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SGLT2i Inhibitor Therapy in the Management of Pulmonary Hypertension: A Literature Review

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Abstract
Pulmonary hypertension (PH) is a complex, progressive condition marked by elevated pulmonary vascular resistance and artery pressure, often leading to right heart failure. Therapeutic options remain limited, especially for PH due to left heart disease (PH-LHD) and pulmonary arterial hypertension (PAH). Sodium—glucose cotransporter 2 inhibitors (SGLT2i), developed for diabetes, show cardiorenal benefits beyond glycemic control, suggesting a role in PH management. This narrative literature review synthesizes evidence on SGLT2i in PH, focusing on mechanisms, preclinical findings, and clinical outcomes. Systematic searches (PubMed, Scopus, ScienceDirect; 2020–2025) reveal SGLT2i modulate PH pathophysiology via mild osmotic diuresis; reduced inflammation and oxidative stress; improved endothelial function; inhibited vascular remodeling; and enhanced right ventricular function. Preclinical animal studies report lower pulmonary artery pressure and remodeling. Early clinical data from observational studies and heart failure trial sub-analyses indicate improved hemodynamics (e.g., pulmonary artery pressure, NT-proBNP) in PH patients, particularly PH-LHD. In conclusion, SGLT2i offer promise as adjunctive therapy for PH linked to left heart disease due to multimodal actions. Evidence remains preliminary from non-PH-specific trials; ongoing randomized controlled trials will clarify efficacy and safety for broader recommendation.

Keywords: *pulmonary hypertension, SGLT2 inhibitors, vascular remodeling, right ventricular function, diuresis, inflammation*

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INTRODUCTION

Pulmonary hypertension (PH) is a complex pathophysiological condition characterized by increased pulmonary vascular resistance and pulmonary arterial pressure (PAP) (Tan et al., 2024; Tekin et al., 2025). Diagnostically, PH is defined by a resting mean pulmonary artery pressure (mPAP) above 20 mmHg (Tan et al., 2024) . This condition can ultimately lead to right heart failure and increased mortality (Tan et al., 2024; Tekin et al., 2025). PH is classified into five groups based on its etiology, pathogenesis, and treatment strategies (Luo et al., 2024; Tan et al., 2024). Pulmonary Arterial Hypertension (PAH) is a subtype of Group 1 PH characterized by pulmonary artery remodeling, increased pulmonary vascular resistance, and blood pressure in the pulmonary artery, leading to right heart failure and increased mortality (Tan et al., 2024). Hemodynamic PAH is defined by mPAP more than 20 mmHg, pulmonary capillary wedge pressure (PCWP) 15 mmHg or less, and pulmonary vascular resistance (PVR) above 2 Wood's units (Tan et al., 2024). PH due to left heart disease (PH-LHD) is the most common form of PH (Group 2), occurring in 40%-75% of patients with heart failure with decreased ejection fraction (HFrEF) and 36%-83% of patients with heart failure with preserved ejection fraction (HFpEF). The prevalence of PH is estimated to be 1% of the global population and increases to 10% in individuals over 65 years, with significant morbidity and mortality (Luo et al., 2024). PH is a significant threat to patient health, often progressive in

nature (Tekin et al., 2025). If left untreated, PAH can progress to inevitable right heart failure and death. The prognosis remains grim, with a 5-year survival rate of approximately 50%, even with combination therapy (Tan et al., 2024) . The presence of PH in HFpEF patients is associated with worse clinical outcomes (Tekin et al., 2025), and progression of PH-LHD has a poor prognosis, with increased mortality beyond left heart failure alone (King & Brittain, 2022).

Treatment options for PH associated with HFpEF are still limited (Tekin et al., 2025). The current management of PH-LHD focuses only on the management of comorbid conditions, and there are no proven effective therapies to prevent or slow its progression. Trials of Group 1 PAH therapies (such as endothelin-1 receptor antagonists or phosphodiesterase-5 inhibitors) have not shown significant results in patients with combined pre- and post-capillary PH (CPH). The challenge in treating PH lies in the complicated pathophysiology, prevalence of comorbidities, and limited efficacy of vasodilator treatment against vascular remodeling (Tan et al., 2024).

Despite limitations in available therapies, a promising new class of drugs has emerged: Sodium-Glucose Co-transporter 2 inhibitors (SGLT2i). SGLT2i are recommended for patients with heart or kidney problems, even without type 2 diabetes mellitus (T2DM) (Allen, 2024; Heidenreich et al., 2022; John, 2020). SGLT2i are considered a new "wonder weapon" in the treatment of HFpEF and HFmrEF, with a Class I recommendation in the revised 2023 European Society of Cardiology (ESC) guidelines for the treatment of acute and chronic heart failure (Herrmann et al., 2025; Zulkarnain & Umini, 2025). SGLT2i show significant therapeutic potential in PH through suppression of inflammation and improvement of vascular remodeling (King & Brittain, 2022; Luo et al., 2024; Memarian & Eskandarian, 2025; Pabel et al., 2021; Rolski & Mączewski, 2025; Tan et al., 2024). These drugs have shown efficacy in reducing vascular smooth muscle cell (VSMC) contraction and proliferation (Luo et al., 2024; Tan et al., 2024) , maintaining nitric oxide (NO) bioavailability (King & Brittain, 2022; Luo et al., 2024; Memarian & Eskandarian, 2025; Pabel et al., 2021; Rolski & Mączewski, 2025; Tan et al., 2024), overcoming insulin resistance (Luo et al., 2024; Tan et al., 2024), and improving hemodynamics through decongestive mechanisms in PH, specifically PH-LHD (King & Brittain, 2022; Memarian & Eskandarian, 2025; Pabel et al., 2021; Tan et al., 2024). Recent small-scale studies indicate that SGLT2i can improve pulmonary artery pressure in PH-LHD patients (Kirschbaum et al., 2022; Luo et al., 2024; Memarian & Eskandarian, 2025; Satoh et al., 2024; Tekin et al., 2025). Animal models of PAH have also shown that SGLT2i can reduce pulmonary vascular remodeling and prevent disease progressivity (King & Brittain, 2022; Luo et al., 2024; Tan et al., 2024). Currently, two clinical trials are evaluating the use of dapagliflozin and empagliflozin in PAH patients (LEMONJAVA et al., 2024; Luo et al., 2024; Tan et al., 2024). SGLT2i are even recognized as a potential fourth treatment pathway alongside traditional therapies for PAH, indicating a significant shift in management approaches (Memarian & Eskandarian, 2025).

The aim of this literature review is to systematically examine the pre-clinical and clinical evidence regarding the potential of Sodium-Glucose Co-transporter 2 inhibitors (SGLT2i) as a novel therapeutic modality in the management of pulmonary hypertension, specifically through mechanisms of mild diuresis, anti-inflammatory and antioxidant effects, and improvement of right ventricular function. The benefit of this research is expected to provide

a comprehensive synthesis of the rationale for using SGLT2i in PH, identify existing knowledge gaps, and offer direction for further clinical research, thereby ultimately contributing to the development of more effective therapeutic strategies to improve the prognosis of patients with pulmonary hypertension.

RESEARCH METHOD

This study employed a literature review method with a narrative approach to examine the potential role of Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) in the management of pulmonary hypertension (PH). The procedure was carried out through a systematic search of relevant scientific literature published between 2020 and 2025 in databases such as PubMed, Scopus, ScienceDirect, and Google Scholar, as well as specialized cardiology and pulmonology journals.

The keywords used in the search included “SGLT2 inhibitors”, “pulmonary hypertension”, “vascular remodeling”, “right ventricular function”, and “diuresis inflammation”. The inclusion criteria comprised original research articles (both pre-clinical and clinical), randomized controlled trials, systematic reviews, and meta-analyses that discussed the effects of SGLT2i on the pathophysiology and treatment of PH. The exclusion criteria were non-scientific articles, publications without full-text availability, and studies not directly relevant to the focus of this review.

The selected studies were analyzed descriptively and synthesized to highlight the mechanisms of action of SGLT2i, pre-clinical and clinical evidence, as well as challenges in their clinical application. The analysis focused on comparing existing findings, identifying current limitations, and outlining potential directions for future research.

RESULTS AND DISCUSSION

A. Mechanism of Action of SGLT2i

Sodium-Glucose Co-transporter 2 inhibitors (SGLT2i) were originally developed as one of the oral antidiabetic drug classes that have high efficacy in reducing blood glucose levels (Fernandez-Fernandez et al., 2020; Teo et al., 2021) . Its mechanism of action is to inhibit glucose reabsorption in the renal tubules, particularly in the early segment of the proximal tubule, where most glucose is absorbed via the SGLT2 transporter (about 97%) and the remainder via SGLT1 (Allen, 2024) . This decrease in glucose reabsorption leads to increased urinary excretion of glucose (glucosuria), which can reach 80 grams per day, and simultaneously decreases sodium absorption(Yohanes, 2020)

Figure 1. Mechanism of action of SGLT2 Inhibition (Kaur et al., 2021)

However, over time, large studies have revealed promising cardioprotective and nephroprotective effects of SGLT2i, even in patients without type 2 diabetes mellitus (T2DM) . Some notable clinical trials demonstrating these benefits include EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI, CREDENCE, EMPEROR-Reduced, EMPEROR-Preserved, DAPA-HF, and DAPA-CKD (Tan et al., 2024) . These benefits include reduced risk of heart failure hospitalization, cardiovascular death, and worsening renal function, which in some studies was even more significant in the dapagliflozin group compared to empagliflozin for cases of heart failure and renal failure) (Allen, 2024) . These cardiovascular benefits appear rapidly and are not solely dependent on lowering glucose levels (Herrmann et al., 2025; Pabel et al., 2021) .

SGLT2i have a multifactorial influence on intravascular volume, blood pressure, and metabolism (Herrmann et al., 2025) . These include:

1. Decreased plasma volume and blood pressure: SGLT2i cause osmotic diuresis and natriuresis (increased sodium excretion), which can reduce body fluid volume and lower blood pressure (Allen, 2024) . Although the blood pressure reduction is moderate, this effect still contributes to the cardiovascular benefits (Wilcox, 2020) .
2. Improvements in cardiac energy metabolism: SGLT2i may shift metabolism from glucose to lipids, increasing the production of ketone bodies (e.g., β-hydroxybutyrate) that become a more efficient energy source for the heart, especially under stress conditions (Tan et al., 2024) .
3. Anti-inflammatory and anti-oxidative effects: SGLT2i can suppress inflammation and oxidative stress, which are important factors in the pathogenesis of cardiovascular diseases (Tan et al., 2024).
4. Improvement of endothelial function and vascular remodeling: These drugs can increase nitric oxide (NO) bioavailability, reduce vascular smooth muscle cell (VSMC) proliferation, and inhibit vascular remodeling (Tan et al., 2024) .

Thus, although originally intended for managing T2DM, the broad spectrum of effects of SGLT2i on the cardiovascular system-including their influence on fluid volume, blood pressure, and metabolism as well as inflammation and vascular remodeling-provides a strong basis for exploring their therapeutic potential in complex conditions such as pulmonary hypertension (PH) (Tan et al., 2024) .

B. Pathophysiology of Pulmonary Hypertension

Pulmonary hypertension (PH) is a complex pathophysiological condition characterized diagnostically by mean pulmonary artery pressure (mPAP) above 20 mmHg at rest (Kopeć et al., 2020) . The condition can progress and is associated with various cardiovascular and respiratory disorders, and can lead to right heart failure and, in severe cases, death (Tekin et al., 2025) .

The classification of PH is divided into five groups based on etiology, pathophysiologic mechanisms, clinical presentation, hemodynamic characteristics, and therapeutic approaches (Tan et al., 2024) .

1. Group 1 (Pulmonary Arterial Hypertension/PAH):

This is a subtype of PH characterized hemodynamically by mPAP above 20 mmHg, pulmonary artery wedge pressure (PAWP) of 15 mmHg or less, and pulmonary vascular resistance (PVR) above 2 Wood units (Tan et al., 2024) . PAH is often genetic and associated with mutations in the bone morphogenetic protein receptor type 2 (BMPR2) pathway, potassium channel subfamily k member 3 (KCNK3) gene, and caveolin 1 (CAV1) gene . If left untreated, PAH progresses to right heart failure and death (Luo et al., 2024; Tan et al., 2024) .

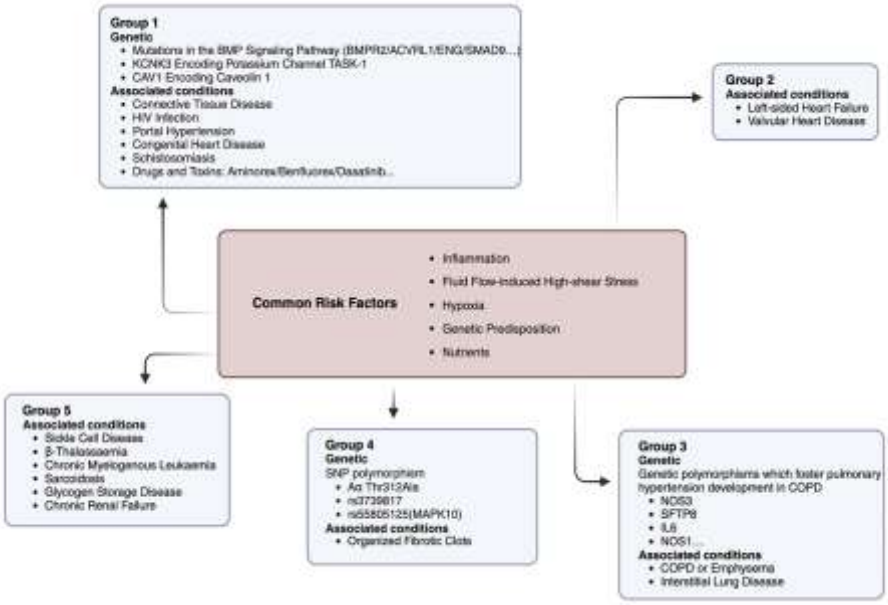

Figure 2. Risk factors of pulmonary hypertension in 5 groups (Tan et al., 2024)

2. Group 2 (PH Associated with Left Heart Disease/PH-LHD):

It is the most common manifestation of PH, occurring in 40%-75% of patients with reduced ejection fraction heart failure (HFrEF) and 36%-83% of patients with preserved ejection fraction heart failure (HFpEF). PH-LHD is caused by increased postcapillary pressure transmitted from the left heart, which can be clinically isolated or occur in conjunction with precapillary PH (CPH)

3. Groups 3, 4, and 5:

Group 3 is associated with lung disease and/or hypoxia, Group 4 with pulmonary artery obstruction, and Group 5 with unclear and/or multifactorial mechanisms, including

hematologic abnormalities, systemic disorders, and metabolic diseases (Luo et al., 2024; Tan et al., 2024) .

The pathogenesis of PH is multifactorial and involves several key mechanisms (Mocumbi et al., 2024; Prins & Thenappan, 2016) .

1. Vascular Remodeling:

This is a key pathological feature of PAH. This process includes proliferation and hypertrophy of pulmonary artery endothelial cells (PAECs), pulmonary artery smooth muscle cells (PASMCs), adventitial thickening, and infiltration of immune cells around blood vessels with chronic inflammatory reaction (Luo et al., 2024) . Endothelial dysfunction, characterized by impaired vasodilation and increased vasoconstriction, is also a hallmark of PAH contributing to increased pulmonary vascular resistance and pressure (Tan et al., 2024) .

2. Pulmonary Vasoconstriction:

There is an imbalance of vasoactive substances in favor of vasoconstrictors (such as thromboxane A2 and endothelin) versus vasodilators (such as prostacyclin and nitric oxide/NO), leading to narrowing of small pulmonary arteries. NO is an important biological signaling molecule produced by vascular endothelial cells and essential for maintaining vascular function and lowering blood pressure (Tan et al., 2024).

3. Inflammation and Oxidative Stress:

Inflammation plays an important role in the pathogenesis of PH (Tan et al., 2024; Tekin et al., 2025) . Pulmonary vascular cells release inflammatory mediators that attract inflammatory cells, which in turn trigger the release of cytokines, chemokines, and growth factors, thus contributing to vascular remodeling (Tekin et al., 2025). This chronic inflammation also reduces NO production, increases fibrosis, and induces endothelial-mesenchymal transition (EMT) (King & Brittain, 2022) . Oxidative stress also plays a role in the pathogenesis of PAH (Memarian & Eskandarian, 2025) .

4. Fibrosis:

Excessive collagen deposition in the pulmonary vascular wall and in the myocardium is part of the vascular and cardiac remodeling process (Luo et al., 2024) . This contributes to vascular stiffness and organ dysfunction.

5. Metabolic Dysfunction:

Growing evidence suggests that metabolic dysfunction is a major driver of PH-LHD and PAH (King & Brittain, 2022) . Conditions such as obesity, insulin resistance, and glucose intolerance are strongly associated with increased risk and severity of pulmonary vascular dysfunction (King & Brittain, 2022; Luo et al., 2024) . Metabolic dysfunction also exacerbates inflammation (King & Brittain, 2022) . Pulmonary artery smooth muscle cells show metabolic reprogramming (Warburg effect) with increased glycolysis, even in the presence of oxygen, which favors cell survival and proliferation (Tan et al., 2024) .

PH progressively leads to right heart failure (RHF) due to increased pressure load on the right ventricle (RV) resulting from high pulmonary vascular resistance (Tekin et al., 2025) . RV dysfunction is frequently found in PH patients and is a major determinant of prognosis (King & Brittain, 2022; Luo et al., 2024) . Increased left ventricular filling pressure can also lead to passive pulmonary venous congestion and postcapillary PH, ultimately increasing the load on the RV (Tekin et al., 2025) . In addition, renal function is also strongly associated.

Renal dysfunction, such as chronic kidney disease (CKD), is a common comorbidity in PH patients and worsens prognosis (King & Brittain, 2022; Zulkarnain & Umini, 2025) .

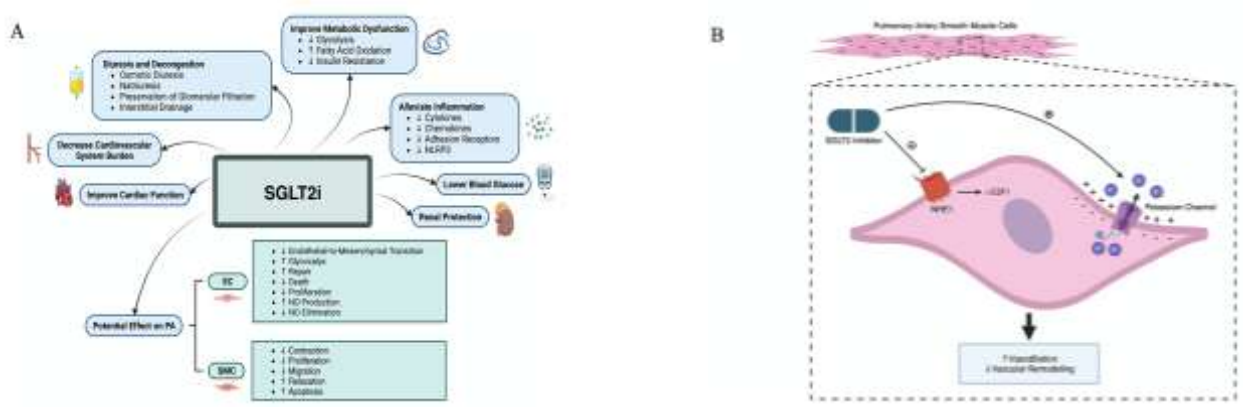

Figure 3. Effects of sGlt2 inhibitor and its potential effects on PA (Tan et al.,2024).

(a) besides its initial usage in lowering blood glucose and protecting renal function, sGlt2i has been proven to have a diuretic effect, decrease cardiovascular burden, and improve cardiac function. its ability to alleviate inflammation and improve metabolism serves as a potential mechanism to inhibit pulmonary arterial remodeling. in addition, sGlt2i has a direct effect on arteries that needs to be verified in pulmonary arteries. it has protective and antiproliferative effects on endothelial cells. it also promotes smooth muscle cell relaxation and apoptosis while inhibiting their contraction, proliferation, and migration. (b) sGlt2i inhibits nHe1 and thus down-regulates e2F1, alleviating hypertrophy and proliferation of pulmonary arterial sMCs. it also promotes K + channel activation, resulting in hyperpolarization of the cell membrane and therefore vasodilation. abbreviation: eC: endothelial cell; nHe1: sodium/proton exchanger 1; nlrP3: noD-, lrr- and pyrin domain-containing protein 3; no: nitroxide; Pa: pulmonary artery; sGlt2i: sodium-glucose co-transporter-2 inhibitor; sMC: smooth muscle cell.

C. Potential Mechanisms of SGLT2i in Modulating Pulmonary Hypertension

The pathophysiology of pulmonary hypertension (PH) is a multifactorial condition involving pulmonary vasoconstriction, vascular remodeling, fibrosis, inflammation, and metabolic dysfunction, ultimately taxing the right heart. Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i), originally developed for diabetes, have shown significant potential in modulating these important components in PH, making them a relevant therapeutic option (Tan et al., 2024). The mild osmotic diuretic mechanism of SGLT2i, which causes glycosuria and natriuresis, may reduce plasma volume, cardiac preload, and pulmonary artery pressure (Wilcox, 2020) . In contrast to traditional diuretics, SGLT2i achieve this decompressive effect without excessive neurohumoral activation, selectively reducing interstitial fluid with minimal changes in intravascular volume (Puglisi et al., 2021) .

Furthermore, SGLT2i plays an important role in decreasing systemic inflammation and oxidative stress, which are the main drivers of pulmonary vascular remodeling (Tan et al., 2024; Tekin et al., 2025) . The drug has been shown to reduce reactive oxygen species (ROS)

(Tan et al., 2024) and suppress inflammatory mediators such as cytokines, chemokines, and adhesion molecules (Rolski & Mączewski, 2025) , as well as inhibit activation of the NLRP3 inflammasome (Rolski & Mączewski, 2025; Tan et al., 2024) . These anti-inflammatory and anti-oxidative effects could potentially prevent and reverse pulmonary vascular remodeling (Tan et al., 2024) .

Several studies, both in animals and humans, have also shown improvements in right ventricular function (King & Brittain, 2022) . SGLT2i can reduce the pressure load on the right ventricle and improve its parameters, as seen from the decrease in tricuspid regurgitation velocity (TRV) and NT-proBNP levels in heart failure patients with preserved ejection fraction (HFpEF) and PH (Tekin et al., 2025) . In addition, SGLT2i may contribute to decreased pulmonary vascular resistance (PVR) and possible improvements in endothelial function (King & Brittain, 2022) . SGLT2i may increase the bioavailability of nitric oxide (NO), an important vasodilator (Wilcox, 2020) , as well as inhibit Endothelial-to-Mesenchymal Transition (EndoMT) which contributes to the pathogenesis of PH . Thus, these various systemic and direct mechanisms confirm that SGLT2i have the potential to modulate key components in the development and progression of PH.

D. Clinical and Pre-Clinical Evidence

The role of Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) in modulating the pathophysiology of pulmonary hypertension (PH) is gaining increasing attention, supported by evidence from pre-clinical and early clinical studies, although further validation through large randomized controlled clinical trials (RCTs) is still urgently needed (Tan et al., 2024).

Pre-clinical evidence suggests promising effects of SGLT2i on pulmonary arterial pressure (PAP) and pulmonary vascular remodeling. For example, empagliflozin has been shown to reduce mortality, right ventricular systolic pressure (RVSP), mean pulmonary artery pressure (mPAP), and maladaptive pulmonary vascular remodeling in a rat model with monocrotaline (MCT)-induced PAH (Tan et al., 2024) . Similarly, dapagliflozin was reported to reduce pulmonary vascular damage, right ventricular (RV) dysfunction, and susceptibility to ventricular arrhythmias in MCT-induced PAH models (Joki et al., 2023) . Canagliflozin has also demonstrated the ability to directly cause pulmonary artery vasodilation in ex-vivo studies (King & Brittain, 2022) .

In terms of clinical evidence, observational studies and sub-analyses in patients with heart failure (HF) who have signs of PH have also shown positive results. In the EMBRACE-HF trial, empagliflozin significantly lowered pulmonary artery diastolic pressure in HF patients (Memarian & Eskandarian, 2025) . A study in patients with type 2 diabetes mellitus (T2DM) and cardiovascular risk showed that dapagliflozin significantly reduced RVSP and left ventricular filling pressure (LVFP) during exercise (King & Brittain, 2022) . A sustained reduction in PAP was also observed after the addition of SGLT2i to optimal medical therapy in heart failure patients (Tan et al., 2024) . Furthermore, dapagliflozin has been shown to reduce pulmonary wedge capillary pressure (PCWP) both at rest and during exercise, as well as reduce pulmonary artery and right atrial pressures during exercise in HF patients with preserved ejection fraction (HFpEF) . A small study also showed that SGLT2i can significantly reduce tricuspid regurgitation velocity (TRV) and NT-proBNP levels in PH-HFpEF patients (Tekin et al., 2025) . In addition, combination therapy of sacubitril/valsartan with

dapagliflozin in patients with PH due to left heart disease (PH-LHD) resulted in improved left heart function, improved endothelial function, and decreased inflammation, thus slowing the progression of PH (Tan et al., 2024) . Recent studies in patients with exercise-induced PH and chronic kidney disease (CKD) have also shown SGLT2i can ameliorate hemodynamic abnormalities and exercise intolerance, and improve left ventricular function global longitudinal strain (LVGLS) (Satoh et al., 2024) .

The potential role of SGLT2i is extended not only to PH group 2 (due to left heart failure), but also to PH group 3 (due to chronic lung disease), although further studies are needed (King & Brittain, 2022). SGLT2i is hypothesized to modulate important components in the pathophysiology of PH, including systemic inflammation, oxidative stress, vascular remodeling, and improvement of right heart function (Tan et al., 2024) .

However, it should be emphasized that the available data still have limitations. Currently, there are not many direct RCTs that have PH as the primary endpoint (Tan et al., 2024) . Much of the existing evidence comes from pre-clinical studies or sub-analyses of clinical trials designed for other conditions such as heart failure or diabetes (King & Brittain, 2022; Tan et al., 2024) . Some studies also had small sample sizes, retrospective designs, or were conducted in single centers, which limits the generalizability of the findings (Tekin et al., 2025) . One study also reported no significant changes in cardiopulmonary interaction parameters after initiation of SGLT2i in HFpEF/HFmrEF patients (Herrmann et al., 2025) . Therefore, although preliminary results are very promising and support the potential of SGLT2i as a novel therapy for PH, more large, specifically designed randomized controlled clinical trials are needed to validate its efficacy and safety in diverse PH patient populations (Tan et al., 2024) . Currently, two ongoing clinical trials (Dapagliflozin in Pulmonary Arterial Hypertension, ClinicalTrials.gov ID: NCT05179356; and Empagliflozin in Pulmonary Arterial Hypertension, ClinicalTrials.gov ID: NCT05493371) are expected to provide more comprehensive clinical data (Luo et al., 2024; Tan et al., 2024) .

E. Limitations and Challenges of Clinical Implementation

Although the potential of Sodium-Glucose Cotransporter 2 inhibitors (SGLT2i) in modulating pulmonary hypertension (PH) is increasingly being investigated, there are several significant limitations and challenges that need to be addressed before their use can be widely recommended.

First, there has been no formal recommendation of SGLT2i use specifically for PH (non-diabetes) from major guidelines. The 2022 guidelines from the European Society of Cardiology/European Respiratory Society (ESC/ERS), for example, currently advise against the use of SGLT2i in pulmonary arterial hypertension (PAH, Group 1) unless it is necessary due to comorbidities (Allen, 2024; Satoh et al., 2024) . Although SGLT2i have been strongly recommended (Class 1) for chronic heart failure with decreased ejection fraction (HFrEF) and shown benefit (Class 2a) for heart failure with preserved ejection fraction (HFpEF) regardless of diabetes status (Heidenreich et al.,2022) , these recommendations are for heart failure and not directly for PH as a primary indication (Allen, 2024) . Pulmonary hypertension due to left heart disease (PH-LHD, Group 2) itself still lacks specific targeted therapy (King & Brittain, 2022; Luo et al., 2024) .

Second, there are still limited specialized clinical trials dedicated to PH. Most of the evidence supporting the potential of SGLT2i in PH comes from pre-clinical animal studies, sub-analyses of large clinical trials focused on heart failure or diabetes, or small-scale observational studies (Tekin et al., 2025) . For example, a case series on HFpEF/HFmrEF patients found no significant changes in pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR), or pulmonary capillary wedge pressure (PCWP) within 6 months of SGLT2i initiation. The study hypothesized that the results may be due to patients still having congestion or their baseline PAP not being high enough (Herrmann et al., 2025) . A retrospective cohort study on PH-HFpEF also explicitly stated larger-scale randomized trials are needed to confirm the results (Tekin et al., 2025) . Similarly, a study on exercise-induced PH (post-EIPH) in chronic kidney disease (CKD) patients acknowledged its limitations as a single-center study with a relatively small sample size, which limits the generalizability of findings and statistical power for subgroup analysis (Satoh et al., 2024) . This underscores the need for further validation through larger, well-defined studies. Fortunately, there are currently two ongoing randomized controlled clinical trials (RCTs) (Dapagliflozin in Pulmonary Arterial Hypertension, ClinicalTrials.gov ID: NCT05179356, and Empagliflozin in Pulmonary Arterial Hypertension, ClinicalTrials.gov ID: NCT05493371) that specifically evaluated SGLT2i in PAH, and the results are still awaited (Luo et al., 2024; Tan et al., 2024).

Third, the effects of SGLT2i likely differ depending on the etiology of PH (Group 1 vs Group 2 vs Group 3). Important heart failure clinical trials generally exclude patients with PAH (Group 1), but do not uniformly exclude individuals with PH-LHD (Group 2) (Luo et al., 2024) . This suggests that most of the existing clinical observations favor Group 2 PH. The role of SGLT2i in PAH (Group 1) is currently still largely unknown (LEMONJAVA et al., 2024) , and strong direct evidence is still lacking (Tan et al., 2024) . However, pre-clinical studies in animal models of monocrotaline-induced PAH (similar to Group 1) showed promising results, including reduced mortality, PAP, right ventricular systolic pressure (RVSP), and vascular remodeling (Allen, 2024) . On the other hand, SGLT2i has shown potential benefit in PH-LHD (Group 2), although a study focusing on this specifically excluded PH patients from groups 1, 3, 4, or 5 (Tekin et al., 2025) . Meanwhile, the potential role of SGLT2i in Group 3 PH (due to chronic lung disease) was mentioned as requiring further research (King & Brittain, 2022).

CONCLUSION

SGLT2 inhibitors offer promising potential in managing pulmonary hypertension (PH) through mechanisms like diuretic effects, anti-inflammation, antioxidation, and right heart function improvement. Preclinical evidence and early clinical studies show encouraging results, particularly in PH due to left heart disease (PH-LHD), though benefits in pulmonary arterial hypertension (PAH) and other PH groups need further exploration. Limitations include the absence of large trials with PH as the primary endpoint, hindering widespread use. Ongoing randomized controlled trials should clarify SGLT2i as adjunctive therapy. Until robust evidence emerges, apply SGLT2i in PH patients with clear cardiovascular or renal indications, while monitoring potential pulmonary hemodynamic benefits. Future research may conduct large-scale, PH-specific randomized controlled trials evaluating SGLT2i efficacy across PH subgroups (e.g., PAH vs. PH-LHD), with endpoints including pulmonary

artery pressure, right ventricular function, and long-term survival, alongside safety in diverse populations.

REFERENCES

Allen. (2024). Peran SGLT2i terhadap Risiko Kardiorenal Pasien dengan atau Tanpa Diabetes Melitus Tipe 2. *Cermin Dunia Kedokteran*, *51*(2), 110–114. https://doi.org/10.55175/cdk.v51i2.873

Fernandez-Fernandez, B., Sarafidis, P., Kanbay, M., Navarro-González, J. F., Soler, M. J., Górriz, J. L., & Ortiz, A. (2020). SGLT2 inhibitors for non-diabetic kidney disease: drugs to treat CKD that also improve glycaemia. In *Clinical kidney journal* (Vol. 13, Issue 5, pp. 728–733). https://doi.org/10.1093/ckj/sfaa198

Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., … Yancy, C. W. (2022). 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. In *Circulation* (Vol. 145, Issue 18). https://doi.org/10.1161/CIR.0000000000001063

Herrmann, E. J., Guckert, M., Gruen, D., Keller, T., Tello, K., Seeger, W., Sossalla, S., & Assmus, B. (2025). Case Series Evaluating the Relationship of SGLT2 Inhibition to Pulmonary Artery Pressure and Non-Invasive Cardiopulmonary Parameters in HFpEF/HFmrEF Patients—A Pilot Study. *Sensors*, *25*(3), 1–14. https://doi.org/10.3390/s25030605

Humbert, M., Kovacs, G., Hoeper, M. M., Badagliacca, R., Berger, R. M. F., Brida, M., Carlsen, J., Coats, A. J. S., Escribano-Subias, P., Ferrari, P., Ferreira, D. S., Ghofrani, H. A., Giannakoulas, G., Kiely, D. G., Mayer, E., Meszaros, G., Nagavci, B., Olsson, K. M., Pepke-Zaba, J., … Rosenkranz, S. (2023). 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Respiratory Journal*, *61*(1), 2200879. https://doi.org/10.1183/13993003.00879-2022

Joki, Y., Konishi, H., Takasu, K., & Minamino, T. (2023). Tofogliflozin, a sodium-glucose cotransporter 2 inhibitor, improves pulmonary vascular remodeling due to left heart disease in mice. *Journal of Cardiology*, *81*(4), 347–355. https://doi.org/10.1016/j.jjcc.2022.10.003

Kaur, P., Behera, B. S., Singh, S., & Munshi, A. (2021). "The pharmacological profile of SGLT2 inhibitors: Focus on mechanistic aspects and pharmacogenomics." *European Journal of Pharmacology*, *904*, 174169. https://doi.org/https://doi.org/10.1016/j.ejphar.2021.174169

King, N. E., & Brittain, E. (2022). Emerging therapies: The potential roles SGLT2 inhibitors, GLP1 agonists, and ARNI therapy for ARNI pulmonary hypertension. *Pulmonary Circulation*, *12*(1), 1–16. https://doi.org/10.1002/pul2.12028

Kopeć, G., Kurzyna, M., Mroczek, E., Chrzanowski, Ł., Mularek-Kubzdela, T., Skoczylas, I., Kuśmierczyk, B., Pruszczyk, P., Błaszczak, P., Lewicka, E., Karasek, D., Mizia-Stec, K., Tomaszewski, M., Jacheć, W., Ptaszyńska-Kopczyńska, K., Peregud-Pogorzelska, M., Doboszyńska, A., Pawlak, A., Gąsior, Z., … Torbicki, A. (2020). Characterization

of Patients with Pulmonary Arterial Hypertension: Data from the Polish Registry of Pulmonary Hypertension (BNP-PL). *Journal of Clinical Medicine*, *9*(1). https://doi.org/10.3390/jcm9010173

Lemonjava, I., Gudushauri, N., Tskhakaia, I., Martinez Manzano, J. M., & AZMAIPARASHVILI, Z. (2024). Impact of Sglt2 Inhibitors on Mortality in Pulmonary Arterial Hypertension: Exploring the Association. *Chest*, *166*(4), A5793. https://doi.org/10.1016/j.chest.2024.06.3435

Luo, T., Wu, H., Zhu, W., Zhang, L., Huang, Y., & Yang, X. (2024). Emerging therapies: Potential roles of SGLT2 inhibitors in the management of pulmonary hypertension. *Respiratory Medicine*, *227*(January), 107631. https://doi.org/10.1016/j.rmed.2024.107631

Memarian, M., & Eskandarian, R. (2025). *SGLT2 inhibitors for the treatment of pulmonary hypertension ; new trends*. *14*(3), 3–5. https://doi.org/10.34172/jrip.2025.38409

Mocumbi, A., Humbert, M., Saxena, A., Jing, Z.-C., Sliwa, K., Thienemann, F., Archer, S. L., & Stewart, S. (2024). Pulmonary hypertension. *Nature Reviews Disease Primers*, *10*(1), 1. https://doi.org/10.1038/s41572-023-00486-7

Pabel, S., Hamdani, N., Luedde, M., & Sossalla, S. (2021). SGLT2 Inhibitors and Their Mode of Action in Heart Failure—Has the Mystery Been Unravelled? *Current Heart Failure Reports*, *18*(5), 315–328. https://doi.org/10.1007/s11897-021-00529-8

Prins, K. W., & Thenappan, T. (2016). World Health Organization Group I Pulmonary Hypertension: Epidemiology and Pathophysiology. *Cardiology Clinics*, *34*(3), 363–374. https://doi.org/https://doi.org/10.1016/j.ccl.2016.04.001

Puglisi, S., Rossini, A., Poli, R., Dughera, F., Pia, A., Terzolo, M., & Reimondo, G. (2021). *Effects of SGLT2 Inhibitors and GLP-1 Receptor Agonists on System*. *12*(October), 1–10. https://doi.org/10.3389/fendo.2021.738848

Rolski, F., & Mączewski, M. (2025). Cardiac Fibrosis: Mechanistic Discoveries Linked to SGLT2 Inhibitors. *Pharmaceuticals*, *18*(3). https://doi.org/10.3390/ph18030313

Satoh, T., Yaoita, N., Higuchi, S., Nochioka, K., Yamamoto, S., Sato, H., Tatebe, S., Yamada, K., Yamada, Y., Komaru, K., Chiba, N., Sarashina, Y., Mori, R., Nakada, M., Hayashi, H., Suzuki, H., Takahama, H., Ota, H., & Yasuda, S. (2024). Impact of Sodium-Glucose Co-Transporter-2 Inhibitors on Exercise-Induced Pulmonary Hypertension. *Pulmonary Circulation*, *14*(4), 1–8. https://doi.org/10.1002/pul2.70026

Tan, J. S., Wei, Y., Chong, L., Yang, Y., Hu, S., & Wang, Y. (2024). SGLT2 inhibitors as a potential therapeutic option for pulmonary hypertension: mechanisms and clinical perspectives. *Critical Reviews in Clinical Laboratory Sciences*, *61*(8), 709–725. https://doi.org/10.1080/10408363.2024.2361012

Tekin, I., Yaylalı, Y. T., & Yaylalı, G. F. (2025). Effects of Sodium-glucose Co-transporter-2 Inhibitors on Pulmonary Hypertension in Heart Failure with Preserved Ejection Fraction. *Interventional Cardiology Perspective*, *1*(1), 23–28.

Teo, Y. H., Teo, Y. N., Syn, N. L., Kow, C. S., Yoong, C. S. Y., Tan, B. Y. Q., Yeo, T.-C., Lee, C.-H., Lin, W., & Sia, C.-H. (2021). Effects of Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitors on Cardiovascular and Metabolic Outcomes in Patients Without Diabetes Mellitus: A Systematic Review and Meta-Analysis of Randomized-Controlled

Trials. *Journal of the American Heart Association*, *10*(5), e019463. https://doi.org/10.1161/JAHA.120.019463

Wilcox, C. S. (2020). Antihypertensive and Renal Mechanisms of SGLT2 (Sodium-Glucose Linked Transporter 2) Inhibitors. *Hypertension*, *75*(4), 894–901. https://doi.org/10.1161/HYPERTENSIONAHA.119.11684

Yohanes, D. C. (2020). Penghambat Sodium-Glucose Cotransporter-2. *Acta Pharmaciae Indonesia : Acta Pharm Indo*, *8*(1), 26. https://doi.org/10.20884/1.api.2020.8.1.2450

Zulkarnain, B. S., & Umini, K. (2025). IMPACT SGLT2 INHIBITORS (Dapagliflozin and Empagliflozin) In Heart Failure With Reduced Ejection Fraction (HFrEF): a scoping review. *MEDFARM: Jurnal Farmasi Dan Kesehatan*, *13*(2), 257–278. https://doi.org/10.48191/medfarm.v13i2.462

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