SGLT2 inhibitors in the Management of Cardiovascular Disease

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Agenda

- Introduction
- Cardiovascular Outcome Trials
- Mechanism of action
- Conclusion

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Phlorizin history

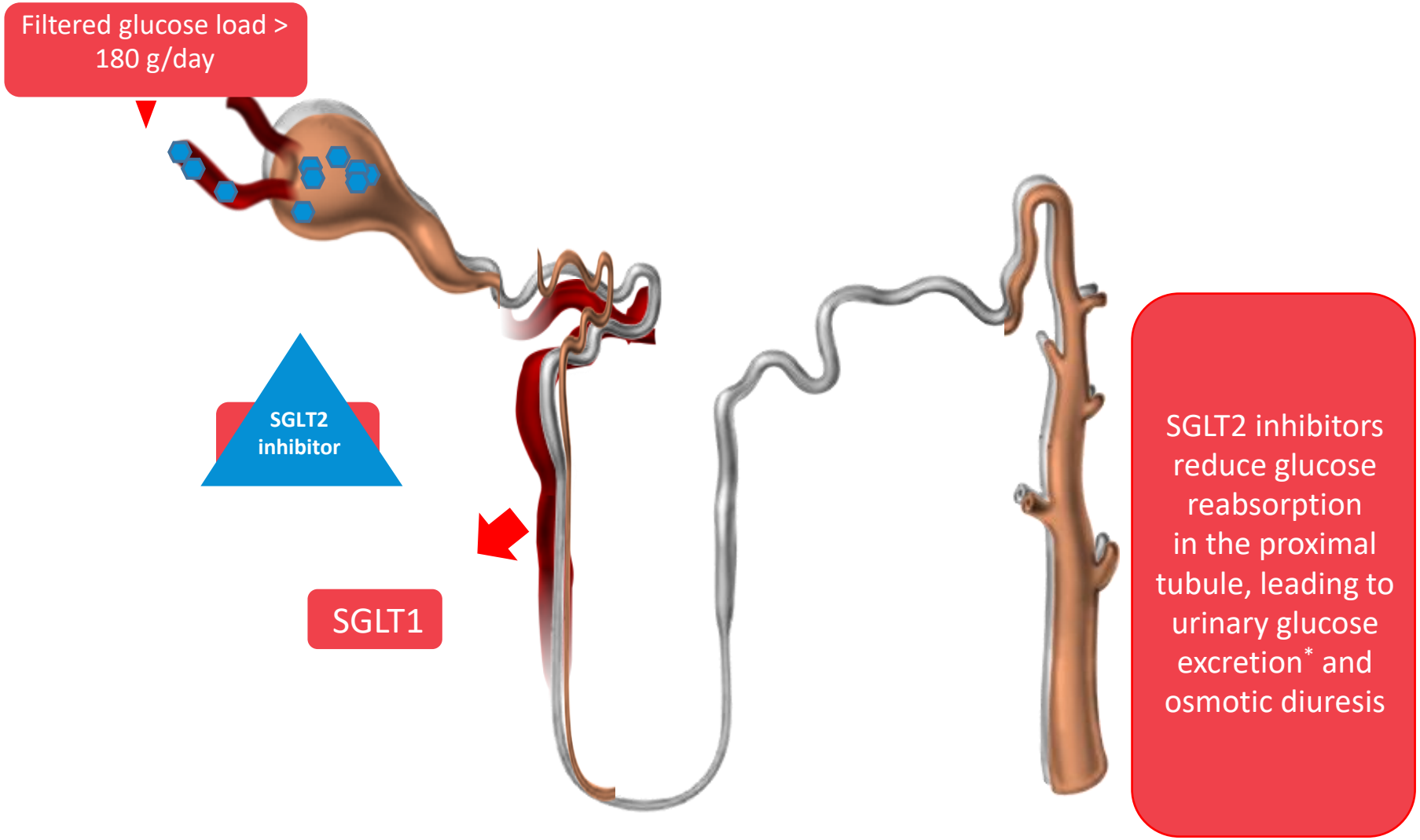
- Isolation from the bark of the apple tree In 1835 by Petersen
- Discovery of glucosuric properties by von Mering
- In the 1980s, mechanism of action was understood and reducing blood glucose concentrations in rats with diabetes observed
- The first synthetic SGLT2 inhibitor developed by Tsujihara et al in the 1990s
- In 1999 represent a new approach to the treatment of type 2 diabetes Oku et al..

- The reabsorption of glucose from the glomerular filtrate is an active process, which is linked to sodium and requires a carrier protein, referred to as a sodium– glucose cotransporter (SGLT)

Two isoforms of SGLT have been described:

- SGLT1: primarily located in the small intestine, with little effect on the renal tubule
- SGLT2: SGLT2 has low-affinity and high-capacity properties and is found almost exclusively in the epithelial cells of the proximal renal tubule, where it is responsible for more than 90% of glucose reabsorption and 65% of sodium reabsorption

Urinary glucose excretion via SGLT2 inhibition[1]

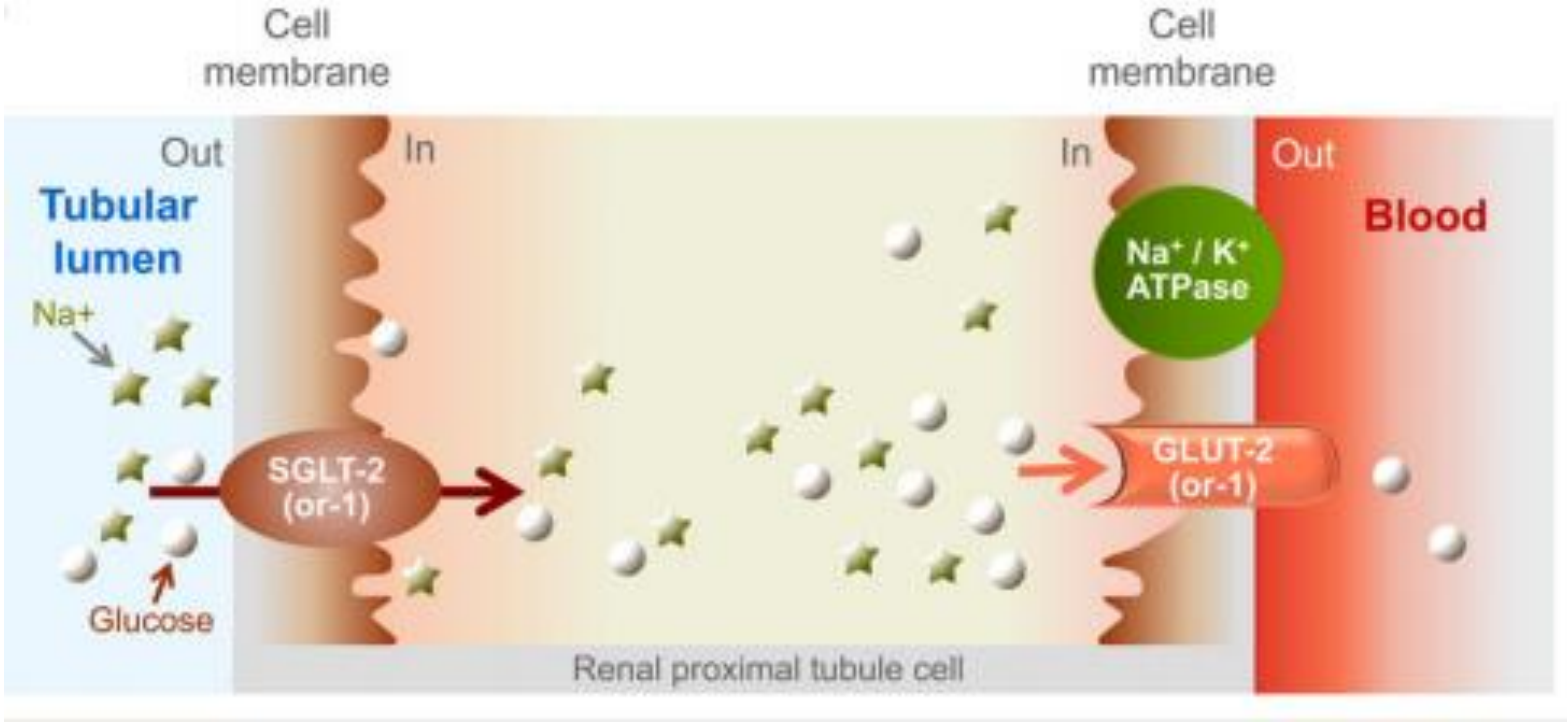


Glucose Transporters

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.

- Clinical trials showed that this class of drugs, also referred to as Gliflozins, was safe, reduced glycated hemoglobin levels by approximately 0.5 to 1.1%

- Because the drugs are not insulin-dependent — did not cause hypoglycemia unless administered with other glucose-lowering agents

- Between 2012 and 2017, FDA and the European Medicines Agency approved Canagliflozin , Dapagliflozin,Empagliflozin, and Ertugliflozin for reducing hyperglycemia in patients with type 2 diabetes

- In 2008, before the approval of the SGLT2 inhibitors, concern about the cardiovascular safety of rosiglitazone ,led the FDA to issue a Guidance for Industry recommending that sponsors of new or recently approved antidiabetic agents “demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk.”

- To satisfy this requirement, a number of large clinical outcome trials were conducted to evaluate such agents, including SGLT2 inhibitors, which had important actions on the heart and kidneys.

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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

Zinman B *et al. N Engl J Med* 2015;373:2117-28

EMPA-REG OUTCOME trial

- EMPA-REG OUTCOME trial compared Empagliflozin with placebo in 7020 patients with CVD
- The primary end point was major adverse cardiac events (i.e., death from cardiovascular causes, nonfatal MI, or nonfatal stroke)
- Not only was empagliflozin shown to be safe, but it also appeared to be cardioprotective.

EMPA-REG OUTCOME trial

- The HR in the empagliflozin group, as compared with the placebo group, was reduced (HR, 0.86, 95% [CI], 0.74 to 0.99)

- The risks of secondary end points were all significantly reduce including cardiovascular death (by 38%); and the risk of hospitalization for heart failure (by 35%) and all-cause death (by 32%) significantly were reduced

- Significant beneficial effects observed as early as 2 to 3 weeks after the start of therapy.

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

Nejm 377;7 , August 17, 2017

CANVAS Program

- The CANVAS Program (CANVAS) and CANVAS-Renal (CANVAS-R), evaluated Canagliflozin in 10,142 patients, two thirds of whom had a history of CVD
- The primary end point was major adverse cardiac events significantly reduced (HR, 0.86; 95% CI, 0.75 to 0.97
- This benefit was observed across a broad range of subgroups defined by baseline glycated hemoglobin level, presence or absence and severity of albuminuria, and duration and intensity of treatment for type 2 diabetes.
- Of the various prespecified secondary end points, hospitalization for heart failure showed the greatest reduction (HR, 0.67; 95% CI, 0.52 to 0.87

CREDENCE

- The Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial

- 4401 patients with type 2 diabetes and arteriosclerotic cardiovascular disease with associated albuminuric renal disease was enrolled

- Major adverse clinical events were all reduced significantly , (HR, 0.80; 95% CI, 0.67 to 0.95), hospitalization for heart failure (HR, 0.61; 95% CI, 0.47 to 0.80), combination of hospitalization for heart failure or cardiovascular death (HR, 0.69; 95% CI, 0.57 to 0.83)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

S.D. Wiviott, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, T.A. Zelniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, J.P.H. Wilding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, A.-M. Langkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

NEJM,2019 Jan 24;380(4):347-5

DECLARE–TIMI 58 trial

- The Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 (DECLARE–TIMI 58) trial enrolled 17,160 patients who had or were at risk for atherosclerotic cardiovascular disease (10,186 without ACVD)

- This trial had the lowest-risk study population of any of the cardiovascular outcome trials

- Dapagliflozin did not result in a lower rate of MACE (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR, 0.93; 95% CI, 0.84 to 1.03; P =0.17) but did result in a lower rate of cardiovascular death or hospitalization for heart failure (hazard ratio, 0.83; 95% CI, 0.73 to 0.95)

- Cardiovascular death and death from any cause were significantly reduced among patients at high risk, which included patients with heart failure and a reduced EF and patients with previous myocardial infarction.

Circulation

ORIGINAL RESEARCH ARTICLE

Efficacy of Ertugliflozin on Heart Failure–Related Events in Patients With Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease

Results of the VERTIS CV Trial

VERTIS CV

- The Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) randomly assigned 8246 patients with type 2 diabetes and established atherosclerotic cardiovascular disease to ertugliflozin or placebo.

- No significant effect on cardiovascular death was observed

- There was a significant reduction in first hospitalizations for heart failure (HR, 0.70; 95% CI, 0.54 to 0.90

SGLT1 and SGLT2 inhibitor

- Sotagliflozin inhibits both SGLT1 and SGLT2

- SGLT1 acts in part by slowing intestinal absorption of glucose, which may cause mild diarrhea

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

D.L. Bhatt, M. Szarek, P.G. Steg, C.P. Cannon, L.A. Leiter, D.K. McGuire, J.B. Lewis, M.C. Riddle, A.A. Voors, M. Metra, L.H. Lund, M. Komajda, J.M. Testani, C.S. Wilcox, P. Ponikowski, R.D. Lopes, S. Verma, P. Lapuerta, and B. Pitt, for the SOLOIST-WHF Trial Investigators*

ABSTRACT

NEJM. 2021 Jan 14;384(2):117-28

SOLOIST-WHF trial

- The Effect of Sotagliflozin on Cardiovascular Events in Patients with Type 2 Diabetes
- Post Worsening Heart Failure (SOLOIST-WHF) trial enrolled 1222 patients who had recently been hospitalized for decompensated heart failure
- Treatment was begun very early either in the hospital or 2 days after discharge.

The primary end point, a composite of cardiovascular death,

hospitalization for heart failure, or urgent visits for heart failure, was

reduced in the sotagliflozin group (hazard ratio, 0.67; 95% CI, 0.52 to 0.85)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease

Deepak L. Bhatt, M.D., M.P.H., Michael Szarek, Ph.D., Bertram Pitt, M.D., Christopher P. Cannon, M.D., Lawrence A. Leiter, M.D., Darren K. McGuire, M.D., M.H.Sc., Julia B. Lewis, M.D., Matthew C. Riddle, M.D., Silvio E. Inzucchi, M.D., Mikhail N. Kosiborod, M.D., David Z.I. Cherney, M.D., Ph.D., Jamie P. Dwyer, M.D., Benjamin M. Scirica, M.D., M.P.H., Clifford J. Bailey, Ph.D., Rafael Díaz, M.D., Kausik K. Ray, M.D., Jacob A. Udell, M.D., M.P.H., Renato D. Lopes, M.D., Ph.D., Pablo Lapuerta, M.D., and P. Gabriel Steg, M.D., for the SCORED Investigators*

NEJM. 2021 Jan 14;384(2):129-39

SCORED trial

- The Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients with Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk (SCORED) trial

- 10,584 patients with type 2 diabetes and chronic kidney disease who were at risk for arteriosclerotic cardiovascular disease was enrolled

- For the original coprimary end point of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, the HR was 0.84 (95% CI, 0.72 to 0.99); for the original coprimary end point of the first occurrence of death from cardiovascular causes or hospitalization for heart failure, the HR was 0.77 (95% CI, 0.66 to 0.91)

- Total numbers of myocardial infarctions and strokes were also reduced.

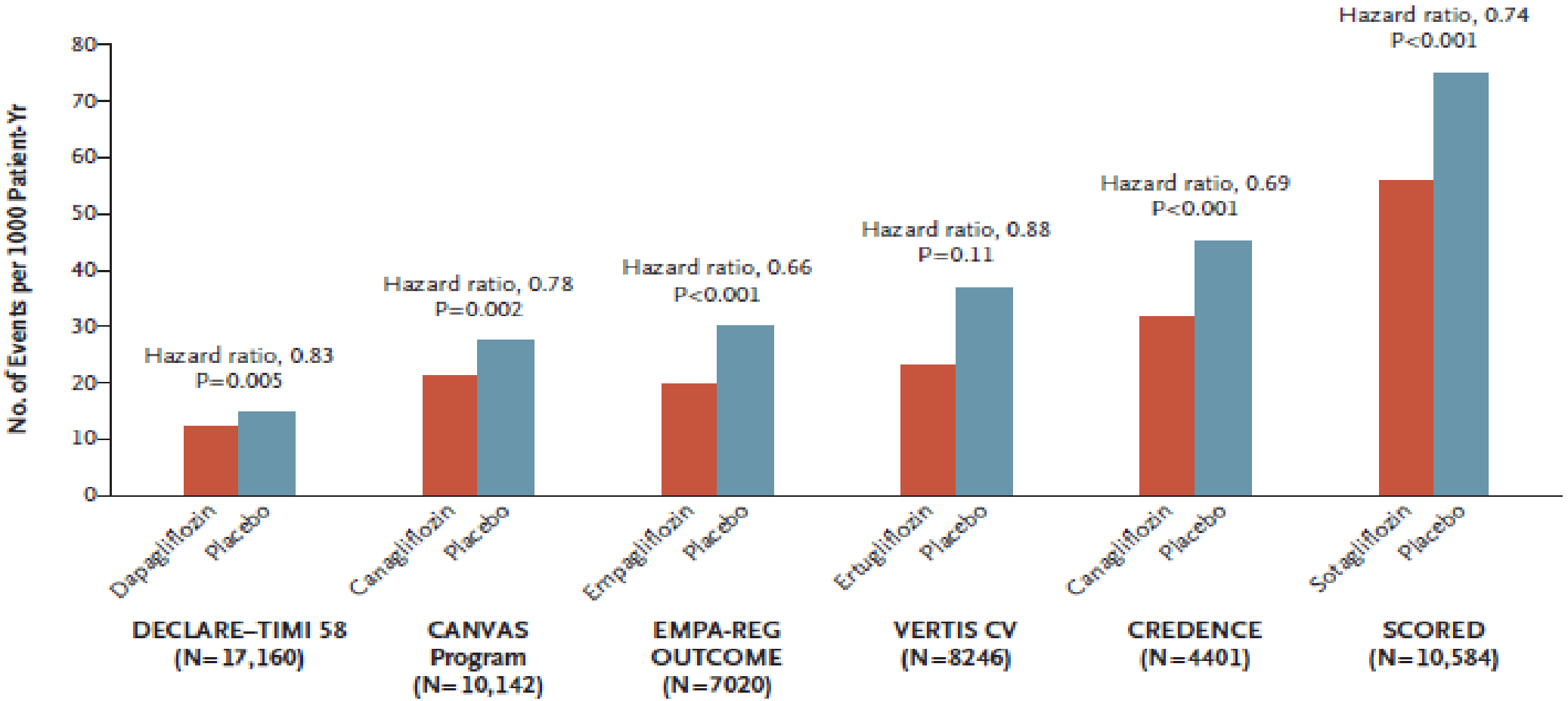

Figure 1. Cardiovascular Death or Hospitalization for Heart Failure among Patients with Type 2 Diabetes Enrolled in Six Treatment Trials.

Outcomes are shown in ascending order of frequency from left to right. Data sources for the six trials are as follows: DECLARE–TIMI 58, Wiviott et al.[17]; CANVAS Program, Young et al.[21]; EMPA-REG OUTCOME, Zinman et al.[14]; VERTIS CV, Cannon et al.[18]; CREDENCE, Perkovic et al.[16]; and SCORED, Bhatt et al.[19]

Patients with Heart Failure

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

September,19, 2019, NEJM

DAPA-HF

- was limited to patients who had heart failure with ejection fractions below 40%
- 55% of the 4744 patients enrolled did not have type 2 diabetes

- The patients randomly assigned to dapagliflozin had significant reductions in cardiovascular death or hospitalization for heart failure (the primary end point) (HR, 0.74; 95% CI, 0.65 to 0.85)

- significant (31%) reduction in All-cause mortality and outpatient worsening of heart failure were also reduced

- The improvements were similar in patients with and in those without type 2 diabetes, indicating that the cardiovascular benefits of the SGLT2 inhibitor were independent of its glucose-lowering properties.

EMPEROR-Reduced

- The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) enrolled patients with more severe systolic dysfunction compare to DAPA HF

- the cardiac benefit was observed both in patients with and in those without type 2 diabetes.

- The benefit was also seen across a spectrum of risk for heart failure, level of N-terminal pro–B-type natriuretic peptide (NT-proBNP), renal function, and glucose level at baseline

EMPEROR-Preserved

- The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPEROR-Preserved) The largest placebo-controlled trial dedicated to this condition

- enrolled 5988 patients with an EF of 40% or higher
- In the group of patients randomly assigned to empagliflozin, the primary end point, cardiovascular death or hospitalization for heart failure, was reduced (hazard ratio, 0.79; 95% CI, 0.69 to 0.90)

- secondary end point of hospitalization for heart failure was reduced (hazard ratio, 0.73; 95% CI, 0.61 to 0.88)

- The benefits of empagliflozin were almost identical in patients with and in those without type 2 diabetes

- The Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial (ClinicalTrials.gov number, NCT03619213) is studying the effect of dapagliflozin in patients with a left ventricular ejection fraction above

  40% Results are expected shortly

Table 2. Cardiovascular Outcome Trials Involving Patients with Heart Failure.*

Variable	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	SOLOIST-WHF
Drug	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
No. of patients	4744	3730	5988	1222
Type 2 diabetes — % of patients	41.7	49.8	49.1	100
LVEF — %	31.1	27.4	54.3	35
Median NT-proBNP — pg/ml	1437	1907	970	1864
Mean eGFR — ml/min/1.73 m^2	65.7	62.0	60.6	49.9
Outcomes — hazard ratio (95% CI)				
Cardiovascular death or hospitalization for heart failure	0.74 (0.65–0.85)	0.75 (0.68–0.86)	0.79 (0.69–0.90)	0.67 (0.52–0.85)
Hospitalization for heart failure	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.64 (0.49–0.83)

- A meta-analysis of four clinical end point trials (EMPA-REG OUTCOME, CANVAS Program, CREDENCE, and DECLARE–TIMI 58)

  involving 38,723 patients with type 2 diabetes

Result: compared with patients receiving placebo, those who received SGLT2 inhibitors had a significant reduction in the risk of progression to dialysis, transplantation, or death due to kidney disease (relative risk, 0.67; 95% CI, 0.52 to 0.86).

Lancet Diabetes Endocrinol 2019; 7: 845-54

Other Clinical Outcomes

- Reduction in atrial fibrillation or atrial flutter by dapagliflozin In the DECLARE–TIMI 58 trial
- Reduction in ventricular arrhythmias, resuscitated cardiac arrest, or sudden death (hazard ratio, 0.73; 95% CI, 0.63 to 0.99)by dapagliflozin in the DAPA-HF trial
- In a meta-analysis of 34 RCT , SGLT2 inhibitors were also associated with significant reductions in atrial arrhythmias (odds ratio, 0.81; 95% CI, 0.69 to 0.95) and sudden cardiac death (odds ratio, 0.72; 95% CI, 0.54 to 0.97)

N Engl J Med 2019; 380: 347-57
N Engl J Med 2019; 381: 1995-2008
Eur Heart J 2021; 42: 3727-38

Other Clinical Outcomes

- In a meta-analysis of 43 randomized, placebo controlled trials involving 22,528 patients with type 2 diabetes, randomized assignment to an SGLT2 inhibitor was associated with modest but significant reductions in arterial pressure (by an average of 2.5 mm Hg systolic and 1.5 mm Hg diastolic), with no increase in heart rate

- Mitigation of anemia (presumably through stimulation of erythropoiesis), and improves oxygen delivery to the heart

- Reduce the risk of obstructive sleep apnea has been reported by empagliflozin

J Am Heart Assoc 2017; 6(6): e004007
J Diabetes Complications 2020; 34:107729
Diabetes Care 2020; 43: 3007-15

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Mechanisms of Action

- In type 2 diabetes, the hyperabsorption of glucose and sodium in the proximal renal tubules by SGLT2 causes afferent arteriolar Vasodilatation leading to glomerular hyperfiltration, and glomerular inflammation, fibrosis, and ultimately, DKD
- The reduction of reabsorption of sodium increases the sodium concentration at the macula densa, specialized cells in the distal renal tubules adjacent to the glomeruli
- Tubuloglomerular feedback activates adenosine receptors, which constrict the afferent glomerular arterioles This constriction reduces glomerular hyperfiltration and thereby reduces further renal damage

Cardiac Actions

- SGLT2 inhibition raises circulating ketone levels, that appears to improve mitochondrial function, increase the production of ATP, and enhance ventricular contractile performance

- Attenuate activation of the nucleotide-binding domain–like protein 3, which stimulates inflammatory responses in experimental models of heart failure

Cardiac Actions

- Reduce free radical formation of human cardiomyocytes, thereby enhancing systolic and diastolic function
- Improve coronary endothelial function and enhance flow-mediated vasodilatation
- Reduce adipose tissue, body weight, waist circumference, visceral and central adiposity, and extracellular volume, aortic stiffness and myocardial fibrosis

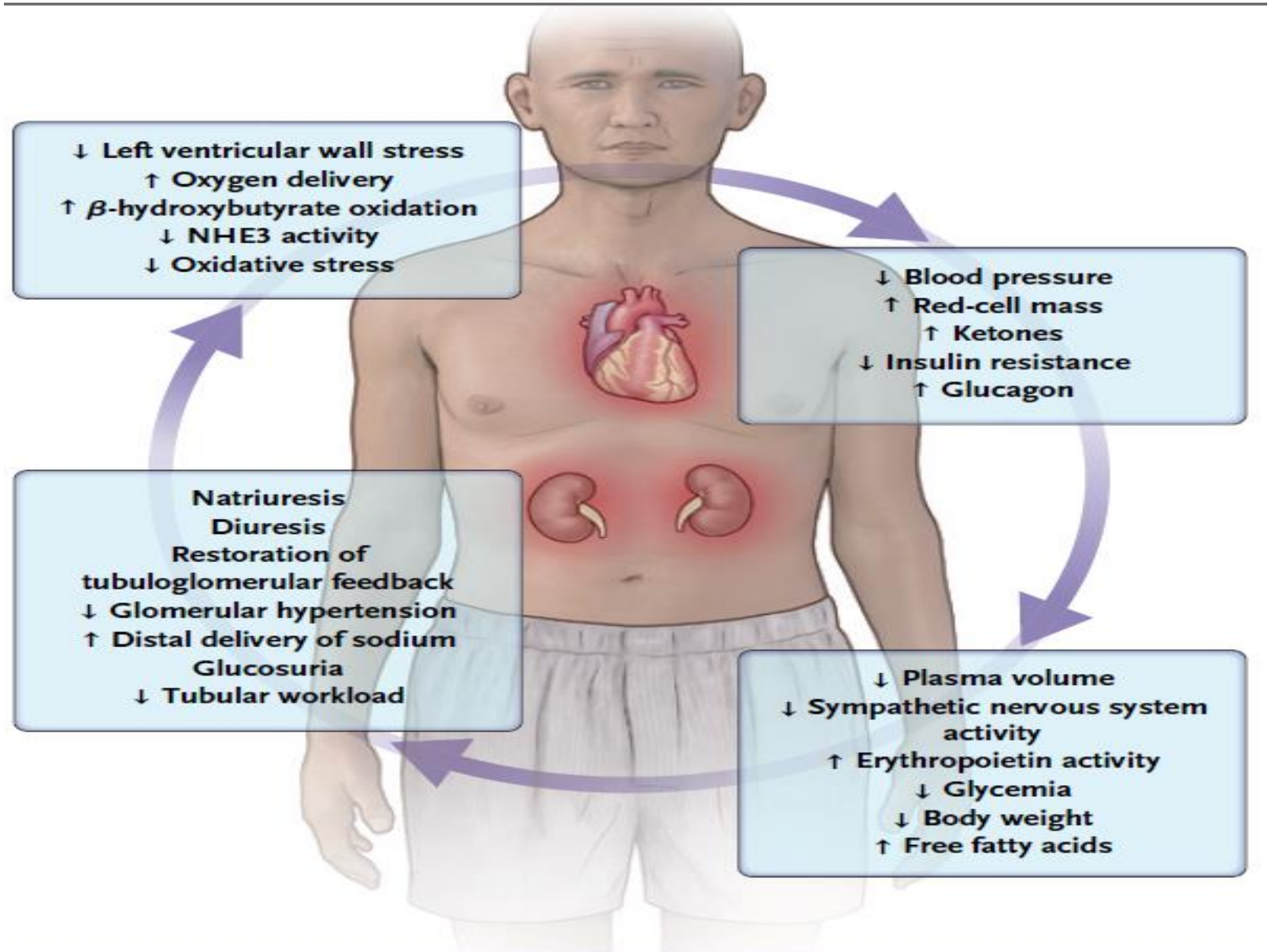
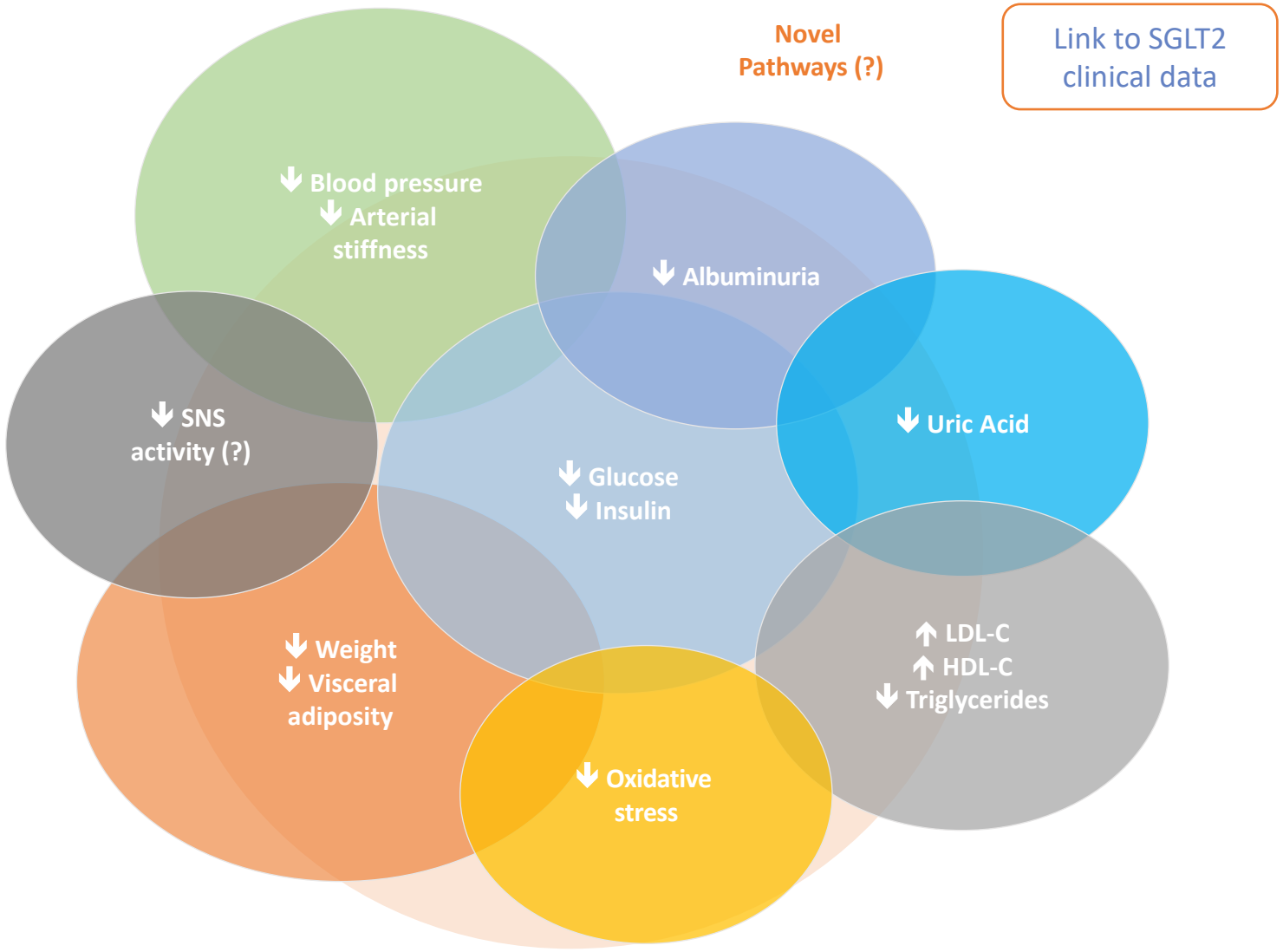


Figure 3. The Kidney–Heart Connection for Organ Protection by SGLT2 Inhibitors.

NHE3 denotes sodium–hydrogen exchanger 3. Modified from Tuttle et al.[39]

SGLT2 inhibitors modulate a range of factors related to CV risk

Based on clinical and mechanistic studies



Inzucchi et al. Diab Vasc Dis Res 2015;12:90–100.

- The FDA has approved Empagliflozin to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure, irrespective of the ejection fraction

- The FDA’s approval of Dapagliflozin was similar but was limited to patients with a reduced ejection fraction
- Canagliflozin has been approved to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular disease
- Dapagliflozin and canagliflozin have also been approved by the FDA for reducing the risk of end-stage kidney disease

Clinical Implications

- The most common adverse effects is: mycotic genital infections more frequently in women than in Men

  Less common adverse effects are:

- urinary tract infections and pyelonephritis
- Diabetic ketoacidosis which is relatively uncommon, may occur, particularly in elderly patients with volume depletion
- A doubling of the incidence of lower-limb amputations and an increase in bone fractures were noted with canagliflozin in the CANVAS Program

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Diabetes guidelines and societies now recommend a cardioprotective glucose-lowering agent for patients with T2D and CV disease

American Diabetes Association®

*"…therapy should […] incorporate an **agent proven to reduce major adverse CV events and CV mortality***

DIABETES CANADA

*"…an antihyperglycemic agent with **demonstrated CV outcome benefit** should be added to **reduce the risk of major CV events**."*[2]

American Diabetes Association®

EASD

*"…Among patients with T2D who have **established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven cardiovascular benefit are recommended** as part of glycaemic management."*[3]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

1. American Diabetes Association. *Diabetes Care* 2021;41:S1; 2. Diabetes Canada. *Can J Diabetes* 2018;42:S162;
3. Davies MJ *et al. Diabetes Care* 2018;41:2669

Cardiology guidelines now recommend a cardioprotective glucose-lowering agent for patients with T2D and CV disease

EUROPEAN SOCIETY OF CARDIOLOGY®

*"In patients with **T2D and CV disease**, the use of an **SGLT2 inhibitor** should be considered early in the course of the disease to **reduce CV and total mortality.**"*[1]

AMERICAN COLLEGE *of* CARDIOLOGY

*"CV specialists should be aware of the **evidence supporting the use of novel therapies, SGLT2 inhibitors and GLP-1 RAs**, to reduce risk in patients with T2D and ASCVD" and "should be both **champions and strong advocates of these agents.**"*[2]

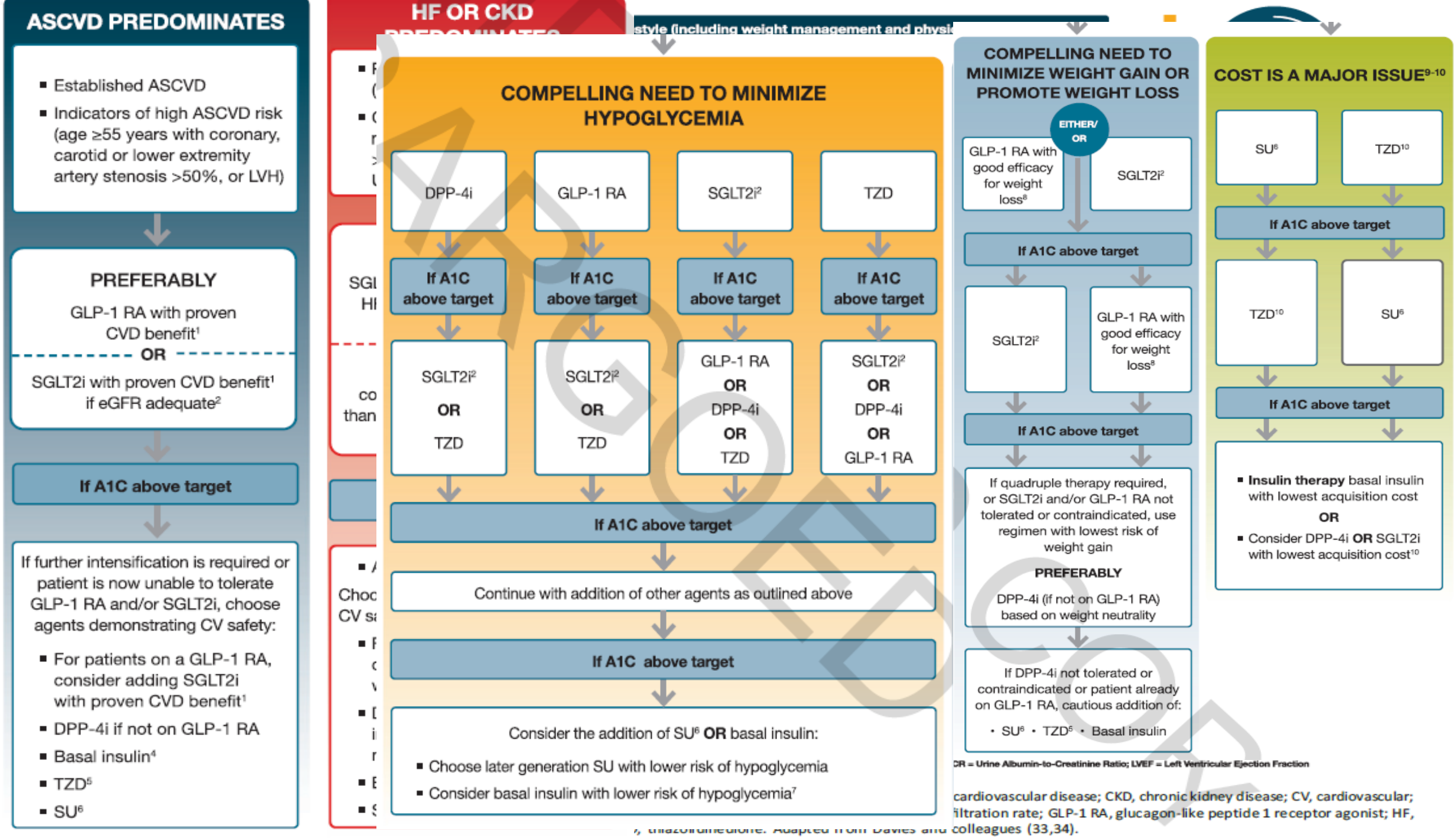
HEART FAILURE ASSOCIATION OF THE ESC

EUROPEAN SOCIETY OF CARDIOLOGY®

*"**Empagliflozin** should be considered in patients with T2D in order to **prevent or delay the onset of HF and prolong life.**"*[3]

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HF, heart failure; SGLT2, sodium-glucose co-transporter-2; T2D, type 2 diabetes

1. Piepoli MF *et al. Eur Heart J* 2016;37:2315; 2. Das SR *et al. J Am Coll Cardiol* 2018;72:3200; 3. Ponikowski P *et al. Eur Heart J* 2016;37:2129



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).

Practice Guidelines

- American Diabetes Association In 2022, recommended treatment with an SGLT2 inhibitor for patients with type 2 diabetes and established arteriosclerotic cardiovascular disease, multiple risk factors, or diabetic kidney disease

- The 2021 guidelines of the European Society of Cardiology and the 2022 guidelines of the American Heart Association for the treatment of heart failure made similar recommendations.

Pharmacological properties of available SGLT2 inhibitors

	Empagliflozin	Dapagliflozin	Canagliflozin
Therapeutic dose (mg/day) Starting dose	10–25 10	5–10 10	100–300 100
Administration	QD With or without food	QD With or without food	QD Before first meal
Peak plasma concentration (hours post-dose)	1.5	Within 2	1–2
Absorption (mean oral bioavailability)	≥ 60%	~ 78%	~ 65%
Metabolism	← Primarily glucuronidation - no active metabolite →		
Elimination (half-life, hours)	Hepatic:renal 43:57 [12.4]	Hepatic:renal 22:78 [12.9]	Hepatic:renal 67:33 [13.1]*
Selectivity over SGLT1	1:5000	> 1:1400	> 1:160[1]
Glucose excretion with higher dose (g/day)	78	~ 70	119

*For the 300 mg dose.

Data from http://www.ema.europa.eu/ (Jardiance SPC, Forxiga SPC , Invokana PI, Invokana SPC, all accessed June 2015); 1. Sha et al. Diab Obes Metab 2015;17:188–97.

Take home message

- SGLT2 inhibitors are responsible for major paradigm shifts in the care of patients with or at high risk for heart failure, progression of chronic kidney disease, or both

- SGLT2 inhibition improves cardiovascular outcomes in patients with heart failure over a wide range of ejection fractions, regardless of whether the patients have type 2 diabetes

- In addition to having glucosuric and natriuretic properties, these agents also reduce the risk of end-stage kidney disease in patients with type 2 diabetes and chronic kidney disease


Thank you