

## SGLT inhibitors for improving Healthspan and lifespan

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### ABSTRACT

Sodium-glucose cotransporter inhibitor/inhibition (SGLTi), initially approved as a glucose-lowering therapy for type 2 diabetes, is associated with decreased risks for many of the most common conditions of aging, including heart failure, chronic kidney disease, all-cause hospitalization, atrial fibrillation, cancer, gout, emphysema, neurodegenerative disease/dementia, emphysema, non-alcoholic fatty liver disease, atherosclerotic disease, and infections. Studies also show that SGLTi improves overall life expectancy and reduces risks of cardiovascular death and cancer death. These wide-ranging health benefits are largely unexplained by the SGLTi's modest improvements in standard risk factors. SGLTi produces upregulation of nutrient deprivation signaling and downregulation of nutrient surplus signaling. This in turn promotes autophagy, which helps to optimize cellular integrity and prevent apoptotic cell death. SGLTi decreases oxidative stress and endoplasmic reticulum stress, restores of mitochondrial health, stimulates mitochondrial biogenesis, and diminishes proinflammatory and profibrotic pathways. These actions help to revitalize senescent cells, tissues, and organs. In summary, SGLTi appears to slow aging, prevent disease, and improve life expectancy, and its mechanisms of action lend strong biological plausibility to this hypothesis. Further randomized trials are warranted to test whether SGLTi, a safe and well-tolerated, once-daily pill, might improve healthspan and lifespan.

### Introduction

The innate aging process is the most important risk factor for the majority of serious chronic disease and death. Aging is characterized by the progressive erosion of optimal physiological function beginning at the cellular level and culminating in musculoskeletal frailty with an increased risk for developing chronic cardiovascular (CV) disease (CVD), metabolic, neurodegenerative, infectious and neoplastic diseases. Due to the increasingly well-understood biological mechanisms of aging, this process may be theoretically modifiable using targeted therapeutic interventions. In recent decades, scientists have explored a range of nutritional and pharmacological interventions aimed at extending lifespan in lower organisms. Optimal diet and exercise appear to be effective at extending lifespan as well as healthspan—the number of years a person lives in a state of good health with full mental and physical capabilities.<sup>1,2</sup> Aerobic exercise/cardiorespiratory fitness and calorie restriction/fasting have been shown to improve insulin

sensitivity, which provides potent protection against age-related disease and premature death.<sup>2,3</sup>

Scientists are actively studying several drugs that have shown potential for slowing aging and improving lifespan and healthspan. Two of the most promising geroprotective (protective against adverse effects of aging) agents, metformin and rapamycin, are already being prescribed off-label to slow aging despite a paucity of evidence showing safety and efficacy.<sup>4–8</sup> Sodium-glucose cotransporter inhibitor/inhibition (SGLTi) works by blocking reuptake of filtered glucose in the proximal tubule of the nephron. These agents all block the SGLT2, but sotogliflozin also blocks SGLT1, which is primarily located in the intestinal wall. Originally formulated to treat type 2 diabetes (T2D), this relatively simple mechanism of action leads to extraordinary downstream effects for preventing and treating many of the most common and serious age-related diseases regardless of T2D status. The aims of this review are a) to propose SGLTi as a potential therapy that may prevent/delay many of the common age-related diseases and improve lifespan and

**Abbreviations:** AF, Atrial Fibrillation; AMPK, Adenosine Monophosphate-activated Protein Kinase; BDNF, Brain-Derived Neurotrophic Factor; BP, Blood Pressure; CKD, Chronic Kidney Disease; CNS, Central Nervous System; CV, Cardiovascular; CVD, Cardiovascular Disease; DPP4i, Dipeptidyl Peptidase-4 inhibitor; HbA1c, Hemoglobin A1c; HF, Heart Failure; mTOR, Mechanistic Target of Rapamycin; PGC1- $\alpha$ , Peroxisome Proliferator-activated Receptor  $\gamma$  Coactivator 1-alpha; RCT, Randomized Controlled Trial; SGLTi, Sodium-Glucose Cotransporter inhibitor; SIRT, Sirtuin; T2D, Type 2 Diabetes; TNF- $\alpha$ , Tumor Necrosis Factor-alpha.

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healthspan, and b) to discuss potential mechanisms of action whereby SGLTi might confer these benefits.

### SGLTi: Effects on standard CVD risk factors

Unlike other proposed geroprotective therapies, a large body of data provides compelling evidence that SGLTi may reduce risks of many age-related diseases and improve life expectancy in humans.<sup>9</sup> This class of medication produces a modest osmotic diuresis through inhibition of renal glucose and sodium reabsorption in patients with or without T2D—urinary glucose losses generally total 60 to 80 g/day (~300 cal/day). Randomized controlled trials (RCT) report that SGLTi used in T2D patients causes statistically significant reductions in hemoglobin A1c (HbA1c) (0.8%), weight (3.75 pounds or 2.4% of body weight) and blood pressure (BP; 4/2 mmHg) with a significant increase in high-density lipoprotein cholesterol (7%).<sup>10</sup>

However, in patients without T2D, these drugs induce small to negligible A1c reductions because the urinary glucose losses are offset by augmented hepatic gluconeogenesis.<sup>11,12</sup> In normotensive, nonobese individuals, SGLTi-induced changes in BP and weight are minimal to absent.<sup>12</sup> Yet, in all patients, the SGLTi-induced glucosuria and natriuresis bestow cardioprotective and renoprotective actions such as decreasing preload and afterload in the heart and suppressing sympathetic overactivity.<sup>9</sup>

SGLTi enhances utilization of body fat stores for energy production and aids transformation of white adipose tissue into brown adipose tissue (abundant mitochondria imbue these adipocytes with a brown color).<sup>13</sup> As compared to white fat, brown fat is more metabolically active, so it burns more calories and generates less inflammation.<sup>13</sup> SGLTi attenuates obesity-induced inflammation and insulin resistance, and decreases levels of proinflammatory mediators including tumor necrosis factor alpha (TNF- $\alpha$ ), C-reactive protein and interleukin-6.<sup>12</sup>

SGLTi is associated with reduced risks for many of the most common conditions of aging including heart failure (HF), chronic kidney disease (CKD), atrial fibrillation (AF), cancer, gout, neurodegenerative disease, emphysema, non-alcoholic fatty liver disease, atherosclerotic CVD and infections.<sup>11,14–49</sup> Studies also consistently report that SGLTi improves overall life expectancy with reduced risk of CVD death and cancer death.<sup>50,51</sup> SGLTi reliably reduces hospitalizations, not only for HF but also all-cause hospitalization.<sup>11,14–16,21</sup> These systemic benefits in healthspan and longevity, however, are not fully explained by the modest improvements in standard modifiable risk factors such as HbA1c, weight, BP and lipids.<sup>52</sup>

### SGLTi and life expectancy

A meta-analysis of 21 randomized trials, mean follow-up of 2 years and inclusive of 39,593 patients in the SGLTi arm and 30,771 patients in the comparator arm, showed that SGLTi was associated with a highly significant 14% relative risk reduction in all-cause mortality ( $p < 0.00001$ ).<sup>19</sup> Another large meta-analysis of five RCTs of HF patients that included 21,947 participants found that SGLTi compared to placebo significantly reduced risk of all-cause mortality despite relatively short study durations (typically 2 to 3 years) (Fig. 1).<sup>21</sup> Other meta-analyses also reported that SGLTi2i decreases risk of death from any cause including CVD and cancer.<sup>11,14,16,21</sup> EMPA-REG was an RCT of 7020 patients with preexisting CVD in which empagliflozin compared to placebo reduced risk of CVD death by 38% ( $p < 0.001$ ).<sup>22</sup> In a “real-world” propensity-matched observational study of ~160,000 patients with newly diagnosed T2D, the patients who were prescribed SGLTi had 45% lower risk of all-cause mortality compared with those not taking SGLTi2 inhibitors ( $p = 0.0001$ ) (Fig. 2).<sup>53</sup>

An observational study of 18,500 T2D patients used propensity score matching to compare SGLTi users to dipeptidyl peptidase-4 inhibitor (DPP4i) users.<sup>20</sup> Observational studies of SGLTi often choose DPP4i as the comparator because in RCTs the latter drug generally produces neutral effects on long term-survival and adverse CVD events. SGLTi users had significantly lower relative risk of all-cause mortality, with a hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.68 to 0.94;  $p = 0.0057$ .<sup>20</sup> Similarly, an observational study of 140,000 T2D patients from Japan, Taiwan and Korea used 70,000 matched patient pairs who used either SGLTi or DPP4i.<sup>17</sup> SGLTi use was associated with lower risk of all-cause mortality (HR 0.60, CI 0.51 to 0.70).<sup>17</sup> Another large, international, observational study of 388,248 T2D patients reported that initiation of SGLTi versus DPP4i was associated with a lower risk of all-cause mortality (HR 0.64, CI 0.57 to 0.72;  $p < 0.0001$ ).<sup>24</sup>

In the Interventions Testing Program, SGLTi2-i consistently extended median survival of male mice by 14%.<sup>18</sup> SGLTi2i led to lower fasting glucose and improved glucose tolerance in both sexes, but that study demonstrated no benefit to longevity in female mice.

### Effects on CVD and respiratory diseases

Age is among the strongest risk factors for HF, and large outcome studies have consistently reported that SGLTi decreases risk of new or worsening HF for both subtypes—HF with reduced ejection fraction and HF with preserved ejection fraction.<sup>21,23,25,26,31,32</sup> In large RCTs, SGLTi therapy demonstrates statistical superiority compared to placebo with

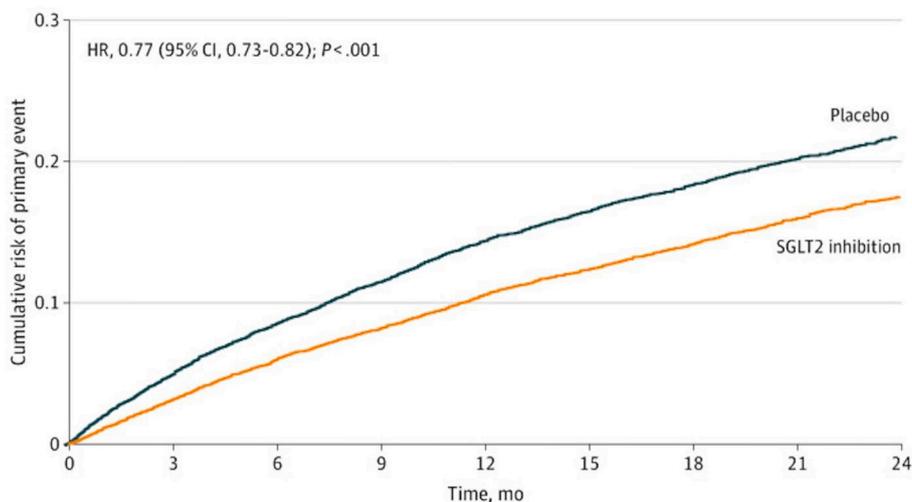


Fig. 1. Kaplan Meier curves for primary endpoint of CV death or worsening HF in 21,947 patients in RCTs. HR hazard ratio, CI confidence interval.<sup>21</sup>

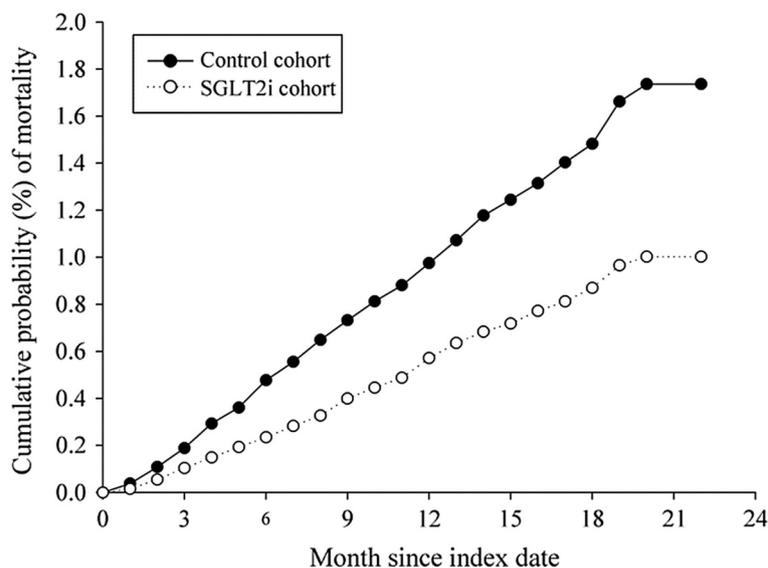


Fig. 2. Cumulative risk curve showing all-cause mortality for the study cohort treated with SGLT2i versus non-SGLT2i cohort.<sup>53</sup> Permission obtained.

respect to HF hospitalization and CVD death within just 12 days of drug initiation.<sup>30</sup> A recent comprehensive meta-analysis of RCTs comprised of 17,000 HF patients reported that SGLT2i significantly decreased relative risks for HF hospitalization (–29%), adverse renal outcomes (–37%), CVD mortality (–13%), and all-cause mortality (–11%).<sup>14</sup>

In patients with atherosclerotic CVD, SGLT2i was shown in a large RCT to reduce risk of major adverse CVD events (myocardial infarction, ischemic stroke, or CVD death).<sup>22</sup> A meta-analysis of nine large RCTs reported that SGLT2i was associated with lower incidence of several CV disorders, including HF, AF, bradycardia, hypertension, hypertensive emergency, and varicose veins.<sup>34</sup> AF is the most common serious arrhythmia, and large studies consistently show that SGLT2i is associated with a ~25% reduction in risk of AF.<sup>53,54</sup> Additionally, SGLT2i was linked with lower rates of respiratory diseases including asthma, bronchitis, emphysema, pulmonary edema, non-small cell lung cancer, pneumonia, pleural effusion, respiratory tract infections and sleep apnea.<sup>34</sup> SGLT2i therapy, compared to DPP4i therapy, has been linked to lower risk for pneumonia and pneumonia-related mortality.<sup>34</sup>

### SGLT2i and CKD

Age is the most prevalent risk factor for CKD, which is present in 34% of people ≥65 years of age.<sup>29</sup> SGLT2i is the most effective drug class for preserving renal function and slowing progression of CKD.<sup>16,21,27</sup> In large RCTs, SGLT2i significantly reduced risk of kidney disease progression and acute kidney injury by 25 to 40%,<sup>16</sup> risk of end-stage renal disease (ESRD) and risk of death from CKD.<sup>16,21,27,33</sup> These renoprotective benefits are similar in patients with and without T2D and are present irrespective of baseline kidney function.<sup>16,21,27</sup> A large meta-analysis of RCTs found that SGLT2i reduces risk of serious hyperkalemia by 16%.<sup>28</sup> A model based on RCT data estimated that SGLT2i has the potential to delay ESRD and the need for dialysis by 15 years.<sup>41</sup> SGLT2i also acts as a functional antagonist of renal sympathetic nerve hyperactivity in the setting of HF.<sup>9</sup> In EMPA-KIDNEY, empagliflozin decreased risk of all-cause hospitalizations by 14%.<sup>16</sup>

Elevated uric acid and gout are common age-related issues that are associated with increased risk of insulin resistance, T2D, CKD, myocardial infarction, stroke and HF. An RCT found that SGLT2i therapy

decreased serum uric acid level by 13% compared with placebo.<sup>44</sup> A recent comprehensive meta-analysis reported that SGLT2i was associated with a 34% lower risk of developing gout among patients with T2D.<sup>39</sup>

### SGLT2i and cancer

The sodium-glucose cotransporter functions as a key channel often overexpressed in cancer, which allows for glucose uptake in malignant cells and fuels tumor growth.<sup>35</sup> Sodium-glucose cotransporters have been reported in adenocarcinomas of the pancreas, breast, kidney and prostate. In animal models, SGLT2i has been shown to interfere with tumor growth and induce tumor necrosis.<sup>35</sup> A retrospective propensity score-matched cohort study comprised of T2D patients diagnosed with cancer found that cancer patients treated with SGLT2i had significantly better survival outcomes compared to patients not treated with SGLT2i (Fig. 3).<sup>50</sup> Emerging evidence suggests that SGLT2i may have anticancer activity against several malignancies, including pancreatic, breast, prostate, liver, thyroid and lung cancers.<sup>35</sup> In an observational study, SGLT2i use was associated with lower risks of new-onset overall cancer, cancer-related mortality and all-cause mortality compared to DPP4i.<sup>36</sup> Observational studies report that SGLT2i is associated with improved

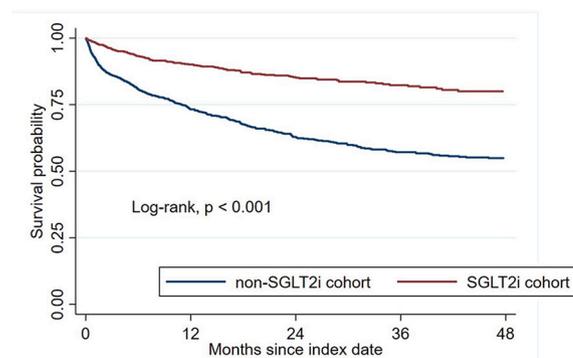


Fig. 3. Kaplan-Meier analysis showing the overall survival for cancer patients treated with SGLT2i compared to those not treated with SGLT2i.<sup>50</sup>

survival among patients with non-small cell lung cancer.<sup>40</sup>

### SGLTi and dementia

Sodium-glucose cotransporters are widely present in the central nervous system (CNS). SGLTi drugs are lipid-soluble and cross the blood-brain barrier with brain/serum ratio of ~0.5; thus are being studied for their potential protective activity against neurodegenerative diseases.<sup>43</sup> SGLTi decreases leakage of the blood-brain barrier, reduces reactive oxygen species, ameliorates microglia dysfunction and improves endothelial function.<sup>39</sup> Empagliflozin significantly increases CNS levels of brain-derived neurotrophic factor (BDNF), which facilitates growth, survival and plasticity of neurons and favorably modulates neurotransmission.<sup>43,46</sup> In animal models, SGLT2i reduces amyloid beta levels, senile plaque density, TNF- $\alpha$  and has neuroprotective effects against Parkinson's disease.<sup>38</sup> Observational studies of patients with T2D consistently show that SGLTi is associated with lower risks for neurodegenerative disorders, such as dementia and Parkinson's disease.<sup>42,47,48</sup> A meta-analysis of 10 observational studies involving 819,511 individuals with T2D reported that SGLTi users had a lower risk of all-cause dementia compared to non-SGLT2 inhibitor users (RR 0.62, CI 0.39–0.97).<sup>45</sup>

### SGLTi enhances autophagy

Autophagy is an evolutionarily conserved intracellular “housecleaning” pathway whereby senescent cellular components are encircled by a double-membrane vesicle (the autophagosome). Subsequent fusion with the lysosome allows degradative enzymes to break down and recycle the contents of the vesicle.<sup>55,56</sup> Nutrient and/or oxygen deprivation are the fundamental stimuli that activate autophagy. Such signaling permits cellular digestion of damaged components like oxidized proteins and dysfunctional organelles for salvage and reuse, which revitalizes mitochondria and generates ATP for energy-depleted cells.<sup>57</sup> Autophagy can be stimulated in response to stressors like fasting, calorie restriction and exercise—both aerobic and resistance training.<sup>58</sup>

Oxidative stress plays a major role in aging. Principal sources of intracellular oxidative stress are dysfunctional mitochondria and endoplasmic reticulum stress. Generally caused by excess glucose or fatty acids or accumulation of misfolded proteins, endoplasmic reticulum stress can lead to apoptosis of the cell and has been associated with neurodegenerative disorders, T2D, atherosclerosis, and cancer.<sup>9,59</sup> Autophagic clearance of this cellular debris—dysfunctional mitochondria and endoplasmic reticulum—ameliorates intracellular oxidative stress and mitigates proinflammatory and profibrotic responses.<sup>9</sup> The cumulative effect of enhanced autophagic flux is the preservation of cellular integrity and prevention apoptotic cell death, thereby helping to restore and maintain optimal structure and function of the cells, tissues and organs.<sup>55,56</sup>

SGLTi reliably amplifies autophagic flux throughout the body and facilitates the disposal of defective mitochondria, rejuvenates healthy mitochondrial function and stimulates mitochondrial biogenesis.<sup>39,60,61</sup> Furthermore, SGLTi alleviates endoplasmic reticulum stress, diminishes the generation of reactive oxygen species and boosts endogenous antioxidant activity.<sup>59,62–64</sup>

### Anti-aging mechanisms of action

As outlined above, SGLTi promotes cellular housekeeping by augmenting autophagic flux, which slows aging at a cellular level. These benefits appear to arise from the ability of SGLTi to simultaneously upregulate nutrient deprivation signaling and downregulate nutrient surplus signaling.<sup>65</sup> These alterations in nutrient sensing reduce activation of mammalian target of rapamycin (mTOR) receptors and increase expression and activity of adenosine monophosphate-activated

protein kinase (AMPK), sirtuin 1 (SIRT1), sirtuin 3 (SIRT3), sirtuin 6 (SIRT6) and peroxisome proliferator-activated receptor  $\gamma$  coactivator 1- $\alpha$  (PGC1- $\alpha$ ).<sup>9,65</sup>

AMPK, sirtuins, PGC-1 $\alpha$  and mTOR are 4 master transcription factors and enzymes that regulate numerous genes and proteins that function to maintain cellular homeostasis and allow organisms to adapt to environmental challenges and opportunities.<sup>9</sup> During times when nutrients are plentiful, and mTOR signaling is robust, organisms prioritize the use of fuels to expand cell mass. Such activity is useful in young organisms while they are still growing, but it is potentially detrimental in mature organisms who may be at risk for cancer and disorders of nutrient excess like obesity and diabetes.<sup>66</sup> Conversely, when nutrients are depleted, organisms shut down anabolic pathways and instead ramp up AMPK, sirtuins and PGC-1 $\alpha$ , which are proteins synthesized in the liver as the body's primary response to starvation.<sup>9,67</sup> For example, AMPK is a fundamental energy sensor of the cell and, in response to energetic stress—starvation, fasting, vigorous exercise—augments energy production, mitochondrial biogenesis and insulin sensitivity.<sup>65</sup>

In the clinical setting, SGLTi-induced nutrient deprivation signaling promotes gluconeogenesis, ketogenesis, erythrocytosis and reduces uric acid levels.<sup>67</sup> By inducing glycosuria, SGLTi mimics a state of starvation characterized by the hepatic production of ketone bodies, predominantly  $\beta$ -hydroxybutyrate.<sup>67</sup> Ketogenesis and erythrocytosis are the key clinical biomarkers of the action of SGLTi because they reflect the typical physiological responses to nutrient deficit and oxygen deprivation, respectively.<sup>65</sup> SGLTi reduces serum uric acid, a marker of oxidative stress.<sup>9</sup> Upregulated nutrient and oxygen deprivation signaling can augment erythropoietin synthesis in the kidney and reduce oxidative stress in cardiomyocytes, neurons and other cells throughout the body.<sup>9,65</sup> Tellingly, large RCTs have consistently identified hemoglobin increases and uric acid reductions as statistical determinants of the ability of SGLTi to decrease risks for HF hospitalizations and major adverse renal events.<sup>9</sup>

These clinical findings, in conjunction with extensive data from experimental studies, support the hypothesis that SGLTi mitigates a number of afflictions associated with aging and improves life expectancy. This ability of this class of therapy to augment healthspan and lifespan arises in part through alterations in nutrient deprivation/surplus signaling with consequent effects in promoting autophagy and restoring mitochondrial vitality, reducing reactive oxygen species, dampening inflammation and fibrosis and enhancing the viability of cells throughout the body.<sup>9</sup> Recent studies have shown that the adaptive cellular reprogramming produced by SGLTi is also seen in isolated cell cultures. Otherwise stated, these agents have direct, glycosuria-independent, effects that decrease cellular stress and enhance cell survival.<sup>65</sup> This finding suggests that SGLTi may bind directly to nutrient sensors to influence their function. Indeed, SGLTi has been shown to bind to mTOR in the same structural domain used by rapamycin.<sup>63</sup>

SGLTi inhibits inflammation and diminishes fibrosis by reducing proinflammatory cytokines and diminishing profibrotic pathways, fibroblast proliferation and collagen deposition.<sup>68,69</sup> Through these actions, SGLTi helps to maintain normal tissue architecture,<sup>68,69</sup> regress of adverse structural remodeling and rejuvenate organ function.<sup>60,70–73</sup>

### Adverse effects

Any candidate compound being considered for use as a geroprotective agent to improve life expectancy should meet the *Primum non nocere* (first do no harm) maxim. A compound to be used for decades by healthy people must have very low risk for serious adverse effects. SGLTi are generally well tolerated, with discontinuation rates in RCTs that are similar to placebo (Fig. 4). A network meta-analysis of 47,000 patients in RCTs reported no significant changes in the risk of adverse events, including hypoglycemia, urinary tract infection, bone fractures or volume depletion.<sup>51,74</sup> RCTs show that SGLTi users report improved quality of life metrics compared to the control group.<sup>15</sup> Notably, SGLTi

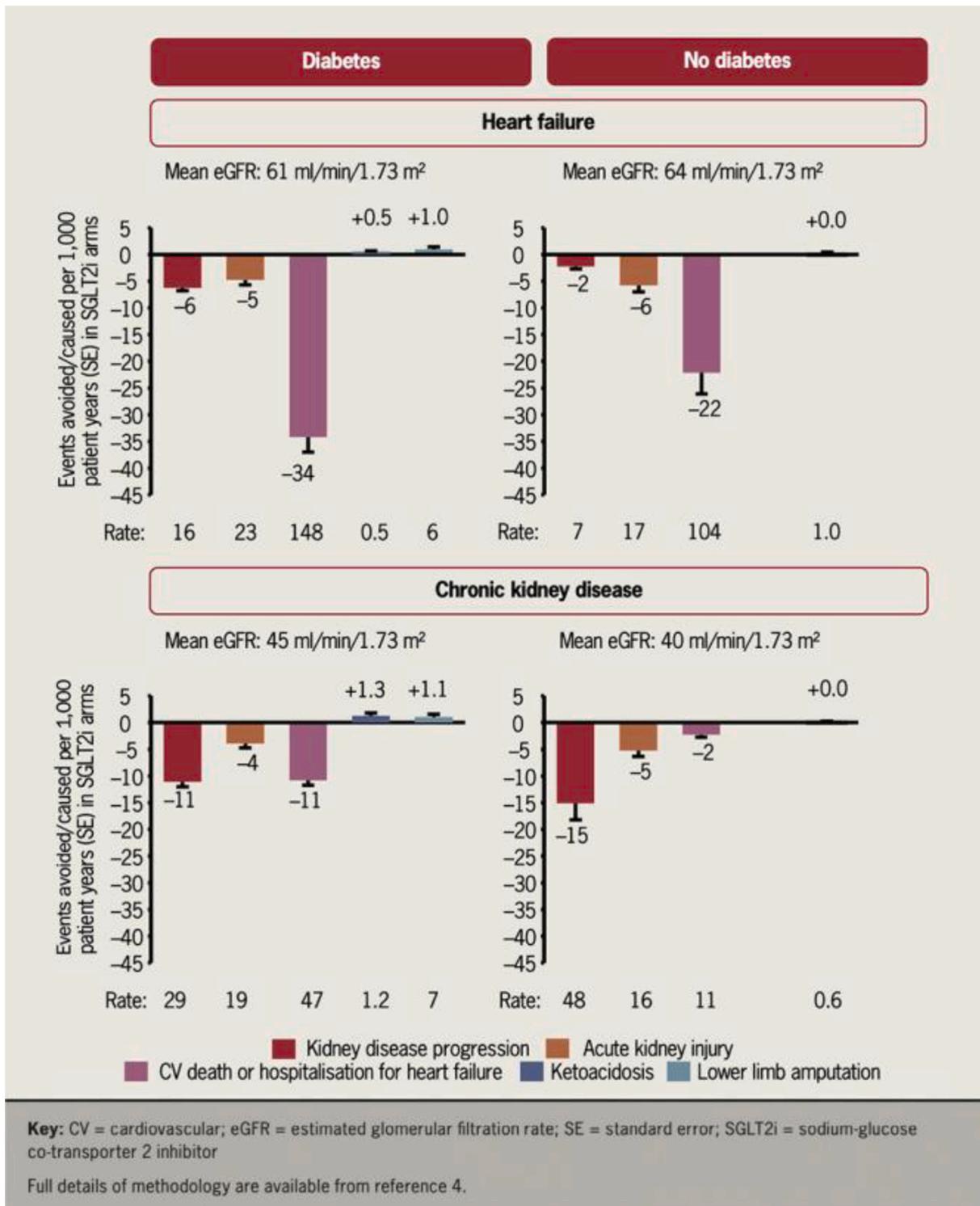


Fig. 4. Results from two recent trials and two recent meta-analyses conclusively demonstrated the cardio-protective and kidney-protective effects of SGLT<sub>i</sub> in HF and CKD populations. The absolute benefits convincingly outweighed the potential harms.<sup>15</sup> Permission obtained.

therapy does increase risk of genital yeast infection due to glycosuria. A large meta-analysis found that SGLT<sub>i</sub> use was associated with statistically significant 3.3-fold increased risk of genital yeast infections compared to controls, but the absolute risk was modest, 6.3% for SGLT<sub>i</sub> versus 1.7% for control.<sup>74</sup>

Although canagliozin in one study was associated with increased risk of lower limb amputation, a recent large meta-analysis showed no increased risk of amputation with any drugs in the SGLT<sub>i</sub> class.<sup>75</sup>

Fournier's gangrene of the perineum is an exceedingly rare infection that occurs in diabetics. A total of 29 cases of Fournier's gangrene have been reported with SGLT<sub>i</sub>.<sup>76</sup> Additionally, SGLT<sub>i</sub> can also cause euglycemic ketoacidosis in patients with diabetes, generally in the context of serious medical illness often in and individual whose pancreas makes little to no insulin. In RCTs, ketoacidosis was a rare event despite a doubling of its risk with SGLT<sub>i</sub>.<sup>16</sup> Only a single starvation ketoacidosis event has been reported in an individual without T2D during ~30,000

years of trial participant follow-up.<sup>16</sup> For nondiabetic individuals, SGLT2i therapy virtually never causes ketoacidosis, lower limb amputation or Fournier's gangrene.<sup>15,16,51</sup> Empagliflozin, dapagliflozin, and sotagliflozin are the agents in the SGLT2i drug class with the strongest safety and efficacy for improving healthspan and lifespan.<sup>51,77,78</sup>

**Conclusion**

SGLT2i simultaneously upregulates nutrient deprivation signaling and downregulates nutrient surplus signaling. This promotes autophagy, restores mitochondrial health, reduces intracellular oxidative stress,

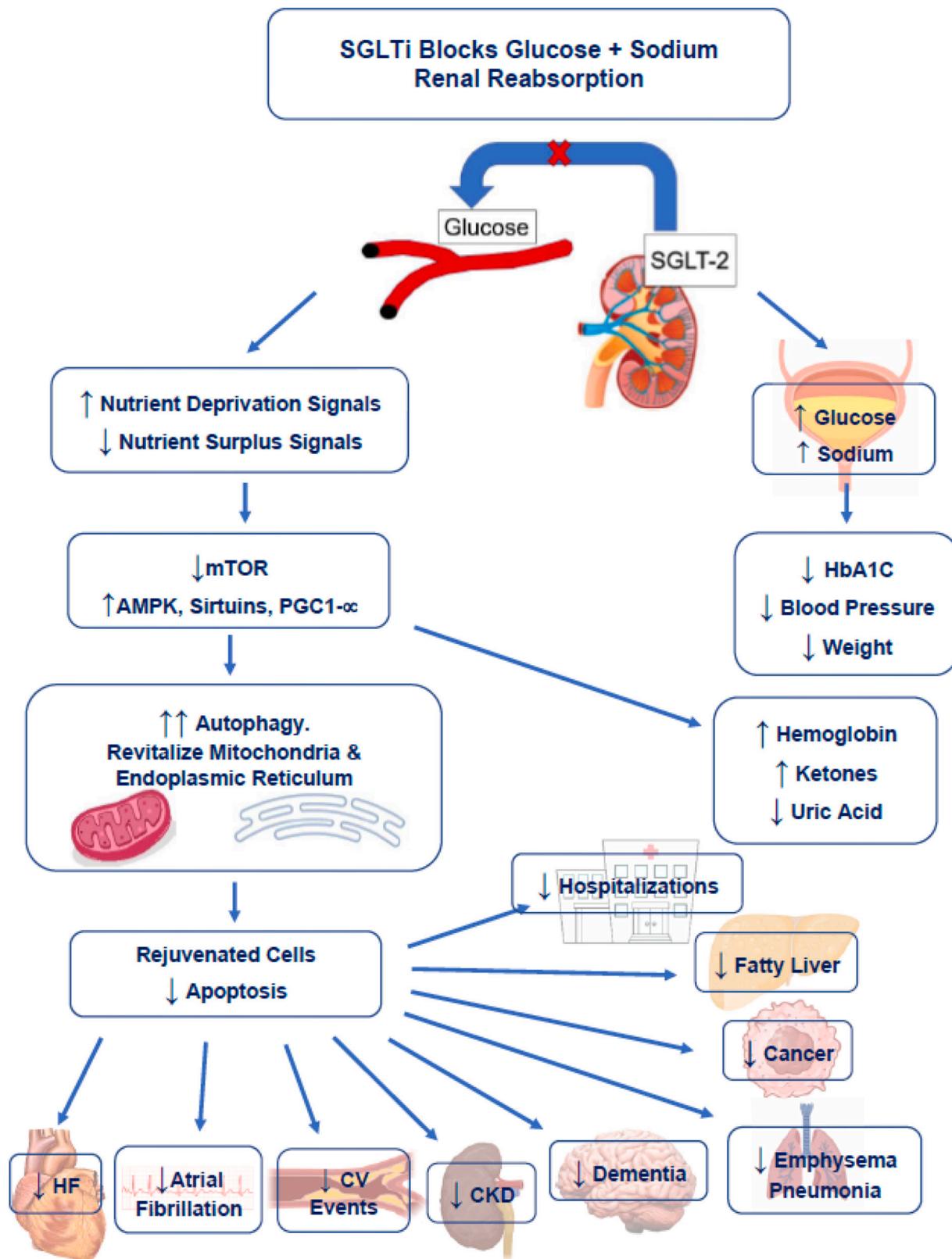


Fig. 5. (Central Figure) – Mechanisms of action whereby SGLT2i improves health and reduces risk of age-related diseases. Figure made by authors.

decreases proinflammatory and profibrotic pathways, and preserves integrity and viability in cells and organs. Clinical studies show SGLT2 lowers risks for premature mortality and many of the diseases of aging (Fig. 5-Central Figure). Of the candidate geroprotective agents including metformin and rapamycin, SGLT2 has the most RCT data for safety and efficacy in humans. Further studies are warranted to assess SGLT2 for reducing age-related disease and improving life expectancy.

### Declaration of Competing Interest

JHO – Speaker for Boehringer Ingelheim.

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