
IN THE NAME OF GOD

Pharmacologic Approaches to Glycemic Treatment ADA 2021 (Updates)

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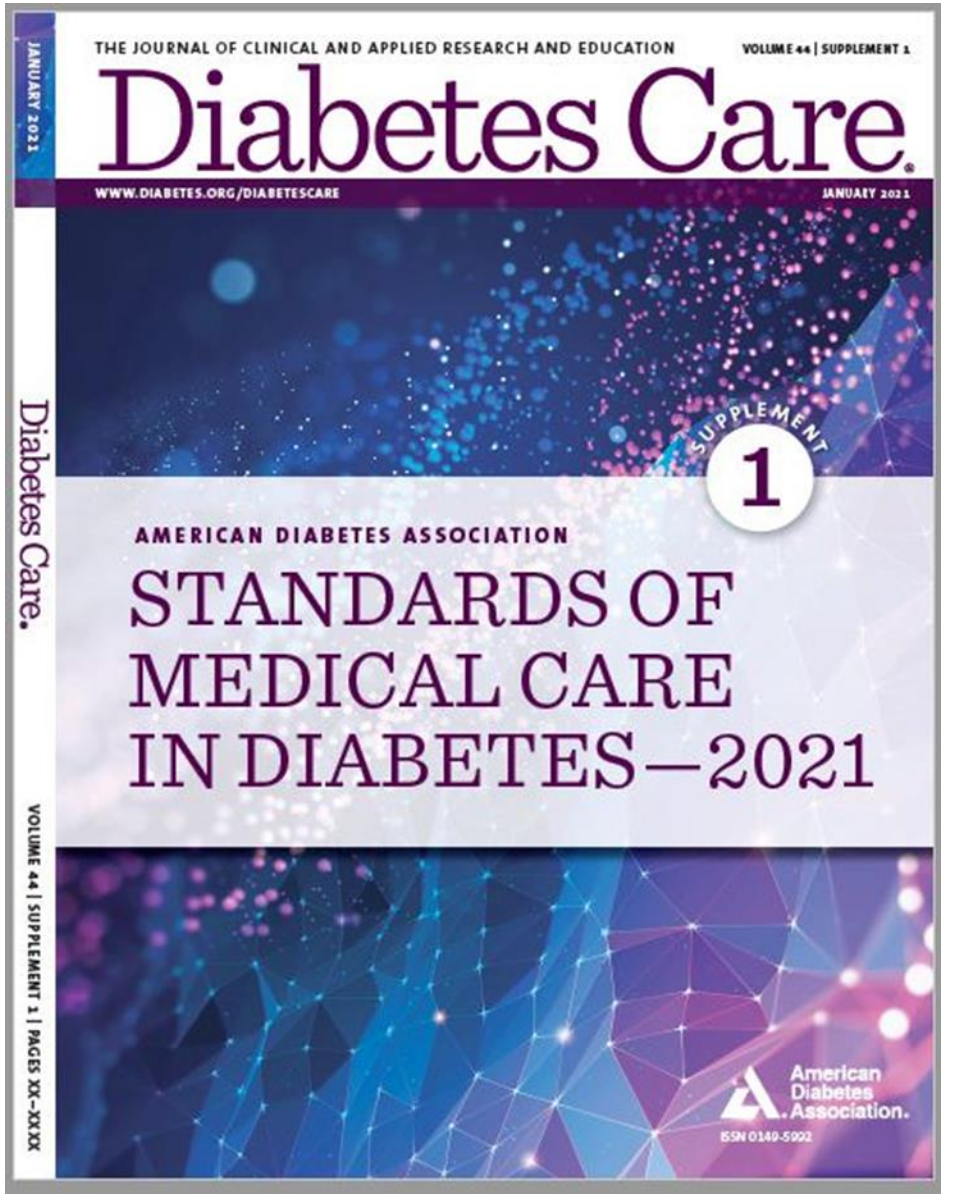
4th Tir , Isfahan

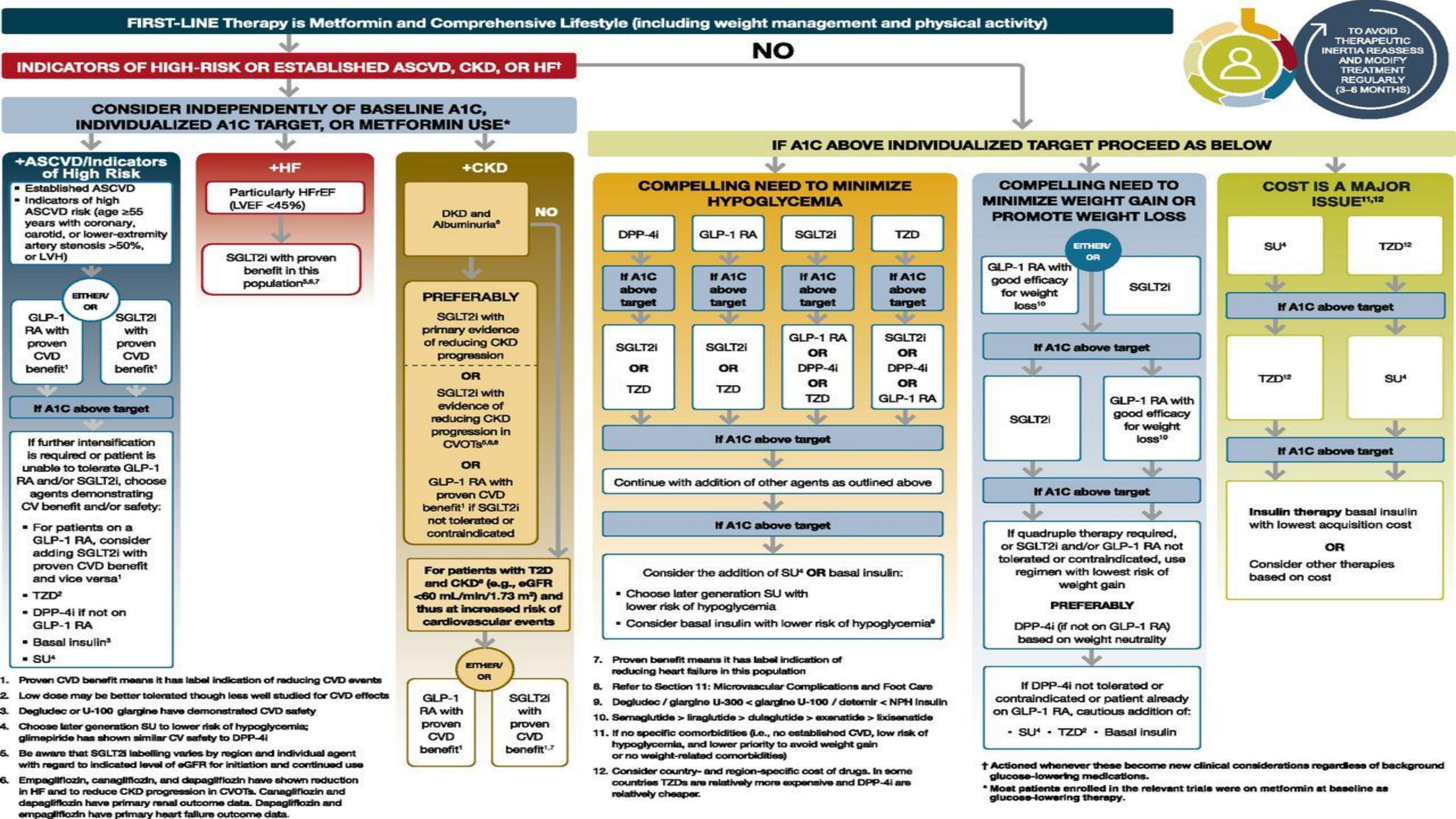
Objectives

- Pharmacologic Approaches to Glycemic Treatment **ADA 2021 (Updates)**
- Pharmacologic Approaches to Glycemic Treatment **KDIGO 2020 (Updates)**
- The Relation Between T2DM and Cardiovascular Disease
- Dosage & Administration of Empagliflozin

Pharmacologic Approaches to Glycemic Treatment



Pharmacologic Approaches to Glycemic Management: *Diabetes Care* 2021;44(Suppl.1):S100-S110.



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.

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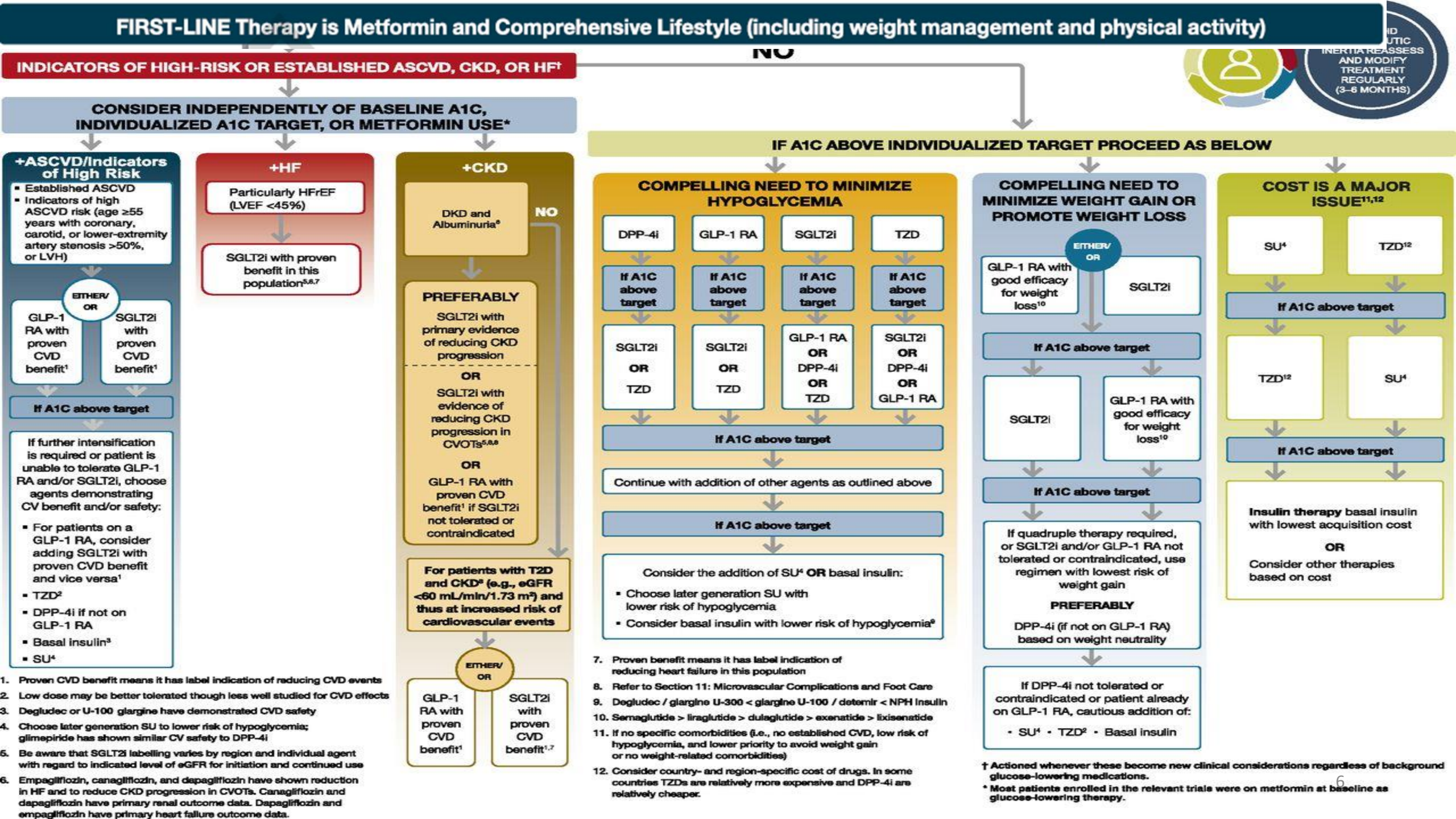

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FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

NO

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

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

INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

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[5,6,8]

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]

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

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

EITHER/OR

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

If A1C above target

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

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

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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

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PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

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COST IS A MAJOR ISSUE[11,12]

- SU[4]
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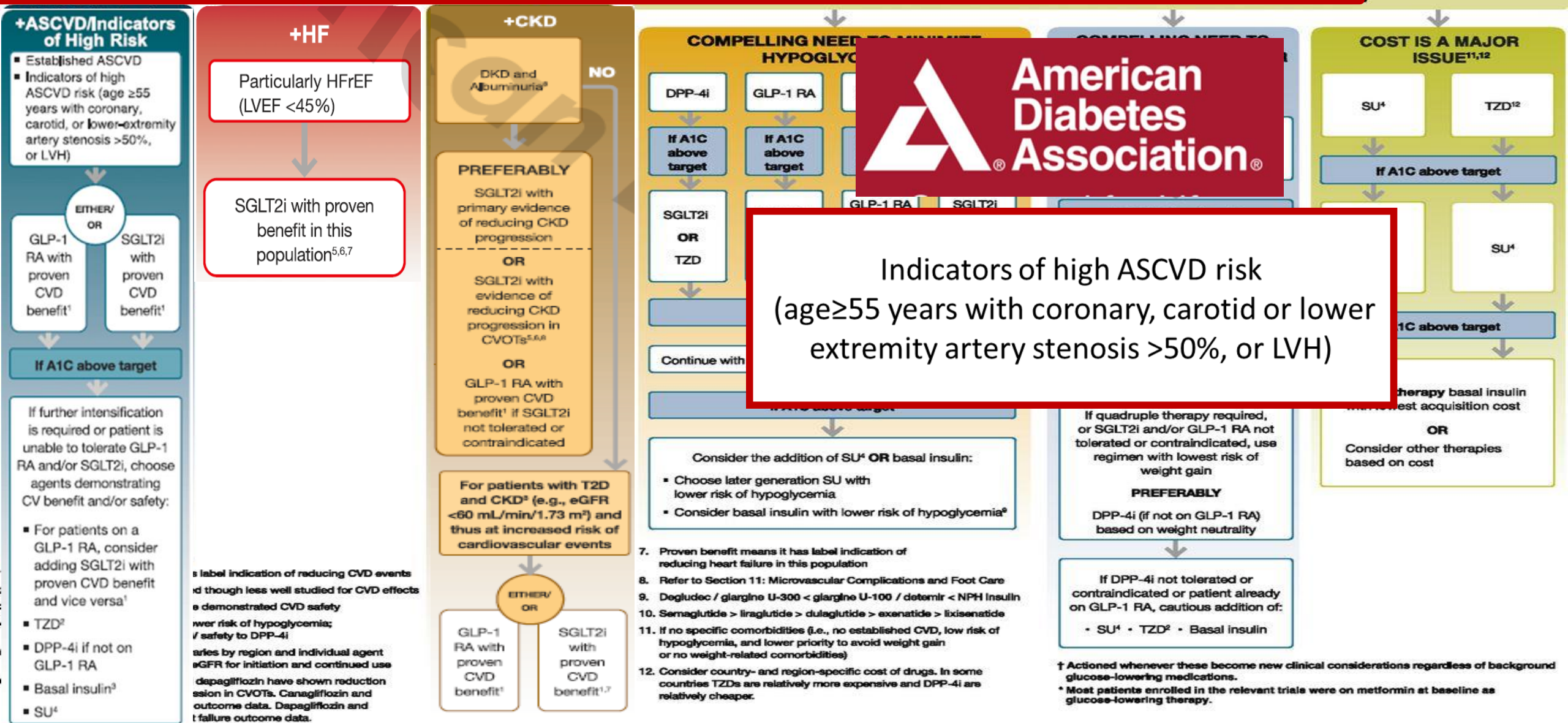

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SGLT2i

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COST IS A MAJOR ISSUE[11,12]

SU[4] TZD[12]

If A1C above target

TZD[12] SU[4]

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COST IS A MAJOR ISSUE[11,12]

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

NO

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

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

+ASCVD/Indicators of High Risk

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid, or lower-extremity artery stenosis >50%, or LVH)

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[5,6,8]

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]

IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW

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

EITHER/OR

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

If A1C above target

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

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.

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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

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SU[4]	TZD[12]
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8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
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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.

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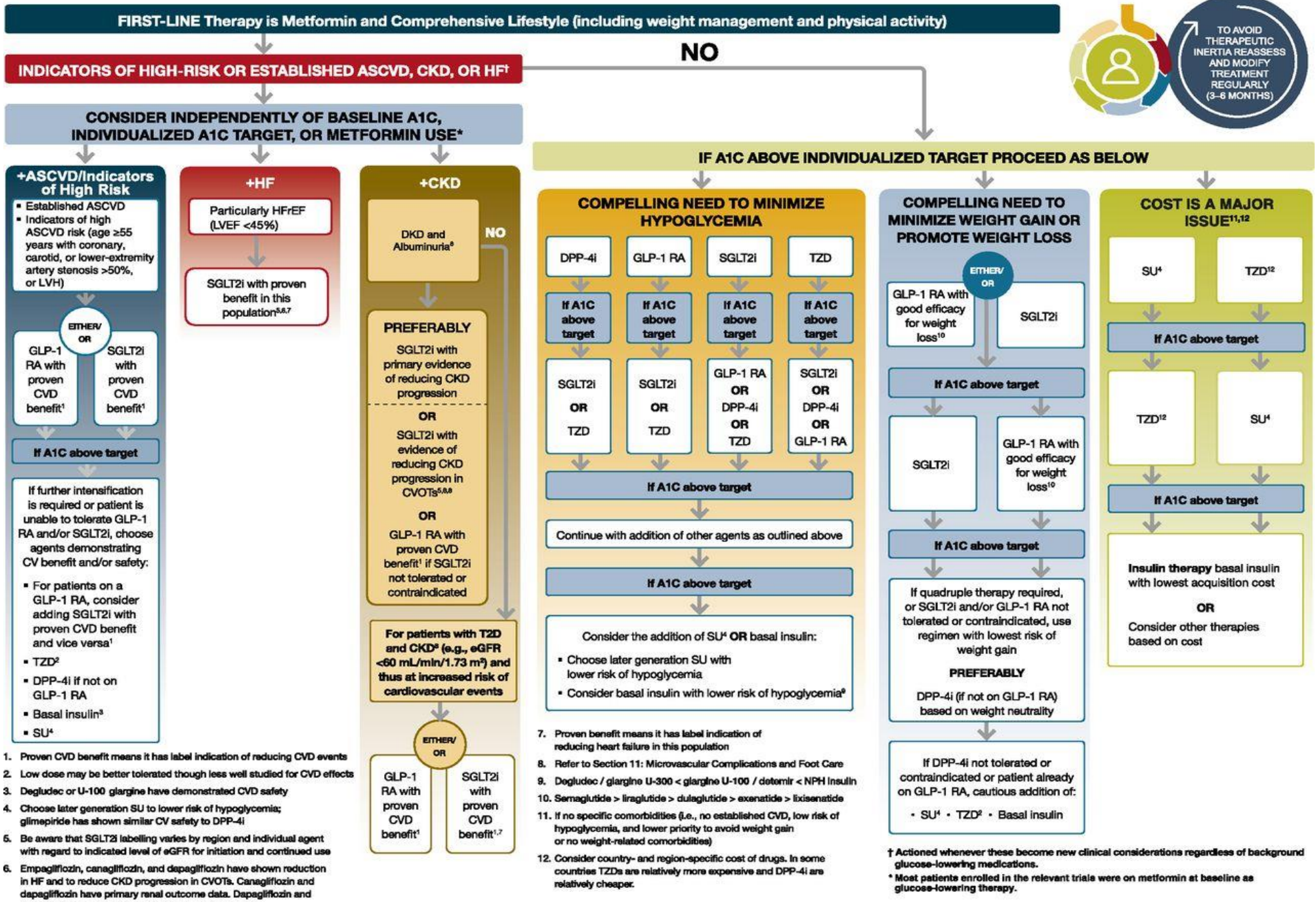

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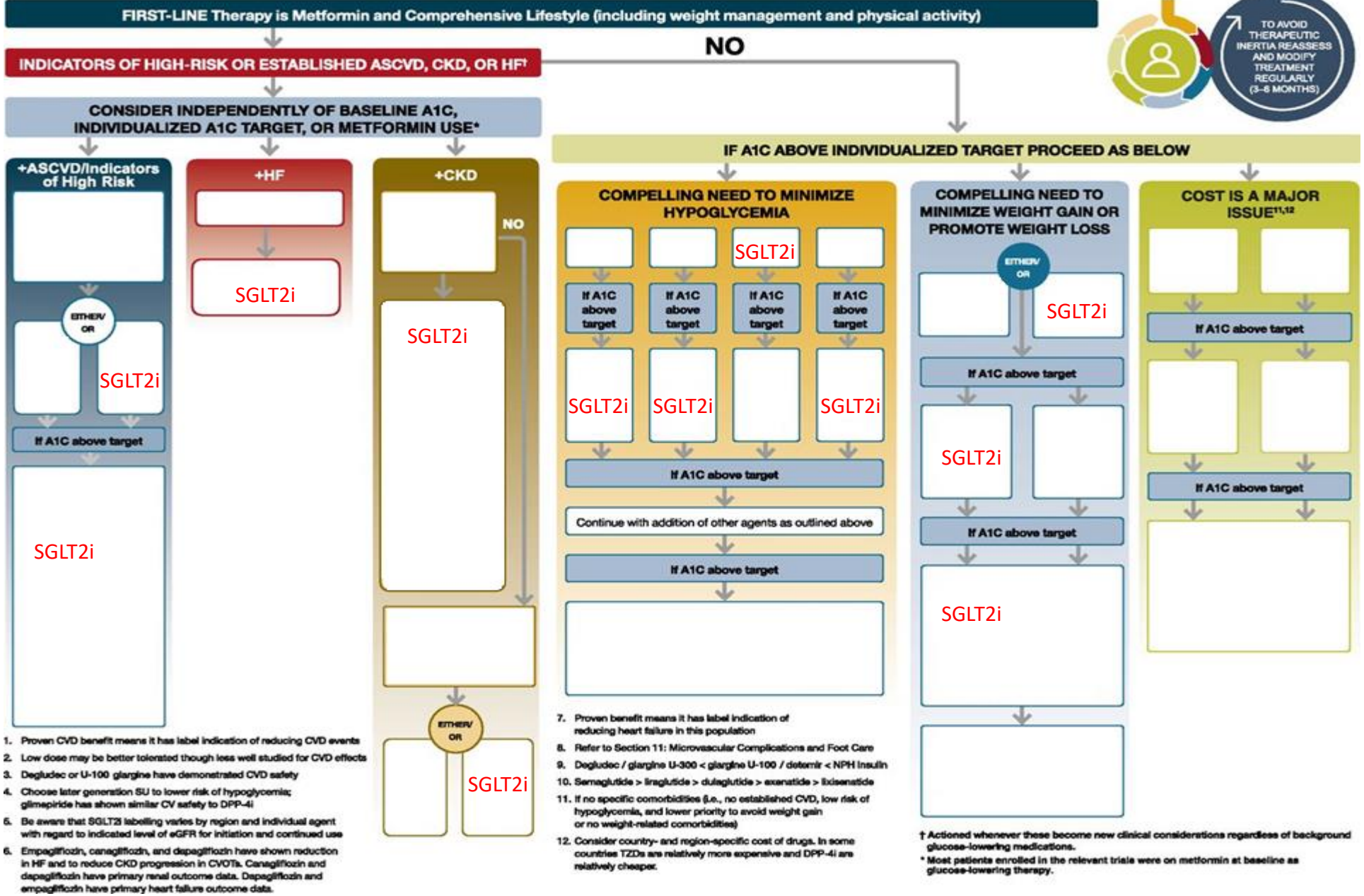
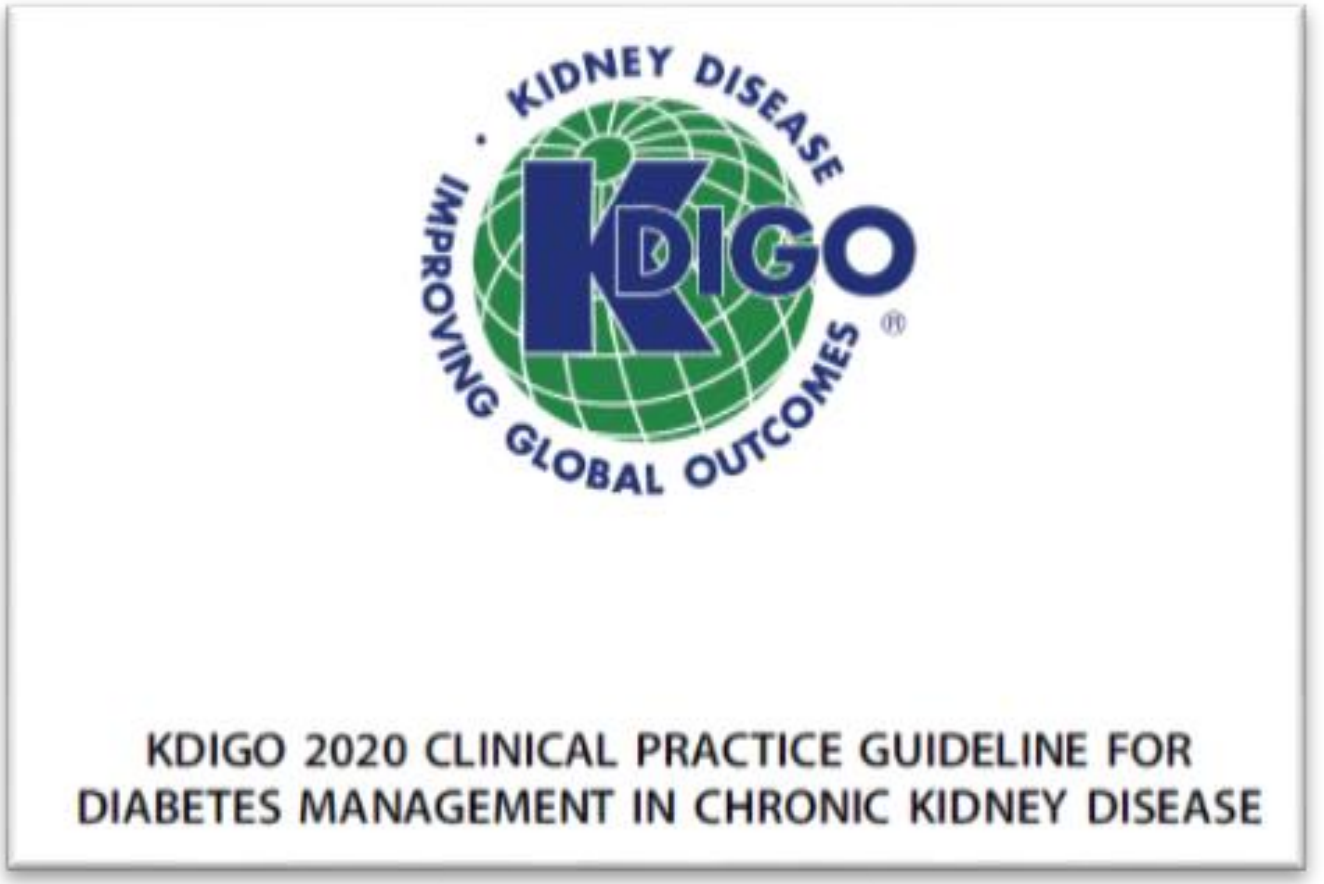
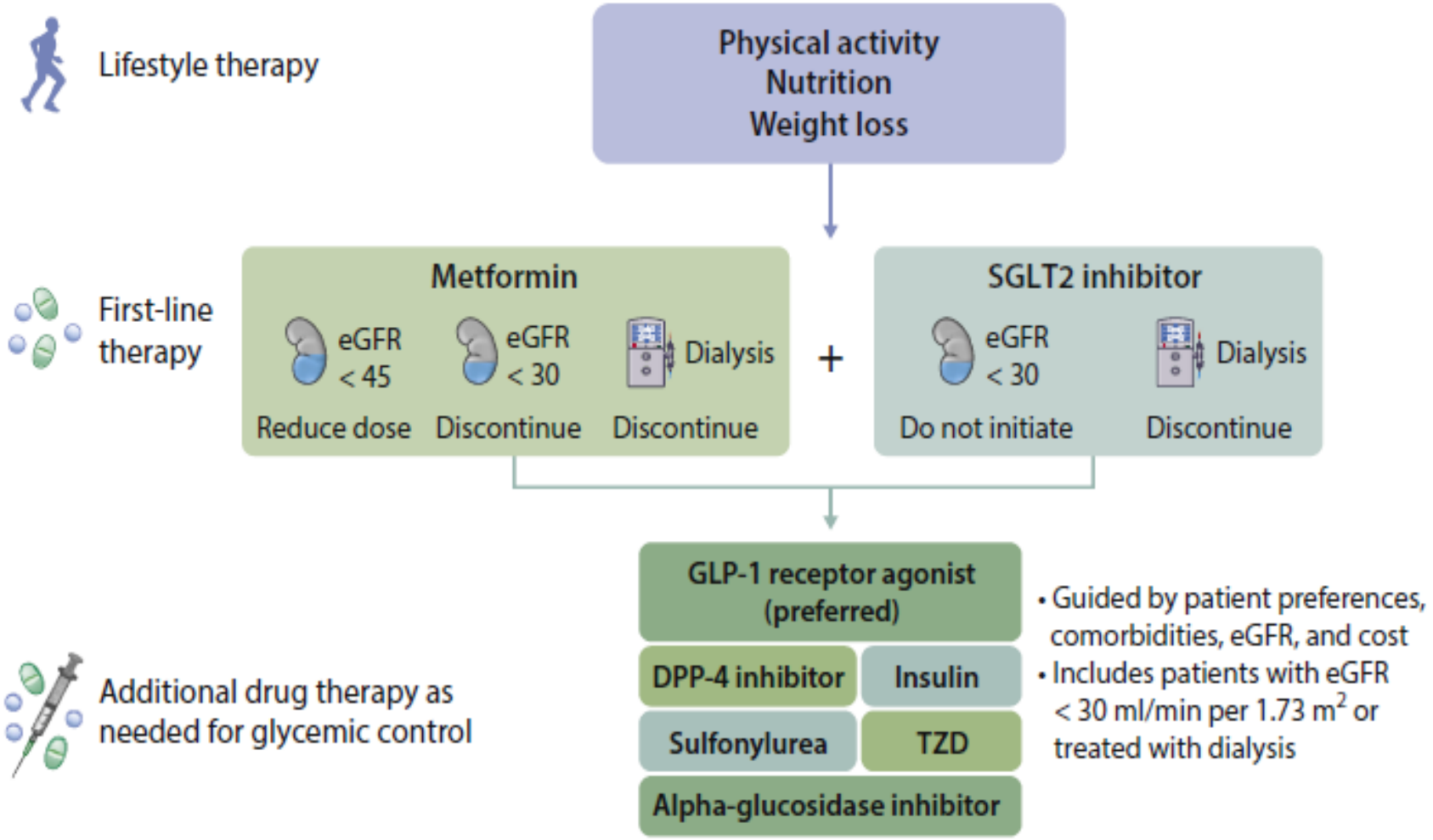


Diabetes Care 2021; 44(Suppl. 1):S111-S124.



Kidney Int. 2020; 98(4S): S1-S115

KDIGO Guideline:
SGLT2 Inhibitors and Metformin Combination Are Recommended as First-Line Therapy for T2D and CKD[1]



1- Kidney Int. 2020; 98(4S): S1-S115

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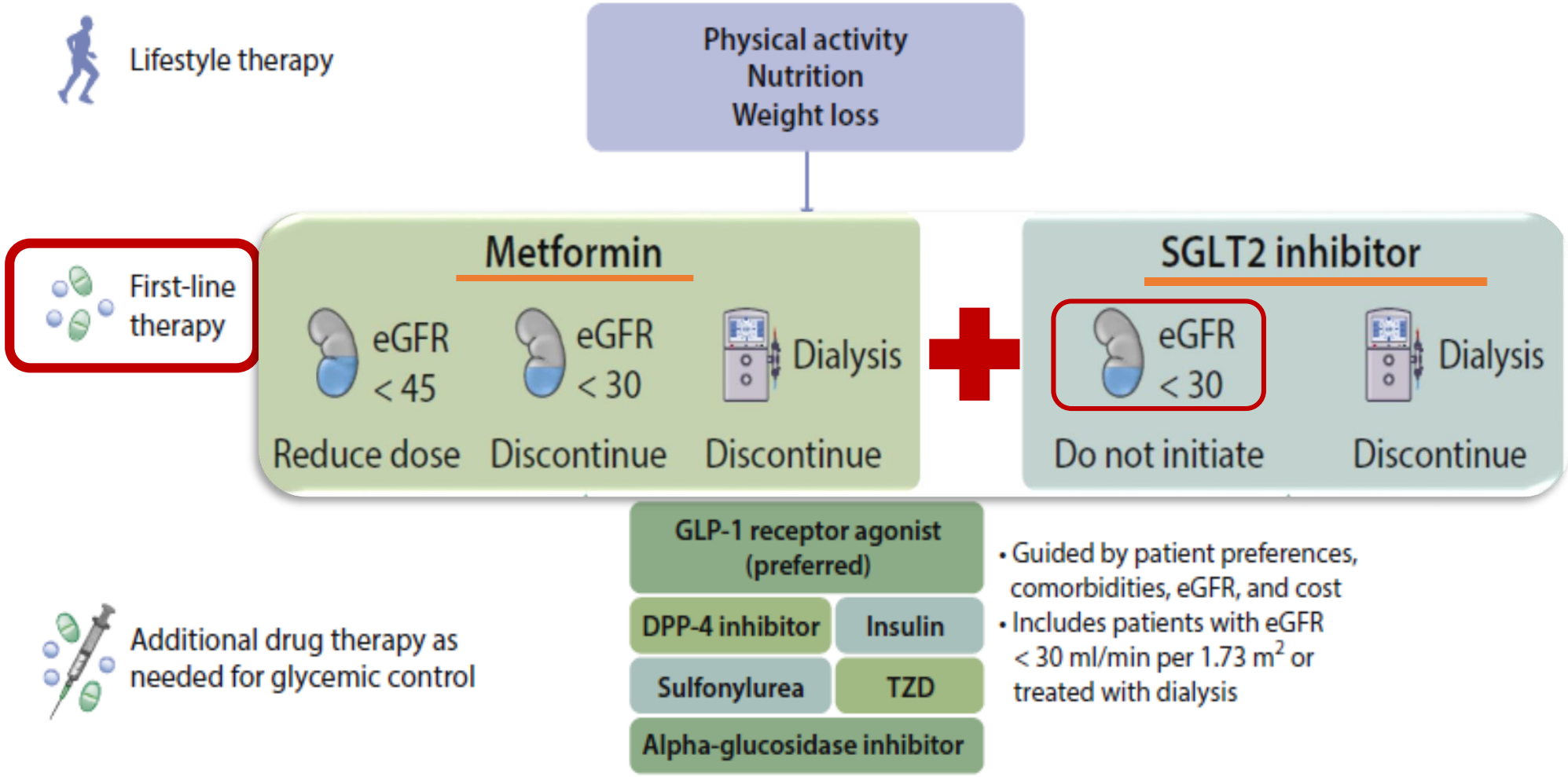


1- Kidney Int. 2020; 98(4S): S1-S115

KDIGO Guideline Recommends Practical Points for Type 2 Diabetes Management in Chronic Kidney Disease[1]

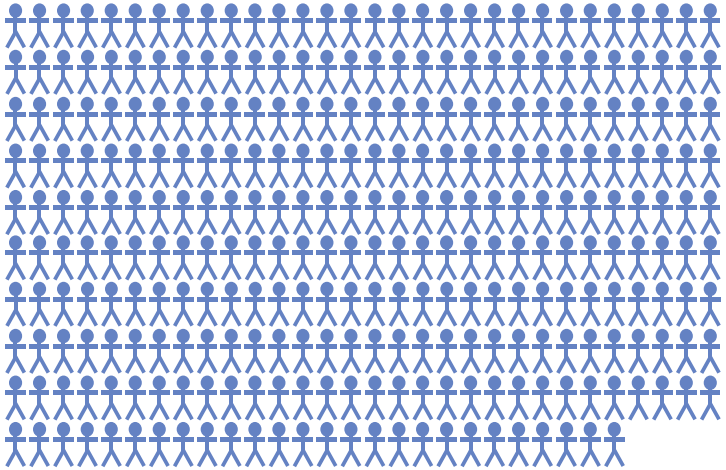
- Most patients with T2DM, CKD, and eGFR ≥ 30ml/min per 1.73 m^2 would benefit from treatment with both **Metformin** and an **SGLT2i**.[1]
- Treating patients with T2DM, CKD, and an **eGFR ≥ 30** ml/min per 1.73 m^2 with an SGLT2i.[1]
- Once an SGLT2i is initiated, it is reasonable to continue an SGLT2i **even if the eGFR falls below 30 ml/min per 1.73 m^2**, unless it is not tolerated or kidney replacement therapy is initiated.[1]

1- Kidney Int. 2020; 98(4S): S1-S115.
KDIGO: Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease;

The Relation Between T2DM and Cardiovascular Disease

T2D Is Increasingly Prevalent and CVD Is the Leading Cause of Death in this Population[1-3]

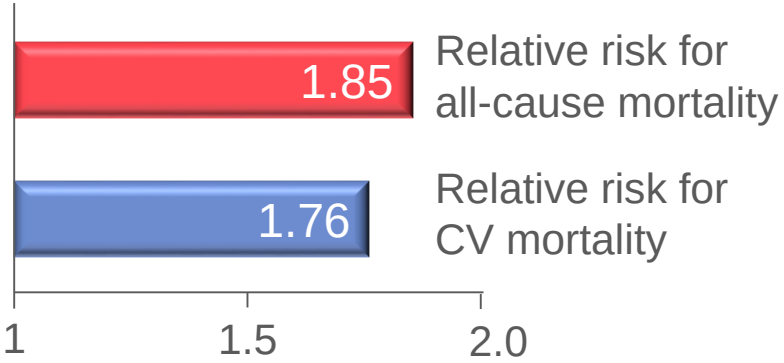
- Globally, 463 million people are living with diabetes[1]



- Rising to 592 million by 2035[1]

Represents 2 million people.
Diabetes is mostly (85–95%) T2D.[1]

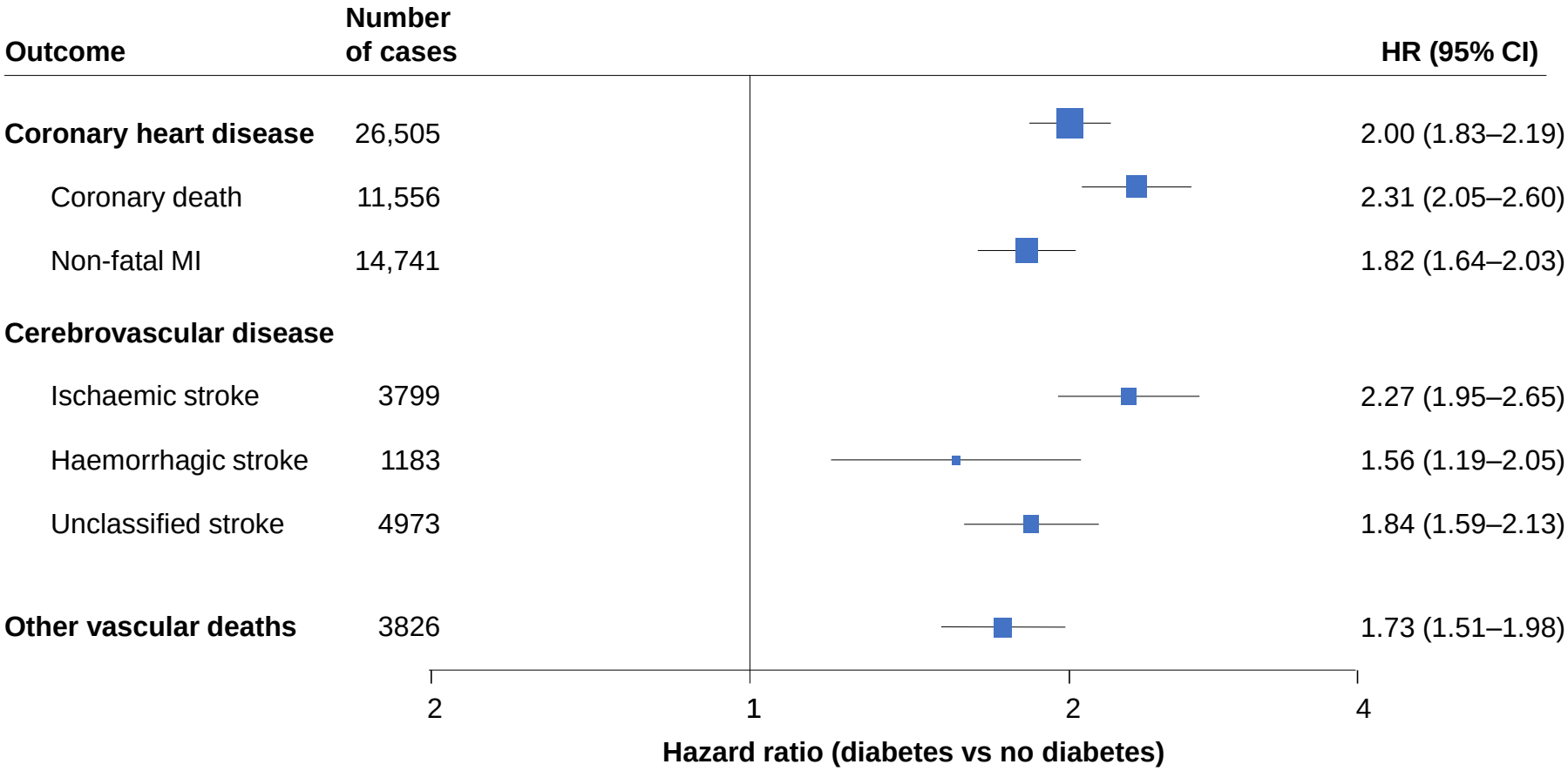
- T2D approximately doubles the risk of death[2]



- The number of deaths resulting from diabetes and its complications in 2019 is estimated to be 4.2 million.[1]
- CVD is the principal cause of death in T2D[2,3]

1- IDF Diabetes Atlas. 2019; 9th edition. 2- Br J Diabetes Vasc Dis 2013;13:192–207. 3-Cardiovasc Diabetol. 2018. 8;17(1):83.

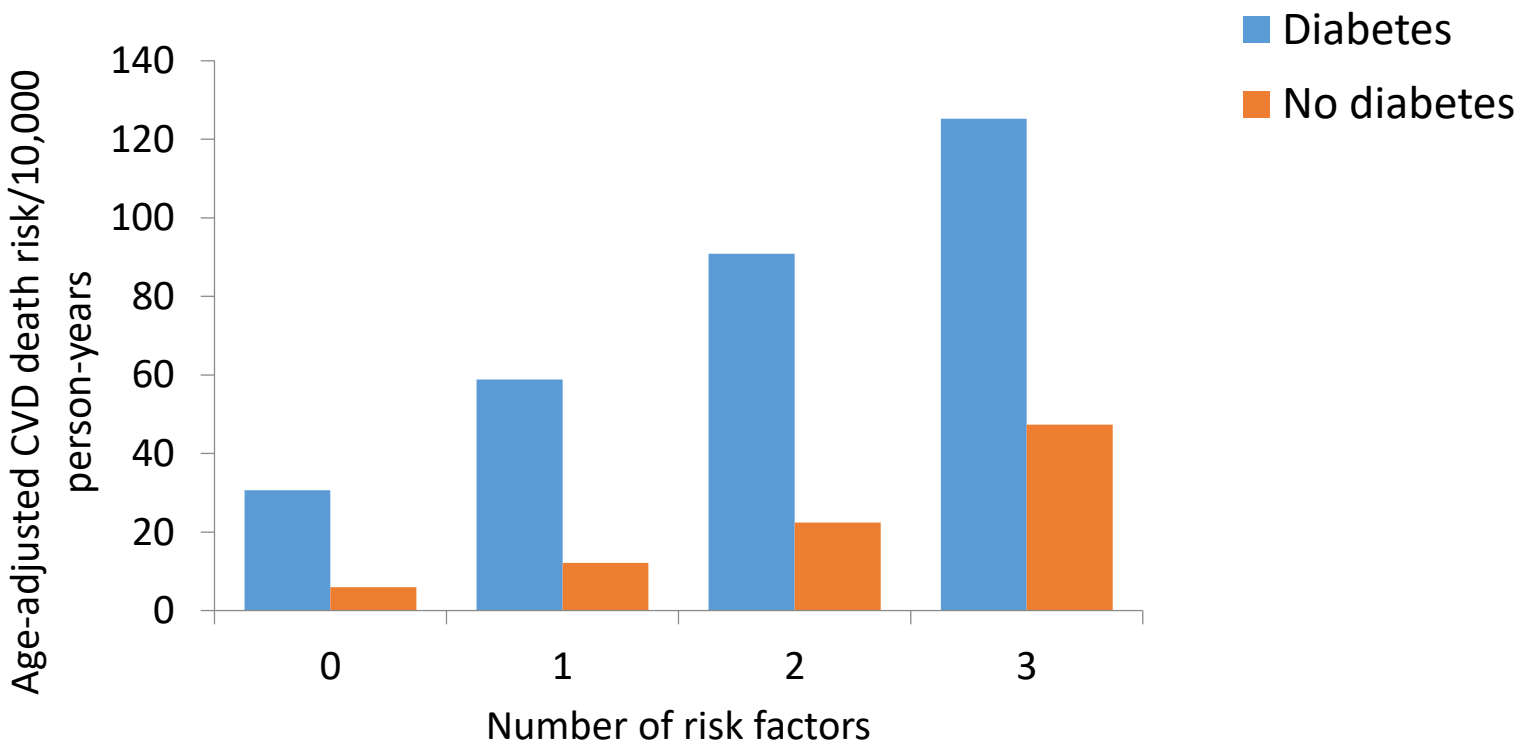
Diabetes Doubles the Risk of Vascular Events[1]



Diabetes confers about a two-fold excess risk for a wide range of vascular diseases, independently from other conventional risk factors.

1-Lancet 2010;375(9733):2215–2222.

CV Death Is Increased in Patients with Diabetes and Multiple Risk Factors[1]

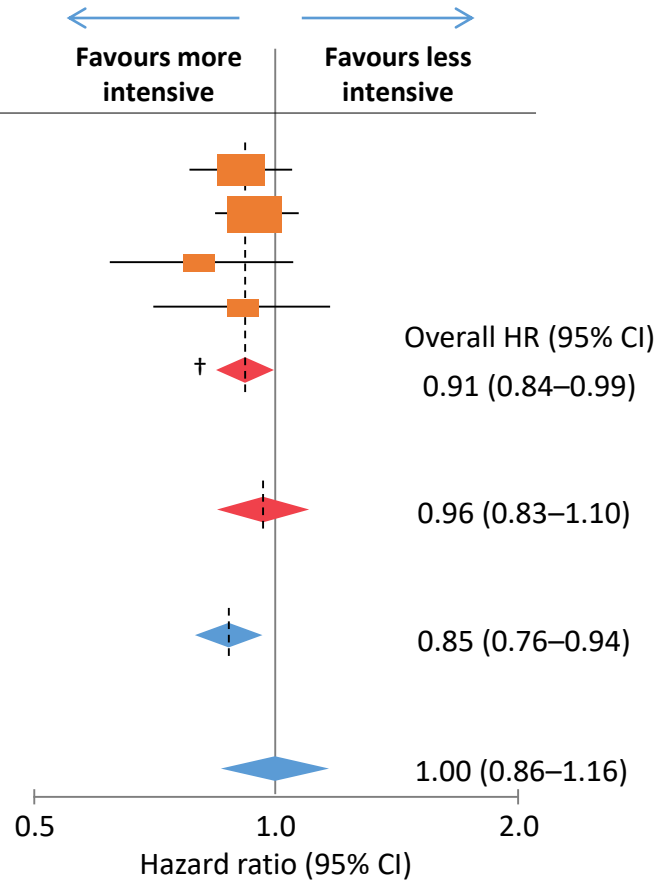


Risk factors were serum cholesterol ≥200 mg/dL, current smoker, SBP ≥120 mmHg

1- Diabetes Care 1993;16:434.

Intensive Glycaemic Control Has Modest Benefits On Macrovascular Risks[1]

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA_{1c} (%)
Major cardiovascular events*			
ACCORD	352 (2.11)	371 (2.29)	-1.01
ADVANCE	557 (2.15)	590 (2.28)	-0.72
UKPDS	169 (1.30)	87 (1.60)	-0.66
VADT	116 (2.68)	128 (2.98)	-1.16
Overall	1194	1176	-0.88
Stroke			
Overall	378	370	-0.88
Myocardial infarction			
Overall	730	745	-0.88
Hospitalised/fatal heart failure			
Overall	459	446	-0.88



- A beneficial effect on macrovascular risk of more intensive glycaemic control in patients with T2D has not been demonstrated in an individual prospective randomised controlled trial, but meta-analysis reveals a small benefit of more intensive glycaemic control on the risk of major CV events.

*Major CV events = CV death or non-fatal stroke or non-fatal MI.
Meta-analysis including 27,049 participants and 2370 major vascular events
†Diamonds incorporate point estimate (vertical dashed line) and encompass 95% CI of overall effect for each outcome.
1- Diabetologia 2009;52:2288–98.

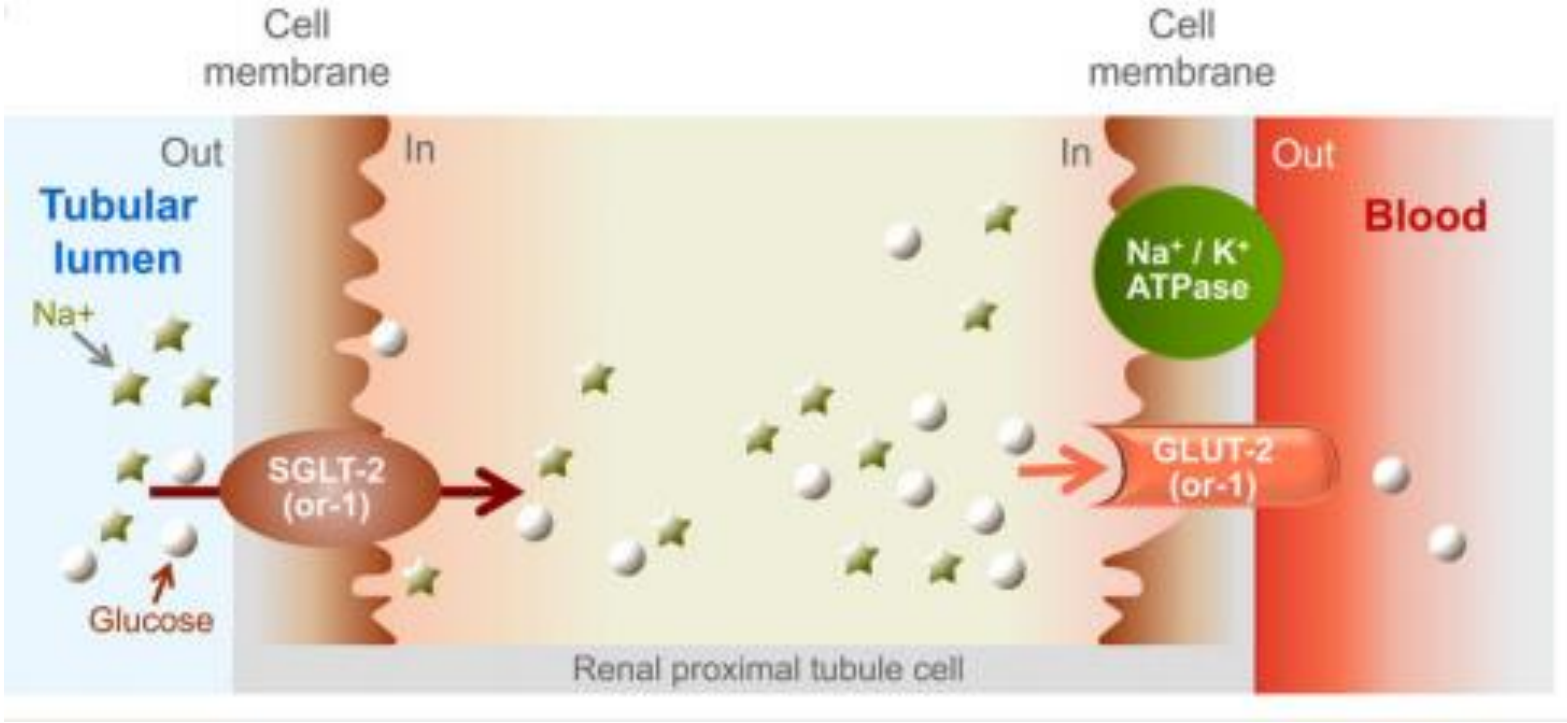
SGLT2 & SGLT2 Inhibitors Introduction

Glucose Transporters

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

facilitative glucose transporters (GLUTs)

sodium-dependent glucose transporters (SGLTs)



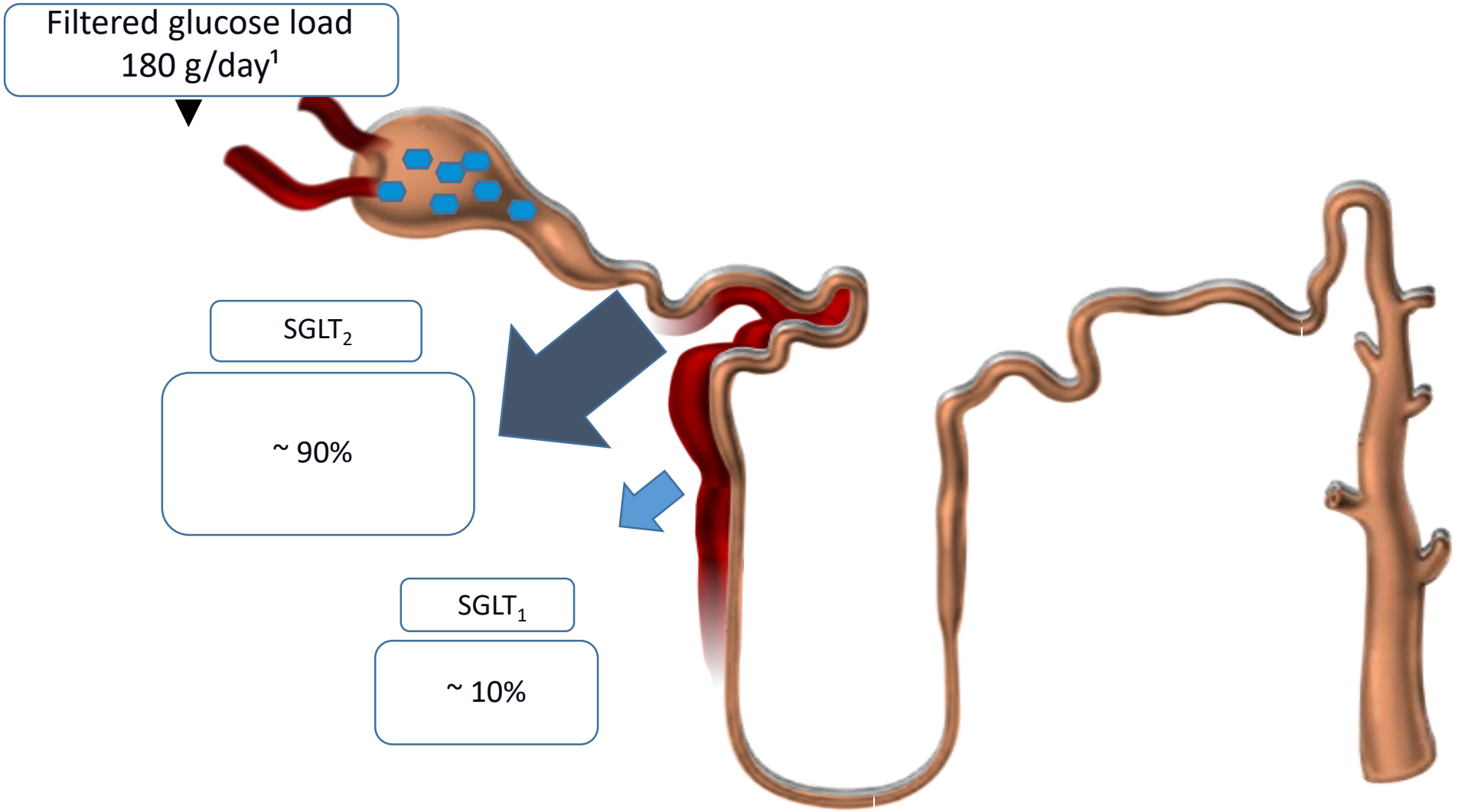
$SGLT_1$: low capacity, high affinity, mostly in intestine

$SGLT_2$: 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.

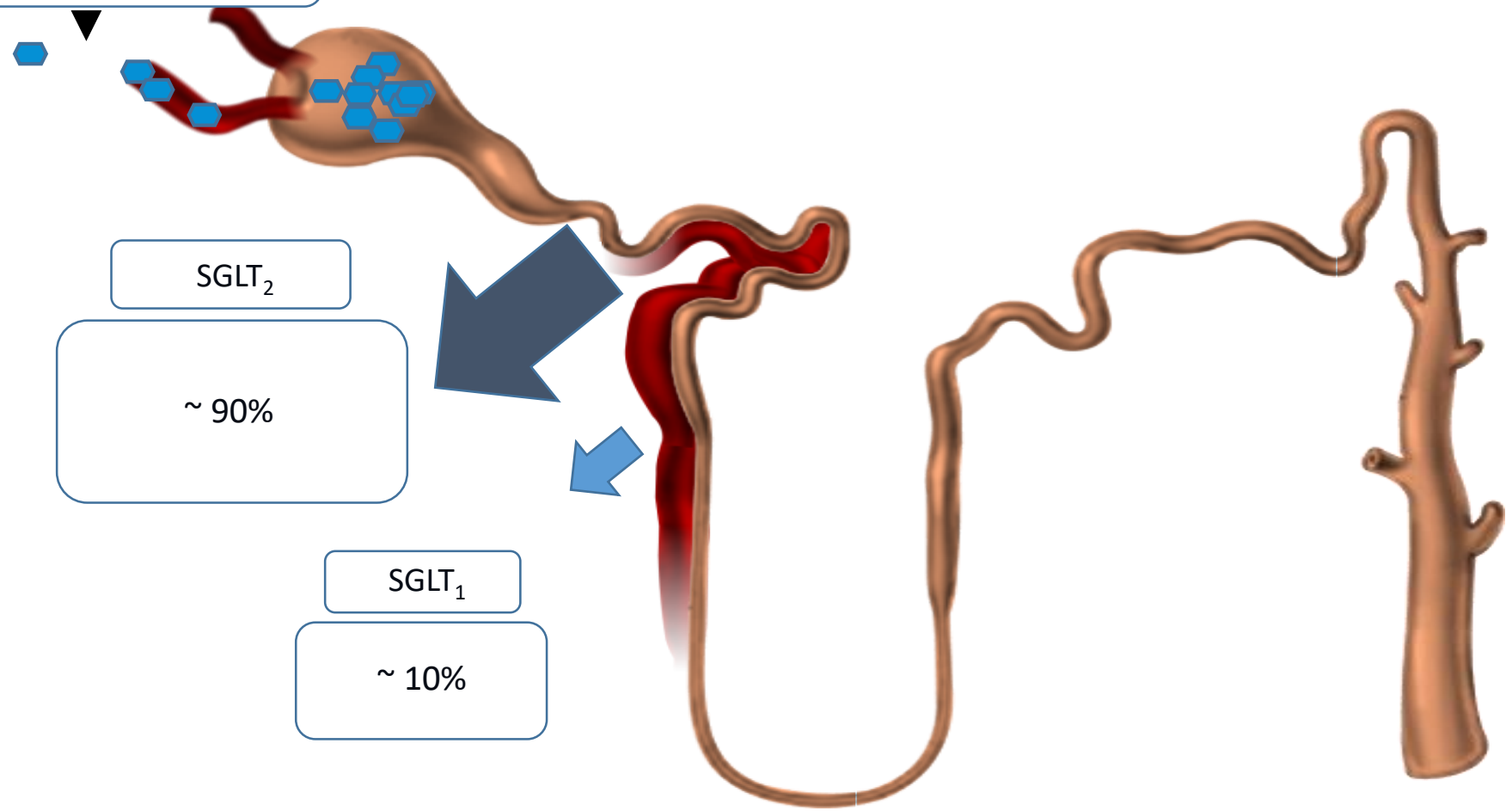
Renal Glucose Re-absorption in Healthy Individuals[1]



1-. Diabetic Medicine. 2010; 27(2): 136-42.

Renal Glucose Re-absorption in Patients with Diabetes[1]

Filtered glucose load > 180[1] g/day



$SGLT_2$

~ 90%

$SGLT_1$

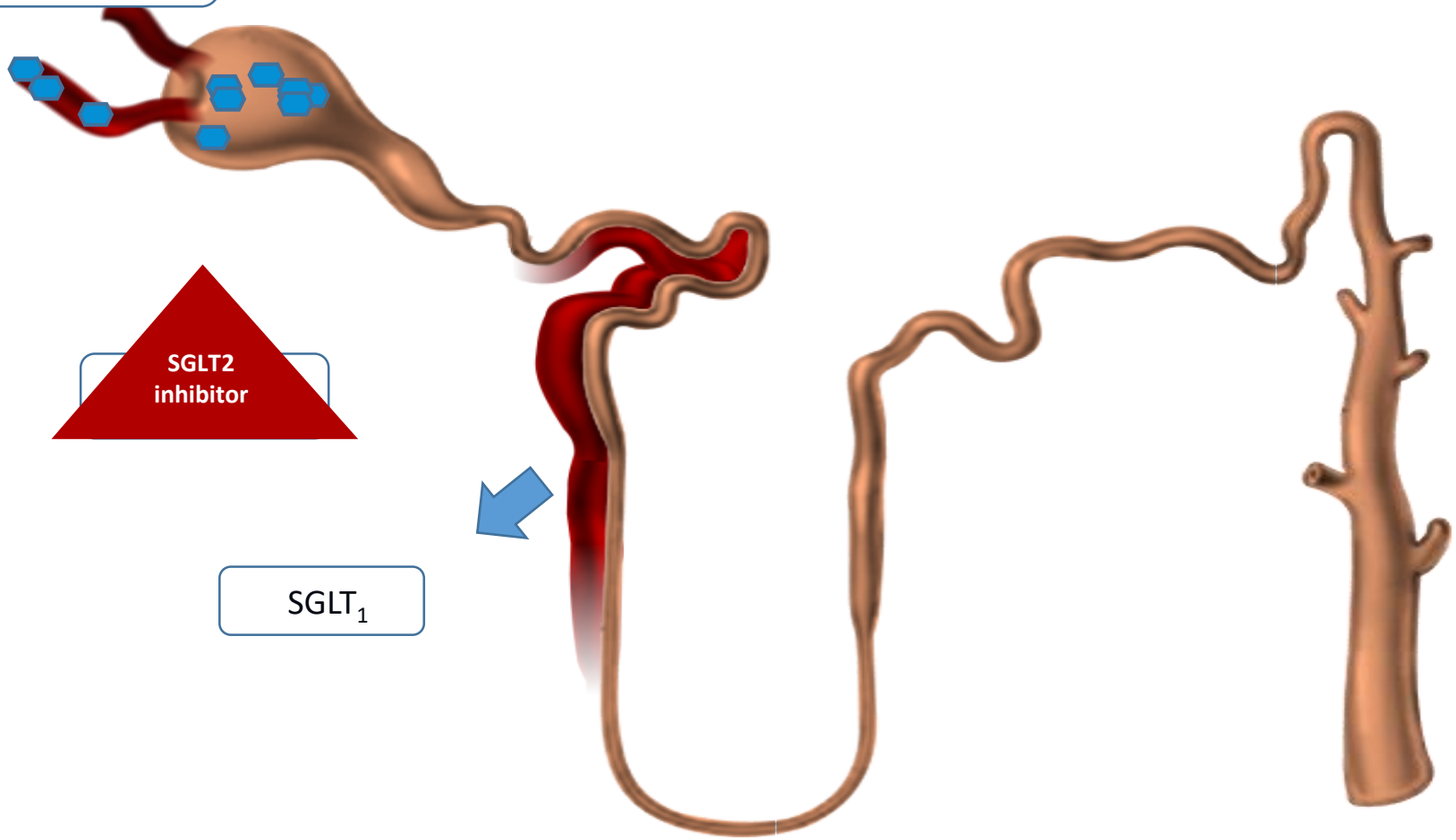
~ 10%

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

1- Diabetic Medicine. 2010; 27(2): 136-42.

Urinary Glucose Excretion via SGLT2 Inhibition[1]

Filtered glucose load
> 180 g/day

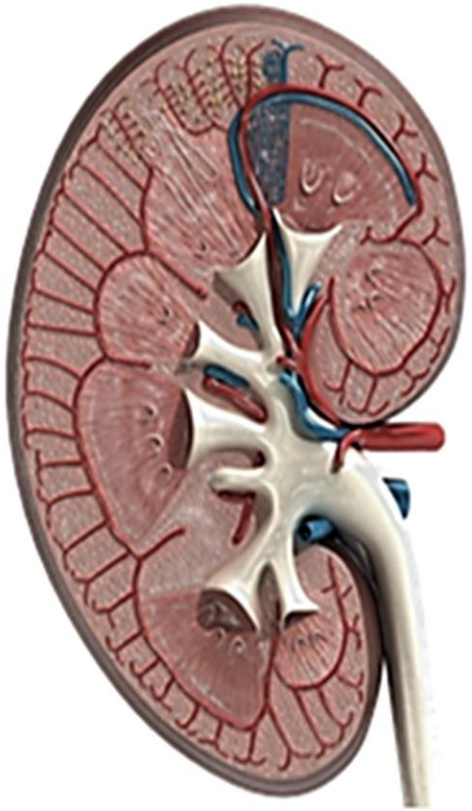


$SGLT_2$ inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis[1]

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

1- Diabetic Medicine. 2010; 27(2): 136-42.

Expected Clinical Effects of SGLT2 Inhibition[1]



Increased glucose excretion → Reduced glycemia → HbA1c reduction

Increased glucose excretion → Loss of energy (calories) → Weight loss

Increased sodium excretion → Reduced sodium load → BP reduction

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

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

Convenience of a once-daily oral treatment[1]

STARTING DOSE	10 mg 1 × daily The recommended starting dose for Empagliflozin is 10 mg once daily
INCREASE TO	25 mg 1 × daily For patients who tolerate 10 mg once daily who have an eGFR ≥ 60 mL/min/1.73 m^2 and need tighter glycemic control, their dose can be increased to 25 mg once daily

Empagliflozin can be taken

With or without food

At any time of day*

When Empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia

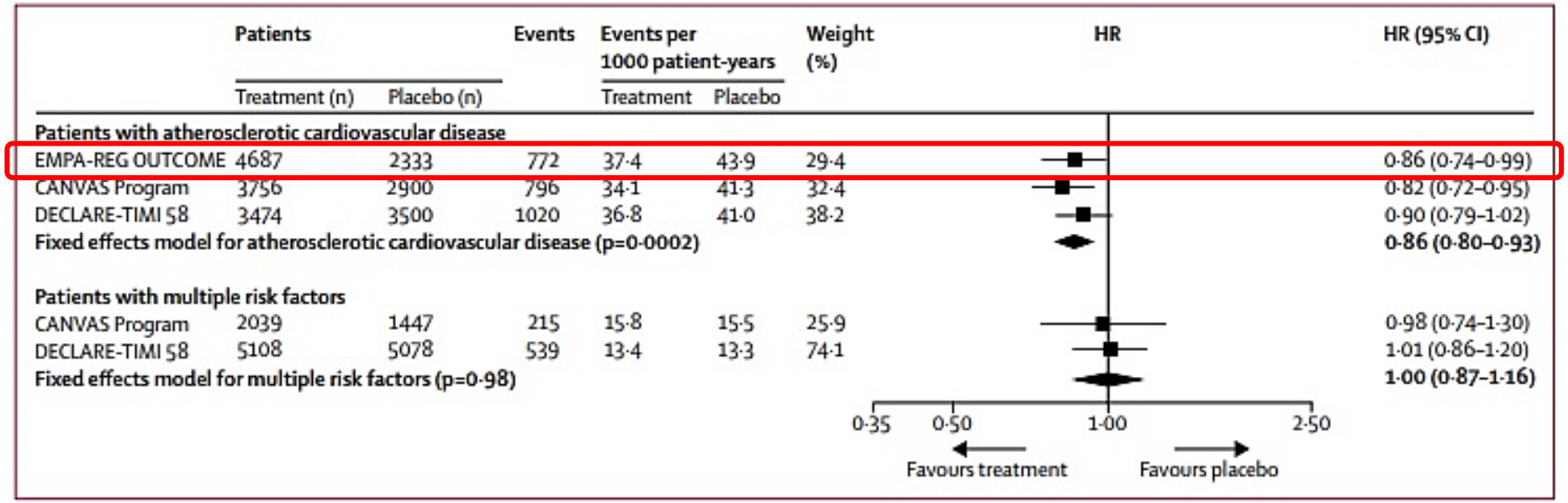
eGFR, estimated glomular filtration rate.
*It is advisable to take JARDIANCE® at the same time each day, which will help with patient adherence.
A missed dose can be taken if it is ≥ 12 hours until the next dose; if it is < 12 hours, the missed dose should be skipped.

1-Jardiance FDA label 2018. Reference ID: 4367802


Thank you

SGLT2 Inhibitors Cardiovascular Outcome

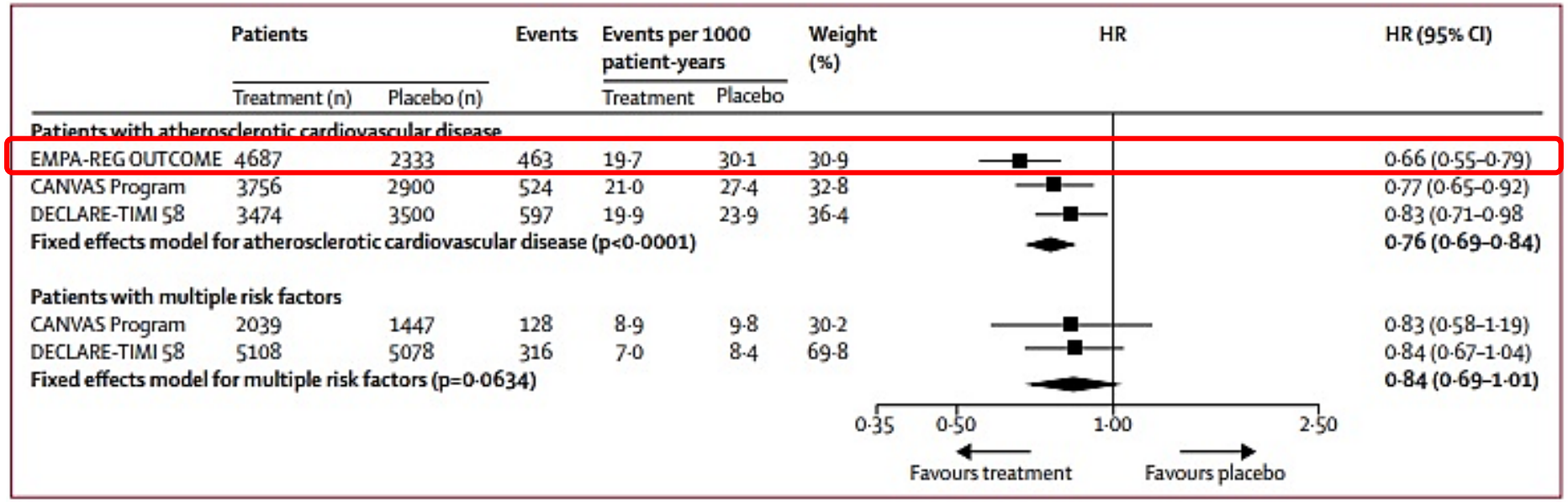
SGLT2 Inhibitors Reduce the Risk of MACE by 11% in Patients with Established CVD[1]



Overall, SGLT2 inhibitors reduced the risk of a major adverse cardiac event; (HR 0·89 [95% CI 0·83–0·96], p=0·0014.

1-Lancet. 2019 Jan 5;393(10166):31-39.
MACE: the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events)
CVD: Cardiovascular Disease

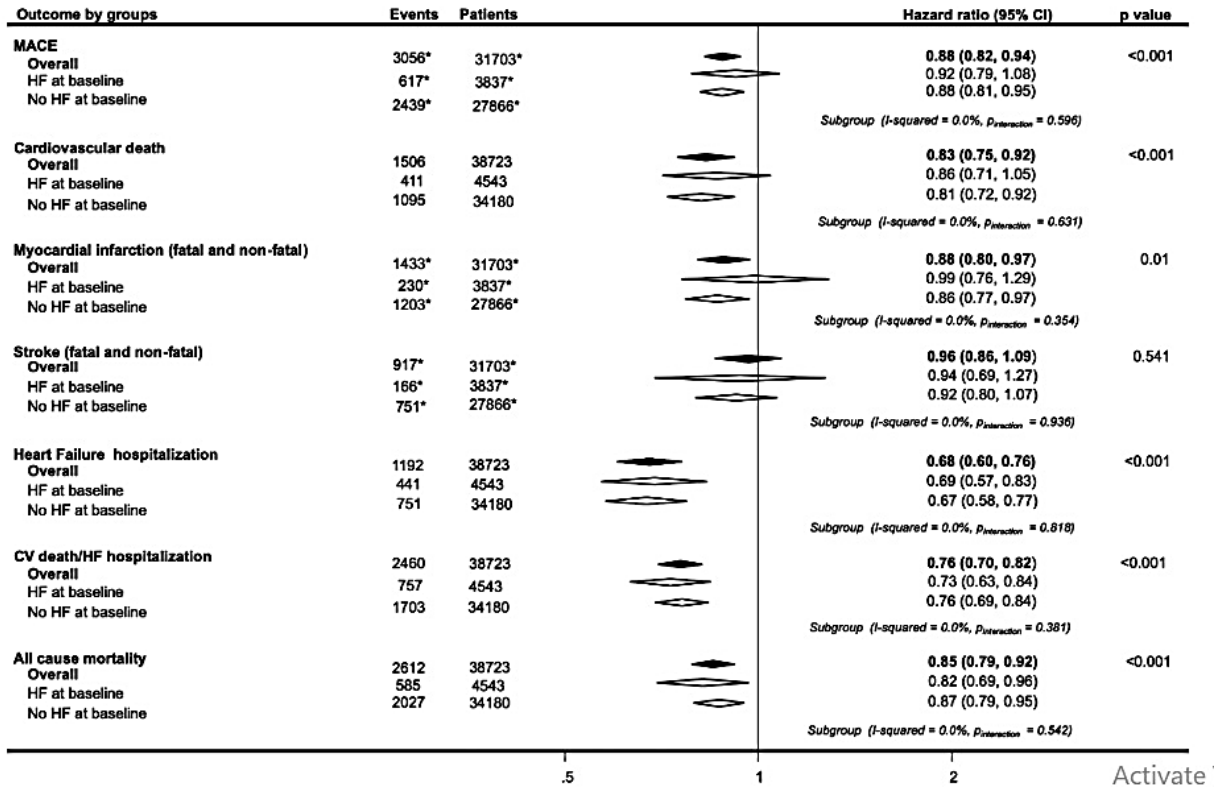
SGLT2 Inhibitors Reduce the Risk of hospitalization for heart failure and cardiovascular death by 23% in Patients with Established CVD[1]



Overall, SGLT2i significantly reduced the risk for the composite of cardiovascular death or hospitalization for heart failure; (HR 0·77 [95% CI 0·71–0·84], p<0·0001).

1-Lancet. 2019 Jan 5;393(10166):31-39.
CVD: Cardiovascular Death

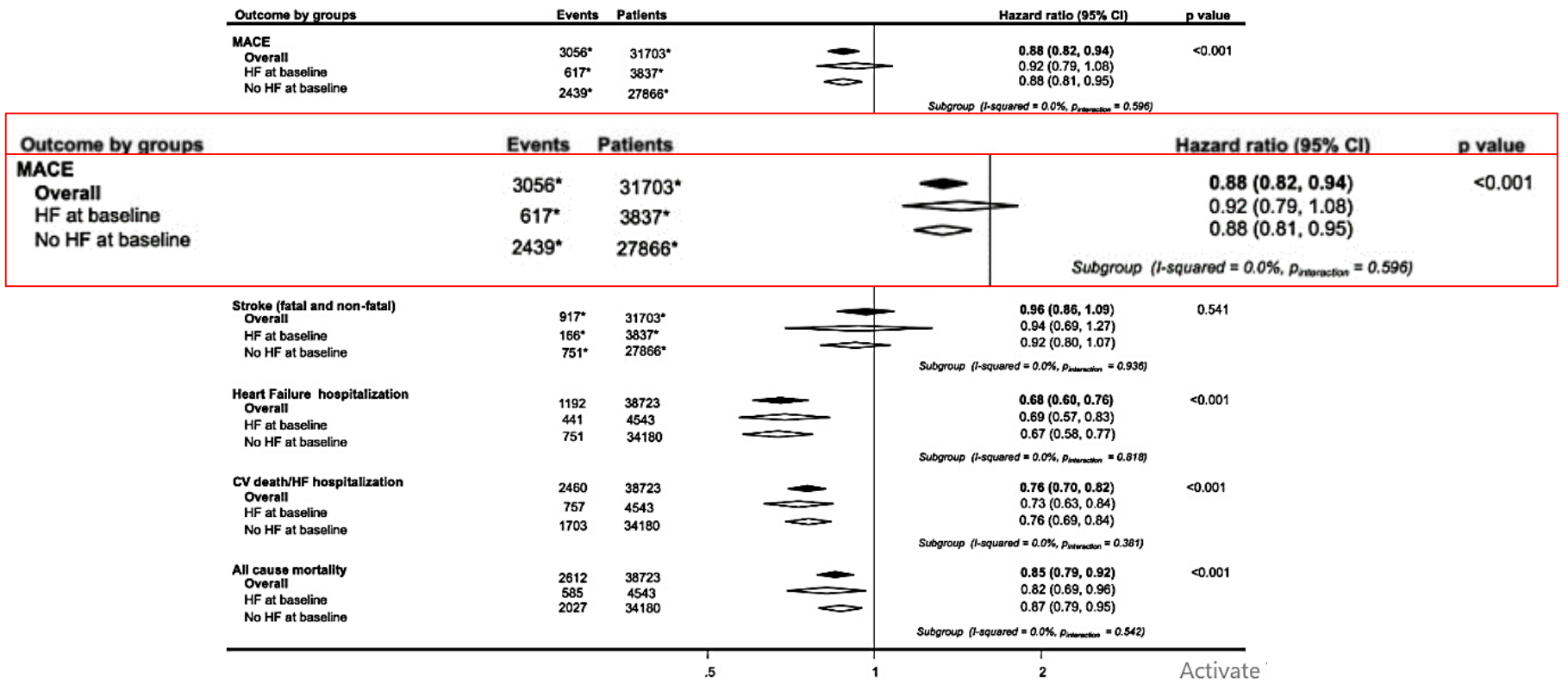
SGLT2 Inhibitors Reduce the Risk of death and cause-specific CV events for patients with and without a history of HF at baseline[1]



There were 4543 patients (12%) with a history of HF at baseline. SGLT2 inhibitors were associated with a reduction in risk of hospitalization for HF, irrespective of baseline HF.

1-Lancet. 2019 Jan 5;393(10166):31-39.
CV: Cardiovascular; HF: Heart Failure

SGLT2 Inhibitors Reduce the Risk of death and cause-specific CV events for patients with and without a history of HF at baseline[1]



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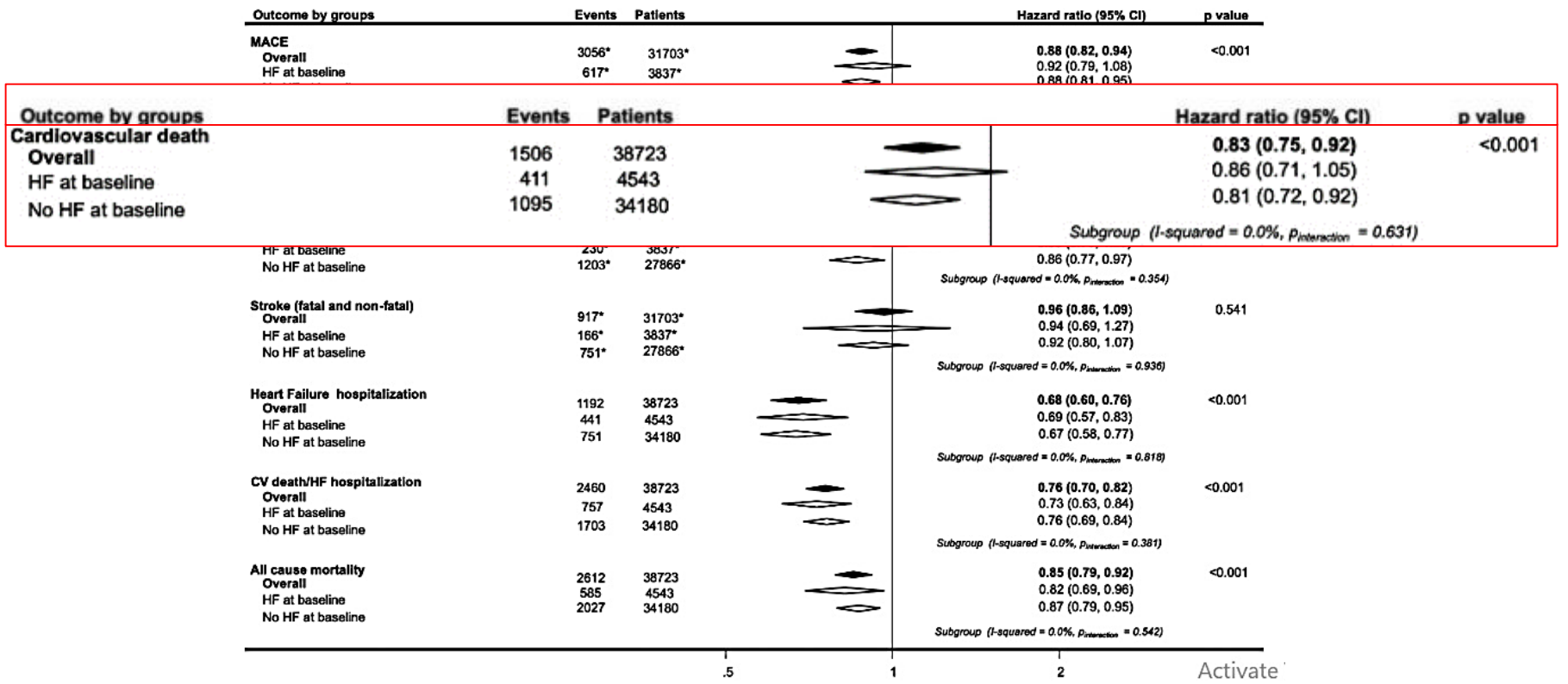

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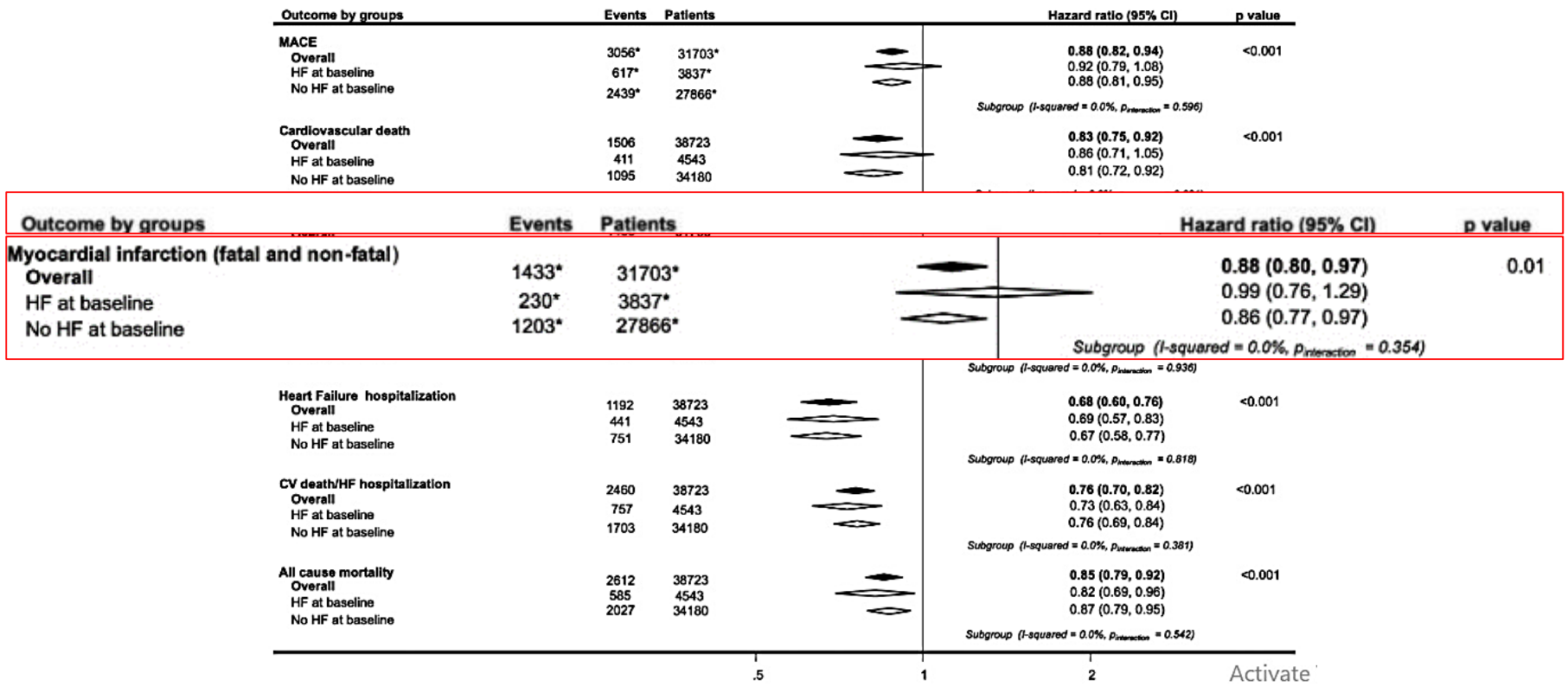

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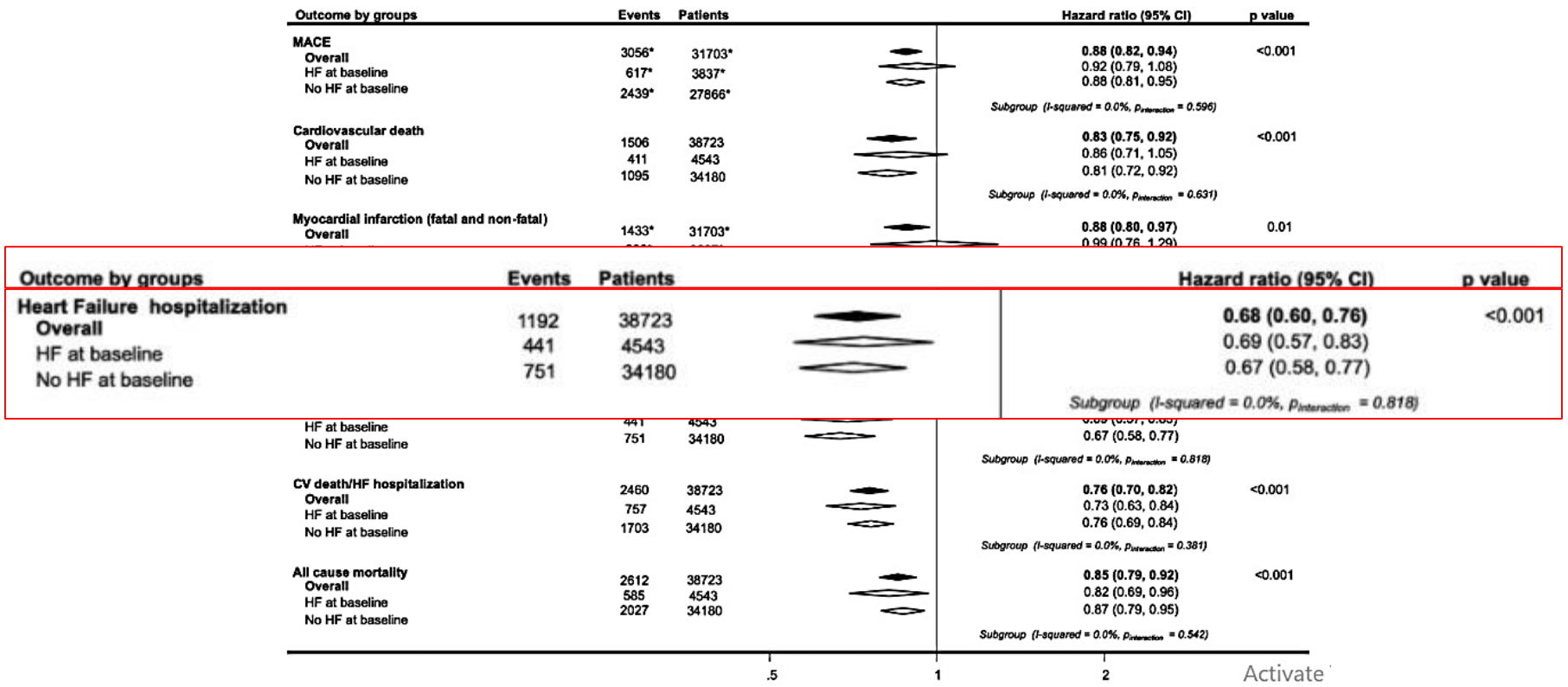
SGLT2 Inhibitors Reduce the Risk of death and cause-specific CV events for patients with and without a history of HF at baseline[1]



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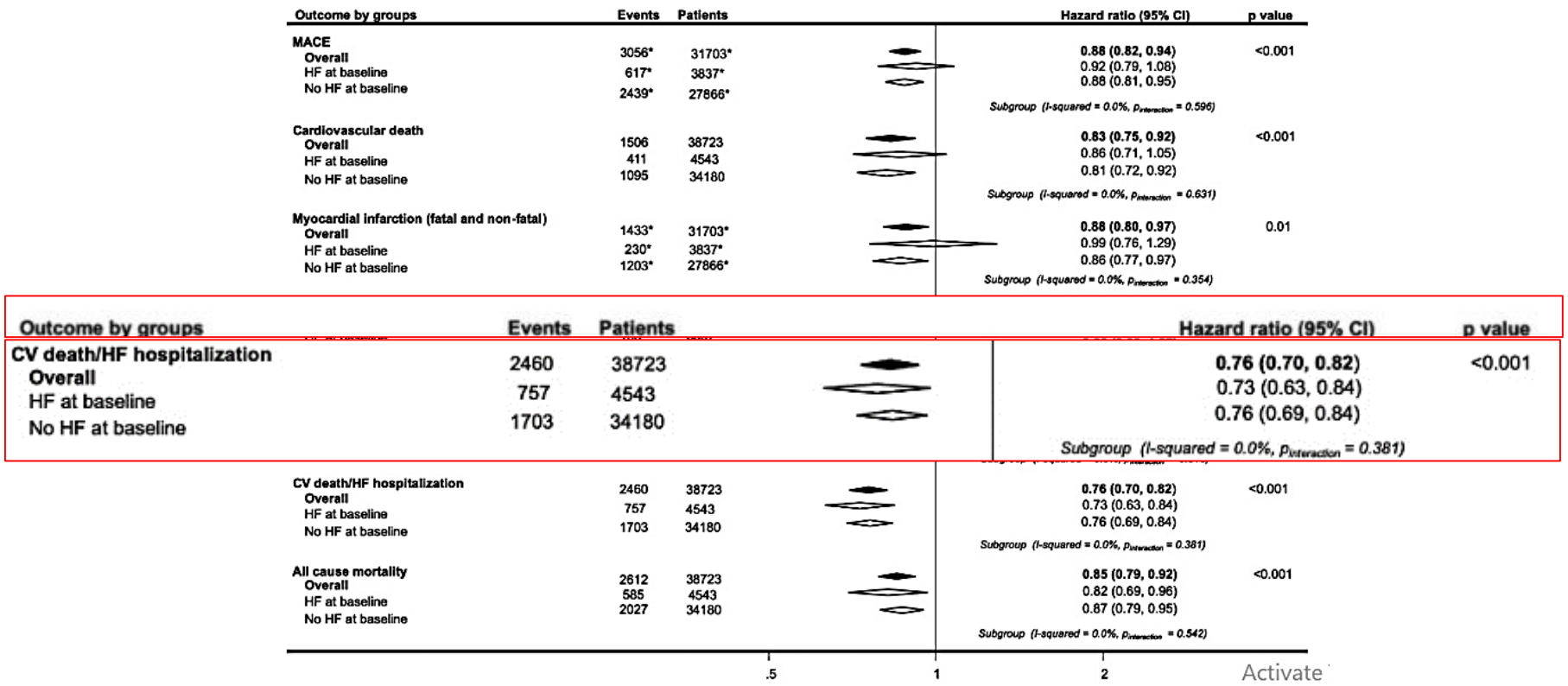

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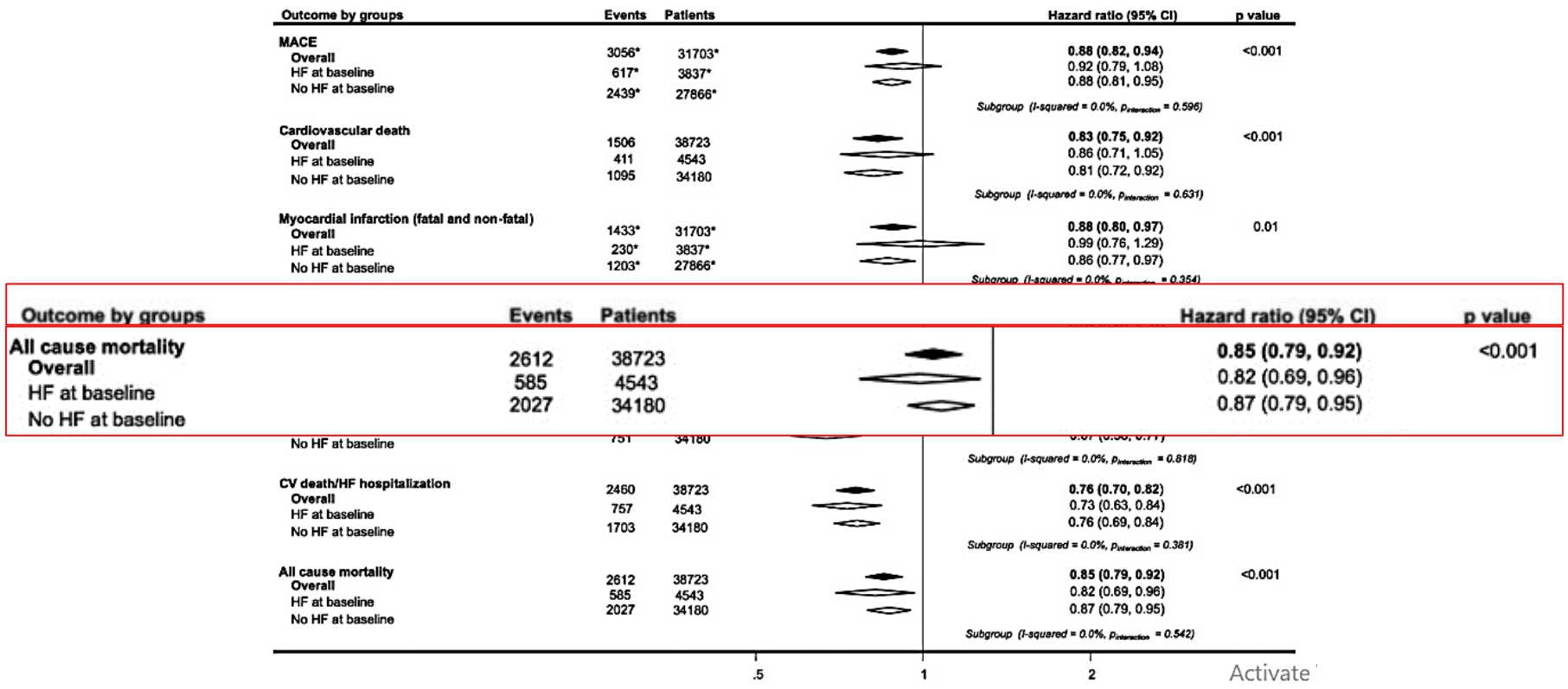

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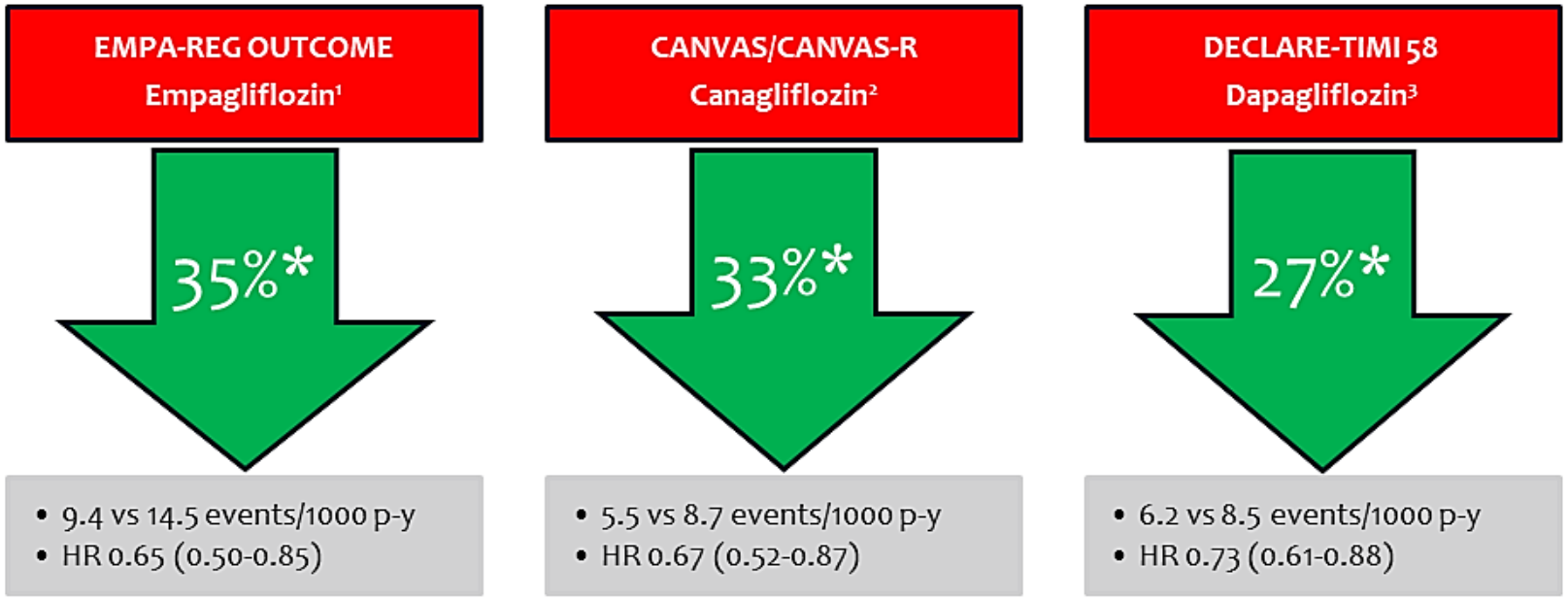
1-Lancet. 2019 Jan 5;393(10166):31-39.
CV: Cardiovascular; HF: Heart Failure

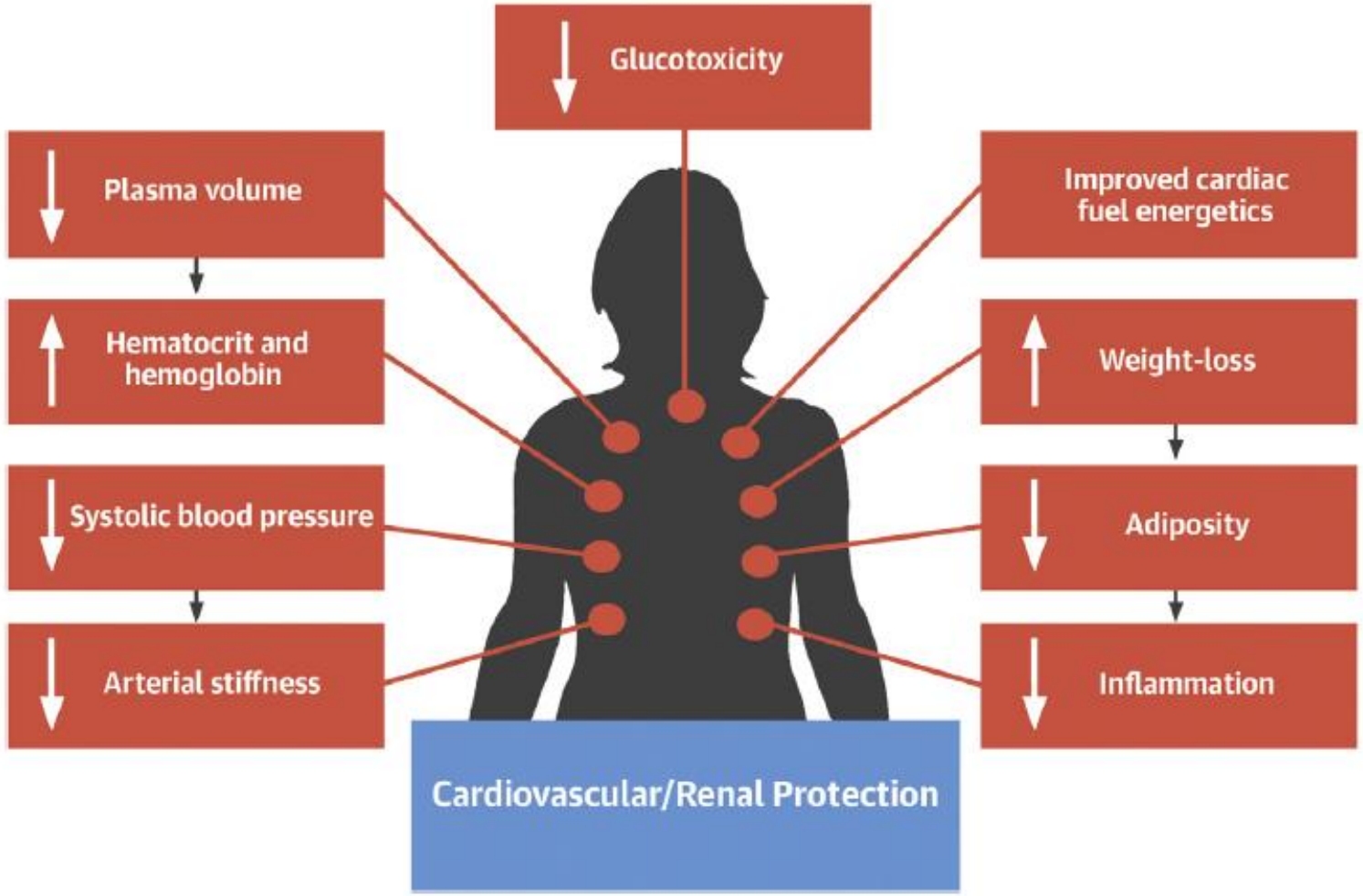
SGLT2 Inhibitors Reduce the Risk of Hospitalization for Heart Failure[1-3]



1-N Engl J Med. 2015 Nov 26;373(22):2117-28. 2-Cardiovasc Diabetol. 2019; 18: 64. 3-N Engl J Med. 2019 Jan 24;380(4):347-357.

Mechanisms of Cardiorenal Effects of Empagliflozin

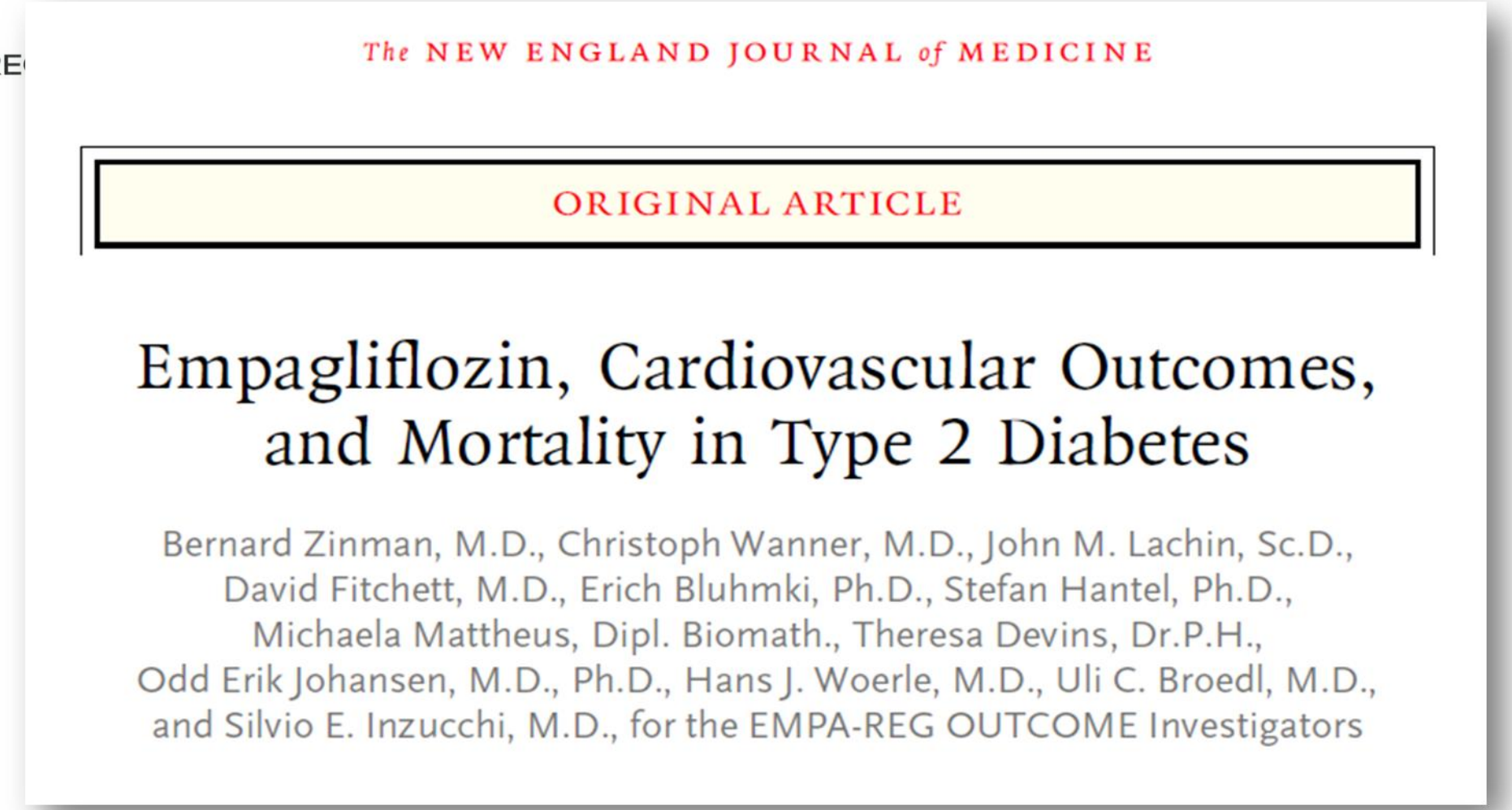
Suggested Mechanisms for Cardiorenal Protection With SGLT2i[1]



1- J Am Coll Cardiol. 2020 Feb 4;75(4):422-434. doi: 10.1016/j.jacc.2019.11.031

EMPA-REG OUTCOME®

EMPA-REG OUTCOME



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

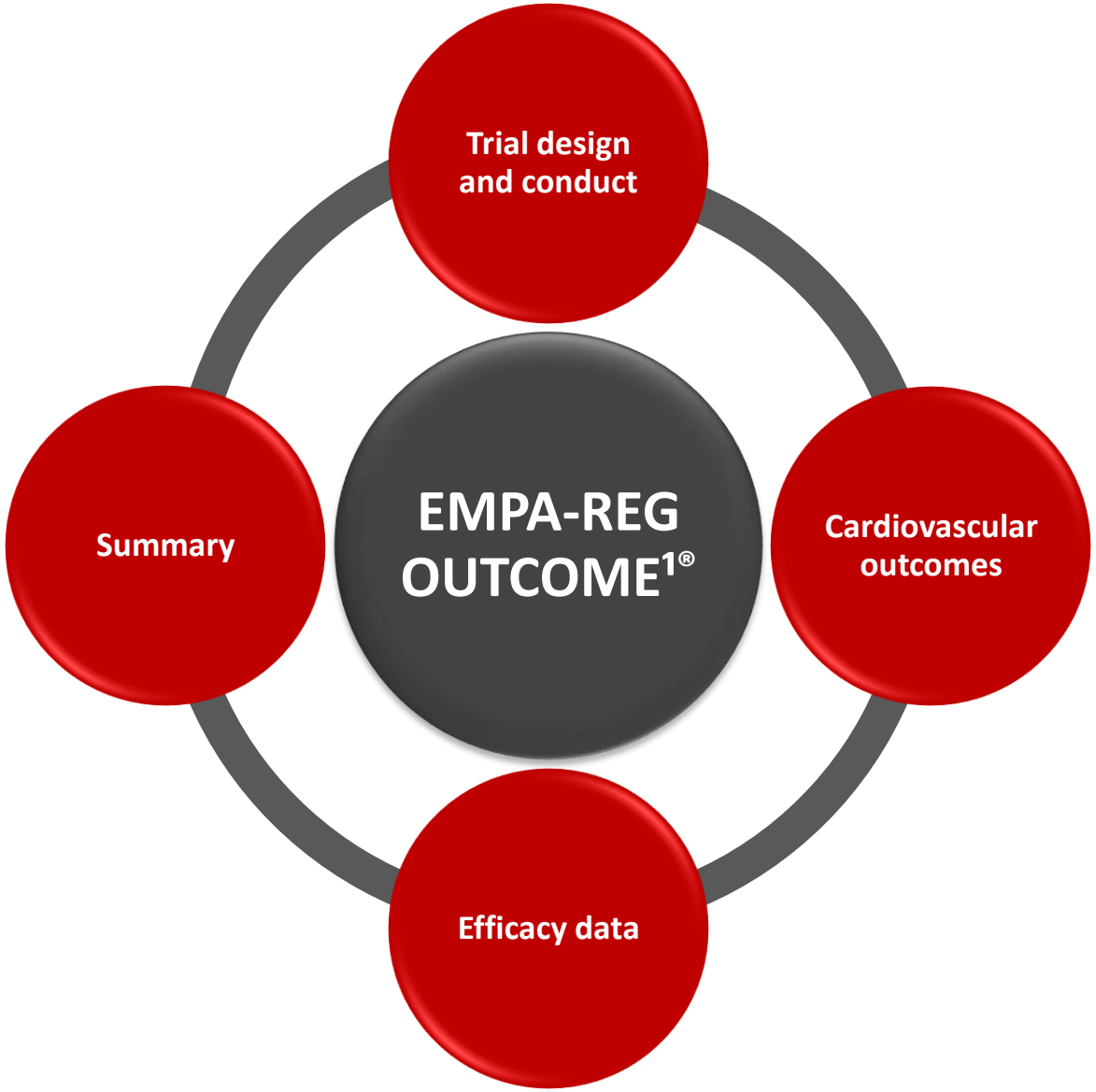
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

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

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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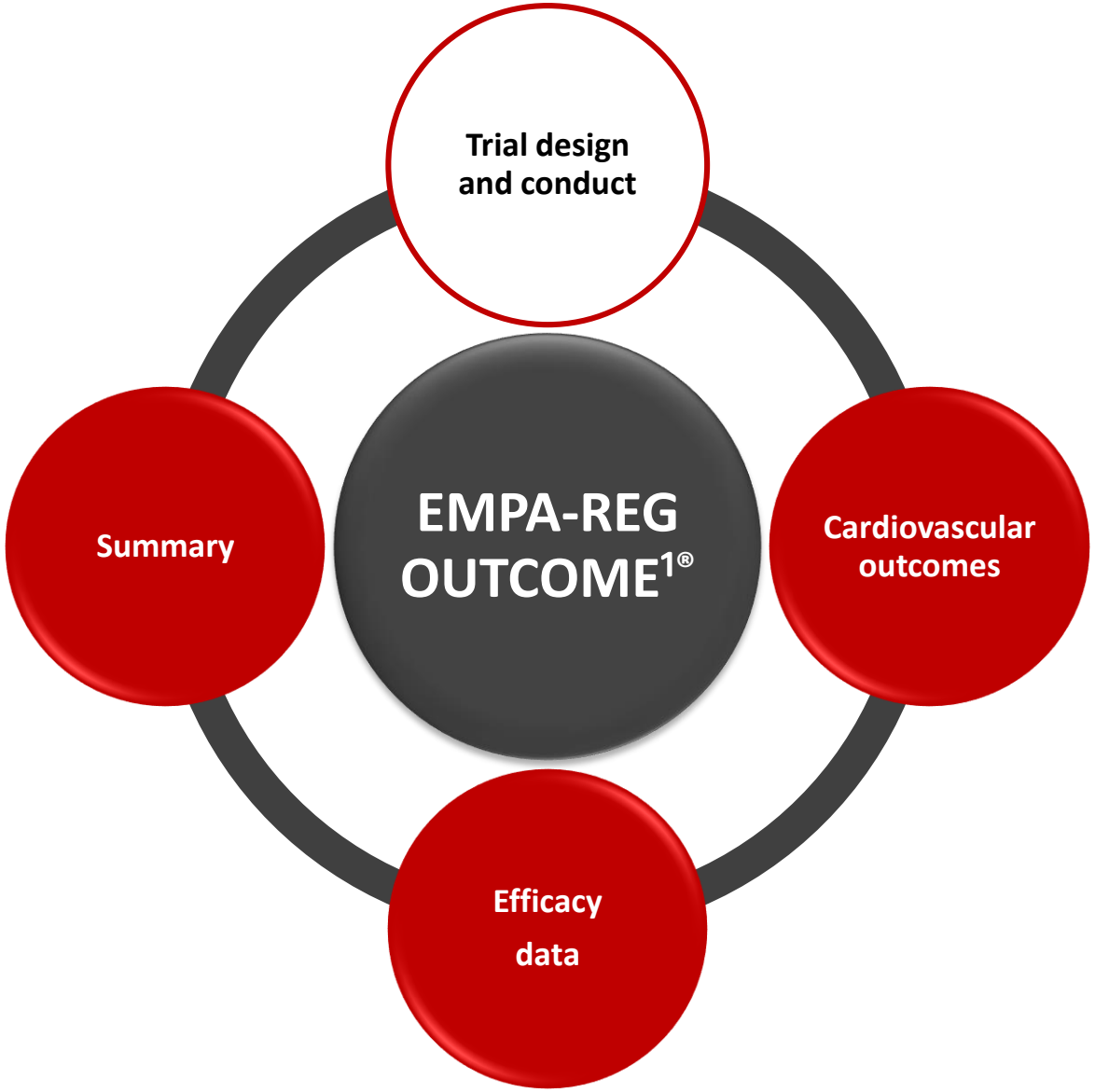
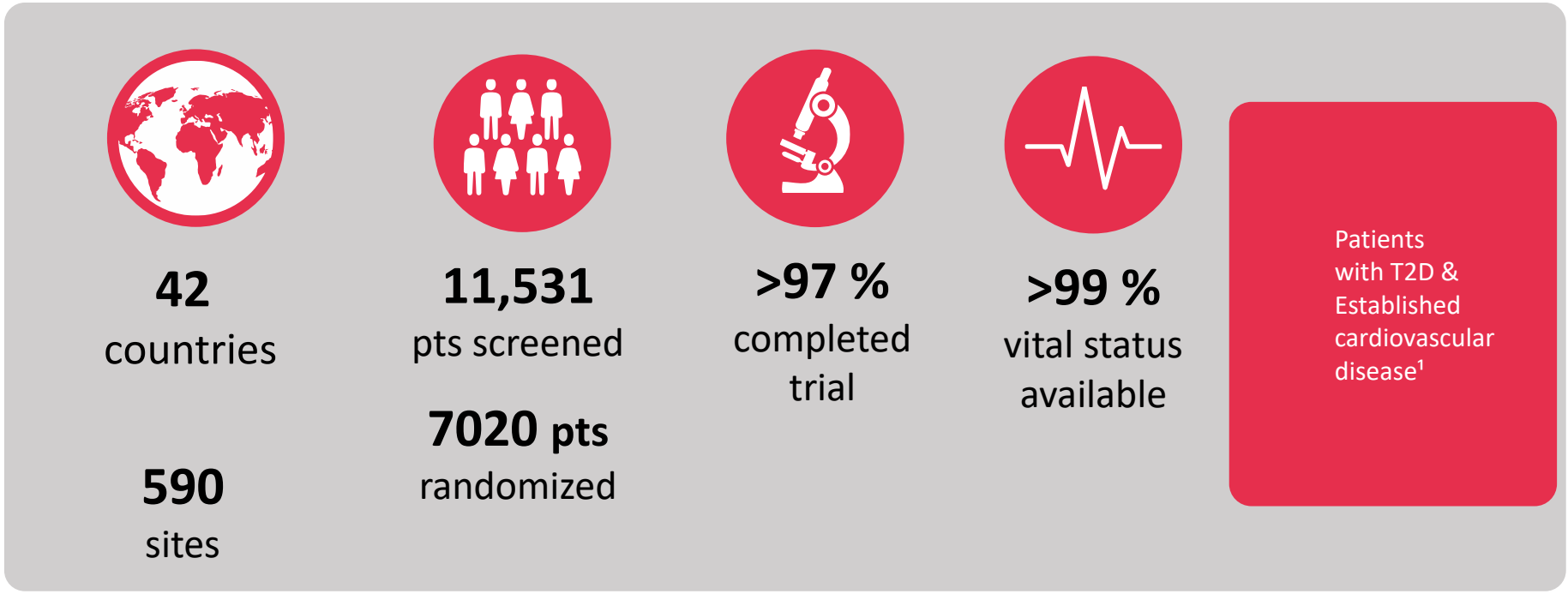


1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Trial Design[1]



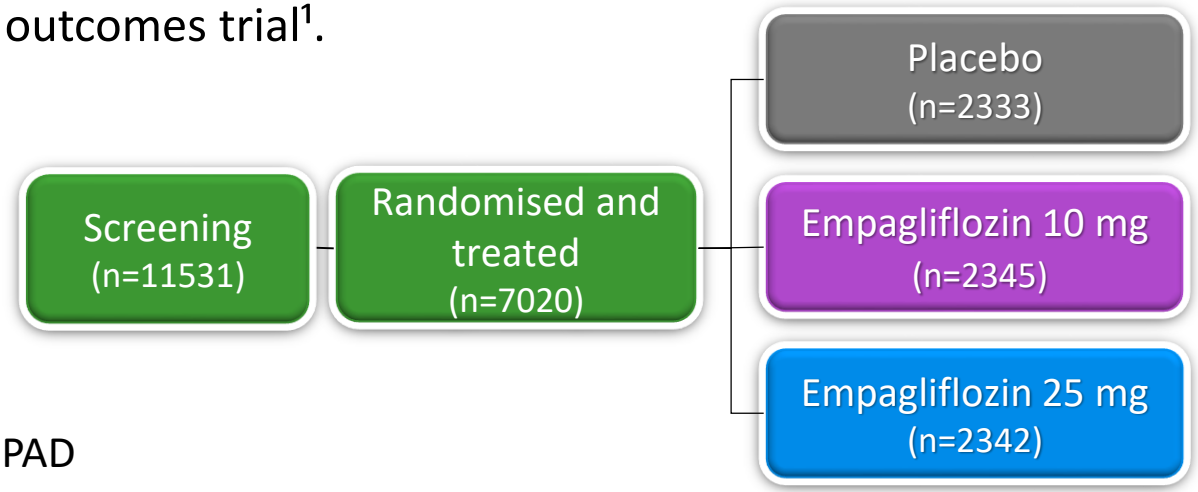
- CV, cardiovascular.

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[1]

EMPA-REG OUTCOME

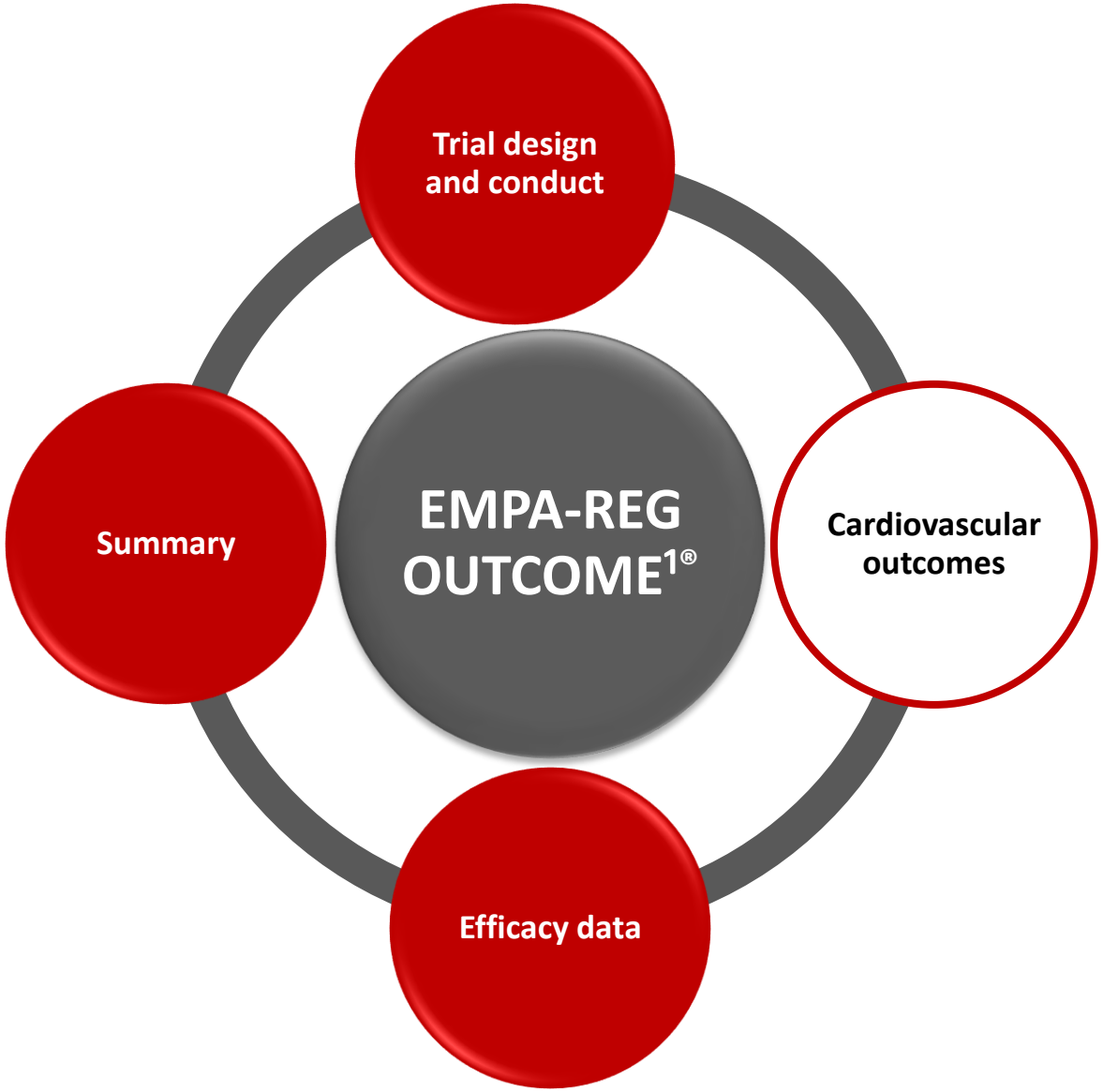
- **Design**
  - Randomized, double-blind, placebo-controlled CV outcomes trial[1].
- **Key inclusion criteria**
  - Adults with T_2DM
  - BMI ≤45 *kg/m2*
  - HbA_{1c} 7–10%*
  - Established cardiovascular disease
    - Prior MI, CAD, stroke, unstable angina or occlusive PAD
- **Key exclusion criteria**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

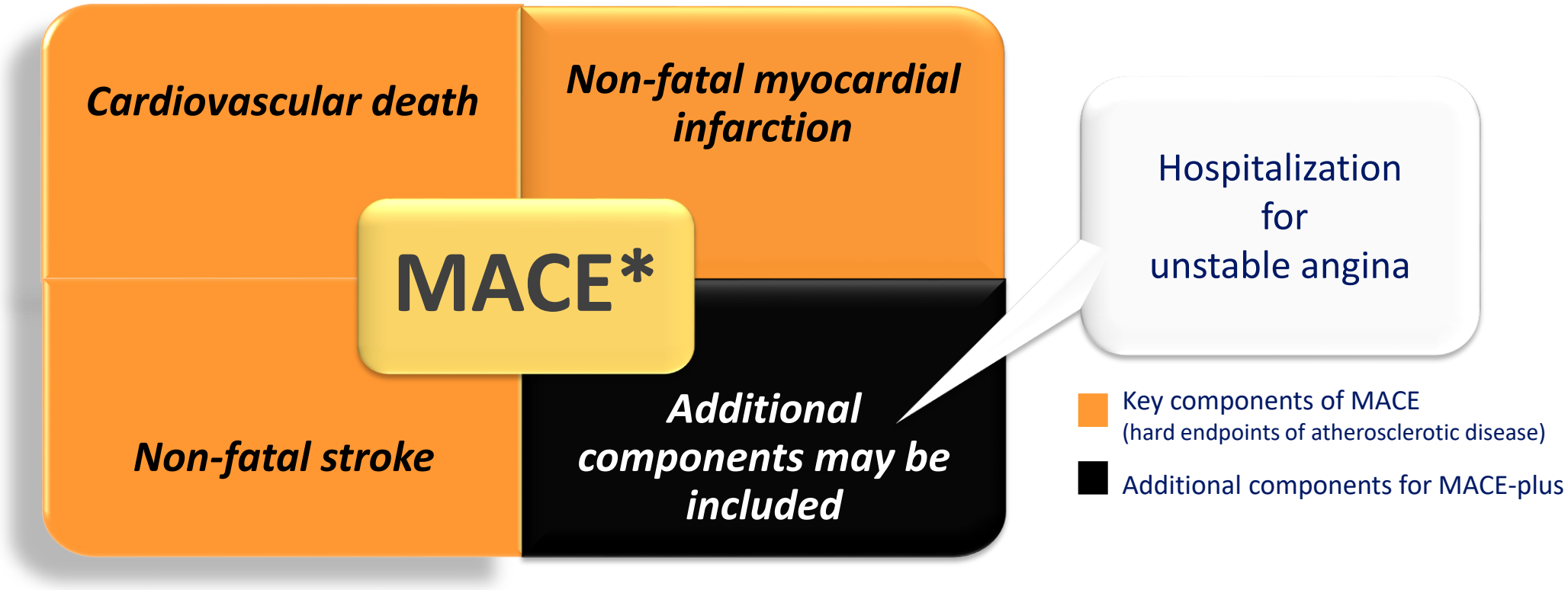
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.



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

Pre-specified primary and key secondary outcomes[1]

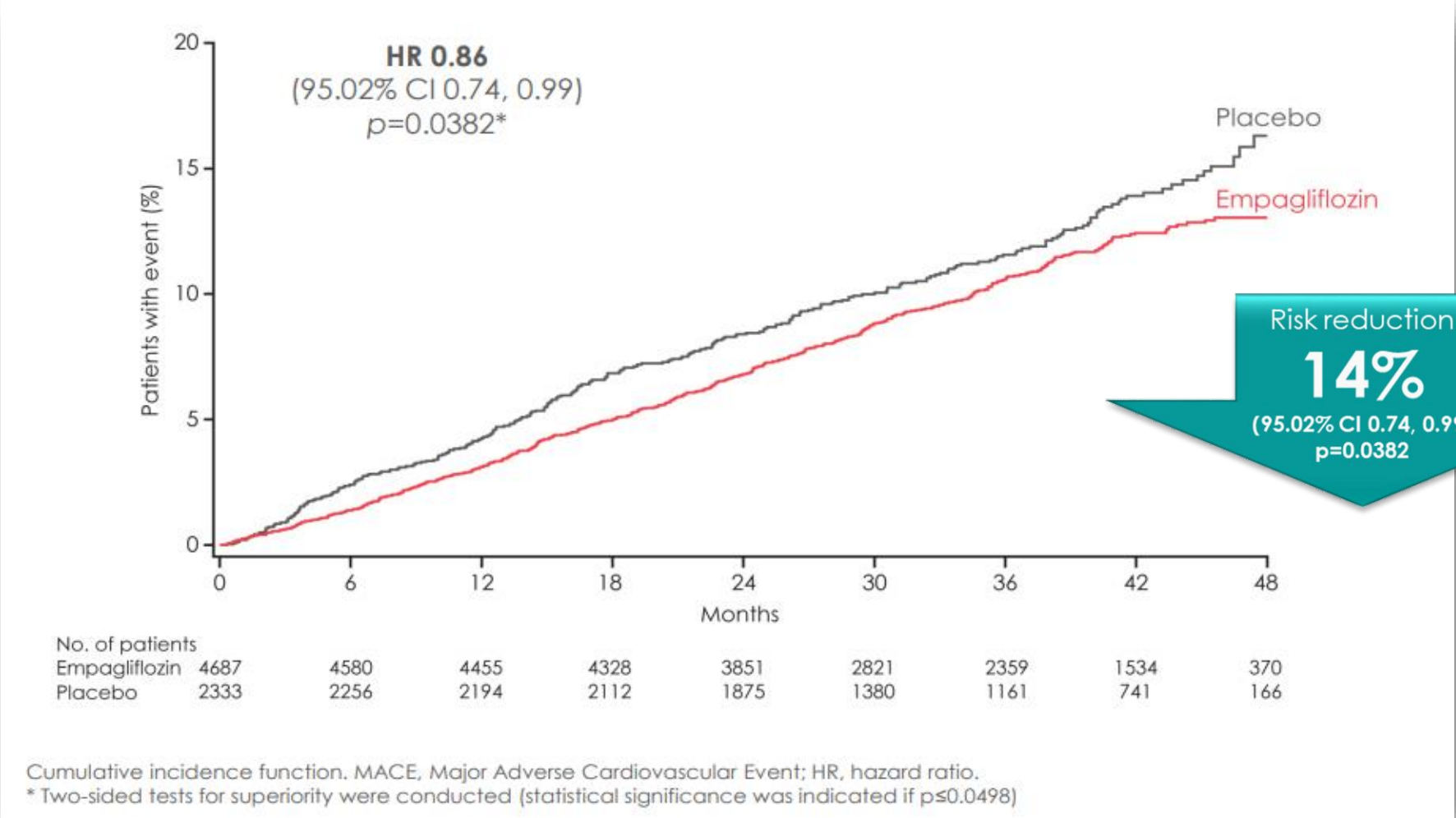
EMPA-REG OUTCOME



*Major Adverse Cardiovascular Events

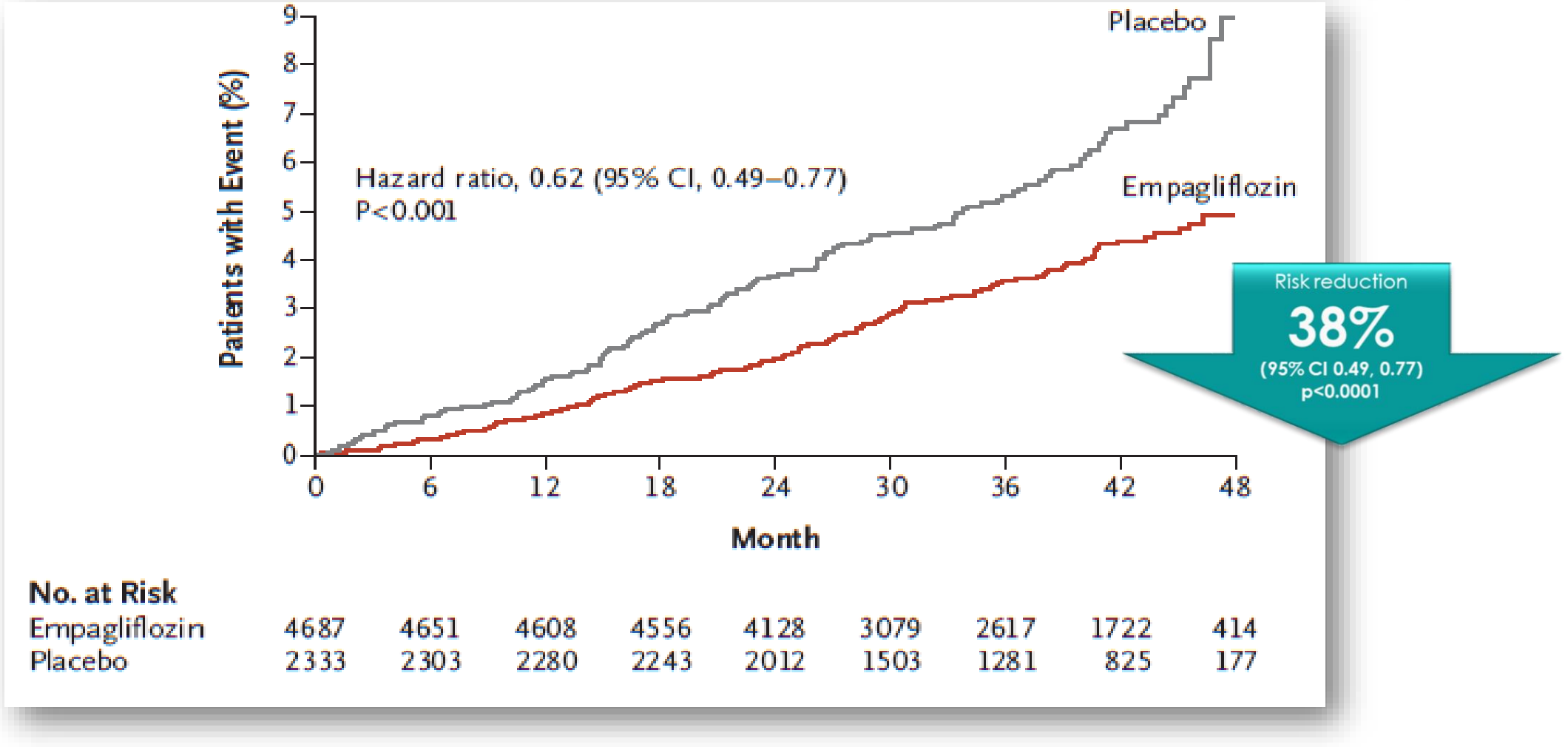
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

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



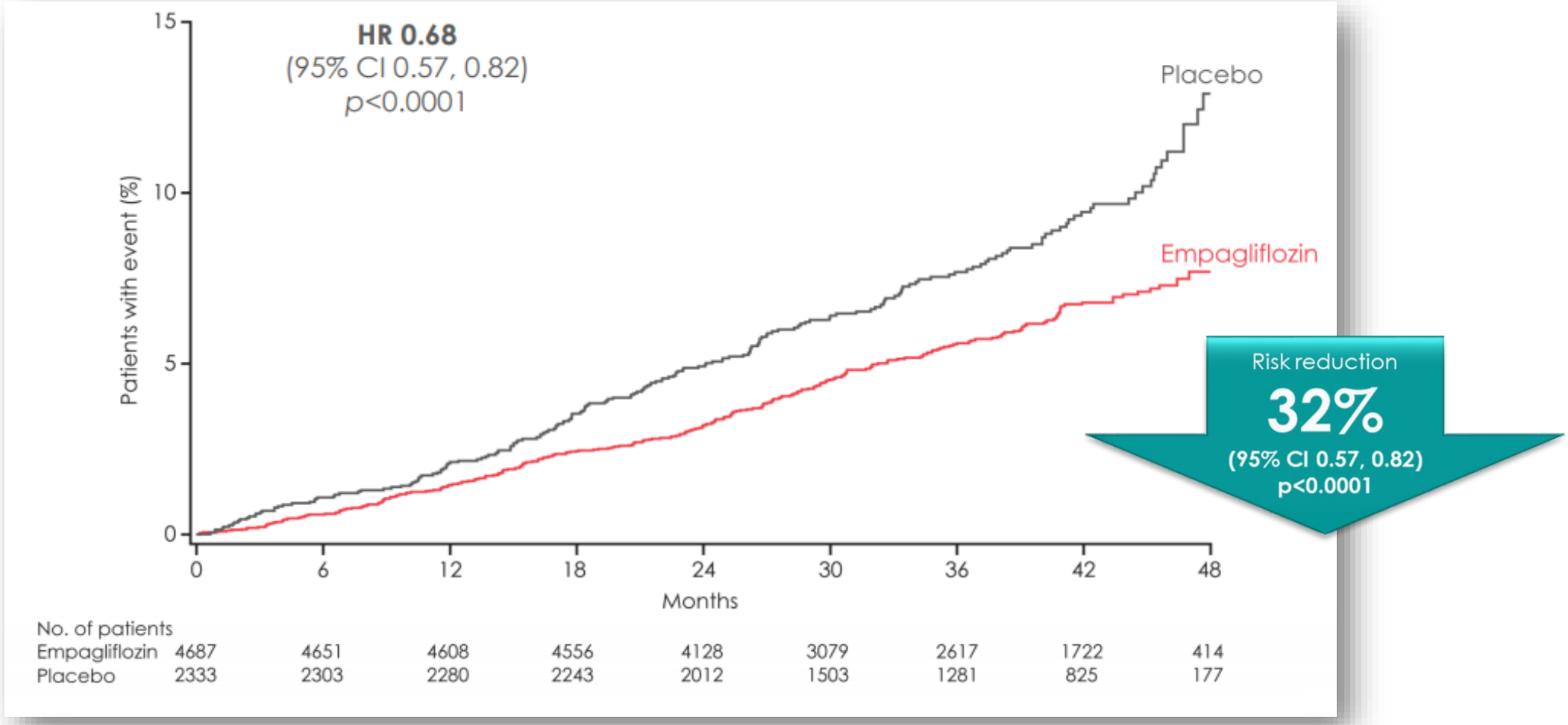
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

EMPA-REG OUTCOME®CV Death[1]



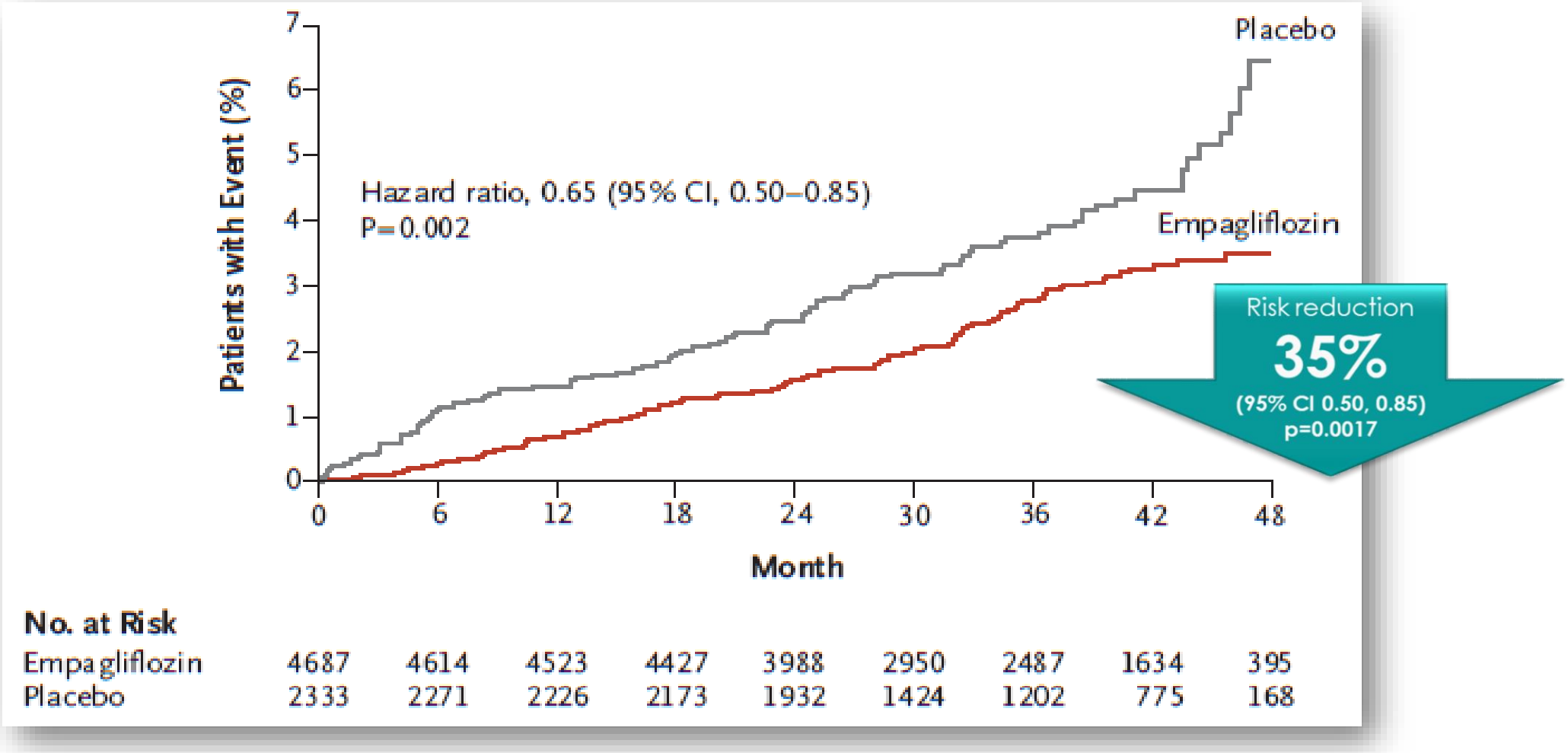
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

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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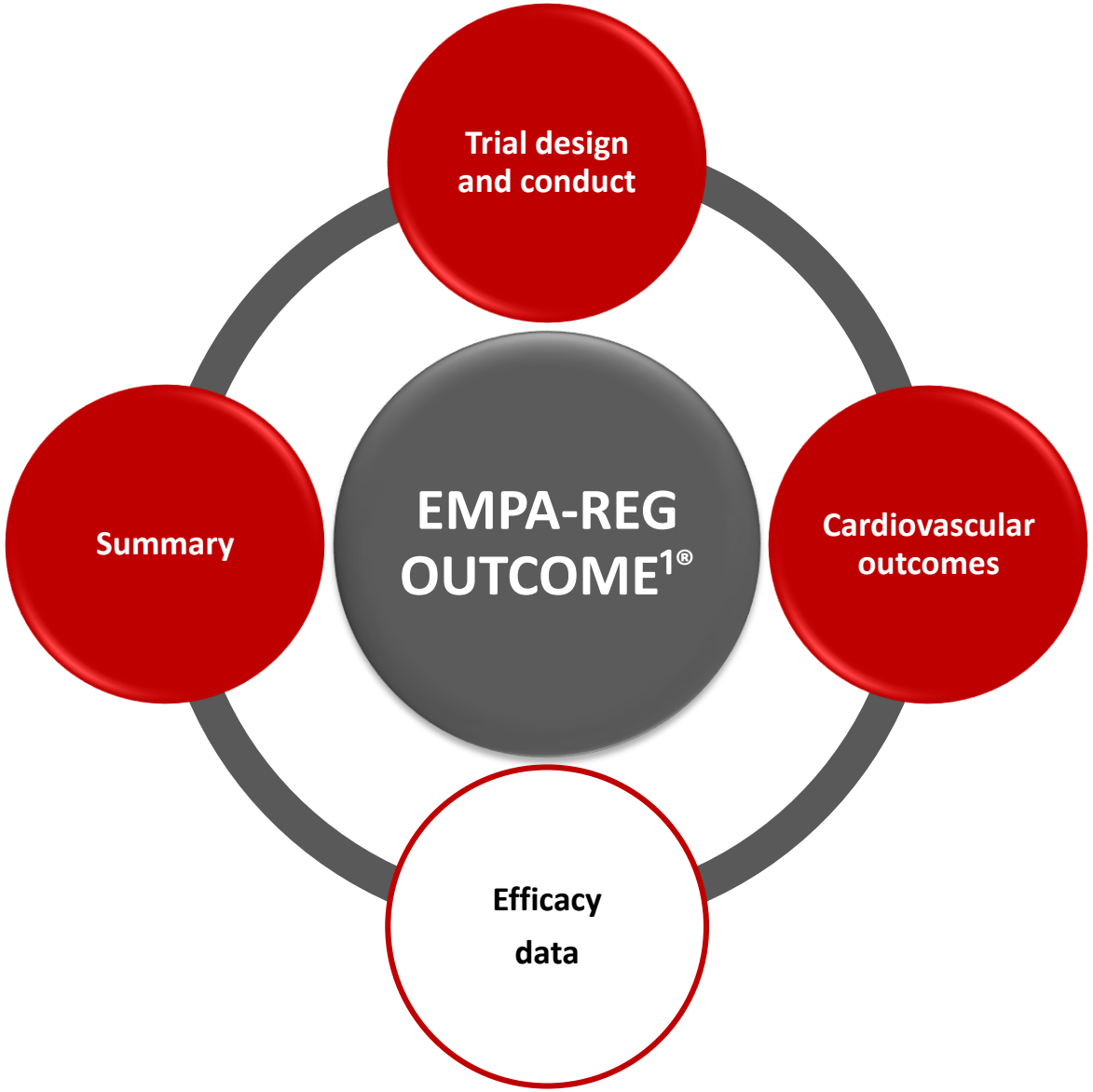
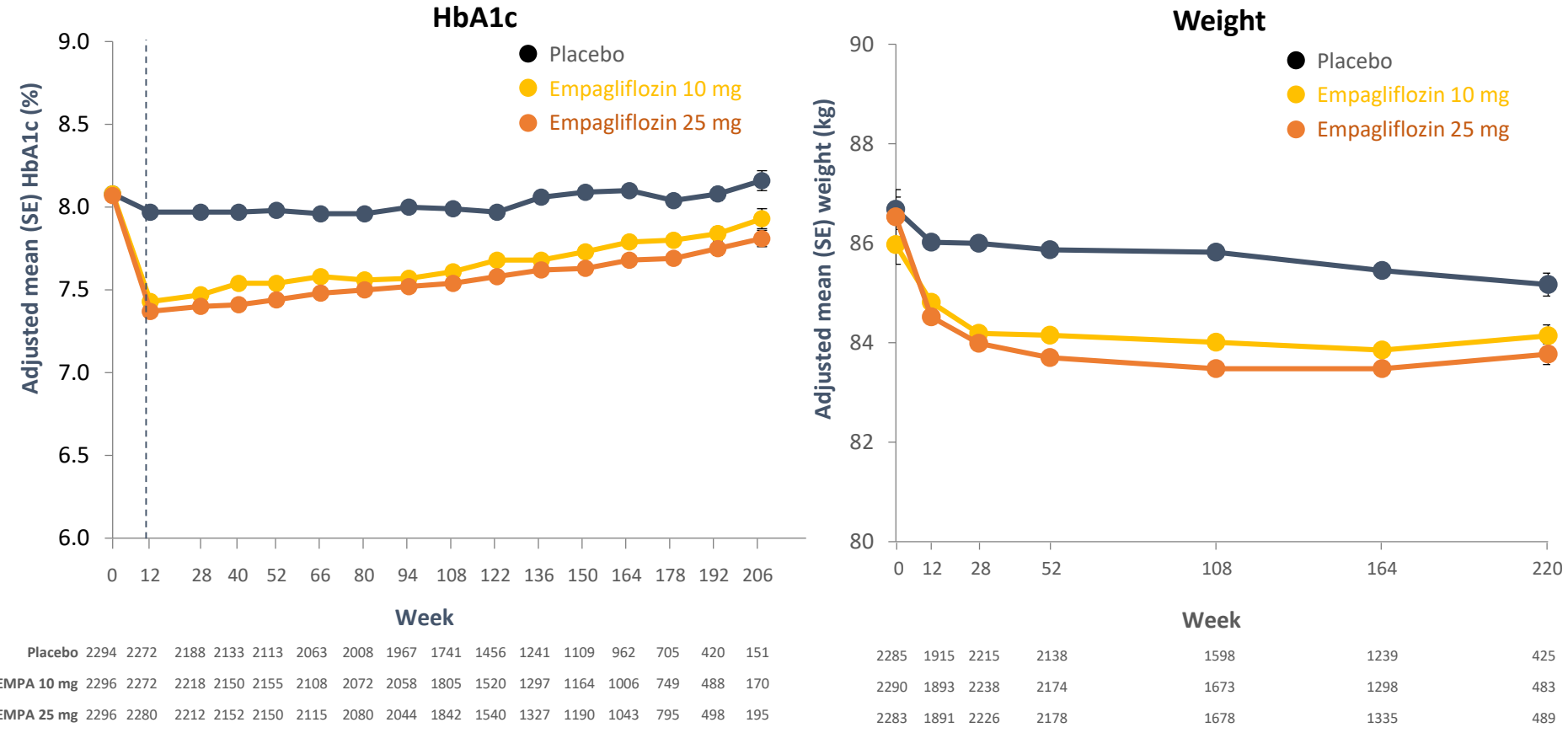


1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

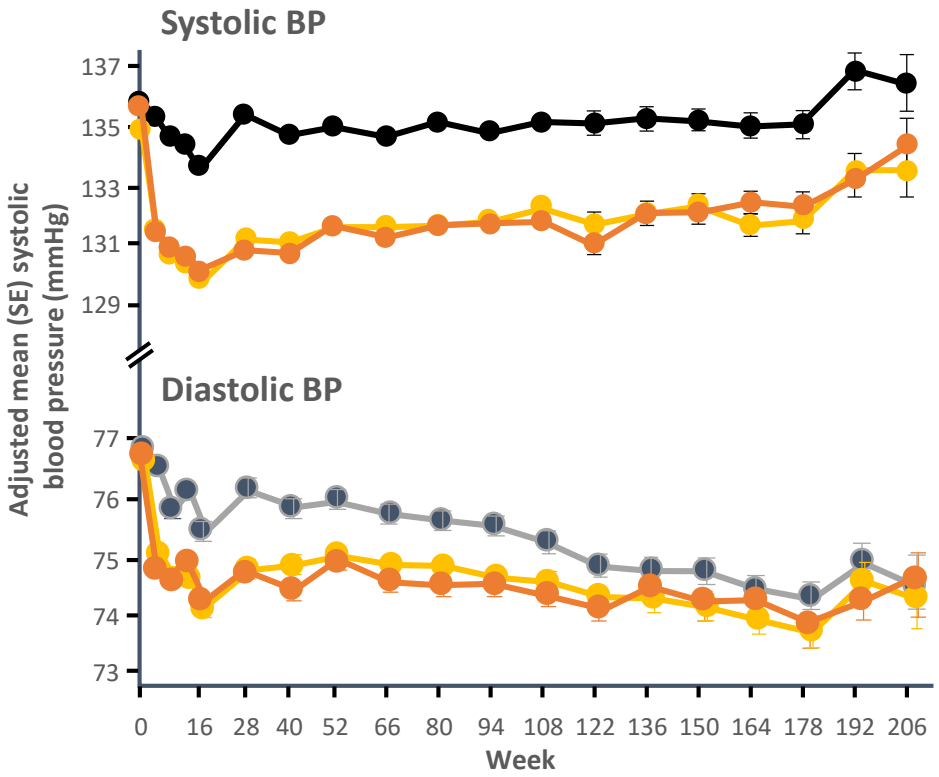
Mean adjusted HbA1c and weight parameters[1]



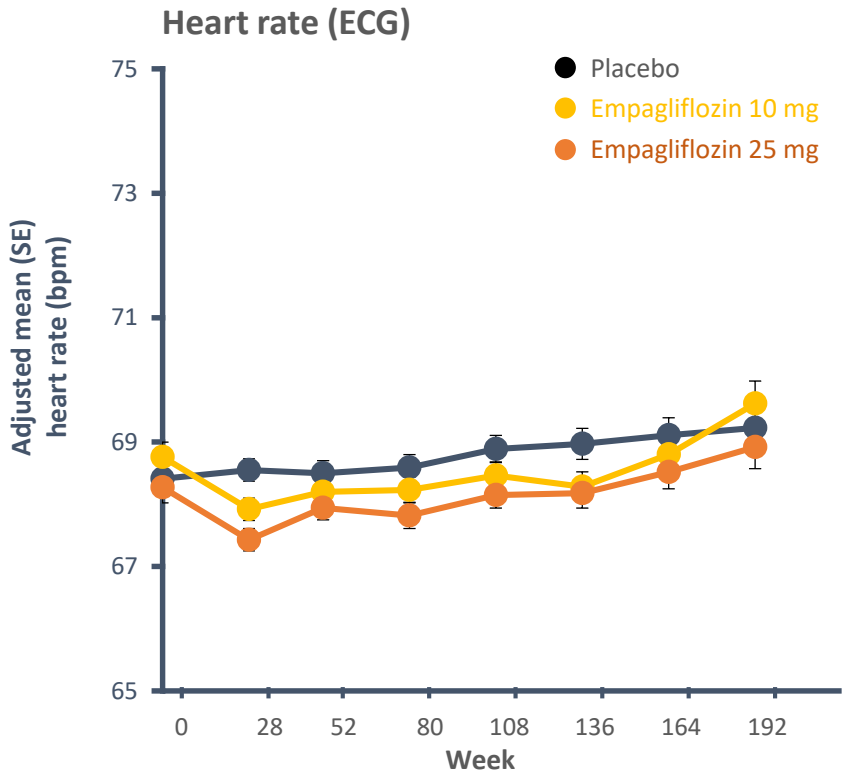
All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent to treat)
X-axis: time points with reasonable amount of data available for prescheduled measurements
EMPA, empagliflozin; HbA1c, glycated haemoglobin

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]



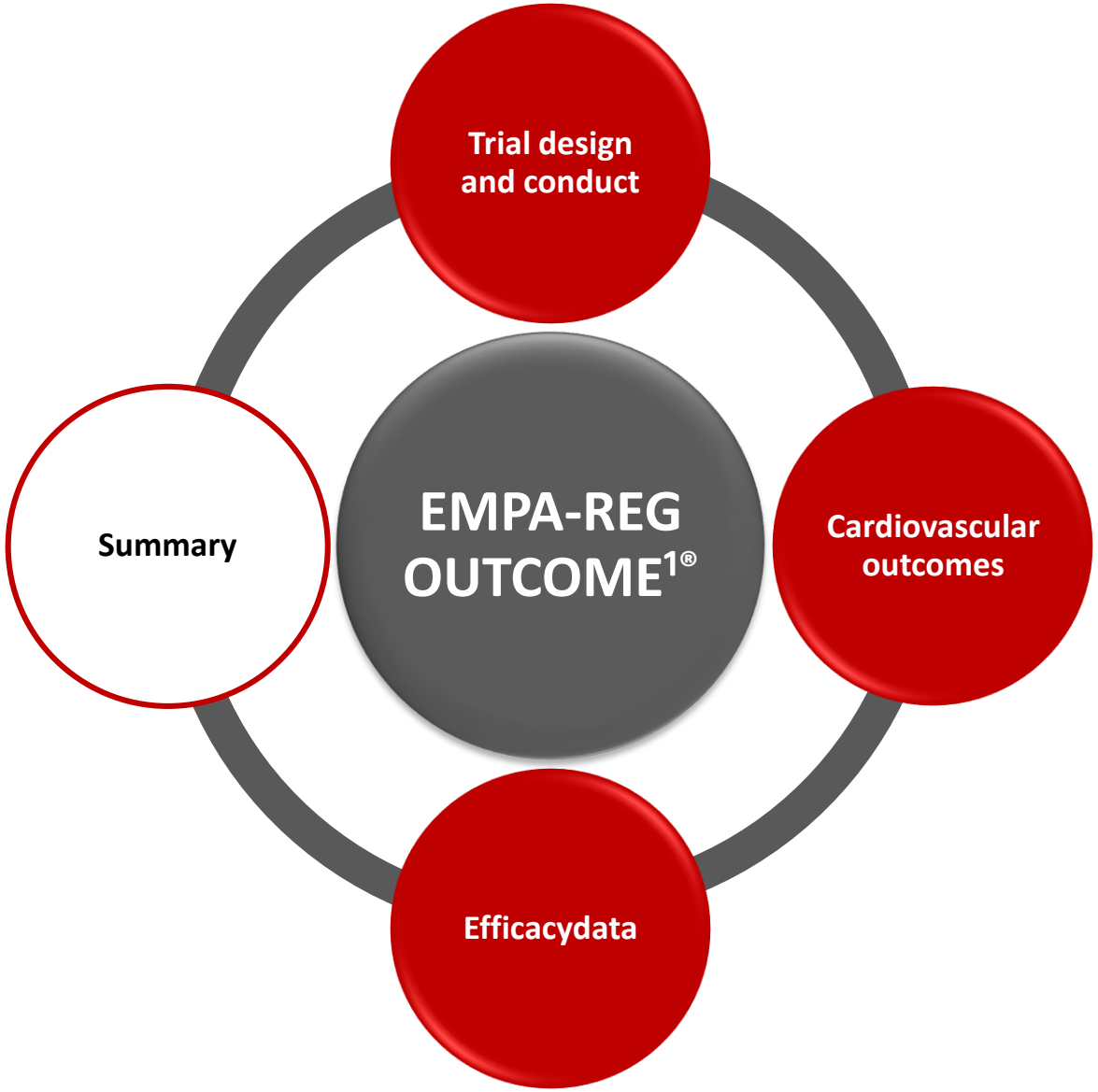
Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
EMPA 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
EMPA 25 mg	2322	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216



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.

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

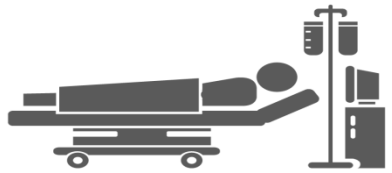
38%

↓ CV death

32%

↓ All-cause mortality

35%

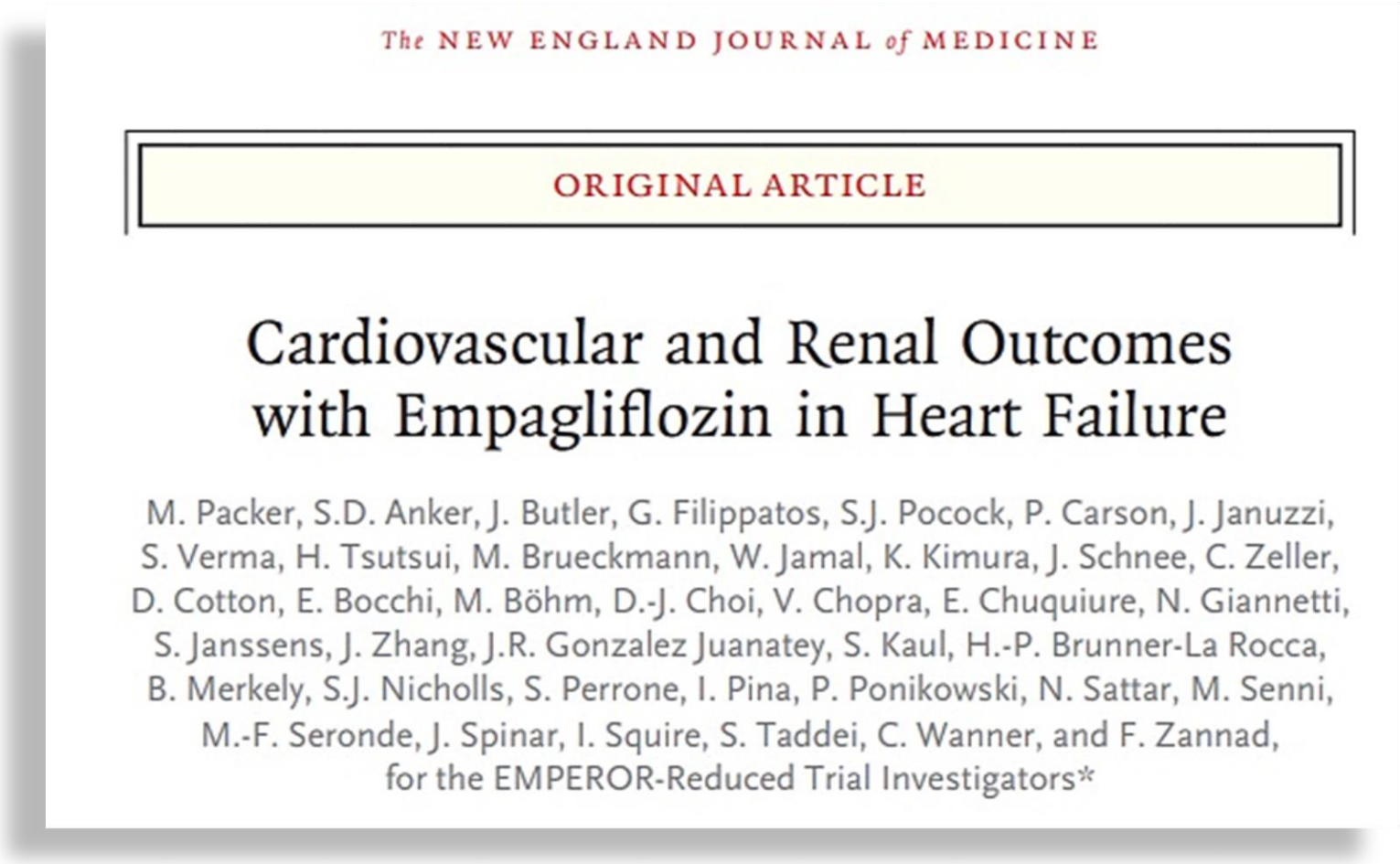


↓ Heart failure hospitalisations

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.

EMPEROR Trial Outcome



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*

Aim[1]:

To investigate the efficacy and safety of Empagliflozin in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction, with or without type 2 diabetes.

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

Trial Design[1]

Patients must be receiving all appropriate treatments for HF

3730 were randomized

≥841 Primary endpoint of the time-to-first event analysis of the combined risk of cardiovascular death and hospitalization for HF

1-N. Engl. J. Med 2020 Aug 29.
SOC: Standards of Medical Care

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)

1-N. Engl. J. Med 2020 Aug 29.
NYHA: Newyork Heart Association

Base-Line Characteristic of Patients[1]

Characteristic	Empagliflozin (N = 1863)	Placebo (N = 1867)
Cause of heart failure — no. (%)		
Ischemic	983 (52.8)	946 (50.7)
Nonischemic	880 (47.2)	921 (49.3)

1-N. Engl. J. Med 2020 Aug 29.
NYHA: Newyork Heart Association

Base-Line Characteristic of Patients[1]

Characteristic	Empagliflozin (N = 1863)	Placebo (N = 1867)
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)

1-N. Engl. J. Med 2020 Aug 29.
NYHA: Newyork Heart Association

Inclusion Criteria[1]

- **Key Inclusion Criteria:**
- NYHA class 2-4 with LVEF≤40%
- Elevated NT-proBNP
- Guideline-recommended medication stable ≥ week prior to first visit
- eGFR ≥20 ml/min/1.73m^2

1-N. Engl. J. Med 2020 Aug 29.
NYHA: Newyourk Heart Association; LVEF: Left Ventricular Ejection Fraction; eGFR: estimated glomerular filtration rate

Trial Endpoints[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

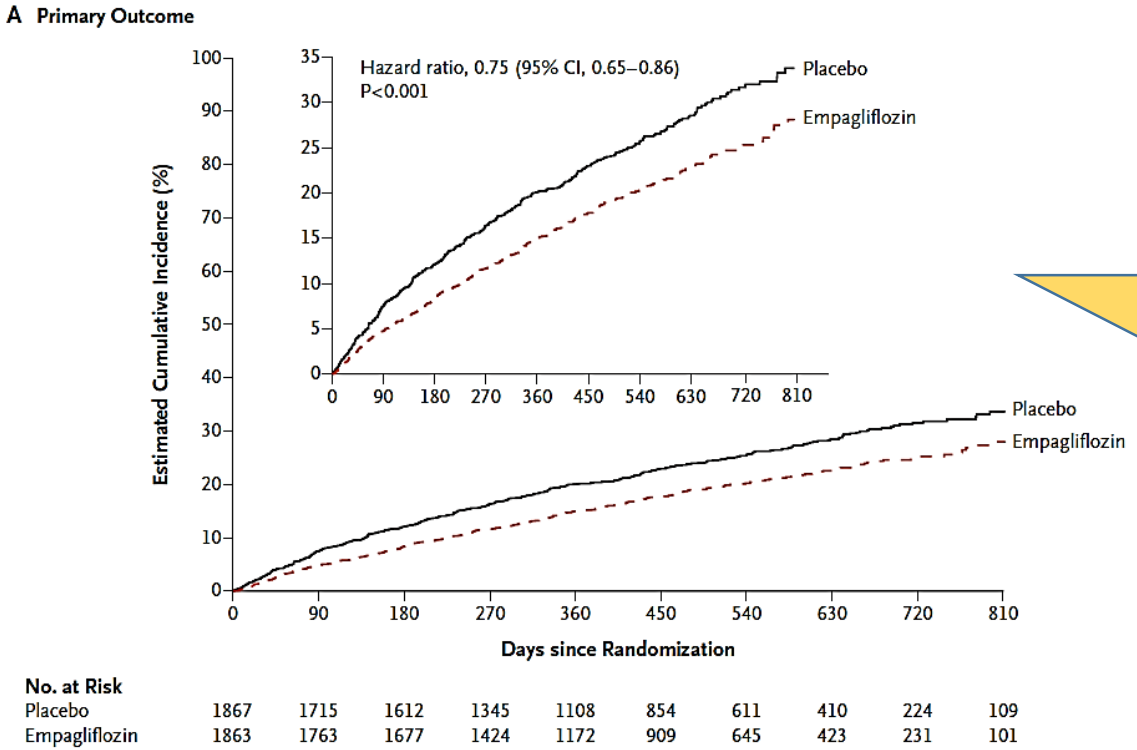
- Slope of decline in glomerular filtration rate over time

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.

Empagliflozin-Treated Patients Had Lower Incidence of Cardiovascular Death or Hospitalization for Heart Failure vs Placebo[1]

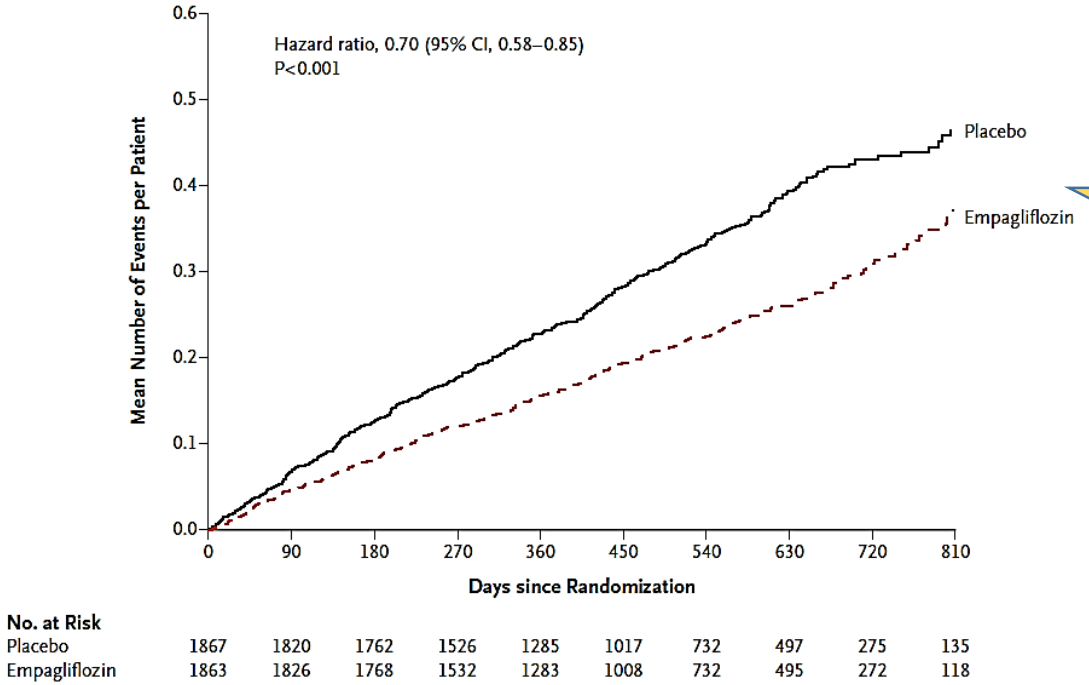


25% RRR
P<0.001
19.4% vs 24.7%
HR=0.75 (0.65-0.86)

The primary composite outcome of death from cardiovascular causes or hospitalization for heart failure occurred in 361 patients (19.4%) in the empagliflozin group and in 462 patients (24.7%) in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001).

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

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



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.

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.

The Relation Between T2DM and Kidney Disease

Growing Problem of Type 2 Diabetes and Kidney Disease[1]

- Diabetes, hypertension, or a combination of both, cause 80% of end-stage renal disease globally.[1]

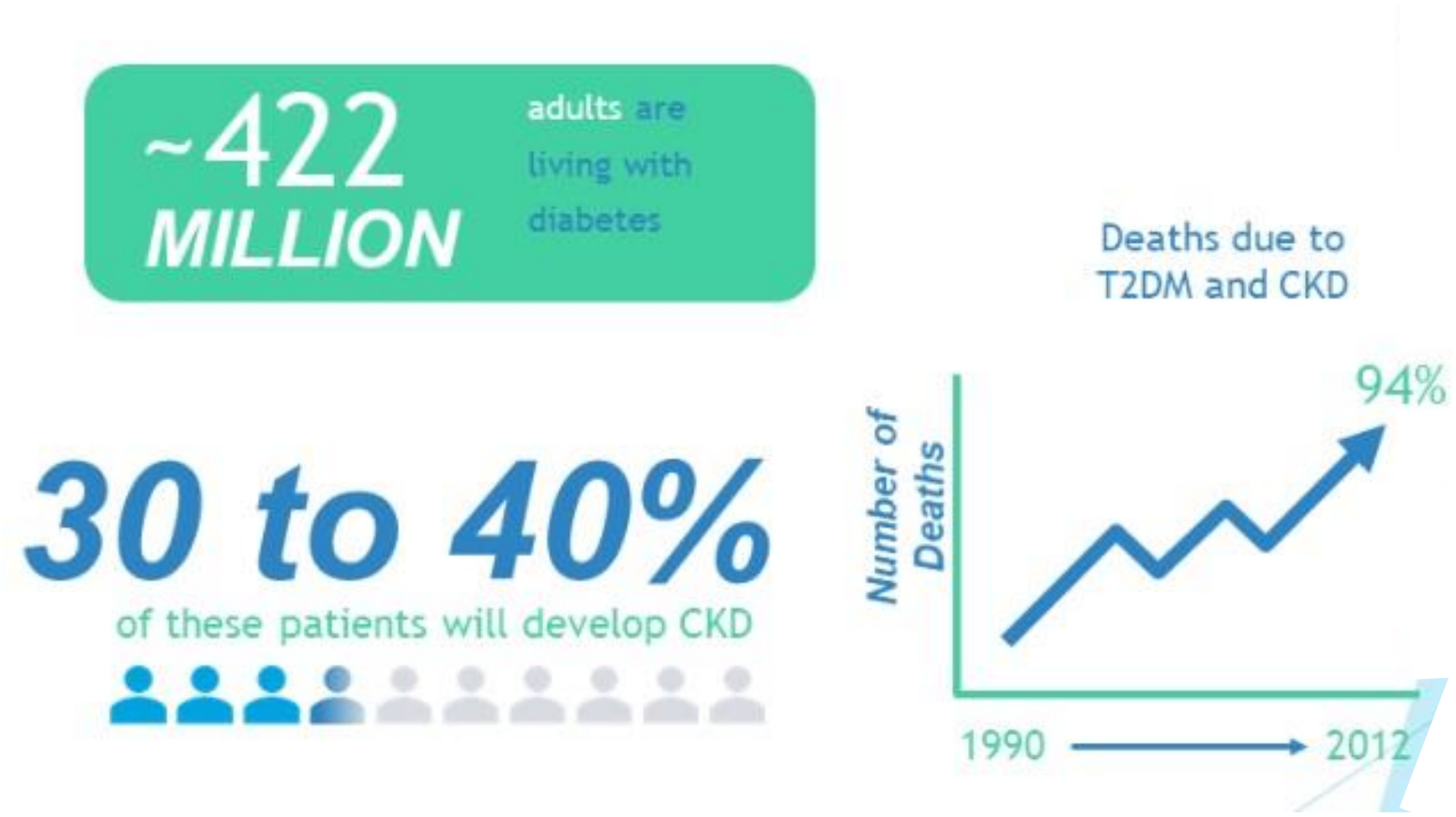
- Both diabetes and chronic kidney disease are strongly associated with cardiovascular diseases.

✓ Controlling blood glucose and blood pressure can reduce associated risks. [1]

- The most effective strategies to reduce the impact of kidney disease in diabetes are to prevent type 2 diabetes and to diagnose and treat kidney disease early and effectively in people already living with diabetes. [1]

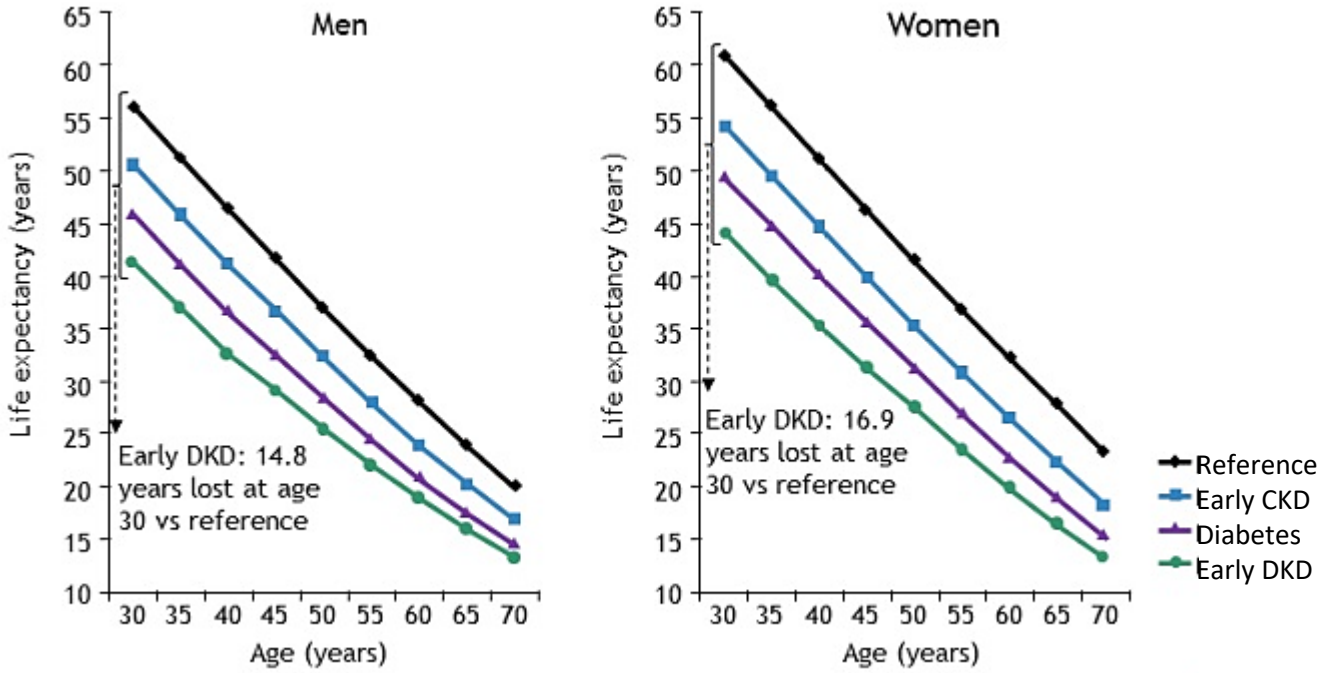
1-IDF Diabetes Atlas. 2019

Kidney Disease Attributed to Diabetes Is a Major But Under-recognized Contributor to the Global Burden of Disease[1]



1-Clin.J. Am Soc. Nephrol 2017. 12 (12).2032-2045

Diabetes Kidney Disease Shortens Life Span By 16 Years[1]

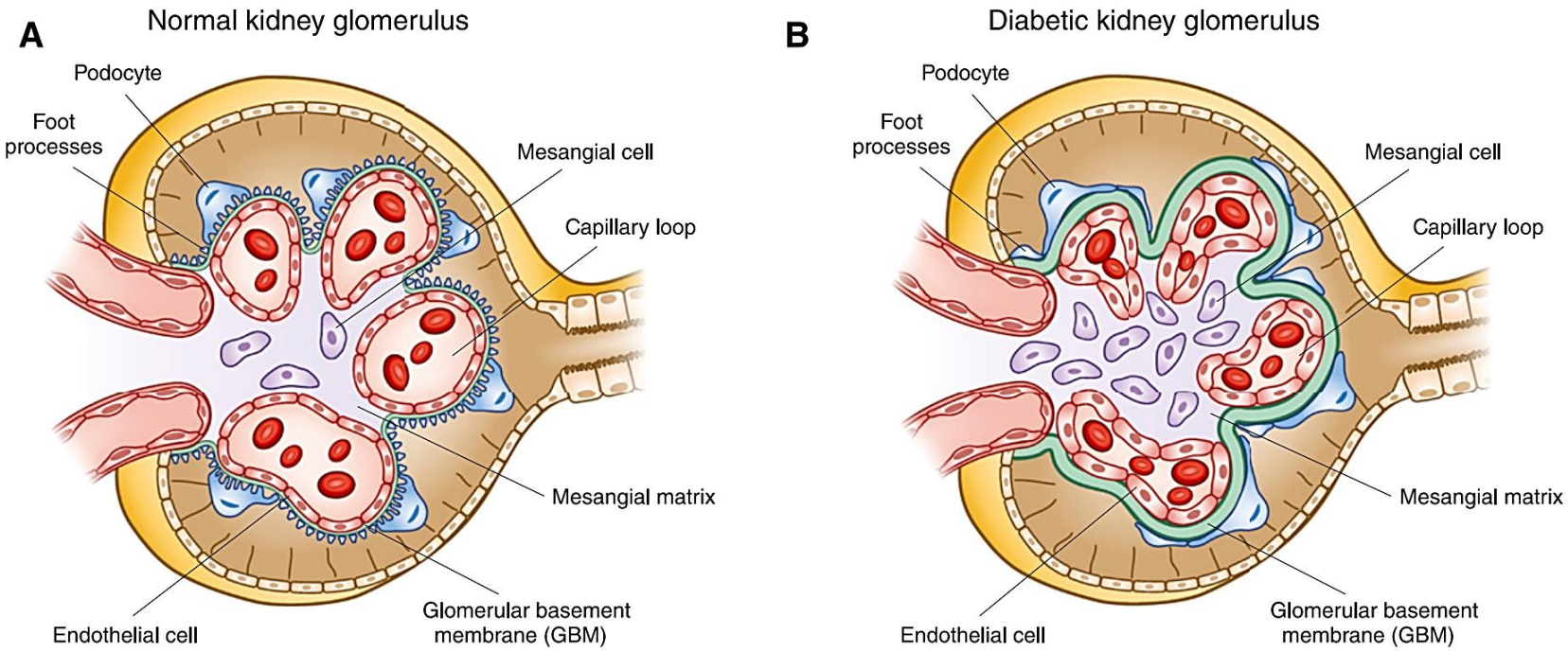


Life span loss with:
Early CKD: 6 years
Diabetes: 10 years
Early DKD: 16 years

At age 30 years, the life expectancy of participants with early DKD was 14.8 years shorter for men and 16.9 years shorter for women compared with the reference group. At age 50 years, the life expectancy of participants with early DKD was 11.5 and 14.1 years shorter for men and women, respectively, compared with the reference group. In comparison, at age 30 years life expectancy was 10.2 years (men) and 11.7 years (women) shorter for the diabetes without CKD group, and 5.7 years (men) and 6.7 years (women) shorter for the CKD without diabetes group.[1]

1-kidney Int.2017.92(2); 388-396.
DKD: Diabetes Kidney Disease
CKD: Chronic Kidney Disease

Normal Kidney Morphology and Structural Changes in Diabetes Mellitus[1]



Diabetic kidney disease induces structural changes, including thickening of the glomerular basement membrane, fusion of foot processes, loss of podocytes with denuding of the glomerular basement membrane, and mesangial matrix expansion.[1]

1-Clin J Am Soc Nephrol. 2017;12(12):2032-2045.

SGLT2 Inhibitors for the Prevention of Kidney Failure in T2DM

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

Brendon L Neuen, Tamara Young, Hiddo J L Heerspink, Bruce Neal, Vlado Perkovic, Laurent Billot, Kenneth W Mahaffey, David M Charytan, David C Wheeler, Clare Arnott, Severine Bompoint, Adeera Levin, Meg J Jardine

Aim:[1] to assess the effects of SGLT2 inhibitors on major kidney outcomes in patients with type 2 diabetes and to determine the consistency of effect size across trials and different levels of eGFR and albuminuria.

1-The lancet diabetes &endocrinology. 2019.S2213-8587(19)30256-6

Characteristics of Included Studies[1]

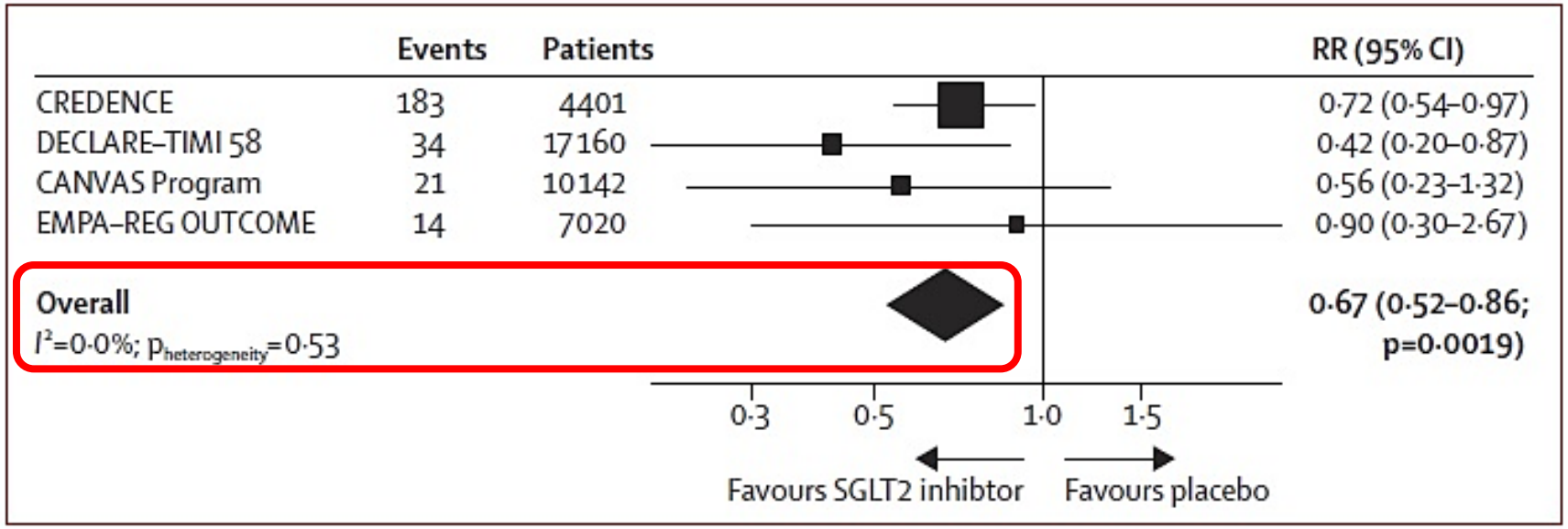
	EMPA-REG OUTCOME	CANVAS Program	DECLARE–TIMI 58	CREDENCE
Drug	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin
Dose (mg)	10 and 25	100 and 300	10	100
Number of participants	7020	10 142	17 160	4401
Mean age (years)	63·1	63·3	63·9	63·0
Sex				
Men	5016 (71·5%)	6509 (64·2%)	10 738 (62·6%)	2907 (66·1%)
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)	1494 (33·9%)
Median follow-up (years)	3·1	2·4	4·2	2·6*
eGFR inclusion criteria	≥30 (MDRD)	≥30 (MDRD)	CrCl ≥60 mL/min (Cockcroft-Gault)	30 to <90 (CKD-EPI)
Baseline eGFR subgroup (mL/min per 1·73 m²)†‡				
≥90	1538 (21·9%)	2476 (24·4%)	8162 (47·6%)	0
60 to <90	3661 (52·2%)	5625 (55·5%)	7732 (45·1%)	1809 (41·1%)
45 to <60	1249 (17·8%)	1485 (14·6%)	1265 (7·4%)§	1279 (29·1%)
<45	570 (8·1%)	554 (5·5%)	NA	1313 (29·8%)
Missing baseline eGFR	2 (<0·1%)	2 (<0·1%)	1 (<0·1%)	0
UACR criteria (mg/g)	None	None	None	>300 to 5000
Baseline UACR subgroup (mg/g)‡				
<30	4171 (59·4%)	7007 (69·1%)	11 644 (67·9%)	0
30–300	2013 (28·7%)	2266 (22·3%)	4030 (23·5%)	0
>300	769 (11·0%)	760 (7·5%)	1169 (6·8%)	4401 (100·0%)
Missing baseline UACR	67 (1·0%)	109 (1·1%)	317 (1·8%)	0
Baseline use of RAS blockade	5666 (80·7%)	8116 (80·0%)	13 950 (81·3%)	4395 (99·9%)

Data are n (%), unless otherwise specified. eGFR=estimate glomerular filtration rate. MDRD=Modification of Diet in Renal Disease equation. CrCl=creatinine clearance. CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration equation. UACR=urine albumin-to-creatinine ratio. RAS=renin–angiotensin system. NA=not available. *Stopped early after a planned interim analysis on the recommendation of the independent data monitoring committee. †Based on the MDRD equation in EMPA-REG OUTCOME and the CANVAS Program and on the CKD-EPI equation in DECLARE–TIMI 58 and CREDENCE. ‡Based on screening (rather than baseline) eGFR and UACR measurements in the CREDENCE trial. §Includes all DECLARE–TIMI 58 participants with eGFR lower than 60 mL/min per 1·73m².

Table: **Characteristics of included studies**

1-The lancet diabetes &endocrinology. 2019.S2213-8587(19)30256-6

SGLT2 Inhibitors reduced the risk of Dialysis, Transplantation, or Death Due to Kidney Disease by 33% compared with placebo [1]

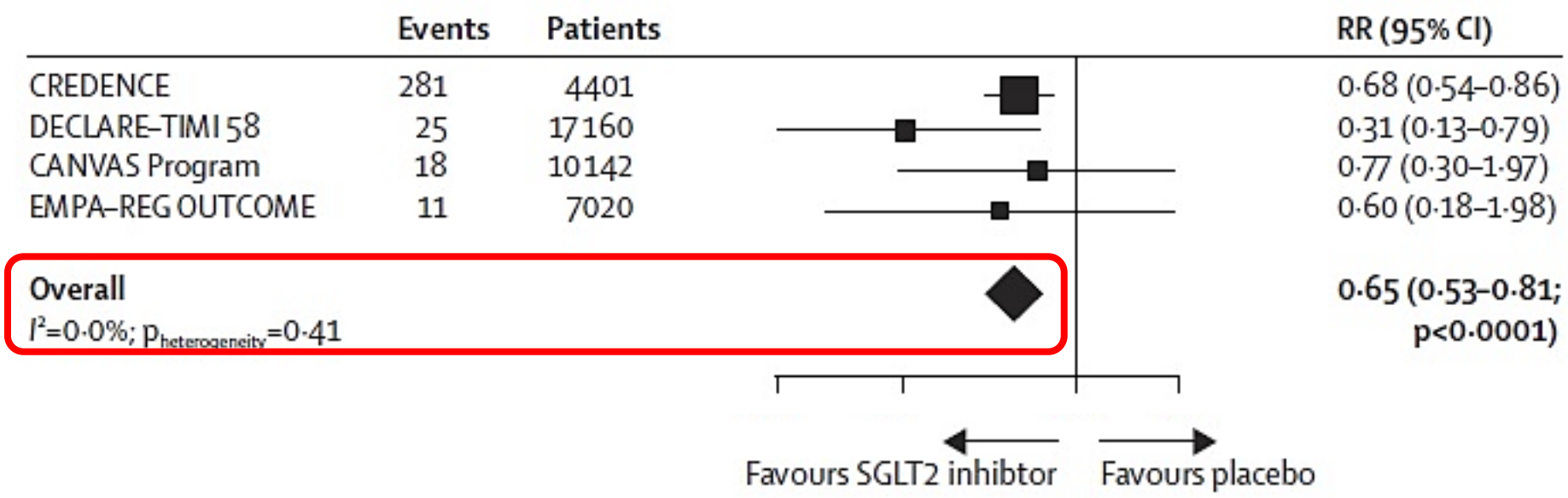


SGLT2 inhibitor treatment reduced the risk of dialysis, transplantation, or death due to kidney disease.

1-The lancet diabetes &endocrinology. 2019.S2213-8587(19)30256-6

Weights were from random-effects meta-analysis. Data from DECLARE-TIMI 58 have not been previously reported. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

SGLT2 Inhibitors Reduced the Risk of End-Stage Kidney Disease by 35% Compared with Placebo.[1]

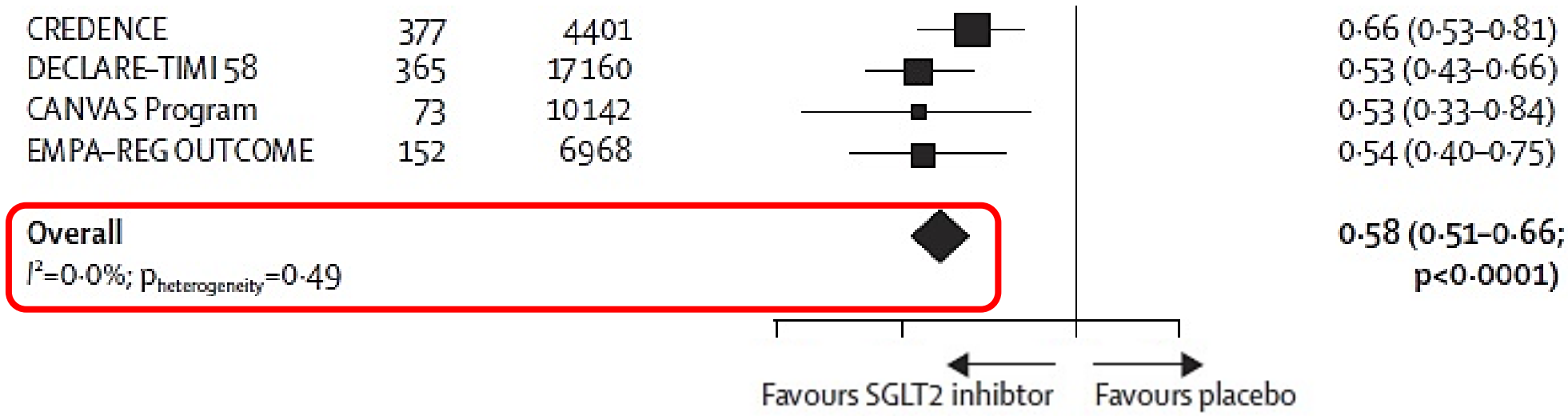


SGLT2 inhibitor treatment reduced the risk of end-stage kidney disease, with no differences in treatment effect across studies.

1-The lancet diabetes &endocrinology. 2019.S2213-8587(19)30256-6

Weights were from random effects meta-analysis. ESKD was defined as chronic dialysis, transplantation, or sustained estimated glomerular filtration rate (eGFR) lower than 15 mL/min per 1·73 m², apart from in the EMPA-REG OUTCOME trial, in which it was defined as chronic dialysis or transplantation. Substantial loss of kidney function was defined as doubling of serum creatinine, apart from in the DECLARE–TIMI 58 trial, in which it was defined as sustained 40% decline in eGFR. ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

SGLT2 Inhibitors Reduced the Risk of Substantial Loss of Kidney Function, ESKD, or Death Due to Kidney Disease by 42% vs Placebo[1]

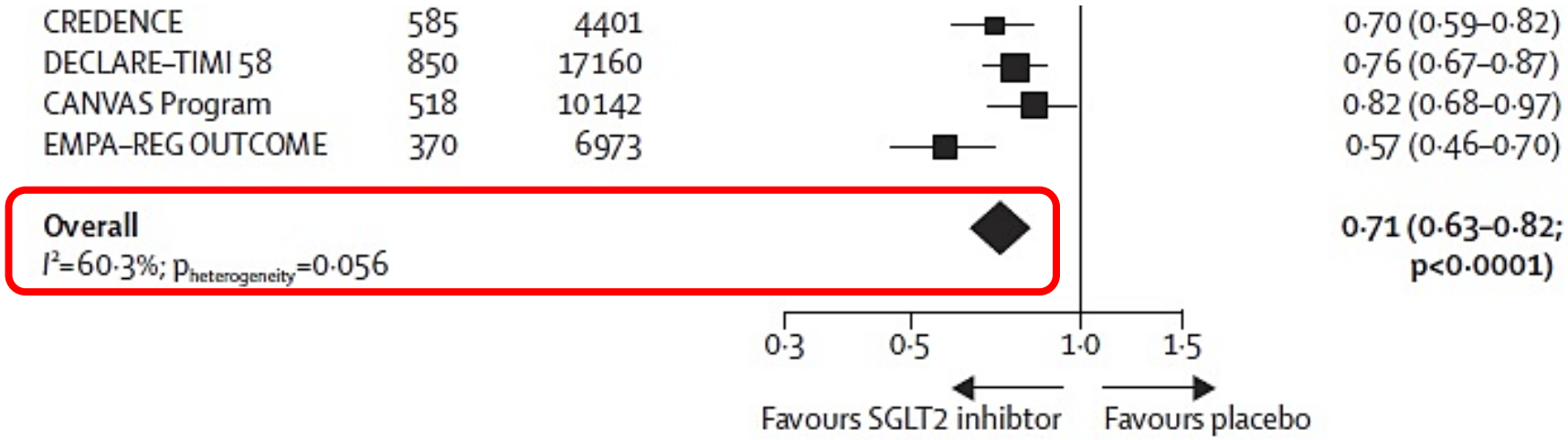


The use of SGLT2 inhibitors also reduced the risk of substantial loss of kidney function, end-stage kidney disease, or death due to kidney disease, with no evidence of differences between studies.

1-The lancet diabetes &endocrinology. 2019.S2213-8587(19)30256-6

Weights were from random effects meta-analysis. ESKD was defined as chronic dialysis, transplantation, or sustained estimated glomerular filtration rate (eGFR) lower than 15 mL/min per 1·73 m², apart from in the EMPA-REG OUTCOME trial, in which it was defined as chronic dialysis or transplantation. Substantial loss of kidney function was defined as doubling of serum creatinine, apart from in the DECLARE–TIMI 58 trial, in which it was defined as sustained 40% decline in eGFR. ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

SGLT2 Inhibitors Reduced the Risk of Substantial Loss of Kidney Function, ESKD, or Death Due to Cardiovascular or Kidney Disease by 29% vs Placebo[1]

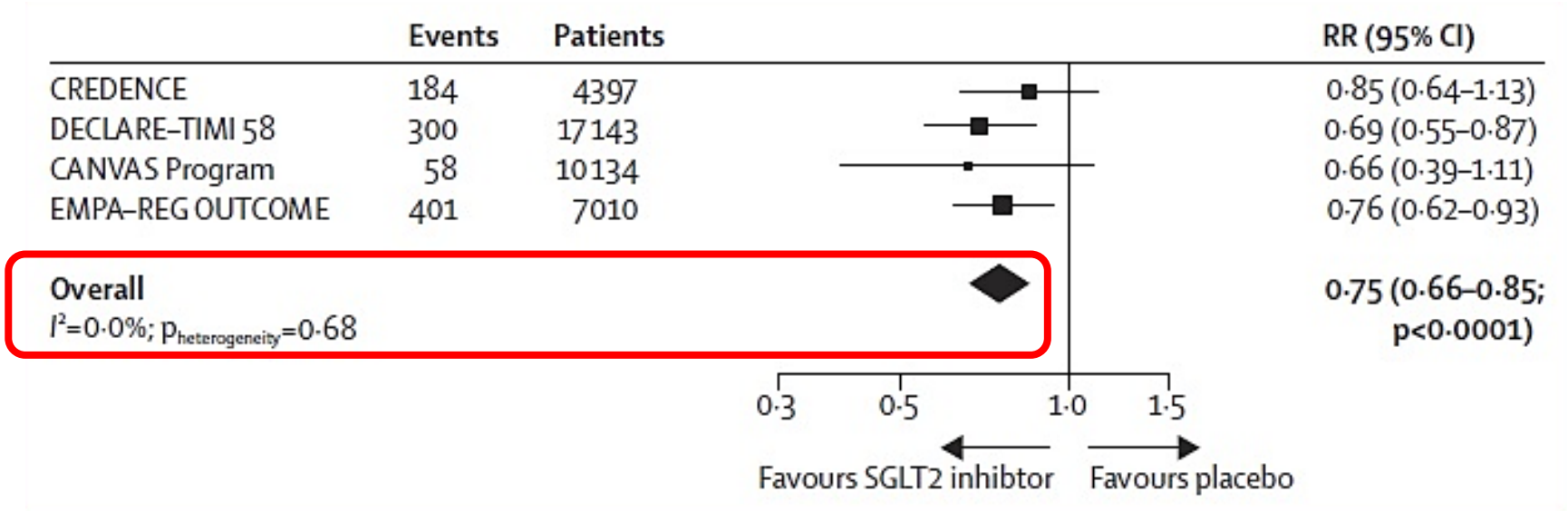


The overall effect of SGLT2 inhibitors on substantial loss of kidney function, end-stage kidney disease, death due to cardiovascular or kidney disease varied across studies, primarily because of the EMPA-REG OUTCOME trial, in which a greater magnitude of effect on death due to cardiovascular disease was observed.

1-The lancet diabetes &endocrinology. 2019.S2213-8587(19)30256-6

Weights were from random effects meta-analysis. ESKD was defined as chronic dialysis, transplantation, or sustained estimated glomerular filtration rate (eGFR) lower than 15 mL/min per 1·73 m², apart from in the EMPA-REG OUTCOME trial, in which it was defined as chronic dialysis or transplantation. Substantial loss of kidney function was defined as doubling of serum creatinine, apart from in the DECLARE–TIMI 58 trial, in which it was defined as sustained 40% decline in eGFR. Data on substantial loss of kidney function, ESKD, or death due to cardiovascular or kidney disease in EMPA-REG OUTCOME have not been previously published. ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

SGLT2 Inhibitors Reduced the Risk of Acute Kidney Injury by 25% vs Placebo[1]

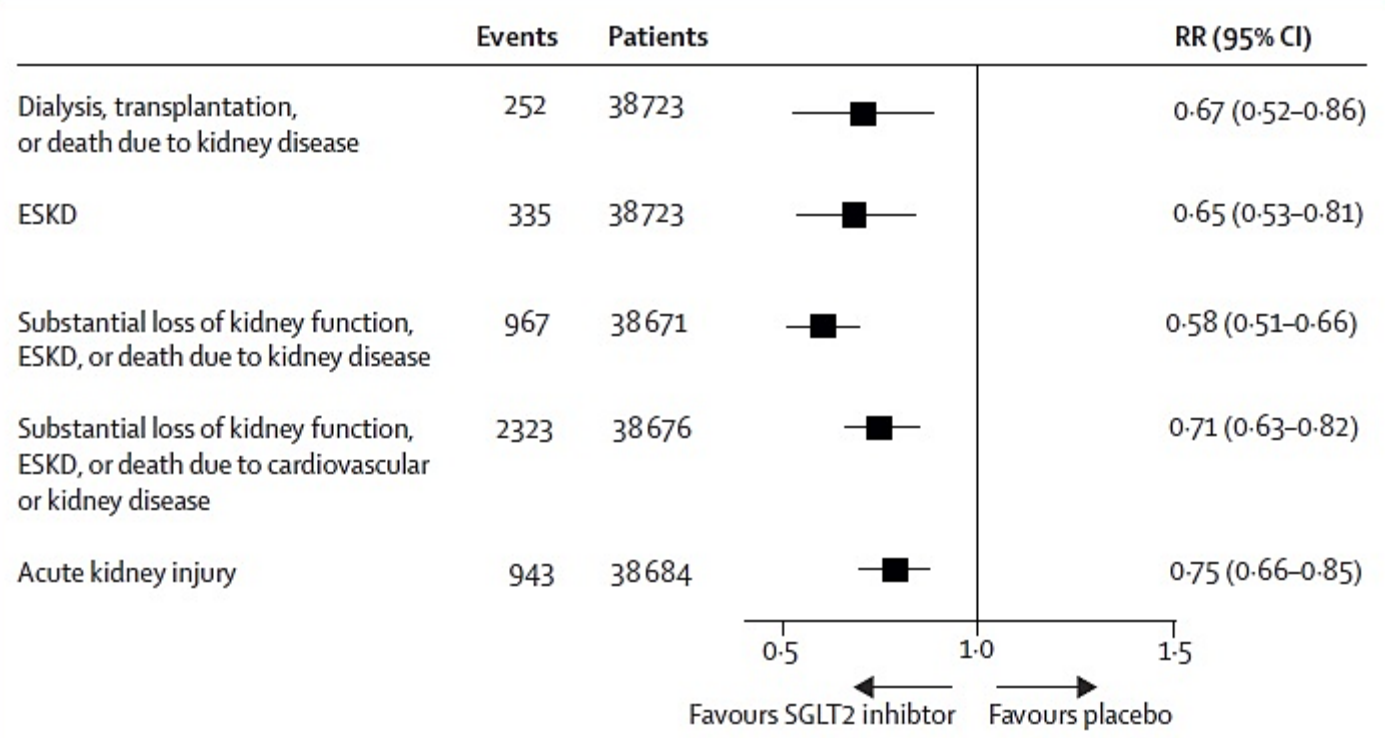


Treatment with SGLT2 inhibitors also lowered the risk of acute kidney injury, with no evidence of differences between studies.

1-The lancet diabetes &endocrinology. 2019.S2213-8587(19)30256-6

Weights were from random-effects meta-analysis. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

SGLT2 Inhibition Resulted in Lower Major Kidney Outcomes[1]



The use of SGLT2 inhibitors prevent major kidney outcomes in people with type 2 diabetes.

1-The Lancet Diabetes & Endocrinology, 7(11), pp.845-854.

ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

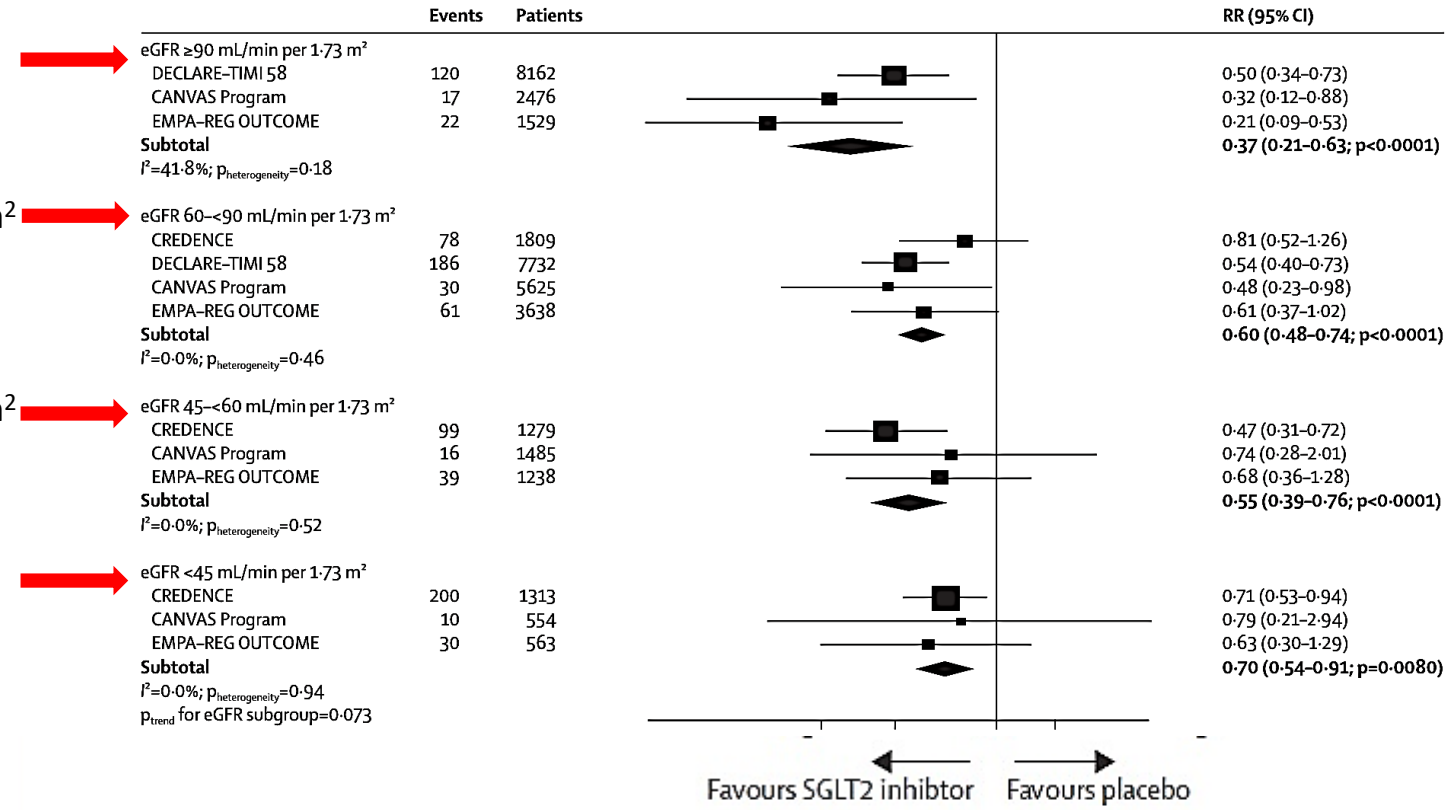
Beneficial Effects of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease is attenuated across all eGFR levels[1]

eGFR>90 mL/min/1.73m^2

eGFR 60-<90 mL/min/1.73m^2

eGFR 45-<60 mL/min/1.73m^2

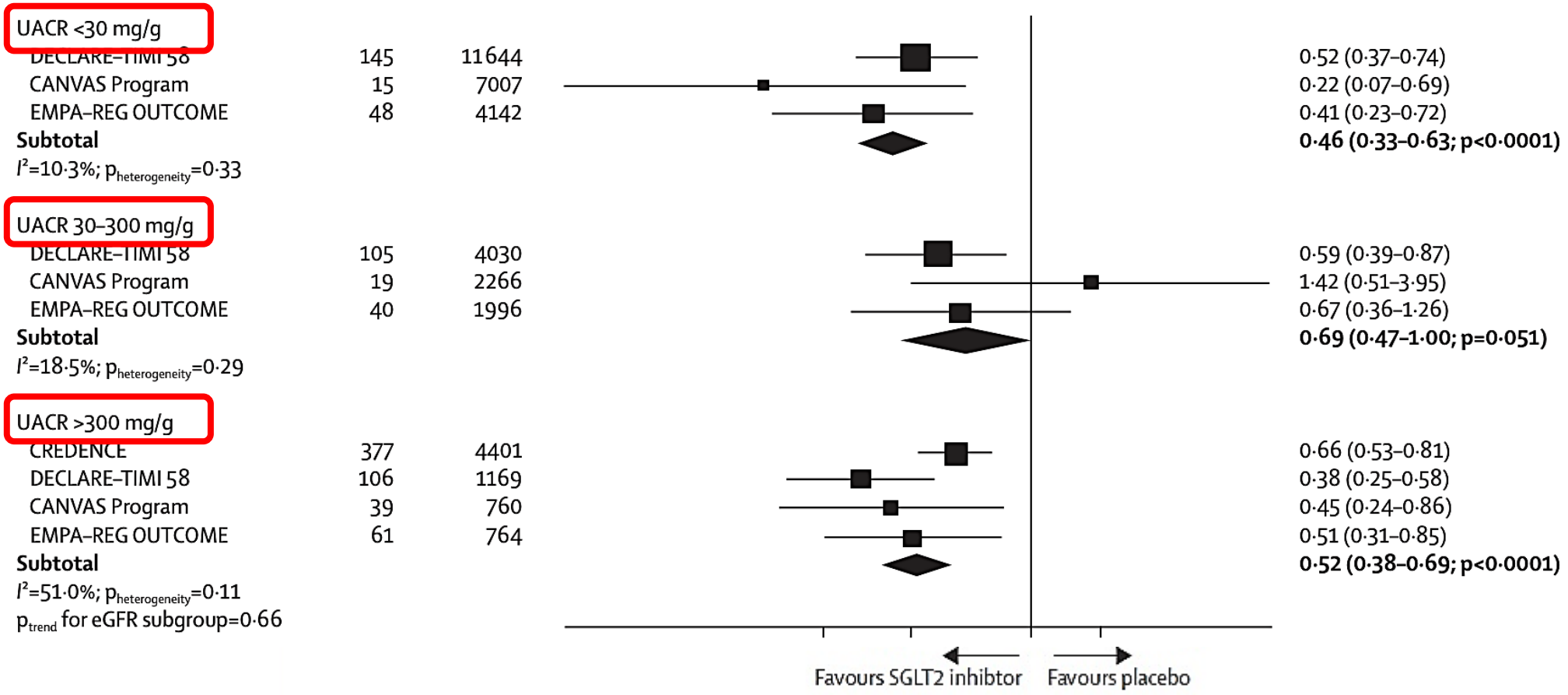
eGFR <45 mL/min/1.73m^2



The magnitude of benefit of SGLT2 inhibitors might be attenuated across progressively lower eGFR subgroups (ptrend=0·073); Separately significant evidence of benefit was apparent for all eGFR subgroups, including for participants with a baseline eGFR lower than 45 mL/min per 1·73 m², in whom a 30% relative risk reduction was identified.

1-The Lancet Diabetes & Endocrinology, 7(11), pp.845-854. ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

SGLT2 inhibitors affect beneficially on substantial loss of kidney function, ESKD, or death due to kidney disease in all baselines of UACR[1]

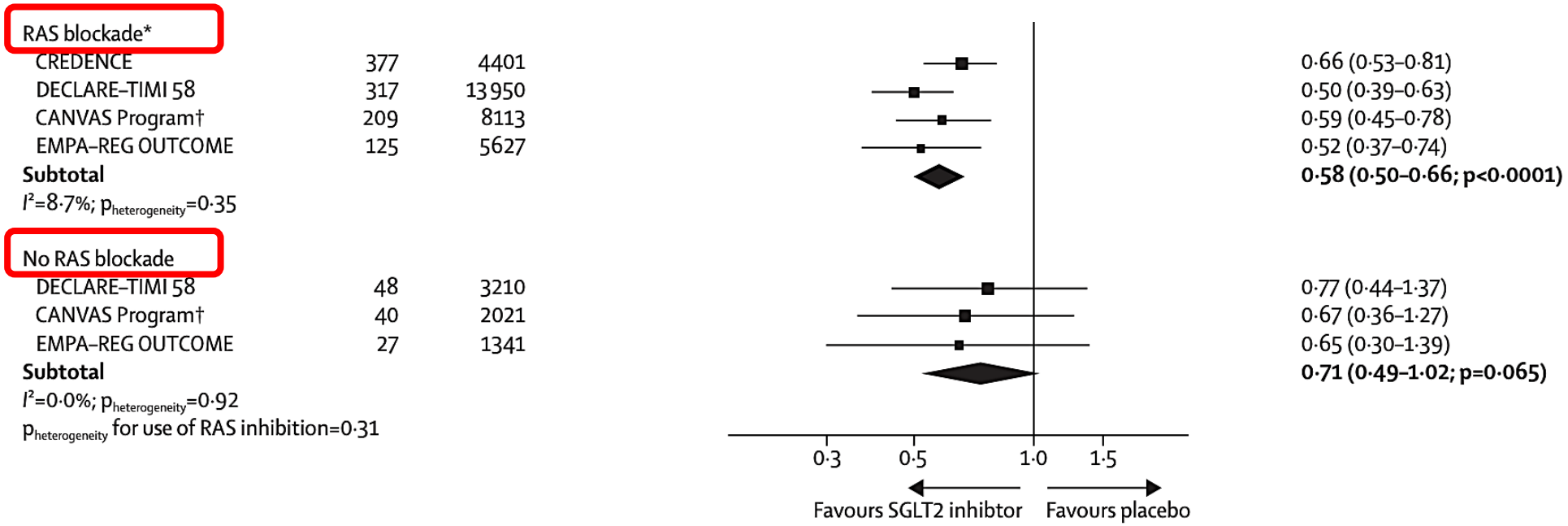


There was no evidence of differences in treatment effect of SGLT2 ihibitors for the composite outcome across UACR subgroups (ptrend=0·66).

1-The Lancet Diabetes & Endocrinology, 7(11), pp.845-854.

ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

Effect of SGLT2 inhibitors on substantial loss of kidney function, ESKD, or death due to kidney disease is not affected by using RAS blockade [1]



The effect of SGLT2 inhibitors was consistent between users and non-users of RAS blockade-based treatments at baseline (P heterogeneity=0·31).

1-The Lancet Diabetes & Endocrinology, 7(11), pp.845-854.

ESKD=end-stage kidney disease. SGLT2=sodium-glucose co-transporter-2. RR=relative risk.

Empa-Reg Renal Outcome

The NEW ENGLAND JOURNAL of MEDICINE

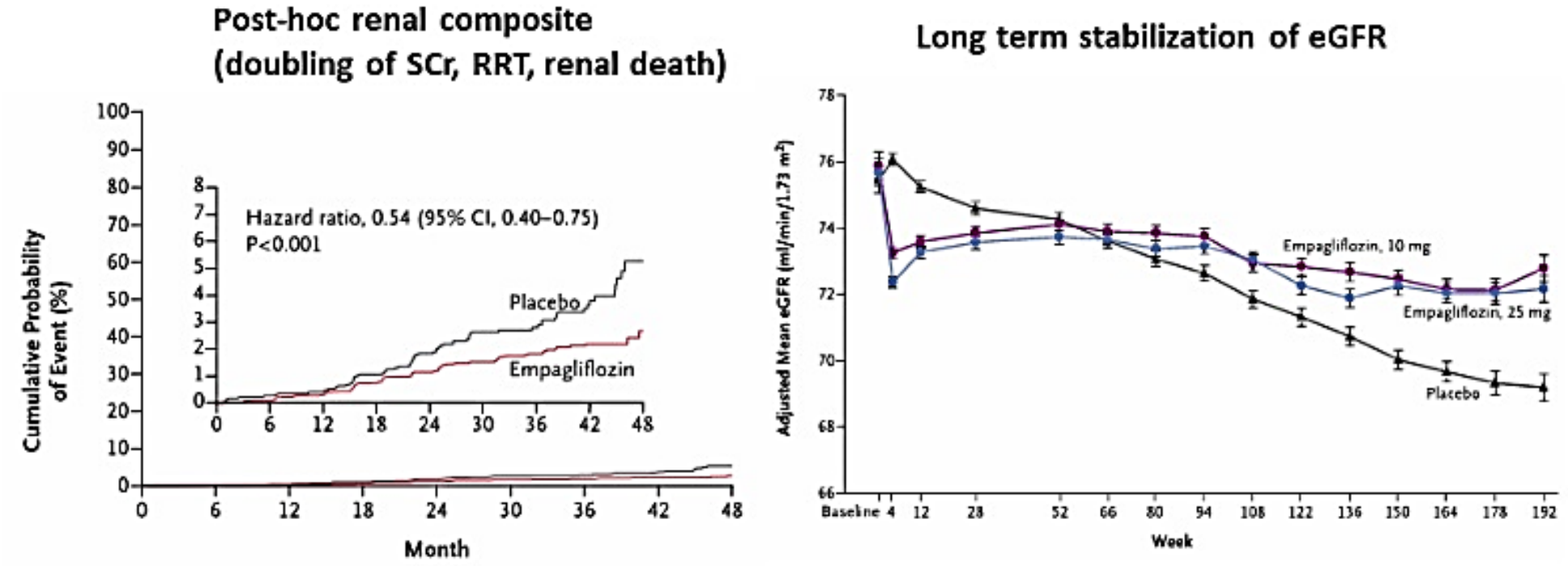
ORIGINAL ARTICLE

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; 28;375(4):323-34.

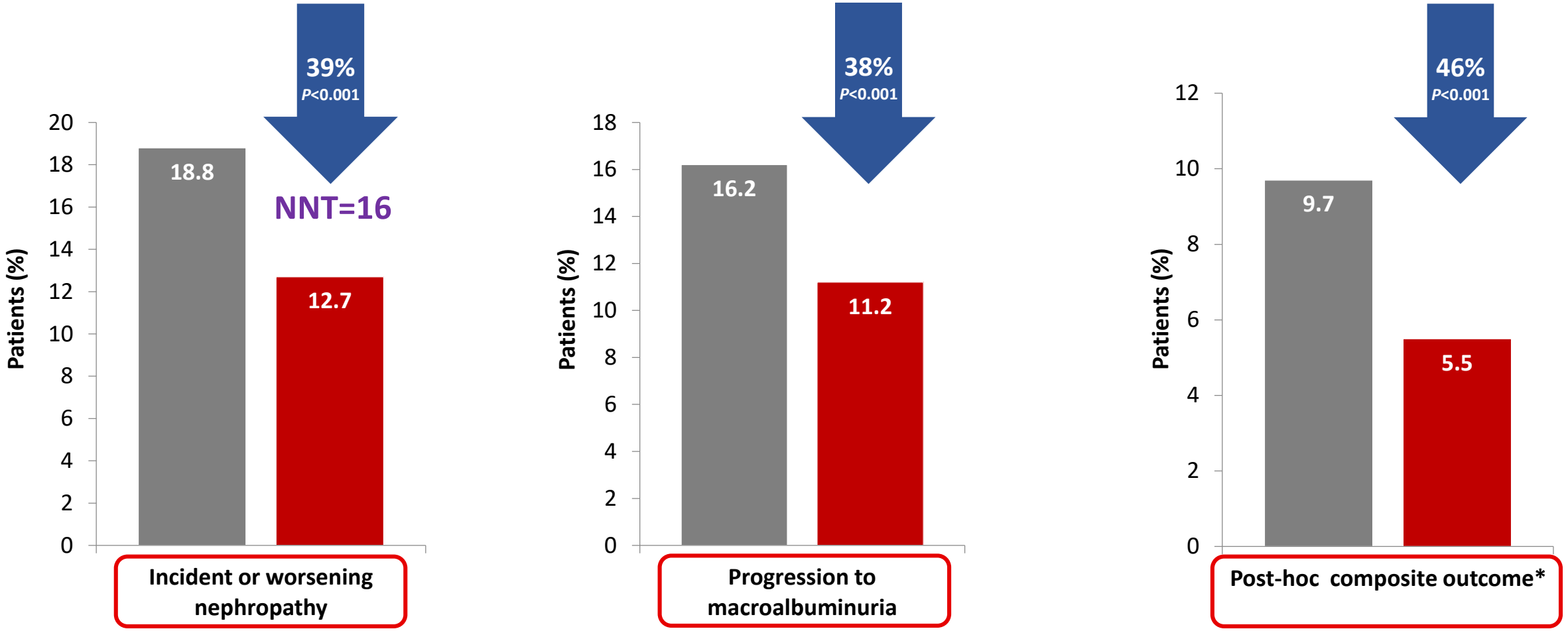
Empagliflozin Suggests Reno-Protection[1]



Empagliflozin reduced eGFR over time and resulted in lower renal composite vs placebo.

1-N. Engl. J. Med. 2016; 28;375(4):323-34.

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

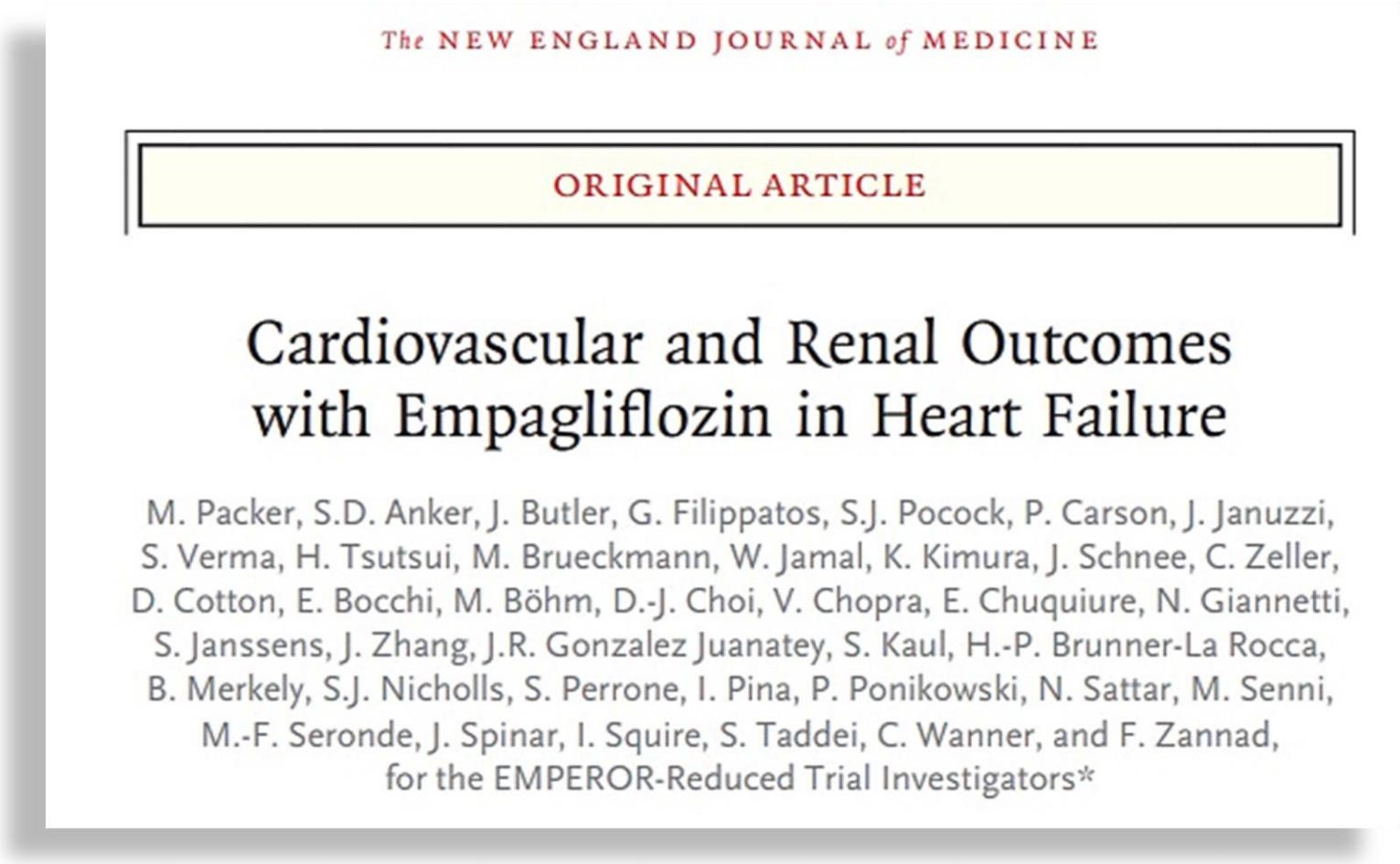


Arrows = relative risk reduction

*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; 28;375(4):323-34.

EMPEROR-Reduced Kidney Results



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

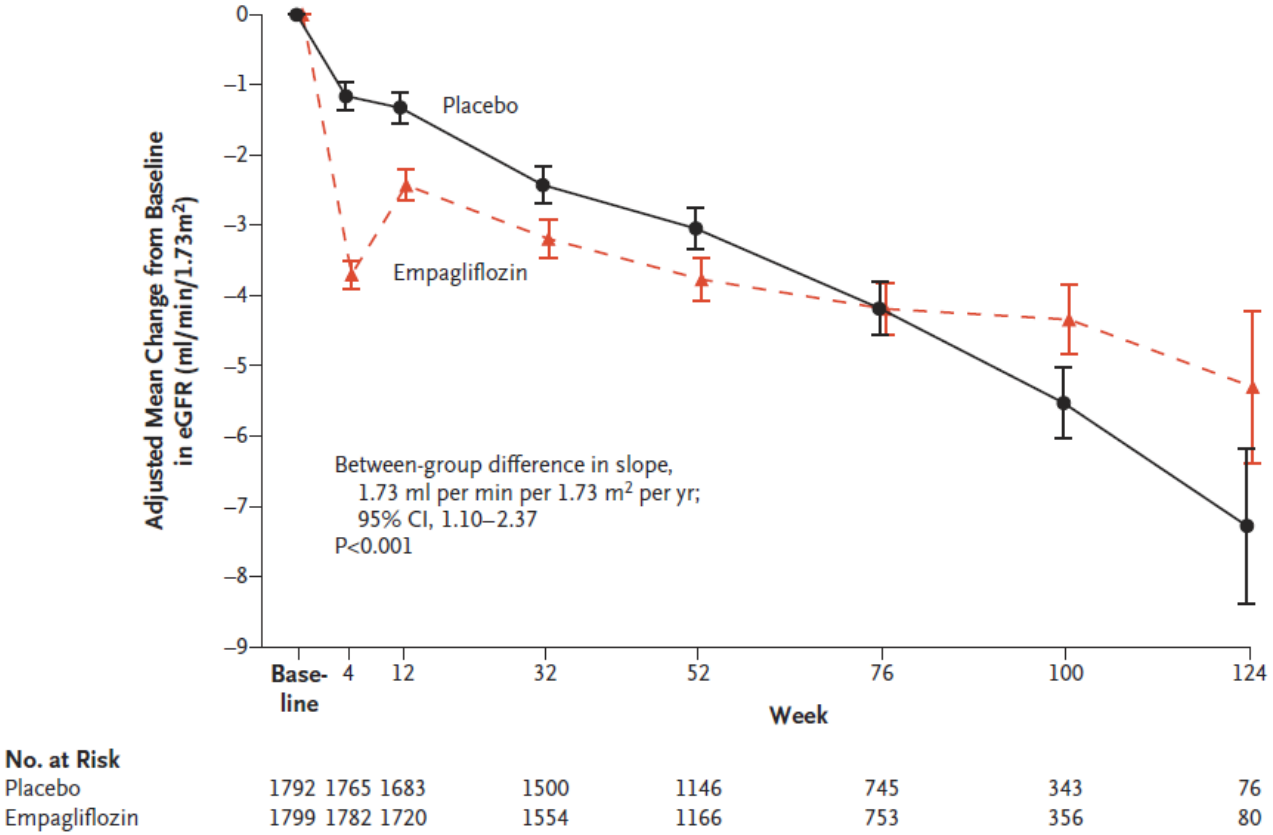
M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, 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*

Aim[1]:

To investigate the efficacy and safety of Empagliflozin in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction, with or without type 2 diabetes.

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

Empagliflozin Reduced the Decline of eGFR Slope Significantly Over Time vs Placebo[1]



–2.28 ml / min / 1.73 m2 / year
On placebo

– 0.55 ml /min/1.73 m2 / year
On Empagliflozin

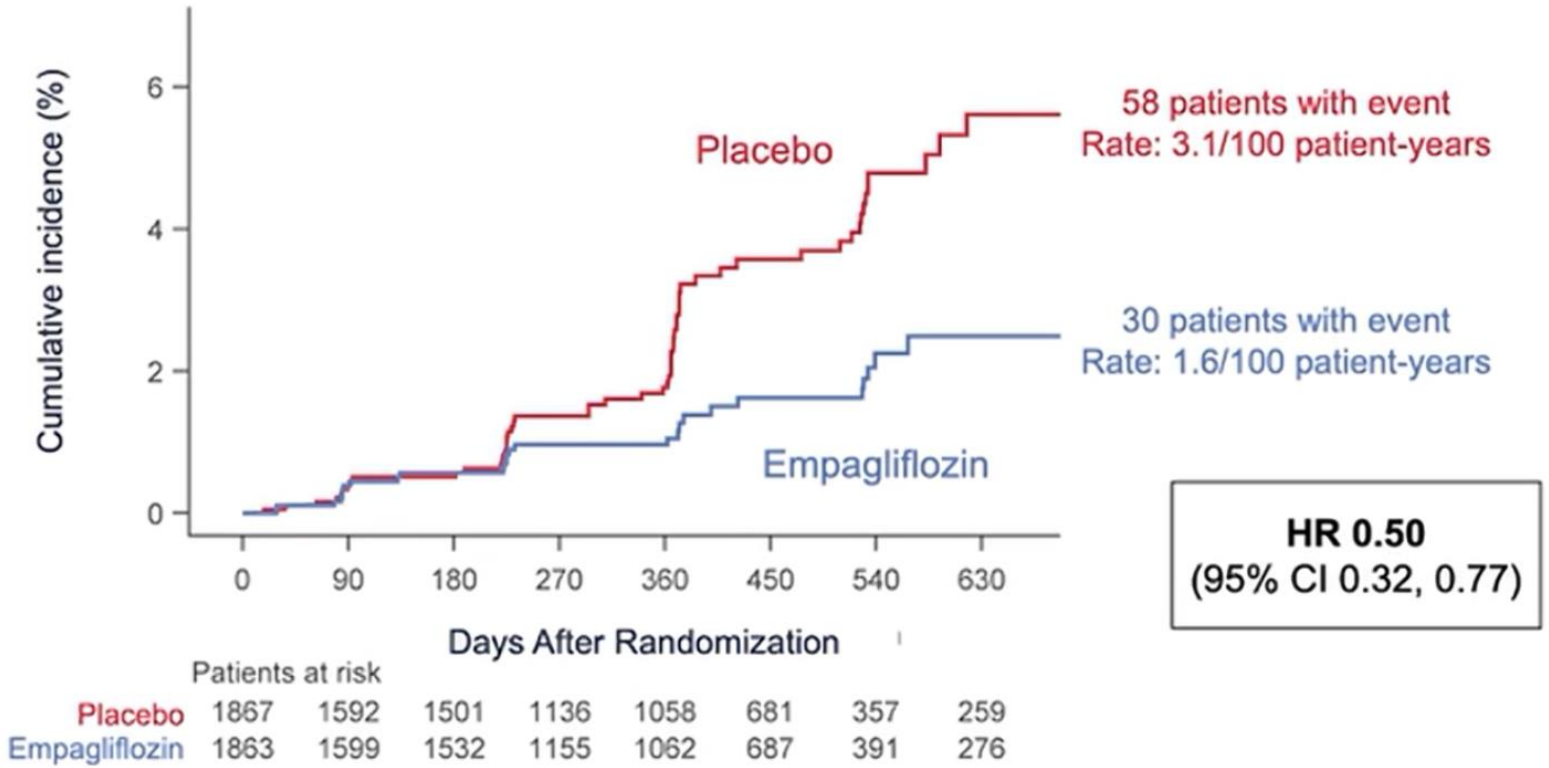
1.73 ml / min / 1.73 m2 / year

P < 0.001

✓ Empagliflozin was associated with a slower progressive decline in renal function in patients with chronic HF and a reduced EF, regardless of the presence or absence of diabetes[2].

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

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).[1]

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

Dosage & Administration of Empagliflozin

Convenience of a once-daily oral treatment[1]

STARTING DOSE	10 mg 1 × daily The recommended starting dose for Empagliflozin is 10 mg once daily
INCREASE TO	25 mg 1 × daily For patients who tolerate 10 mg once daily who have an eGFR ≥ 60 mL/min/1.73 m^2 and need tighter glycemic control, their dose can be increased to 25 mg once daily

Empagliflozin can be taken

With or without food

At any time of day*

When Empagliflozin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia

eGFR, estimated glomular filtration rate.
*It is advisable to take JARDIANCE® at the same time each day, which will help with patient adherence.
A missed dose can be taken if it is ≥ 12 hours until the next dose; if it is < 12 hours, the missed dose should be skipped.

1-Jardiance FDA label 2018. Reference ID: 4367802


Thank you