SGLT2 Inhibitors in ESRD: A Shifting Paradigm?

Explore the emerging role of SGLT2 inhibitors in End-Stage Renal Disease (ESRD). This presentation covers evidence, controversies, and clinical perspectives for better decision-making.

F by Farhad Khoshjou

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MECHANISMS OF HYPERTENSION AND TARGET-ORGAN DAMAGE (JE HALL AND ME HALL, SECTION EDITORS)

Is There a Role for SGLT2 Inhibitors in Patients with End-Stage Kidney Disease?

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Purpose of Review Chronic kidney disease and end-stage kidney disease (ESKD) are well-established risk factors for cardiovascular disease (CVD), the leading cause of mortality in the dialysis population. Conventional therapies, such as statins, blood pressure control, and renin-angiotensin-aldosterone system blockade, have inadequately addressed this cardiovascular risk, highlighting the unmet need for effective treatment strategies. Sodium–glucose transporter 2 (SGLT2) inhibitors have demonstrated significant renal and cardiovascular benefits among patients with type 2 diabetes, heart failure, or CKD at risk of progression. Unfortunately, efficacy data in dialysis patients is lacking as ESKD was an exclusion criterion for all major clinical trials of SGLT2 inhibitors. This review explores the potential of SGLT2 inhibitors in improving cardiovascular outcomes among patients with ESKD, focusing on their direct cardiac effects.

Recent Findings Recent clinical and preclinical studies have shown promising data for the application of SGLT2 inhibitors to the dialysis population. SGLT2 inhibitors may provide cardiovascular benefits to dialysis patients, not only indirectly by preserving the remaining kidney function and improving anemia but also directly by lowering intracellular sodium and calcium levels, reducing inflammation, regulating autophagy, and alleviating oxidative stress and endoplasmic reticulum stress within cardiomyocytes and endothelial cells.

Summary This review examines the current clinical evidence and experimental data supporting the use of SGLT2 inhibitors, discusses its potential safety concerns, and outlines ongoing clinical trials in the dialysis population. Further research is needed to evaluate the safety and effectiveness of SGLT2 inhibitor use among patients with ESKD.

Keywords Sodium-glucose cotransporter-2 inhibitors · End-stage kidney disease · Dialysis · Residual kidney function · Chronic kidney disease · Heart failure · Mortality · Oxydative stress · Autophagy · Inflammation

Introduction

Chronic kidney disease (CKD) and end-stage kidney disease (ESKD) are associated with an increased risk of CVD and mortality. CKD has the bidirectional relationship with cardiovascular disease (CVD). The manifestations of CVD in CKD can be broadly classified as myocardial remodeling (i.e., left ventricular hypertrophy, systolic and diastolic dysfunction) and vascular remodeling (i.e., atherosclerosis, arteriosclerosis, vascular calcification), which interact with each other [1]. CVD is the leading cause of mortality in the dialysis population, accounting for 45% of all deaths. The prevalence of coronary heart disease, heart failure, and left ventricular hypertrophy is reported as high as 40%, 43%, and 70%, respectively [2, 3]. Particularly, heart failure poses a significant challenge in the management of ESKD. It frequently develops after initiation of dialysis and is a prominent mortality risk factor among these patients [4]. Traditional therapies to prevent CVD complications in the general population have shown to be ineffective in CKD. To address the unmet need, further research is needed to evaluate novel therapeutic strategies to improve cardiovascular outcomes among patients on dialysis.

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SGLT1 vs SGLT2

Mechanism of inhibition

SGLT1

Intestinal Glucose Absorption

31% decreased intestinal glucose absorption

50% decreased GIP

60% increased PYY

35% increased GLP-1

SGLT2

Renal Glucose Reabsorption

Adverse side effects

SGLT1

Osmotic diarrhea

Gut microbiome proliferation

Enteric inflammation

SGLT2

Genital Mycotic Infections

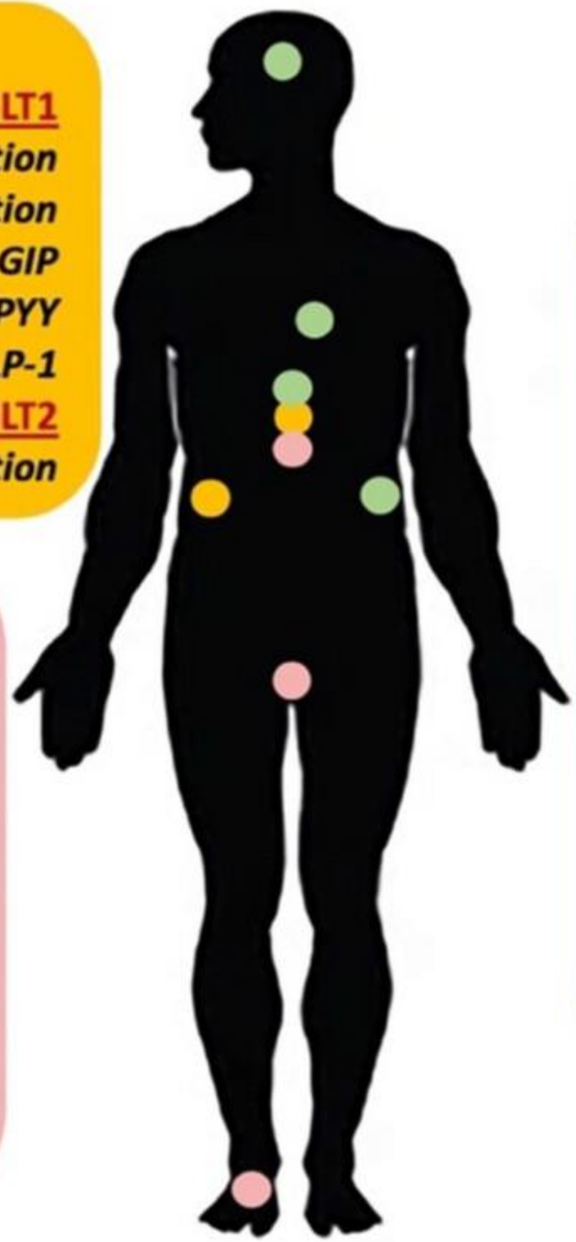
Urinary Tract Infections

Acute Renal Failure

Diabetic Ketoacidosis

Fractures

Amputations



Beneficial side effects

SGLT1

Prevents cerebral ischemia

Prevents Type2 DM related heart failure

Prevents myocardial ischemia

Prevents cardiomyopathy

Prevents effects of acute kidney injury

SGLT2

14% reduced major adverse cardiac events

Reduced systolic blood pressure

Increased urinary glucose excretion

Increased HDL levels

Lowered triglyceride levels

Decreased body weight

Reduced albuminuria progression

Reduced Glomerular Filtration Rate

Lowered TNF receptor-1

Lowered IL-6

SGLT2 inhibitors have variable selectivity for SGLT2 vs. SGLT1

2500× selectivity for empagliflozin

1200× selectivity for dapagliflozin,

250× selectivity for canagliflozin

20x selectivity for sotagliflozin

less selective SGLT2 inhibitors was associated with a lower risk of heart failure

SGLT2 Inhibitors in End-Stage Kidney Disease: Exploring New Frontiers

Chronic kidney disease (CKD) and end-stage kidney disease (ESKD) significantly increase cardiovascular disease risk, the leading cause of mortality in dialysis patients. While conventional therapies have inadequately addressed this risk, sodium-glucose transporter 2 (SGLT2) inhibitors have shown promising renal and cardiovascular benefits in patients with type 2 diabetes, heart failure, or CKD.

This presentation explores the potential application of SGLT2 inhibitors in improving cardiovascular outcomes among ESKD patients, focusing on their direct cardiac effects and safety considerations in the dialysis population.

F by Farhad Khoshjou

Understanding ESKD and Cardiovascular Risk

High Prevalence of Heart Disease

Cardiovascular disease accounts for 45% of all deaths in the dialysis population, with coronary heart disease, heart failure, and left ventricular hypertrophy reported in up to 40%, 43%, and 70% of patients, respectively.

Bidirectional Relationship

CKD has a bidirectional relationship with cardiovascular disease, manifesting as myocardial remodeling (left ventricular hypertrophy, systolic and diastolic dysfunction) and vascular remodeling (atherosclerosis, arteriosclerosis, vascular calcification).

Treatment Challenges

Traditional therapies to prevent cardiovascular complications in the general population have shown limited effectiveness in CKD patients, highlighting the need for novel therapeutic strategies.

SGLT2 Inhibitors: Mechanism and Current Evidence

Primary Mechanism

SGLT2 inhibitors block sodium and glucose reabsorption in the proximal tubule of the kidneys, inducing glycosuria and natriuresis. This leads to improved glycemic control, reduced blood pressure, and modest weight loss in diabetic patients.

Unlike traditional diuretics, SGLT2 inhibitor-induced diuresis is associated with fewer electrolyte abnormalities, decreased risk of acute kidney injury, and less neurohormonal activation.

Clinical Evidence

Clinical trials have demonstrated that SGLT2 inhibitors reduce the risk of cardiovascular events, mortality, and heart failure hospitalizations in patients with type 2 diabetes.

Recent studies show these benefits extend to non-diabetic patients with heart failure (both reduced and preserved ejection fraction) and chronic kidney disease, suggesting mechanisms beyond glycemic control.

Potential Benefits in Dialysis Patients

Preserving Residual Kidney Function

Many incident ESKD patients still have some kidney function, with approximately 27% starting dialysis with an eGFR of 10-14 ml/min/1.73 m².

SGLT2 inhibitors may help preserve this residual function, which is associated with better clinical outcomes.

Improving Anemia

SGLT2 inhibitors can increase hematocrit levels, reduce anemia risk, and decrease the need for iron supplements or erythropoietin stimulating agents.

This effect occurs through stimulation of erythropoietin production and reduced inflammation.

Direct Cardiovascular Benefits

Preclinical studies show SGLT2 inhibitors directly benefit cardiomyocytes, endothelial cells, and smooth muscle cells through multiple pathways.

These effects appear to be independent of their action on the kidneys.

Background: SGLT2 Inhibitors and CKD

Mechanism of Action

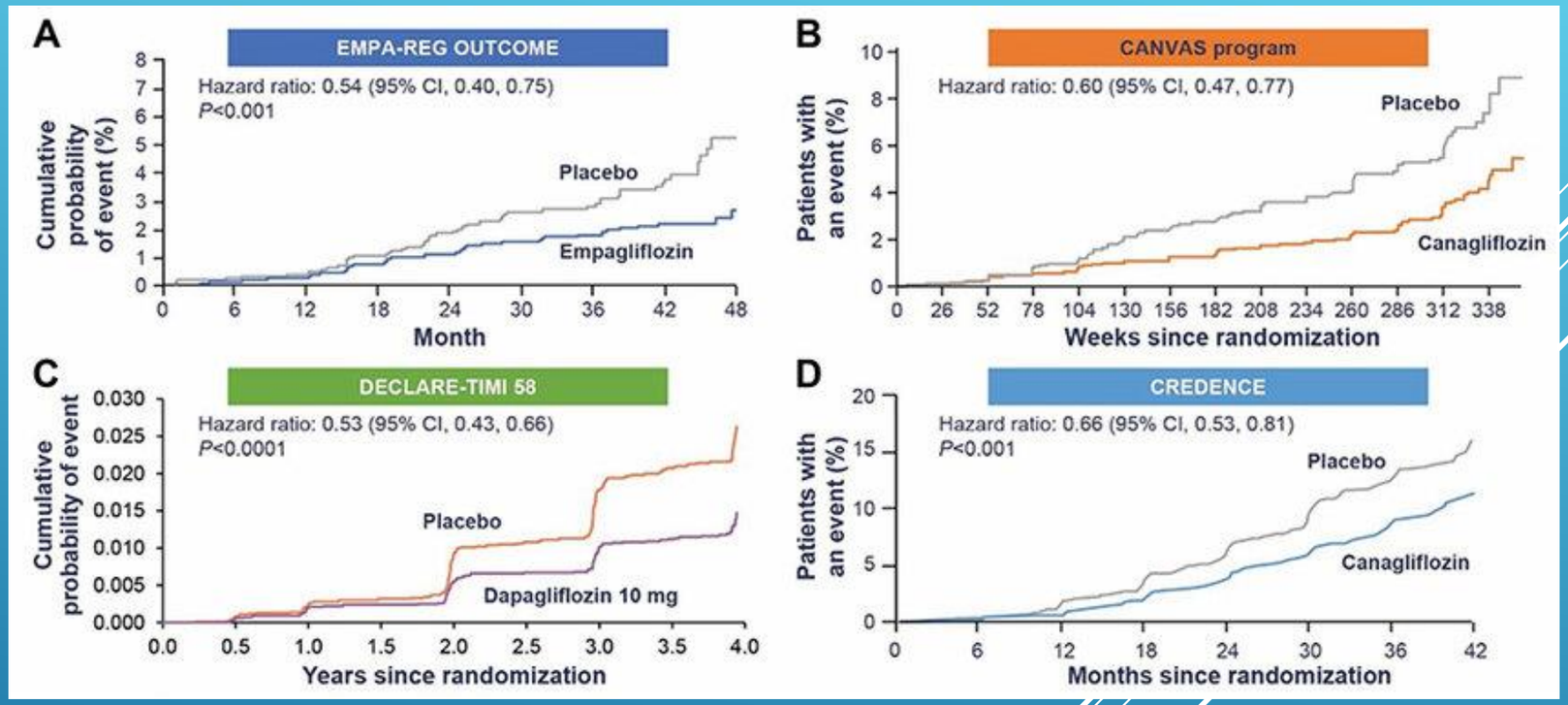
SGLT2 inhibitors block renal glucose reabsorption, lowering blood sugar.

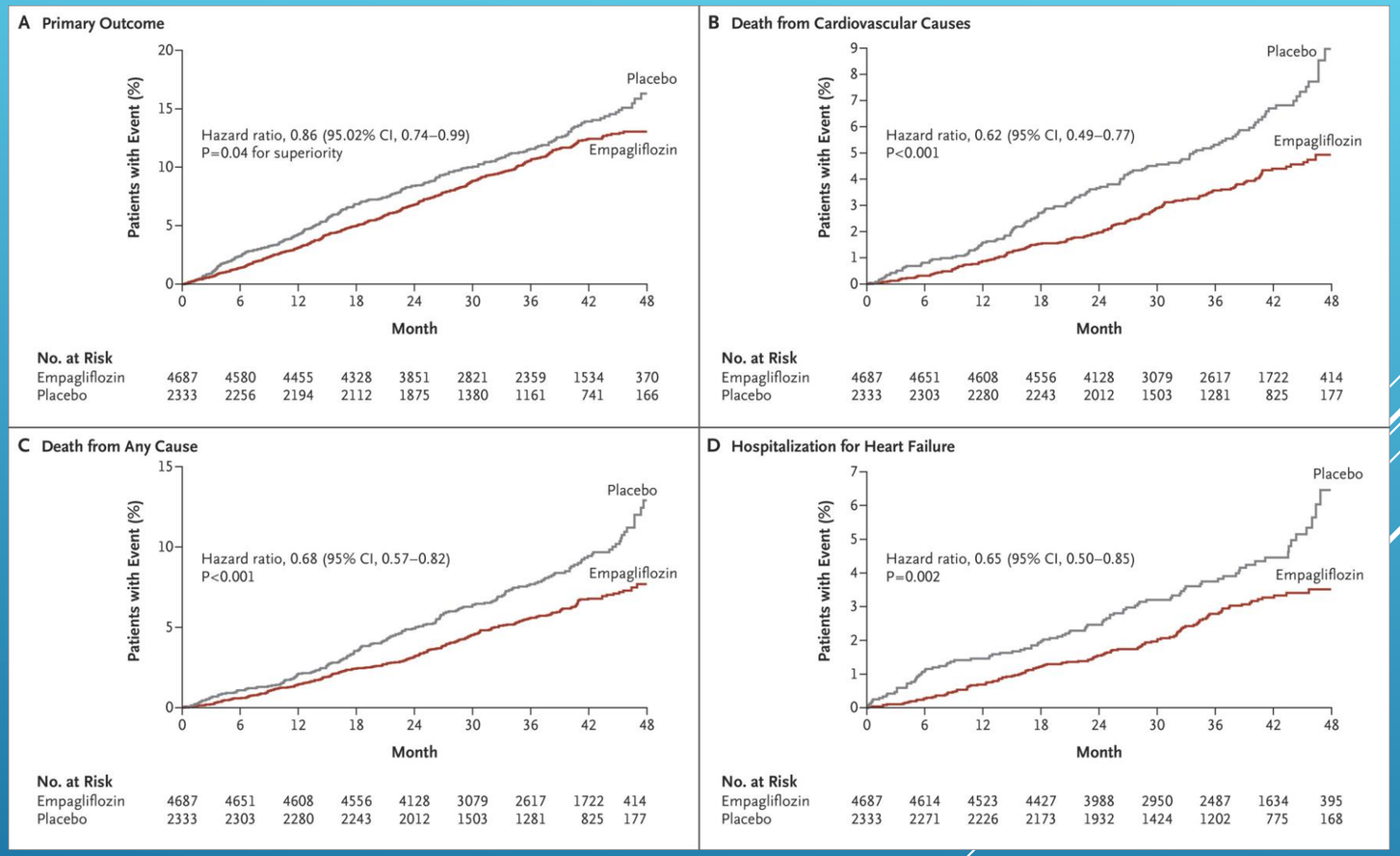
Landmark Trials

- EMPA-REG OUTCOME
- CREDENCE
- DAPA-CKD

Clinical Benefits

They slow CKD progression and reduce cardiovascular risk.


A
EMPA-REG OUTCOME
Hazard ratio: 0.54 (95% CI, 0.40, 0.75)
P<0.001
Cumulative probability of event (%)
Placebo
Empagliflozin
Month
B
CANVAS program
Hazard ratio: 0.60 (95% CI, 0.47, 0.77)
Patients with an event (%)
Placebo
Canagliflozin
Weeks since randomization
C
DECLARE-TIMI 58
Hazard ratio: 0.53 (95% CI, 0.43, 0.66)
P<0.0001
Cumulative probability of event
Placebo
Dapagliflozin 10 mg
Years since randomization
D
CREDENCE
Hazard ratio: 0.66 (95% CI, 0.53, 0.81)
P<0.001
Patients with an event (%)
Placebo
Canagliflozin
Months since randomization


A Primary Outcome
Patients with Event (%)
Placebo
Empagliflozin
Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P=0.04 for superiority
Month
No. at Risk
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166
B Death from Cardiovascular Causes
Patients with Event (%)
Placebo
Empagliflozin
Hazard ratio, 0.62 (95% CI, 0.49–0.77)
P<0.001
Month
No. at Risk
Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414
Placebo 2333 2303 2280 2243 2012 1503 1281 825 177
C Death from Any Cause
Patients with Event (%)
Placebo
Empagliflozin
Hazard ratio, 0.68 (95% CI, 0.57–0.82)
P<0.001
Month
No. at Risk
Empagliflozin 4687 4651 4608 4556 4128 3079 2617 1722 414
Placebo 2333 2303 2280 2243 2012 1503 1281 825 177
D Hospitalization for Heart Failure
Patients with Event (%)
Placebo
Empagliflozin
Hazard ratio, 0.65 (95% CI, 0.50–0.85)
P=0.002
Month
No. at Risk
Empagliflozin 4687 4614 4523 4427 3988 2950 2487 1634 395
Placebo 2333 2271 2226 2173 1932 1424 1202 775 168

EMPA-REG

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Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

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ABSTRACT

BACKGROUND

Type 2 diabetes mellitus is the leading cause of kidney failure worldwide, but few effective long-term treatments are available. In cardiovascular trials of inhibitors of sodium–glucose cotransporter 2 (SGLT2), exploratory results have suggested that such drugs may improve renal outcomes in patients with type 2 diabetes.

METHODS

In this double-blind, randomized trial, we assigned patients with type 2 diabetes and albuminuric chronic kidney disease to receive canagliflozin, an oral SGLT2 inhibitor, at a dose of 100 mg daily or placebo. All the patients had an estimated glomerular filtration rate (GFR) of 30 to <90 ml per minute per 1.73 m^2 of body-surface area and albuminuria (ratio of albumin [mg] to creatinine [g], >300 to 5000) and were treated with renin–angiotensin system blockade. The primary outcome was a composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <15 ml per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes. Prespecified secondary outcomes were tested hierarchically.

RESULTS

The trial was stopped early after a planned interim analysis on the recommendation of the data and safety monitoring committee. At that time, 4401 patients had undergone randomization, with a median follow-up of 2.62 years. The relative risk of the primary outcome was 30% lower in the canagliflozin group than in the placebo group, with event rates of 43.2 and 61.2 per 1000 patient-years, respectively (hazard ratio, 0.70; 95% confidence interval [CI], 0.59 to 0.82; P=0.00001). The relative risk of the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes was lower by 34% (hazard ratio, 0.66; 95% CI, 0.53 to 0.81; P<0.001), and the relative risk of end-stage kidney disease was lower by 32% (hazard ratio, 0.68; 95% CI, 0.54 to 0.86; P=0.002). The canagliflozin group also had a lower risk of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.80; 95% CI, 0.67 to 0.95; P=0.01) and hospitalization for heart failure (hazard ratio, 0.61; 95% CI, 0.47 to 0.80; P<0.001). There were no significant differences in rates of amputation or fracture.

CONCLUSIONS

In patients with type 2 diabetes and kidney disease, the risk of kidney failure and cardiovascular events was lower in the canagliflozin group than in the placebo group at a median follow-up of 2.62 years. (Funded by Janssen Research and Development; CREDENCE ClinicalTrials.gov number, NCT02065791.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Perkovic at the George Institute for Global Health, University of New South Wales Sydney, Level 5, 1 King St., Newtown, NSW 2042, Australia, or at vperkovic@georgeinstitute.org.au.

*A complete list of the CREDENCE trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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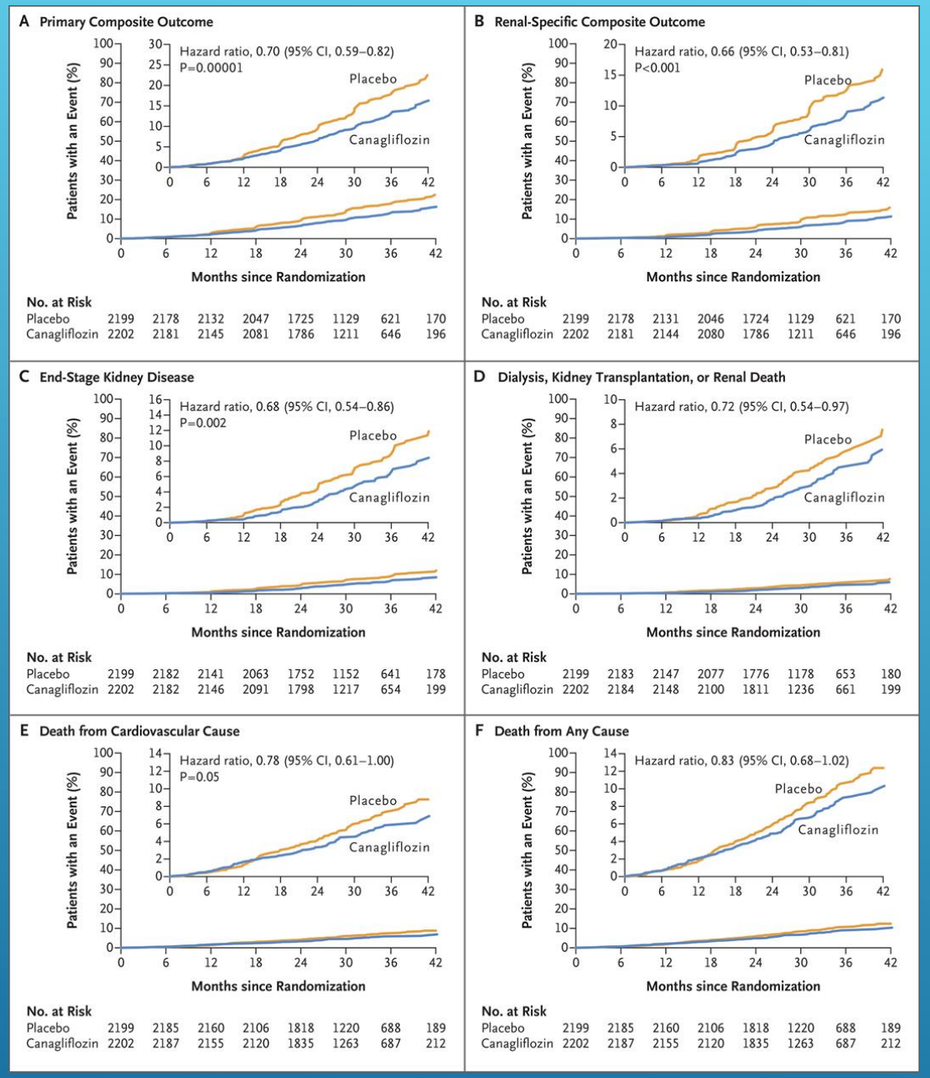
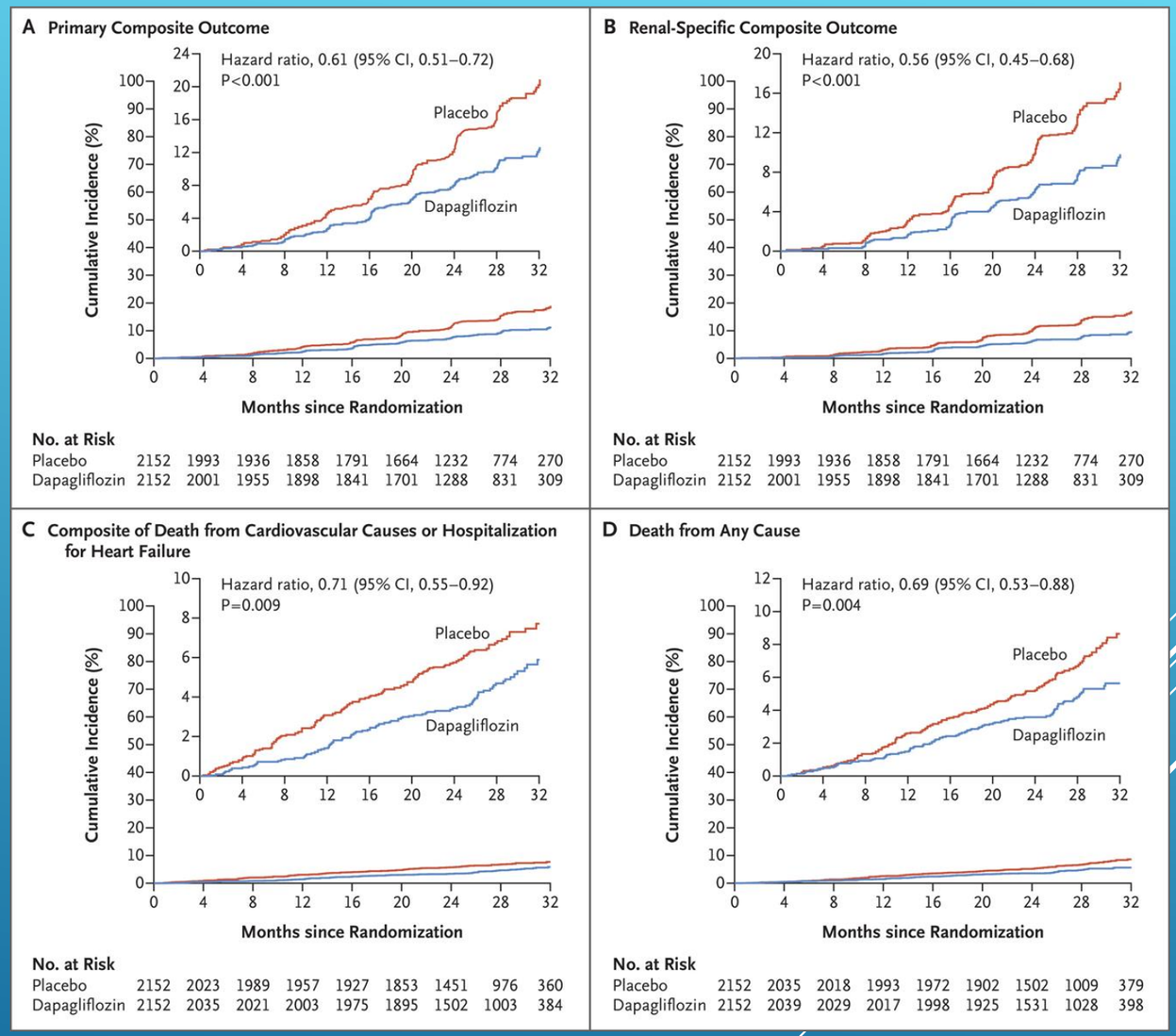

A Primary Composite Outcome
Hazard ratio, 0.70 (95% CI, 0.59–0.82)
P=0.00001
Placebo
Canagliflozin
Patients with an Event (%)
Months since Randomization
No. at Risk
Placebo 2199 2178 2132 2047 1725 1129 621 170
Canagliflozin 2202 2181 2145 2081 1786 1211 646 196
B Renal-Specific Composite Outcome
Hazard ratio, 0.66 (95% CI, 0.53–0.81)
P<0.001
Placebo
Canagliflozin
Patients with an Event (%)
Months since Randomization
No. at Risk
Placebo 2199 2178 2131 2046 1724 1129 621 170
Canagliflozin 2202 2181 2144 2080 1786 1211 646 196
C End-Stage Kidney Disease
Hazard ratio, 0.68 (95% CI, 0.54–0.86)
P=0.002
Placebo
Canagliflozin
Patients with an Event (%)
Months since Randomization
No. at Risk
Placebo 2199 2182 2141 2063 1752 1152 641 178
Canagliflozin 2202 2182 2146 2091 1798 1217 654 199
D Dialysis, Kidney Transplantation, or Renal Death
Hazard ratio, 0.72 (95% CI, 0.54–0.97)
Placebo
Canagliflozin
Patients with an Event (%)
Months since Randomization
No. at Risk
Placebo 2199 2183 2147 2077 1776 1178 653 180
Canagliflozin 2202 2184 2148 2100 1811 1236 661 199
E Death from Cardiovascular Cause
Hazard ratio, 0.78 (95% CI, 0.61–1.00)
P=0.05
Placebo
Canagliflozin
Patients with an Event (%)
Months since Randomization
No. at Risk
Placebo 2199 2185 2160 2106 1818 1220 688 189
Canagliflozin 2202 2187 2155 2120 1835 1263 687 212
F Death from Any Cause
Hazard ratio, 0.83 (95% CI, 0.68–1.02)
Placebo
Canagliflozin
Patients with an Event (%)
Months since Randomization
No. at Risk
Placebo 2199 2185 2160 2106 1818 1220 688 189
Canagliflozin 2202 2187 2155 2120 1835 1263 687 212

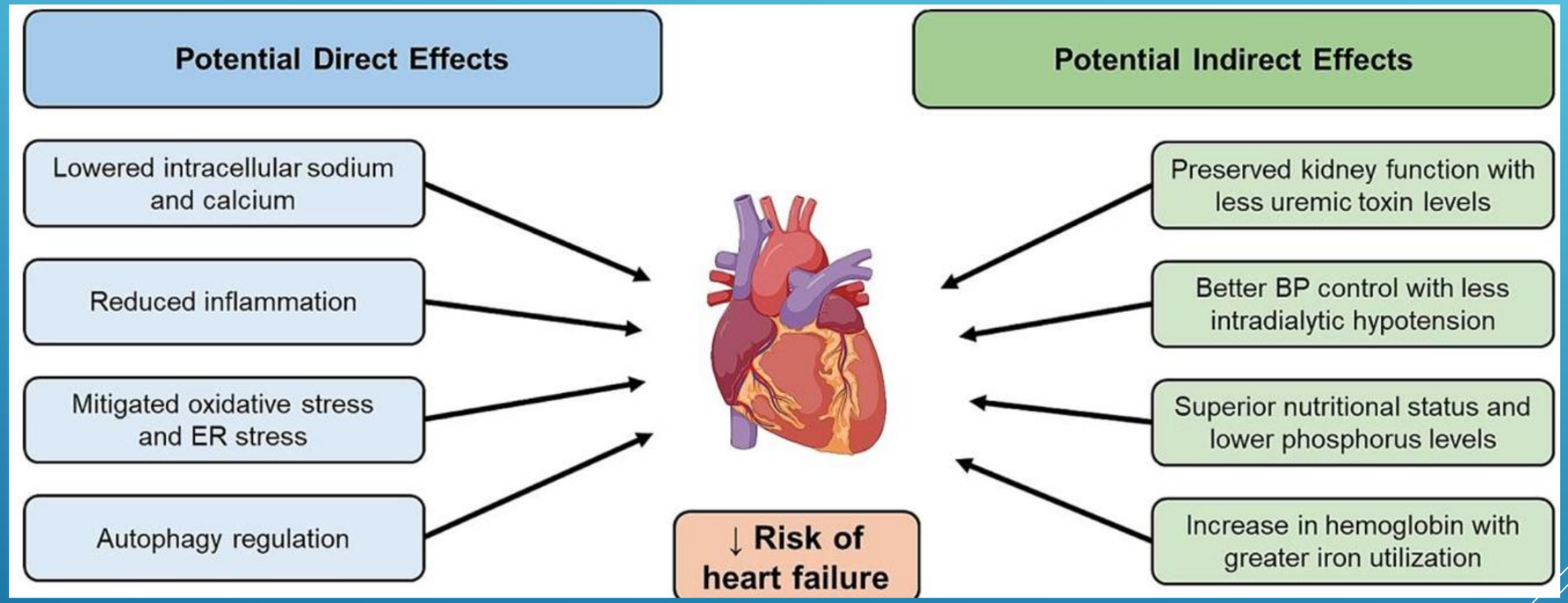
CREDENCE


A Primary Composite Outcome
Hazard ratio, 0.61 (95% CI, 0.51–0.72)
P<0.001
Placebo
Dapagliflozin
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2152 1993 1936 1858 1791 1664 1232 774 270
Dapagliflozin 2152 2001 1955 1898 1841 1701 1288 831 309
B Renal-Specific Composite Outcome
Hazard ratio, 0.56 (95% CI, 0.45–0.68)
P<0.001
Placebo
Dapagliflozin
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2152 1993 1936 1858 1791 1664 1232 774 270
Dapagliflozin 2152 2001 1955 1898 1841 1701 1288 831 309
C Composite of Death from Cardiovascular Causes or Hospitalization for Heart Failure
Hazard ratio, 0.71 (95% CI, 0.55–0.92)
P=0.009
Placebo
Dapagliflozin
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2152 2023 1989 1957 1927 1853 1451 976 360
Dapagliflozin 2152 2035 2021 2003 1975 1895 1502 1003 384
D Death from Any Cause
Hazard ratio, 0.69 (95% CI, 0.53–0.88)
P=0.004
Placebo
Dapagliflozin
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2152 2035 2018 1993 1972 1902 1502 1009 379
Dapagliflozin 2152 2039 2029 2017 1998 1925 1531 1028 398

DAPA-CKD

The EMPA-REG Renal trial showed the risk of mild to moderate urinary tract infection associated with empagliflozin use was more pronounced among patients with more advanced CKD (no acute pyelonephritis or urosepsis was reported).

DAPA-CKD trial, dapagliflozin did not show increased risk of adverse events eGFR declined to < 15 ml/min per 1.73m2


Potential Direct Effects
Lowered intracellular sodium and calcium
Reduced inflammation
Mitigated oxidative stress and ER stress
Autophagy regulation
↓ Risk of heart failure
Potential Indirect Effects
Preserved kidney function with less uremic toxin levels
Better BP control with less intradialytic hypotension
Superior nutritional status and lower phosphorus levels
Increase in hemoglobin with greater iron utilization

Direct Cardiovascular Effects: Electrolyte Regulation

Sodium-Hydrogen Exchanger Inhibition

SGLT2 inhibitors can directly inhibit sodium-hydrogen exchanger 1 (NHE-1) in cardiomyocytes and endothelial cells.

Reduced Intracellular Sodium

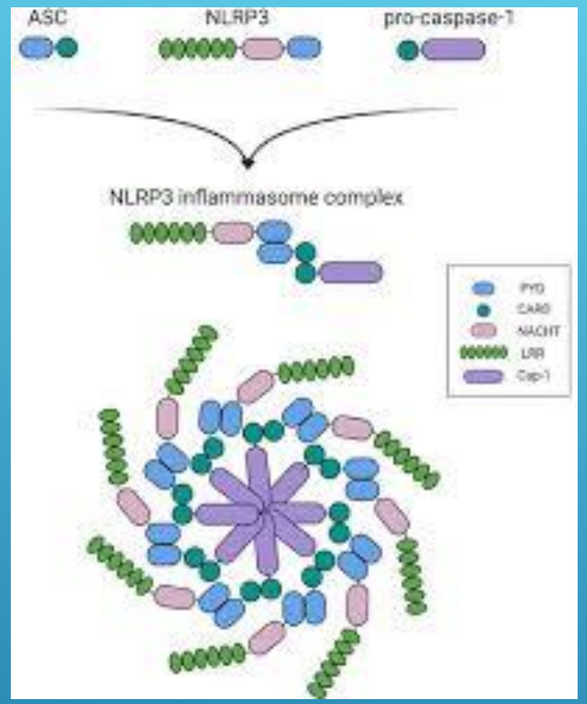
This inhibition leads to reduced intracellular sodium levels in cardiac cells.

Improved Calcium Handling

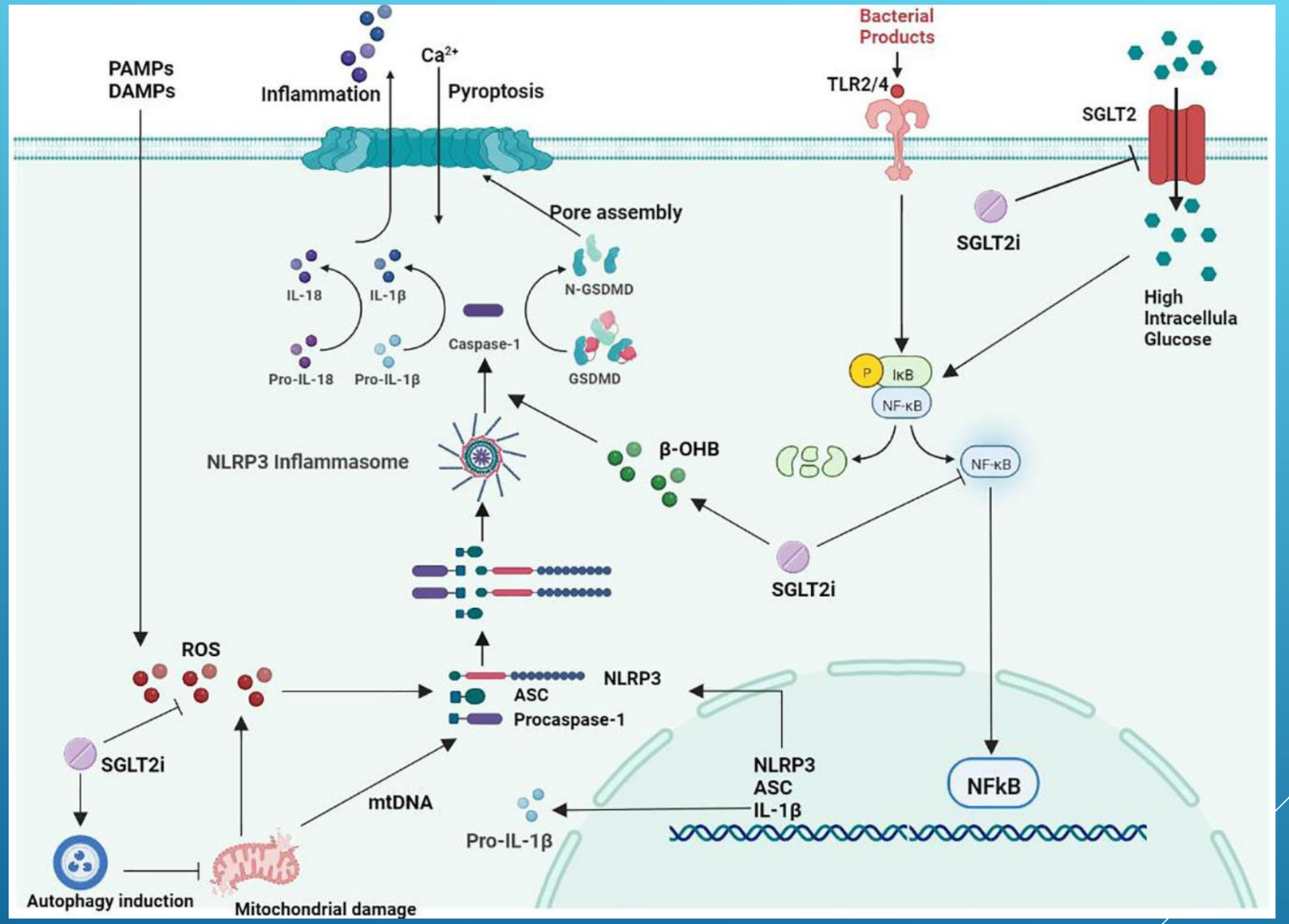
Lower intracellular sodium results in decreased intracellular calcium and increased mitochondrial calcium levels.

Cardiac Function Improvement

These electrolyte changes improve cardiac contractility and reduce arrhythmia vulnerability.



NLRP3 INFLAMMASOME COMPLEX


PAMPs
DAMPs
Inflammation
Ca2+
Pyroptosis
Bacterial
Products
TLR2/4
SGLT2
Pore assembly
SGLT2i
IL-18
IL-1β
N-GSDMD
Caspase-1
Pro-IL-18
Pro-IL-1β
GSDMD
High
Intracellula
Glucose
P
IκB
NF-κB
NLRP3 Inflammasome
β-OHB
NF-κB
SGLT2i
ROS
NLRP3
ASC
Procaspase-1
SGLT2i
mtDNA
NLRP3
ASC
IL-1β
NFkB
Pro-IL-1β
Autophagy induction
Mitochondrial damage

Direct Cardiovascular Effects: Inflammation and Oxidative Stress

Reduced Inflammatory Markers

SGLT2 inhibitors reduce the expression of various circulating inflammatory molecules (IL-1β, IL-6, IL-18, TNF-α, MCP-1) and cell adhesion molecules.

They suppress NLRP3 inflammasome activation through reduced intracellular calcium levels and AMPK activation.

Oxidative Stress Reduction

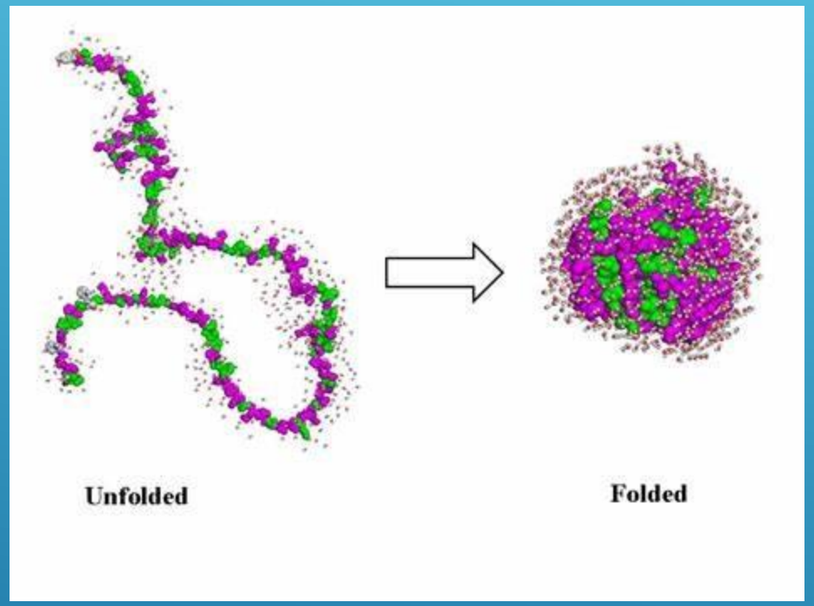
Studies show SGLT2 inhibitors attenuate cardiomyocyte hypertrophy, diminish interstitial fibrosis, and reduce myocardial oxidative stress in animal models.

Empagliflozin restored endothelium-mediated cardiomyocyte function impaired by uremic serum from ESKD patients.

Endothelial Function Improvement

Anti-inflammatory and anti-oxidative properties lead to improvements in endothelial function and arterial wall stiffness.

These effects may mitigate cardiac fibrosis and atherosclerosis by inhibiting macrophage infiltration and promoting anti-inflammatory responses.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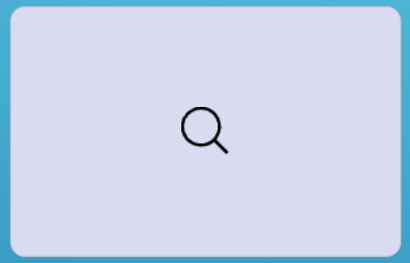
Direct Cardiovascular Effects: Autophagy and ER Stress

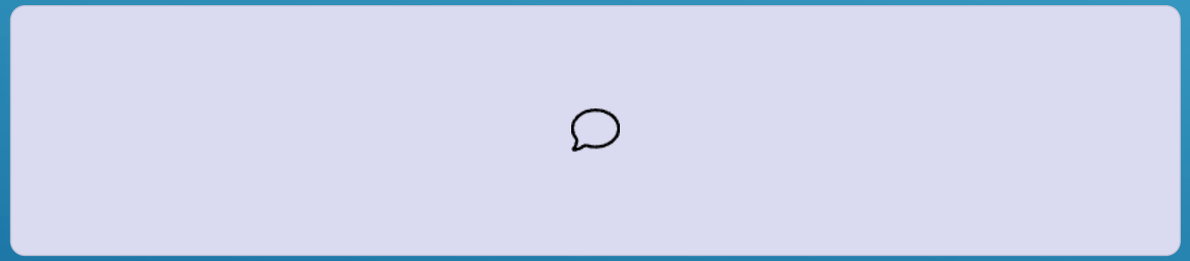


Autophagy Regulation

SGLT2 inhibitors modulate cardiac autophagy, a critical process for maintaining cellular homeostasis in cardiomyocytes.

Endoplasmic Reticulum Stress Reduction

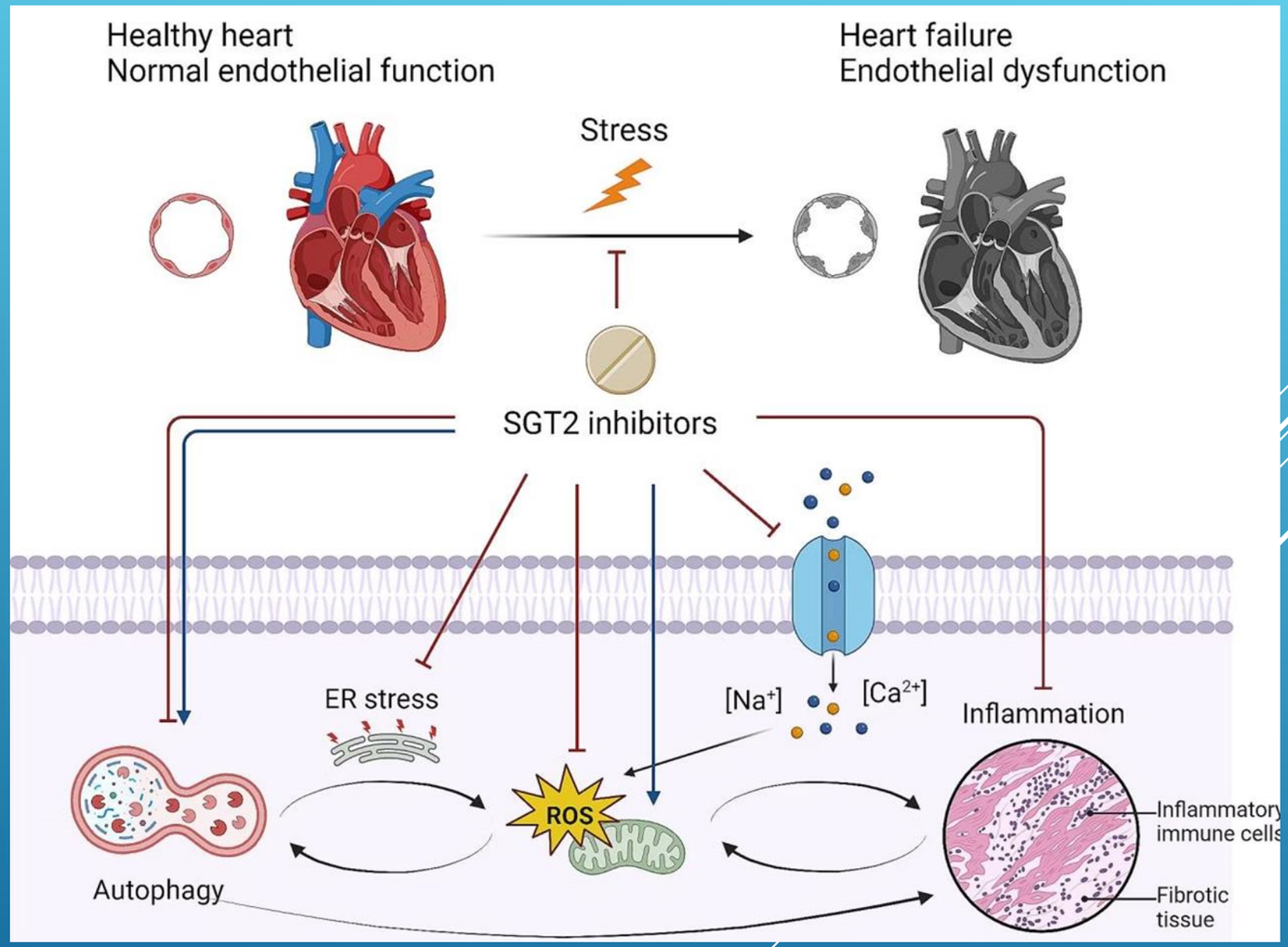
Treatment reduces key ER stress markers in cardiomyocytes exposed to various stressors.



Improved Mitochondrial Function

These effects contribute to improved mitochondrial morphology, function, and biogenesis in the heart.

Autophagy is particularly important for cardiomyocytes as terminally differentiated cells. SGLT2 inhibitors promote autophagy through upregulation of nutrient deprivation signals (AMPK, sirtuins, PGC-1α) while downregulating nutrient surplus signals (mTOR). They can also prevent excessive autophagy in certain disease conditions, maintaining an "optimal window" of autophagy activity.


Healthy heart
Normal endothelial function
Heart failure
Endothelial dysfunction
Stress
SGT2 inhibitors
ER stress
[Na+]
[Ca2+]
Inflammation
ROS
Autophagy
Inflammatory immune cells
Fibrotic tissue

Safety Considerations in ESKD

1

Pharmacokinetics

Studies show similar peak plasma levels in ESKD patients compared to those with normal kidney function, with only mildly prolonged half-life and approximately 1.5 times larger AUC.

2

Drug Accumulation

Seven days of dapagliflozin 10 mg/day in dialysis patients resulted in no significant drug accumulation, with peak concentrations similar to those in patients with normal kidney function.

3

Infection Risk

The EMPA-REG Renal trial showed increased risk of mild to moderate urinary tract infections with empagliflozin in advanced CKD, warranting caution in oliguric dialysis patients.

4

Regulatory Changes

In 2023, the FDA removed dialysis dependency from contraindications for SGLT2 inhibitors, acknowledging evolving understanding of these agents.

Ongoing Clinical Trials

Trial Name	Intervention	Primary Outcome	Target N
RENAL LIFE-CYCLES	Dapagliflozin	All-cause mortality, kidney failure, heart failure	1500
DAPA-HD	Dapagliflozin	Cardiac MRI parameters	108
EMPA-PRED	Empagliflozin	Echocardiogram parameters	150
CARe-MRI	Canagliflozin	Cardiac MRI parameters	92
SEED	Empagliflozin	Body fluid distributions	60

Several clinical trials are currently investigating the effects of SGLT2 inhibitors in the dialysis population. These studies aim to provide proof-of-concept evidence on the efficacy and safety of these drugs in ESKD patients, potentially opening new avenues for cardiovascular risk management in this population.

SGLT2 inhibitors in peritoneal dialysis

Reduction in glucose uptake and an increase in ultrafltration through the rat peritoneum, as well as an inhibition of glucose uptake by human PMCs mediated by empaglifozin.

The genital infections remains consistent across various SGLT2 inhibitors and persists throughout the duration of therapy .

Risk factors include : Female sex, diabetes duration of more than 10 years, and a previous genital infection.

Potential Benefits in ESRD

Cardiovascular Protection

May reduce heart failure risk even in ESRD.

Fluid Management

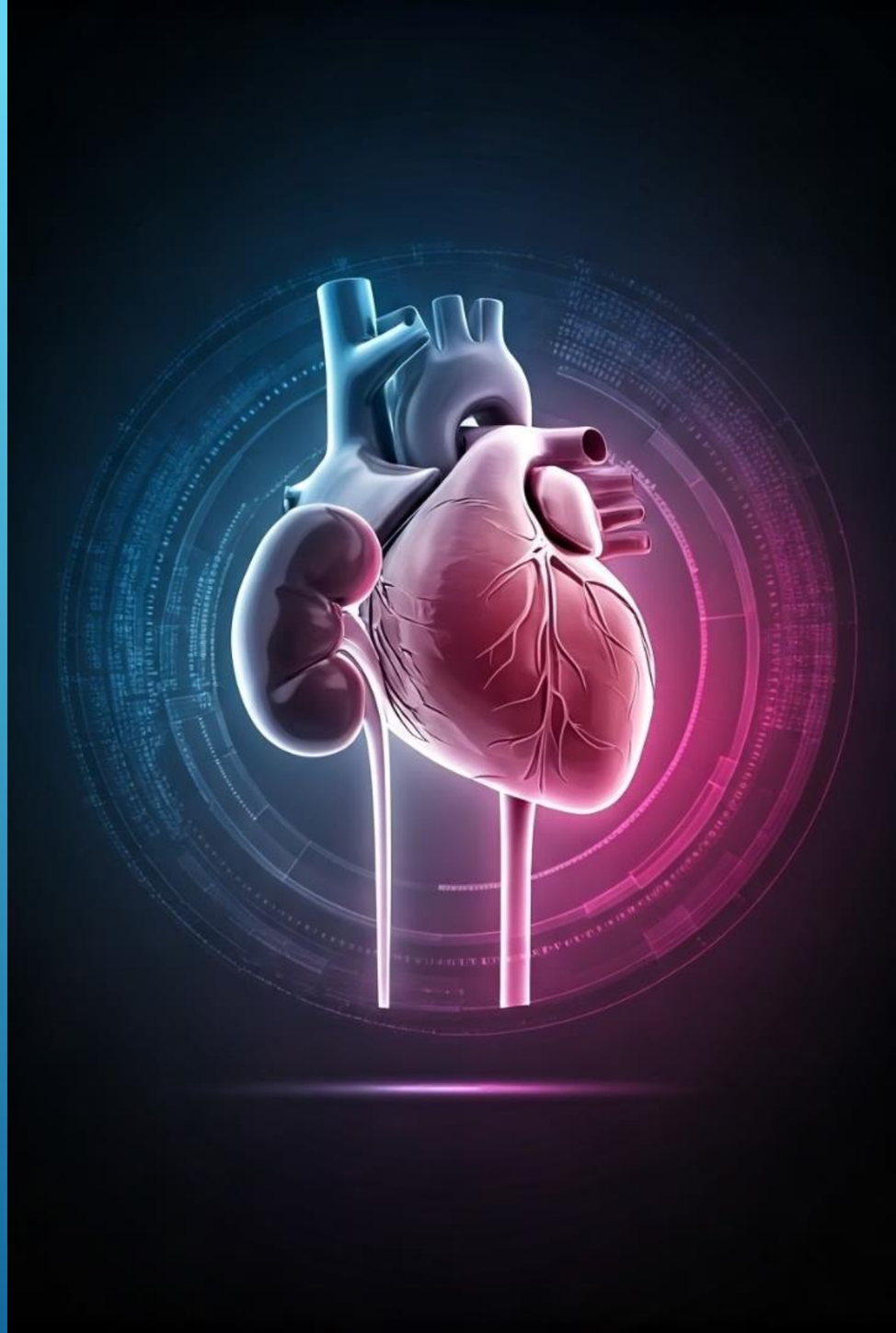
Diuretic effects might aid dialysis patients.

Inflammation Reduction

Could modulate oxidative stress pathways.

Metabolic Improvement

Possible glucose control benefits in diabetic ESRD.



Expert Opinion and Guidelines

KDIGO 2024 Conference

Highlighted areas of uncertainty around SGLT2i in ESRD.

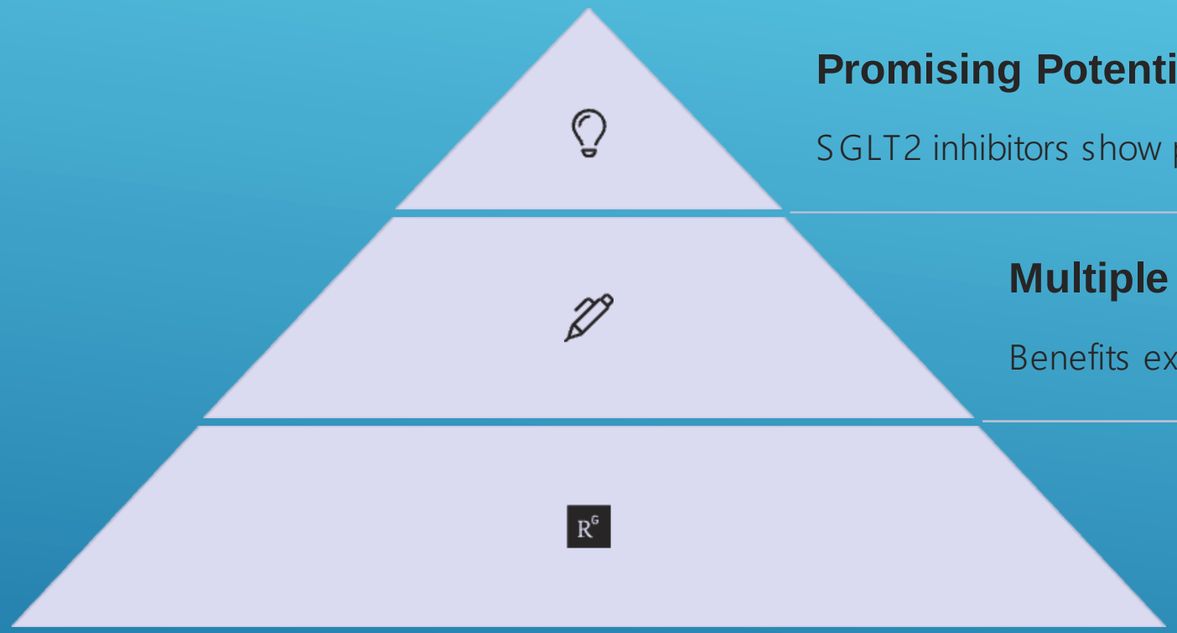
Guideline Evolution

Recommendations are cautious and evolving.

Risk-Benefit Assessment

Individualized approach with multidisciplinary care essential.

Conclusions and Future Directions



Promising Potential

SGLT2 inhibitors show promise for cardiovascular protection in ESKD

Multiple Mechanisms

Benefits extend beyond glycosuria to direct cardiac effects

Ongoing Research

Clinical trials will determine safety and efficacy in dialysis patients

The pleiotropic effects of SGLT2 inhibitors, including their benefits on preserving kidney function and improving cardiovascular health, make them promising therapeutic agents for dialysis patients. Preclinical studies suggest direct actions on the cardiovascular system, even where SGLT2 expression is minimal or negligible.

Ongoing clinical trials will provide critical data on safety and efficacy, potentially transforming cardiovascular risk management in this vulnerable population. If successful, SGLT2 inhibitors could address a significant unmet need in ESKD patient care.