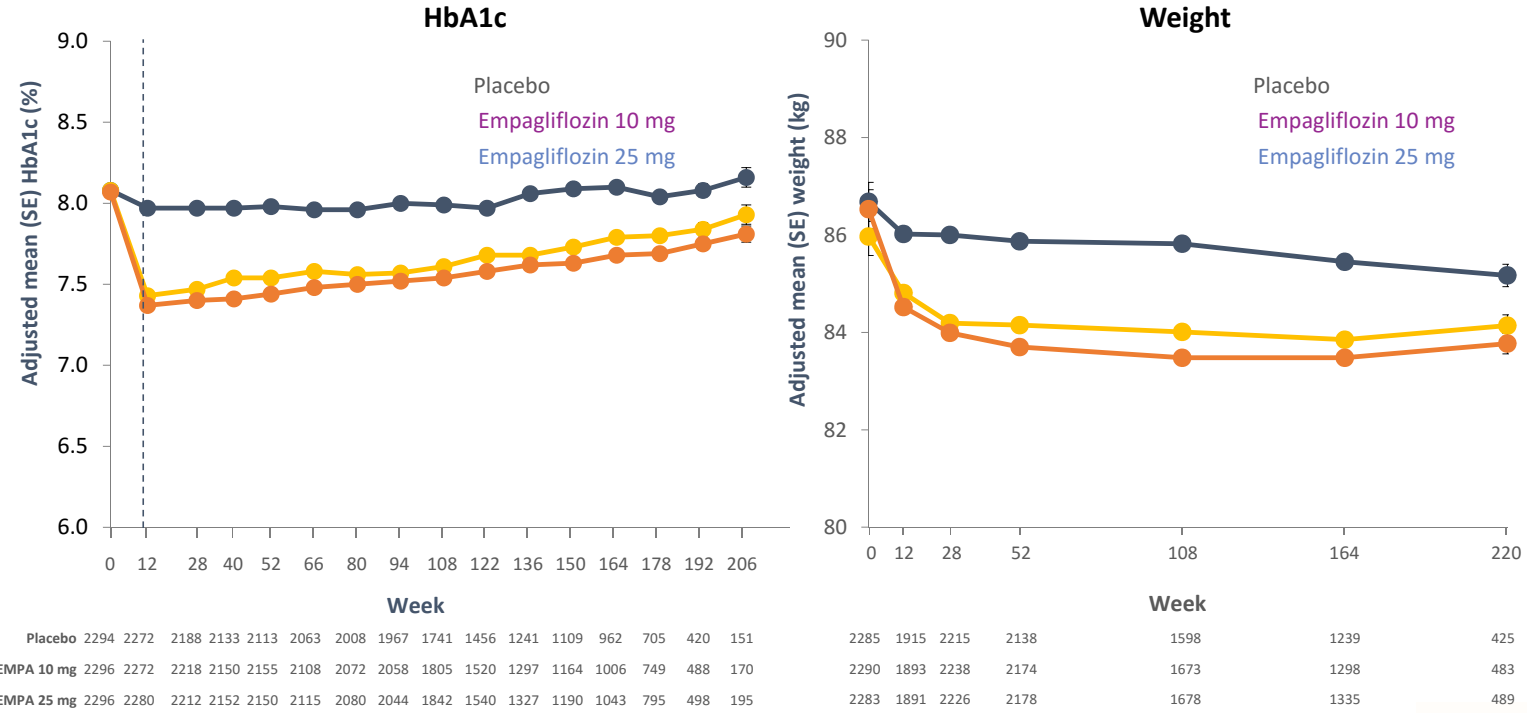


1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Mean adjusted HbA1c and weight parameters[1]



All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent to treat)
X-axis: time points with reasonable amount of data available for prescheduled measurements
EMPA, empagliflozin; HbA1c, glycated haemoglobin

1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Mean adjusted blood pressure parameters[1]

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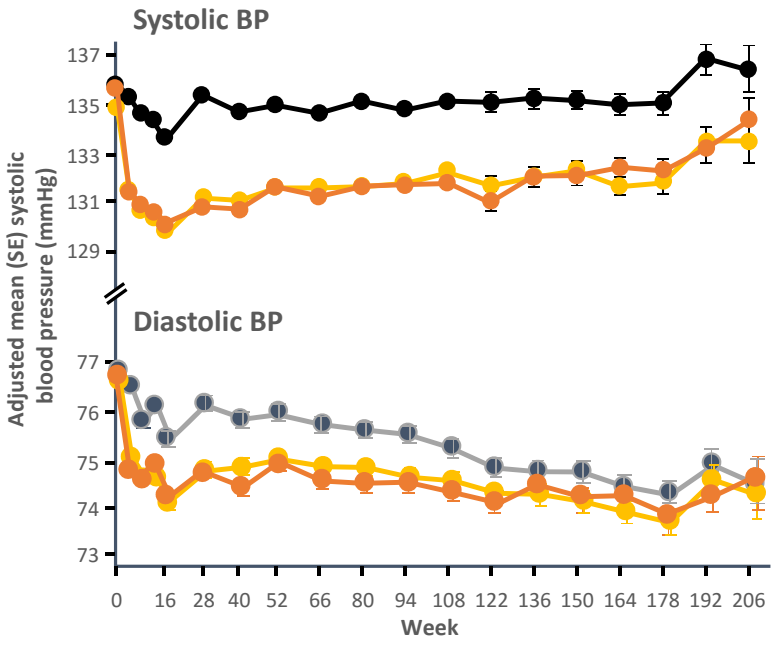
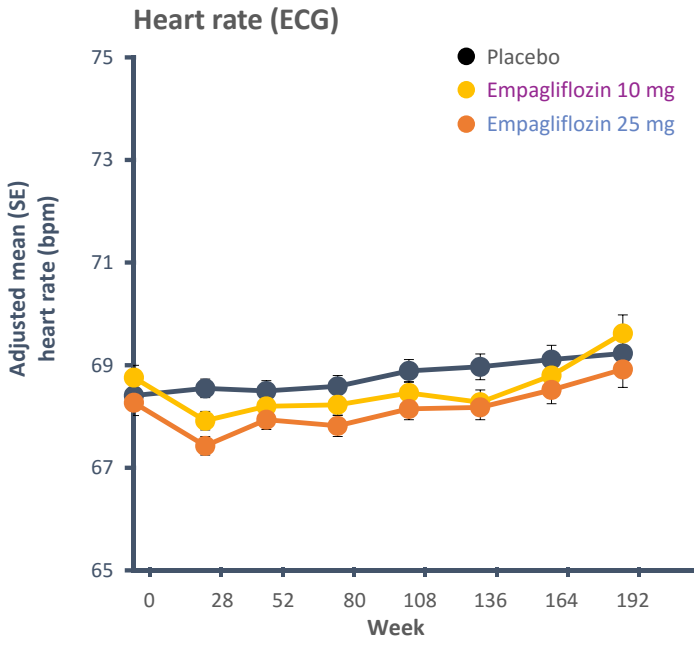


Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
EMPA 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
EMPA 25 mg	2322	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216



Placebo	2174	2127	2032	1928	1796	1300	1002	552
EMPA 10 mg	2205	2137	2064	2006	1877	1366	1045	597
EMPA 25 mg	2192	2127	2066	2006	1907	1383	1086	633

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent to treat)
X-axis: time points with reasonable amount of data available for prescheduled measurements
BP, blood pressure; ECG, electrocardiogram; EMPA, empagliflozin

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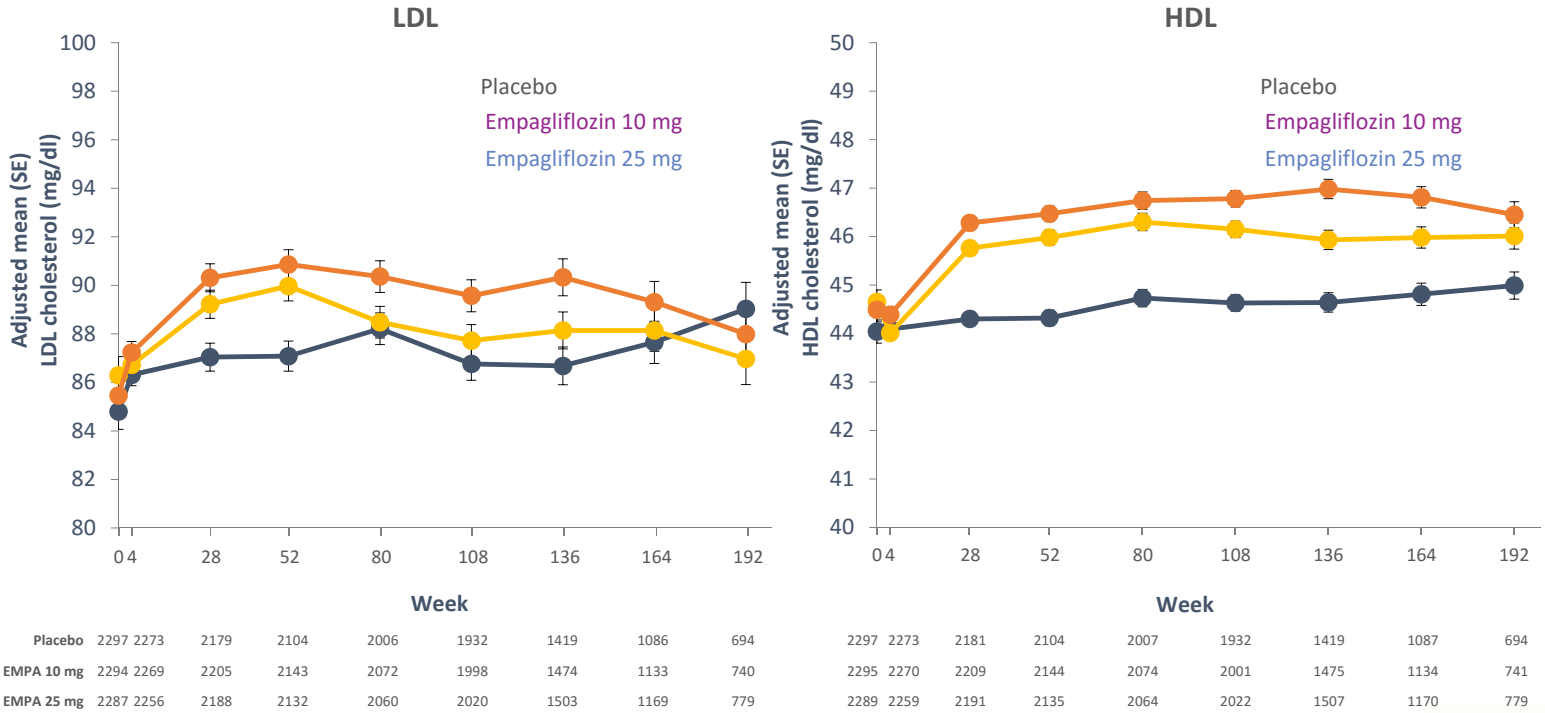
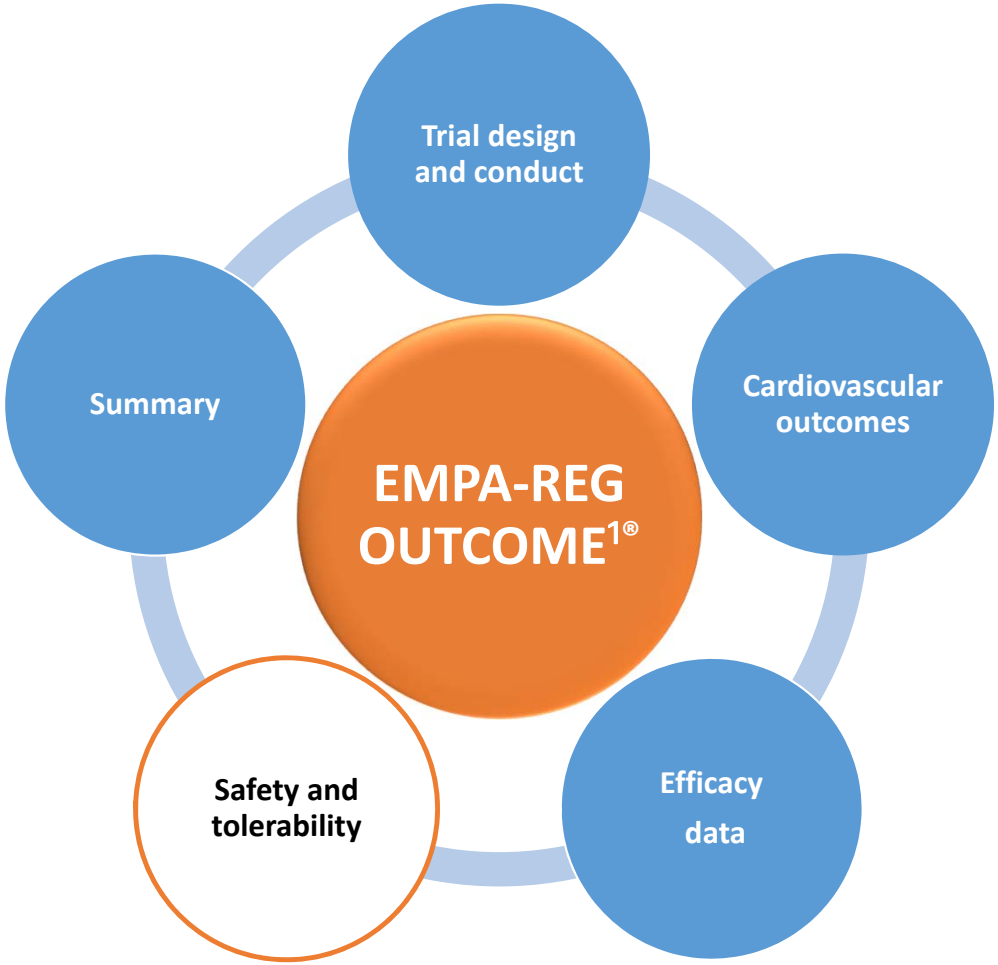
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Mean adjusted LDL/HDL[1]



All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent to treat)
X-axis: time points with reasonable amount of data available for prescheduled measurements
EMPA, empagliflozin; HDL, high-density lipoprotein; LDL, low-density lipoprotein

1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.



1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Adverse events[1,2]

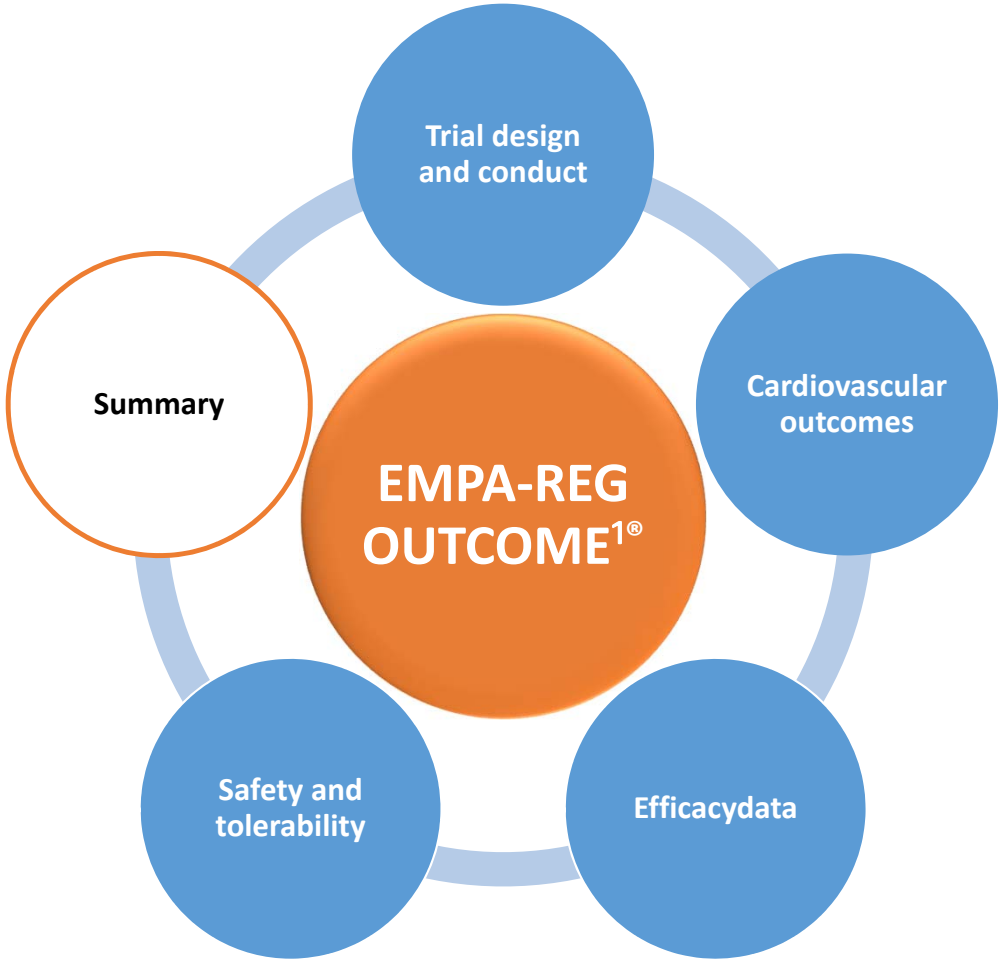
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
One or more AE[1]	2139 (91.7)	178.67	2112 (90.1)	150.34	2118 (90.4)	148.36
One or more drug-related* AE[2]	549 (23.5)	11.33	666 (28.4)	14.15	643 (27.5)	13.38
One or more AE leading to discontinuation[1]	453 (19.4)	8.26	416 (17.7)	7.28	397 (17.0)	6.89
One or more serious AE[1]	988 (42.3)	22.34	876 (37.4)	18.20	913 (39.0)	19.39

Rate = per100 patient-years

*As reported by the investigator
Patients treated with ≥1 dose of study drug

1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

2-Zinman B. EASD 2015; Oral presentation



1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

EMPA-REG OUTCOME®: summary

Empagliflozin in addition to standard of care reduced CV risk and improved overall survival in adults with T2D at high CV risk[1]

14%	38%	32%	35%
			
↓ 3P-MACE	**↓ CV death**	**↓ All-cause mortality**	**↓ Heart failure hospitalisations**

The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information[1]

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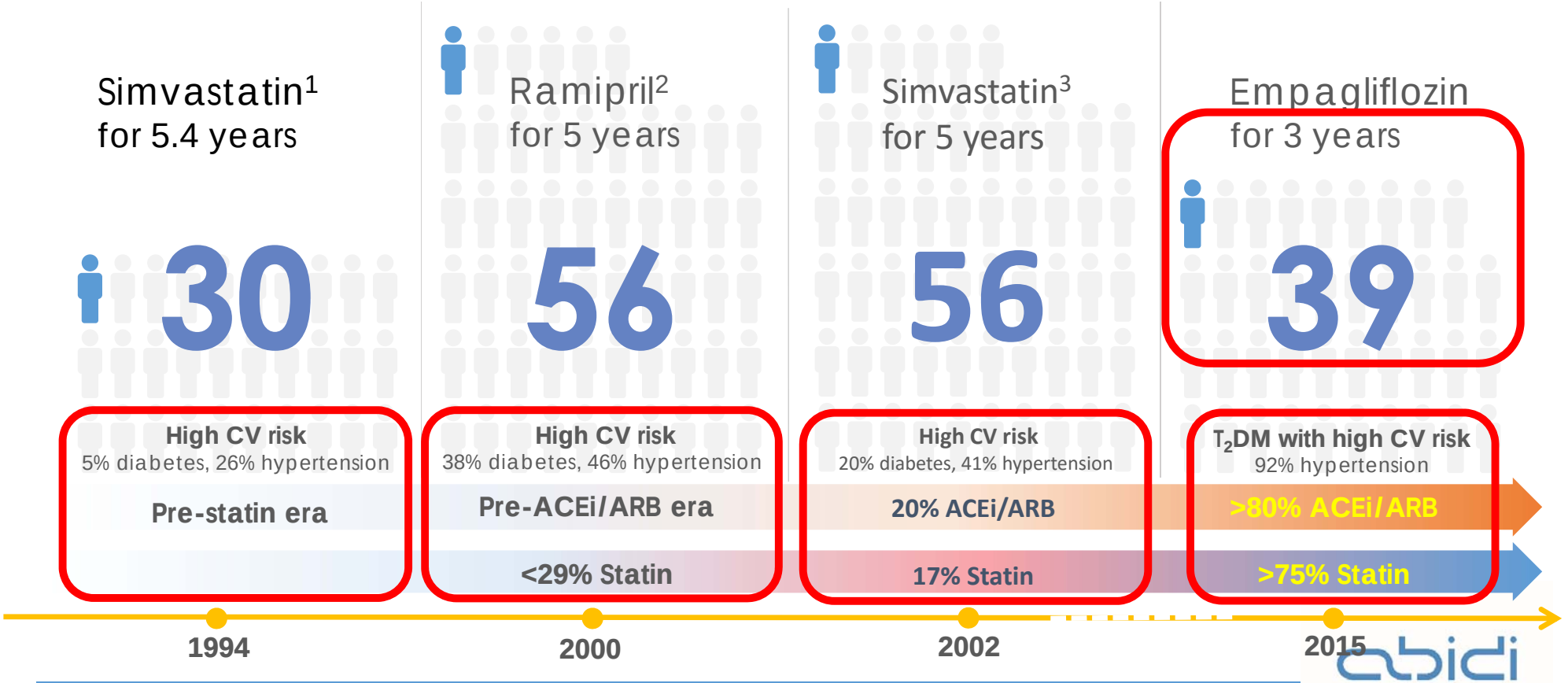
3P-MACE, 3-point major adverse cardiovascular events
Empagliflozin is not indicated for CV risk reduction. CV, cardiovascular; T2D, type 2 diabetes
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

NNT to Prevent One Death Across Major Trials in Patients with High CV Risk



1. 4S investigators. Lancet 1994; 344: 1383-89. 2. HOPE investigators. N Engl J Med 2000;342:145-53, EBM2000;5:47; HOPE investigators. Evid Based Med 2000;5:47.
3. HPS group Lancet 2002; 360: 7–22.
4. Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

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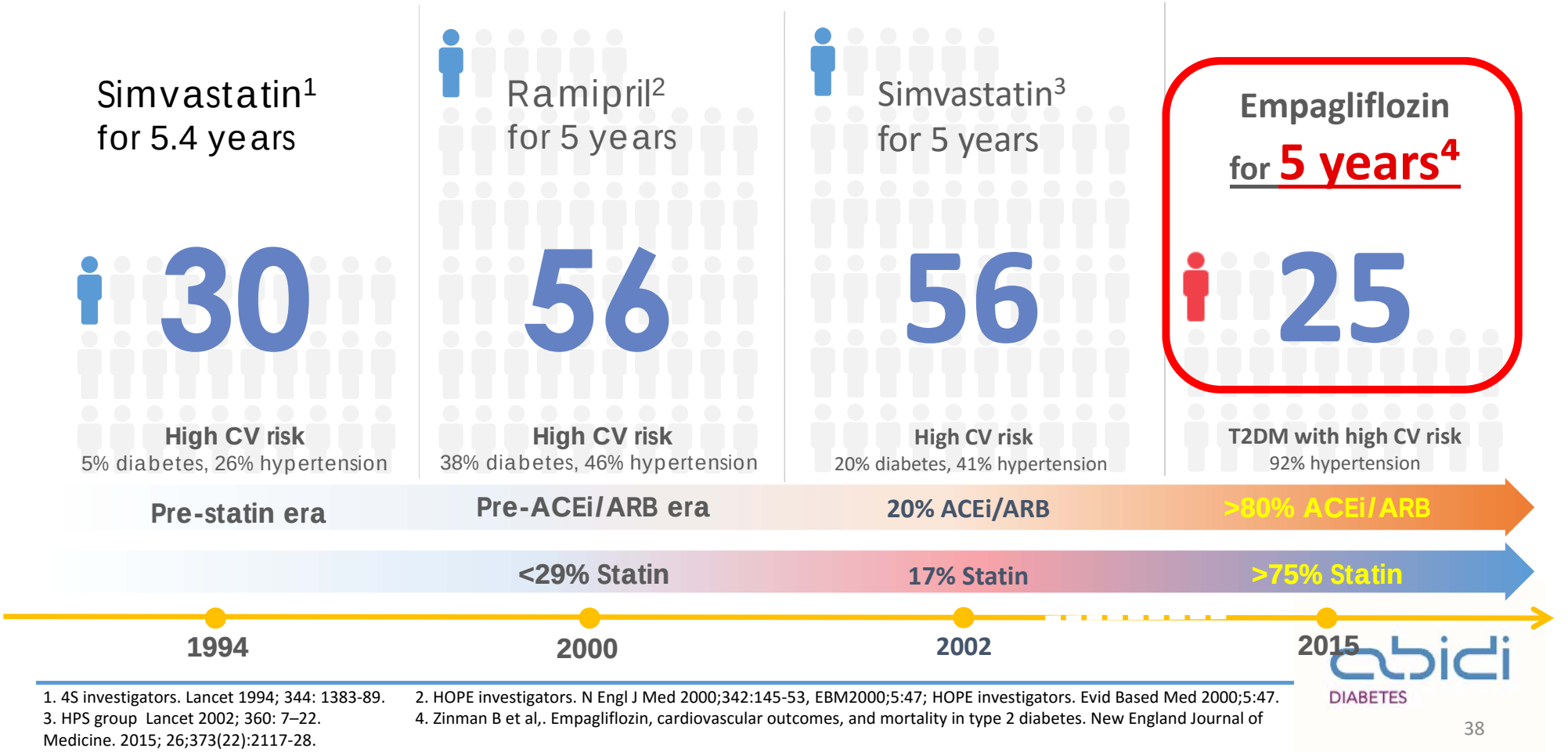

1. 4S investigators. Lancet 1994; 344: 1383-89.
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3. HPS group Lancet 2002; 360: 7–22.
4. Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

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EMPA-REG RENAL®

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

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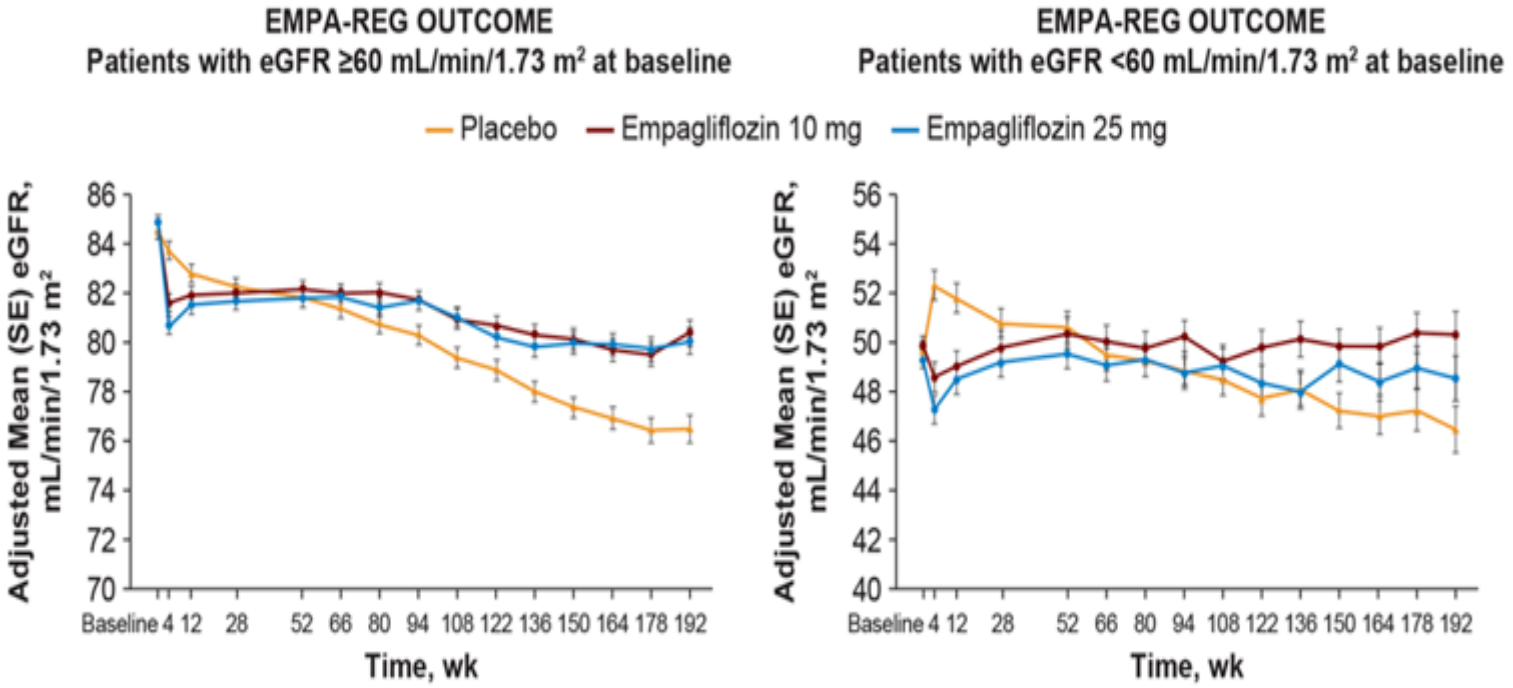
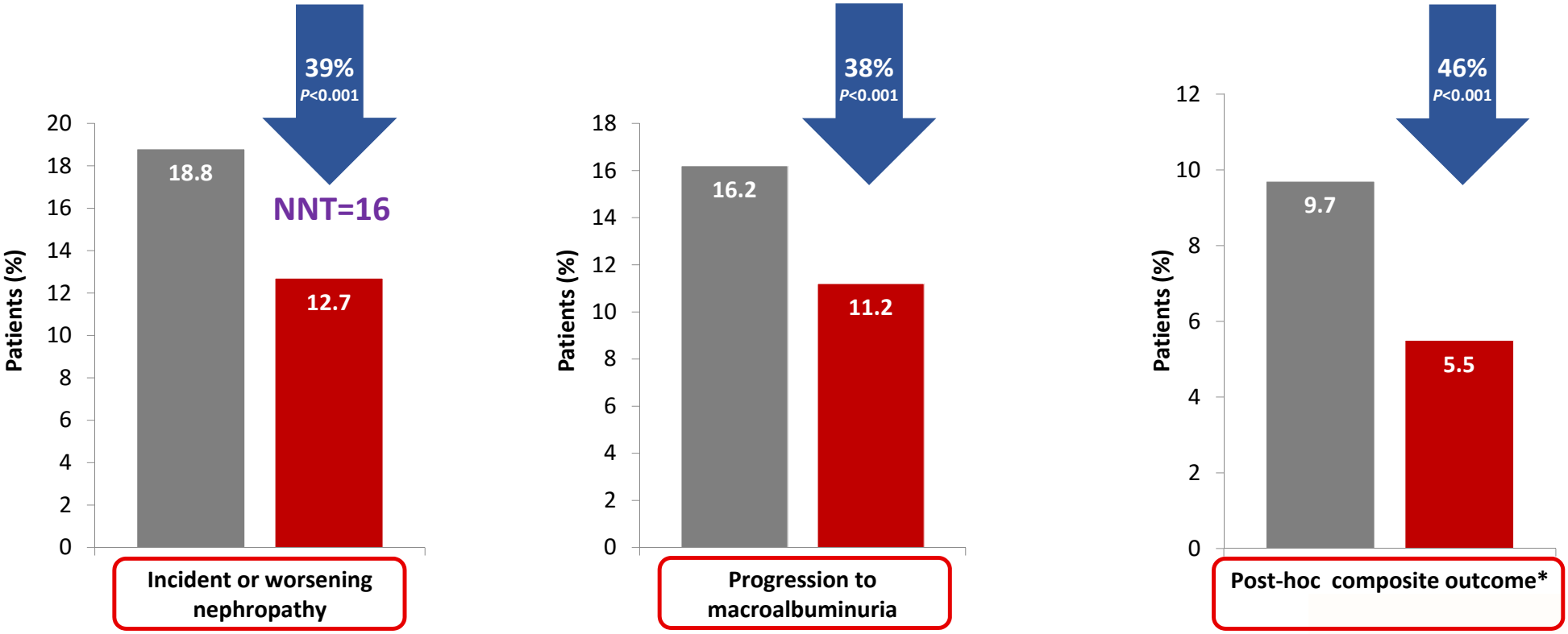
Wanner C et al,. Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine. 2016; 28;375(4):323-34.

SGLT2 Inhibitors Induce a Temporary Reduction in eGFR, but Preserve Renal Function Overtime[1]



1-Wanner C et al,. Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine. 2016; 28;375(4):323-34.

Renal Outcomes with Empagliflozin over 3.2 Years (EMPA-REG RENAL)[1]



Arrows = relative risk reduction

*Doubling of SCr + eGFR ≤45 *mL/min/1.73 m²*, initiation of renal replacement therapy, or death from renal disease.

1-Wanner C et al,. Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine. 2016; 28;375(4):323-34.

Cardio and Renal potential mechanisms of Empagliflozin

Suggested Mechanisms Explaining Reduction in CV Events with SGLT2 Inhibition[1]

Effect	Consequence
H_2O Diuresis	• Reduced filling pressures, pre-/afterload reduction
Na^+ Natriuresis	• Reduced filling pressures, pre-/afterload reduction
BP lowering	• Reduced myocardial work, reduced filling pressures, pre-/afterload reduction
Weight loss	• Improved CV risk profile, lower blood pressure
Reduction in/prevention of albuminuria, slowing of kidney function decline	• Reduction in kidney risk profile, possibly fewer incident CV events, including less HF
Effects on myocardial and kidney metabolism: shift to more efficient ketone-based metabolism	• Improved metabolic efficiency, less myocardial workload
Blockade of sodium-hydrogen cotransporter	• Tissue protection: reduction in kidney and myocardial injury
Reduction in sympathetic tone	• Reduce blood pressure and arrhythmia

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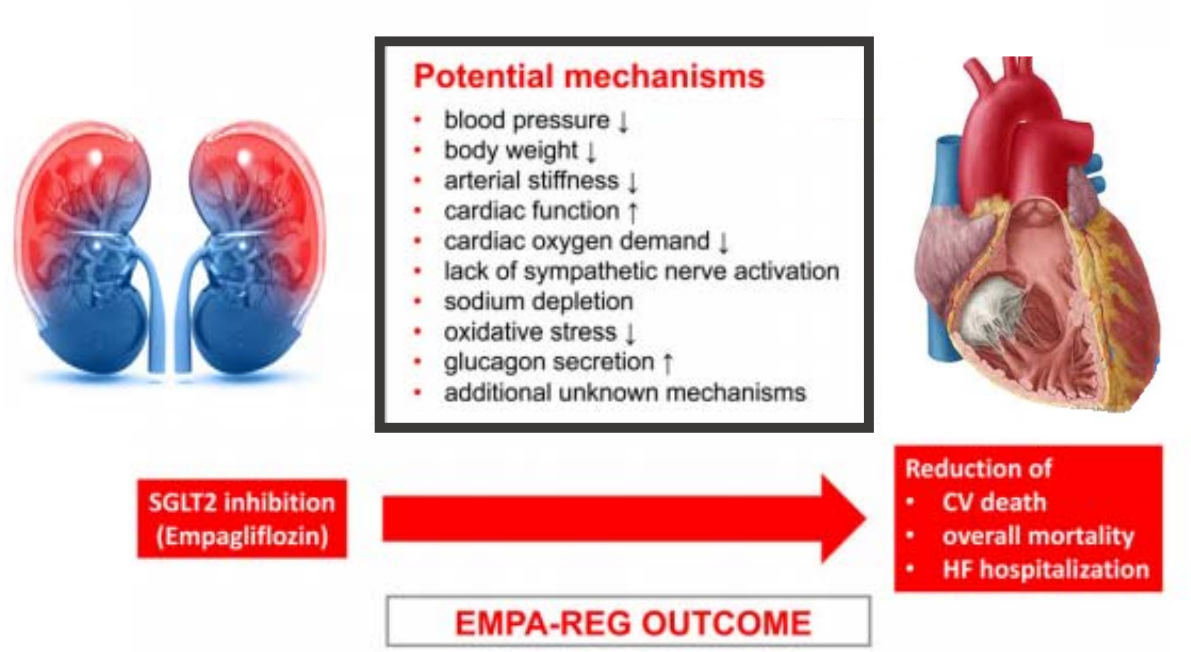
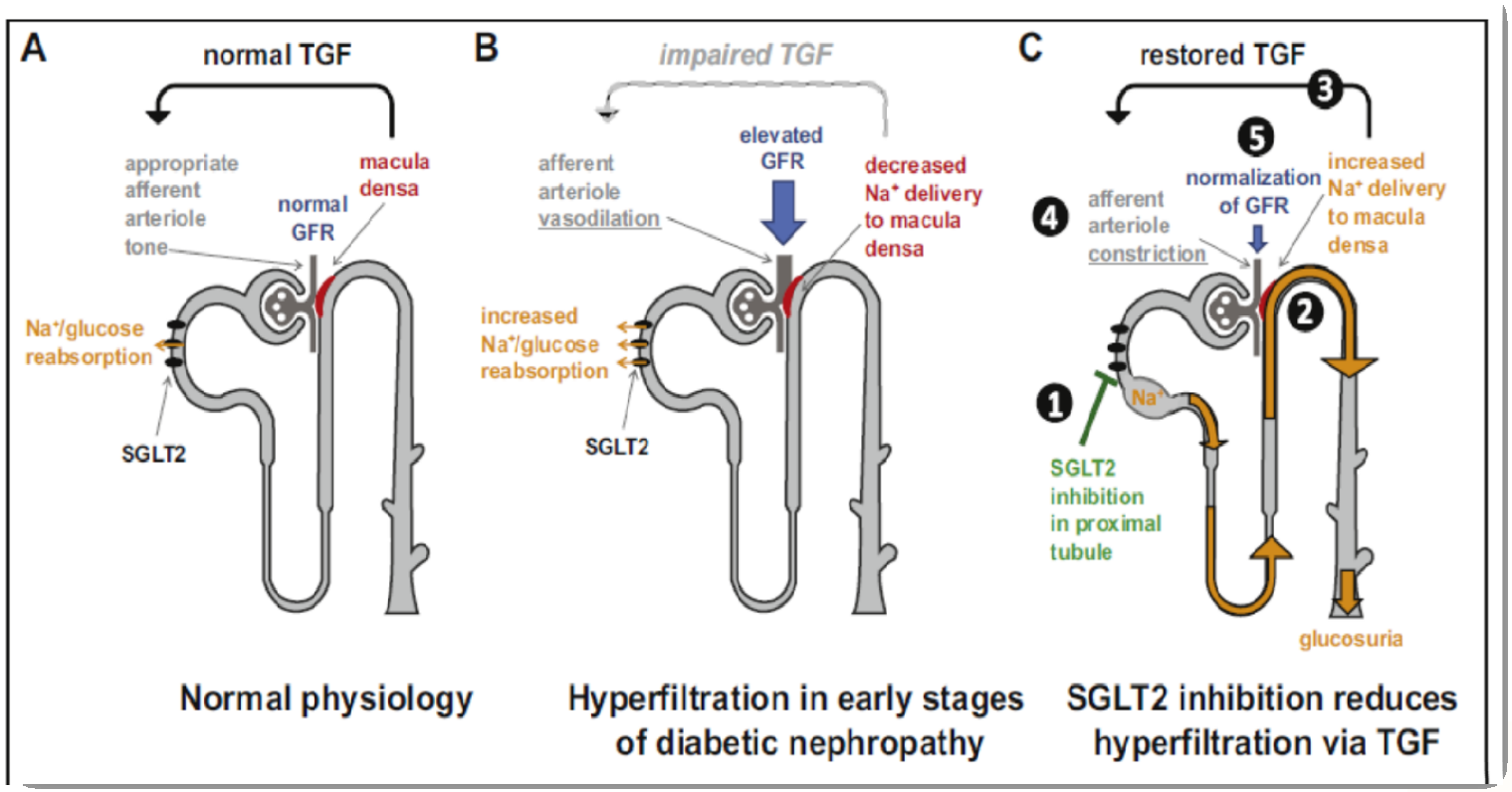
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Potential mechanisms involved in the reduction of cardiovascular events for empagliflozin-treated patients with T2DM[1]



1-Kramer CK et al,. Sodium–glucose co-transporter-2 (SGLT-2) inhibitors in patients with type 2 diabetes mellitus: the road ahead. (2016): 3201-3202

TGF Restoration by SGLT2 Inhibition[1]



1-Wanner C et al,. Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine. 2016; 28;375(4):323-34.

Initial Combination of Empagliflozin and Metformin

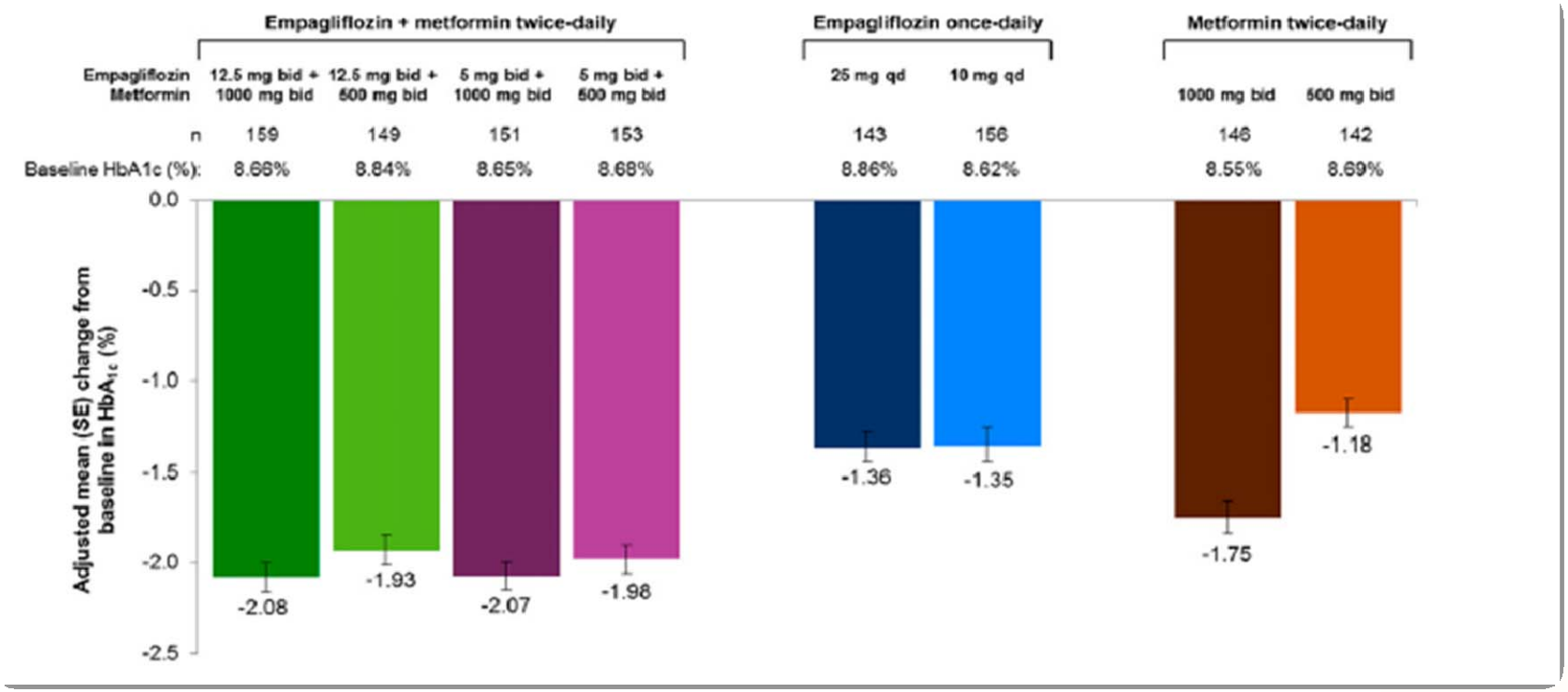
Initial Combination of Empagliflozin and Metformin in Patients With Type 2 Diabetes

Samy Hadjadj,[1] Julio Rosenstock,[2] Thomas Meinicke,[3] Hans J. Woerle,[4] and Uli C. Broedl[4]

Diabetes Care 2016;39:1718–1728 | DOI: 10.2337/dc16-0522

Hadjadj S et al, Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016 1;39(10):1718-28.

Change from Baseline in HbA1c[1]



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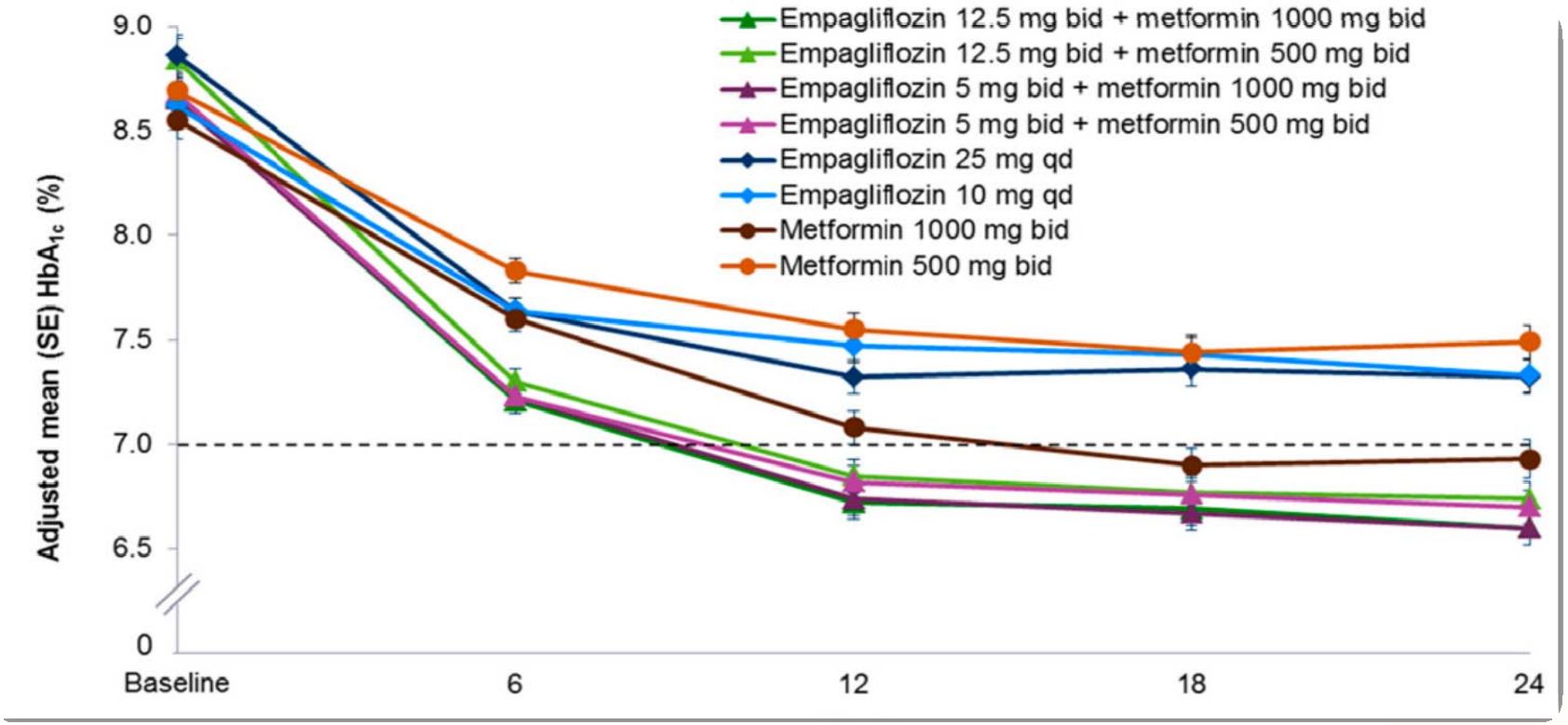
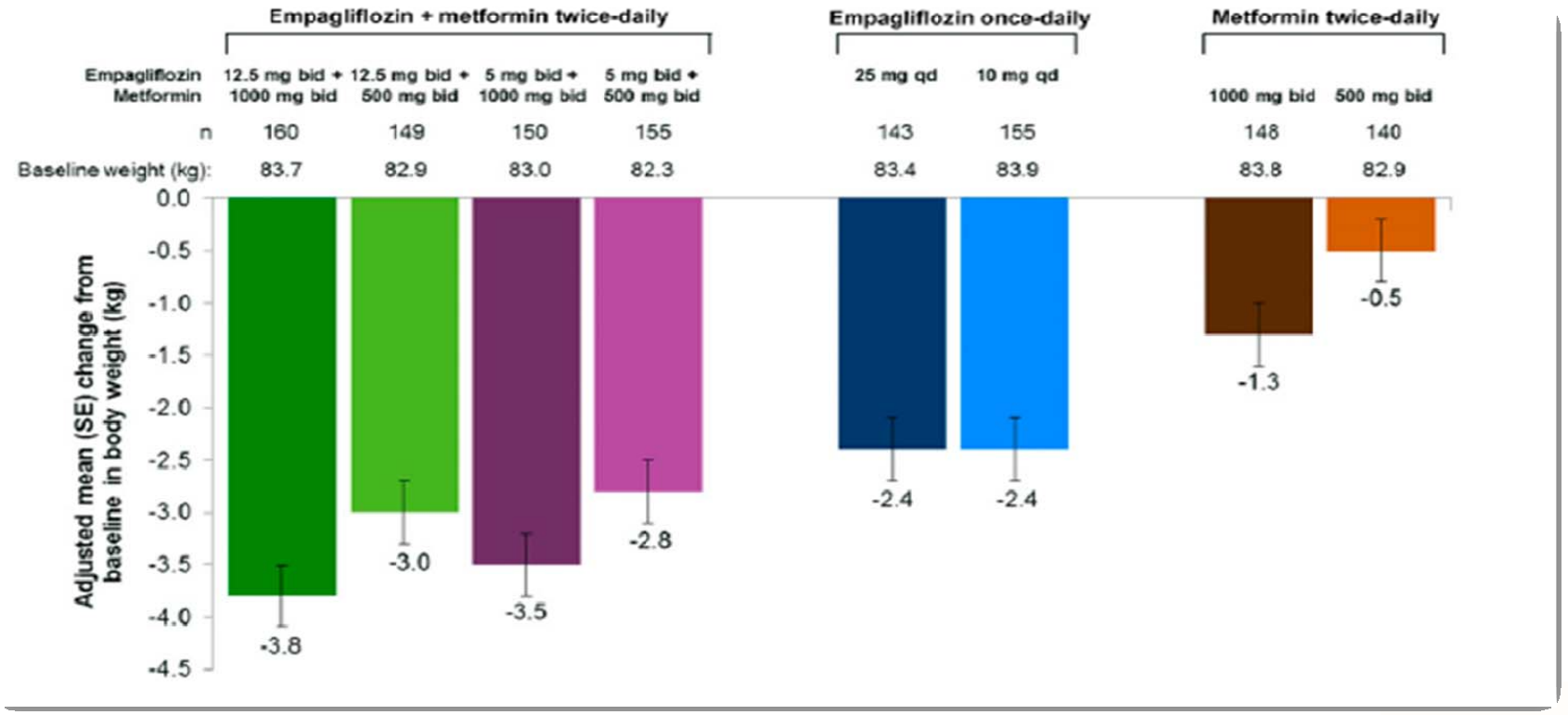
Change from Baseline in HbA1c[1]



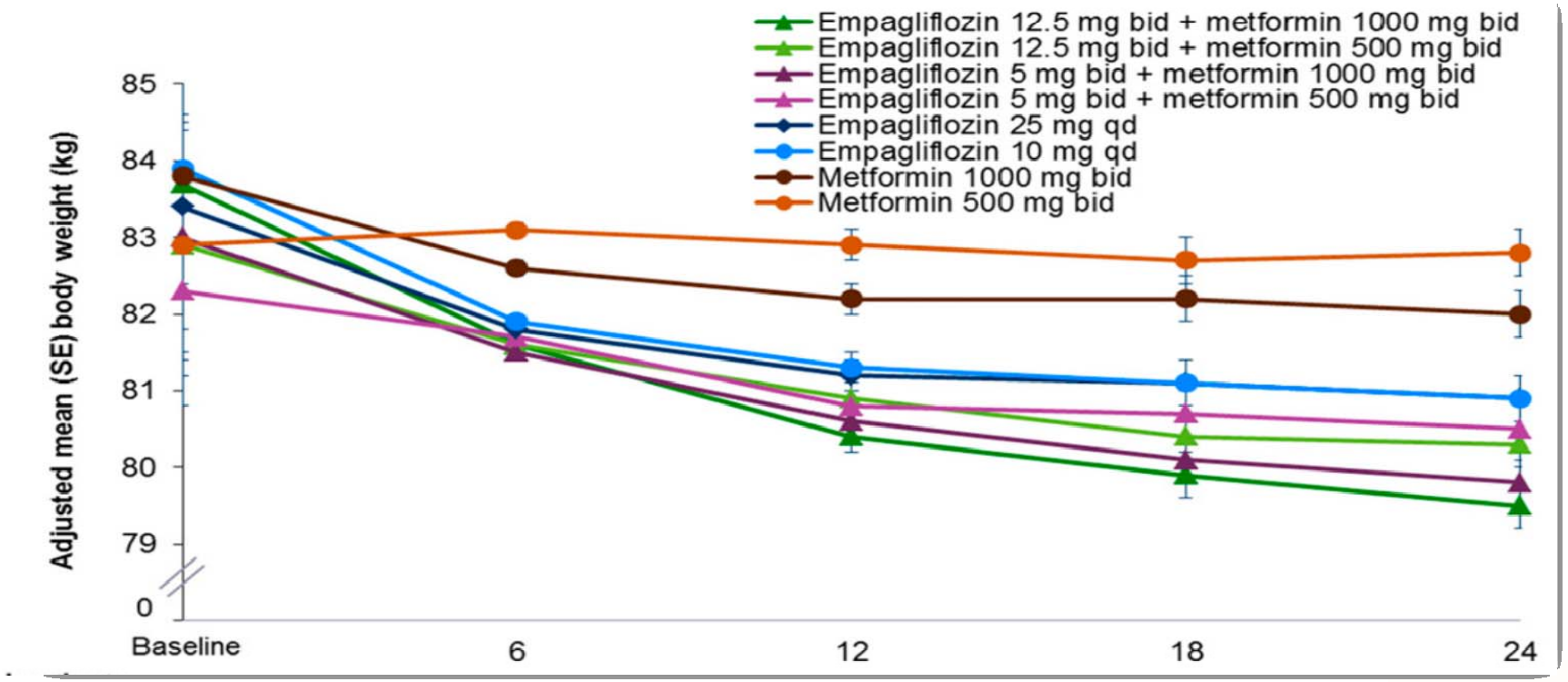
1-Hadjadj S et al, Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016 1;39(10):1718-28.

Change from Baseline in Weight[1]



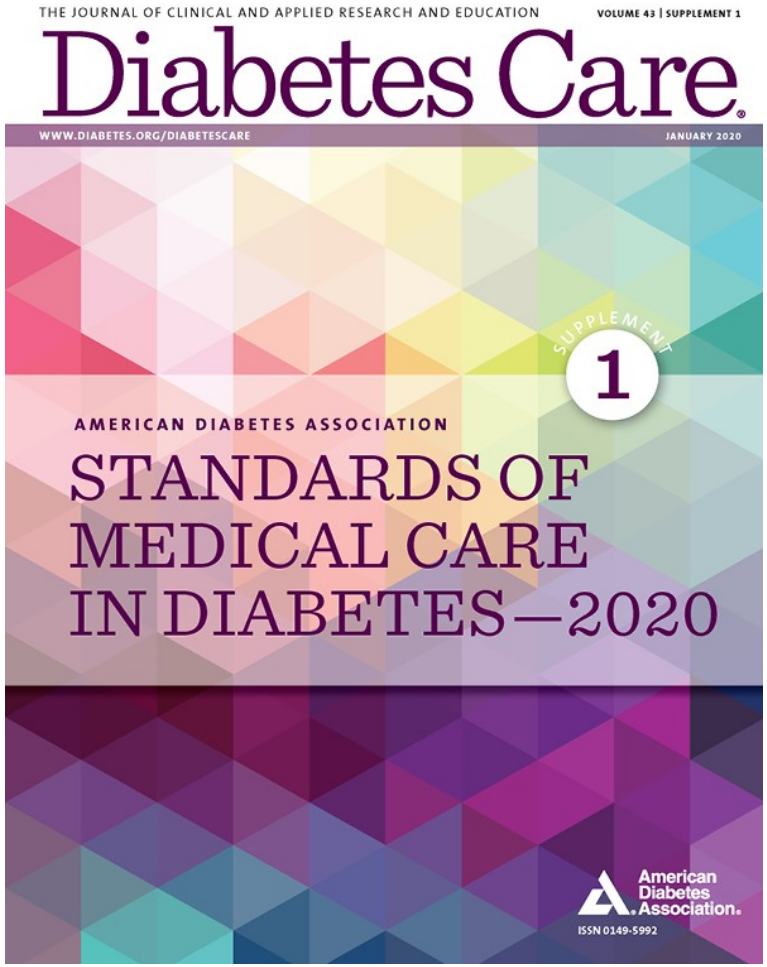
1-Hadjadj S et al, Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016 1;39(10):1718-28.

Change from Baseline in Weight[1]



1-Hadjadj S et al, Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016 1;39(10):1718-28.

Guidelines Recommendations


THE JOURNAL OF CLINICAL AND APPLIED RESEARCH AND EDUCATION
VOLUME 43 | SUPPLEMENT 1
Diabetes Care
WWW.DIABETES.ORG/DIABETESCARE
JANUARY 2020
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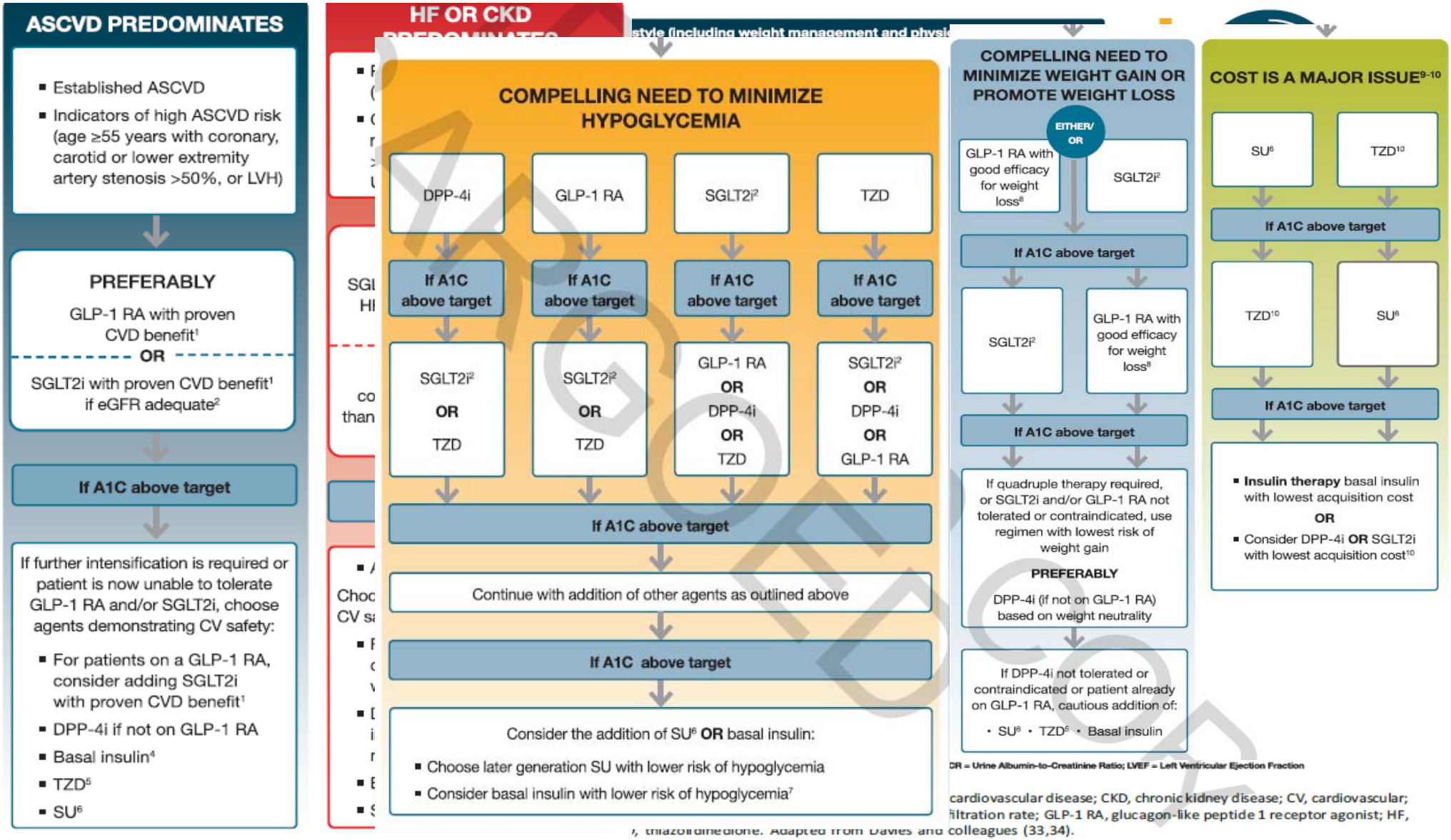
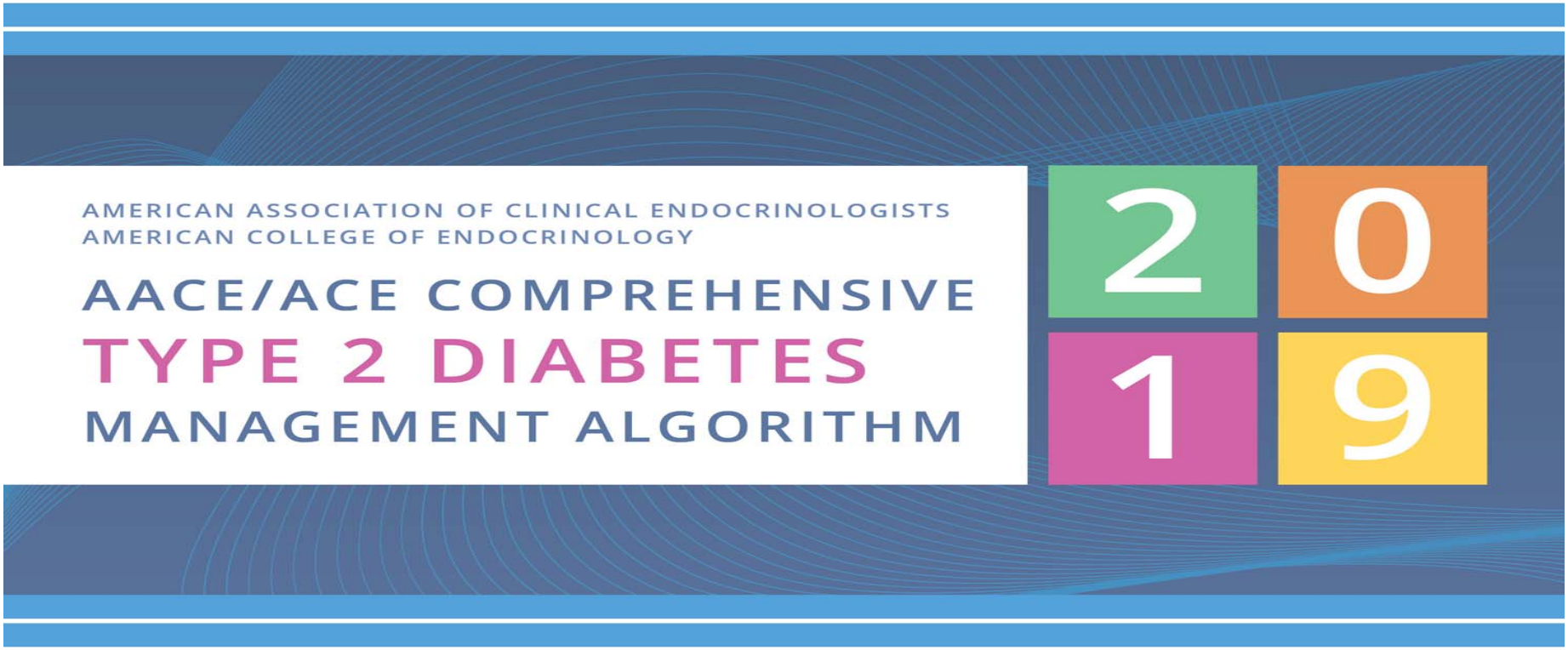
AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2020
American Diabetes Association.
ISSN 0149-5992

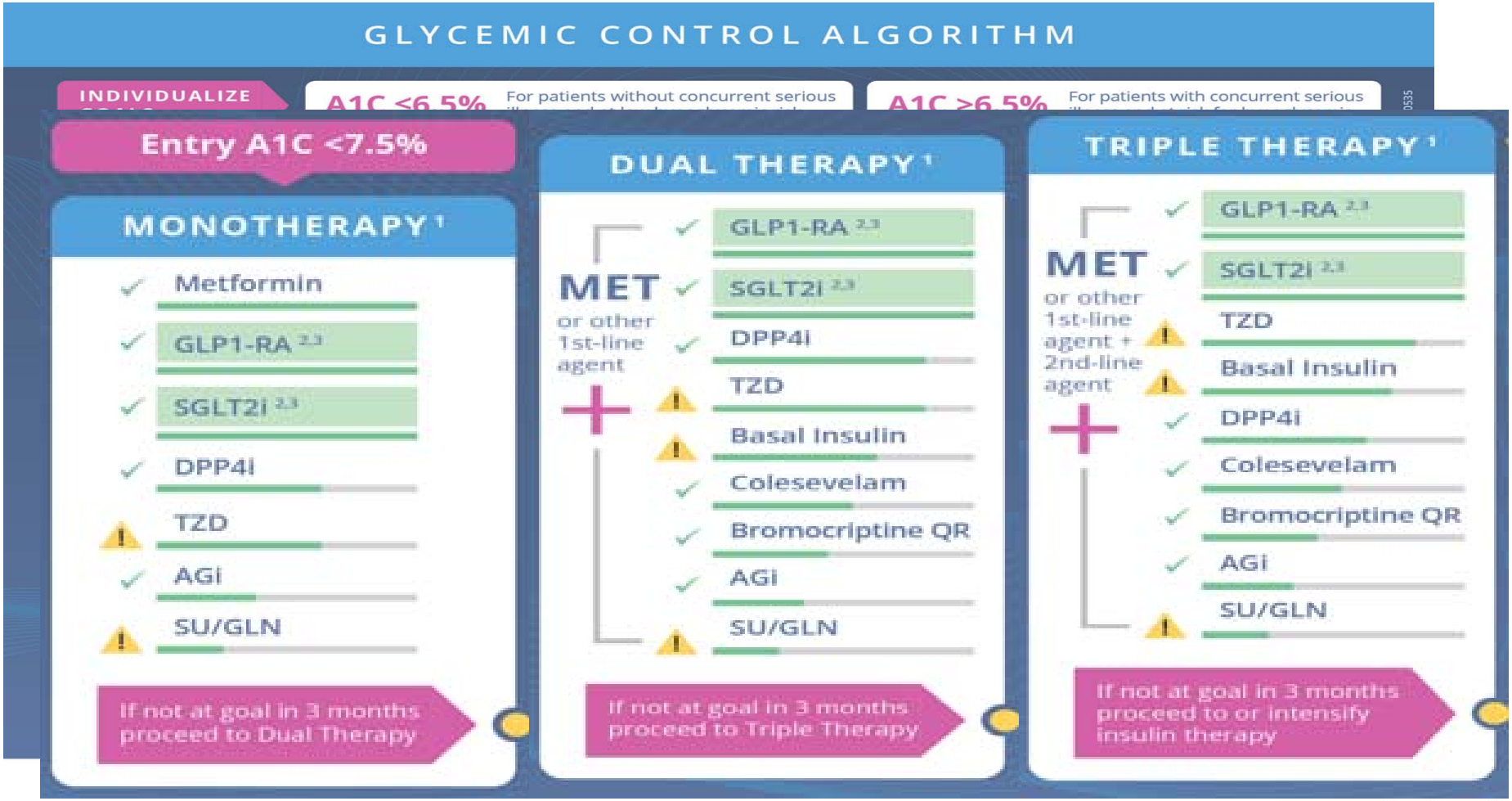


CR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, , thiazolidinedione. Adapted from Davies and colleagues (33,34).



1-Garber AJ et al, Consensus statement by the American association of clinical endocrinologists and American college of endocrinology on the comprehensive type 2 diabetes management algorithm–2019 executive summary. Endocrine Practice. 2019; 25(1):69-100.



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ESC European Society of Cardiology
European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

abcdi DIABETES

Lars R, Anker SD, Christian B, Francesco C, Nicolas D, Christi D, Javier E, Hammes HP, Heikki H, Michel M, Nikolaus M. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD.

Cardiovascular risk categories in patients with diabetes[1]

Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

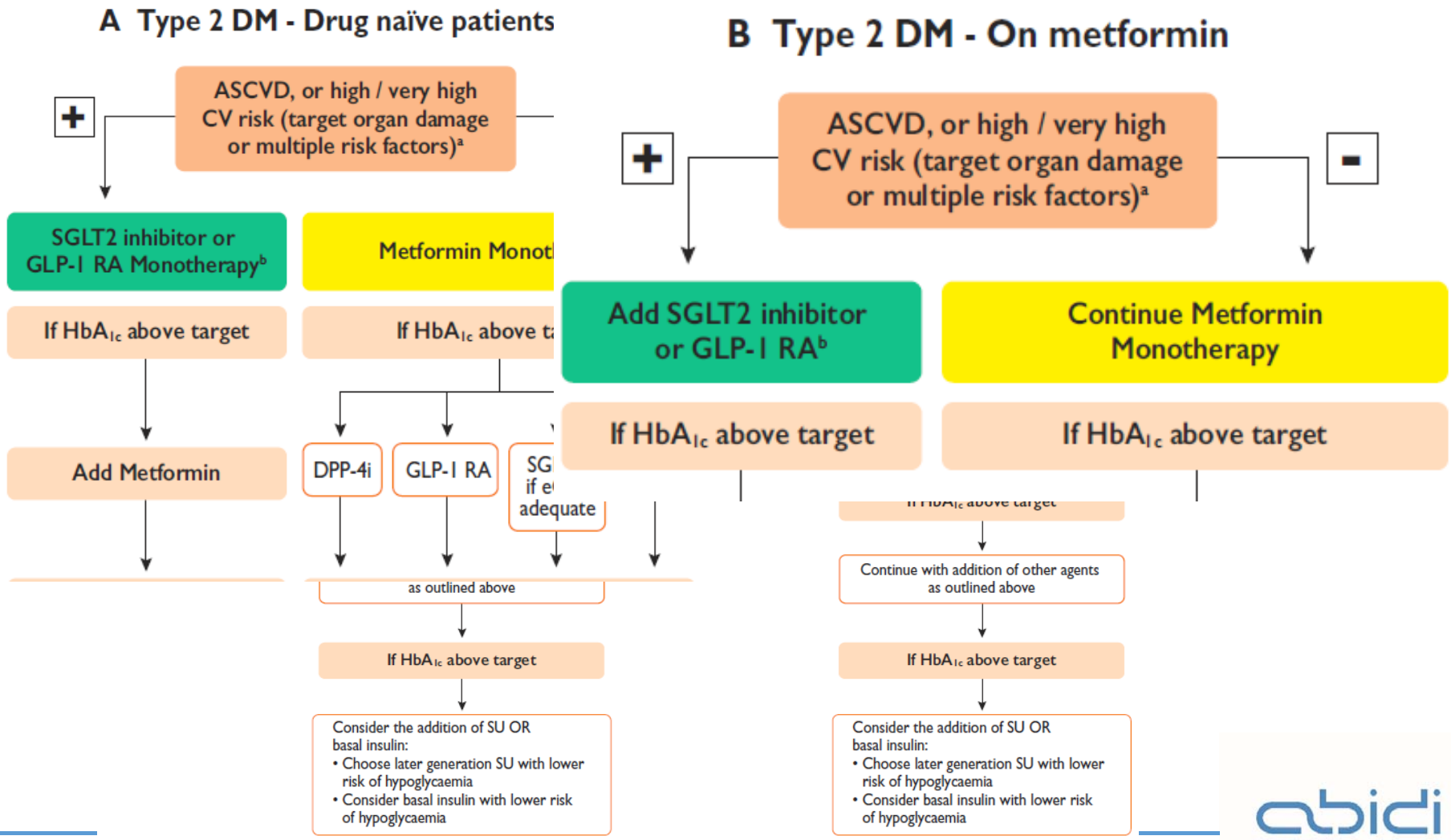
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

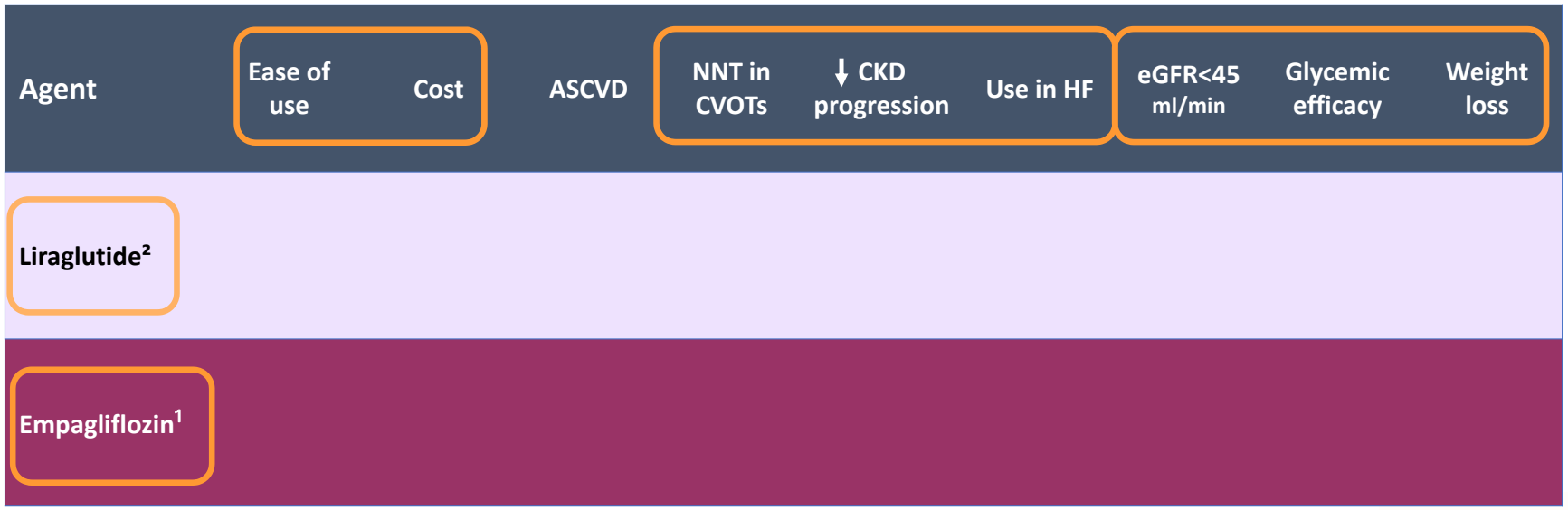
[c]Age, hypertension, dyslipidemia, smoking, obesity.

1-Piepoli, Massimo F., et al. "2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)." *European heart journal* 37.29 (2016): 2315-2381.



1-Lars R, Anker SD, Christian B, Francesco C, Nicolas D, Christi D, Javier E, Hammes HP, Heikki H, Michel M, Nikolaus M. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD.

Empagliflozin vs. Liraglutide



1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.
2-Marso SP et al,. Liraglutide and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine. 2016; 28;375(4):311-22.

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Administration, Cautions, Side effects, Safety profile

Convenience of a once-daily oral treatment[1]

STARTING DOSE	10 mg 1 × daily The recommended starting dose for Empagliflozin is 10 mg once daily
INCREASE TO	25 mg 1 × daily For patients who tolerate 10 mg once daily who have an eGFR ≥ 60 mL/min/1.73 m^2 and need tighter glycemic control, their dose can be increased to 25 mg once daily

Empagliflozin can be taken

With or without food

At any time of day*

When Empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia

eGFR, estimated glomular filtration rate.
*It is advisable to take JARDIANCE® at the same time each day, which will help with patient adherence.
A missed dose can be taken if it is ≥ 12 hours until the next dose; if it is < 12 hours, the missed dose should be skipped.

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1-Jardiance FDA label 2018. Reference ID: 4367802

Empagliflozin Clinical Pharmacokinetics[1]

Tablet intake:

10 mg, QD

25 mg, QD

Absorption:

Peak levels at 1.5 hrs after dosing

No clinically relevant food effect

Metabolism:

No active metabolite

Half-life:

Estimated to be 12.4 hrs, steady state reached by ~Day 5

1-Jardiance FDA label 2018. Reference ID: 4367802

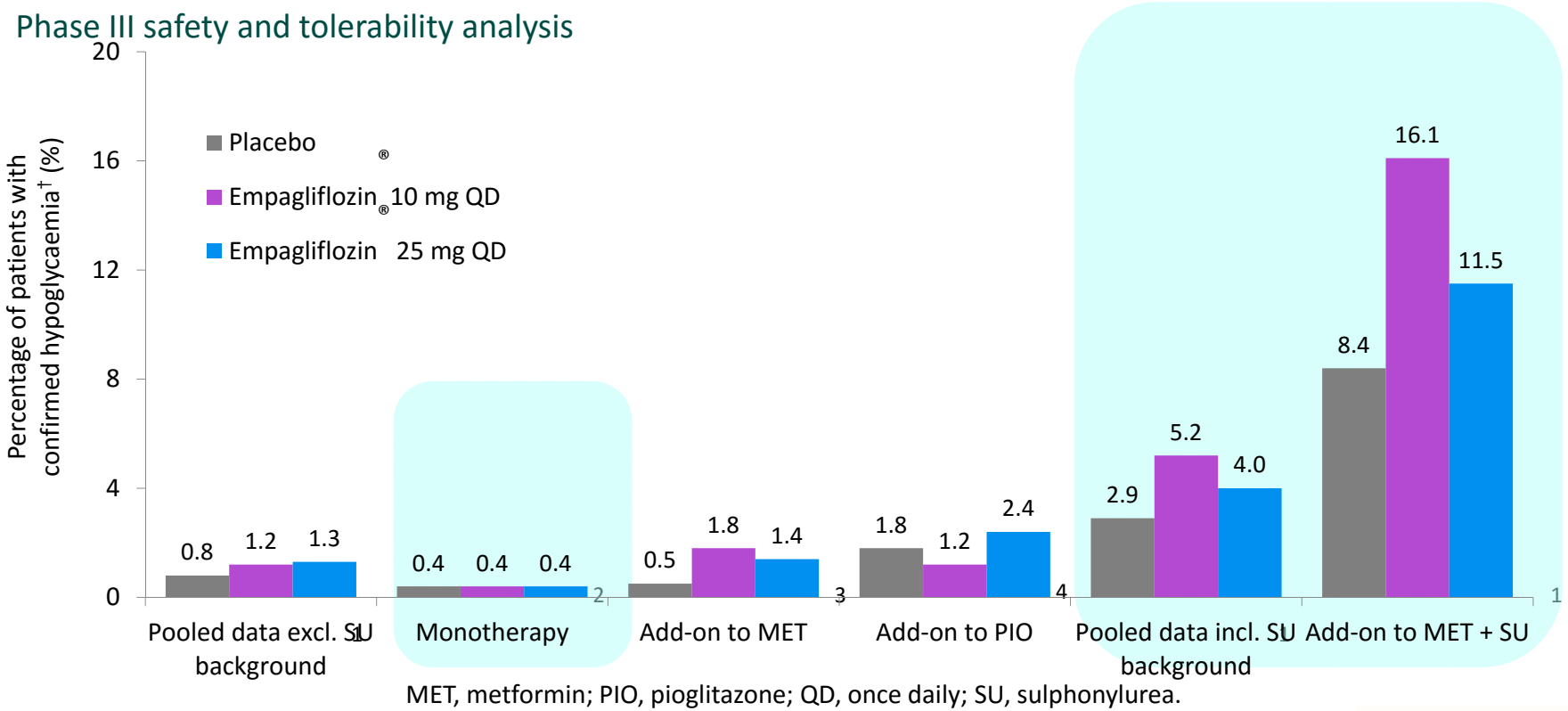
Empagliflozin Safety Profile[1]

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Infections and infestations		Vaginal moniliasis, vulvovaginitis, balanitis and other genital infection Urinary tract infection		
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)			Diabetic Ketoacidosis*
Skin and subcutaneous disorders		Pruritis (generalised)		
Vascular disorders			Volume depletion	
Renal and urinary disorders		Increased urination	Dysuria	

1-Jardiance FDA label 2018. Reference ID: 4367802

Hypoglycemic Events

- Phase III safety and tolerability analysis



MET, metformin; PIO, pioglitazone; QD, once daily; SU, sulphonylurea.

†Confirmed events; plasma glucose ≤ 70 mg/dL and/or requiring assistance

Roden M, et al. Lancet Diabetes Endocrinol. 2013;1(3):208–219 (EMPA-REG MONO®);
Häring H-U, et al. Diabetes Care. 2014 (EMPA-REG MET® - in press); Kovacs C, et al. Diabetes Obes Metab. 2014;16(2):147–158 (EMPA-REG PIO®; Häring H-U, et al. Diabetes Care. 2013;36(11):3396–404 (EMPA-REG METSU®);
Kim G, et al. Diabetes. 2013;(suppl 1):(P74-LB).

Summary

Favorable effects of empagliflozin:

- Weight loss
- HbA_{1c} lowering
- Reduced blood pressure
- Renal & cardiac protection
- Improved beta cell function
- Independent to insulin presence
- Mechanism complementary to other therapies
- Reduction of Heart failure hospitalisations in patients with T2D

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Gloripa®
Empagliflozin

Synoripa®
Empagliflozin / Metformin

Thank you for your attention

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Diabetes