

"درمان های جدید دیابت نوع 2"

مهار کننده های ترانسپورتر ۲ سدیم گلوکوز

دکتر ناصر آقامحمدزاده

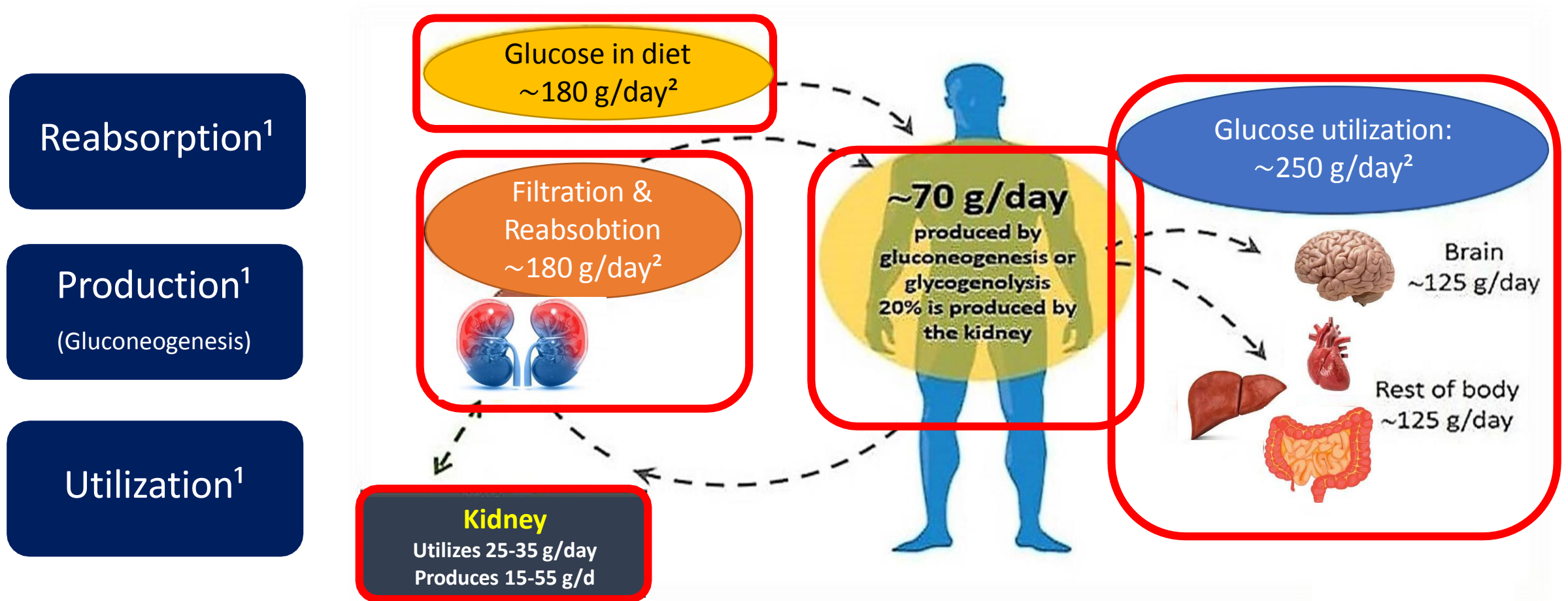
فوق تخصص غدد درون ریز

دانشیار دانشگاه علوم پزشکی تبریز

Objectives

- Brief review of kidney role in glucose homeostasis
- SGLT2 & SGLT2 inhibitors
- Efficacy Studies
- EMPA-REG OUTCOME®
- EMPEROR-Reduced trial
- European Society of Cardiology Guideline (ESC 2019)
- Administration, Cautions, Side effects
- Conclusion

Kidney Plays a Significant Role in Glucose Balance



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.

2-Wright EM et al,. Active sugar transport in health and disease. Journal of internal medicine. 2007; 261(1):32-43.

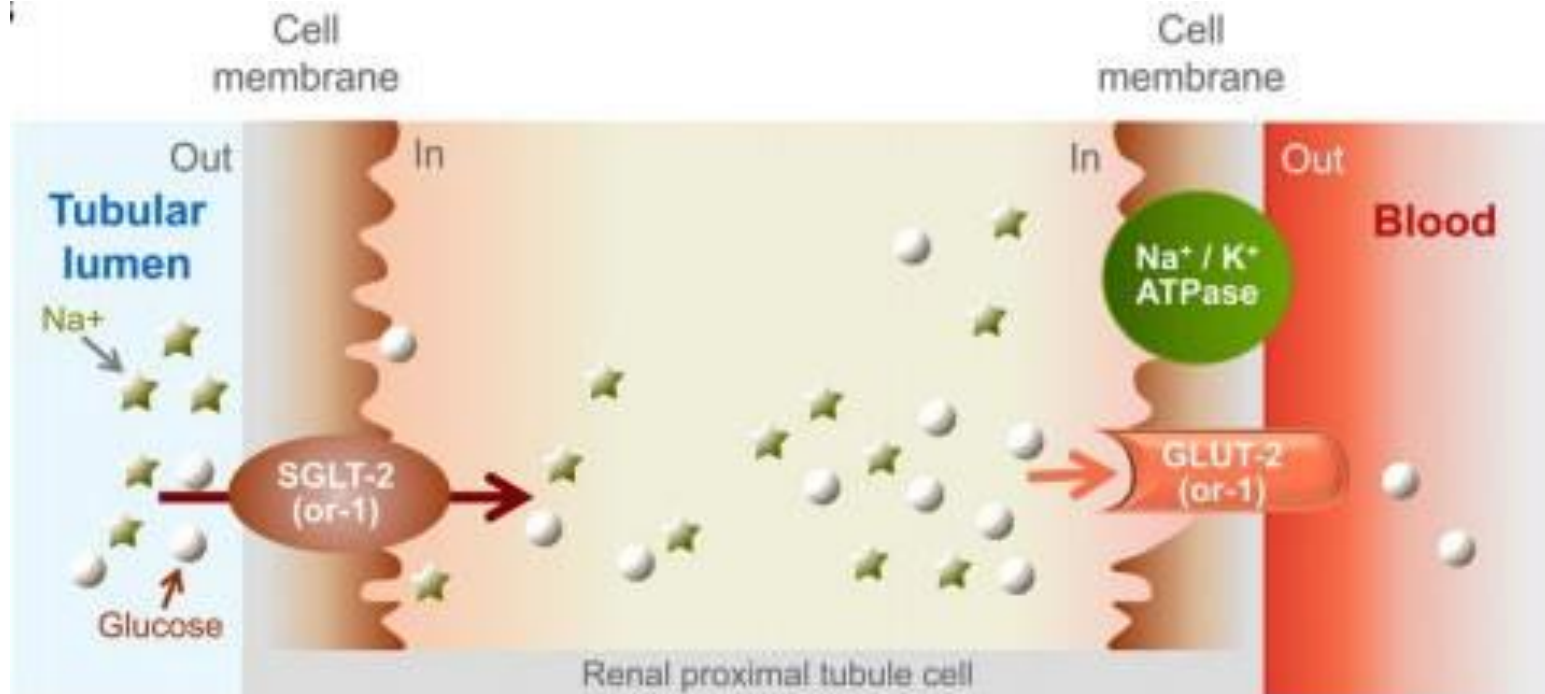
SGLT2 & SGLT2 inhibitors

Glucose Transporters

They are classified into two families^{1,2}:

facilitative glucose transporters (GLUTs)

sodium-dependent glucose transporters (SGLTs)



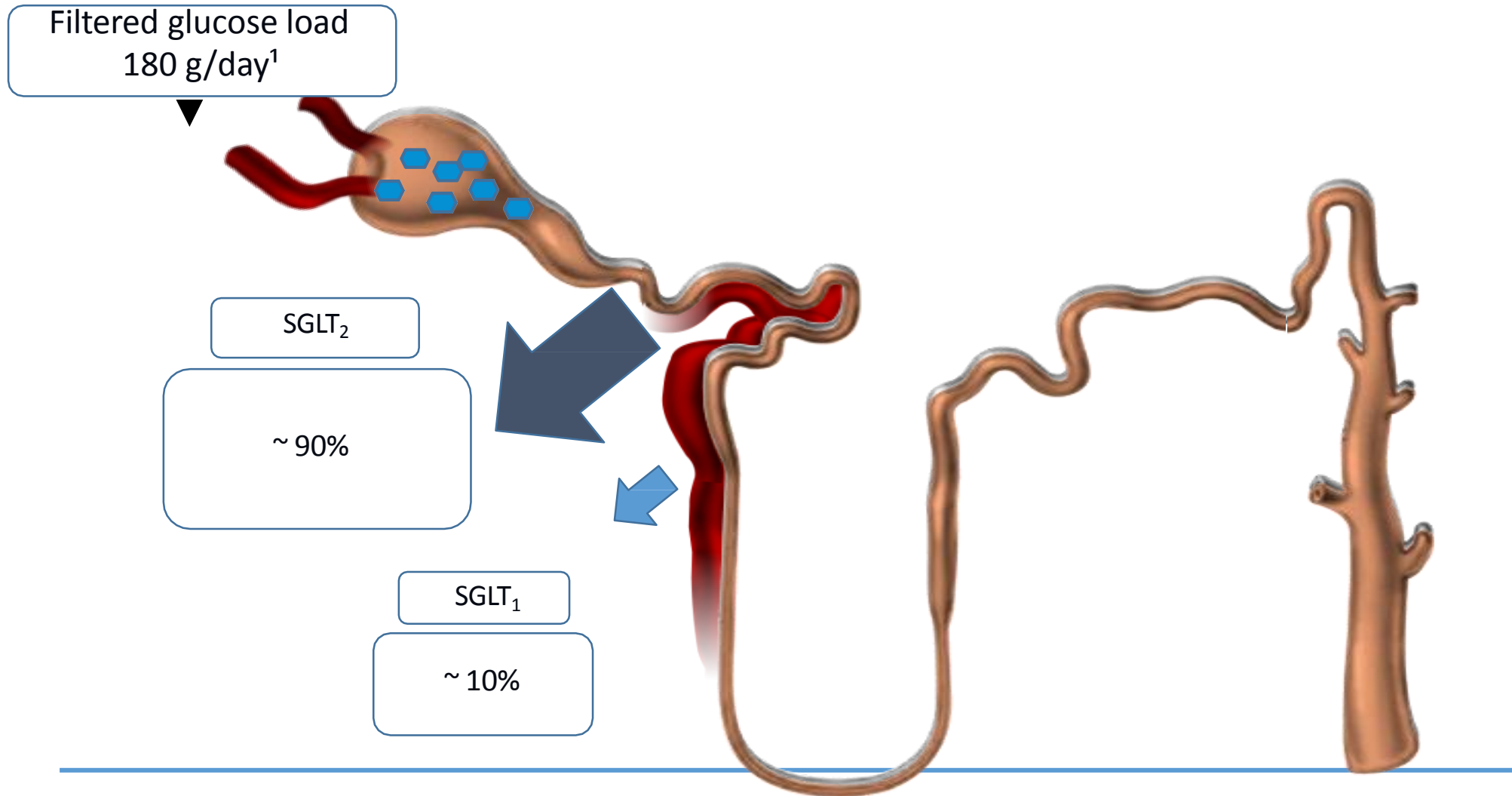
SGLT₁: low capacity, high affinity, mostly in intestine

SGLT₂: high capacity, low affinity, mostly in kidney

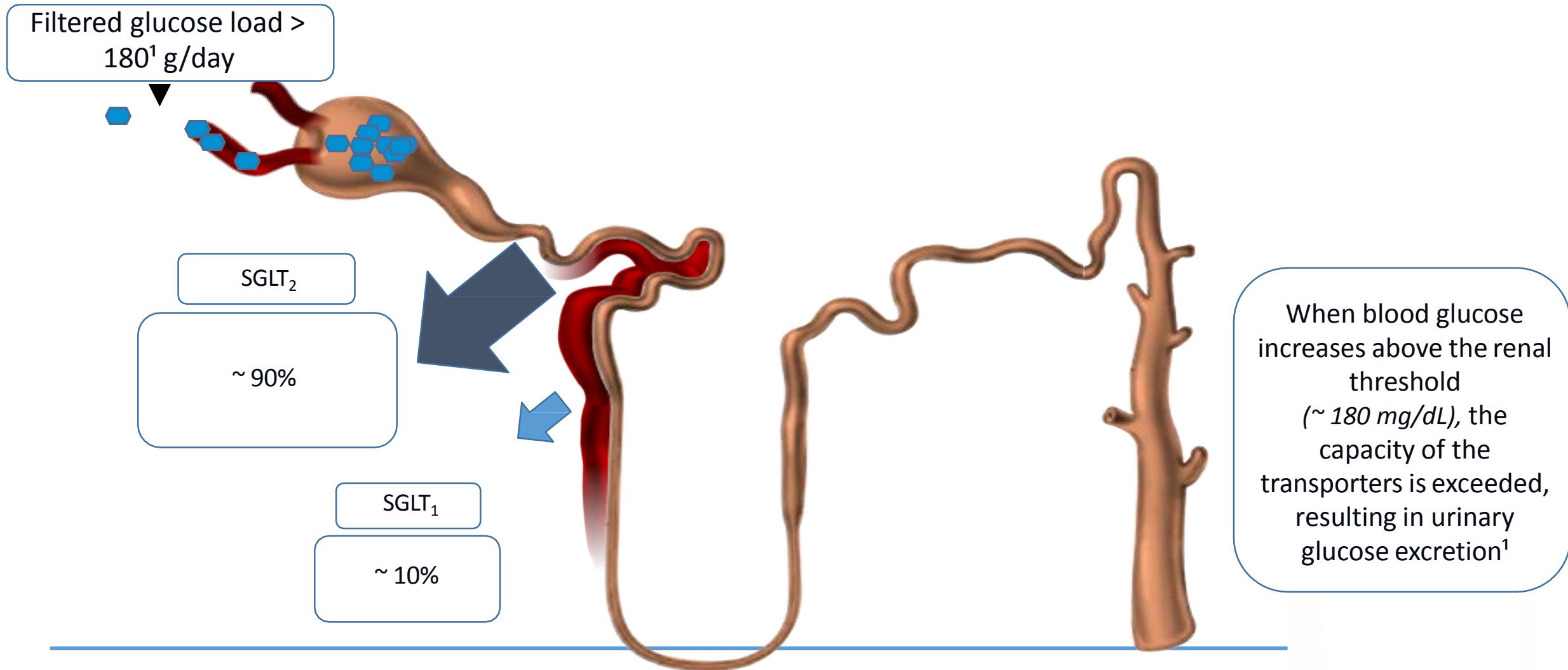
1-Bays H. Sodium glucose co-transporter type 2 (SGLT2) inhibitors: targeting the kidney to improve glycemic control in diabetes mellitus. Diabetes Therapy. 2013; 4(2):195-22

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.

Renal glucose re-absorption in healthy individuals

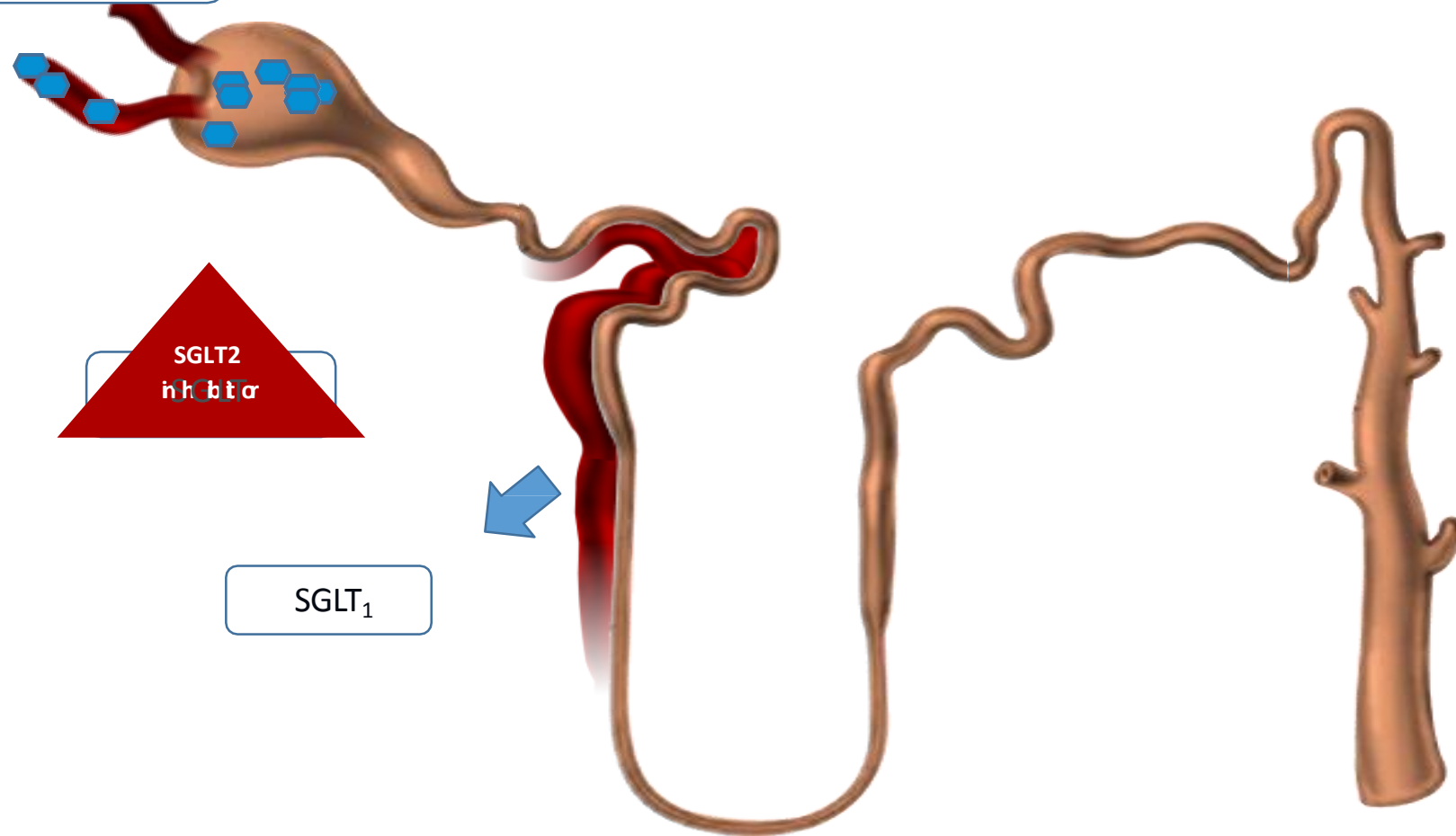


Renal glucose re-absorption in patients with diabetes



Urinary glucose excretion via SGLT2 inhibition

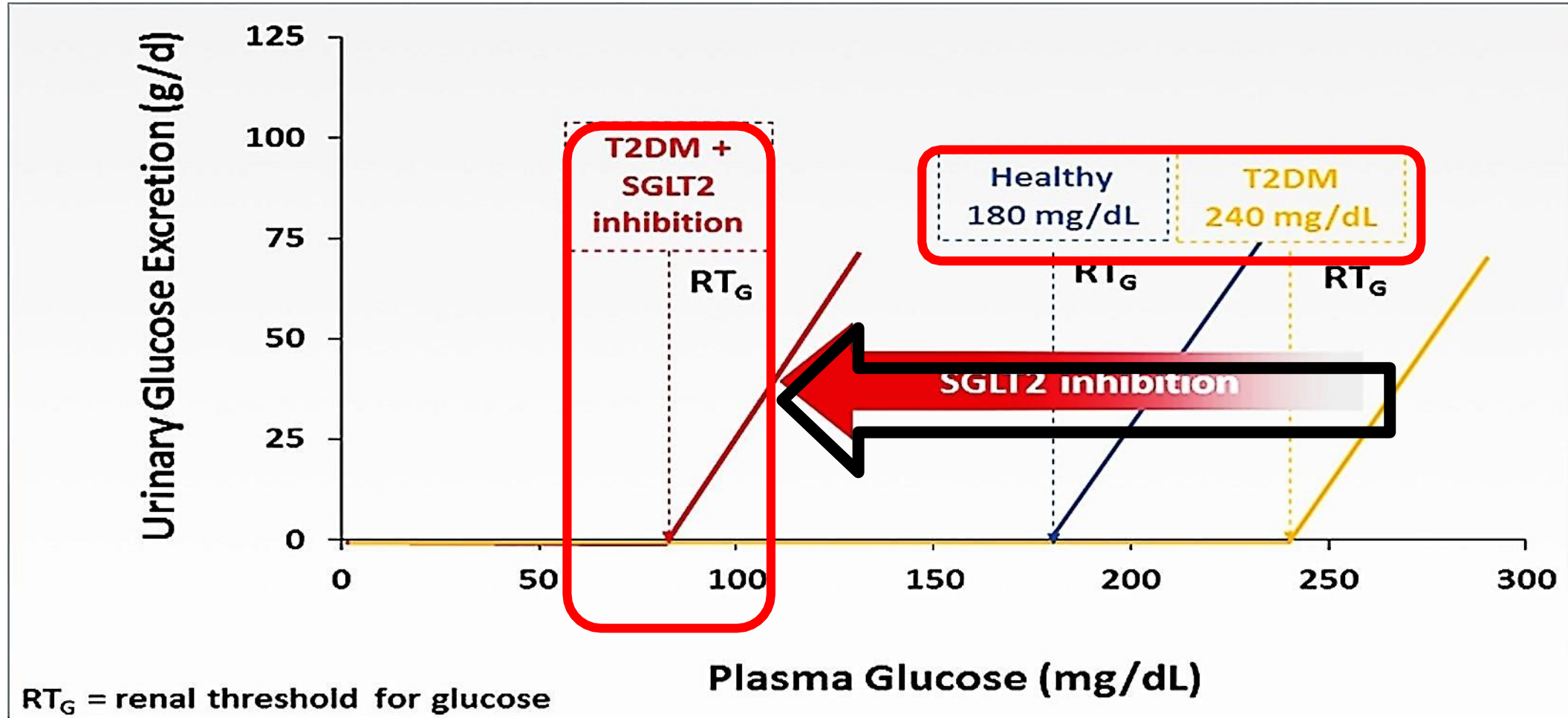
Filtered glucose load
> 180 g/day



SGLT₂ inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis¹

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

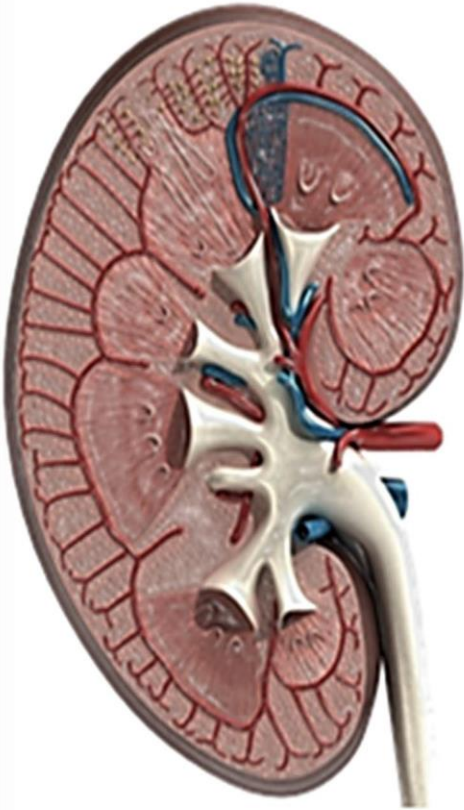
SGLT2i lowers renal threshold for glucose excretion^{1,2}



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. 2000; 14(1): 102-10.

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.

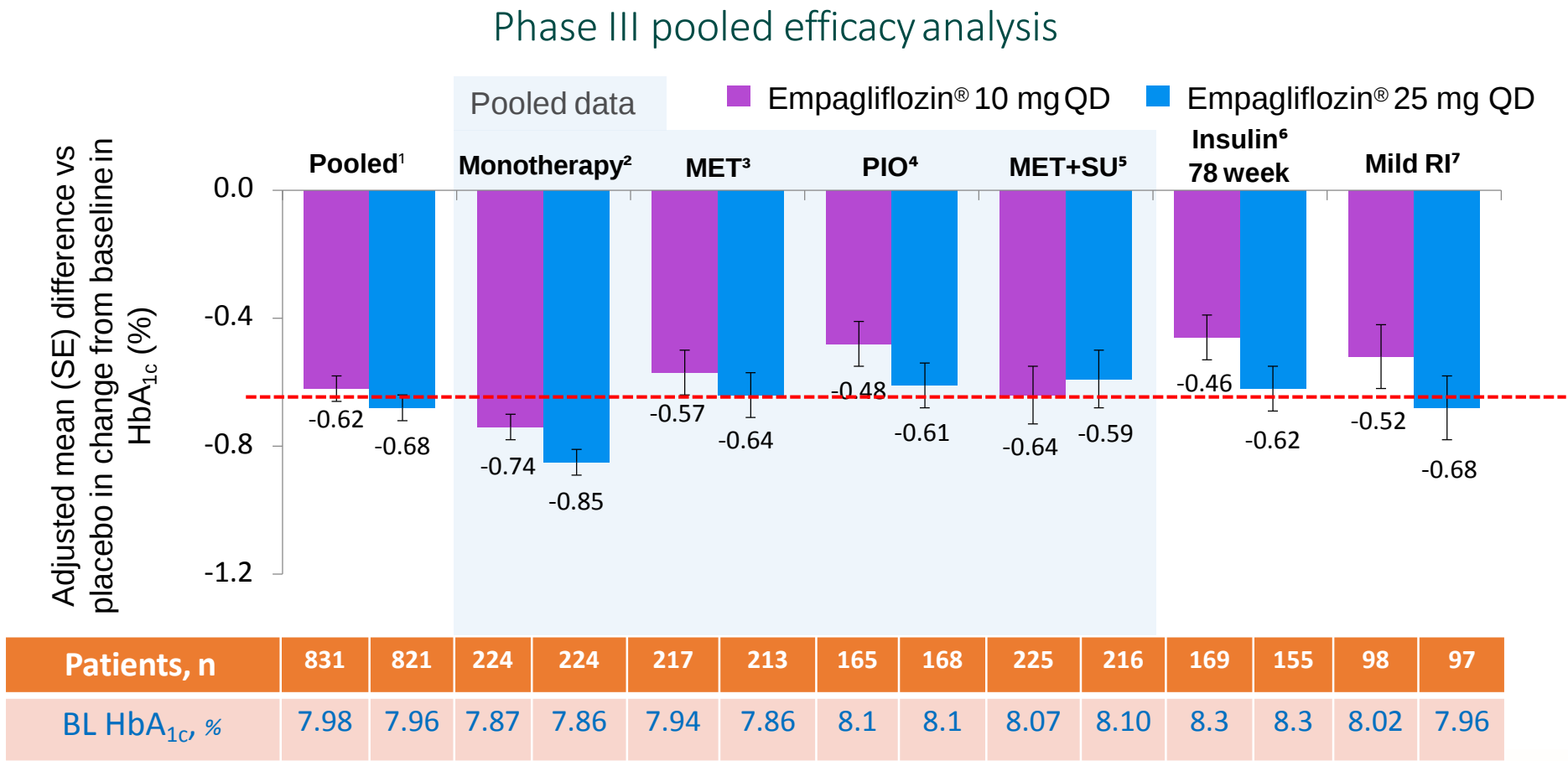
Expected Clinical Effects of SGLT2 Inhibition¹



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): 782-90¹⁰

Efficacy Studies

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

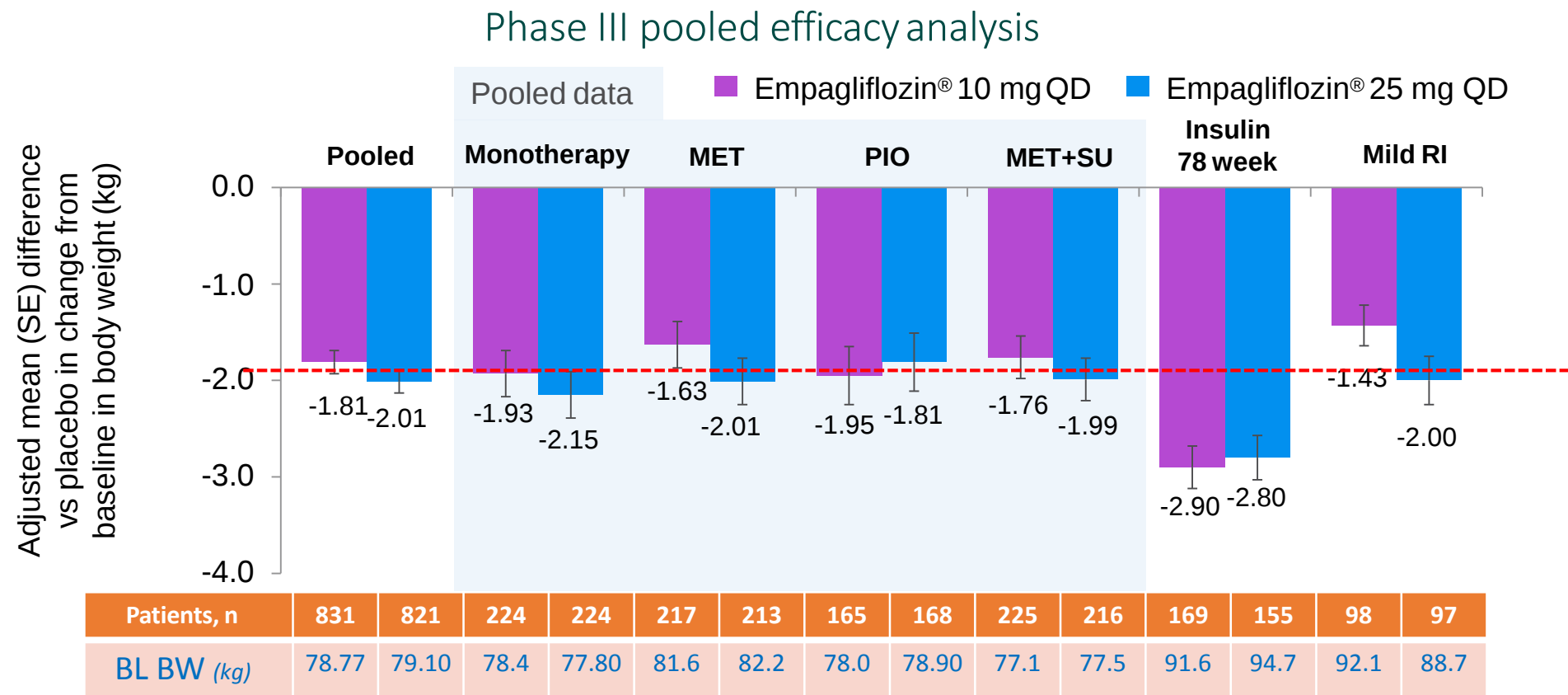


BL, baseline; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SE, standard error; SU, sulphonylu

* 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*. 2013;62(suppl 1A):A21 (P69-LB);
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 (P91321);
7-Barnett A, et al, *Lancet Diabetes Endocrinol*. 2014; doi:10.1016/S2213-8587(13)70208-0.

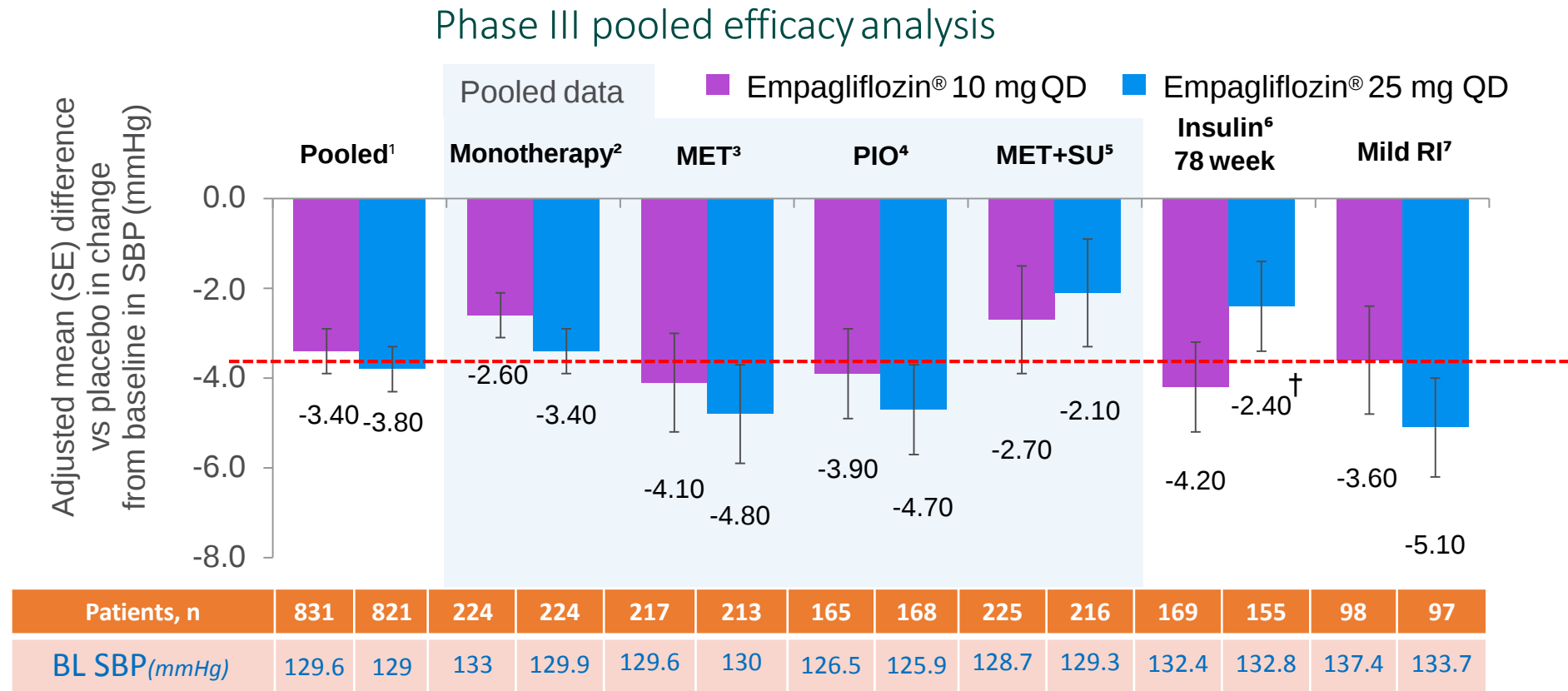
Δ Body Weight Across Different Background Therapy Empagliflozin® vs. Placebo*



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*. 2013;54(suppl 1);S372 (P91331);
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 (P91331);
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*



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*

4-Kovacs C, et al. *Diabetes Obes Metab*. 2014;16(2):147–158;

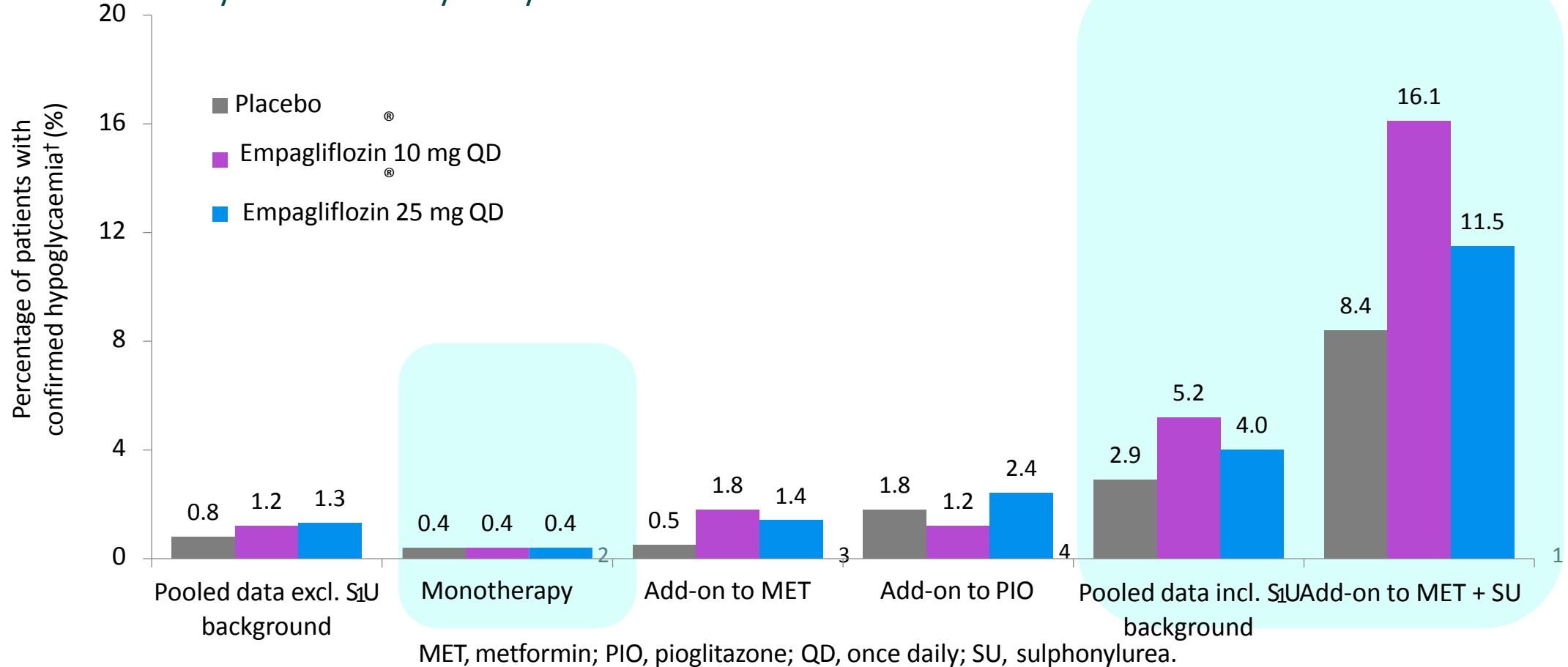
5- Häring H-U, et al. *Diabetes Care*. 2013;36(11):3396–404;

6- Rosenstock J, et al. *Diabetologia*. 2013;56(suppl 1):S372 (P9314);

7-Barnett A, et al, *Lancet Diabetes Endocrinol*. 2014; doi:10.1016/S2213-8587(13)70208-0.

Hypoglycemic Events

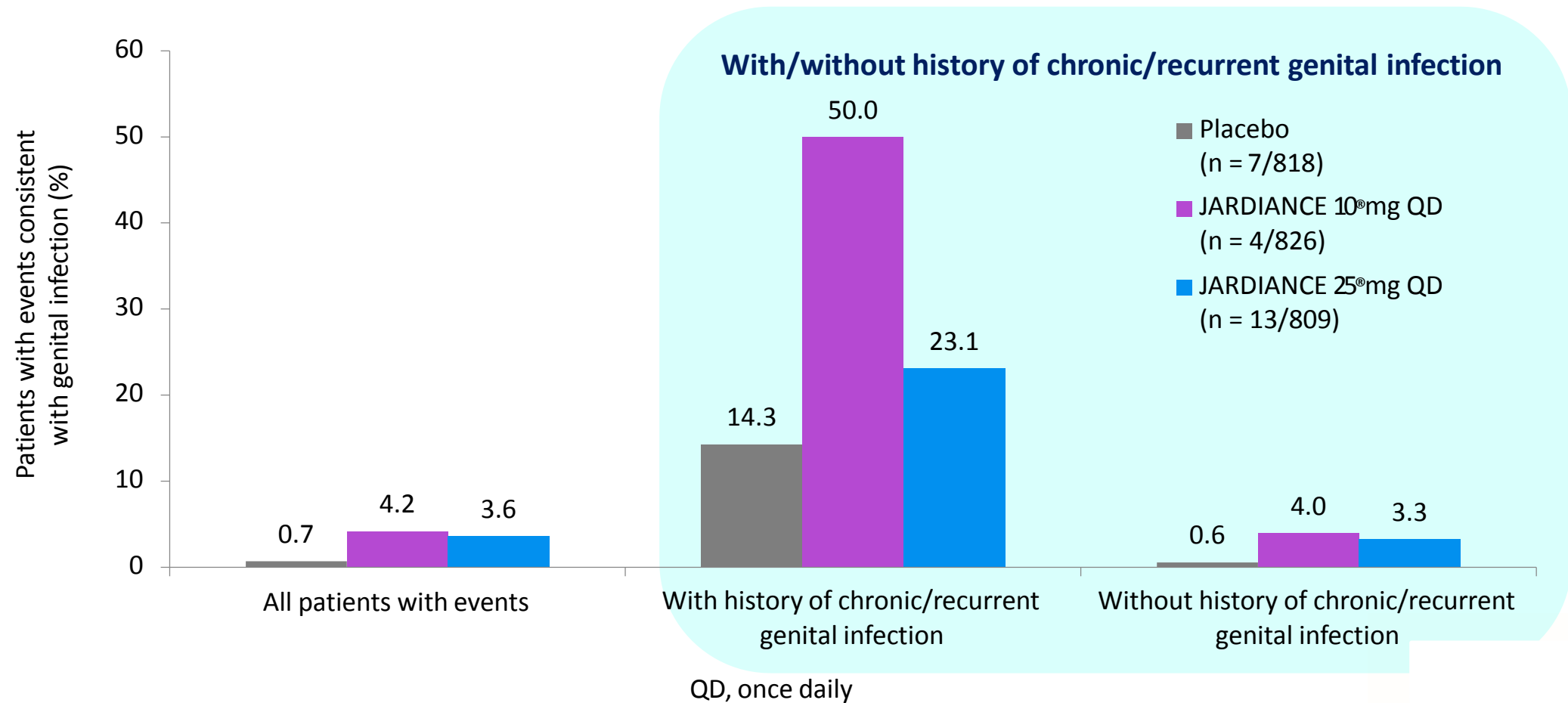
- Phase III safety and tolerability analysis



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

Genital infection stratified by previous history

Phase III pooled[†] safety and tolerability analysis

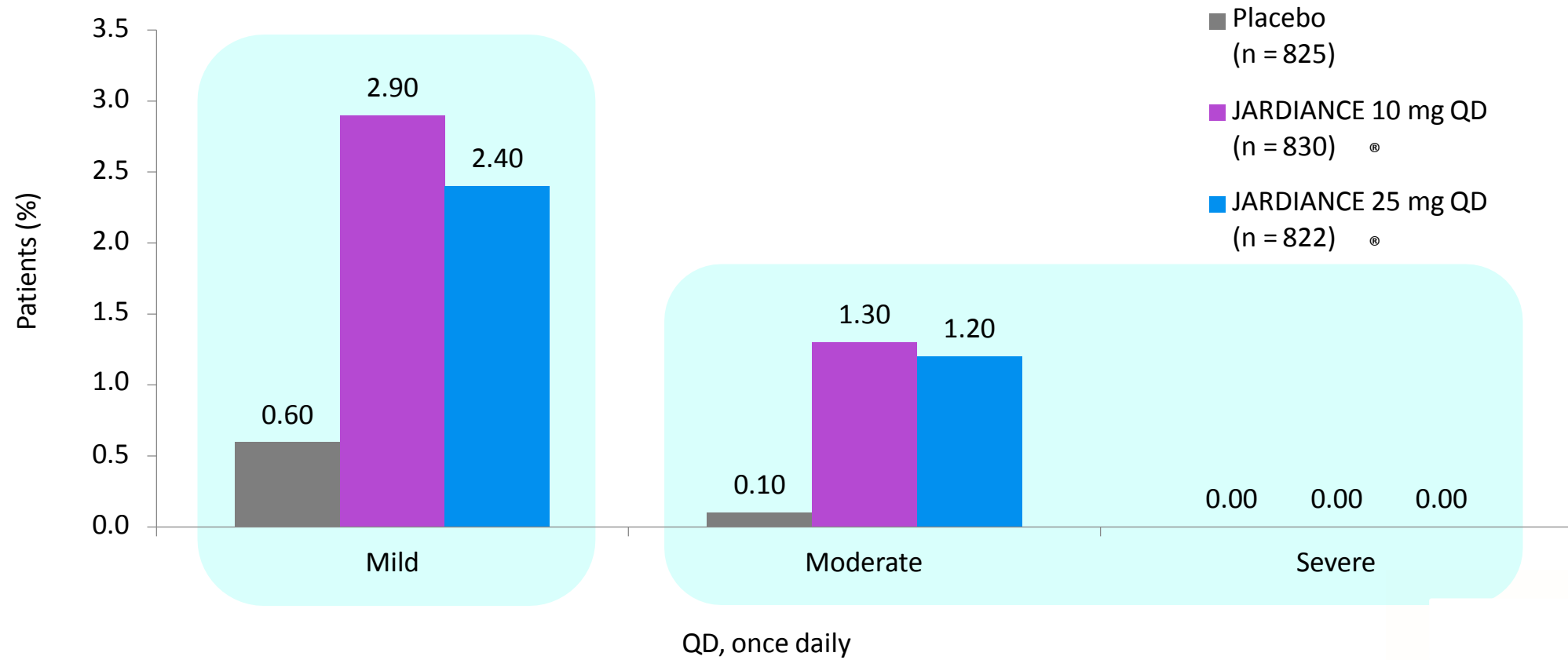


[†]The following studies were included in the pooled analysis:

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 Care.* 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).

Genital infection distribution of events severity

Phase III pooled[†] safety and tolerability analysis



[†]The following studies were included in the pooled analysis:

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 Care.* 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).

EMPA-REG OUTCOME®

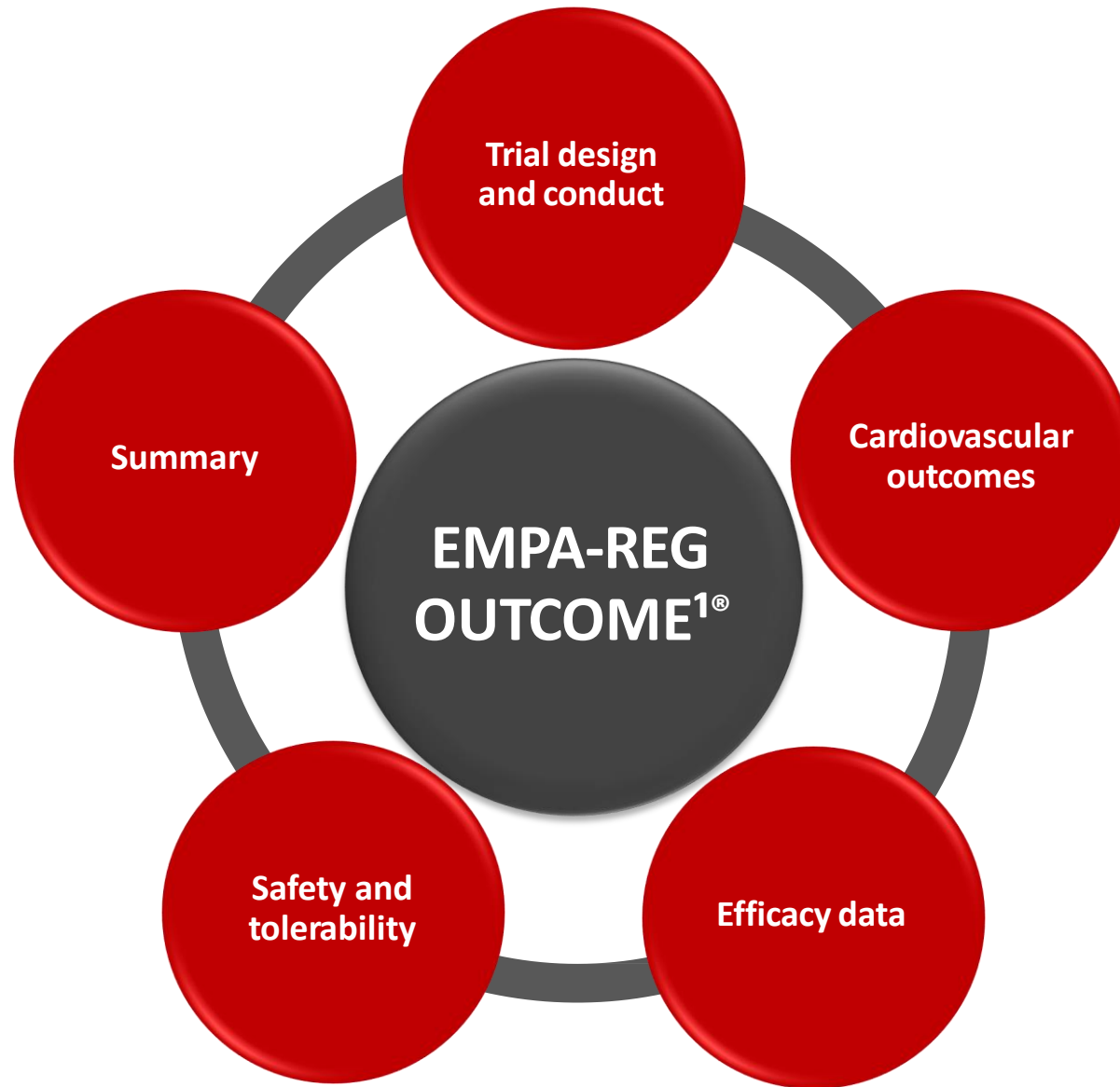
ORIGINAL ARTICLE

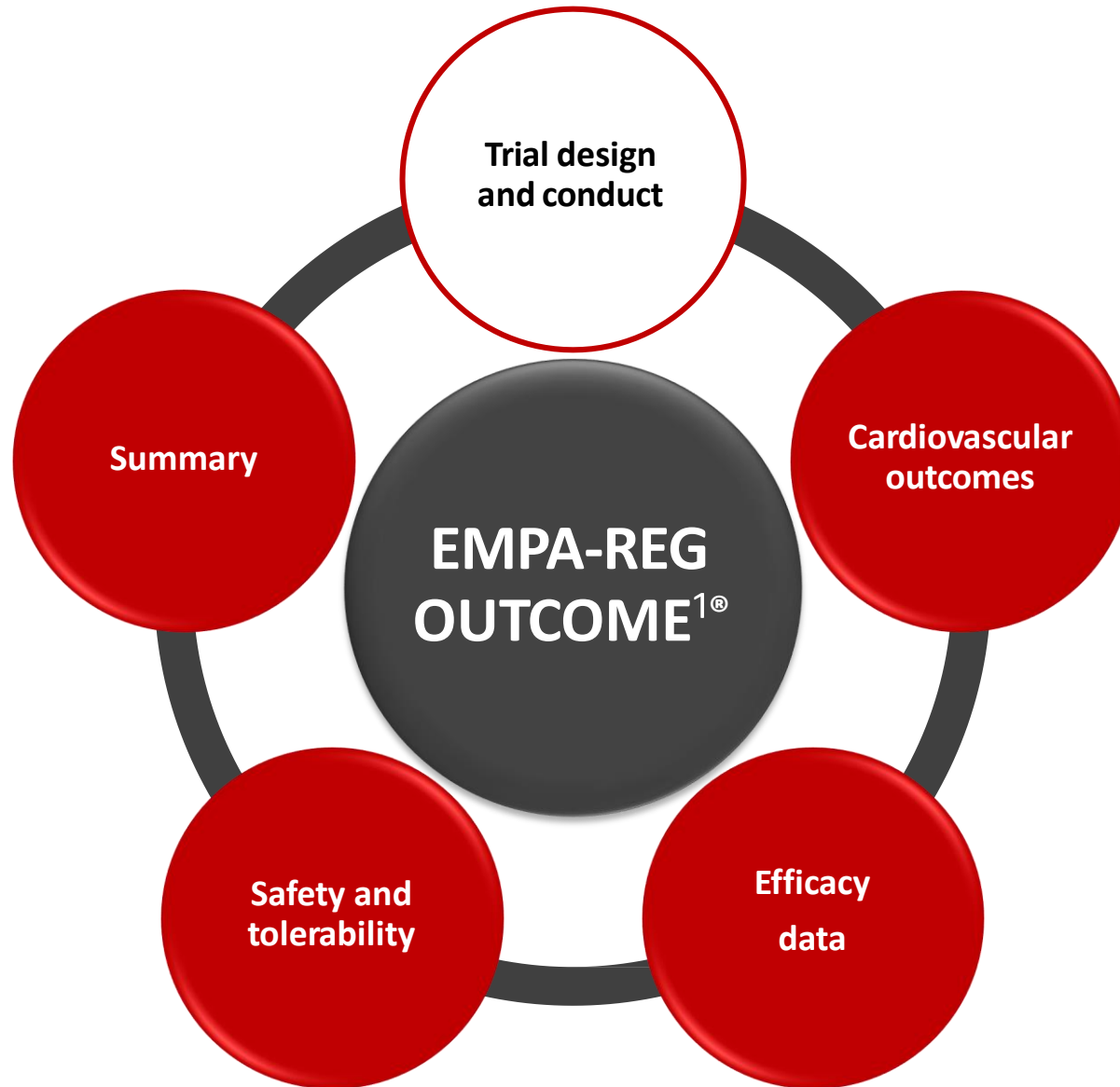
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D.,
David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D.,
Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H.,
Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D.,
and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

Objective¹

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





Trial Design¹



- **Design**

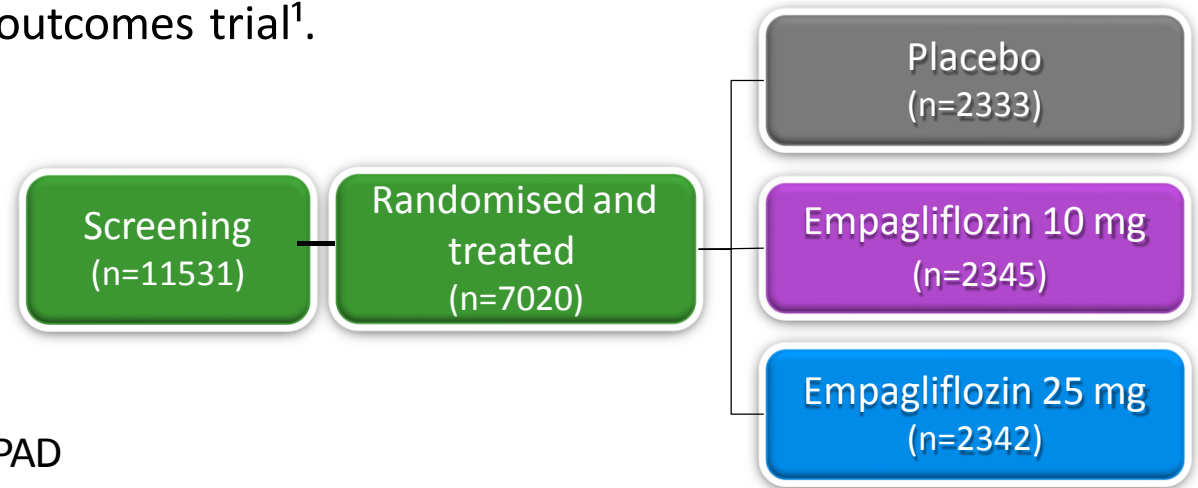
- Randomized, double-blind, placebo-controlled CV outcomes trial¹.

- **Key inclusion criteria**

- Adults with T₂DM
- BMI ≤ 45 kg/m²
- HbA_{1c} 7–10%*
- Established cardiovascular disease
 - Prior MI, CAD, stroke, unstable angina or occlusive PAD

- **Key exclusion criteria**

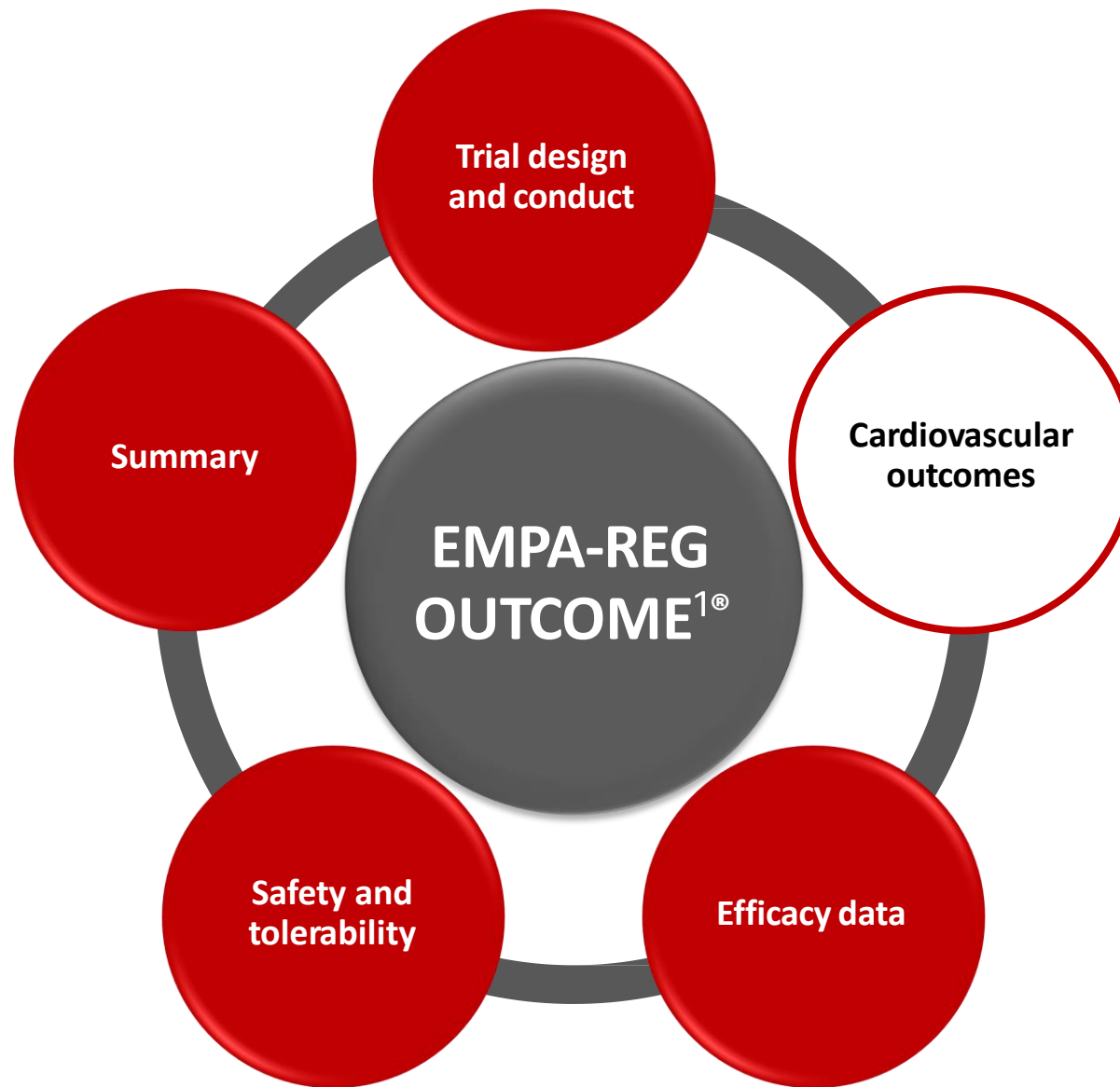
- eGFR < 30 mL/min/1.73m² (MDRD)



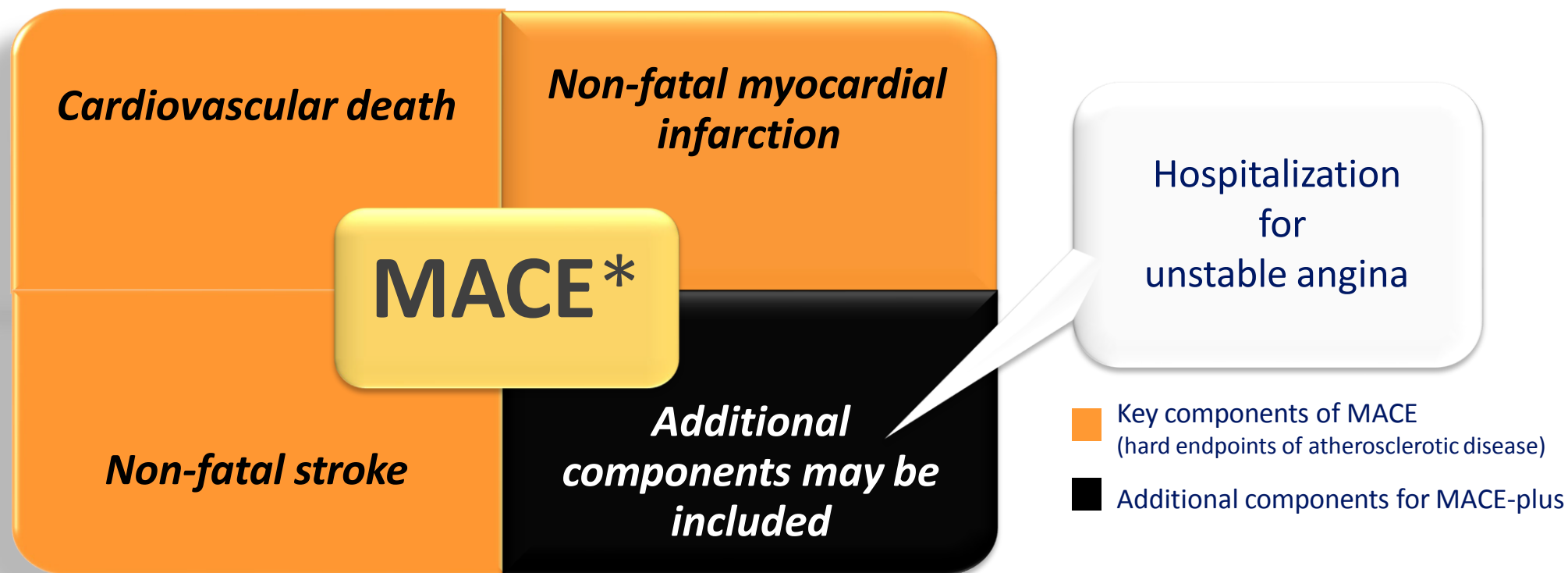
☐ The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event.

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

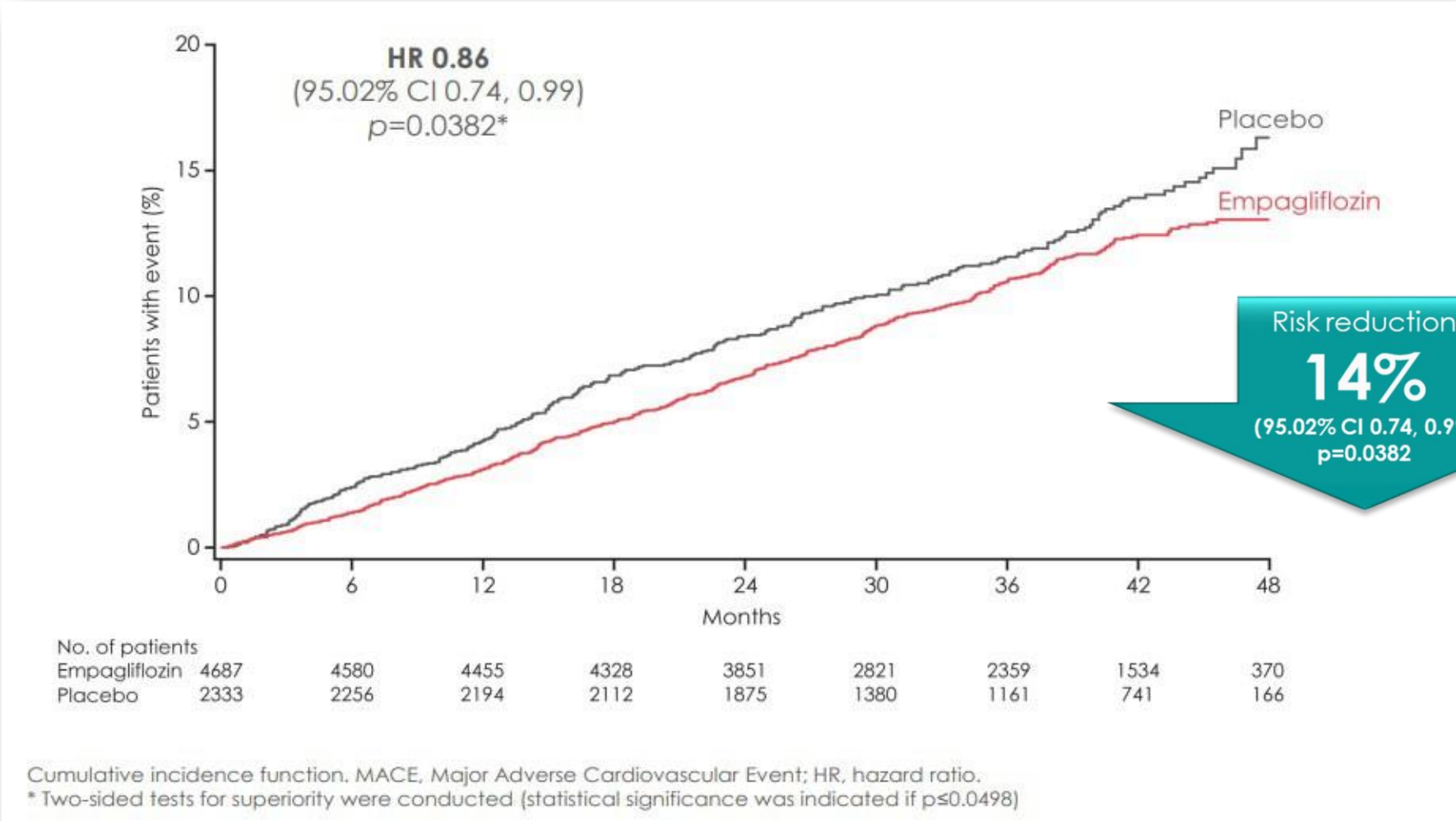


Pre-specified primary and key secondary outcomes¹



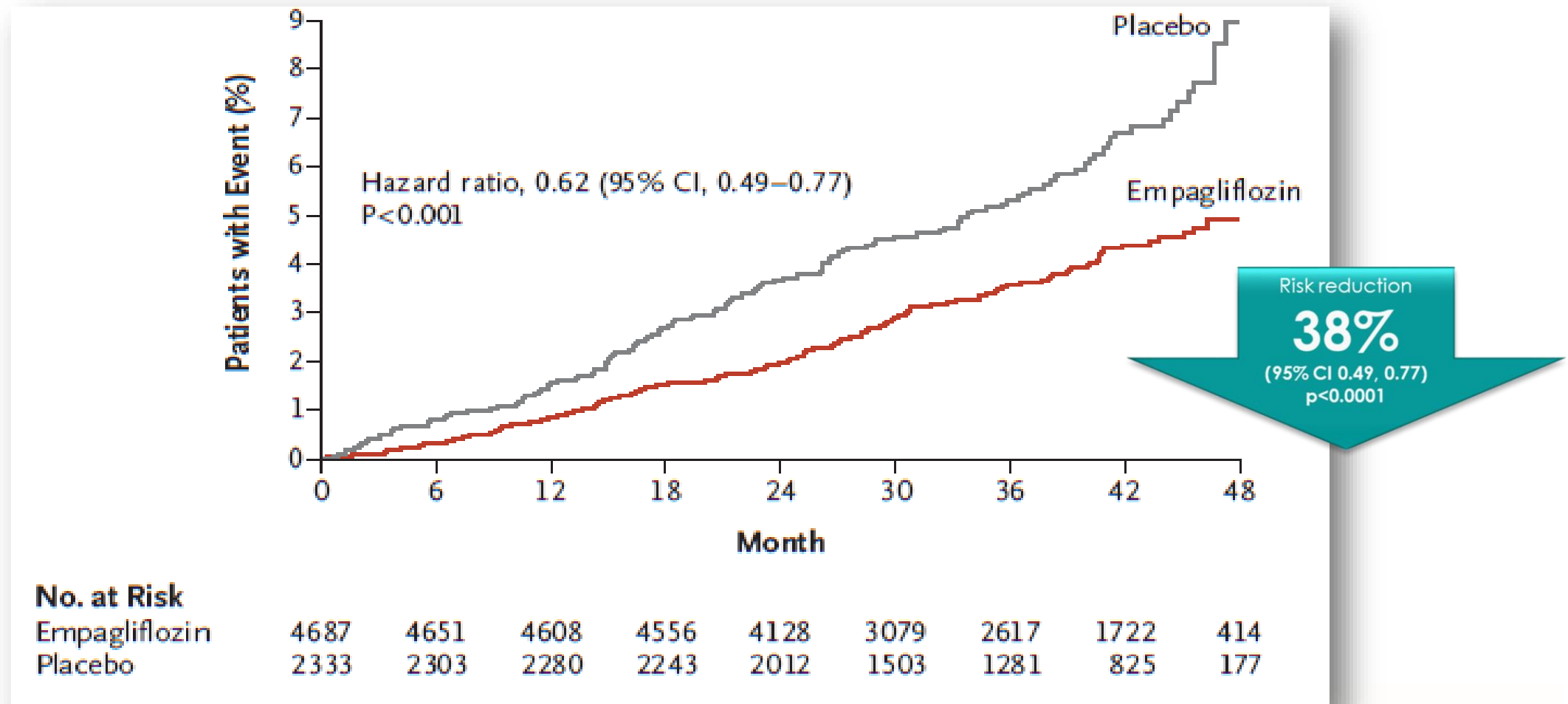
*Major Adverse Cardiovascular Events

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

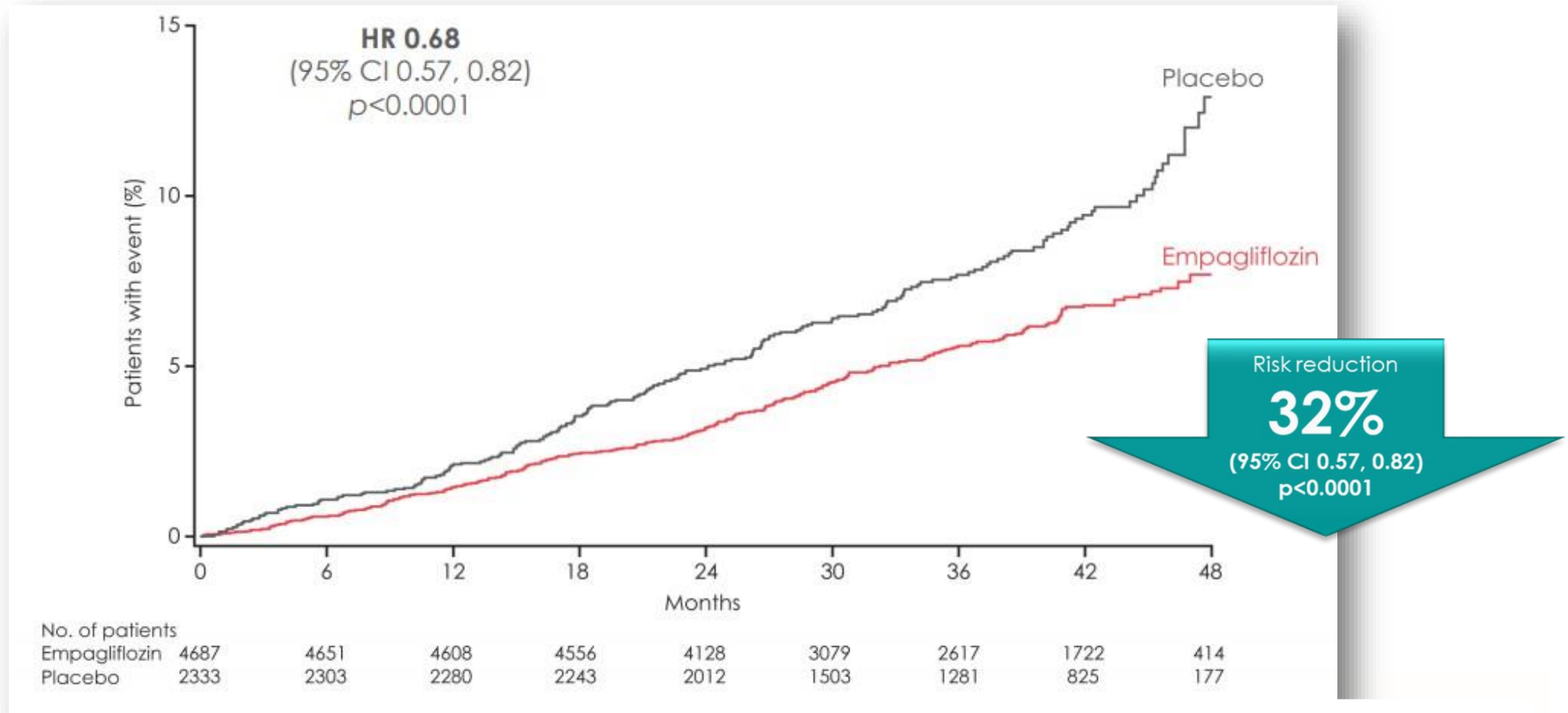


1-Zinman B et al.,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

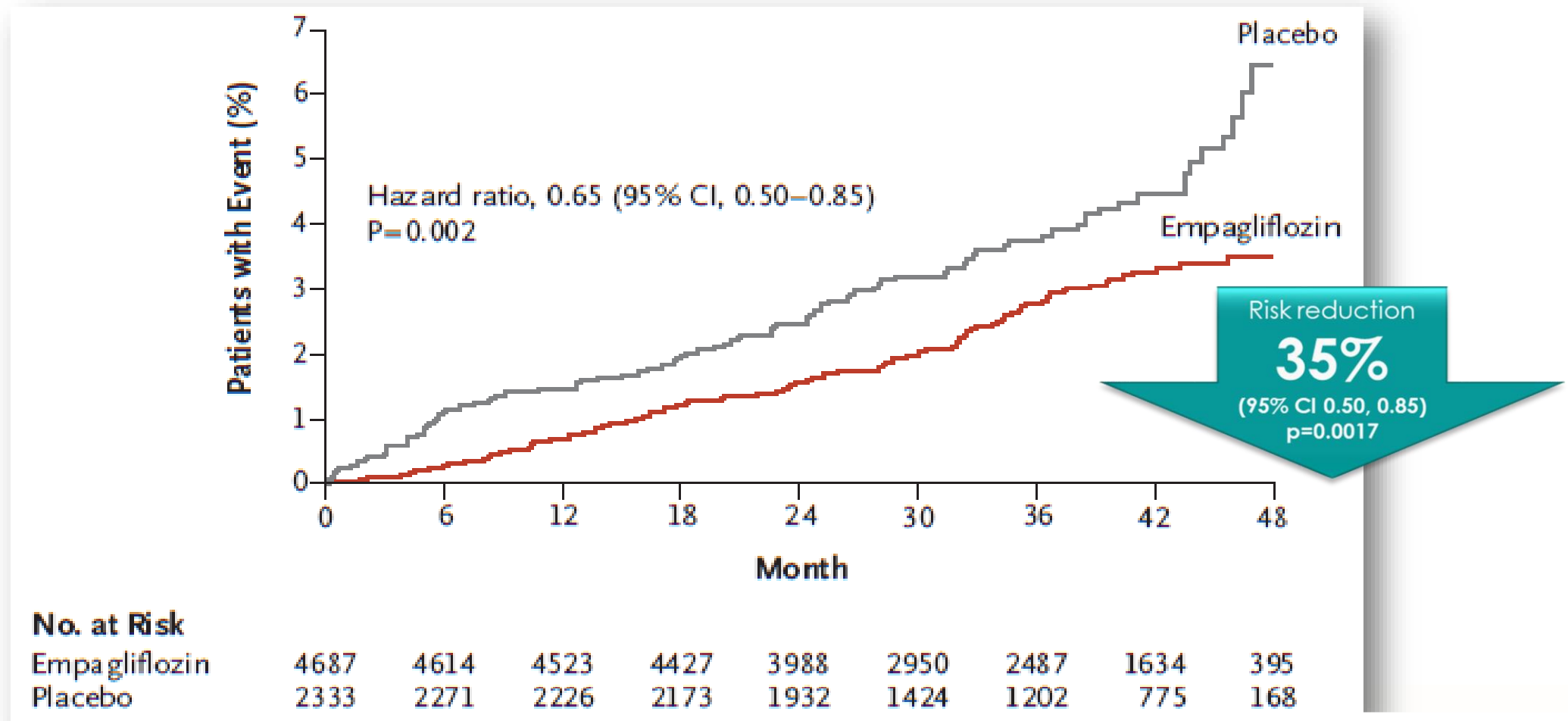
EMPA-REG OUTCOME® CV Death¹

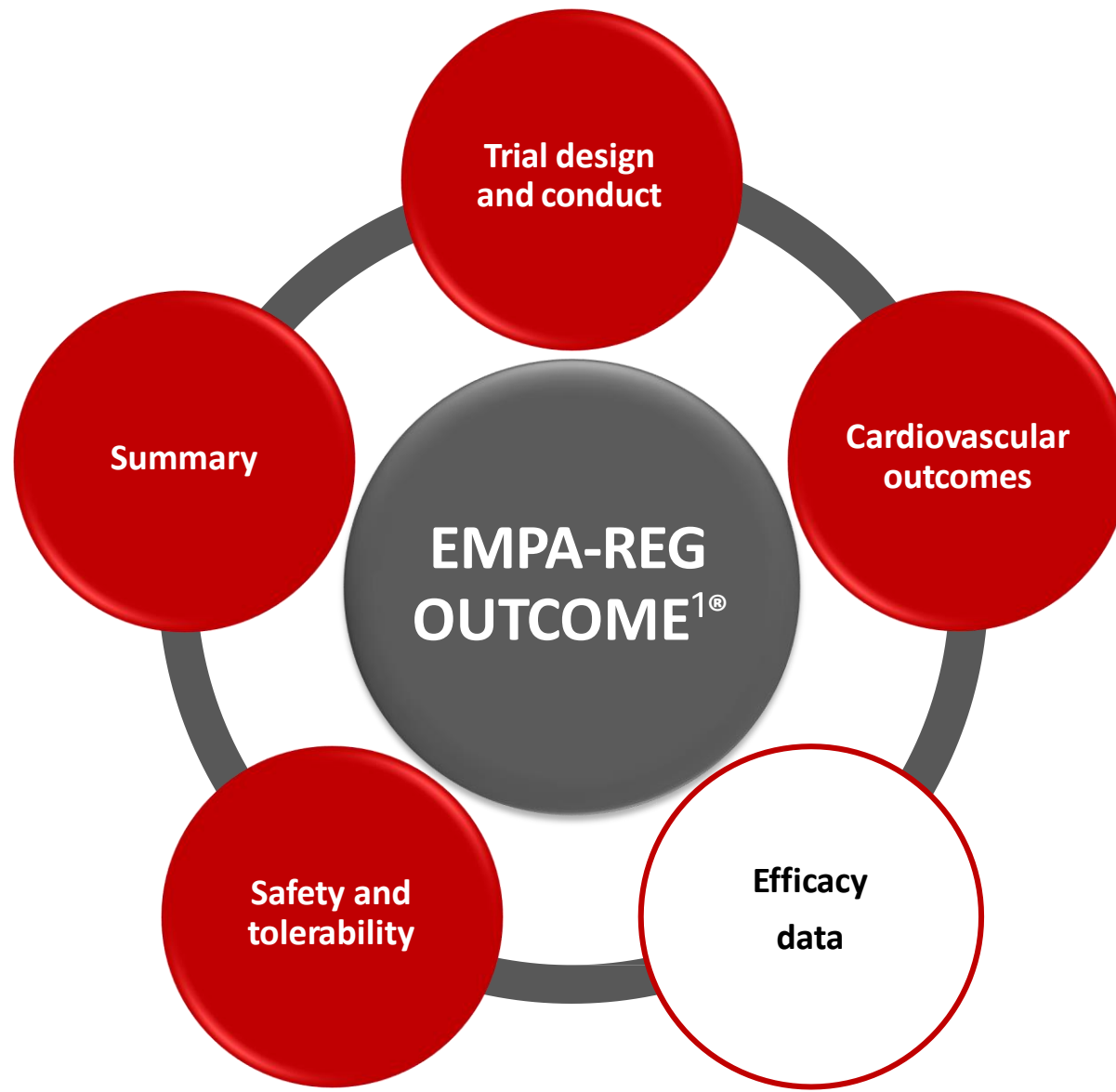


EMPA-REG OUTCOME® All-cause Mortality¹

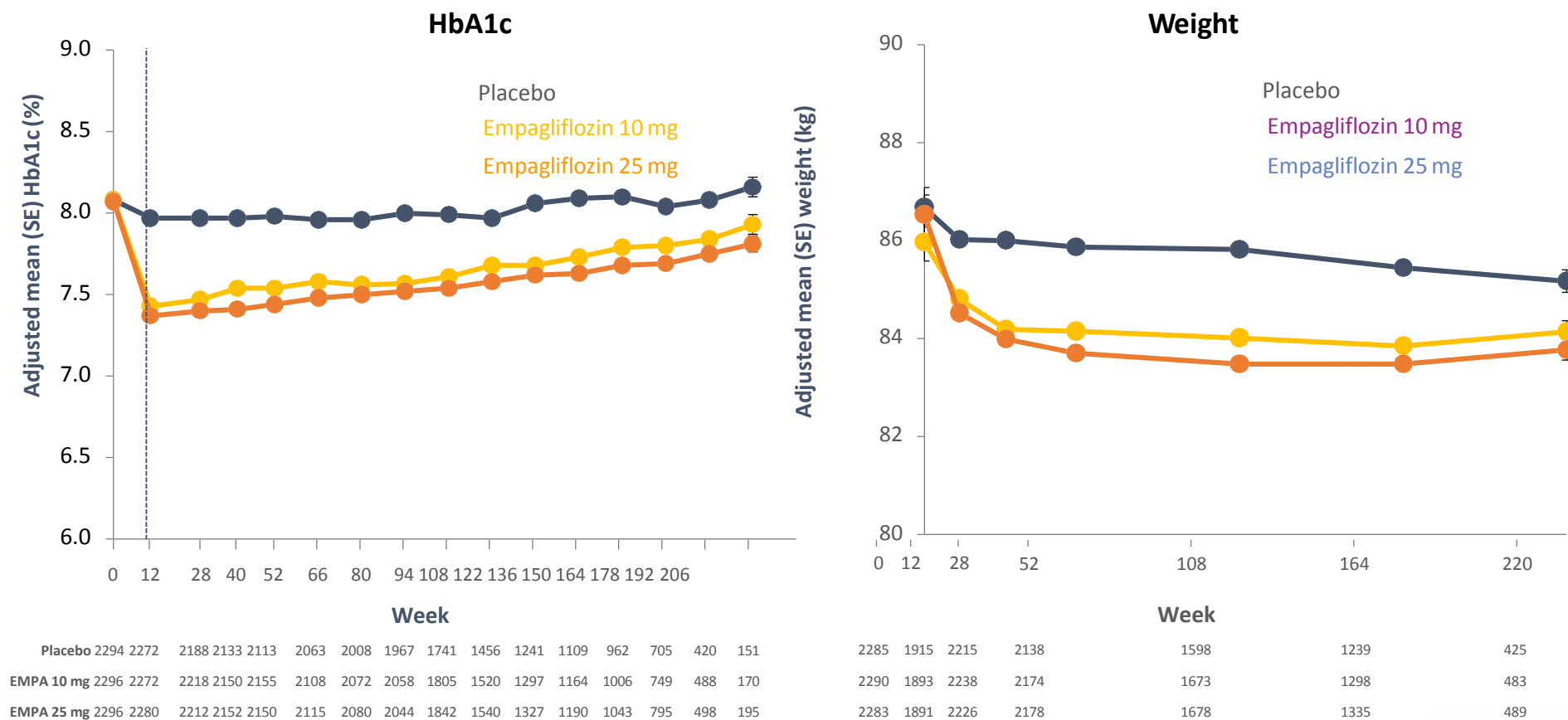


EMPA-REG OUTCOME® Hospitalization for Heart Failure¹





Mean adjusted HbA1c and weight parameters¹

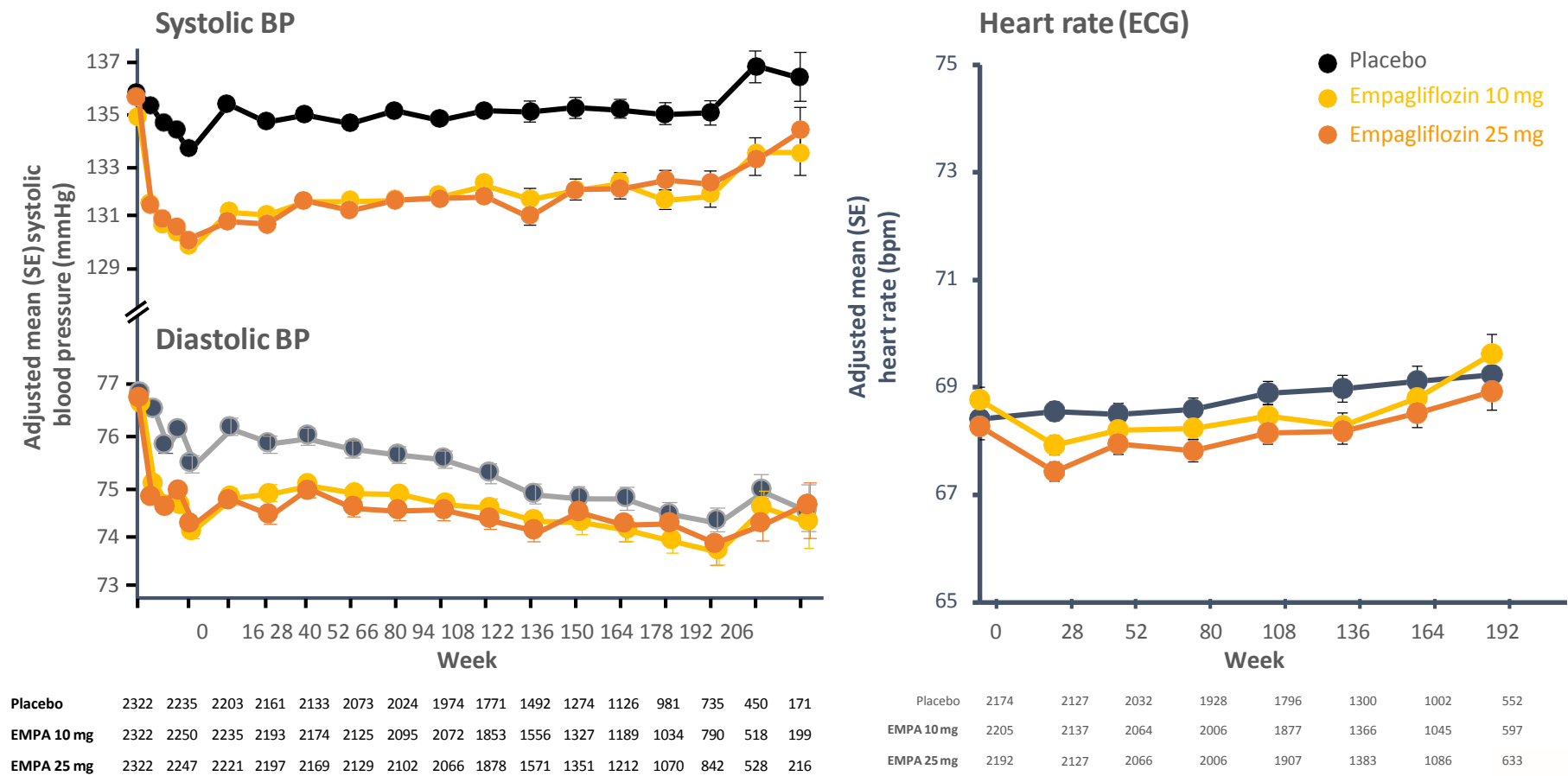


All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent to treat)

X-axis: time points with reasonable amount of data available for prescheduled measurements

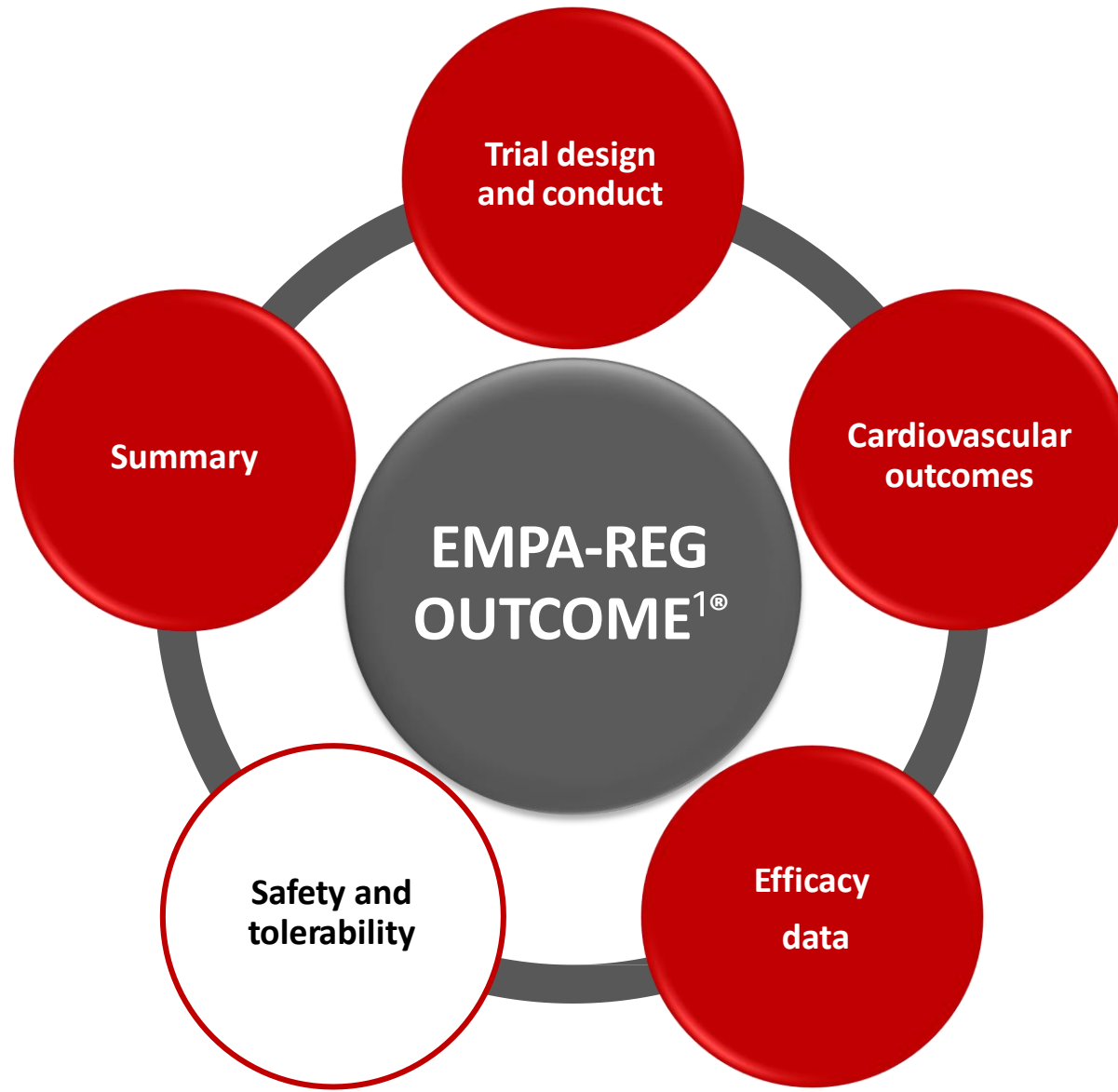
EMPA, empagliflozin; HbA1c, glycated hemoglobin

Mean adjusted blood pressure parameters¹



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

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

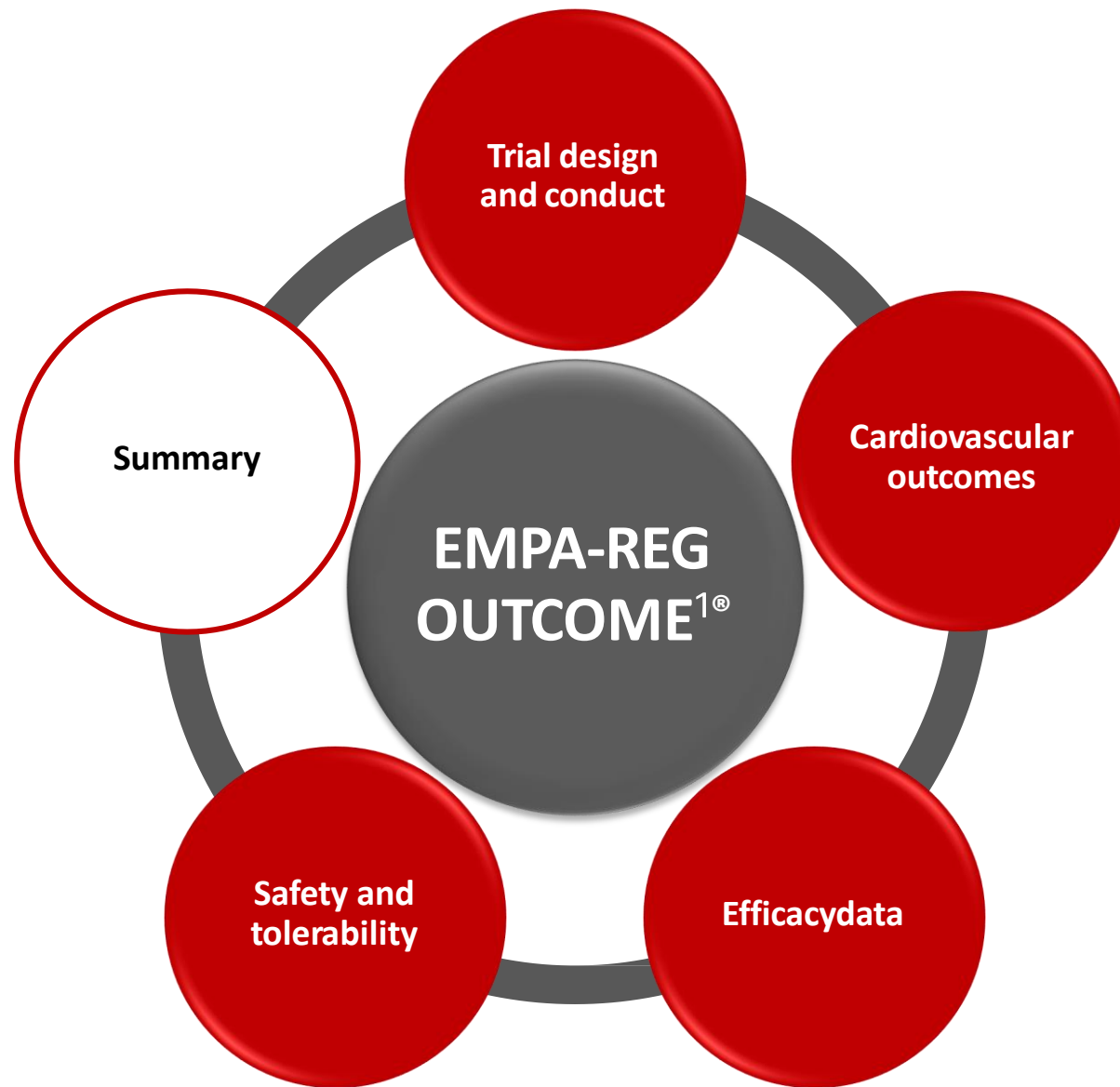
Rate = per100 patient-years

*As reported by the investigator

Patients treated with ≥1 dose of study drug

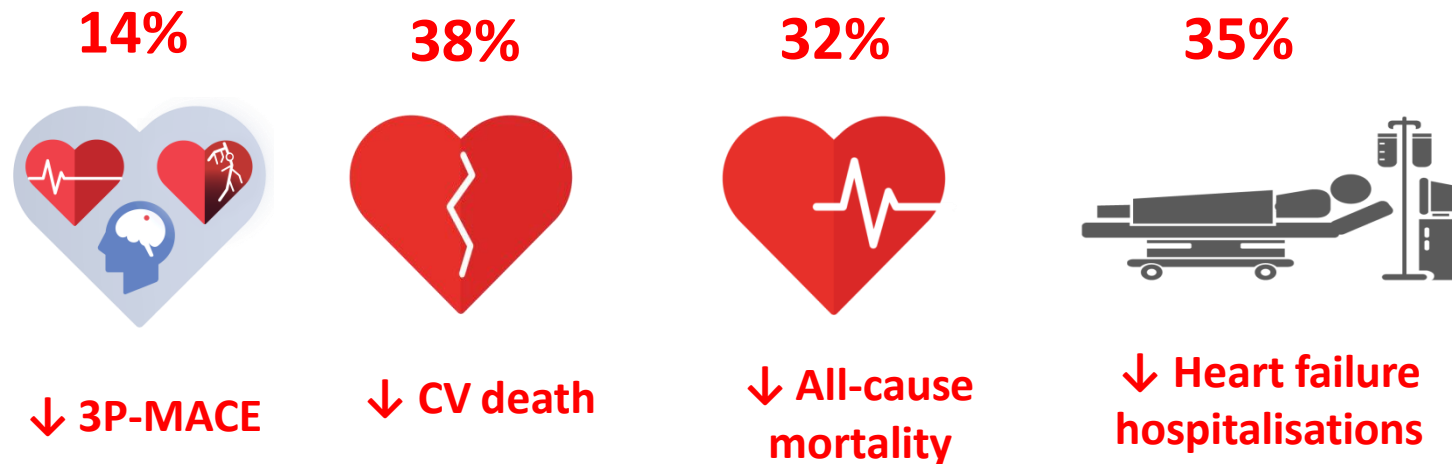
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

2-Zinman B. EASD 2015; Oral presentation



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 risk¹



The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information¹

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.

EMPEROR-Reduced trial

ORIGINAL ARTICLE

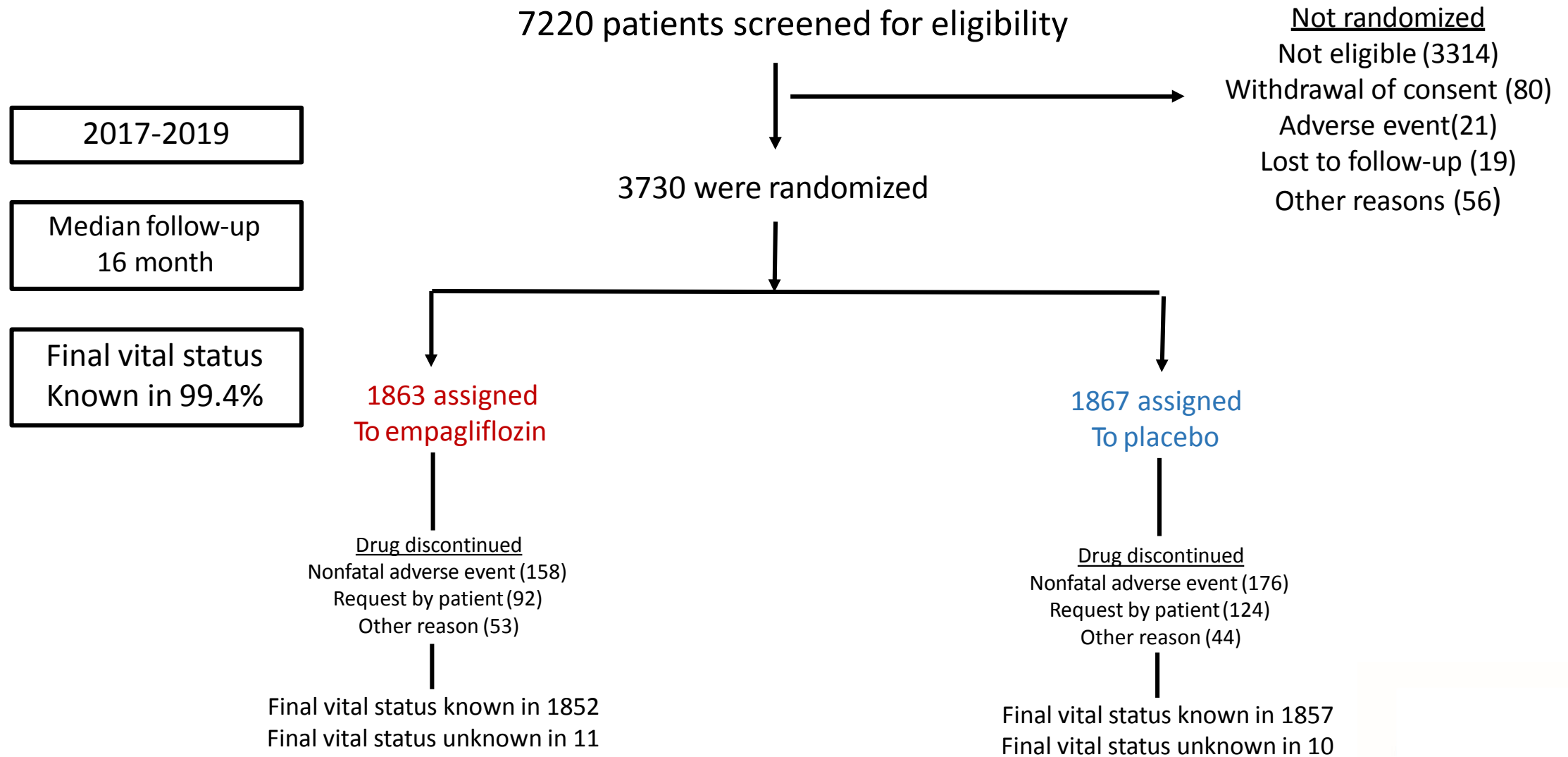
Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

Objective¹:

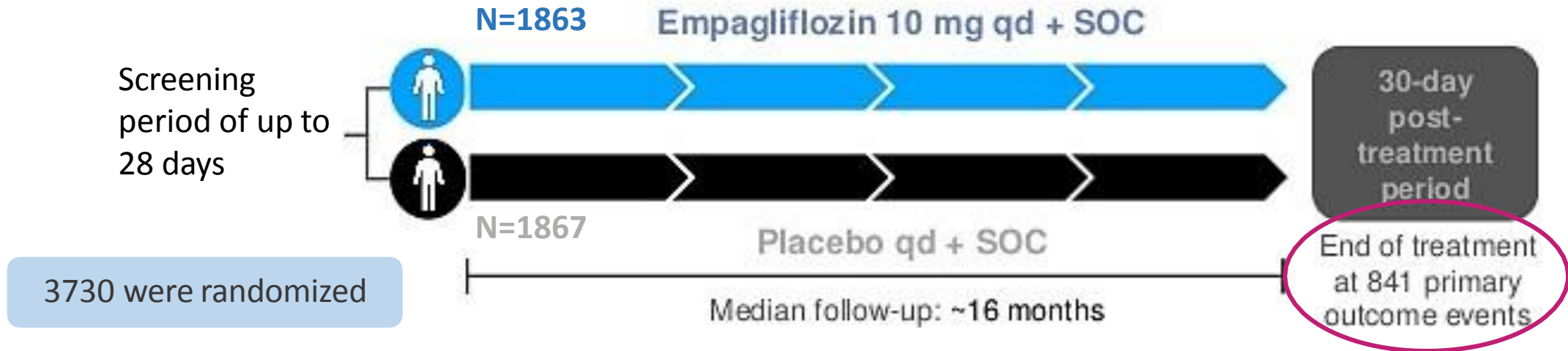
The **EMPEROR-Reduced** trial was designed to evaluate the effects of empagliflozin 10 mg once daily (as compared with placebo) in patients with heart failure and a **reduced** ejection fraction, with or without diabetes, who were already receiving all appropriate treatments for heart failure.

EMPEROR-Reduced: Patient Disposition¹



Trial Design¹

Patients must be receiving all appropriate treatments for HF



SOC; Standard Of Care

EMPEROR-Reduced trial specified only three endpoints to be tested in hierarchical manner¹



☐ Primary End point

Composite of cardiovascular death Or heart failure hospitalization



☐ First Secondary End point

Total (first and recurrent) heart failure hospitalization



☐ Second Secondary End point

Slope of decline in glomerular Filtration rate over time

☐ Other pre-specific end points:

Composite renal endpoints, KCCQ clinical summary score, total number of hospitalization for any reason , all-cause mortality, new onset diabetes

Inclusion criteria¹

The study included patients with **Chronic HF** with reduced ejection fraction

Key inclusion criteria:

- NYHA class II-IV
- Elevated NT-pro BNP
- Guideline recommendation medication stable ≥ 1 week prior to first visit
- eGFR ≥ 20 ml/min/1.73 m²

EF%	NT-proBNP (pg/ml) Patients without AF	NT-proBNP (pg/ml) Patients with AF
≥ 36 to ≤ 40	≥ 2500	≥ 5000
≥ 31 to ≤ 35	≥ 1000	≥ 2000
≤ 30	≥ 600	≥ 1200
> 40+HHF within 12 months	≥ 600	≥ 1200

NYHA; New York Heart Association

1- EMPEROR-Reduced Trial Marta Cobo Marcos M. Packer presentation ESC 2020

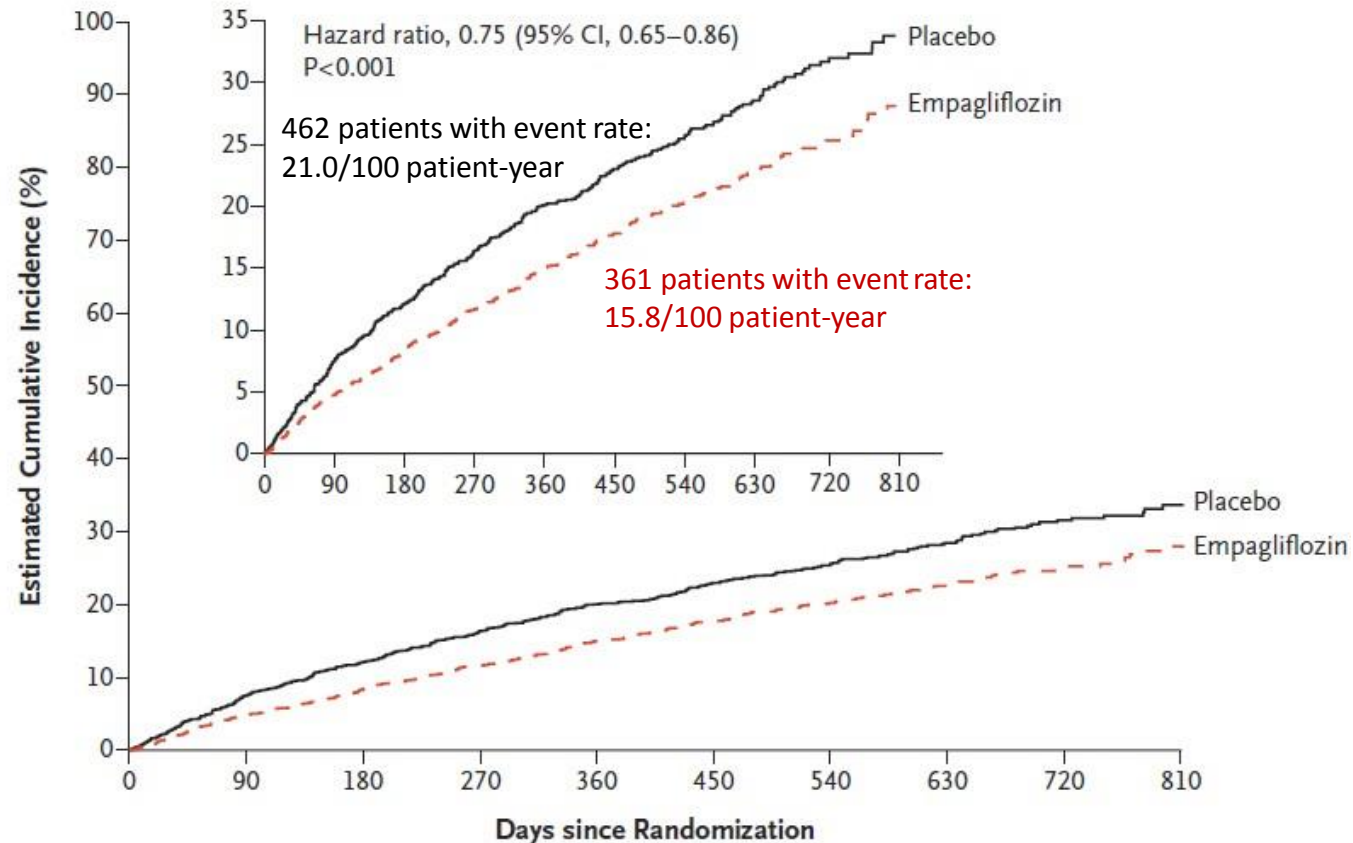
Base-Line Characteristic of Patients¹

Characteristic	Empagliflozin (N= 1863)	Placebo (N= 1867)
NYHA functional class — no. (%)		
II	1399 (75.1)	1401 (75.0)
III	455 (24.4)	455 (24.4)
IV	9 (0.5)	11 (0.6)
Left ventricular ejection fraction		
Mean value	27.7±6.0	27.2±6.1
Value of ≤30% — no. (%)	1337 (71.8)	1392 (74.6)
Cardiovascular history — no. (%)		
Hospitalization for heart failure in ≤12 mo	577 (31.0)	574 (30.7)
Atrial fibrillation	664 (35.6)	705 (37.8)
Diabetes mellitus	927 (49.8)	929 (49.8)
Hypertension	1349 (72.4)	1349 (72.3)
NT-proBNP		
Median value (IQR) — pg/ml	1887 (1077–3429)	1926 (1153–3525)
Value of ≥1000 pg/ml — no./total no. (%)	1463/1862 (78.6)	1488/1866 (79.7)
Estimated glomerular filtration rate		
Mean value — ml/min/1.73 m ²	61.8±21.7	62.2±21.5
Value of <60 ml/min/1.73 m ² — no./total no. (%)	893/1862 (48.0)	906/1866 (48.6)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)

1-N. Engl. J. Med 2020 Aug 20

Empagliflozin Group Had Lower Incidence of Cardiovascular Death or Hospitalization for Heart Failure¹

A Primary Outcome



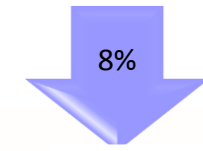
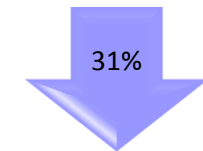
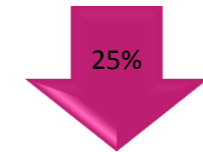
No. at Risk

Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

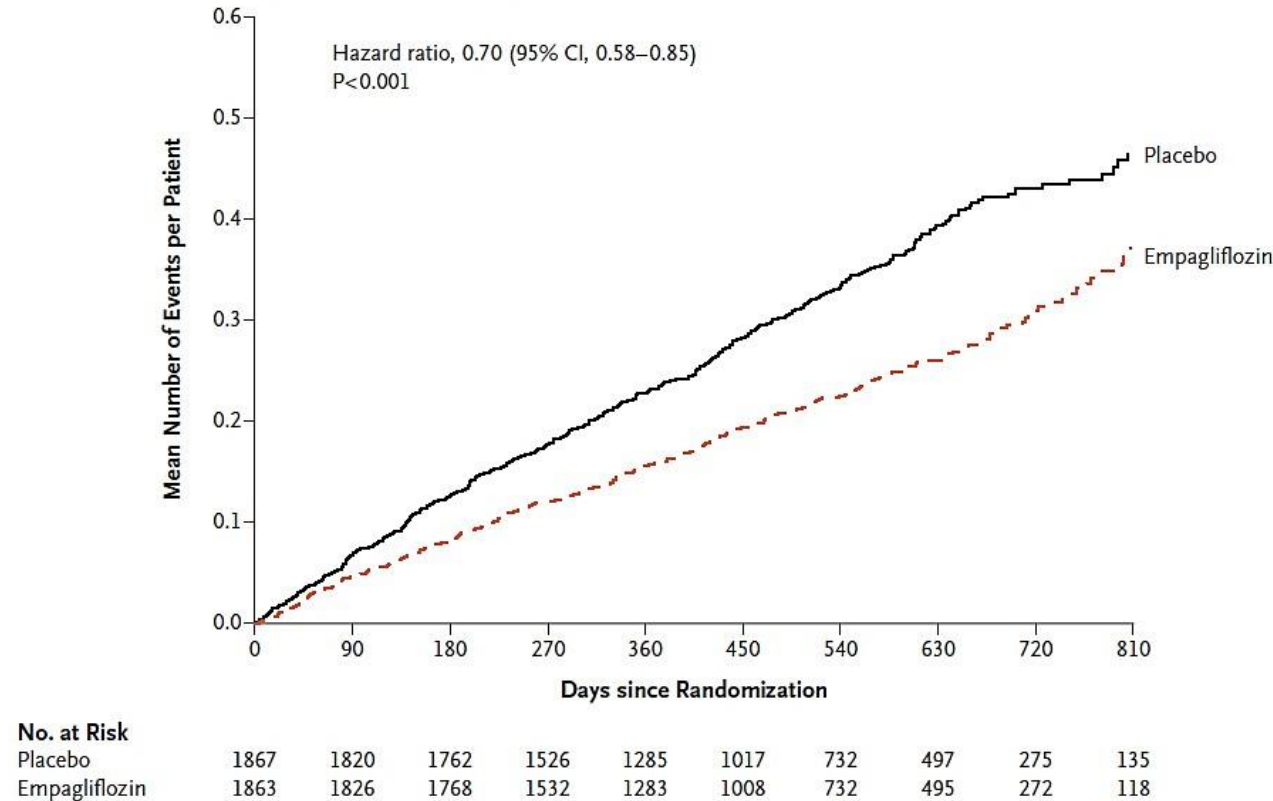


Effect on individual components of the primary endpoint¹

	Empagliflozin (n=1863)		Placebo (n=1867)		Hazard Ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yr	Number of events (%)	Events/100 patient-yr		
Primary composite outcome	361 (19.4%)	15.8	462 (24.7%)	21.0	0.75 (0.65 – 0.86)	<0.001
First hospitalization for heart failure	246 (13.2%)	10.7	342 (18.3%)	15.5	0.69 (0.59 – 0.81)	
Cardiovascular death	187 (10.0%)	7.6	202 (10.8%)	8.1	0.92 (0.75 – 1.12)	



Empagliflozin-Treated Patients Had lower Risk of Hospitalization for Heart Failure¹



30% RRR

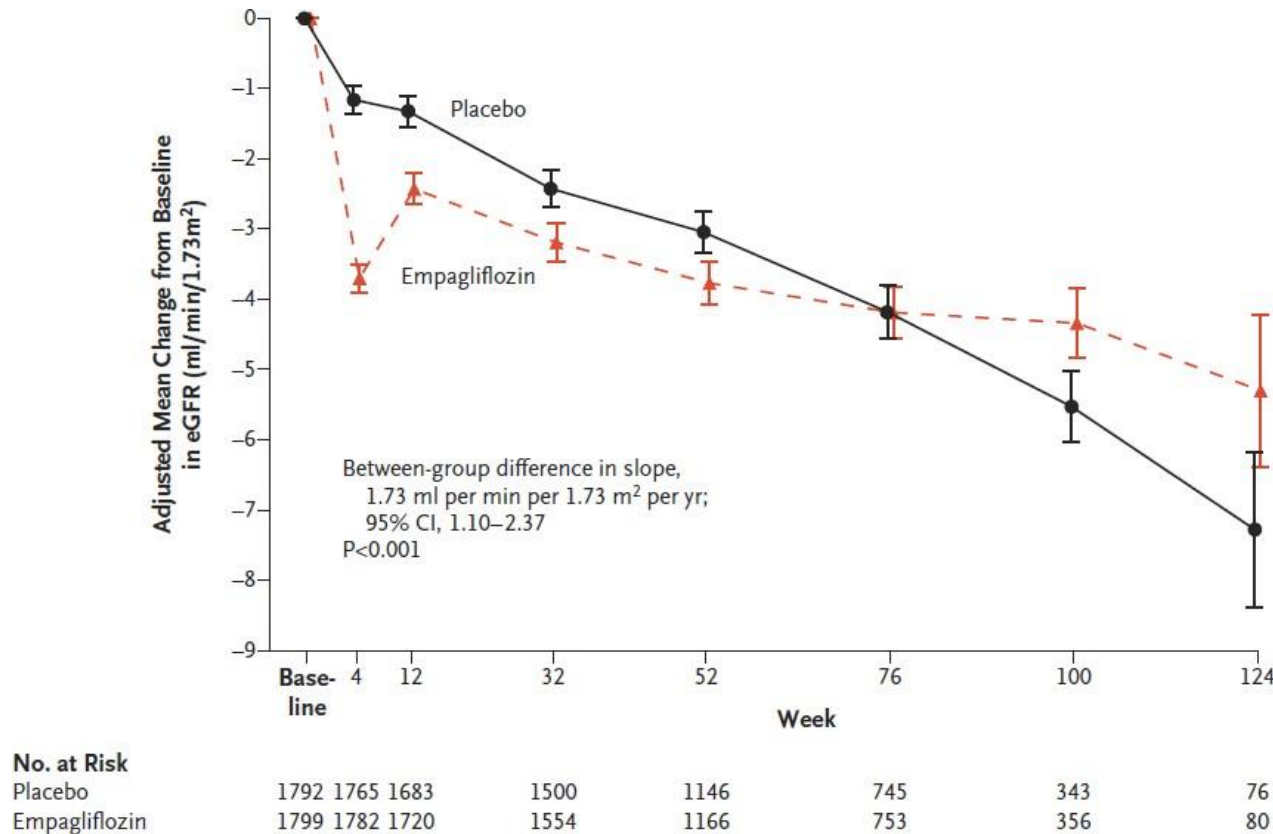
$p < 0.001$

388 Vs 553

$HR = 0.70 (0.58-0.85)$

- ☐ The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group, with 388 events and 553 events, respectively (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001)

Empagliflozin Reduced eGFR Significantly Over the Time vs Placebo¹



–2.28 ml / min / 1.73
m² / year
On placebo

– 0.55 ml / min / 1.73 m²
/ year
On Empagliflozin

1.73 ml / min / 1.73 m²
/ year

P < 0.001

- ☐ Empagliflozin was associated with a slower progressive decline in renal function in patients with chronic HF and a reduced EF, regardless of the presence or absence of diabetes².

1 N. Engl. J. Med 2020 Aug 29.

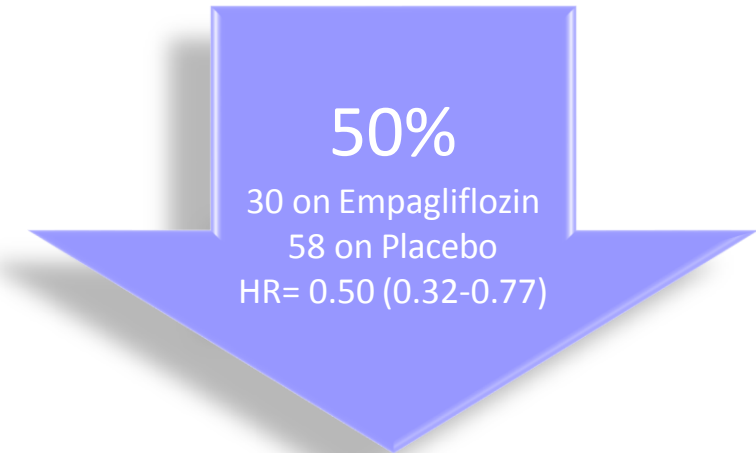
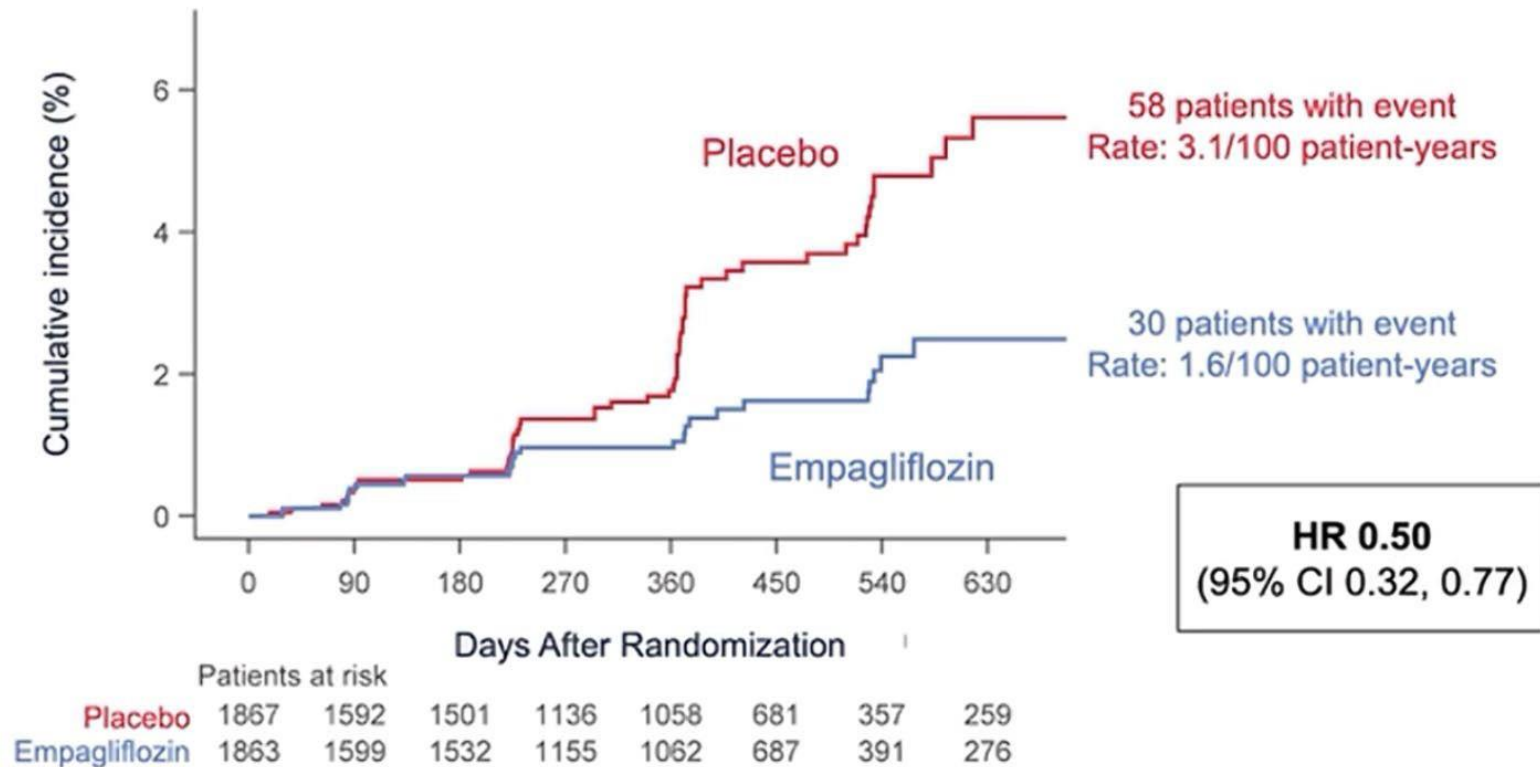
2 EMPEROR-Reduced Trial Marta Cobo Marcos M. Packer presentation ESC 2020

EMPEROR-Reduced trial achieved all three hierarchically specified endpoints at $p < 0.001$ ¹

	Primary Endpoint Composite of cardiovascular death or heart failure hospitalization	Achieved $P < 0.001$
	First Secondary Endpoint Total (first and recurrent heart failure hospitalizations)	Achieved $P < 0.001$
	Second Secondary Endpoint Slope of decline in glomerular filtration rate over time	Achieved $P < 0.001$

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal $P < 0.01$)

Empagliflozin reduced composite renal endpoint by 50%¹



□ a composite renal outcome (chronic dialysis or renal transplantation or a profound, sustained reduction in the estimated GFR) occurred in 30 patients (1.6%) in the empagliflozin group and in 58 patients (3.1%) in the placebo group (hazard ratio, 0.50; 95% CI, 0.32 to 0.77)

EMPEROR-Reduced: Adverse events¹

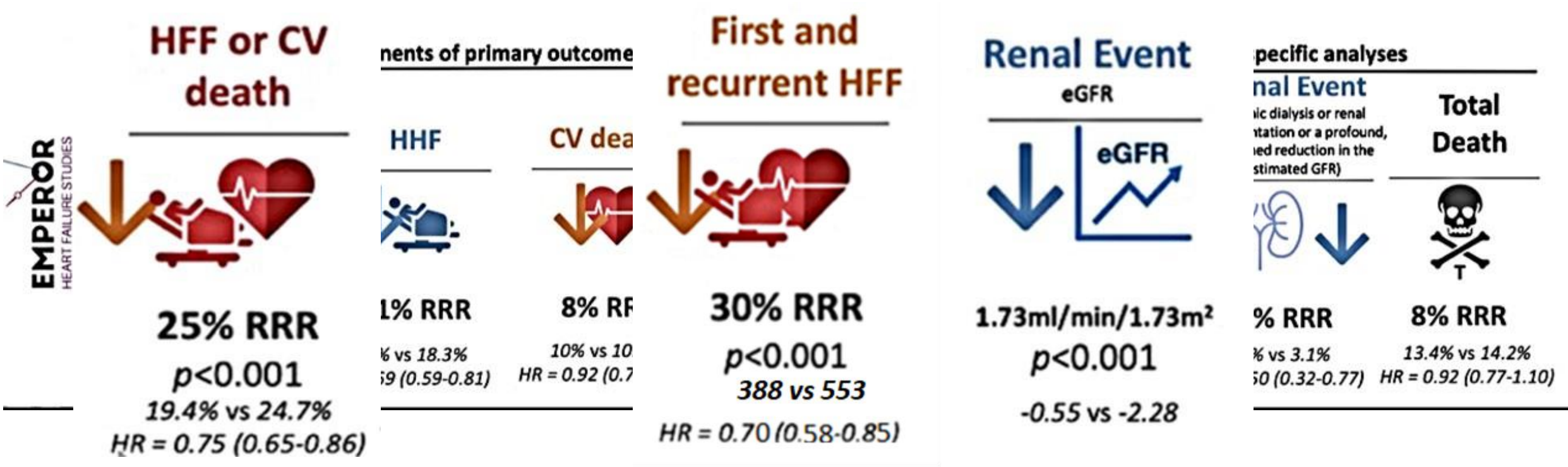
- ☐ Uncomplicated genital tract infection was reported more frequently with empagliflozin than with placebo².
- ☐ Safety concerns that have been seen with other drugs for heart failure (e.g., hypotension, volume depletion, renal dysfunction, bradycardia, and hyperkalemia) were not evident with empagliflozin².

	Empagliflozin (n=1863)	Placebo (n=1863)
Serious adverse events	772 (41.4)	896 (48.1)
Related to cardiac disorder	500 (26.8)	634 (34.0)
Related to worsening renal function	59 (3.2)	95 (5.1)
<i>Selected adverse events of special interest</i>		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Hypoglycemia	27 (1.4)	28 (1.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Urinary tract infections	91 (4.9)	83 (4.5)
Genital tract infections	31 (1.7)	12 (0.6)
Bone fractures	45 (2.4)	42 (2.3)
Lower limb amputations	13 (0.7)	10 (0.5)

1- EMPEROR-Reduced Trial Marta Cobo Marcos M. Packer presentation ESC 2020

2- N. Engl. J. Med 2020 Aug 29.

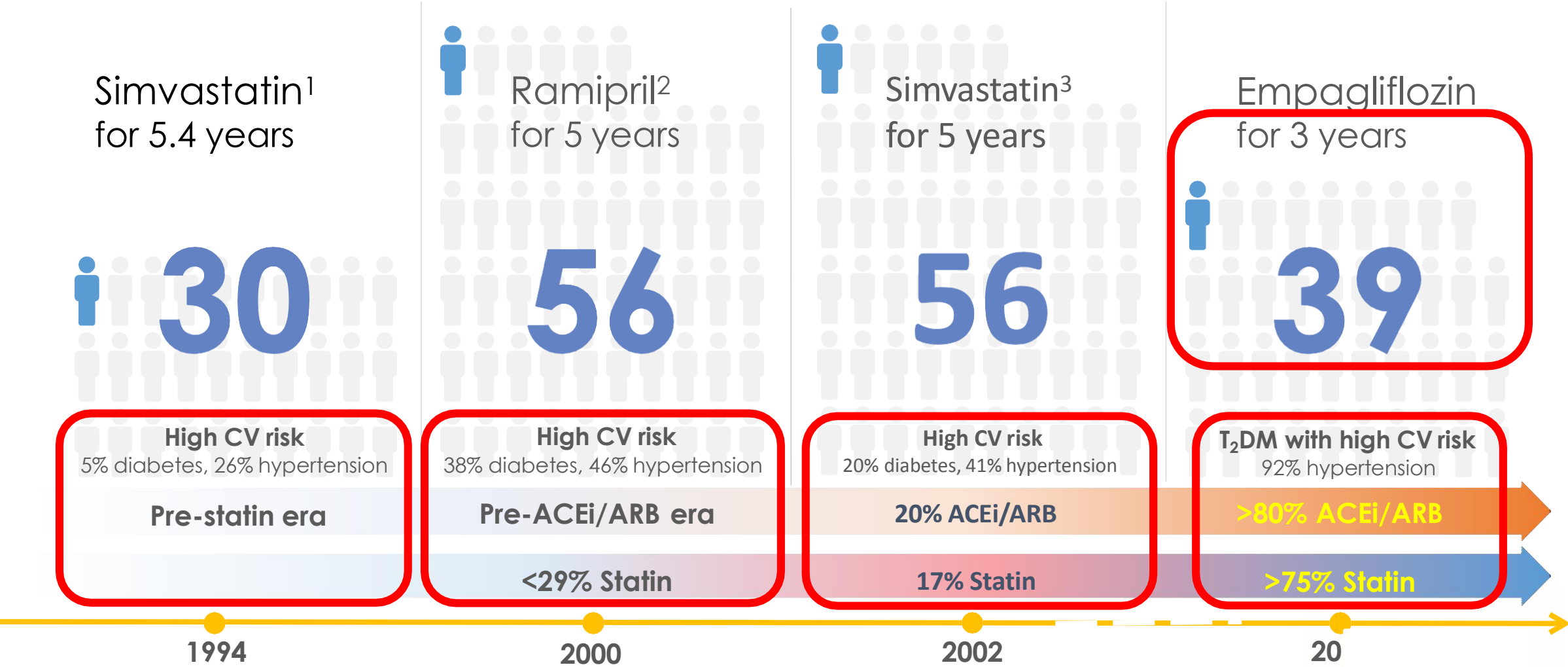
Conclusion¹



- Overall, in this trial, empagliflozin was associated with a lower combined risk of cardiovascular death or hospitalization for heart failure than placebo and with a slower progressive decline in renal function in patients with chronic heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes.

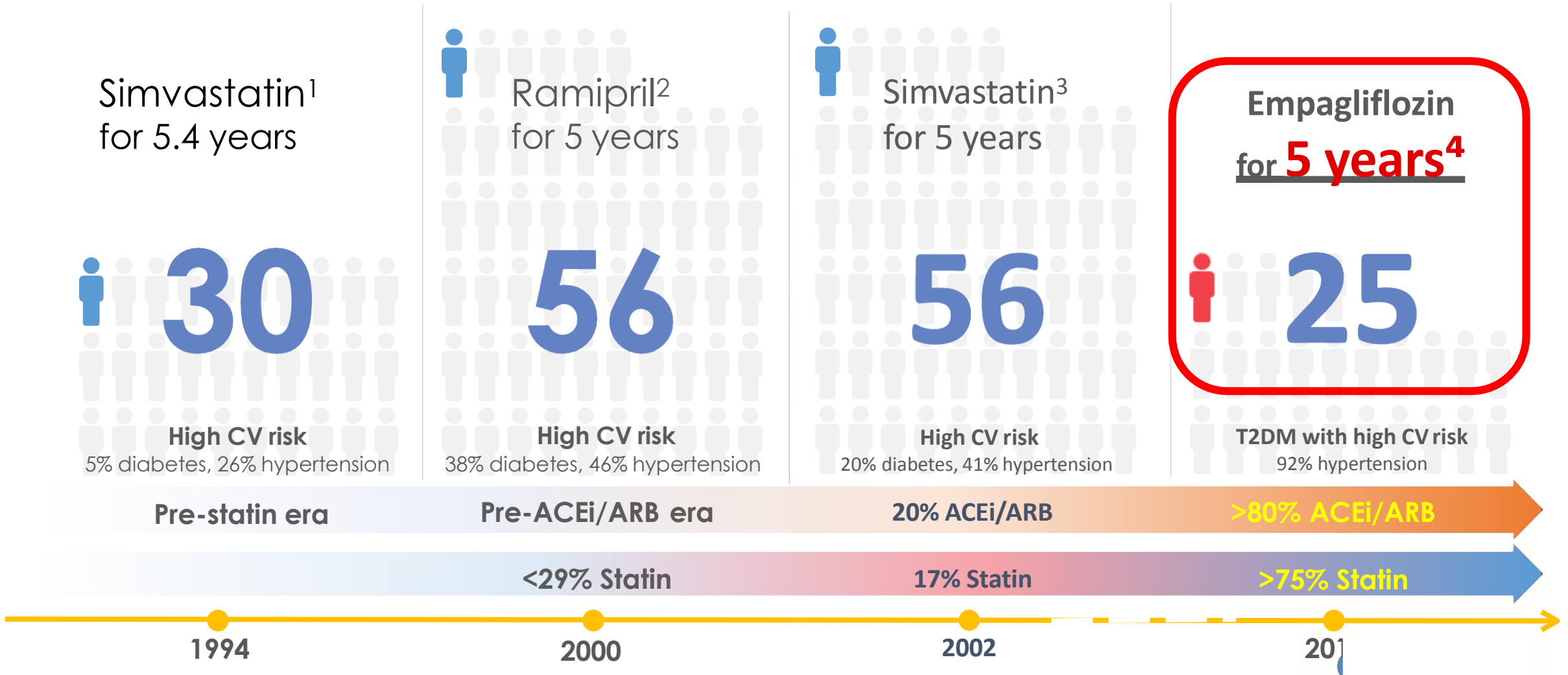
1-N. Engl. J. Med 2020 Aug 29.

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.

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



1. 4S investigators. Lancet 1994; 344: 1383-89.

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Medicine. 2015; 26;373(22):2117-28.

2. HOPE investigators. N Engl J Med 2000;342:145-53, EBM2000;5:47; HOPE investigators. Evid Based Med 2000;5:47.

4. Zinman B et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of

FDC & Initial combination therapy of Empagliflozin and Metformin



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

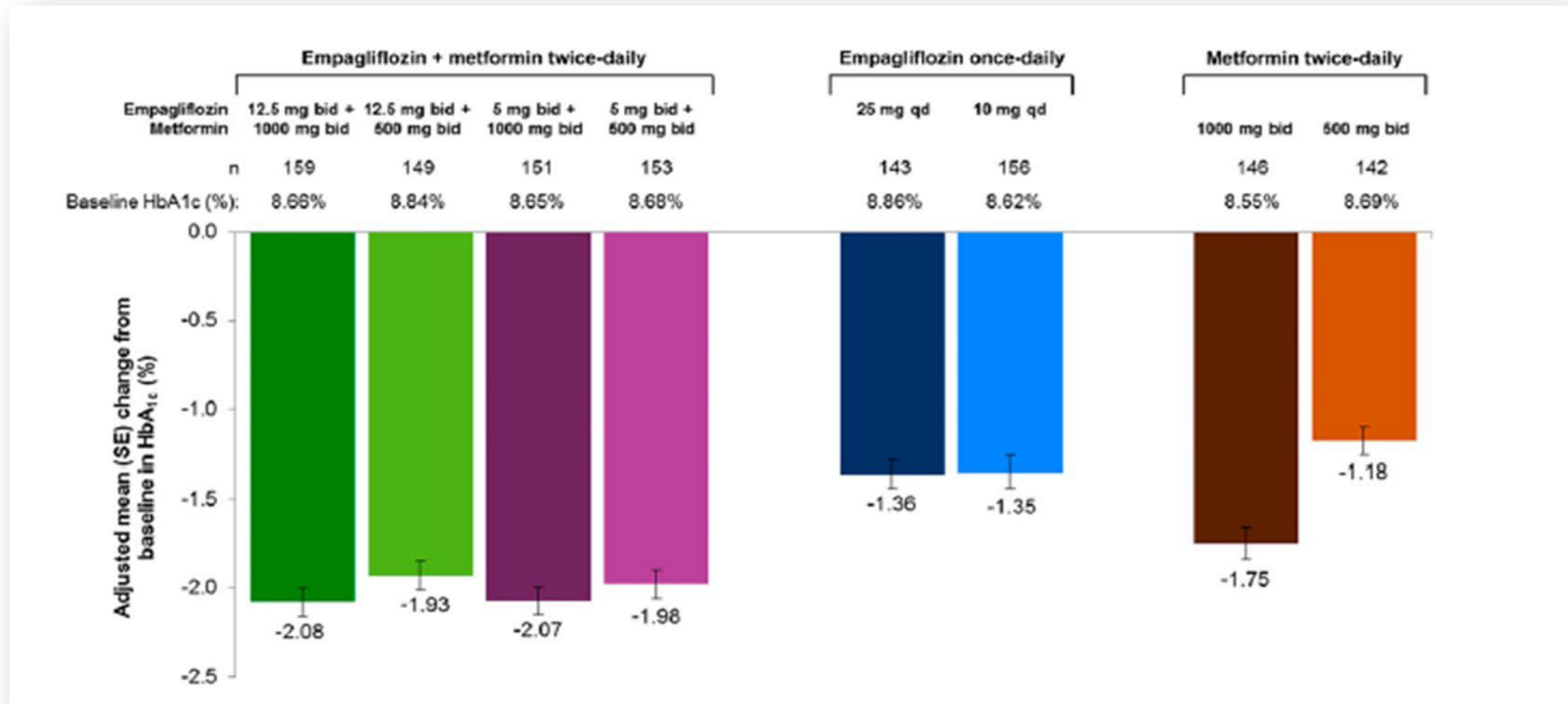
*Samy Hadjadj,¹ Julio Rosenstock,²
Thomas Meinicke,³ Hans J. Woerle,⁴ and
Uli C. Broedl⁴*

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

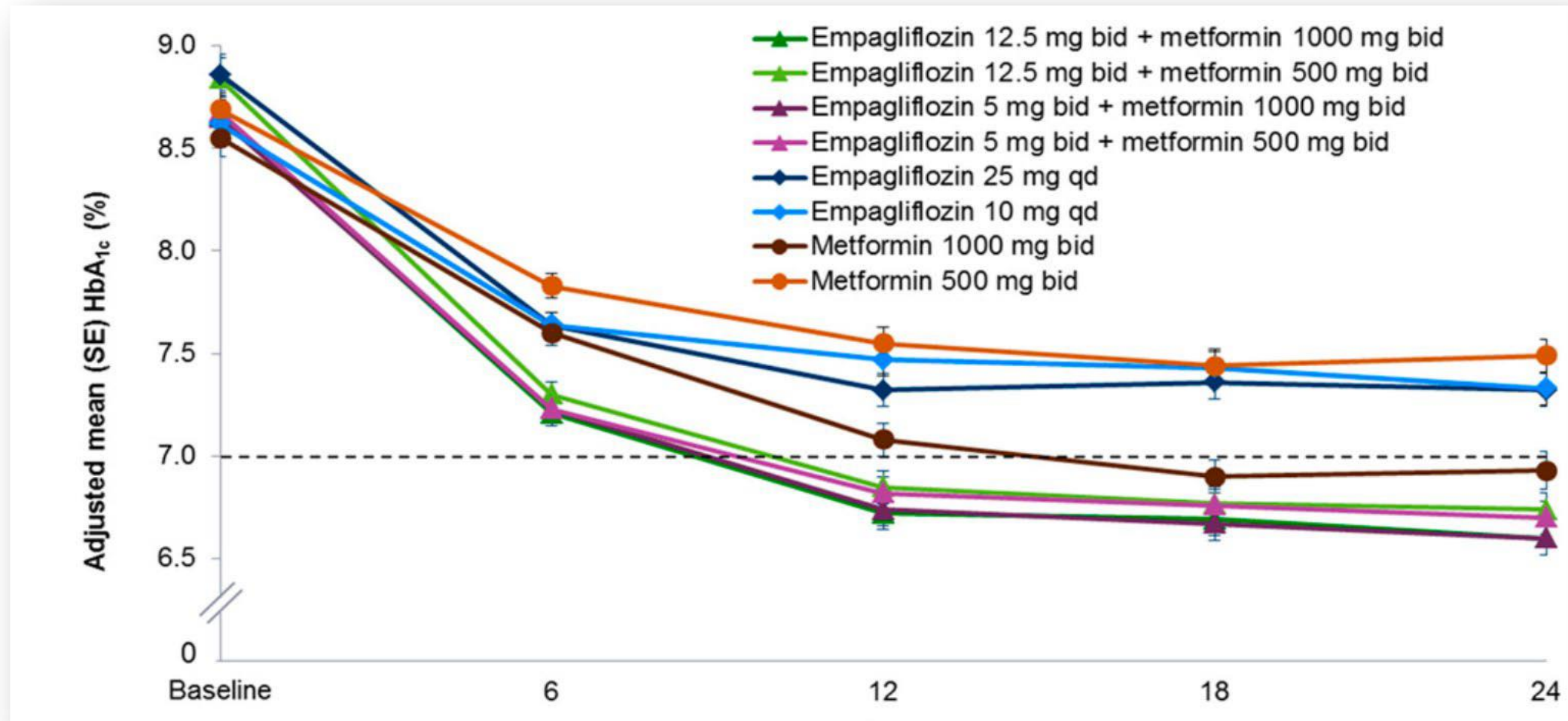
OBJECTIVE:

This study compared the efficacy and safety of initial combinations of empagliflozin + metformin with empagliflozin and metformin monotherapy in patients with type 2 diabetes.

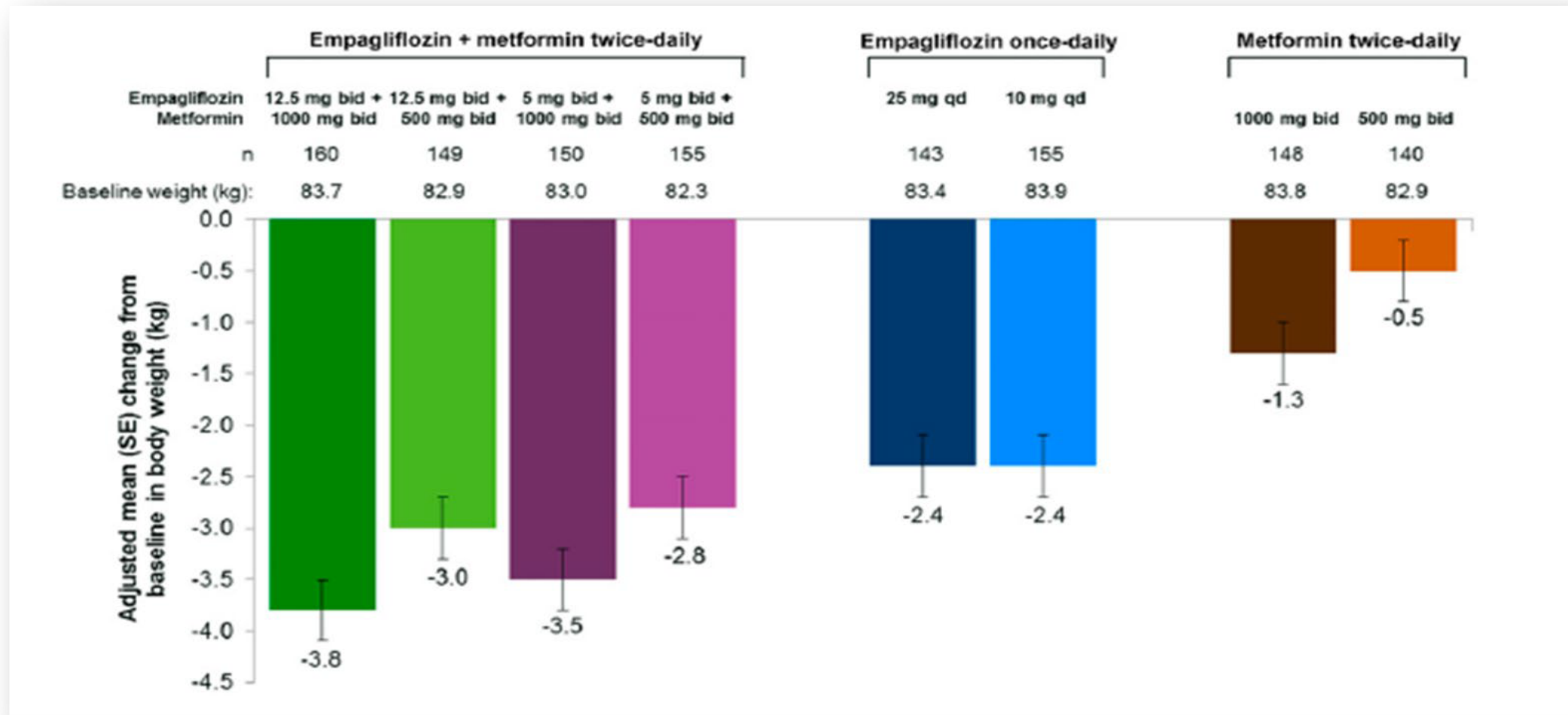
Change from Baseline in HbA1c¹



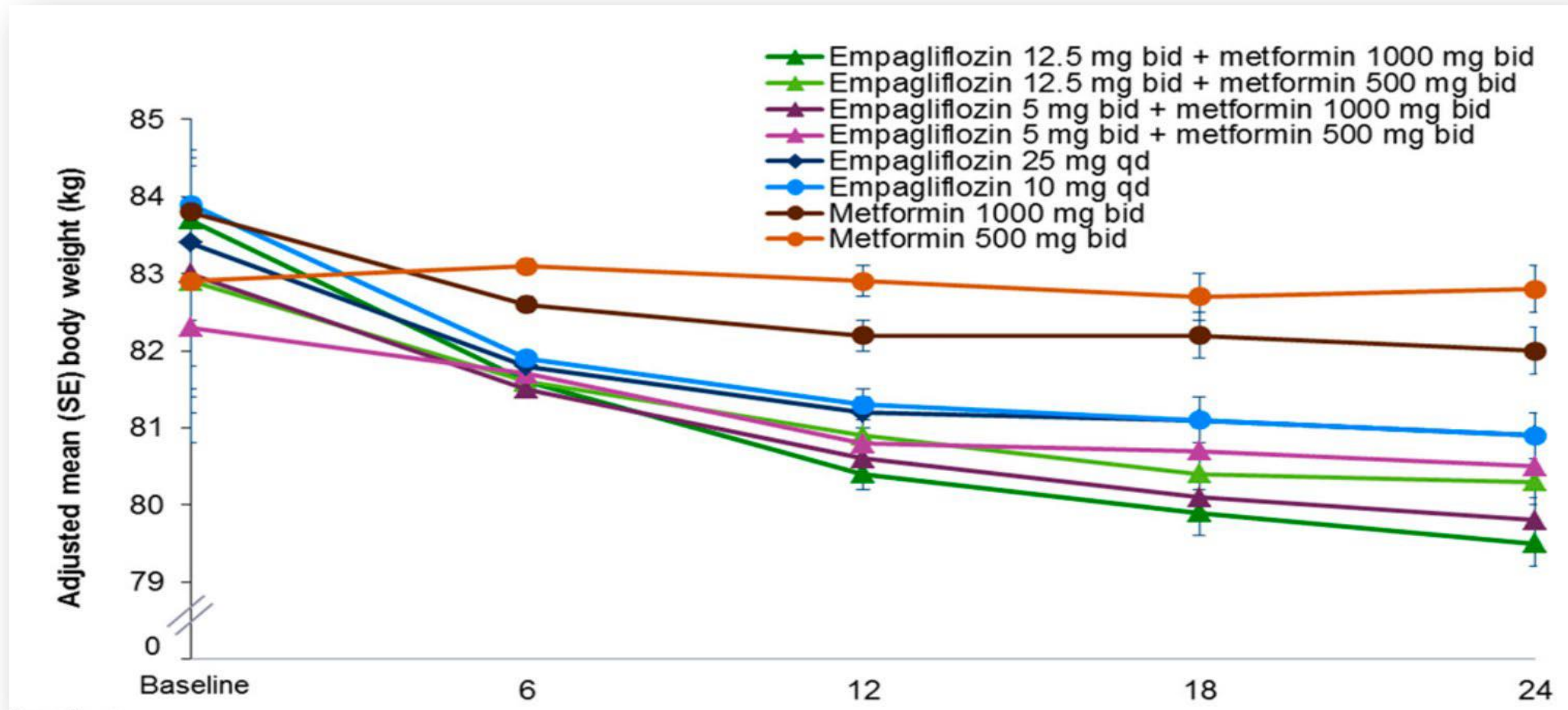
Change from Baseline in HbA_{1c}¹



Change from Baseline in Weight¹



Change from Baseline in Weight¹



conclusion

- Initial combinations of empagliflozin + metformin for 24 weeks significantly reduced HbA1c versus empagliflozin once daily and metformin twice daily, without increased hypoglycemia, reduced weight versus metformin twice daily, and were well tolerated.

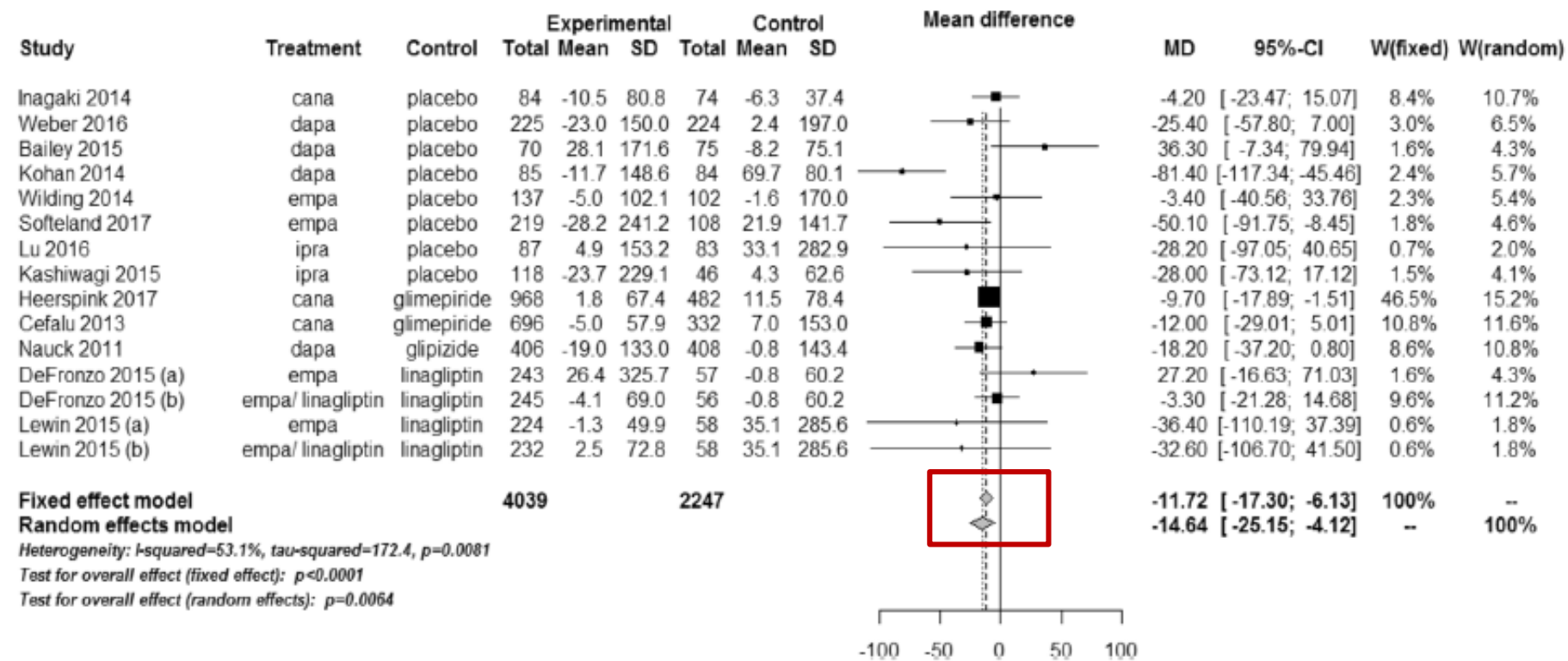
Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Jae Hyun Bae¹, Eun-Gee Park², Sunhee Kim², Sin Gon Kim¹, Seokyoung Hahn^{3,4} & Nam Hoon Kim¹

Objective:

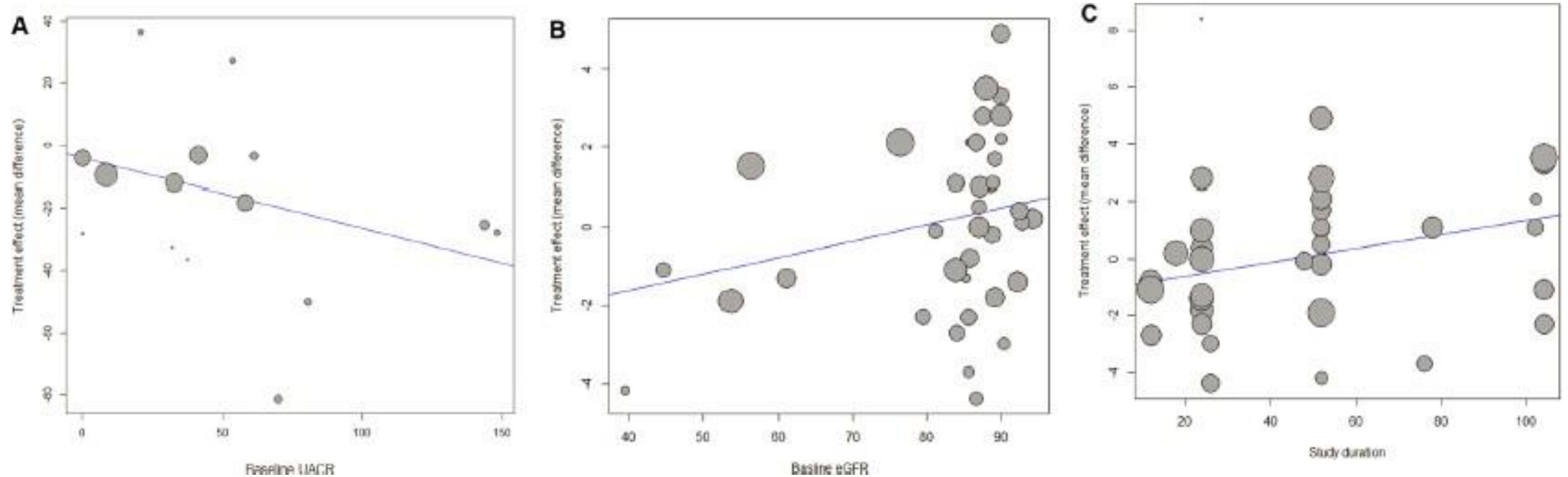
This study was conducted to investigate the effects of sodium-glucose cotransporter 2 (SGLT2) inhibitors on individual renal outcomes in patients with type 2 diabetes¹.

Weighted mean differences in changes in UACR from baseline (mg/g) for SGLT2i versus placebo or other antidiabetic drugs¹



UACR,urine albumin-to-creatinine ratio; CI, confidence interval; MD, mean difference; SD, standard deviation; W, weight.

Meta-regression of changes in (UACR*) and (eGFR) for SGLT2 inhibitors versus placebo or other antidiabetic drugs¹



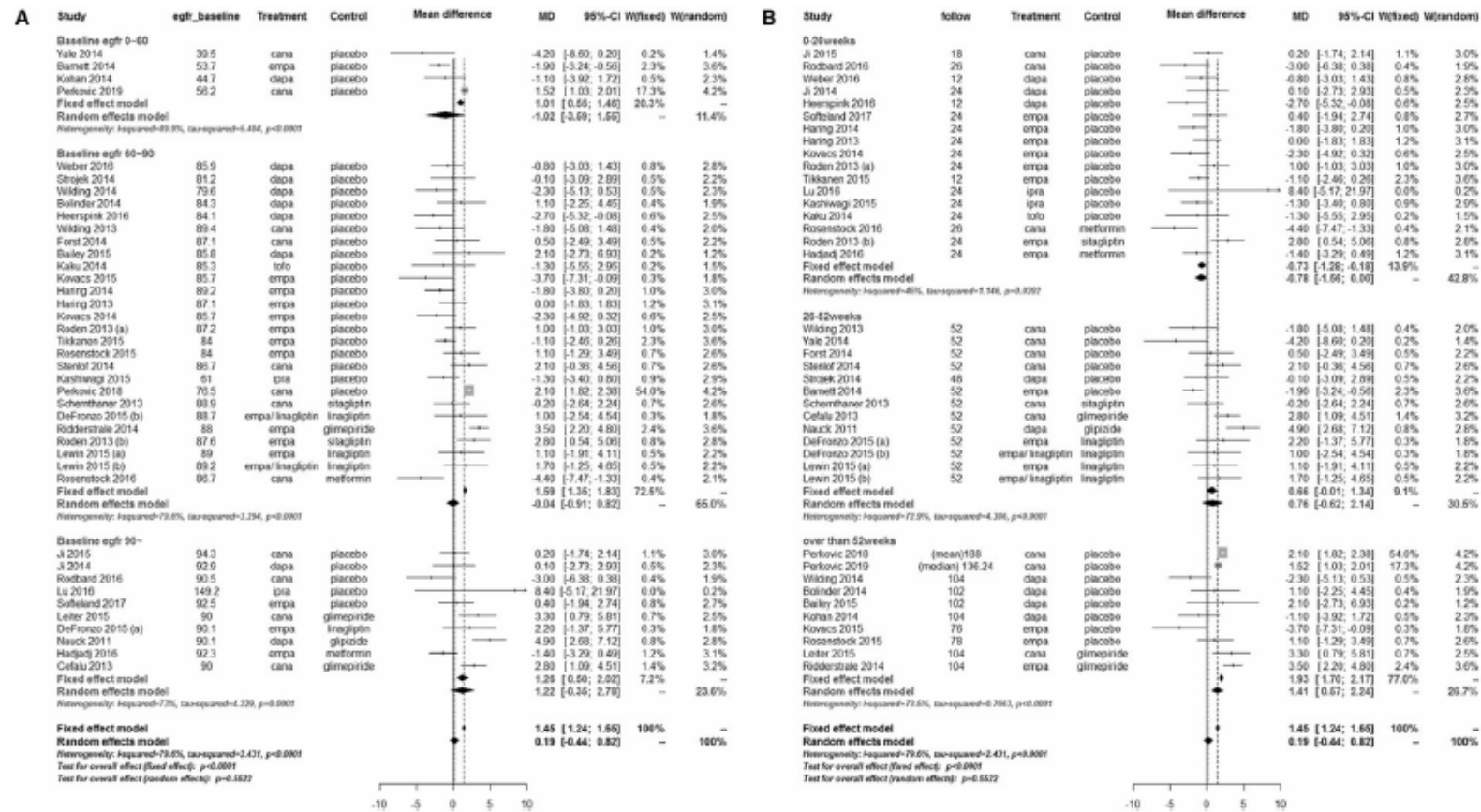
(A) Changes in UACR according to baseline UACR.

(B) Changes in eGFR according to baseline eGFR

(C) Changes in eGFR according to treatment duration.

UACR,urine albumin-to-creatinine ratio

Weighted mean differences in eGFR from baseline for SGLT2 inhibitors versus placebo or other antidiabetic drugs¹



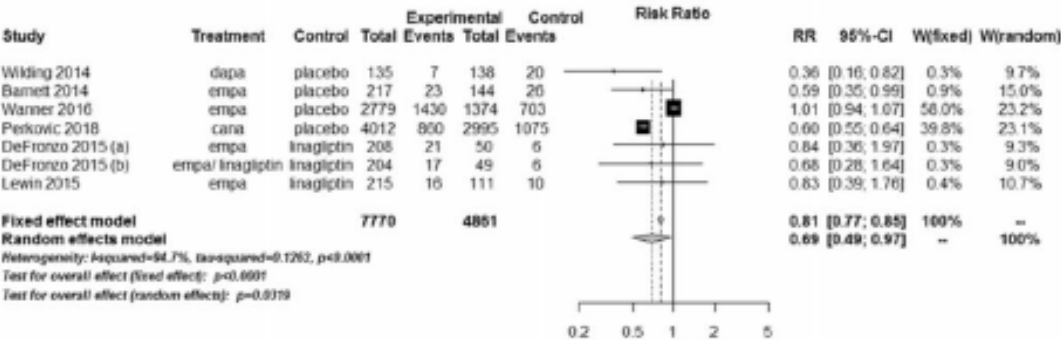
(A) According to baseline estimated glomerular filtration rate

(B) According to treatment duration

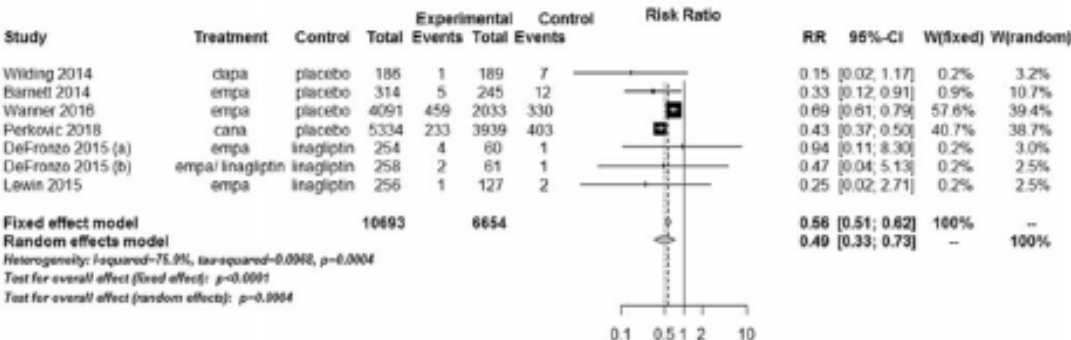
CI, confidence interval; MD, mean difference; SD, standard deviation; W, weight.

Relative risks of microalbuminuria, macroalbuminuria, worsening nephropathy, and ESRD for SGLT2 inhibitors versus placebo or other antidiabetic drugs¹

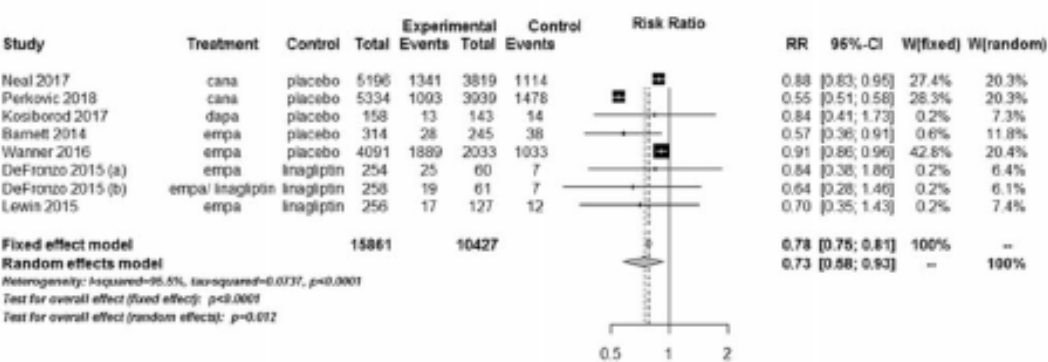
A Microalbuminuria



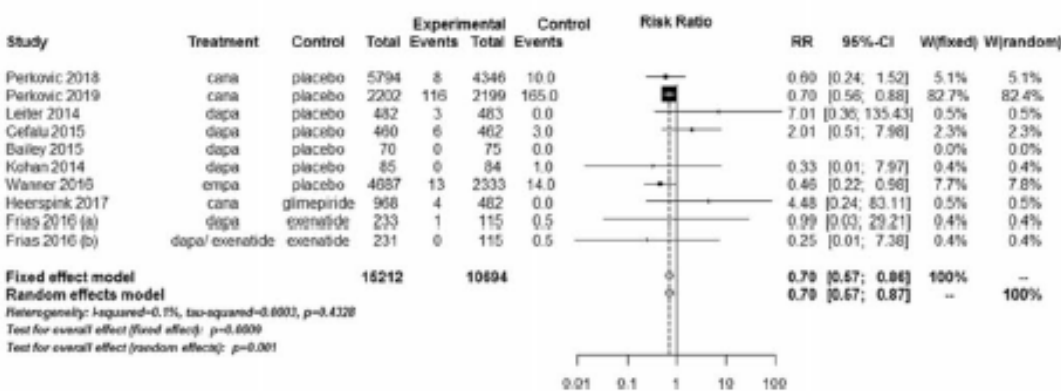
B Macroalbuminuria



C Worsening nephropathy



D End-stage renal disease



CI, confidence interval; RR, relative risk; W, weight.

Discussion

- ☐ SGLT2 inhibitors were associated with a significantly lower risk of development or progression of albuminuria compared with placebo or other antidiabetic drugs in patients with type 2 diabetes¹.
- ☐ The UACR-lowering effects of SGLT2 inhibitors were associated with a higher baseline UACR¹.
- ☐ The overall changes in eGFR were not different between two groups. However, SGLT2 inhibitors slowed the decline in eGFR in patients with a higher baseline eGFR and a longer duration of treatment¹.
- ☐ SGLT2 inhibitor significantly reduced the risk of ESRD compared with controls¹.
- ☐ Considering the direct action of SGLT2 inhibitors on the renal tubules and their favorable effects on BP, body weight, and heart failure, these agents have been suggested theoretically to improve renal outcomes in patients with type 2 diabetes¹.

UACR, urine albumin-to-creatinine ratio; ESRD, end stage renal disease.

Discussion

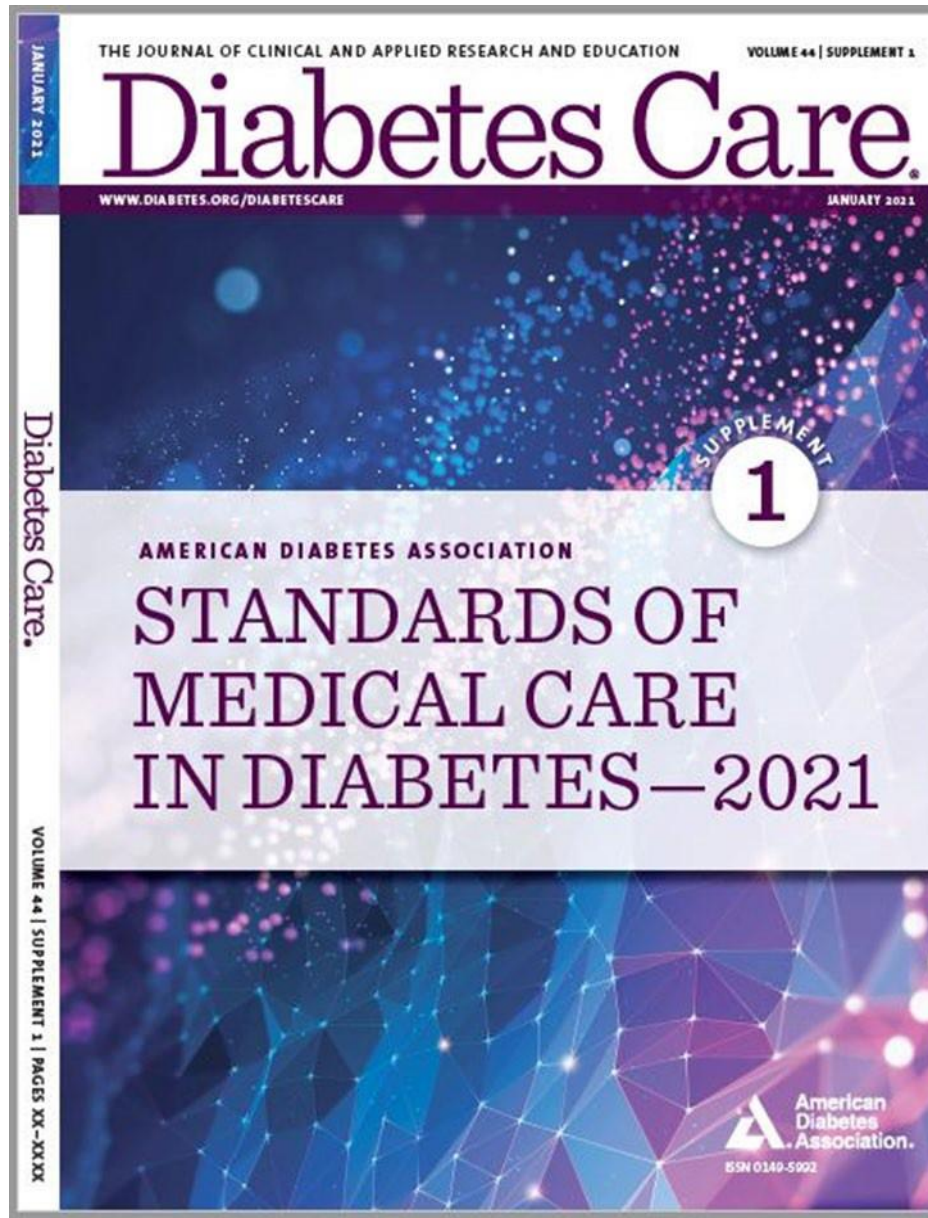
- SGLT2 inhibitors had the renoprotective effects by reducing the risk of albuminuria and ESRD in patients with a wide range of cardiovascular risk¹.
- SGLT2 inhibitors may reduce albuminuria by several mechanisms including a decrease in glomerular hyperfiltration, improvement in tubulointerstitial fibrosis, systemic BP reduction, changes in plasma volume expansion, and a decrease in uric acid levels¹.
- In patients with type 2 diabetes and either microalbuminuria or macroalbuminuria, empagliflozin reduced the UACR independent of changes in hemoglobin A1c (HbA1c), BP, and body weight¹.
- Albuminuria-lowering effects of SGLT2 inhibitors were higher on macroalbuminuria than on microalbuminuria. It could be partly explained by the greater UACR reduction in patients with a higher baseline UACR after SGLT2 inhibitor treatment. Therefore, SGLT2 inhibitors may have beneficial effects on albuminuria in the later stage rather than the early stage of DKD¹.

UACR, urine albumin-to-creatinine ratio; DKD, diabetic kidney disease

Conclusion

- This meta-analysis demonstrated that SGLT2 inhibitors had beneficial effects on the kidney by lowering the risk of albuminuria development or progression and reducing the risk of ESRD compared with placebo or other antidiabetic drugs in patients with type 2 diabetes. In addition, the renoprotective effects of SGLT2 inhibitors were greater in patients with a higher UACR and GFR, and a long duration of treatment¹.

UACR, urine albumin-to-creatinine ratio; ESRD, end stage renal disease.



FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†

NO

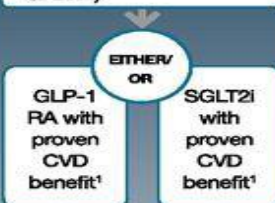
IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW



CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥ 55 years with coronary, carotid, or lower-extremity artery stenosis $>50\%$, or LVH)



If A1C above target

If further intensification is required or patient is unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV benefit and/or safety:

- For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit and vice versa¹
- TZD²
- DPP-4i if not on GLP-1 RA
- Basal insulin³
- SU⁴

+HF

Particularly HFrEF (LVEF $<45\%$)

SGLT2i with proven benefit in this population^{5,6,7}

+CKD

DKD and Albuminuria⁸

NO

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

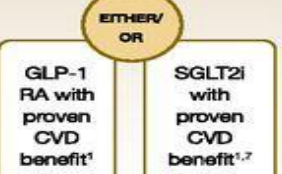
OR

SGLT2i with evidence of reducing CKD progression in CVOTs^{5,8,9}

OR

GLP-1 RA with proven CVD benefit¹ if SGLT2i not tolerated or contraindicated

For patients with TZD and CKD² (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events



COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA



If A1C above target

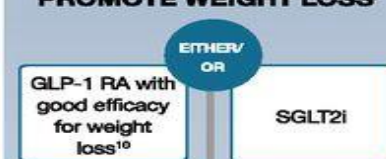
Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU⁴ OR basal insulin:

- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia⁹

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



If A1C above target

SGLT2i

GLP-1 RA with good efficacy for weight loss¹⁰

If A1C above target

If quadruple therapy required, or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of:

- SU⁴ • TZD² • Basal insulin

COST IS A MAJOR ISSUE^{11,12}



If A1C above target

TZD¹²

SU⁴

If A1C above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

- Proven CVD benefit means it has label indication of reducing CVD events
- Low dose may be better tolerated though less well studied for CVD effects
- Degludec or U-100 glargine have demonstrated CVD safety
- Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
- Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
- Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.

- Proven benefit means it has label indication of reducing heart failure in this population
- Refer to Section 11: Microvascular Complications and Foot Care
- Degludec / glargine U-300 < glargine U-100 / detemir < NPH Insulin
- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
- If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
- Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ESC 2019

European Society of Cardiology Guideline



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)

Cardiovascular risk categories in patients with diabetes¹

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

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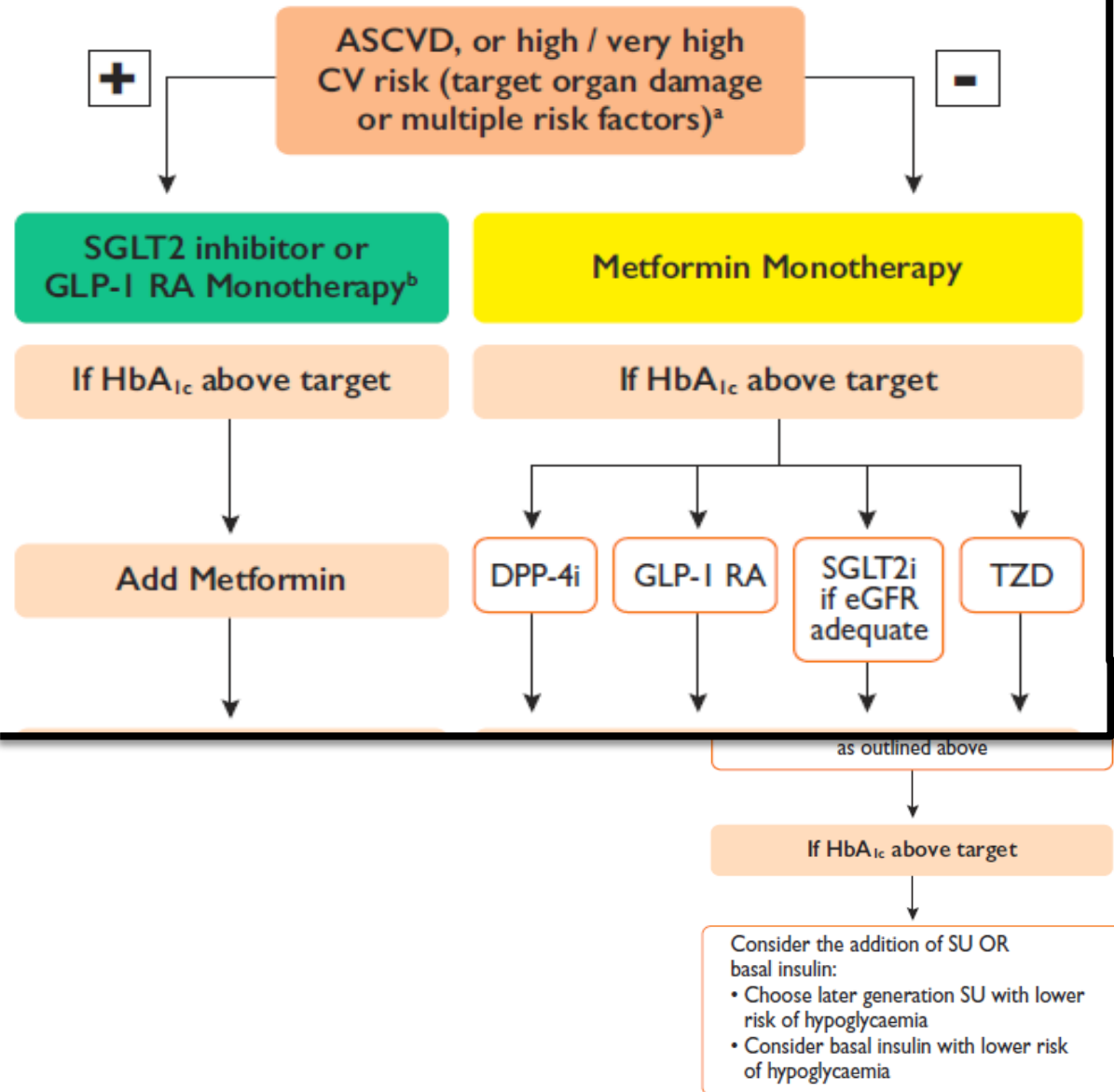
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

^aModified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.²⁷

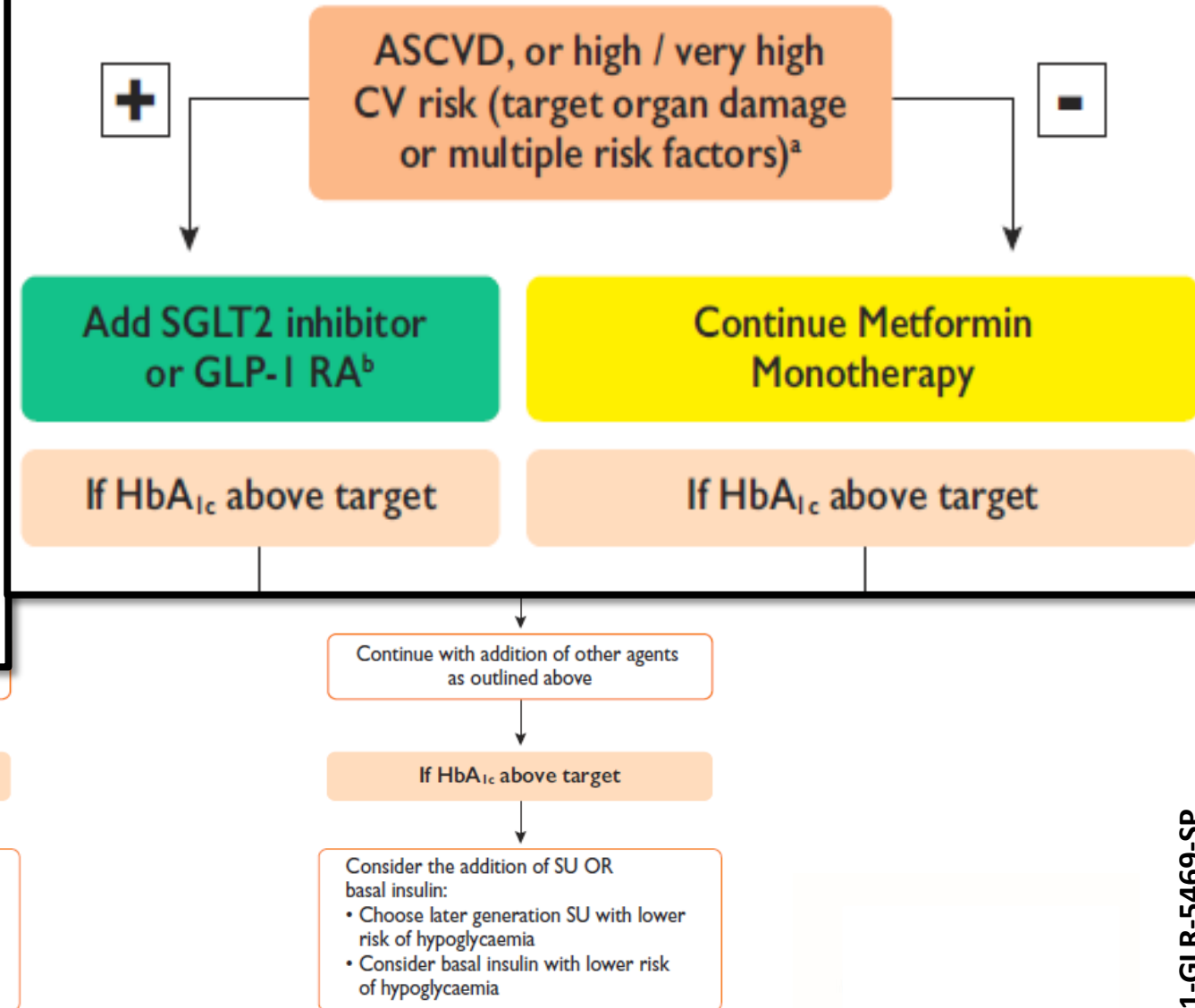
^bProteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy.

^cAge, hypertension, dyslipidemia, smoking, obesity.

A Type 2 DM - Drug naïve patients



B Type 2 DM - On metformin



Heart failure and diabetes¹

Key messages

- Patients with pre-DM and DM are at increased risk of developing HF.
- Patients with DM are at greater risk of HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF); conversely, HF increases the risk of DM.
- The coexistence of DM and HF imparts a higher risk of HF hospitalization, all-cause death, and CV death.
- Guideline-based medical and device therapies are equally effective in patients with and without DM; as renal dysfunction and hyperkalaemia are more prevalent in patients with DM, dose adjustments of some HF drugs (e.g. RAAS blockers) are advised.
- First-line treatment of DM in HF should include metformin and SGLT2 inhibitors; conversely, saxagliptin, pioglitazone, and rosiglitazone are not recommended for patients with DM and HF.

Empagliflozin vs. Liraglutide

Agent	Ease of use	Cost	ASCVD	NNT in CVOTs	↓ CKD progression	Use in HF	eGFR<45 ml/min	Glycemic efficacy	Weight loss
Liraglutide ²									
Empagliflozin 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.

2-Marso SP et al,. Liraglutide and cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine. 2016; 28;375(4):311-22.

Administration, Cautions, Side effects, Safety profile

Convenience of a once-daily oral treatment¹

- ☐ Recommended starting dose 10 mg once daily
- ☐ Can be taken with/without food in the morning
- ☐ Dose may be increased to 25 mg once daily
- ☐ Can be used alone or in combination with other common therapies:
 - ☐ A lower dose of insulin or insulin secretagogues (eg, sulphonylureas) may be needed to reduce the risk of hypoglycaemia when empagliflozin is used in combination with these agents

Empagliflozin in Patients with Renal Impairment

- ☐ No dose adjustment is needed if $\text{eGFR} \geq 45 \text{ mL/min/1.73 m}^2$
- ☐ Empagliflozin should not be initiated in patients with an $\text{eGFR} < 45 \text{ mL/min/1.73 m}^2$
- ☐ Discontinue JARDIANCE if eGFR falls persistently below $45 \text{ mL/min/1.73 m}^2$
- ☐ Assess renal function prior to initiating SGLT2 inhibitor treatment and periodically thereafter

Empagliflozin Safety Profile¹

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	

Summary

Favorable effects of empagliflozin:

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

Q a.:->ici
Diabetes



Thank you