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
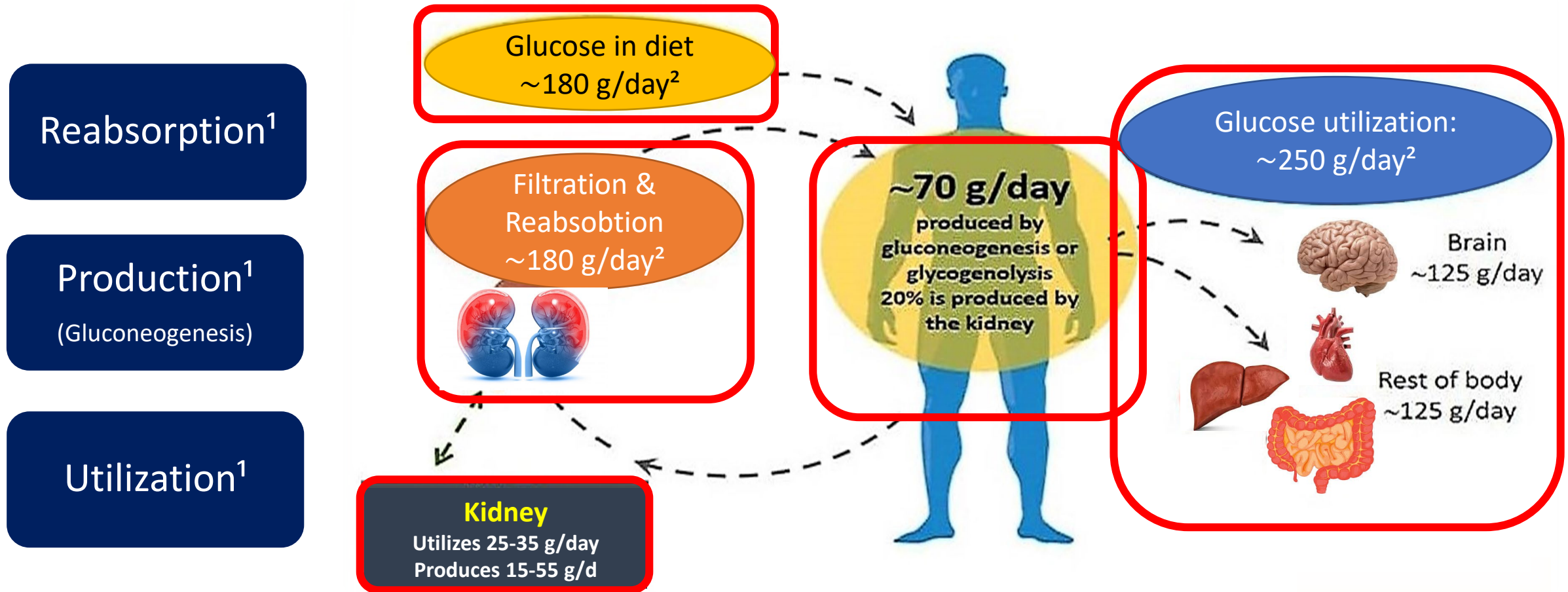
Reabsorption[1]

Production[1]
(Gluconeogenesis)

Utilization[1]

Glucose in diet
~180 g/day[2]

Filtration &
Reabsobtion
~180 g/day[2]

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

~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

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.
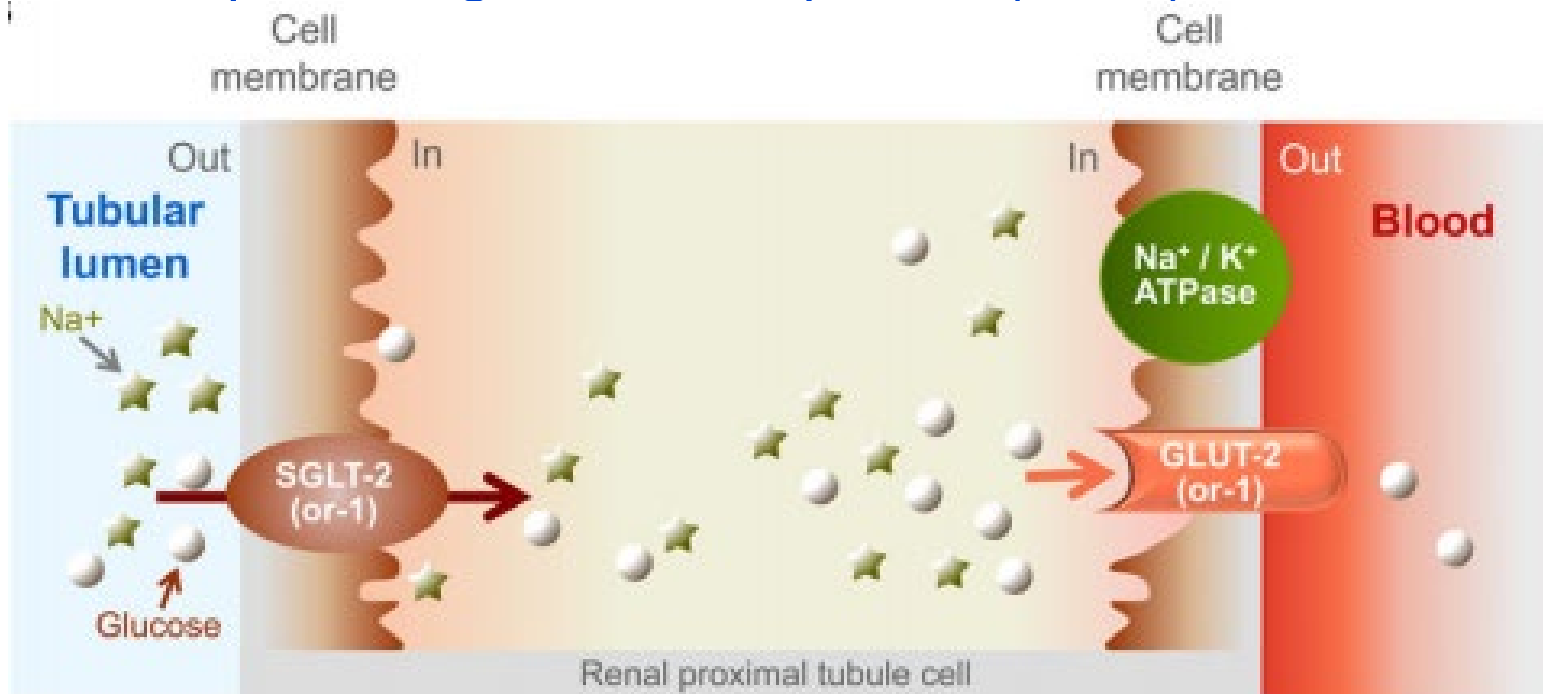
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SGLT2 & SGLT2 inhibitors

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Glucose Transporters

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

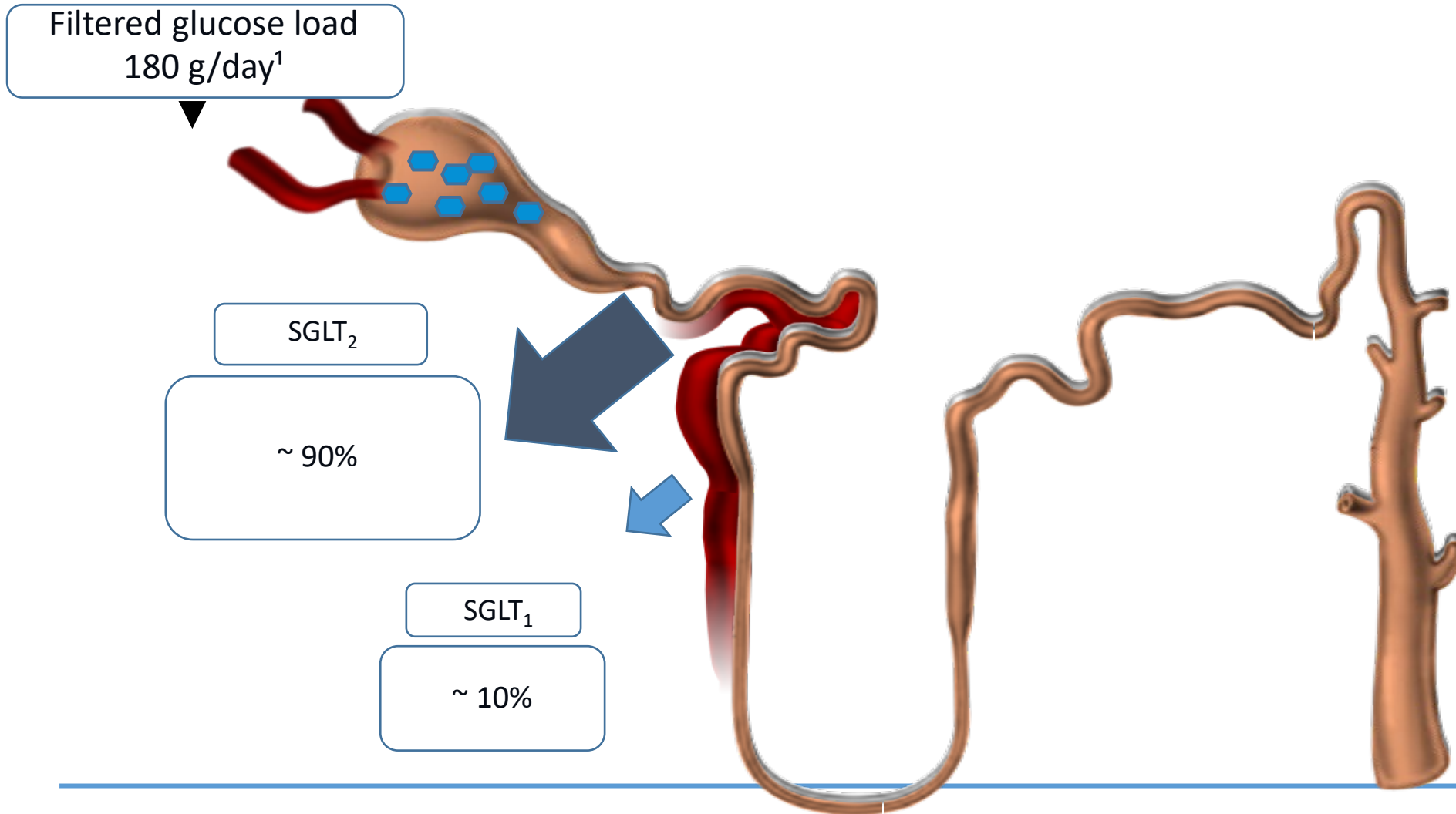facilitative glucose transporters (GLUTs)

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.

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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]

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

Urinary glucose excretion via SGLT2 inhibition

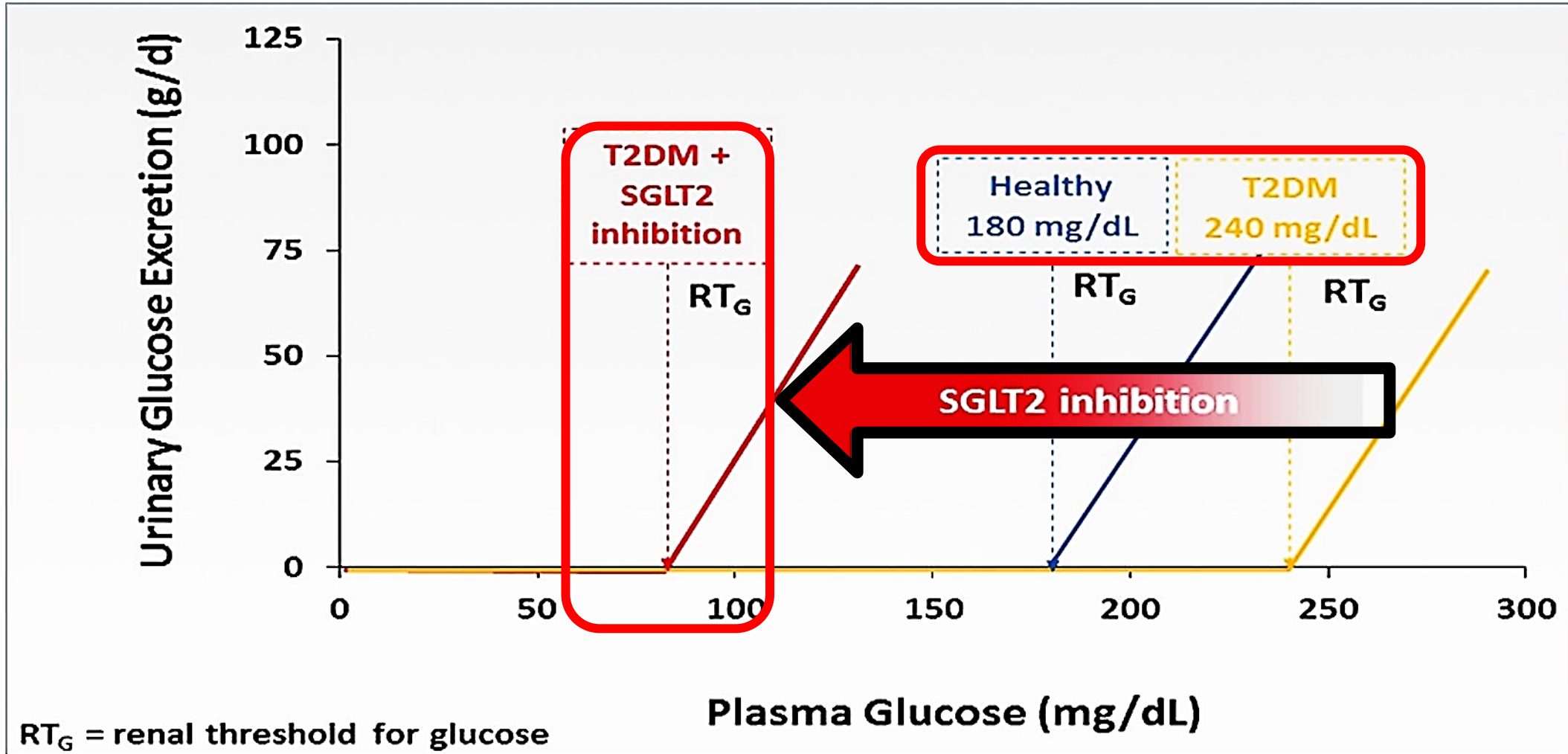Filtered glucose load
> 180 g/day

SGLT2
inhibitor

$SGLT_1$
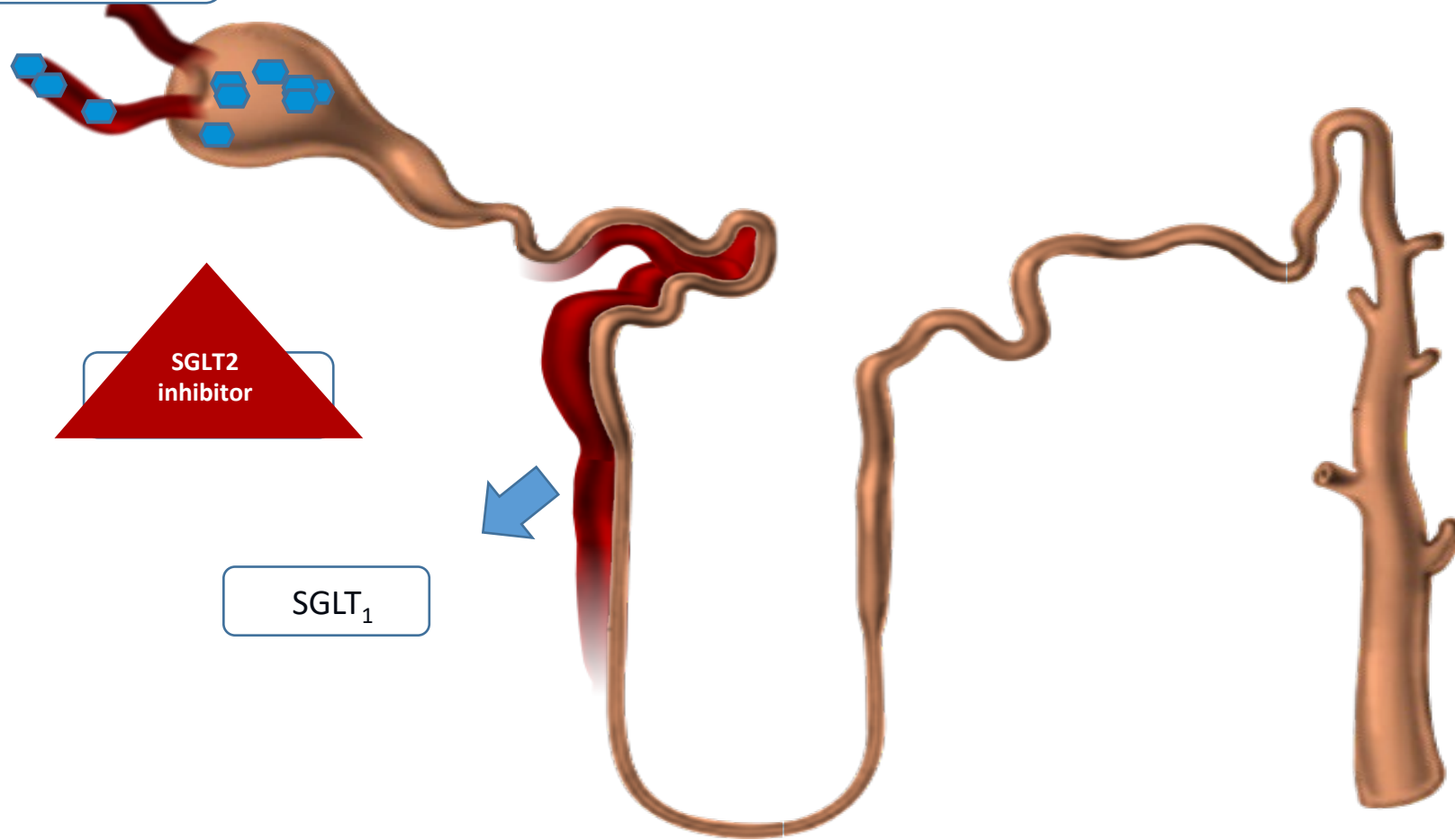
$SGLT_2$ inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis[1]

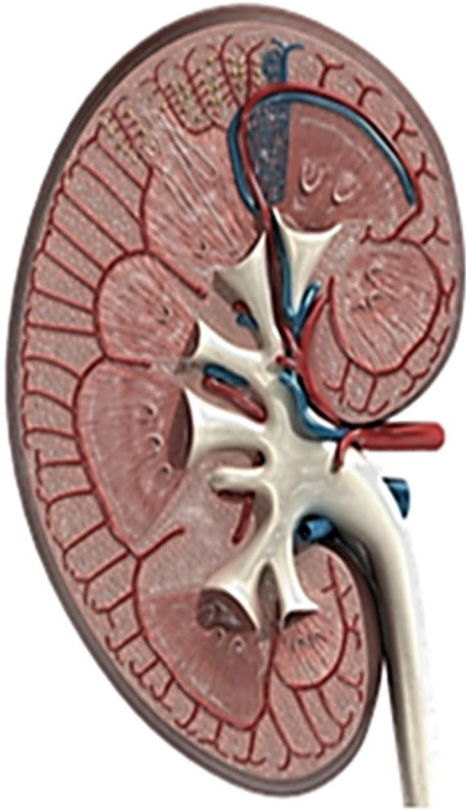*Loss of ~ 80 g of glucose/day

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DIABETES

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.

Expected Clinical Effects of SGLT2 Inhibition[1]

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

Efficacy Studies

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

Phase III pooled efficacy analysis

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

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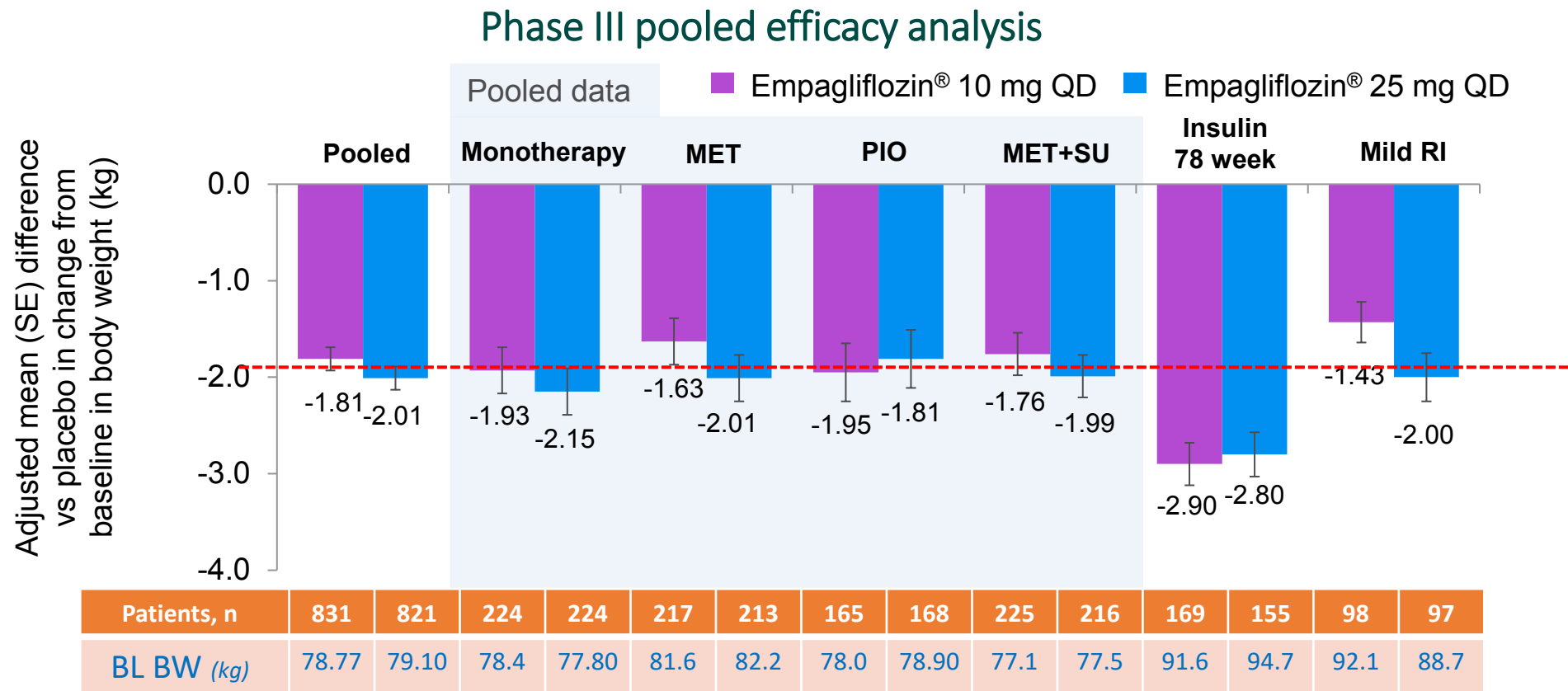4-Kovacs C, et al. *Diabetes Obes Metab*. 2014;16(2):147–158;   5- Häring H-U, et al. *Diabetes Care*. 2013;36(11):3396–404;   6- Rosenstock J, et al. *Diabetologia*. 2013;56(suppl 1);S372 (P931);
7-Barnett A, et al, *Lancet Diabetes Endocrinol*. 2014; doi:10.1016/S2213-8587(13)70208-0.

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

Phase III pooled efficacy analysis

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

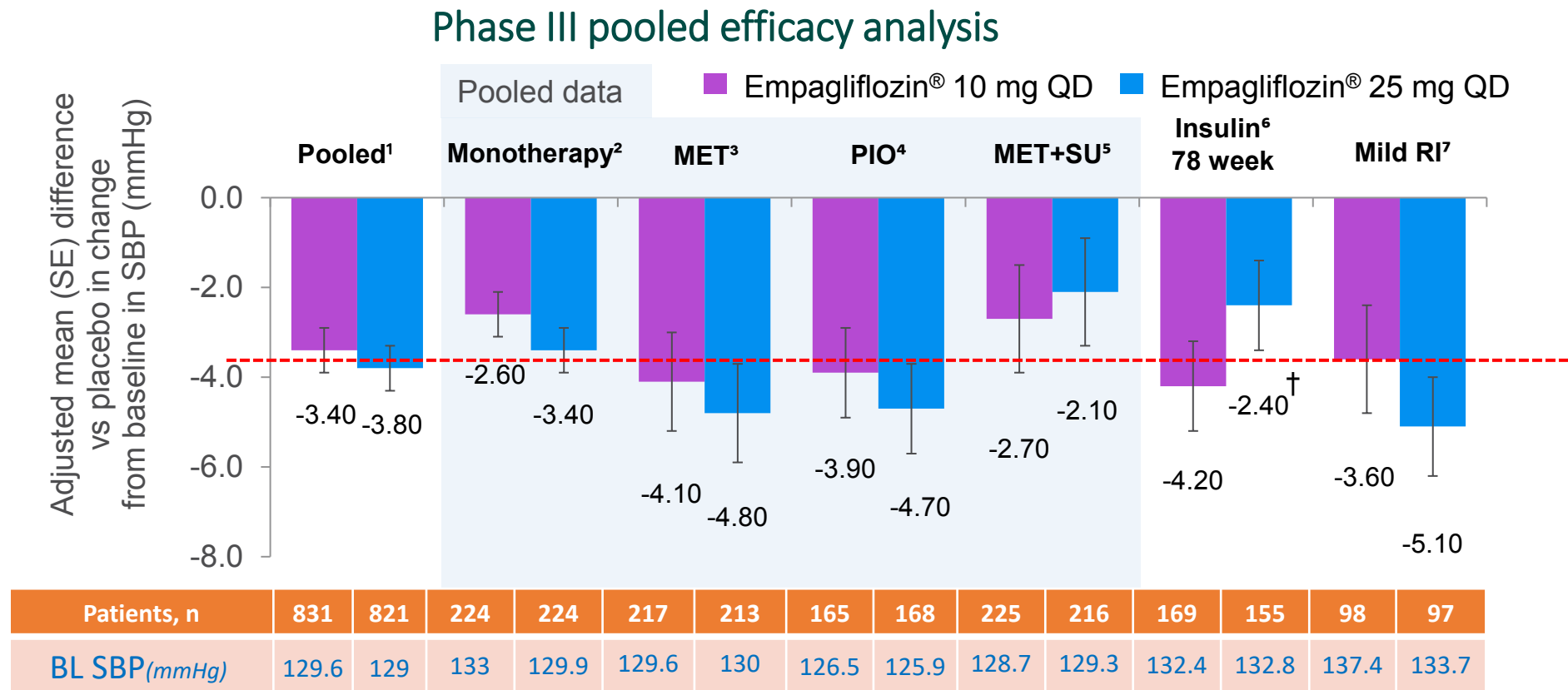| Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL BW (kg)	78.77	79.10	78.4	77.80	81.6	82.2	78.0	78.90	77.1	77.5	91.6	94.7	92.1	88.7

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

Adjusted mean (SE) difference vs placebo in change from baseline in SBP (mmHg)

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

	Pooled[1]		Monotherapy[2]		MET[3]		PIO[4]		MET+SU[5]		Insulin[6] 78 week		Mild RI[7]	
Values	-3.40	-3.80	-2.60	-3.40	-4.10	-4.80	-3.90	-4.70	-2.70	-2.10	-4.20	-2.40†	-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.
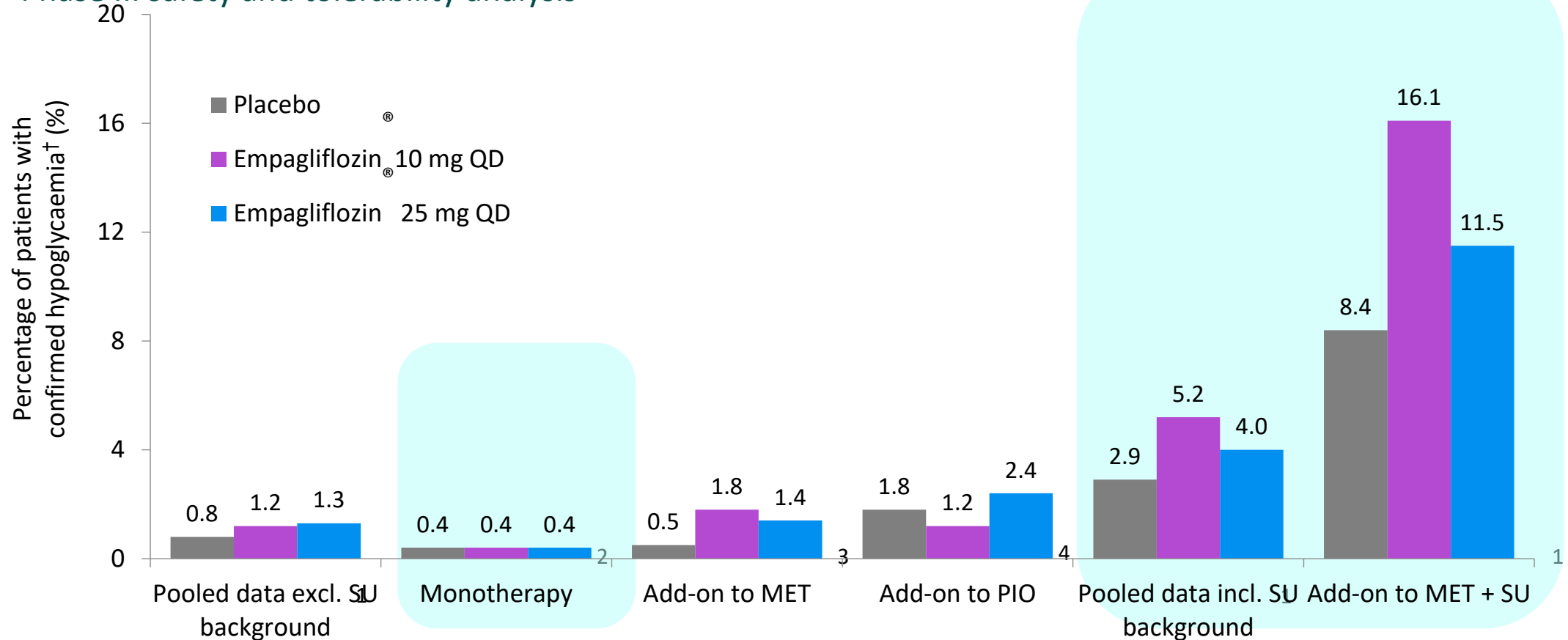*All statistically significant except when marked as †.

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
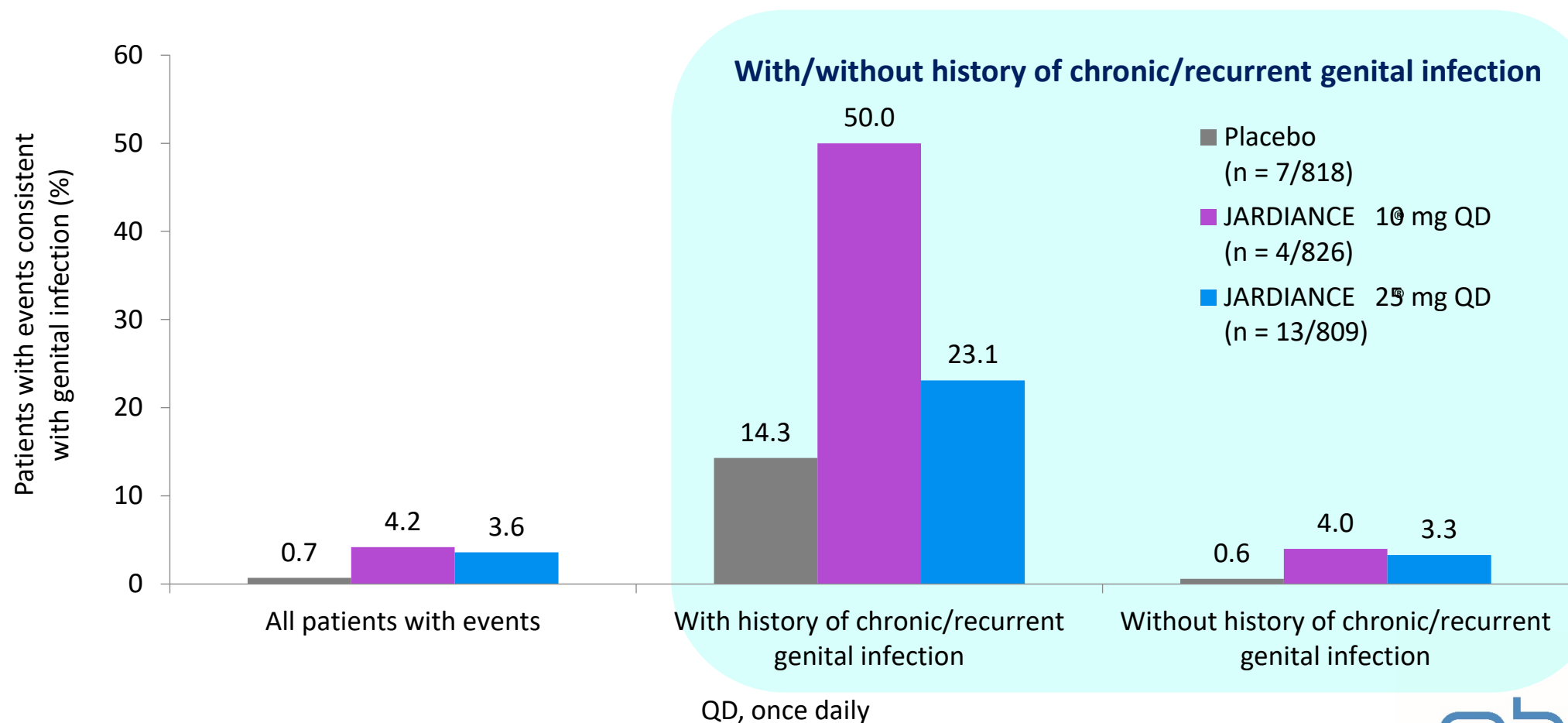
- Phase III safety and tolerability analysis

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

- 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).

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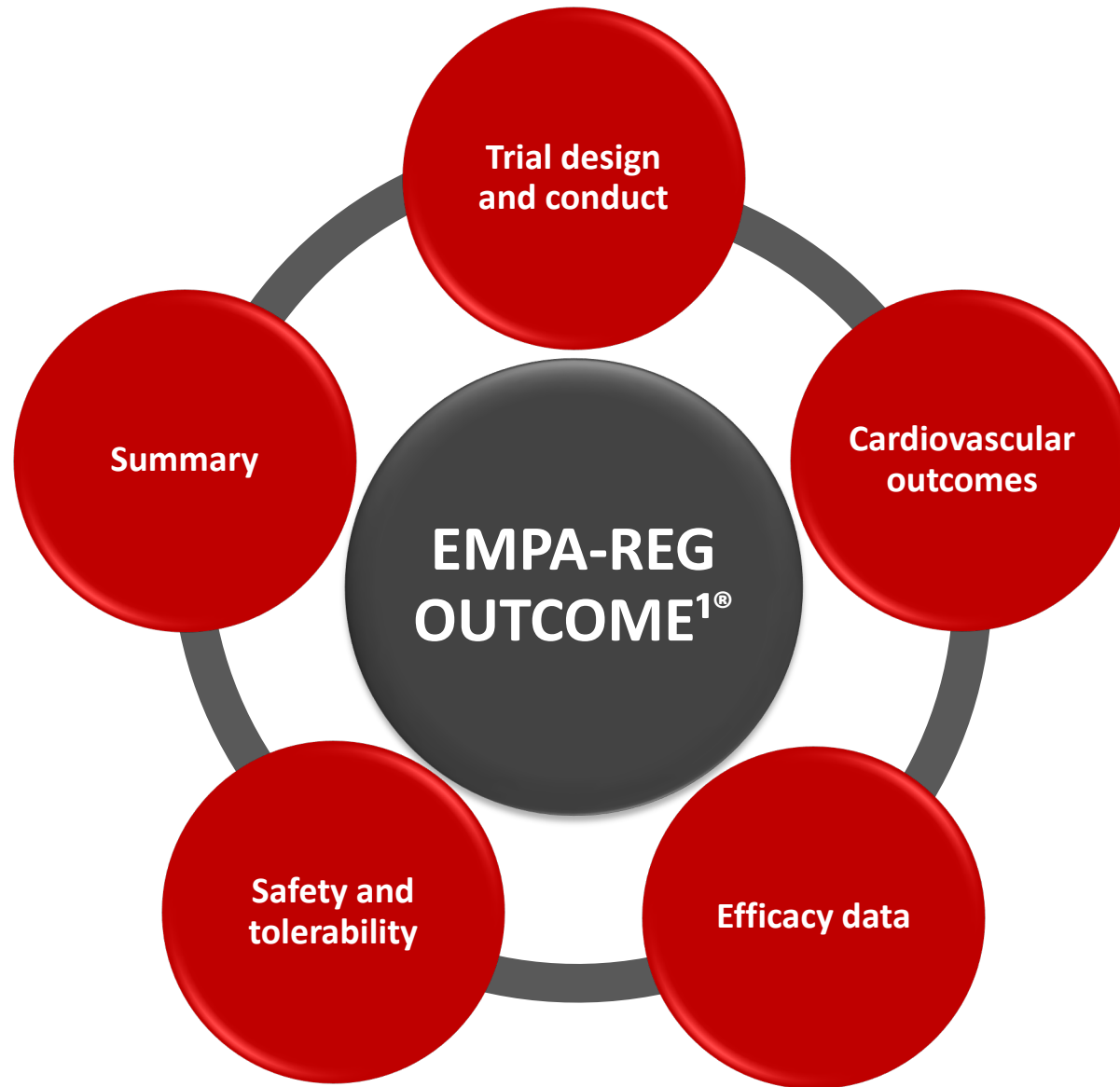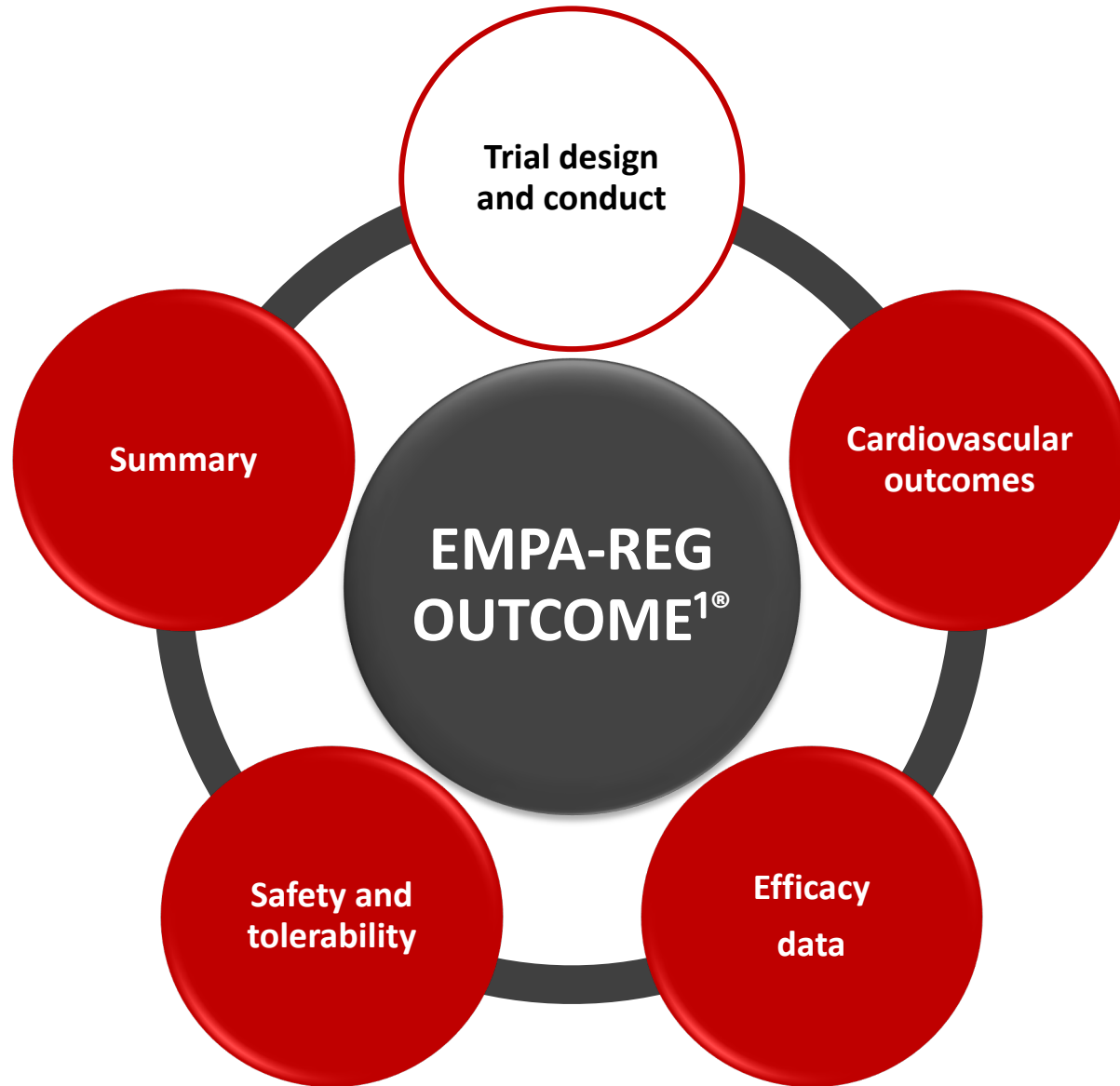# Genital infection distribution of events severity

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®

DIABETES

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
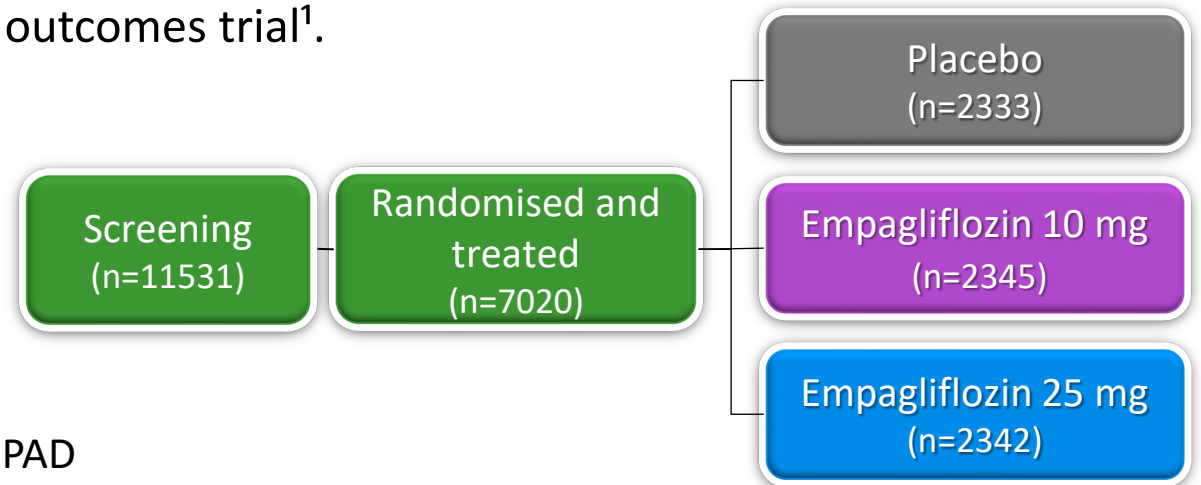
- **Key exclusion criteria**
  - eGFR <30 *mL/min/1.73m²* (MDRD)

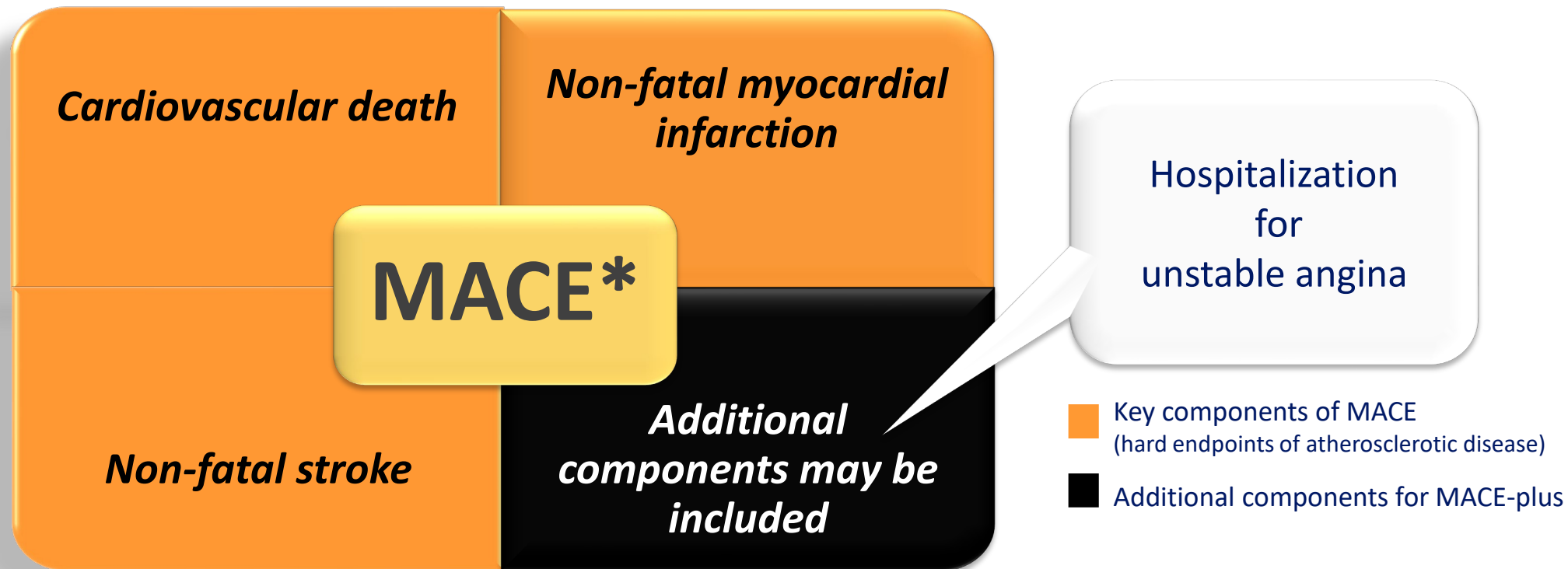 ✓ The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event.

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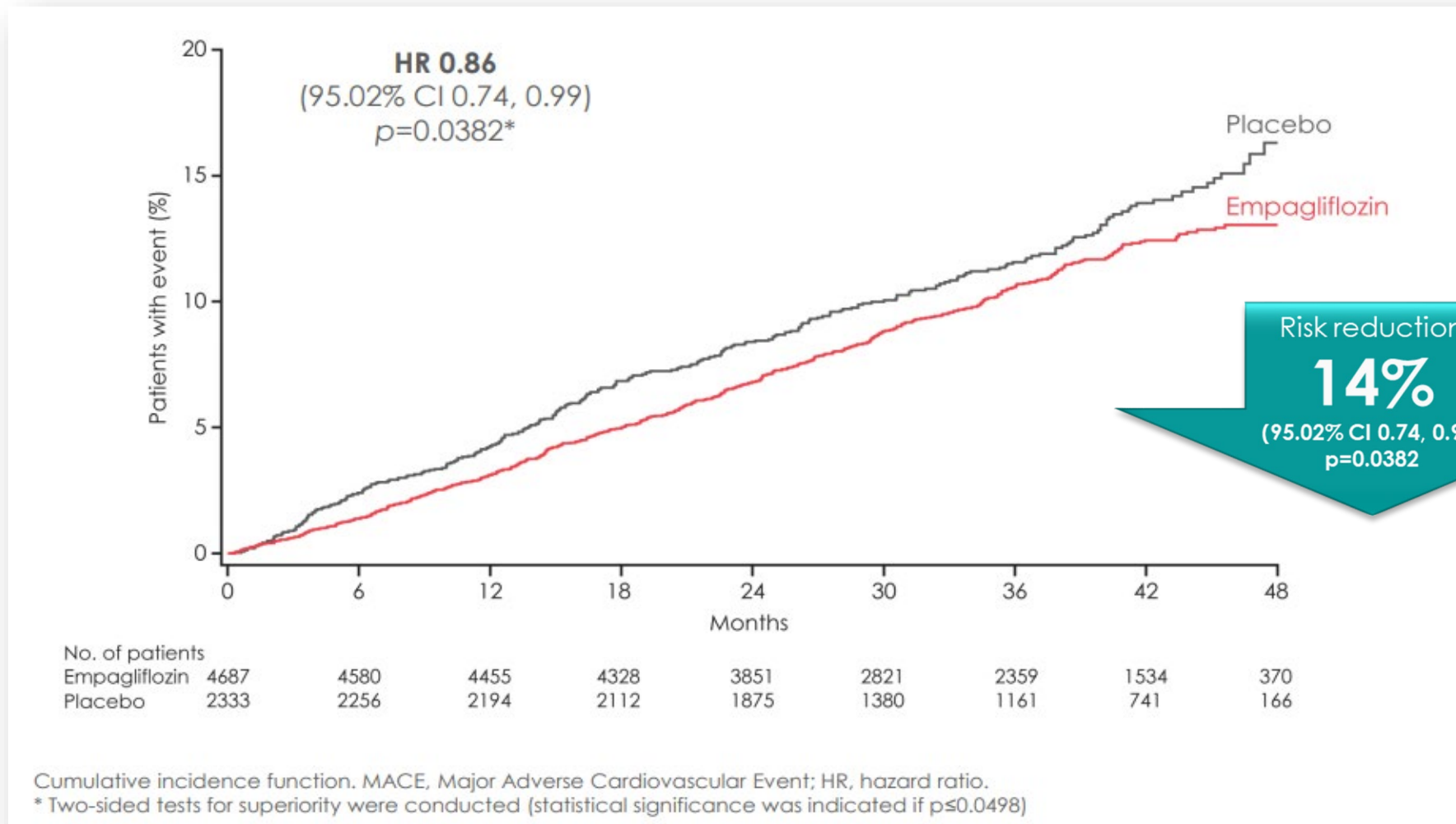
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Trial design and conduct

Summary

Cardiovascular outcomes

EMPA-REG OUTCOME[1]®

Safety and tolerability

Efficacy data

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)
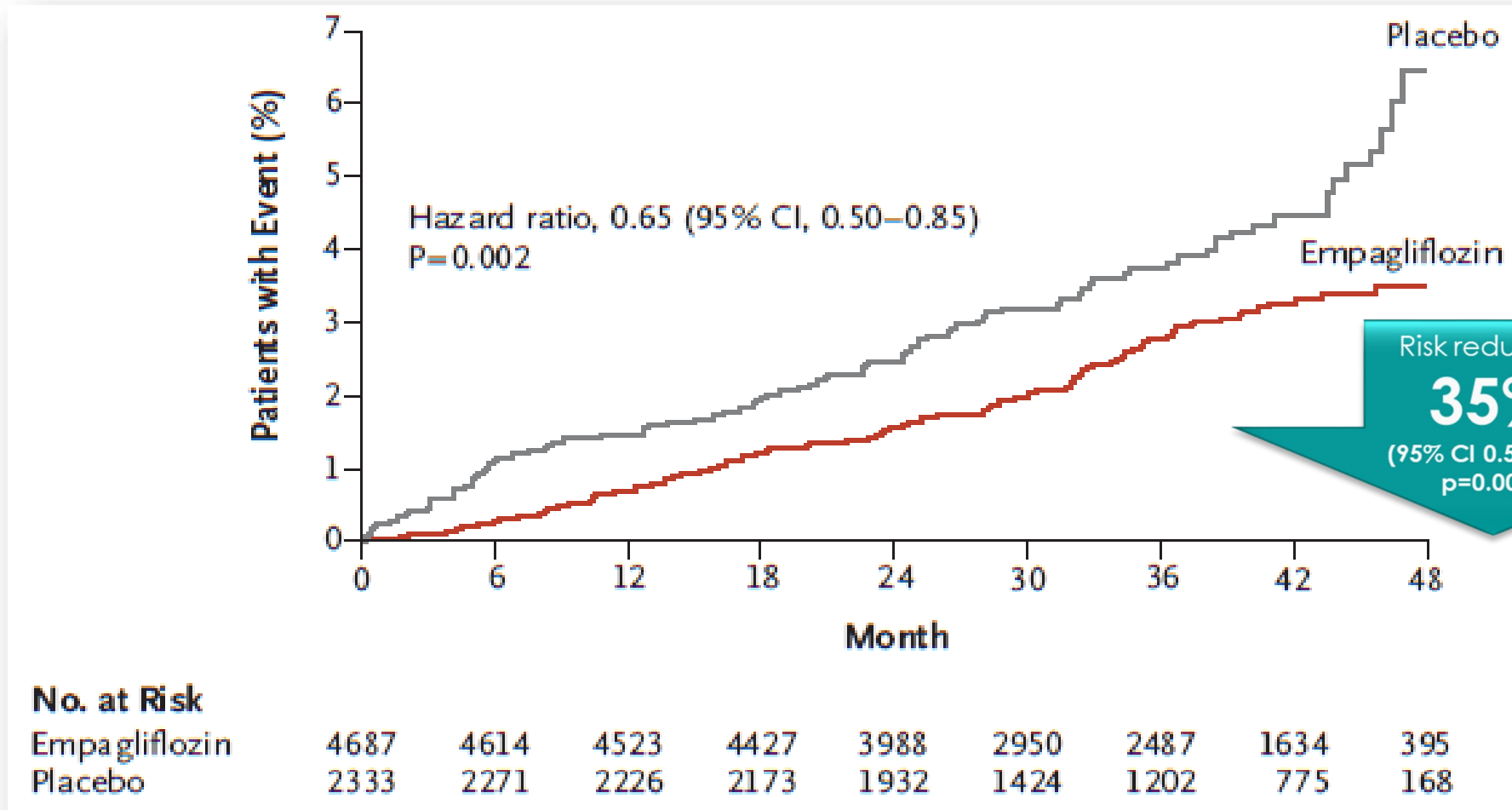- Additional components for MACE-plus

*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.
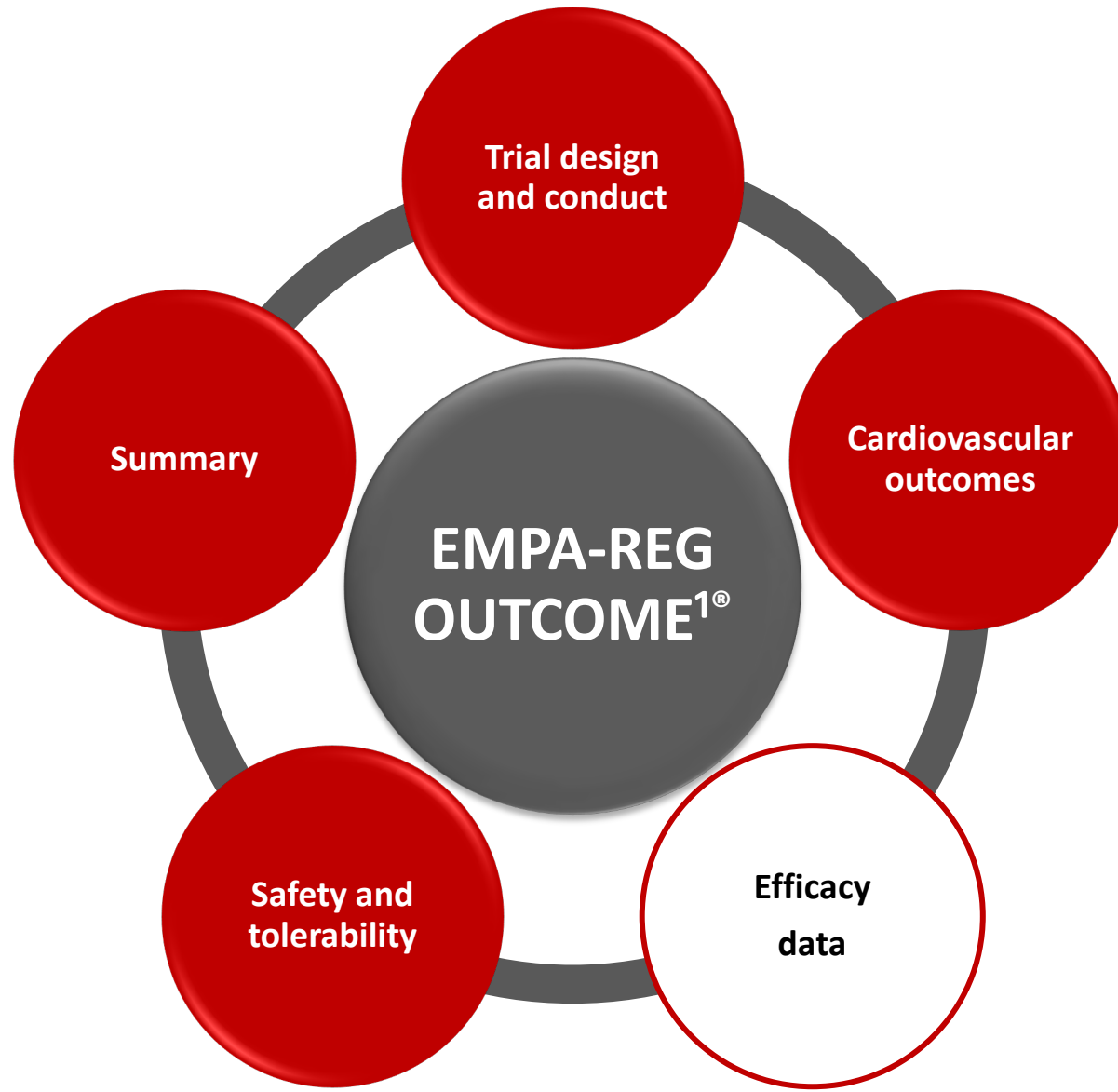
EMPA-REG OUTCOME®CV Death[1]

Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001
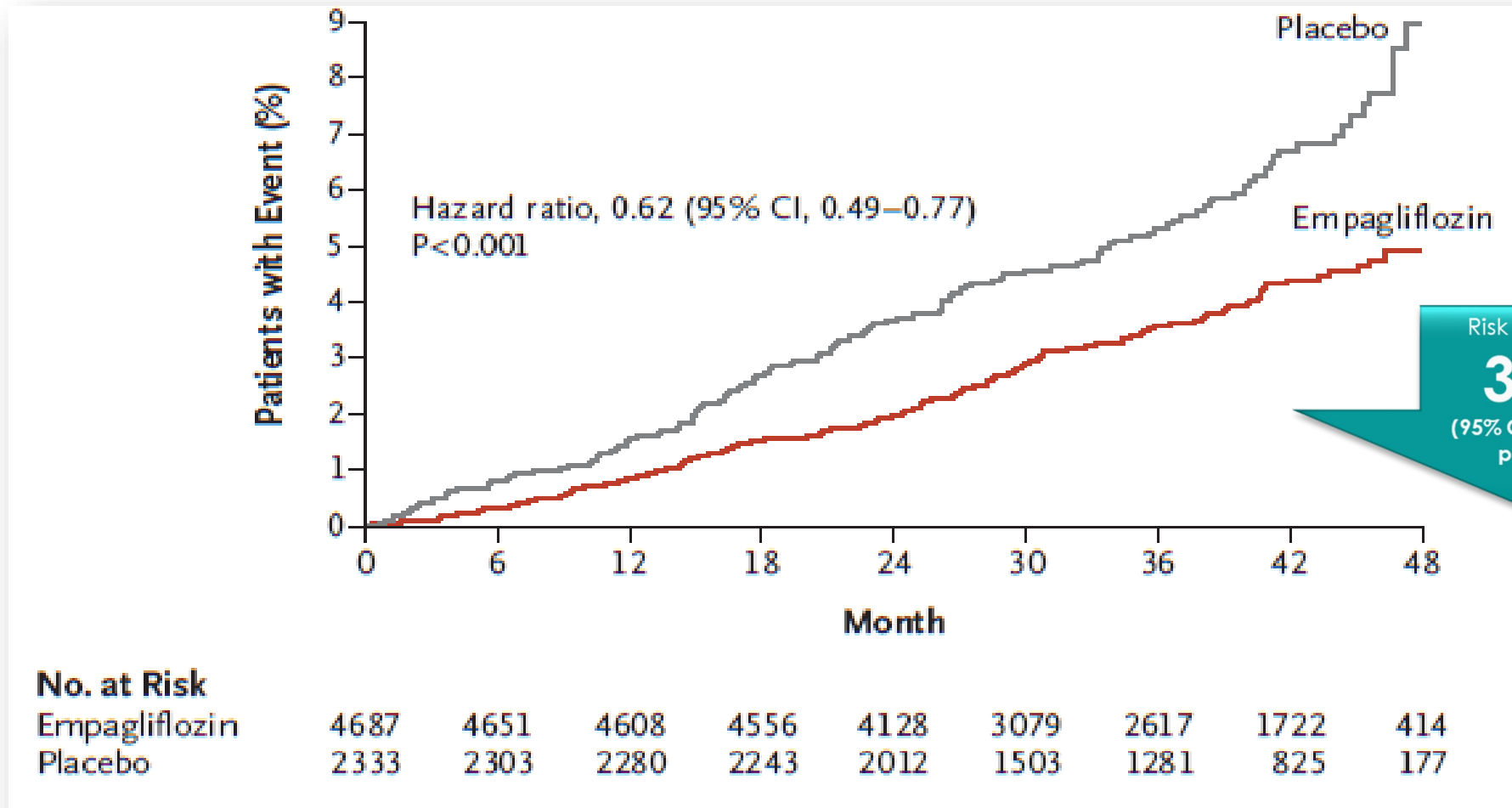
Risk reduction
38%
(95% CI 0.49, 0.77)
p<0.0001

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]

HR 0.68
(95% CI 0.57, 0.82)
p<0.0001

Placebo
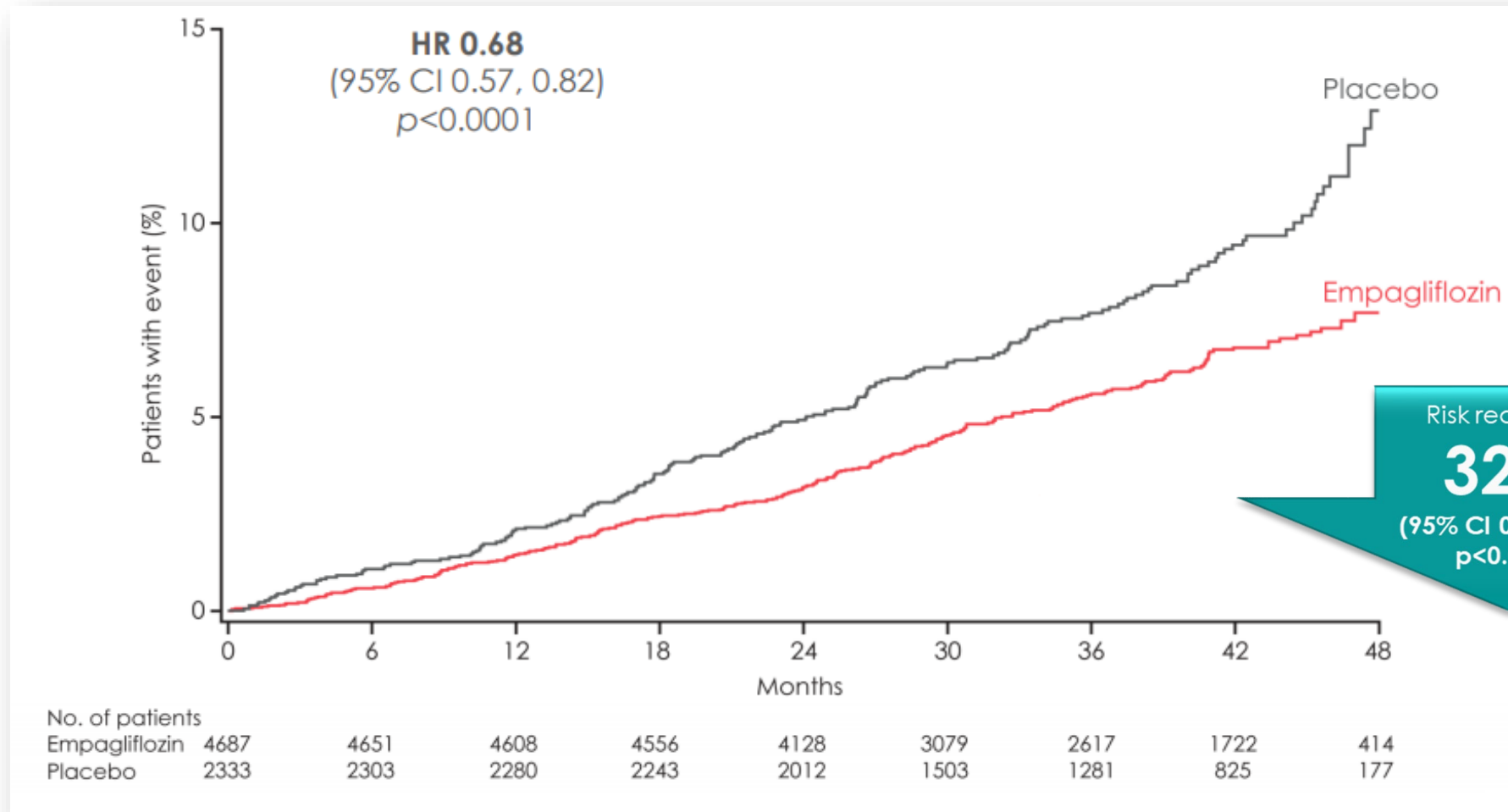
Empagliflozin

Risk reduction
32%
(95% CI 0.57, 0.82)
p<0.0001

No. of patients

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

1-Zinman B et al,. 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

Placebo

Empagliflozin

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

Patients with Event (%) — y-axis: 0, 1, 2, 3, 4, 5, 6, 7

Month — x-axis: 0, 6, 12, 18, 24, 30, 36, 42, 48

No. at Risk

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

1-Zinman B et al,. 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]

HbA1c

Adjusted mean (SE) HbA1c (%)

Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg

Week

Weight

Adjusted mean (SE) weight (kg)

Placebo
Empagliflozin 10 mg
Empagliflozin 25 mg

Week
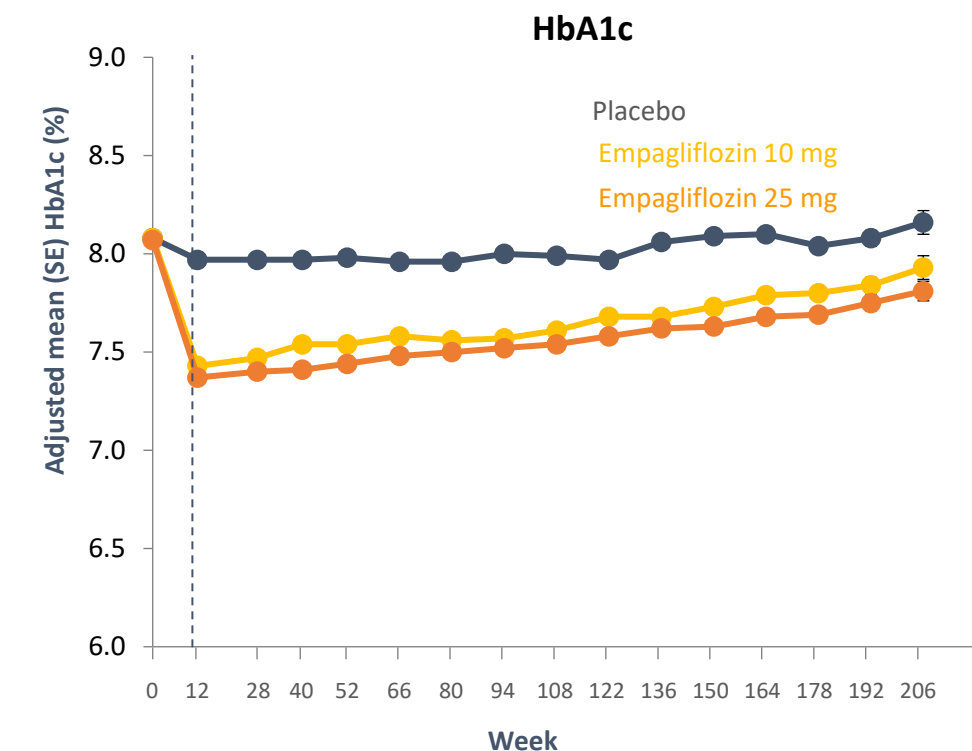
	0	12	28	40	52	66	80	94	108	122	136	150	164	178	192	206
Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
EMPA 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
EMPA 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195
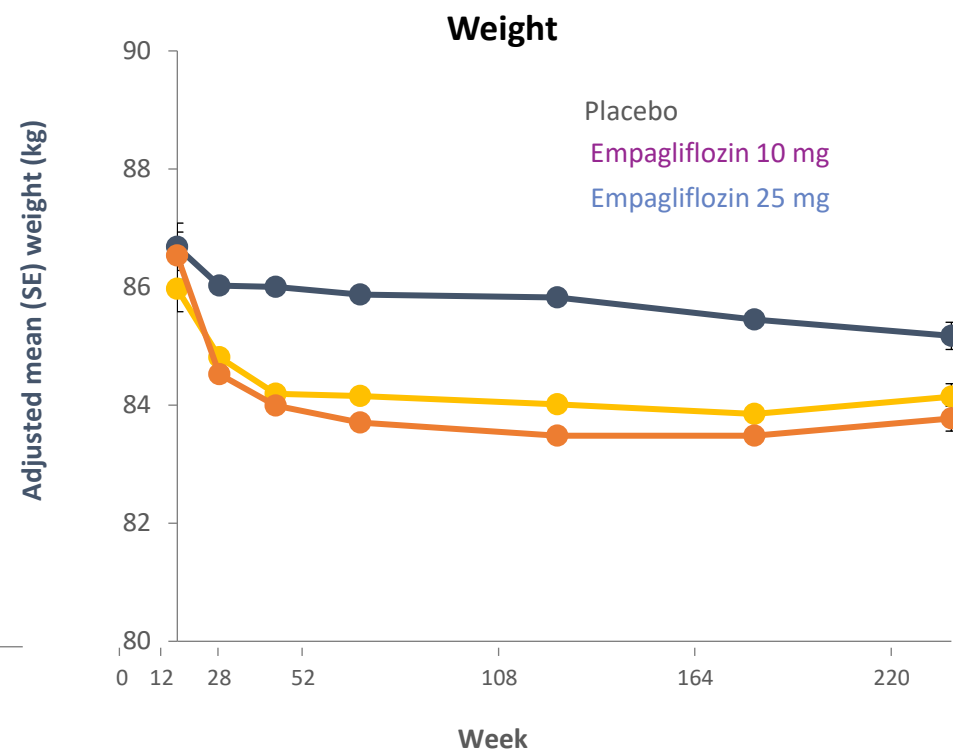
2285	1915	2215	2138	1598	1239	425
2290	1893	2238	2174	1673	1298	483
2283	1891	2226	2178	1678	1335	489

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

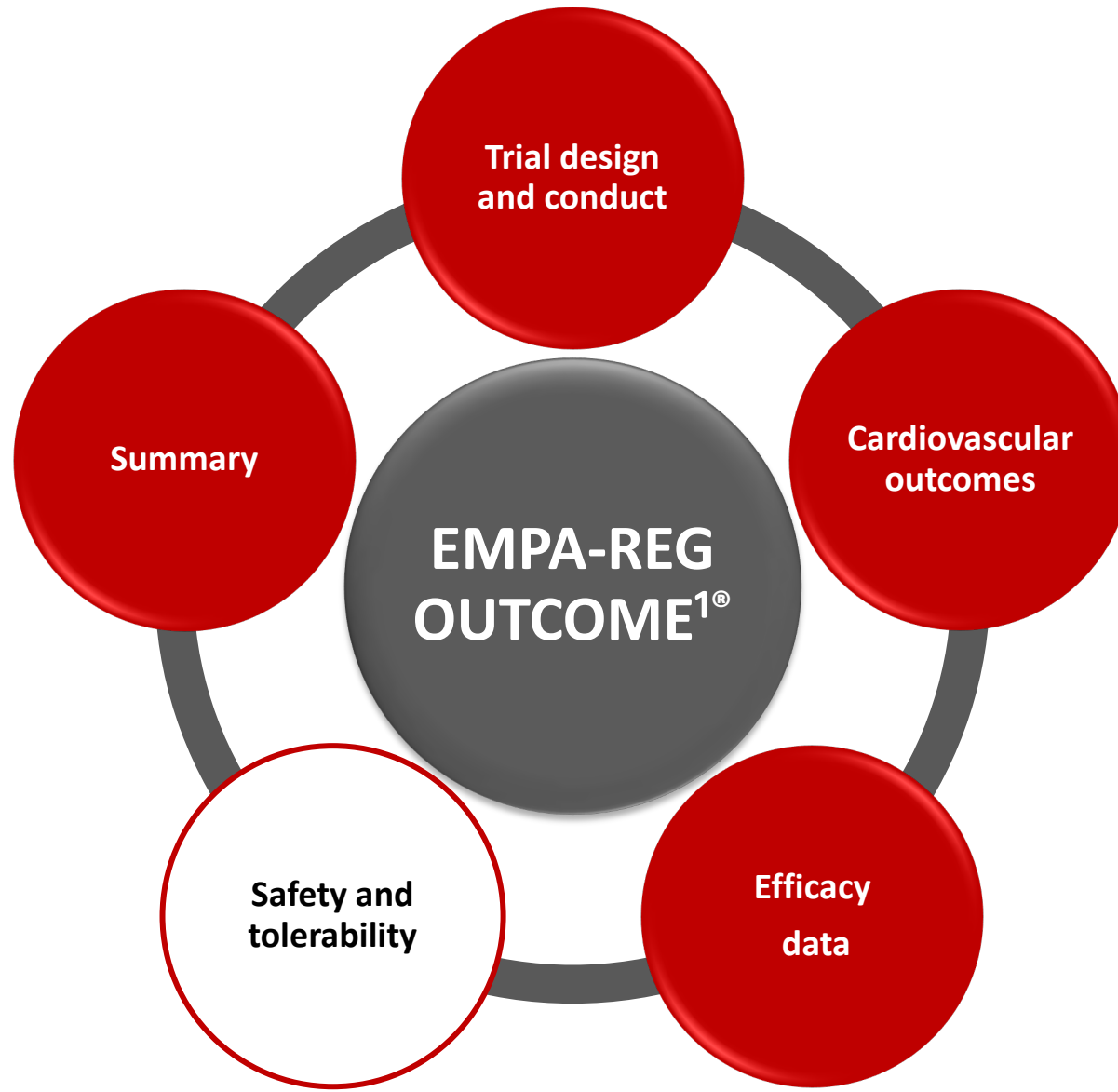1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Mean adjusted blood pressure parameters[1]

EMPA-REG OUTCOME

Systolic BP

Diastolic BP

Heart rate (ECG)

- ● Placebo
- ● Empagliflozin 10 mg
- ● Empagliflozin 25 mg

Adjusted mean (SE) systolic blood pressure (mmHg)

Adjusted mean (SE) heart rate (bpm)

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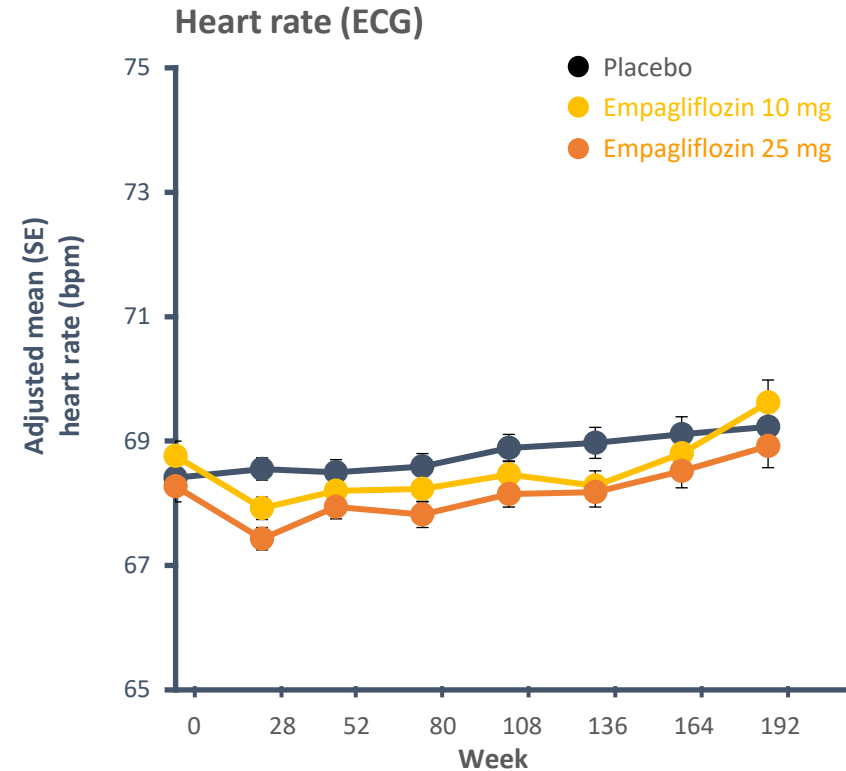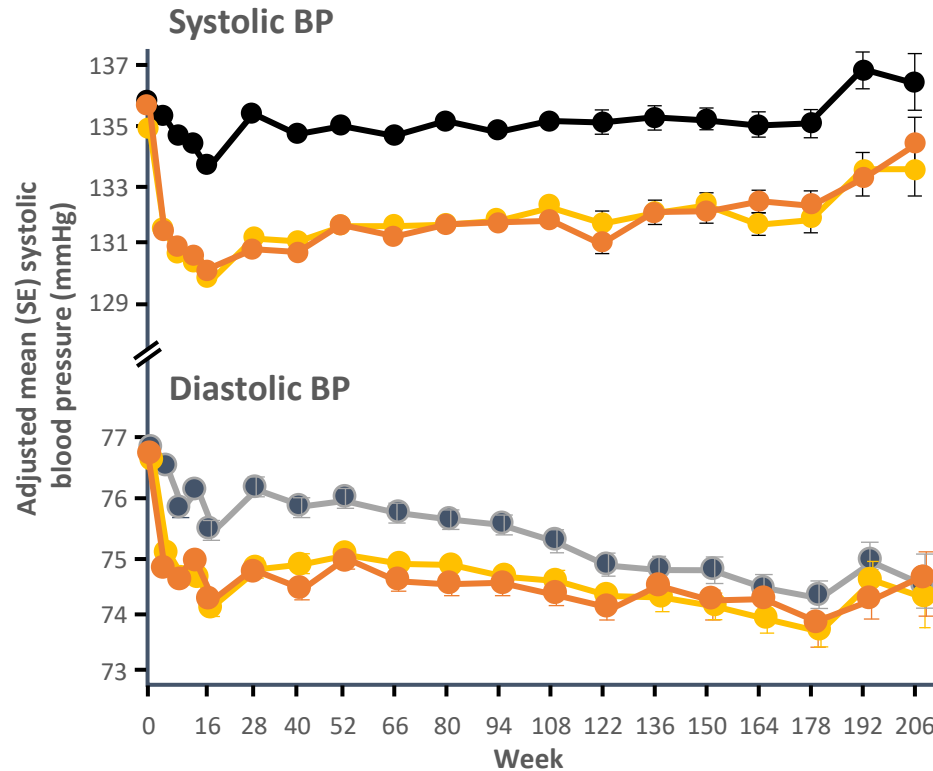
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
EMPA 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
EMPA 25 mg	2322	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

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

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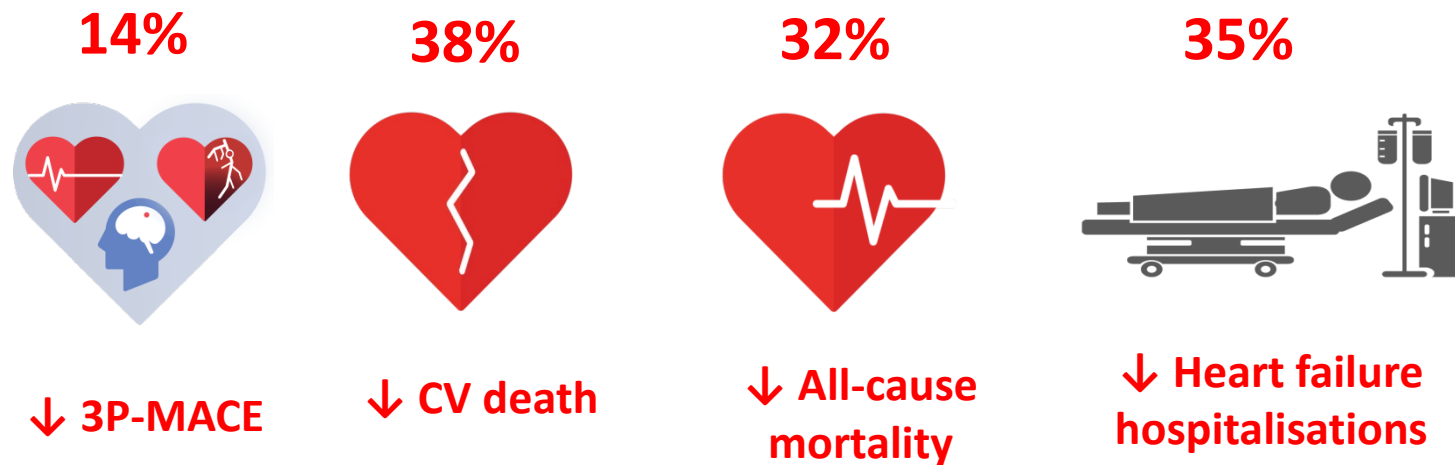BP, blood pressure; ECG, electrocardiogram; EMPA, empagliflozin

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

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

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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.
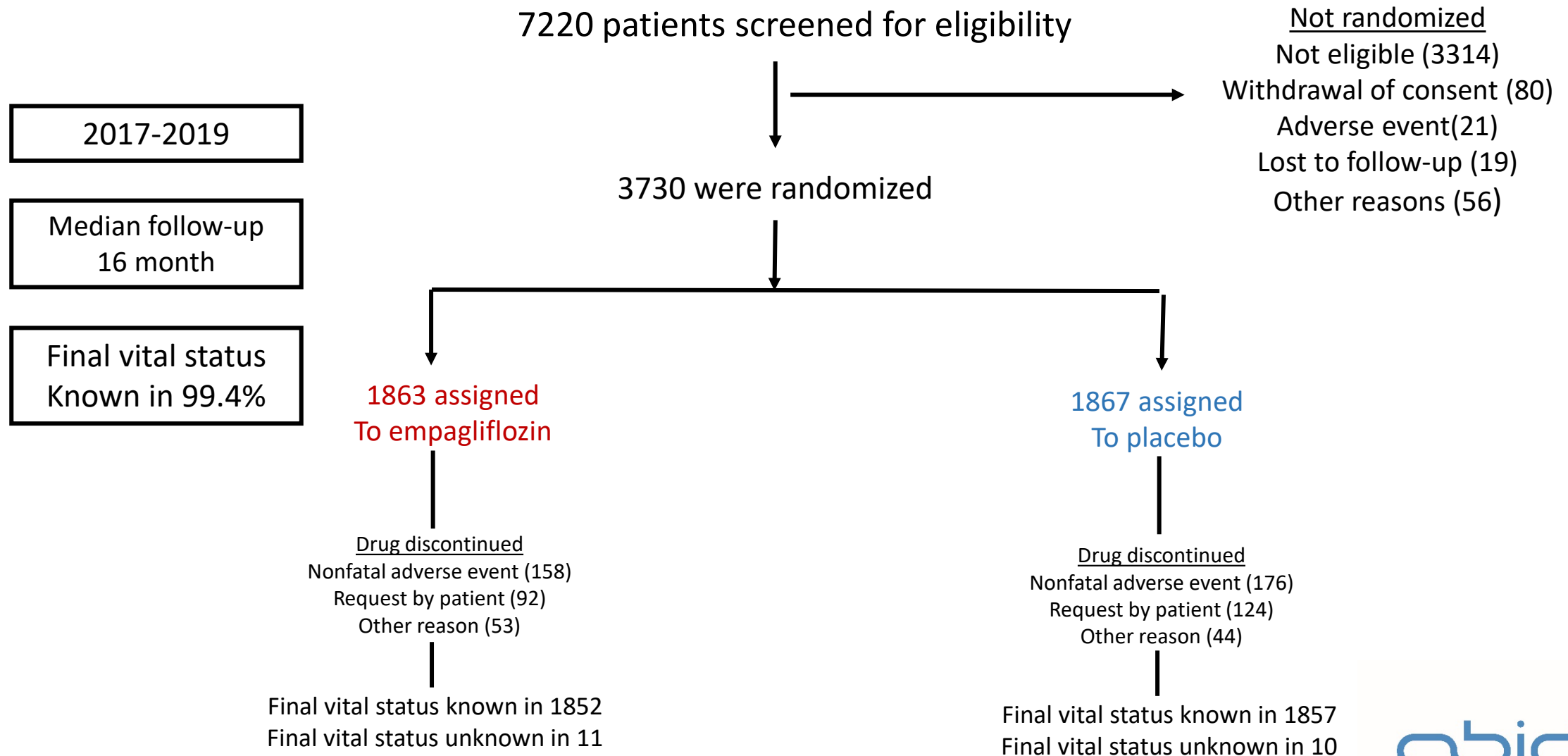
2-Zinman B. EASD 2015; Oral presentation

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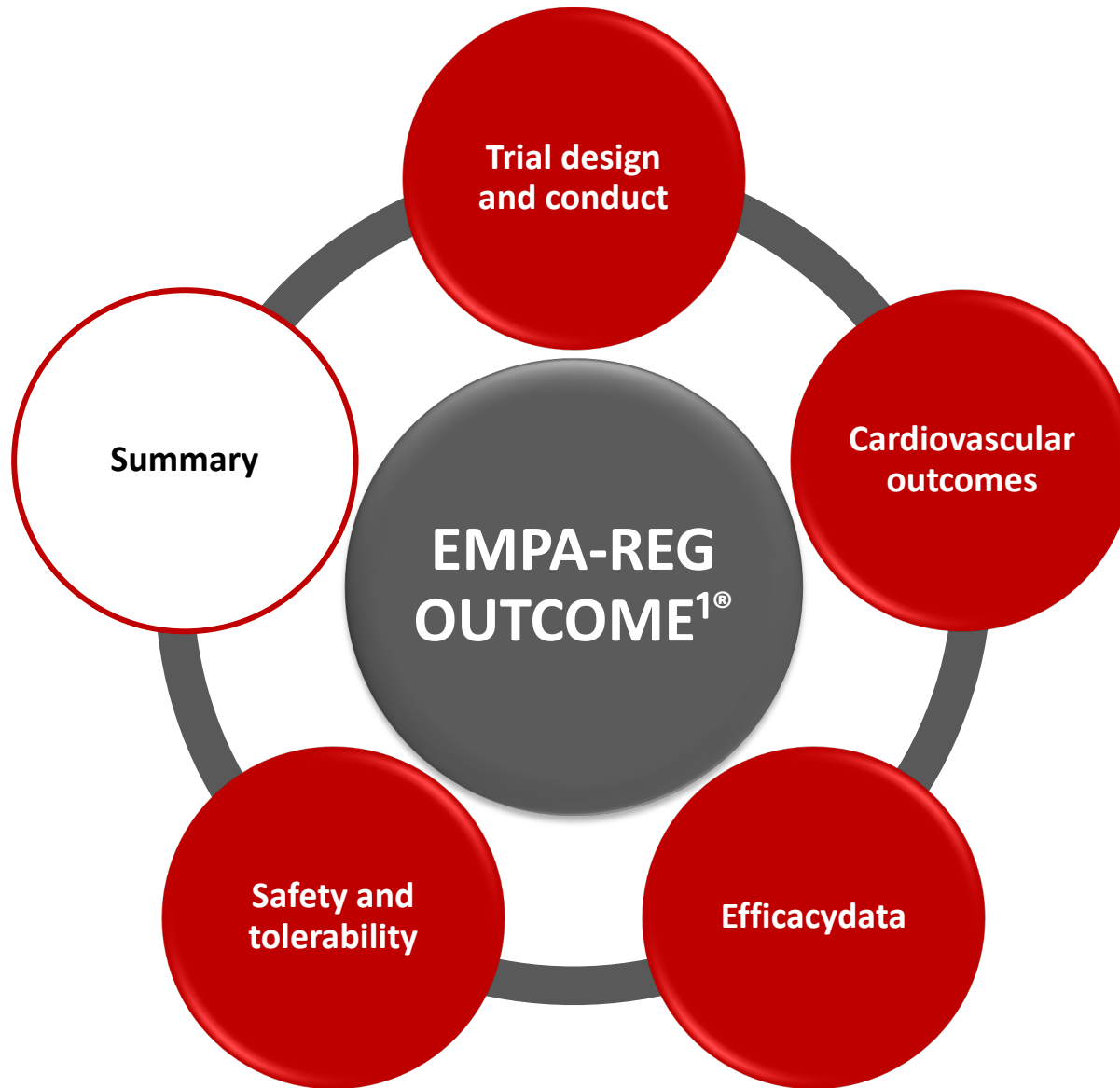
EMPA-REG OUTCOME®: summary

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

14%

38%

32%

35%

↓ 3P-MACE

↓ CV death

↓ All-cause mortality

↓ Heart failure hospitalisations

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

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35

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.

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

EMPEROR-Reduced: Patient Disposition[1]

7220 patients screened for eligibility

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

3730 were randomized

2017-2019

Median follow-up
16 month

Final vital status
Known in 99.4%

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

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DIABETES

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

Trial Design[1]

Patients must be receiving all appropriate treatments for HF

N=1863   Empagliflozin 10 mg qd + SOC

Screening period of up to 28 days

N=1867   Placebo qd + SOC

3730 were randomized

30-day post-treatment period

End of treatment at 841 primary outcome events

Median follow-up: ~16 months

SOC; Standard Of Care

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

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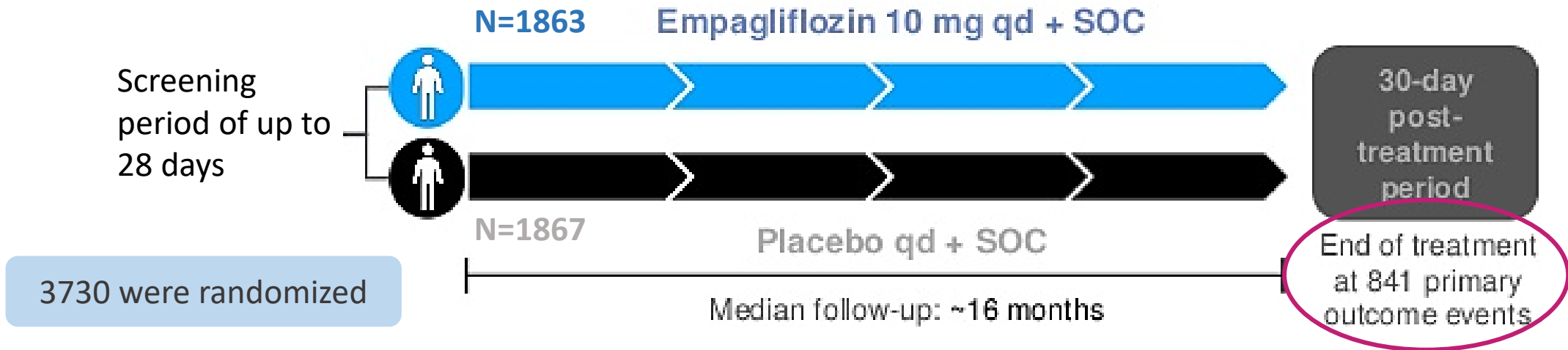
EMPEROR-Reduced trial specified only three endpoints to be tested in hierarchical manner[1]

✓ Primary End point
Composite of cardiovascular death Or heart failure hospitalization
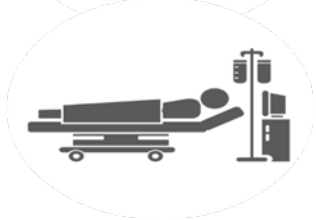
✓ First Secondary End point
Total (first and recurrent) heart failure hospitalization

✓ 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.

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Inclusion criteria[1]

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

Key inclusion criteria:	EF%	NT-proBNP (pg/ml) Patients without AF	NT-proBNP (pg/ml) Patients with AF
• NYHA class II-IV	≥36 to ≤40	≥2500	≥5000
• Elevated NT-pro BNP	≥31 to ≤35	≥1000	≥2000
• Guideline recommendation medication stable ≥1 week prior to first visit	≤30	≥600	≥1200
• eGFR ≥20 ml/min/1.73 m^2	> 40+HHF within 12 months	≥600	≥1200

NYHA; New York Heart Association

DIABETES

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 Au

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DIABETES

Empagliflozin Group Had Lower Incidence of Cardiovascular Death or Hospitalization for Heart Failure[1]

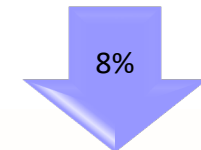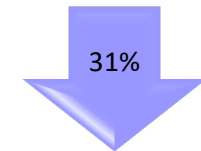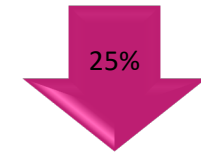**A Primary Outcome**

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

Estimated Cumulative Incidence (%)

Placebo
Empagliflozin

Days since Randomization

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
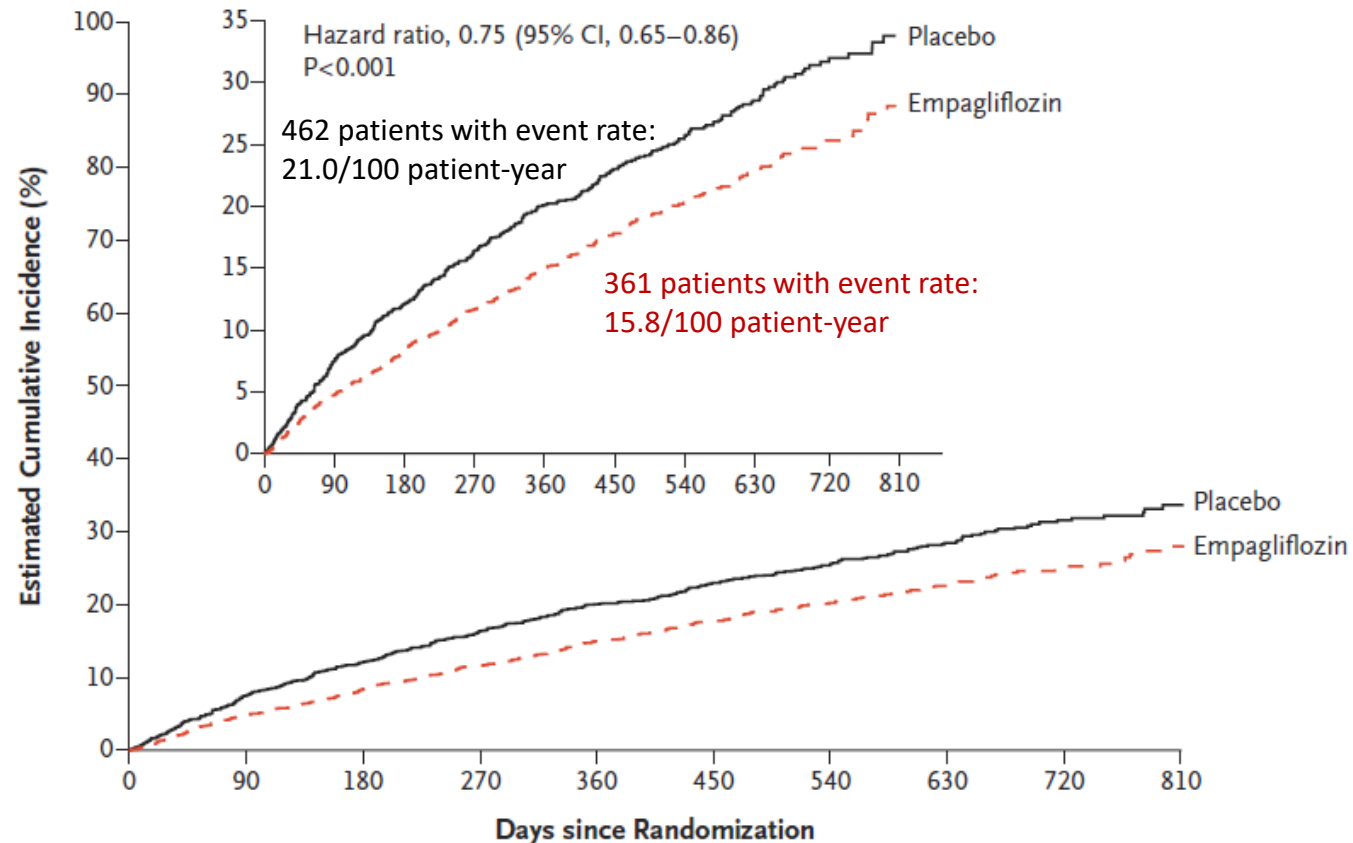
25% RRR

p<0.001

19.4% vs 24.7%

HR = 0.75 (0.65-0.86)

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

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DIABETES

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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DIABETES

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

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
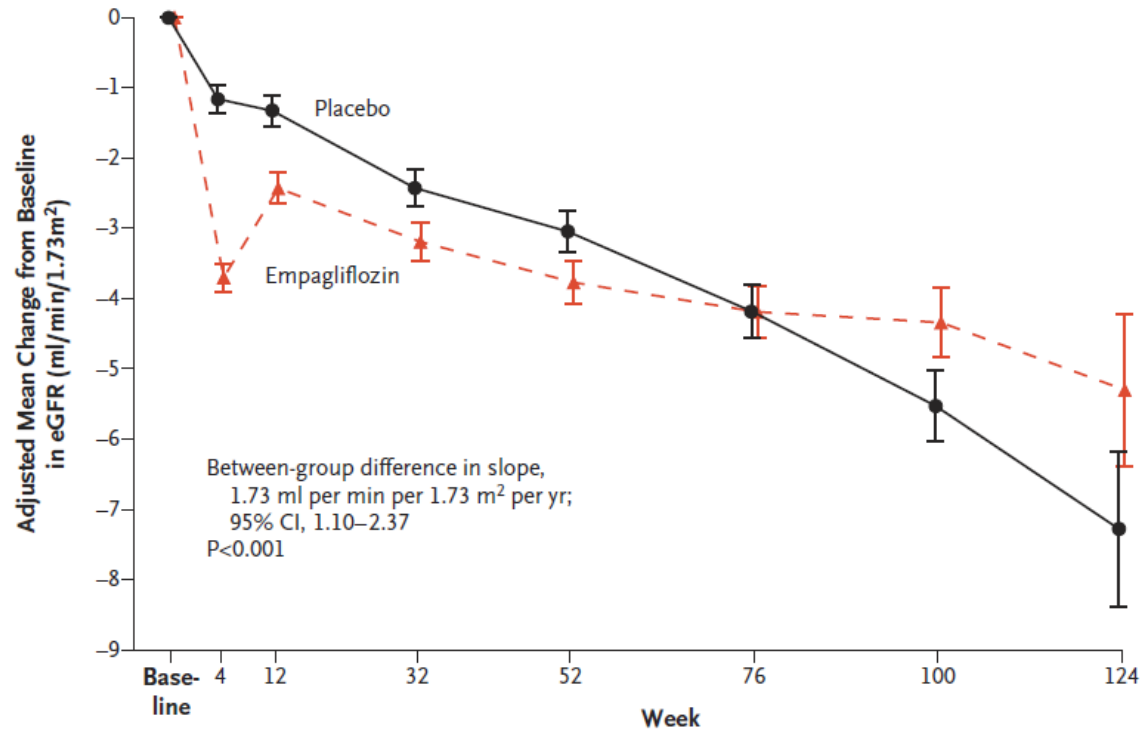- Placebo
- Empagliflozin

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

✓ 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
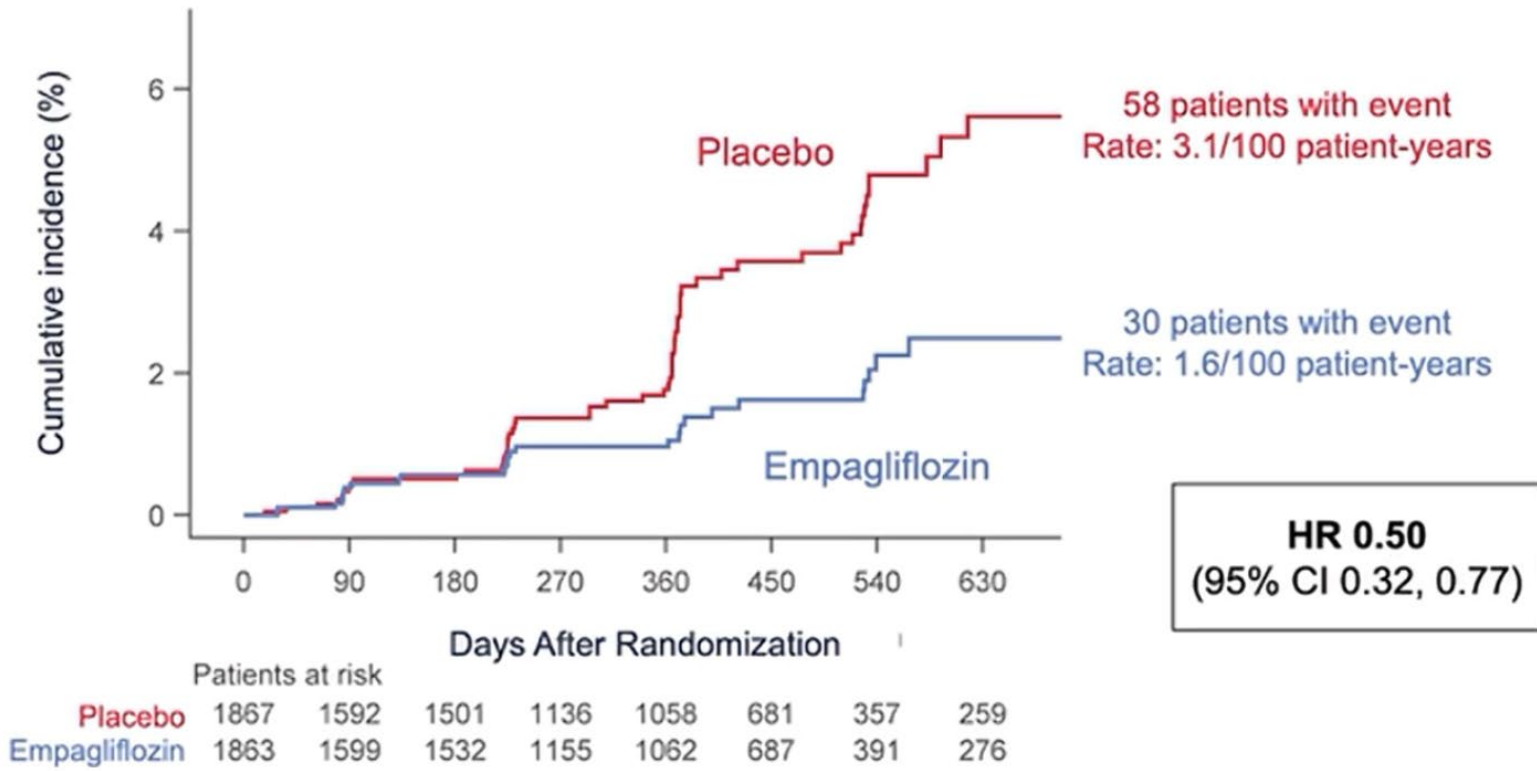
1.73 ml / min / 1.73 m2 / year

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].

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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]

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

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

HR 0.50
(95% CI 0.32, 0.77)

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)

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DIABETES

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)

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DIABETES

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

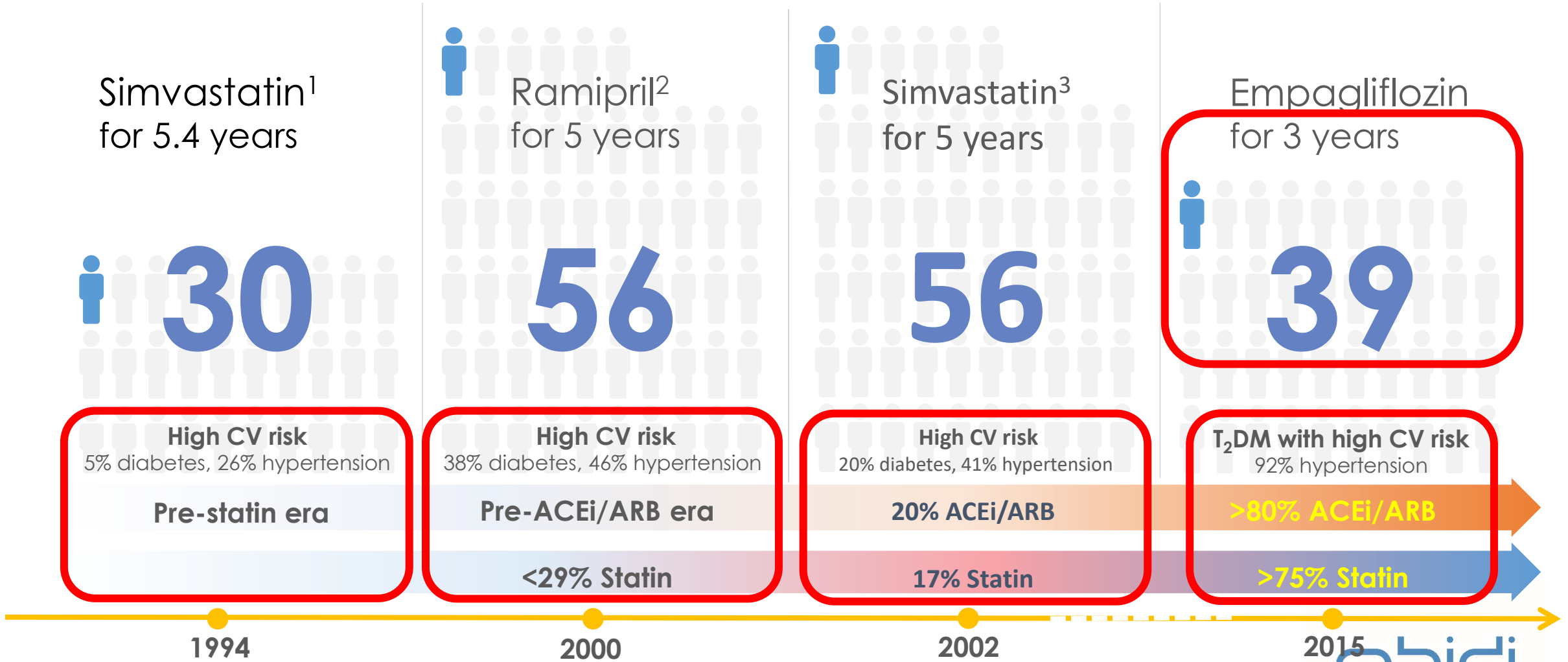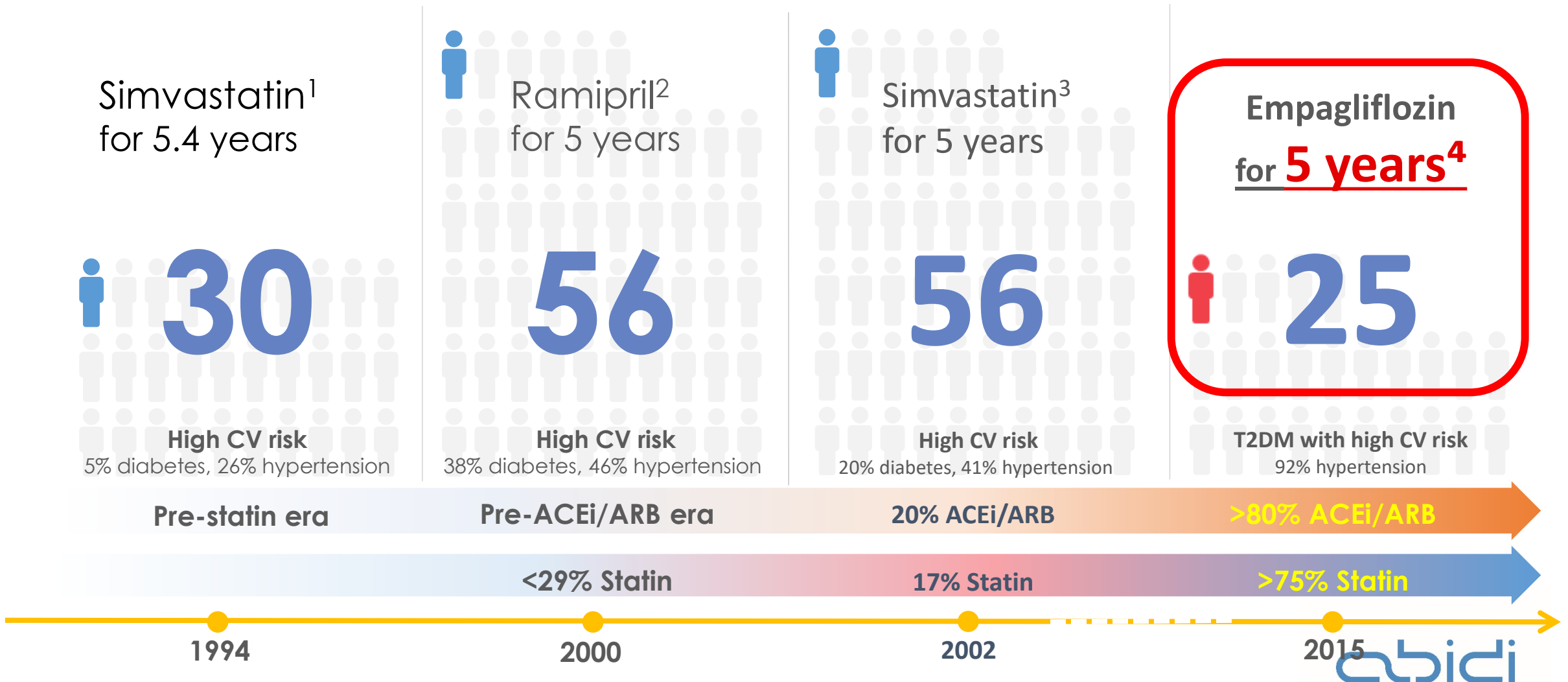# Conclusion[1]
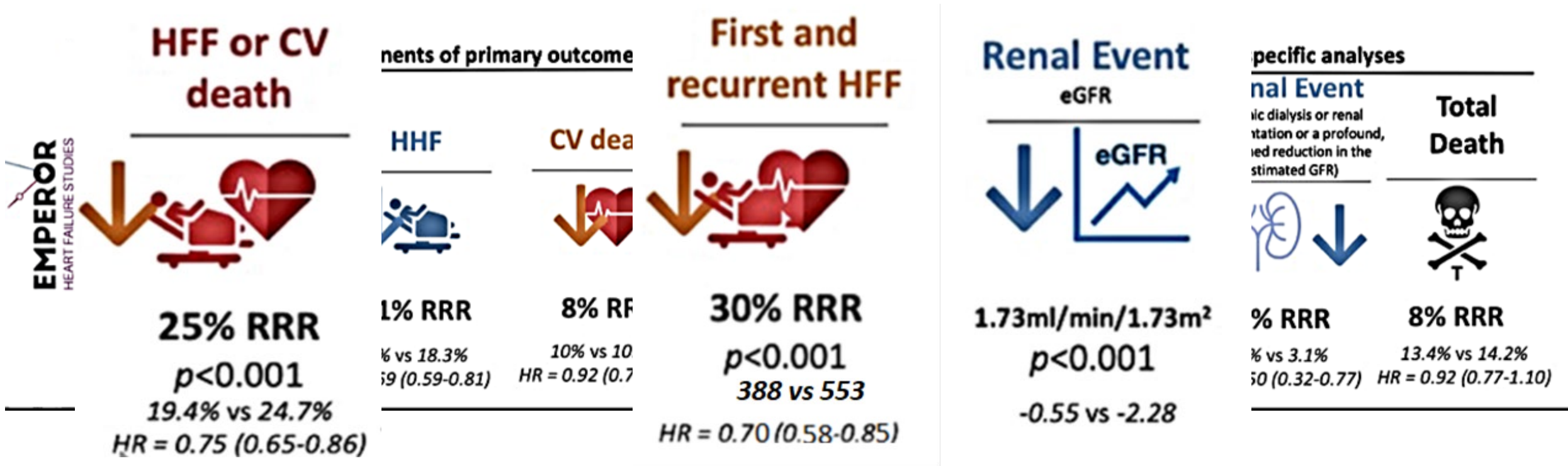
✓ Overall, in this trial, empagliflozin was associated with a lower combined risk of cardiovascular death or hospitalization for heart failure than placebo and with a slower progressive decline in renal function in patients with chronic heart failure and a reduced ejection fraction, regardless of the presence or absence of diabetes.

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

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DIABETES

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

Simvastatin[1] for 5.4 years	Ramipril[2] for 5 years	Simvastatin[3] for 5 years	Empagliflozin for 3 years
30	**56**	**56**	**39**
High CV risk 5% diabetes, 26% hypertension	**High CV risk** 38% diabetes, 46% hypertension	**High CV risk** 20% diabetes, 41% hypertension	**T$_2$DM 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.   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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DIABETES

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

Simvastatin[1]
for 5.4 years

30

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

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DIABETES

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.

FDC & Initial combination therapy of Empagliflozin and Metformin

Initial Combination of Empagliflozin and Metformin in Patients With Type 2 Diabetes
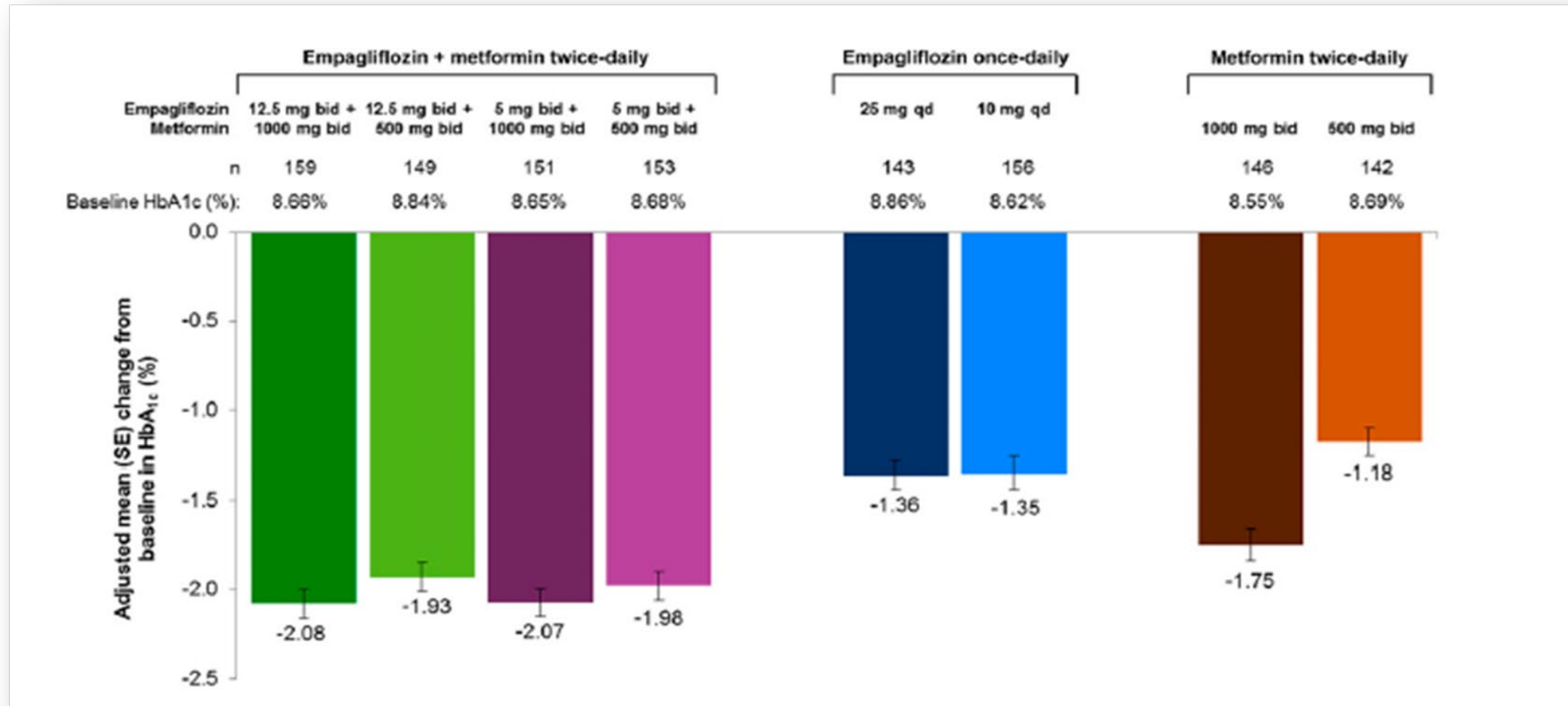
Samy Hadjadj,[1] Julio Rosenstock,[2] Thomas Meinicke,[3] Hans J. Woerle,[4] and Uli C. Broedl[4]

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.

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

54

Change from Baseline in HbA1c[1]

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

Change from Baseline in HbA1c[1]

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

Change from Baseline in Weight[1]

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

Change from Baseline in Weight[1]

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

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.

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

SCIENTIFIC REPORTS
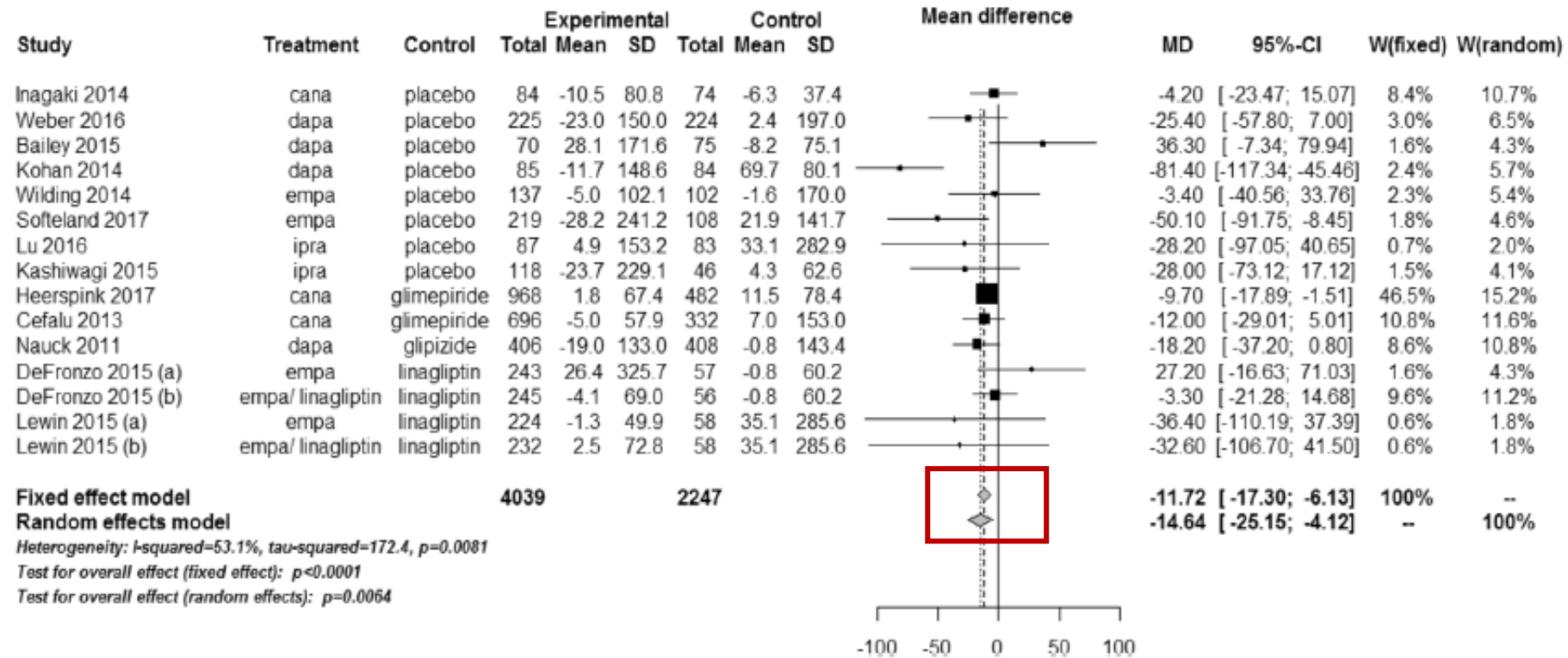natureresearch

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 Bae[1], Eun-Gee Park[2], Sunhee Kim[2], Sin Gon Kim[1], Seokyung Hahn[3,4] & Nam Hoon Kim[1]

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 diabetes[1].

1-Sci Rep. 2019 Sep 10;9(1):13009.

DIABETES

Weighted mean differences in changes in UACR from baseline (mg/g) for SGLT2i versus placebo or other antidiabetic drugs[1]

| Study	Treatment	Control	Experimental			Control			Mean difference	MD	95%-CI	W(fixed)	W(random)
			Total	Mean	SD	Total	Mean	SD					
Inagaki 2014	cana	placebo	84	-10.5	80.8	74	-6.3	37.4		-4.20	[-23.47; 15.07]	8.4%	10.7%
Weber 2016	dapa	placebo	225	-23.0	150.0	224	2.4	197.0		-25.40	[-57.80; 7.00]	3.0%	6.5%
Bailey 2015	dapa	placebo	70	28.1	171.6	75	-8.2	75.1		36.30	[-7.34; 79.94]	1.6%	4.3%
Kohan 2014	dapa	placebo	85	-11.7	148.6	84	69.7	80.1		-81.40	[-117.34; -45.46]	2.4%	5.7%
Wilding 2014	empa	placebo	137	-5.0	102.1	102	-1.6	170.0		-3.40	[-40.56; 33.76]	2.3%	5.4%
Softeland 2017	empa	placebo	219	-28.2	241.2	108	21.9	141.7		-50.10	[-91.75; -8.45]	1.8%	4.6%
Lu 2016	ipra	placebo	87	4.9	153.2	83	33.1	282.9		-28.20	[-97.05; 40.65]	0.7%	2.0%
Kashiwagi 2015	ipra	placebo	118	-23.7	229.1	46	4.3	62.6		-28.00	[-73.12; 17.12]	1.5%	4.1%
Heerspink 2017	cana	glimepiride	968	1.8	67.4	482	11.5	78.4		-9.70	[-17.89; -1.51]	46.5%	15.2%
Cefalu 2013	cana	glimepiride	696	-5.0	57.9	332	7.0	153.0		-12.00	[-29.01; 5.01]	10.8%	11.6%
Nauck 2011	dapa	glipizide	406	-19.0	133.0	408	-0.8	143.4		-18.20	[-37.20; 0.80]	8.6%	10.8%
DeFronzo 2015 (a)	empa	linagliptin	243	26.4	325.7	57	-0.8	60.2		27.20	[-16.63; 71.03]	1.6%	4.3%
DeFronzo 2015 (b)	empa/ linagliptin	linagliptin	245	-4.1	69.0	56	-0.8	60.2		-3.30	[-21.28; 14.68]	9.6%	11.2%
Lewin 2015 (a)	empa	linagliptin	224	-1.3	49.9	58	35.1	285.6		-36.40	[-110.19; 37.39]	0.6%	1.8%
Lewin 2015 (b)	empa/ linagliptin	linagliptin	232	2.5	72.8	58	35.1	285.6		-32.60	[-106.70; 41.50]	0.6%	1.8%
Fixed effect model			**4039**			**2247**				**-11.72**	**[-17.30; -6.13]**	**100%**	**--**
Random effects model										**-14.64**	**[-25.15; -4.12]**	**--**	**100%**

Heterogeneity: I-squared=53.1%, tau-squared=172.4, p=0.0081
Test for overall effect (fixed effect): p<0.0001
Test for overall effect (random effects): p=0.0064

UACR,urine albumin-to-creatinine ratio; CI, confidence interval; MD, mean difference; SD, standard deviation; W, weight.
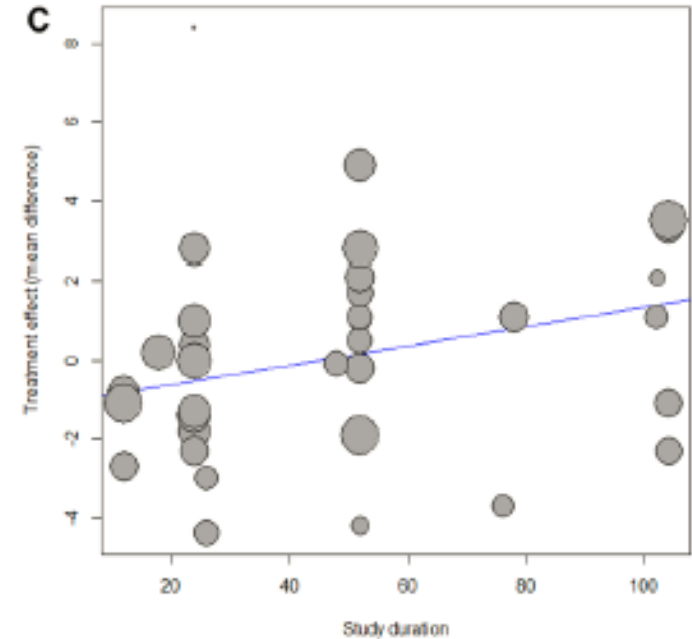
1-Sci Rep. 2019 Sep 10;9(1):13009.

Meta-regression of changes in (UACR*) and (eGFR) for SGLT2 inhibitors versus placebo or other antidiabetic drugs[1]
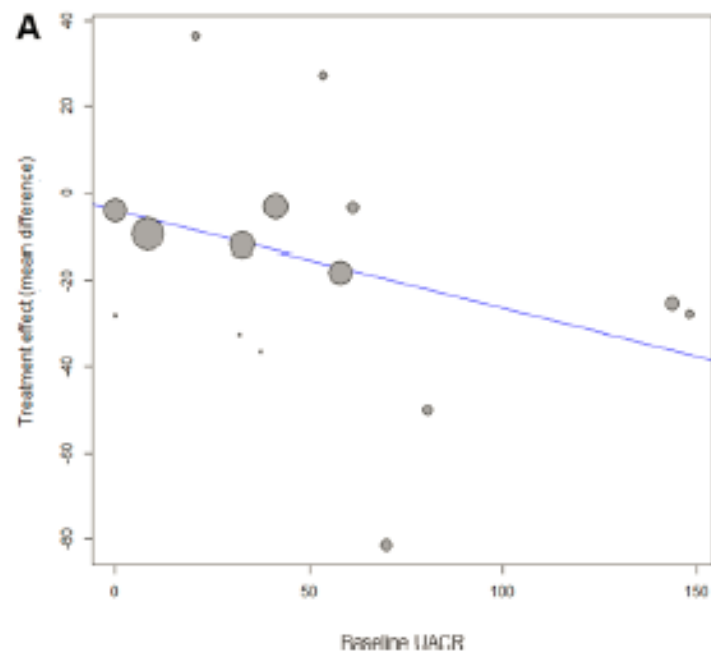
(A) Changes in UACR according to baseline UACR.
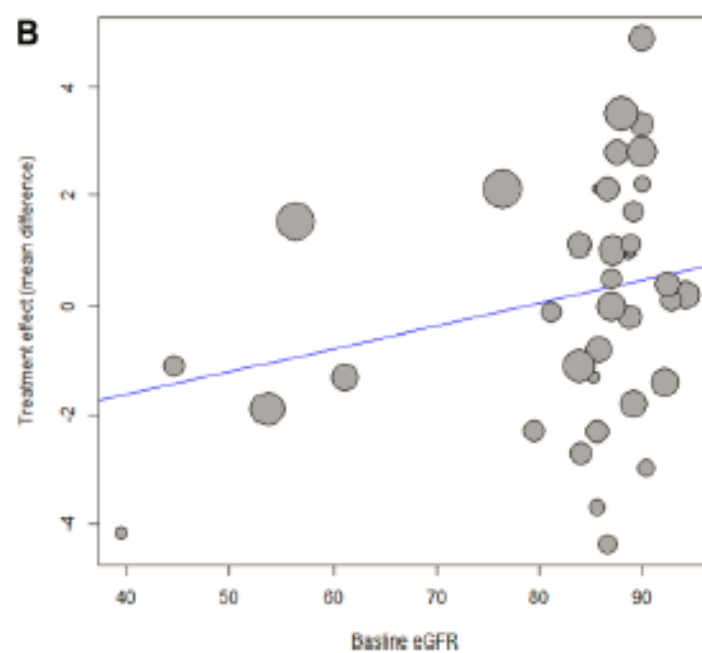
(B) Changes in eGFR according to baseline eGFR

(C) Changes in eGFR according to treatment duration.

UACR, urine albumin-to-creatinine ratio

1-Sci Rep. 2019 Sep 10;9(1):13009.

Weighted mean differences in eGFR from baseline for SGLT2 inhibitors versus placebo or other antidiabetic drugs[1]

(A) According to baseline estimated glomerular filtration rate

(B) According to treatment duration

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

1-Sci Rep. 2019 Sep 10;9(1):13009.

Relative risks of microalbuminuria, macroalbuminuria, worsening nephropathy, and ESRD for SGLT2 inhibitors versus placebo or other antidiabetic drugs[1]
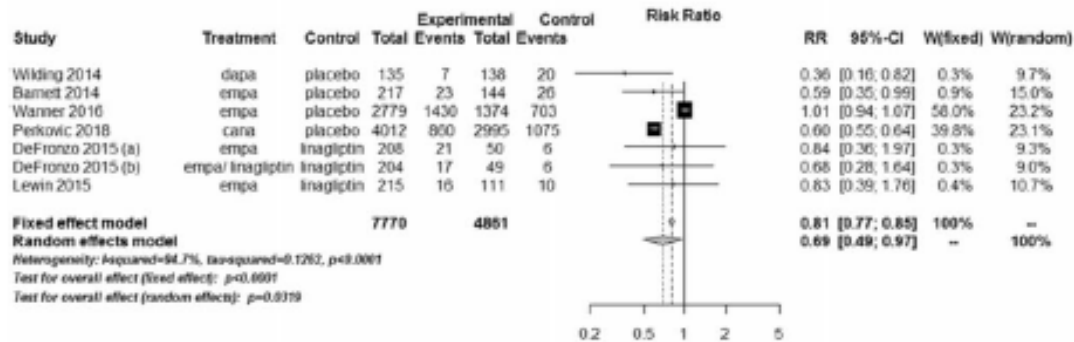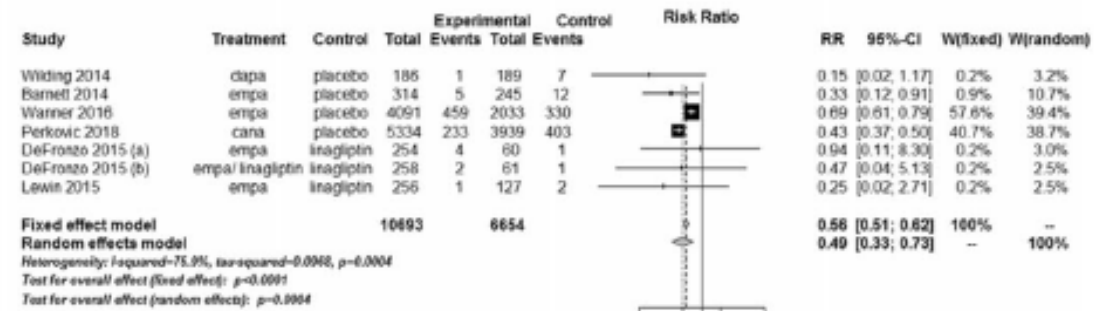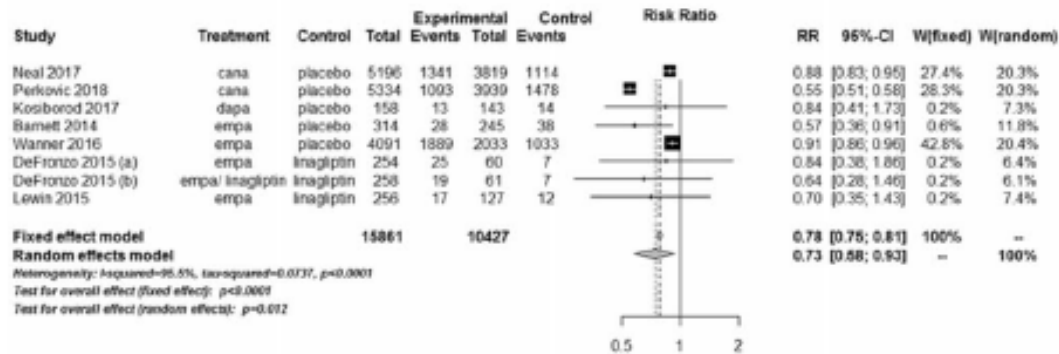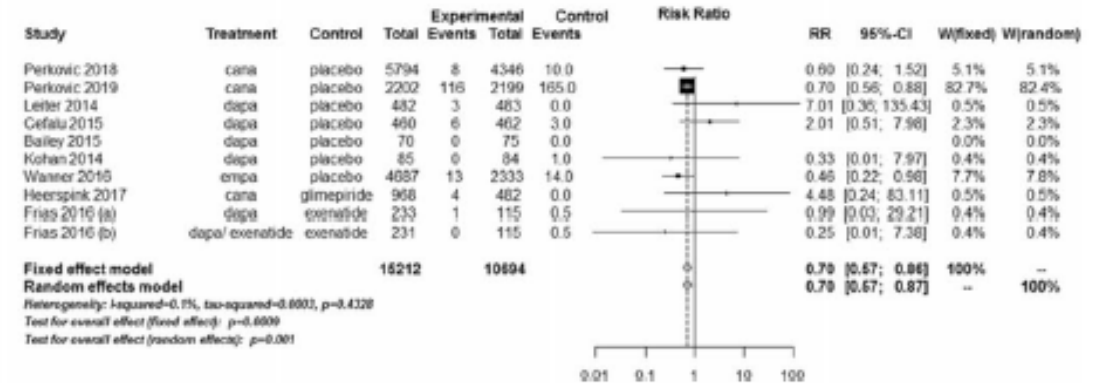

CI, confidence interval; RR, relative risk; W, weight.

1-Sci Rep. 2019 Sep 10;9(1):13009.

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 diabetes[1].

- ✓ The UACR-lowering effects of SGLT2 inhibitors were associated with a higher baseline UACR[1].

- ✓ 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 treatment[1].

- ✓ SGLT2 inhibitor significantly reduced the risk of ESRD compared with controls[1].

- ✓ 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 diabetes[1].

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

1-Sci Rep. 2019 Sep 10;9(1):13009.

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Discussion

✓ SGLT2 inhibitors had the renoprotective effects by reducing the risk of albuminuria and ESRD in patients with a wide range of cardiovascular risk[1].

✓ 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 levels[1].

✓ 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 weight[1].

✓ 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 DKD[1].

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

1-Sci Rep. 2019 Sep 10;9(1):13009.

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 treatment[1].

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

1-Sci Rep. 2019 Sep 10;9(1):13009.

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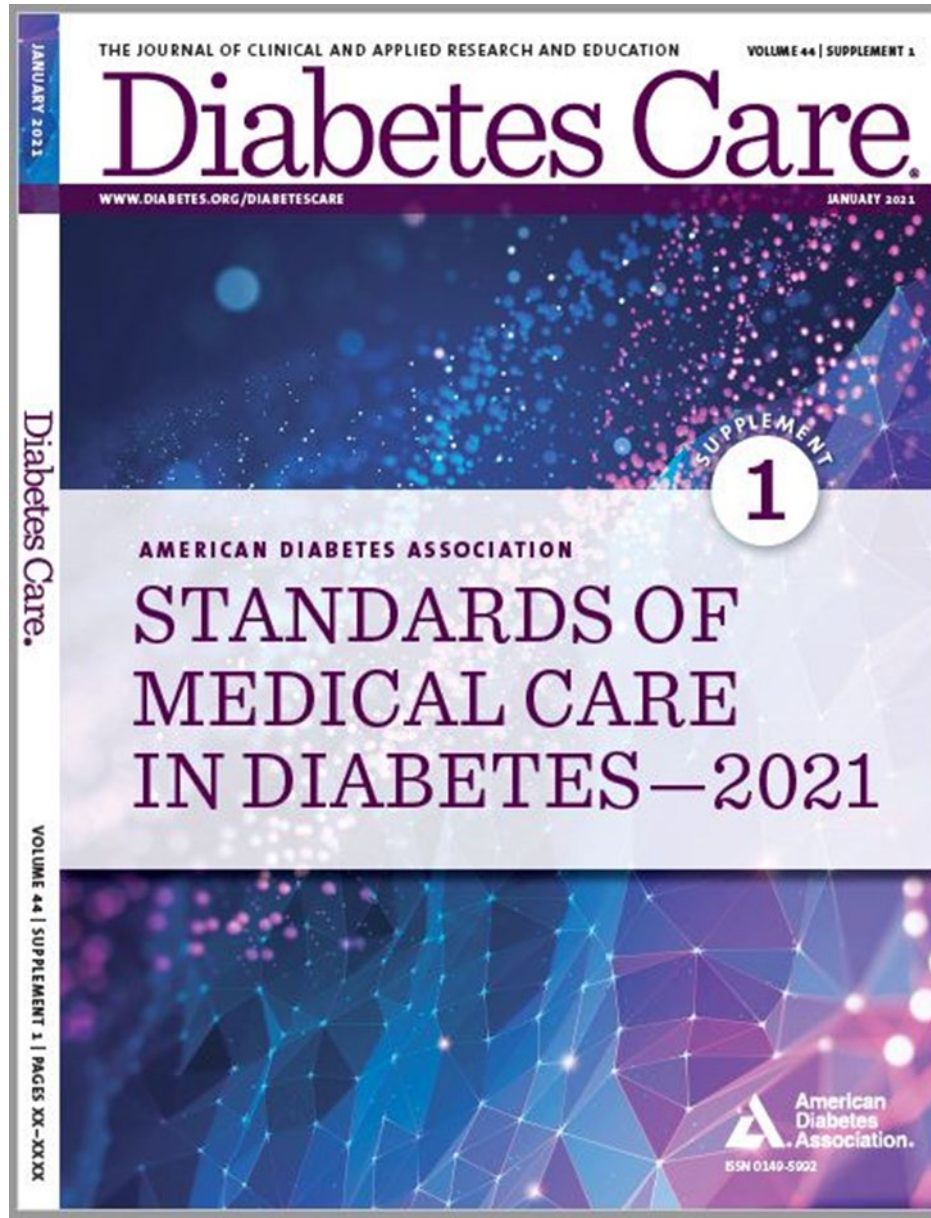
FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

NO

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

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)

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

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

+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)

EITHER/OR

GLP-1 RA with proven CVD benefit[1] | SGLT2i with proven CVD benefit[1]

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 versa[1]
- TZD[2]
- DPP-4i if not on GLP-1 RA
- Basal insulin[3]
- SU[4]

+HF

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

+CKD

DKD and Albuminuria[8]   NO

PREFERABLY
SGLT2i with primary evidence of reducing CKD progression

OR
SGLT2i with evidence of reducing CKD progression in CVOTs[5,8,8]

OR
GLP-1 RA with proven CVD benefit[1] if SGLT2i not tolerated or contraindicated

For patients with T2D and CKD[8] (e.g., eGFR <60 mL/min/1.73 m²) and thus at increased risk of cardiovascular events

EITHER/OR

GLP-1 RA with proven CVD benefit[1] | SGLT2i with proven CVD benefit[1,7]

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA

DPP-4i | GLP-1 RA | SGLT2i | TZD

If A1C above target | If A1C above target | If A1C above target | If A1C above target

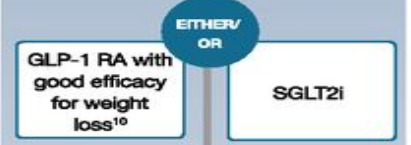SGLT2i OR TZD | SGLT2i OR TZD | GLP-1 RA OR DPP-4i OR TZD | SGLT2i OR DPP-4i OR GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

If A1C above target

Consider the addition of SU[4] OR basal insulin:
- Choose later generation SU with lower risk of hypoglycemia
- Consider basal insulin with lower risk of hypoglycemia[9]

COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

GLP-1 RA with good efficacy for weight loss[10] — EITHER/OR — SGLT2i

If A1C above target

SGLT2i | GLP-1 RA with good efficacy for weight loss[10]

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:
- SU[4] · TZD[2] · Basal insulin

COST IS A MAJOR ISSUE[11,12]

SU[4] | TZD[12]

If A1C above target

TZD[12] | SU[4]

If A1C above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider other therapies based on cost

1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. 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.

7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. 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)
12. 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.

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

ESC 2019

European Society of Cardiology Guideline

DIABETES

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)

IR-1121-GLR-5469-SP

71

Cardiovascular risk categories in patients with diabetes[1]

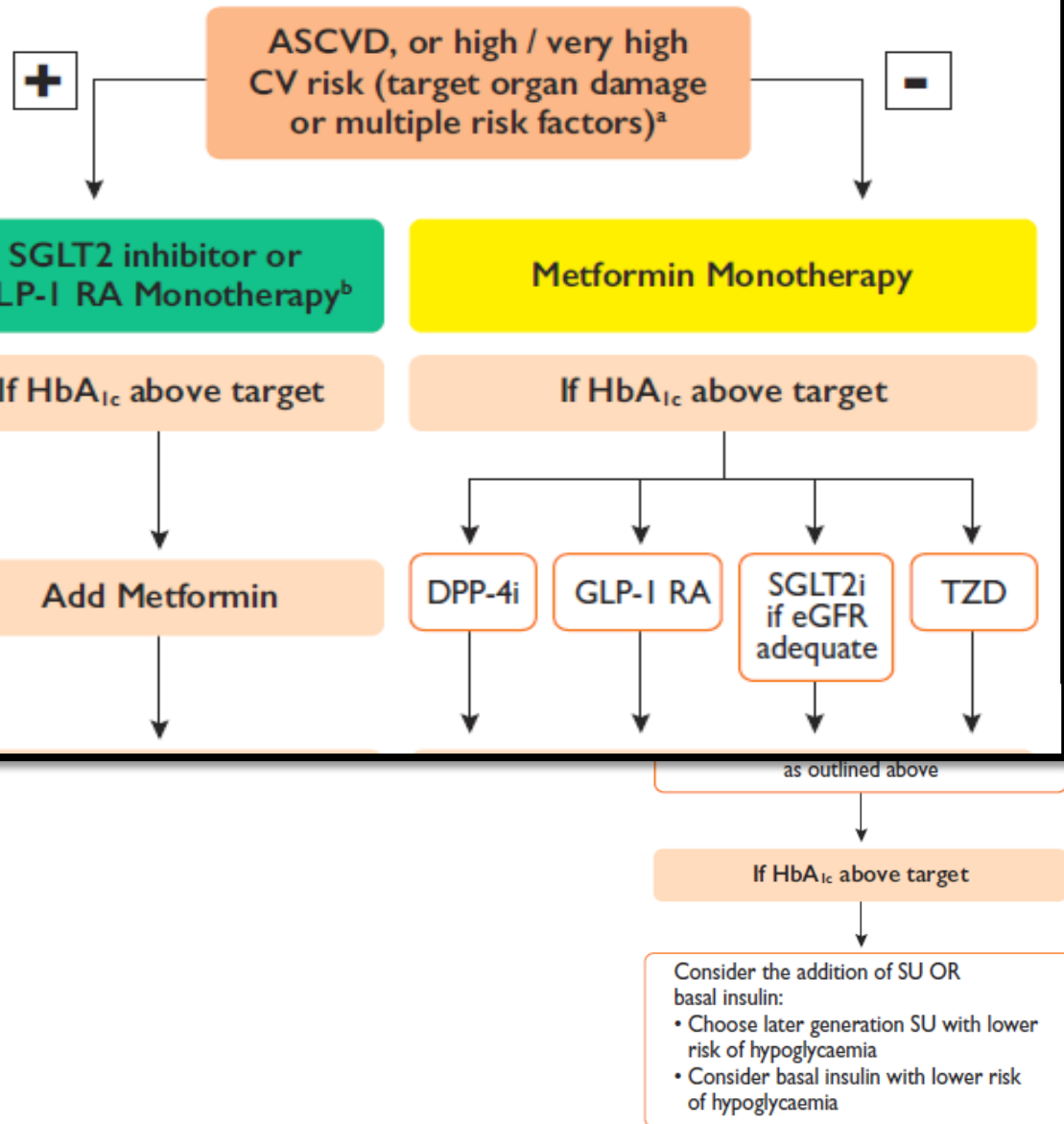|	
Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor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

©ESC 20

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]
[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m², left ventricular hypertrophy, or retinopathy.
[c]Age, hypertension, dyslipidemia, smoking, obesity.

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

A Type 2 DM - Drug naïve patients

+ ← ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a] → **−**

SGLT2 inhibitor or GLP-1 RA Monotherapy[b]	Metformin Monotherapy
If HbA$_{1c}$ above target	If HbA$_{1c}$ above target
Add Metformin	DPP-4i / GLP-1 RA / SGLT2i if eGFR adequate / TZD

as outlined above

If HbA$_{1c}$ above target

Consider the addition of SU OR basal insulin:
- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia

B Type 2 DM - On metformin

+ ← ASCVD, or high / very high CV risk (target organ damage or multiple risk factors)[a] → **−**

Add SGLT2 inhibitor or GLP-1 RA[b]	Continue Metformin Monotherapy
If HbA$_{1c}$ above target	If HbA$_{1c}$ above target

Continue with addition of other agents as outlined above

If HbA$_{1c}$ above target

Consider the addition of SU OR basal insulin:
- Choose later generation SU with lower risk of hypoglycaemia
- Consider basal insulin with lower risk of hypoglycaemia

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Heart failure and diabetes[1]

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.

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

DIABETES

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.

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Administration, Cautions, Side effects, Safety profile

DIABETES

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≥ 45 mL/min/1.73 m2

✓Empagliflozin should not be initiated in patients with an eGFR <45 mL/min/1.73 m2

✓Discontinue JARDIANCE 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 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

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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

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Diabetes

Thank you