

Effects of SGLT 2 inhibitors on Cardiovascular system

- ▶ Dr Nasser Aghamohammadzadeh
 - ▶ Professor of Endocrinology
- ▶ Tabriz University of Medical Sciences



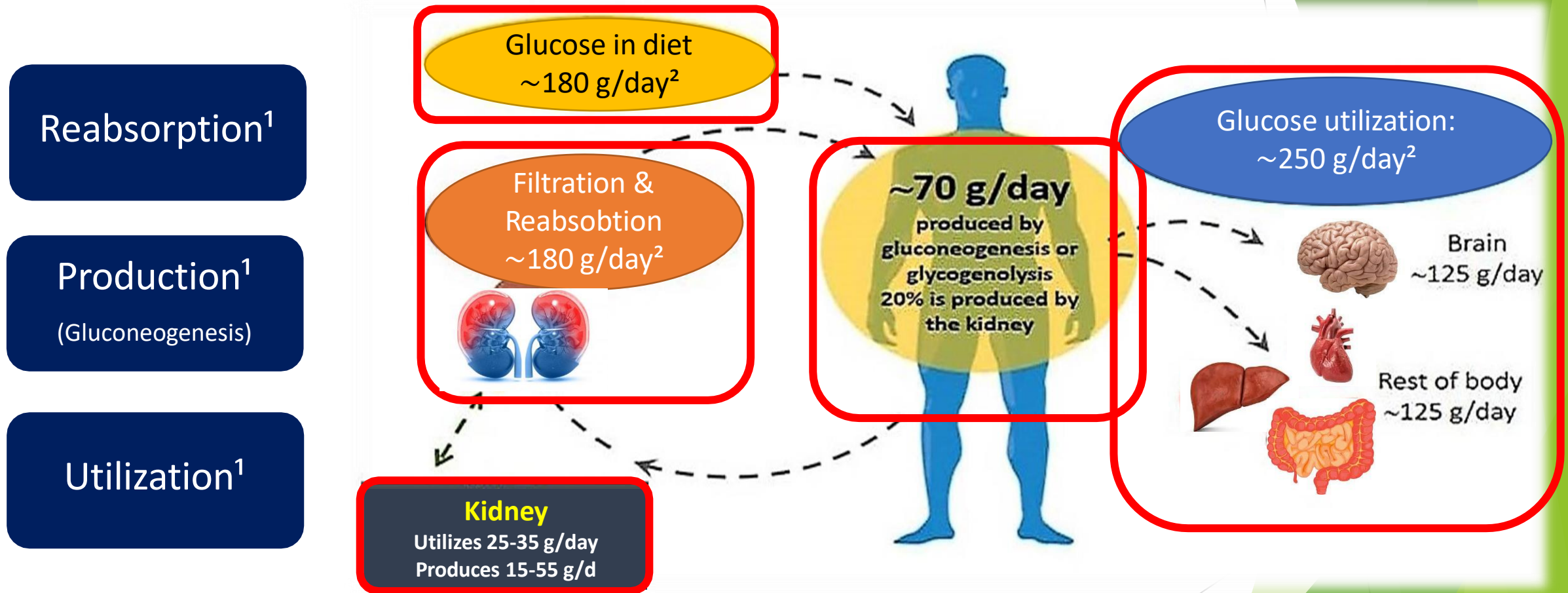
Objectives

- *Brief review of kidney role in glucose homeostasis*
- *SGLT2 & SGLT2 inhibitors*
- *Efficacy Studies*
- *EMPA-REG OUTCOME®*
- *EMPEROR-Reduced trial*
- *Administration, Cautions, Side effects*
- *Conclusion*

Empagluco® | 10
Empagliflozin | 25

Emzip® | 5/1000
12.5/1000
Empagliflozin ⊕ Metformin

Kidney Plays a Significant Role in Glucose Balance

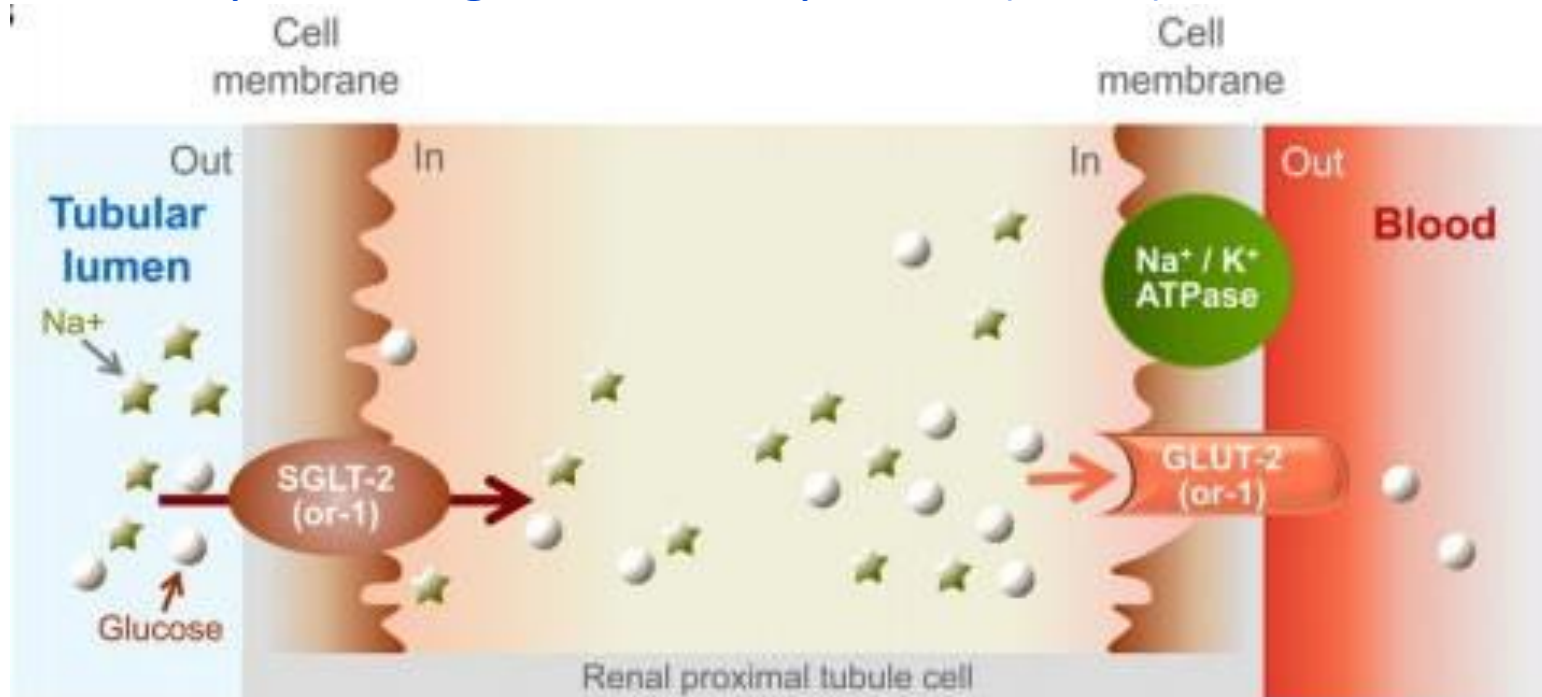


Glucose Transporters:

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

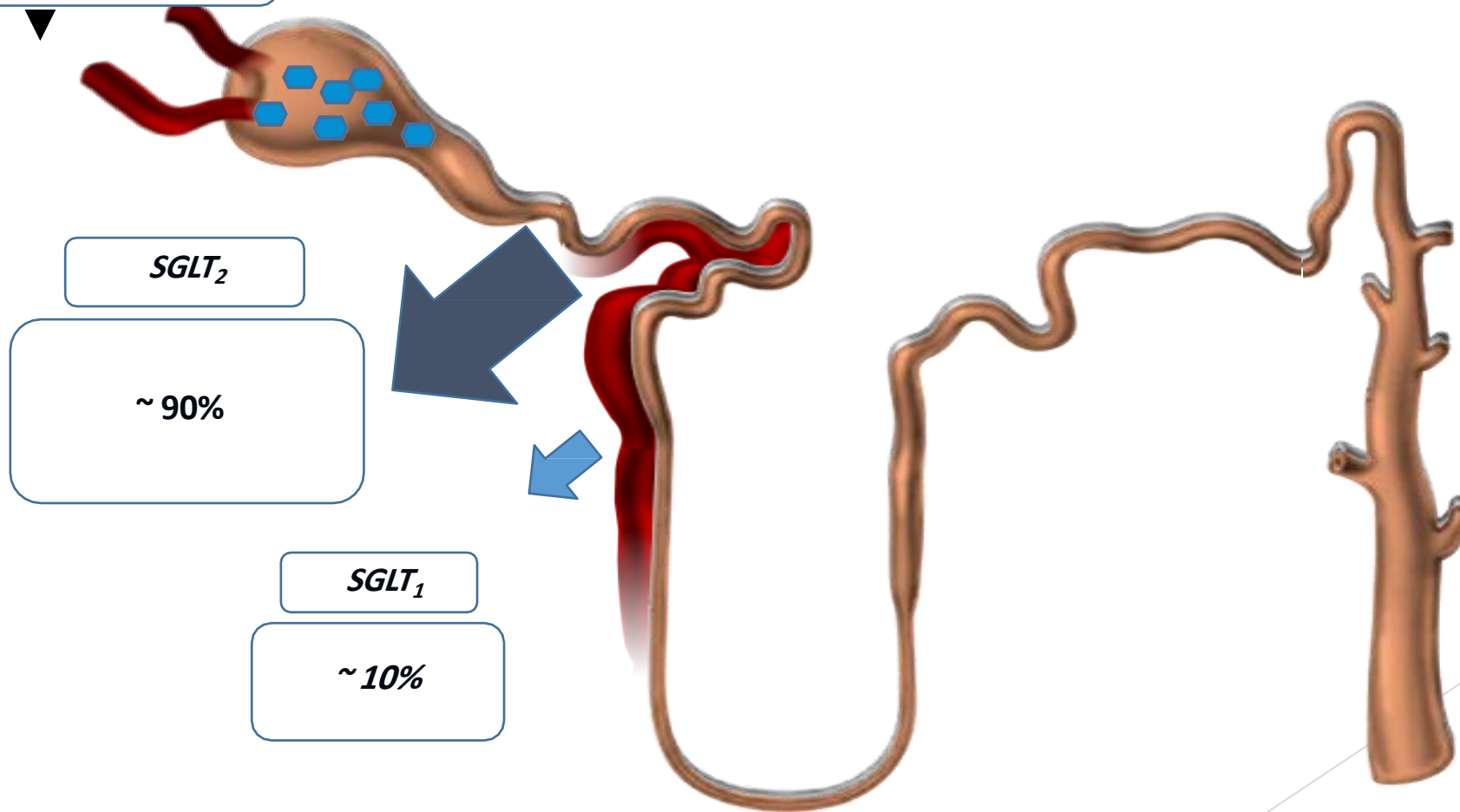
SGLT₂: high capacity, low affinity, mostly in kidney

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

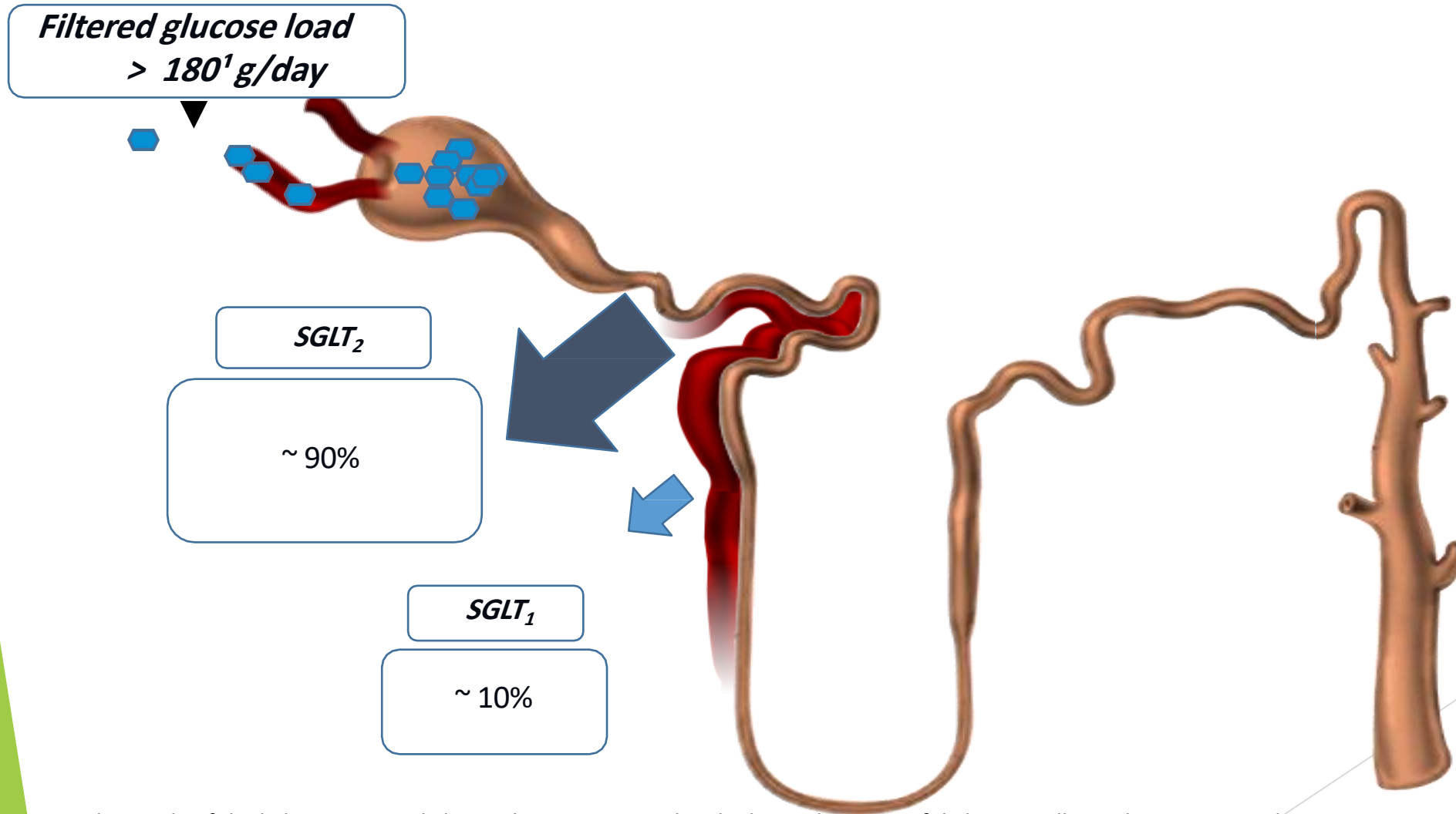
2-Nair S et al., Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism. 2010;95(1):34-42.

Renal glucose re-absorption in healthy individuals

Filtered glucose load 180 g/day¹



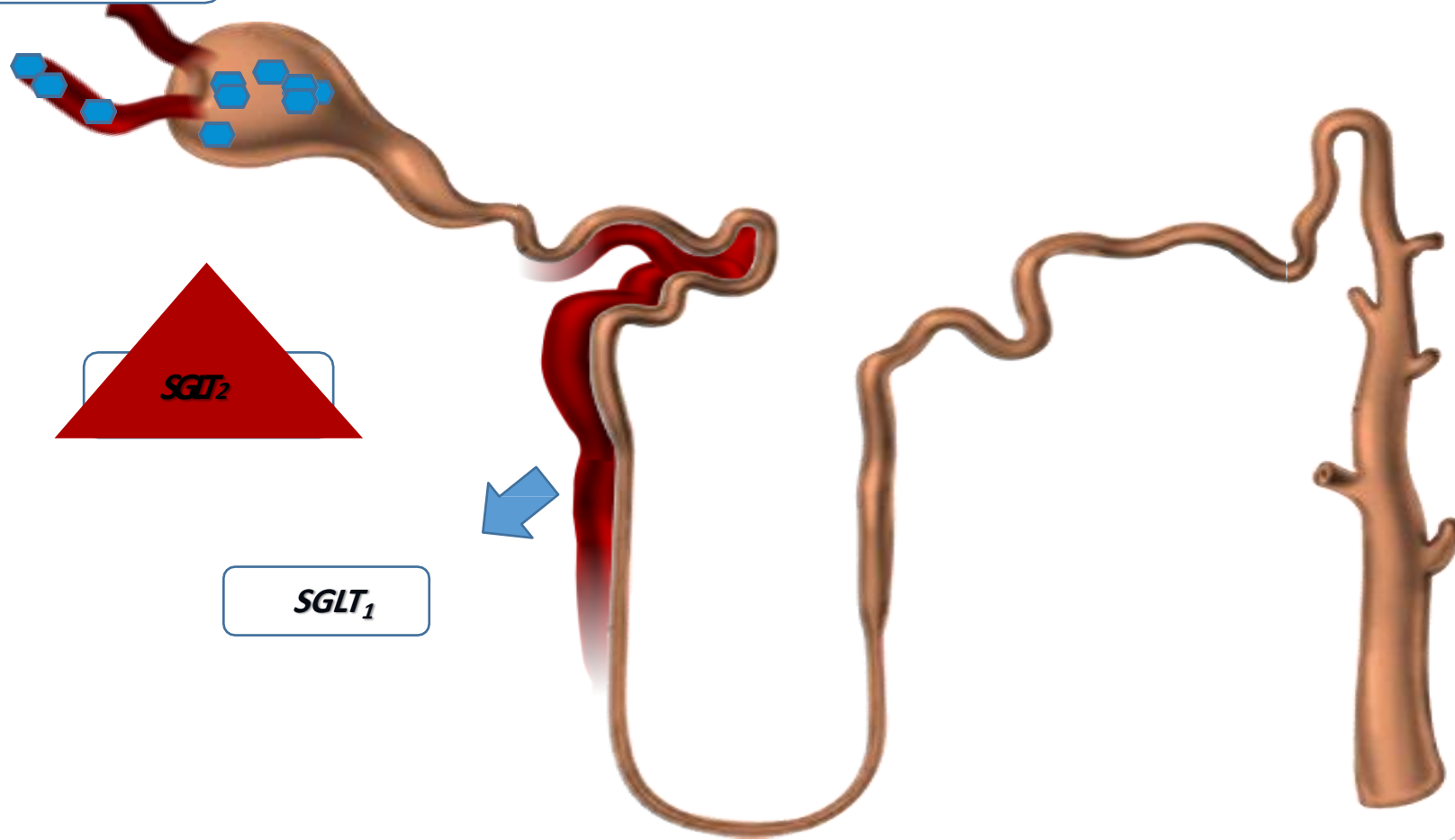
Renal glucose re-absorption in patients with diabetes:



When blood glucose increases above the renal threshold (~ 180 mg/dL), the capacity of the transporters is exceeded, resulting in urinary glucose excretion¹

Urinary glucose excretion via SGLT2 inhibition

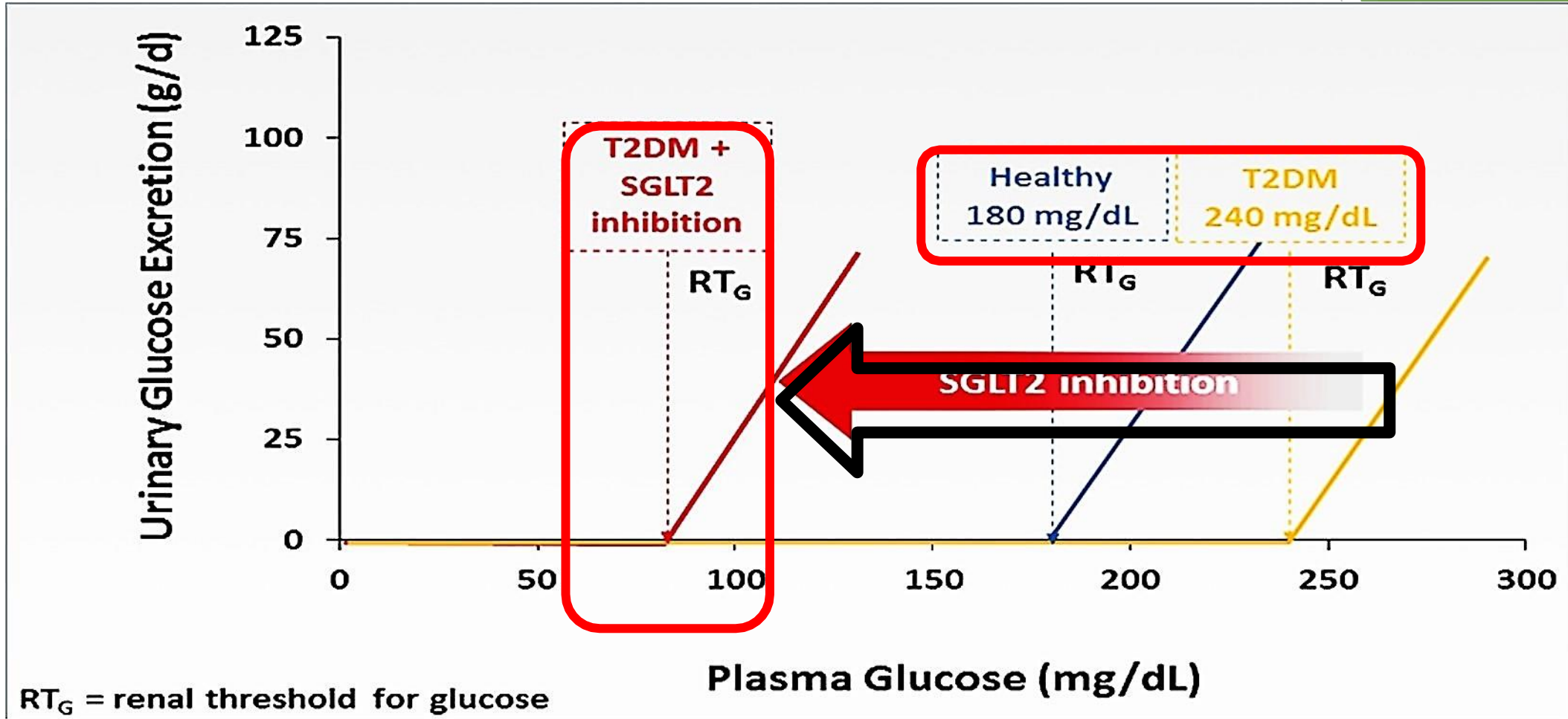
Filtered glucose load
> 180 g/day



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. 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.

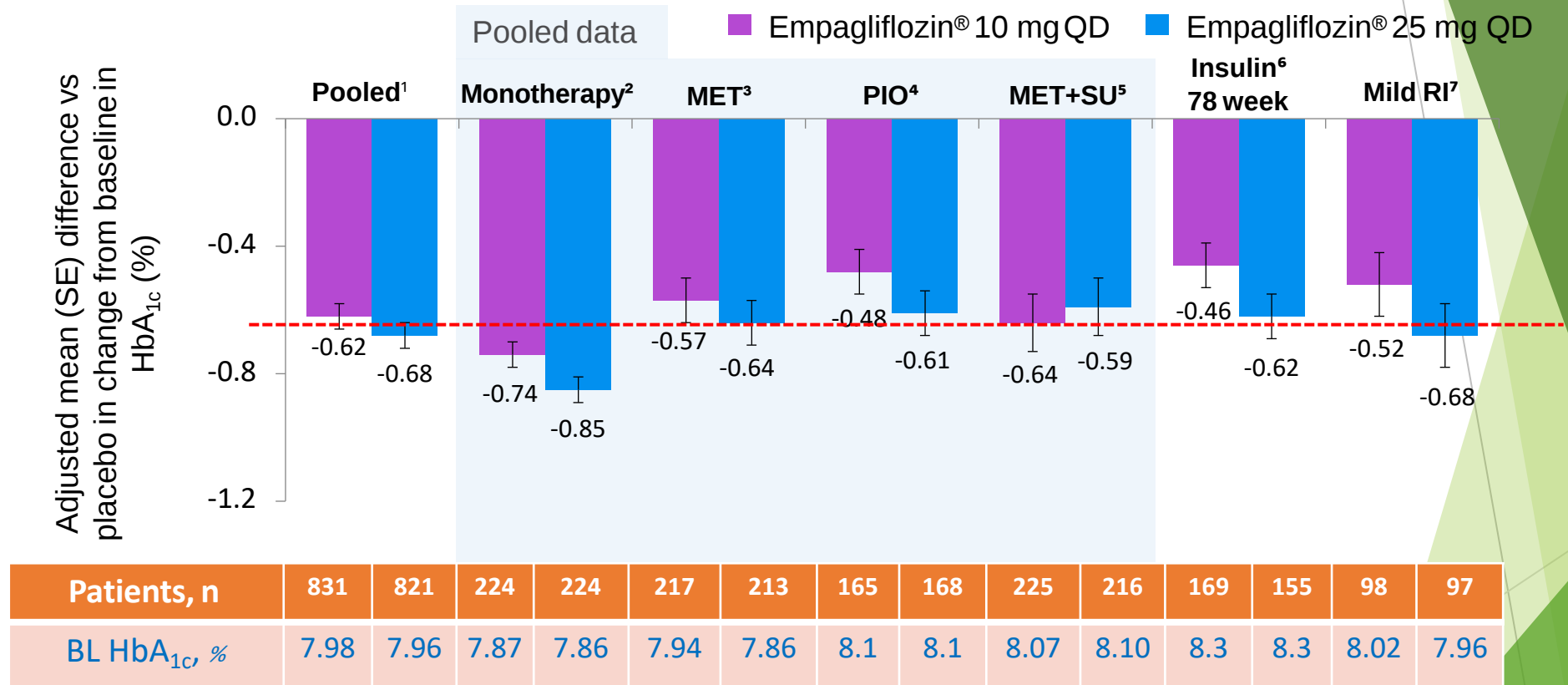
Efficacy Studies

Empagluco[®] | 10
Empagliflozin 25

Emzip[®] | 5/1000
12.5/1000
Empagliflozin ⊕ Metformin

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

Phase III pooled efficacy analysis



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);

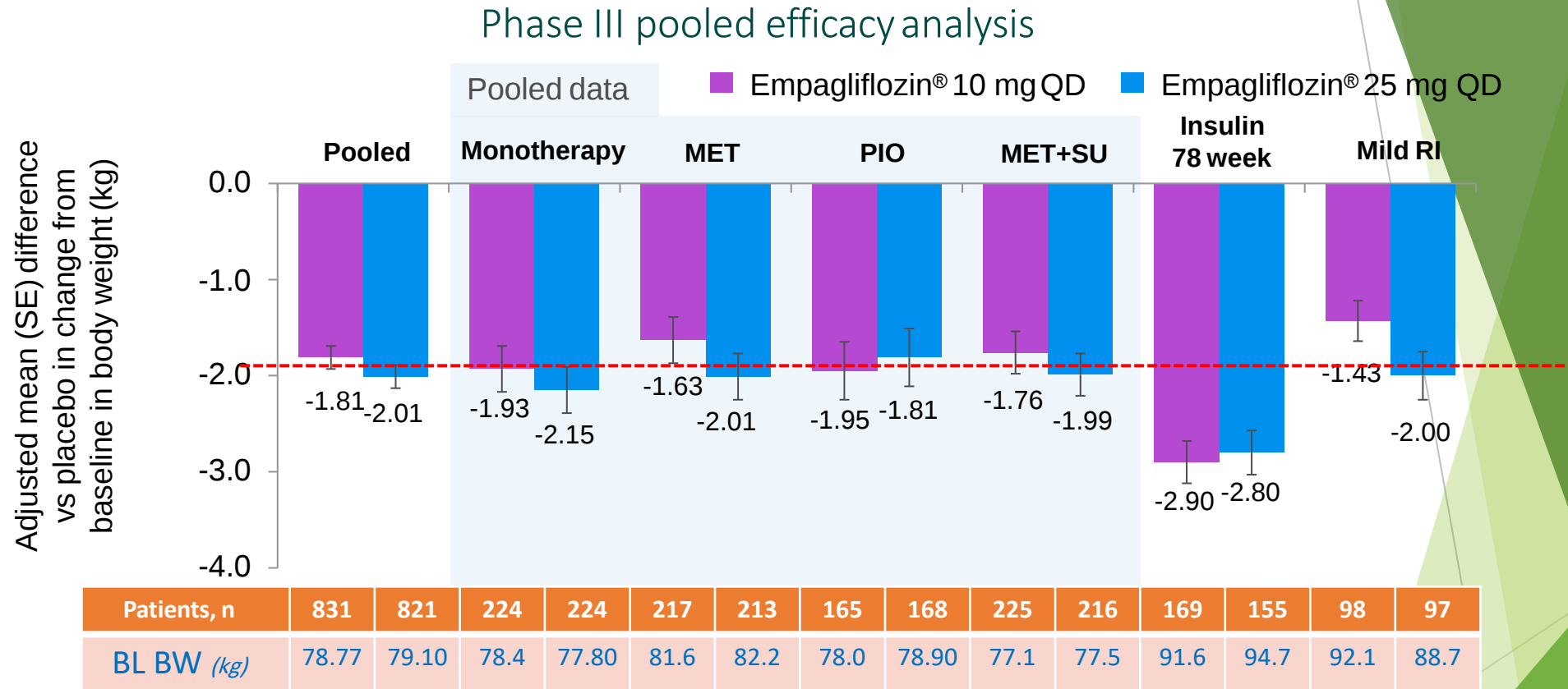
4-Kovacs C, et al. *Diabetes Obes Metab*. 2014;16(2):147–158;

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

6- Rosenstock J, et al. *Diabetologia*. 2013;56(suppl 1):S372 (P913.1);

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

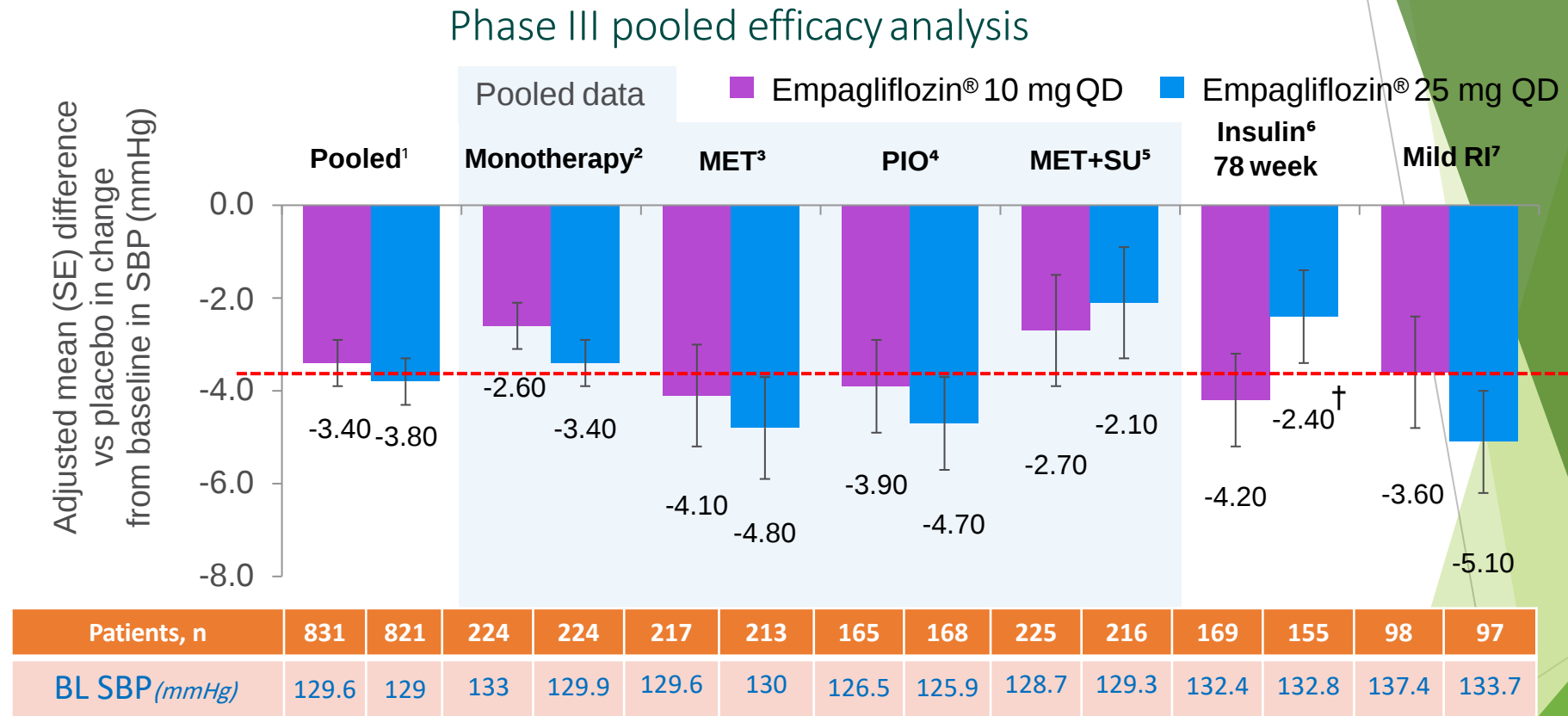
Δ Body Weight Across Different Background Therapy Empagliflozin® vs. Placebo*



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

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 Care*. 2014 (in press);

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

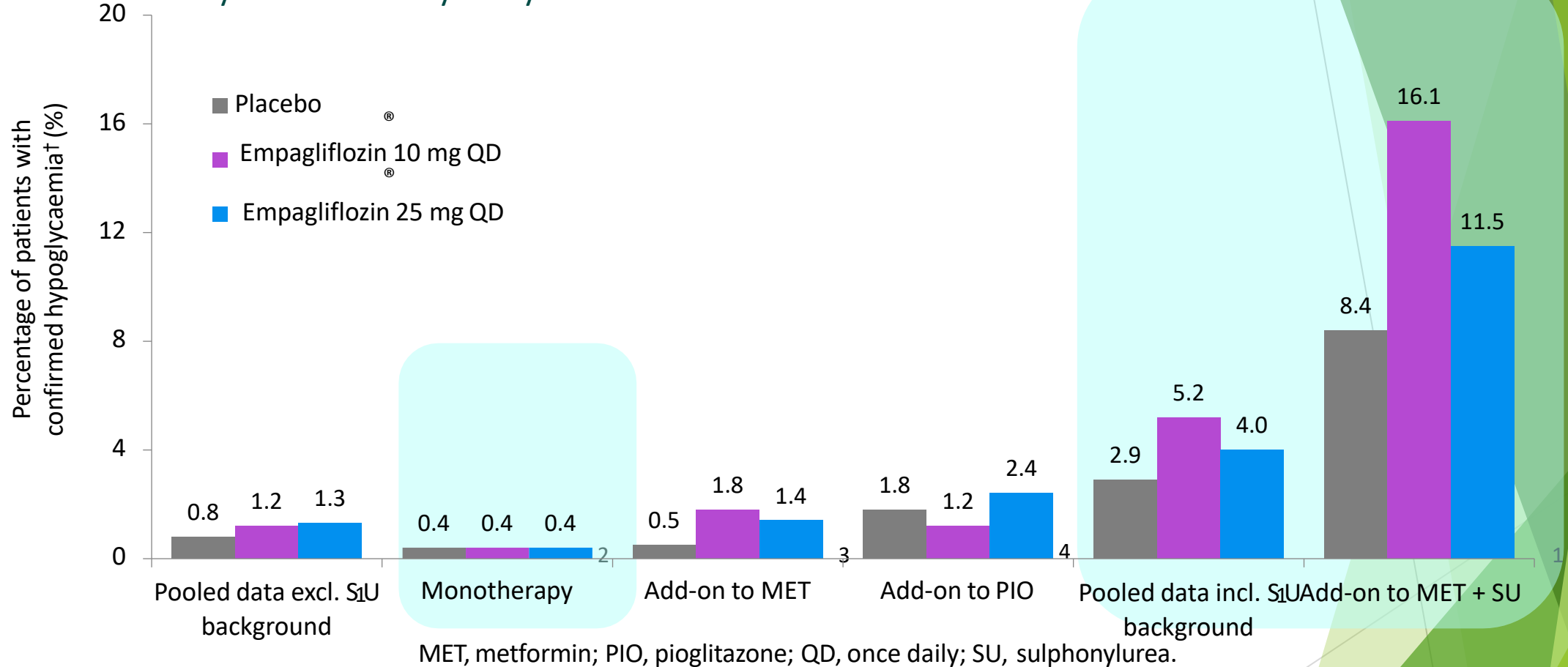
5- Häring H-U, et al. *Diabetes Care*. 2013;36(11):3396–404;

6- Rosenstock J, et al. *Diabetologia*. 2013;56(suppl 1):S372 (P93_14);

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

Hypoglycemic Events

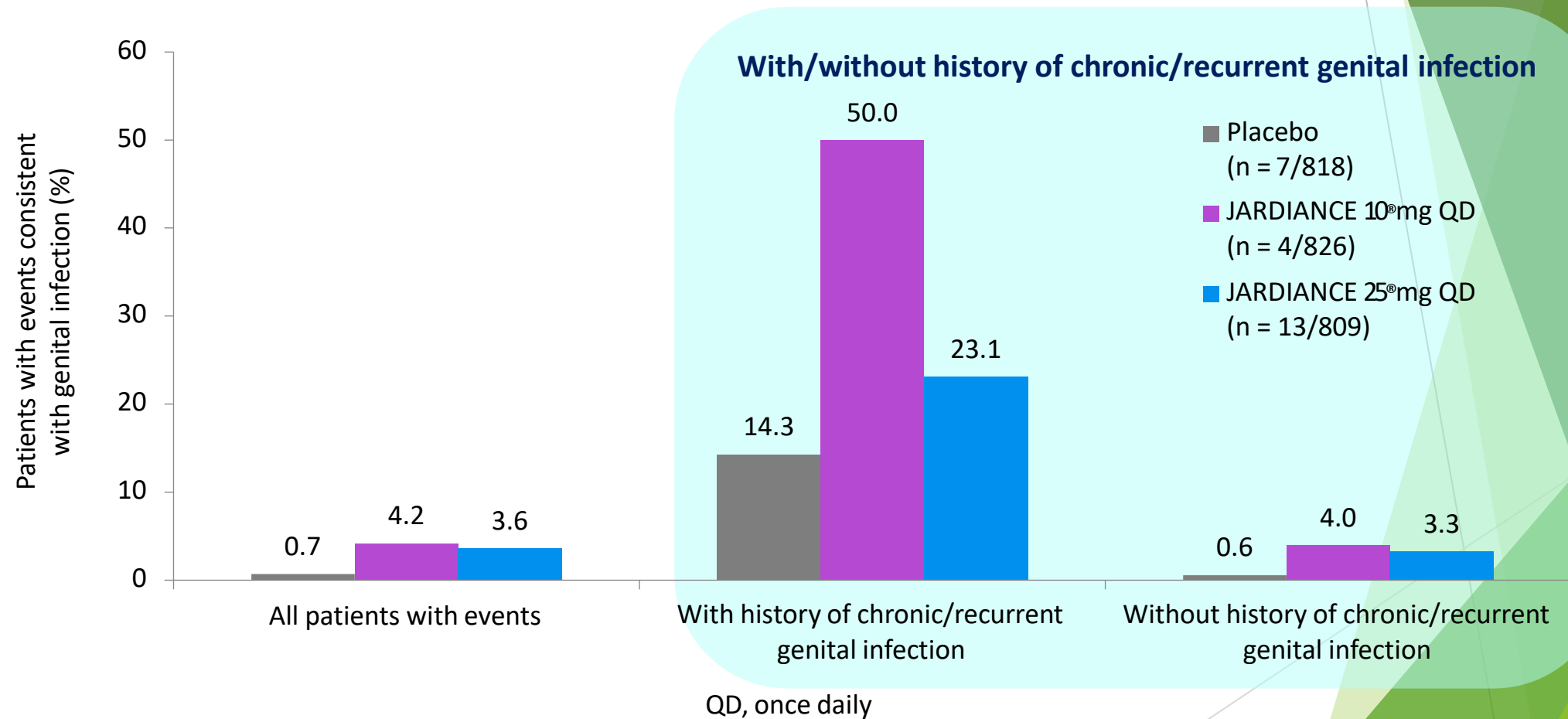
- Phase III safety and tolerability analysis



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

Genital infection stratified by previous history

Phase III pooled[†] safety and tolerability analysis

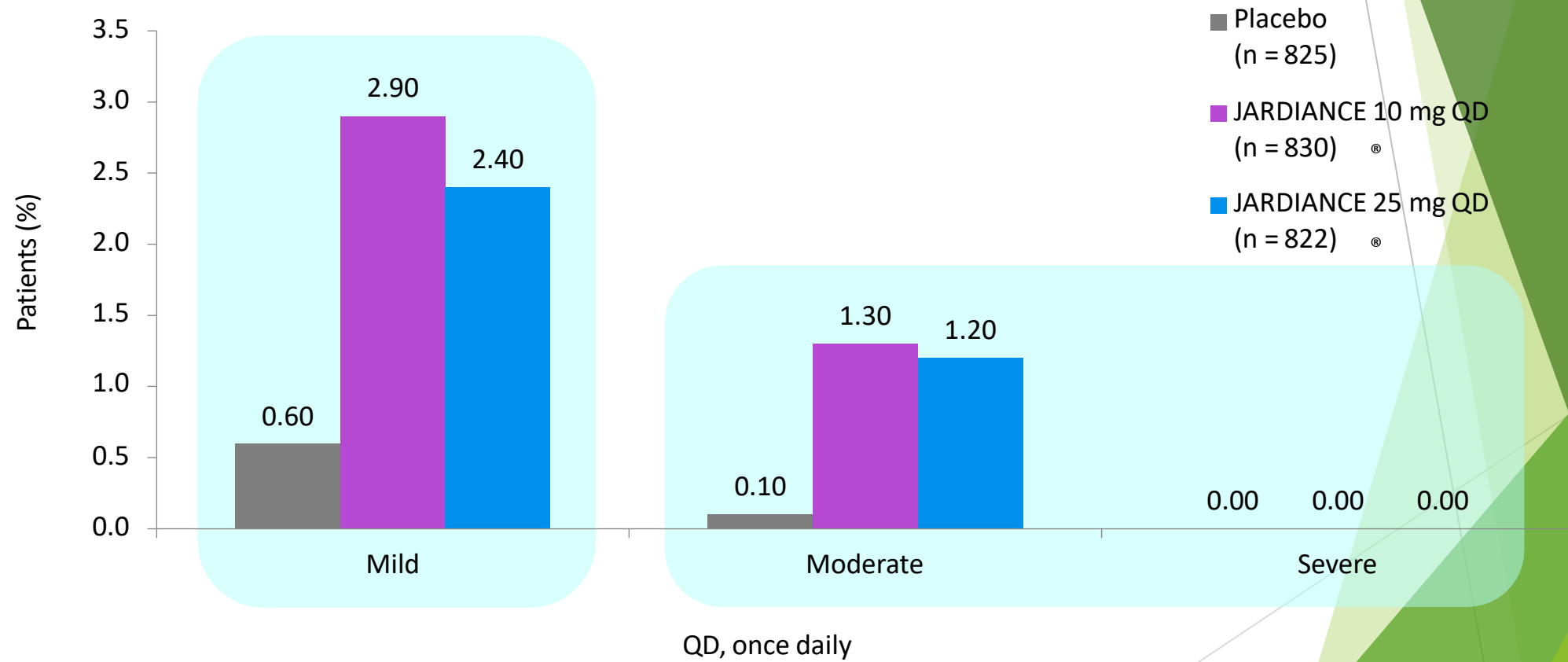


[†]The following studies were included in the pooled analysis:

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 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).

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 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).

EMPA-REG OUTCOME®

Empagluco® | 10
Empagliflozin | 25

Emzip® | 5/1000
Empagliflozin + Metformin | 12.5/1000

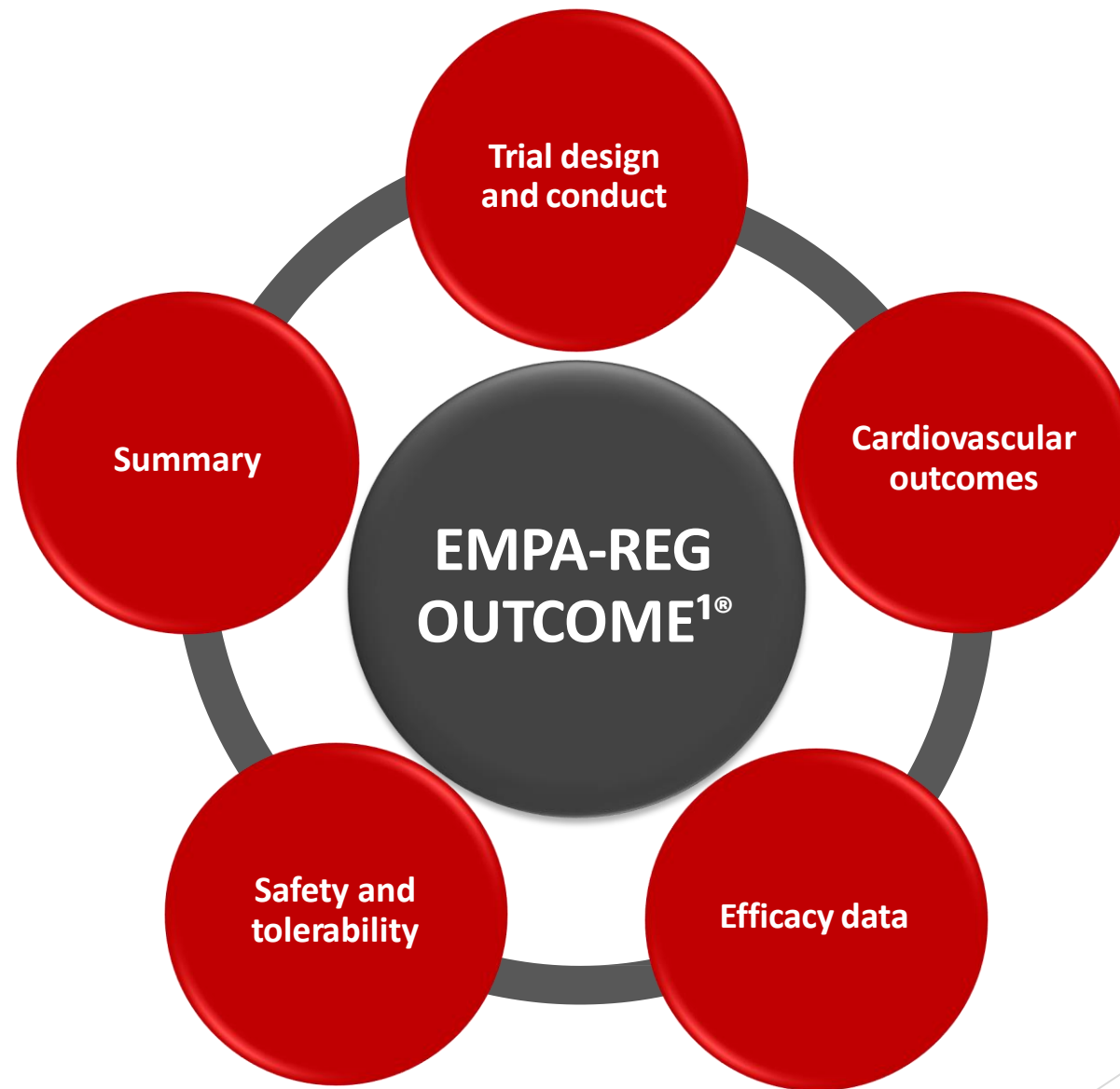
ORIGINAL ARTICLE

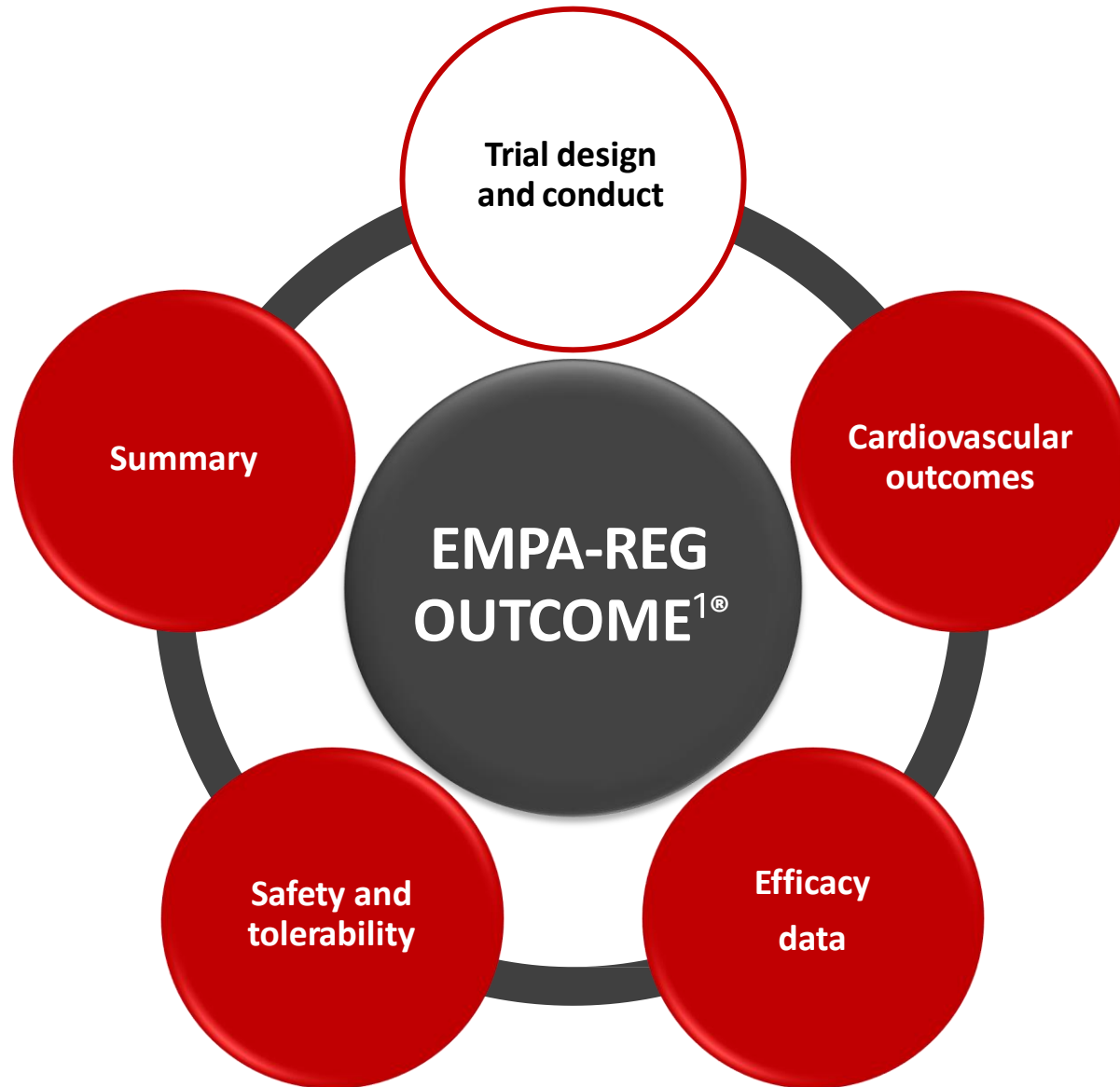
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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**

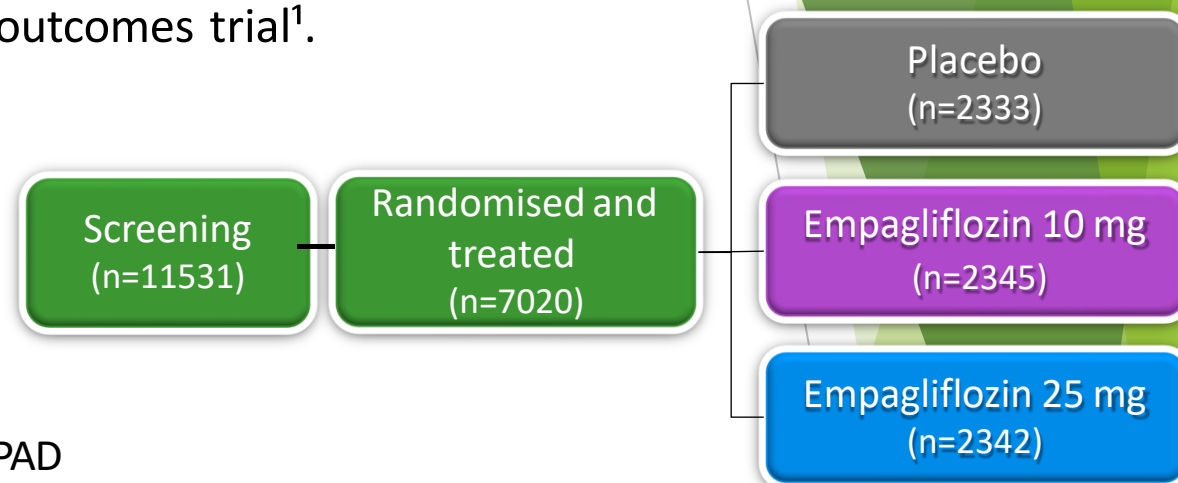
- Randomized, double-blind, placebo-controlled CV outcomes trial¹.

- **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**

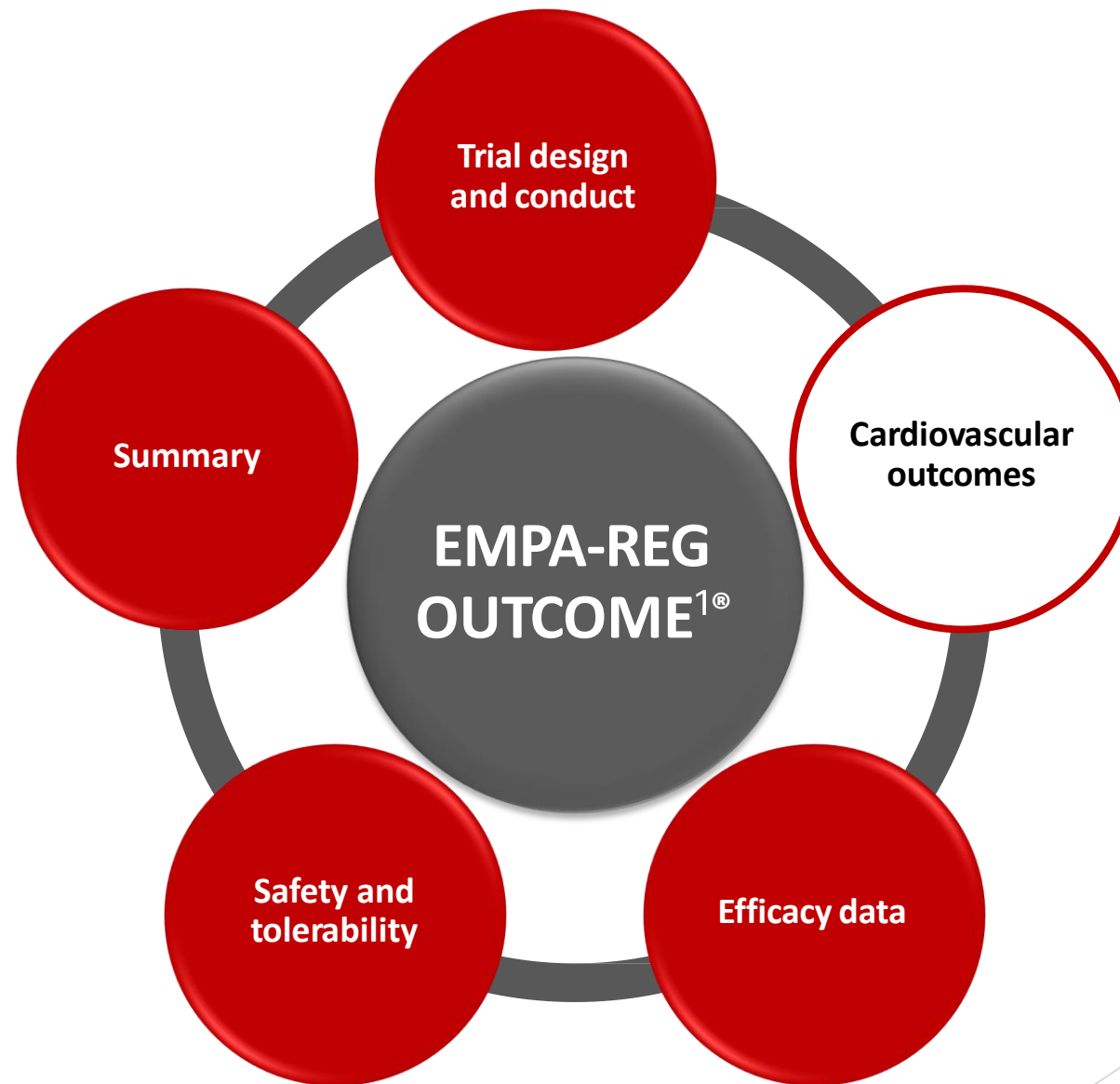
- eGFR < 30 mL/min/1.73m² (MDRD)



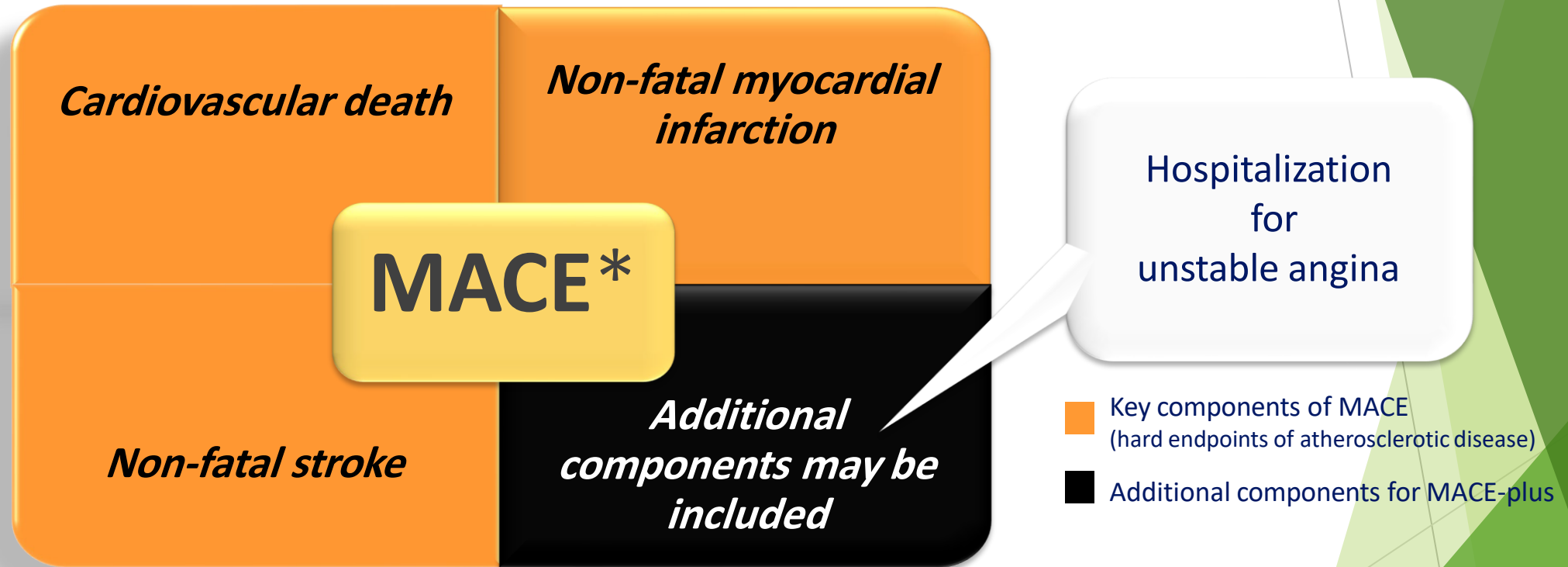
✓ The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event.

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



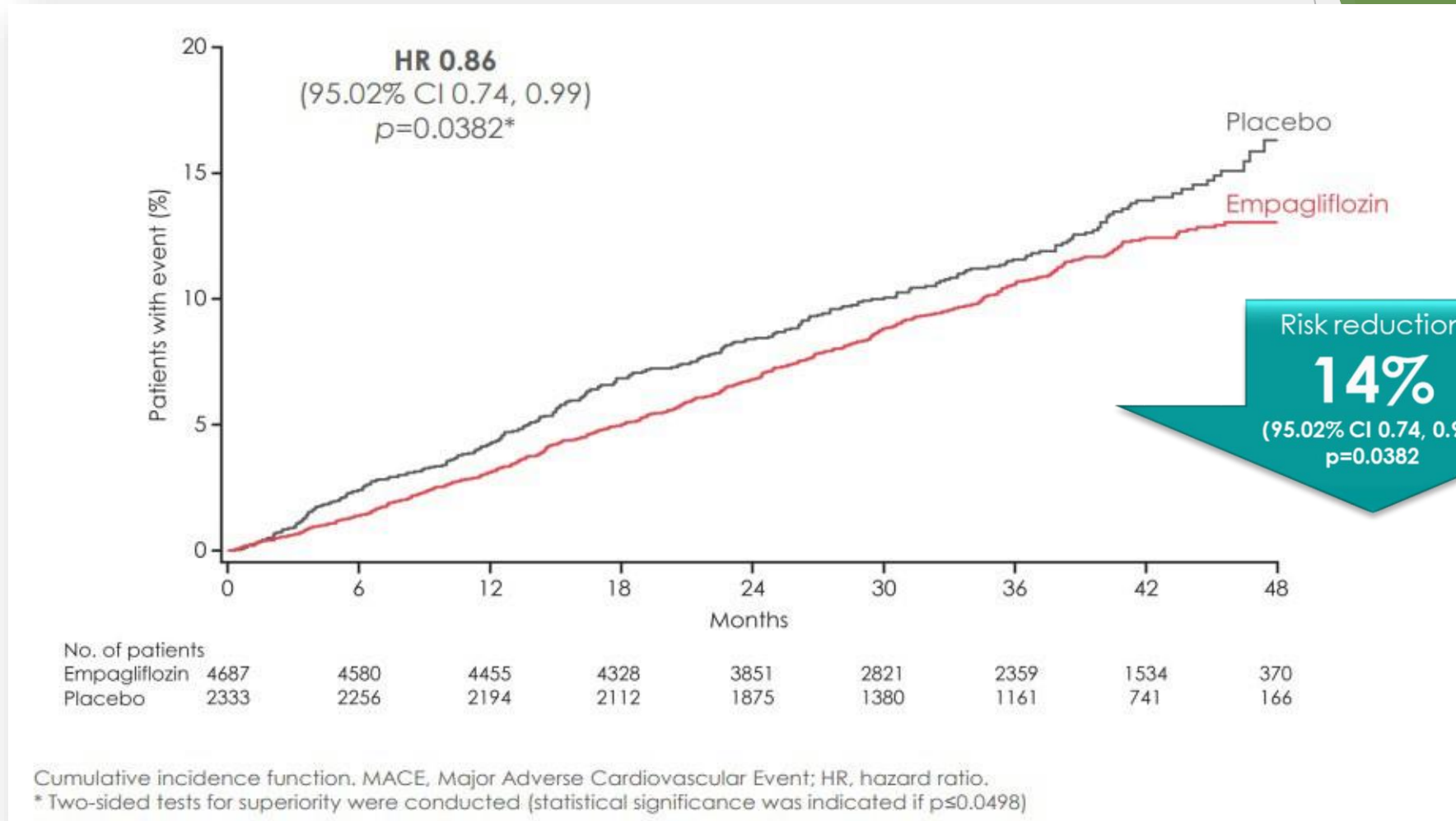
Pre-specified primary and key secondary outcomes¹



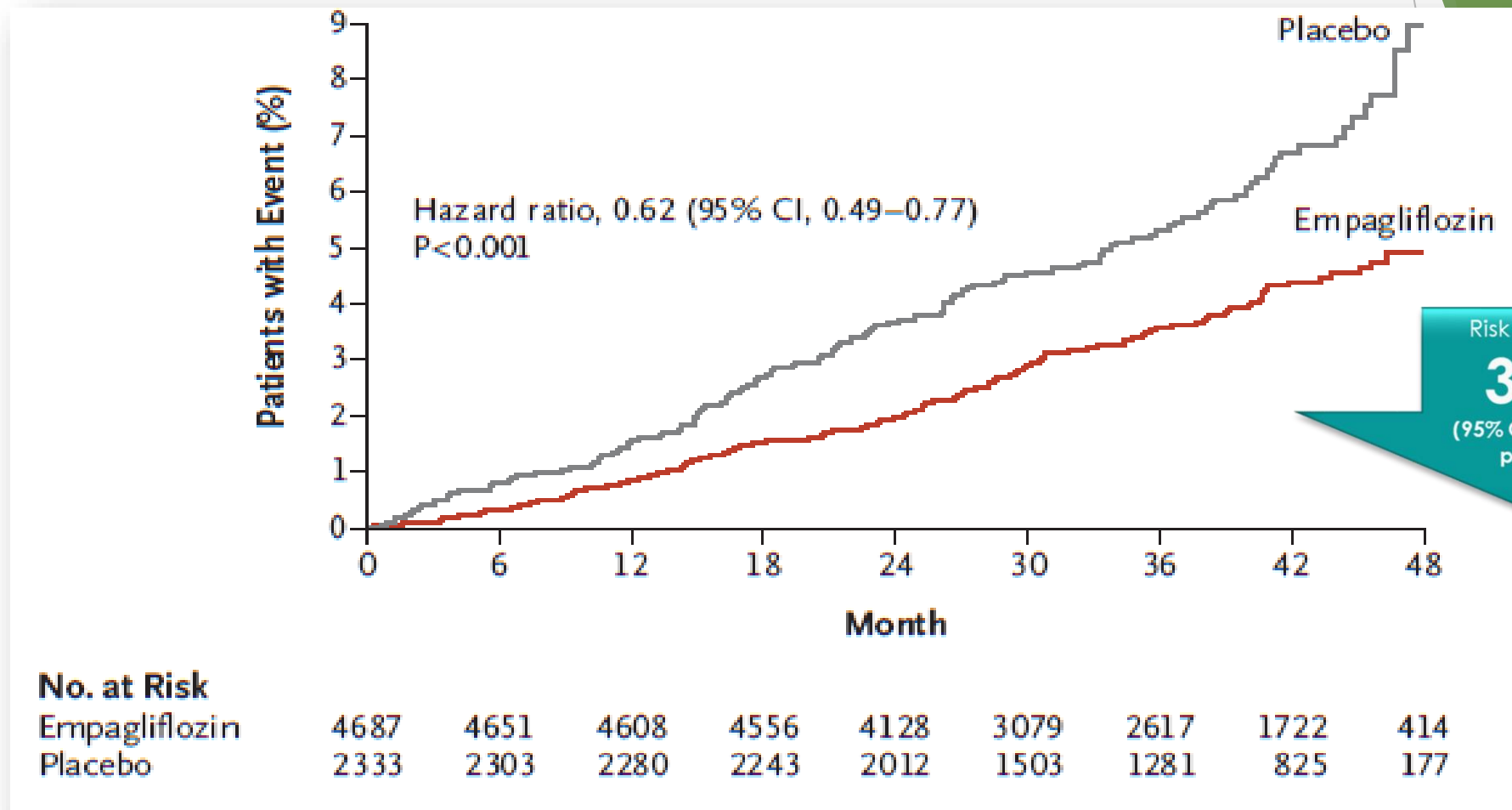
*Major Adverse Cardiovascular Events

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

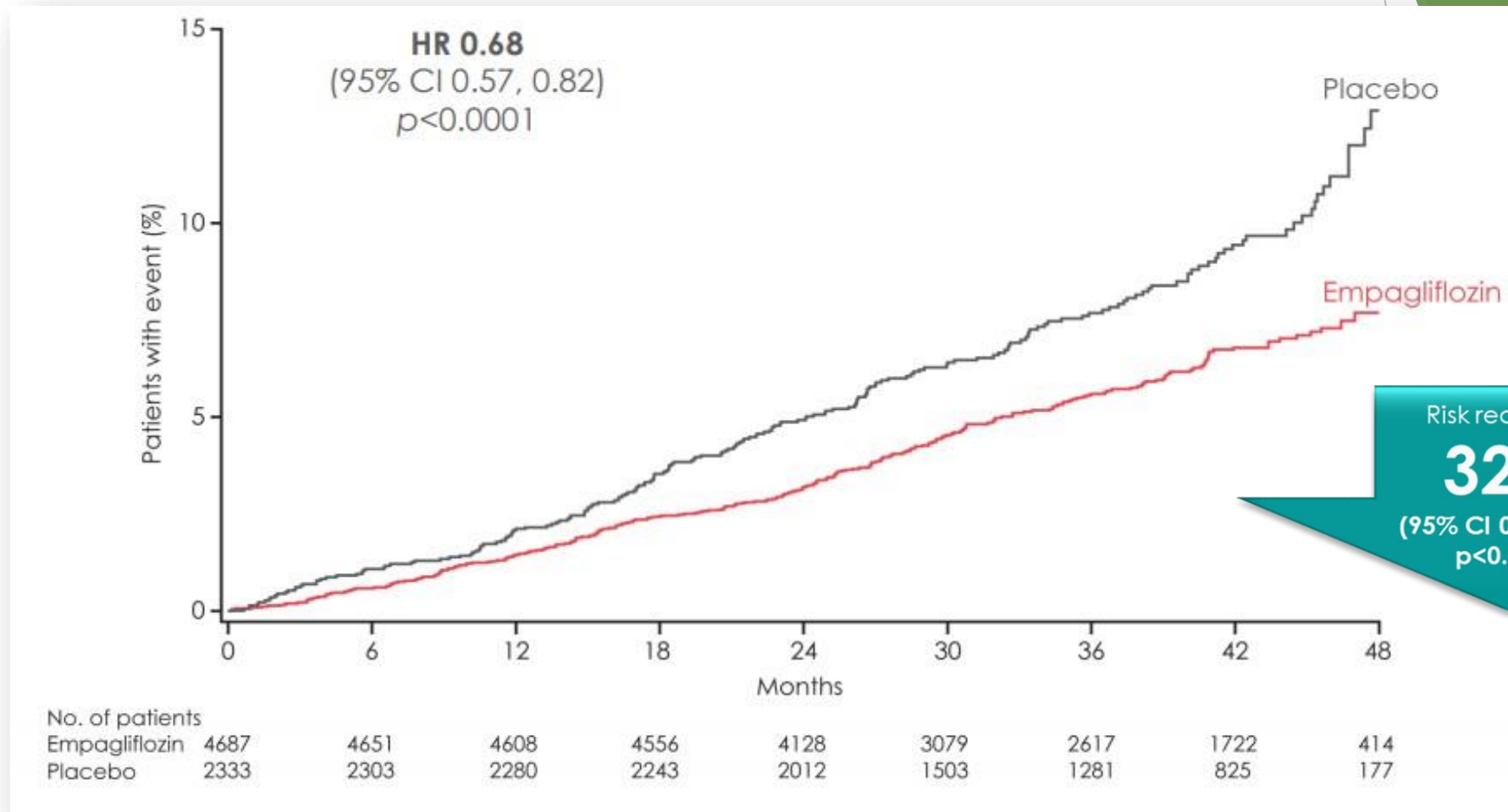
Primary Outcome: 3-point MACE (CV death, Nonfatal MI, Nonfatal stroke)¹



EMPA-REG OUTCOME® CV Death¹

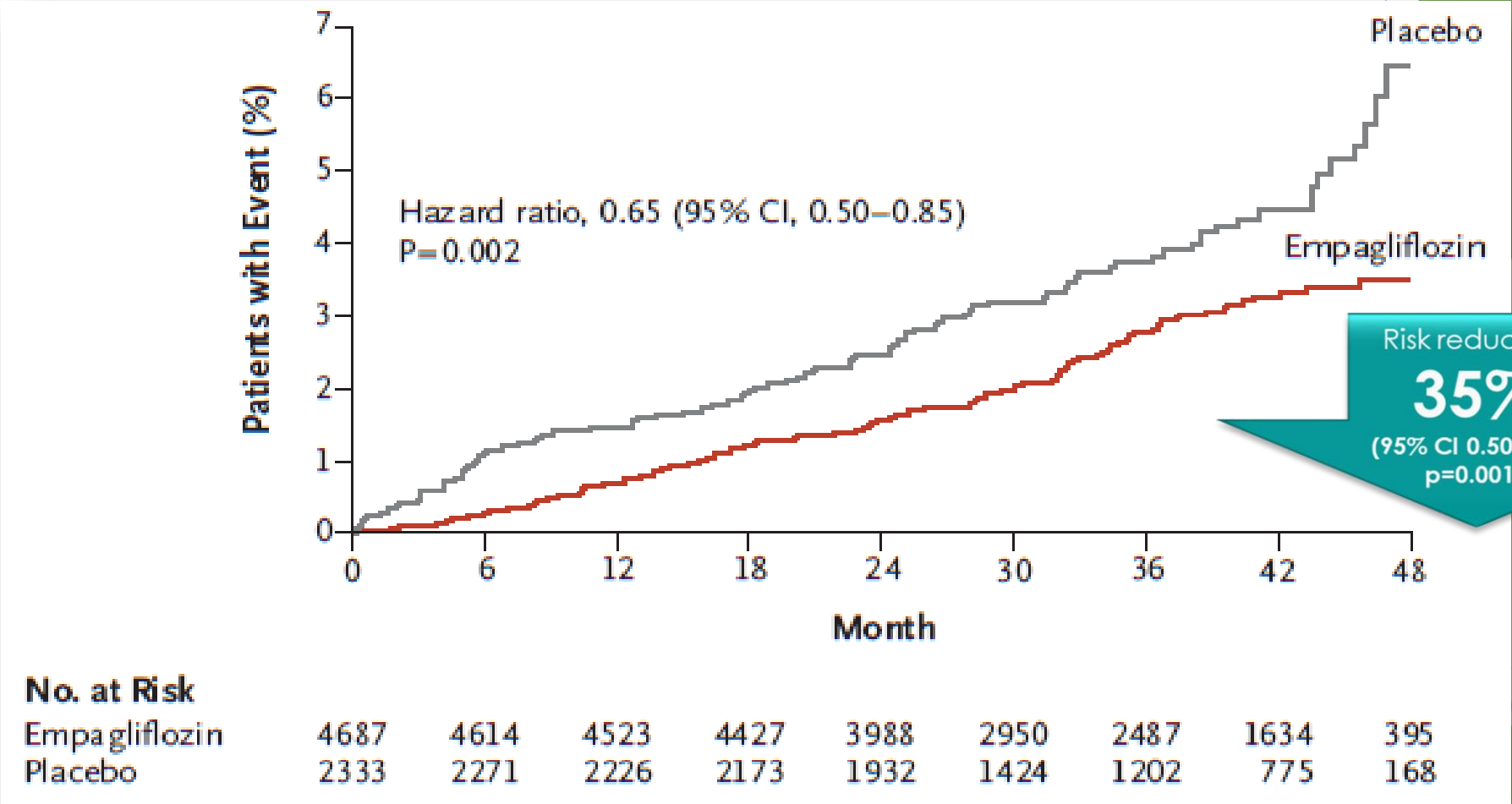


EMPA-REG OUTCOME® All-cause Mortality¹

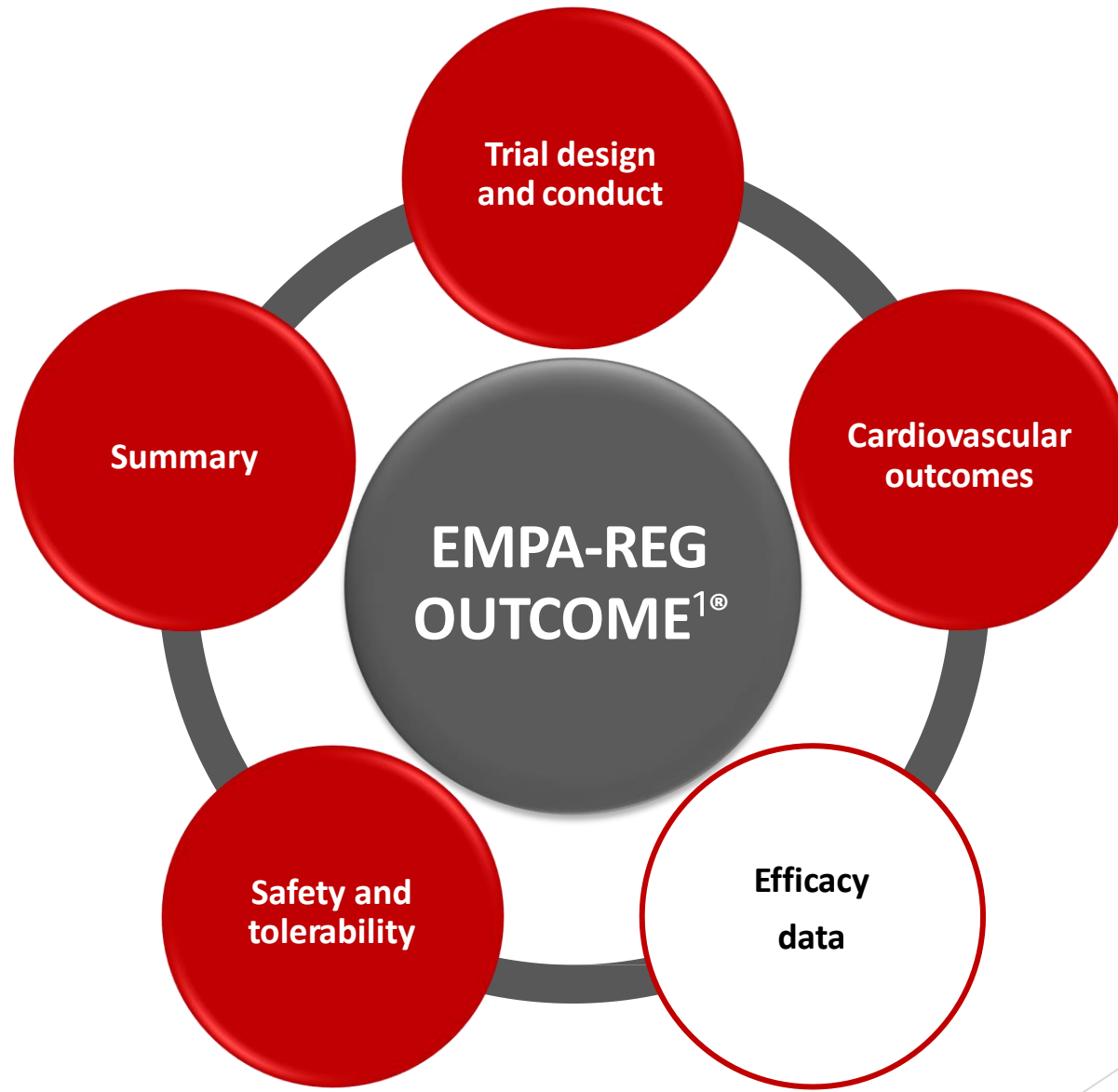


1-Zinman B et al., Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

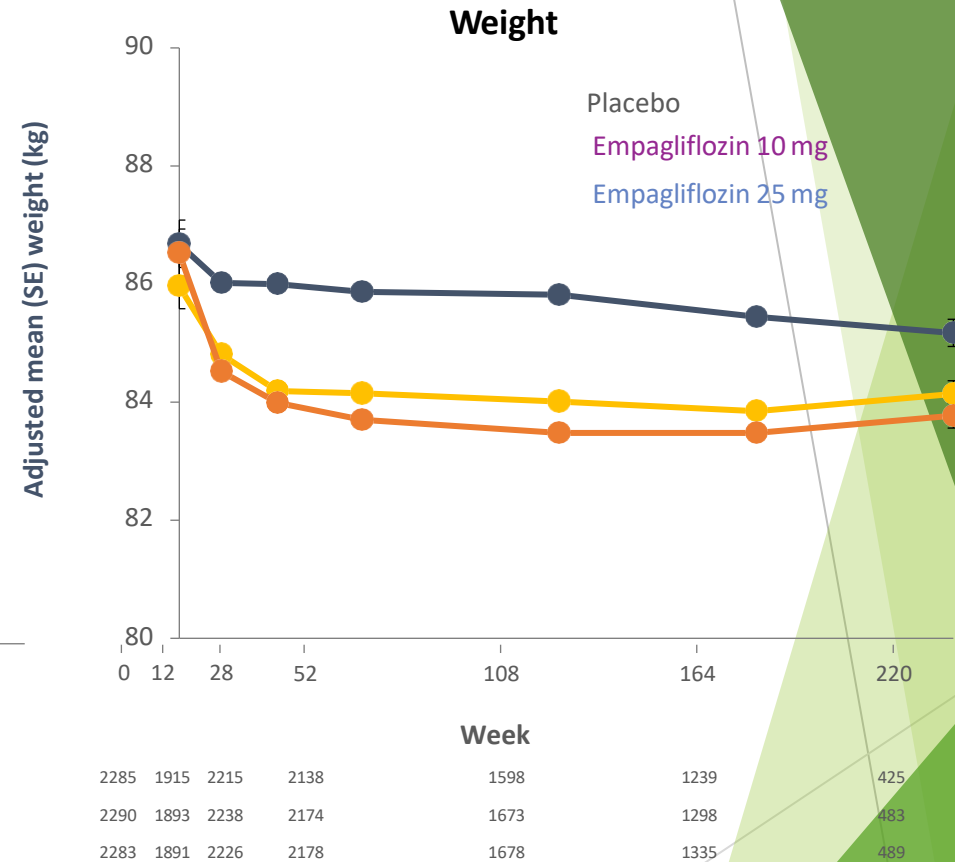
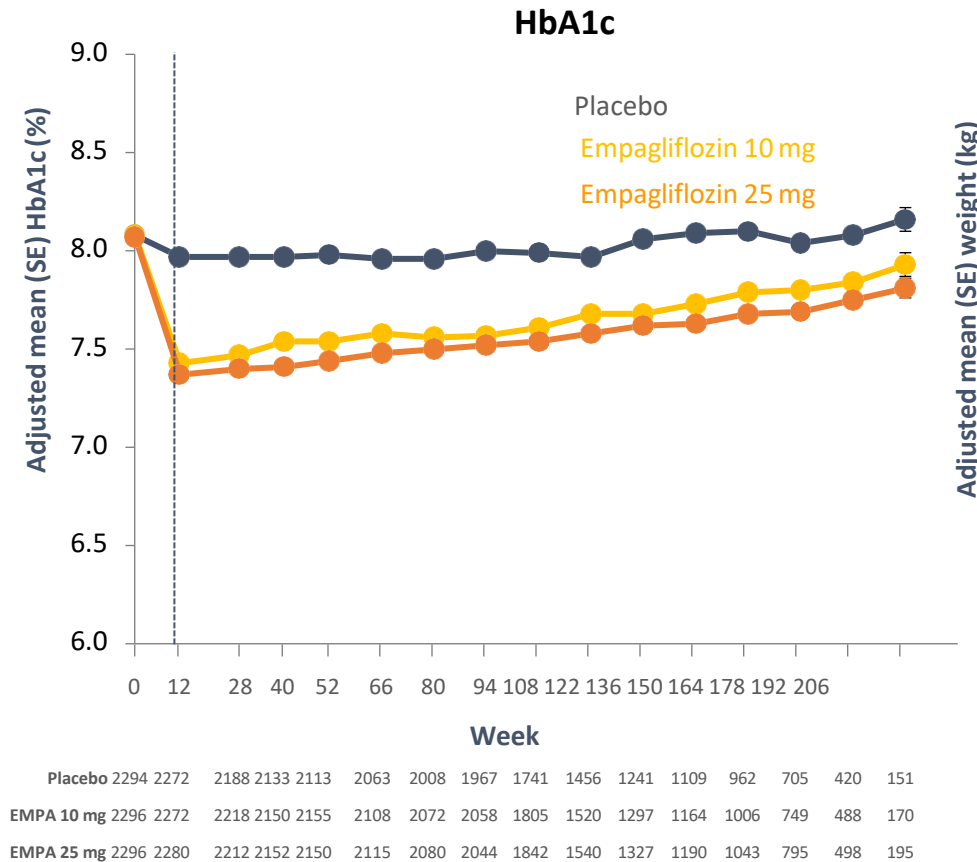
EMPA-REG OUTCOME® Hospitalization for Heart Failure¹



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 parameters¹

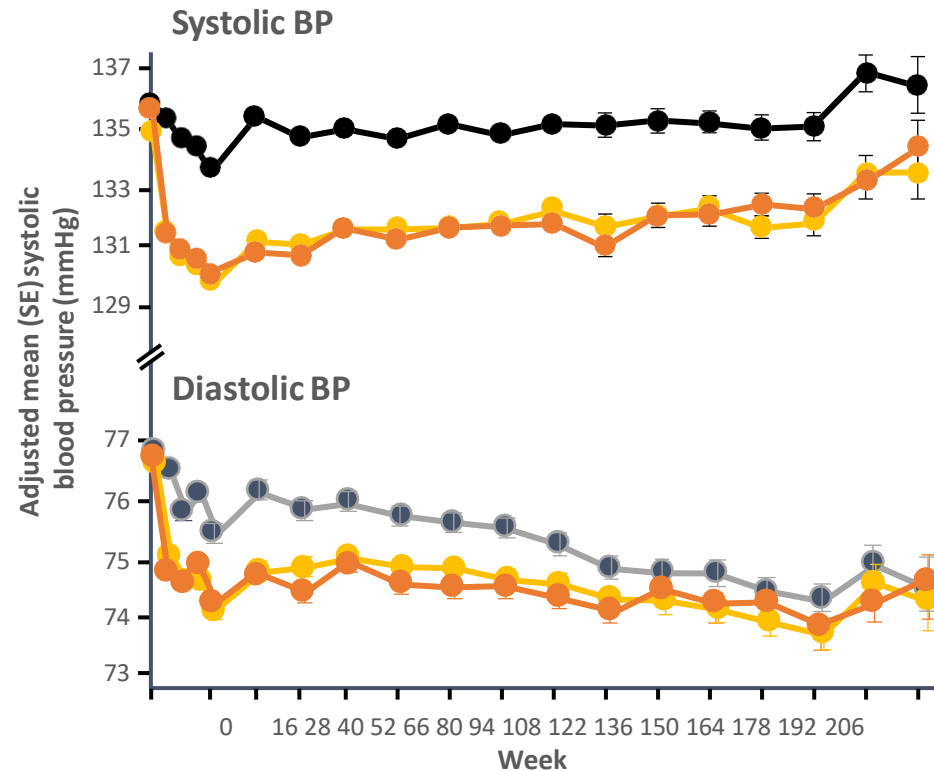


All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent to treat)

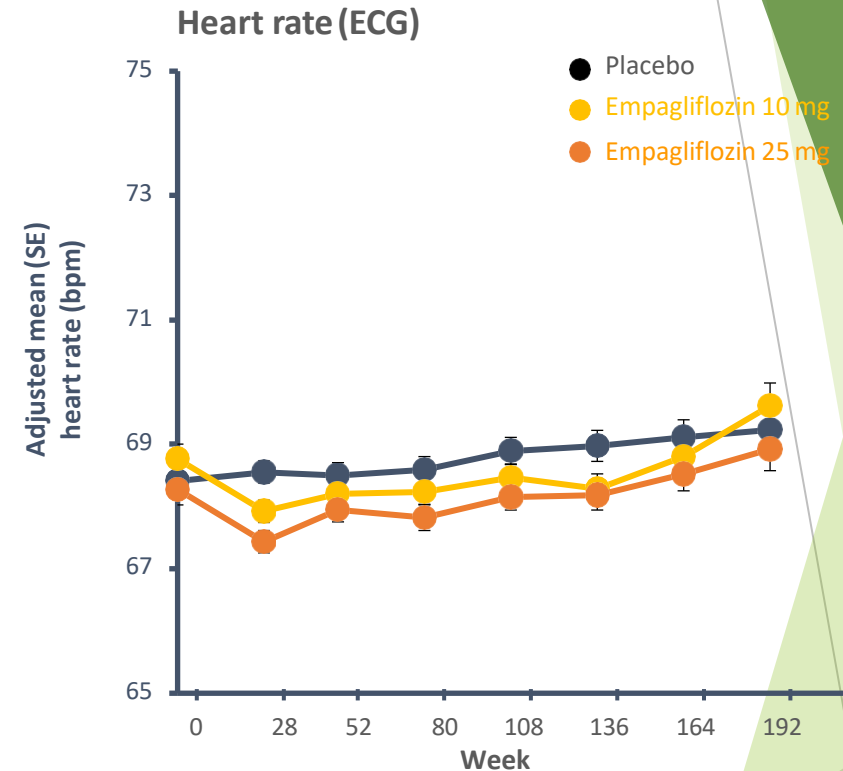
X-axis: time points with reasonable amount of data available for prescheduled measurements

EMPA, empagliflozin; HbA1c, glycated hemoglobin

Mean adjusted blood pressure parameters¹

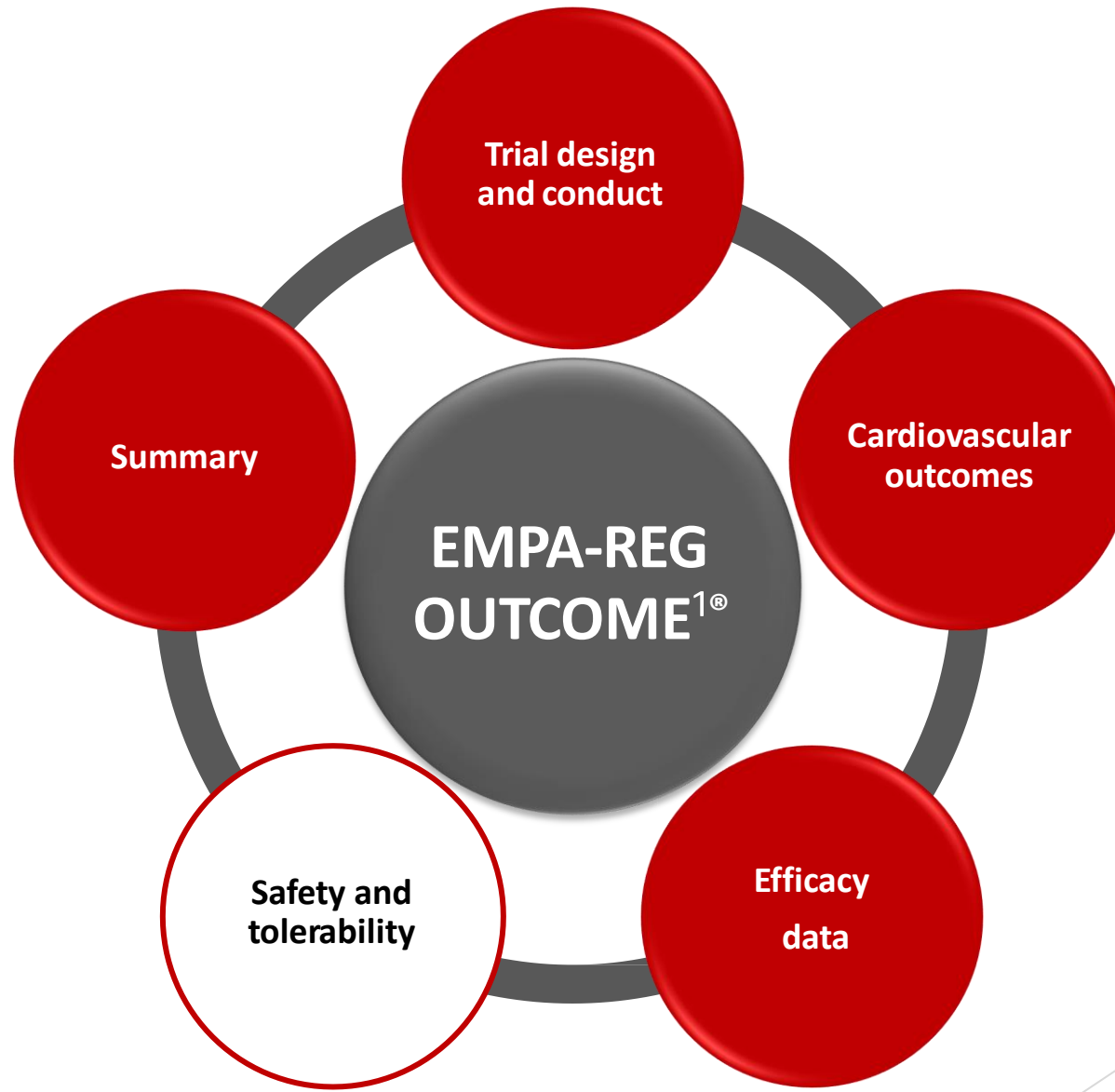


Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
EMPA 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
EMPA 25 mg	2322	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216



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



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

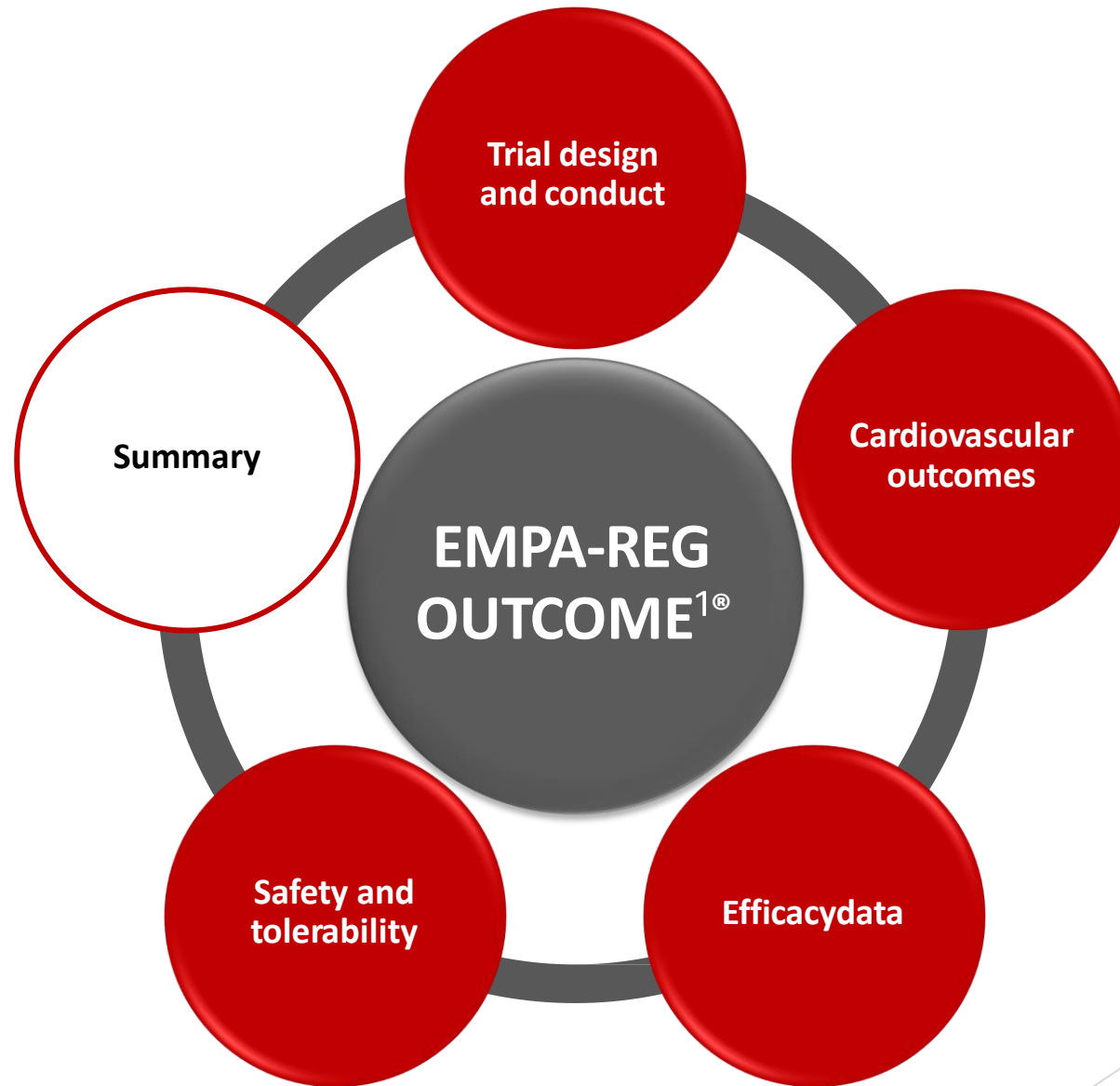
Rate = per100 patient-years

*As reported by the investigator

Patients treated with ≥1 dose of study drug

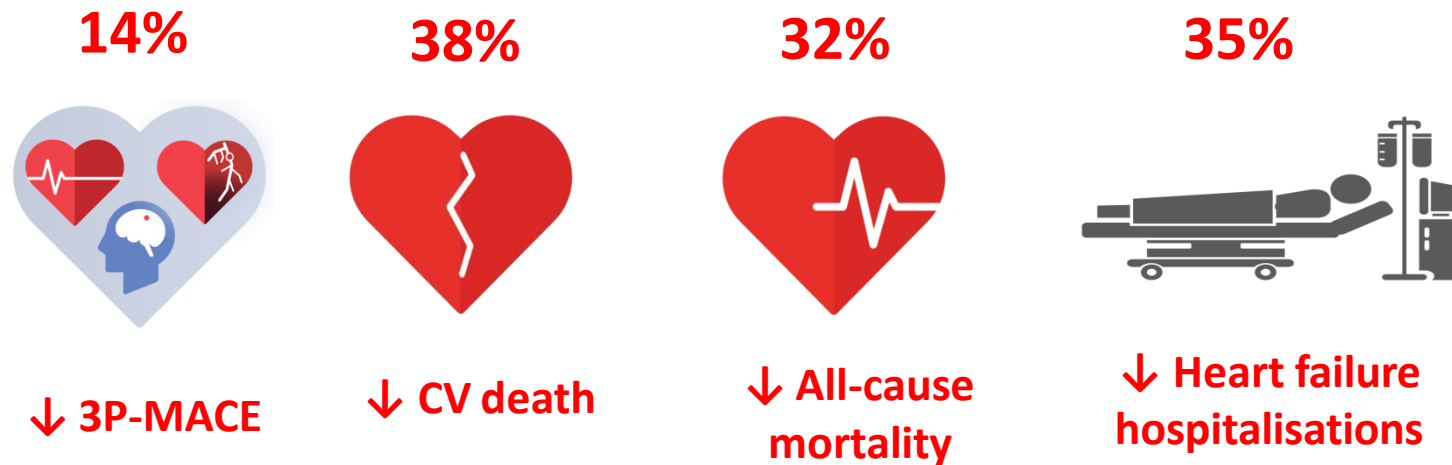
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

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

Empagluco[®] | 10
Empagliflozin | 25

Emzip[®] | 5/1000
12.5/1000
Empagliflozin ⊕ Metformin

ORIGINAL ARTICLE

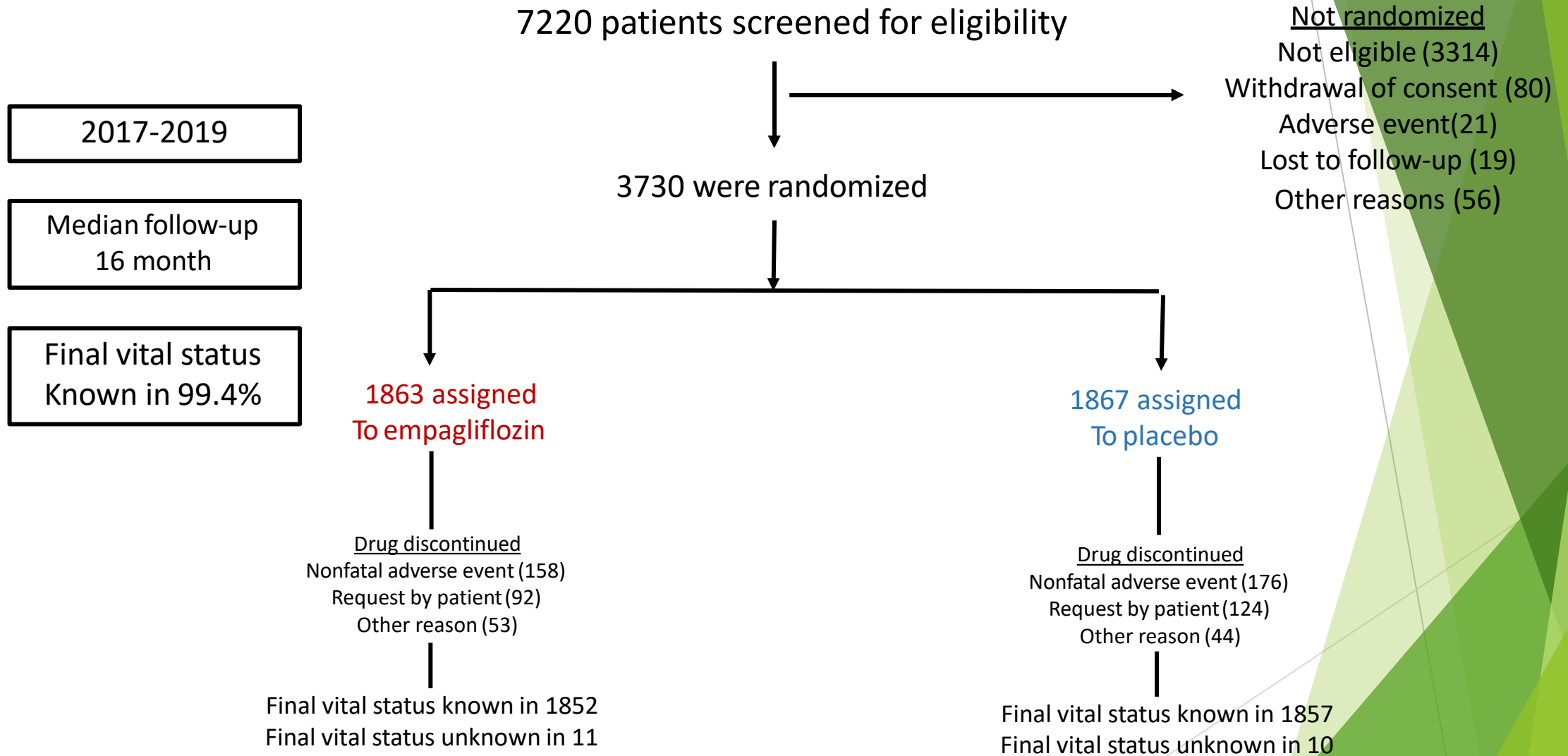
Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

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:

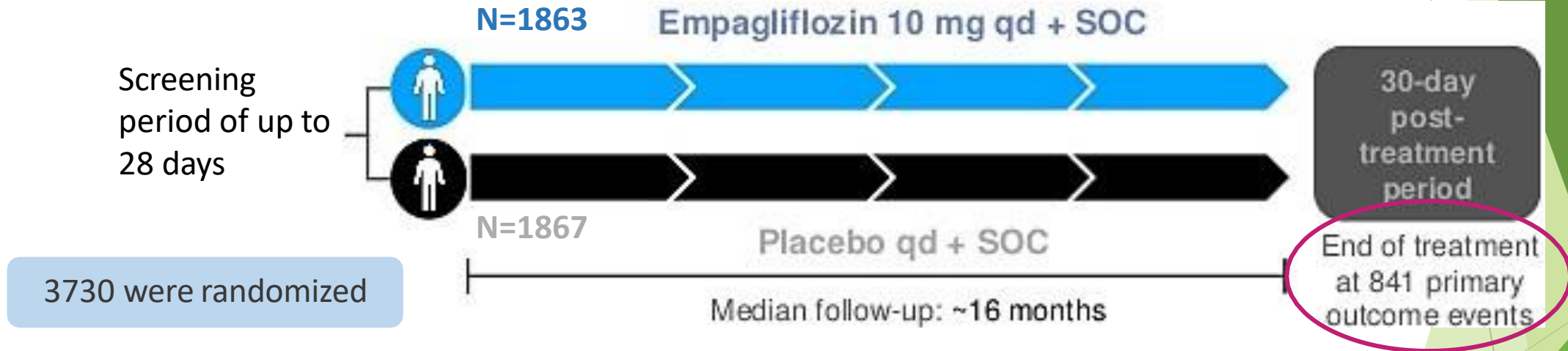
The **EMPEROR-Reduced trial** was designed to evaluate the effects of empagliflozin 10 mg once daily (as compared with placebo) in patients with heart failure and a **reduced** ejection fraction, with or without diabetes, who were already receiving all appropriate treatments for heart failure.

EMPEROR-Reduced: Patient Disposition¹



Trial Design¹

Patients must be receiving all appropriate treatments for HF



SOC; Standard Of Care

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

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

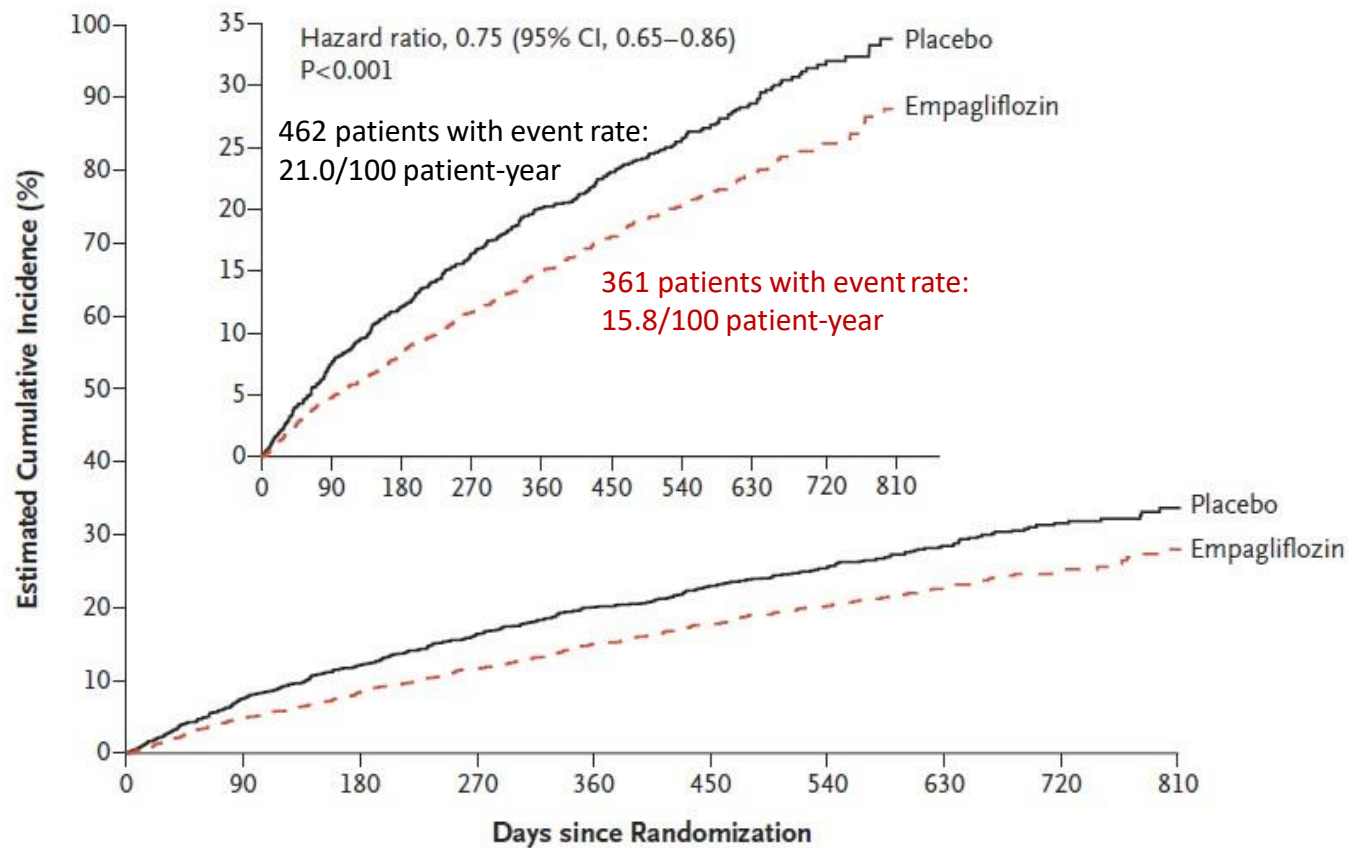
Base-Line Characteristic of Patients¹

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



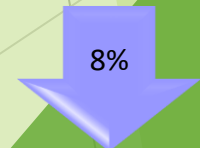
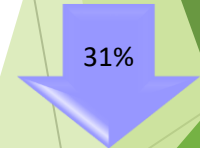
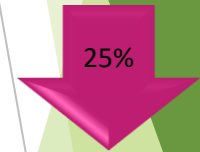
No. at Risk

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

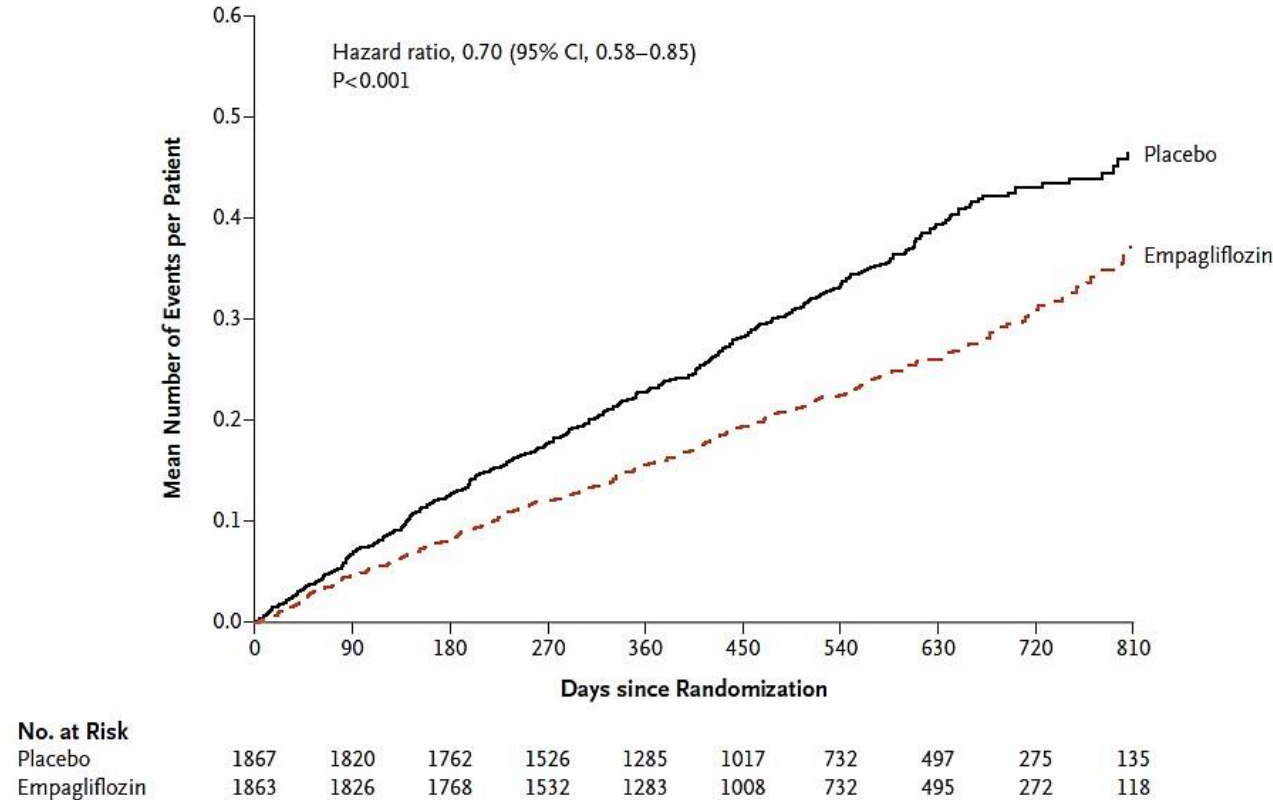


Effect on individual components of the primary endpoint¹

	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

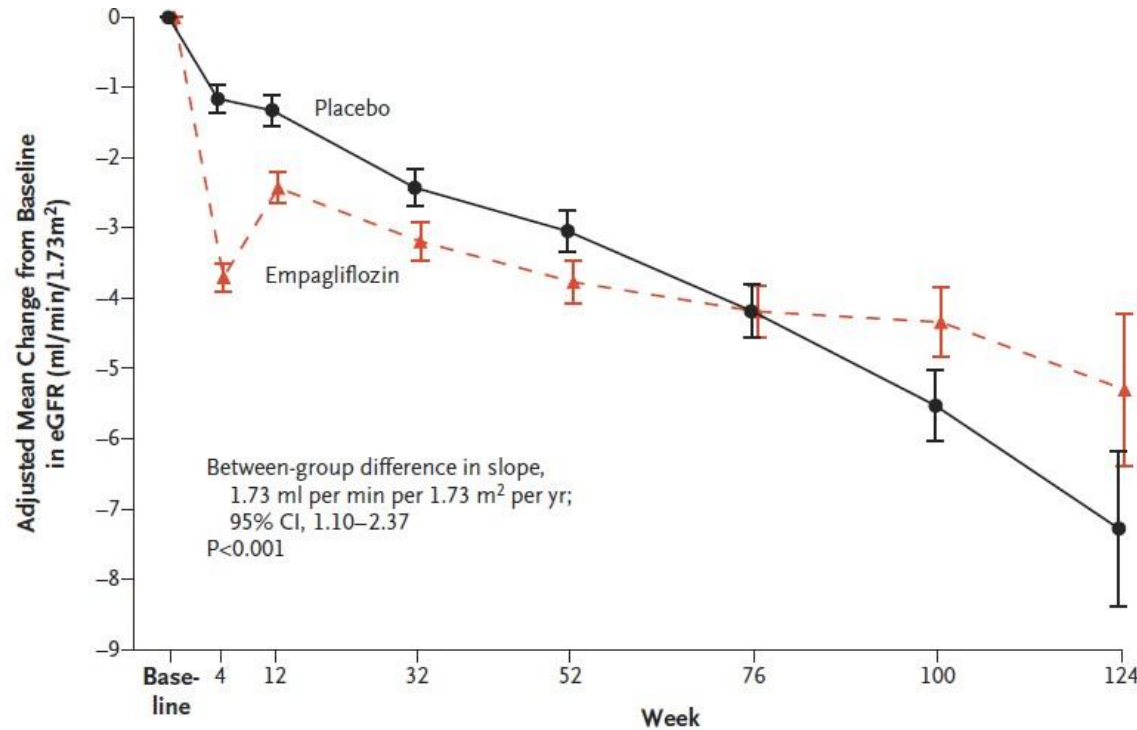
$p < 0.001$

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



No. at Risk
Placebo
Empagliflozin

1792	1765	1683	1500	1146	745	343	76
1799	1782	1720	1554	1166	753	356	80

-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.

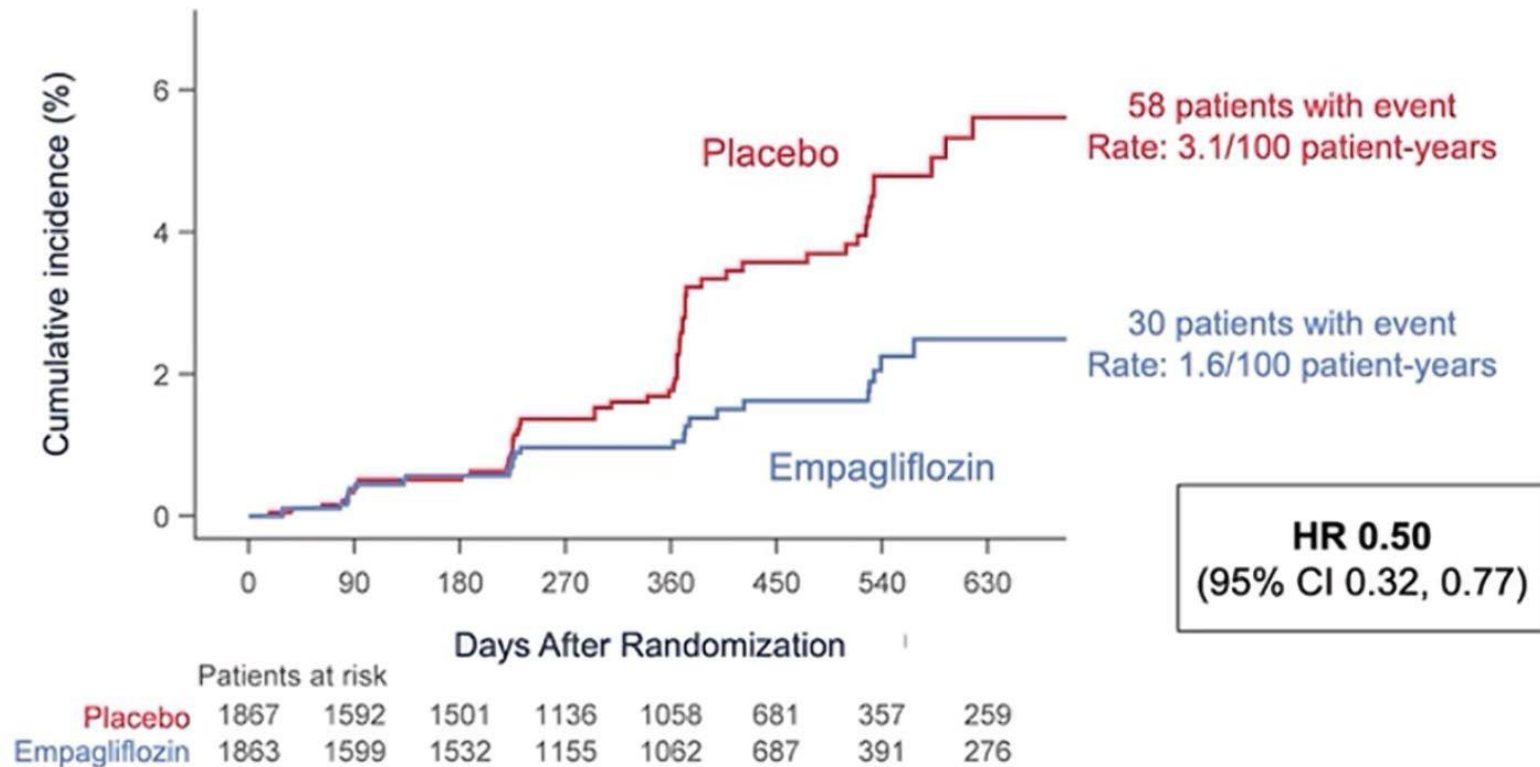
2 EMPEROR-Reduced Trial Marta Cobo Marcos M. Packer presentation ESC 2020

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



50%
30 on Empagliflozin
58 on Placebo
HR= 0.50 (0.32-0.77)

- ✓ 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

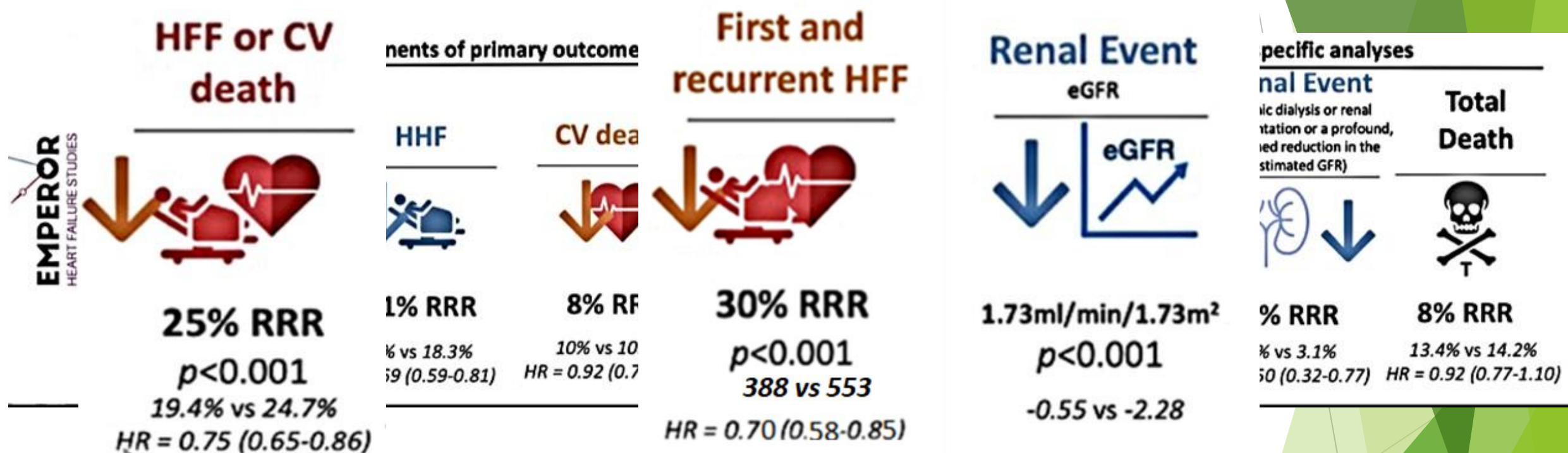
- ✓ Uncomplicated genital tract infection was reported more frequently with empagliflozin than with placebo².
- ✓ Safety concerns that have been seen with other drugs for heart failure (e.g., hypotension, volume depletion, renal dysfunction, bradycardia, and hyperkalemia) were not evident with empagliflozin².

	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

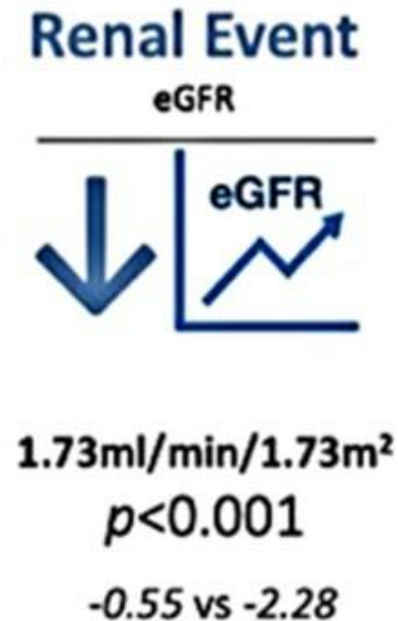
2- N. Engl. J. Med 2020 Aug 29.

Conclusion¹



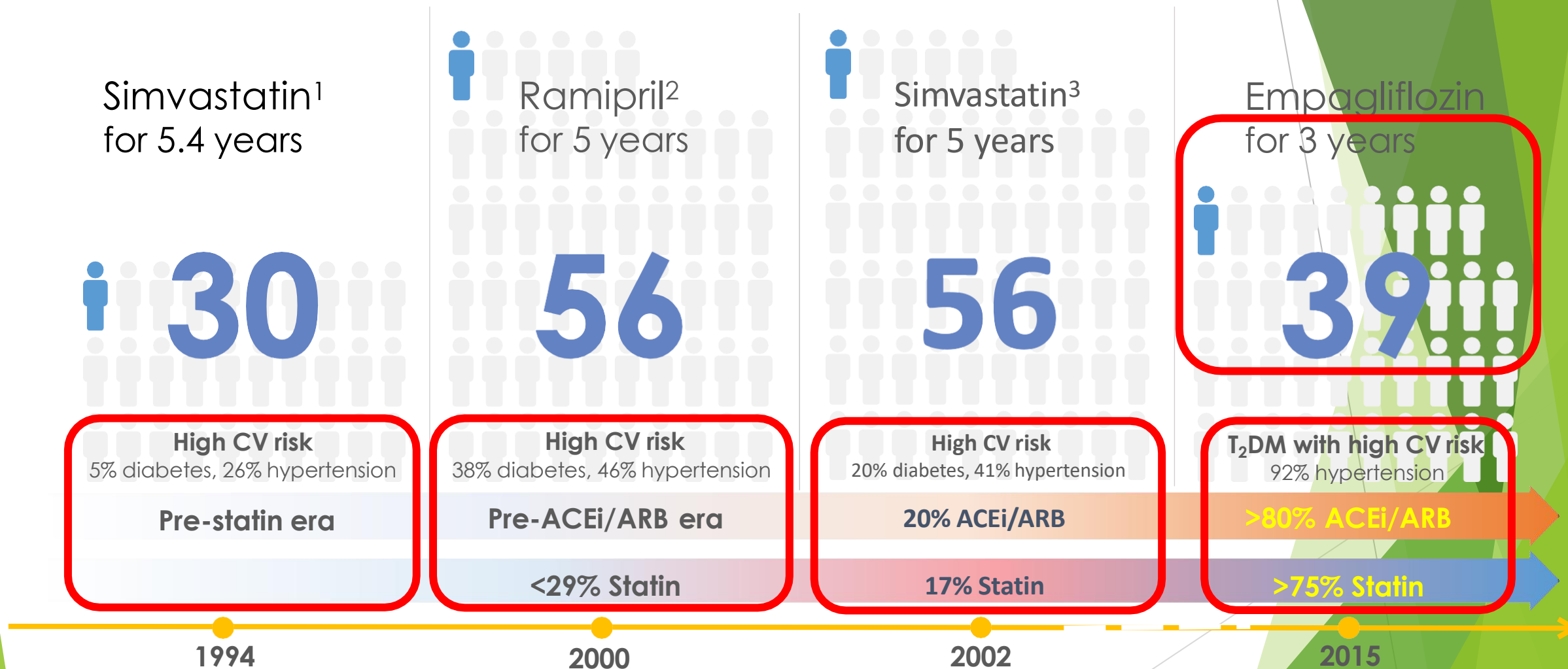
- ✓ Overall, in this trial, empagliflozin was associated with a lower combined risk of cardiovascular death or hospitalization for heart failure than placebo and with a slower progressive decline in renal function in patients with chronic heart failure and a reduced ejection fraction, regardless of the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

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.

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



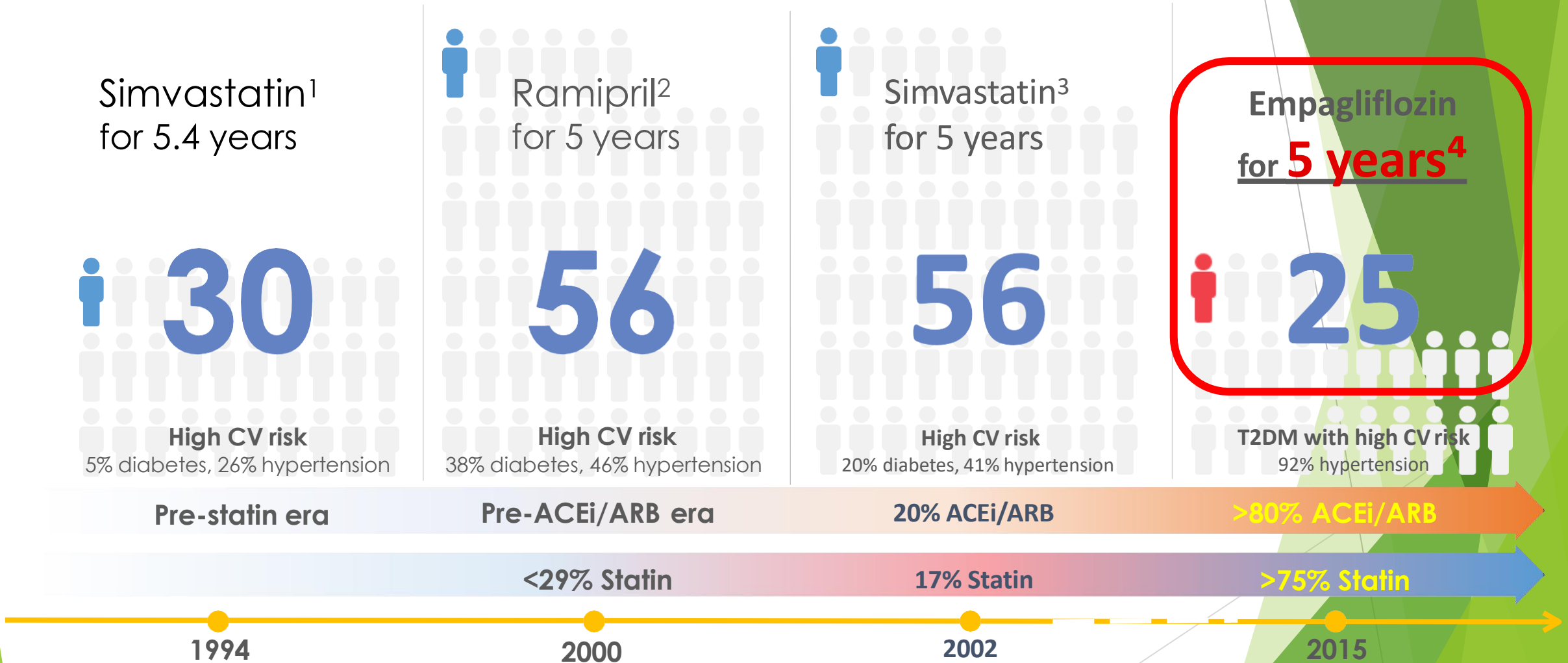
1. 4S investigators. Lancet 1994; 344: 1383-89.

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

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



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

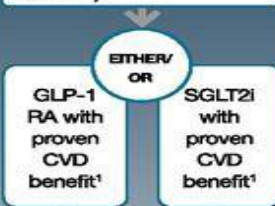
NO

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

- 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.

+HF

Particularly HFrEF (LVEF $<45\%$)

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

+CKD

DKD and Albuminuria⁸

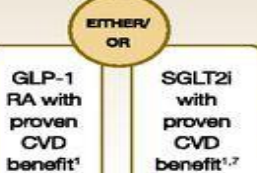
NO

PREFERABLY
SGLT2i with primary evidence of reducing CKD progression

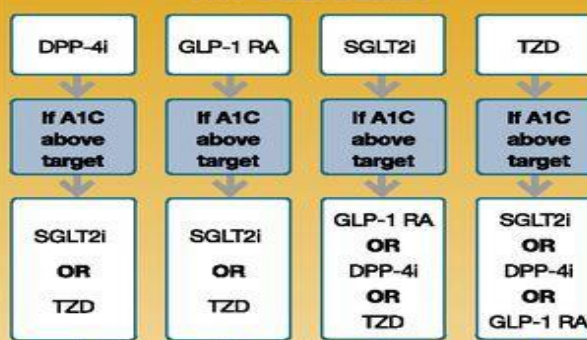
OR
SGLT2i with evidence of reducing CKD progression in CVOTs^{5,6,8}

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

For patients with TZD and CKD⁹ (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

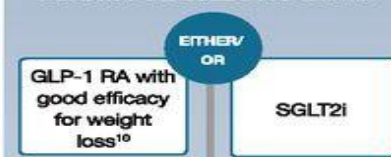
If A1C above target

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

- 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.

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS



If A1C above target



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

† Acted 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.

COST IS A MAJOR ISSUE^{11,12}



If A1C above target



If A1C above target

Insulin therapy basal insulin with lowest acquisition cost
OR
Consider other therapies based on cost

Administration, Cautions, Side effects, Safety profile

Empagluco® | 10
Empagliflozin | 25

Emzip® | 5/1000
12.5/1000
Empagliflozin & Metformin

Convenience of a once-daily oral treatment: ¹

- ✓ ***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 $eGFR \geq 45$ mL/min/1.73 m²*
- ✓ *Empagliflozin should not be initiated in patients with an $eGFR < 45$ mL/min/1.73 m²*
- ✓ *Discontinue Empagliflozin if $eGFR$ falls persistently below 45 mL/min/1.73 m²*
- ✓ *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*

Empagluco®

Empagliflozin Tablets
10 mg / 25 mg



Your Health, Our Ambition



It's Time To Get To The Heart Of What Matters

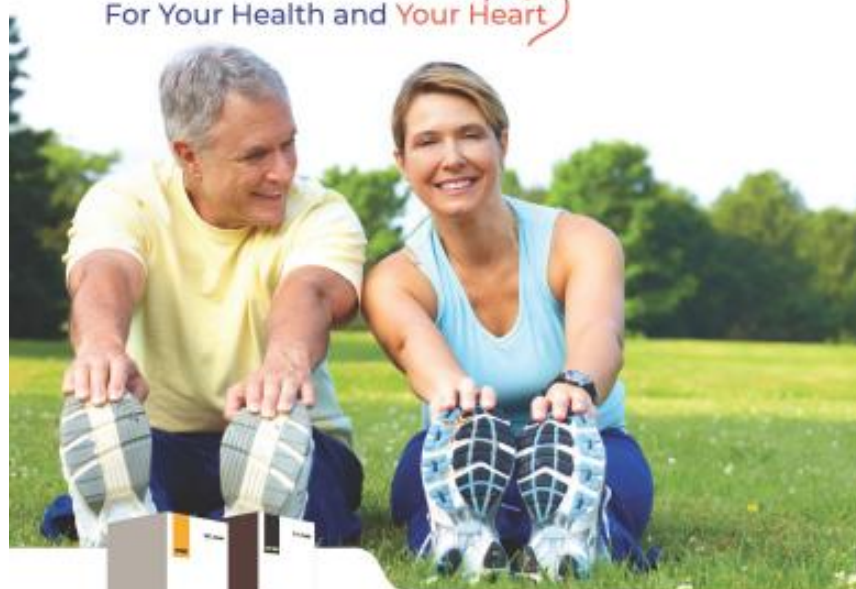
Significantly reduced risk of cv death for adults who have type 2 diabetes and known heart disease.

Emzip

5mg / 1000mg
12.5mg / 1000mg

Empagliflozin + Metformin

For Your Health and Your Heart



Save Your Heart, Save Your Life!

Significantly reduced risk of cv death for adults who have type 2 diabetes and known heart disease.





Thank you