Circulation: Heart Failure

ADVANCES IN HEART FAILURE, MECHANICAL CIRCULATORY SUPPORT AND TRANSPLANT

Use of SGLT2 (Sodium-Glucose Cotransporter 2) Inhibitors in Pulmonary Hypertension

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ABSTRACT: Inhibiting SGLT2 (sodium-glucose cotransporter 2) has recently transformed the medical care of patients with left heart disease. Right ventricular failure is a major predictor for patients suffering from pulmonary hypertension of various causes, including those with postcapillary pulmonary hypertension due to left heart disease. Similar to how SGLT2 inhibition benefits patients with left heart failure, recent studies have suggested utilizing these molecules to enhance right ventricular function in pulmonary hypertension. In this review, we summarize the current knowledge on the use of SGLT2is (SGLT2 inhibitors) in pulmonary hypertension. Further dedicated trials are necessary to establish their role in right ventricular pulmonary vascular disease.

Key Words: blood pressure ■ heart failure ■ heart ventricles ■ hypertension ■ lung

SGLT2is (SGLT2 [sodium-glucose cotransporter 2] inhibitors), acting on SGLT2 proteins, have emerged as a transformative class of medications in cardiometabolic health. Initially approved for glycemic control in type 2 diabetes, large-scale cardiovascular outcome trials such as EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 demonstrated reductions in heart failure (HF) hospitalizations and cardiovascular mortality.[1–3] These findings catalyzed a broader focus on the pleiotropic effects of SGLT2i. The cardiovascular benefits of these molecules in HF with reduced ejection fraction and HF with preserved ejection fraction have been demonstrated[4–7] (Figure 1). These successes prompted researchers to investigate the benefits of SGLT2i for treating right ventricular (RV) dysfunction associated with pulmonary hypertension (PH). There are 5 clinical categories of PH, each with its underlying cause of elevated pulmonary artery pressure: pulmonary arterial hypertension (PAH or group 1), PH due to left heart disease (group 2), PH due to lung diseases and hypoxia (group 3), PH with pulmonary artery obstructions, particularly thromboembolic syndromes (group 4), and PH with undifferentiated or multifactorial causes (group 5).[8]

In PH, increased pulmonary vascular resistance places a chronic pressure overload on the RV, which may induce RV hypertrophy, yet always triggers decompensation, leading to RV failure and death. Therapeutic strategies targeting this pathophysiological cascade, especially those that can enhance vascular compliance, decrease inflammation, and safeguard the RV myocardium, are urgently needed. SGLT2is are currently being investigated as potential candidates in this therapeutic niche. In this review, we summarized the current knowledge on the use of SGLT2i in left HF, as well as their potential perspectives on PH.

SODIUM-GLUCOSE COTRANSPORTER

SGLTs (sodium-glucose cotransporters) are responsible for the active transport of glucose across cell membranes, and in humans, there are a total of 12 SGLTs corresponding to the SLC5 (solute carrier 5)

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Nonstandard Abbreviations and Acronyms

AMPK	AMP-activated protein kinase
CCR2$^+$	C-C chemokine receptor type 2
EMBRACE-HF	Empagliflozin Evaluation by Measuring the Impact on Hemodynamics in Patients With HF
EVENT	Enavogliflozin Outcome Trial in Functional Tricuspid Regurgitation
HF	heart failure
IL-6	interleukin-6
LR	leucine-rich repeat
NHE1	Na^+/h^+ exchanger isoform 1
NLRP3	NLR pyrin domain-containing protein 3
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PAH	pulmonary arterial hypertension
PASMC	pulmonary arterial smooth muscle cell
PH	pulmonary hypertension
PPAR-γ	peroxisome proliferator-activated receptor gamma
RV	right ventricular
SERCA2a	sarcoplasmic reticulum calcium-ATPase isoform 2a
SGLT	sodium-glucose cotransporter
SGLT2	sodium-glucose cotransporter 2
SGLT2i	sodium-glucose cotransporter 2 inhibitor
SLC5	solute carrier 5
TNF-α	tumor necrosis factor-α

family.[9] The SLC5 family includes the high-affinity Na^+-glucose transporter SGLT1 (SLC5A1); the 3 low-affinity isoforms, SGLT2 (SLC5A2), SGLT3 (SLC5A4 and SAAT1), and SGLT4 (SLC5A9); 2 inositol transporters, SMIT1 (SLC5A3) and SGLT6 (SMIT2 and SLC5A11); 1 iodide transporter NIS (SLC5A5); the vitamin transporter SMVT (SLC5A6); a choline transporter CHT1 (SLC5A7); 2 monocarboxylate transporters, SMCT1 (SLC5A8) and SMCT2 (SLC5A12); and the incompletely characterized Na^+ cotransporter SLGT5 (SLC5A10).

Among all SLC5 members, SGLT1 and SGLT2 are the most studied members. SGLT1 is primarily located in the late proximal tubule and the small intestine. SGLT2 has been described as being expressed primarily in the apical membrane of the S1 and S2 segments of the proximal renal tubule. SGLT1 and SGLT2 use energy from the sodium gradient created by Na^+/K^+ ATPase to transport glucose against its concentration gradient.

SGLT2 INHIBITORS

SGLT2is, also named gliflozins or flozins, were initially developed to help control glucose in patients with diabetes by blocking SGLT2 in the proximal convoluted tubule of the kidney, resulting in glucosuria. SGLT2i shows significant pharmacological selectivity to SGLT2 over SGLT1. Sotaglifozin is considered a dual SGLT1/2 inhibitor. However, canagliflozin also shows clinically relevant renal, gastrointestinal, and myocardial SGLT1 inhibition. In contrast, the SGLT2i empagliflozin, dapagliflozin, and ertugliflozin are highly selective for SGLT2. These differences could have profound clinical consequences because SGLT1 is responsible for glucose reabsorption in the gastrointestinal system,[10] and the loss of function of SGLT1 mutations protects against the development of HF.[11] SGLT2i reduces filtered glucose reabsorption, lowers renal threshold for glucose, and promotes urinary glucose excretion.[12] The cardioprotection observed in humans, as well as several experimental models, could be attributed to their diuretic effects, the reduction of blood pressure, anti-inflammatory properties, and metabolic benefits. Most of these cardioprotective effects can be directly attributed to SGLT2/SGLT1 inhibition, but some of them can be due to off-target effects. Experimental evidence in *Sglt2* knockout mice showing a cardioprotective benefit of SGLT2i must lead researchers to consider SGLT2-independent mechanisms.[13] Indeed, gliflozins have several additional targets that could also contribute to their cardioprotective benefits.[14,15]

Although limited evidence exists in PAH, the potential benefits of SGLT2is likely involve hemodynamic, metabolic, and anti-inflammatory mechanisms, which will be explored in the following sections.[16]

PULMONARY HYPERTENSION ASSOCIATED WITH HF

A major limitation of the available clinical studies in HF is the paucity of detailed hemodynamic data obtained by right heart catheterization, which restricts a precise understanding of the mechanisms of action of SGLT2i. Nevertheless, in patients with HF, SGLT2is have been shown to decrease pulmonary arterial pressure. In the EMBRACE-HF trial (Empagliflozin Evaluation by Measuring the Impact on Hemodynamics in Patients With HF), 62 patients with HF and a remote PA pressure monitoring device were randomized to empagliflozin versus placebo for 12 weeks.[17] Both NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels and PA diastolic pressures were significantly improved, suggesting that the effect of empagliflozin was mediated by a reduction of pulmonary arterial wedge pressure. It has, therefore, been suggested that SGLT2i may play a role in the prevention of PH associated with HF[18] (Figure 1).

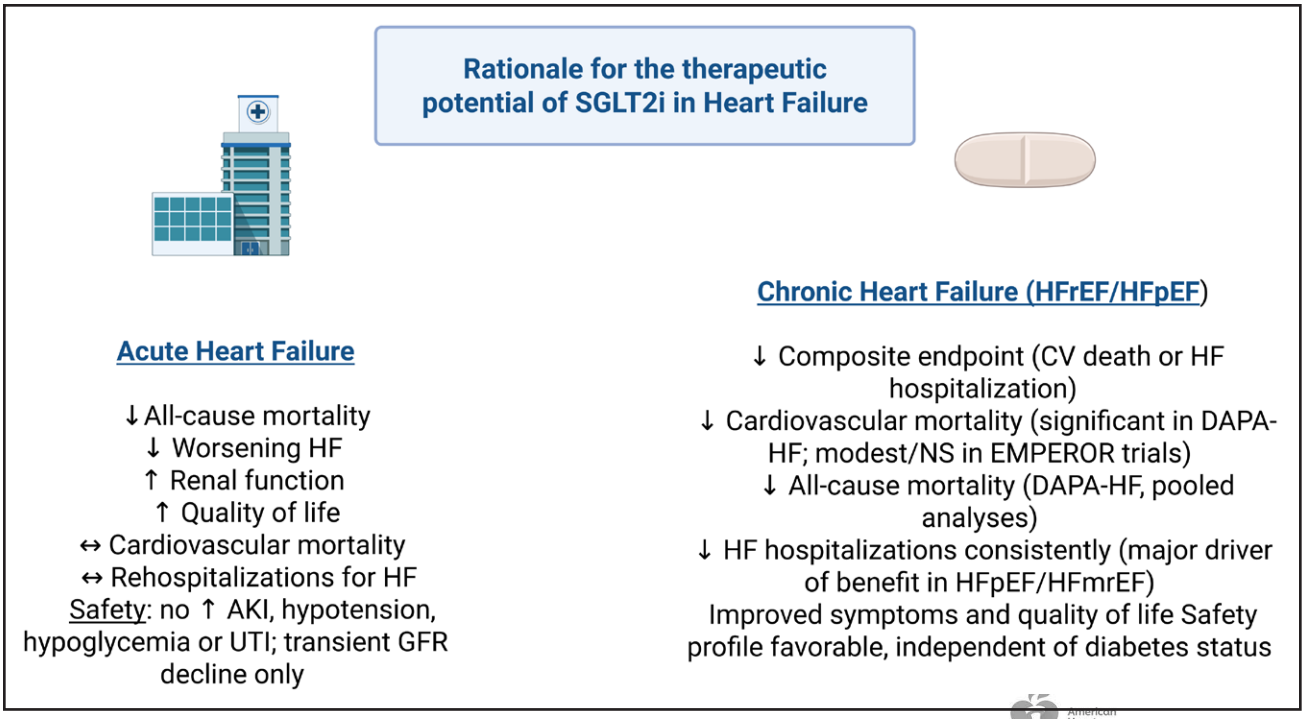

Figure 1. Therapeutic rationale for SGLT2is (sodium-glucose cotransporter 2 inhibitors) in acute vs chronic heart failure (HF). This figure was created using Biorender. AKI indicates acute kidney injury; CV, cardiovascular; GFR, glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and UTI, urinary tract infection.

HEMODYNAMIC AND METABOLIC MECHANISMS OF SGLT2 INHIBITION

Diuretic and Volume-Reducing Effects

SGLT2i promotes glycosuria and natriuresis by blocking glucose and Na^+ reabsorption in the proximal tubules. The osmotic diuresis that follows leads to a reduction in plasma volume and interstitial fluid content. This pharmacological profile is particularly advantageous in patients with HF, where volume overload plays a central role in symptomatology and disease progression. Unlike loop diuretics, which may activate neurohormonal pathways and worsen renal perfusion, SGLT2i achieves a more balanced and sustained volume reduction, potentially contributing to reduced cardiac preload and improved filling pressures in both ventricles.[19–22]

The role of the gut-lung axis in PAH is increasingly recognized. Experimental and clinical data suggest that intestinal barrier dysfunction and subsequent bacterial translocation contribute to pulmonary vascular inflammation and remodeling. In patients with idiopathic and heritable PAH, elevated circulating levels of sCD14 and LPS have been reported, consistent with enhanced macrophage activation and systemic inflammation.[23] Similar findings were reproduced in monocrotaline-induced PH rats, where gut leakiness and bacterial translocation paralleled RV hypertrophy. This gut-lung vicious circle may be amplified by right HF itself because venous congestion and intestinal edema further increase gut permeability and translocation of bacterial products. In this context, SGLT2is, by its diuretic effect and reducing right-sided filling pressures, could help to mitigate systemic and intestinal congestion. Such an effect may not only improve right heart function but also indirectly reduce bacterial translocation and the associated inflammatory drive that fuels pulmonary vascular remodeling.

Reduction of Afterload and Arterial Stiffness

Several studies have noted reductions in systolic blood pressure and arterial stiffness among patients treated with SGLT2i.[24] These agents decrease systemic vascular resistance, which lowers cardiac afterload and may also benefit the pulmonary circuit well.[25] However, in clinical trials, the magnitude of systolic blood pressure reduction has generally been modest, limiting its contribution as the sole explanation for the observed cardiopulmonary benefits.[5]

Metabolic Modulation and Improved Myocardial Efficiency

One of the most intriguing benefits of SGLT2i lies in its ability to reprogram myocardial energetics. By increasing circulating ketone bodies and promoting a shift toward ketone metabolism, SGLT2i provides the myocardium

with a more oxygen-efficient fuel source. This is particularly significant in failing hearts, where oxidative phosphorylation is impaired. The RV is particularly sensitive to changes in the balance between oxygen supply and demand due to its thin wall and lower coronary perfusion.

These metabolic advantages may, therefore, contribute significantly to preserved contractile function.[26–28]

Water Conservation and Hemodynamic Stability

Marton et al[22] highlighted an important nuance in SGLT2 physiology: although these agents induce osmotic diuresis, they also seem to promote water conservation by increasing urea reabsorption. This mechanism may help maintain blood pressure and renal perfusion, mitigating the risk of hypotension often observed with traditional diuretics. The preservation of intravascular volume, alongside natriuresis, creates a unique hemodynamic profile that supports both systemic and pulmonary circulatory balance.

SGLT2 INHIBITION AND THE SYMPATHETIC NERVOUS SYSTEM

In addition to their well-characterized hemodynamic and metabolic effects, SGLT2i exert significant sympathoinhibitory actions that are increasingly recognized as a key mechanism contributing to their cardiorenal benefits. Recent studies have shown that SGLT2 expression is upregulated under conditions of enhanced sympathetic nervous system activation, as observed in HF, hypertension, and chronic kidney disease models[29–31]

In the case of PH, where sympathetic may participate in pulmonary vascular remodeling, RV dysfunction, and increased arrhythmogenic risk,[32,33] the modulation of sympathetic nervous system activity by SGLT2i could serve as a significant therapeutic option.

ANTI-INFLAMMATORY AND ANTIOXIDANT EFFECTS OF SGLT2IS

Chronic inflammation and oxidative stress are central features of pulmonary vascular remodeling and RV dysfunction in PH.[34] In this context, the pleiotropic anti-inflammatory properties of SGLT2i are becoming increasingly acknowledged as an essential aspect of their cardioprotective profile. At the cellular level, these inhibitors block the activation of the NOD (nucleotide-binding oligomerization domain), LRRs (leucine-rich repeats), and NLRP3 (NLR pyrin domain-containing protein 3) inflammasome, which is essential for innate immune responses linked to cardiac fibrosis and endothelial damage.[35] In a high-fat diet animal model, Joki et al[36] demonstrated that tofogliflozin significantly reduces serum levels of inflammatory cytokines, including TNF-α (tumor necrosis factor-α) and IL-6 (interleukin-6), both of which are known to contribute to vascular dysfunction through smooth muscle cell proliferation and endothelial cell apoptosis. This effect has been noted in both cardiac and vascular tissues, demonstrating that SGLT2i not only reduces systemic inflammation but also exerts localized anti-inflammatory effects within the pulmonary vasculature.[37] In models of monocrotaline-induced PH, dapagliflozin administration decreases vascular wall inflammation and fibrotic remodeling. Histological analysis revealed fewer perivascular inflammatory infiltrates and reduced collagen deposition in treated animals.[38] These results support the notion that SGLT2i directly modulates inflammatory cascades implicated in the pathogenesis of pulmonary vascular disease.

From an oxidative stress perspective, SGLT2 inhibition improves mitochondrial function, enhances the antioxidant defense system, and reduces reactive oxygen species generation.[39] These effects have been linked to improved myocardial efficiency and preserved RV systolic function under stress conditions.[40]

Overall, the anti-inflammatory and antioxidant actions of SGLT2i are likely to contribute significantly to their observed benefits in PH and RV dysfunction. These effects may complement their hemodynamic benefits, reinforcing the rationale for their use in right heart-pulmonary vascular diseases.

SGLT2IS AND PULMONARY VASCULAR REMODELING IN PH

Pulmonary vascular remodeling is a hallmark of PH, and it is characterized by a combination of endothelial dysfunction, intimal thickening, medial hypertrophy and excessive proliferation of pulmonary arterial smooth muscle cells (PASMCs), and adventitial fibrosis, all contributing to vascular remodeling.[8] These histopathologic changes result in increased pulmonary vascular resistance and RV afterload.[41] In patients with PH, RV function is the primary determinant of PH severity and the most important predictor of clinical outcome.[42] Recent data suggest that SGLT2i may exert protective effects against these processes by directly modulating PASMC proliferation and promoting endothelial homeostasis.

In a model of hypobaric hypoxia-induced PH, Tang et al[43] demonstrated that canagliflozin significantly reduced pulmonary artery wall thickness and improved right heart hemodynamics. These findings were mechanistically linked to the inhibition of PASMC proliferation and downregulation of proliferative signaling pathways.[43]

Chen et al[44] further clarified the intracellular signaling mechanisms, revealing that canagliflozin modulates the SGLT1/AMPK axis. Activation of AMPK (AMP-activated protein kinase), a cellular energy sensor, was shown to reduce mTOR (mammalian target of rapamycin) signaling and PASMC proliferation in monocrotaline-induced

PH models. This supports a broader role for SGLT2i in controlling metabolic dysregulation and hyperproliferative states within the pulmonary vasculature. Complementary findings showed that empagliflozin activates the PPAR-γ (peroxisome proliferator-activated receptor gamma), which is known to inhibit PASMC proliferation and promote apoptosis in PH.[45] The activation of PPAR-γ by SGLT2i may contribute to the normalization of pulmonary artery structure and function.

In the context of left heart disease, Joki et al[36] reported that tofogliflozin ameliorates pulmonary vascular remodeling secondary to elevated left atrial pressure in a murine model. This suggests that SGLT2i could also be effective in group 2 PH, where backward transmission of pressure leads to secondary vascular changes. Histological studies from experimental models consistently demonstrate reduced medial wall thickness, decreased muscularization of distal pulmonary arterioles, and attenuated lung perivascular fibrosis in tofogliflozin-treated animals. These structural improvements are accompanied by functional benefits, such as reductions in RV systolic pressure and enhanced RV-arterial coupling[25,38]

Together, these data indicate that SGLT2i exerts multifactorial effects on the pulmonary vasculature through metabolic reprogramming, antiproliferative signaling, and antifibrotic action (Figure 2), ultimately reducing pulmonary vascular resistance and alleviating RV strain.

RIGHT ATRIAL AND VENTRICULAR ADAPTATIONS IN PH: STRUCTURAL AND FUNCTIONAL BENEFITS OF SGLT2IS

The RV plays a critical role in the prognosis of patients with PH, yet it has historically been underappreciated in clinical trials and pharmacological research. Under normal conditions, the RV is a thin-walled, compliant chamber adapted to a low-resistance pulmonary circuit. In the setting of increased afterload, such as in PH, the RV undergoes adaptive hypertrophy to maintain stroke volume. However, prolonged pressure overload leads to

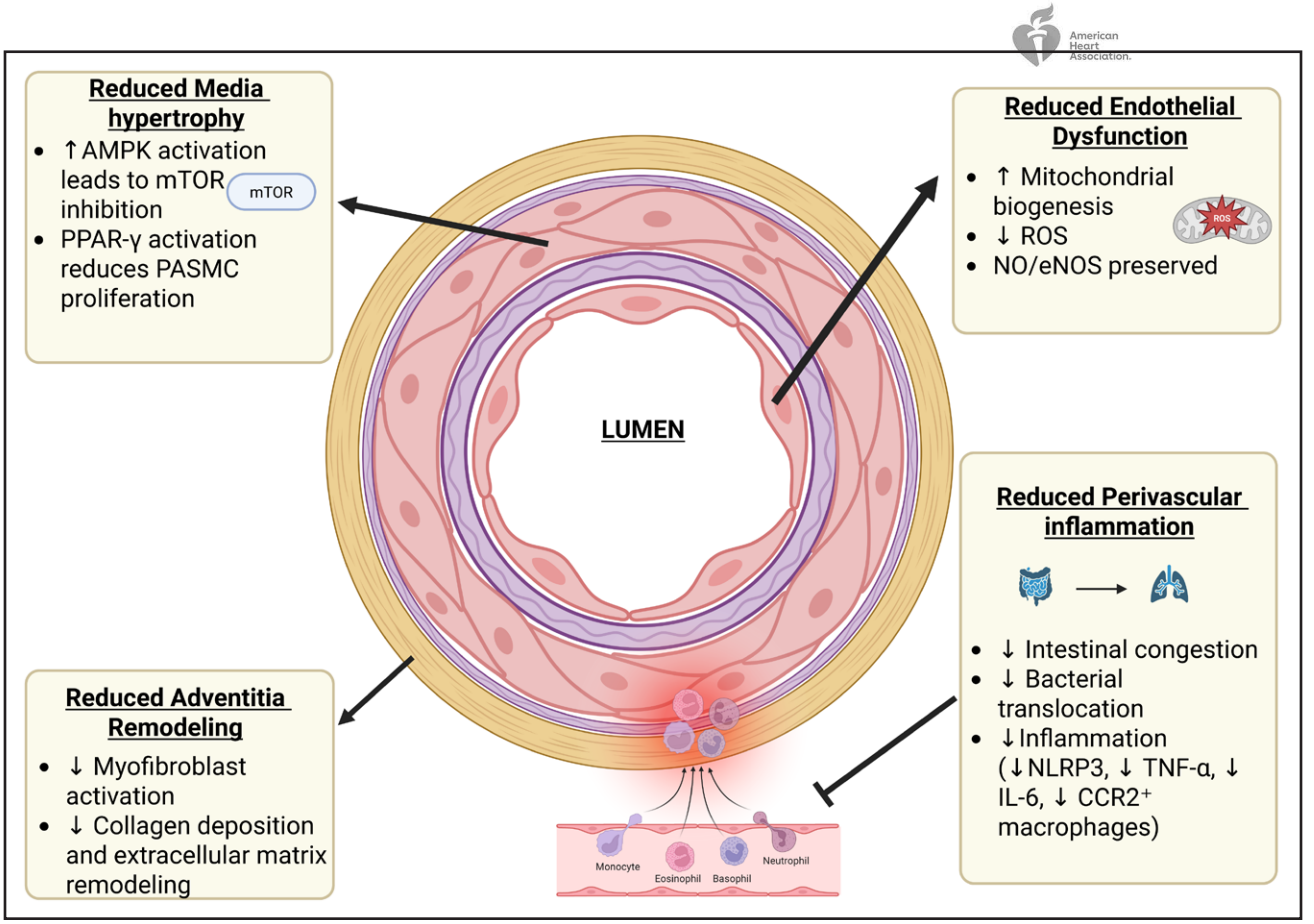

Figure 2. Proposed mechanisms of SGLT2i (sodium-glucose cotransporter 2 inhibitor) effects on pulmonary vascular remodeling. SGLT2i modulate endothelial, medial, and adventitial layers through metabolic, anti-inflammatory, and antifibrotic effects. They improve mitochondrial biogenesis and NO signaling, inhibit smooth muscle cell proliferation via AMPK (AMP-activated protein kinase)-mTOR (mammalian target of rapamycin) and PPAR-γ (peroxisome proliferator-activated receptor gamma) pathways, and reduce collagen deposition and perivascular inflammation, also mitigating gut-lung axis activation. This figure was created using Biorender. CCR2+ indicates C-C chemokine receptor type 2; eNOS, endothelial nitric oxide synthase; IL-6, interleukin-6; NLRP3, NOD-like receptor family pyrin domain-containing protein 3; PASMC, pulmonary artery smooth muscle cell; ROS, reactive oxygen species; and TNF-α, tumor necrosis factor alpha.

maladaptive remodeling, including fibrosis, capillary rarefaction, mitochondrial dysfunction, and, ultimately, RV failure.[46]

In addition to their impact on RV remodeling, accumulating evidence suggests that SGLT2is may exert beneficial effects on atrial electrophysiology and arrhythmogenesis. Preclinical studies have shown that dapagliflozin reduced the susceptibility to atrial fibrillation in the monocrotaline-induced PH model, an effect associated with improved mitochondrial ultrastructure, attenuation of oxidative stress, and normalization of calcium handling, all of which are critical for the maintenance of atrial electrical stability.[38,47] Beyond the PH setting, experimental data in diabetic and pressure-overload models similarly indicate that SGLT2 inhibition decreases atrial fibrosis, reduces atrial enlargement, and improves connexin expression and gap junction integrity, thereby lowering the arrhythmogenic substrate.[48] These findings are consistent with clinical observations from HF trials, where SGLT2i therapy was associated with a reduced incidence of new-onset atrial fibrillation or atrial flutter.[5] Together, these data support the concept that SGLT2i may confer a dual benefit in right heart disease not only by preserving RV structure and function but also by modulating atrial remodeling and susceptibility to atrial fibrillation, a common and morbid complication in PH.

There is still a lack of randomized controlled trial data specifically addressing outcomes such as tricuspid regurgitation burden, RV end-diastolic pressure, and atrial function. We think that this represents a clear unmet need and a call to arms for the design of prospective randomized studies dedicated to right-sided heart outcomes. Of note, the ongoing EVENT (Enavogliflozin Outcome Trial in Functional Tricuspid Regurgitation; Unique identifier: NCT06027307) will provide valuable insights into whether SGLT2 inhibition can improve both clinical and echocardiographic outcomes in patients with functional tricuspid regurgitation.

Additional preclinical results demonstrated that SGLT2 inhibition in rats with RV failure restored calcium cycling proteins such as SERCA2a (sarcoplasmic reticulum calcium-ATPase isoform 2a) and phospholamban, thereby reducing the incidence of ventricular arrhythmias.[49] These molecular changes were accompanied by better systolic function and preserved RV architecture.

In a study by Connelly et al,[50] treatment with the SGLT2i dapagliflozin in a rat model of RV pressure overload resulted in the normalization of SERCA2a protein expression, suggesting that SGLT2 inhibition can restore impaired calcium handling in the RV heart. Dapagliflozin reduced cardiomyocyte hypertrophy, interstitial fibrosis, and capillary rarefaction within the RV myocardium. The effects are thought to result from lower oxidative stress, anti-inflammatory signals, and improved heart energy under low oxygen and high pressure.[44,51,52]

Clinical trials have begun to reflect these experimental insights. In a secondary analysis of the PRESERVED-HF trial, Reddy et al[53] showed that patients treated with dapagliflozin experienced improved RV-pulmonary artery coupling, a key determinant of exercise capacity and prognosis in PH. Similarly, Kirschbaum et al[54] observed reductions in pulmonary artery pressures and improved right heart congestion markers in patients with chronic HF treated with empagliflozin, measured via remote pressure monitoring.

These data suggest that SGLT2i targets multiple pathophysiological processes in the RV, including myocardial hypertrophy, fibrosis, energy metabolism, and electrophysiological stability (Figure 3). Their ability to influence both structure and function makes them promising agents in the management of RV dysfunction in various PH phenotypes.

Building on these findings, a recent study by Yoshida et al[55] explored the specific role of SGLT2 inhibition in pulmonary vascular remodeling and RV dysfunction in PAH. Using both in vitro and in vivo models, the authors demonstrated that the SGLT2 expression is upregulated in pulmonary endothelial cells from patients with PAH, and the empagliflozin treatment restores mitochondrial biogenesis, reduces oxidative stress, and attenuates pulmonary endothelial cell hyperproliferation. In the severe sugen/hypoxia model of PAH, empagliflozin significantly reduced pulmonary vascular resistance, pulmonary vascular remodeling, and RV hypertrophy while preserving RV function. These preclinical data suggest that beyond systemic hemodynamic effects, SGLT2i exerts direct pulmonary vascular and myocardial protective actions. However, the accompanying phase IIa EMPHOWER trial in patients with idiopathic and heritable PAH yielded more cautious results, with empagliflozin being well tolerated but associated with a slight deterioration of RV function as assessed by cardiac magnetic resonance imaging.[55] These findings highlight the complexity of translating preclinical SGLT2i benefits into human PAH and underline the need for further mechanistic and clinical investigations.

CONFLICTING EVIDENCE AND LIMITATIONS

Despite the promising evidence outlined above, not all studies report the beneficial effects of SGLT2i in PH or RV dysfunction. These conflicting findings highlight the complexity of disease modeling and suggest that therapeutic responses may depend heavily on experimental design, disease stage, and specific PH cause.

A notable study by Li et al[56] investigated the effect of dapagliflozin in 2 distinct rat models of PH: monocrotaline-induced and pulmonary trunk banding. In

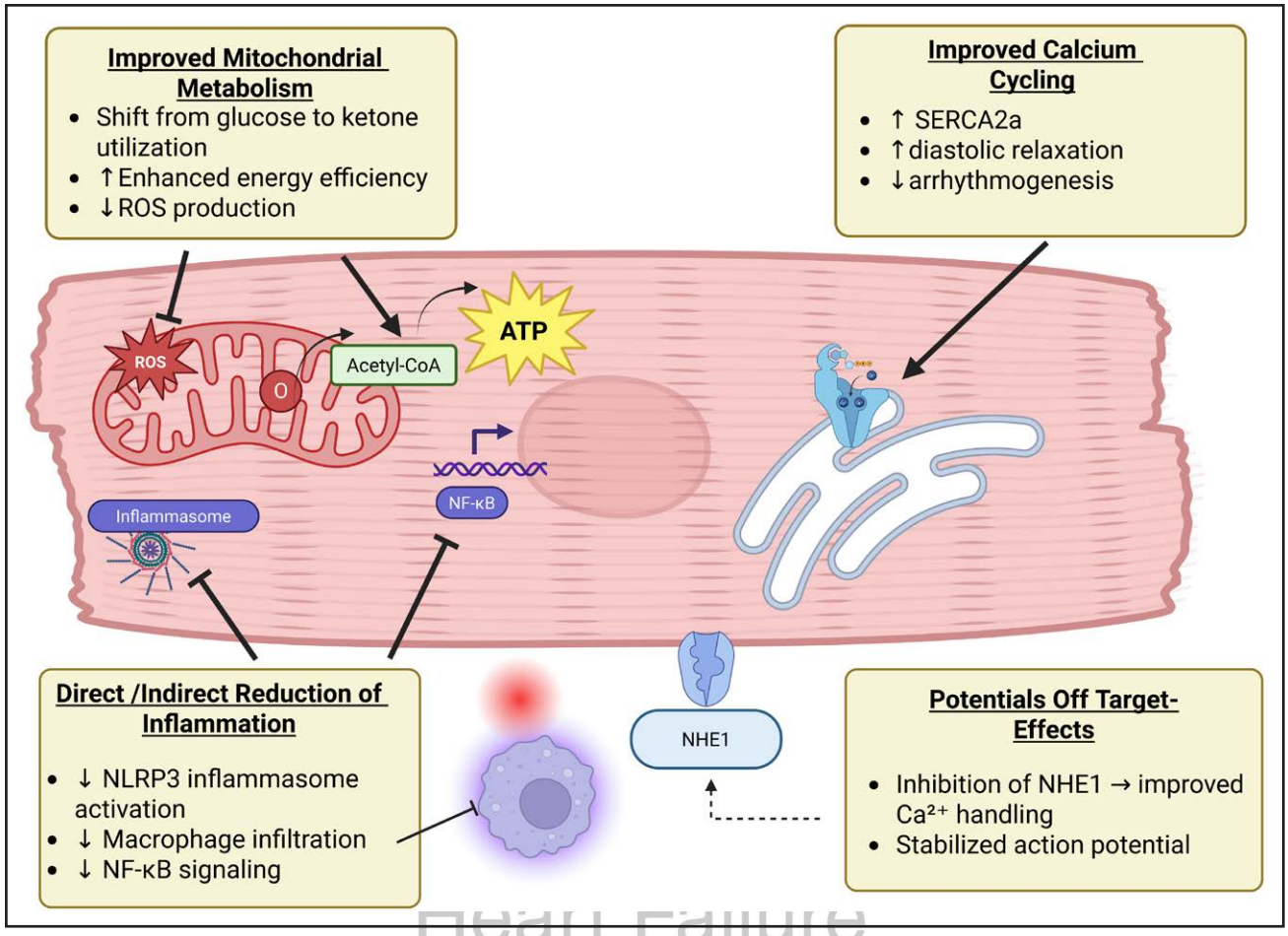

Figure 3. Proposed cellular mechanisms of SGLT2i (sodium-glucose cotransporter 2 inhibitor) in cardiomyocytes.
This figure was created using Biorender. SGLT2is modulate ionic homeostasis, energy metabolism, and stress signaling pathways in cardiomyocytes. Through indirect inhibition of NHE1 (Na^+/h^+ exchanger isoform 1), activation of AMPK (AMP-activated protein kinase) and PPAR-γ (peroxisome proliferator-activated receptor gamma), and improved mitochondrial efficiency, they reduce oxidative stress, fibrosis, and Ca^{2+} overload, thereby enhancing right ventricular contractility and diastolic relaxation in pulmonary hypertension. Acetyl-CoA indicates acetyl coenzyme A; Ca^{2+}, calcium ion; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain-containing protein 3; ROS, reactive oxygen species; and SERCA2a, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase isoform 2a.

both models, the authors found that dapagliflozin failed to improve pulmonary hemodynamics, vascular remodeling, or RV function. These findings contrast sharply with the positive outcomes reported in other monocrotaline studies and suggest that the timing of treatment initiation, dosage, and duration may critically influence outcomes. In addition, it remains unclear whether the lack of benefit in pulmonary trunk banding, a purely pressure-overload model, reflects a limitation of SGLT2i in settings of fixed mechanical obstruction.

Further complicating the interpretation of preclinical data is the heterogeneity among animal models. While the monocrotaline model is widely used, it has limitations in replicating the multifactorial pathophysiology of human PH. For example, monocrotaline induces inflammation and endothelial injury but does not fully recapitulate the vascular lesions seen in human PAH. Similarly, hypoxia-induced models often lack the degree of RV failure observed in more advanced diseases. As such, the generalizability of findings from these models to human disease remains an open question.

Another consideration is species-specific differences in drug metabolism and cardiovascular physiology. Rodents, for instance, exhibit higher heart rates, lower vascular resistance, and different patterns of cardiac remodeling compared with humans.[57–59] These differences may contribute to inconsistent findings across studies and necessitate cautious extrapolation of animal data to clinical settings.

In clinical trials, subgroup analyses have occasionally failed to demonstrate significant improvements in right-sided parameters. While large trials such as DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved consistently show reduced hospitalizations and mortality,[4,5] detailed RV-specific metrics were often not reported or evaluated systematically. This gap underscores the need for dedicated clinical trials focusing explicitly on RV outcomes and PH subgroups. Therefore, while the

mechanistic rationale for SGLT2 inhibition in PH and RV dysfunction remains strong, the field must reconcile conflicting findings through more refined experimental designs, standardized disease models, and RV-focused clinical end points.

Preclinical studies exploring the effects of SGLT2is in PH and RV dysfunction are markedly heterogeneous, which likely contributes to the variability of results reported. This heterogeneity arises from several factors, including the different molecules studied (empagliflozin, dapagliflozin, canagliflozin, and so on), variability in dosing regimens, and differences in routes of administration (oral gavage versus delivery in drinking water).

At present, it remains difficult to determine whether SGLT2is should be envisioned primarily as rescue therapies in established maladaptive RV remodeling or as agents for long-term management of chronic RV failure. Most experimental studies have been conducted in a preventive setting, rather than in curative strategies or at advanced maladaptive stages of RV dysfunction. This limits the translational insight into how these drugs might perform in patients with overt right HF. One promising avenue for chronic therapeutic implications relates to their potential antifibrotic effects. RNA-sequencing analyses have identified SGLT2 expression in cardiac fibroblasts, suggesting that direct modulation of fibroblast biology could contribute to attenuation of pathological fibrosis over time.[60] The increase in hematocrit observed with SGLT2is was first described in large pivotal trials, notably EMPA-REG, where it appeared as a mean rise of 2% to 4%. At that time, it was mainly interpreted as a simple hemoconcentration related to osmotic diuresis and was considered a potential mediator of cardiovascular benefit rather than an adverse effect.[1] Subsequent mechanistic studies have shown that this explanation was incomplete. Kinetic analyses revealed that diuresis normalizes rapidly, whereas hematocrit continues to rise for several weeks. A proposed mechanism involves the reduction of metabolic stress and cortical renal hypoxia caused by SGLT2 inhibition, which enables the redifferentiation of fibroblasts that had transformed into myofibroblasts back into erythropoietin-producing cells. Restoration of endogenous erythropoietin production would, thus, account for the sustained stimulation of erythropoiesis and the increase in hemoglobin and hematocrit.[61] A large Korean cohort study published in 2025 quantified this phenomenon in real-world practice: among 6787 patients exposed to SGLT2is, 16.9% developed erythrocytosis according to WHO thresholds, with a median hemoglobin increase of 1 g/dL and a median time to peak of about 7 months. Risk factors identified included male sex, obesity, and smoking. Thromboembolic events were rare (0.5%) and most often related to preexisting cardiovascular comorbidities rather than directly to SGLT2i-induced erythrocytosis.[62] Rare cases of marked, symptomatic polycythemia do occur, particularly in patients with comorbidities.[63] This evolving body of evidence supports regular monitoring of hemoglobin and hematocrit, with heightened vigilance in patients with thrombotic risk factors or concomitant use of other erythropoietic agents. This evolving body of evidence supports regular monitoring of hemoglobin and hematocrit, with heightened vigilance in patients with thrombotic risk factors and particularly in those receiving concomitant sotatercept, given its additional erythropoietic effect.[64]

SYNERGISTIC PATHWAYS AND COMBINED THERAPIES IN PAH

Beyond their standalone effects, SGLT2i may provide enhanced therapeutic efficacy when combined with other pharmacological agents that target different facets of pulmonary vascular disease. Combination therapy is a cornerstone in the management of PAH, where endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs are commonly coadministered. In this context, SGLT2i has shown potential as an adjunctive treatment, working synergistically with established agents.[65]

Tang et al[66] explored the combined use of dapagliflozin and sildenafil in a monocrotaline-induced PH model. However, their findings revealed conflicting results regarding potential synergy: while each agent individually improved RV systolic pressure and attenuated pulmonary vascular remodeling, their combination did not lead to additive benefits, suggesting that synergistic effects may be limited or context-dependent in PH models.

Furthermore, synergistic benefits have been proposed in the context of HF with pulmonary congestion. For instance, SGLT2i may augment the decongestive and hemodynamic actions of loop diuretics without the adverse neurohormonal activation associated with high-dose diuretic therapy. Mullens et al[67] reported that dapagliflozin significantly reduced pulmonary artery pressures in patients with HF monitored via implantable devices, supporting a potential additive role in volume management.

These data underscore the potential value of integrating SGLT2i into existing therapeutic regimens for PH and RV failure. However, clinical trials explicitly designed to test such combinations remain limited, and further research is required to identify the most effective and safe therapeutic pairings.

GENETIC AND MOLECULAR INSIGHTS IN PH

The beneficial effects of SGLT2i in PH and RV dysfunction extend into the molecular and genetic domains, suggesting that these drugs may modulate core pathways implicated in disease pathogenesis. Notably, recent

studies have uncovered molecular interactions between SGLT2 inhibition and key signaling cascades involved in cell proliferation, inflammation, and metabolism.

Lai et al[45] demonstrated that empagliflozin activates the PPAR-γ in pulmonary vascular tissue. PPAR-γ is a nuclear receptor known to exert antiproliferative and antifibrotic effects on PASMCs, as well as to promote endothelial function. Activation of this pathway by empagliflozin led to reduced medial hypertrophy and attenuated vascular remodeling in experimental models of PH, suggesting a transcriptional basis for some of the observed vascular benefits.

Additional insights have been offered by Marfella et al,[52] who showed that SGLT2 is expressed in both diabetic and nondiabetic failing human cardiomyocytes, indicating a broader relevance of SGLT2 pathways in myocardial pathology. Their work suggests that SGLT2 inhibition may influence gene expression related to calcium handling, oxidative stress regulation, and mitochondrial metabolism, all critical for RV performance under pressure overload.

Furthermore, Qu et al[68] emphasized the importance of focusing on the forgotten RV in cardiovascular research. Their analysis revealed that SGLT2i can preserve the expression of genes associated with mitochondrial biogenesis and contractile integrity in RV cardiomyocytes subjected to stress. These findings support a paradigm shift in which RV-specific molecular adaptations are considered integral to evaluating therapeutic efficacy.

Taken together, these data suggest that the benefits of SGLT2 inhibition extend beyond systemic hemodynamics and local anti-inflammatory effects. By modulating genetic and molecular pathways, SGLT2i may offer disease-modifying potential in PH and RV failure, a hypothesis warranting further investigation in translational and clinical studies.

SUMMARY AND MECHANISTIC OVERVIEW

The expression of SGLT2, primarily localized in the renal proximal tubule, has recently become a subject of debate regarding its presence and potential role in myocardial tissue (Figure 4). This question is fundamental in light of the cardioprotective effects demonstrated by SGLT2i. These benefits have raised the hypothesis of a direct expression, and possibly function, of SGLT2 in the heart. Some studies support this hypothesis. Marfella et al[52] reported significant expression of SGLT2 in human cardiomyocytes from patients with diabetes compared with nondiabetic controls, with overexpression induced by high glucose concentrations. Similarly, an experimental study in a porcine model of myocardial infarction showed transient induction of SGLT2 in ischemic cardiac tissue.[69] More recently, it has been demonstrated that SGLT2 cardiac expression may be upregulated under pathological conditions such as HF, reinforcing the idea of an adaptive regulation of the transporter under cellular stress.[70] Recent work has further highlighted the dynamic regulation of both SGLT1 and SGLT2 expression in the vascular endothelium, particularly within the coronary arteries, the aorta, and regions exposed to disturbed flow. While their expression is minimal under physiological conditions, it is significantly upregulated in response to stimuli such as angiotensin II, circulating microparticles derived from patients with coronary artery disease, and inflammatory cytokines, including IL-1β, IL-6, and TNF-α.[71]

In the lungs, although SGLT2 is not constitutively expressed in endothelial cells, it can be induced during systemic inflammatory states, such as in COVID-19, which contributes to endothelial senescence and thrombosis.[70,72] In support of this concept, the study by Mroueh et al[70] demonstrated a marked overexpression of SGLT2 in human cardiovascular tissues, particularly in the left ventricle and internal thoracic artery, in response to low-grade inflammation. SGLT2 expression was correlated with endothelial activation, oxidative stress, and senescence markers and, inversely, with eNOS levels. In vitro, proinflammatory cytokines induced SGLT2 upregulation, which was attenuated by SGLT2i, suggesting a causal role.[70]

However, these findings are contradicted by numerous studies using high-resolution transcriptomic techniques. A recent single-cell RNA-seq analysis[1] found no expression of the *SLC5A2* gene (encoding SGLT2) in human myocardial cells, whether in healthy or diseased hearts, suggesting that the cardiovascular effects of SGLT2i are unlikely to result from direct cardiac action. Moreover, several experimental studies, including animal models, confirm the absence or low expression of SGLT2 in the myocardium while highlighting the predominant role of SGLT1, a related transporter more ubiquitously expressed in the heart.[73–75] Berger et al[13] demonstrated, in a murine model of HF with reduced ejection fraction, that the beneficial effects of empagliflozin are independent of SGLT2 expression, which is absent in the heart. Although both pharmacological inhibition and genetic deletion of SGLT2 induce similar metabolic effects (glucosuria, increased ketogenesis, and enhanced lipolysis), only empagliflozin improves cardiac function and reduces pathological remodeling. These benefits are maintained in *Sglt2* knockout mice, confirming an off-target mechanism of action.[13] Altogether, current data indicate that SGLT2 expression in cardiac tissue is, at best, minimal and highly conditional. The observed benefits of SGLT2i are, therefore, more likely to stem from indirect mechanisms such as reduced sodium and fluid overload, improved myocardial metabolism, or effects on ion transporters rather than direct SGLT2 inhibition in the heart.

Thus, many cardiovascular benefits of SGLT2i likely arise from off-target effects, including the inhibition of the NHE1 (Na^+/h^+ exchanger isoform 1) in the myocardium.

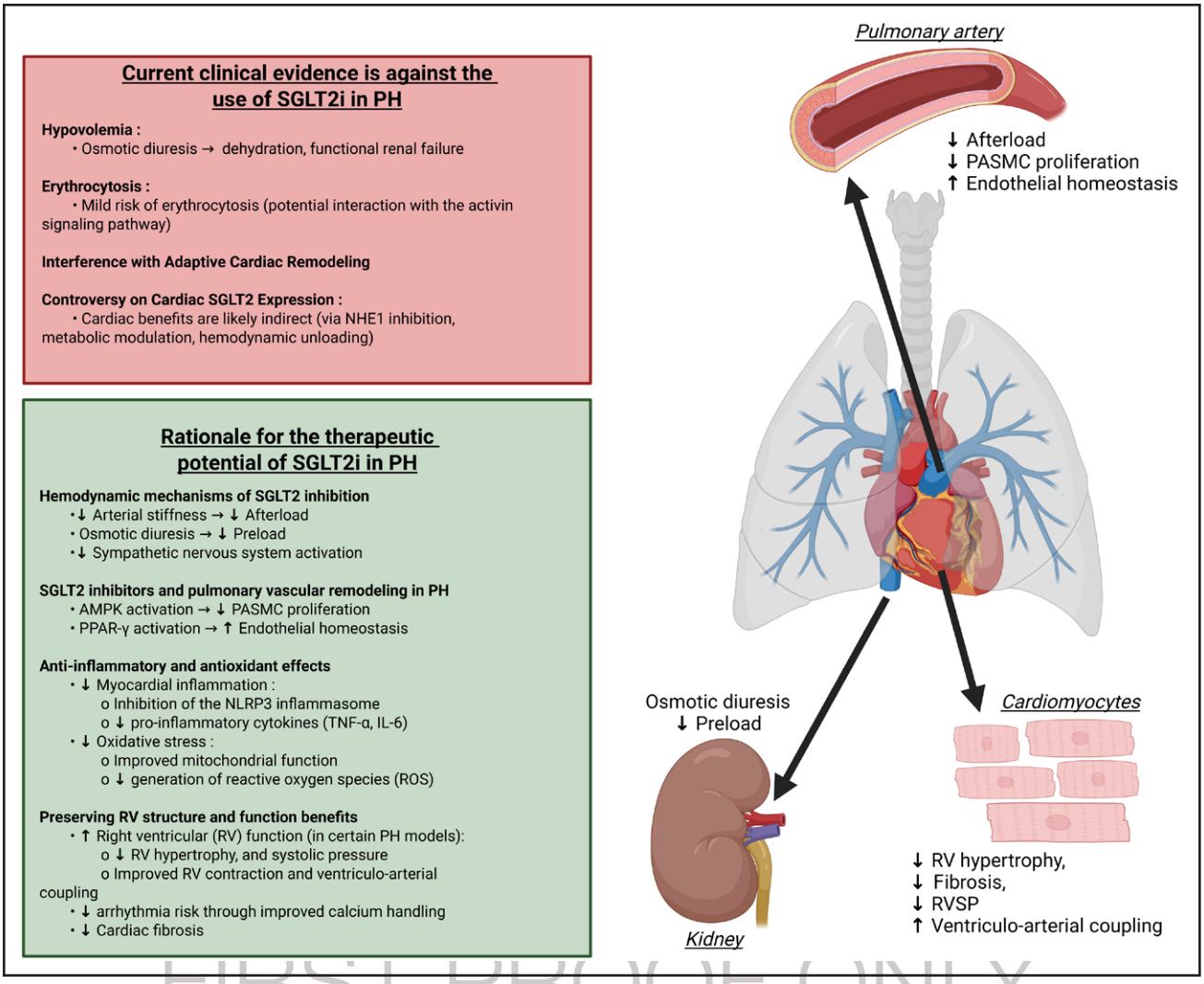

Figure 4. Potential effects of SGLT2 (sodium-glucose cotransporter 2) inhibitors in pulmonary hypertension based on theoretical/experimental data.

This figure was created using Biorender. AMPK indicates AMP-activated protein kinase; IL-6, interleukin-6; NHE1, sodium-hydrogen antiporter 1; NLRP3, NOD-like receptor family, pyrin domain-containing 3; PASMC, pulmonary artery smooth muscle cell; PPAR-γ, peroxisome proliferator-activated receptor gamma; RV, right ventricle; RVSP, right ventricular systolic pressure; and TNF-α, tumor necrosis factor α.

Inhibiting NHE1 has been shown to reduce intracellular sodium and calcium overload, improve mitochondrial function, and attenuate oxidative stress, especially under pressure overload.[76,77] These indirect effects may underlie many of the observed benefits in the RV and pulmonary vasculature.[27,51]

Given the growing evidence that the cardiovascular benefits of SGLT2i may stem from off-target actions, particularly the inhibition of the myocardial NHE1, a logical next step in therapeutic exploration would be the direct investigation of NHE1 inhibitors in PH. Specific NHE1 blockade could offer a more targeted modulation of intracellular sodium and calcium handling, mitochondrial function, and oxidative stress responses, particularly within RV cardiomyocytes. Considering that SGLT2 is not significantly expressed in the heart yet produces consistent RV benefits, further studies comparing SGLT2i to direct NHE1 inhibitors in both animal models and clinical settings may yield critical insights into their shared and distinct mechanisms of action (Table 1). Interestingly, some preclinical studies have already investigated NHE1 inhibitors in left ventricular failure and ischemia-reperfusion injury,[78,79] but their role in PH and RV dysfunction remains underexplored.

Recent studies using rimeporide, a selective NHE1 inhibitor, have shown promising results: in a sugen/hypoxia rat model, it significantly ameliorated RV dysfunction and reduced pulmonary pressures.[80,81] Such studies could ultimately help to isolate the precise molecular pathways responsible for RV improvement. They could also lead to the development of highly specific treatments for pulmonary vascular disease.

SGLT2i has transitioned from glucose-lowering agents to cornerstone therapies in cardiometabolic disease.

Table 1. Summary of Studies Supporting or Refuting Cardiac SGLT2 Expression

Study	Methodology	Findings	Conclusion
Marfella et al (2022)[52]	Immunohistochemistry on human cardiomyocytes	SGLT2 expression detected in diabetic cardiomyocytes	Supports cardiac SGLT2 expression
Harris et al (2024)[69]	Postischemic analysis in a porcine model	Transient SGLT2 upregulation in ischemic heart tissue	Supports (in acute pathological state)
Rolski and Mączewski (2025)[16]	Experimental and clinical synthesis	Increased expression in heart failure	Supports (conditionally expressed)
Mroueh et al (2024)[70]	Human tissue analysis+in vitro cytokine stimulation	SGLT2 overexpression in the left ventricle and vessels under inflammation	Supports (inflammatory regulation)
Mourad et al (2025)[60]	Single-cell transcriptomics	No SGLT2 expression in human cardiomyocytes	Against cardiac SGLT2 expression
Sayour et al (2020)[73]	RT-qPCR on human left myocardium	No SGLT2 mRNA in the left myocardium	Against
Di Franco et al (2017)[74]	Review of human and animal models	SGLT2 has no expression of the protein; SGLT1 is predominant.	Against

RT-qPCR indicates reverse-transcription quantitative polymerase chain reaction; SGLT1, sodium-glucose cotransporter 1; and SGLT2, sodium-glucose cotransporter 2.

Their pleiotropic effects extend beyond glycemic control, encompassing cardiovascular, renal, and potentially pulmonary vascular benefits. This review has examined the expanding body of evidence supporting their role in PH and RV dysfunction.

SGLT2i demonstrates significant hemodynamic effects by reducing preload through osmotic diuresis and decreasing afterload via improved arterial compliance. Metabolically, they shift myocardial substrate utilization toward ketone bodies, enhancing oxygen efficiency.[27] These adaptations are particularly beneficial to the RV, which is more sensitive to changes in pressure and volume loading. Anti-inflammatory and antioxidant effects, mediated through NLRP3 inflammasome suppression and oxidative stress reduction, further support myocardial and vascular health.[49,82] In addition, the inhibition of PASMC proliferation, likely via AMPK and PPAR-γ pathways, suggests a direct impact on pulmonary vascular remodeling[44,45] (Table 2). The study by Wu et al[83] shows that dapagliflozin protects against HF by inhibiting macrophage-driven inflammation independently of SGLT2. By targeting CCR2+ (C-C chemokine receptor type 2) macrophages, cardiac fibrosis is reduced through immunomodulation.[83] These mechanisms collectively contribute to improved RV-pulmonary arterial coupling, reduced RV hypertrophy, and better overall cardiopulmonary function in experimental models and select clinical populations.

CONCLUSIONS

SGLT2i has rapidly evolved from antidiabetic agents into modulators of cardiopulmonary health. Their ability to improve RV function and reduce PH stems from a combination of hemodynamic, metabolic, anti-inflammatory, and antifibrotic effects. Experimental models consistently show benefits in pulmonary vascular remodeling, RV hypertrophy, and RV-arterial coupling. However, clinical translation, particularly in group 1 PAH, remains challenging, with mixed results thus far. Given their favorable

Table 2. Summary of Preclinical Studies Assessing the Effects of SGLT2 Inhibitors in Rat Models of Pulmonary Hypertension

Study	Animal model	Compound	Main findings	Dose	Treatment duration, wk
Chen et al (2024)[44]	Rat MCT	Canagliflozin	↓ PASMC proliferation via SGLT1/AMPK signaling and ↓ pulmonary arterial remodeling	30 mg/kg	4 wk
Tang et al (2023)[43]	Mice hypobaric hypoxia	Canagliflozin	↓ Vascular wall thickening and ↓ RV pressure	10 mg/kg	4 wk
Lai et al (2024)[45]	Rat MCT	Empagliflozin	Activation of PPAR-γ, ↓ pulmonary arterial remodeling	10 mg/kg	3 wk
Qin et al (2022)[47]	Rat MCT	Dapagliflozin	↓ RVSP, improved RV function, and fewer arrhythmias	60 mg/L (drinking water)	4 wk
Dai et al (2022)[38]	Rat MCT	Dapagliflozin	↓ Vascular remodeling and ↓ susceptibility to atrial fibrillation and improved mitochondrial function	60 mg/L (drinking water)	4 wk
Li et al (2021)[56]	Rat MCT+PTB	Dapagliflozin	No beneficial effect detected on RV or pulmonary arteries	1,5 mg/kg	3 wk
Tang et al (2022)[66]	Mice MCT	Dapagliflozin+ sildenafil	No additive effect on vascular remodeling and cardiac function	1 mg/kg	3 wk
Chowdhury et al (2020)[25]	Rat MCT	Empagliflozin	↓ Mortality, slowed PH progression, and antifibrotic effect	10 mg/kg	3 wk

↑ indicates increase; ↓, decrease; AMPK, AMP-activated protein kinase; MCT, monocrotaline; PASMC, pulmonary arterial smooth muscle cell; PH, pulmonary hypertension; PPAR-γ, peroxisome proliferator-activated receptor gamma; PTB, pulmonary trunk banding; RV, right ventricle; RVSP, right ventricular systolic pressure; and SGLT1/SGLT2, sodium-glucose cotransporter 1/2.

safety profile and multifaceted mechanisms, SGLT2i warrants further investigation in dedicated RV and PH-focused trials, ideally with advanced imaging and biomarker-based end points. Overall, SGLT2i represents an exciting new endeavor in right heart-pulmonary vascular disease therapeutics.

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REFERENCES

1. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720
2. 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;377:644–657. doi: 10.1056/NEJMoa1611925
3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380:347–357. doi: 10.1056/NEJMoa1812389
4. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med.* 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303
5. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca H-P, Choi D-J, Chopra V, Chuquiure-Valenzuela E, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451–1461. doi: 10.1056/NEJMoa2107038
6. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, et al; Authors/Task Force Members: ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2024;26:5–17. doi: 10.1002/ejhf.3024
7. Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, Ferreira JP, Nassif ME, Psotka MA, Tromp J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. *Nat Med.* 2022;28:568–574. doi: 10.1038/s41591-021-01659-1
8. Kovacs G, Bartolome S, Denton CP, Gatzoulis MA, Gu S, Khanna D, Badesch D, Montani D. Definition, classification and diagnosis of pulmonary hypertension. *Eur Respir J.* 2024;64:2401324. doi: 10.1183/13993003.01324-2024
9. Landowski CP, Suzuki Y, Hediger MA. CHAPTER 4 - the Mammalian transporter families. In: Alpern RJ, Hebert SC, eds. *Seldin and Giebisch's The Kidney (Fourth Edition).* San Diego: Academic Press; 2008:91–146. https://www.sciencedirect.com/science/article/pii/B9780120884889500073
10. Pitt B, Steg G, Leiter LA, Bhatt DL. The role of combined SGLT1/SGLT2 inhibition in reducing the incidence of stroke and myocardial infarction in patients with type 2 diabetes mellitus. *Cardiovasc Drugs Ther.* 2022;36:561–567. doi: 10.1007/s10557-021-07291-y
11. Seidelmann SB, Feofanova E, Yu B, Franceschini N, Claggett B, Kuokkanen M, Puolijoki H, Ebeling T, Perola M, Salomaa V, et al. Genetic variants in SGLT1, glucose tolerance, and cardiometabolic risk. *J Am Coll Cardiol.* 2018;72:1763–1773. doi: 10.1016/j.jacc.2018.07.061
12. Padda IS, Mahtani AU, Parmar M. Sodium-Glucose Transport Protein 2 (SGLT2) Inhibitors. In: *StatPearls.* Treasure Island (FL): StatPearls Publishing; 2025. Accessed May 4, 2025. http://www.ncbi.nlm.nih.gov/books/NBK576405/
13. Berger JH, Finck BN. Beyond ketosis: the search for the mechanism underlying SGLT2-inhibitor benefit continues. *J Clin Invest.* 2024;134:e187097. doi: 10.1172/JCI187097
14. Hwang J, Kim DB, Park HJ. Off-target effects of sodium-glucose cotransporter 2 (SGLT-2) inhibitor in cardiovascular disease. *Korean Circ J.* 2020;50:458–460. doi: 10.4070/kcj.2020.0066
15. Forelli N, Eaton D, Patel J, Bowman CE, Kawakami R, Kuznetsov IA, Li K, Brady C, Bedi K, Yang Y, et al. SGLT2 inhibitors activate pantothenate kinase in the human heart. *bioRxiv.* 2024;2024.07.26.605401. doi: 10.1101/2024.07.26.605401
16. Rolski F, Mączewski M. Cardiac fibrosis: mechanistic discoveries linked to SGLT2 inhibitors. *Pharmaceuticals (Basel).* 2025;18:313. doi: 10.3390/ph18030313
17. Nassif ME, Nguyen D, Spertus JA, Gosch KL, Tang F, Windsor SL, Jones P, Khariton Y, Sauer AJ, Kosiborod MN. Association between change in ambulatory pulmonary artery pressures and natriuretic peptides in patients with heart failure: results from the EMBRACE-HF trial. *J Card Fail.* 2023;29:1324–1328. doi: 10.1016/j.cardfail.2023.05.009
18. Cascino TM, Maron BA, Vachiéry J-L, McLAUGHLIN VV, Tedford RJ. Highlights for the heart failure cardiologist from the seventh world symposium on pulmonary hypertension: are we out of the woods yet? *J Card Fail.* 2025;31:127–131. doi: 10.1016/j.cardfail.2024.09.009
19. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. *Circulation.* 2017;136:1643–1658. doi: 10.1161/CIRCULATIONAHA.117.030012
20. Boorsma EM, Beusekamp JC, Ter Maaten JM, Figarska SM, Danser AHJ, Van Veldhuisen DJ, Van Der Meer P, Heerspink HJL, Damman K, Voors AA. Effects of empagliflozin on renal sodium and glucose handling in patients with acute heart failure. *Eur J Heart Fail.* 2021;23:68–78. doi: 10.1002/ejhf.2066
21. Vallon V. Renoprotective effects of SGLT2 inhibitors. *Heart Fail Clin.* 2022;18:539–549. doi: 10.1016/j.hfc.2022.03.005
22. Marton A, Saffari SE, Rauh M, Sun R-N, Nagel AM, Linz P, Lim TT, Takase-Minegishi K, Pajarillaga A, Saw S, et al. Water conservation overrides osmotic diuresis during SGLT2 inhibition in patients with heart failure. *J Am Coll Cardiol.* 2024;83:1386–1398. doi: 10.1016/j.jacc.2024.02.020
23. Ranchoux B, Bigorgne A, Hautefort A, Girerd B, Sitbon O, Montani D, Humbert M, Tcherakian C, Perros F. Gut-lung connection in pulmonary arterial hypertension. *Am J Respir Cell Mol Biol.* 2017;56:402–405. doi: 10.1165/rcmb.2015-0404LE

24. Asensio Lopez MDC, Lax A, Hernandez Vicente A, Saura Guillen E, Hernandez-Martinez A, Fernandez Del Palacio MJ, Bayes-Genis A, Pascual Figal DA. Empagliflozin improves post-infarction cardiac remodeling through GTP enzyme cyclohydrolase 1 and irrespective of diabetes status. *Sci Rep*. 2020;10:13553. doi: 10.1038/s41598-020-70454-8
25. Chowdhury B, Luu AZ, Luu VZ, Kabir MG, Pan Y, Teoh H, Quan A, Sabongui S, Al-Omran M, Bhatt DL, et al. The SGLT2 inhibitor empagliflozin reduces mortality and prevents progression in experimental pulmonary hypertension. *Biochem Biophys Res Commun*. 2020;524:50–56. doi: 10.1016/j.bbrc.2020.01.015
26. Selvaraj S, Patel S, Sauer AJ, McGarrah RW, Jones P, Kwee LC, Windsor SL, Ilkayeva O, Muehlbauer MJ, Newgard CB, et al. Metabolic effects of the SGLT2 inhibitor dapagliflozin in heart failure across the spectrum of ejection fraction. *Circ Heart Fail*. 2024;17:e011980. doi: 10.1161/CIRCHEARTFAILURE.124.011980
27. Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *JACC Basic Transl Sci*. 2020;5:632–644. doi: 10.1016/j.jacbts.2020.02.004
28. Su S, Ji X, Li T, Teng Y, Wang B, Han X, Zhao M. The changes of cardiac energy metabolism with sodium-glucose transporter 2 inhibitor therapy. *Front Cardiovasc Med*. 2023;10:1291450. doi: 10.3389/fcvm.2023.1291450
29. Herat LY, Magno AL, Rudnicka C, Hricova J, Carnagarin R, Ward NC, Arcambal A, Kiuchi MG, Head GA, Schlaich MP, et al. SGLT2 inhibitor–induced sympathoinhibition. *JACC Basic Transl Sci*. 2020;5:169–179. doi: 10.1016/j.jacbts.2019.11.007
30. Borges-Júnior FA, Silva Dos Santos D, Benetti A, Polidoro JZ, Wisnivesky ACT, Crajoinas RO, Antônio EL, Jensen L, Caramelli B, Malnic G, et al. Empagliflozin inhibits proximal tubule NHE3 activity, preserves GFR, and restores euvolemia in nondiabetic rats with induced heart failure. *J Am Soc Nephrol*. 2021;32:1616–1629. doi: 10.1681/ASN.2020071029
31. Yoshikawa T, Kishi T, Shinohara K, Takesue K, Shibata R, Sonoda N, Inoguchi T, Sunagawa K, Tsutsui H, Hirooka Y. Arterial pressure lability is improved by sodium-glucose cotransporter 2 inhibitor in streptozotocin-induced diabetic rats. *Hypertens Res*. 2017;40:646–651. doi: 10.1038/hr.2017.14
32. Vaillancourt M, Chia P, Sarji S, Nguyen J, Hoftman N, Ruffenach G, Eghbali M, Mahajan A, Umar S. Autonomic nervous system involvement in pulmonary arterial hypertension. *Respir Res*. 2017;18:201. doi: 10.1186/s12931-017-0679-6
33. Velez-Roa S, Ciarka A, Najem B, Vachiery J-L, Naeije R, Van De Borne P. Increased sympathetic nerve activity in pulmonary artery hypertension. *Circulation*. 2004;110:1308–1312. doi: 10.1161/01.CIR.0000140724.90898.D3
34. Evans CE, Cober ND, Dai Z, Stewart DJ, Zhao Y-Y. Endothelial cells in the pathogenesis of pulmonary arterial hypertension. *Eur Respir J*. 2021;58:2003957. doi: 10.1183/13993003.03957-2020
35. Byrne NJ, Matsumura N, Maayah ZH, Ferdaoussi M, Takahara S, Darwesh AM, Levasseur JL, Jahng JWS, Vos D, Parajuli N, et al. Empagliflozin blunts worsening cardiac dysfunction associated with reduced NLRP3 (nucleotide-binding domain-like receptor protein 3) inflammasome activation in heart failure. *Circ Heart Fail*. 2020;13:e006277. doi: 10.1161/CIRCHEARTFAILURE.119.006277
36. Joki Y, Konishi H, Takasu K, Minamino T. Tofogliflozin, a sodium-glucose cotransporter 2 inhibitor, improves pulmonary vascular remodeling due to left heart disease in mice. *J Cardiol*. 2023;81:347–355. doi: 10.1016/j.jjcc.2022.10.003
37. Zhang R, Xie Q, Lu X, Fan R, Tong N. Research advances in the anti-inflammatory effects of SGLT inhibitors in type 2 diabetes mellitus. *Diabetol Metab Syndr*. 2024;16:99. doi: 10.1186/s13098-024-01325-9
38. Dai C, Kong B, Shuai W, Xiao Z, Qin T, Fang J, Gong Y, Zhu J, Liu Q, Fu H, et al. Dapagliflozin reduces pulmonary vascular damage and susceptibility to atrial fibrillation in right heart disease. *ESC Heart Fail*. 2022;10:578–593. doi: 10.1002/ehf2.14169
39. Packer M. Critical reanalysis of the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors and reaffirmation of the nutrient deprivation signaling/autophagy hypothesis. *Circulation*. 2022;146:1383–1405. doi: 10.1161/CIRCULATIONAHA.122.061732
40. Li X, Flynn ER, Do Carmo JM, Wang Z, Da Silva AA, Mouton AJ, Omoto ACM, Hall ME, Hall JE. Direct cardiac actions of sodium-glucose cotransporter 2 inhibition improve mitochondrial function and attenuate oxidative stress in pressure overload-induced heart failure. *Front Cardiovasc Med*. 2022;9:859253. doi: 10.3389/fcvm.2022.859253
41. Guignabert C, Aman J, Bonnet S, Dorfmüller P, Olschewski AJ, Pullamsetti S, Rabinovitch M, Schermuly RT, Humbert M, Stenmark KR. Pathology and pathobiology of pulmonary hypertension: current insights and future directions. *Eur Respir J*. 2024;64:2401095. doi: 10.1183/13993003.01095-2024
42. Naeije R, Manes A. The right ventricle in pulmonary arterial hypertension. *Eur Respir Rev*. 2014;23:476–487. doi: 10.1183/09059180.00007414
43. Tang L, Cai Q, Wang X, Li X, Li X, Chen L, Yang Y. Canagliflozin ameliorates hypobaric hypoxia-induced pulmonary arterial hypertension by inhibiting pulmonary arterial smooth muscle cell proliferation. *Clin Exp Hypertens*. 2023;45:2278205. doi: 10.1080/10641963.2023.2278205
44. Chen X, Yu X, Lian G, Tang H, Yan Y, Gao G, Huang B, Luo L, Xie L. Canagliflozin inhibits PASMCs proliferation via regulating SGLT1/AMPK signaling and attenuates artery remodeling in MCT-induced pulmonary arterial hypertension. *Biomed Pharmacother*. 2024;174:116505. doi: 10.1016/j.biopha.2024.116505
45. Lai Y-J, Yeh Y-H, Huang Y-L, De Almeida C, Chang G-J, Chen W-J, Hsu H-H. Empagliflozin attenuates pulmonary arterial remodeling through peroxisome proliferator-activated receptor gamma activation. *ACS Pharmacol Transl Sci*. 2024;7:2725–2738. doi: 10.1021/acsptsci.4c00127
46. Vonk Noordegraaf A, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, Kawut SM, Langleben D, Lumens J, Naeije R. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: an update. *Eur Respir J*. 2019;53:1801900. doi: 10.1183/13993003.01900-2018
47. Qin T, Kong B, Dai C, Xiao Z, Fang J, Shuai W, Huang H. Protective effects of Dapagliflozin on the vulnerability of ventricular arrhythmia in rats with pulmonary artery hypertension induced by monocrotaline. *Bioengineered*. 2022;13:2697–2709. doi: 10.1080/21655979.2021.2017652
48. Peng X, Li L, Zhang M, Zhao Q, Wu K, Bai R, Ruan Y, Liu N. Sodium-glucose cotransporter 2 inhibitors potentially prevent atrial fibrillation by ameliorating ion handling and mitochondrial dysfunction. *Front Physiol*. 2020;11:912. doi: 10.3389/fphys.2020.00912
49. Wu J, Liu T, Shi S, Fan Z, Hiram R, Xiong F, Cui B, Su X, Chang R, Zhang W, et al. Dapagliflozin reduces the vulnerability of rats with pulmonary arterial hypertension-induced right heart failure to ventricular arrhythmia by restoring calcium handling. *Cardiovasc Diabetol*. 2022;21:197. doi: 10.1186/s12933-022-01614-5
50. Connelly KA, Wu E, Visram A, Friedberg MK, Batchu SN, Yerra VG, Thai K, Nghiem L, Zhang Y, Kabir G, et al. The SGLT2i dapagliflozin reduces RV mass independent of changes in RV pressure induced by pulmonary artery banding. *Cardiovasc Drugs Ther*. 2024;38:57–68. doi: 10.1007/s10557-022-07377-1
51. Ng K-M, Lau Y-M, Dhandhania V, Cai Z-J, Lee Y-K, Lai W-H, Tse H-F, Siu C-W. Empagliflozin ammeliorates high glucose induced-cardiac dysfuntion in human iPSC-derived cardiomyocytes. *Sci Rep*. 2018;8:14872. doi: 10.1038/s41598-018-33293-2
52. Marfella R, Scisciola L, D'Onofrio N, Maiello C, Trotta MC, Sardu C, Panarese I, Ferraraccio F, Capuano A, Barbieri M, et al. Sodium-glucose cotransporter-2 (SGLT2) expression in diabetic and non-diabetic failing human cardiomyocytes. *Pharmacol Res*. 2022;184:106448. doi: 10.1016/j.phrs.2022.106448
53. Reddy YNV, Carter RE, Sorimachi H, Omar M, Popovic D, Alogna A, Jensen MD, Borlaug BA. Dapagliflozin and right ventricular–pulmonary vascular interaction in heart failure with preserved ejection fraction: a secondary analysis of a randomized clinical trial. *JAMA Cardiol*. 2024;9:843–851. doi: 10.1001/jamacardio.2024.1914
54. Kirschbaum K, Vasa-Nicotera M, Zeiher AM, Cremer S. SGLT2 inhibitor therapy and pulmonary artery pressure in patients with chronic heart failure-further evidence for improved hemodynamics by continuous pressure monitoring. *Clin Res Cardiol*. 2022;111:469–472. doi: 10.1007/s00392-021-01954-4
55. Yoshida K, Toth E, Duijvelaar E, Neep B, Agarwal S, Pan X, Sanada T, Yoshida Y, Aman J, De Jesus Perez VA, et al. Empagliflozin improves mitochondrial biogenesis and ameliorates experimental pulmonary vascular remodeling, but may not benefit patients with pulmonary arterial hypertension. 2025. Accessed May 13, 2025. http://medrxiv.org/lookup/doi/10.1101/2025.01.27.25321226
56. Li H, Zhang Y, Wang S, Yue Y, Liu Q, Huang S, Peng H, Zhang Y, Zeng W, Wu Z. Dapagliflozin has no protective effect on experimental pulmonary arterial hypertension and pulmonary trunk banding rat models. *Front Pharmacol*. 2021;12:756226. doi: 10.3389/fphar.2021.756226
57. Milani-Nejad N, Janssen PML. Small and large animal models in cardiac contraction research: advantages and disadvantages. *Pharmacol Ther*. 2014;141:235–249. doi: 10.1016/j.pharmthera.2013.10.007
58. Riehle C, Bauersachs J. Small animal models of heart failure. *Cardiovasc Res*. 2019;115:1838–1849. doi: 10.1093/cvr/cvz161
59. Hopper SE, Cuomo F, Ferruzzi J, Burris NS, Roccabianca S, Humphrey JD, Figueroa CA. Comparative study of human and murine aortic biomechanics

and hemodynamics in vascular aging. *Front Physiol*. 2021;12:746796. doi: 10.3389/fphys.2021.746796
60. Mourad O, Vohra S, Nunes SS. Single cell transcriptomic analysis of SGLT2 expression supports an indirect or off-target role for the cardioprotective benefits of empagliflozin in heart failure. *Sci Rep*. 2025;15:8265. doi: 10.1038/s41598-025-93144-9
61. Sano M, Goto S. Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 inhibitors and associated beneficial renal and cardiovascular effects. *Circulation*. 2019;139:1985–1987. doi: 10.1161/CIRCULATIONAHA.118.038881
62. Lee JY, Lee J-H, Jung E-J, Park W, Seo J, Kang M, Jung EH, Kim S-A, Suh KJ, Kim J-W, et al. Prevalence and thrombotic risk of SGLT-2 inhibitor-associated erythrocytosis: a retrospective cohort study. *Cardiovasc Diabetol*. 2025;24:276. doi: 10.1186/s12933-025-02805-6
63. Tukker M, Bruwiere E, Bos S, Caliskan K. SGLT2 inhibitor–related polycythemia in a patient with chronic heart failure: a potential severe adverse event. *Circ Heart Fail*. 2023;16:e010613. doi: 10.1161/CIRCHEARTFAILURE.123.010613
64. Humbert M, McLaughlin V, Gibbs JSR, Gomberg-Maitland M, Hoeper MM, Preston IR, Souza R, Waxman A, Escribano Subias P, Feldman J, et al; PULSAR Trial Investigators. Sotatercept for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2021;384:1204–1215. doi: 10.1056/NEJMoa2024277
65. Chin KM, Gaine SP, Gerges C, Jing Z-C, Mathai SC, Tamura Y, McLaughlin VV, Sitbon O. Treatment algorithm for pulmonary arterial hypertension. *Eur Respir J*. 2024;64:2401325. doi: 10.1183/13993003.01325-2024
66. Tang Y, Tan S, Li M, Tang Y, Xu X, Zhang Q, Fu Q, Tang M, He J, Zhang Y, et al. Dapagliflozin, sildenafil and their combination in monocrotaline-induced pulmonary arterial hypertension. *BMC Pulm Med*. 2022;22:142. doi: 10.1186/s12890-022-01939-7
67. Mullens W, Martens P, Forouzan O, Dauw J, Vercammen J, Luwel E, Ceyssens W, Kockaerts V, Ameloot K, Dupont M. Effects of dapagliflozin on congestion assessed by remote pulmonary artery pressure monitoring. *ESC Heart Fail*. 2020;7:2071–2073. doi: 10.1002/ehf2.12850
68. Qu L, Duan X, Chen H. The effects of sodium-glucose cotransporter 2 inhibitors on the "forgotten" right ventricle. *ESC Heart Fail*. 2025;2:1045–1058. doi: 10.1002/ehf2.15103
69. Harris DD, Sabe SA, Broadwin M, Stone C, Xu C, Hu J, Kanuparthy M, Abid MR, Sellke FW. Proteomic profiling of SGLT-2 inhibitor canagliflozin in a swine model of chronic myocardial ischemia. *Biomedicines*. 2024;12:588. doi: 10.3390/biomedicines12030588
70. Mroueh A, Algara-Suarez P, Fakih W, Gong D-S, Matsushita K, Park S-H, Amissi S, Auger C, Kauffenstein G, Meyer N, et al. SGLT2 expression in human vasculature and heart correlates with low-grade inflammation and causes eNOS-NO/ROS imbalance. *Cardiovasc Res*. 2024;121:643–657. doi: 10.1093/cvr/cvae257
71. Park S-H, Belcastro E, Hasan H, Matsushita K, Marchandot B, Abbas M, Toti F, Auger C, Jesel L, Ohlmann P, et al. Angiotensin II-induced upregulation of SGLT1 and 2 contributes to human microparticle-stimulated endothelial senescence and dysfunction: protective effect of gliflozins. *Cardiovasc Diabetol*. 2021;20:65. doi: 10.1186/s12933-021-01252-3
72. Hmadeh S, Trimaille A, Matsushita K, Marchandot B, Carmona A, Zobairi F, Sato C, Kindo M, Hoang TM, Toti F, et al. Human aortic stenotic valve-derived extracellular vesicles induce endothelial dysfunction and thrombogenicity through AT1R/NADPH oxidases/SGLT2 pro-oxidant pathway. *JACC Basic Transl Sci*. 2024;9:845–864. doi: 10.1016/j.jacbts.2024.02.012
73. Sayour AA, Oláh A, Ruppert M, Barta BA, Horváth EM, Benke K, Pólos M, Hartyánszky I, Merkely B, Radovits T. Characterization of left ventricular myocardial sodium-glucose cotransporter 1 expression in patients with end-stage heart failure. *Cardiovasc Diabetol*. 2020;19:159. doi: 10.1186/s12933-020-01141-1
74. Di Franco A, Cantini G, Tani A, Coppini R, Zecchi-Orlandini S, Raimondi L, Luconi M, Mannucci E. Sodium-dependent glucose transporters (SGLT) in human ischemic heart: a new potential pharmacological target. *Int J Cardiol*. 2017;243:86–90. doi: 10.1016/j.ijcard.2017.05.032
75. Von Lewinski D, Rainer PP, Gasser R, Huber M-S, Khafaga M, Wilhelm B, Haas T, Mächler H, Rössl U, Pieske B. Glucose-transporter–mediated positive inotropic effects in human myocardium of diabetic and nondiabetic patients. *Metabolism*. 2010;59:1020–1028. doi: 10.1016/j.metabol.2009.10.025
76. Duan H-Y, Barajas-Martinez H, Antzelevitch C, Hu D. The potential antiarrhythmic effect of SGLT2 inhibitors. *Cardiovasc Diabetol*. 2024;23:252. doi: 10.1186/s12933-024-02312-0
77. Chen S, Wang Q, Bakker D, Hu X, Zhang L, Van Der Made I, Tebbens AM, Kovácsházi C, Giricz Z, Brenner GB, et al. Empagliflozin prevents heart failure through inhibition of the NHE1-NO pathway, independent of SGLT2. *Basic Res Cardiol*. 2024;119:751–772. doi: 10.1007/s00395-024-01067-9
78. Gumina RJ, Buerger E, Eickmeier C, Moore J, Daemmgen J, Gross GJ. Inhibition of the Na^+/H^+ exchanger confers greater cardioprotection against 90 minutes of myocardial ischemia than ischemic preconditioning in dogs. *Circulation*. 1999;100:2519–26; discussion 2469. doi: 10.1161/01.cir.100.25.2519
79. 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;61:375–389. doi: 10.2165/00003495-200161030-00006
80. Milano G, Reinero M, Puyal J, Tozzi P, Samaja M, Porte-Thomé F, Beghetti M. Inhibition of sodium/hydrogen exchanger-1 in the right ventricle and lung dysfunction induced by experimental pulmonary arterial hypertension in rats. *J Am Heart Assoc*. 2025;14:e036859. doi: 10.1161/JAHA.124.036859
81. Milano G, Reinero M, Sameere A, Porte-Thome F, Beghetti M. Rimeporide, a first in class Na/H exchanger-1 inhibitor, ameliorates right ventricular dysfunction and pulmonary arterial hypertension in a SuHx model. *Eur Heart J*. 2023;44:ehad655.3142. doi: 10.1093/eurheartj/ehad655.3142
82. Silva Dos Santos D, Polidoro JZ, Borges-Júnior FA, Girardi ACC. Cardioprotection conferred by sodium-glucose cotransporter 2 inhibitors: a renal proximal tubule perspective. *Am J Physiol Cell Physiol*. 2020;318:C328–C336. doi: 10.1152/ajpcell.00275.2019
83. Wu Q, Yao Q, Hu T, Yu J, Jiang K, Wan Y, Tang Q. Dapagliflozin protects against chronic heart failure in mice by inhibiting macrophage-mediated inflammation, independent of SGLT2. *Cell Rep Med*. 2023;4:101334. doi: 10.1016/j.xcrm.2023.101334