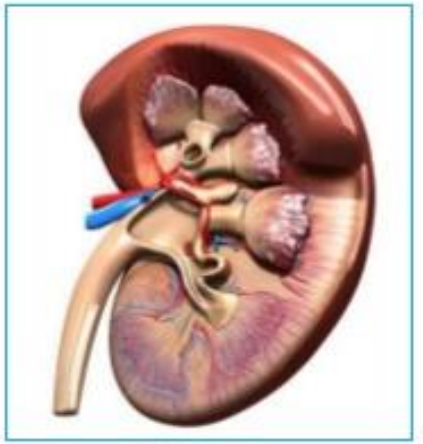
SODIUM–GLUCOSE CO-TRANSPORTERS (SGLTS) INHIBITORS



Dr.vahideh sadra

Endocrinologist

Tabriz university of medical science 2021

SGLT2 INHIBITION—

A NEW KIDNEY- BASED STRATEGY TO REDUCE HYPERGLYCEMIA

1

Objectives

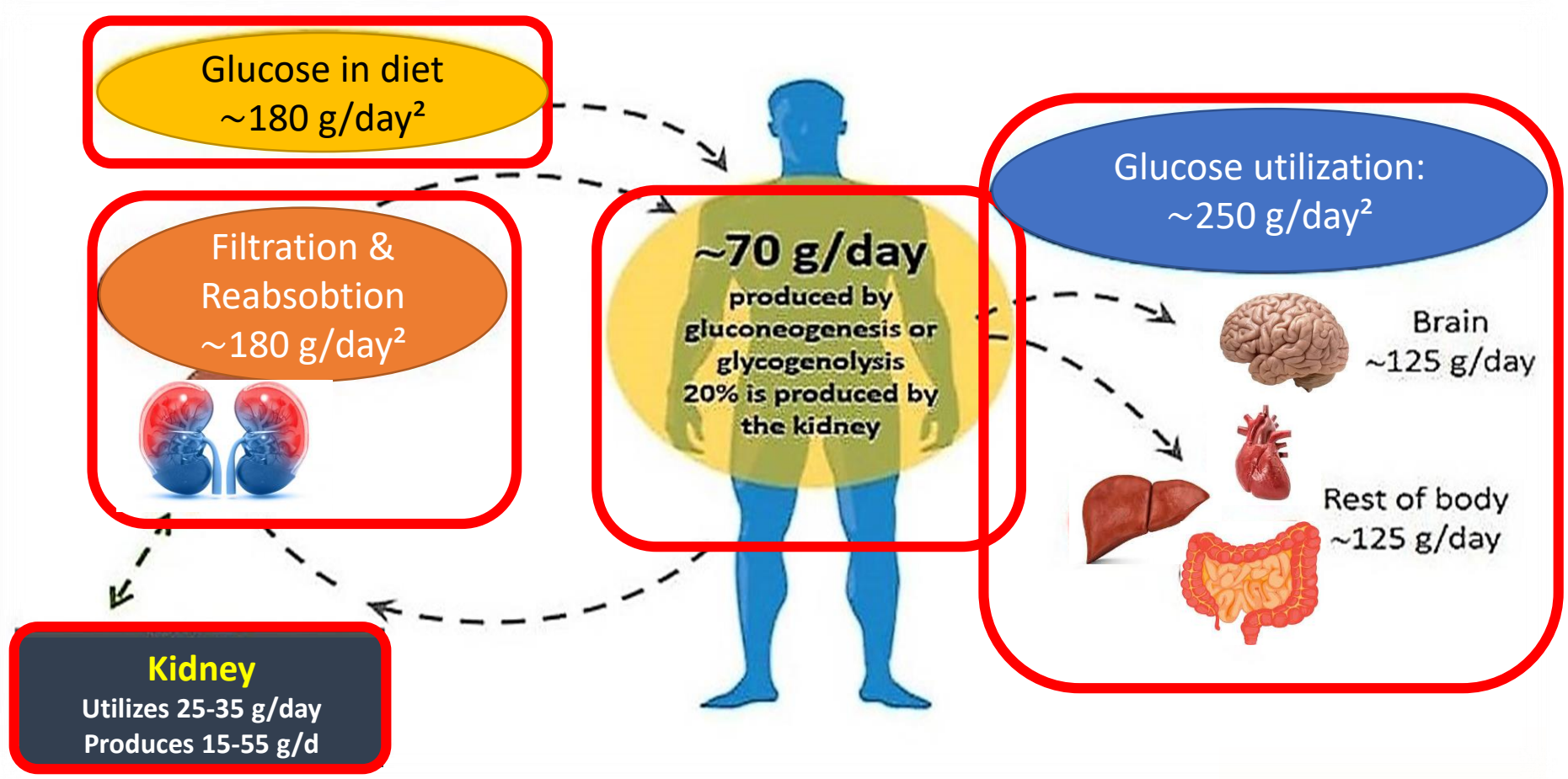
- Brief review of kidney role in glucose homeostasis
- SGLT2 & SGLT2 inhibitors
- Efficacy Studies
- Adverse events studies
- EMPA-REG OUTCOME
- EMPEROR- Reduced
- Guidelines Recommendations
- Administration, Cautions, Side effects
- Conclusion

Kidney Plays a Significant Role in Glucose Balance

Reabsorption[1]

Production[1]
(Gluconeogenesis)

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

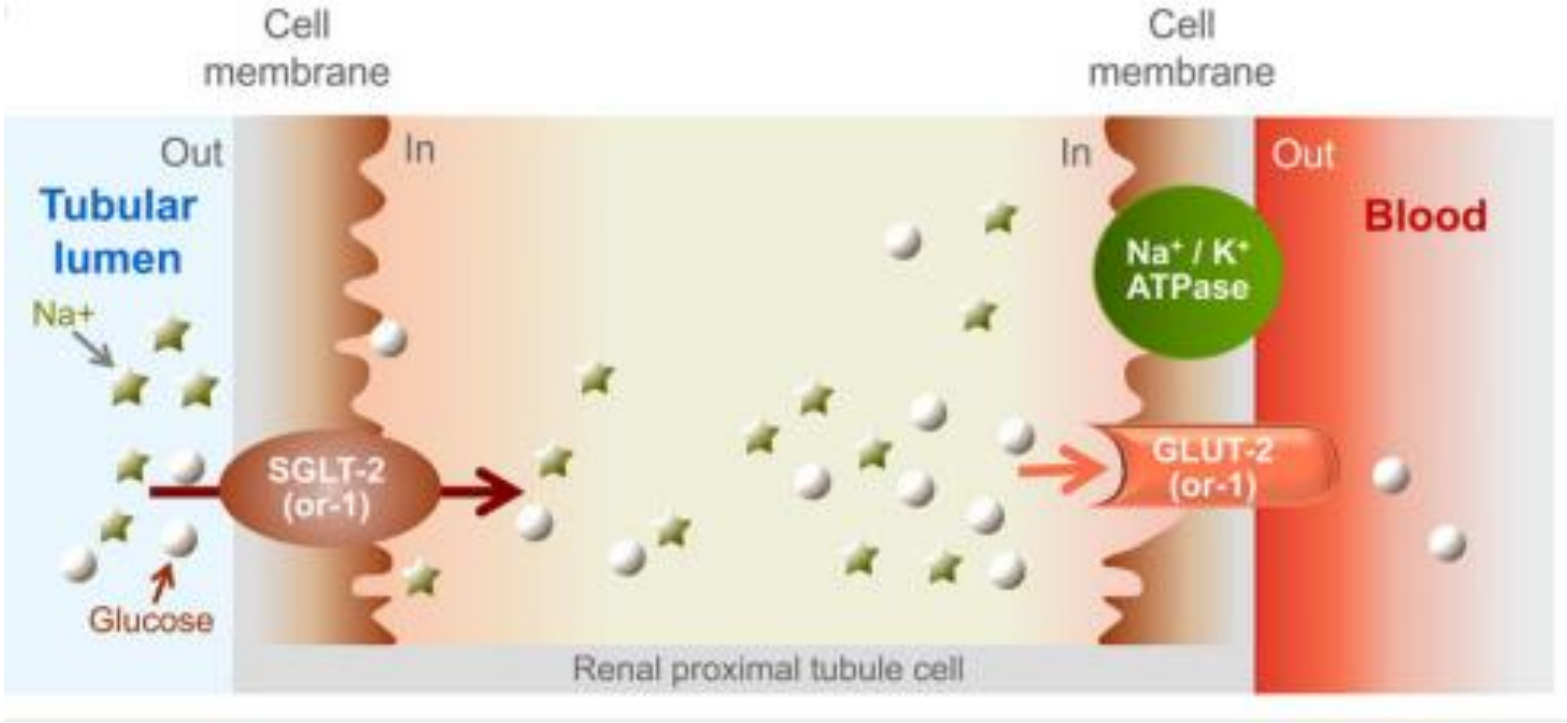
SGLT2 & SGLT2 inhibitors

Glucose Transporters

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

facilitative glucose transporters (GLUTs)

sodium-dependent glucose transporters (SGLTs)



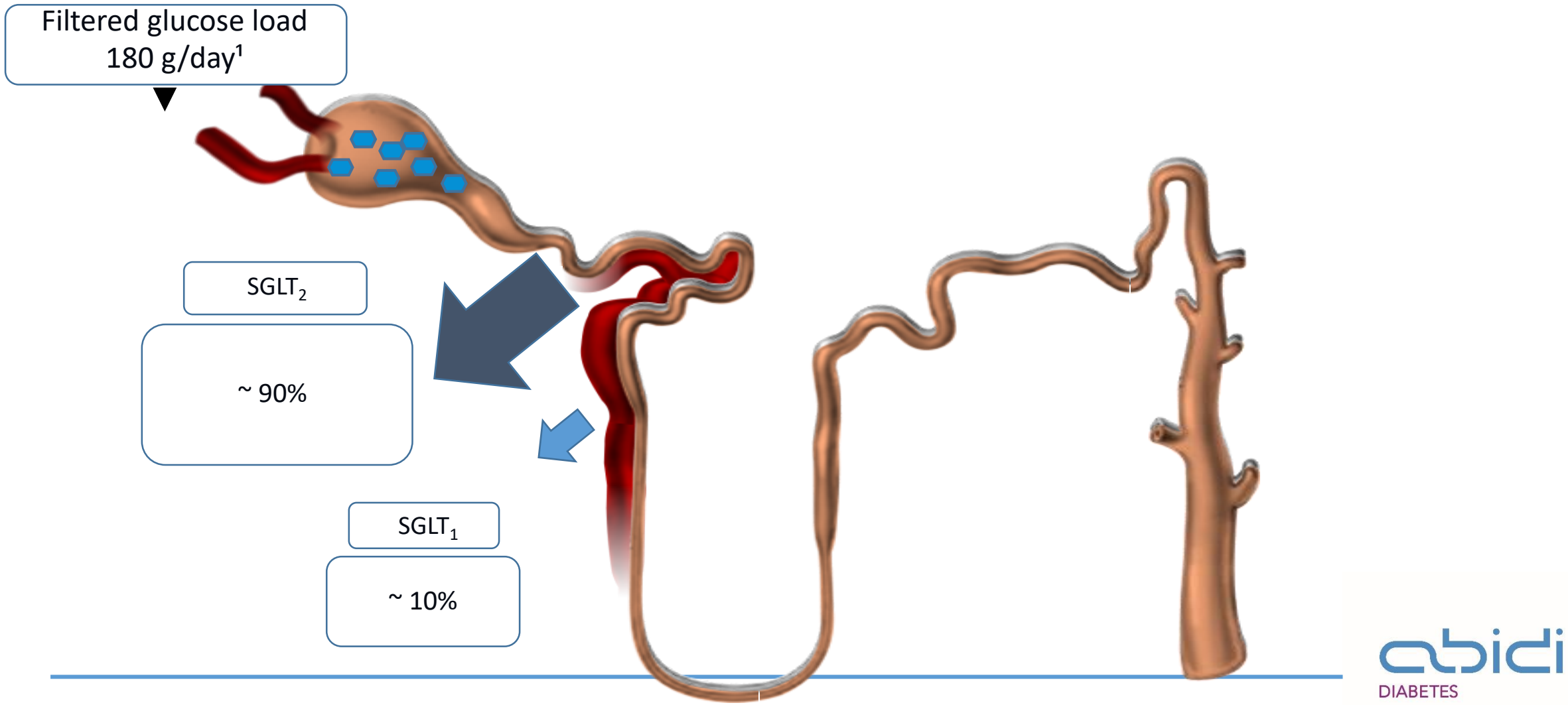
$SGLT_1$: low capacity, high affinity, mostly in intestine

$SGLT_2$: 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.

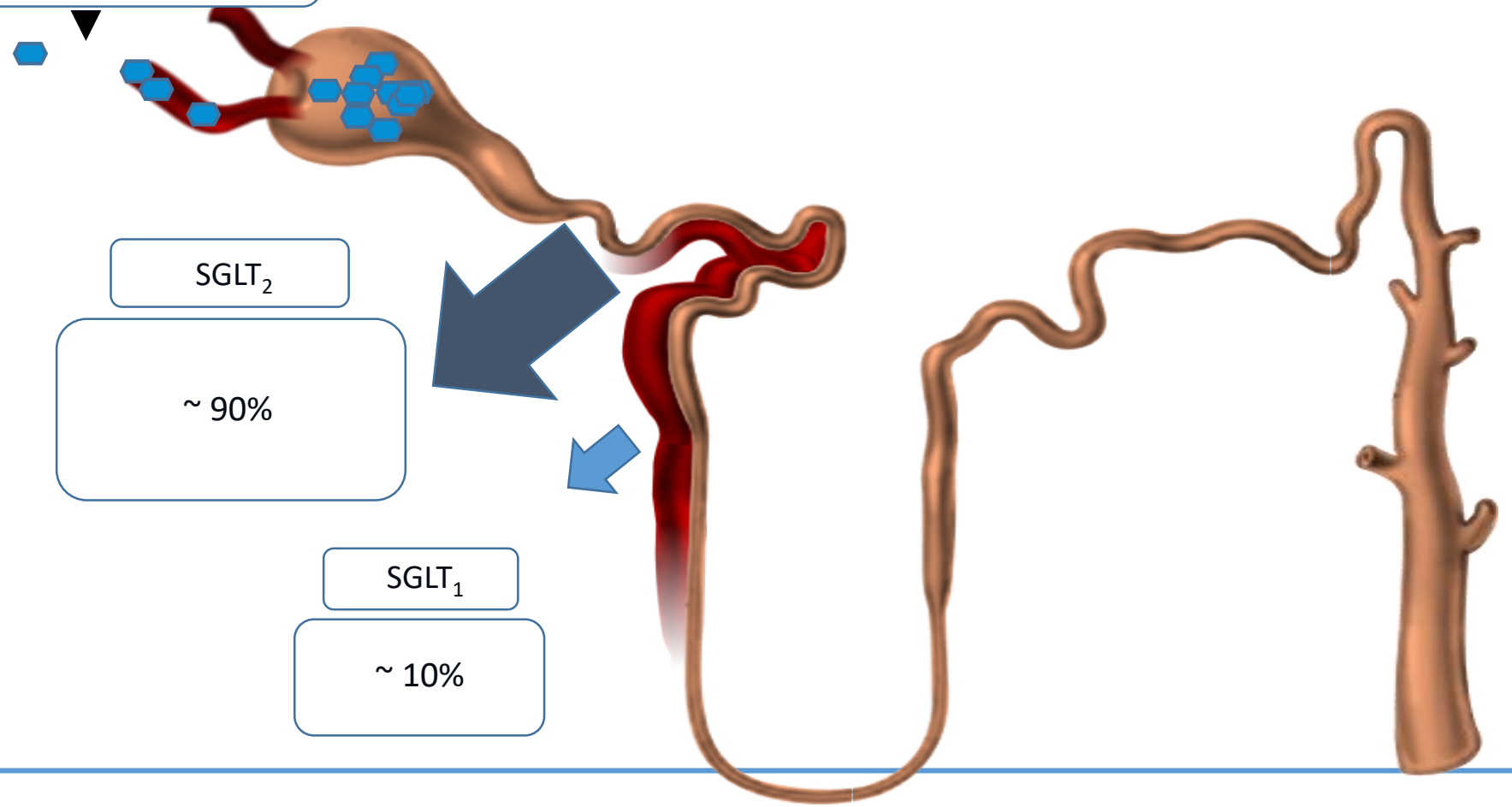
Renal glucose re-absorption in healthy individuals



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



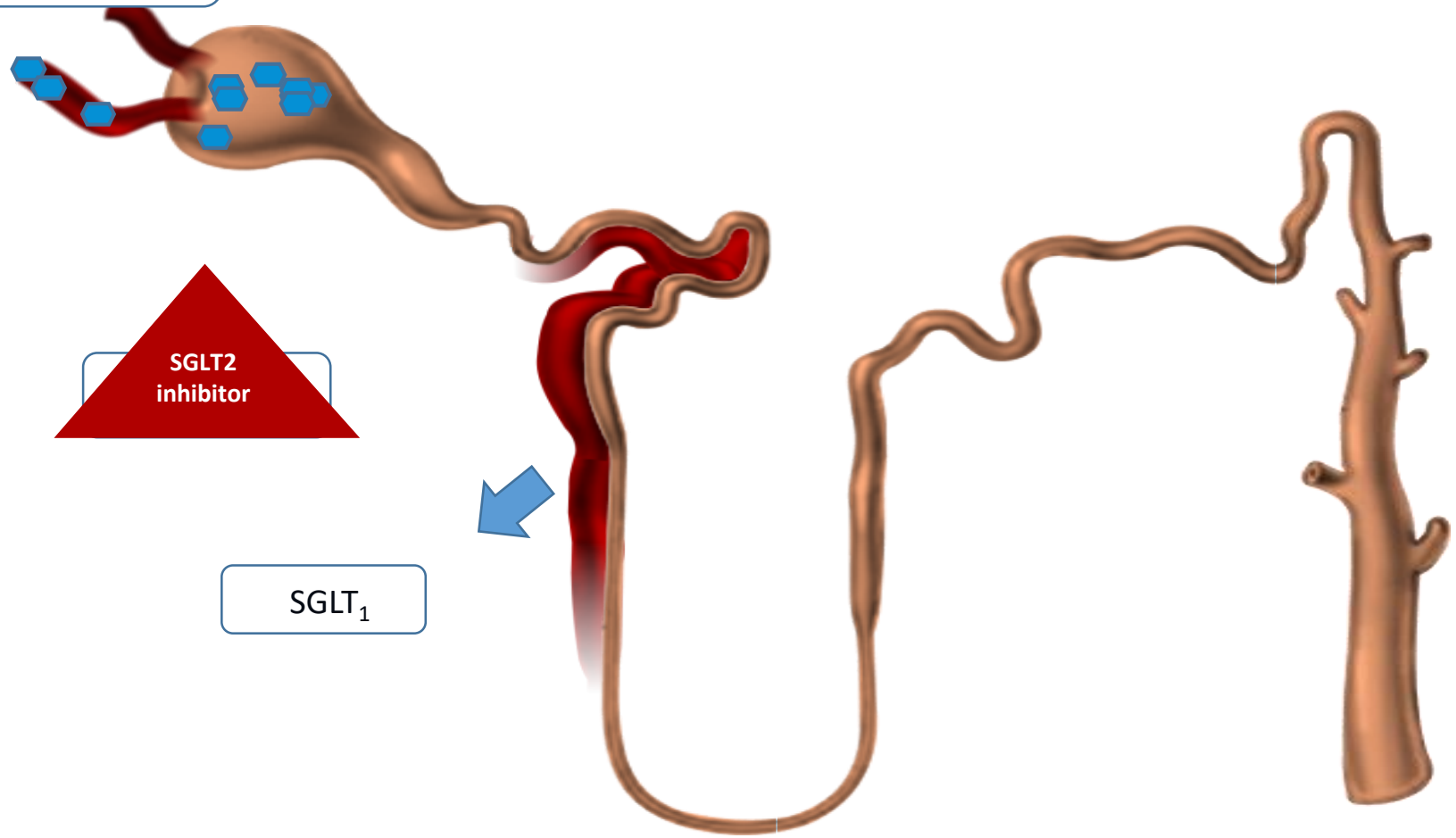
When blood glucose increases above the renal threshold *(~ 180 mg/dL),* the capacity of the transporters is exceeded, resulting in urinary glucose excretion[1]

abidi 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.

Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load
> 180 g/day



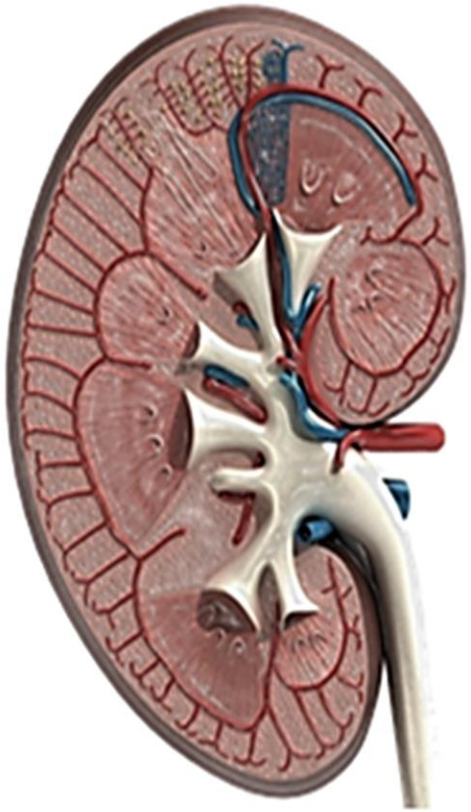
$SGLT_2$ inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis[1]

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

abidi DIABETES

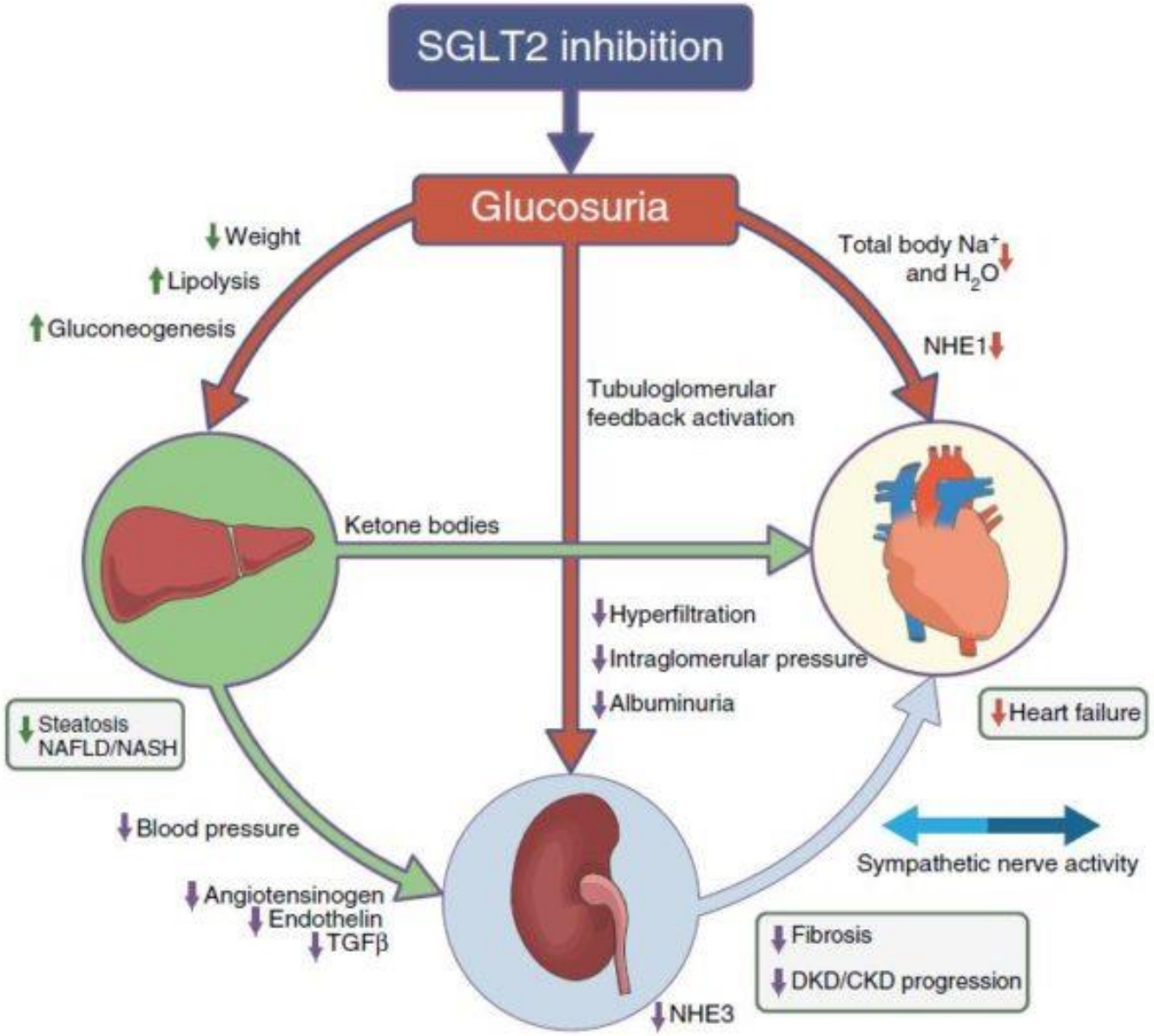
1-Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2):136-42.

Expected Clinical Effects of SGLT2 Inhibition[1]



DIABETES

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

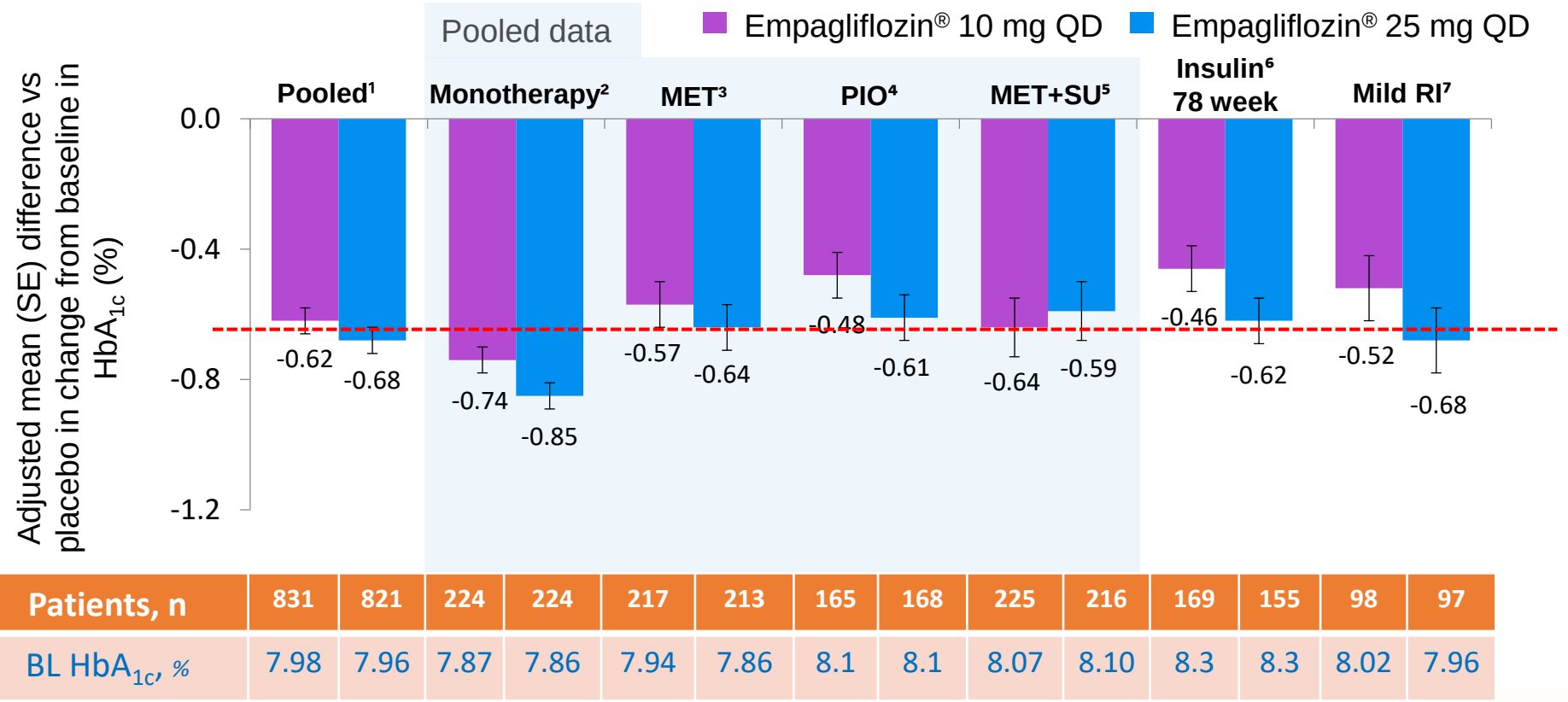


abidi DIABETES

Efficacy Studies

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

Phase III pooled efficacy analysis



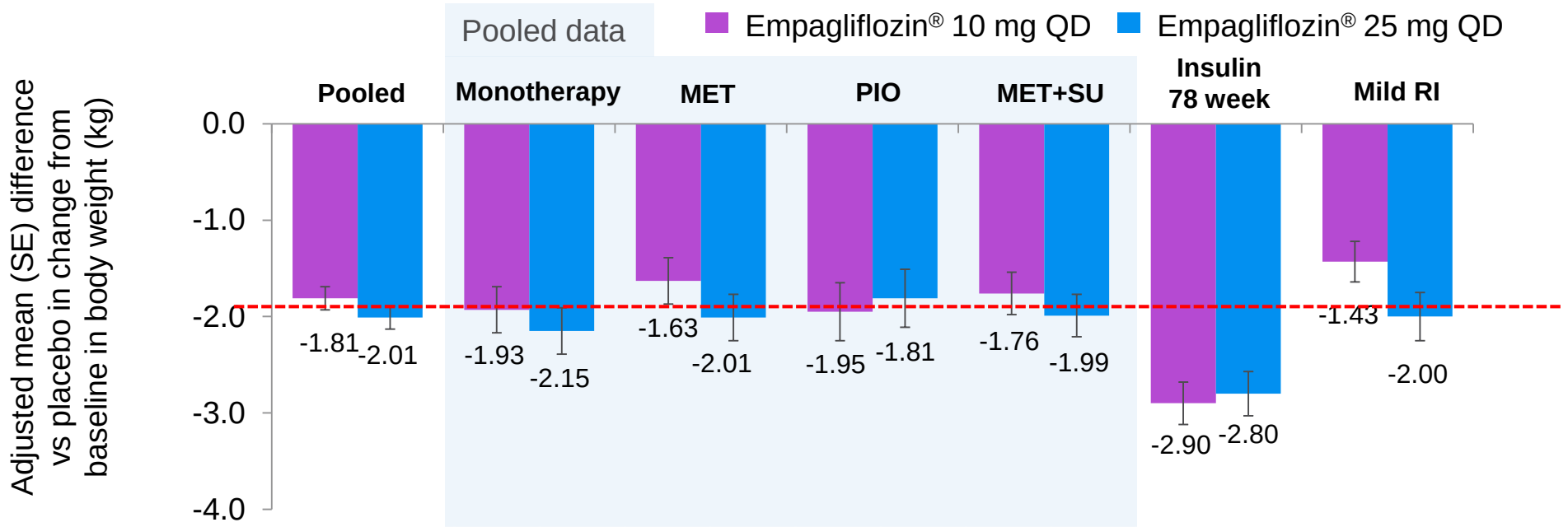
Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL HbA_{1c}, %	7.98	7.96	7.87	7.86	7.94	7.86	8.1	8.1	8.07	8.10	8.3	8.3	8.02	7.96

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

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

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

Phase III pooled efficacy analysis

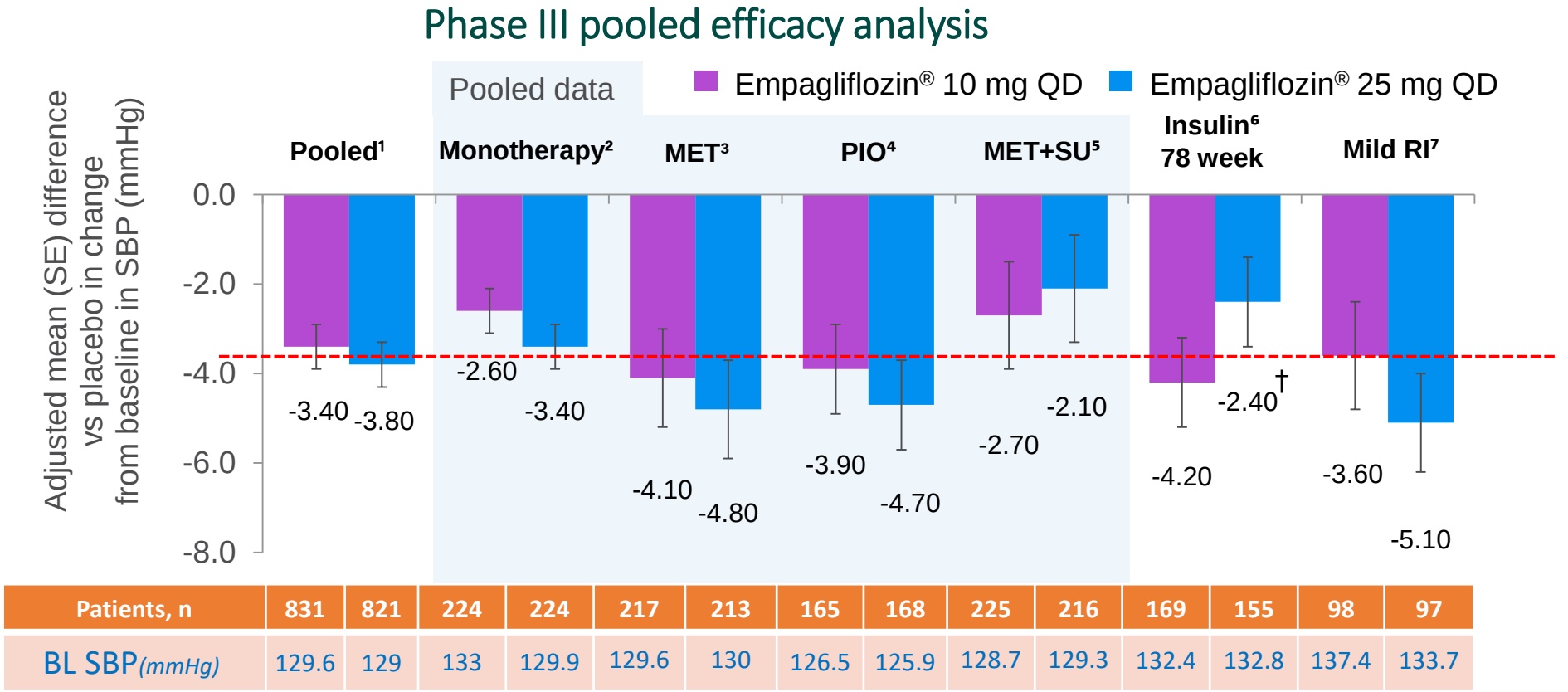


Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL BW *(kg)*	78.77	79.10	78.4	77.80	81.6	82.2	78.0	78.90	77.1	77.5	91.6	94.7	92.1	88.7

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*

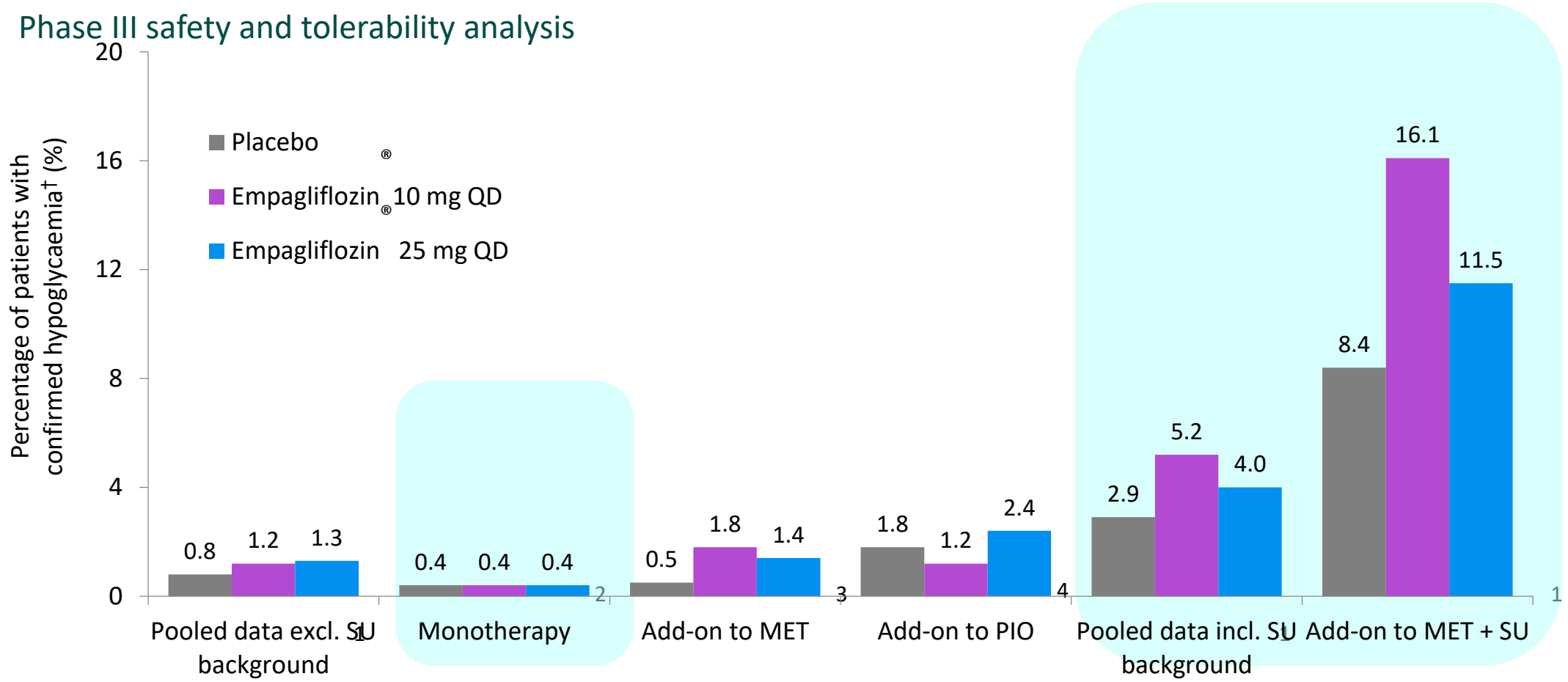


BL, baseline; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea.
*All statistically significant except when marked as †.

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.

Hypoglycemic Events

- Phase III safety and tolerability analysis



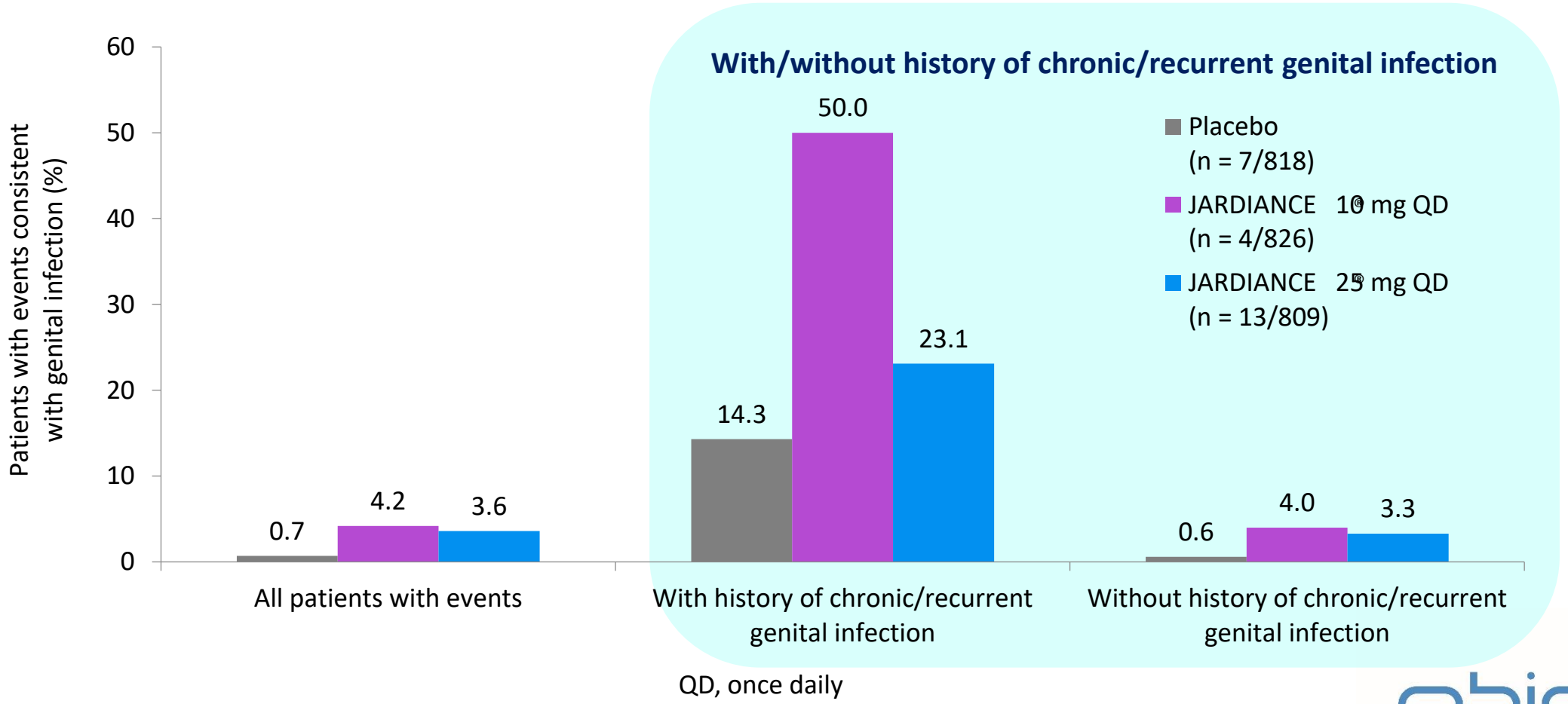
MET, metformin; PIO, pioglitazone; QD, once daily; SU, sulphonylurea.

†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

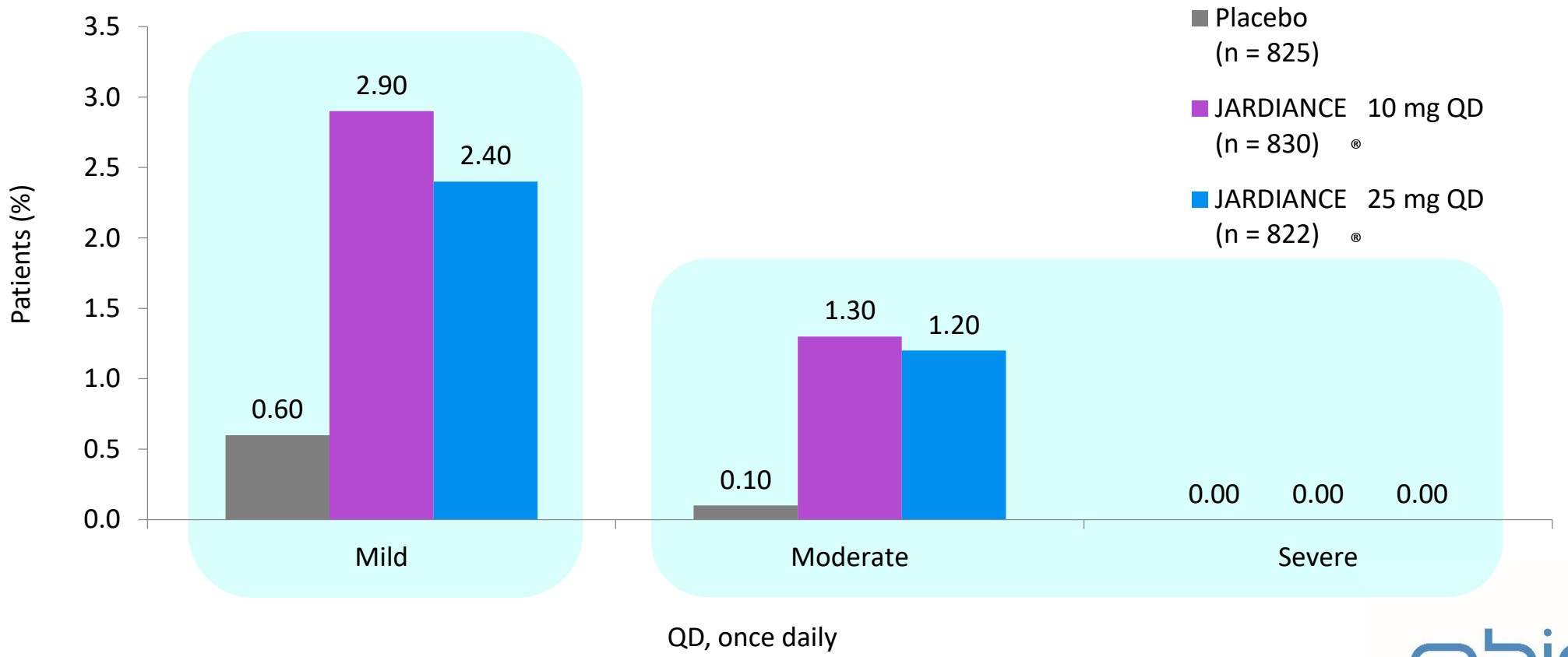


†The following studies were included in the pooled analysis:

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



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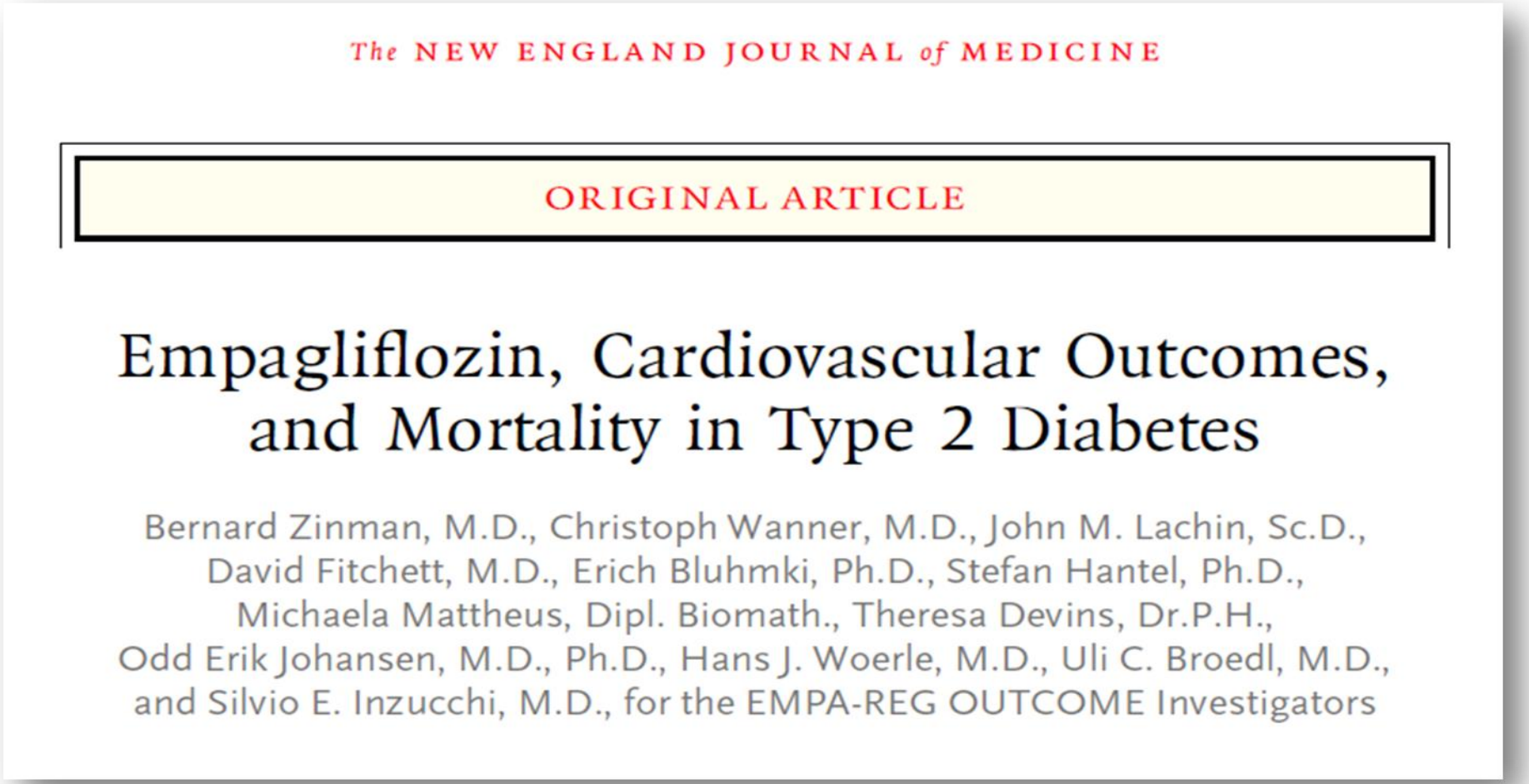
EMPA-REG OUTCOME®

EMPA-REG OUTCOME



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

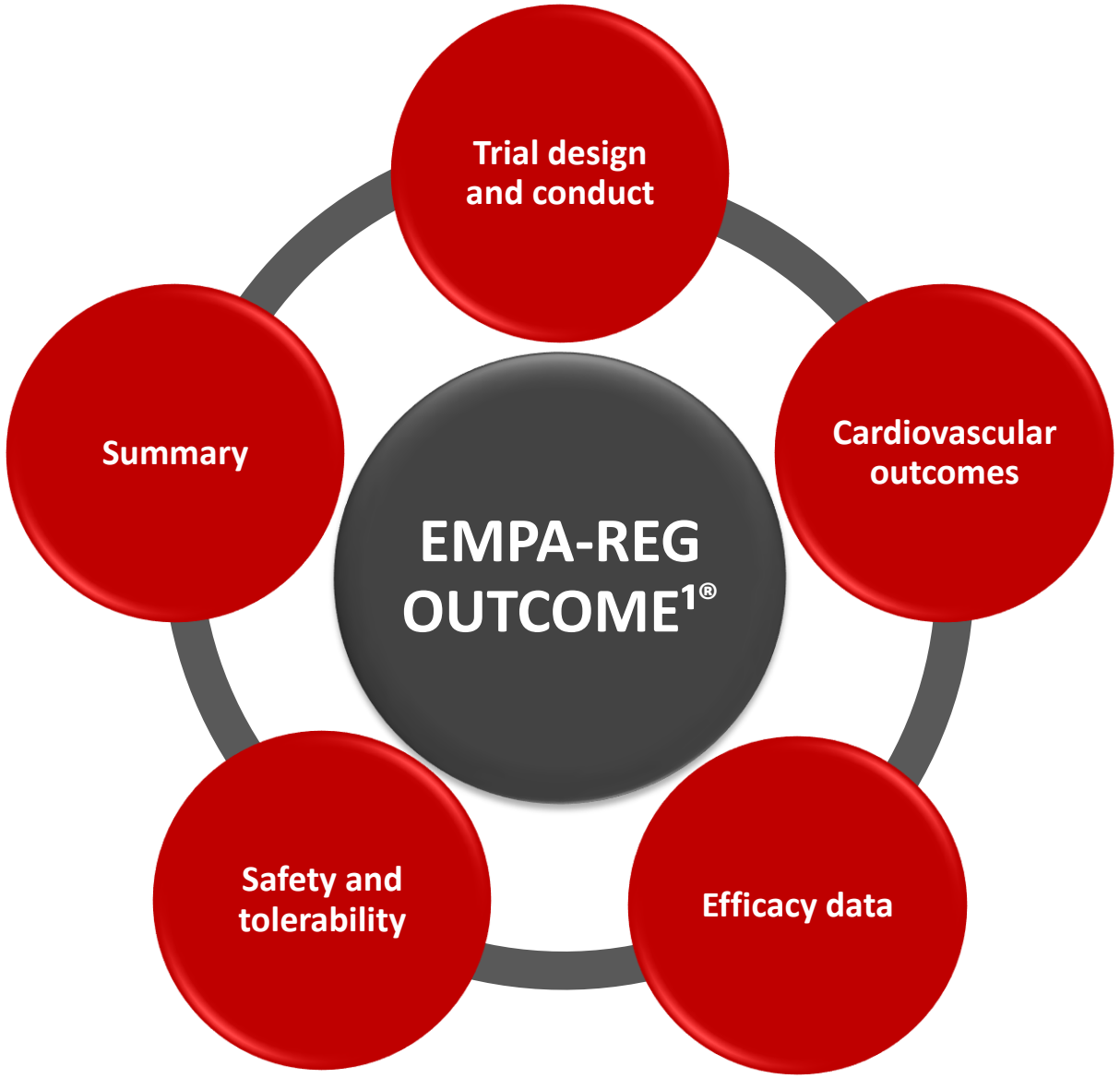
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for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

abidi 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.



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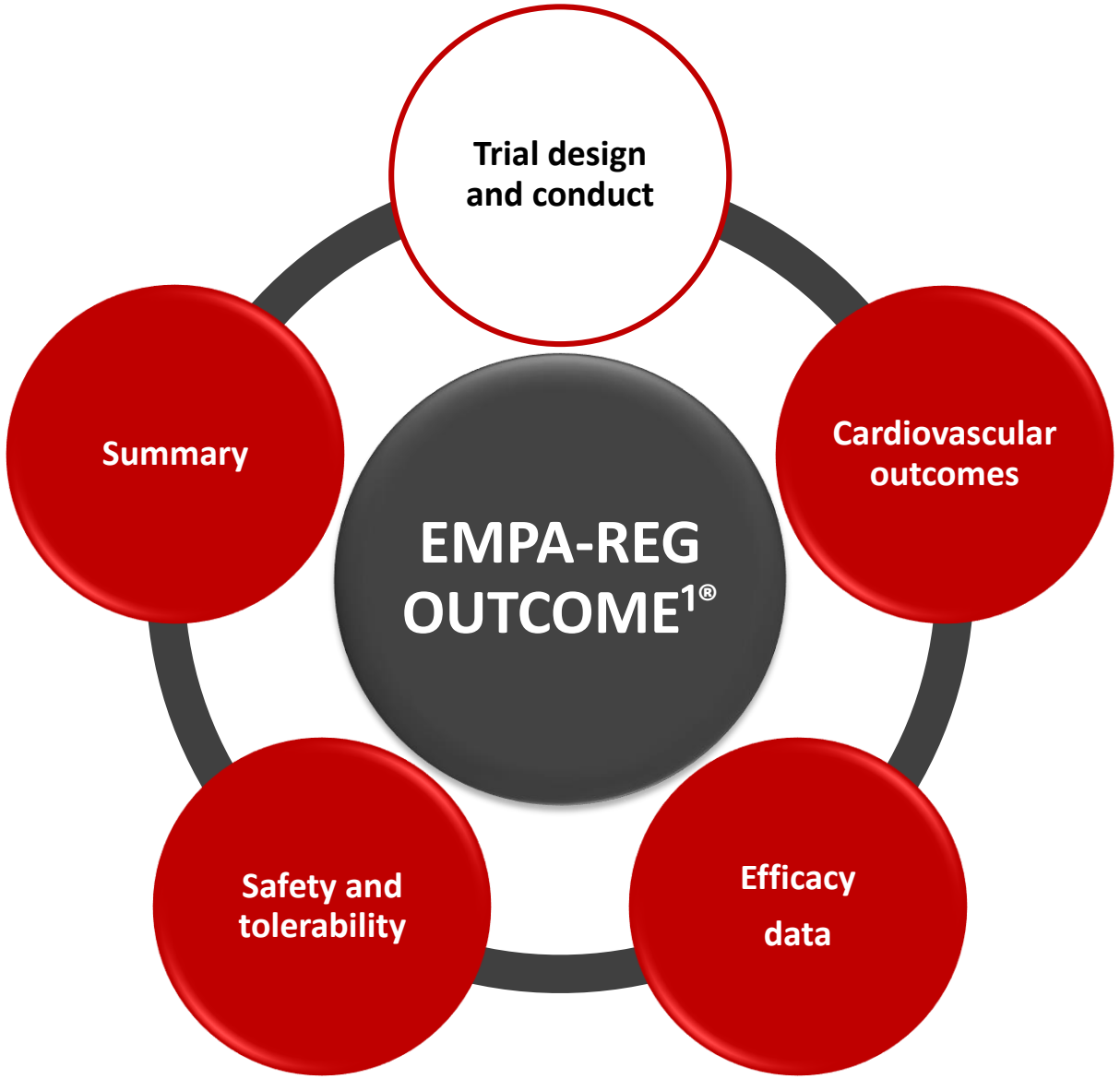
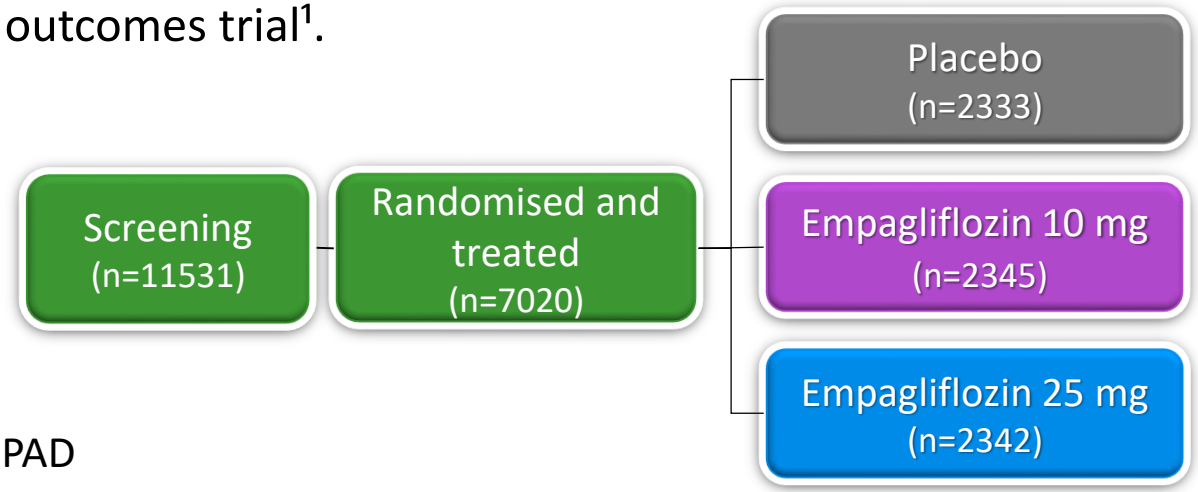


1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Trial Design[1]

EMPA-REG OUTCOME

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

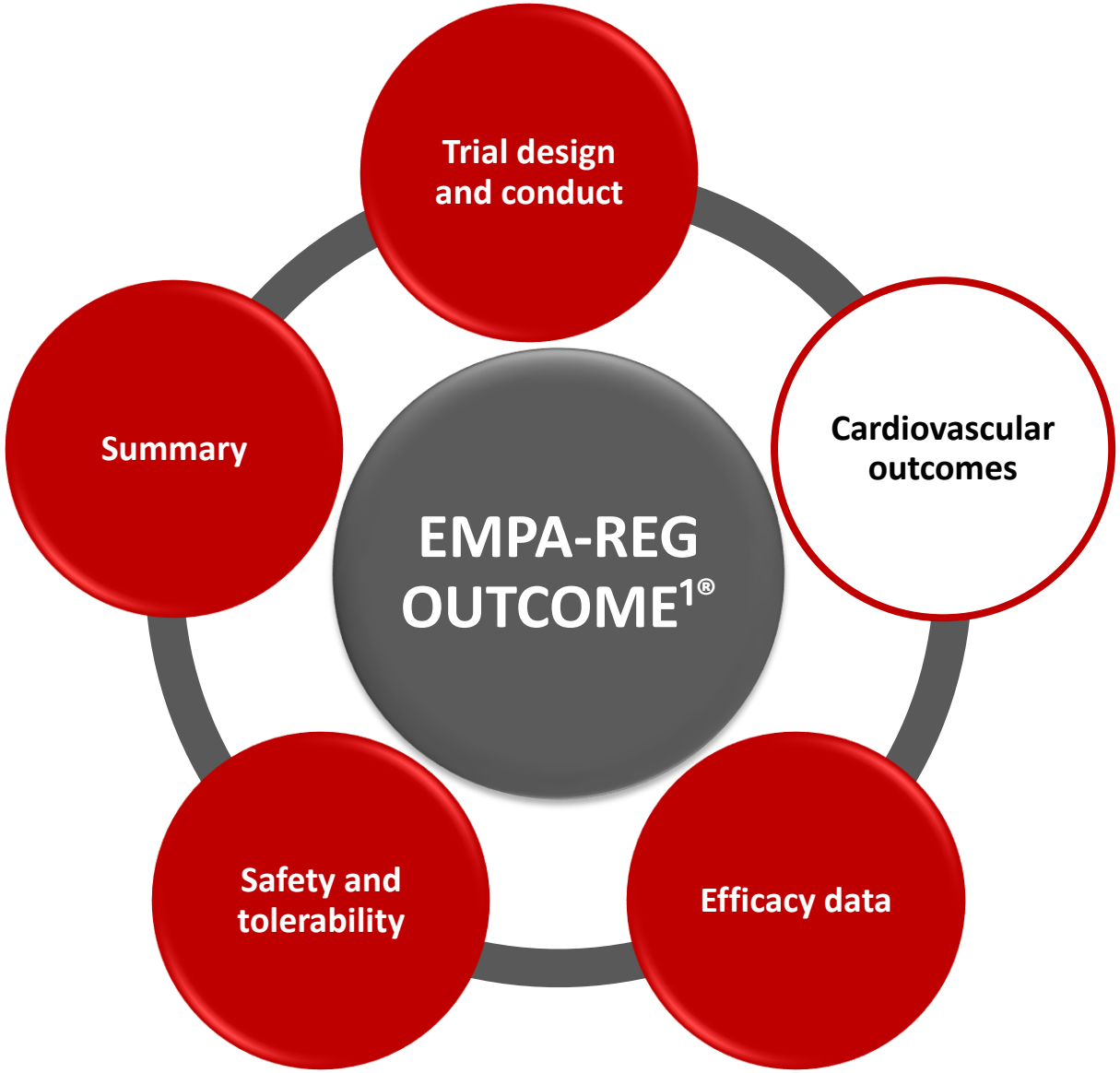


✓ The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event.

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

abidi 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.

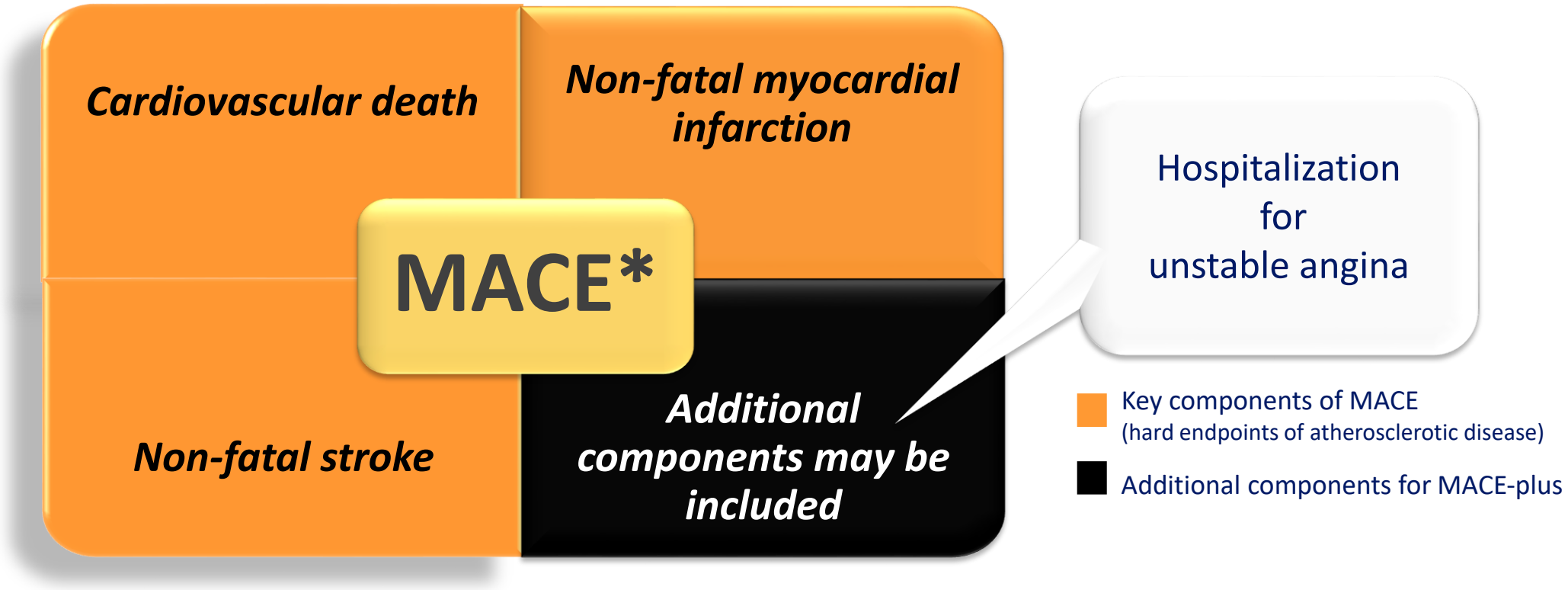


abidi DIABETES

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.

Pre-specified primary and key secondary outcomes[1]

EMPA-REG OUTCOME

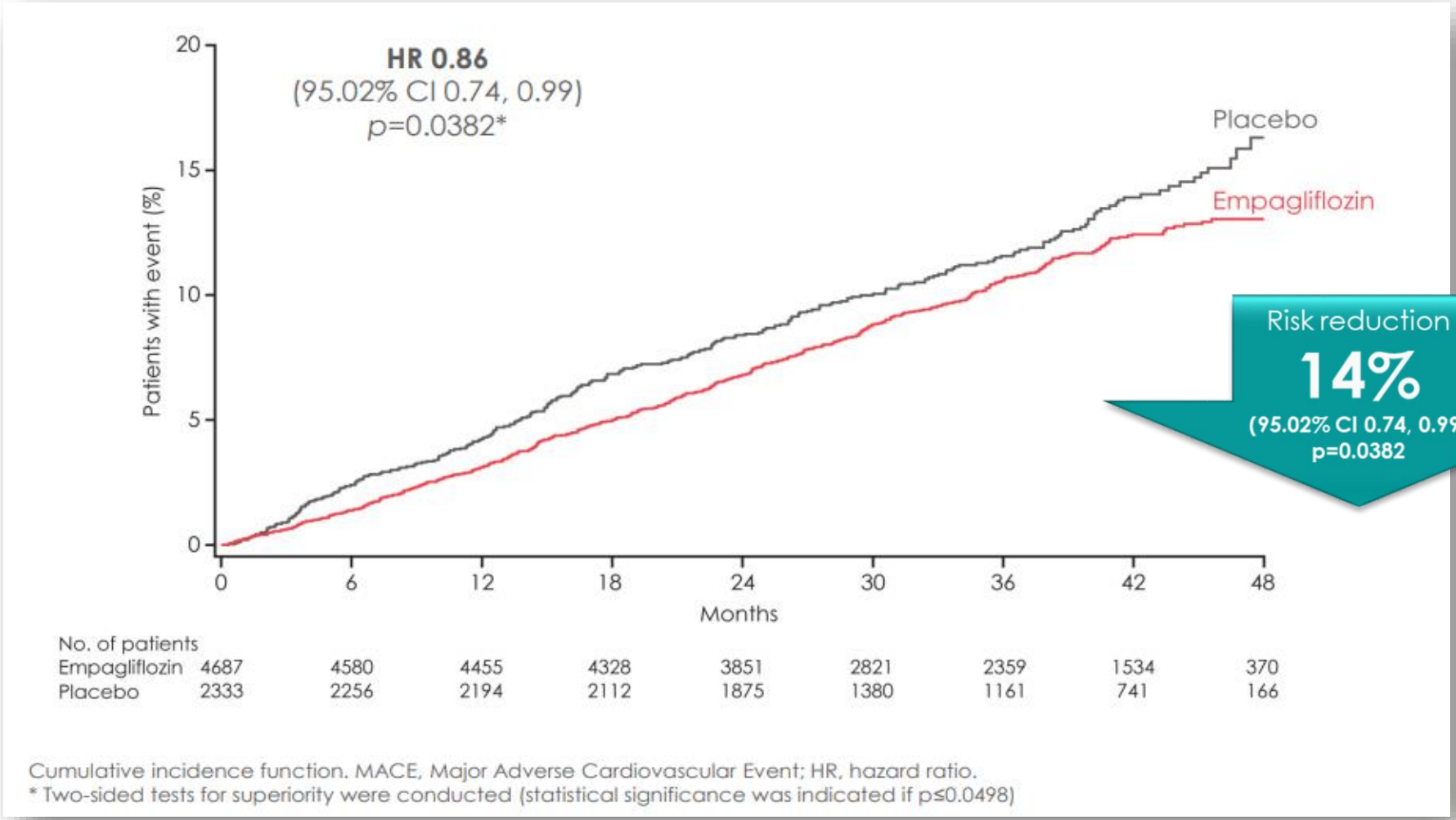


*Major Adverse Cardiovascular Events

abidi DIABETES

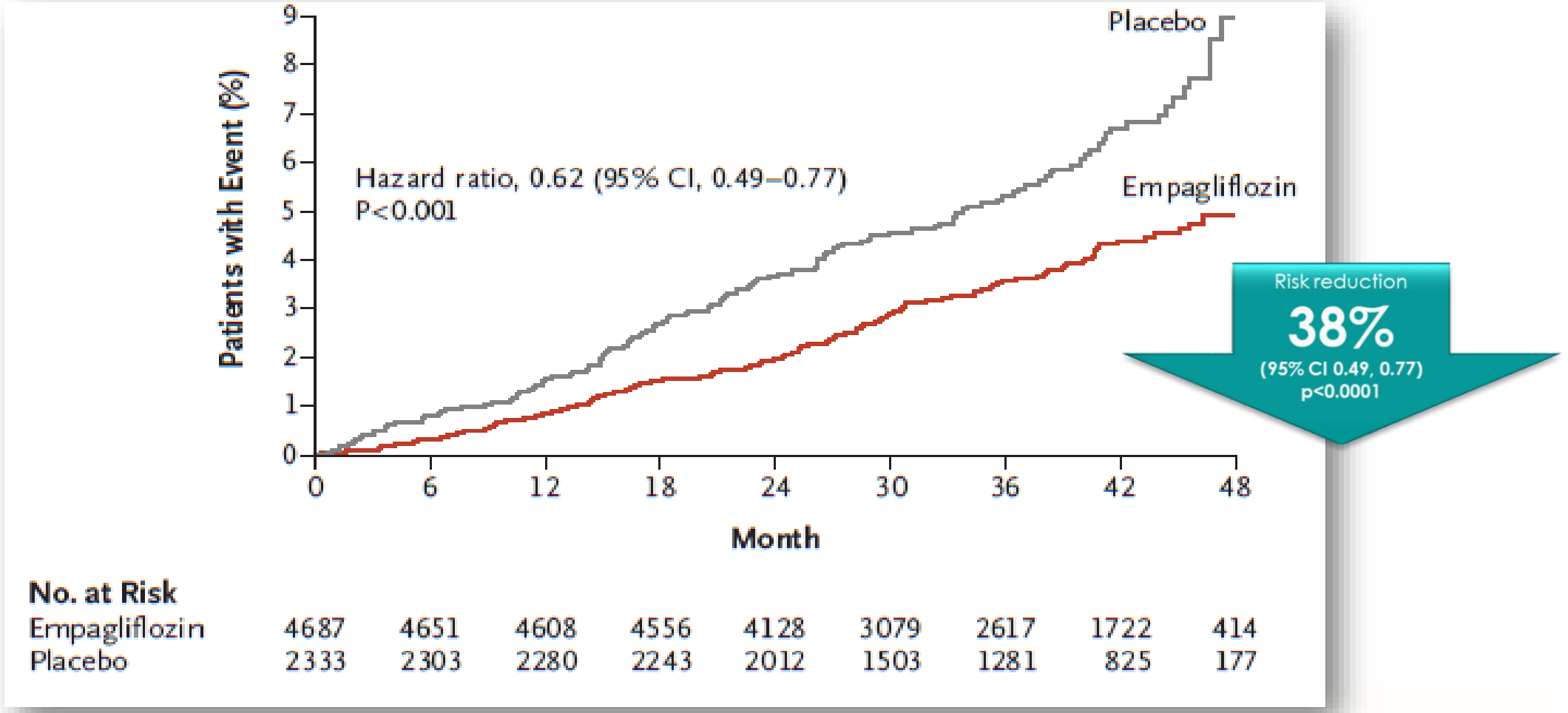
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

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



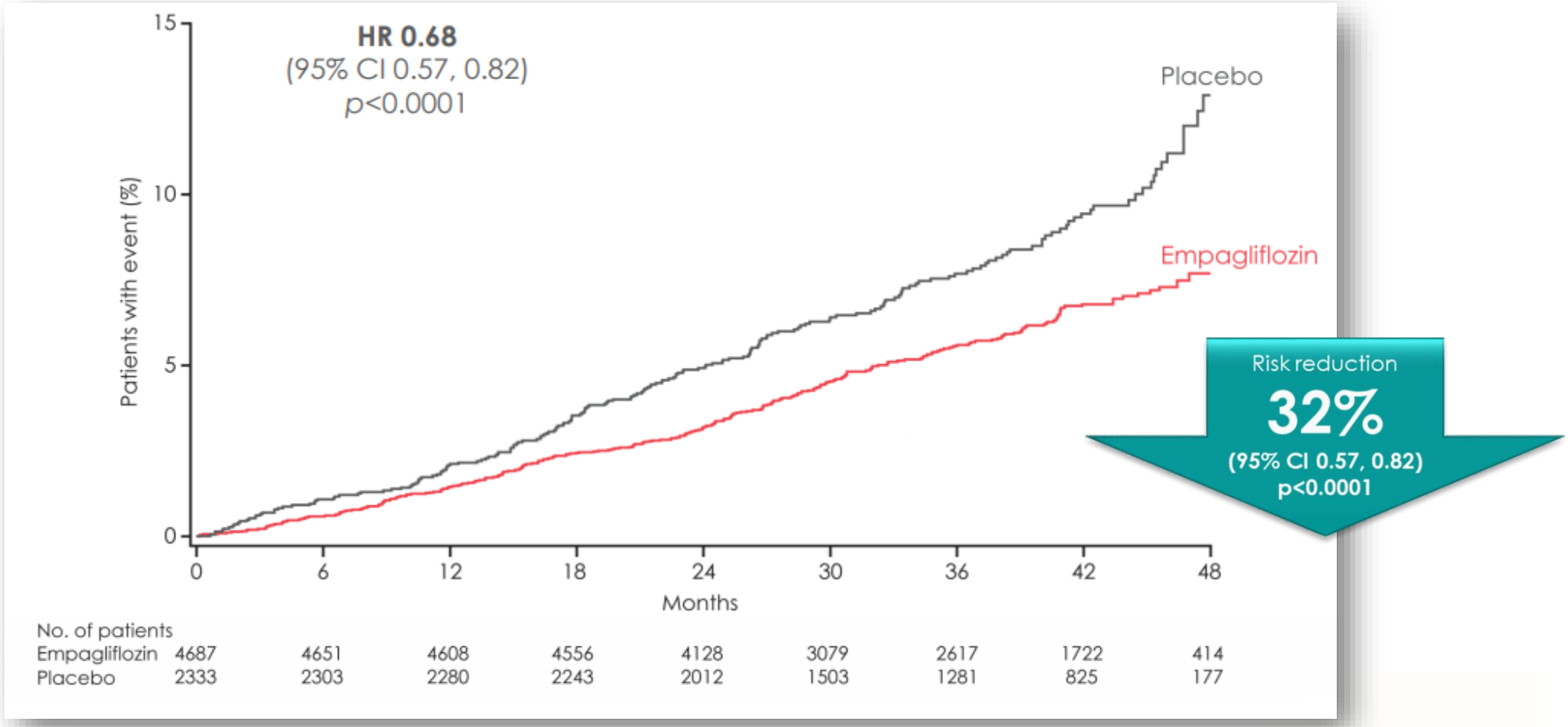
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

EMPA-REG OUTCOME®CV Death[1]



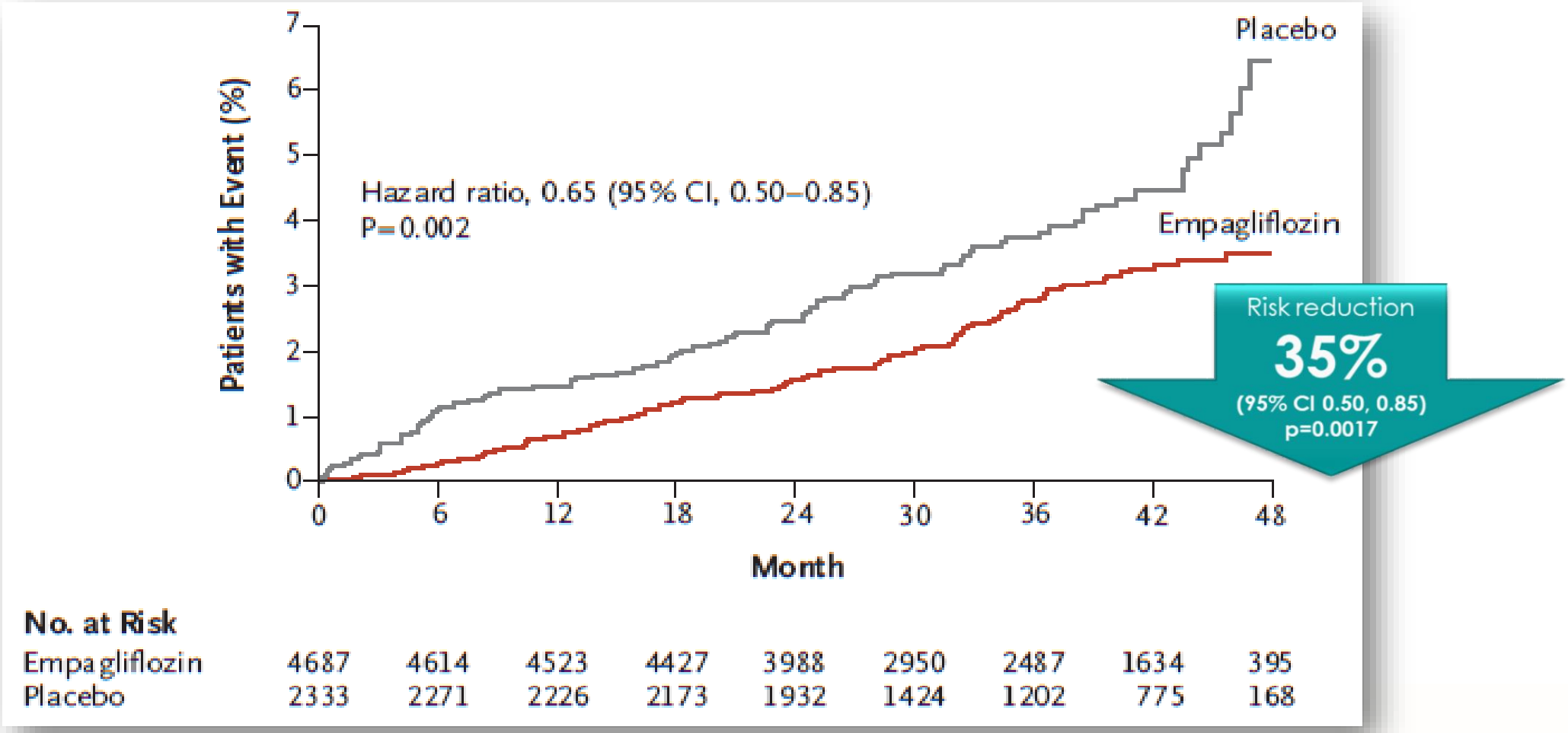
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

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]



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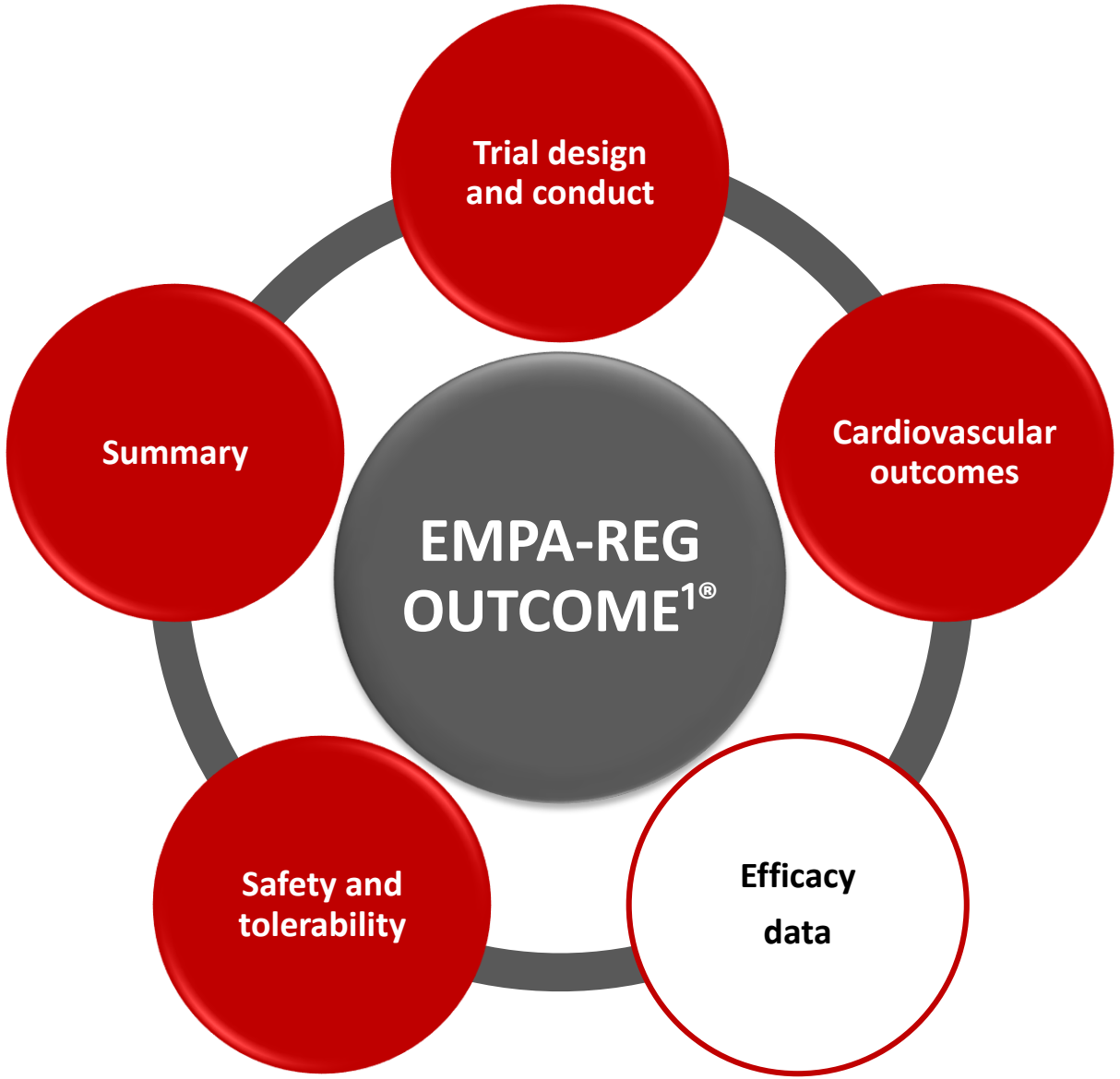
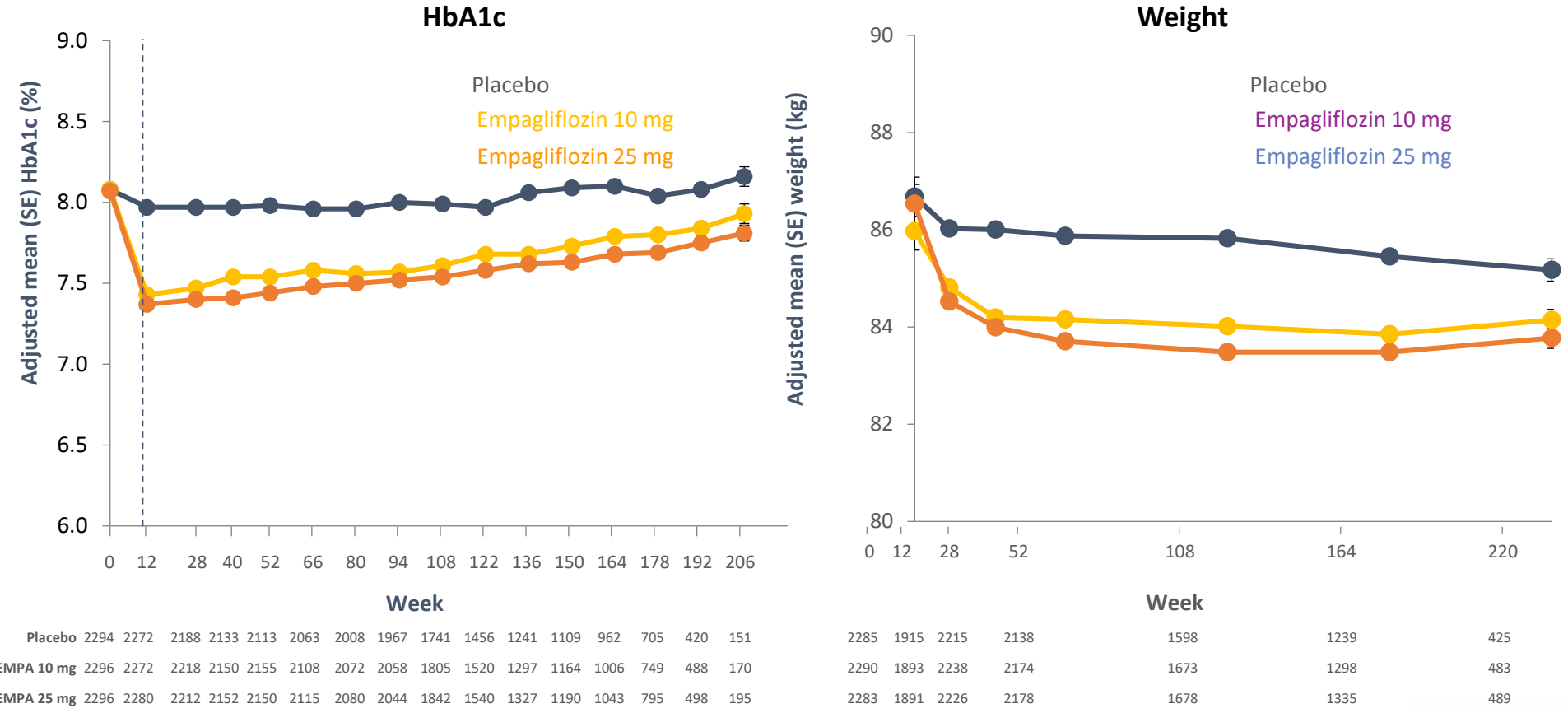


1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

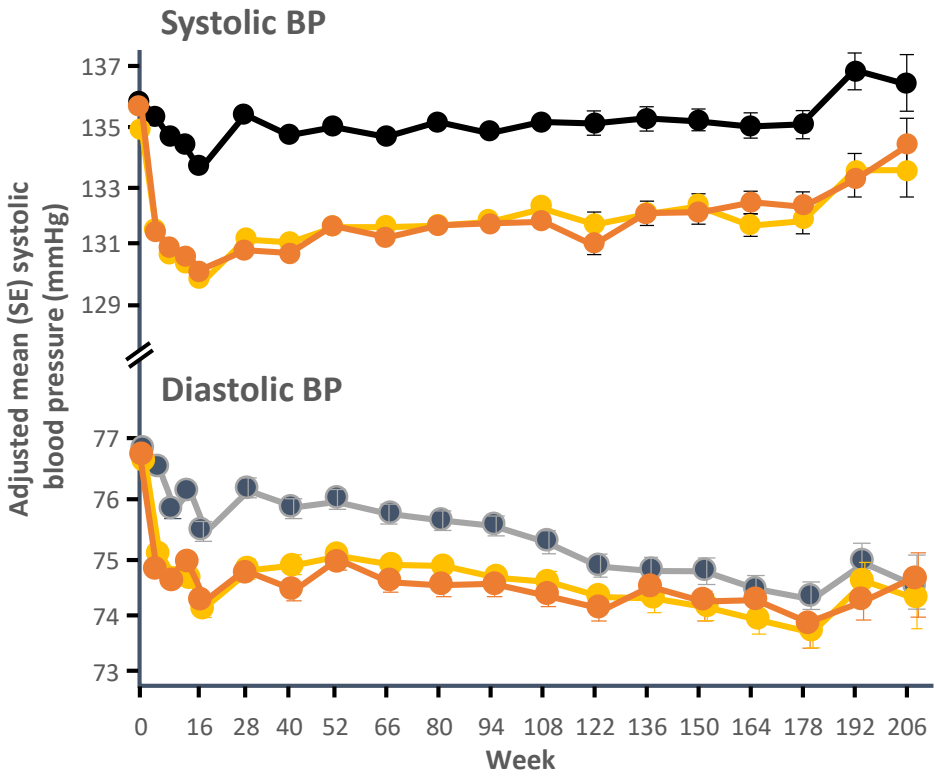
Mean adjusted HbA1c and weight parameters[1]



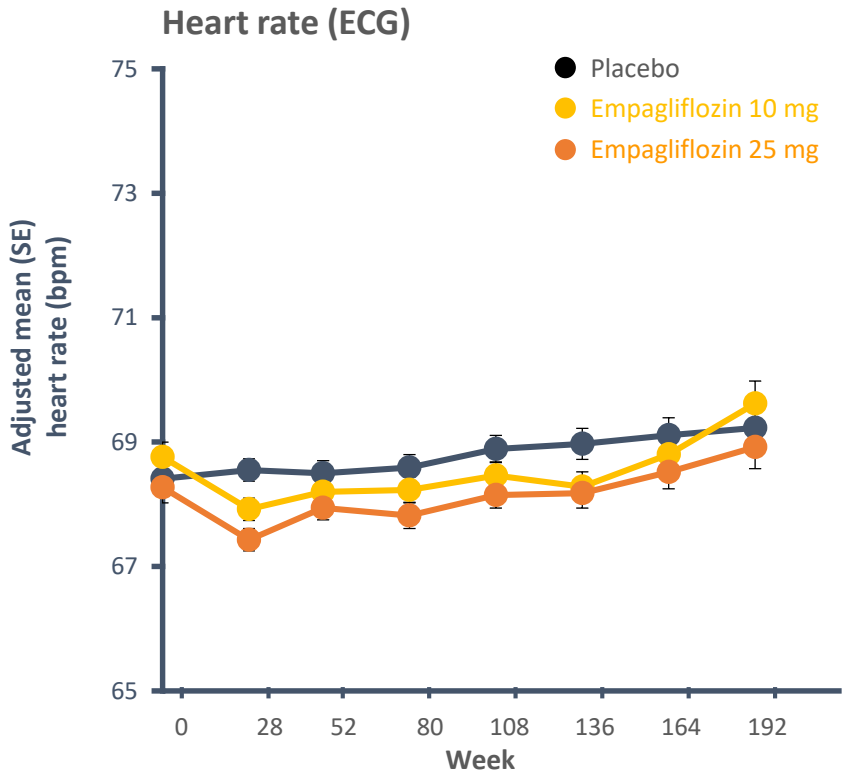
All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent to treat)
X-axis: time points with reasonable amount of data available for prescheduled measurements
EMPA, empagliflozin; HbA1c, glycated hemoglobin

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]



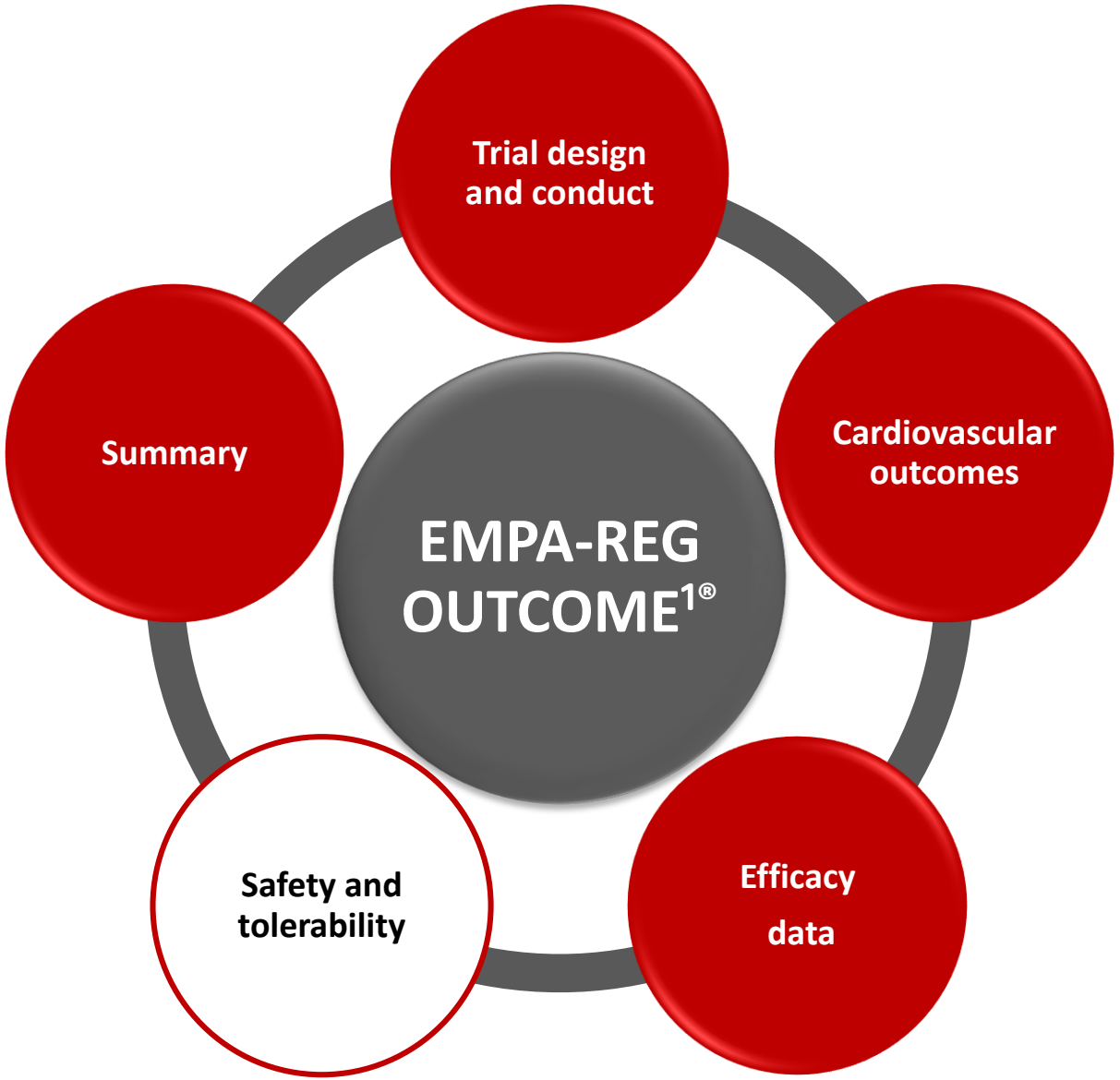
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
EMPA 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
EMPA 25 mg	2322	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216



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.



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]

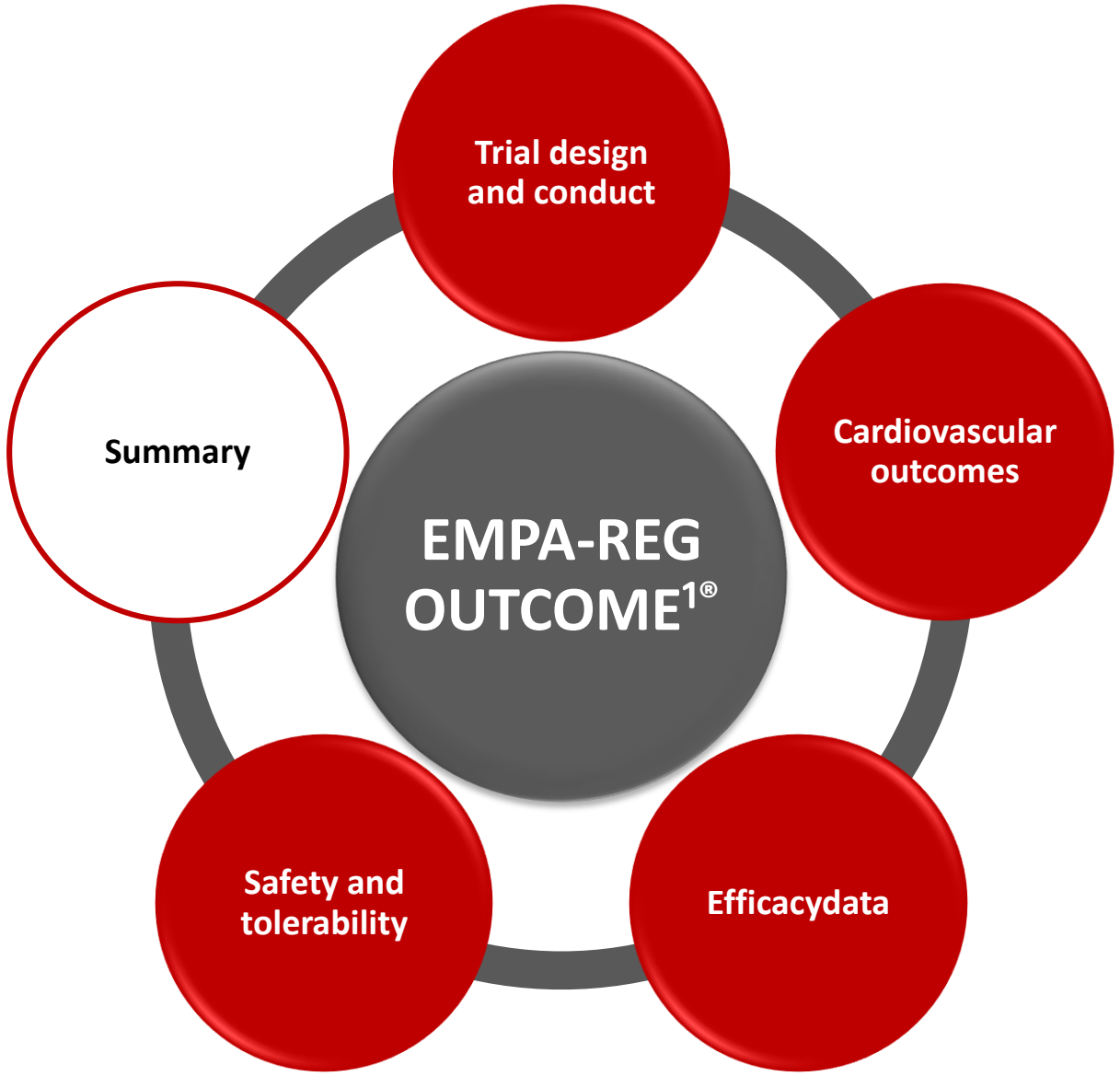
	Placebo (n=2333)		Empagliflozin 10 mg (n=2345)		Empagliflozin 25 mg (n=2342)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
One or more AE[1]	2139 (91.7)	178.67	2112 (90.1)	150.34	2118 (90.4)	148.36
One or more drug-related* AE[2]	549 (23.5)	11.33	666 (28.4)	14.15	643 (27.5)	13.38
One or more AE leading to discontinuation[1]	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%

↓ 3P-MACE

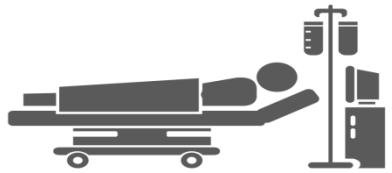
38%

↓ CV death

32%

↓ All-cause mortality

35%

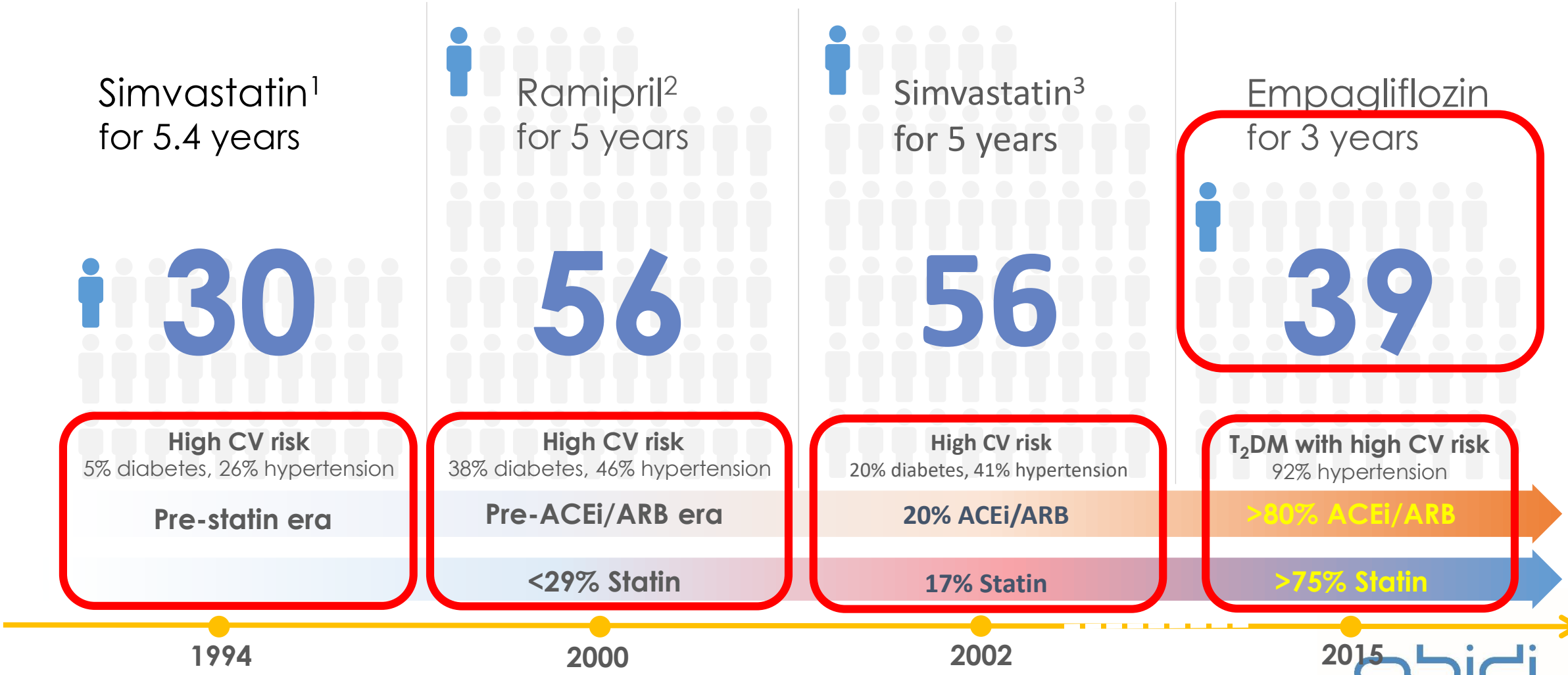


↓ Heart failure hospitalisations

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.

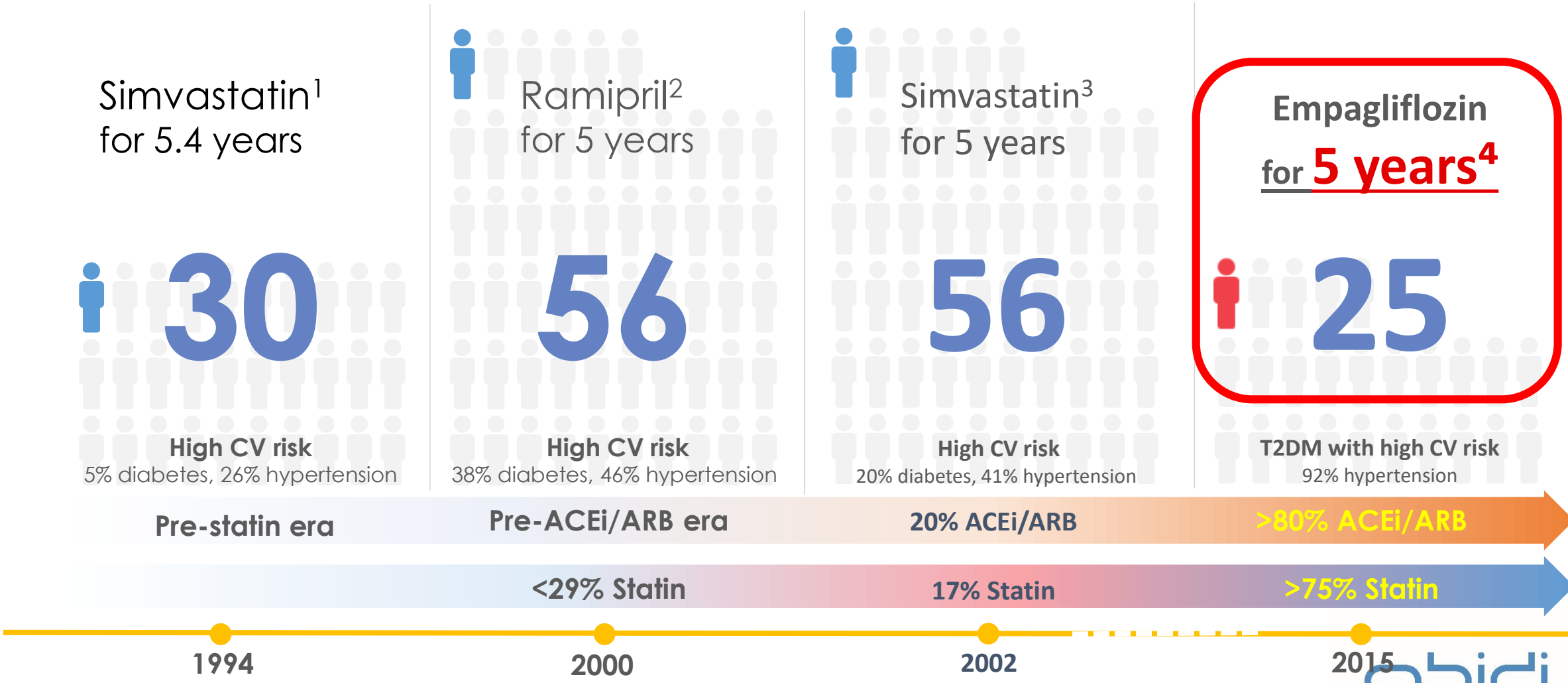
NNT to Prevent One Death Across Major Trials in Patients with High CV Risk



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

DIABETES

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



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

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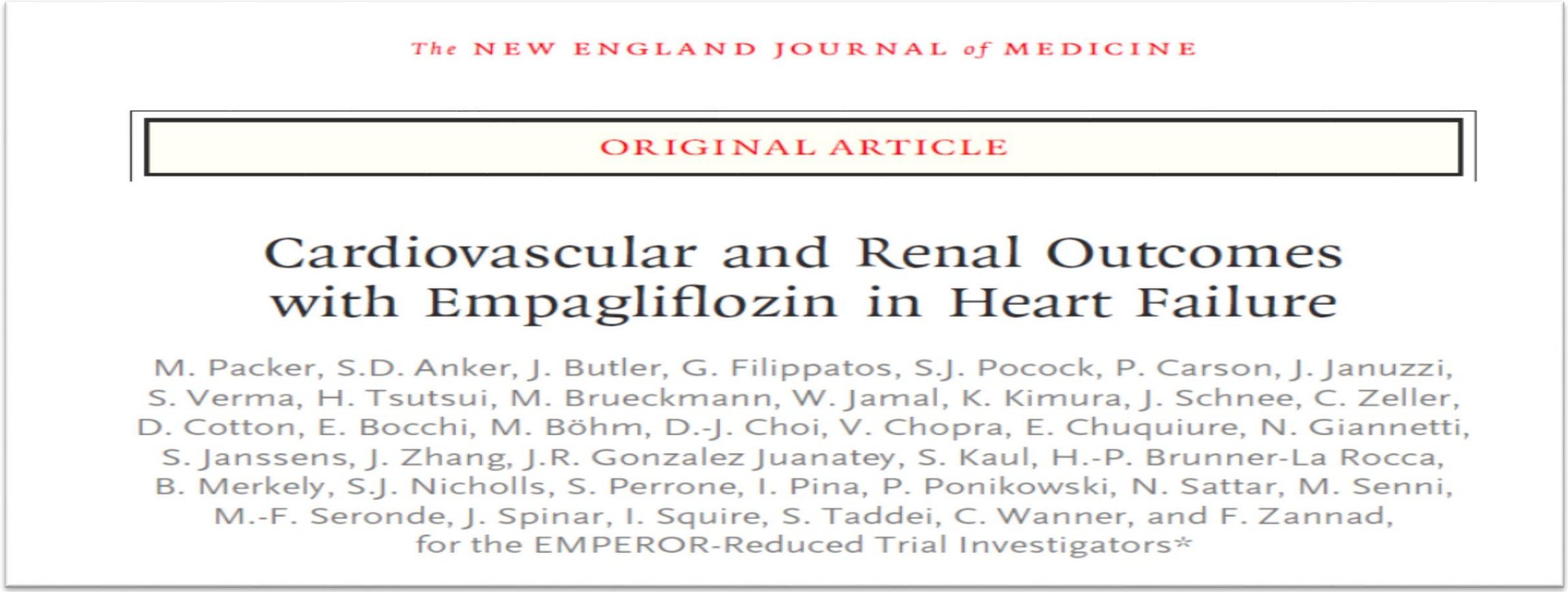
EMPEROR-Reduced trial



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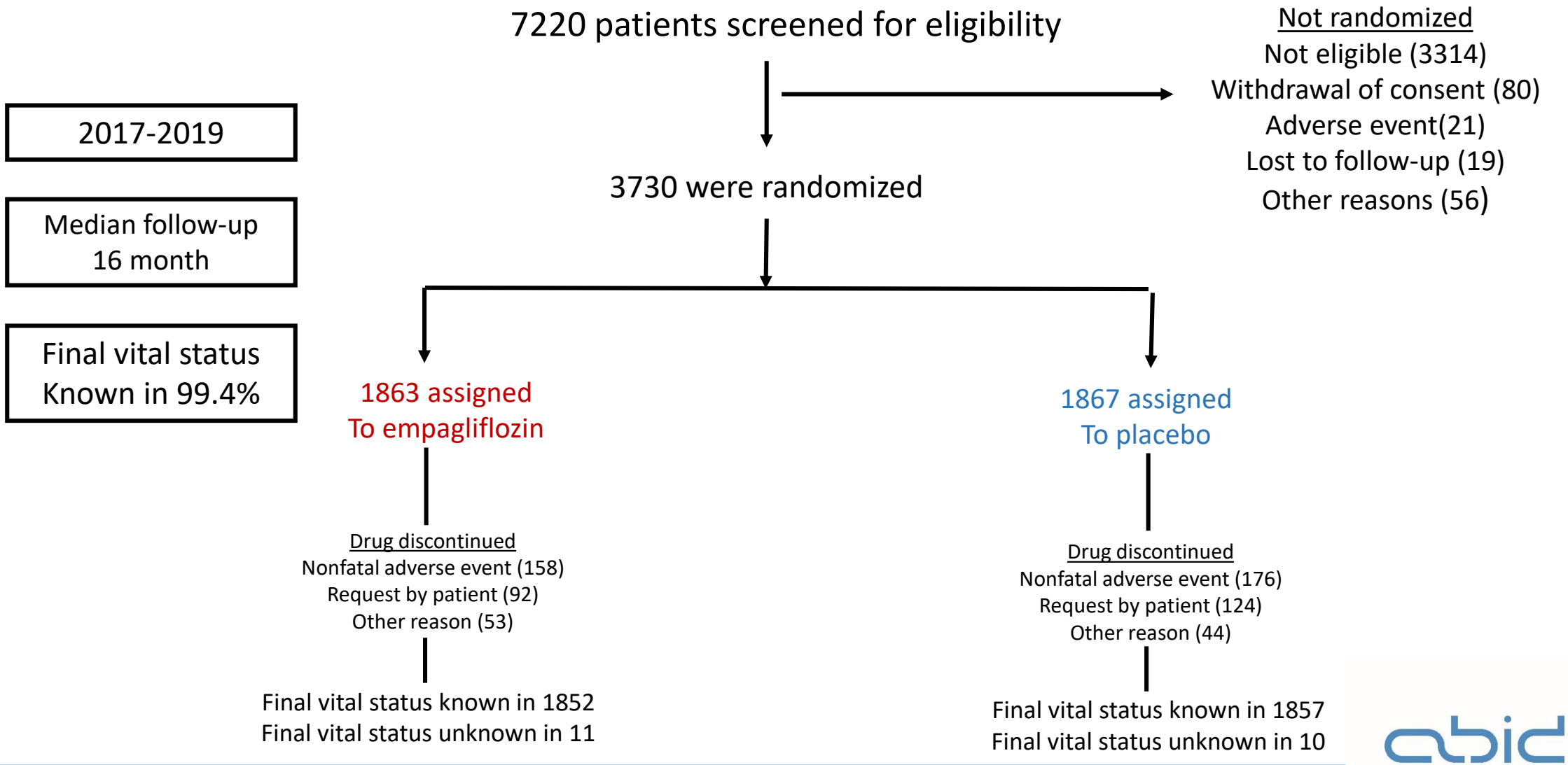
1-N. Engl. J. Med 2020 Aug 29.

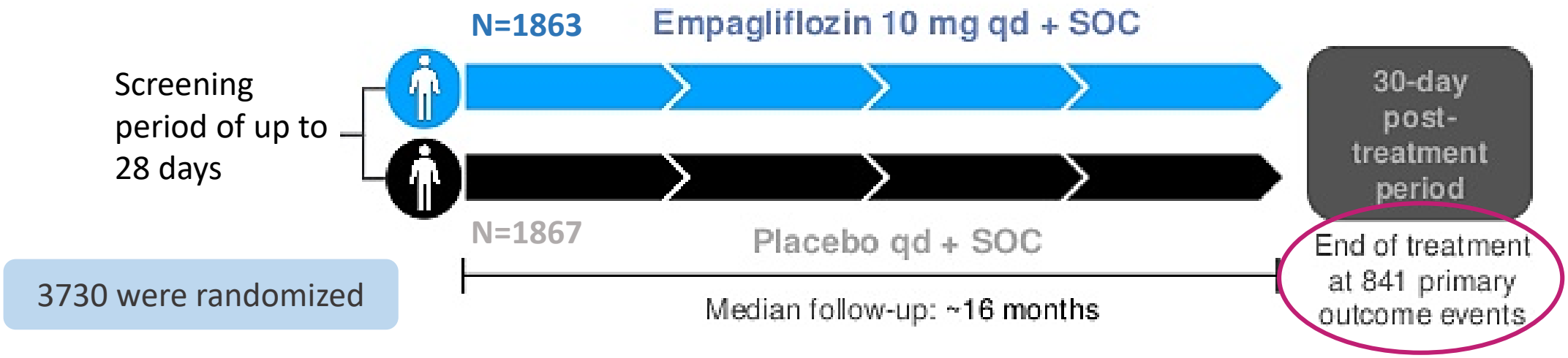
EMPEROR-Reduced: Patient Disposition[1]



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

Trial Design[1]

Patients must be receiving all appropriate treatments for HF



SOC; Standard Of Care

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

EMPEROR-Reduced trial specified only three endpoints to be tested in hierarchical 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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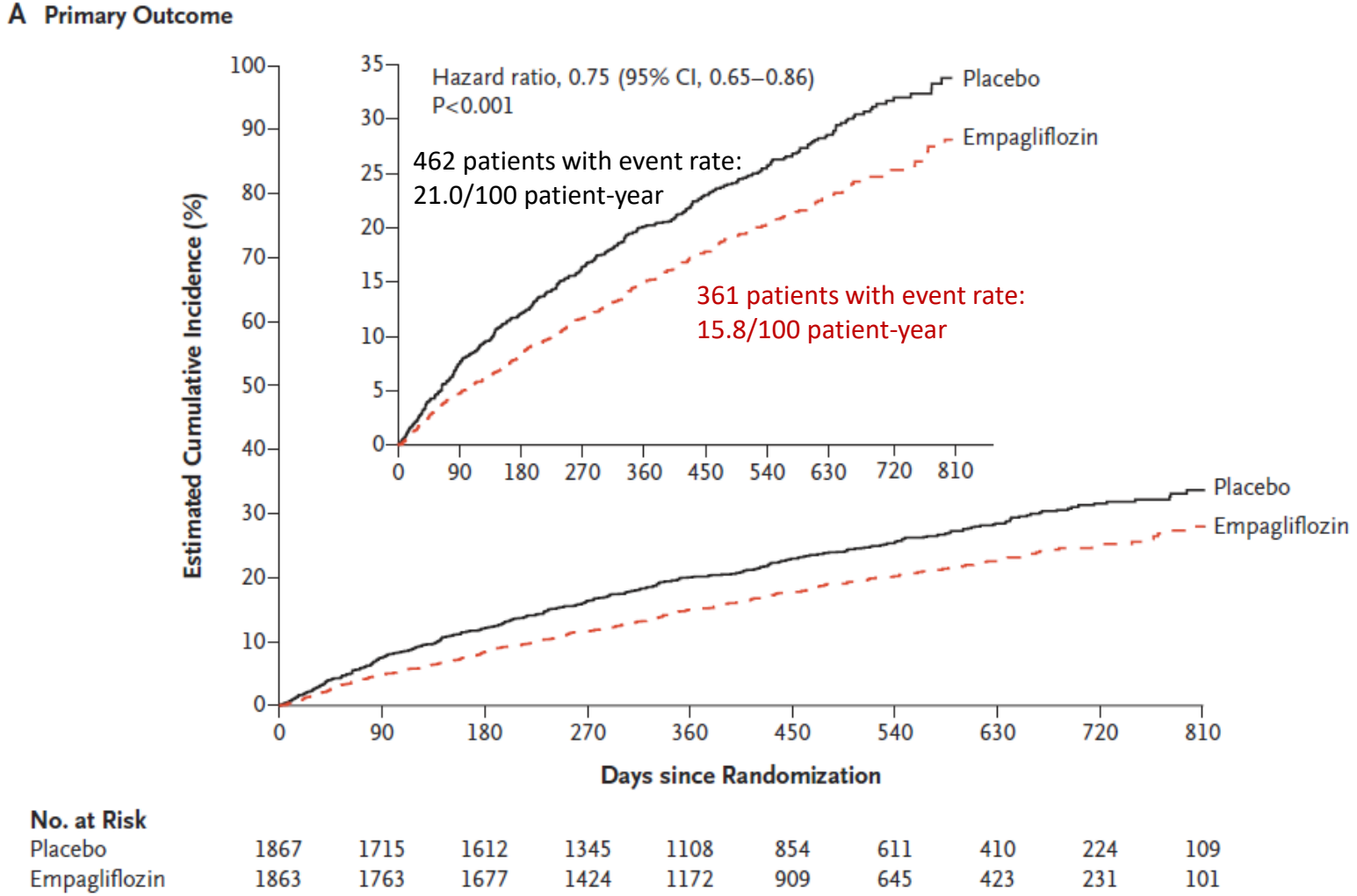
Empagliflozin Group Had Lower Incidence of Cardiovascular Death or Hospitalization for Heart Failure[1]



25% RRR

p<0.001

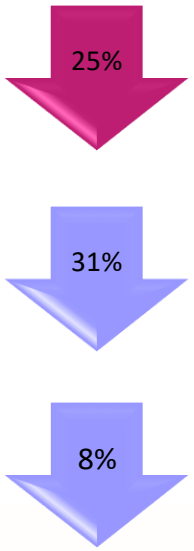
19.4% vs 24.7%

HR = 0.75 (0.65-0.86)

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

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)	



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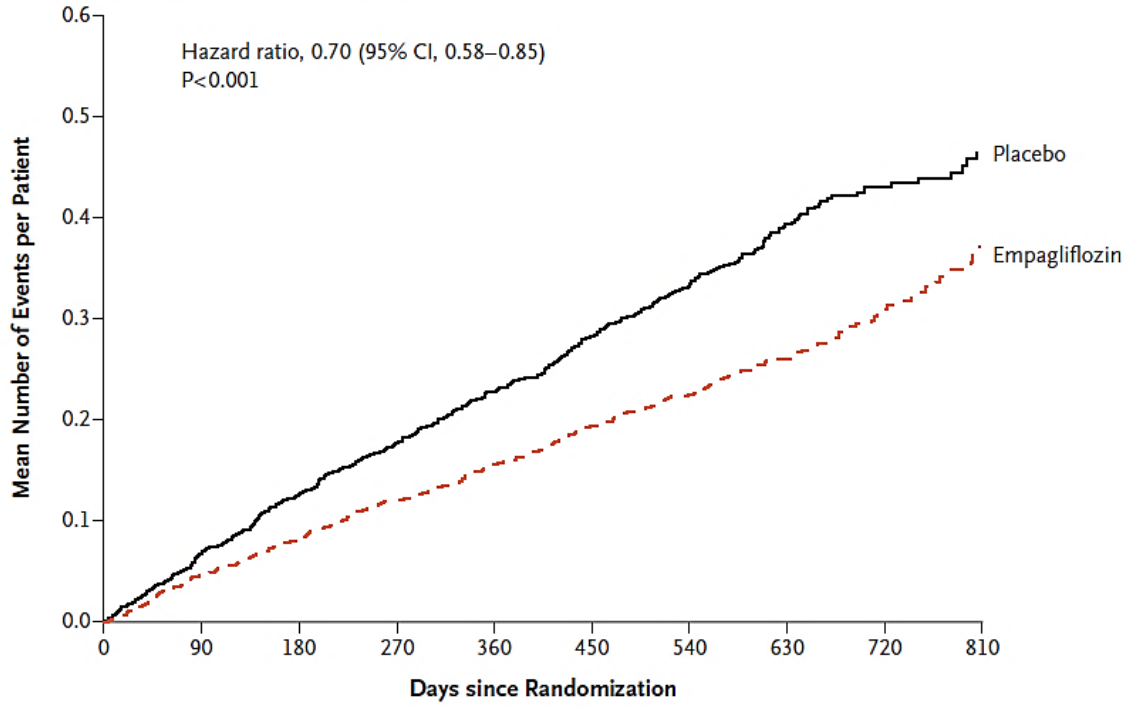
1-N. Engl. J. Med 2020 Aug 29.

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



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

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)

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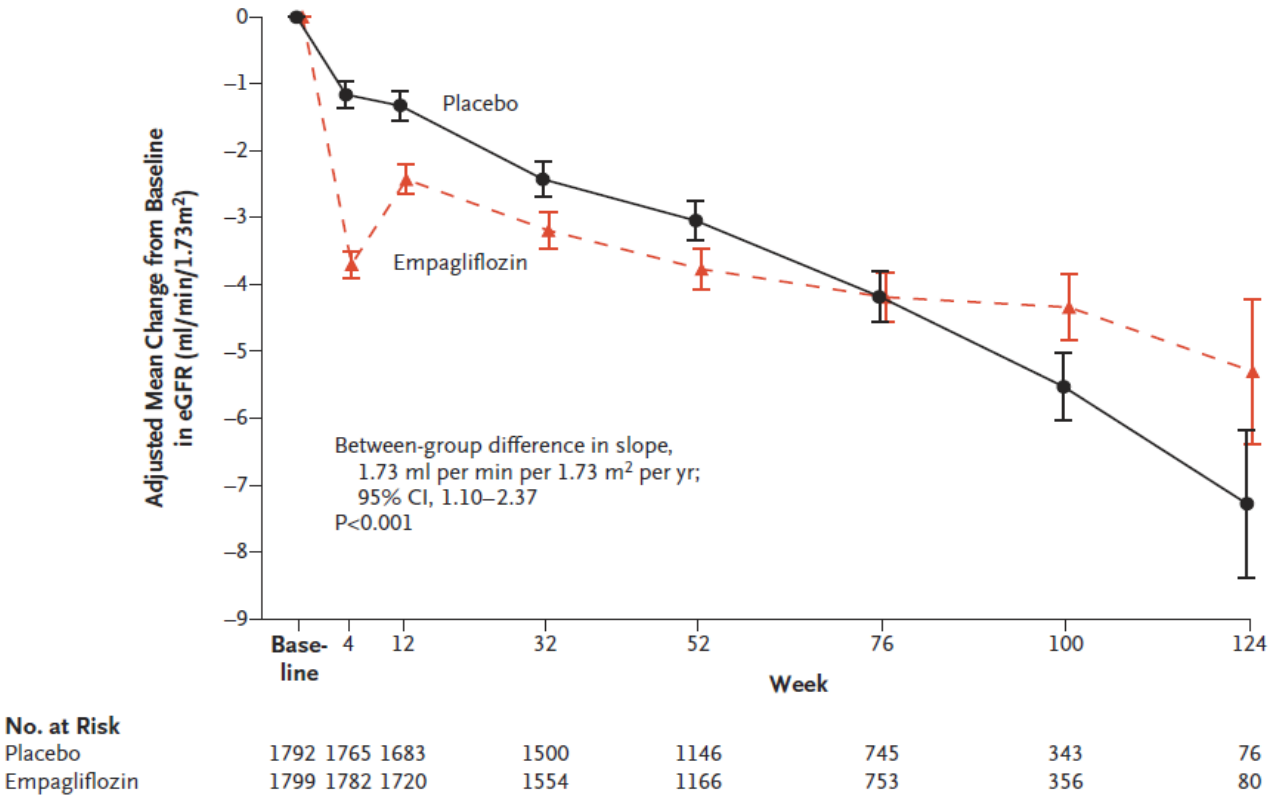
1-N. Engl. J. Med 2020 Aug 29.

Empagliflozin Decreased the Slope of eGFR Reduction 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)

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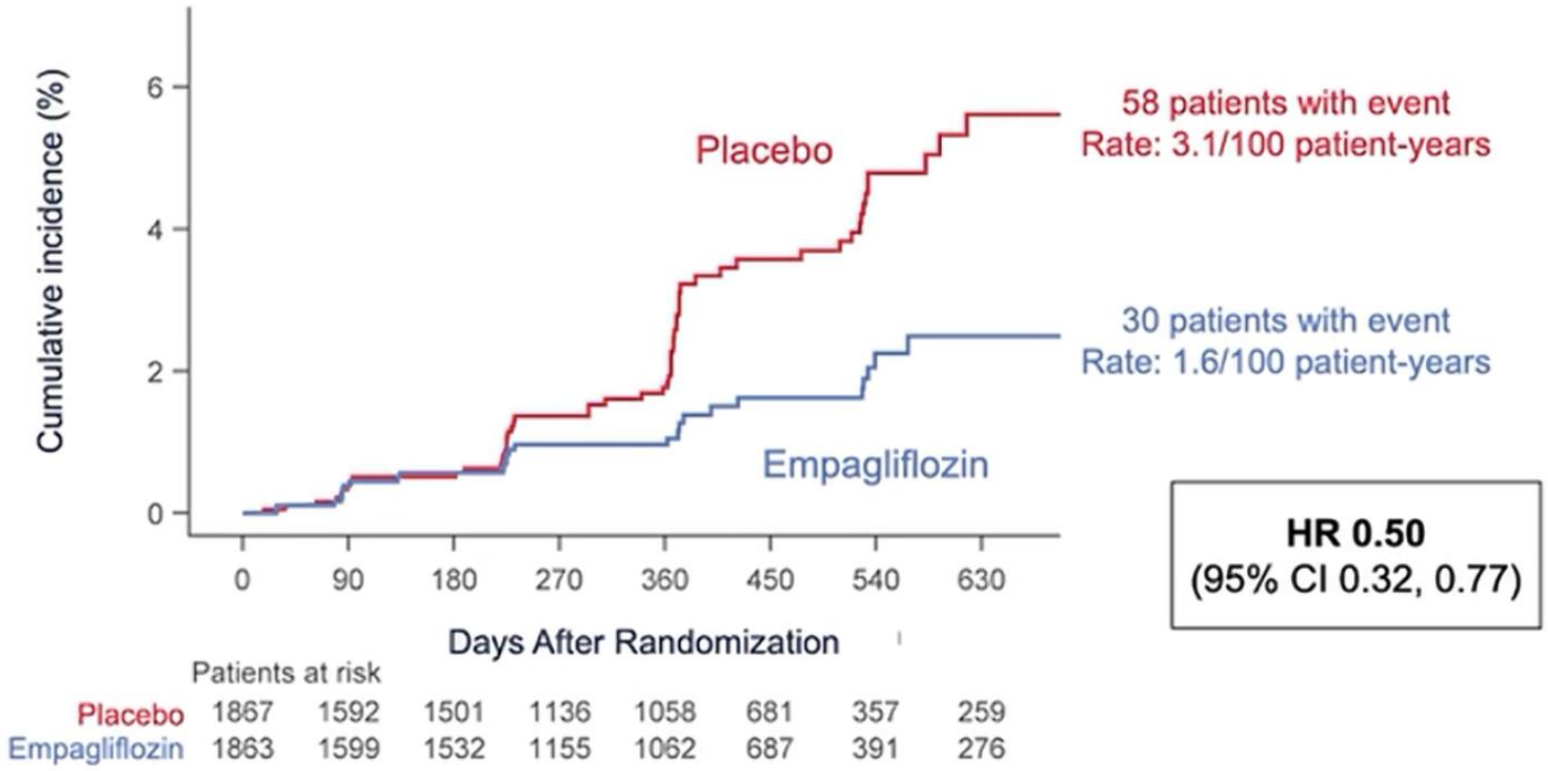
1- EMPEROR-Reduced Trial Marta Cobo Marcos M. Packer presentation ESC 2020

Empagliflozin reduced composite renal endpoint by 50%[1]



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

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

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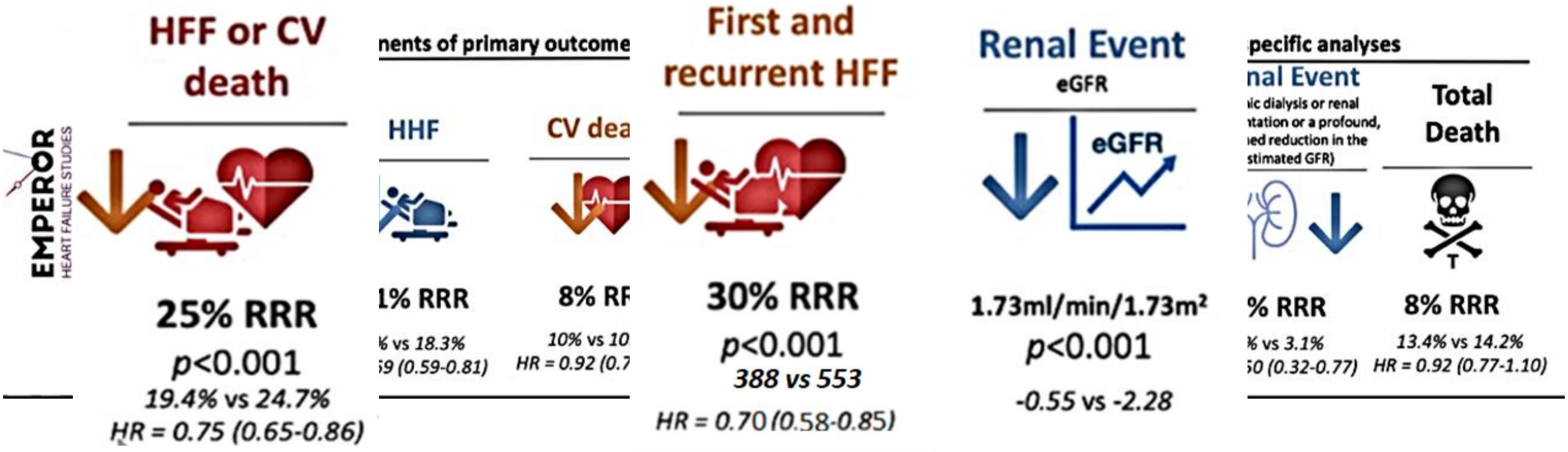
1- EMPEROR-Reduced Trial Marta Cobo Marcos M. Packer presentation ESC 2020
2- N. Engl. J. Med 2020 Aug 29.

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.

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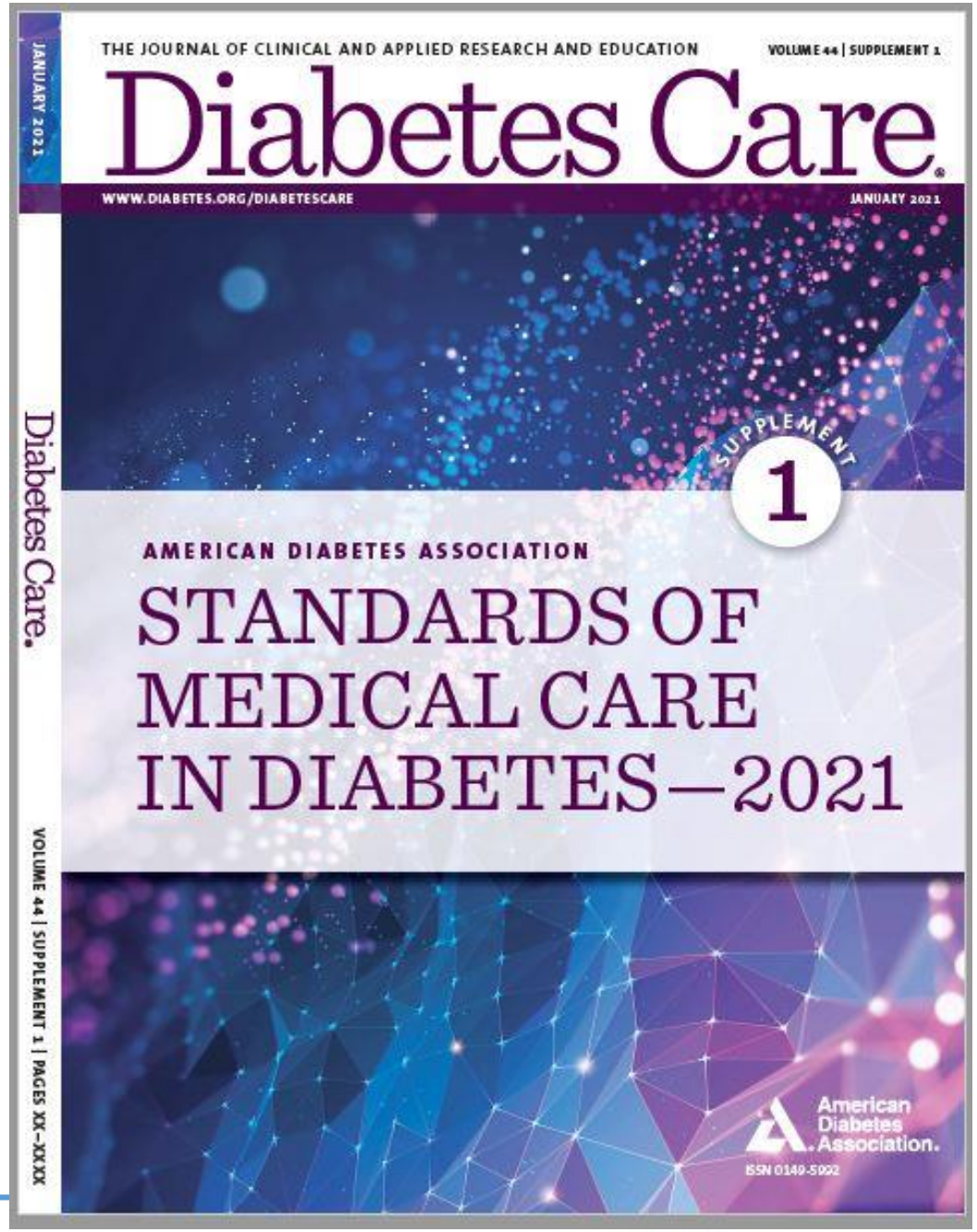
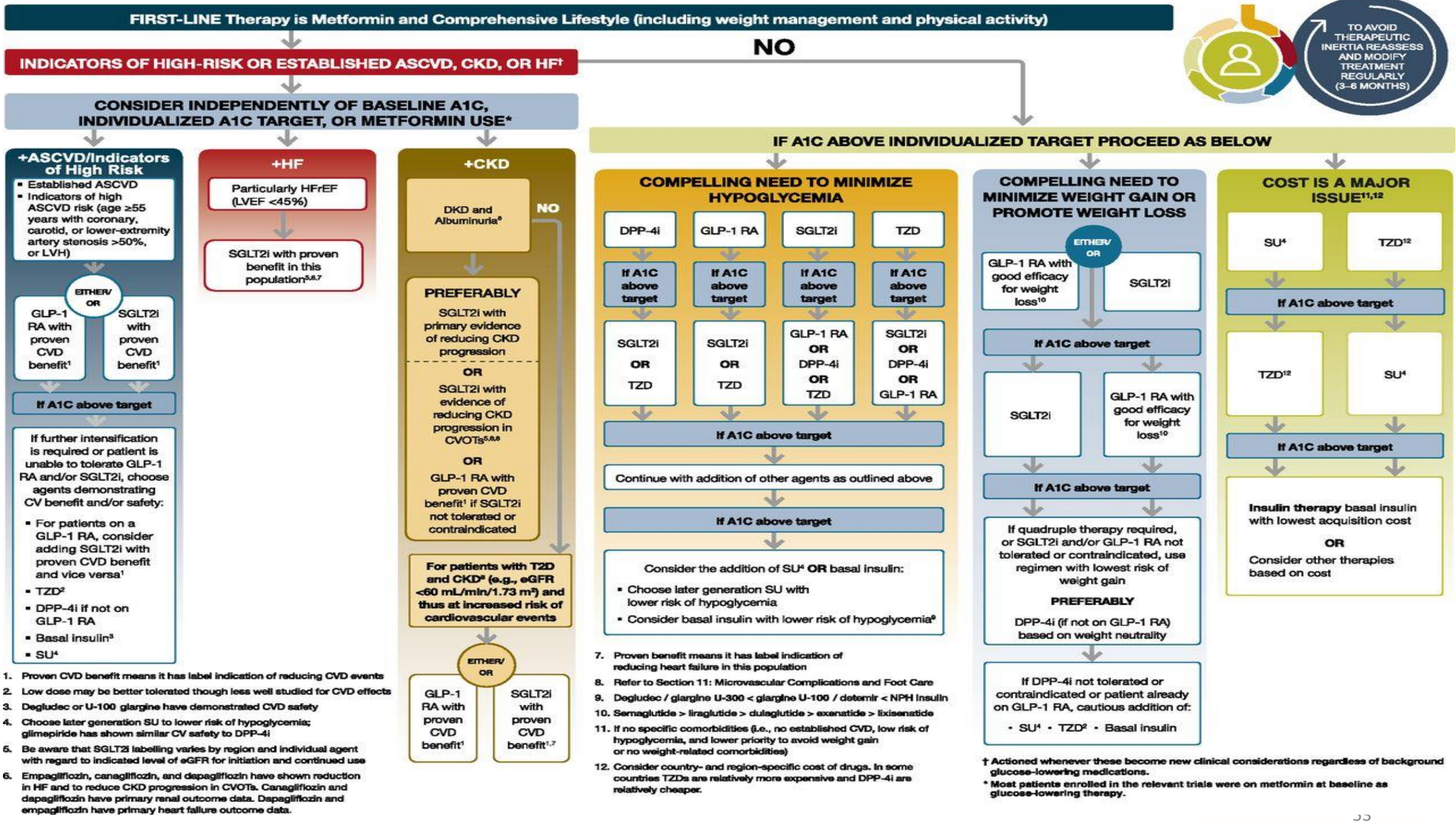
1-N. Engl. J. Med 2020 Aug 29.

Guidelines Recommendations ADA2021



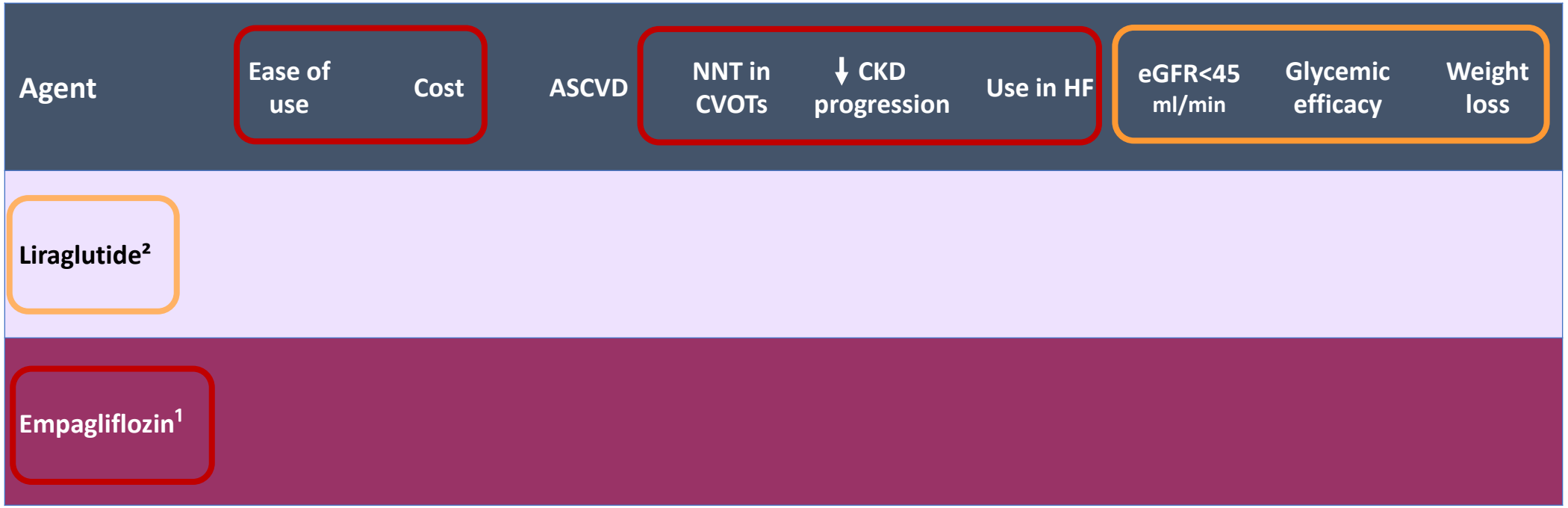


1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar 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.

Empagliflozin vs. Liraglutide



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

Administration, Cautions, Side effects, Safety profile

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

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1-Jardiance FDA label 2018. Reference ID: 4367802

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

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1-Jardiance FDA label 2018. Reference ID: 4367802

Empagliflozin Safety Profile[1]

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

1-Jardiance FDA label 2018. Reference ID: 4367802

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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Thank you