**Inhibition of the Sodium–Proton Antiporter (Exchanger) is a Plausible Mechanism of Potential Benefit and Harm for Drugs Designed to Block Sodium Glucose Co-transporter 2**

**Brief Title: Organ System Impact of NHE Inhibition by SGLT2i**

Peter A. McCullough, MD, MPH1 2 3 4, Aaron Y. Kluger, MPH3 5, Kristen M. Tecson, PhD3 4 5, Clay M. Barbin, MD1 2, Andy Y. Lee, MD1 2, Edgar V. Lerma, MD, MPH6, Zachary P. Rosol, MD1 2, Sivan L. Kluger, Janani Rangaswami, MD7 8

1Baylor University Medical Center, Dallas, TX; 2Baylor Heart and Vascular Hospital, Dallas, TX; 3Baylor Heart and Vascular Institute, Dallas, TX; 4Texas A&M College of Medicine Health Science Center, Dallas, TX; 5Baylor Scott & White Research Institute, Dallas, TX; 6Advocate Health System, Chicago, IL; 7Einstein Medical Center, Philadelphia, PA; 8Sidney Kimmel College of Thomas Jefferson University, Philadelphia, PA

**Word Count**: 4000

**Address correspondence to**: Peter A. McCullough, MD, MPH, Baylor Heart and Vascular Institute, 621 N. Hall #H030, Dallas TX 75226, phone: 214-820-7997, e-mail: peteramccullough@gmail.com

**ABSTRACT**

Clinical trials of sodium glucose co-transporter 2 inhibitors (SGLT2i) in patients with type 2 diabetes and comorbid cardiovascular and kidney disease have shown reductions in major adverse cardiovascular events, heart failure hospitalizations, and attenuation of the progression of kidney disease. The magnitude of benefit appears to be greater than expected due to glycemic control, reduced blood pressure, and loss of adiposity. This impact is also independent from reduced renal function and lesser degrees of natriuresis and glycosuria. However, these agents have also been associated with limb amputation, Fournier’s gangrene, diabetic ketoacidosis, metabolic bone disease, and increased hematopoiesis. A strong off-target effect of SGLT2i on the sodium–proton antiporter (exchanger) on the cell surface and intracellular organelles explains the wide-ranging effects of these agents. By slowing the restoration of pH within cells, SGLT2i activate secondary processes that mimic ischemic preconditioning in the heart and kidney and increased hematopoiesis in bone marrow which would explain salutary effects. Conversely, the inability to rapidly recover pH in ischemic peripheral tissues explains the progression of diabetic extremity ulcers, gangrene, propensity for metabolic bone disease, and diabetic ketoacidosis in patients who are predisposed. This paper will review the evidence for the strong off-target effect of SGLT2i on the sodium-proton exchanger and its potential effect on the organ systems and processes in which SGLT2i appear to have activity.

**Keywords:** SGLT-2 inhibitor, sodium-proton exchanger, sodium-hydrogen exchanger, empagliflozin, canagliflozin, dapagliflozin, ertugliflozin, sotagliflozin, cardiovascular disease, chronic kidney disease, adverse effects

**INTRODUCTION**

Patients with type 2 diabetes mellitus (T2DM) frequently develop cardiovascular and and/or kidney disease. [[1]](#endnote-1) [[2]](#endnote-2) The deleterious effects of T2DM have been described as microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (coronary disease, stroke, peripheral arterial disease).[[3]](#endnote-3) In recent decades, T2DM has been described as an independent risk factor for the two major phenotypes of heart failure (HF)—preserved and reduced ejection fraction.[[4]](#endnote-4) [[5]](#endnote-5) [[6]](#endnote-6) [[7]](#endnote-7) Further, it is associated with a four-fold increase in the rate of HF hospitalizations compared to those without T2DM.[[8]](#endnote-8) T2DM is also associated with non-healing lower extremity wounds such as foot ulcers, deep tissue osteomyelitis, metabolic bone disease, anemia, pancreatitis, and in advanced insulinopenic patients--diabetic ketoacidosis (DKA).[[9]](#endnote-9) [[10]](#endnote-10) [[11]](#endnote-11)

The treatments for T2DM have been scrutinized for their independent link to organ system diseases above and beyond the risk of T2DM. Thiazolidinediones have been associated with worsening edema and increased risk for HF hospitalization, cardiovascular death, but not all-cause mortality.[[12]](#endnote-12) [[13]](#endnote-13) [[14]](#endnote-14) Oral sulfonylureas are mechanistically associated with hypoglycemia and the catecholamine surge that occurs with it provoking myocardial infarction (MI), stroke, and cardiovascular death.[[15]](#endnote-15) [[16]](#endnote-16) Other safety events associated with particular agents are disputed with additional analyses over time such as pancreatitis (originally associated with glucagon-like peptide-1 agonists) and HF (originally associated with thiazolidinediones and dipeptidyl peptidase-4 inhibitors).[[17]](#endnote-17) [[18]](#endnote-18)

**CARDIOVASCULAR SAFETY ASSESSED IN CLINICAL TRIALS OF ANTIDIABETIC AGENTS**

In 2008, the United States Food and Drug Administration (FDA) put forth guidelines for drug manufacturers to demonstrate that new anti-hyperglycemic medications should not increase the risk for MI, stroke, or cardiovascular death.[[19]](#endnote-19) Specifically, the upper bound of the 95% confidence limit of the hazard ratio for major adverse cardiac events (nonfatal myocardial infarction, non-fatal stroke, or cardiovascular death) should not exceed 1.30 at the end of the trial nor > 1.80 at any interim analysis.[[20]](#endnote-20) The shortcoming of this guidance is that it ignored the important connections between T2DM and the risk of HF, progression of kidney disease, and other organ system illnesses.[[21]](#endnote-21) Additionally, while it leveraged the endpoints that were associated with hyperglycemia (MI, stroke, cardiovascular death) it failed to provide a framework that could adapt to the mechanism of action of the drug or consider important unique safety events for adjudication (e.g. extremity amputation, DKA, acute kidney injury). In the United States, there have been four FDA approved sodium glucose co-transporter inhibitors (SGLT2i) based on this guidance; their clinical implications have been well-demonstrated and are promising new tools for the care of T2DM patients with established cardiovascular disease, as evidenced by the recent 2018 American College of Cardiology Expert Consensus Decision.[[22]](#endnote-22) However, there are concerning potential adverse effects – for example, a registry-based cohort study (n=34,426) comparing outcomes between new users of SGLT2i and GLP1 receptor agonists found that SGLT2i were associated with increased risk of lower limb amputation and DKA compared to GLP1 receptor agonists.[[23]](#endnote-23) In 2017 the European Medicines Agency a warning for this SGLT2i class limited at that time to canagliflozin, empagliflozin, and dapagliflozin concerning the risk of lower limb amputations.[[24]](#endnote-24) The array of clinical responses to this class of agents calls for an in-depth consideration of both target-mediated and off-target effects. Such an analysis of biologic mechanisms would account for positive outcomes such as a reduction in HF hospitalization, cardiovascular death, and attenuation of progression of diabetic kidney disease (Figure 1), as well as adverse outcomes such as an increased risk of limb amputation, Fournier’s gangrene, DKA, metabolic bone disease, and increased hematopoiesis.

**The *EMPA-REG OUTCOME* Trial**

The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial was the first to show cardiovascular mortality reduction in T2DM patients with established cardiovascular disease treated with the SGLT2i empagliflozin. This trial randomized 7020 patients with T2DM, estimated glomerular filtration rate (eGFR)>30 ml/min/1.73 m2 and cardiovascular disease (CVD) to 10mg or 25mg of empagliflozin daily or to placebo.[[25]](#endnote-25) The primary composite endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke occurred in 10.5% in the pooled empagliflozin group vs. 12.1% in placebo (hazard ratio [HR] = 0.86, 95% confidence interval [CI] = 0.74-0.99. p=0.04) in the 3.1 year follow up period. There were no significant differences in rates of MI or stroke, but there was a 38% lower risk of cardiovascular death and a 32% risk reduction for all-cause death (p-values<0.001) with empagliflozin. The mortality effects were concordant with a reduction of HF hospitalization by 35% and HF death or hospitalization by 39% (p-values<0.001), with these benefits seen in patients with (10%) and without (90%) documented HF at baseline.22 [[26]](#endnote-26) The reduced adjudicated endpoint of HF hospitalization was supported by similar reductions of investigator-reported HF, and the introduction of loop diuretics as a proxy for HF symptoms. In the same trial, there was a 39% reduction in the relative hazard of incident or worsening nephropathy defined as either progression to macroalbuminuria (>300 mg of albumin per gram of creatinine in spot urine), a doubling of the serum creatinine accompanied by an eGFR of ≤45 ml/min/1.73 m2, the initiation of renal-replacement therapy, or death from renal disease (HR=0.61, 95% CI = 0.53-0.71, p<0.001). These findings appeared to be out of proportion to the 0.54% reduction in hemoglobin A1C, decrease (~4 mmHg) in systolic blood pressure, and decline (~2.0 kg) in body weight observed in the treatment group. Additionally, the cardiovascular outcomes were independent of baseline eGFR.[[27]](#endnote-27)

**The *CANVAS* Program**

The Canagliflozin Cardiovascular Assessment Study (CANVAS) Program included the CANVAS and CANVAS-Renal (CANVAS-R) study cohorts assembled into a randomized trial comparing canagliflozin 100 mg or 300 mg (100 mg with optional increase to 300 mg) to placebo control in 10,142 patients with T2DM and eGFR >30 ml/min/1.73m2.[[28]](#endnote-28) [[29]](#endnote-29) Unlike EMPA-REG, CANVAS included only 56% of patients with established cardiovascular disease. Like EMPA-REG OUTCOME, the cardiovascular and renal benefits were evident with SGLT2i. The primary composite outcome of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was lower with canagliflozin than with placebo, (HR= 0.86, 95% CI = 0.75-0.97, p=0.02). HF hospitalization or cardiovascular death was reduced with canagliflozin compared with placebo (HR=0.78, 95% CI = 0.67–0.91) as was fatal or hospitalized HF (HR=0.70, 95% CI = 0.55–0.89) and hospitalized HF alone (HR=0.67, 95% CI = 0.52–0.87).[[30]](#endnote-30) Canagliflozin reduced the progression of albuminuria (HR=0.73, 95% CI = 0.67-0.79) and the composite outcome of a sustained 40% eGFR reduction, the need for renal-replacement therapy, or death from renal causes (HR=0.60, 95% CI = 0.47-0.77). Patients treated with canagliflozin had nearly a two-fold increased risk of limb amputation (6.3 vs. 3.4 participants per 1000 patient-years; HR=1.97, 95% CI = 1.41-2.75); amputations were primarily of the toe or metatarsal.24 As in the EMPA-REG OUTCOME trial, the reductions in cardiorenal endpoints were out of proportion to changes in glycemic control, blood pressure, and body weight.

**The *DECLARE-TIMI 58* Trial**

Unlike EMPA-REG OUTCOME and CANVAS, the Dapagliflozin Effect on CardiovasculAR Events (DECLARE-TIMI 58) trial recruited 17,160 T2DM patients (66% with cardiovascular disease) with eGFR >60 ml/min/1.73 m2. In the primary endpoint analyses, dapagliflozin 10 mg daily did not reduce major adverse cardiovascular events (MACE) (HR=0.93, 95% CI = 0.84-1.03, p=0.17), but did result in a lower rate of HF hospitalization or cardiovascular death (HR=0.83, 95% CI = 0.73-0.95, p=0.005).[[31]](#endnote-31) The renal composite endpoint of sustained 40% eGFR reduction to <60 ml/min/1.73 m2, end stage renal disease, or death from renal causes was reduced with dapagliflozin (HR=0.76, 95% CI = 0.67-0.87). DKA was more common with dapagliflozin than with placebo (0.3% vs. 0.1%, p=0.02) and there were similar rates of amputation for dapagliflozin vs. placebo (1.4% vs. 1.3%, HR=1.09, 95% CI = 0.84-1.4, p=0.53). As in the EMPA-REG OUTCOME and CANVAS trials, the cardiorenal benefit was somewhat out of proportion to changes in glycemic control, blood pressure, and body weight.

**The *CVD-REAL* and *CVD-REAL 2* Studies**

EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 provided evidence of the efficacy and safety of currently approved SGLT2i in the randomized controlled trial setting. However, each trial had stringent inclusion and exclusion criteria, affecting the “real-world” applicability of these drugs.[[32]](#endnote-32) Therefore, in support of these trials, the investigators in the Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors (CVD-REAL) study sought to evaluate the efficacy but not safety of SGLT2i in reducing cardiovascular death and HF hospitalization in patients with T2DM in a large, multination, observational study. Patients on SGLT2i were compared to patients on other glucose-lowering drugs. Data from 309,056 patients were collected from the US, Norway, Denmark, Sweden, Germany and the UK. Thirteen percent of patients had established ASCVD. There was an overall lower risk of HF hospitalization (HR=0.61, 95% CI = 0.51-0.73, p<0.001); death (HR=0.49, 95% CI = 0.41-0.57, p< 0.001); and composite HF hospitalization or death (HR=0.54, 95% CI = 0.48-0.60, p<0.001) in patients treated with SGLT2i compared to other glucose-lowering agents.There were geographic differences noted among the utilization of specific SGLT2i (92% dapagliflozin in Europe and 76% canagliflozin in the US); however, there was no significant absolute or relative difference in outcomes which suggests a class effect of SGLT2i in lowering cardiovascular risk.

In a subsequent study, the CVD-REAL 2 study, the investigators evaluated a broad range of cardiovascular outcomes in patients on SGLT2i compared with other antidiabetic agents. This study included over 400,000 patients from South Korea, Japan, Singapore, Israel, Australia and Canada; 27% had established cardiovascular disease.[[33]](#endnote-33) Pooled analyses showed that the use of SGLT2i was associated with a lower risk of all cause death (HR=0.51, 95% CI = 0.37-0.70, p<0.001), HF hospitalization (HR=0.64, 95% CI = 0.50-0.82, p<0.001), composite death or HF hospitalization (HR=0.60, 95% CI = 0.47-0.76, p<0.001), MI (HR=0.81, 95% CI = 0.74-0.88, p<0.001), and stroke (HR=0.68, 95% CI = 0.55-0.84, p<0.001). These results were similar regardless of country and patient subgroup.

**COMMON MECHANISMS OF CARDIORENAL BENEFIT**

Any potential mechanism of SGLT2i benefiting the heart and the kidneys should consider the simultaneous impact on known and accepted risk factors for disease progression. For the outcome of HF and cardiovascular death, there are three principles of disease progression: 1) pressure overload, 2) volume overload, and 3) cardiomyopathy as it relates to structure, function, or resilience of the myocardium in response to disease. For diabetic nephropathy there are two mechanistic principles of treatment: 1) glycemic control and 2) blood pressure control.

***Improvements in Glycemic Control:*** SGLT2 is located almost exclusively in the proximal renal tubule, while SGLT1 transporters are also located in the intestines, heart, and skeletal muscles.[[34]](#endnote-34) Glucose reabsorption in the kidneys occurs in a sodium-dependent manner via SGLT transporters, with most reabsorption occurring at the proximal convoluted tubule through SGLT2 and a smaller portion in the distal segment of the proximal tubule by SGLT1.[[35]](#endnote-35) Once the maximum glucose transport capacity has been reached, excess glucose is excreted into the urine. SGLT2i lead to increased urinary glucose excretion by blocking SGLT2-mediated glucose reabsorption which is dependent upon the number of functioning nephrons and by proxy, the eGFR. SGLT2i as monotherapy and in combination with oral medications in T2DM as well as injectable therapies consistently improves glycemic control to a modest degree. Because SGLT2i increase glucose excretion in the urine, causing increased calorie loss and thus body weight reduction, there is less need for therapies that may have no benefit on cardiovascular and renal risk such as oral hypoglycemic agents and insulin, respectively. If we consider in context the pharmacologic inhibition of SGLT2 channels taken as a sole mechanism, there is no parallel antidiabetic agent that reduces hemoglobin A1c by ~0.5% and results in ~20-40% reductions in cardiovascular and renal events.

***Blood Pressure Control:*** SGLT2i treatment is associated with reductions in systolic and diastolic blood pressure. Unlike vasodilators, this change in blood pressure is not associated with an increase in heart rate, suggesting that the sympathetic nervous system is not activated and that plasma volume is not persistently contracted.[[36]](#endnote-36) [[37]](#endnote-37) Reduction in blood pressure is likely multifactorial and related to natriuresis, non-fluid weight loss, as well as direct vascular effects.[[38]](#endnote-38) The blood pressure reduction of ~4 mmHg is significant enough to partly influence both heart and kidney outcomes. This is supported by the observation that HF was the most responsive endpoint to SGLT2i, which is consistent with blood-pressure lowering trials.[[39]](#endnote-39)

***Sodium and Fluid Loss:*** SGLT2i induce osmotic diuresis and natriuresis through the decreased reabsorption of glucose and sodium, resulting in decreased extracellular volume, possible reduction of vascular wall stress, improved cardiac function and potentially reduced congestion.[[40]](#endnote-40) An initial reduction in plasma volume may also lead to reduced myocardial stretch and natriuretic peptide levels, as well as improving symptom and functional capacity.[[41]](#endnote-41) SGLT2i have been shown to reduce the sodium content in skin which correlates with left ventricular mass.[[42]](#endnote-42) [[43]](#endnote-43) In clinical practice, there may be a reduction in the need for thiazide and loop diuretics, and as a result, less diuretic-induced activation of the renin-angiotensin system, hypokalemia, and metabolic alkalosis. Unlike thiazide diuretics, SGLT2i induce natriuresis as well as osmotic diuresis via glucosuria which may decline over time with lower daily plasma glucose levels and compensatory renal mechanisms for sodium reabsorption. The increase in sodium excretion with SGLT2i may be long-lasting having an effect on blood pressure reduction in sustained and synergistic with other blood pressure lowering medication, perhaps due to whole body sodium content.[[44]](#endnote-44) While thiazides act on the distal convoluted tubule and are associated with hypokalemia, increased serum uric acid, and impaired glucose tolerance, SGLT2i act on the proximal renal tubule and are associated with reductions in serum uric acid and no changes in serum potassium.[[45]](#endnote-45) In summary, the diuretic-like properties of SGLT2i appear to account for the blood pressure reductions seen in T2DM; however. these effects do not appear to be substantial enough to account for the cardiorenal benefits of SGLT2i in clinical trials.

***Weight Loss*:** SGLT2i are associated with modest (1.8 kg) short term but sustained reductions in body weight.[[46]](#endnote-46) This occurs rapidly initially with diuresis and then is gradually consistent with daily caloric losses of glucose in urine until a plateau is reached; the weight reduction is sustained over time. Outside of bariatric surgery trials, which yield large reductions in body weight, clinical trials attempting to reduce body weight and improve cardiovascular outcomes have been disappointing. A greater than 10% loss of body weight with medication has been associated with reductions in cardiovascular deaths and adverse cardiovascular outcomes in patients with diabetes over the long term.[[47]](#endnote-47) However, the modest ~2 kg (<5%) reduction in body weight is unlikely to completely account for the large reductions in HF, cardiovascular death, and/or progression of chronic kidney disease (CKD) observed in SGLT2i trials.

**the Sodium–Proton antiporter (EXCHANger) CHANNELS**

There are 10 described sodium-proton antiporters or sodium-hydrogen exchangers (NHE) in mammalian cells (Table 1, Figure 2).[[48]](#endnote-48) These anti-porters exchange sodium for protons and work to restore pH in the setting of intracellular accumulation of acid. Additionally, there are NHE antiporters on the sarcolemmal membrane in cardiomyocytes which work as critical regulators of sodium within the sarcolemma at the level of intercalated discs and T-tubules.[[49]](#endnote-49) Increased intracellular concentration of sodium has been demonstrated to have deleterious effects on cardiomyocytes, altering the efficiency of calcium and hydrogen exchange.[[50]](#endnote-50) [[51]](#endnote-51) This increased intracellular sodium tendency has been well demonstrated in myocardial hypertrophy and HF states, both acute and chronic. Isoforms of NHE and tissue types are shown in Table 1. The NHE family has homology in structure to the SGLT family in terms of a funnel shape for sodium transport.39 It is well established that reductions in intracellular and tissue pH occur in the setting of systemic acidosis, hypoxia, and/or tissue ischemia due to impaired blood flow. The rapid restoration of intracellular pH is a normal function of all cells, and when this process is impaired, it results in both gene activation and repression governing a variety of metabolic processes in cells known as ischemic preconditioning. In short, provided the exposure to ischemia is sufficiently brief, ischemic preconditioning improves the hardiness of cells to the subsequent bout of ischemia; NHE upregulation occurs ischemic preconditioning as well as in many disease states. These changes may modulate responses to infarction, apoptosis, fibrosis, and have been important for drug development.[[52]](#endnote-52) In the setting of chronic disease, NHE is upregulated and related to maladaptive processes including myocardial hypertrophy, sodium reabsorption, intracellular sodium accumulation, and fluid retention.[[53]](#endnote-53)

**DRUGS THAT INHIBIT THE Sodium–Proton antiporter (EXHANGER)**

The known and developed pharmacologic inhibitors of NHE include cariporide, zoniporide, rimeporide, eniporide, and the clinically utilized diuretic, amiloride. Cariporide (an NHE1 inhibitor) was developed as an adjunct to cardiac revascularization with the intent of preventing intracellular calcium overload by NHE1 inhibition. In the Guard During Ischemia Against Necrosis (GUARDIAN) trial, 11,590 patients who were hospitalized for an acute coronary syndrome or undergoing high-risk percutaneous coronary intervention or coronary artery bypass grafting (CABG) were randomized to one of three doses of cariporide (20, 80, or 120 mg), or placebo, administered as a 60-minute infusion every 8 hours for two to seven days.[[54]](#endnote-54) At day 36, patients treated with cariporide 120 mg demonstrated a nonsignificant 10% risk reduction in the primary endpoint of death or MI compared with placebo (p=0.12). At this dose, patients undergoing CABG experienced a 25% risk reduction in death or MI (p = 0.03), which was sustained through six months (p=0.033). The improvement resulted primarily from a 32% risk reduction in nonfatal MI (p=0.007). Cardiovascular benefit was associated with the degree to which creatine kinase isoenzyme excursions were attenuated by cariporide. This very short-term exposure to a strong NHE inhibitor suggested cardiovascular benefit, but unlike the SGLT2i trials, there was not a long period of exposure and there was a limited opportunity to characterize other changes such as blood pressure or changes in renal function/albuminuria. In contrast, the phase 2 placebo-controlled Evaluation of the Safety and Cardioprotective Effects of Eniporide in Acute Myocardial Infarction (ESCAMI) trial failed show reductions in cumulative cardiac enzyme release when administered close to thrombolysis or percutaneous coronary intervention in acute myocardial infarction.[[55]](#endnote-55) An interpretation of GAURDIAN and ESCAMI pointed out that NHE1 inhibition would need to be pharmacologically present before the ischemic insult and additionally, there would need to be prompt reperfusion in order to have benefit of this mechanism of action.[[56]](#endnote-56) These principles would explain the disparate results of these trials and would also support the concept that long-term daily NHE1 inhibition would have a rationale as a myocardial protectant for bouts of ischemia.

Zoniporide is a parental NHE1 antagonist that in clinical models had a similar ischemic-protective effect as cariporide.[[57]](#endnote-57) In a pig model of cardiac arrest, zoniporide prevented reductions in left ventricular myocardial distensibility during the interval of cardiac arrest and extracorporeal circulation. Additionally, zoniporide was resulted in greater effectiveness in termination and prevention of recurrent ventricular fibrillation. These energy effects are consistent with NHE-1 inhibition protecting mitochondrial bioenergetic function and limiting Ca2+ overload.[[58]](#endnote-58) [[59]](#endnote-59) Rimeporide is an oral NHE1 inhibitor being tested in Duchenne’s muscular dystrophy (Rimeporide in Patients with Duchenne Muscular Dystrophy [RIM4DMD] Trial).[[60]](#endnote-60) Amiloride was approved by the US FDA in 1981 and works by inhibiting epithelial sodium channel in the distal nephron. It has also been shown to block the NHE3 antiporter on the apical surface of the proximal tubule cells in the nephron, abolishing more than 80% of the action of angiotensin II on the secretion of hydrogen ions in proximal tubule cells. Finally, spironolactone has been indirectly linked to NHE1 inhibition in models where desoxycorticosterone induced hypertension results in an upregulation in aortic NHE1 and spironolactone prevents this injury without a change in the transcription of NHE1.[[61]](#endnote-61)

**SGLT2i PLEIOTROPIC INHIBITION OF CARDIORENAL SODIUM-PROTON EXCHANGE**

We recognize that SGLT2i inhibition of the family of NHE’s is speculative and much remains to be proven in testable hypotheses. In preclinical models, empagliflozin has been demonstrated to have 80% of the NHE1 inhibitory effect of cariporide in both rat and rabbit ventricular myocytes.[[62]](#endnote-62) These preclinical trials treated healthy cardiomyocytes with physiologically relevant concentrations 0.25- 1 μmol/l of empagliflozin, 5.5 mmol/l or 11 mmol/l glucose, 10 μmol/l cariporide, or 20 mmol NH4Cl (NH+) either alone or in combination. NHE1 inhibition was inferred by the delay in pH recovery after an acute acidic load via a pulse of NH4+. In control conditions, pH quickly recovered to normal values after NH4+ pulse. Recovery of pH was totally inhibited as expected by cariporide. In the presence of empagliflozin, the NHE flux was strongly reduced by approximately 80% of that with cariporide. This effect was independent of glucose and SGLT1 in cardiomyocytes. Isolated healthy mouse ventricular cardiomyocytes were treated with 1 μmol/l empagliflozin, 1 μmol/l dapagliflozin, 3 μmol/l canagliflozin or control vehicle (note that these concentrations were based on the maximum plasma concentration of each drug at physiologic doses[[63]](#endnote-63)). As shown in Figure 3, all three compounds considerably slowed the restoration of intracellular pH after an NH4 pulse. Additionally, in a model of NHE1 binding, all three SGLT2i were found to bind efficiently at the Na pocket of NHE1 (815 amino acids) as shown in Figure 4 (note glucose was used as a control as it binds weakly to the Na pocket at much lower affinities). The glucoside portion of the drug molecule bound toward the Na+ binding site on the extracellular side of the channel and the aglycone portion of the drug molecule blocks the aperture. SGLT2 inhibition of NHE1 on cardiomyocytes reduced intracellular concentrations of sodium, subsequently reducing calcium overloading which is a common pathophysiologic mechanism of contractile failure.[[64]](#endnote-64) The reduction in intracellular sodium influx was significant and clearly associated with the introduction of the SGLT2i in the experimental model. Langendorff constant-flow perfused mouse hearts were treated with SGLT2i for 30 minutes; there was coronary dilation with a modest reduction in coronary perfusion pressure and no change in rate-pressure product or measures of myocardial energetics. It is also has been known that SGLT2i do not influence the cardiomyocyte action potential. At this time, the physiologic impact and direct cardiac tissue effect of SGLT2i have not been fully assessed, but we believe preclinical data suggest blunting of the recovery of pH may mimic ischemic preconditioning which is a set of actions that have protective effects on cell survival, function, and organ adaptation.[[65]](#endnote-65) Finally, dapagliflozin has been demonstrated to attenuate the upregulation of NHE1 in response to injury due to lipoprotein polysaccharide in preclinical models using rat cardiac fibroblasts.[[66]](#endnote-66)

In the kidney, under physiologic concentrations of glucose, SGLT2-mediated glucose uptake has been shown to stimulate NHE3 (834 amino acids) which is involved in the secretion of ammonia and reabsorption of sodium bicarbonate.[[67]](#endnote-67) [[68]](#endnote-68) Under normal conditions, NHE3 is responsible for a considerable amount of sodium reabsorption in the proximal tubule.[[69]](#endnote-69) NHE3 transcription is upregulated by angiotensin II which itself is activated in CKD and HF. In a HF rat model, the upregulation of NHE3 likely contributed to attenuation of the natriuresis and volume expansion.[[70]](#endnote-70) SGLT2i has resulted in decreased activity and function of NHE3, possibly contributing to natriuresis, reduction in blood pressure, and a tissue protective effect at the level of the renal tubule.[[71]](#endnote-71) As with NHE1, glucose binds to NHE3, and while one would expect SGLT2i to bind directly to NHE3, at the time of this writing, we could find no report of binding models or attempted provocative studies of SGLT2i on NHE3.39 NHE3 inhibition may work in concert with natriuresis and glycosuria to trigger tubuloglomerular feedback and reduce glomerular blood flow.[[72]](#endnote-72) By this mechanism, the hyperfiltration glomerular injury in T2DM may be attenuated.

**SGLT2i AND SODIUM-PROTON ANTIPORTER (EXCHANGER) MEDIATED EFFECTS IN OTHER ORGAN SYSTEMS**

***Hematopoietic System***: SGLT2i result in increased hemoglobin and hematocrit levels.[[73]](#endnote-73) Univariate analysis of potential mediators for empagliflozin's reduction in cardiovascular demonstrated that hematocrit (increase of 5%) – a surrogate for both hemoglobin concentration and plasma volume reduction – was associated with a 52% risk reduction cardiovascular mortality, however, the associations with both lower and higher hemoglobin concentrations is complex and this relationship may be spurious.[[74]](#endnote-74) [[75]](#endnote-75) [[76]](#endnote-76) This increase in hemoglobin and hematocrit has been hypothesized to also coincide with the renal tubular benefit of SGLT2i.[[77]](#endnote-77) Erythroblasts and reticulocytes express NHE 1 which is reduced as the red cell matures.[[78]](#endnote-78) It has been demonstrated that NHE participates in the regulation of hematopoiesis.[[79]](#endnote-79) Hemoglobin provides better tissue oxygenation and is regulated through hypoxia-inducible factor 1-alpha expression and subsequent erythropoietin secretion, factors that influenced by SGLT2i inhibition of NHE1.[[80]](#endnote-80) Note that while the rise in hematocrit was thought to increase stroke risk, a post-hoc analysis of EMPA-REG OUTCOME found no elevated risk and CVD-REAL observed a reduced risk.[[81]](#endnote-81) Thus we believe the rise in hemoglobin and hematocrit with SGLT2i may not all be attributed to a diuretic effect and while yet not demonstrated with NHE1 inhibition, an increase in erythropoiesis should be considered. At this time we are not aware of studies evaluating SGLT2i on red cell mass or measured plasma volume, hence this is a current knowledge gap.

***Vasculature*:** Empagliflozin has been shown to reduce arterial stiffness in patients with type I DM.[[82]](#endnote-82) The improved arterial compliance and smooth muscle relaxation mediated through NHE1 inhibition may be beneficial in patients at risk for HF and the progression of CKD. In patients with T2DM and hypertension, empagliflozin was associated with reductions in markers of arterial stiffness and vascular resistance.[[83]](#endnote-83) Thus, the dual diuretic-like effect of SGLT2i combined with the vascular effects of NHE1 inhibition may explain the sustained reduction of blood pressure in SGLT2i trials across a range of eGFR at the lower ends which would normally not be as responsive to diuretics alone.

***Cellular Metabolism:*** The ketone genesis observed with SGLT2i is likely independent of NHE blockade.[[84]](#endnote-84) However the elevated level of beta hydroxybutyrate seen with SGLT2i results in a shift in metabolism from fatty acids and glucose – which are less energy efficient in the setting of T2DM – towards the more energy-efficient ketones.[[85]](#endnote-85) This in turn improves myocardial and renal metabolic efficiency while reducing oxygen consumption.[[86]](#endnote-86) [[87]](#endnote-87) The ketone hypothesis is under study for cardiovascular and renal benefit and is potentially positioned to explore the proclivity for T2DM patients who are ketosis prone, to develop DKA while administered SGLT2i in the absence of hyperglycemia or insulinopenia.[[88]](#endnote-88) The NHE family of channels may be influenced by ketogenesis, for example, NHE1 appears to mediate the brain swelling that occurs in preclinical models of DKA.[[89]](#endnote-89)

***Metabolic Bone Disease:*** Chronic metabolic acidosis is associated with activation of osteoclastic activity and suppression of osteoblasts. Likewise, a chronically impaired NHE mechanism in osteocytes is a tractable mechanism for metabolic bone disease that is akin to that of CKD.[[90]](#endnote-90) NHE1, NHE3, and NHE5 are all expressed in bone cells, although inhibition of these channels has not been performed to evaluate the effects on bone cells. In trials of dapagliflozin, there were higher rates of fracture with SGLT2i. In a dedicated bone mineral density study, dapagliflozin 10 mg compared to metformin had no impact on imaging or biochemical measures of bone health.[[91]](#endnote-91) Canagliflozin in a dedicated bone mineral density study was associated with markers of bone resorption consistent with the activation of osteoclasts potentially through NHE.[[92]](#endnote-92) There are potentially kidney-bone metabolic effects to consider with SGLT2i including renal phosphate retention which has been shown over the short term to induce the secretion of fibroblast-growth factor-23 in health volunteers.[[93]](#endnote-93) Accordingly, there were numerically higher rates of fracture in EMPA-REG OUTCOME and CANVAS which did not meet statistical significance.[[94]](#endnote-94) [[95]](#endnote-95) [[96]](#endnote-96)

***Diabetic Non-Healing Ulcers, Extremity Amputation, Fournier’s Gangrene:*** Tissue hypoxia and acidosis is an accepted model for the progression of non-healing diabetic ulcers most commonly seen in the diabetic foot. The same factors contribute to arterial ulcers and critical limb ischemia as it occurs in those with and without T2DM. NHE1 is active in neuronal cells, fibroblasts, subcutaneous stromal cells, and on the vascular endothelium.[[97]](#endnote-97) In this setting, NHE1 is essential for the restoration of intracellular pH after bouts of ischemia. Thus, it is conceivable that NHE1 inhibition by SGLT2i is the mechanism by which these agents, most notably canagliflozin, have been associated with lower extremity amputations and rare cases of Fournier’s gangrene, which may be an extension of the well-recognized genital mycotic infections associated with SGLT2i.[[98]](#endnote-98) Because canagliflozin is used clinically at doses corresponding to highest tissue concentration in preclinical models, it is congruous that canagliflozin has had the strongest differential amputation risk among the SGLT2i.[[99]](#endnote-99) [[100]](#endnote-100)

**DISCUSSION**

We have described in detail how a strong, off-target effect on NHE1 and NHE3 could explain the substantial clinical effects seen in terms of HF hospitalization, cardiovascular death, and attenuation of the progression of kidney disease reported in the EMPA-REG OUTCOME, CANVAS, and DECLARE TIMI-58 trials. A meta-analysis of the three trials found that the reduction in atherosclerotic events and cardiovascular death was dependent on patients having known atherosclerotic disease at the time of event.[[101]](#endnote-101) While there was a trend towards significance for patients with multiple risk factors, it was not statistically significant. However, reductions in HF hospitalization were consistently reduced across all patients. Additional retrospective studies have also observed these clinical findings.[[102]](#endnote-102) Upregulation of NHE1 in the setting of known myocardial disease and pharmacologic inhibition of NHE1 with SGLT2i would also explain the effects reported on the rates of fatal ischemic stroke and MI; importantly, NHE1 inhibition as a mechanism is more likely to impact the survivability of these events and hence is part of the explanation of the greater reduction cardiovascular death than in the nonfatal events themselves. The biologic plausibility that SGLT2i are also NHE inhibitors is very strong. It is based on what is known about the molecular homology of SGLT and NHE channels, binding studies, and interventional physiologic experiments which all demonstrate a direct NHE inhibitory of three SGLT2i: empagliflozin, canagliflozin, and dapagliflozin.[[103]](#endnote-103)

Recent reviews have called attention to NHE1 and relationships to myocardial energetics as the most plausible mechanism explaining the favorable impact on both phenotypes in HF.[[104]](#endnote-104) [[105]](#endnote-105) [[106]](#endnote-106) [[107]](#endnote-107) Mimicking the physiology of ischemic preconditioning and favorable upregulation of gene programs that result in improved myocardial performance and resistance to hypoxic injury at the cellular level would explain benefit in HF with preserved or reduced ejection fraction. Because the cardiovascular benefits of SGLT2i are independent from the degree of HbA1C reduction and baseline eGFR, it is very likely that pharmacologic ischemic preconditioning and or more favorable myocardial energetics are the mechanisms of myocardial benefit as opposed to diuresis or theorized chronic volume contraction. In support of this idea, inhibition of hematoblast NHE1 and upregulation of erythropoiesis are concordant with the cardiovascular benefits of SGLT2i. The improvement of T2DM and CKD associated anemia could be viewed as salutary effects for the heart as well.[[108]](#endnote-108)

Inhibition of renal NHE3 with SGLT2i may be a mechanism to explain further protection against the adverse impact of angiotensin II in the proximal tubules. As in the heart, SGLT2i inhibition of NHE attenuates renal ischemia reperfusion injury.[[109]](#endnote-109) Additionally, the role of NHE3 inhibition in concert with glycosuria and natriuresis on tubulo-glomerular feedback resulting in an increase in afferent arteriolar tone and a reduction in glomerular blood flow are areas of active research to explain the renal impact of SGLT2i. This clinical effect appears to be a relatively immediate minor reduction in eGFR which is then sustained and protected from the time related loss of eGFR seen in T2DM. There is a reduction in the progression of albuminuria, but this appears to be a minor effect.

In our view, SGLT2i inhibition of NHE represents a plausible mechanistic pathway for the positive cardiorenal effects as well as the potential adverse effects of DKA, metabolic bone disease, amputation, and Fournier’s gangrene (Figure 5). Of these three, the amputation risk is most plausibly explained by NHE inhibition. The progression of diabetic foot ulcers, critical limb ischemia, deep tissue infection, and osteomyelitis are all related to tissue hypoxia and acidosis. If SGLT2i can slow the restoration of pH in the setting of ischemia or acid loading as well as inhibit the upregulation of NHE in the setting of infection, it is understandable how SGLT2i – despite improving glycemic control and exerting cardiorenal benefit – could accelerate the risks of amputations in T2DM patients with foot ulcers/gangrene/critical limb ischemia. In one analysis from CANVAS, patients who suffered one or more amputations had the greatest relative risk reductions in cardiovascular endpoints. While a sub-analysis of the EMPA-REG OUTCOME trial did not find an increased amputation risk, the trial did not specifically report critical limb ischemia as an adverse outcome, while CANVAS did.[[110]](#endnote-110) Thus, the differential amputation risk between the two studies may be partly attributable to a difference in definitions. NHE inhibition appears to be a logical explanation that could account for the amputation risk.

There are many ongoing large clinical trials with SGLT2i as a treatment for HF and CKD in those with T2DM and in some trials, even those without T2DM.[[111]](#endnote-111) The off-target NHE inhibitory effects of SGLT2i support the rationale for SGLT2i in patients without T2DM. If positive outcomes are observed in the absence of smaller reductions in HbA1C, body weight, and blood pressure, then inhibition of NHE as a global mechanism would be further supported. There is a great need for additional preclinical investment in SGLT2i and NHE inhibition as this off-target effect may be amenable to drug design changes to optimize this important cellular metabolic effect.

**SUMMARY**

The class of SGLT2i agents as strong inhibitors of NHE1 will likely be shown to either moderate or inhibit NHE3 resulting in favorable changes at the cellular and tissue levels in the heart and kidney. NHE inhibition is the most plausible explanation for the cardiorenal benefit of these agents. In contrast, careful consideration of NHE inhibition brings to light the notion that this same mechanism likely explains the adverse effects of these agents described in human use including DKA, metabolic bone disease, amputations, and Fournier’s gangrene.

The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

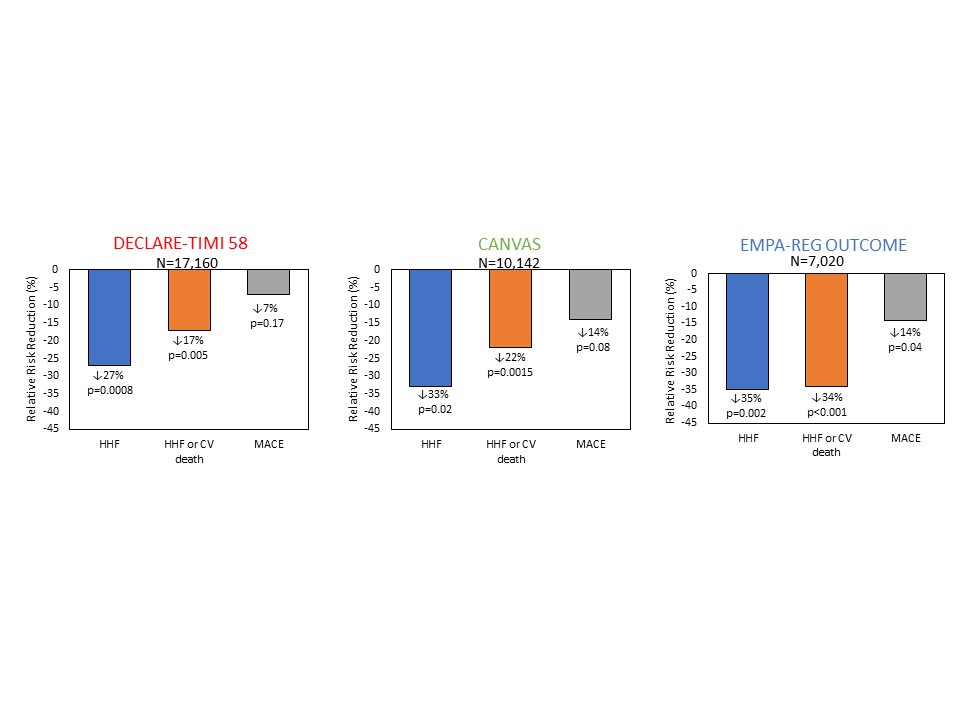
**Funding**: No extramural funding was used to support this work.

**Conflicts of Interest**: None

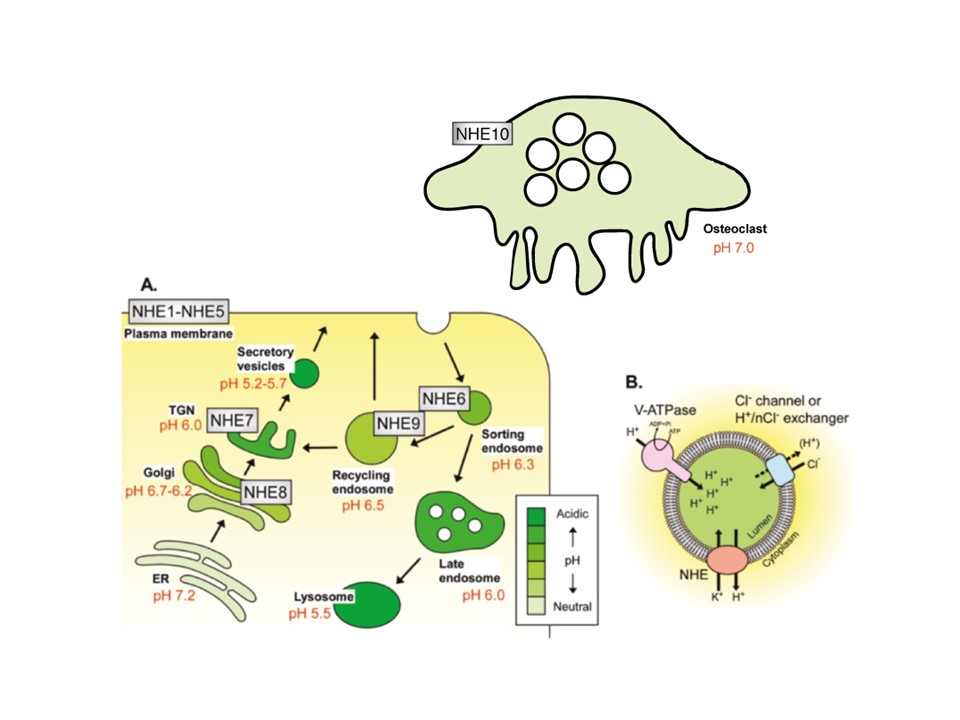
**Table 1.** Subtypes of sodium-proton antiporters otherwise known as sodium hydrogen exchangers. These antiporter channels on the cell surface and surface of some organelles function by exchanging one proton out of the cell and one sodium into the cell, restoring intracellular pH.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **NHE Subtype** | **Chromosome** | **Tissue/Cell Type** | **Comments** | **Inhibitor** |
| NHE1[[112]](#endnote-112) | 1 | Cardiomyocyte, fibroblast, erythroblast, vascular endothelium | Upregulated in ischemic heart disease, heart failure, mediates hypertrophy | SGLT2i  Cariporide  Zoniporide  Remiporide  Amiloride |
| NHE2[[113]](#endnote-113) | 2 | Renal collecting duct | Co-dependent on aquaporin channels | Amiloride |
| NHE350 | 5 | Renal tubular epithelium  Intestinal epithelium | Co-dependent on angiotensin II | SGLT2i?  Tenapanor |
| NHE4[[114]](#endnote-114) | 2 | Renal thick ascending limb of Henle, distal tubule | Ammonia efflux into urine |  |
| NHE5[[115]](#endnote-115) | 16 | Neurons | Regulates endosome pH |  |
| NHE6[[116]](#endnote-116) | X | Mitochondria,  neurons, skeletal muscle, cardiomyocyte | Mutation results in Christianson Syndrome |  |
| NHE7[[117]](#endnote-117) | X | Intracellular Golgi apparatus | Involved in lithium uptake |  |
| NHE8[[118]](#endnote-118) | 20 | Retina, intestinal epithelium, testes | Responsible for mucosal integrity |  |
| NHE9[[119]](#endnote-119) | 3 | Brain microvasculature | Upregulated in glioblastoma |  |
| NHE10[[120]](#endnote-120) | 4 | Bone osteoclasts |  |  |

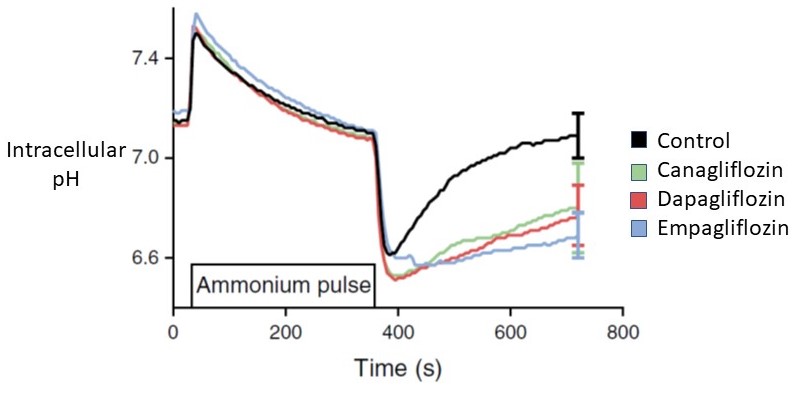
**Figures and lagends**

****

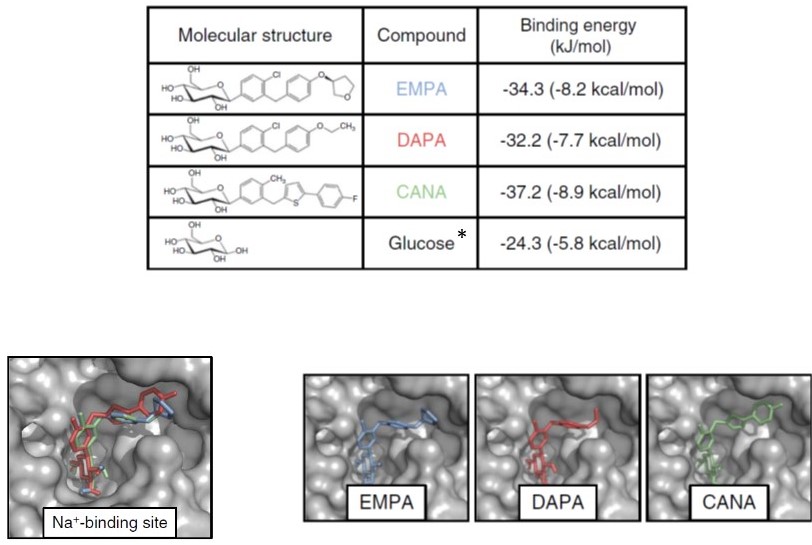
**Figure 1.** Figure 1. Cardiovascular outcomes from: the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58) trial, the Canagliflozin Cardiovascular Assessment Study (CANVAS), the Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME). Data reported as relative risk (RR) reduction percentage, p-value. RR reduction percentages calculated from hazard ratios for event rates per 1000 patient-years. HHF=heart failure hospitalization; CV=cardiovascular; MACE=major adverse cardiovascular event.

****

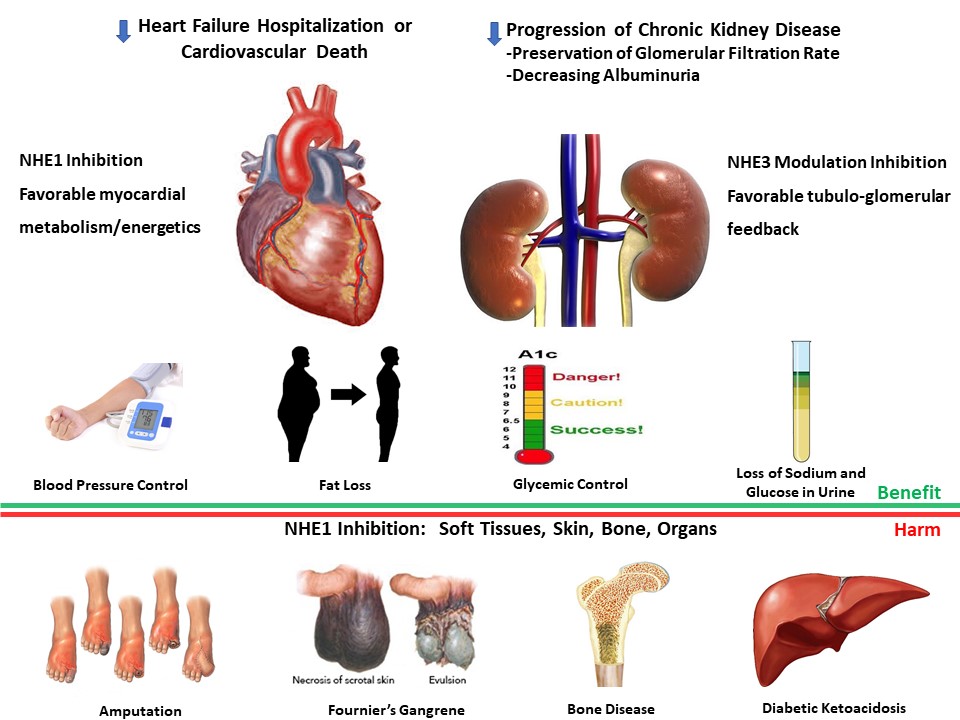
**Figure 2.** Sodium-hydrogen exchanger (NHE) functions and locations within cells. (A) Locations of NHEs 1-5 in the plasma membrane and NHEs 6-9 in the organelles of somatic cells, and NHE10 in osteoclastic cells. (B) Illustration of pH regulation in somatic organelles. TGN=trans-Golgi network; ER=endoplasmic reticulum. Adapted from Ohgaki et al. and Yuan et al.[[121]](#endnote-121) [[122]](#endnote-122)

****

**Figure 3.** Sodium glucose co-transporter 2 inhibitorsmediate sodium-hydrogen exchanger 1 inhibition and blunting of the restoration of pH of cardiomyocytes in response to an acid challenge. All p-values < 0.001. Adapted from Uthman et al.58

****

**Figure 4.** Molecular structure and binding energy of sodium glucose co-transporter 2 inhibitorson the sodium-hydrogen exchanger 1 channel. Glucose was used as a negative control. EMPA=empagliflozin; DAPA=dapagliflozin; CANA=canagliflozin. Adapted from Uthman et al.58

****

**Figure 5.** Inhibition of sodium-proton antiporters in the heart, kidney, bone, and peripheral tissues account for cardiorenal benefit as well as the known serious adverse effects of sodium glucose co-transporter 2 inhibitors. NHE=sodium-hydrogen exchanger.

1. WHO. Global Report on Diabetes. 2016; http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257\_eng.pdf?ua=1, Accessed December 20, 2016. [↑](#endnote-ref-1)
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER, 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW and Turner MB. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133:e38-360. [↑](#endnote-ref-2)
3. Ray KK, Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Preiss D, Erqou S and Sattar N. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet. 2009;373:1765-72. [↑](#endnote-ref-3)
4. Fitchett DH, Udell JA and Inzucchi SE. Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes. Eur J Heart Fail. 2017;19:43-53. [↑](#endnote-ref-4)
5. Lloyd-Jones DM, Larson MG, Leip EP, Beiser A, D'Agostino RB, Kannel WB, Murabito JM, Vasan RS, Benjamin EJ and Levy D. Lifetime risk for developing congestive heart failure: the Framingham Heart Study. Circulation. 2002;106:3068-72. [↑](#endnote-ref-5)
6. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL and Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. The New England journal of medicine. 2006;355:251-9. [↑](#endnote-ref-6)
7. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL and Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. The New England journal of medicine. 2006;355:251-9. [↑](#endnote-ref-7)
8. Zelniker TA, Braunwald E. Cardiac and Renal Effects of Sodium-Glucose

   Co-Transporter 2 Inhibitors in Diabetes: JACC State-of-the-Art Review. J Am Coll

   Cardiol. 2018 Oct 9;72(15):1845-1855. doi: 10.1016/j.jacc.2018.06.040. Epub 2018

   Jul 31. Review. PubMed PMID: 30075873. [↑](#endnote-ref-8)
9. Armstrong DG, Boulton AJM, Bus SA. Diabetic Foot Ulcers and Their Recurrence.

   N Engl J Med. 2017 Jun 15;376(24):2367-2375. doi: 10.1056/NEJMra1615439. Review.

   PubMed PMID: 28614678. [↑](#endnote-ref-9)
10. Gilbert MP, Pratley RE. The impact of diabetes and diabetes medications on

    bone health. Endocr Rev. 2015 Apr;36(2):194-213. doi: 10.1210/er.2012-1042. Epub

    2015 Mar 4. Review. PubMed PMID: 25738213. [↑](#endnote-ref-10)
11. Thomas MC, Tsalamandris C, MacIsaac RJ, Jerums G. The epidemiology of

    hemoglobin levels in patients with type 2 diabetes. Am J Kidney Dis. 2006

    Oct;48(4):537-45. PubMed PMID: 16997049. [↑](#endnote-ref-11)
12. Kaul S, Bolger AF, Herrington D, Giugliano RP, Eckel RH; American Heart

    Association; American College Of Cardiology Foundation. Thiazolidinedione drugs

    and cardiovascular risks: a science advisory from the American Heart Association

    and American College Of Cardiology Foundation. J Am Coll Cardiol. 2010 Apr

    27;55(17):1885-94. doi: 10.1016/j.jacc.2010.02.014. PubMed PMID: 20413044. [↑](#endnote-ref-12)
13. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M and McMurray JJ. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet. 2009;373:2125-35. [↑](#endnote-ref-13)
14. Lincoff AM, Wolski K, Nicholls SJ and Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. Jama. 2007;298:1180-8. [↑](#endnote-ref-14)
15. Douros A, Dell'Aniello S, Yu OHY, Filion KB, Azoulay L, Suissa S.

    Sulfonylureas as second line drugs in type 2 diabetes and the risk of

    cardiovascular and hypoglycaemic events: population based cohort study. BMJ. 2018

    Jul 18;362:k2693. doi: 10.1136/bmj.k2693. PubMed PMID: 30021781; PubMed Central

    PMCID: PMC6050517. [↑](#endnote-ref-15)
16. Powell WR, Christiansen CL, Miller DR. Meta-Analysis of Sulfonylurea Therapy

    on Long-Term Risk of Mortality and Cardiovascular Events Compared to Other Oral

    Glucose-Lowering Treatments. Diabetes Ther. 2018 Aug;9(4):1431-1440. doi:

    10.1007/s13300-018-0443-z. Epub 2018 May 28. Review. PubMed PMID: 29808360;

    PubMed Central PMCID: PMC6064594. [↑](#endnote-ref-16)
17. Li L, Shen J, Bala MM, Busse JW, Ebrahim S, Vandvik PO, Rios LP, Malaga G,

    Wong E, Sohani Z, Guyatt GH, Sun X. Incretin treatment and risk of pancreatitis

    in patients with type 2 diabetes mellitus: systematic review and meta-analysis of

    randomised and non-randomised studies. BMJ. 2014 Apr 15;348:g2366. doi:

    10.1136/bmj.g2366. Review. PubMed PMID: 24736555; PubMed Central PMCID:

    PMC3987051. [↑](#endnote-ref-17)
18. Kaneko M, Narukawa M. Assessment of the Risk of Hospitalization for Heart

    Failure With Dipeptidyl Peptidase-4 Inhibitors, Saxagliptin, Alogliptin, and

    Sitagliptin in Patients With Type 2 Diabetes, Using an Alternative Measure to the

    Hazard Ratio. Ann Pharmacother. 2017 Jul;51(7):570-576. doi:

    10.1177/1060028017698496. Epub 2017 Mar 1. PubMed PMID: 28622738. [↑](#endnote-ref-18)
19. McMurray JJ, Gerstein HC, Holman RR and Pfeffer MA. Heart failure: a cardiovascular outcome in diabetes that can no longer be ignored. Lancet Diabetes Endocrinol. 2014;2:843-51. [↑](#endnote-ref-19)
20. Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New

    Antidiabetic Therapies to Treat Type 2 Diabetes. U.S. Department of Health and Human Services

    Food and Drug Administration Center for Drug Evaluation and Research (CDER)

    December 2008 [↑](#endnote-ref-20)
21. Zannad F, Stough WG, Lipicky RJ, Tamargo J, Bakris GL, Borer JS, Alonso García

    Mde L, Hadjadj S, Koenig W, Kupfer S, McCullough PA, Mosenzon O, Pocock S, Scheen

    AJ, Sourij H, Van der Schueren B, Stahre C, White WB, Calvo G. Assessment of

    cardiovascular risk of new drugs for the treatment of diabetes mellitus: risk

    assessment vs. risk aversion. Eur Heart J Cardiovasc Pharmacother. 2016

    Jul;2(3):200-5. doi: 10.1093/ehjcvp/pvw007. Epub 2016 Apr 3. Review. PubMed PMID:

    27418973; PubMed Central PMCID: PMC4907355. [↑](#endnote-ref-21)
22. Writing Committee, Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT,

    Januzzi JL Jr, Rastogi Kalyani R, Kosiborod M, Magwire ML, Morris PB, Sperling

    LS. 2018 ACC Expert Consensus Decision Pathway on Novel Therapies for

    Cardiovascular Risk Reduction in Patients With Type 2 Diabetes and

    Atherosclerotic Cardiovascular Disease: A Report of the American College of

    Cardiology Task Force on Expert Consensus Decision Pathways. J Am Coll Cardiol.

    2018 Nov 24. pii: S0735-1097(18)38498-5. doi: 10.1016/j.jacc.2018.09.020. [Epub

    ahead of print] PubMed PMID: 30497881. [↑](#endnote-ref-22)
23. Ueda P, Svanström H, Melbye M, Eliasson B, Svensson AM, Franzén S,

    Gudbjörnsdottir S, Hveem K, Jonasson C, Pasternak B. Sodium glucose cotransporter

    2 inhibitors and risk of serious adverse events: nationwide register based cohort

    study. BMJ. 2018 Nov 14;363:k4365. doi: 10.1136/bmj.k4365. PubMed PMID: 30429124;

    PubMed Central PMCID: PMC6233755. [↑](#endnote-ref-23)
24. https://www.ema.europa.eu/en/medicines/human/referrals/sglt2-inhibitors-previously-canagliflozin [↑](#endnote-ref-24)
25. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE and Woerle HJ. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. The New England journal of medicine. 2015;373:2117-28. [↑](#endnote-ref-25)
26. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, Johansen OE, Woerle HJ, Broedl UC and Inzucchi SE. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J. 2016;37:1526-34. [↑](#endnote-ref-26)
27. Cherney DZI, Cooper ME, Tikkanen I, Pfarr E, Johansen OE, Woerle HJ, Broedl

    UC, Lund SS. Pooled analysis of Phase III trials indicate contrasting influences

    of renal function on blood pressure, body weight, and HbA1c reductions with

    empagliflozin. Kidney Int. 2018 Jan;93(1):231-244. doi:

    10.1016/j.kint.2017.06.017. Epub 2017 Aug 30. PubMed PMID: 28860019. [↑](#endnote-ref-27)
28. Neal B, Perkovic V, Zeeuw D, Mahaffey KW, Fulcher G, Stein P, Desai M, Shaw W, Jiang J and Vercruysse F. Rationale, design, and baseline characteristics of the Canagliflozin cardiovascular assessment study (CANVAS)–a randomized placebo-controlled trial. Am Heart J. 2013;166:217-223. [↑](#endnote-ref-28)
29. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law

    G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and

    Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017 Aug

    17;377(7):644-657. doi: 10.1056/NEJMoa1611925. Epub 2017 Jun 12. PubMed PMID:

    28605608. [↑](#endnote-ref-29)
30. Rådholm K, Figtree G, Perkovic V, Solomon SD, Mahaffey KW, de Zeeuw D, Fulcher

    G, Barrett TD, Shaw W, Desai M, Matthews DR, Neal B. Canagliflozin and Heart

    Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program

    (Canagliflozin Cardiovascular Assessment Study). Circulation. 2018 Mar 11. pii:

    CIRCULATIONAHA.118.034222. doi: 10.1161/CIRCULATIONAHA.118.034222. [Epub ahead of

    print] PubMed PMID: 29526832; PubMed Central PMCID: PMC6075881. [↑](#endnote-ref-30)
31. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG,

    Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH,

    Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine

    MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and Cardiovascular Outcomes in

    Type 2 Diabetes. N Engl J Med. 2018 Nov 10. doi: 10.1056/NEJMoa1812389. [Epub

    ahead of print] PubMed PMID: 30415602. [↑](#endnote-ref-31)
32. Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Holl RW, Norhammar A,

    Birkeland KI, Jørgensen ME, Thuresson M, Arya N, Bodegård J, Hammar N, Fenici P;

    CVD-REAL Investigators and Study Group\*. Lower Risk of Heart Failure and Death in

    Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other

    Glucose-Lowering Drugs: The CVD-REAL Study (Comparative Effectiveness of

    Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2

    Inhibitors). Circulation. 2017 Jul 18;136(3):249-259. doi:

    10.1161/CIRCULATIONAHA.117.029190. Epub 2017 May 18. PubMed PMID: 28522450;

    PubMed Central PMCID: PMC5515629. [↑](#endnote-ref-32)
33. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, Tangri N, Goh SY,

    Thuresson M, Chen H, Surmont F, Hammar N, Fenici P; CVD-REAL Investigators and

    Study Group. Cardiovascular Events Associated With SGLT-2 Inhibitors Versus Other

    Glucose-Lowering Drugs: The CVD-REAL 2 Study. J Am Coll Cardiol. 2018 Jun

    12;71(23):2628-2639. doi: 10.1016/j.jacc.2018.03.009. Epub 2018 Mar 11. PubMed

    PMID: 29540325. [↑](#endnote-ref-33)
34. Heerspink HJ, Perkins BA, Fitchett DH, Husain M and Cherney DZ. Sodium Glucose Cotransporter 2 Inhibitors in the Treatment of Diabetes Mellitus: Cardiovascular and Kidney Effects, Potential Mechanisms, and Clinical Applications. Circulation. 2016;134:752-72. [↑](#endnote-ref-34)
35. Nauck MA. Update on developments with SGLT2 inhibitors in the management of type 2 diabetes. Drug Des Devel Ther. 2014;8:1335-80. [↑](#endnote-ref-35)
36. Baker WL, Smyth LR, Riche DM, Bourret EM, Chamberlin KW and White WB. Effects of sodium-glucose co-transporter 2 inhibitors on blood pressure: a systematic review and meta-analysis. J Am Soc Hypertens. 2014;8:262-75.e9. [↑](#endnote-ref-36)
37. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle HJ, von Eynatten M and Broedl UC. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol. 2014;13:28. [↑](#endnote-ref-37)
38. Inzucchi SE, Zinman B, Wanner C, Ferrari R, Fitchett D, Hantel S, Espadero RM, Woerle HJ, Broedl UC and Johansen OE. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res. 2015;12:90-100. [↑](#endnote-ref-38)
39. Brouwer TF, Vehmeijer JT, Kalkman DN, Berger WR, van den Born BH, Peters RJ,

    Knops RE. Intensive Blood Pressure Lowering in Patients With and Patients Without

    Type 2 Diabetes: A Pooled Analysis From Two Randomized Trials. Diabetes Care.

    2018 Jun;41(6):1142-1148. doi: 10.2337/dc17-1722. Epub 2017 Dec 6. PubMed PMID:

    29212825. [↑](#endnote-ref-39)
40. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, Fagan NM, Woerle HJ, Johansen OE, Broedl UC and von Eynatten M. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. Circulation. 2014;129:587-97. [↑](#endnote-ref-40)
41. Rajasekeran H, Lytvyn Y and Cherney DZ. Sodium-glucose cotransporter 2 inhibition and cardiovascular risk reduction in patients with type 2 diabetes: the emerging role of natriuresis. Kidney Int. 2016;89:524-6. [↑](#endnote-ref-41)
42. Schmieder R, Ott C, Linz P, Jumar A, Friedrich S, Titze J, Hammon M, Uder M, Kistner I. OS 12-03 SGLT-2-inhibition with dapagliflozin reduces tissue sodium content. J Hypertens. 2016;34(suppl 1):ISH 2016 Abstract Book:e76. [↑](#endnote-ref-42)
43. Schneider MP, Raff U, Kopp C, Scheppach JB, Toncar S, Wanner C, Schlieper G, Saritas T, Floege J, Schmid M, Birukov A, Dahlmann A, Linz P, Janka R, Uder M, Schmieder RE, Titze JM, Eckardt KU. Skin sodium concentration correlates with left ventricular hypertrophy in CKD. J Am Soc Nephrol. 2017;28:1867–1876. doi: 10.1681/ASN.2016060662 [↑](#endnote-ref-43)
44. Heise T, Jordan J, Wanner C, Heer M, Macha S, Mattheus M, Lund SS, Woerle HJ and Broedl UC. Pharmacodynamic Effects of Single and Multiple Doses of Empagliflozin in Patients With Type 2 Diabetes. Clin Ther. 2016;38:2265-2276. [↑](#endnote-ref-44)
45. Scheen AJ. Reappraisal of the diuretic effect of empagliflozin in the EMPA-REG OUTCOME trial: Comparison with classic diuretics. Diabetes & metabolism. 2016;42:224-33. [↑](#endnote-ref-45)
46. Vasilakou D, Karagiannis T, Athanasiadou E, Mainou M, Liakos A, Bekiari E, Sarigianni M, Matthews DR and Tsapas A. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159:262-74. [↑](#endnote-ref-46)
47. Look AHEAD Research Group, Gregg EW, Jakicic JM, Blackburn G, Bloomquist P,

    Bray GA, Clark JM, Coday M, Curtis JM, Egan C, Evans M, Foreyt J, Foster G,

    Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jeffery RW, Johnson KC, Kitabchi AE,

    Knowler WC, Kriska A, Lang W, Lewis CE, Montez MG, Nathan DM, Neiberg RH,

    Patricio J, Peters A, Pi-Sunyer X, Pownall H, Redmon B, Regensteiner J, Rejeski

    J, Ribisl PM, Safford M, Stewart K, Trence D, Wadden TA, Wing RR, Yanovski SZ.

    Association of the magnitude of weight loss and changes in physical fitness with

    long-term cardiovascular disease outcomes in overweight or obese people with type

    2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial.

    Lancet Diabetes Endocrinol. 2016 Nov;4(11):913-921. doi:

    10.1016/S2213-8587(16)30162-0. Epub 2016 Aug 30. PubMed PMID: 27595918; PubMed

    Central PMCID: PMC5094846. [↑](#endnote-ref-47)
48. Kilić A, Huang CX, Rajapurohitam V, Madwed JB, Karmazyn M. Early and transient

    sodium-hydrogen exchanger isoform 1 inhibition attenuates subsequent cardiac

    hypertrophy and heart failure following coronary artery ligation. J Pharmacol Exp

    Ther. 2014 Dec;351(3):492-9. doi: 10.1124/jpet.114.217091. Epub 2014 Sep 12.

    PubMed PMID: 25216745. [↑](#endnote-ref-48)
49. Fliegel L, Dyck JR. Molecular biology of the cardiac sodium/hydrogen

    exchanger. Cardiovasc Res 29: 155–159, 1995. [↑](#endnote-ref-49)
50. Pogwizd SM, Sipido KR, Verdonck F, Bers DM. Intracellular Na in animal models

    of hypertrophy and heart failure: contractile function and arrhythmogenesis.

    Cardiovasc Res. 2003 Mar 15;57(4):887-96. Review. PubMed PMID: 12650867. [↑](#endnote-ref-50)
51. Cingolani HE, Ennis IL. Sodium-hydrogen exchanger, cardiac overload, and

    myocardial hypertrophy. Circulation. 2007 Mar 6;115(9):1090-100. Review. PubMed

    PMID: 17339567. [↑](#endnote-ref-51)
52. Madonna R, De Caterina R. Sodium-hydrogen exchangers (NHE) in human

    cardiovascular diseases: interfering strategies and their therapeutic

    applications. Vascul Pharmacol. 2013 Nov-Dec;59(5-6):127-30. doi:

    10.1016/j.vph.2013.10.001. Epub 2013 Oct 15. Review. PubMed PMID: 24140414. [↑](#endnote-ref-52)
53. Donowitz M, Ming Tse C, Fuster D. SLC9/NHE gene family, a plasma membrane and

    organellar family of Na⁺/H⁺ exchangers. Mol Aspects Med. 2013

    Apr-Jun;34(2-3):236-51. doi: 10.1016/j.mam.2012.05.001. Review. PubMed PMID:

    23506868; PubMed Central PMCID: PMC3724465. [↑](#endnote-ref-53)
54. Chaitman BR. A review of the GUARDIAN trial results: clinical implications and

    the significance of elevated perioperative CK-MB on 6-month survival. J Card

    Surg. 2003 Jan-Feb;18 Suppl 1:13-20. Review. PubMed PMID: 12691375. [↑](#endnote-ref-54)
55. U. Zeymer, H. Suryapranata, J.P. Monassier, et al.The Na+/H+exchange inhibitor eniporide as an adjunct to early reperfusion therapy for acute myocardial infarction: results of the Evaluation of the Safety and Cardioprotective Effects of Eniporide in Acute Myocardial Infarction (ESCAMI) trial

    J Am Coll Cardiol, 38 (2001), pp. 1644-1650. [↑](#endnote-ref-55)
56. Avkiran M, Marber MS. Na(+)/H(+) exchange inhibitors for cardioprotective

    therapy: progress, problems and prospects. J Am Coll Cardiol. 2002 Mar

    6;39(5):747-53. Review. PubMed PMID: 11869836. [↑](#endnote-ref-56)
57. Clements-Jewery H, Sutherland FJ, Allen MC, Tracey WR, Avkiran M.

    Cardioprotective efficacy of zoniporide, a potent and selective inhibitor of

    Na+/H+ exchanger isoform 1, in an experimental model of cardiopulmonary bypass.

    Br J Pharmacol. 2004 May;142(1):57-66. Epub 2004 Mar 22. PubMed PMID: 15037516;

    PubMed Central PMCID: PMC1574931. [↑](#endnote-ref-57)
58. Ayoub IM, Kolarova J, Gazmuri RJ. Cariporide given during resuscitation

    promotes return of electrically stable and mechanically competent cardiac

    activity. Resuscitation. 2010 Jan;81(1):106-10. doi:

    10.1016/j.resuscitation.2009.09.013. Epub 2009 Oct 22. PubMed PMID: 19853351;

    PubMed Central PMCID: PMC2814946. [↑](#endnote-ref-58)
59. Lamoureux L, Radhakrishnan J, Mason TG, Kraut JA, Gazmuri RJ. Adverse

    postresuscitation myocardial effects elicited by buffer-induced alkalemia

    ameliorated by NHE-1 inhibition in a rat model of ventricular fibrillation. J

    Appl Physiol (1985). 2016 Nov 1;121(5):1160-1168. doi:

    10.1152/japplphysiol.00336.2016. Epub 2016 Sep 15. PubMed PMID: 27633736. [↑](#endnote-ref-59)
60. https://clinicaltrials.gov/ct2/show/NCT02710591 [↑](#endnote-ref-60)
61. Carreño JE, Verdugo FJ, Contreras F, Montellano FA, Veloso S, Schalper KA,

    Sandoval M, Villanueva S, Marusic E, Irarrazabal CE. Spironolactone inhibits the

    activity of the Na+/H+ exchanger in the aorta of mineralocorticoid-induced

    hypertensive rats. J Renin Angiotensin Aldosterone Syst. 2015 Dec;16(4):1225-31.

    doi: 10.1177/1470320315587193. Epub 2015 May 21. PubMed PMID: 25997821. [↑](#endnote-ref-61)
62. Baartscheer A, Schumacher CA, Wüst RC, Fiolet JW, Stienen GJ, Coronel R,

    Zuurbier CJ. Empagliflozin decreases myocardial cytoplasmic Na(+) through

    inhibition of the cardiac Na(+)/H(+) exchanger in rats and rabbits. Diabetologia.

    2017 Mar;60(3):568-573. doi: 10.1007/s00125-016-4134-x. Epub 2016 Oct 17. PubMed

    PMID: 27752710. [↑](#endnote-ref-62)
63. Scheen AJ (2014) Evaluating SGLT2 inhibitors for type 2 diabetes:

    pharmacokinetic and toxicological considerations. Expert Opin

    Drug Metab Toxicol 10:647–663 [↑](#endnote-ref-63)
64. Uthman L, Baartscheer A, Bleijlevens B, Schumacher CA, Fiolet JWT, Koeman A,

    Jancev M, Hollmann MW, Weber NC, Coronel R, Zuurbier CJ. Class effects of SGLT2

    inhibitors in mouse cardiomyocytes and hearts: inhibition of Na(+)/H(+)

    exchanger, lowering of cytosolic Na(+) and vasodilation. Diabetologia. 2018

    Mar;61(3):722-726. doi: 10.1007/s00125-017-4509-7. Epub 2017 Dec 2. PubMed PMID:

    29197997. [↑](#endnote-ref-64)
65. Karmazyn M, Sostaric JV, Gan XT. The myocardial Na+/H+ exchanger: a potential

    therapeutic target for the prevention of myocardial ischaemic and reperfusion

    injury and attenuation of postinfarction heart failure. Drugs. 2001;61(3):375-89.

    Review. PubMed PMID: 11293648. [↑](#endnote-ref-65)
66. Ye Y, Jia X, Bajaj M, Birnbaum Y. Dapagliflozin Attenuates Na(+)/H(+)

    Exchanger-1 in Cardiofibroblasts via AMPK Activation. Cardiovasc Drugs Ther. 2018

    Oct 26. doi: 10.1007/s10557-018-6837-3. [Epub ahead of print] PubMed PMID:

    30367338. [↑](#endnote-ref-66)
67. Pessoa TD, Campos LC, Carraro-Lacroix L, Girardi AC and Malnic G. Functional role of glucose metabolism, osmotic stress, and sodium-glucose cotransporter isoform-mediated transport on Na+/H+ exchanger isoform 3 activity in the renal proximal tubule. J Am Soc Nephrol. 2014;25:2028-39. [↑](#endnote-ref-67)
68. Layton AT, Vallon V and Edwards A. Modeling oxygen consumption in the proximal tubule: effects of NHE and SGLT2 inhibition. Am J Physiol Renal Physiol. 2015;308:F1343-57. [↑](#endnote-ref-68)
69. Fenton RA, Poulsen SB, de la Mora Chavez S, Soleimani M, Dominguez Rieg JA,

    Rieg T. Renal tubular NHE3 is required in the maintenance of water and sodium

    chloride homeostasis. Kidney Int. 2017 Aug;92(2):397-414. doi:

    10.1016/j.kint.2017.02.001. Epub 2017 Apr 3. PubMed PMID: 28385297; PubMed

    Central PMCID: PMC5511580. [↑](#endnote-ref-69)
70. Inoue BH, dos Santos L, Pessoa TD, Antonio EL, Pacheco BP, Savignano FA, Carraro-Lacroix LR, Tucci PJ, Malnic G and Girardi AC. Increased NHE3 abundance and transport activity in renal proximal tubule of rats with heart failure. Am J Physiol Regul Integr Comp Physiol. 2012;302:R166-74. [↑](#endnote-ref-70)
71. Gallo LA, Wright EM and Vallon V. Probing SGLT2 as a therapeutic target for diabetes: basic physiology and consequences. Diab Vasc Dis Res. 2015;12:78-89. [↑](#endnote-ref-71)
72. de Albuquerque Rocha N, Neeland IJ, McCullough PA, Toto RD, McGuire DK.

    Effects of sodium glucose co-transporter 2 inhibitors on the kidney. Diab Vasc

    Dis Res. 2018 Sep;15(5):375-386. doi: 10.1177/1479164118783756. Epub 2018 Jul 2.

    Review. PubMed PMID: 29963920. [↑](#endnote-ref-72)
73. Zinman B, Lachin JM and Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. The New England journal of medicine. 2016;374:1094. [↑](#endnote-ref-73)
74. Inzucchi S. SGLT2 inhibition and cardiovascular outcomes. EASD Virtual Meeting. 2016. http://www.easdvirtualmeeting.org/resources/sglt2-inhibition-and-cardiovascular-outcomes; Accessed May 23, 2017. [↑](#endnote-ref-74)
75. Brown DW, Giles WH, Croft JB. Hematocrit and the risk of coronary heart

    disease mortality. Am Heart J. 2001 Oct;142(4):657-63. PubMed PMID: 11579356. [↑](#endnote-ref-75)
76. Lee G, Choi S, Kim K, Yun JM, Son JS, Jeong SM, Kim SM, Park SM. Association

    of Hemoglobin Concentration and Its Change With Cardiovascular and All-Cause

    Mortality. J Am Heart Assoc. 2018 Jan 29;7(3). pii: e007723. doi:

    10.1161/JAHA.117.007723. PubMed PMID: 29378732; PubMed Central PMCID: PMC5850255. [↑](#endnote-ref-76)
77. Sano M, Takei M, Shiraishi Y and Suzuki Y. Increased Hematocrit During Sodium-Glucose Cotransporter 2 Inhibitor Therapy Indicates Recovery of Tubulointerstitial Function in Diabetic Kidneys. J Clin Med Res. 2016;8:844-847. [↑](#endnote-ref-77)
78. Liu J, Guo X, Mohandas N, Chasis JA, An X. Membrane remodeling during

    reticulocyte maturation. Blood. 2010 Mar 11;115(10):2021-7. doi:

    10.1182/blood-2009-08-241182. Epub 2009 Dec 28. PubMed PMID: 20038785; PubMed

    Central PMCID: PMC2837329. [↑](#endnote-ref-78)
79. Zerbini G, Maestroni A, Mangili R, Pozza G. Amiloride-insensitive Na+-H+

    exchange: a candidate mediator of erythrocyte Na+-Li+ countertransport. J Am Soc

    Nephrol. 1998 Dec;9(12):2203-11. PubMed PMID: 9848774. [↑](#endnote-ref-79)
80. Chang YK, Choi H, Jeong JY, Na KR, Lee KW, Lim BJ and Choi DE. Dapagliflozin, SGLT2 Inhibitor, Attenuates Renal Ischemia-Reperfusion Injury. PloS one. 2016;11:e0158810. [↑](#endnote-ref-80)
81. Zinman B, Inzucchi SE, Lachin JM, Wanner C, Fitchett D, Kohler S, Mattheus M,

    Woerle HJ, Broedl UC, Johansen OE, Albers GW, Diener HC; EMPA-REG OUTCOME

    Investigators (Empagliflozin Cardiovascular Outcome Event Trial in Type 2

    Diabetes Mellitus Patients). Empagliflozin and Cerebrovascular Events in Patients

    With Type 2 Diabetes Mellitus at High Cardiovascular Risk. Stroke. 2017

    May;48(5):1218-1225. doi: 10.1161/STROKEAHA.116.015756. Epub 2017 Apr 6. PubMed

    PMID: 28386035; PubMed Central PMCID: PMC5404404. [↑](#endnote-ref-81)
82. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle HJ, von Eynatten M and Broedl UC. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. Cardiovasc Diabetol. 2014;13:28. [↑](#endnote-ref-82)
83. Chilton R, Tikkanen I, Cannon CP, Crowe S, Woerle HJ, Broedl UC and Johansen OE. Effects of empagliflozin on blood pressure and markers of arterial stiffness and vascular resistance in patients with type 2 diabetes. Diabetes, obesity & metabolism. 2015;17:1180-93. [↑](#endnote-ref-83)
84. Soler C, Cragoe EJ Jr, Soley M. Effects of epidermal growth factor on

    gluconeogenesis and cellular redox state do not require Na+/H+ exchange or

    Na+/K(+)-ATPase activities. Regul Pept. 1994 Jun 16;52(1):1-6. PubMed PMID:

    7972927. [↑](#endnote-ref-84)
85. Ferrannini E, Baldi S, Frascerra S, Astiarraga B, Heise T, Bizzotto R, Mari A, Pieber TR and Muscelli E. Shift to Fatty Substrate Utilization in Response to Sodium-Glucose Cotransporter 2 Inhibition in Subjects Without Diabetes and Patients With Type 2 Diabetes. Diabetes. 2016;65:1190-5. [↑](#endnote-ref-85)
86. Ferrannini E, Mark M and Mayoux E. CV Protection in the EMPA-REG OUTCOME Trial: A "Thrifty Substrate" Hypothesis. Diabetes Care. 2016;39:1108-14. [↑](#endnote-ref-86)
87. Mudaliar S, Alloju S and Henry RR. Can a Shift in Fuel Energetics Explain the Beneficial Cardiorenal Outcomes in the EMPA-REG OUTCOME Study? A Unifying Hypothesis. Diabetes Care. 2016;39:1115-22. [↑](#endnote-ref-87)
88. Lopaschuk GD and Verma S. Empagliflozin's Fuel Hypothesis: Not so Soon. Cell Metab. 2016;24:200-2. [↑](#endnote-ref-88)
89. Rose KL, Watson AJ, Drysdale TA, Cepinskas G, Chan M, Rupar CA, Fraser DD.

    Simulated diabetic ketoacidosis therapy in vitro elicits brain cell swelling via

    sodium-hydrogen exchange and anion transport. Am J Physiol Endocrinol Metab. 2015

    Aug 15;309(4):E370-9. doi: 10.1152/ajpendo.00107.2015. Epub 2015 Jun 16. PubMed

    PMID: 26081282. [↑](#endnote-ref-89)
90. Blair HC, Larrouture QC, Tourkova IL, Liu L, Bian JH, Stolz DB, Nelson DJ,

    Schlesinger PH. Support of bone mineral deposition by regulation of pH. Am J

    Physiol Cell Physiol. 2018 Oct 1;315(4):C587-C597. doi:

    10.1152/ajpcell.00056.2018. Epub 2018 Jul 25. PubMed PMID: 30044661; PubMed

    Central PMCID: PMC6230682 [↑](#endnote-ref-90)
91. Ljunggren Ö, Bolinder J, Johansson L, Wilding J, Langkilde AM, Sjöström CD,

    Sugg J, Parikh S. Dapagliflozin has no effect on markers of bone formation and

    resorption or bone mineral density in patients with inadequately controlled type

    2 diabetes mellitus on metformin. Diabetes Obes Metab. 2012 Nov;14(11):990-9.

    doi: 10.1111/j.1463-1326.2012.01630.x. Epub 2012 Jun 29. PubMed PMID: 22651373. [↑](#endnote-ref-91)
92. Bilezikian JP, Watts NB, Usiskin K, Polidori D, Fung A, Sullivan D, Rosenthal

    N. Evaluation of Bone Mineral Density and Bone Biomarkers in Patients With Type 2

    Diabetes Treated With Canagliflozin. J Clin Endocrinol Metab. 2016

    Jan;101(1):44-51. doi: 10.1210/jc.2015-1860. Epub 2015 Nov 18. PubMed PMID:

    26580234; PubMed Central PMCID: PMC4701848. [↑](#endnote-ref-92)
93. Blau JE, Bauman V, Conway EM, Piaggi P, Walter MF, Wright EC, Bernstein S,

    Courville AB, Collins MT, Rother KI, Taylor SI. Canagliflozin triggers the

    FGF23/1,25-dihydroxyvitamin D/PTH axis in healthy volunteers in a randomized

    crossover study. JCI Insight. 2018 Apr 19;3(8). pii: 99123. doi:

    10.1172/jci.insight.99123. [Epub ahead of print] PubMed PMID: 29669938; PubMed

    Central PMCID: PMC5931122. [↑](#endnote-ref-93)
94. FDA Briefing Document: Endocrine and Metabolic Drug Advisory Committee Meeting Empagliflozin. Food and Drug Administration.

    https://www.fda.gov/downloads/AdvisoryCommittees/UCM508422.pdf. Published June 28, 2016. [↑](#endnote-ref-94)
95. Invokana and Invokamet (canagliflozin): Drug Safety Communication - New Information on Bone Fracture Risk and Decreased Bone Mineral Density. Food and Drug Administration. https://www.fda.gov/Drugs/DrugSafety/ucm461449.htm. Access April 13, 2018. [↑](#endnote-ref-95)
96. Watts NB, Bilezikian JP, Usiskin K, Edwards R, Desai M, Law G, Meininger G.

    Effects of Canagliflozin on Fracture Risk in Patients With Type 2 Diabetes

    Mellitus. J Clin Endocrinol Metab. 2016 Jan;101(1):157-66. doi:

    10.1210/jc.2015-3167. Epub 2015 Nov 18. PubMed PMID: 26580237; PubMed Central

    PMCID: PMC4701850. [↑](#endnote-ref-96)
97. Castañeda-Corral G, Rocha-González HI, Araiza-Saldaña CI, Vidal-Cantú GC,

    Miguel Jiménez-Andrade J, Murbartián J, Granados-Soto V. Blockade of peripheral

    and spinal Na+/H+ exchanger increases formalin-induced long-lasting mechanical

    allodynia and hyperalgesia in rats. Brain Res. 2012 Sep 26;1475:19-30. doi:

    10.1016/j.brainres.2012.08.001. Epub 2012 Aug 8. PubMed PMID: 22898152. [↑](#endnote-ref-97)
98. Kumar S, Costello AJ, Colman PG. Fournier's gangrene in a man on empagliflozin

    for treatment of Type 2 diabetes. Diabet Med. 2017 Nov;34(11):1646-1648. doi:

    10.1111/dme.13508. PubMed PMID: 28887847 [↑](#endnote-ref-98)
99. Ohgaki R, Wei L, Yamada K, Hara T, Kuriyama C, Okuda S, Ueta K, Shiotani M,

    Nagamori S, Kanai Y. Interaction of the Sodium/Glucose Cotransporter (SGLT) 2

    inhibitor Canagliflozin with SGLT1 and SGLT2. J Pharmacol Exp Ther. 2016

    Jul;358(1):94-102. doi: 10.1124/jpet.116.232025. Epub 2016 Apr 27. PubMed PMID:

    27189972. [↑](#endnote-ref-99)
100. Mudaliar S, Polidori D, Zambrowicz B, Henry RR. Sodium-Glucose Cotransporter

     Inhibitors: Effects on Renal and Intestinal Glucose Transport: From Bench to

     Bedside. Diabetes Care. 2015 Dec;38(12):2344-53. doi: 10.2337/dc15-0642. Review.

     PubMed PMID: 26604280. [↑](#endnote-ref-100)
101. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato

     ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine

     MS. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and

     renal outcomes in type 2 diabetes: a systematic review and meta-analysis of

     cardiovascular outcome trials. Lancet. 2018 Nov 9. pii: S0140-6736(18)32590-X.

     doi: 10.1016/S0140-6736(18)32590-X. [Epub ahead of print] PubMed PMID: 30424892. [↑](#endnote-ref-101)
102. Clegg LE, Heerspink HJL, Penland RC, Tang W, Boulton DW, Bachina S, Fox RD,

     Fenici P, Thuresson M, Mentz RJ, Hernandez AF, Holman RR. Reduction of

     Cardiovascular Risk and Improved Estimated Glomerular Filtration Rate by SGLT2

     Inhibitors, Including Dapagliflozin, Is Consistent Across the Class: An Analysis

     of the Placebo Arm of EXSCEL. Diabetes Care. 2019 Feb;42(2):318-326. doi:

     10.2337/dc18-1871. Epub 2018 Dec 6. PubMed PMID: 30523029. [↑](#endnote-ref-102)
103. Uthman L, Baartscheer A, Schumacher CA, Fiolet JWT, Kuschma MC, Hollmann MW,

     Coronel R, Weber NC, Zuurbier CJ. Direct Cardiac Actions of Sodium Glucose

     Cotransporter 2 Inhibitors Target Pathogenic Mechanisms Underlying Heart Failure

     in Diabetic Patients. Front Physiol. 2018 Nov 21;9:1575. doi:

     10.3389/fphys.2018.01575. eCollection 2018. Review. PubMed PMID: 30519189; PubMed

     Central PMCID: PMC6259641. [↑](#endnote-ref-103)
104. Packer M. Activation and Inhibition of Sodium-Hydrogen Exchanger Is a

     Mechanism That Links the Pathophysiology and Treatment of Diabetes Mellitus With

     That of Heart Failure. Circulation. 2017 Oct 17;136(16):1548-1559. doi:

     10.1161/CIRCULATIONAHA.117.030418. Review. PubMed PMID: 29038209. [↑](#endnote-ref-104)
105. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of

     Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With

     Heart Failure: Proposal of a Novel Mechanism of Action. JAMA Cardiol. 2017 Sep

     1;2(9):1025-1029. doi: 10.1001/jamacardio.2017.2275. PubMed PMID: 28768320. [↑](#endnote-ref-105)
106. Verma S, Rawat S, Ho KL, Wagg CS, Zhang L, Teoh H, Dyck JE, Uddin GM, Oudit

     GY, Mayoux E, Lehrke M, Marx N, Lopaschuk GD. Empagliflozin Increases Cardiac

     Energy Production in Diabetes: Novel Translational Insights Into the Heart

     Failure Benefits of SGLT2 Inhibitors. JACC Basic Transl Sci. 2018 Aug

     26;3(5):575-587. doi: 10.1016/j.jacbts.2018.07.006. eCollection 2018 Oct. PubMed

     PMID: 30456329; PubMed Central PMCID: PMC6234616. [↑](#endnote-ref-106)
107. Chin KL, Ofori-Asenso R, Hopper I, von Lueder TG, Reid CM, Zoungas S, Wang BH,

     Liew D. Potential mechanisms underlying the cardiovascular benefits of sodium

     glucose cotransporter 2 inhibitors: a systematic review of data from preclinical

     studies. Cardiovasc Res. 2018 Nov 26. doi: 10.1093/cvr/cvy295. [Epub ahead of

     print] PubMed PMID: 30475996. [↑](#endnote-ref-107)
108. McCullough PA, Barnard D, Clare R, Ellis SJ, Fleg JL, Fonarow GC, Franklin BA,

     Kilpatrick RD, Kitzman DW, O'Connor CM, Piña IL, Thadani U, Thohan V, Whellan DJ;

     HF-ACTION Investigators. Anemia and associated clinical outcomes in patients with

     heart failure due to reduced left ventricular systolic function. Clin Cardiol.

     2013 Oct;36(10):611-20. doi: 10.1002/clc.22181. Epub 2013 Aug 8. PubMed PMID:

     23929781; PubMed Central PMCID: PMC4008125. [↑](#endnote-ref-108)
109. Chang YK, Choi H, Jeong JY, Na KR, Lee KW, Lim BJ and Choi DE. Dapagliflozin, SGLT2 Inhibitor, Attenuates Renal Ischemia-Reperfusion Injury. PloS one. 2016;11:e0158810. [↑](#endnote-ref-109)
110. Inzucchi SE, Iliev H, Pfarr E, Zinman B. Empagliflozin and Assessment of

     Lower-Limb Amputations in the EMPA-REG OUTCOME Trial. Diabetes Care. 2018

     Jan;41(1):e4-e5. doi: 10.2337/dc17-1551. Epub 2017 Nov 13. PubMed PMID: 29133344. [↑](#endnote-ref-110)
111. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular

     benefit: a state-of-the-art review. Diabetologia. 2018 Oct;61(10):2108-2117. doi:

     10.1007/s00125-018-4670-7. Epub 2018 Aug 22. Review. PubMed PMID: 30132036. [↑](#endnote-ref-111)
112. Wakabayashi S, Hisamitsu T, Nakamura TY. Regulation of the cardiac Na⁺/H⁺

     exchanger in health and disease. J Mol Cell Cardiol. 2013 Aug;61:68-76. doi:

     10.1016/j.yjmcc.2013.02.007. Epub 2013 Feb 18. Review. PubMed PMID: 23429007. [↑](#endnote-ref-112)
113. Rivarola V, Di Giusto G, Christensen MJ, Ford P, Capurro C. AQP2-Induced

     Acceleration of Renal Cell Proliferation Involves the Activation of a Regulatory

     Volume Increase Mechanism Dependent on NHE2. J Cell Biochem. 2017

     May;118(5):967-978. doi: 10.1002/jcb.25602. Epub 2017 Jan 5. PubMed PMID:

     27191152. [↑](#endnote-ref-113)
114. Bourgeois S, Meer LV, Wootla B, Bloch-Faure M, Chambrey R, Shull GE, Gawenis

     LR, Houillier P. NHE4 is critical for the renal handling of ammonia in rodents. J

     Clin Invest. 2010 Jun;120(6):1895-904. doi: 10.1172/JCI36581. Epub 2010 May 17.

     PubMed PMID: 20484819; PubMed Central PMCID: PMC2877923. [↑](#endnote-ref-114)
115. Diering GH, Numata M. Endosomal pH in neuronal signaling and synaptic

     transmission: role of Na(+)/H(+) exchanger NHE5. Front Physiol. 2014 Jan

     13;4:412. doi: 10.3389/fphys.2013.00412. eCollection 2014 Jan 13. Review. PubMed

     PMID: 24454292; PubMed Central PMCID: PMC3888932. [↑](#endnote-ref-115)
116. Xu M, Ouyang Q, Gong J, Pescosolido MF, Pruett BS, Mishra S, Schmidt M, Jones

     RN, Gamsiz Uzun ED, Lizarraga SB, Morrow EM. Mixed Neurodevelopmental and

     Neurodegenerative Pathology in Nhe6-Null Mouse Model of Christianson Syndrome.

     eNeuro. 2018 Jan 17;4(6). pii: ENEURO.0388-17.2017. doi:

     10.1523/ENEURO.0388-17.2017. eCollection 2017 Nov-Dec. PubMed PMID: 29349289;

     PubMed Central PMCID: PMC5771691. [↑](#endnote-ref-116)
117. Lin PJ, Williams WP, Luu Y, Molday RS, Orlowski J, Numata M. Secretory carrier

     membrane proteins interact and regulate trafficking of the organellar (Na+,K+)/H+

     exchanger NHE7. J Cell Sci. 2005 May 1;118(Pt 9):1885-97. Epub 2005 Apr 19.

     PubMed PMID: 15840657 [↑](#endnote-ref-117)
118. Wang A, Li J, Zhao Y, Johansson ME, Xu H, Ghishan FK. Loss of NHE8 expression

     impairs intestinal mucosal integrity. Am J Physiol Gastrointest Liver Physiol.

     2015 Dec 1;309(11):G855-64. doi: 10.1152/ajpgi.00278.2015. Epub 2015 Oct 1.

     PubMed PMID: 26505975; PubMed Central PMCID: PMC4669351. [↑](#endnote-ref-118)
119. Beydoun R, Hamood MA, Gomez Zubieta DM, Kondapalli KC. Na(+)/H(+) Exchanger 9

     Regulates Iron Mobilization at the Blood-Brain Barrier in Response to Iron

     Starvation. J Biol Chem. 2017 Mar 10;292(10):4293-4301. doi:

     10.1074/jbc.M116.769240. Epub 2017 Jan 27. PubMed PMID: 28130443; PubMed Central

     PMCID: PMC5354498. [↑](#endnote-ref-119)
120. Lee SH, Kim T, Park ES, Yang S, Jeong D, Choi Y, Rho J. NHE10, an

     osteoclast-specific member of the Na+/H+ exchanger family, regulates osteoclast

     differentiation and survival [corrected]. Biochem Biophys Res Commun. 2008 May

     2;369(2):320-6. doi: 10.1016/j.bbrc.2008.01.168. Epub 2008 Feb 11. Erratum in:

     Biochem Biophys Res Commun. 2008 Aug 15;373(1):174. PubMed PMID: 18269914. [↑](#endnote-ref-120)
121. Ohgaki R, van IJzendoorn SC, Matsushita M, Hoekstra D, Kanazawa H. Organellar

     Na+/H+ exchangers: novel players in organelle pH regulation and their emerging

     functions. Biochemistry. 2011 Feb 1;50(4):443-50. doi: 10.1021/bi101082e. Epub

     2010 Dec 30. Review. PubMed PMID: 21171650. [↑](#endnote-ref-121)
122. Yuan FL, Wu QY, Miao ZN, Xu MH, Xu RS, Jiang DL, Ye JX, Chen FH, Zhao MD, Wang

     HJ, Li X. Osteoclast-Derived Extracellular Vesicles: Novel Regulators of

     Osteoclastogenesis and Osteoclast-Osteoblasts Communication in Bone Remodeling.

     Front Physiol. 2018 May 30;9:628. doi: 10.3389/fphys.2018.00628. eCollection

     2018. Review. PubMed PMID: 29910740; PubMed Central PMCID: PMC5992398. [↑](#endnote-ref-122)