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SGLT2 Inhibitors and Potential Applications in Treating Metabolic Syndrome

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Abstract

SGLT2 inhibitors act to induce glucosuria and have been shown to be efficacious in the treatment of type II diabetes mellitus but have also been shown to positively affect cardiovascular conditions and some benefitting kidney function. SGLT2i have shown to be effective in more advanced conditions but may eventually be a treatment in more general metabolic dysfunction. Metabolic syndrome is a clinical diagnosis for establishing risk for ischemic heart disease and diabetes. The prevalence of type II diabetes mellitus, heart disease, and severe vascular events steadily increased over recent decades. In addition to the established benefits of diet and exercise, SGLT2 inhibitor therapy may be able to aid in the treatment of metabolic syndrome from its proven cardiovascular and anti-hyperglycemic benefits. Pharmacologic modeling in canines is also considered, as they present with similar diagnoses and offer a model that shares many of the characteristics of humans in metabolic dysfunction.

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Introduction

SGLTs | A member of the SLC5 family, sodium-glucose cotransporter 2 (SGLT2) is a low affinity, high-capacity membrane protein located principally in the basolateral membrane of the early proximal tubules. The SGLT2 transporter is responsible for 90% of the filtered glucose reabsorption, approximately 140 grams per day. This is compared to SGLT1, which is involved in high affinity and low-capacity glucose reabsorption in the late proximal tubule and accounts for the remainder of glucose reabsorption. SGLT1 is also found in various places throughout the body but concentrated in the small intestine. Human SGLT2 and SGLT1 share similar architecture with a 59% sequence homology.[1] SGLT2 is unique from other proteins in the SLC5 family as it is almost exclusively expressed in the early proximal tubule of the kidneys; this characteristic of SGLT2 makes it a prime target for drugs that induce glycosuria.

Drug Development | The first known inhibitor of the SGLTs was phlorizin, a plant O-glycoside that was known to have the effect of inducing glycosuria as a non-selective inhibitor of SGLT1 and SGLT2. Phlorizin led to the development of T-1095, a more selective SGLT2 inhibitor, and eventually the development of drugs that almost exclusively target SGLT2. As mentioned earlier, SGLT2 is principally located in the proximal tubule of nephrons; as such, the main concern for targeting SGLT2 for therapeutic treatment is to select compounds with a high affinity to the transporter. It has been shown that the O-glycoside, Phlorizin has a four-fold higher affinity for SGLT2 over SGLT1. Modern therapeutics using SGLT2 inhibitors (SGLT2i)

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demonstrate much higher affinities for SGLT2, with the C-glycosides generally having much more selective profiles compared to the few O-glycosides used as SGLT2 inhibitors. The most selective drug is Empagliflozin, with an SLGT2/1 selectivity ratio of over 2,600, making it 190x more selective than phlorizin.[2]

Canagliflozin was the first SGLT2 inhibitor approved by the FDA to treat type II diabetes mellitus (T2D) in March of 2013, under the brand name Invokana®. Following this approval, both dapagliflozin and empagliflozin were approved for the same treatment in 2014. Since their initial approvals for implications of T2D, all three SGLT2i have been approved for use in implications of various cardiovascular events. Empagliflozin was first shown to reduce the risk for severe cardiovascular events; the EMPEROR-Reduced trial showed treatment was associated with a 38% risk reduction in cardiovascular death in T2D patients at risk of heart failure with reduced ejection fraction.[3] Empagliflozin was the first SGLT2 inhibitor approved for cardiovascular use in patients with T2D in 2016. This evidence led to trials investigating the same effects using canagliflozin (CANVAS) and dapagliflozin (DECLARE-TIMI 58), both showing similar cardiovascular outcomes in patients with T2D.[4, 5] Both canagliflozin and dapagliflozin received FDA approvals for cardiovascular conditions in 2018 and 2019, respectively. Since their first approvals for treating diabetics, empagliflozin and dapagliflozin have since been approved to reduce cardiovascular risks in non-diabetic patients.

Along with their approval for treating T2D, three SGLT2i have also been approved to treat kidney disease. Between the DECLARE-TIMI-58, CANVAS, and EMPA-REG OUTCOME trials, there was an overall 45% reduction in the risk of

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kidney disease progression.[6] Currently, canagliflozin is indicated for treating T2D and diabetic nephropathy based on outcomes of the CREDENCE trial.[7] Dapagliflozin is indicated for general use in reducing the risk of worsening kidney disease based on outcomes from the DAPA-CKD trial.[8]

Drug Indications | The emergence of various SGLT2i as a treatment for adequately controlling blood glucose is similar to the use of GLP agonists or biguanide, metformin. Metformin has clinical use in controlling blood glucose and can effectively alter cellular metabolism by opposing the actions of glucagon. Specifically, Metformin effectively lowers carbohydrate absorption, reduces hepatic glucose production, increases skeletal muscle glucose uptake, and reduces circulating low-density and very low-density lipoprotein (LDL VLDL). Metformin is not well tolerated as long-term therapy, is contradicted in patients with severe renal impairment, and treatment is often associated with adverse gastrointestinal effects. Metformin is often regimented into a dual therapy or triple when treating T2D with combinations with dipeptidyl peptidase-4 (DDP-4) inhibitors, sulfonylureas, or other drugs that assist in controlling blood glucose. SGLT2i are an effective treatment for glycemic control in combination with Metformin, with many SGLT2i being approved as dual therapies alongside Metformin for the treatment of T2D.

There are a few SGLT2i that are well established in the treatment of T2D, namely canagliflozin, dapagliflozin, and empagliflozin. From the trials mentioned earlier, SGLT2i have all been shown to be effective in controlling blood glucose. Findings of additional cardiovascular benefits have spurred interest in further trials expanding indications for wider treatment of cardiovascular conditions for both

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diabetics and non-diabetics. In addition to the three main SGLT2i, a fourth drug named ertugliflozin was also developed. It is currently indicated only for glycemic control in T2D. A small number of trials are active to expand the use of ertugliflozin, many aimed at similar secondary outcomes that have been recorded previously. Contrary to the measured cardiovascular outcomes seen with dapagliflozin and empagliflozin, ertugliflozin was not found to significantly reduce cardiovascular events in patients with T2D and vascular diseases.[9] These results come from the VERTIS-CV trial conducted in 2018. Regardless of this past result, current studies are measuring the cardiovascular benefits of treatment using ertugliflozin. A table showing the current indications of SGLT2i is shown in Appendix B.

The established SGLT2i have similar broad effects but seem to have minute differences in their effect. The different SGLT2i may have slightly different effects that must be explained by their similar but distinct chemical compositions. There are currently over 150 phase 3 or phase 4 trials active or recruiting. These trials include trials measuring SGLT2i effects on heart fibrosis and inflammation, heart remodeling, heart perfusion in prediabetics, heart attack prevention, and ventricular arrhythmias, to name a few. With many trials currently underway, it is likely that indications of SGLT2i are expanded further in the coming years. A highlight of some current late phase SGLT2i trials are listed in Appendix C.

Side Effects | SGLT2i have been well researched, and the side effects of the treatment's interim period are well known. In diabetes, treatment of SGLT2i places a risk of ketoacidosis. A meta-analysis of two different cohorts comparing the risk of

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diabetic ketoacidosis between SGLT2i to that of sulfonylureas and DPP-4 inhibitors showed that diabetics using SGLT2i were at a higher risk of 6.0% compared to 4.3% of DPP-4 inhibitors, and 6.3% compared to 4.5% of sulfonylureas.[10] This incidence likely results from the effectiveness of SGLT2i at reducing blood glucose compared to that of traditional DDP-4 inhibitors and sulfonylureas.

There has been some contention on whether lower limb amputations are attributed to treatment utilizing SGLT2i in diabetic patients. Lower-limb amputations stem from the prevalence of peripheral artery disease (PAD) in patients with T2D. In the case of SGLT2 inhibitors, lower limb complications would arise from the reduction in blood pressure from the volume decreases experienced in treatment or the changes in hemodynamic status. This contrasts with lower limb complications during disease from endothelial damage and clotting from abnormal metabolism and inflammation. In a meta-analysis of reported complications in studies using four different SGLT2 inhibitors, canagliflozin was the only drug to have shown a correlation in the aggregated data to an increase in lower limb complications.[11] There have been many recent analyses conducted with mixed conclusions on the significance of lower limb amputations being correlated to SGLT2 inhibitor therapy.[12, 13] Clinically, patient risk of lower limb complications should be considered when administering treatment involving SGLT2i

Side effects of SGLT2i mainly occur in conjunction with its glucosuric effects. The most prevalent side effect is genital infection, which has a risk ratio of 3.75 in aggregate data.[13] The risk of genital infections has been correlated to every SGLT2 inhibitor and is the main adverse event that may result in the discontinuation of

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treatment. The risk of genital infection is inherent to the induction of glycosuria and should be closely monitored in any treatment involving SGLT2 inhibitors. The safety concerns of SGLT2 inhibitor treatment are correlated with the significant intended response. Many drug trials have been conducted, and the use of SGLT2i has been approved for the treatment of several conditions. The modern SGLT2 inhibitor drug class has been found to be efficacious and safe, with the known side effects monitored during treatment.

SGLT2 Inhibitors & Metabolic Syndrome

Overview of Metabolic Syndrome | In 2019, global deaths from stroke, ischemic heart disease, or chronic obstructive pulmonary disease accounted for 33% of all deaths and are the top three causes of death.[14] The growth rates of these diseases are currently on the decline, but cardiovascular disease has been the number one cause of death for some time. A relatively new diagnosis was coined around 2005 to assist in realizing the severity of risk factors contributing to CVD and related metabolic diseases known as Metabolic Syndrome. Metabolic syndrome is a non-congenital disease mostly induced by frequent states of overnutrition.

Metabolic Syndrome (MetS) comes with risks for type 2 Diabetes mellitus (T2D) and cardiovascular disease (CVD). The criteria for diagnosing metabolic syndrome are the presence of at least three of the criteria from Table 1. A criterion is also met if the patient is prescribed drug treatment to control any parameters. These criteria have all been correlated with an increased risk for cardiovascular disease and T2D. An important point to consider is that the presence of one marker places a

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greater risk for others; even one of these criteria is linked to an increased risk of CVD.

Standards of Diagnosing Metabolic Syndrome

Measurement	Male	Female
Abdominal waist circumference	>94 cm	>80 cm
Serum High-Density Lipoprotein	<40 mg/dl	<50 mg/dl
Blood Pressure	≥130/85 mmHg	
Fasting Glucose	≥100 mg/dl	
Serum triglyceride	≥150 mg/dl	

Table 1: Parameters of diagnosing metabolic syndrome, measures from Ferri's Clinical Advisor 2021[15]

There is currently not an analysis on the prevalence of MetS today, but one of the most recent analyses from 2017 suggests that the prevalence of MetS in the United States was at least 33% of the population between 2007-2012, growing from 25% between the years of 1988-1994.[16] More specific numbers that estimate the prevalence of specific criteria of MetS are available through the National Center for Health Statistics, showing in the years of 2017-2018 of the US population ≥18 years old: 16% fell below 40 mg/dL of serum high-density lipoprotein concentration (HDL), 45% were hypertensive, and 42% of the population are obese (BMI ≥ 30 kg/m^2).[17-19] These data points by themselves are not an accurate way to determine the prevalence of MetS but provide an indicator of overall health and risk of MetS in the

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US population. It is also important to consider that these statistics on the population with low HDL or hypertension do not show the prevalence of individuals that have controlled either condition with prescription treatment.

Two of the five criteria of MetS are concerned with cholesterol and fatty acid homeostasis, showing the connection of fatty acid homeostasis with CVD and T2D. The importance of low HDL and free triglyceride levels is their critical role in lipid homeostasis and markers of metabolic dysfunction. The imbalance of plasma lipids is termed dyslipidemia, and chronic dyslipidemia strongly correlates to stroke, arterial diseases, and cardiovascular events. HDL plays a key role in the pathway of reverse cholesterol transport, returning excess cholesterol from peripheral tissues to the liver to be either redistributed or removed in bile. HDL has had an inverse association with CVD for some time. More recent findings suggest that HDL cholesterol concentration (HDL-c) and cardiovascular outcomes is a paradoxical relationship, but HDL particle concentration (HDL-p), small-sized HDL (ssHDL), and apolipoprotein A1 (apoA1) are more accurate measures. HDL-p, ssHDL, and apoA1 have a far more accurate inverse relationship with individual risk of coronary artery disease compared to the concentration of HDL-c.[20] This evidence does not discredit general HDL-c concentration as a measure of MetS and cardiovascular outcomes but acknowledges that there has been an improvement on the association.

Pathophysiology of Metabolic Syndrome | The combined presence of multiple signs signals the critical need for intervention. The best form of prevention is in the form of habit, with a balanced diet and adequate exercise, but by the time drug

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intervention is prescribed, there is often difficulty reversing symptoms. With increases in adipose tissue due to anabolic pathways induced by high-fat diets, excess caloric intake, and elevated blood glucose, there is also an increase in inflammation derived from adipose tissue itself. Adipose tissue plays a key role as an endocrine gland secreting adiponectin, leptin to modulate metabolism and increase energy expenditure. Inherent to adipose tissue is the excretion of inflammatory cytokines like TNF-α and IL-6 from residing macrophages. With obesity comes low levels of chronic inflammation, and the released inflammatory cytokines have been shown to be associated with insulin resistance.[21] It is known that excess body fat is detrimental to health, but ongoing research shows there is a complexity to metabolic dysregulation and common themes shared by different diseases.

In 2021, the International Diabetes Federation estimated that 537 million people globally have diabetes.[22] The pathogenesis of T2D is characterized by overactive pancreatic beta cells secreting insulin, resulting in an abundance of serum insulin and leading to desensitization of the liver, muscle, and adipose tissue to its effect. A clinical diagnosis of prediabetes is defined as high serum insulin but not high enough to be diagnosed as diabetes. It has been found that abnormal insulin sensitivity precedes a clinical diagnosis of diabetes for up to 15 years.[23] The desensitization ultimately leads to a progression to the increased homeostatic level of blood glucose. Increases in blood glucose are associated with increased oxidative stress from upregulating metabolism to cope with the available energy. The excess energy is normally stored as glycogen or converted into adipose tissue. Diabetics are

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at an inherent risk for CVD, neuropathy, kidney damage, retinopathy, and many others if blood glucose is unable to be adequately controlled.

High blood glucose triggers a cellular response to increasing glucose metabolism, which is inherently related to oxidative stress. Oxidative stress refers to damage incurred by abnormal levels of reactive oxygen species (ROS). The most well-known generation of ROS is in the mitochondria during oxidative phosphorylation but are also generated in peroxisomes, the pentose phosphate pathway, and various biological redox reactions. The accumulation of ROS leads to even further inflammation. Oxidative damage can lead to atherosclerosis, neurodegeneration, diabetes, and accelerated biological aging.[24] Oxidative damage and inflammation are a common intersection for the origin of much of the metabolic dysfunction that presents in the markers of MetS, markers that can be traced to an excess of energy substrates such as glucose or fatty acids.

Therapeutic Relevance | Considering that many of the markers for MetS stem from the excess availability of energy throughout the body, an effective strategy for treatment is clearing excess circulating glucose. SGLT2i may have a use in the disease prevention of MetS as they have shown to have significant outcomes in terms of their efficacy and associated side effects. Using SGLT2i to treat MetS may be able to prevent serious conditions such as CVD and diabetes and has proven nephroprotective properties. It is important to consider their use in the treatment of CVD and T2D, as these are the more advanced conditions that patients with MetS

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are at risk for. The glucosuric action of SGLT2 inhibition is precise, but the overall effect of SGLT2i has been reported to be widespread in patients' health.

The efficacy of SGLT2i is well proven, and the excretion of circulating glucose is clearly beneficial in reducing hyperglycemia. An associated benefit of this function is increasing lipid metabolism when insufficient glucose is available. Decreasing the amount of excess energy that the body has can assist in the switching from the anabolic nature that occurs in the storage of excess glucose and fat. The clinical presentation of this metabolic switch may first present in weight loss. The use of SGLT2i have been found to induce glycosuria that excretes around 200-300 calories per day.[24] Rapid changes in weight would best be attributed to the diuretic effects of decreasing fluid volume, but the calorie excretion would be eventually evident. A kilogram of human body fat is estimated to contain 7,700 calories (kcal), assuming no change in lifestyle; this is approximately a kilogram of fat for every 30 days of treatment. The change of body composition is slow, but if used for metabolic pathologies, the effects would be accelerated if combined with a recommended diet and adequate exercise.

Reducing blood glucose shifts metabolism to lipolysis resulting in a reduction of adipose tissue, reducing the amount of systemic inflammation and overall oxidative stress. The simple shift in metabolism induces a fasting-like state that raises levels of circulating ketone bodies. Ketone bodies production and a shift from glucose oxidation have been proposed as a potential mechanism for the benefits of SGLT2 inhibitor therapy, and SGLT2i have been shown to reduce epicardial adipose tissue.[25] The production of ketone bodies resulting from fat catabolism lowers overall

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body composition of fat, thereby offering a decreased production of inflammatory cytokines from adipose tissue and offering ketone bodies as efficient fuel for the heart.

Overall lipid metabolism is improved from treatment with SGLT2 inhibitors. Metadata of the effects on serum lipids at 24 weeks reports triglycerides decreased and HDL increased dose-dependently with treatment.[26] Along with HDL increases, there are also notable increases in LDL. The increasing concentration of serum LDL is most likely related to reducing LDL catabolism. With both HDL and LDL increasing, there is no overall change in the ratio of HDL to LDL but has been shown in trials to not hinder outcomes of SGLT2 inhibitor trials. The reduction in serum triglycerides is most relevant for this reason, as treatment has shown an approximate 5% decrease.[27]

The improvement of glycemic control is excellent in the SGLT2 inhibitor class, comes the question of how their effects compared to other treatments used to control blood glucose. Metformin remains the primary drug to aid in glycemic control. Sulfonylureas and DPP-4 inhibitors are traditional drugs prescribed with Metformin as combination therapies and act to raise insulin levels, increasing its effect on energy storage. Evidence shows that the major SGLT2i approved for treatment today achieve similar short-term glycemic compared to DPP-4 inhibitors and sulfonylureas and better achieve better long-term control of blood glucose.[28-30]

The low energy produces a state of cellular starvation and increases enzymes levels like AMPK, which is a key indicator of low energy and metabolic stress. AMPK

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is involved in signaling for cell growth, metabolism, and autophagy. With AMPK being pivotal in metabolic signaling, it has been indicated as a primary marker for which the cardiovascular benefits of SGLT2 inhibitor therapy are seen. Increasing levels of AMPK has been a proven effect of SGLT2i with a reduction in cardiac iNOS, plasma TNF and creatinine kinase levels. [31] This shows that there is systemic change in the overall energy utilization, reducing inflammation and factors of cardiovascular dysfunction.

Some SGLT2i also offer protection to the kidneys. The shift to a higher filtrate osmolarity in the nephron increases urine volume and reduces blood volume. There are only small natriuretic effects of SGLT2i that wane after the first hours of dosing. The increased filtrate osmolarity induces compensatory activation of the renin-angiotensin system but returns to normal values 3-6 months into treatment.[32] Dapagliflozin was shown to induce a 2.6-6.4 mmHg drop in systolic blood pressure at 12 weeks, and all SGLT2i have shown long-term decreases in extracellular fluid volume.[33] The volume depletion effects are beneficial in controlling blood pressure and have positive outcomes on kidney function. Albuminuria is one of the hallmarks of declining kidney function. The main renal effect of SGLT2i is the attenuation of albuminuria by reducing intraglomerular hydrostatic pressure. The compensatory sodium/chloride reabsorption increases delivery to the macula densa and triggers tubuloglomerular feedback resulting in vasoconstriction of the afferent arteriole and further reducing intraglomerular hydrostatic pressure.[34] The long-term renal benefits of SGLT2 inhibition are correlated to their associated benefits in endothelial health.

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There is also evidence that SGLT2i may impact cardiovascular architecture. Since SGLT2 expression is limited to the kidneys, this stems from the diuretic effects that these drugs display in treatment. Specifically, SGLT2i induces favorable effects on left ventricular remodeling in patients with heart failure and reduced ejection fraction. [35, 36] These outcomes were recorded in the SUGAR-DM-HF and EMPEROR-Reduced trials, looking at cardiovascular outcomes for patients with heart failure and reduced ejection fraction. SGLT2i have been shown to affect the pathways of cardiac fibrosis, ER stress, and calcium signaling. Alongside this, there is evidence that supports increased cellular and organelle autophagy.[37] The structural effects of SGLT2 inhibition must also be related to changes in both systolic and diastolic blood pressure from reductions in blood volume. From the vast cardiovascular effects seen with SGLT2i; cardiovascular outcomes are currently the most widely studied.

There has been speculation on how SGLT2i are able to provide the vast cardiovascular observed. Aside from reducing blood glucose and blood pressure, there is speculation that SGLT2 inhibitors, specifically empagliflozin, antagonize the Na^+/H^+ exchanger (NHE) 1 in cardiomyocytes and reduce the intracellular concentration of Na^+, thereby reducing excitability and damage from formed ROS.[38-40] However, the activity of NHE-1 activity at physiologic pH (7.2) has negligible activity (<1mmol/min) and would not result in the changes in intracellular Na^+ proposed if there is functional activity of sodium-potassium pumps.[41] A critical aspect of SGLT2i affecting myocardial NHE is that experiments were all conducted in vitro, and this cardiovascular benefit has yet to be demonstrated in live specimens of

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knockout mice. Some SGLT2i have been shown to have a binding affinity to NHE-1, but the full story of SGLT2i affecting cardiac ion handling remains an area of interest.

SGLT2i have been shown to have therapeutic effects aside from their diuretic action. There are likely off-target effects with any treatment, and aside from the proposed inhibition of NHE transporters in the heart, there is substantial evidence that SGLT2i reduces inflammation in myocardial tissue, possibly through the low-affinity inhibition of SGLT1. Aside from shifting from glucose metabolism, there is evidence that SGLT2i reduce the activation of nucleotide binding domain-like receptor protein 3 (NLRP3) in macrophages, dependent on calcium modulation.[42] This is significant as it suggests secondary actions of SGLT2i, acting to blunt worsening cardiac dysfunction by preventing worsening cardiac fibrosis.

MetS is a disease stemming from overstimulation of anabolic pathways increasing energy storage and producing various consequential effects. It seems reasonable that SGLT2i would provide benefits with shifting metabolism to mimic a fasting state that acts on increasing the available energy from adipose stores. Lowering body composition of adipose tissue and reducing blood glucose levels reduces the amount of glucose oxidation associated with oxidative stress. It has also been shown that SGLT2 inhibition can reduce blood pressure and provide a small reduction in serum triglyceride levels. The fasting-like state induced by SGLT2i is an optimal treatment for a disease of overnutrition that encompasses MetS.

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Perspective

SGLT2i may be the standard of care in treating T2D and CVD and would certainly benefit patients with abnormal metabolism defined by excess available energy. It is unforeseeable that any other animal will displace rodents as the primary model in research as they are a well-established, cost-effective method of modeling in research. Especially with the modern advancements in genetic engineering, rodents are certainly going to remain the standard. With the requirement of non-rodent models in pharmaceutical testing, dogs present as a primary animal model for researching pharmacological effects. Research using dogs would be secondary to rodent models and more cost-effective than modeling in primates. Particularly in researching non-congenital diseases, dogs have numerous advantages for preclinical models of drug discovery.

Dogs were believed to be domesticated around 30,000 years ago, and similar environmental factors must play a role in the shared diseases between dogs and humans. With the extensive history of a shared environment, dogs offer various comparisons regarding the similarity of diseases between dogs and humans. Dogs share approximately 80% of their diseases and have a 60% taxonomic and functional overlap of the gut microbiome with humans.[43, 44] Also, a study conducted in private practice veterinary offices found that approximately 34% of dogs are either overweight or obese, reported from a population of over 21,000.[45] These similarities exemplify how dogs represent a great preclinical model of metabolic dysfunction.

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Considering dogs as preclinical models for drug discovery, it is necessary to understand the differences between humans and dogs. There has been extensive research into the pharmacokinetic differences between dogs and humans, which is shown in Martinez, et all. 2021, and many drugs are used for the same indications in both dogs and humans. Specifically, Metformin is indicated for use in treating diabetes in dogs and has been shown to reduce oxidation stress in cardiovascular dysfunction.[46, 47] Alongside therapeutics of diabetes, dogs are used in modeling various cardiovascular conditions and are currently used for research for veterinary treatments of metabolic dysfunction.

Turning back to the case of MetS and SGLT2 inhibitors, dogs are being used to study therapeutics for metabolic dysfunction. There have been studies using dogs as models for SGLT2i already, with significant results showing that canagliflozin reduced atrial remodeling in Beagle dogs.[48] Further research may provide indications in veterinary medicine and a better understanding of SGLT2 inhibitors. At Iowa State University, 10 Beagles were subjected to a high-fat, high-sugar diet intended to mimic a western diet. With this mimetic diet, a baseline of metabolic dysfunction was established in these Beagles. The next step of this research involving inhibition of SGLT2 using dapagliflozin for treatment of metabolic dysfunction is currently pending release.

Conclusion | The principle that SGLT2 is located exclusively in the proximal tubule of the kidneys and is responsible for the majority of glucose reabsorption

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makes it an ideal drug target. With the ability to inhibit SGLT2 activity and induce glycosuria, it is a significant treatment to lower blood sugar. SGLT2i induces cardiovascular benefits; the impact of treatment can not be solely attributed to the slight volume reduction but must result from alternative drug interaction that is currently an area of interest. The reasoning for alternative drug interaction is that cardiovascular

outcomes are different from changes seen in treatment involving diuretics for treating congestive heart failure or a shift from glucose metabolism. SGLT2i have been shown to have many systemic benefits of treatment and would be logical for advanced treatment of metabolic syndrome. Originally a treatment for T2D, SGLT2i have shown pronounced cardiovascular and renal benefits in addition to the intended glycemic control. With ongoing trials, it is likely that SGLT2i are more widely prescribed with their secondary outcomes showing benefits beyond diabetic patients. Although the complete mechanism of how SGLT2i provide such significant cardiovascular benefits is not well understood, this is not halting the expanding trials measuring various outcomes in the cardiovascular, renal, and metabolic effects of SGLT2i. SGLT2 inhibition seems to be a logical solution for treating diseases related to overnutrition and metabolic dysregulation.

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Appendix A: Current indications of SGLT2i

Drug	Indication
Canagliflozin (Invokana®)	• Glycemic control in T2D • Risk of heart failure in type II diabetics • Risk of heart failure in CVD • Reduce the risk of kidney disease, cardiovascular death, and hospitalization in T2D and diabetic nephropathy
Dapagliflozin (Farxiga®)	• Glycemic control in T2D • Risk of heart failure in type II diabetics • Risk of heart failure in CVD • Risk of cardiovascular death and hospitalization in T2D • Risk of cardiovascular death/hospitalization in CVD • Risk of cardiovascular death and hospitalization in adults with HFrEF • Reduce the risk of worsening kidney disease
Empagliflozin (Jardiance®)	• Glycemic control in T2D • Risk of cardiovascular death in T2D • Risk of cardiovascular death in CVD
Ertugliflozin (Steglatro®)	• Glycemic control in T2D

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Appendix B: Select current phase 3 and 4 trials involving SGLT2 inhibitors[49]

Study (ID)	Outcome	Phase
Dapagliflozin		
DELIVER (NCT03619213)	Reduction in CV death or HF events	3
MODA (NCT04707352)	Change in left atrium volume index	3
DAPA-MI (NCT04564742)	Prevention of hospitalization for HF or CV death	3
CARDIA-STIFF (NCT04739215)	Mechanism of CV benefit in T2D with HFpEF	4
DAPA-VOLVO (NCT04869124)	Plasma volume and vascular function	4
ADIDAS (NCT04707261)	Risk reduction and anemia in HF patients	4
ENTRY (NCT04330079)	Heart perfusion reserve in prediabetics	4
* (NCT03782259)	Heart fibrosis and inflammation in T2D	4
Empagliflozin		
EMPA-KIDNEY	Improvement of kidney disease and CV death	3

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(NCT03594110)		
EMPACT-MI (NCT04509674)	CV event post heart attack	3
EMMY (NCT03087773)	Cardiac function and biomarkers of HF	3
EMPA-SNS (NCT03912909)	Inhibition of Sympathetic nervous system activation	3
EMPA-REPAIR (NCT05182658)	Hypertrophic Cardiomyopathy	3
EMPATHYHEART (NCT04117763)	Ventricular repolarization	4
EMPA-HEART 2 (NCT04461041)	Heart remodeling in non-diabetics	4
SAFE-PCI (NCT05037695)	Prevention of post-procedure complications after PCI	4
Canagliflozin		
** (NCT02964585)	Effect on endothelial progenitor cells	3
Ertugliflozin		
ERTU-GLS (NCT03717194)	Cardiac function in T2D	3
ERASE	Impact on ventricular arrhythmias	3

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(NCT04600921)		
VERTICAL (NCT04490681)	Cardiac Fibrosis	3
EFFORT (NCT04231331)	Functional mitral regurgitation	3
EMMED-HF (NCT04071626)	Metabolic mechanism in T2D and HF	4
ERTU-SODIUM (NCT05152940)	Na+ storage, interstitial volume, and plasma volume	4

CV: Cardiovascular, HF: Heart Failure, HFpEF: Heart Failure with preserved Ejection Fraction, SNS: Sympathetic Nervous System, PCI: Percutaneous Coronary Intervention
* Effect of SGLT-2 Inhibition on Myocardial Fibrosis and Inflammation as Assessed by Cardiac MRI in Patients with DM, University of Washington
**Role of Canagliflozin on CD34+ Cells in Patients with Type 2 Diabetes, George Washington University

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