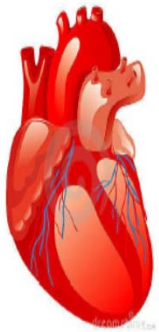
Emerging **Insulin-Independent Approaches** for the Management of T2DM

Cardiovascular disease and diabetes

~65% of deaths are due to CV disease



Coronary heart disease deaths ↑2- to 4-fold

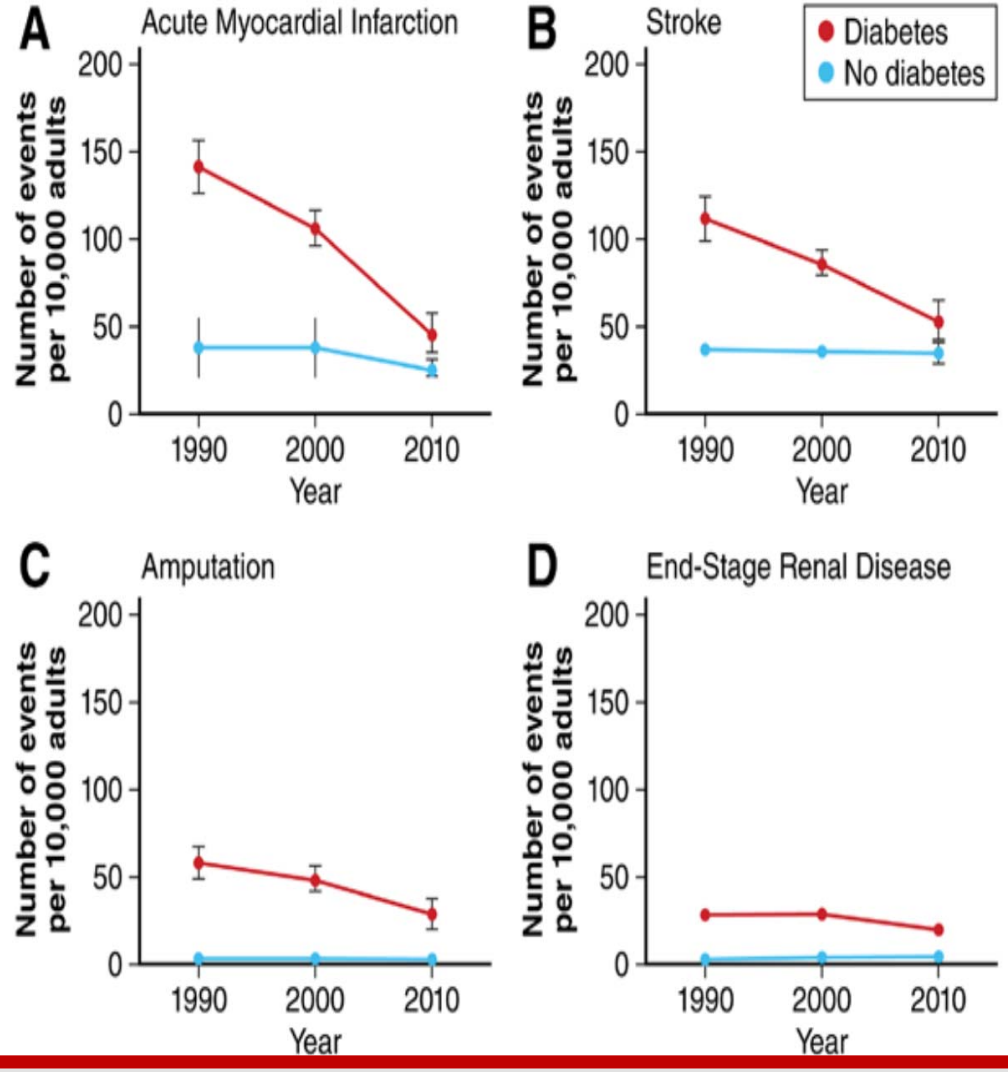
Cardiovascular complications of T2DM

Stroke risk ↑2- to 4-fold

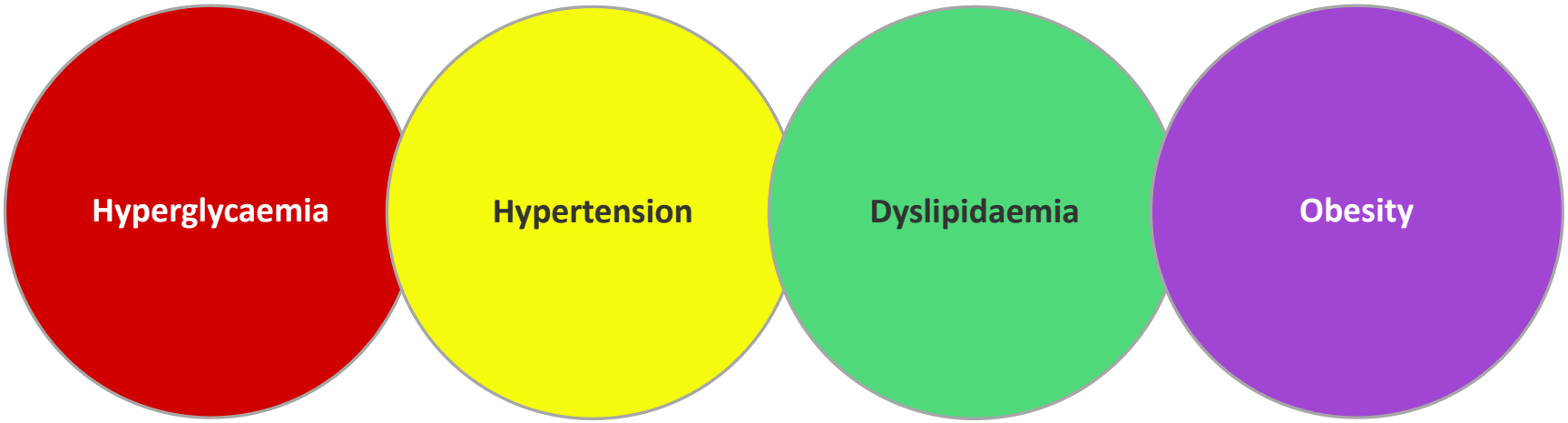
Heart failure ↑2- to 5-fold

T2DM = type 2 diabetes mellitus

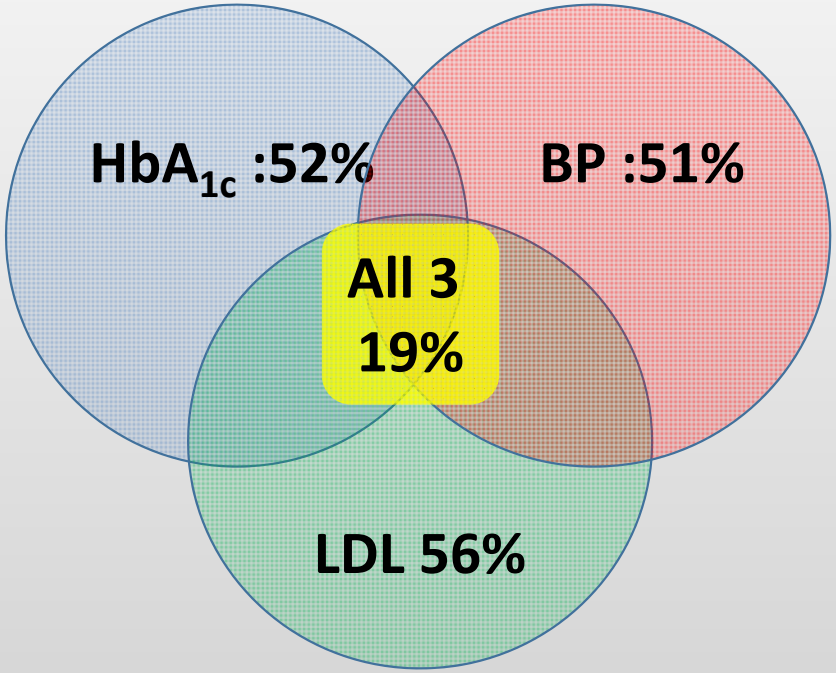
Bell DSH. *Diabetes Care*. 2003;26:2433-41.
Centers for Disease Control (CDC). www.cdc.gov.



Modifiable CV risk factors are common in **T2DM**



Diabetes Patients at Goal



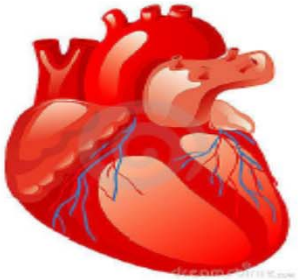
Points in choosing a proper medication

- Safety profiles
- Effectiveness
- Side effects
- Patient satisfaction
- Extra-glycemic effects
- Cost

Extraglycemic effects

Cardiovascular disease and diabetes

~65% of deaths are due to CV disease



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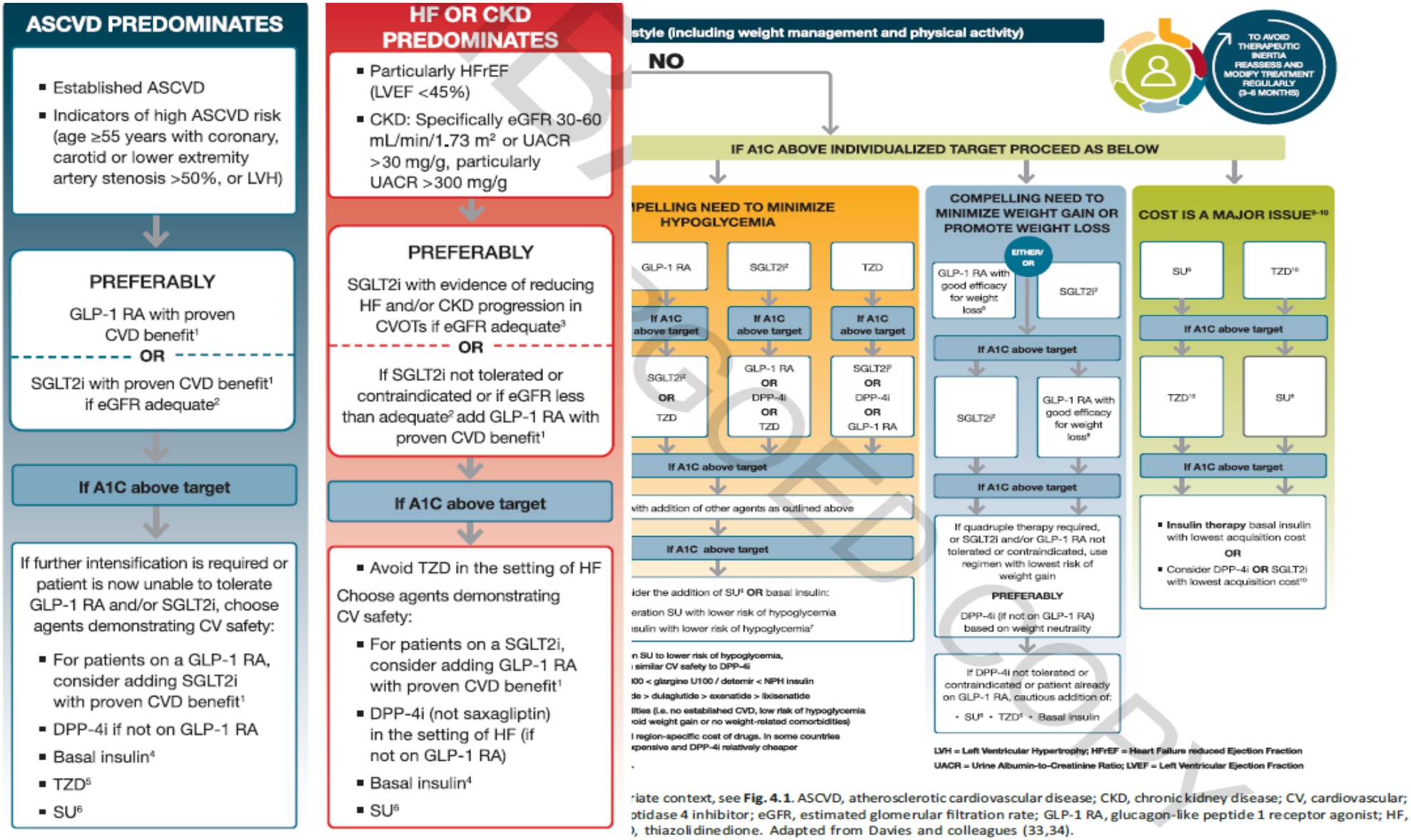

riate context, see **Fig. 4.1**. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; ptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF,), thiazolidinedione. Adapted from Davies and colleagues (33,34).

ey in
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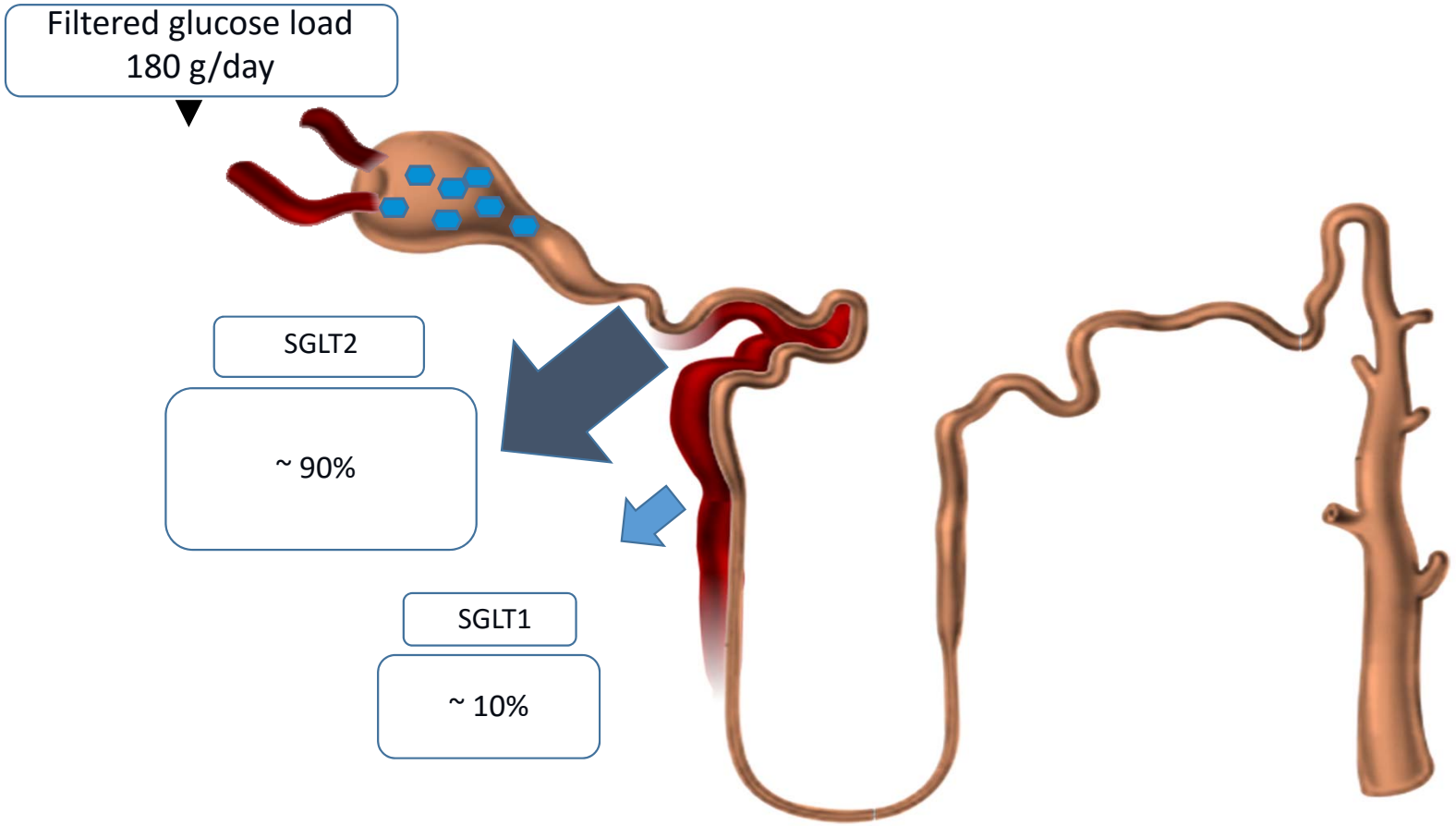
Utilization

n

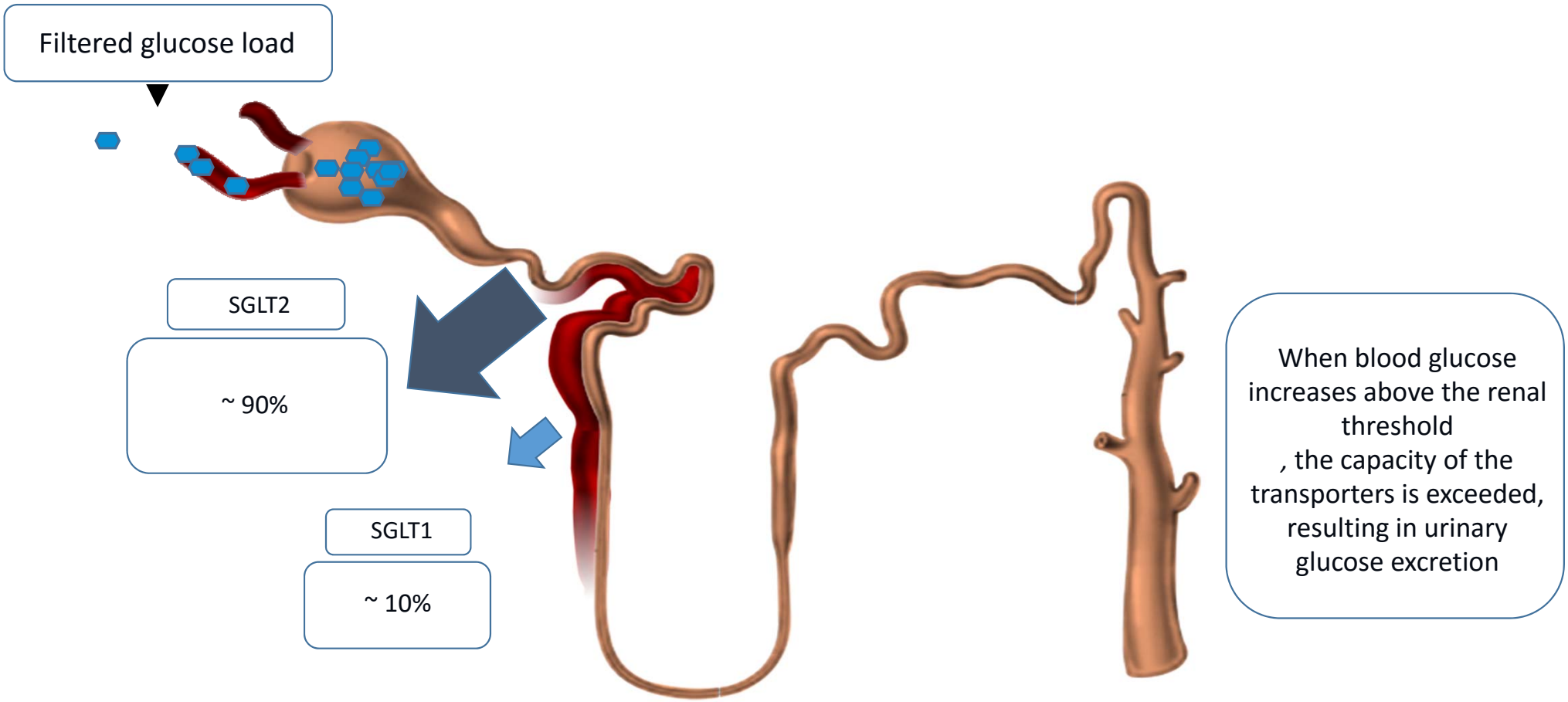
- sodium-dependent glucose transporters (SGLTs)

Renal glucose re-absorption in healthy individuals



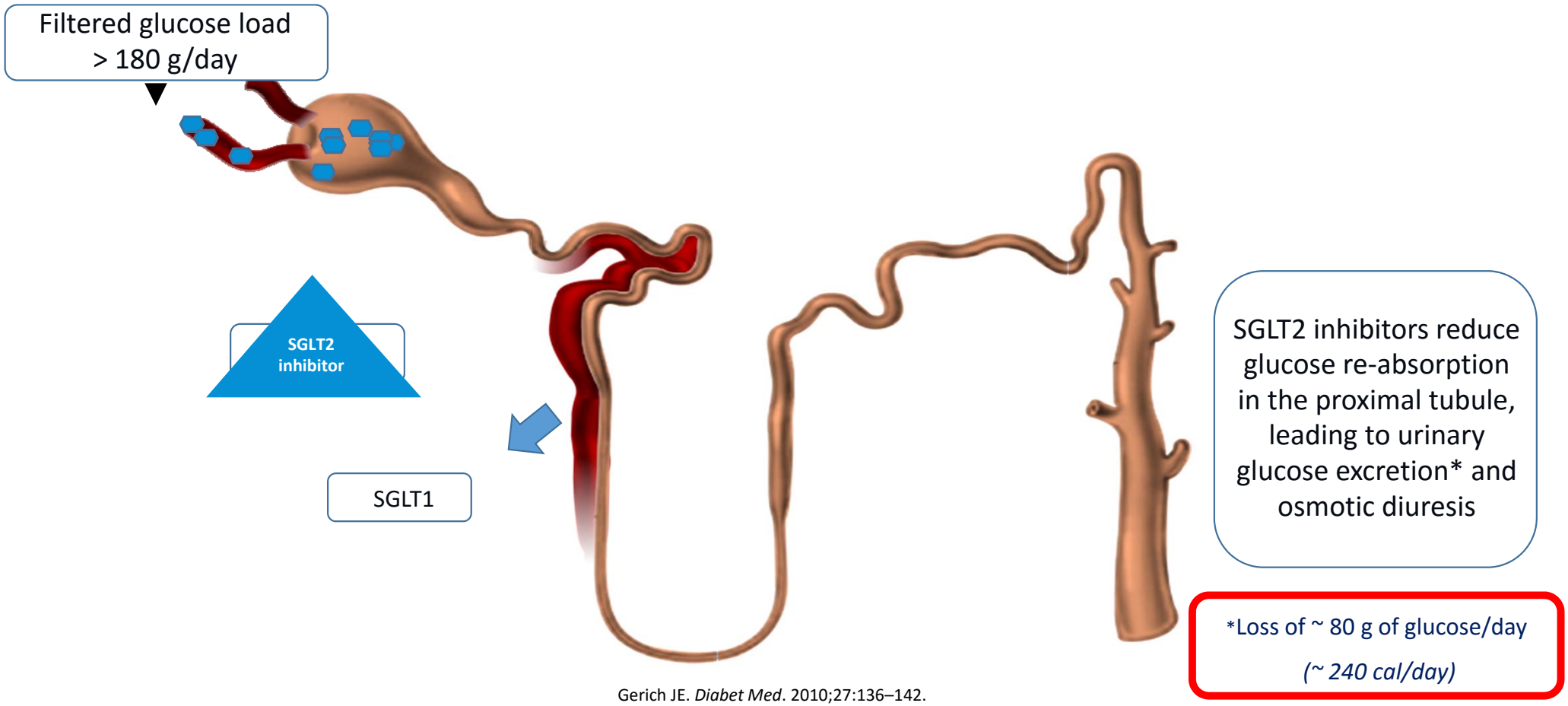
Gerich JE. *Diabet Med*. 2010;27:136–142.

Renal glucose re-absorption in patients with hyperglycaemia



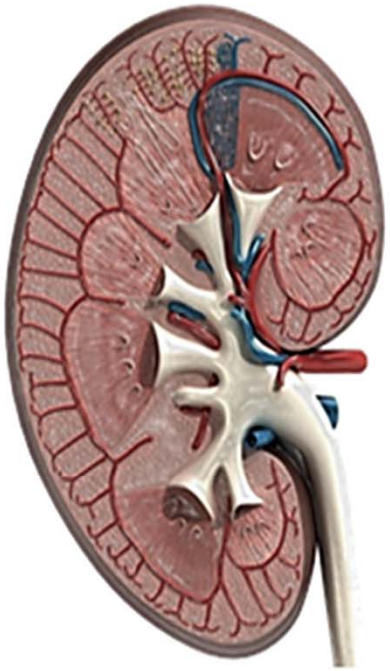
Gerich JE. *Diabet Med*. 2010;27:136–142.

Urinary glucose excretion via SGLT2 inhibition

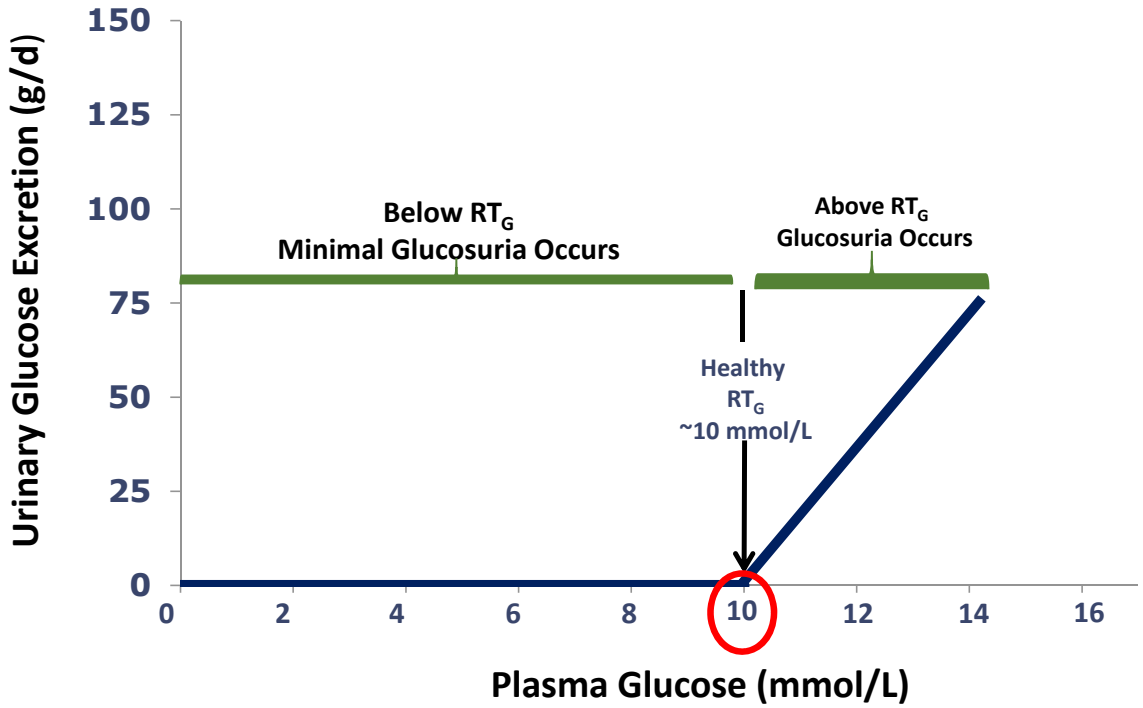


Gerich JE. *Diabet Med*. 2010;27:136–142.

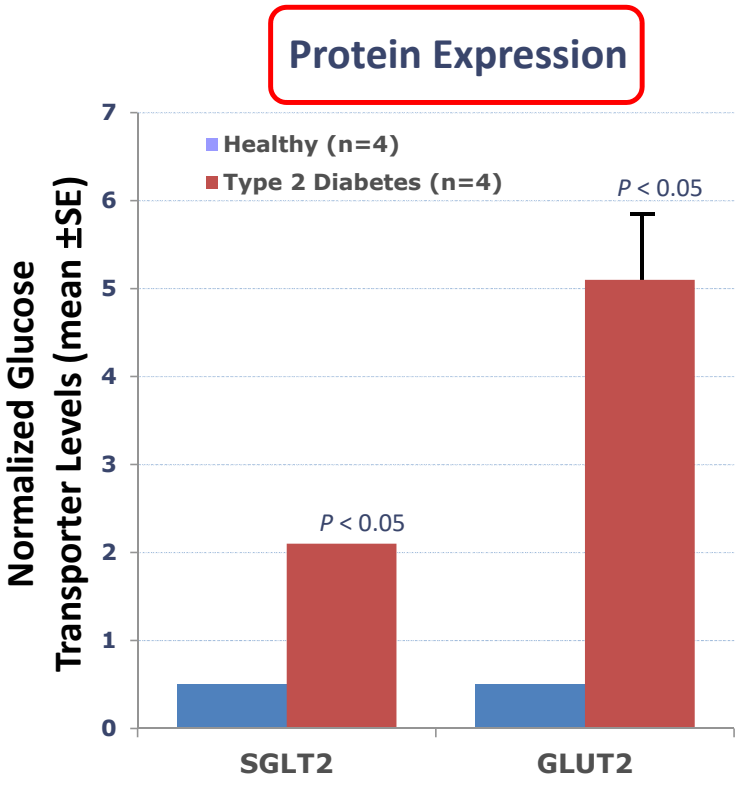
Expected clinical effects of $SGLT_2$ inhibition

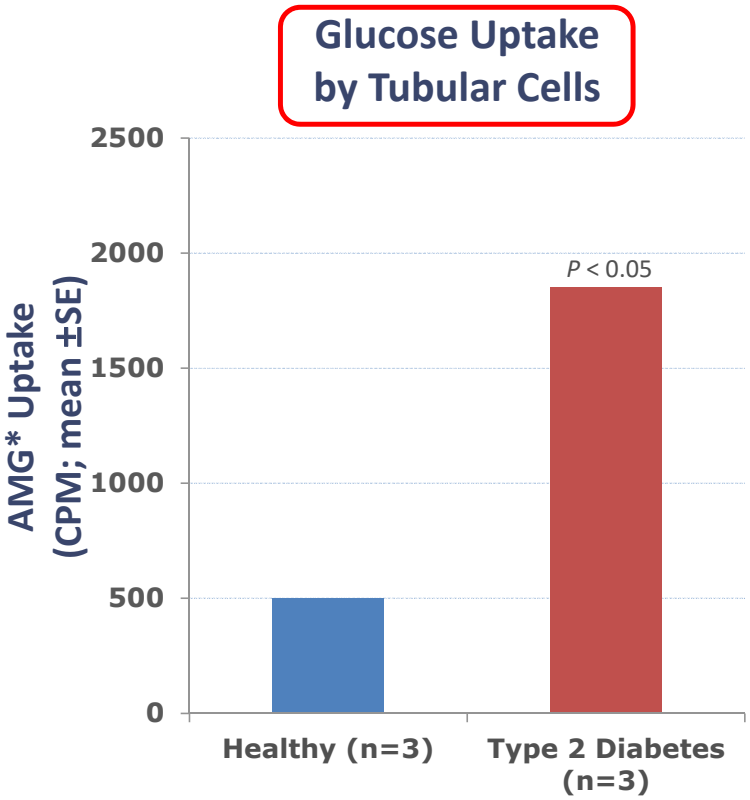


The Renal Glucose Threshold (RT_G) Concept in Healthy Subjects

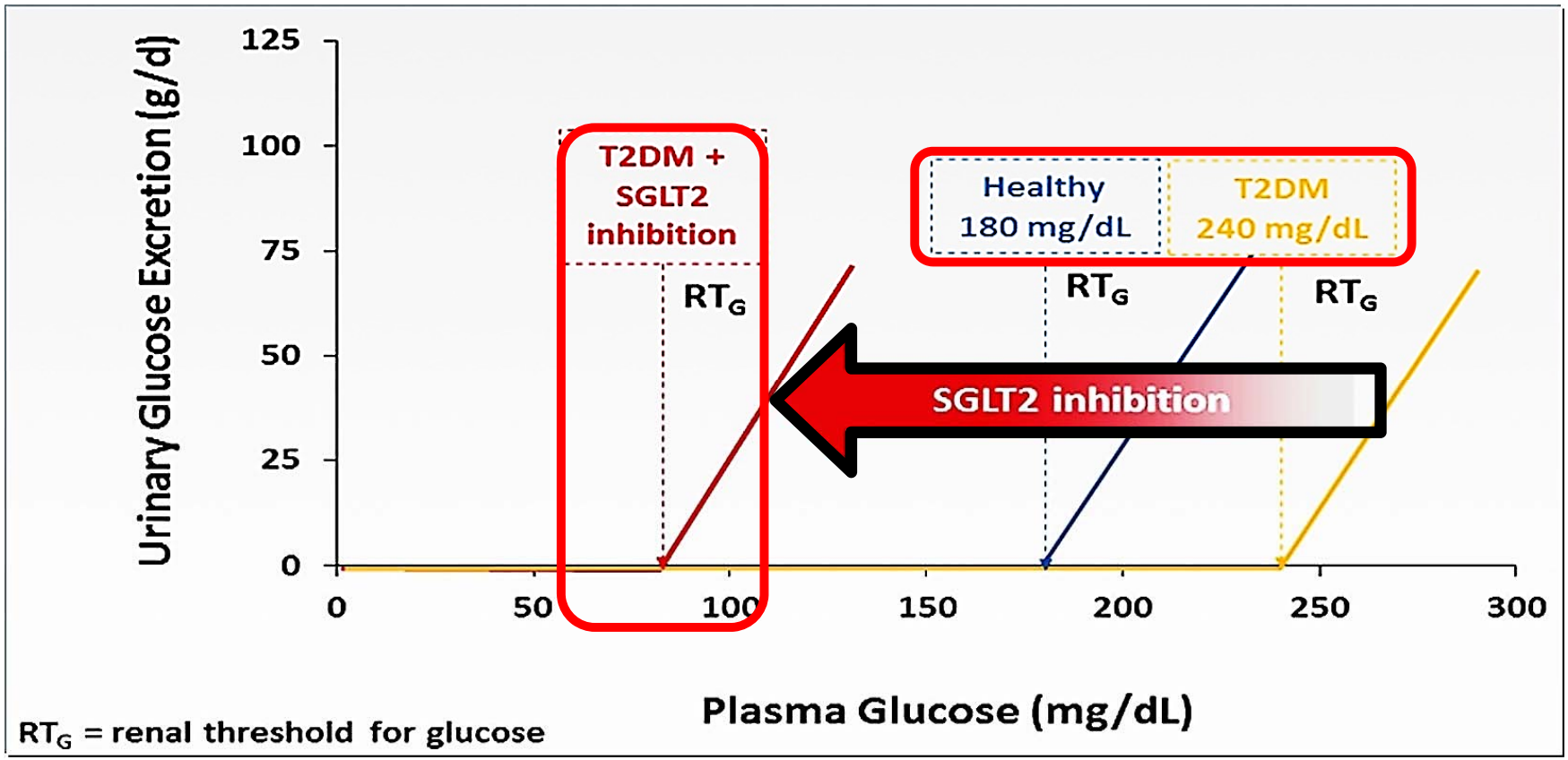


Upregulation of SGLT2 Transporter and Enhanced Cellular Glucose Uptake in Type 2 Diabetes





$SGLT_2i$ lowers renal threshold for glucose excretion



Abdul-Ghani M, et al. *Endocr Pract*. 2008; 14: 782-90.

Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010; 95: 34-42.

↓Plasma Glucose **proportional to the:**

- Ambient glucose concentration
- Glomerular filtration of this glucose

Greater reductions may be seen in patients with **poor glycemic control**, potentially to a greater extent than with other agents

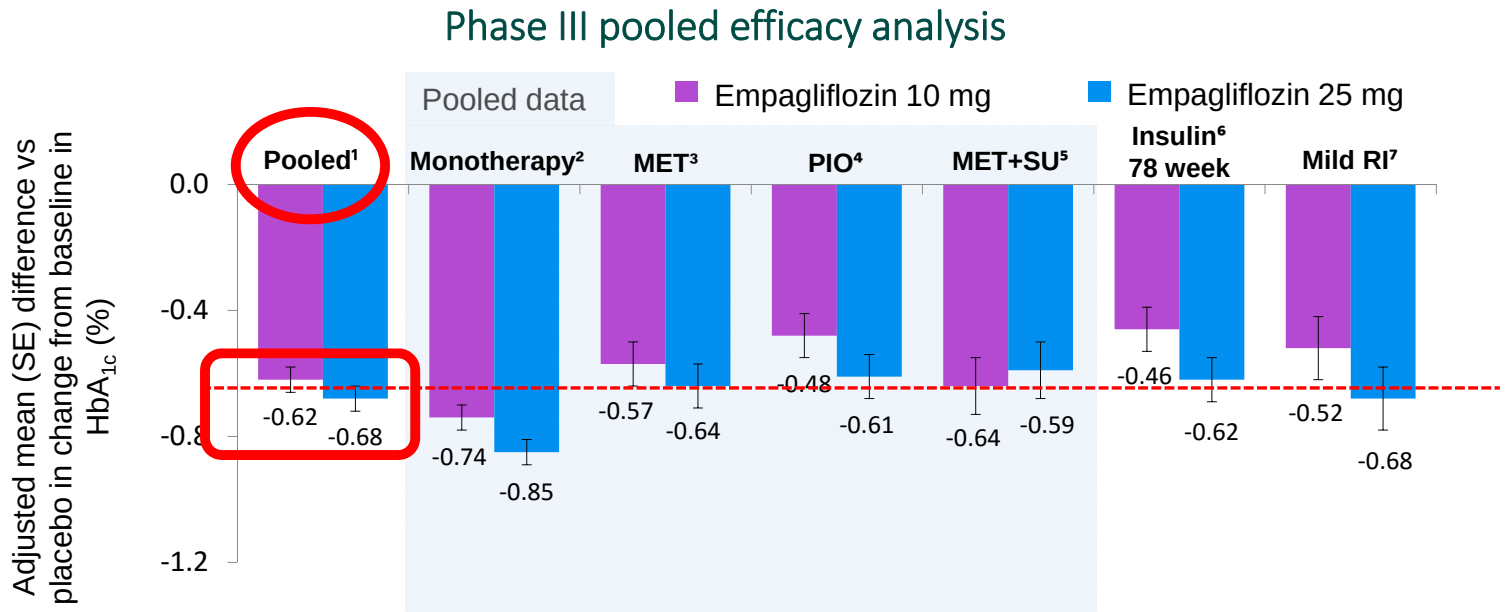
- lowering effects of SGLT2 inhibitors are ↓ in patients with GFR <60 and almost absent when GFR is <30
- ↓HbA1c by 0.6–0.9% vs placebo, regardless of background therapy

↓ FPG

↓ PPG

Glucose-lowering effect of SGLT2 inhibitors **is dose dependent**, at least in patients with **HbA1c < 8%,** in whom high-dose therapy produces superior glucose lowering compared with low-dose

Δ HbA1c Across Different Background Therapy Empagliflozin versus Placebo



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

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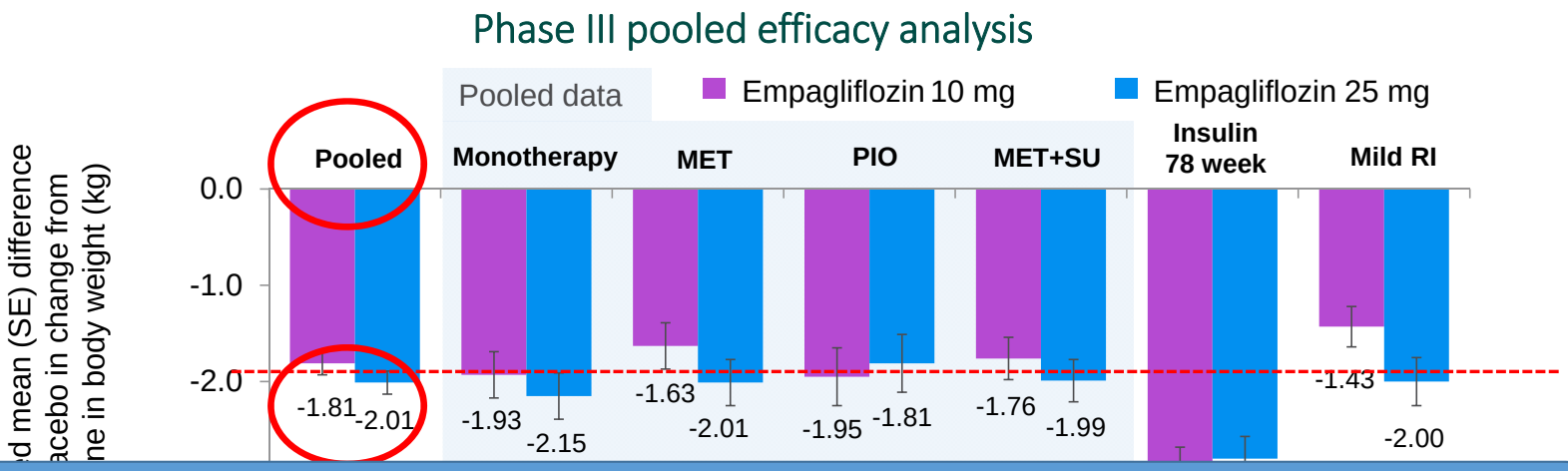
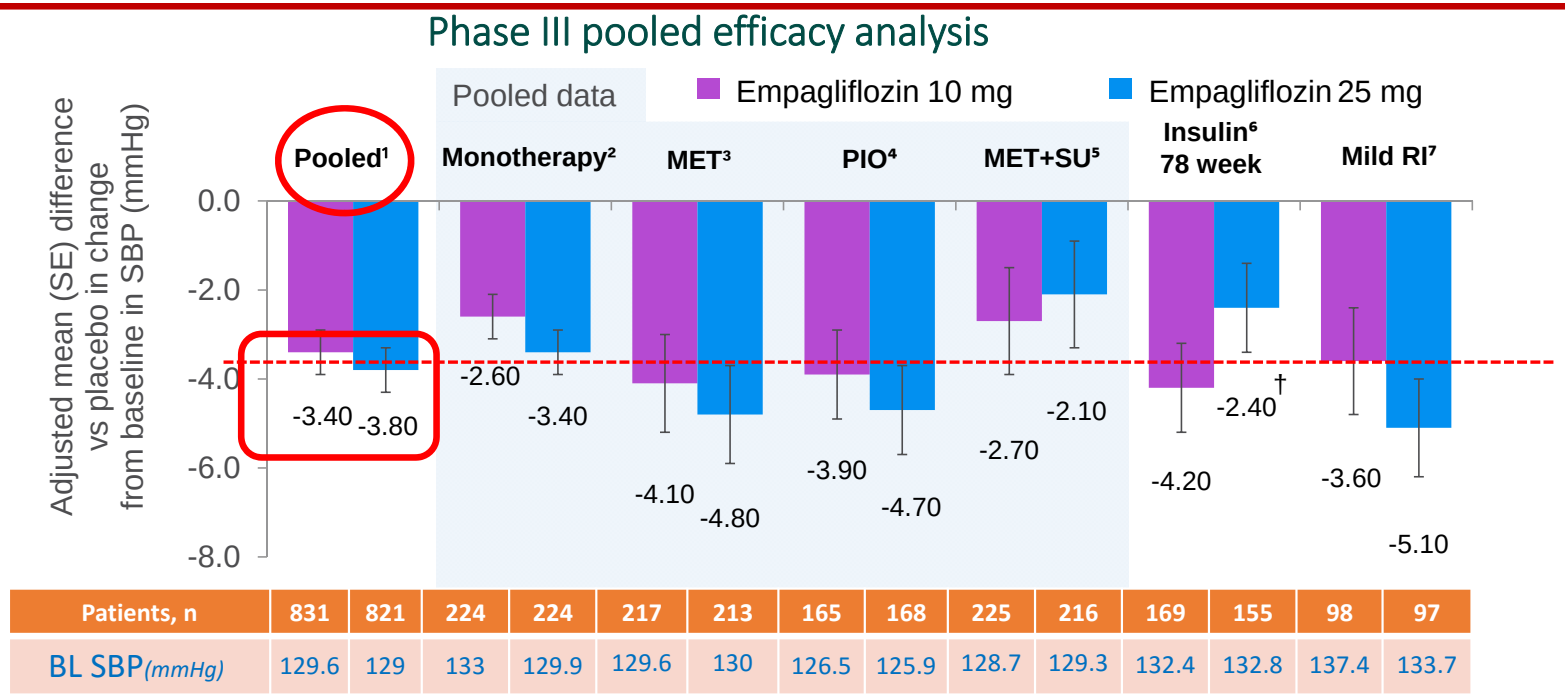
Δ body weight† across different background therapy
Empagliflozin *vs* placebo



Weight reduction is also greater in individuals with the highest HbA1c at baseline and is attenuated in those with good glucose control at baseline

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

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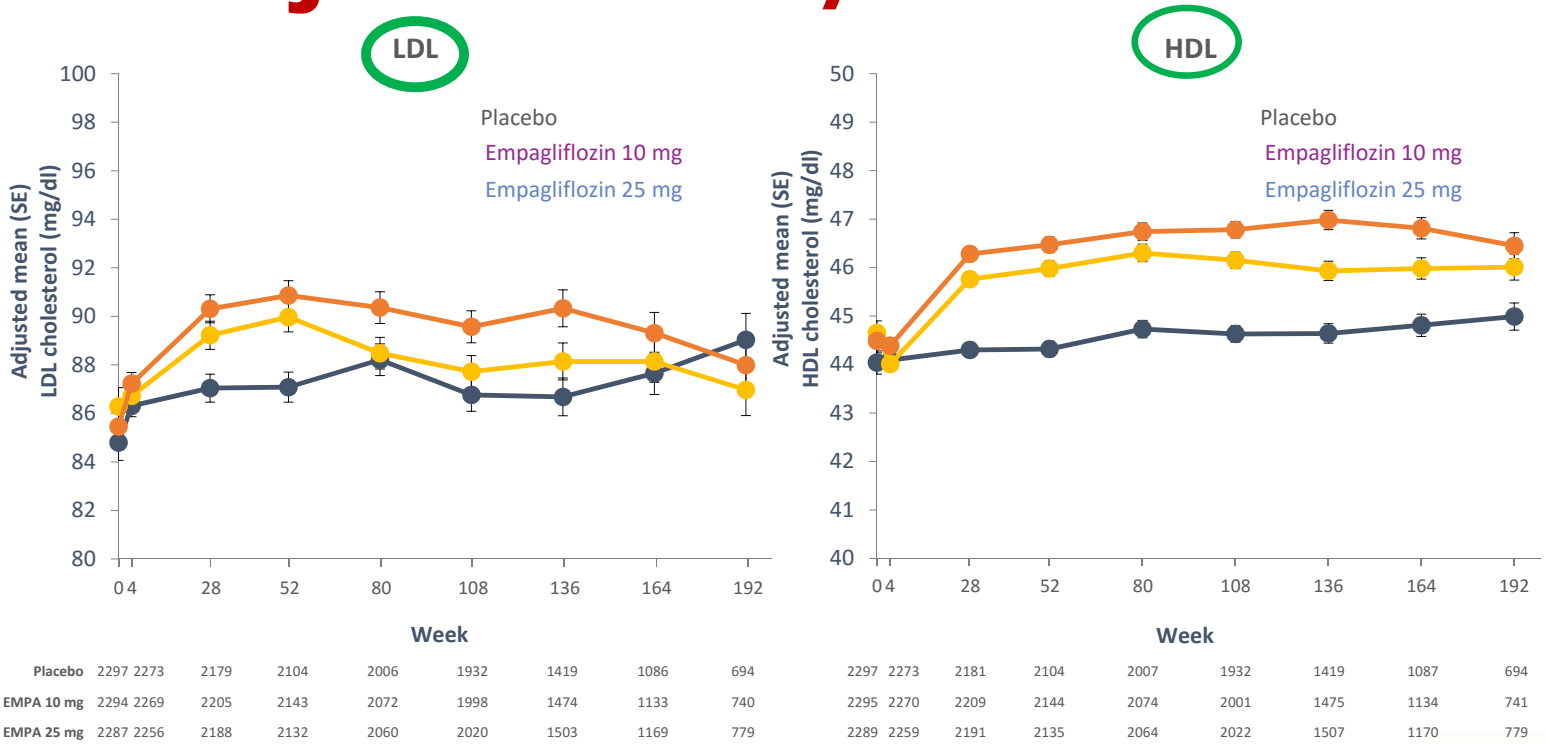
Mean adjusted LDL/HDL

EMPA-REG OUTCOME



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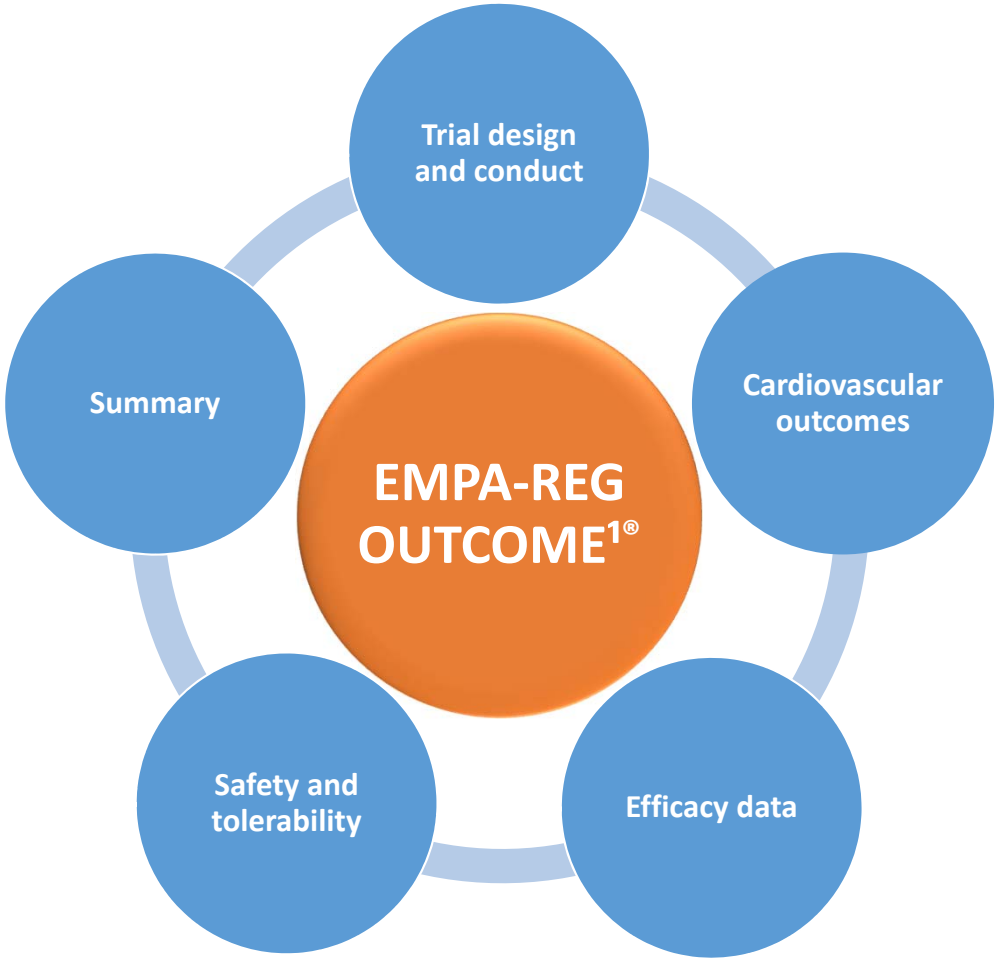
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.



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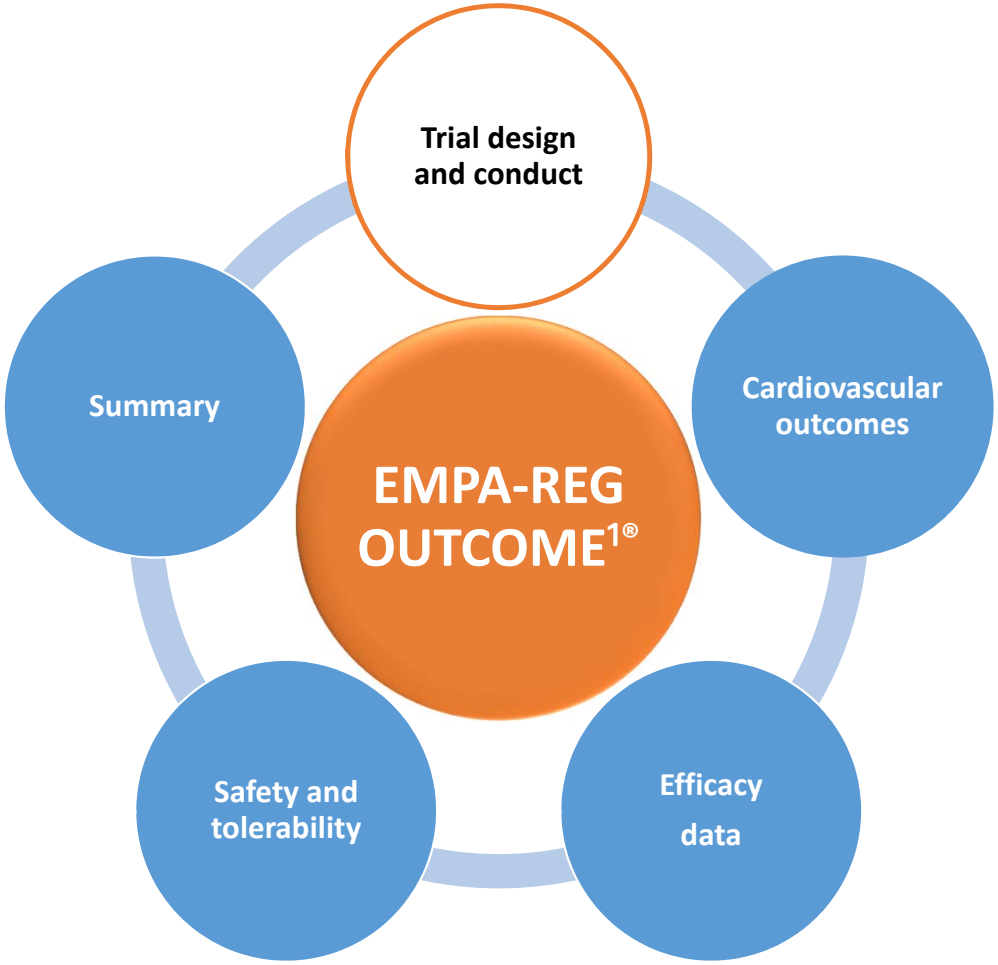

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Trial Design[1]

EMPA-REG OUTCOME®

42
countries

590
sites

11,531
pts screened

7020 pts
randomized

>97 %
completed trial

>99 %
vital status available

Patients with T2D & Established cardiovascular disease[1]

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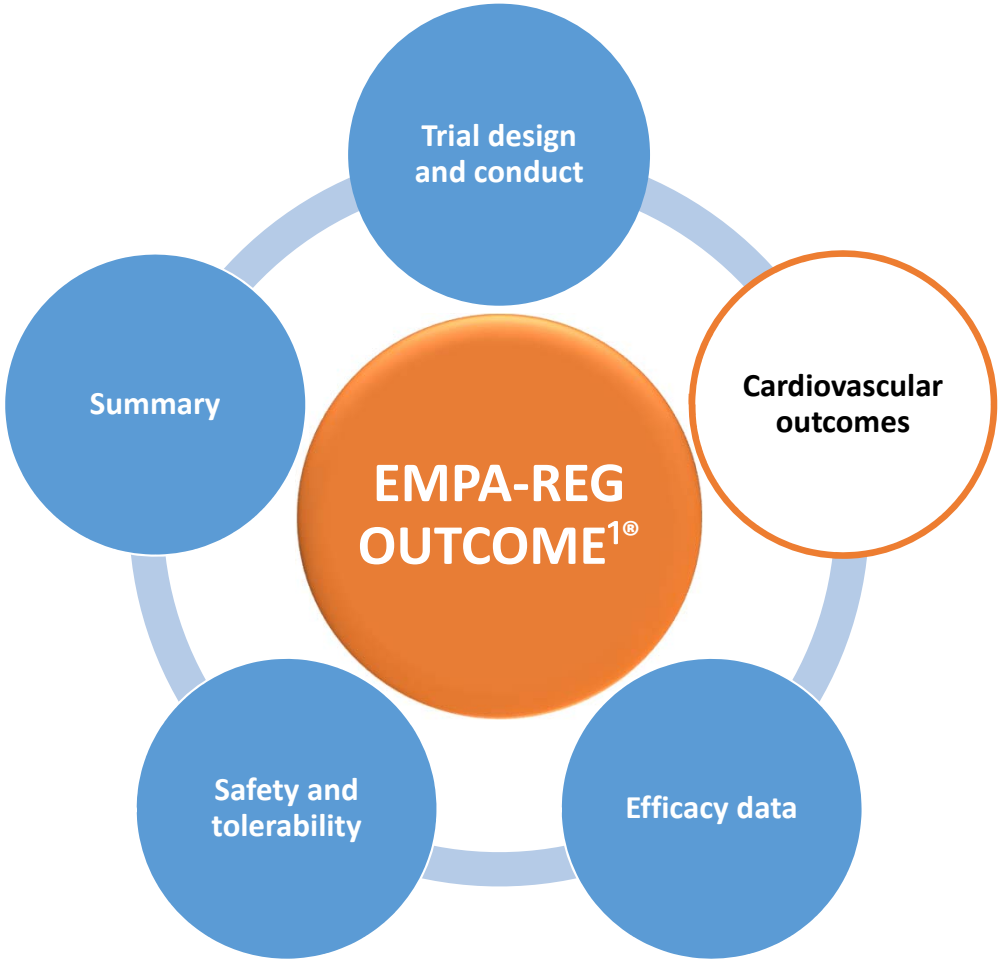

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Pre-specified primary and key secondary outcomes[1]

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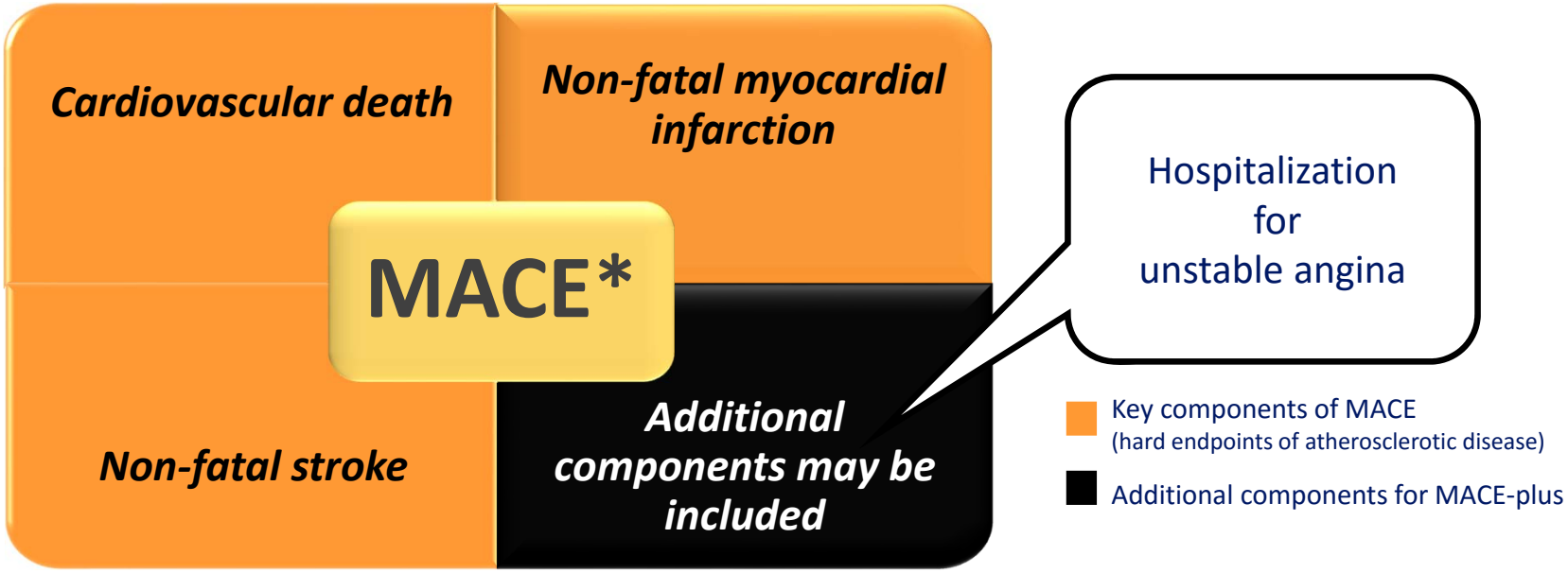

*Major Adverse Cardiovascular Events

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

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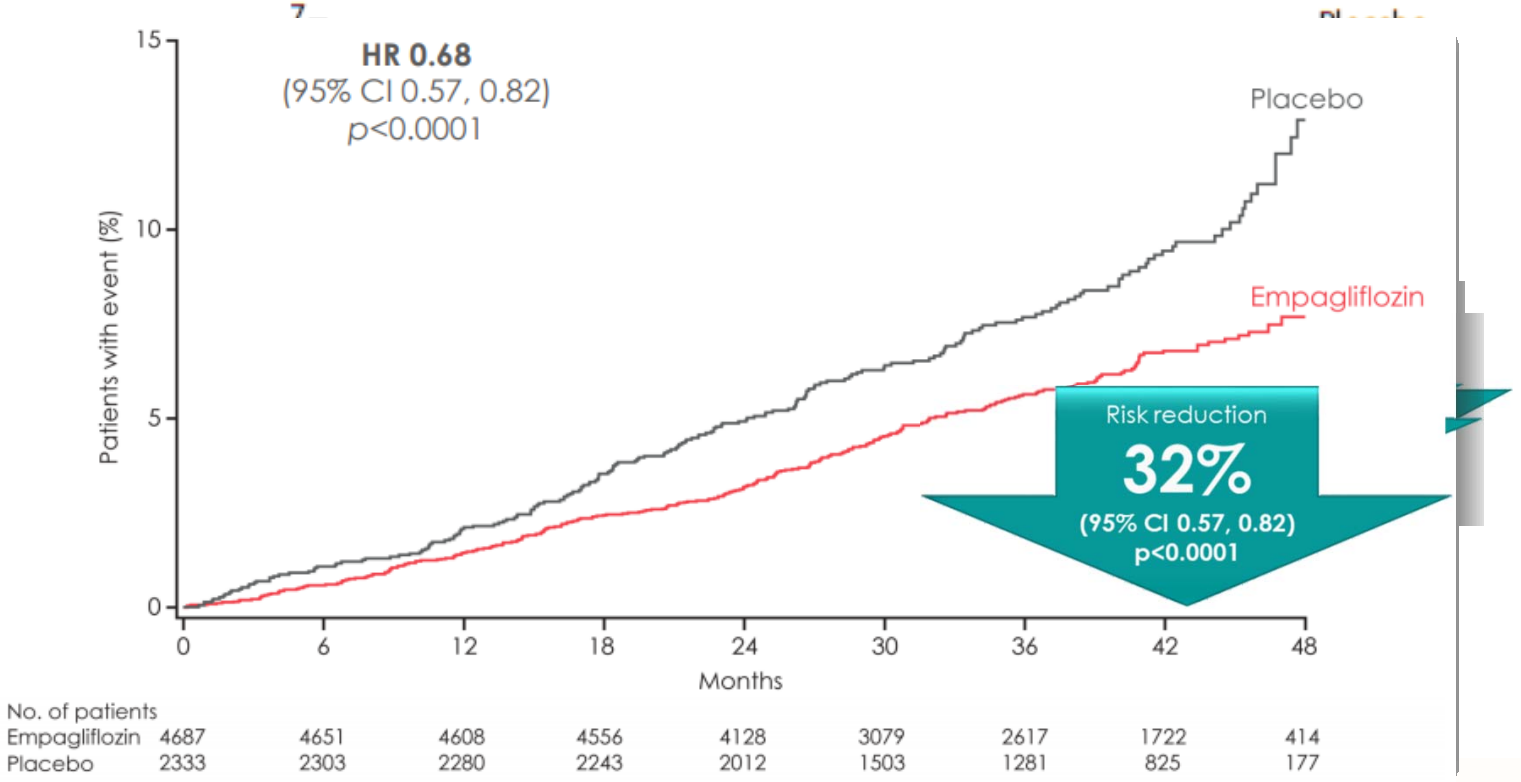

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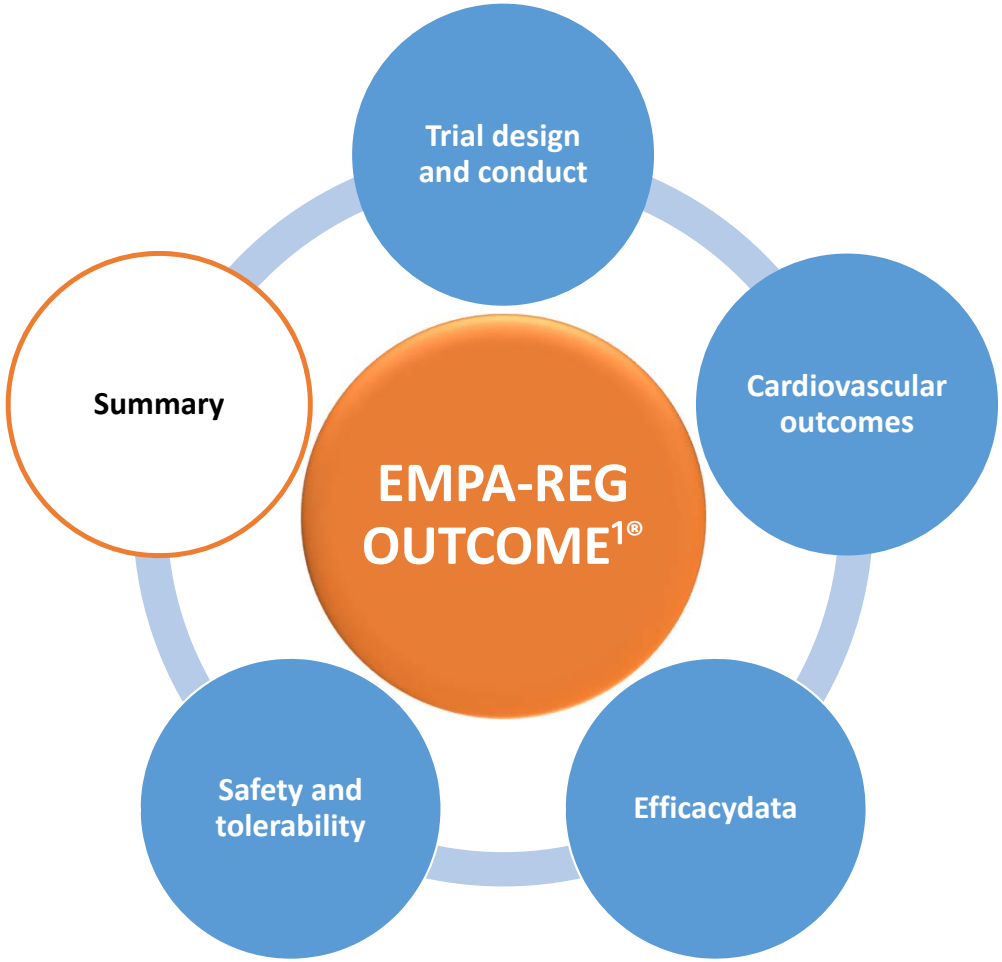

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EMPA-REG OUTCOME®: summary

***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]

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NNT

How to Calculate NNT

Find results of study.

↓

Find the rate in the control group.

↓

Find the rate in the treatment group.

↓

Subtract the treatment group rate from the control group rate (ignore a minus sign, if present), and divide the result into 100.

Example

In a trial of cholesterol lowering over five years, 8 percent of patients died in the treatment group, and 12 percent died in the control group.

↓

Control group rate: 12 percent

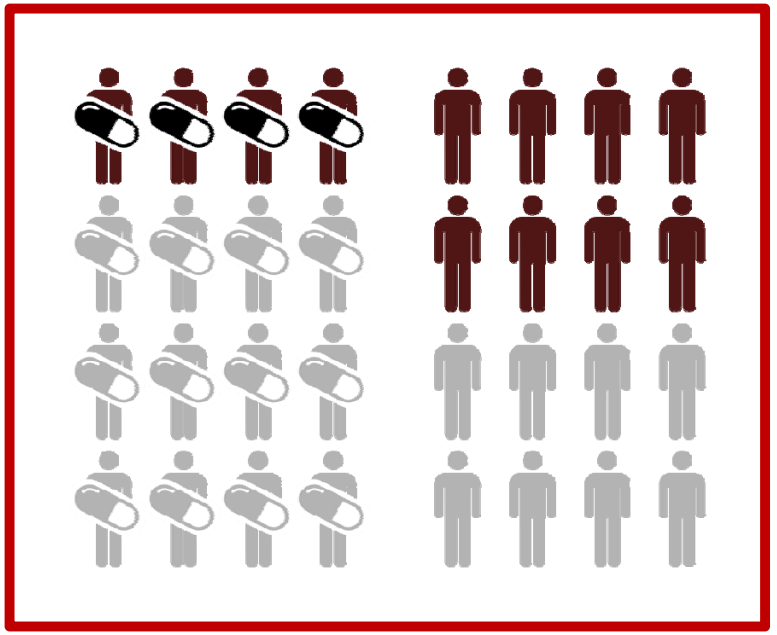
↓

Treatment group rate: 8 percent

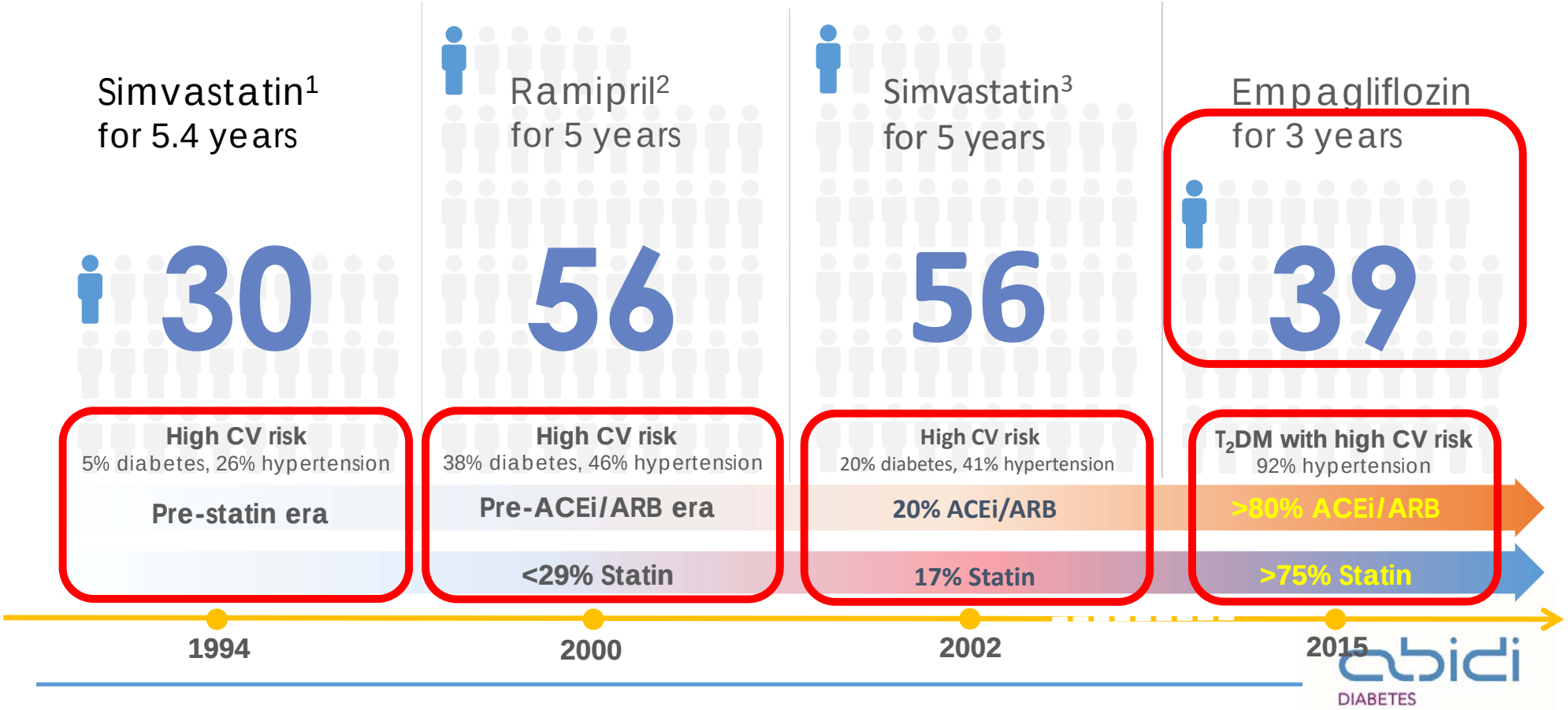
↓

Difference: 4 percent

NNT = 100/4 = 25



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



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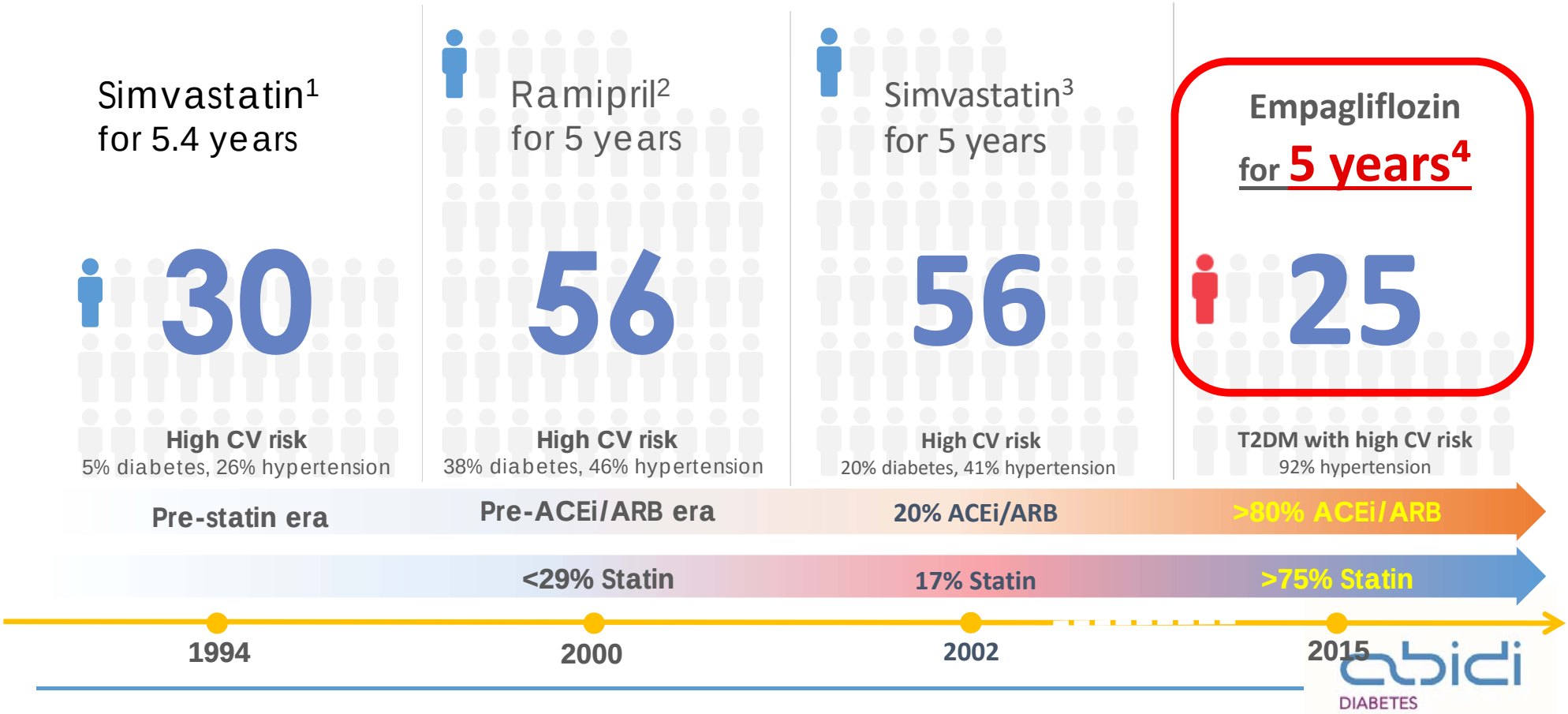
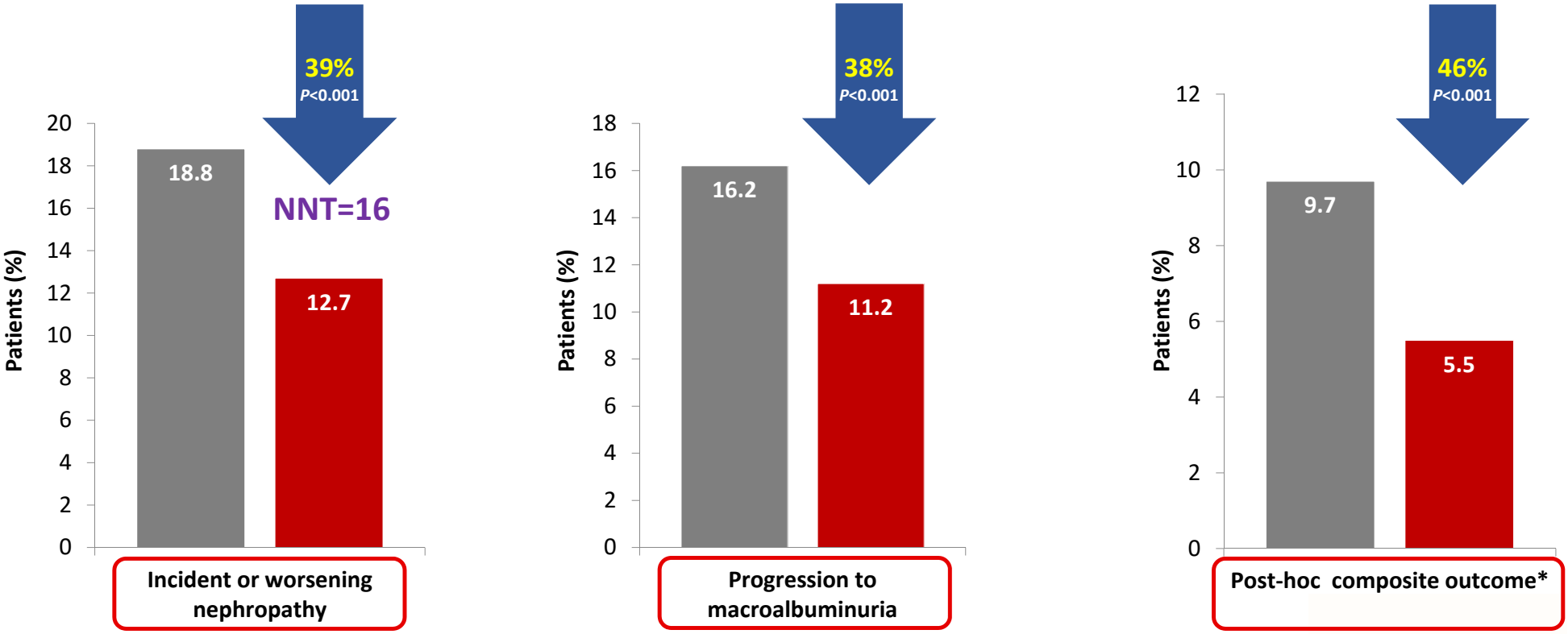


Renal Outcomes with Empagliflozin over 3.2 Years (**EMPA-REG RENAL**)[1]



Arrows = relative risk reduction

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

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Cardio and Renal potential mechanisms of Empagliflozin

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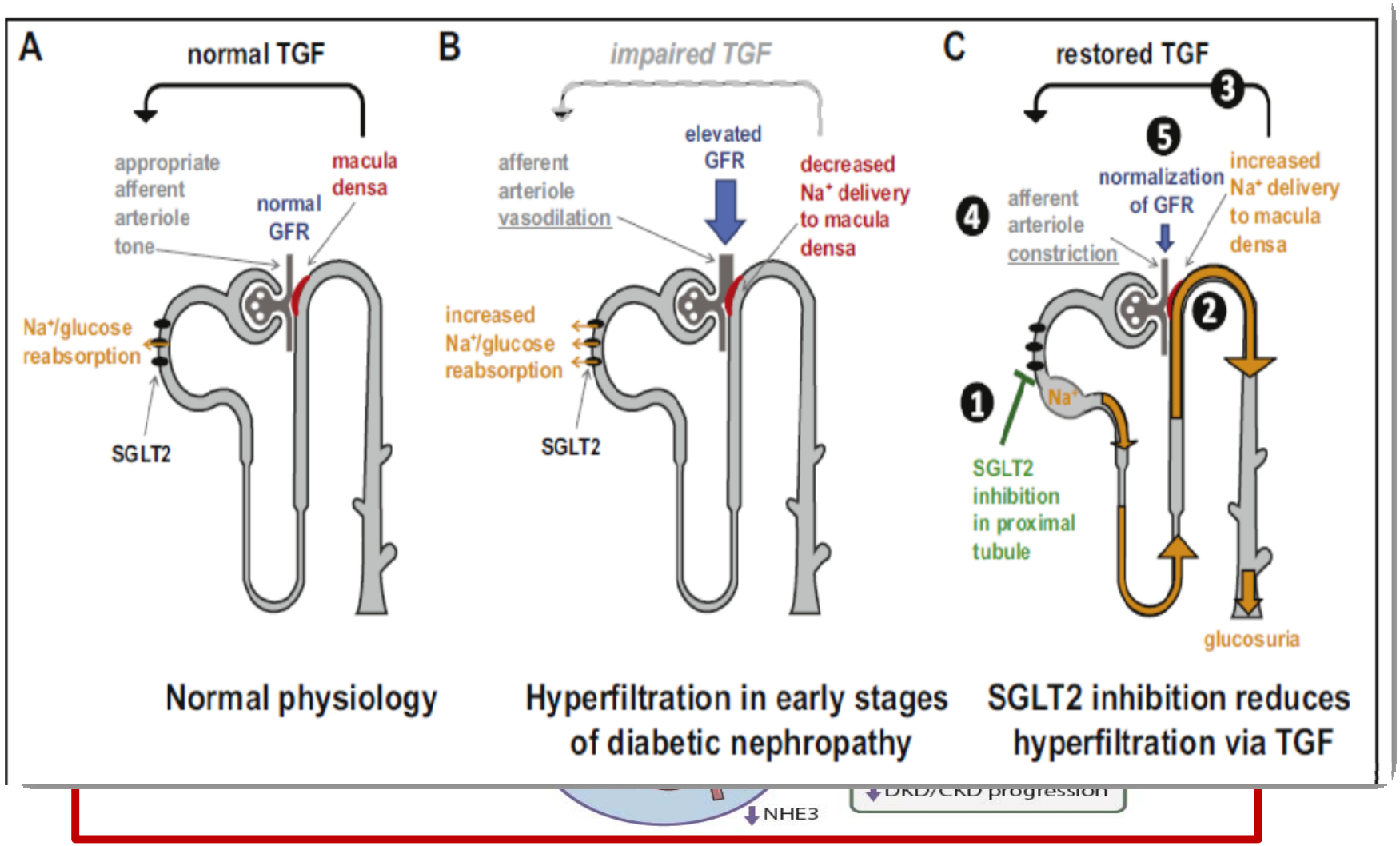
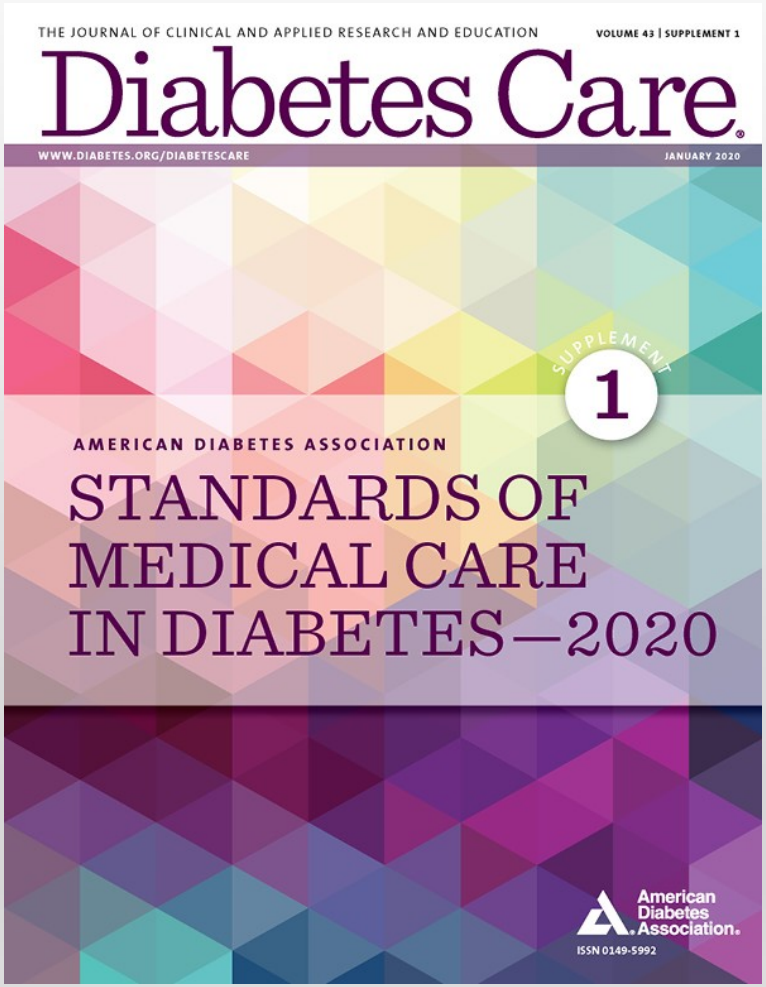
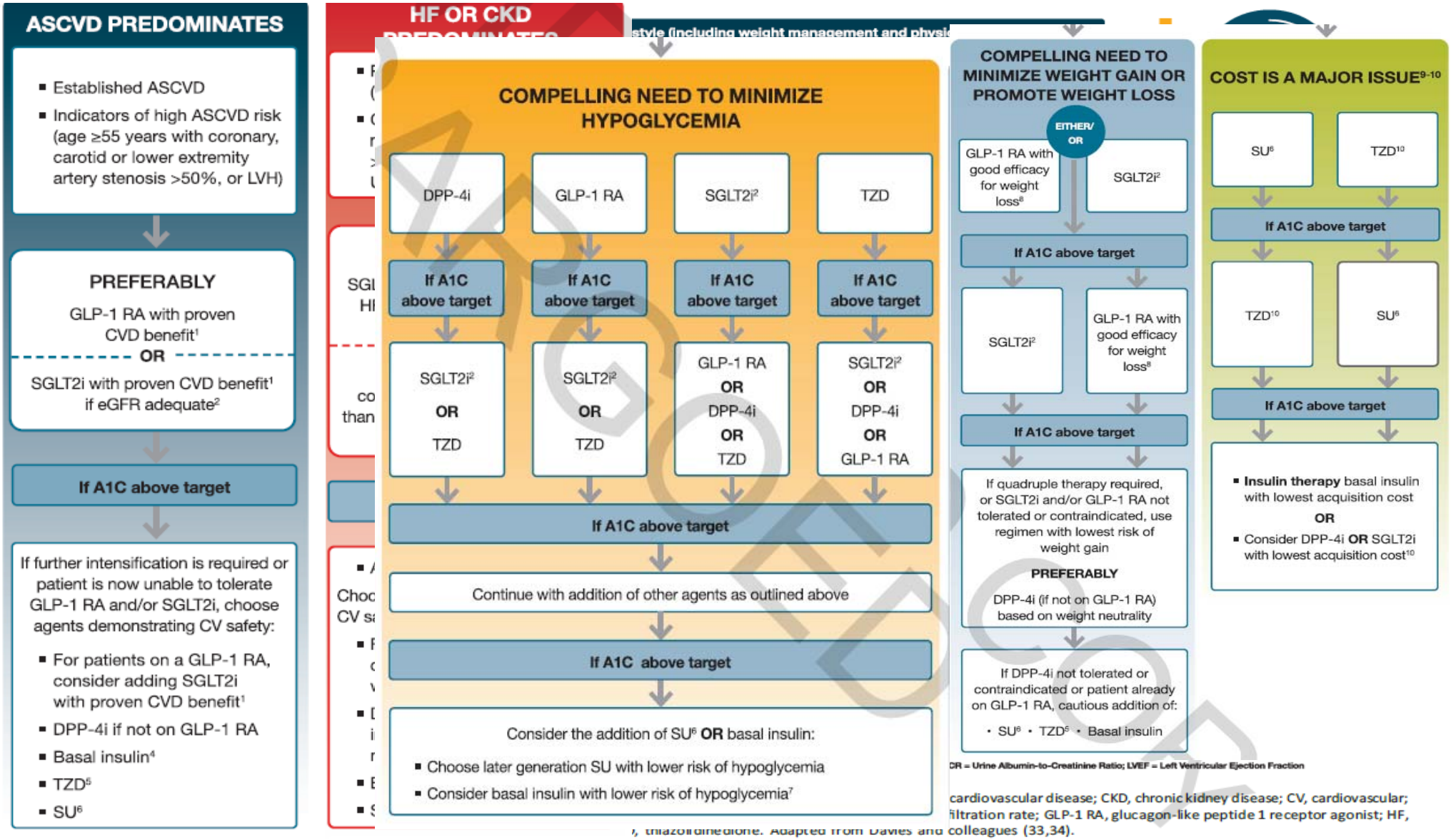
Cardiovascular protection by SGLT2 inhibitors

Effect	Consequence
H_2O Diuresis	• Reduced filling pressures, pre-/afterload reduction
Na^+ Natriuresis	• Reduced filling pressures, pre-/afterload reduction
BP lowering	• Reduced myocardial work, reduced filling pressures, pre-/afterload reduction
Weight loss	• Improved CV risk profile, lower blood pressure
Reduction in/prevention of albuminuria, slowing of kidney function decline	• Reduction in kidney risk profile, possibly fewer incident CV events, including less HF
Effects on myocardial and kidney metabolism: shift to more efficient ketone-based metabolism	• Improved metabolic efficiency, less myocardial workload
Blockade of sodium-hydrogen cotransporter	• Tissue protection: reduction in kidney and myocardial injury
Reduction in sympathetic tone	• Reduce blood pressure and arrhythmia


A
normal TGF
appropriate afferent arteriole tone
normal GFR
macula densa
Na+/glucose reabsorption
SGLT2
Normal physiology
B
impaired TGF
elevated GFR
afferent arteriole vasodilation
decreased Na+ delivery to macula densa
increased Na+/glucose reabsorption
SGLT2
Hyperfiltration in early stages of diabetic nephropathy
C
restored TGF
3
5
normalization of GFR
increased Na+ delivery to macula densa
4
afferent arteriole constriction
2
1
Na+
SGLT2 inhibition in proximal tubule
glucosuria
SGLT2 inhibition reduces hyperfiltration via TGF
NHE3
DKD/CKD progression

Guidelines Recommendations

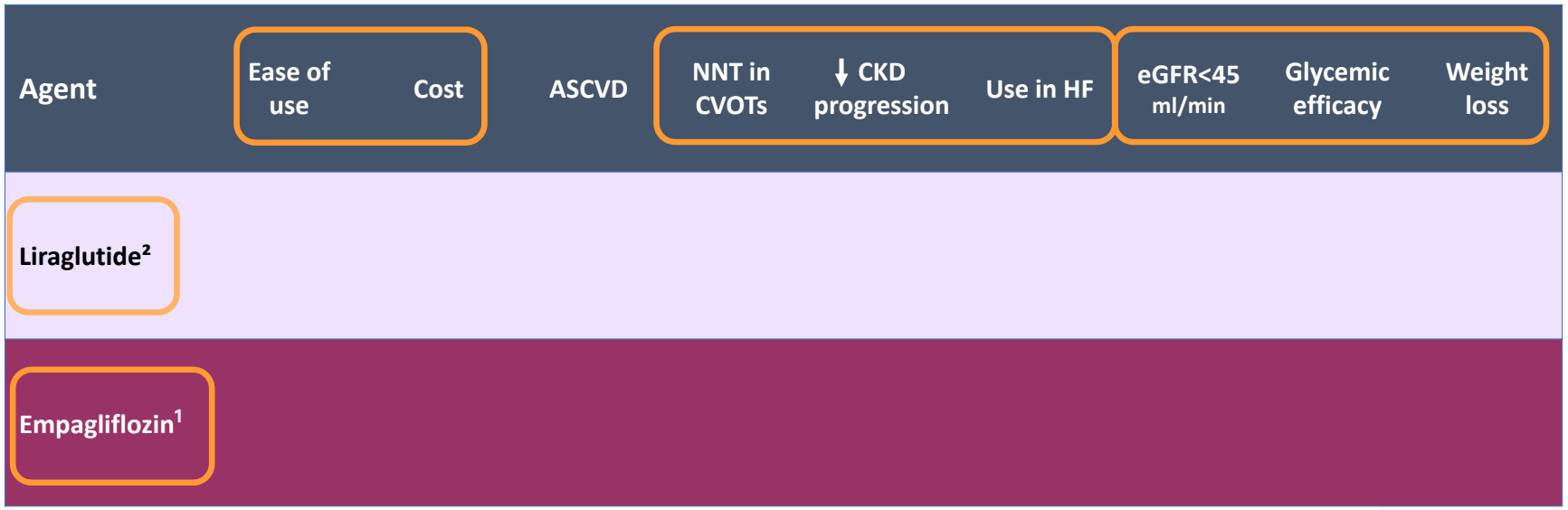




CR = Urine Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction

cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; filtration rate; GLP-1 RA, glucagon-like peptide 1 receptor agonist; HF, , thiazolidinedione. Adapted from Davies and colleagues (33,34).

Empagliflozin versus Liraglutide



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Practical points in using Empagliflozin

Administration, cautions, side effects

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

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Empagliflozin safety profile

Safety data reported in placebo controlled studies

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

The majority of patients who experienced a UTI or genital infection reported a single event

Overall incidences of hypoglycaemic events

	Placebo (n=229)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=223)
Monotherapy[1]	<1%	<1%	<1%
	Placebo (n=206)	Empagliflozin 10 mg (n=217)	Empagliflozin 25 mg (n=214)
Add-on to metformin[2]	<1%	<2%	<1.5%
	Placebo (n=225)	Empagliflozin 10 mg (n=224)	Empagliflozin 25 mg (n=217)
Add-on to metformin + SU[3]	8.4%	16.1%	11.5%
	Placebo (n=170)	Empagliflozin 10mg (n=169)	Empagliflozin 25 mg (n=155)
Add-on to insulin +/- metformin/SU[4]	35%	36%	36%

- A lower dose of insulin or insulin secretagogues (eg, SUs) may be needed to reduce the risk of hypoglycaemia when empagliflozin is used in combination with these agents

$SGLT_2$ inhibition: PROs & CONs

Potential benefits

- Weight loss
- HbA_{1c} lowering
- Reduced blood pressure
- Renal & cardiac protection
- Improved beta cell function
- Independent to insulin presence
- Mechanism complementary to other therapies

Potential risks

- Hypovolemia symptoms
- Vaginitis, balanitis
- Euglycemic DKA
- Increased LDL
- Hyperkalemia
- Polyuria