Effects of SGLT 2 inhibitors on Cardiovascular system

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

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P H A R M E D

Objectives

- *Brief review of kidney role in glucose homeostasis*

- *SGLT2 & SGLT2 inhibitors*

- *Efficacy Studies*

- *EMPA-REG OUTCOME®*

- *EMPEROR-Reduced trial*

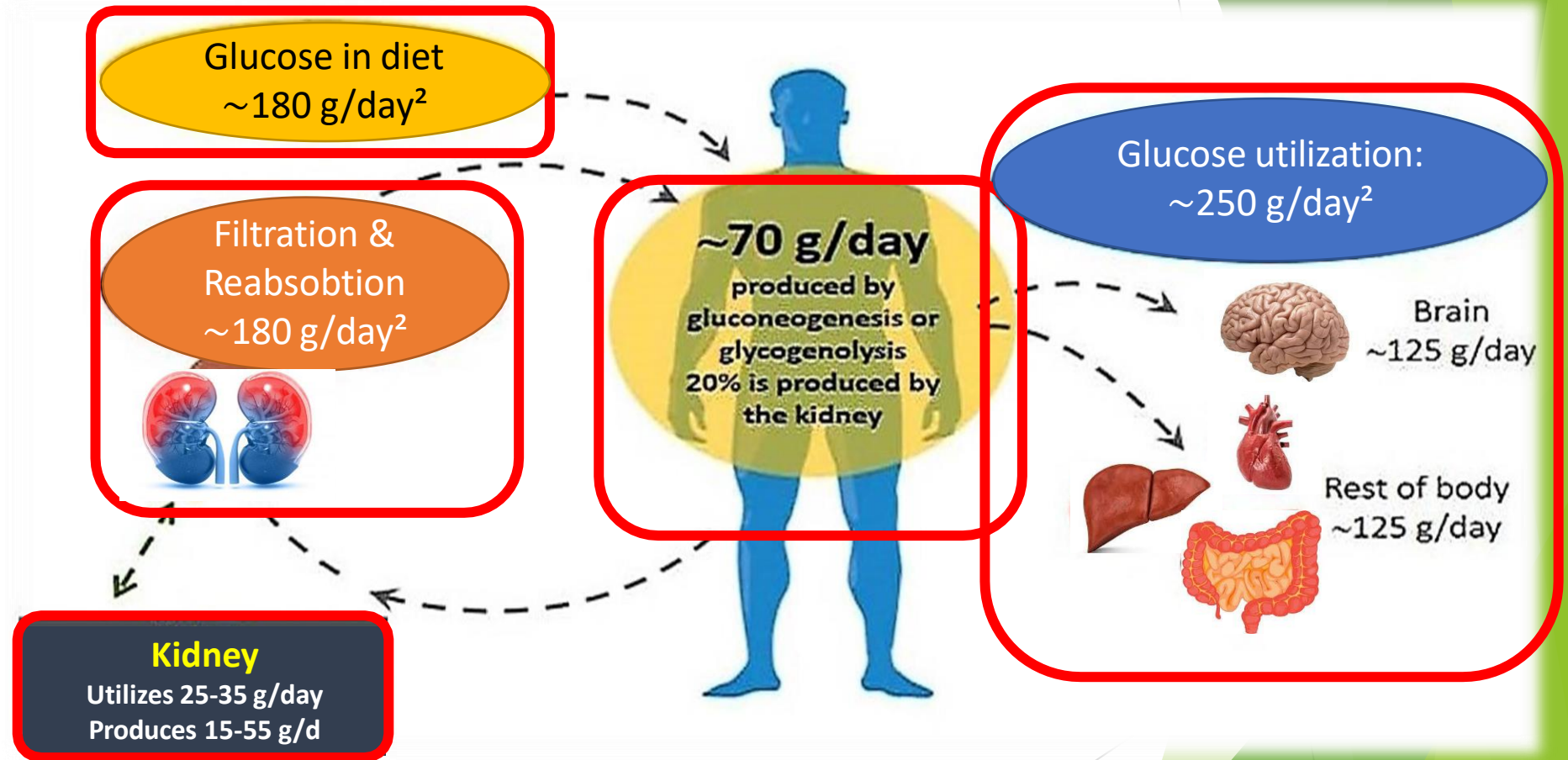- *Administration, Cautions, Side effects*

- *Conclusion*

Kidney Plays a Significant Role in Glucose Balance

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Reabsorption[1]

Production[1]
(Gluconeogenesis)

Utilization[1]

Glucose in diet
~180 g/day[2]

Filtration &
Reabsobtion
~180 g/day[2]

~70 g/day
produced by
gluconeogenesis or
glycogenolysis
20% is produced by
the kidney

Glucose utilization:
~250 g/day[2]

Brain
~125 g/day

Rest of body
~125 g/day

Kidney
Utilizes 25-35 g/day
Produces 15-55 g/d

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.
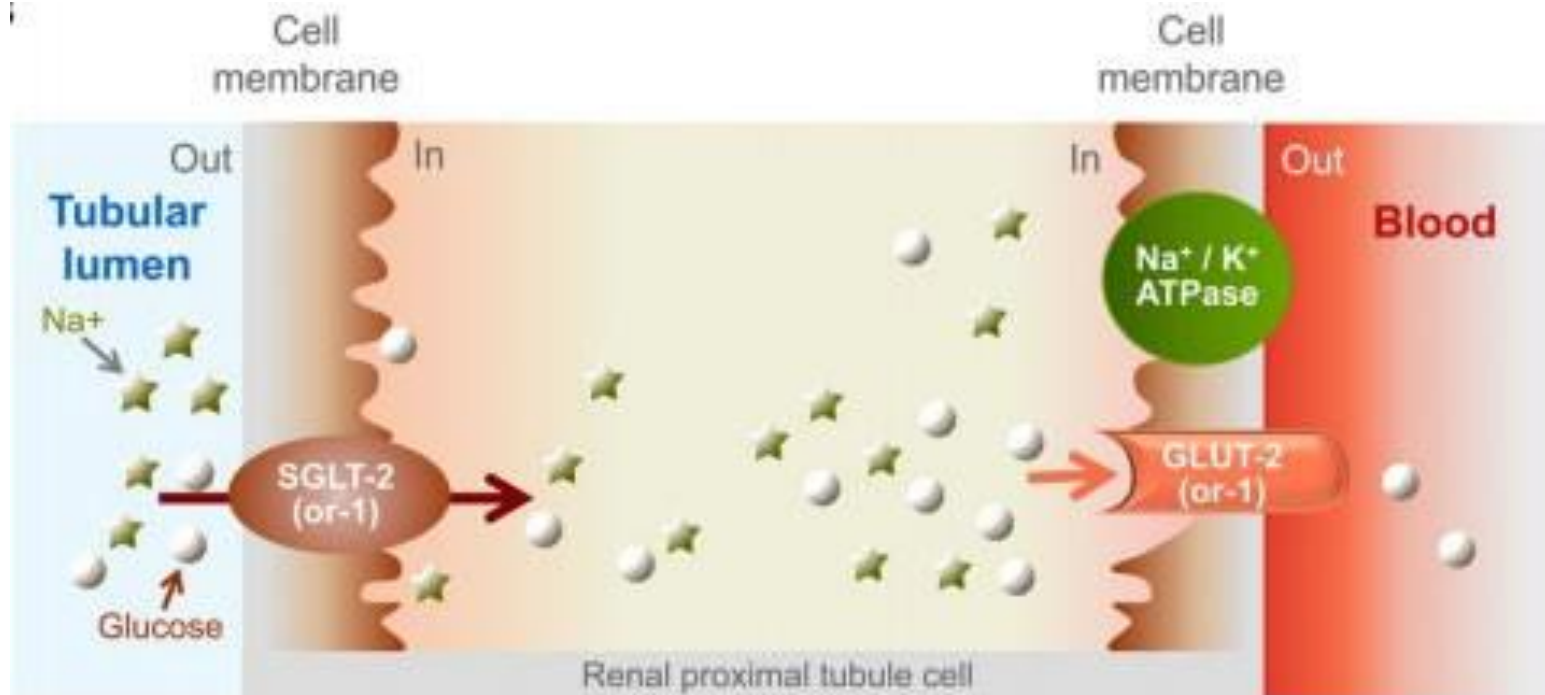
Glucose Transporters:

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

facilitative glucose transporters (GLUTs)

sodium-dependent glucose transporters (SGLTs)

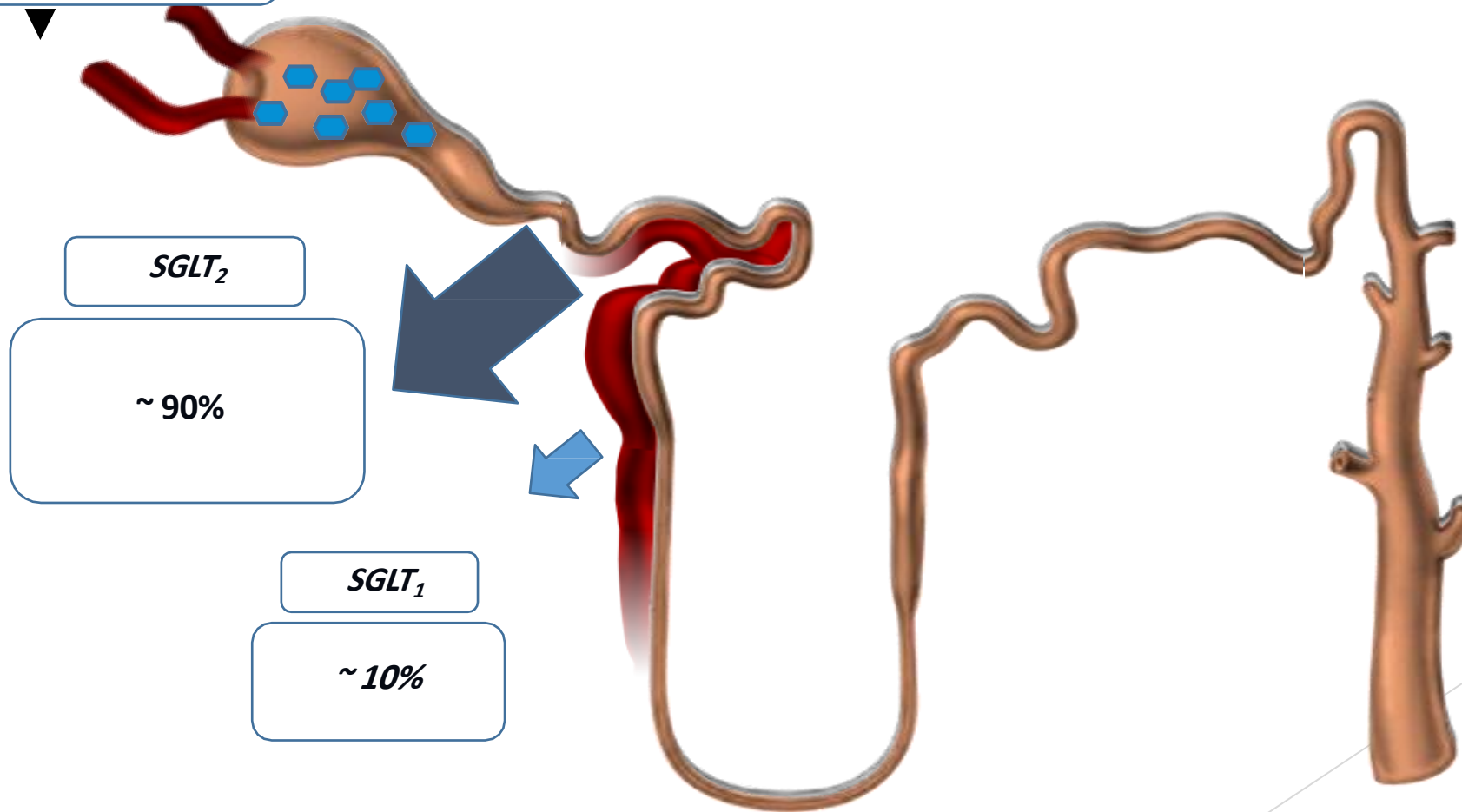$SGLT_1$: low capacity, high affinity, mostly in intestine
$SGLT_2$: high capacity, low affinity, mostly in kidney

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.
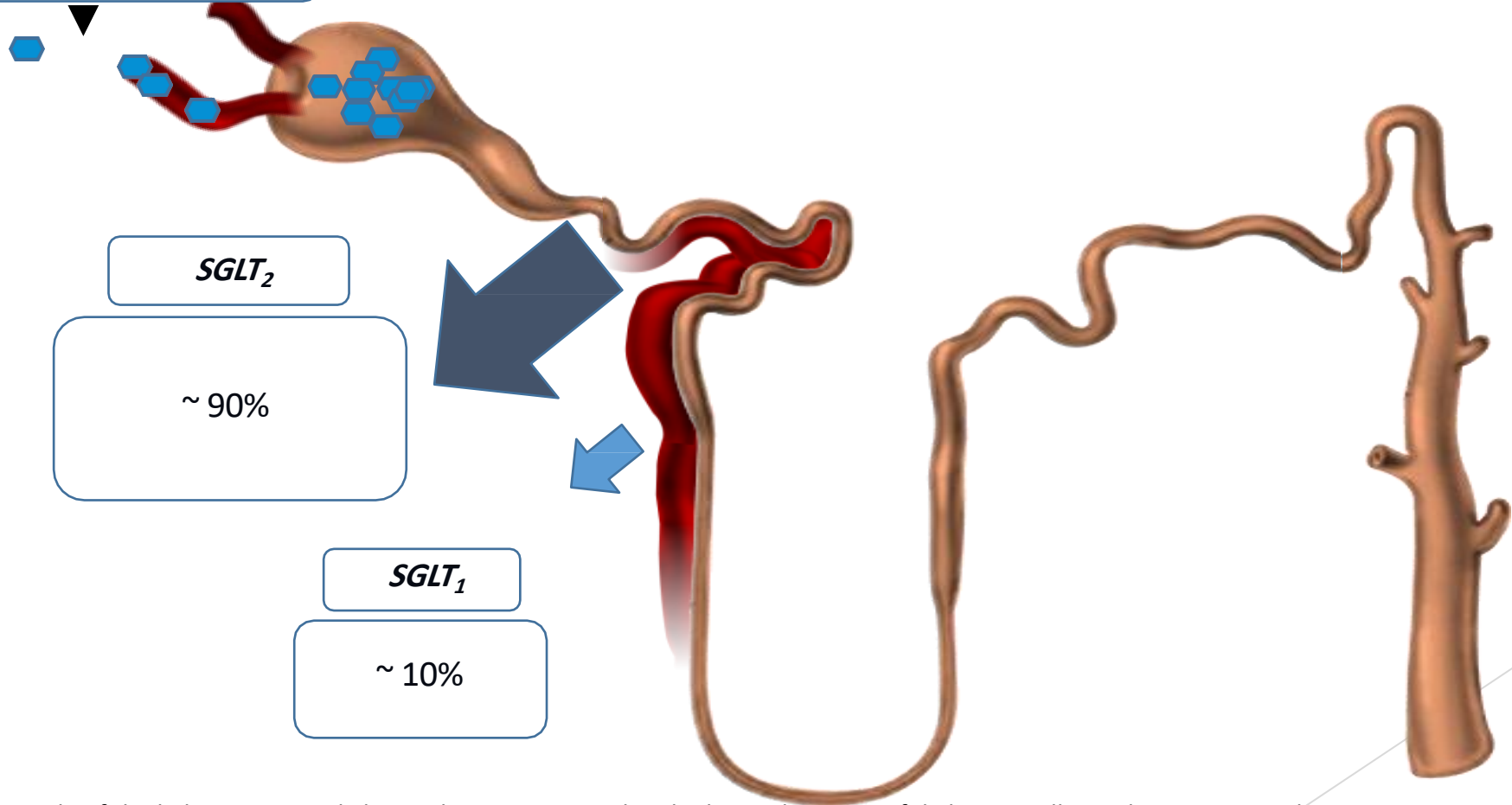
Renal glucose re-absorption in healthy individuals

Filtered glucose load 180 g/day[1]

$SGLT_2$

~ 90%

$SGLT_1$

~ 10%

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:

Filtered glucose load > 180^1 g/day

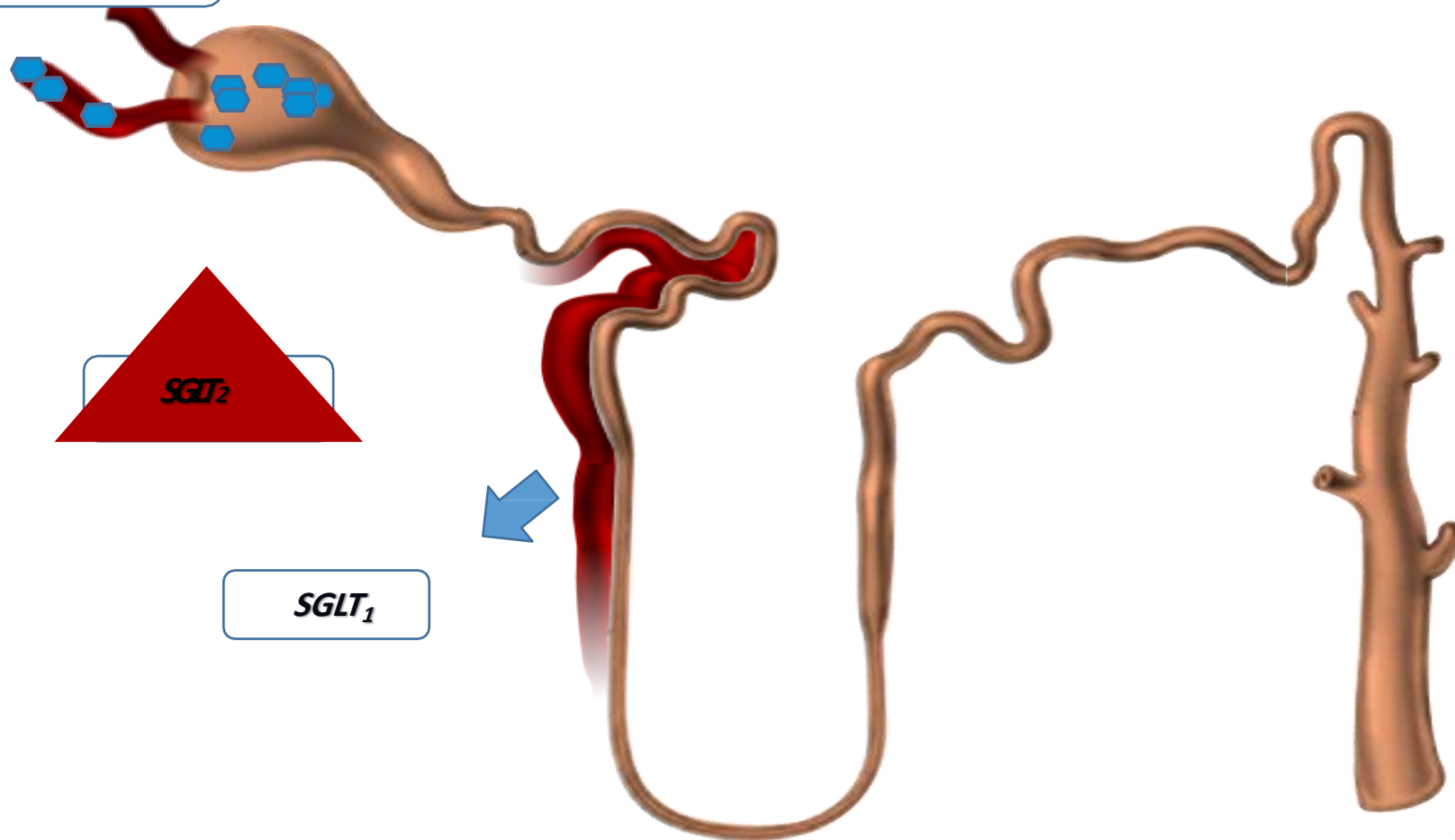**$SGLT_2$**

~ 90%

$SGLT_1$

~ 10%

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

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.

Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load > 180 g/day

SGLT$_2$

SGLT$_1$

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.

SGLT2i lowers renal threshold for glucose excretion[1,2]
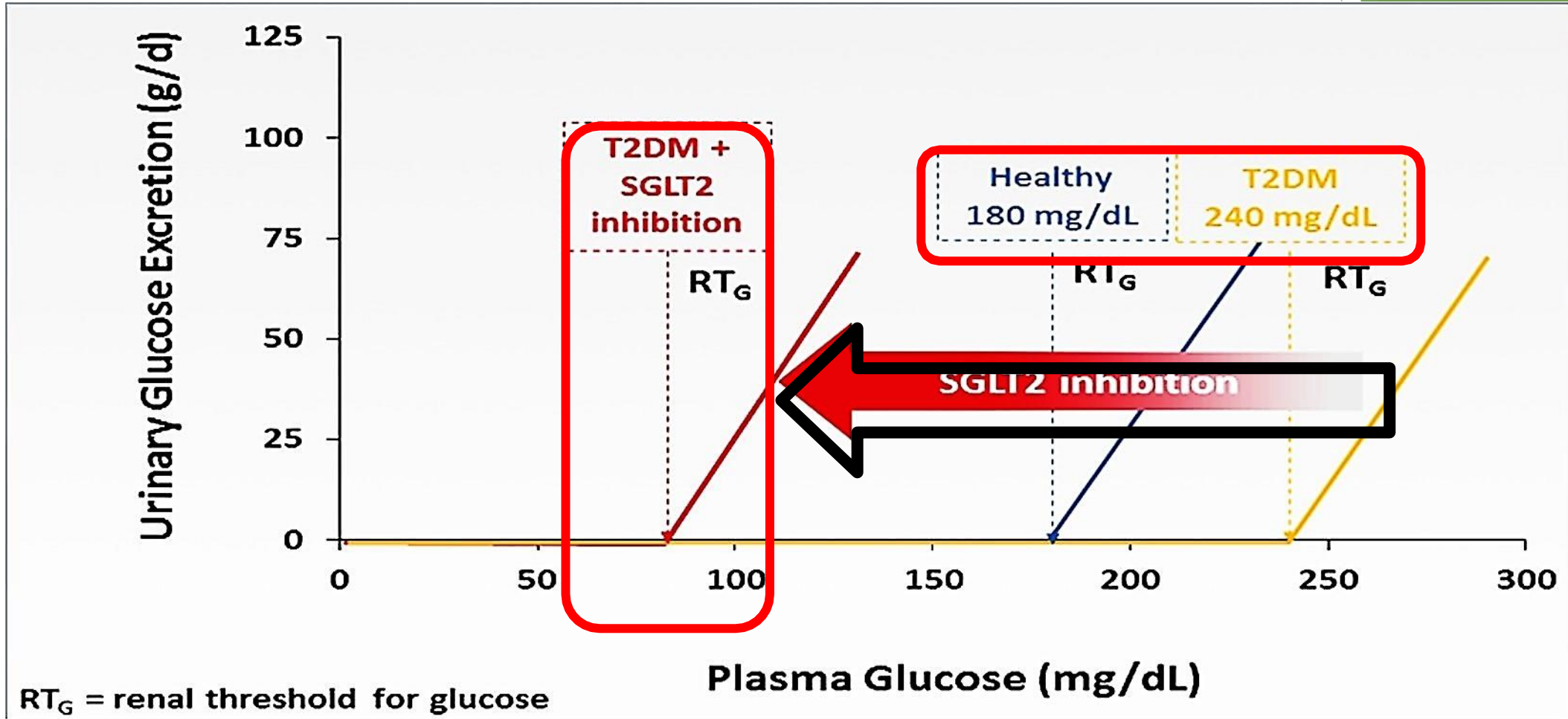
1-Abdul-Ghani M et al, Inhibition of renal glucose reabsorption: a novel strategy for achieving glucose control in type 2 diabetes mellitus. Endocrine Practice. 2008; 14(6): 782-90. 2-Nair S et al, Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism. 2010; 95(1): 34-42.
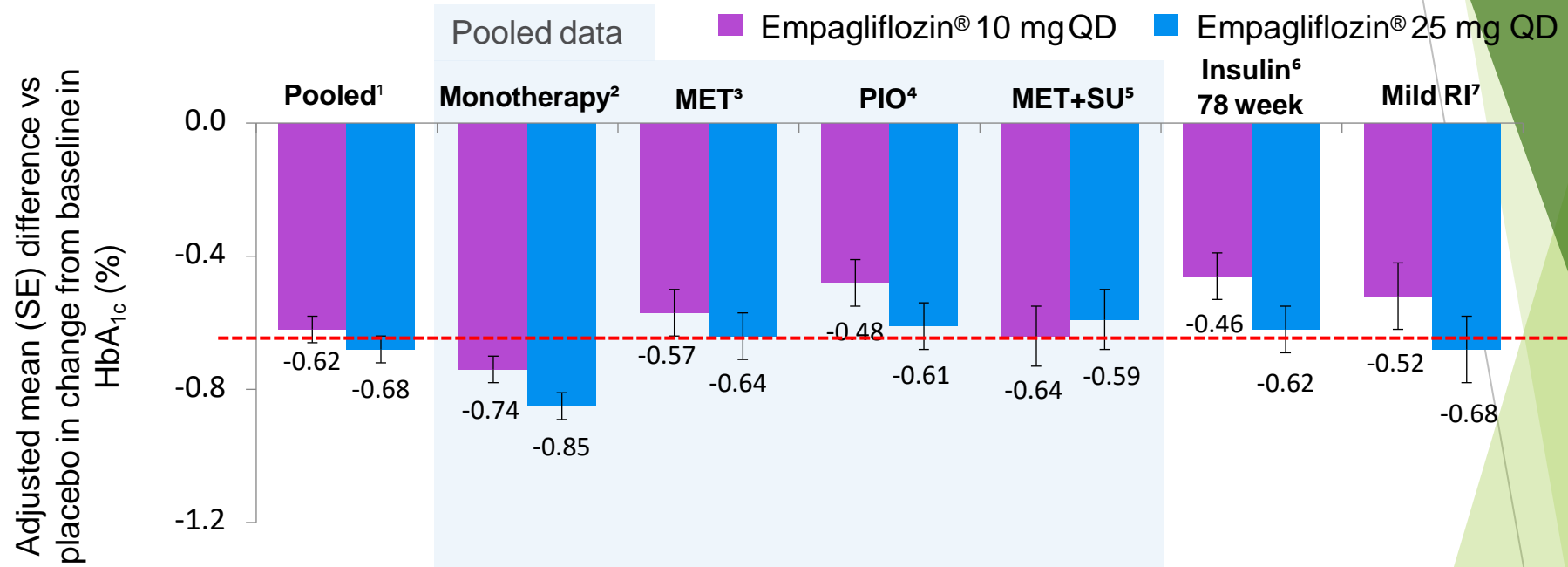
Efficacy Studies

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);
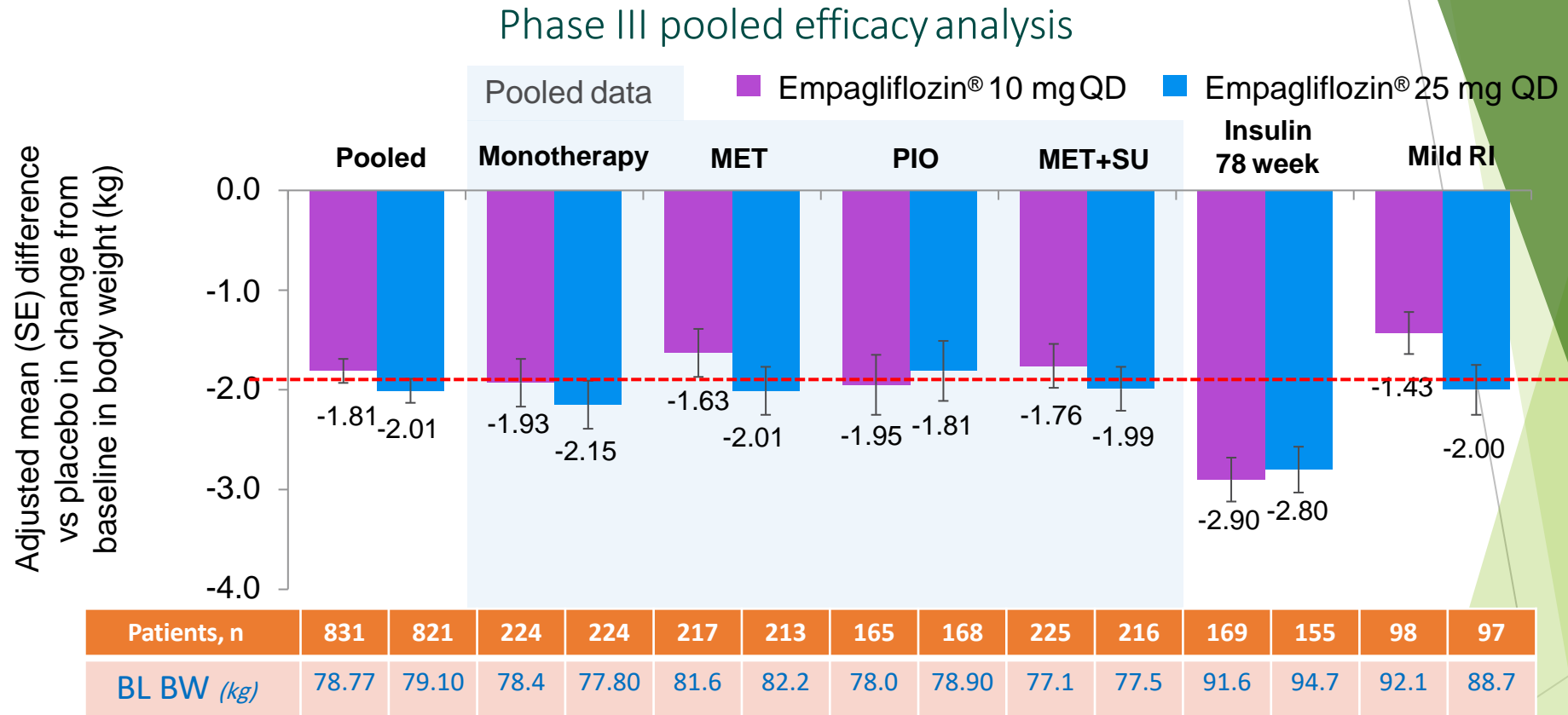4-Kovacs C, et al. *Diabetes Obes Metab*. 2014;16(2):147–158;   5- Häring H-U, et al. *Diabetes Care*. 2013;36(11):3396–404;   6- Rosenstock J, et al. *Diabetologia*. 2013;56(suppl 1);S372 (P9321);
7-Barnett A, et al, *Lancet Diabetes Endocrinol*. 2014; doi:10.1016/S2213-8587(13)70208-0.

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

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Phase III pooled efficacy analysis

Pooled data ■ Empagliflozin® 10 mg QD ■ Empagliflozin® 25 mg QD

Adjusted mean (SE) difference vs placebo in change from baseline in body weight (kg)

	Pooled		Monotherapy		MET		PIO		MET+SU		Insulin 78 week		Mild RI	

Values shown on bars:
- Pooled: -1.81, -2.01
- Monotherapy: -1.93, -2.15
- MET: -1.63, -2.01
- PIO: -1.95, -1.81
- MET+SU: -1.76, -1.99
- Insulin 78 week: -2.90, -2.80
- Mild RI: -1.43, -2.00

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);
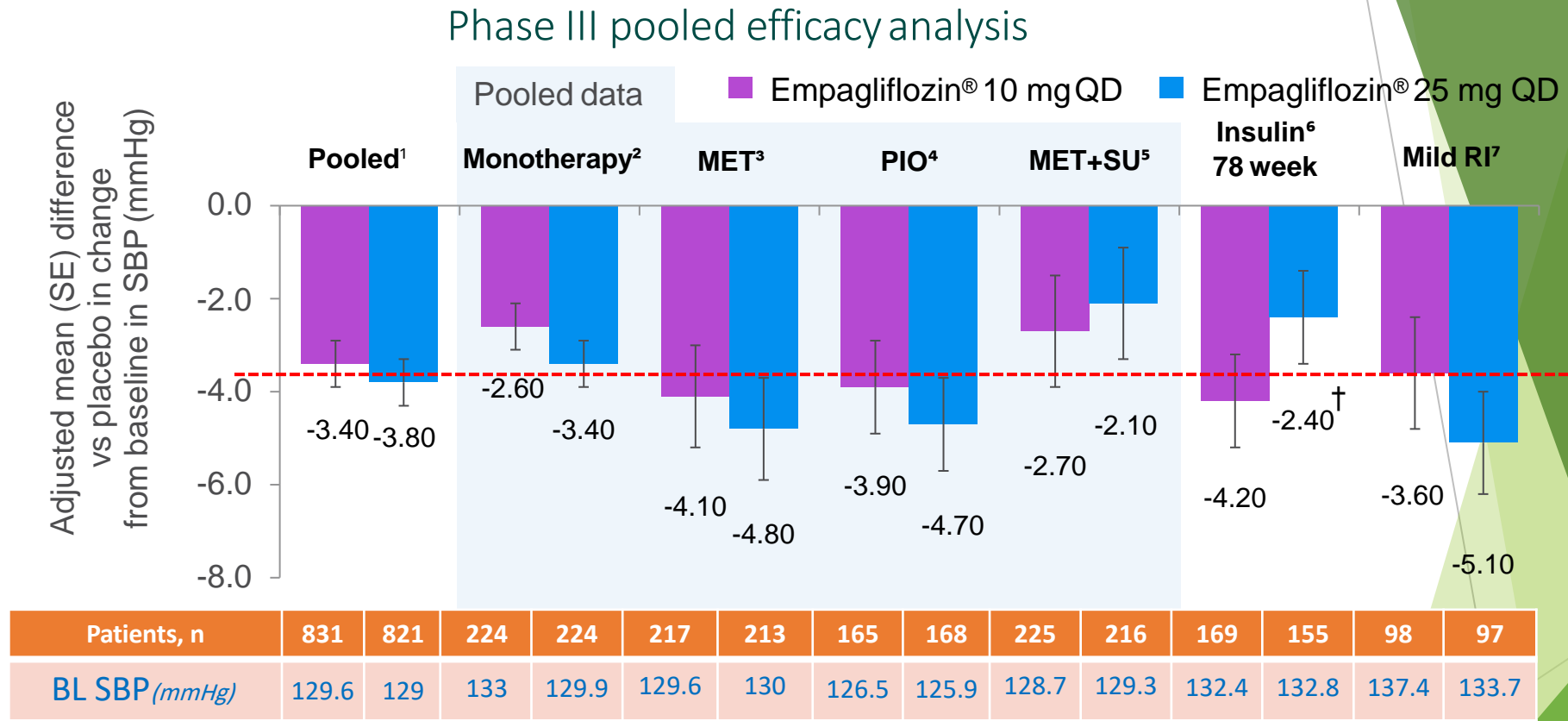4-Kovacs C, et al. Diabetes Obes Metab. 2014;16(2):147–158;   5- Häring H-U, et al. Diabetes Care. 2013;36(11):3396–404;   6- Rosenstock J, et al. Diabetologia. 2013;56(suppl 1);S372 (P931);
7-Barnett A, et al, Lancet Diabetes Endocrinol. 2014; doi:10.1016/S2213-8587(13)70208-0.

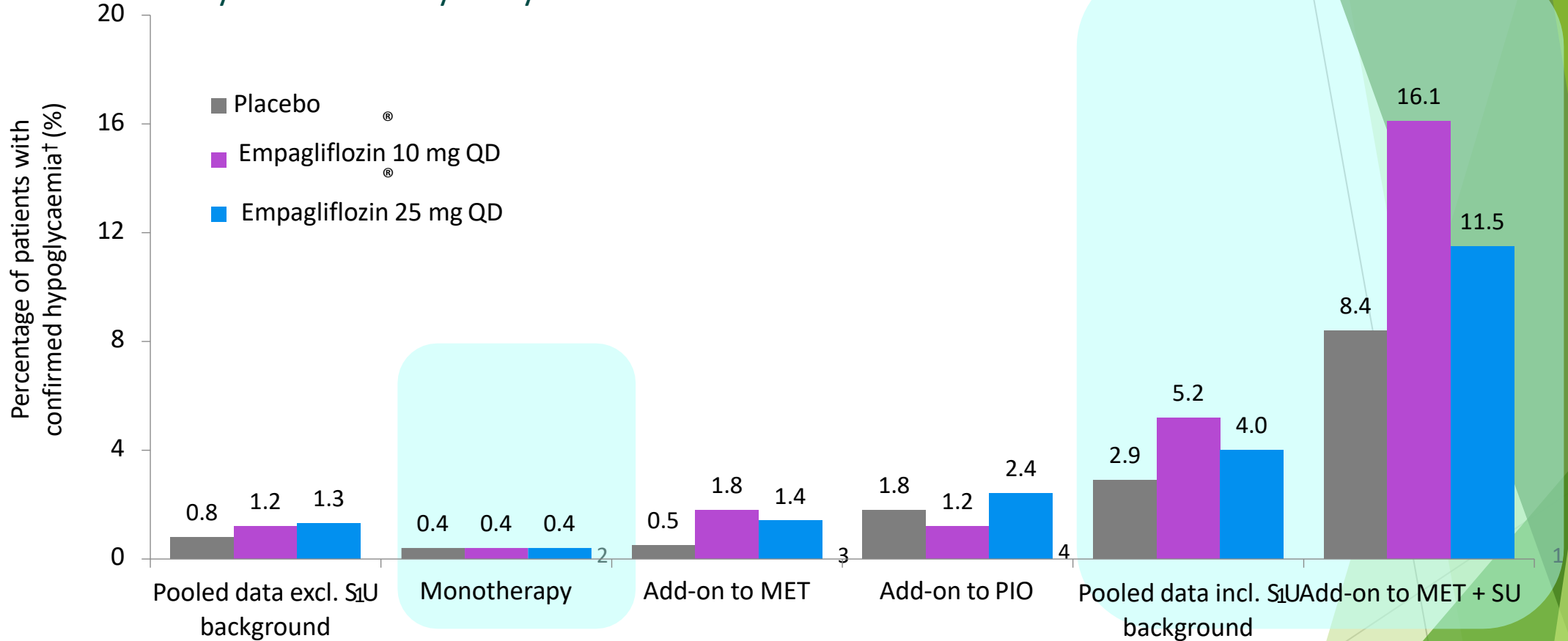# Δ SBP Across Different Background Therapy Empagliflozin® vs. Placebo*

Phase III pooled efficacy analysis

Pooled data █ Empagliflozin® 10 mg QD   █ Empagliflozin® 25 mg QD

Y-axis: Adjusted mean (SE) difference vs placebo in change from baseline in SBP (mmHg)

Categories: Pooled[1], Monotherapy[2], MET[3], PIO[4], MET+SU[5], Insulin[6] 78 week, Mild RI[7]

Bar values:
- Pooled[1]: -3.40, -3.80
- Monotherapy[2]: -2.60, -3.40
- MET[3]: -4.10, -4.80
- PIO[4]: -3.90, -4.70
- MET+SU[5]: -2.70, -2.10
- Insulin[6] 78 week: -4.20, -2.40 †
- Mild RI[7]: -3.60, -5.10

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.

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Hypoglycemic Events

- Phase III safety and tolerability analysis

Percentage of patients with confirmed hypoglycaemia† (%)

Legend:
- Placebo
- Empagliflozin 10 mg QD®
- Empagliflozin 25 mg QD®

Category	Placebo	Empagliflozin 10 mg QD	Empagliflozin 25 mg QD
Pooled data excl. SU background	0.8	1.2	1.3
Monotherapy	0.4	0.4	0.4
Add-on to MET	0.5	1.8	1.4
Add-on to PIO	1.8	1.2	2.4
Pooled data incl. SU background	2.9	5.2	4.0
Add-on to MET + SU	8.4	16.1	11.5

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).

Genital infection stratified by previous history

Phase III pooled[†] safety and tolerability analysis
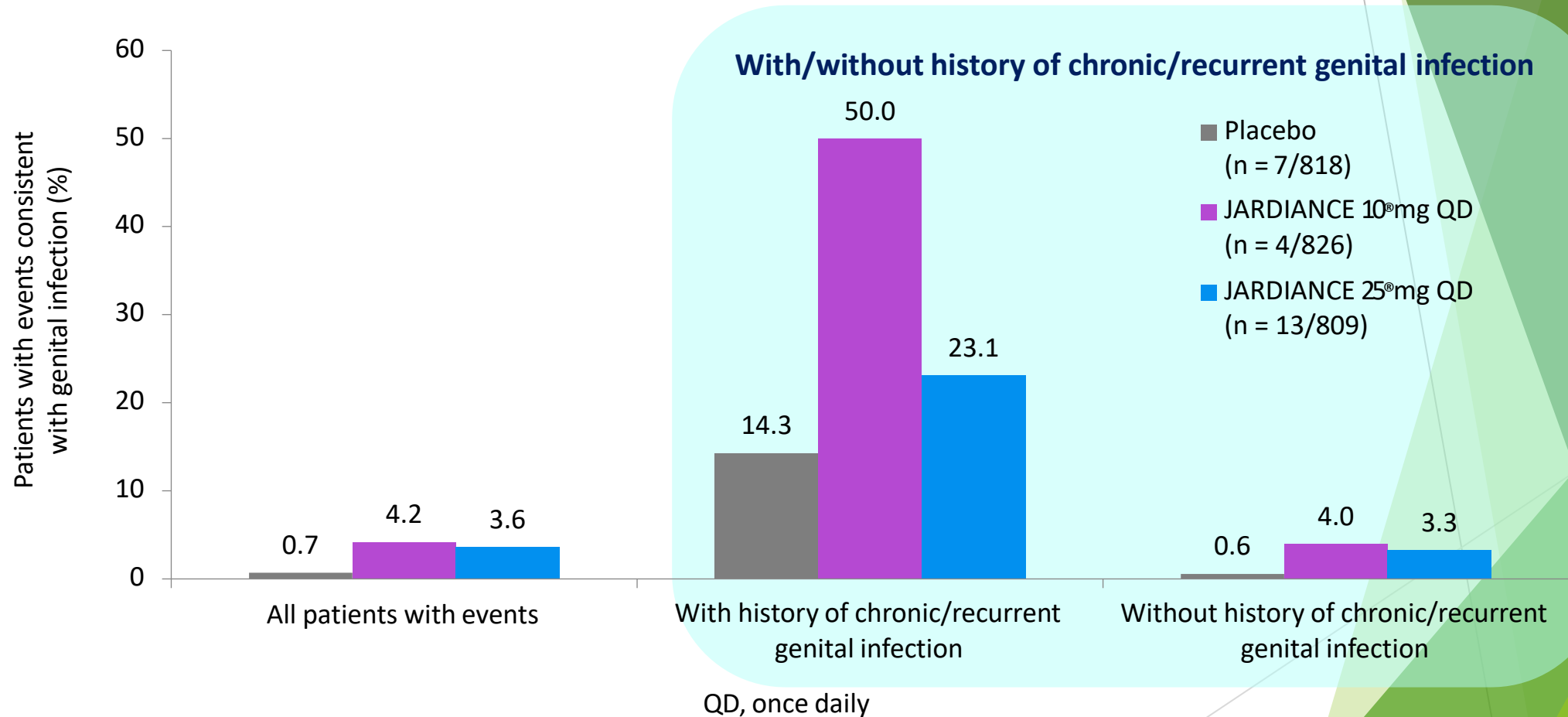
With/without history of chronic/recurrent genital infection

Legend:
- Placebo (n = 7/818)
- JARDIANCE 10®mg QD (n = 4/826)
- JARDIANCE 25®mg QD (n = 13/809)

Y-axis: Patients with events consistent with genital infection (%)

All patients with events: 0.7, 4.2, 3.6

With history of chronic/recurrent genital infection: 14.3, 50.0, 23.1

Without history of chronic/recurrent genital infection: 0.6, 4.0, 3.3

QD, once daily

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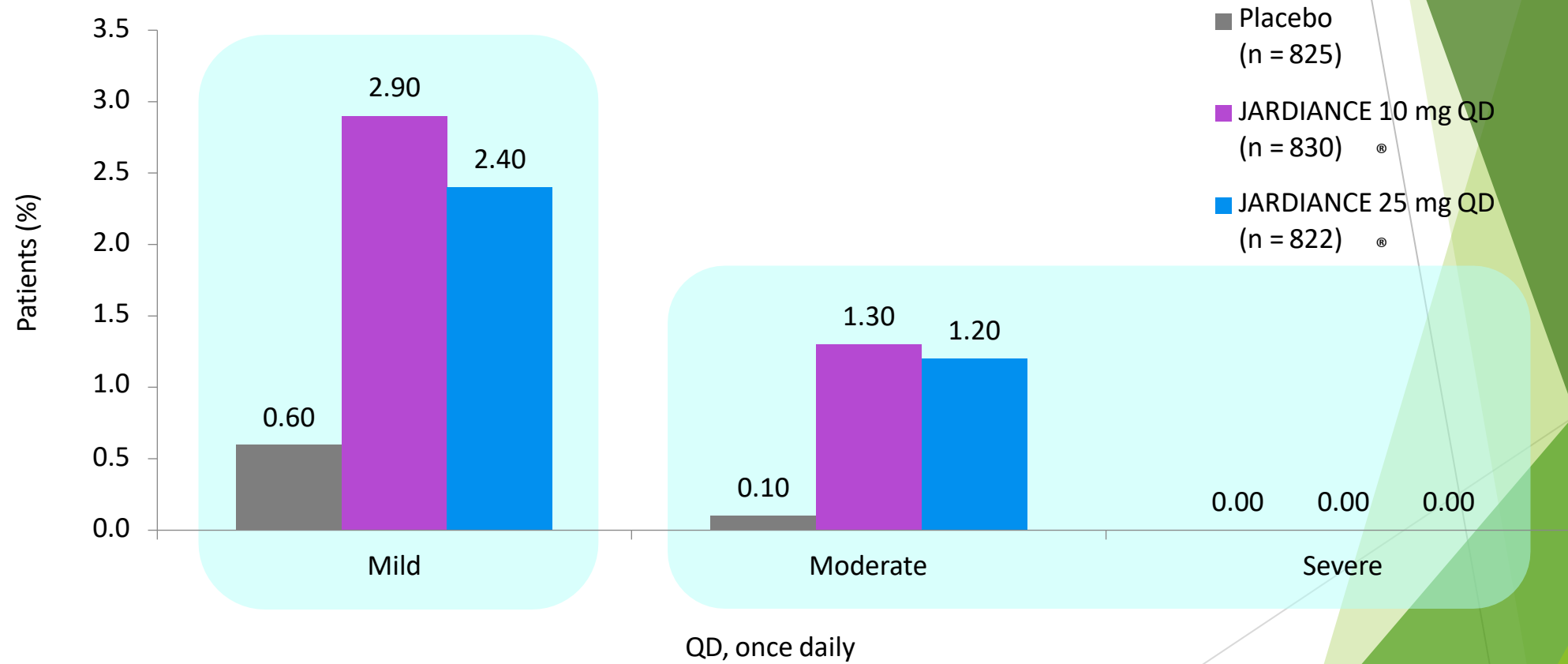
†The following studies were included in the pooled analysis:

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®

The NEW ENGLAND JOURNAL of MEDICINE

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

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

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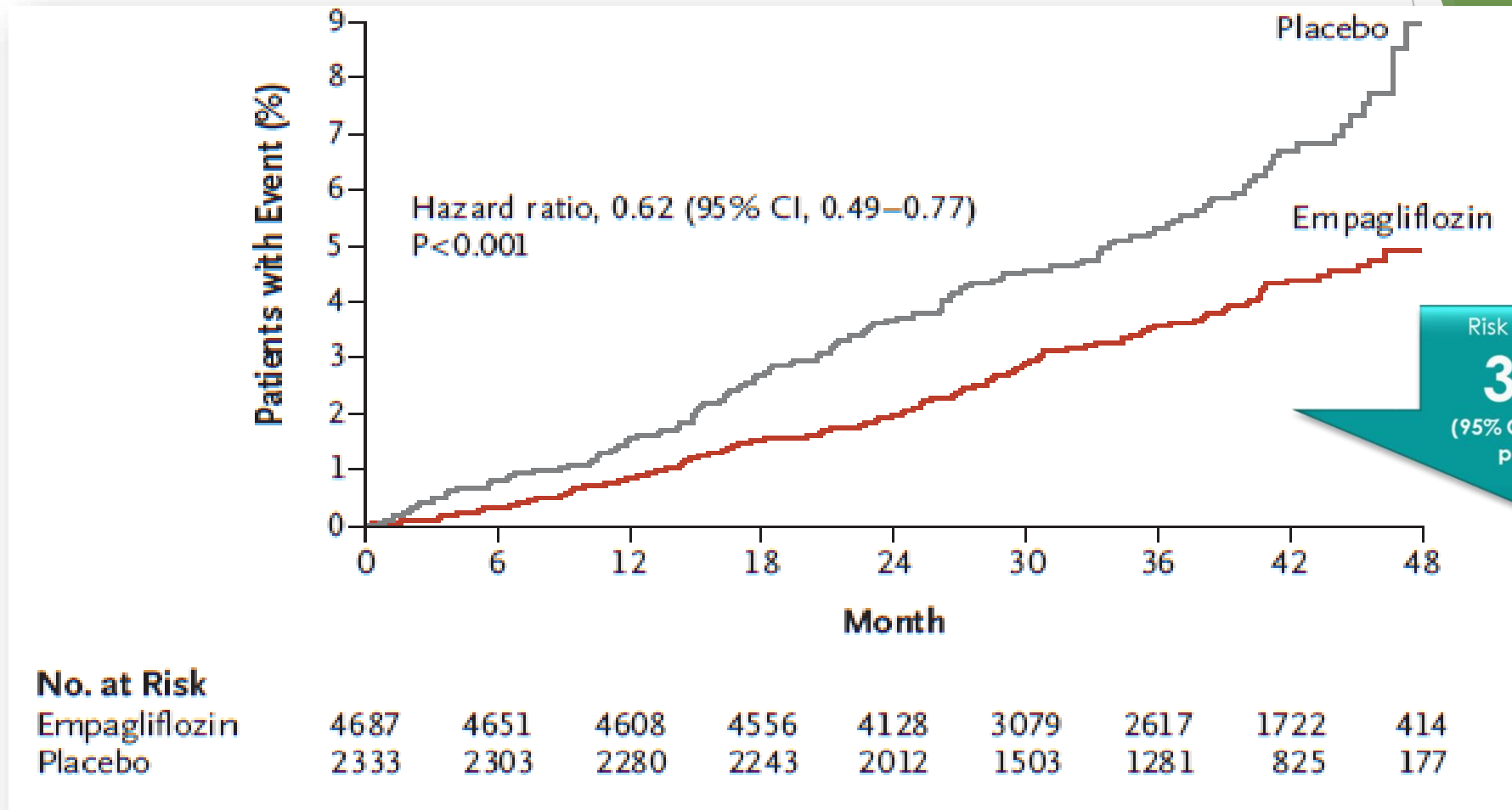
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Trial Design[1]

- **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.

Screening (n=11531) — Randomised and treated (n=7020)

Placebo (n=2333)

Empagliflozin 10 mg (n=2345)

Empagliflozin 25 mg (n=2342)
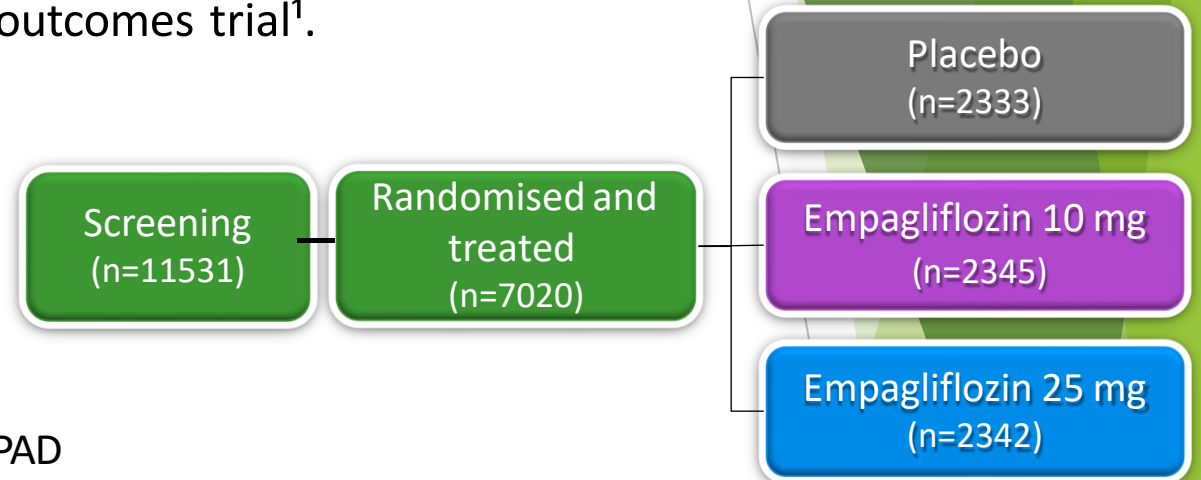
BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
*No glucose-lowering therapy for ≥12 weeks prior to randomisation or no change in dose for ≥12 weeks prior to randomisation or, in the case of insulin, unchanged by >10% compared to the dose at randomisation
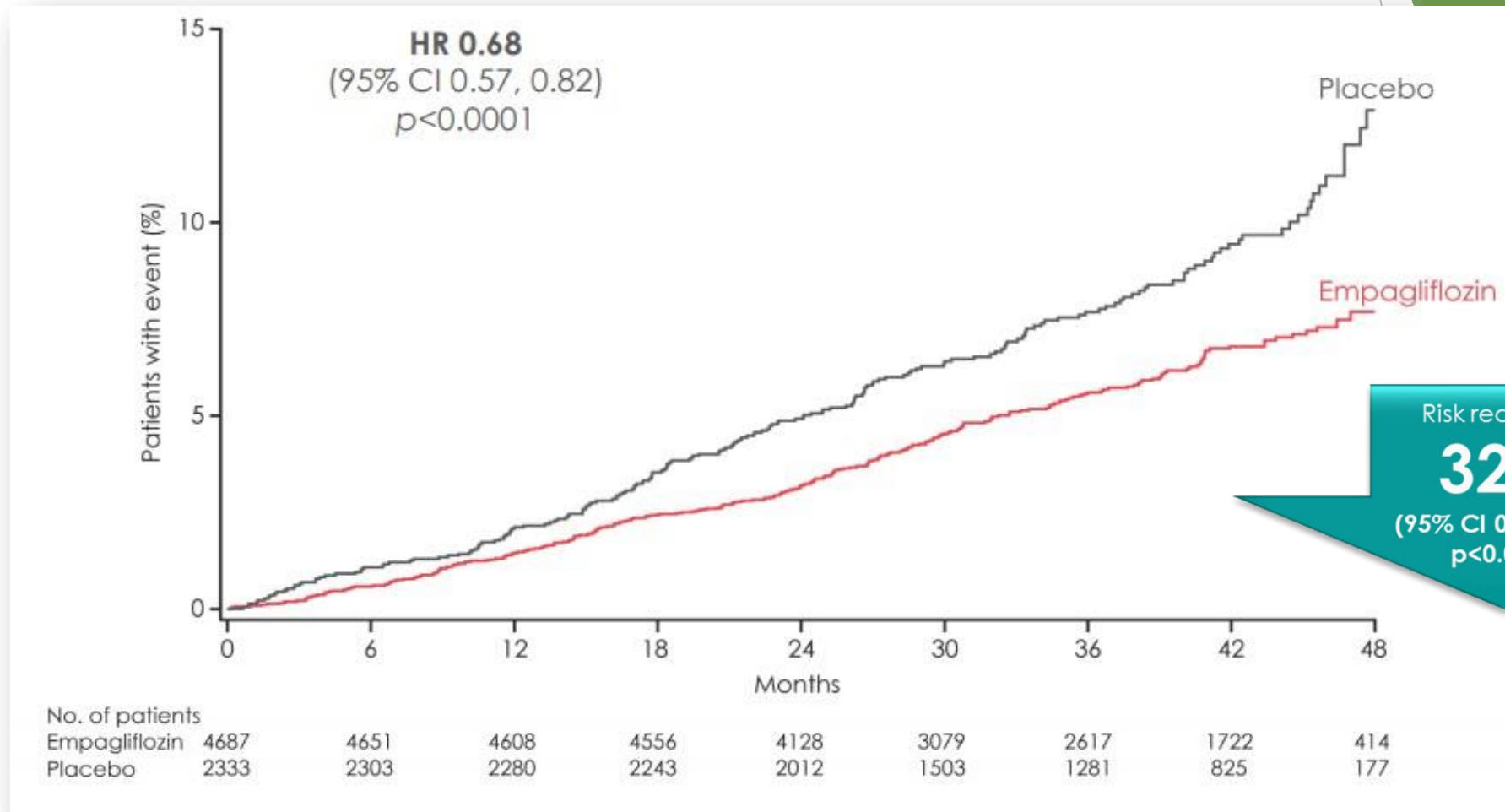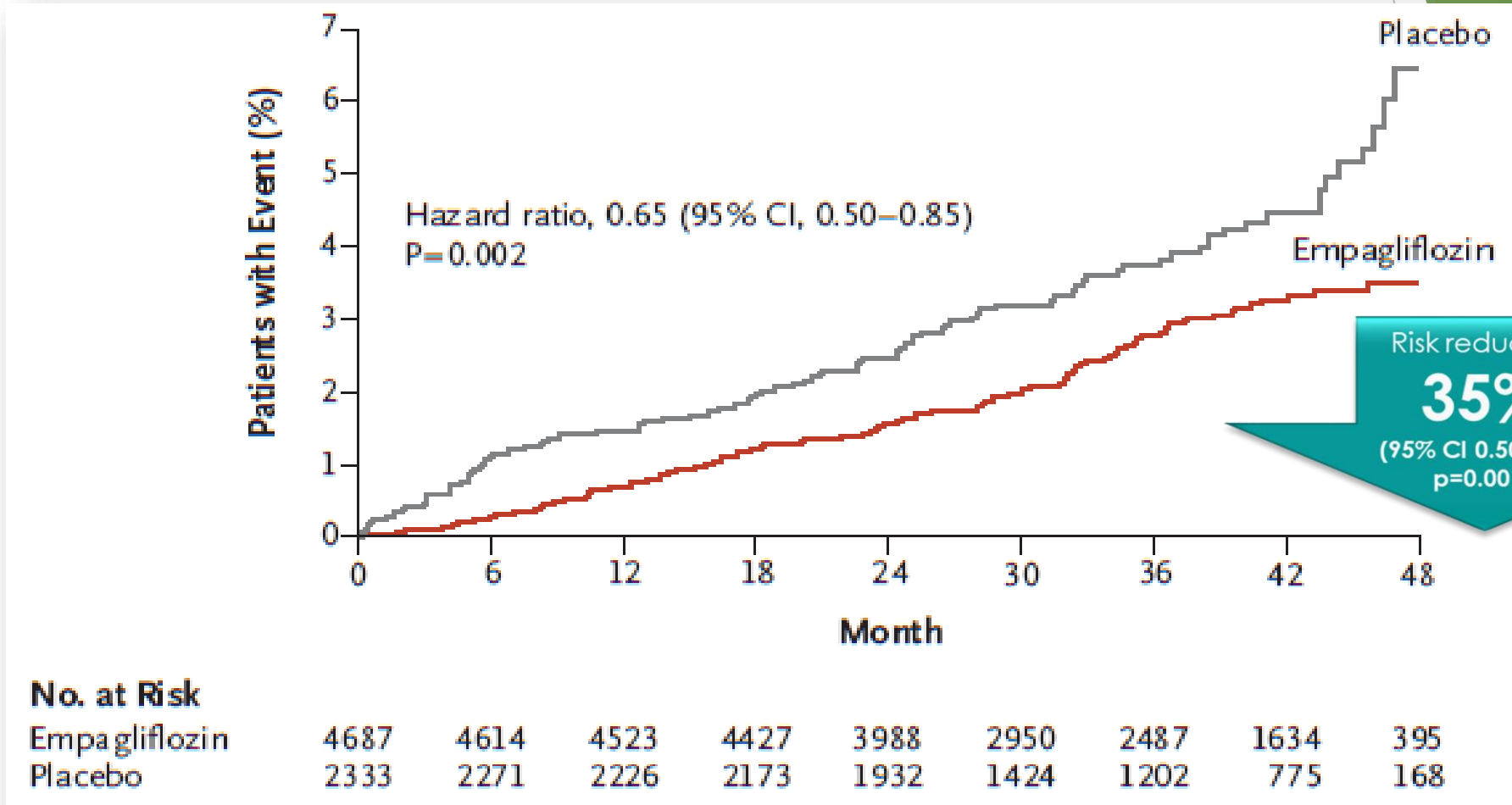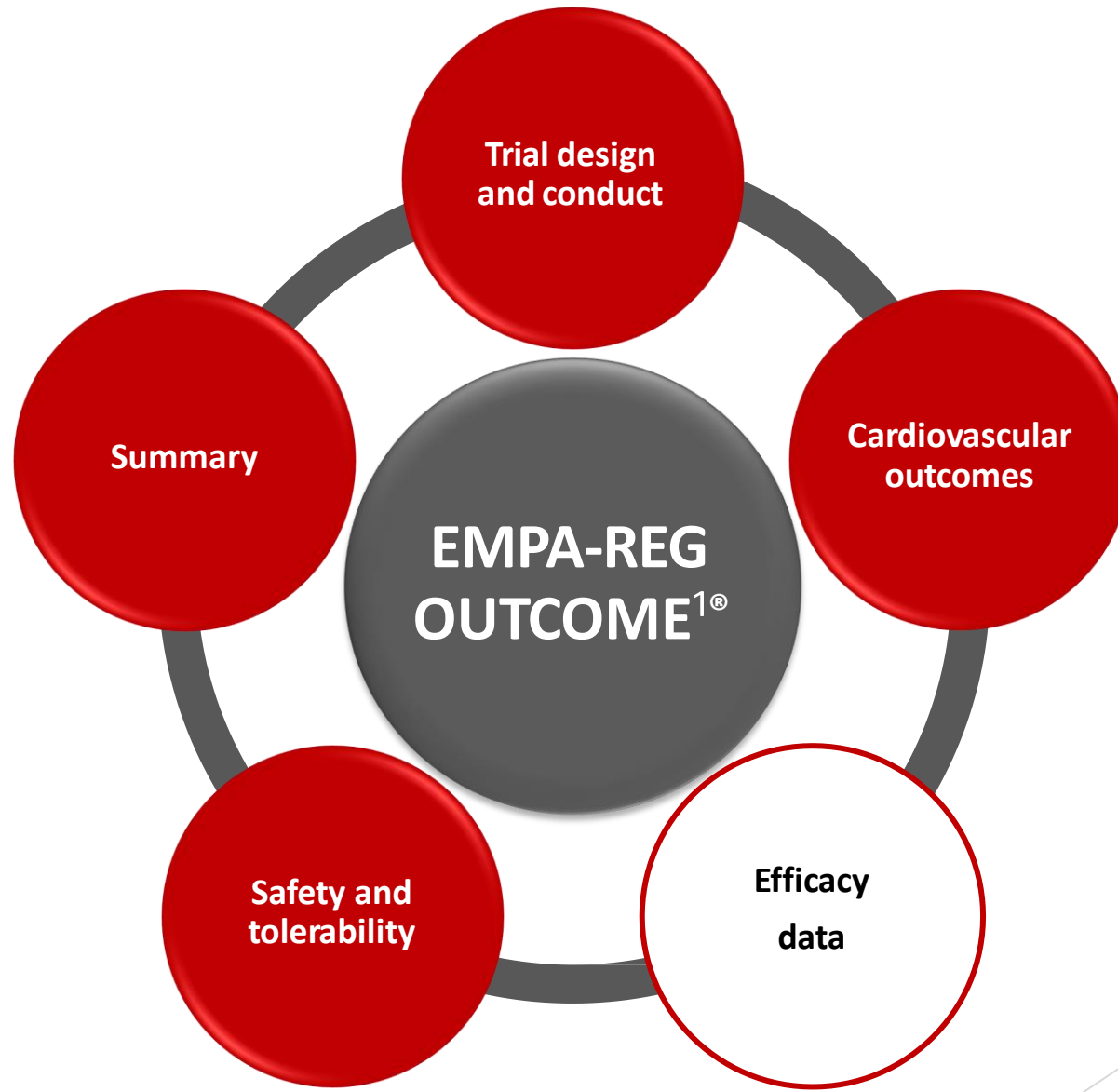
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

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.
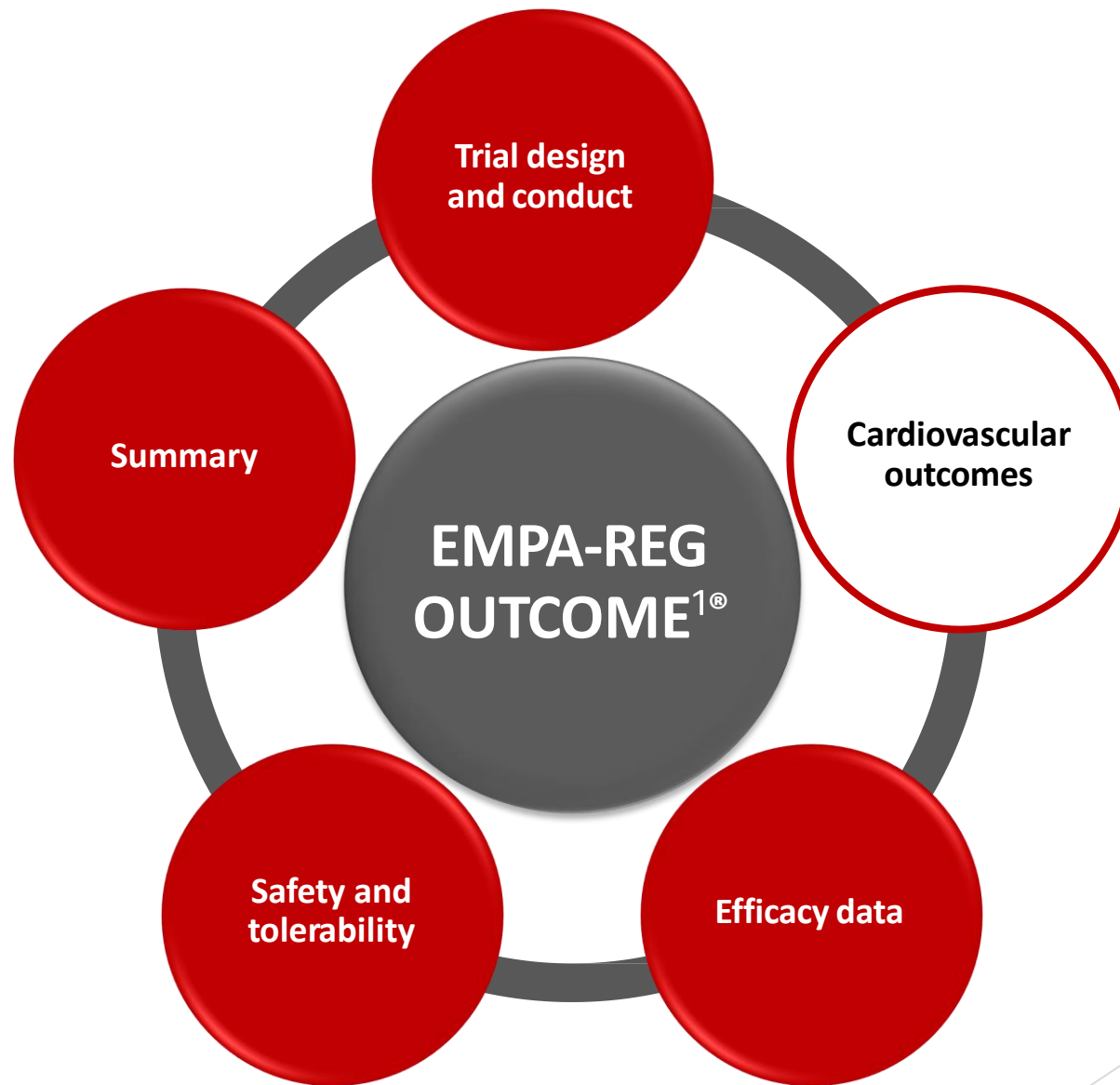
Pre-specified primary and key secondary outcomes[1]

Cardiovascular death

Non-fatal myocardial infarction

MACE*

Non-fatal stroke

Additional components may be included

Hospitalization for unstable angina

Key components of MACE
(hard endpoints of atherosclerotic disease)

Additional components for MACE-plus
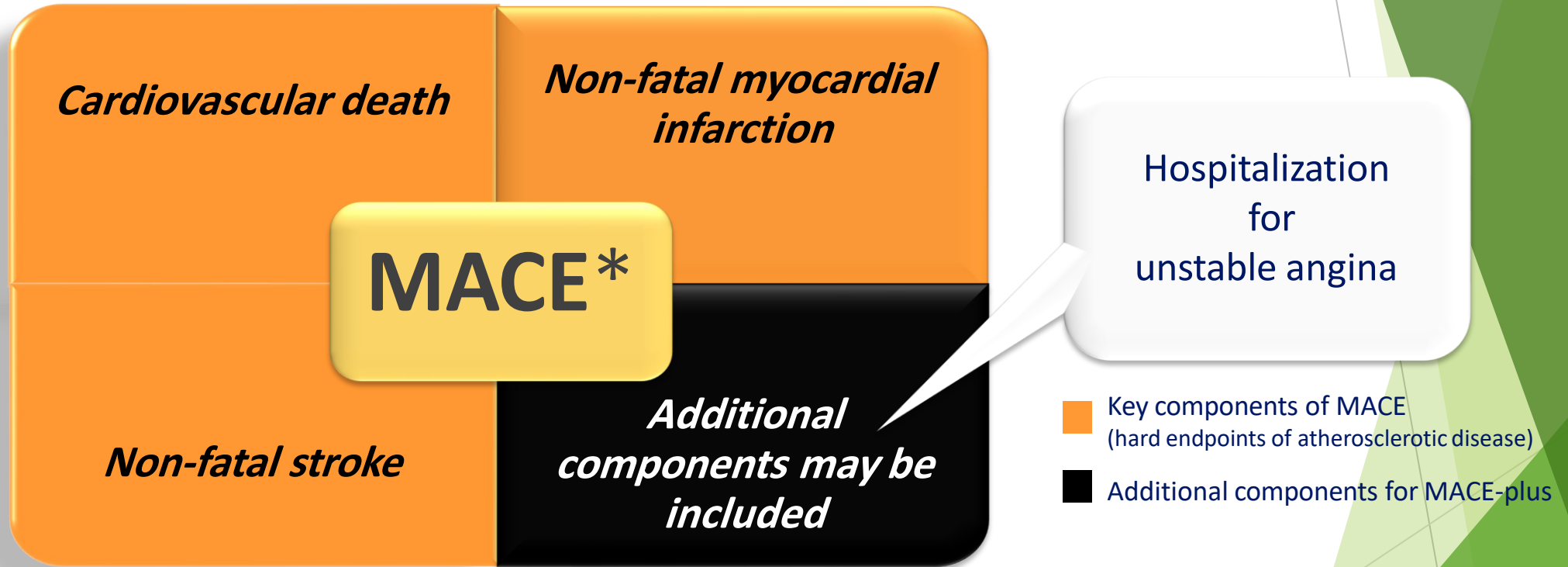
*Major Adverse Cardiovascular Events

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.
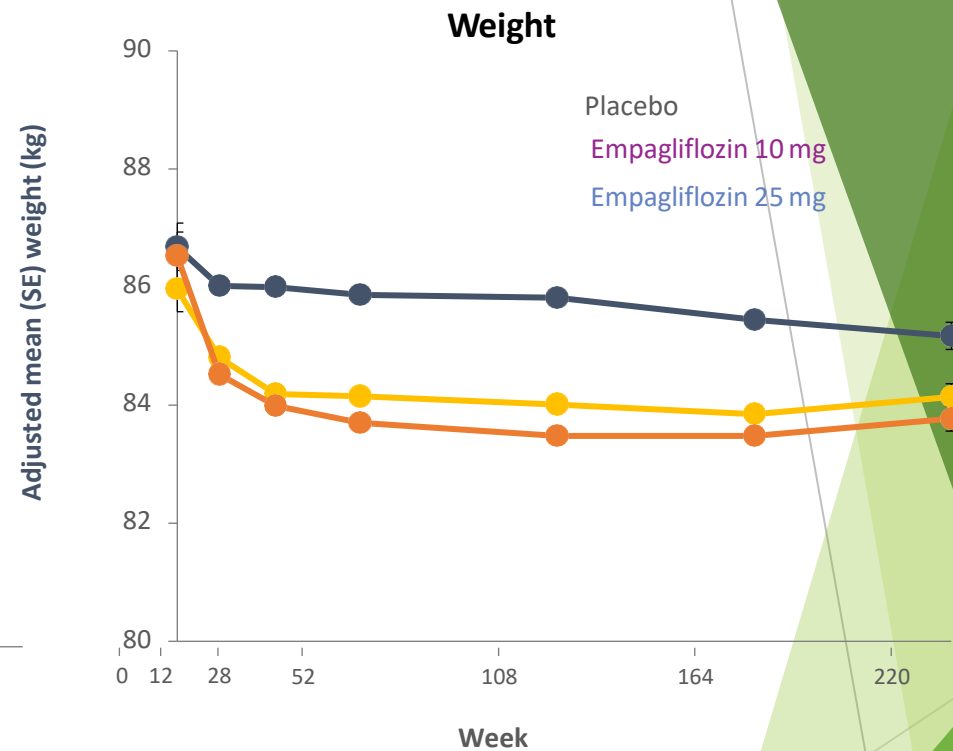
Primary Outcome: 3-point MACE (CV death, Nonfatal MI, Nonfatal stroke)[1]
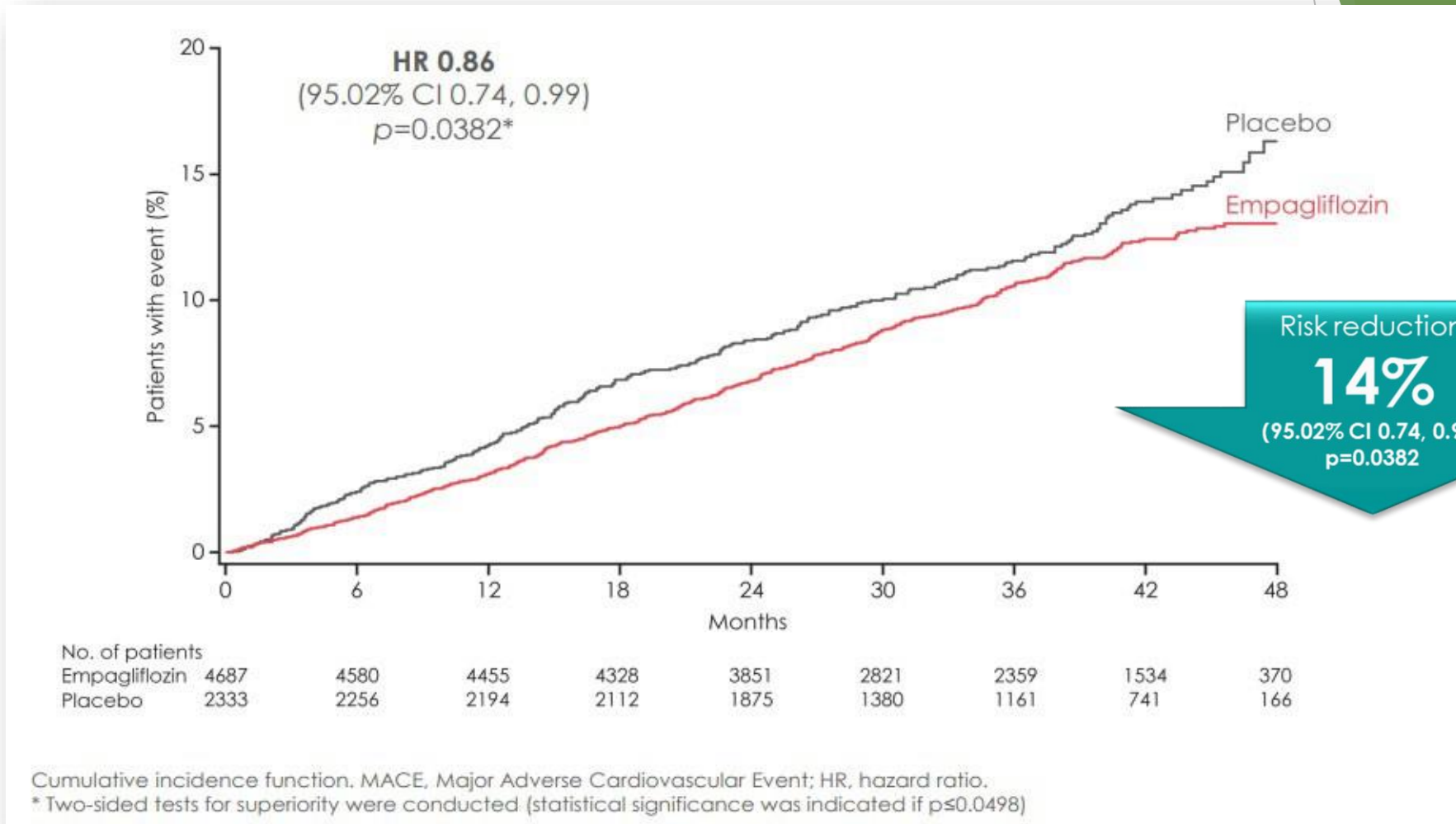
Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

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®CV Death[1]

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001

Risk reduction
38%
(95% CI 0.49, 0.77)
p<0.0001

No. at Risk

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

1-Zinman B et al,. 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]

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]

Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002

Risk reduction
35%
(95% CI 0.50, 0.85)
p=0.0017

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.

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]

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HbA1c

Adjusted mean (SE) HbA1c (%)

- Placebo
- Empagliflozin 10 mg
- Empagliflozin 25 mg

Week
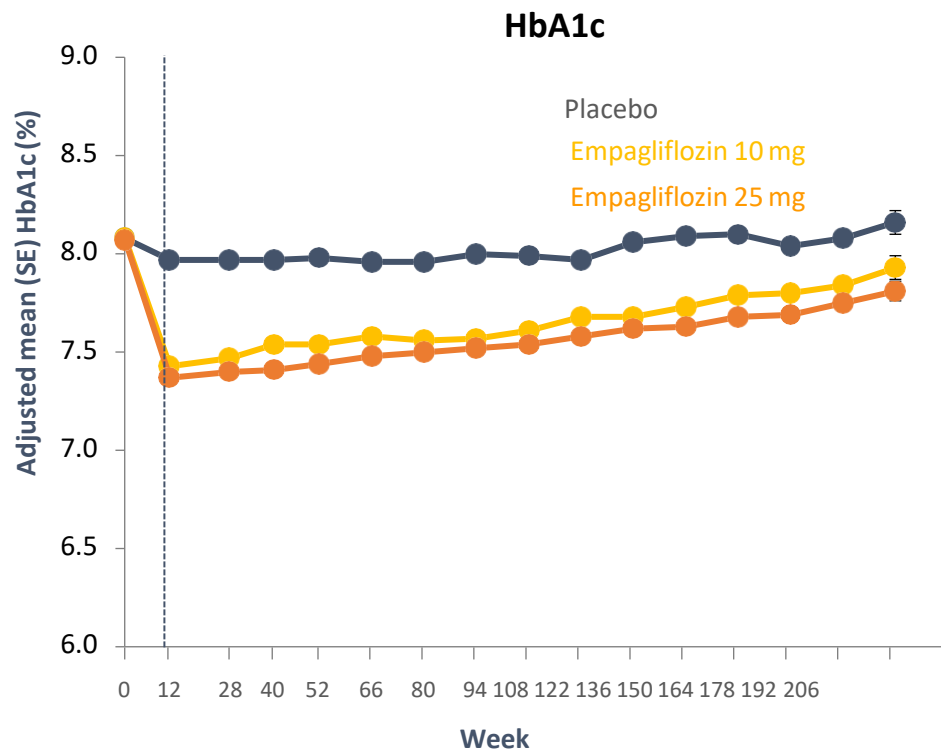
	0	12	28	40	52	66	80	94	108	122	136	150	164	178	192	206
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
EMPA 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
EMPA 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Weight

Adjusted mean (SE) weight (kg)

- Placebo
- Empagliflozin 10 mg
- Empagliflozin 25 mg

Week

	0	12	28	52	108	164	220
	2285	1915	2215	2138	1598	1239	425
	2290	1893	2238	2174	1673	1298	483
	2283	1891	2226	2178	1678	1335	489

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

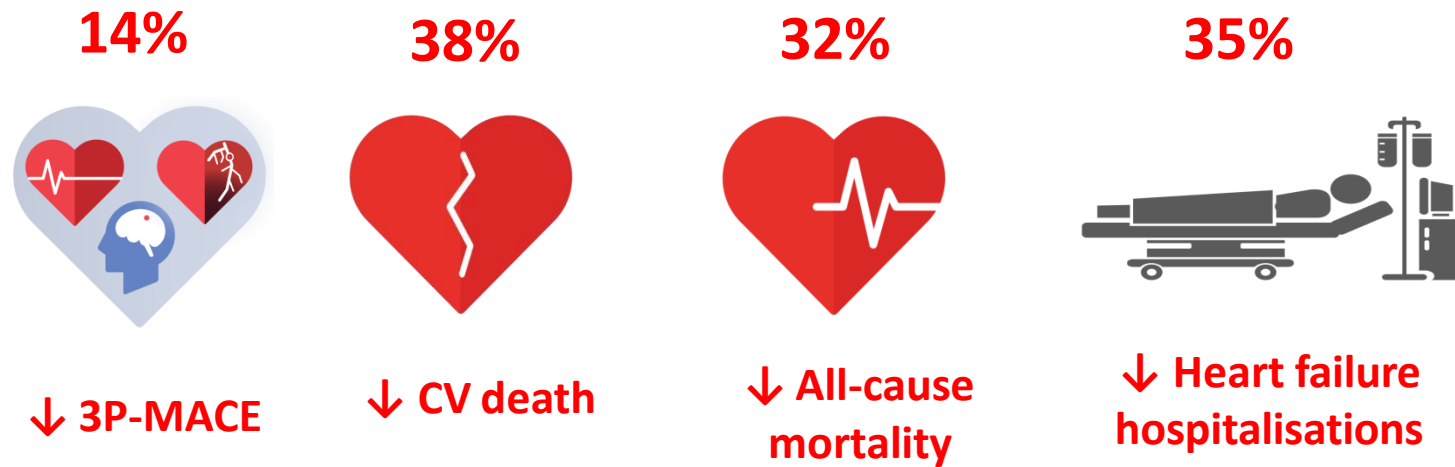EMPA, empagliflozin; HbA1c, glycated hemoglobin

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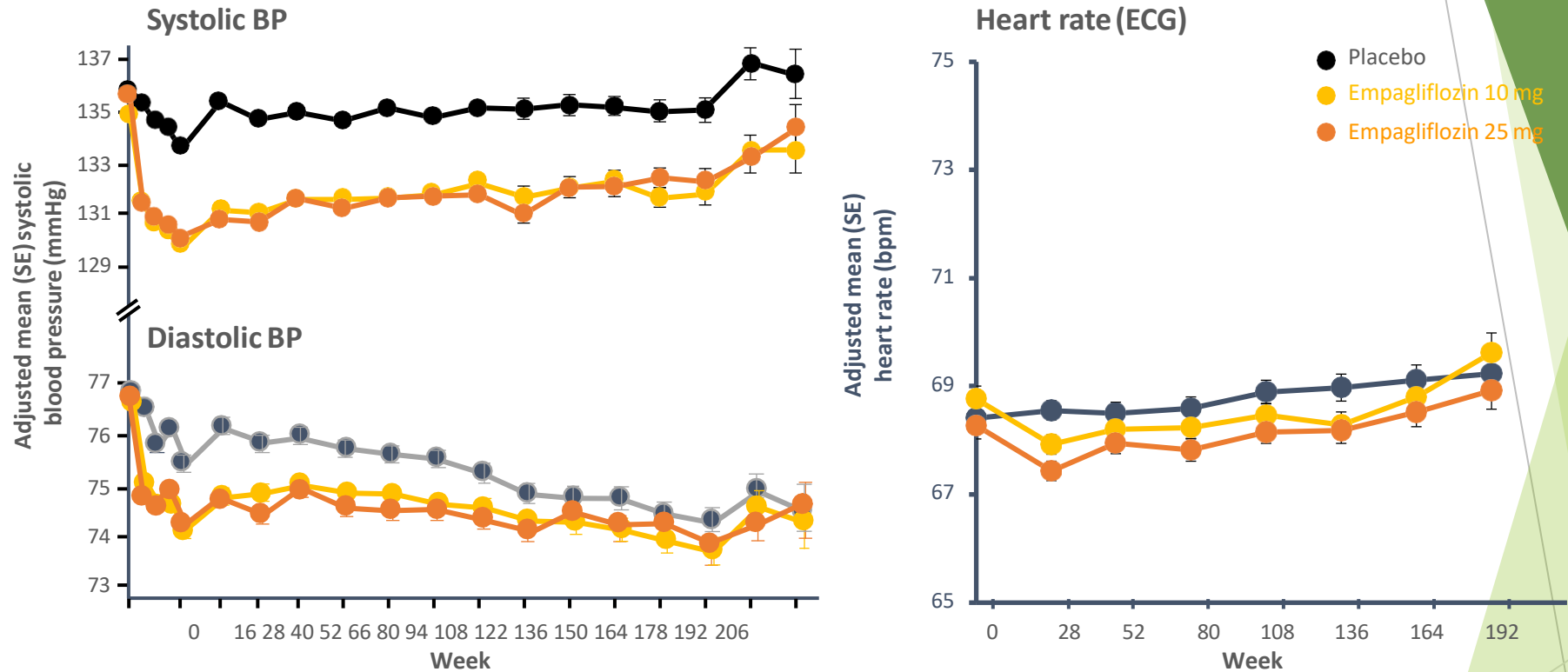
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
EMPA 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
EMPA 25 mg	2322	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

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

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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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.
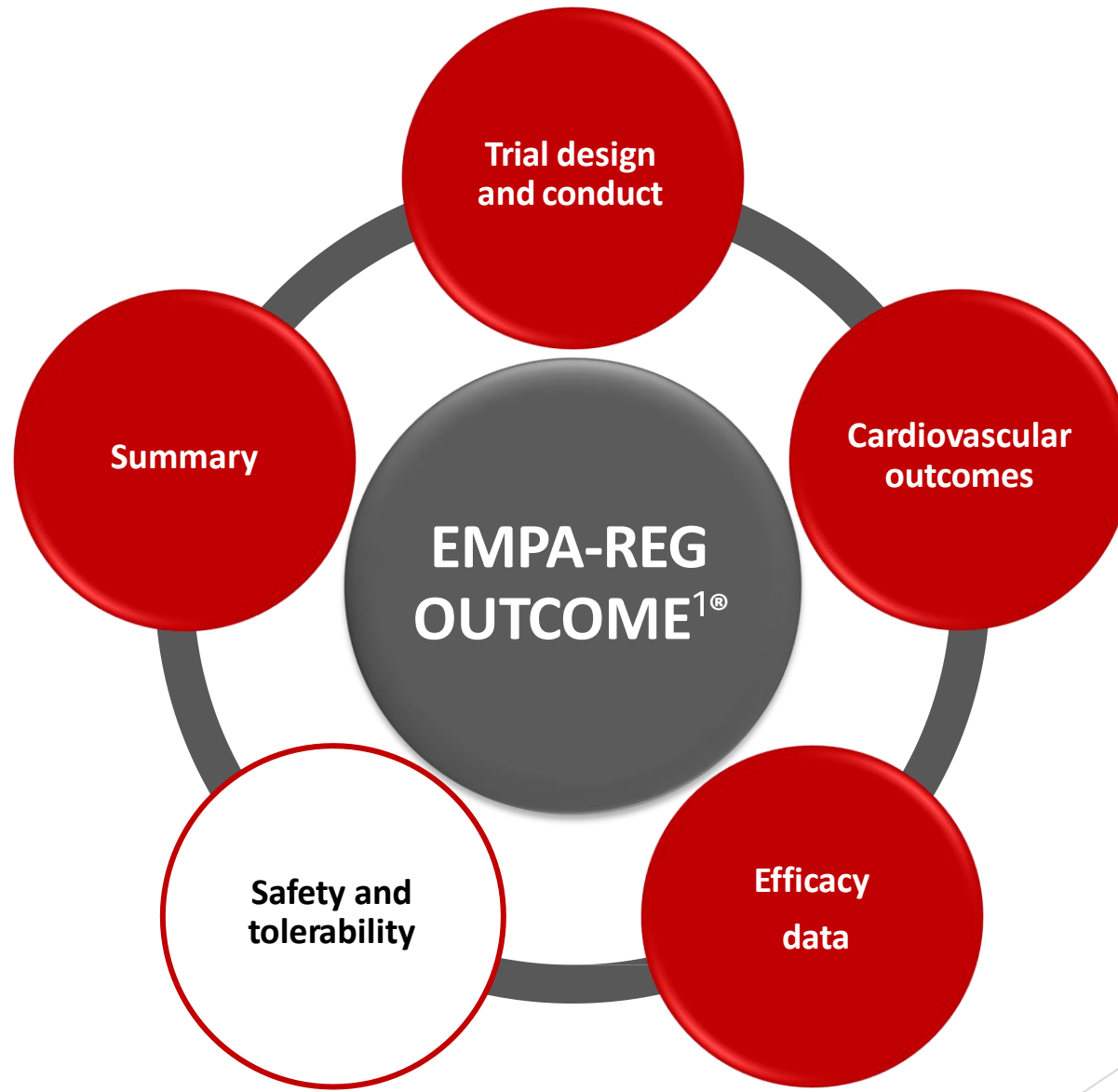
Adverse events[1,2]

	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.
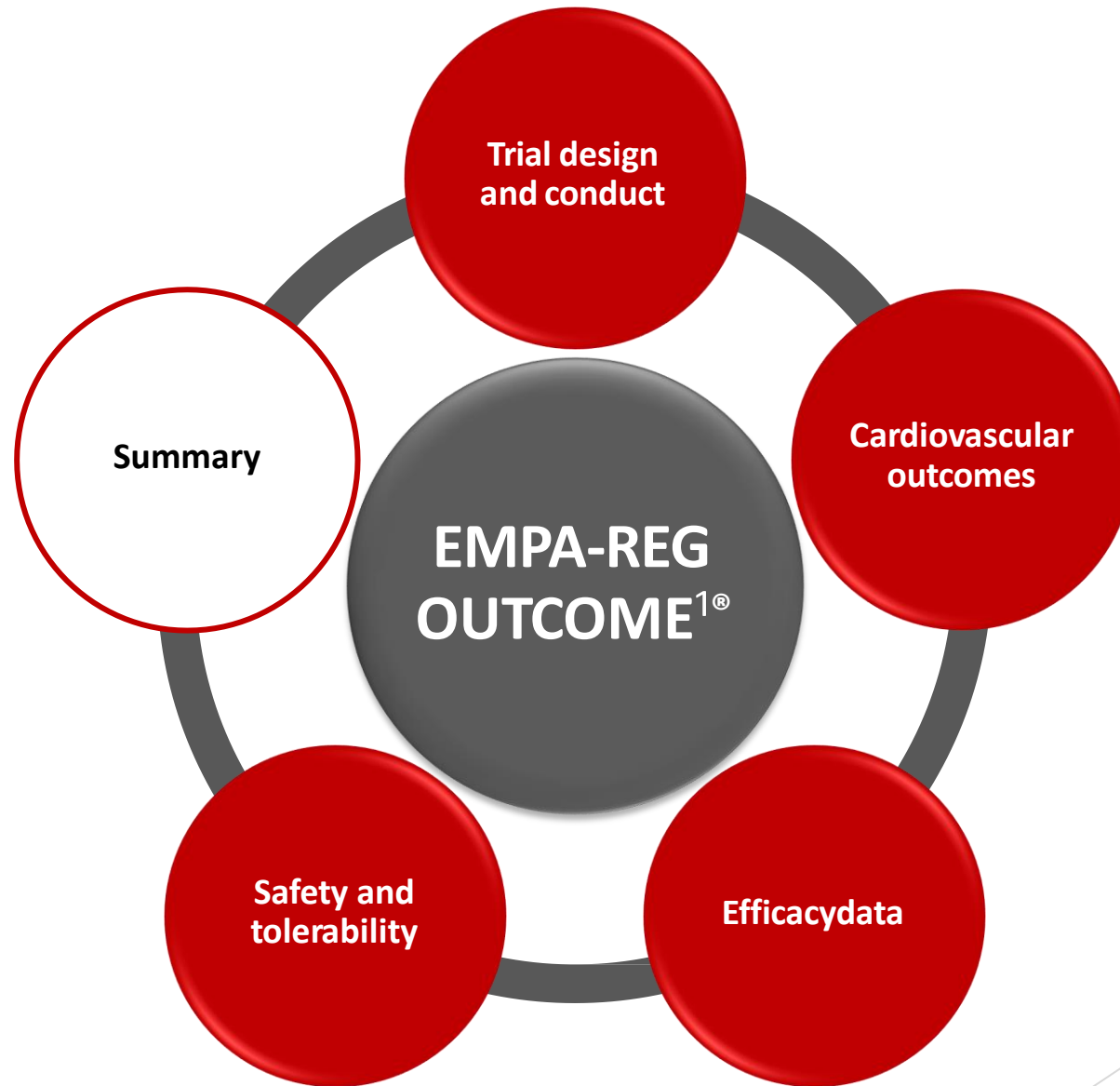
EMPA-REG OUTCOME®: summary

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]

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*

Objective[1]:

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.

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

EMPEROR-Reduced: Patient Disposition[1]

7220 patients screened for eligibility

2017-2019

Median follow-up
16 month

Final vital status
Known in 99.4%

Not randomized
Not eligible (3314)
Withdrawal of consent (80)
Adverse event(21)
Lost to follow-up (19)
Other reasons (56)

3730 were randomized

1863 assigned
To empagliflozin

1867 assigned
To placebo

Drug discontinued
Nonfatal adverse event (158)
Request by patient (92)
Other reason (53)

Drug discontinued
Nonfatal adverse event (176)
Request by patient (124)
Other reason (44)

Final vital status known in 1852
Final vital status unknown in 11

Final vital status known in 1857
Final vital status unknown in 10

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

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Trial Design[1]

Patients must be receiving all appropriate treatments for HF

Screening period of up to 28 days

3730 were randomized

N=1863 Empagliflozin 10 mg qd + SOC

N=1867 Placebo qd + SOC

Median follow-up: ~16 months

30-day post-treatment period

End of treatment at 841 primary outcome events
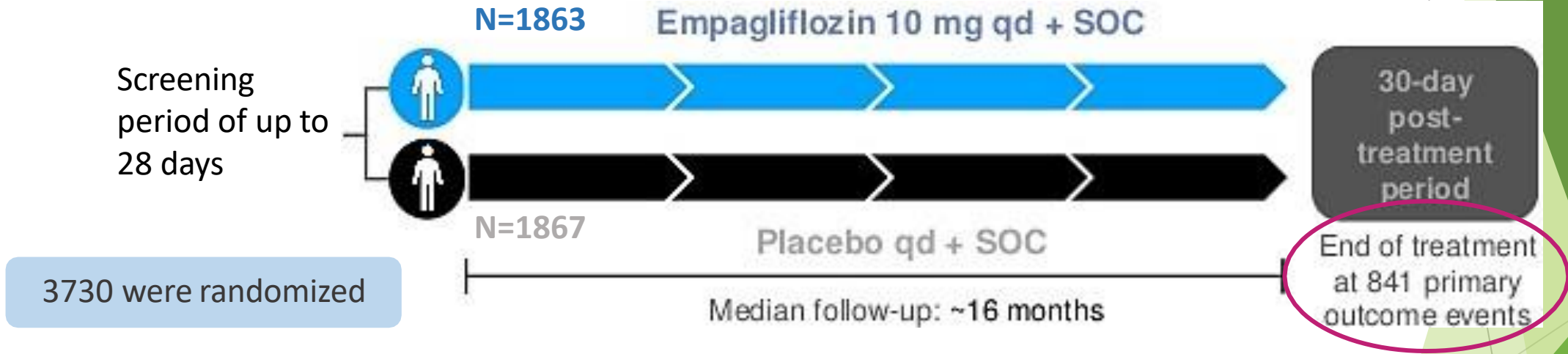
SOC; Standard Of Care

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

EMPEROR-Reduced trial specified only three endpoints to be tested in hierarchical manner[1]

✓ **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

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

Inclusion criteria[1]

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 m^2

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 Patients[1]

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 A

A Primary Outcome

Hazard ratio, 0.75 (95% CI, 0.65–0.86)
P<0.001

462 patients with event rate:
21.0/100 patient-year

361 patients with event rate:
15.8/100 patient-year

25% RRR
p<0.001
19.4% vs 24.7%
HR = 0.75 (0.65-0.86)
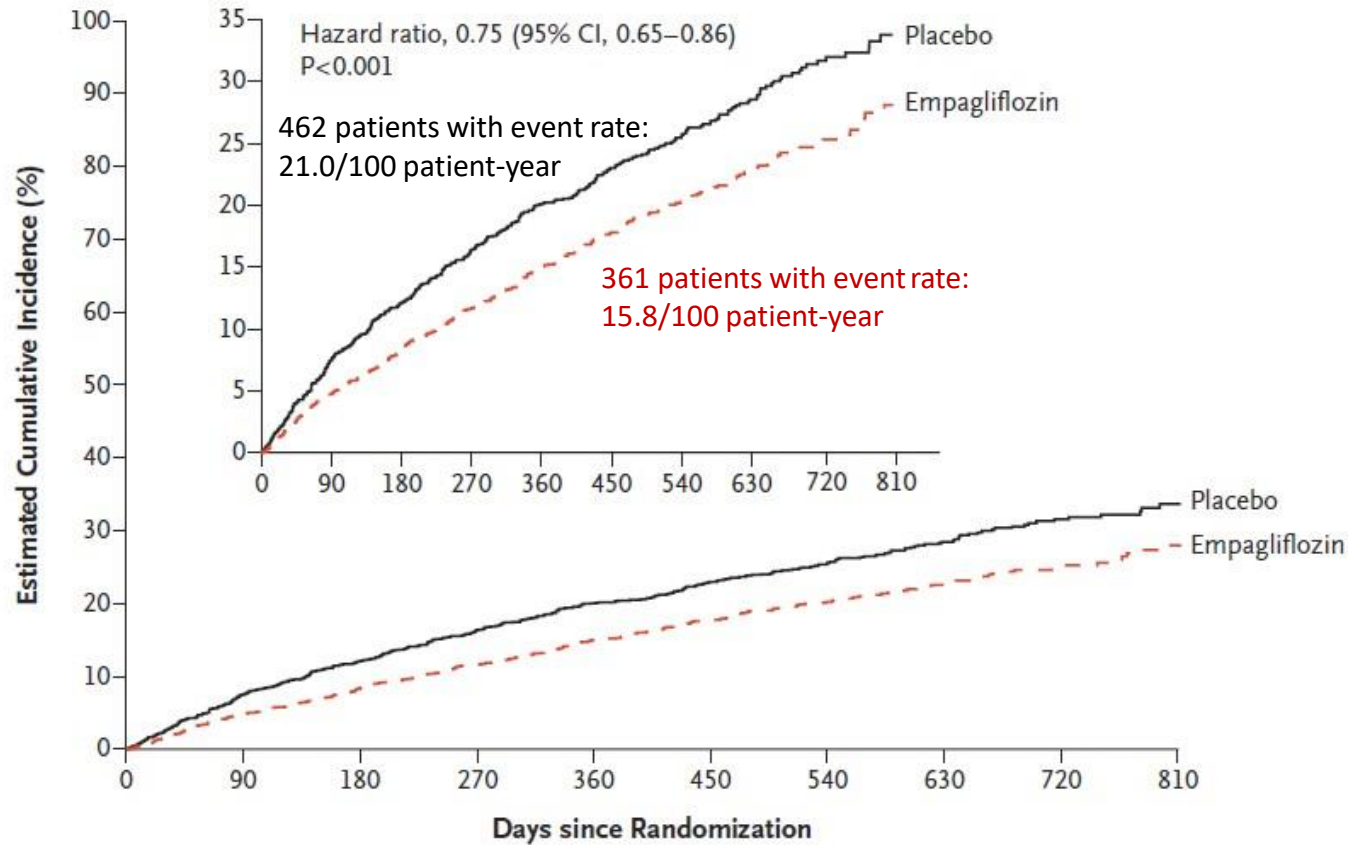
No. at Risk

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

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

Effect on individual components of the primary endpoint[1]

	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)	

25%

31%

8%

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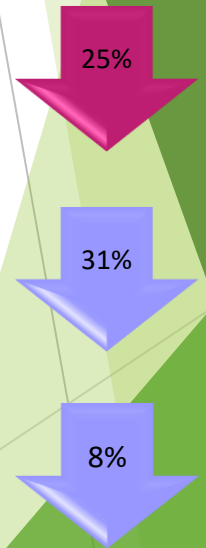
Empagliflozin-Treated Patients Had lower Risk of Hospitalization for Heart Failure[1]

Hazard ratio, 0.70 (95% CI, 0.58–0.85)
P<0.001

Placebo

Empagliflozin

30% RRR
p<0.001

388 Vs 553
HR=0.70 (0.58-0.85)
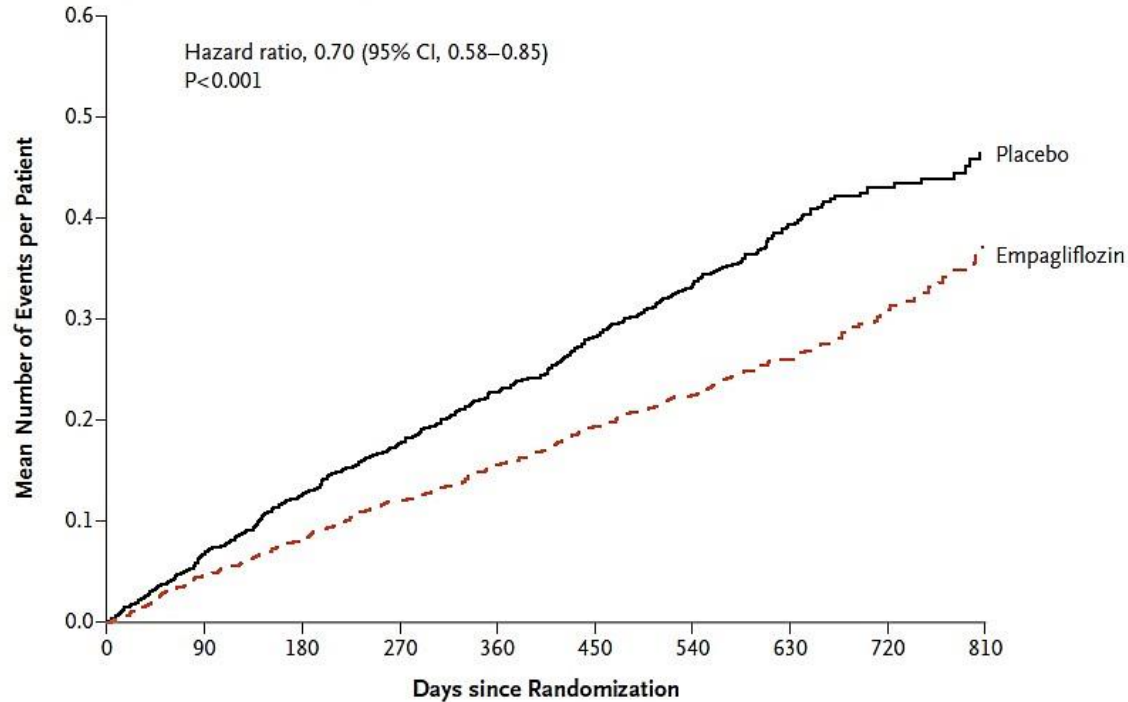
No. at Risk									
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

✓ 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)

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

Empagliflozin Reduced eGFR Significantly Over the Time vs Placebo[1]
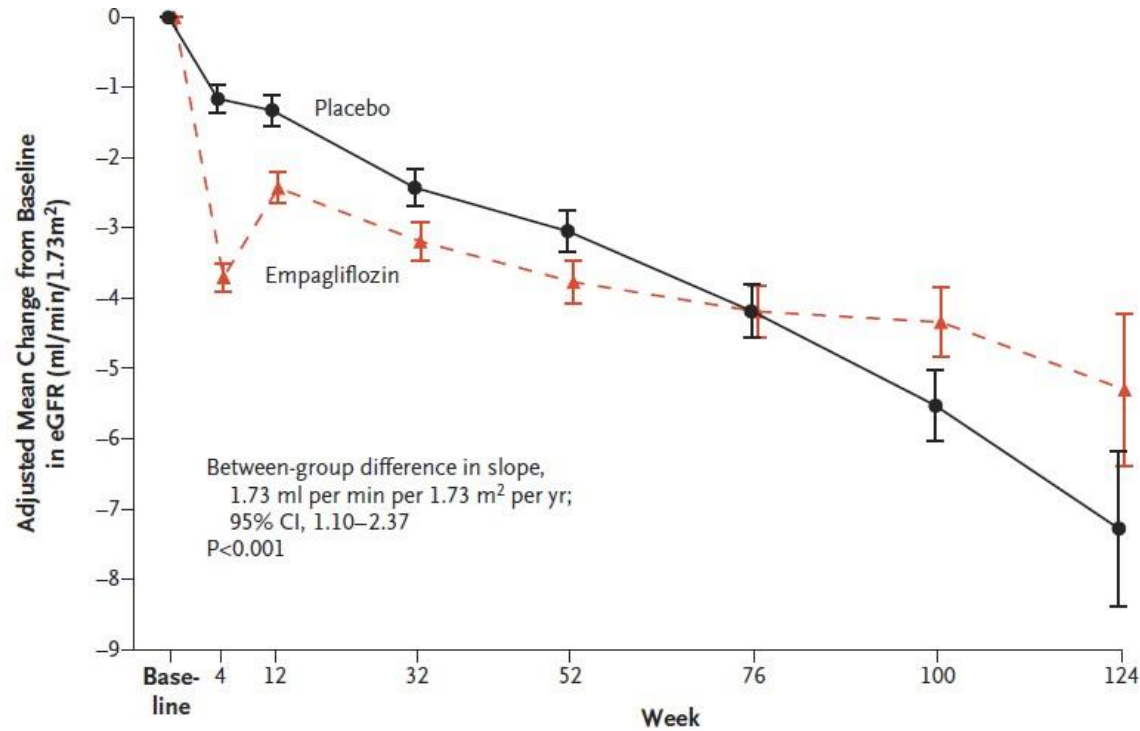
−2.28 ml / min / 1.73 m2 / year
On placebo

− 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 diabetes[2].

1 N. Engl. J. Med 2020 Aug 29.
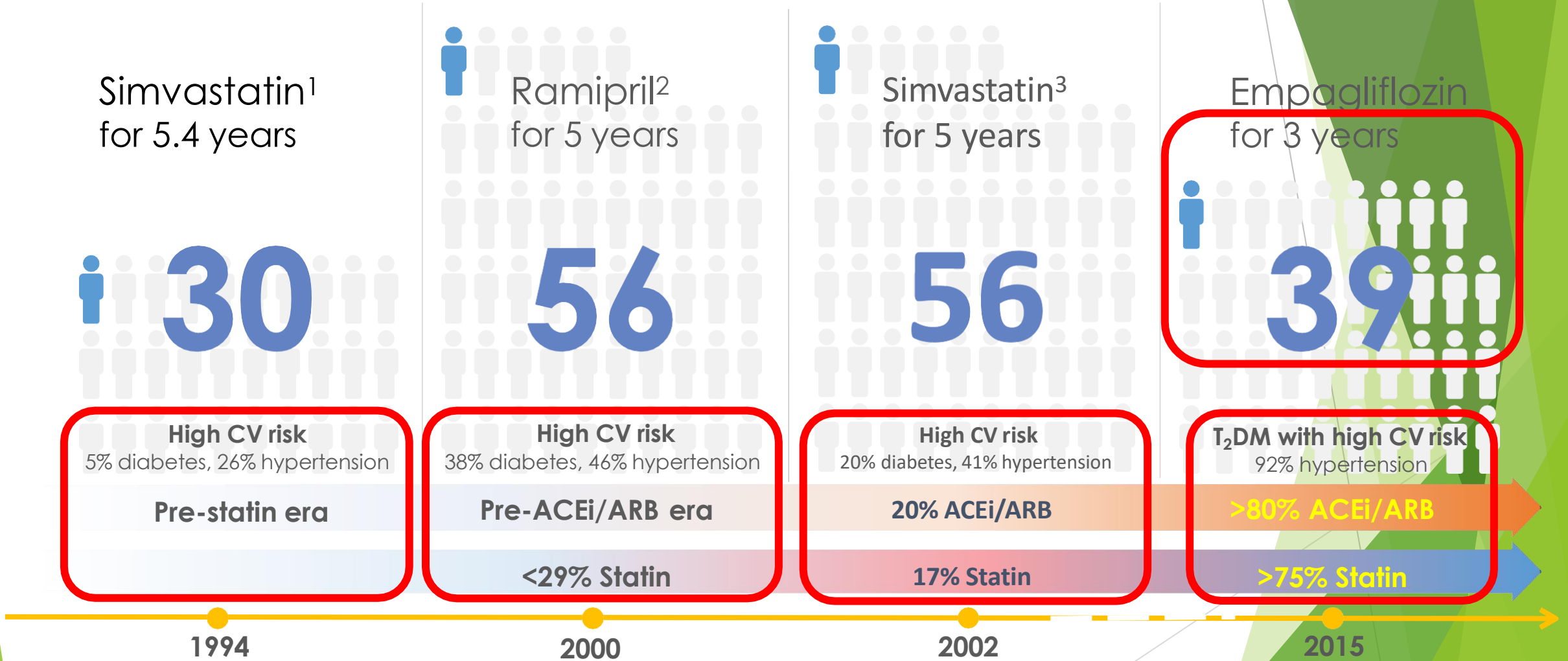2   EMPEROR-Reduced Trial Marta Cobo Marcos M. Packer presentation ESC 2020

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)

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

Empagliflozin reduced composite renal endpoint by 50%[1]

Placebo

58 patients with event
Rate: 3.1/100 patient-years

30 patients with event
Rate: 1.6/100 patient-years

Empagliflozin

HR 0.50
(95% CI 0.32, 0.77)

Cumulative incidence (%) — y-axis: 0, 2, 4, 6

Days After Randomization — x-axis: 0, 90, 180, 270, 360, 450, 540, 630

Patients at risk								
Placebo	1867	1592	1501	1136	1058	681	357	259
Empagliflozin	1863	1599	1532	1155	1062	687	391	276
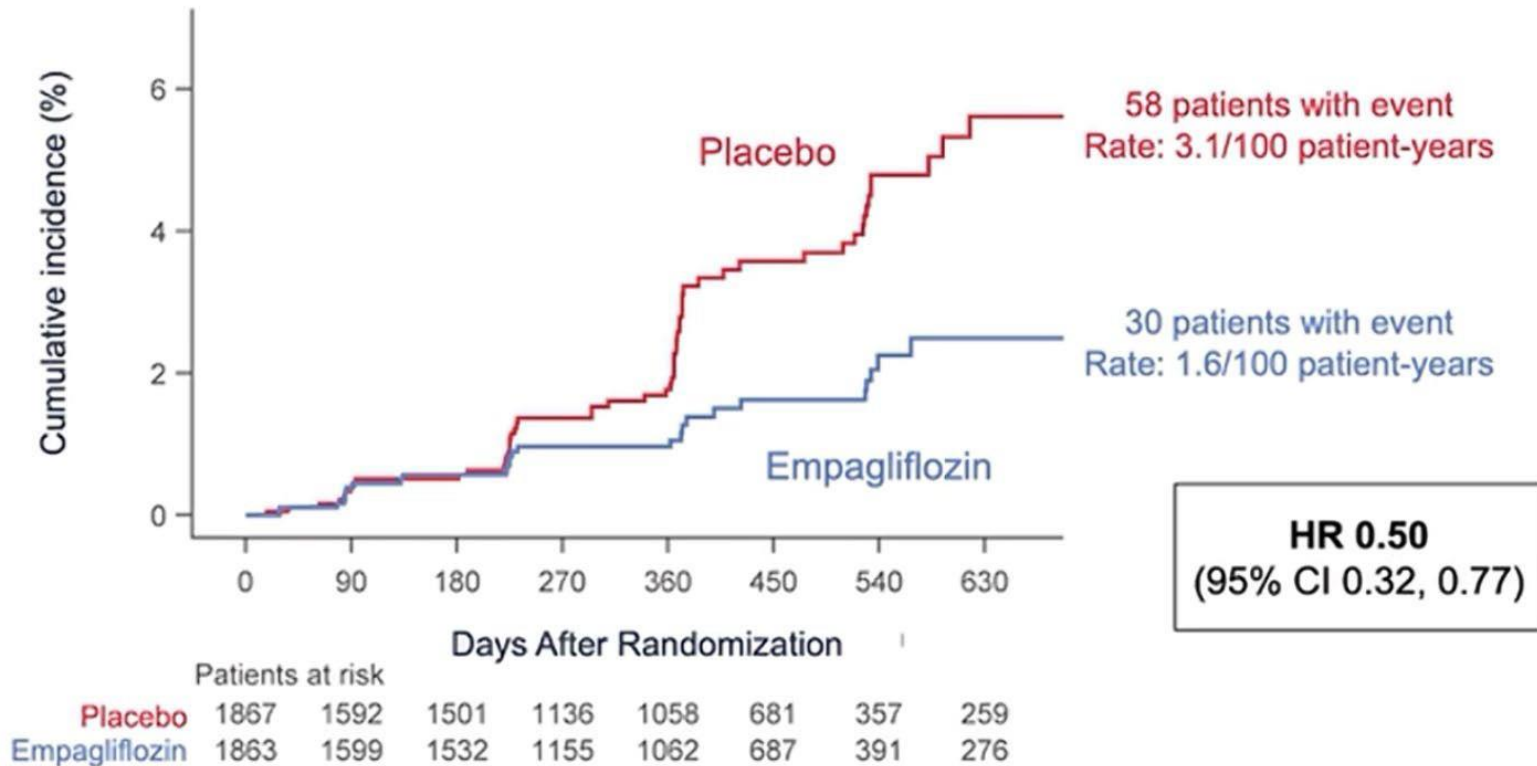
50%
30 on Empagliflozin
58 on Placebo
HR= 0.50 (0.32-0.77)

✓ 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)

1-https://www.radcliffecardiology.com/emperor-reduced-milton-packer-harriette-van-spall

EMPEROR-Reduced: Adverse events[1]

✓ Uncomplicated genital tract infection was reported more frequently with empagliflozin than with placebo[2].

✓ 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 empagliflozin[2].

	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)**
Selected adverse events of special interest		
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.
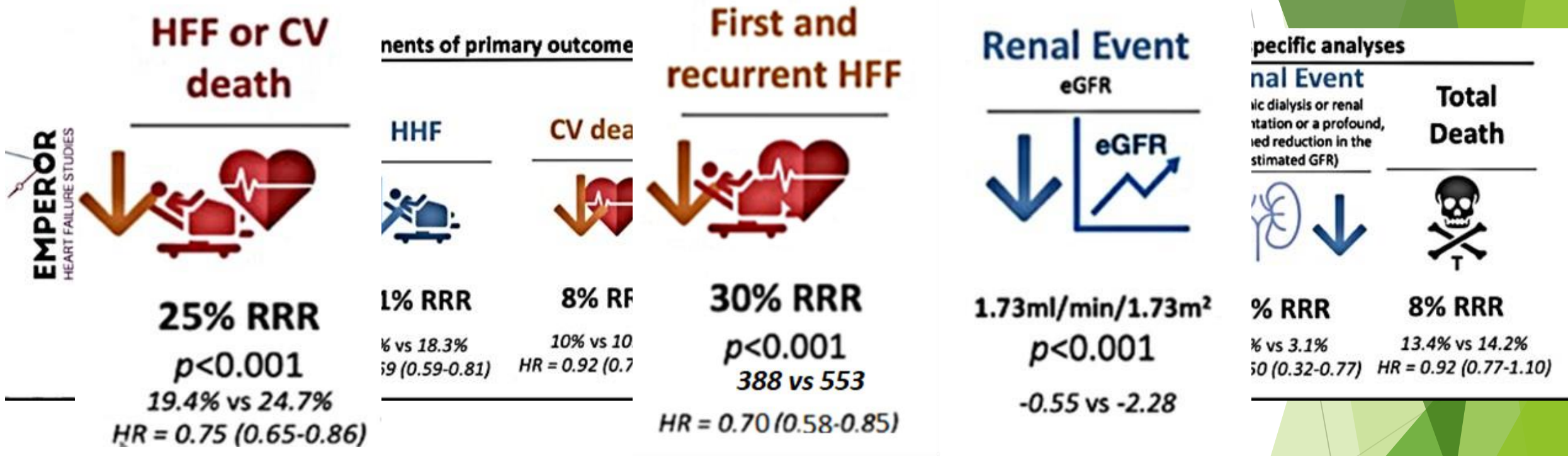
Conclusion[1]

✓ 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.

Conclusion[1]

HFF or CV death

25% RRR
p<0.001
19.4% vs 24.7%
HR = 0.75 (0.65-0.86)

First and recurrent HFF

30% RRR
p<0.001
388 vs 553
HR = 0.70 (0.58-0.85)

Renal Event
eGFR

1.73ml/min/1.73m²
p<0.001
-0.55 vs -2.28
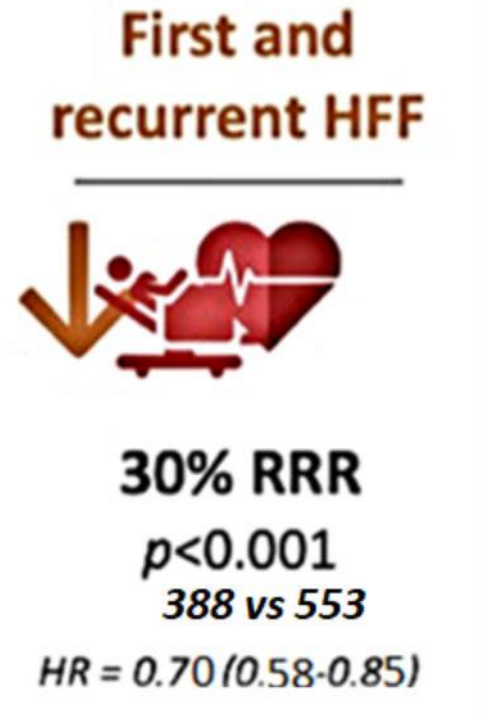
✓ Overall, in this trial, empagliflozin was associated with a lower combined risk of cardiovascular death or hospitalization for heart failure than placebo and with a slower progressive decline in renal function in patients with chronic heart failure and a reduced ejection fraction, regardless of the 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

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Simvastatin[1] for 5.4 years

30

High CV risk
5% diabetes, 26% hypertension

Pre-statin era

Ramipril[2] for 5 years

56

High CV risk
38% diabetes, 46% hypertension

Pre-ACEi/ARB era

<29% Statin

Simvastatin[3] for 5 years

56

High CV risk
20% diabetes, 41% hypertension

20% ACEi/ARB

17% Statin

Empagliflozin for 3 years

39

T$_2$DM with high CV risk
92% hypertension

>80% ACEi/ARB

>75% Statin

1994   2000   2002   2015

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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Simvastatin[1]
for 5.4 years

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High CV risk
5% diabetes, 26% hypertension

Ramipril[2]
for 5 years

56

High CV risk
38% diabetes, 46% hypertension

Simvastatin[3]
for 5 years

56

High CV risk
20% diabetes, 41% hypertension

Empagliflozin
for **5 years[4]**

25

T2DM with high CV risk
92% hypertension

| Pre-statin era | Pre-ACEi/ARB era | 20% ACEi/ARB | >80% ACEi/ARB |

| | <29% Statin | 17% Statin | >75% Statin |

| 1994 | 2000 | 2002 | 2015 |

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

Diabetes Care 2021; 44(Suppl. 1):S111-S124.

Administration, Cautions, Side effects, Safety profile

Empagluco® | 10 25
Empagliflozin

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

Convenience of a once-daily oral treatment Cont:[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*

1-Jardiance FDA label 2018. Reference ID: 4367802

Empagluco® | **10** **25**
Empagliflozin

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

Empagliflozin in Patients with Renal Impairment:

✓ *No dose adjustment is needed if eGFR≥ 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*

Empagluco® | 10 | 25
Empagliflozin

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

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

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® | 10 / 25
Empagliflozin

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

Thank you