Empagliflozin: Glycemic control and lifesaving cardiovascular and renal benefits

Dr. Habibeh Taghavi, MD

Endocrinologist, Assistant Professor of Alborz university of medical science

1400.05.15

Objectives

- Brief Review of Kidney Role in Glucose Homeostasis.
- Empagliflozin Mechanism of Action.
- Empagliflozin Efficacy Studies.
- Empagliflozin Safety Profile.
- EMPA-REG OUTCOME® Trial.
- EMPA-REG RENAL® Trial.
- EMPEROR-REDUCED Trial.
- Diabetes Guideline & New Recommendations.
- Conclusion.

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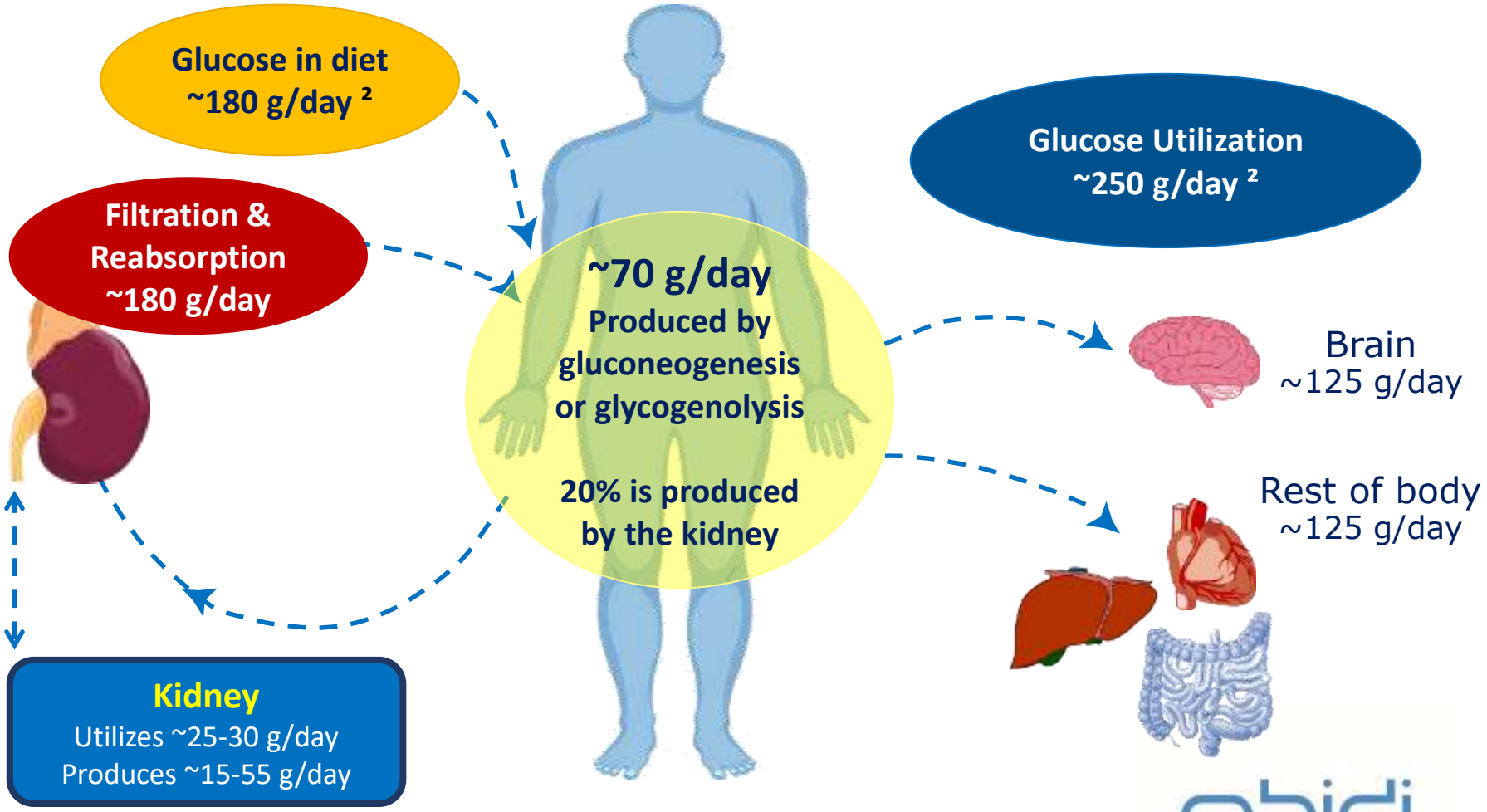
Brief Review of Kidney Role in Glucose Homeostasis

Kidney Plays a Significant Role in Glucose Balance

Reabsorption[1]

Utilization[1]

Production[1]
(gluconeogenesis)

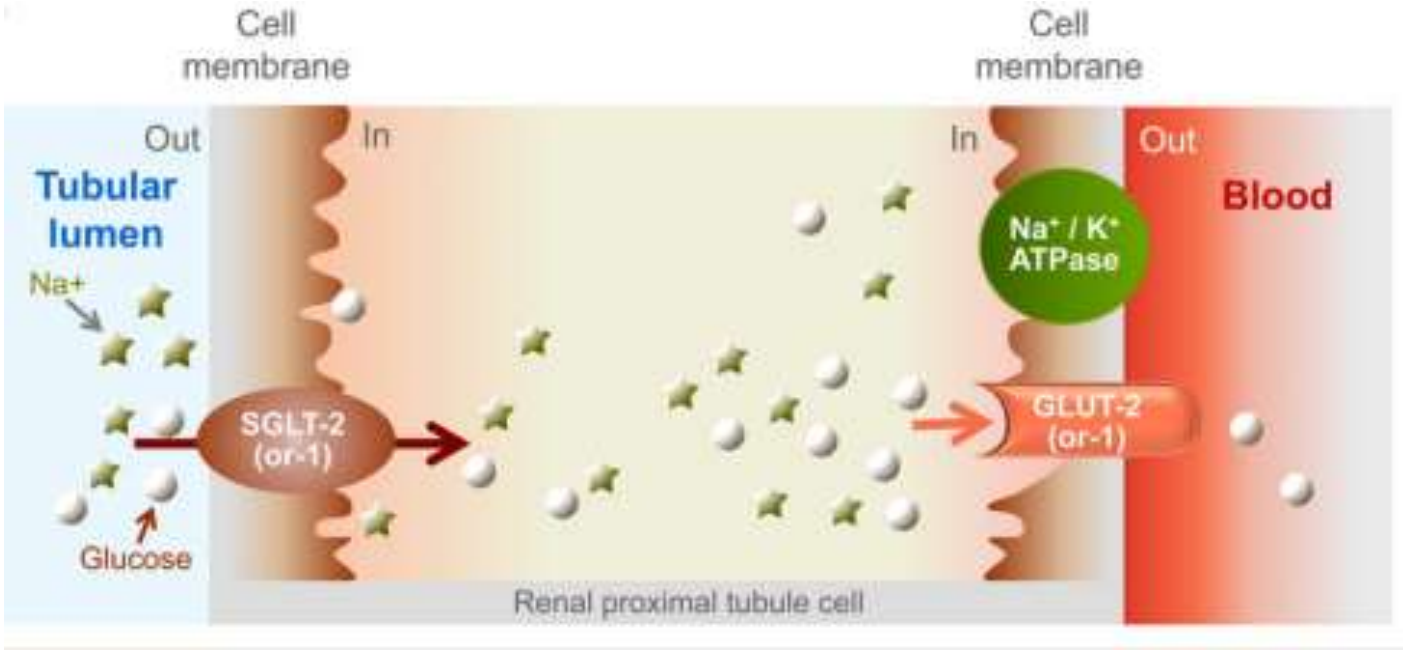


1. Diabetes Med 2010; 27(2):136-42 , 2. J Intern Med 2007; 261(1):32-4

Glucose Transporters

- Glucose transporters play a critical role in various organs.
- They are classified into two families:
  - *facilitative glucose transporters (**GLUTs**)*
  - *sodium-dependent glucose transporters (**SGLTs**)*

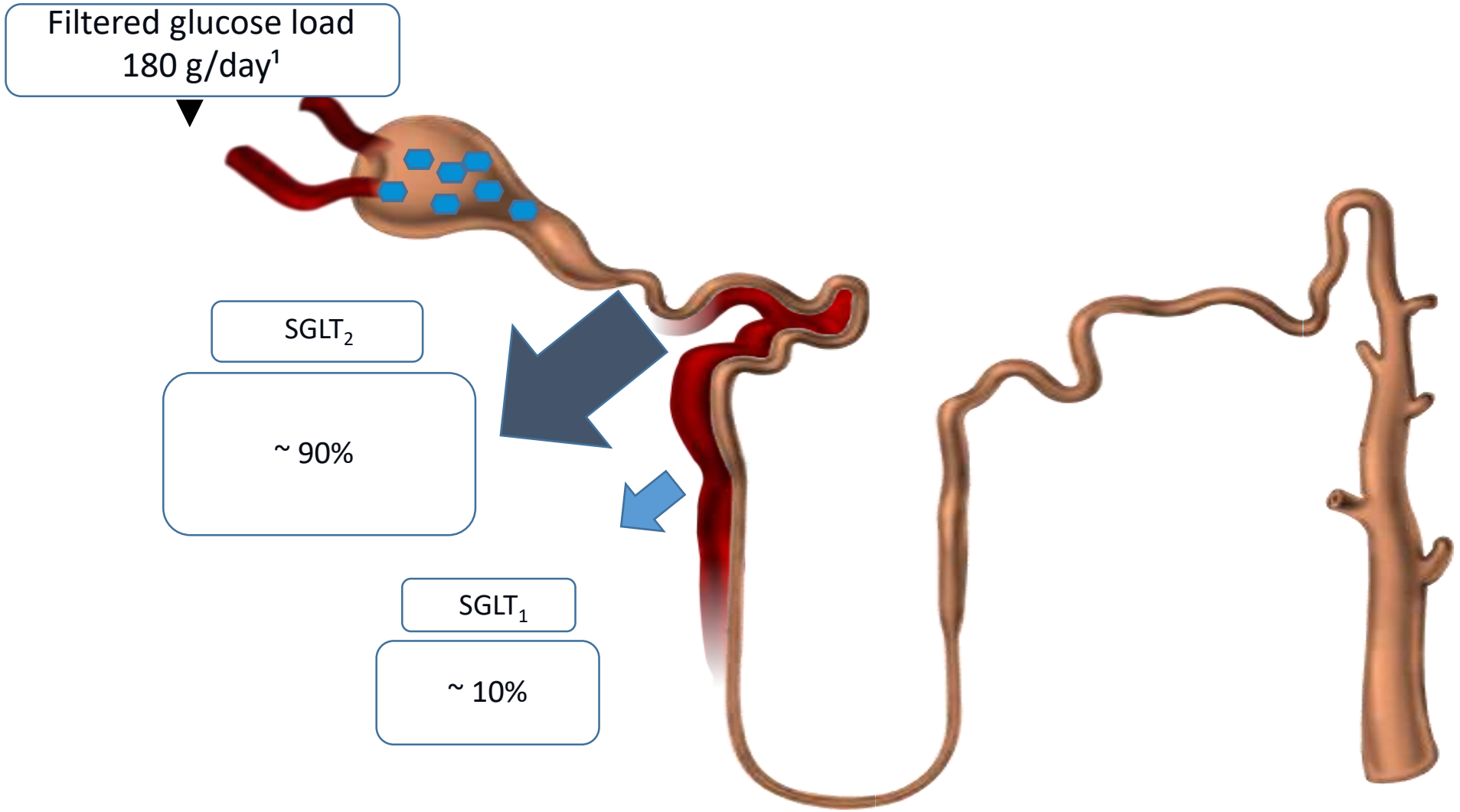
- **SGLTs 1-6: active energy dependent glucose transporters:**
  - ***SGLT$_1$**: low capacity, high affinity, mostly in intestine*
  - ***SGLT$_2$**: high capacity, low affinity, mostly in kidney*



1. Diabetes Ther. 2013; 4(2): 195–220, 2. J Clin Endocrinol Metab. 2010; 95(1):34-42

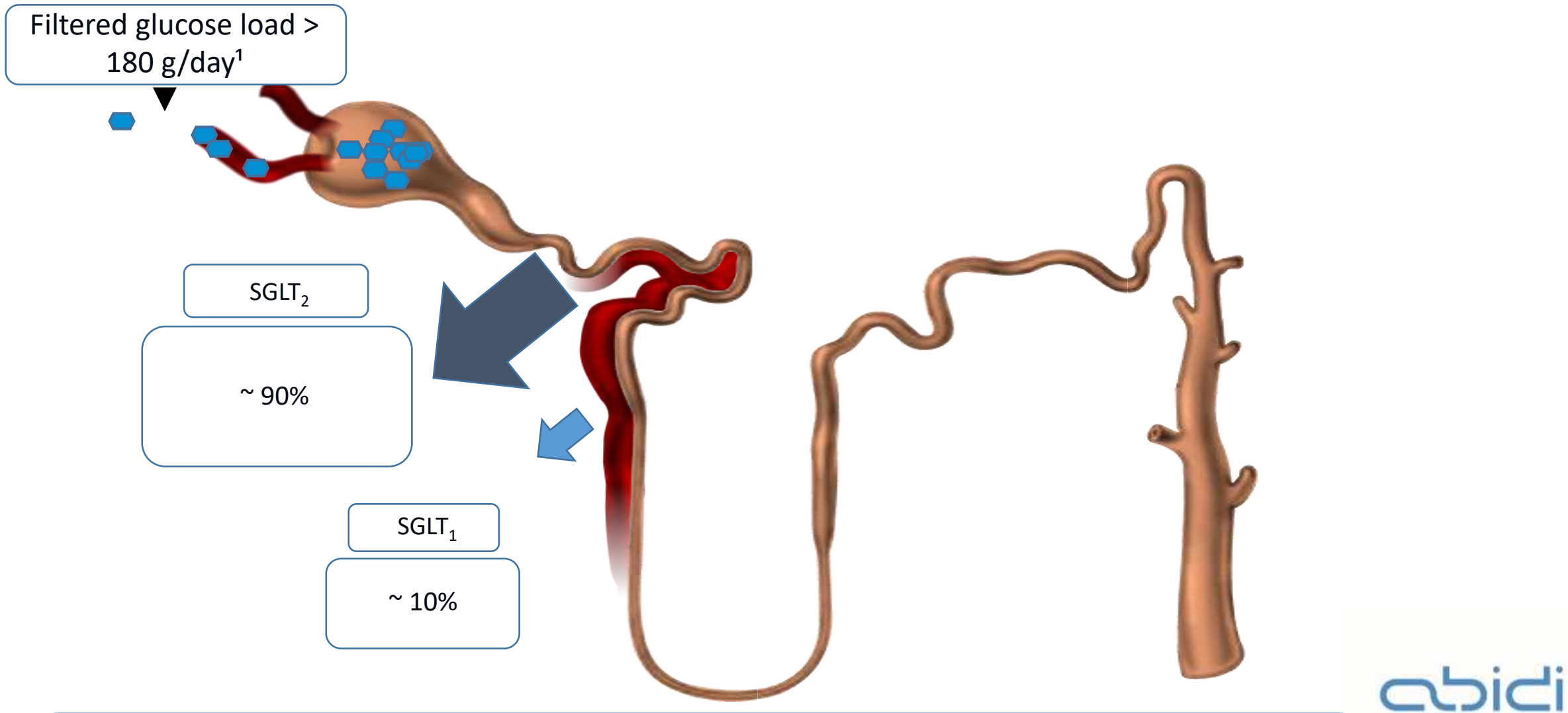
Empagliflozin Mechanism of Action

Renal glucose re-absorption in healthy individuals



1. Diabet Med. 2010; 27(2):136-42

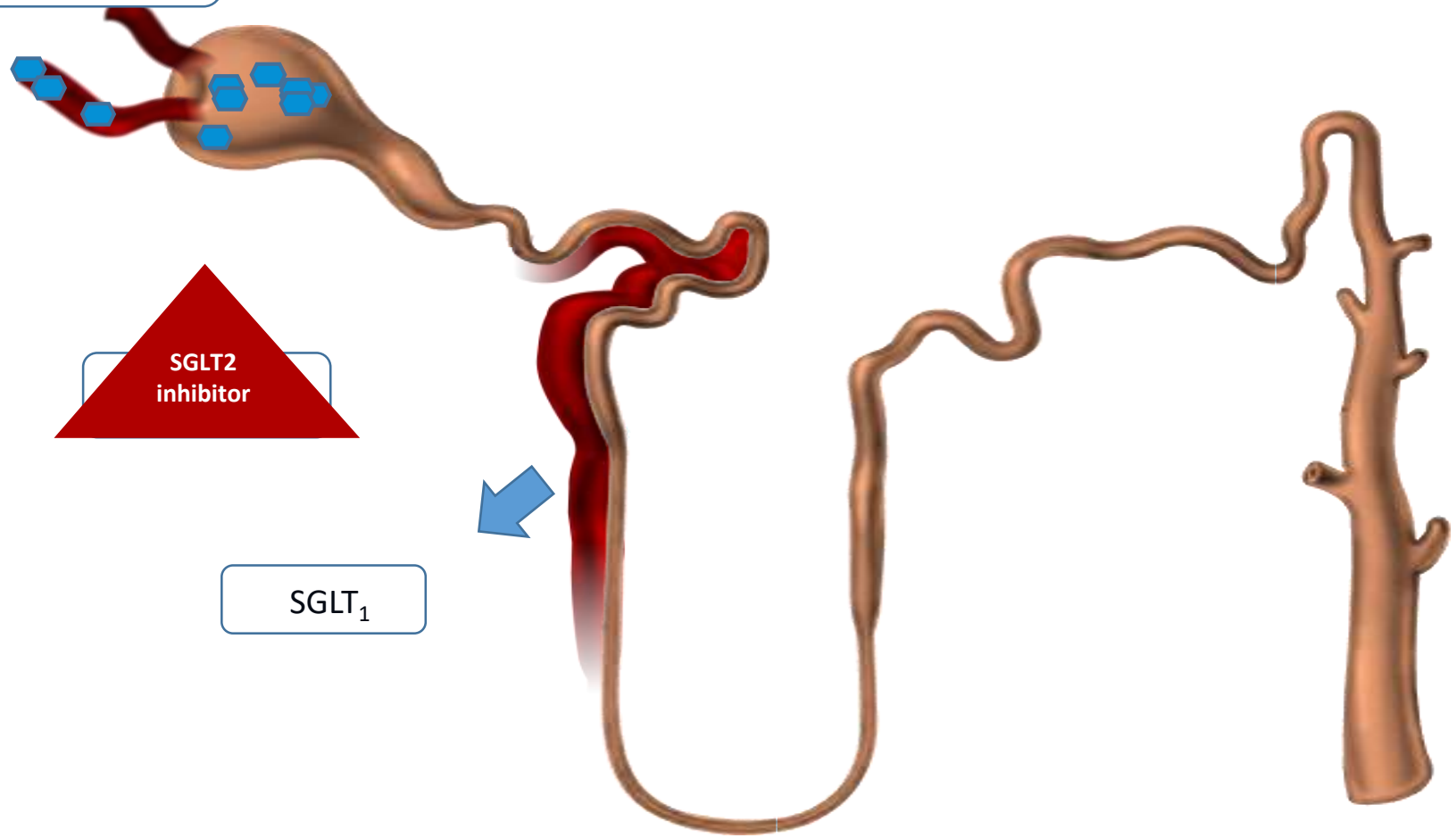
Renal glucose re-absorption in patients with diabetes



1. Diabet Med. 2010; 27(2):136-42

Urinary glucose excretion via SGLT2 inhibition

Filtered glucose load
> 180 g/day

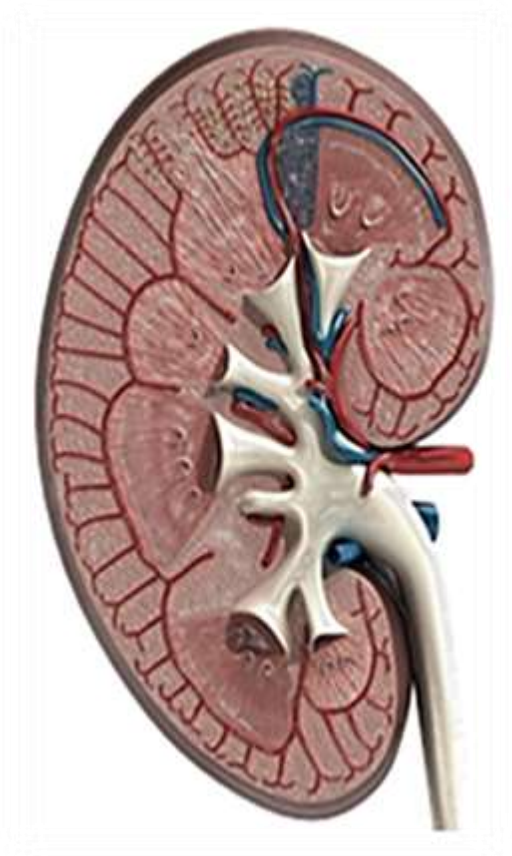


SGLT$_2$ inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis[1]

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

1. Diabet Med. 2010; 27(2):136-42

Expected Clinical Effects of SGLT2 Inhibition



Increased glucose excretion

- → **Reduced glycemia** → **HbA1c Reduction 0.6 - 1%**
- → **Loss of calories** → **Weight loss 2 – 3 kg**

Increased sodium excretion → **Reduced sodium load** → **BP reduction 3 – 5 mmHg**

Abdul-Ghani MA, et al. *Endocri Rev.* 2011; 32:S15-S31.

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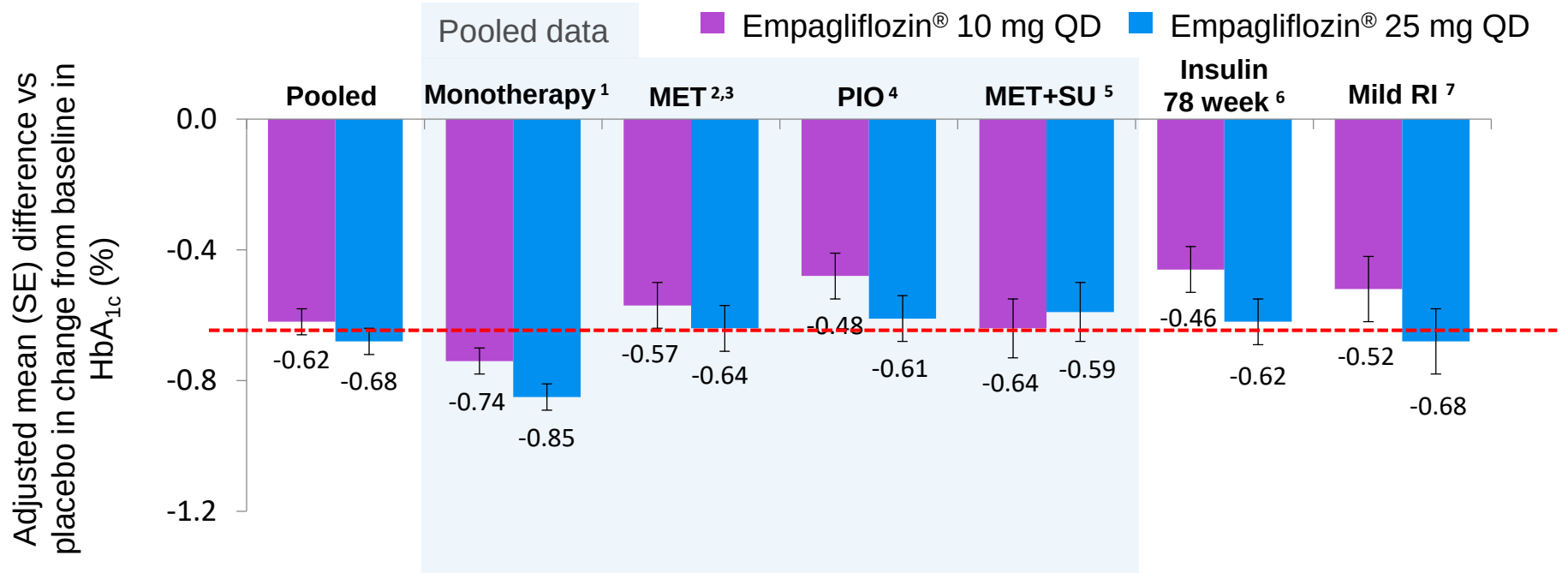
Empagliflozin in clinical studies:

Efficacy

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

Phase III pooled efficacy analysis



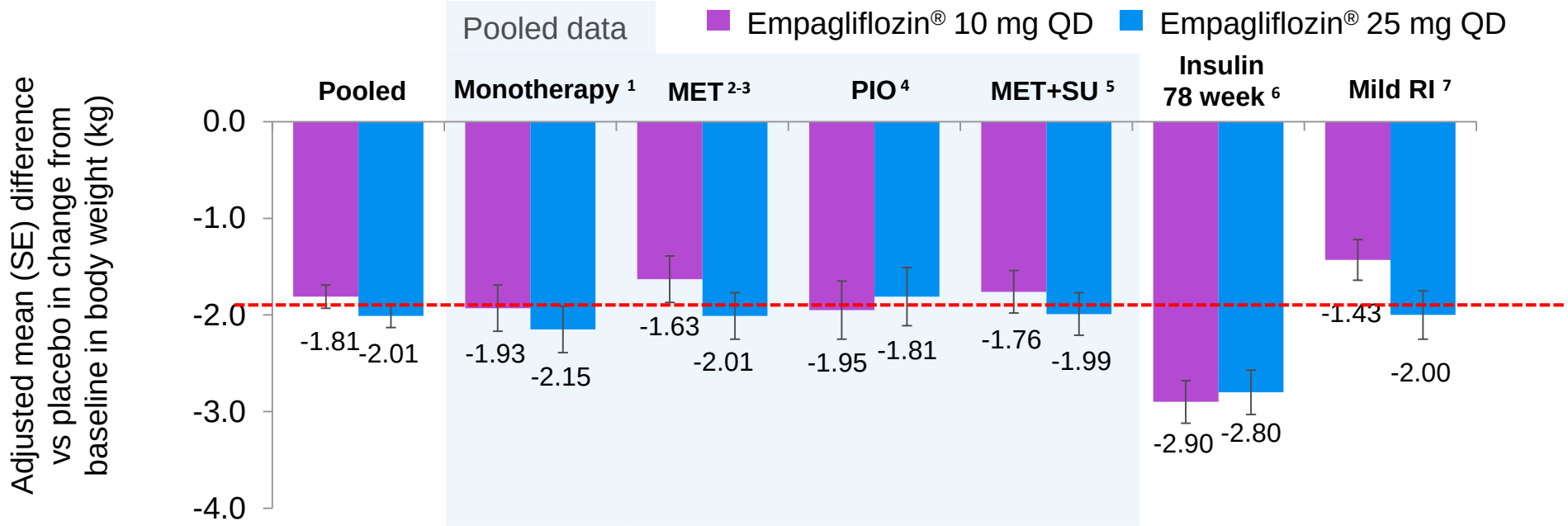
Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL HbA_{1c}, %	7.98	7.96	7.87	7.86	7.94	7.86	8.1	8.1	8.07	8.10	8.3	8.3	8.02	7.96

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. Lancet Diabetes Endocrinol. 2013; 1(3):208-19; 2. Diabetes. 2013; 62(suppl 1A);A21 (P69-LB); 3. Diabetes Care. 2014; 37(6):1650-9
4. Diabetes Obes Metab. 2014; 16(2):147–158; 5. Diabetes Care. 2013; 36(11):3396–404; 6. Diabetologia. 2013; 56(suppl 1);S372 (P931); 7. The Lancet Diabetes & Endocrinology 2014; 2(5), 369–384.

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

Phase III pooled efficacy analysis

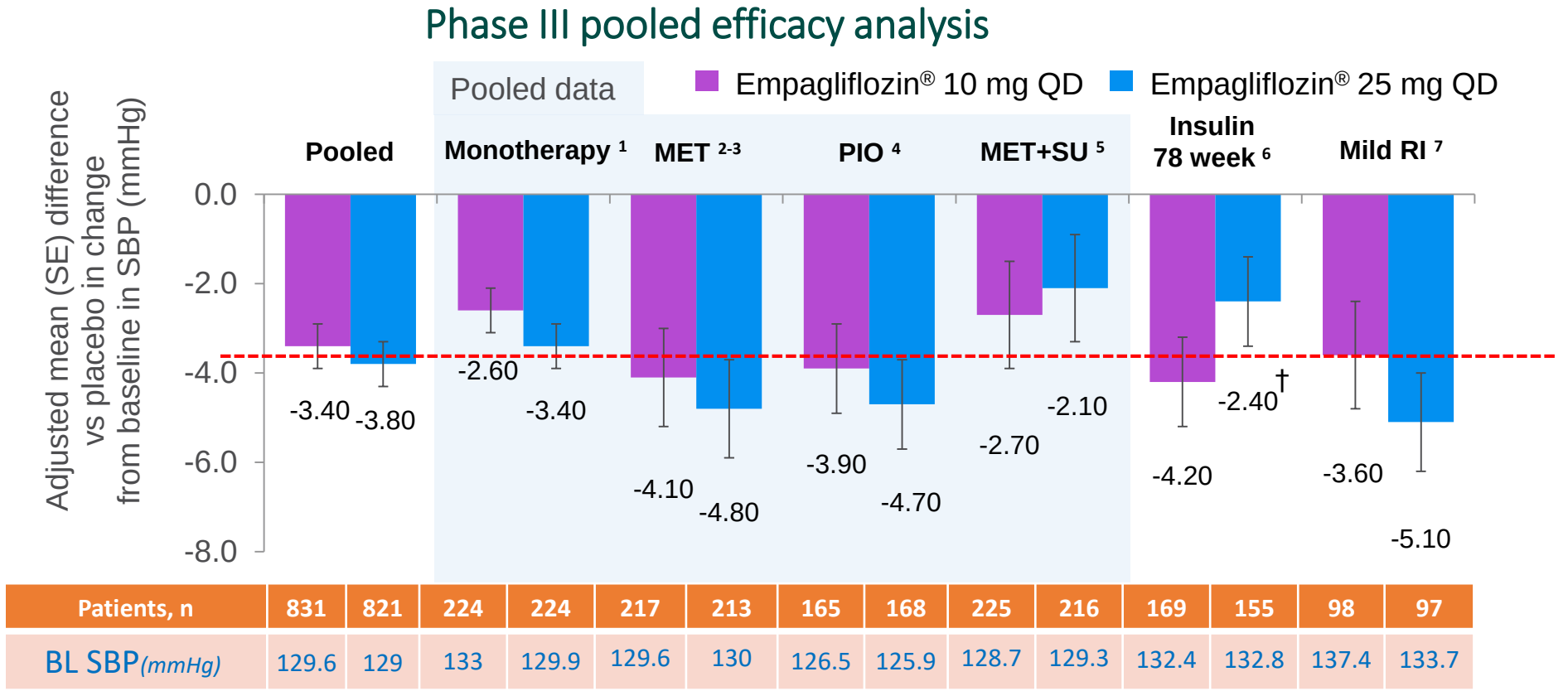


Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL BW *(kg)*	78.77	79.10	78.4	77.80	81.6	82.2	78.0	78.90	77.1	77.5	91.6	94.7	92.1	88.7

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. Lancet Diabetes Endocrinol. 2013; 1(3):208-19; 2. Diabetes. 2013; 62(suppl 1A);A21 (P69-LB); 3. Diabetes Care. 2014; 37(6):1650-9
4. Diabetes Obes Metab. 2014; 16(2):147–158; 5. Diabetes Care. 2013; 36(11):3396–404; 6. Diabetologia. 2013; 56(suppl 1);S372 (P931); 7. The Lancet Diabetes & Endocrinology 2014; 2(5), 369–384.

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



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

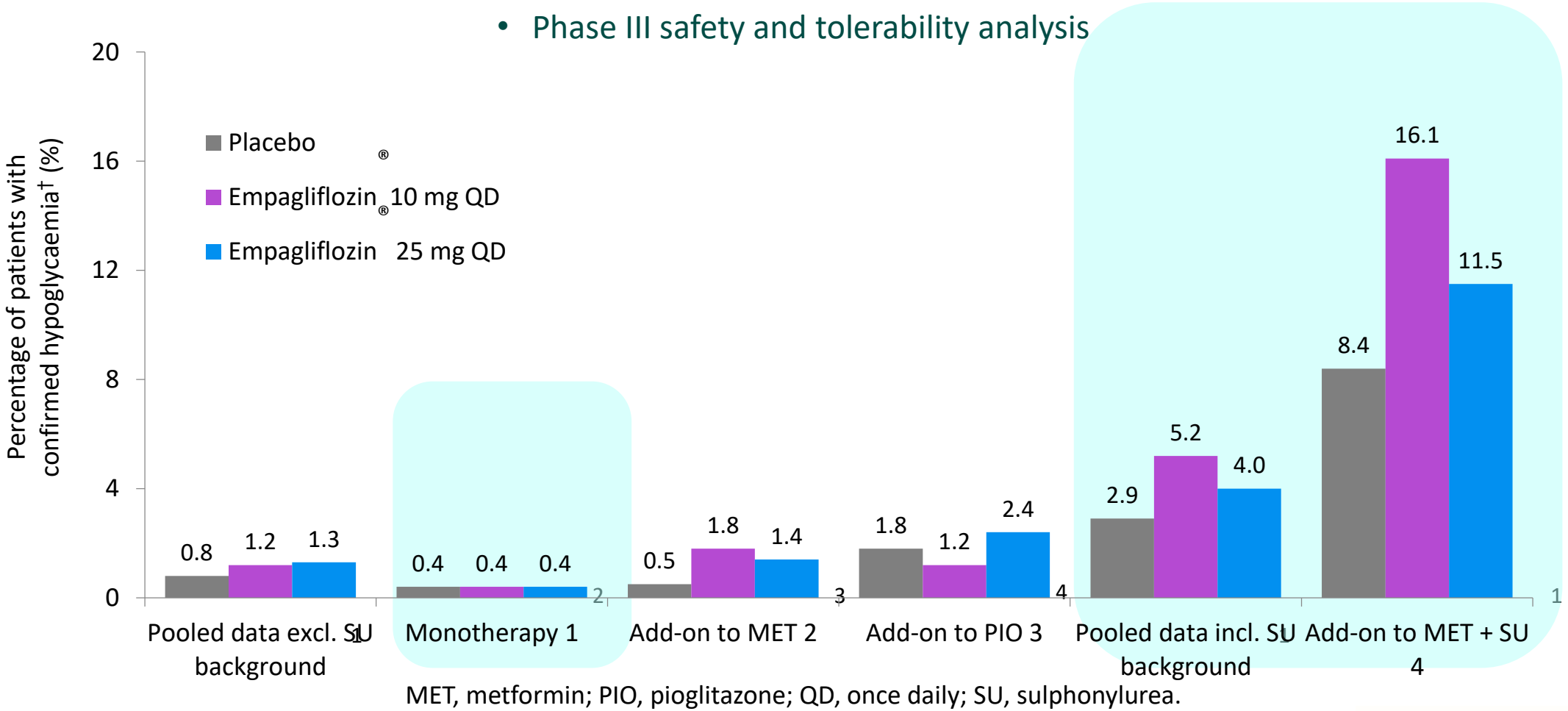
BL, baseline; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea.
*All statistically significant except when marked as †.

1. Lancet Diabetes Endocrinol. 2013; 1(3):208-19; 2. Diabetes. 2013; 62(suppl 1A);A21 (P69-LB); 3. Diabetes Care. 2014; 37(6):1650-9
4. Diabetes Obes Metab. 2014; 16(2):147–158; 5. Diabetes Care. 2013; 36(11):3396–404; 6. Diabetologia. 2013; 56(suppl 1);S372 (P931); 7. The Lancet Diabetes & Endocrinology 2014; 2(5), 369–384.

Empagliflozin **Safety** profile

Hypoglycaemic Events

- Phase III safety and tolerability analysis



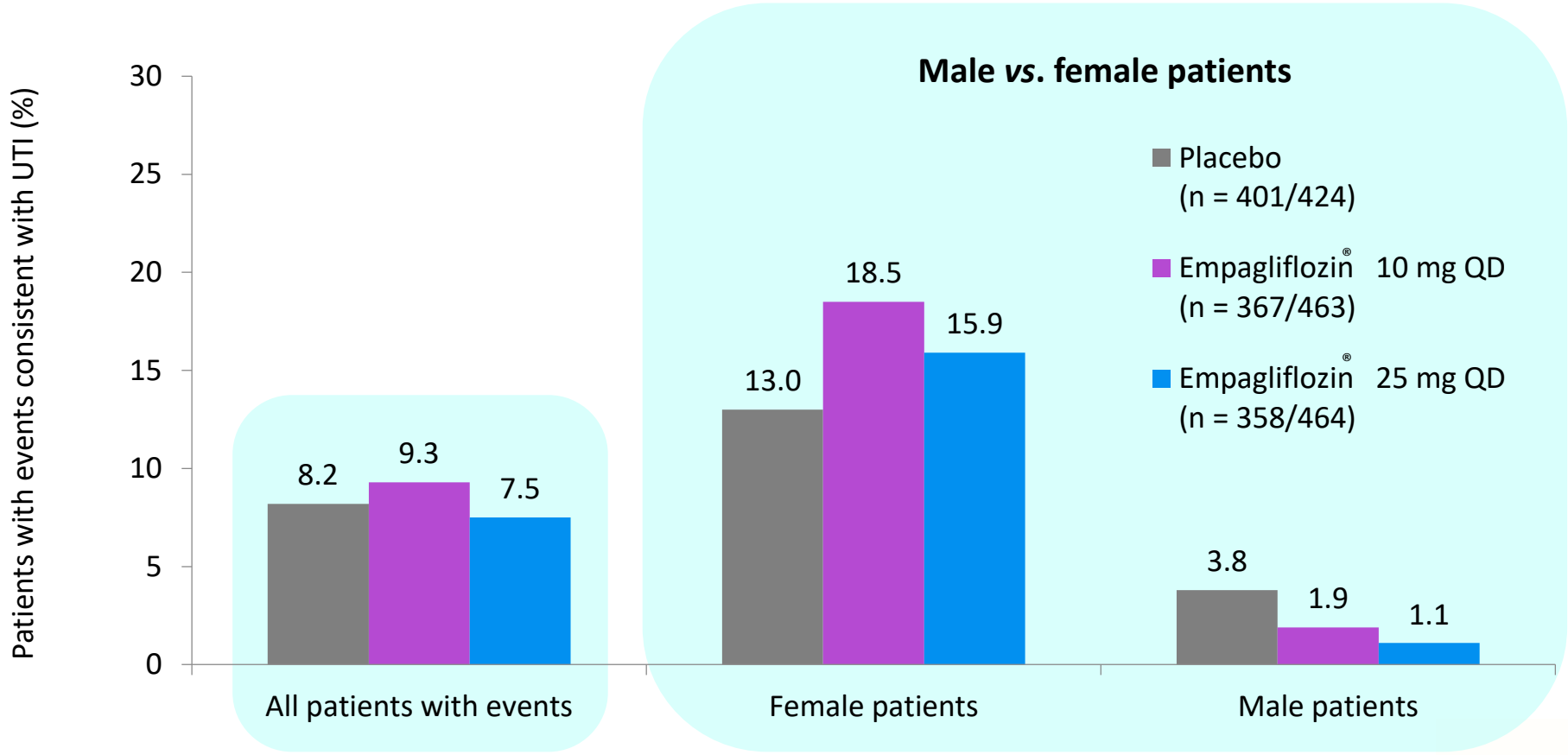
MET, metformin; PIO, pioglitazone; QD, once daily; SU, sulphonylurea.

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

1. Lancet Diabetes Endocrinol. 2013; 1(3):208–219; 2. Diabetes Care. **2014 ;37(6):1650-9** 3. Diabetes Obes Metab. 2014; 16(2):147–158; 4. Diabetes Care. 2013; 36(11):3396–404

Events Consistent with UTI Stratified by Gender

Phase III pooled safety and tolerability analysis

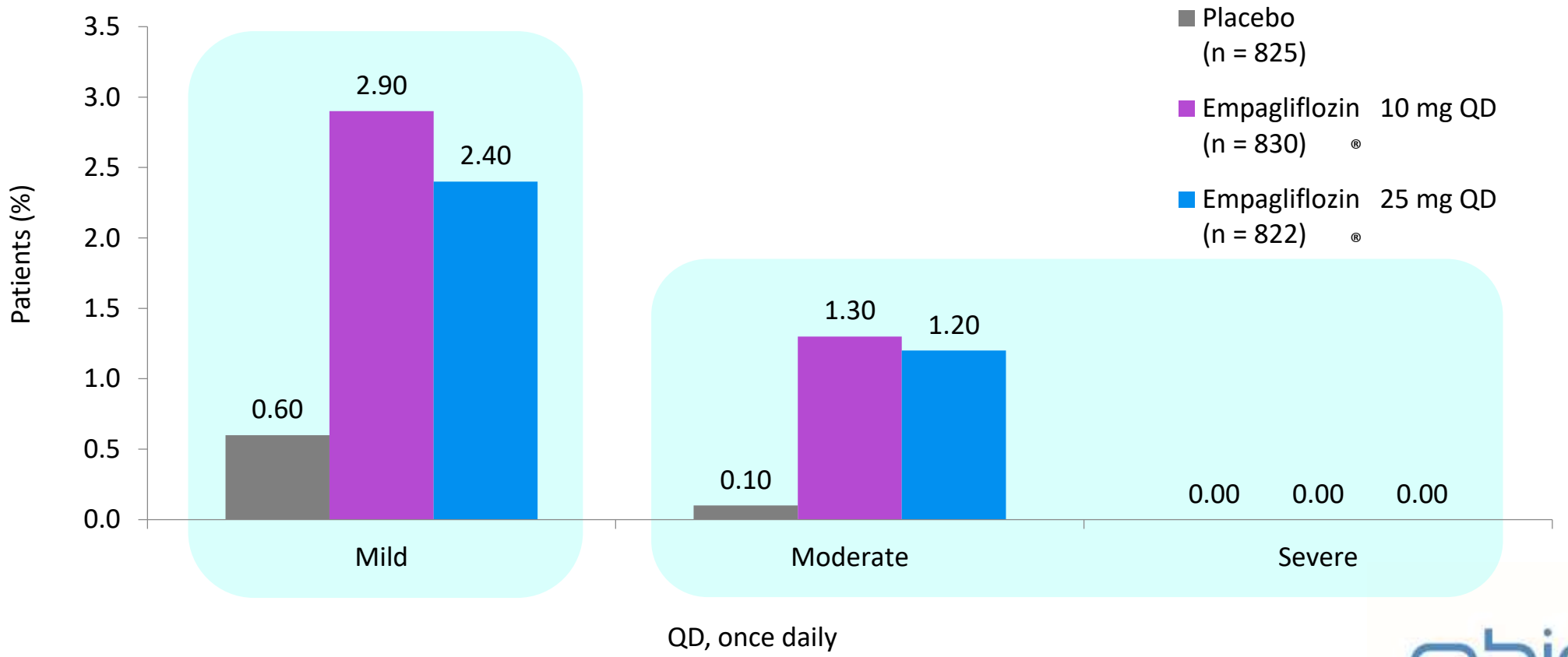


QD, once daily; UTI, urinary tract infection.

1. Lancet Diabetes Endocrinol. 2013; 1(3):208–219; 2. Diabetes Care. **2014 ;37(6):1650-9** 3. Diabetes Obes Metab. 2014; 16(2):147–158; 4. Diabetes Care. 2013; 36(11):3396–404

Genital Infection Distribution of Events Severity[1-4]

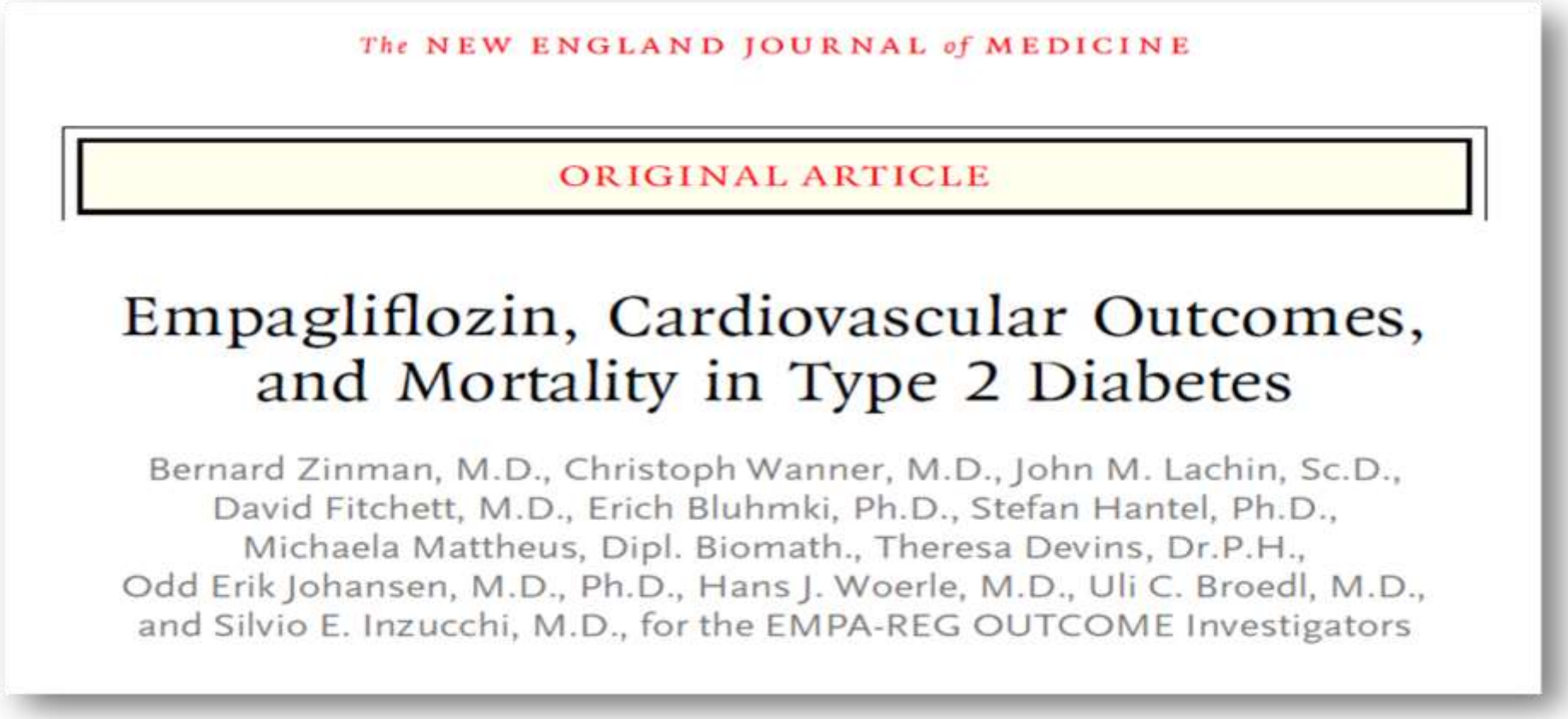
Phase III pooled safety and tolerability analysis



1. Lancet Diabetes Endocrinol. 2013; 1(3):208–219; 2. Diabetes Care. **2014 ;37(6):1650-9** 3. Diabetes Obes Metab. 2014; 16(2):147–158; 4. Diabetes Care. 2013; 36(11):3396–404

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

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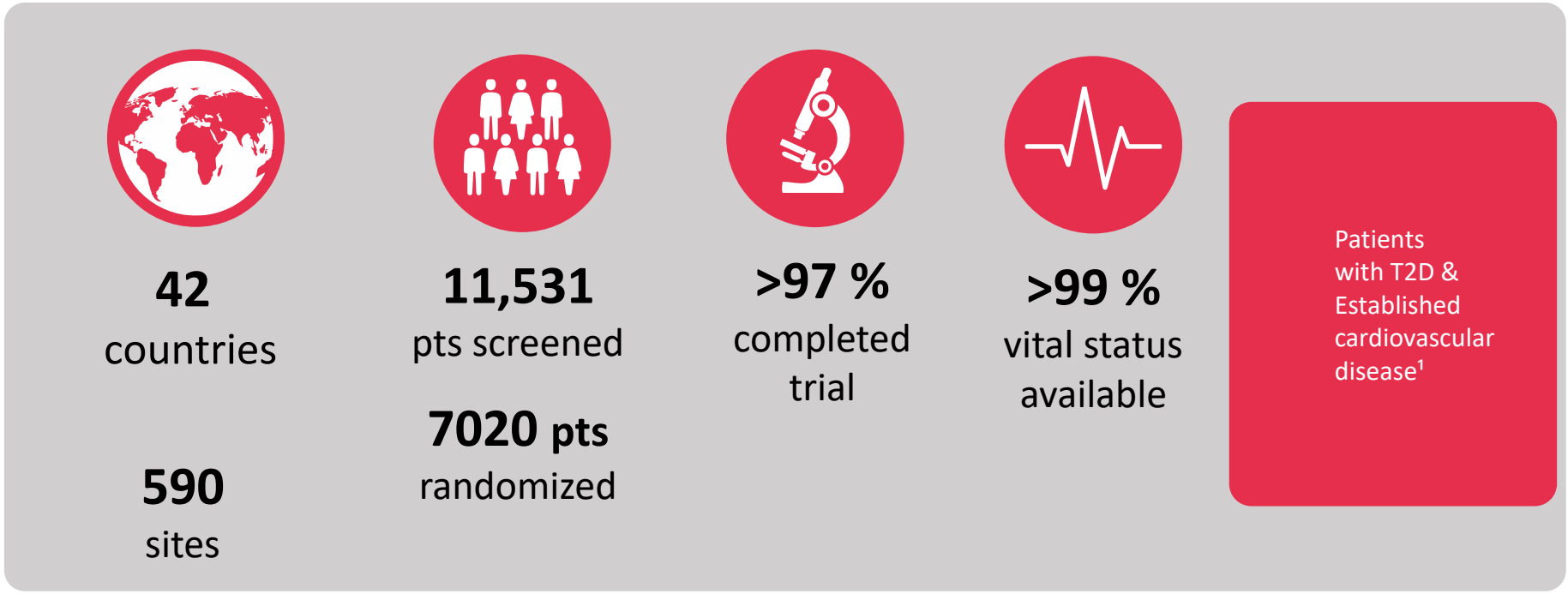
1. N Engl J Med 2015; 373:2117-2128

Trial Design



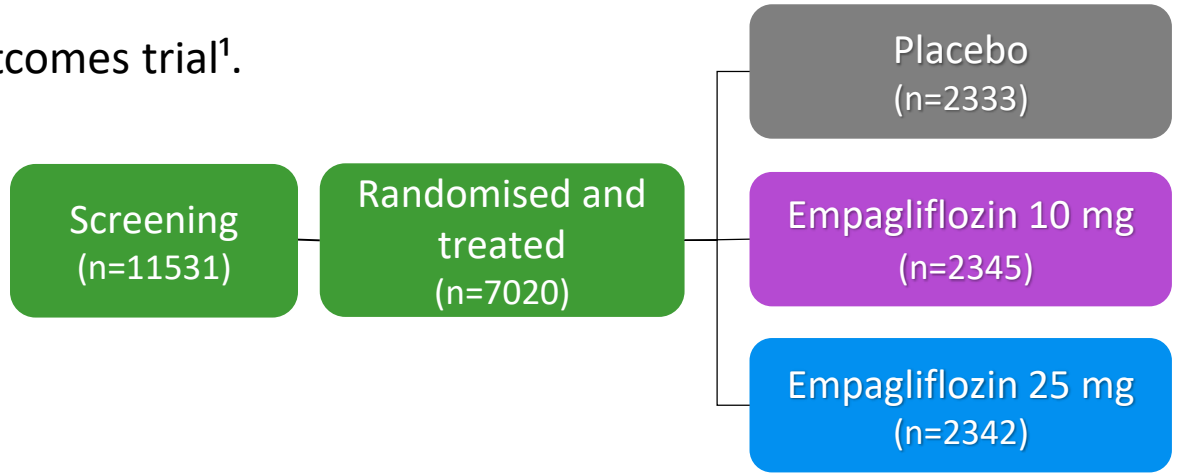
- CV, cardiovascular.

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

EMPA-REG OUTCOME

- **Design**
  - 42 Countries, 590 sites
  - 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

1. N Engl J Med 2015; 373:2117-2128

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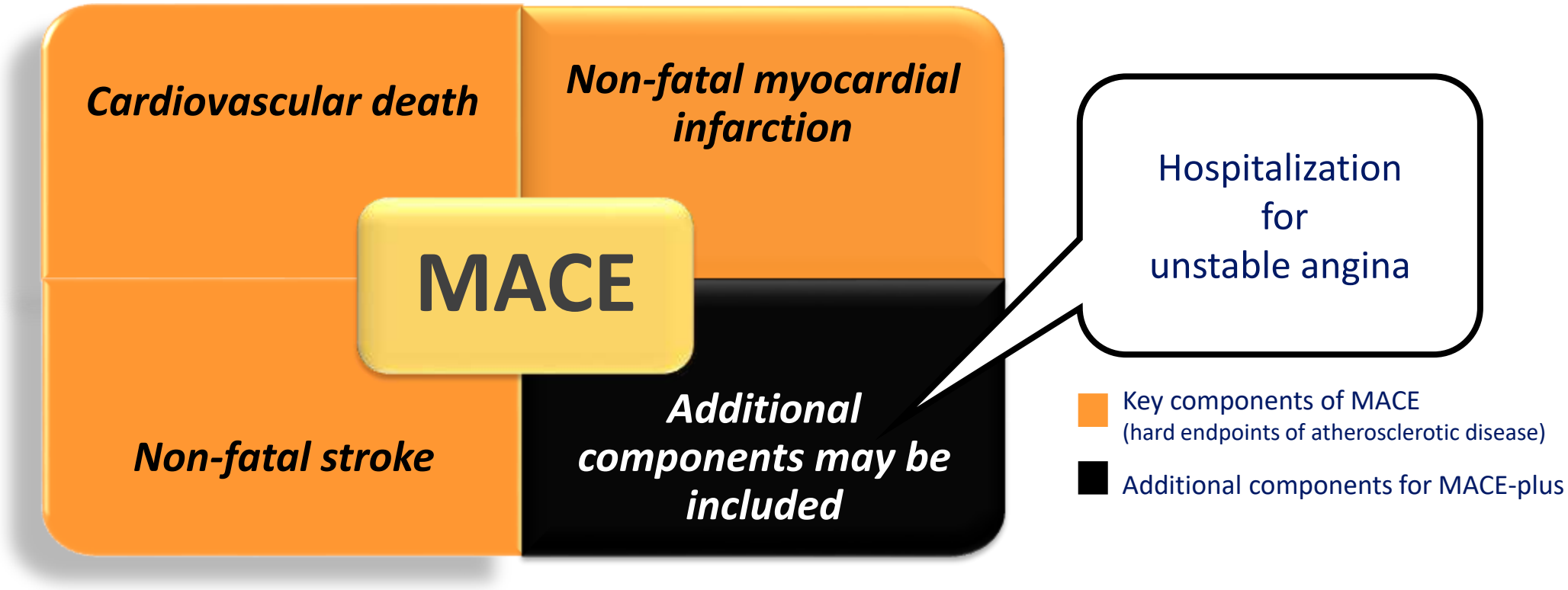
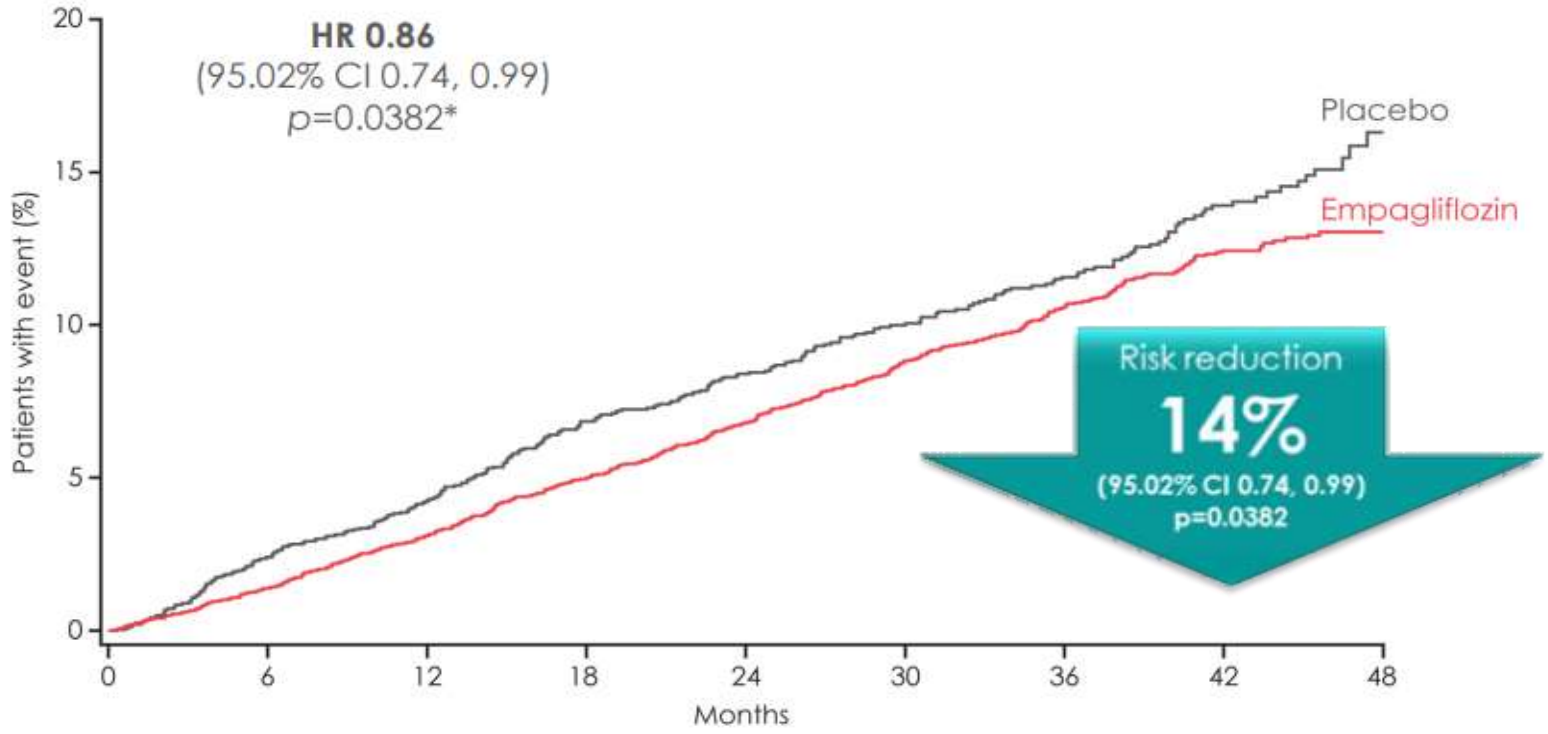
Pre-specified primary and key secondary outcomes



1. N Engl J Med 2015; 373:2117-2128

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

EMPA-REG OUTCOME



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)

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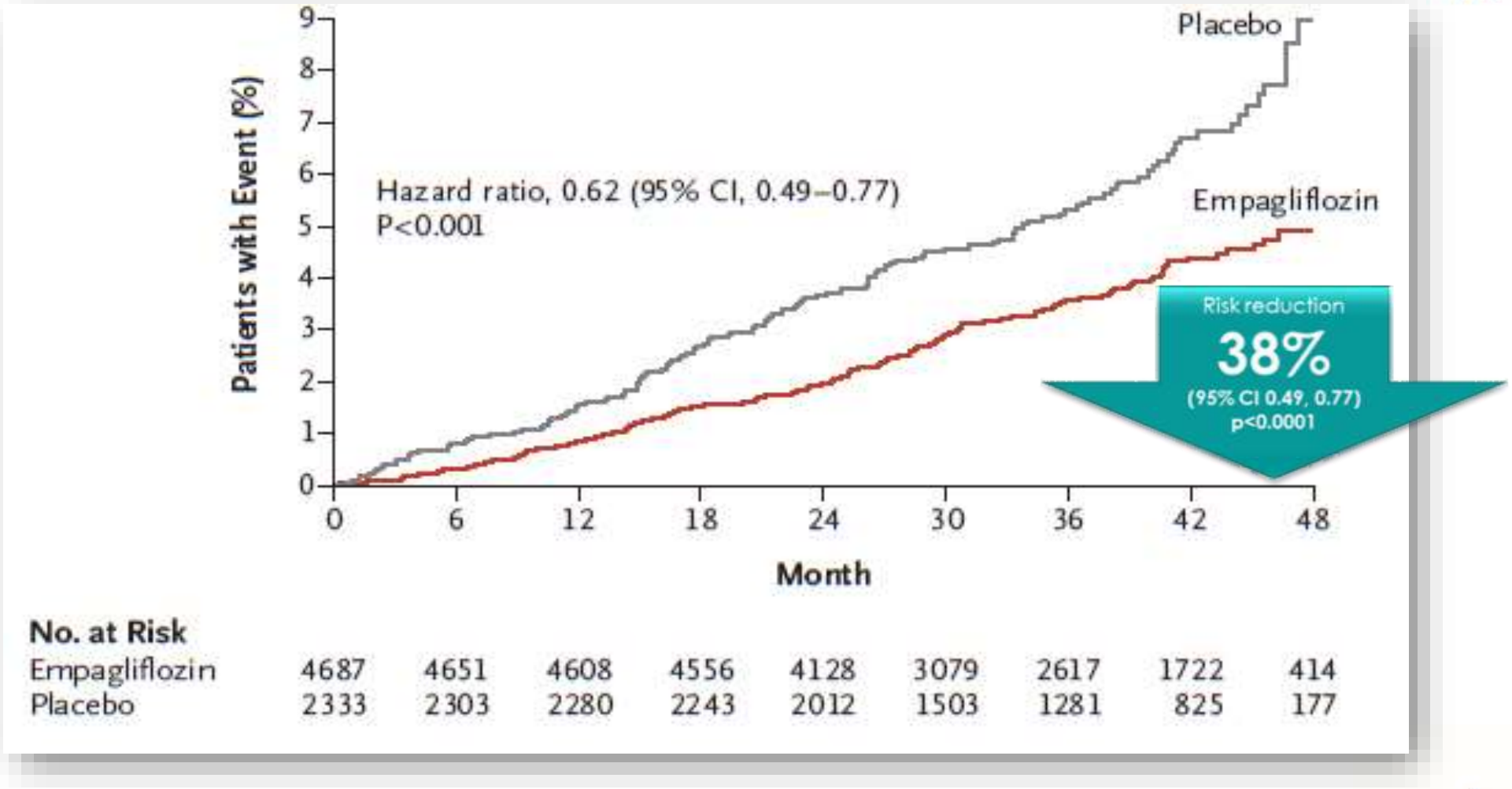
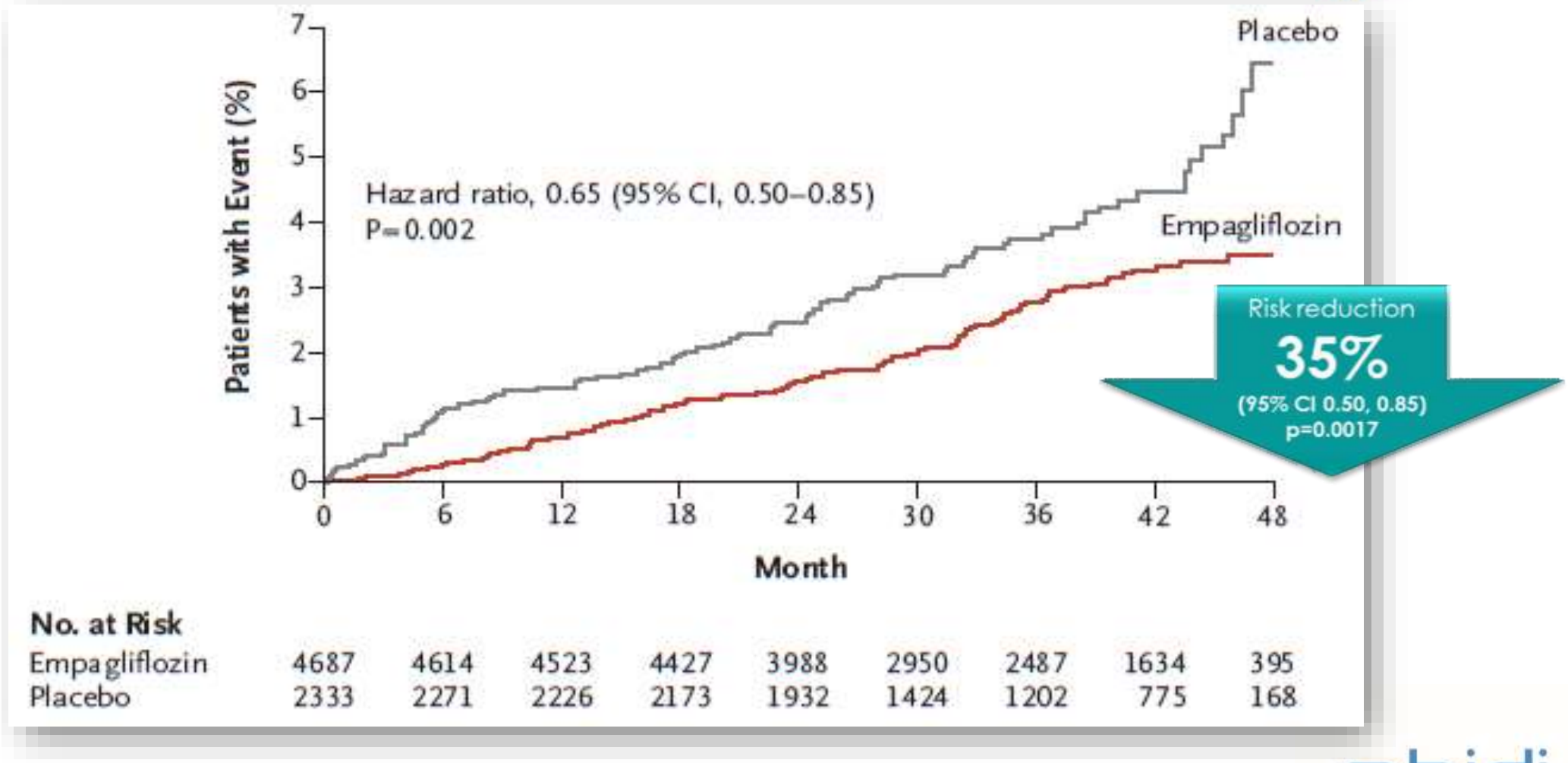
1. N Engl J Med 2015; 373:2117-2128

EMPA-REG OUTCOME® CV Death[1]



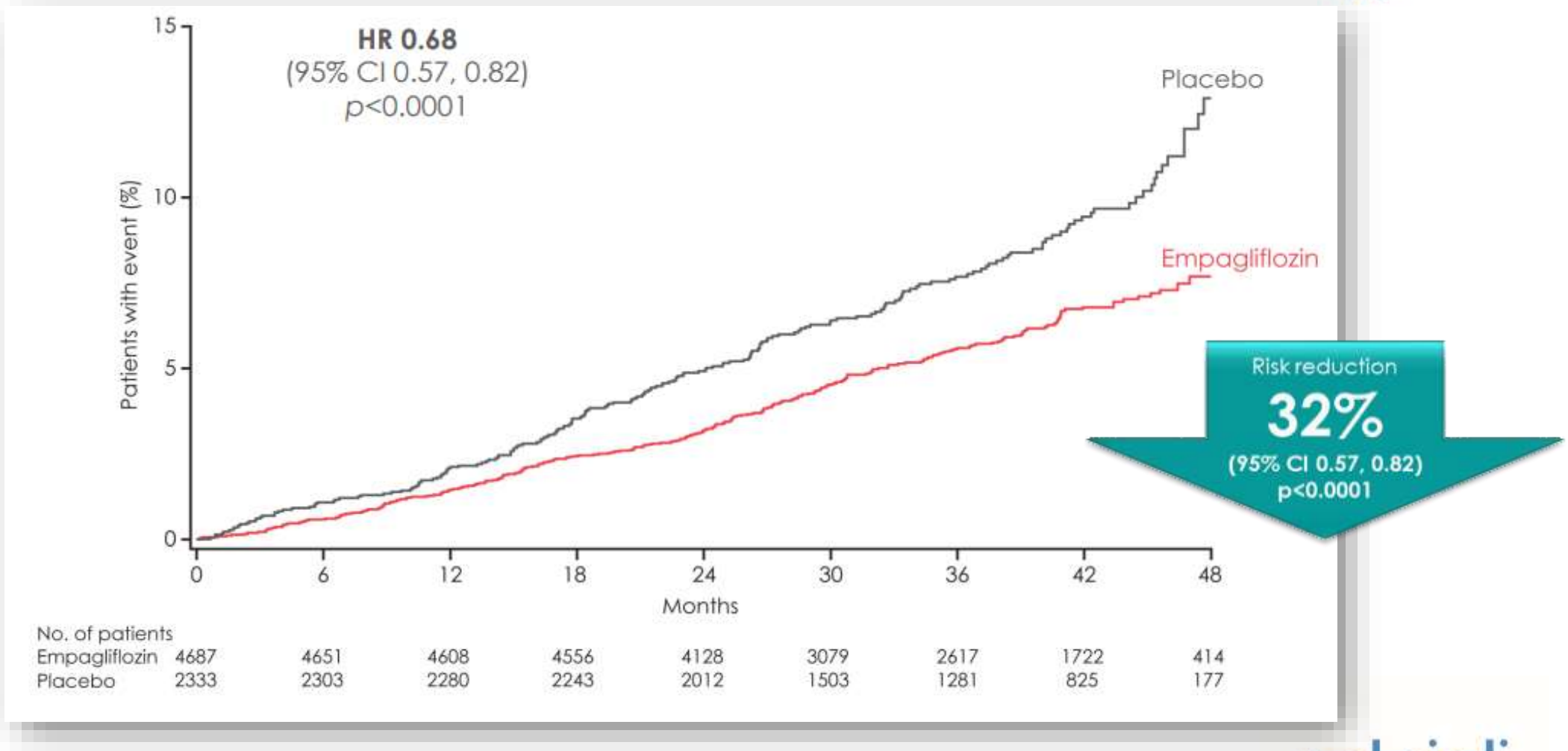
1. N Engl J Med 2015; 373:2117-2128

EMPA-REG OUTCOME® Hospitalization for Heart Failure[1]



1. N Engl J Med 2015; 373:2117-2128

EMPA-REG OUTCOME® All-cause Mortality [1]



1. N Engl J Med 2015; 373:2117-2128

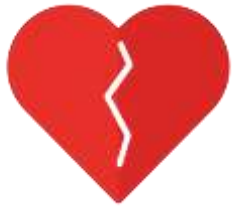
EMPA-REG OUTCOME®: summary

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.

EMPA-REG RENAL®

The NEW ENGLAND JOURNAL of MEDICINE

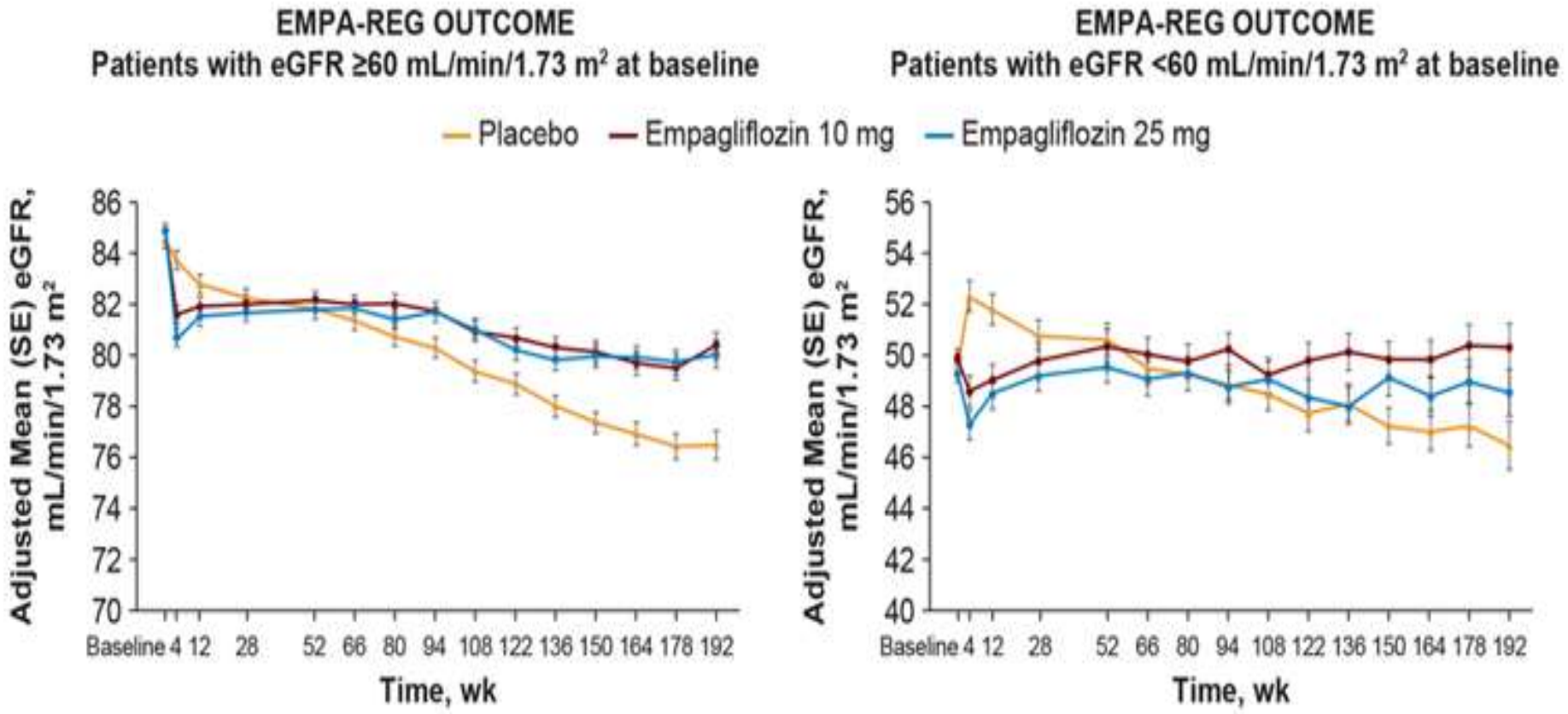
ORIGINAL ARTICLE

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

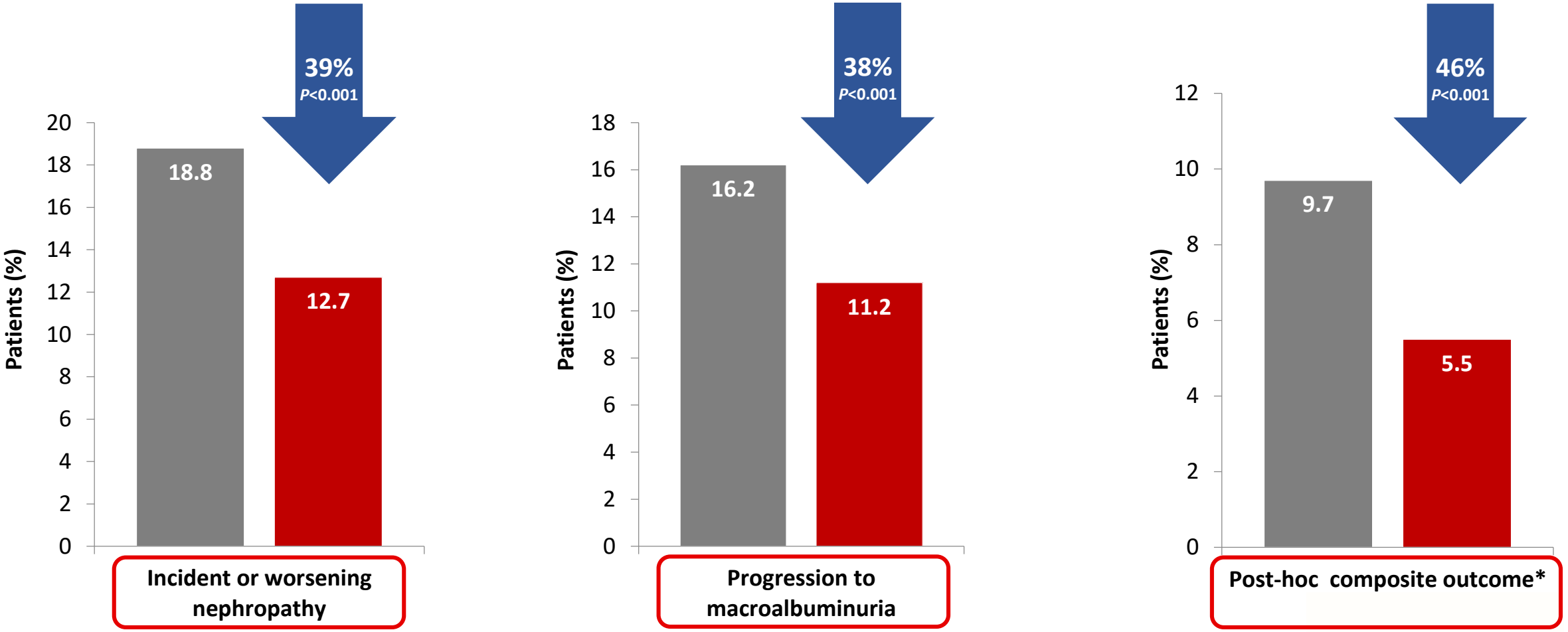
1. N Engl J Med 2016; 375:323-334

SGLT2 Inhibitors Induce a Temporary Reduction in eGFR, but Preserve Renal Function Overtime[1]



1-Wanner C et al,. Empagliflozin and progression of kidney disease in type 2 diabetes. New England Journal of Medicine. 2016; 28;375(4):323-34.

Renal Outcomes with Empagliflozin over 3.2 Years (EMPA-REG RENAL)[1]



Arrows = relative risk reduction

*Doubling of SCr + eGFR ≤45 *mL/min/1.73 m²*, initiation of renal replacement therapy, or death from renal disease.

1. N Engl J Med 2016; 375:323-334

The EMPEROR-Reduced trial

Background

- ✓SGLT2 inhibitors may prevent the onset of HF in high-risk patients, but can these drugs ***treat*** HF in those with an established diagnosis?
- ✓If the benefits of SGLT2 inhibitors on HF are unrelated to their actions on blood glucose, could these drugs exert favorable effects in patients who ***have HF*** but ***who do not have diabetes***?
- ✓Would such benefits be seen in those who are ***already receiving appropriate drug treatments for HF***?

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1-N. Engl. J. Med 2020.8;383(15)1413-1424

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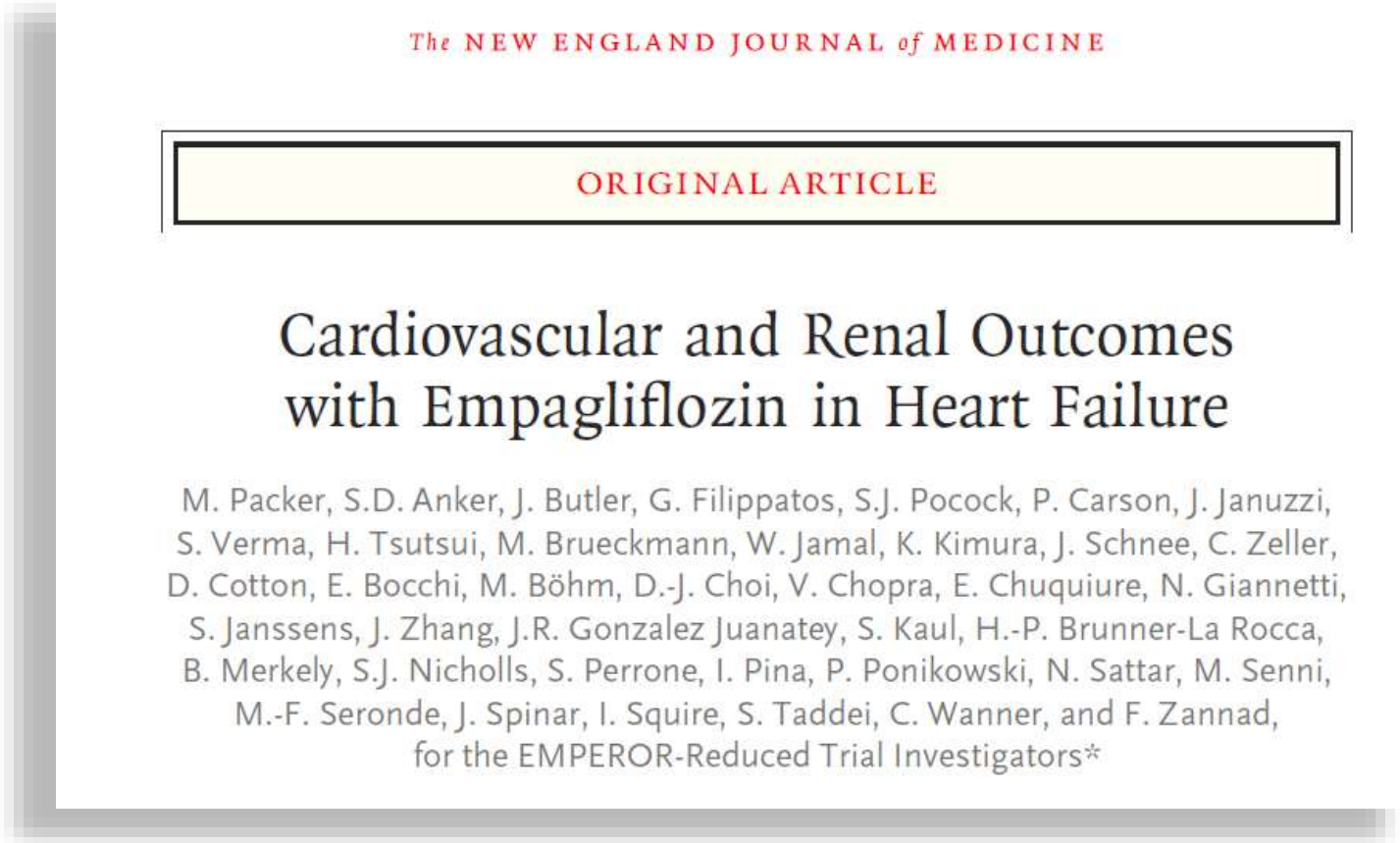

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

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

Objective[1]:

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

1-N. Engl. J. Med 2020.8;383(15)1413-1424

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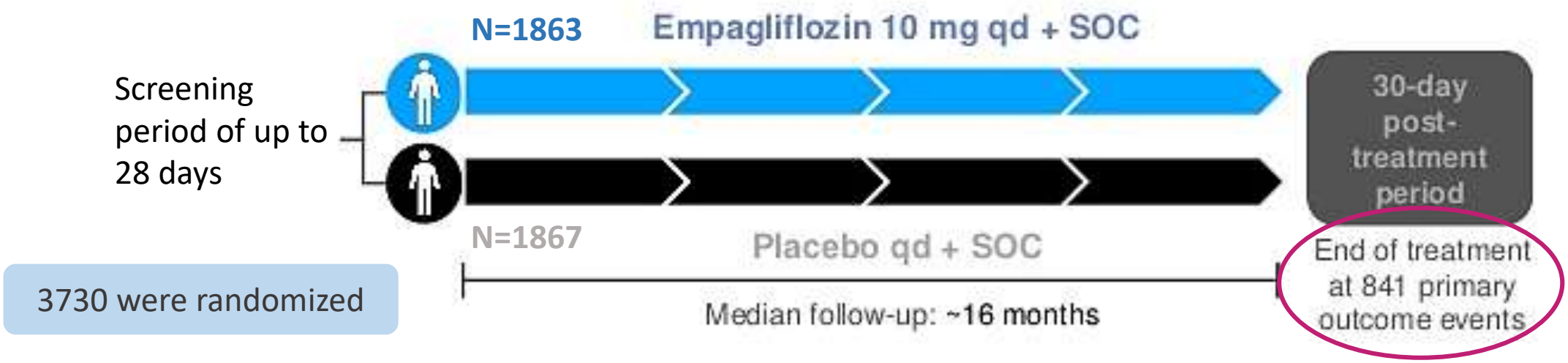
Trial Design

Patients must be receiving all appropriate treatments for HF



3730 were randomized

SOC; Standard Of Care

1-N. Engl. J. Med 2020.8;383(15)1413-1424

.

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

✓ 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 2020.8;383(15)1413-1424

.

Inclusion criteria

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

Key inclusion criteria:

- NYHA class II-IV
- Elevated NT-pro BNP
- Guideline recommendation medication stable ≥1 week prior to first visit
- eGFR ≥20 ml/min/1.73 m^2

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

NYHA; New York Heart Association

1-N. Engl. J. Med 2020.8;383(15)1413-1424

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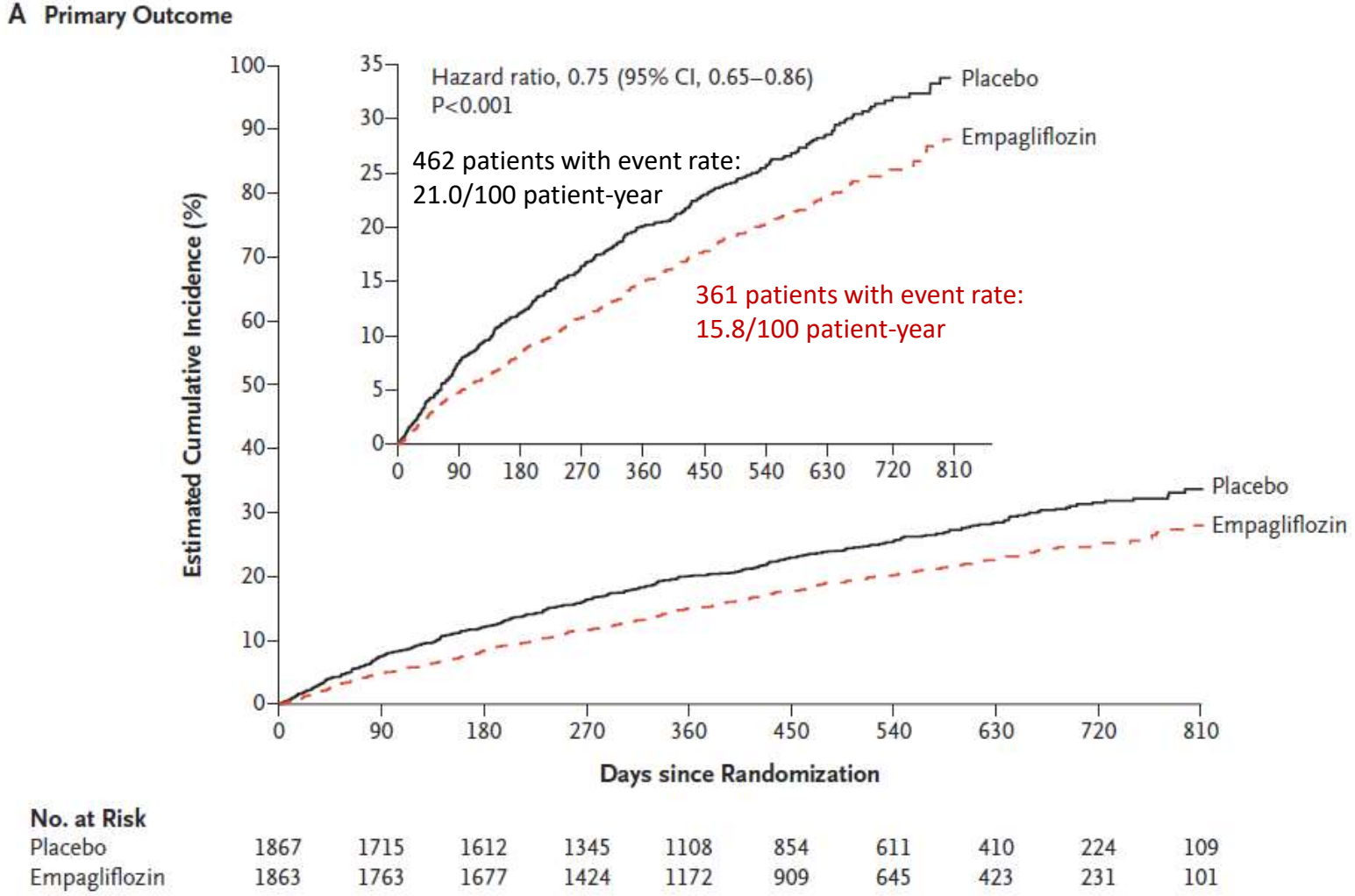
Empagliflozin Group Had Lower Incidence of Cardiovascular Death or Hospitalization for Heart Failure



25% RRR

p<0.001

19.4% vs 24.7%

HR = 0.75 (0.65-0.86)

1-N. Engl. J. Med 2020.8;383(15)1413-1424

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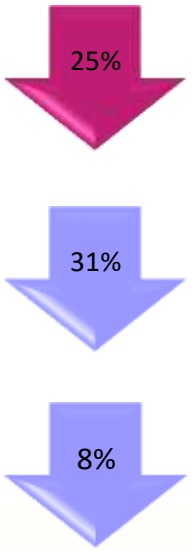
Effect on individual components of the primary endpoint

	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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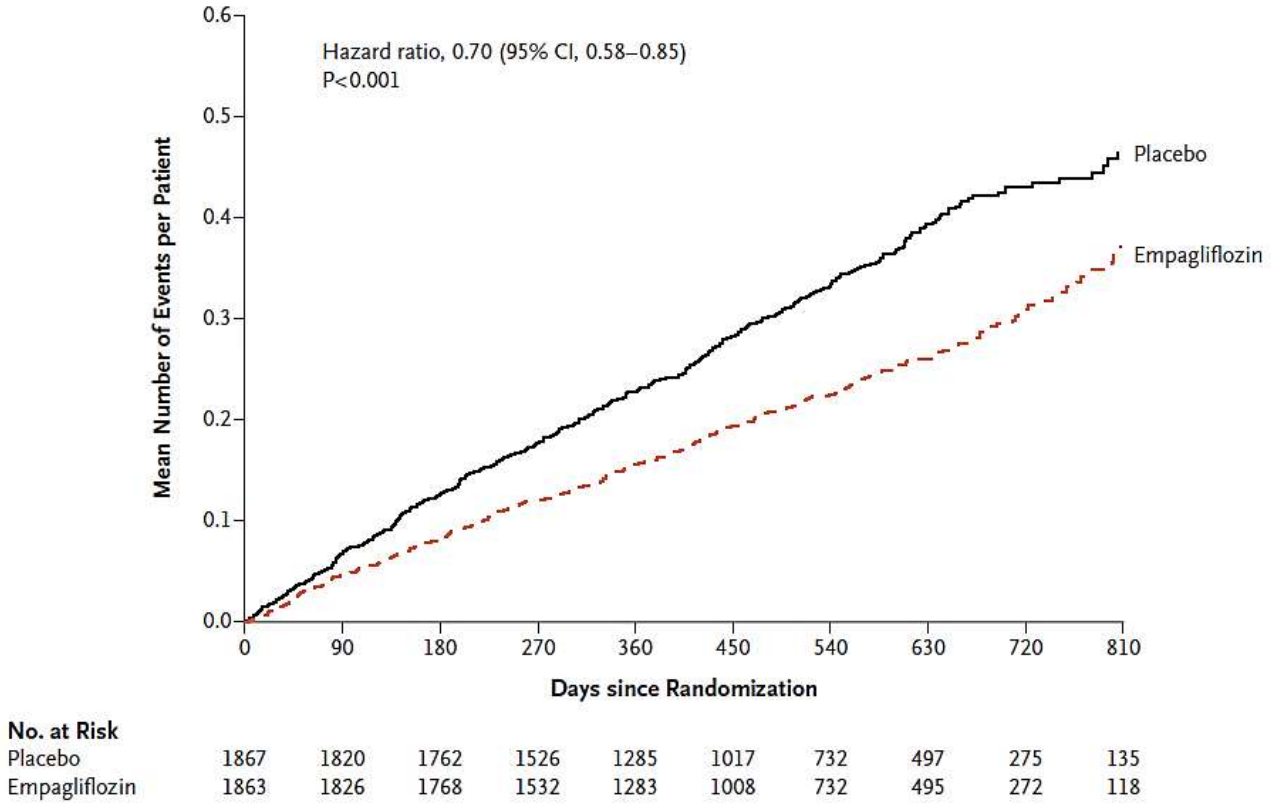
1-N. Engl. J. Med 2020.8;383(15)1413-1424

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



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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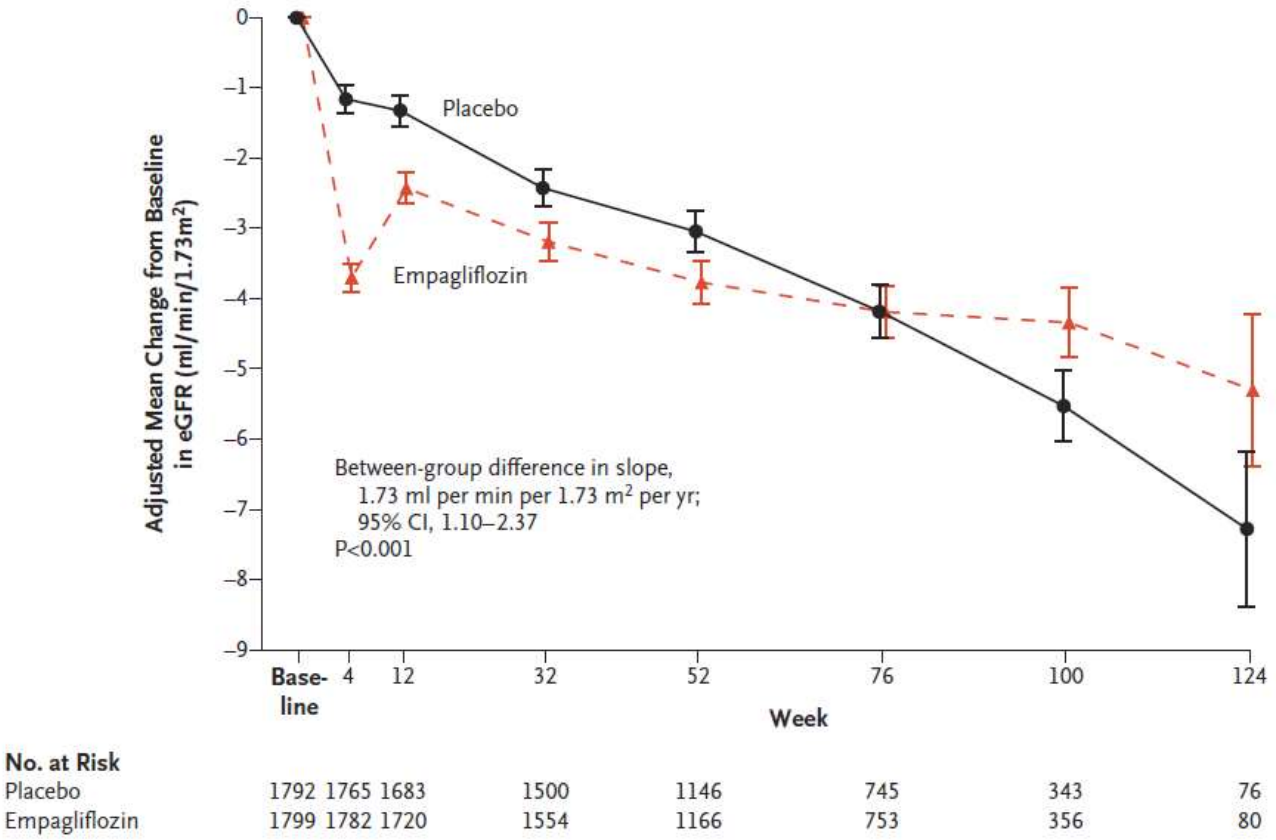
1-N. Engl. J. Med 2020. 8;383(15):1413-1424

Empagliflozin Reduced eGFR Significantly less Over the Time vs Placebo



–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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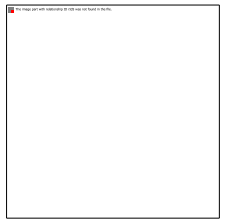
1-N. Engl. J. Med 2020. 8;383(15):1413-1424

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

	**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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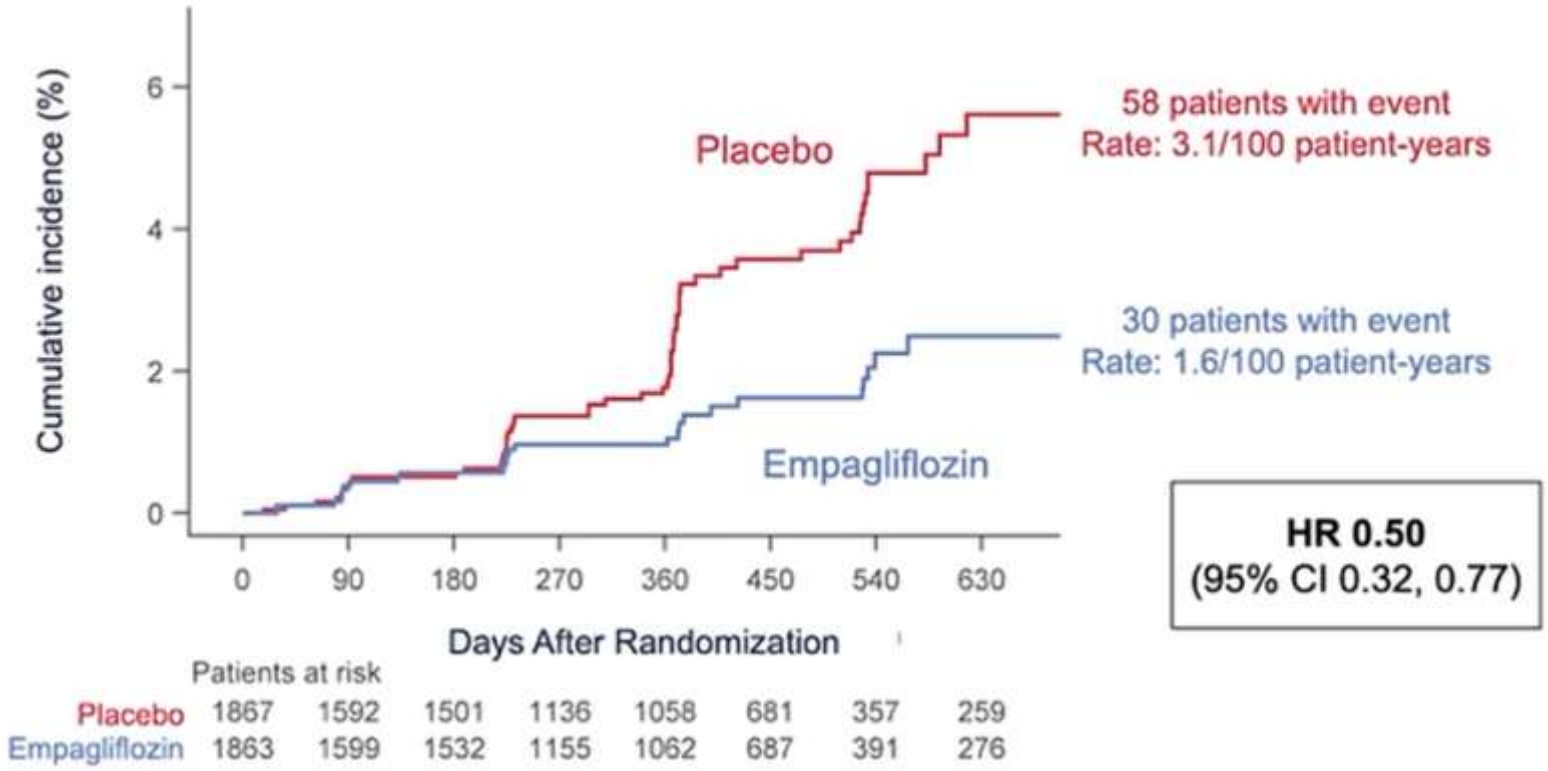
1-N. Engl. J. Med 2020. 8;383(15):1413-1424

Empagliflozin reduced composite renal endpoint by 50%



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

- ✓ 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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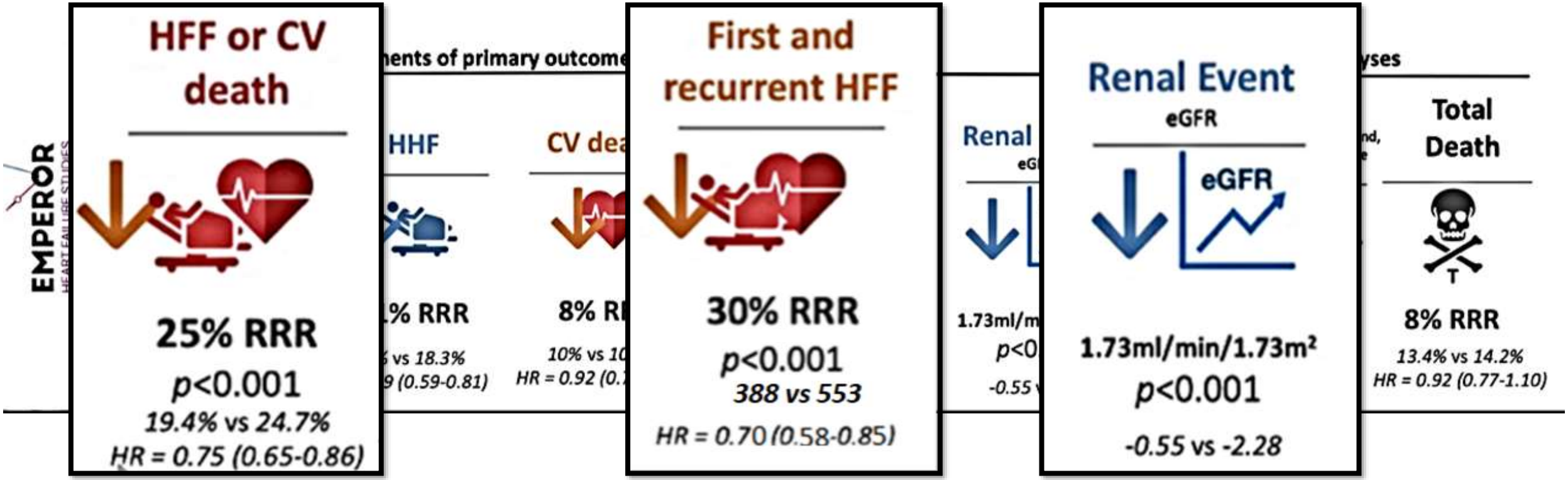
1-N. Engl. J. Med 2020. 8;383(15):1413-1424

Conclusion



- ✓ 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. 8;383(15):1413-1424

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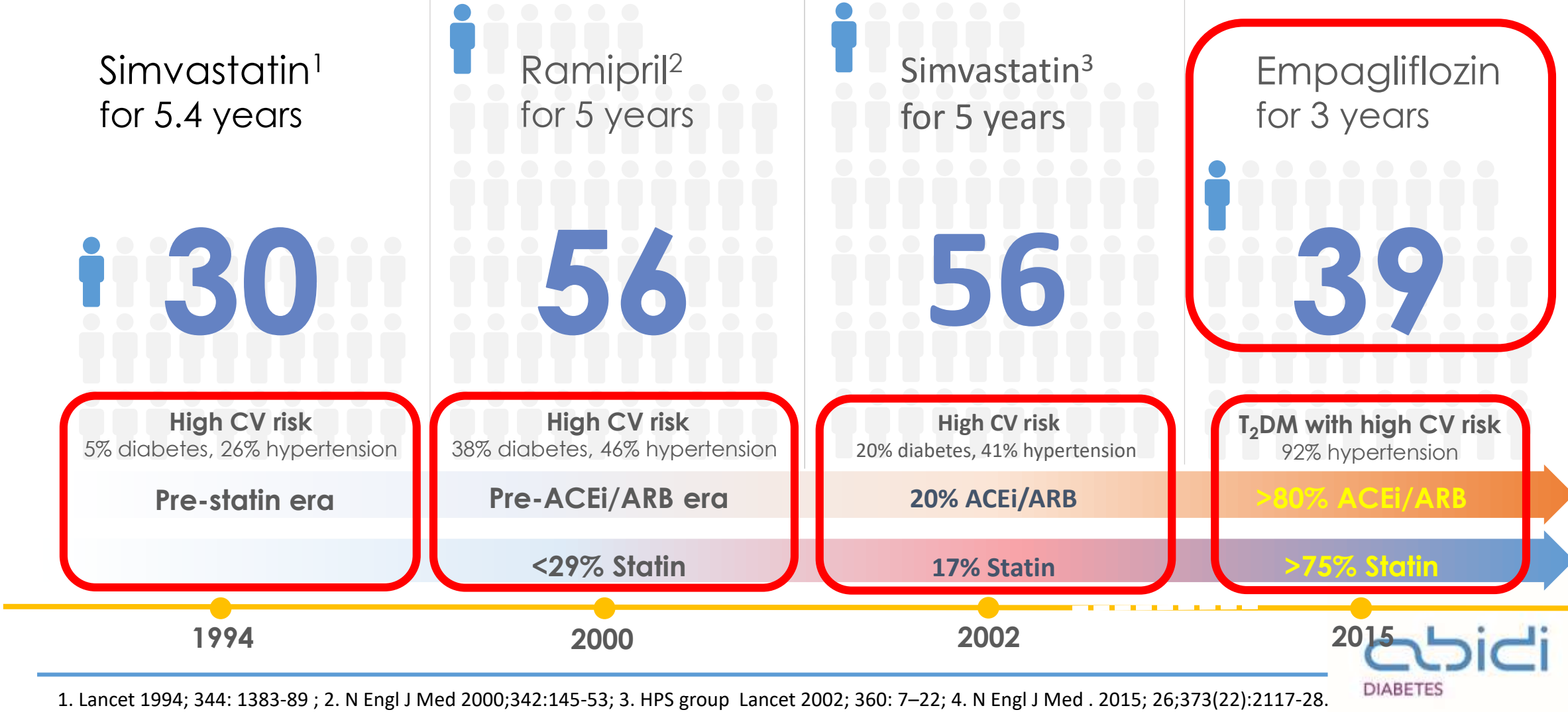
NNT to Prevent One Death Across Major Trials in Patients with High CV Risk



1. Lancet 1994; 344: 1383-89 ; 2. N Engl J Med 2000;342:145-53; 3. HPS group Lancet 2002; 360: 7–22; 4. N Engl J Med . 2015; 26;373(22):2117-28.

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

25

T2DM with high CV risk
92% hypertension

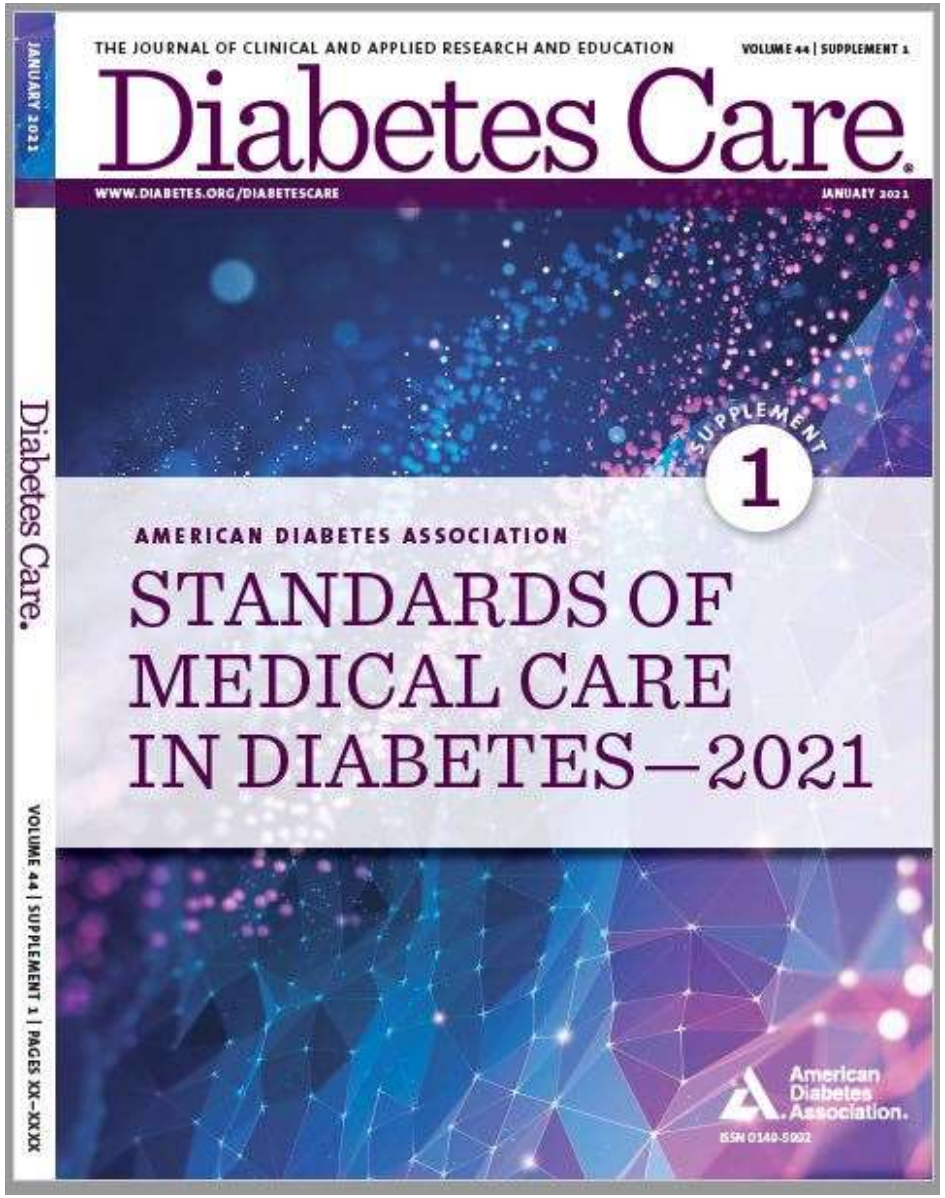
Pre-statin era | **Pre-ACEi/ARB era** | **20% ACEi/ARB** | **>80% ACEi/ARB**

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

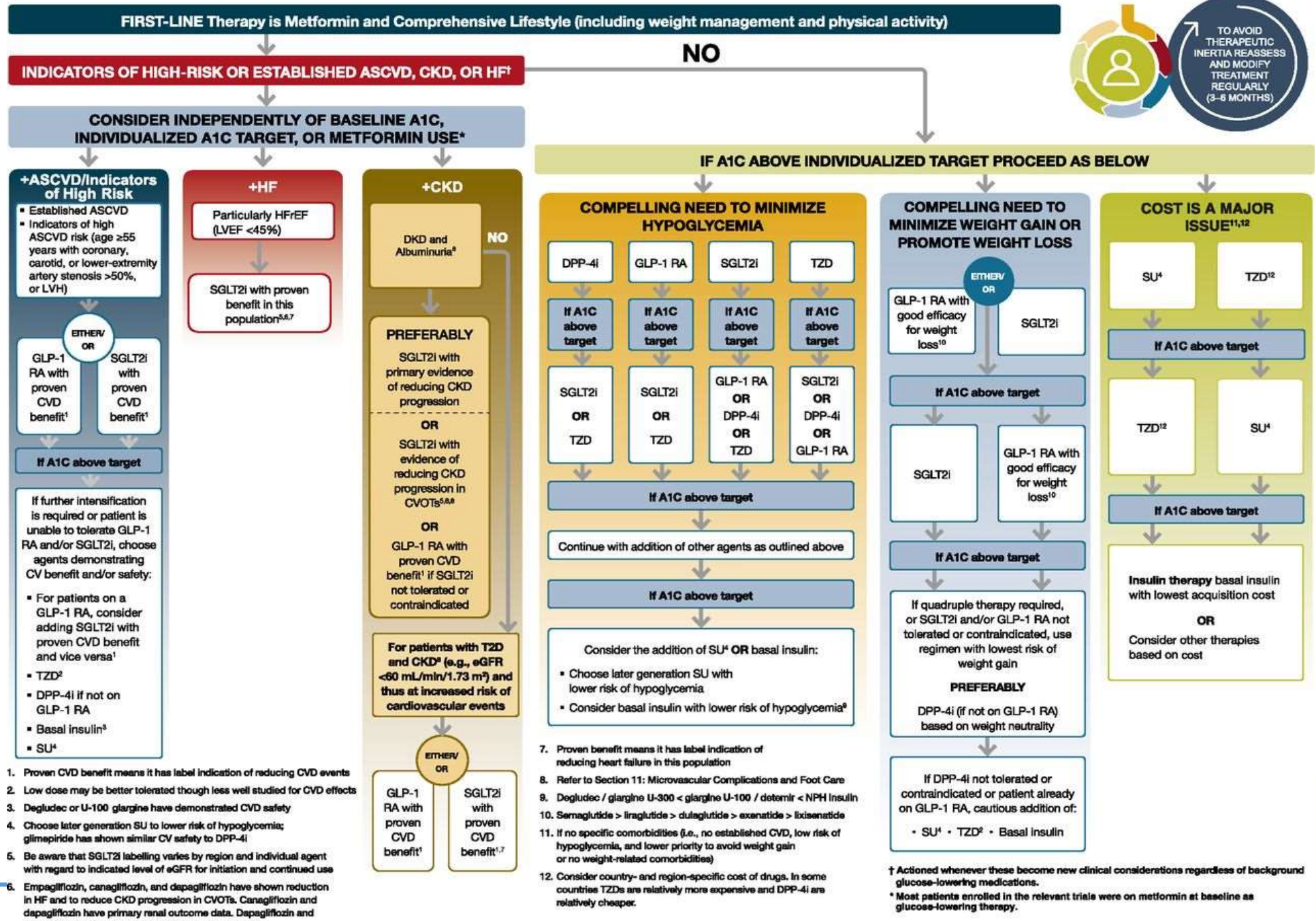
1994 — 2000 — 2002 — 2015

1. Lancet 1994; 344: 1383-89 ; 2. N Engl J Med 2000;342:145-53; 3. HPS group Lancet 2002; 360: 7–22; 4. N Engl J Med . 2015; 26;373(22):2117-28.

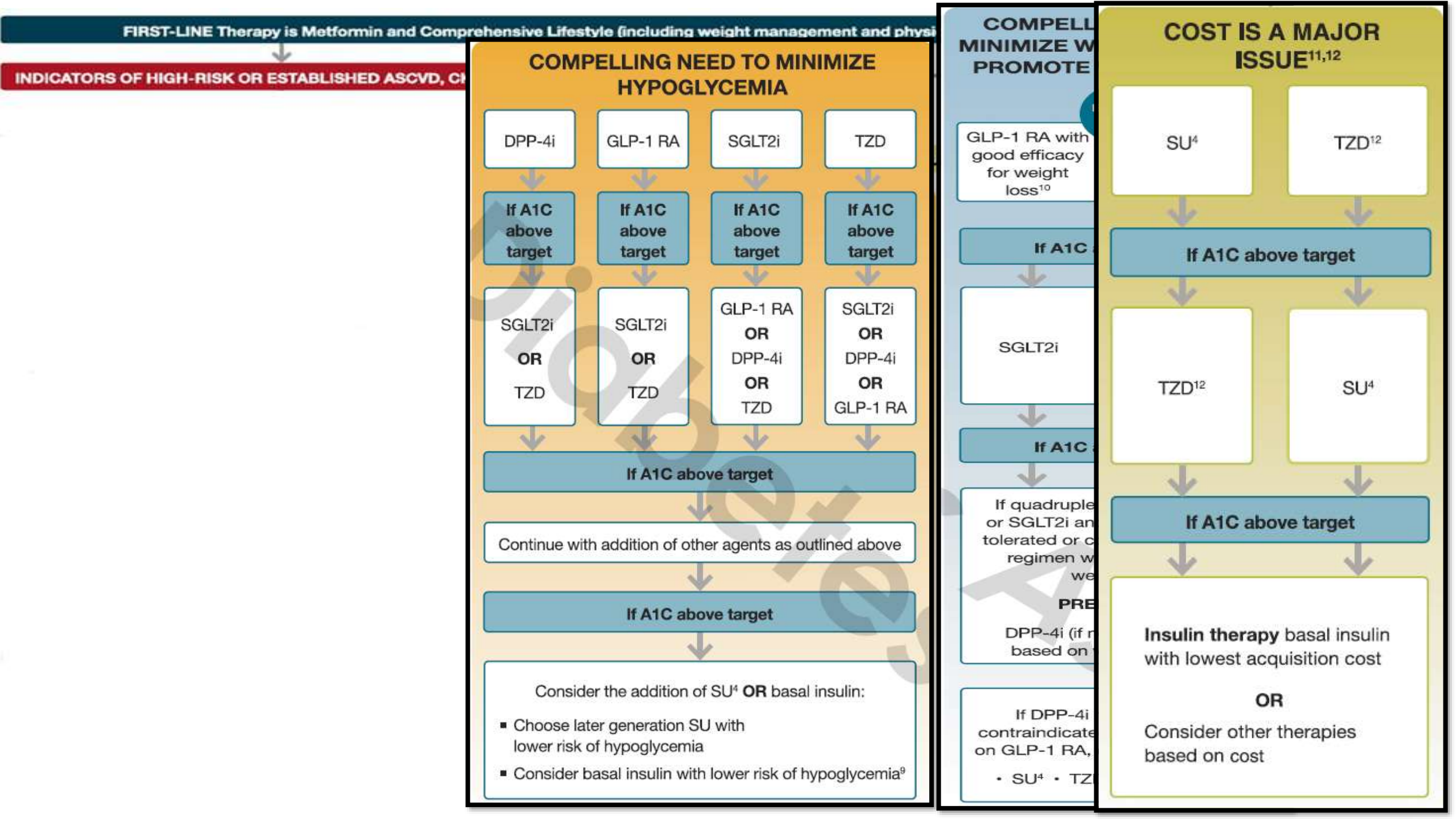
Diabetes Guidelines & New Recommendations



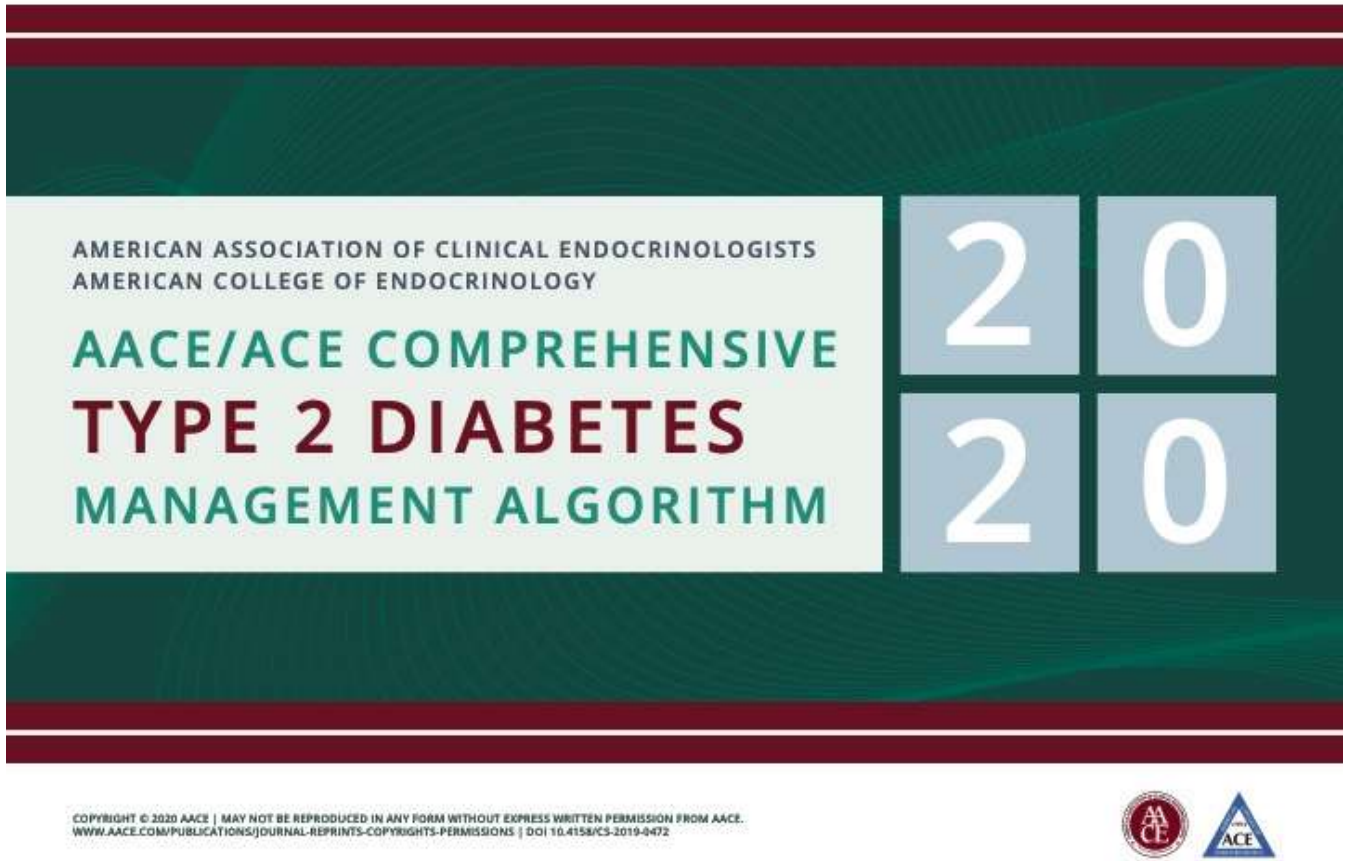
1-American Diabetes Association. standards of medical care in diabetes—2021. Diabetes Care. 2021 Jan



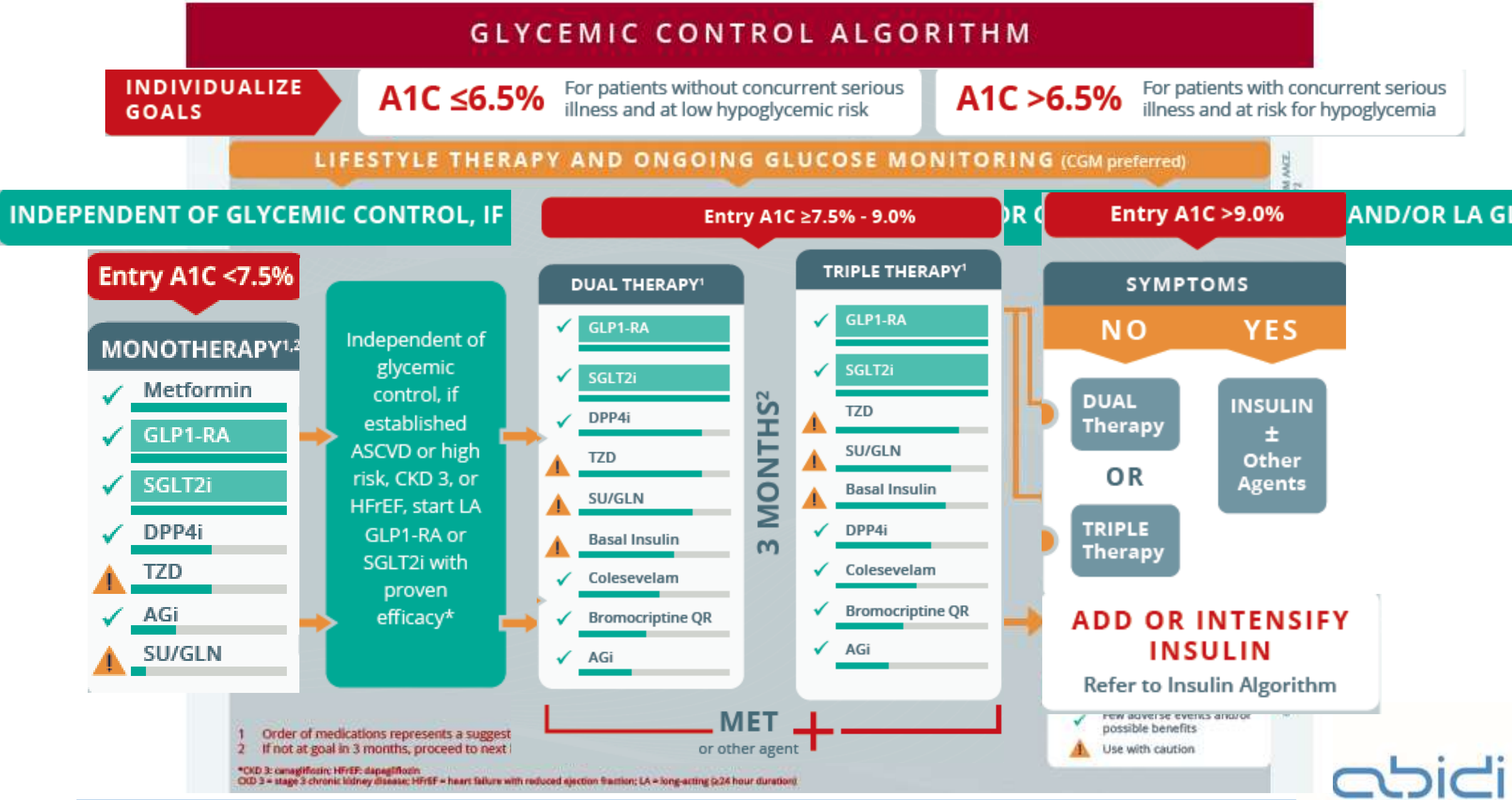
Diabetes Care 2021; 44(Suppl. 1):S111-S124.


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physi
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CI
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]
COMPELL
MINIMIZE W
PROMOTE
GLP-1 RA with good efficacy for weight loss[10]
If A1C
SGLT2i
If A1C
If quadruple or SGLT2i an tolerated or c regimen w we
PRE
DPP-4i (if r based on
If DPP-4i contraindicate on GLP-1 RA,
• SU[4] • TZ
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

Pharmacologic Approaches to Glycemic Treatment



Diabetes Management Algorithm*, Endocr Pract*. 2020;26(No. 1)



Diabetes Management Algorithm, *Endocr Pract*. 2020;26(No. 1)

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ESC European Society of Cardiology

European Heart Journal (2019) **00**, 1–69
doi:10.1093/eurheartj/ehz486

ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

European Heart Journal 2019; 00, 169

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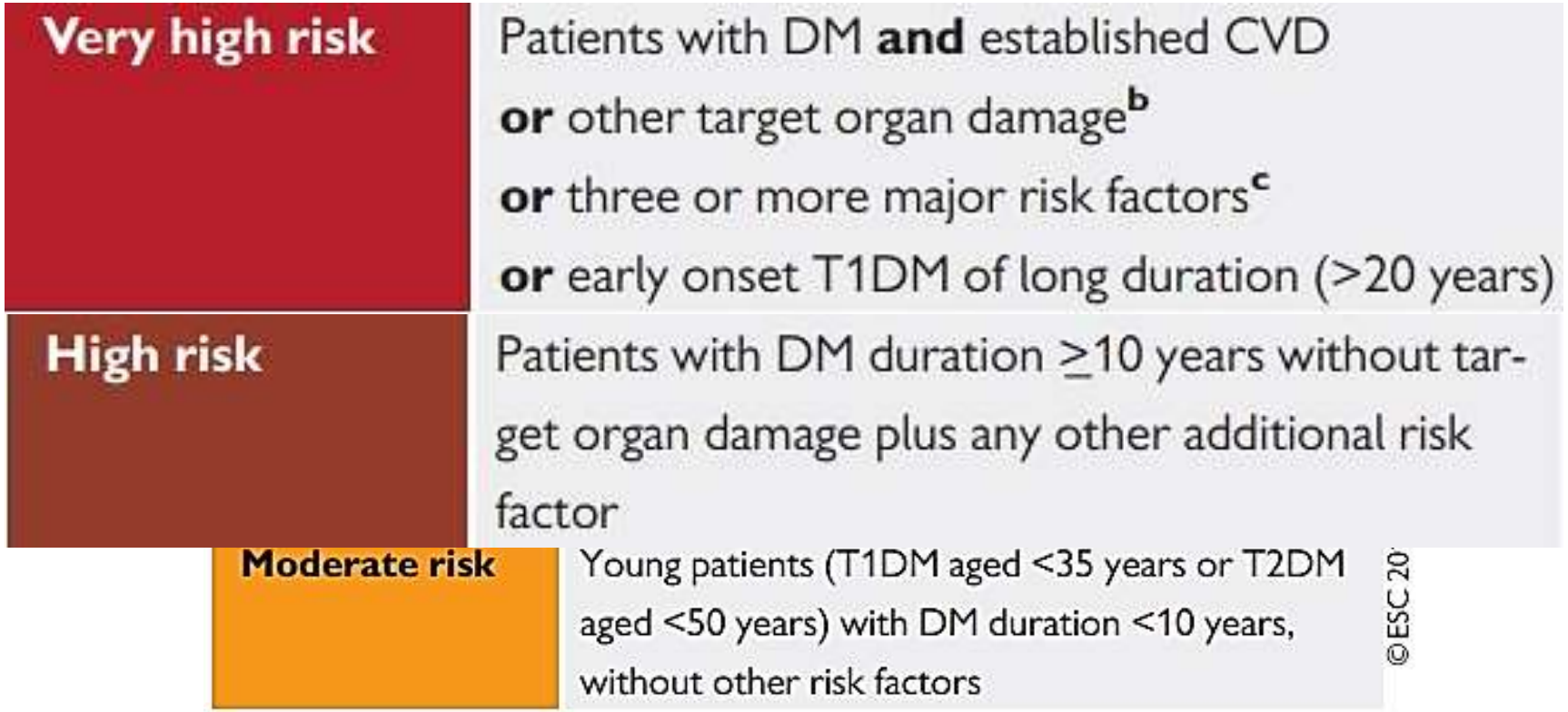
Cardiovascular risk categories in patients with diabetes



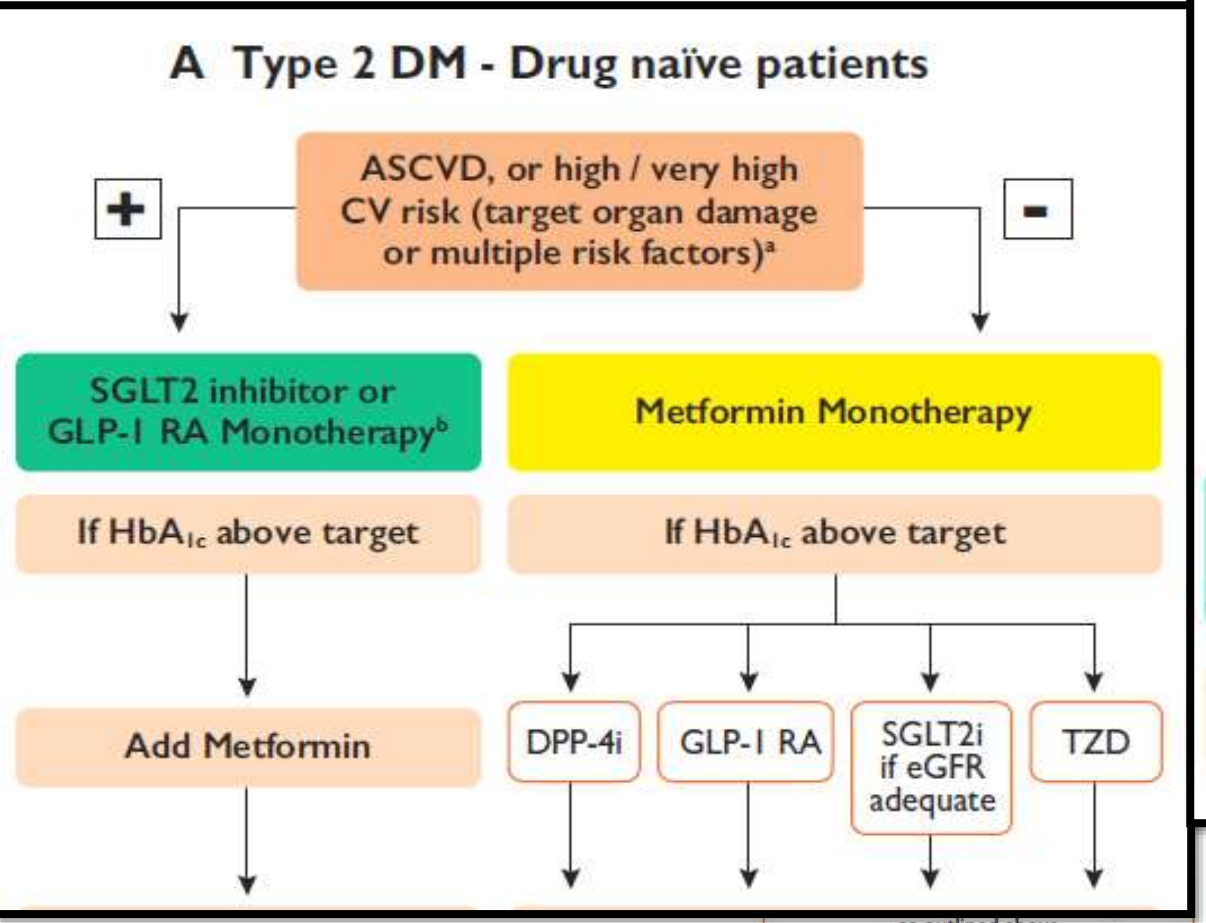
CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

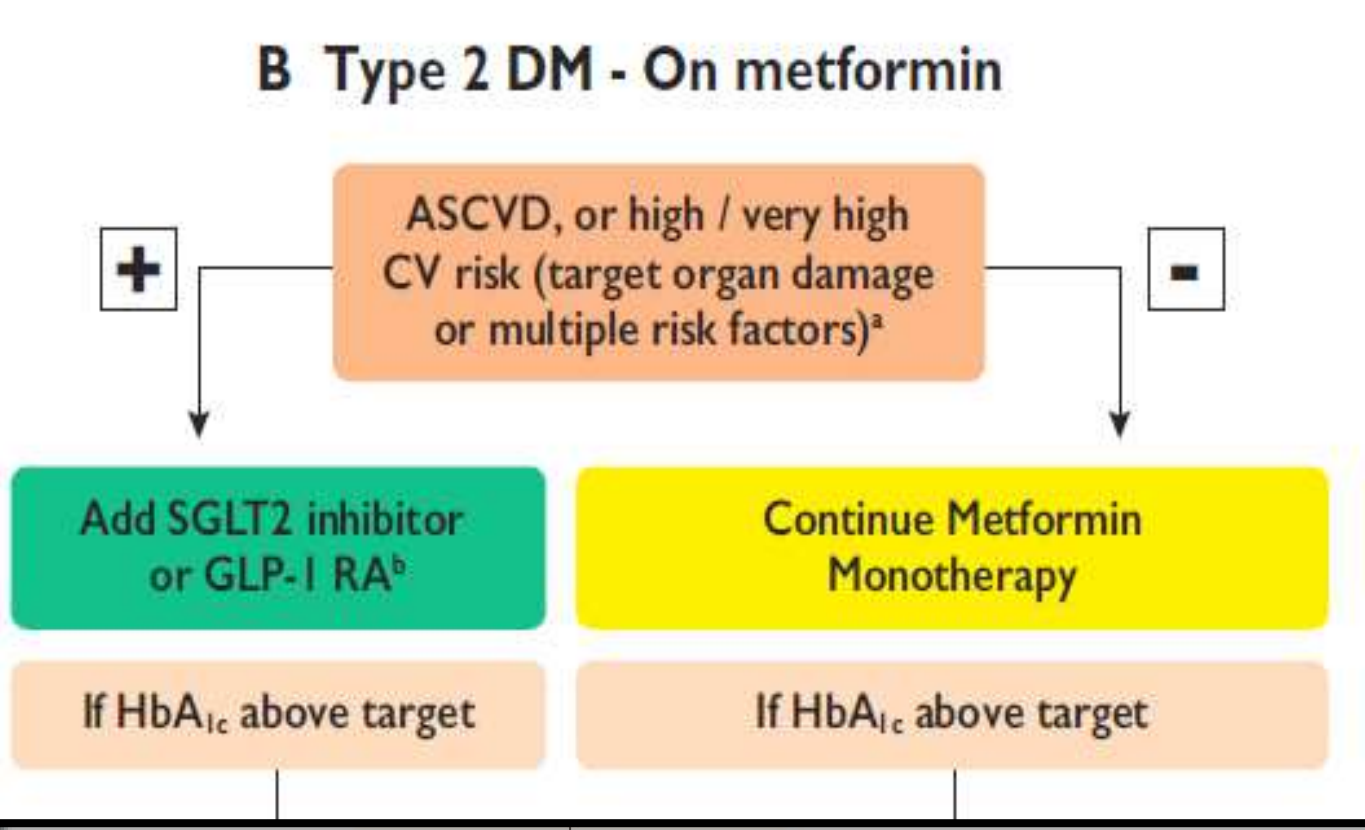
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]

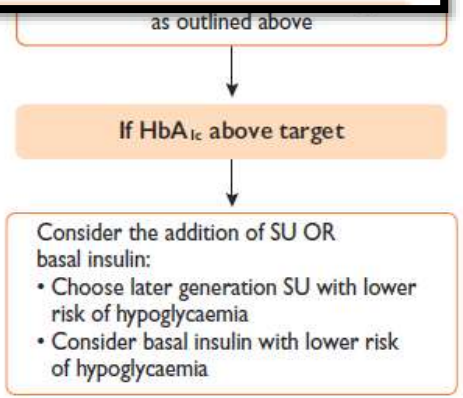
[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

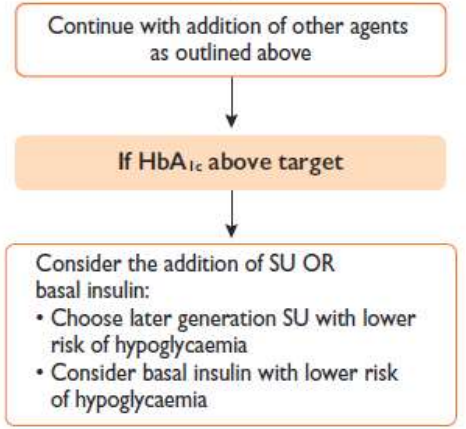
[c]Age, hypertension, dyslipidemia, smoking, obesity.

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.









European Heart Journal 2019; 00, 169

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GLP1-RA vs. SGLT2i [1-5]

Agent	Ease of use	Cost	ASCVD	NNT in CVOTs	↓ CKD progression	Use in HF	eGFR<30 ml/min	Glycemic efficacy	Weight loss
Liraglutide									
Empagliflozin									

1. N Engl J Med 2016; 375:323-334, 2. N Engl J Med 2017; 377:839-848, 3.The Lancet Diabetes & Endocrinology, 2016; 4(10), 812–814, 4. N Engl J Med 2016; 375:311-322,5. N Engl J Med 2015; 373:2117-2128

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Empagliflozin: **Dosage and Administration**

- **Contra-indicated in severe renal impairment / T1DM.**
- **Recommended starting dose: 10 mg once daily.**
- **For patients who tolerate 10 mg and need further glycaemic control, their dose can be increased to 25 mg once daily.**
- **Can be taken with/without food in the morning.**
- **Can be used alone or in combination with other common therapies:**
  - ***No clinically meaningful interactions were observed when Empagliflozin was co-administered with other commonly used medications, including pioglitazone***

Jardiance FDA label 2017
Jardiance (empagliflozin) Summary of Product Characteristics. Available at: https://www.medicines.org.uk/emc/medicine/28973 (accessed July 2016).

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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Conclusion

- Based on proven good efficacy, safety and also its ability to weight and blood pressure reduction, empagliflozin can play a unique role in the management of T2DM patients.

- In addition to its use as an anti-hyperglycemic agent, Empagliflozin have proven cardiac and renal benefits in patients with established or at high risk of ASCVD.

State of the art

Treat the patient Not his sugar

Reduce the CV risk Not only the HbA1c

The Changing Landscape of Diabetes Therapy
Improving outcomes in T2DM
Focus on cardiovascular & renal safety


Thank you