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REVIEW ARTICLE

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Emerging therapies: The potential roles SGLT2 inhibitors, GLP1 agonists, and ARNI therapy for ARNI pulmonary hypertension

Nicholas E. King[1] | **Evan Brittain**[2]

[1]Vanderbilt University Medical Center, Nashville, Tennessee, USA

[2]Department of Medicine, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

Correspondence
Evan Brittain, Department of Medicine, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, 2525 West End Bldg., Room/Suite #300-A, Nashville, TN 37232, USA.
Email: evan.brittain@vumc.org

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Abstract

Pulmonary hypertension (PH) is a highly morbid condition. PH due to left heart disease (PH-LHD) has no specific therapies and pulmonary arterial hypertension (PAH) has substantial residual risk despite several approved therapies. Multiple lines of experimental evidence link metabolic dysfunction to the pathogenesis and outcomes in PH-LHD and PAH, and novel metabolic agents hold promise to improve outcomes in these populations. The anti-diabetic sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP1) agonists targeting metabolic dysfunction and improve outcomes in patients with LHD but have not been tested specifically in patients with PH. The angiotensin receptor/neprilysin inhibitors (ARNIs) produce significant improvements in cardiac hemodynamics and may improve metabolic dysfunction that could benefit the pulmonary circulation and right ventricle function. On the basis of promising preclinical work with these medications and clinical rationale, we explore the potential of SGLT2 inhibitors, GLP1 agonists, and ARNIs as therapies for both PH-LHD and PAH.

KEYWORDS
metabolic dysfuction, pulmonary arterial hypertension

INTRODUCTION

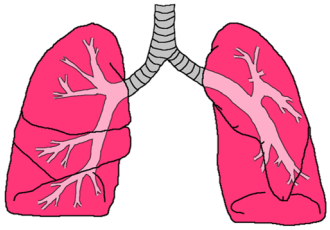
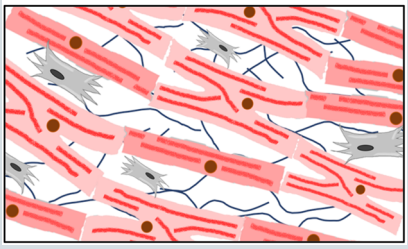
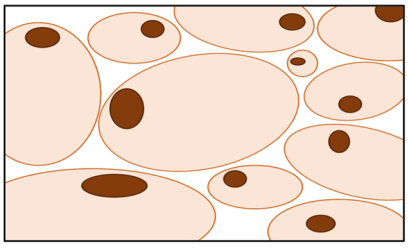
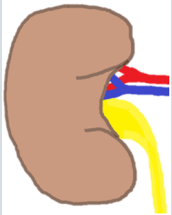
Group II pulmonary hypertension (PH) is a hemodynamic change of the pulmonary venous vasculature driven by elevated postcapillary pressure transmitted from the left heart from either heart failure with reduced or preserved ejection fraction (HFrEF and HFpEF, respectively).[1–3] Group II PH driven by left heart disease (PH-LHD) can be clinically isolated or occur in conjunction with elevated precapillary pulmonary arterial hypertension (combined pre- and postcapillary PH [CPH]), giving a spectrum of disease across the pulmonary vascular bed.[1–3]

PH-LHD is the most common manifestation of PH, occurring in 40%–75% of patients with HFrEF and 36%–83% with HFpEF.[4–10] The prognosis following the development of PH-LHD is poor, with multiple studies showing increased mortality beyond that of left heart failure.[5,7,11–14] Management for PH-LHD is limited to management of any co-occurring conditions, and to date no therapies have been shown to be effective for the prevention or progression of PH-LHD.[3] Even for those patients with CPH, trials of

treatment with typical Group I pulmonary arterial hypertension (PAH) therapies such as endothelin-1 (ET-1) receptor antagonists or phosphodiesterase-5 (PDE5) inhibitors have not shown meaningfully improved outcomes.[15–17] Additional studies, including ones investigating prostanoids, are ongoing; however alternative therapies need to be investigated given the lack of clear benefit in the PH-LHD and CPH populations.[3]

Recently, several classes of medication have been or are anticipated to be approved to reduce clinical events in heart failure. The mechanisms of these agents suggest that they may be beneficial in patients with PH-LHD and perhaps even PAH. Accordingly, this review will investigate the work of three novel classes of medication in the setting of PH-LHD and PAH: the sodium–glucose cotransporter 2 (SGLT2) inhibitors, the glucagon-like peptide-1 (GLP1) receptor agonists, and the angiotensin receptor/neprilysin inhibitors (ARNIs) (Table 1). These agents show promise as potential therapies for both myocardial diseases that

TABLE 1 Overview of the effects of SGLT2 inhibitor, GLP1 agonist, and ARNI therapy 2

Organ	SGLT2 inhibitors	GLP1 agonists	ANRI therapy
Pulmonary Vasculature 	• Reduce PA pressures • Reduce adverse remodeling	• Reduce inflammation, fibrosis, and adverse remodeling • Increase nitric oxide	• Reduce PA pressures • Reduce adverse remodeling
RV myocardium 	• Reduce RV pressures • Improve metabolism • Reduce inflammation • Reduce adverse remodeling	• Improved RV function • Reduce inflammation • Cardioprotective in ischemia • Reduce adverse remodeling	• Reduce RV pressures • Reduce adverse remodeling • Reduce hypertrophy
Adipose 	• Improve insulin sensitivity	• Improve insulin sensitivity • Weight loss • Brown fat thermogenesis	• Potentially improve insulin sensitivity
Renal 	• Enhance osmotic diuresis		• Enhance natriuresis

Abbreviations: ARNI, angiotensin receptor (blocker)/neprilysin inhibitor; GLP1, glucose-like peptide (1); PA, pulmonary artery; RV, right ventricle; SGLT2, sodium–glucose cotransporter.

leads to Group II PH and for pulmonary vascular dysfunction in patients CPH or PAH.

Metabolic dysfunction as a driver of pulmonary vascular disease and myocardial dysfunction

While the precise mechanisms of PH-LHD and PAH remain unclear, there is growing evidence that metabolic dysfunction is injurious to the right ventricle (RV) and pulmonary vasculature. Obesity and insulin resistance/glucose intolerance are strongly associated with increased risk of developing and can modify the severity of pulmonary vascular dysfunction manifested as Group II PH-LHD (particularly CPH) and PAH.[7,12,18–29] Exposure to a high-fat diet (HFD), an inducer of metabolic dysfunction, can produce pulmonary vascular dysfunction in multiple animal models and is enhanced by alterations in apolipoprotein E, a protein involved in lipid metabolism.[30–34] The HFD results in increased pulmonary vascular reactive oxygen species, inflammation, and remodeling, leading to increased pulmonary artery stiffness and pressure.[33–35] Bone morphogenic protein receptor type 2 (BMPR2) mutations appear to contribute to the development of insulin resistance and weight gain in mice models of PAH.[36–38] HFD exposure in BMPR2 mutant models augments the severity of PAH and is strongly correlated with fasting insulin levels rather than glucose, further suggesting metabolic dysfunction is deleterious to the pulmonary vasculature.[35] This is significant when considering that BMPR2 mutations drive ~25% of idiopathic PAH and its expression is altered in almost all cases of connective tissue-associated PAH.[39–41] Several of these HFD models have shown that the metabolic sensitizers metformin and rosiglitazone can rescue (i.e improve insulin sensitivity, RV function, and pulmonary artery pressures in) the PAH phenotype.[32,34]

Metabolic dysfunction is also toxic to the myocardium. Under normal conditions, the heart preferentially uses lipids in the form of fatty acids for energy production which is pathologically shifted to glycolysis in PAH and PH-LHD.[42,43] Metabolomic profiling of PAH patients shows abnormal lipid homeostasis with increased proinflammatory lipids.[44] The RVs of PAH patients mirror this disruption, with increased myocardial triglyceride levels and elevated markers of lipotoxic ceramides on cardiac magnetic resonance imaging.[45] A mouse model of HFD-induced PAH showed increased myocardial lipid accumulation and hypertrophy, which correlated with impaired RV diastolic and systolic function.[34] In well-controlled, type-2 diabetic patients without complications, myocardial triglyceride levels correlate with impaired echocardiographic strain, a marker of subclinical myocardial dysfunction.[46,47] Moreover, individuals with metabolic syndrome are more likely to have RV dysfunction, with an increased incidence of RV hypertrophy, elevated pulmonary artery systolic pressures, and abnormal RV diastolic function.[48,49] This unaddressed myocardial dysfunction might explain the continued deterioration of RV function in PAH despite full medical treatment with current indicated therapy such as prostacyclins, ET-1 receptor antagonists, and PDE5 inhibitors.[50] Preclinical and clinical studies suggest that RV dysfunction may be modifiable with exposure to therapies that improve metabolic status. For example, an 8-week-long phase-2 clinical trial of metformin in patients with PAH showed significant improvement in RV fractional area change on echocardiography and decreased RV lipid content as exploratory endpoints, indicating that metabolic dysfunction is a promising therapeutic target.[51]

Metabolic dysfunction also drives inflammation that contributes to PH. Metabolic function is closely linked to immune regulation as part of an organism's homeostatic equilibrium.[52] Obesity is associated with elevations in inflammatory markers such as C-reactive protein, transforming growth factor-β (TGFβ), neutrophil myeloperoxidase, and calprotectin.[53–57] Adipocytes themselves produce proinflammatory signals including inflammatory fatty acids, interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNFa) which stimulate immune system activation and in turn worsen metabolic dysfunction.[58] Animal models have shown that increased inflammatory signaling can also lead to the development of PH. Treatment of mice with exogenous IL-6 has been shown to induce PH, with animals showing increased RV pressures and RV hypertrophy. This effect was augmented by exposure to hypoxia chronic.[59] A mouse model of IL-6 overexpression resulted in PH with the formation of T cell lesions in the pulmonary vasculature.[60] Overexpression of Fos-related antigen 2 and resultant activation of the Fos pathway, a downstream pathway of inflammatory signaling, has been shown to result in the development of pulmonary fibrosis in mice.[61] Lung tissue from PAH samples shows increased pulmonary vascular infiltration of chronic inflammatory cells such as T cells, B cells, and macrophages.[62,63] Depletion of T cells with anti-CD4 monoclonal antibodies in an ovalbumin-induced mouse model of PH reduced pulmonary artery muscularization, further reinforcing the pathogenic nature of chronic inflammation in PH.[64] Chronic inflammation in the pulmonary vasculature reduces nitric oxide (NO) production, increases fibrosis, and induces an endothelial to mesenchymal transition (EMT).[65] EMT is implicated in a variety of pathologic vascular phenotypes, including

PAH where it contributes to the muscularization of the pulmonary vasculature.[66–69] Chronic inflammation is also found in the RV and likely contributes to the myocardial dysfunction that exacerbates clinical deterioration in PAH.[70,71] A mouse model of HFD-induced PAH showed that the anti-inflammatory fatty acid nitrooctadecenoic acid could rescue the PAH phenotype, including the metabolic dysfunction.[33] Work is ongoing to elucidate if targeting this proinflammatory environment has a potential therapeutic target for PAH.[70,72,73]

SGLT2 inhibitor therapy

The sodium–glucose cotransporter 2 (SGLT2) is a transport protein located in the proximal tubule of the nephron responsible for the reuptake of filtered glucose from the glomerular filtrate.[74] The SGLT2 inhibitors block the transporter thereby lowering the reabsorption threshold of glucose, resulting in glucosuria which lowers serum glucose.[74] Four SGLT2 inhibitors have been approved after trials showed them to be efficacious in lowering hemoglobin A1c, starting with first-in-class canagliflozin in 2013 and subsequently followed by dapagliflozin, empagliflozin, and ertugliflozin.[75–83] Subsequent Food and Drug Administration (FDA)-mandated cardiovascular outcome trials of novel antidiabetic agents showed treatment with canagliflozin, dapagliflozin, and empagliflozin resulted in significant improvements in a composite outcome of major adverse cardiovascular events (MACE; cardiovascular death, nonfatal stroke or myocardial infarction), with secondary endpoints suggesting improvement in renal function. Dapagliflozin and empagliflozin additionally showed reduced hospitalizations for heart failure.[84–87] Ertugliflozin showed no significant difference in either cardiovascular or renal outcomes.[88] This led to subsequent studies showing that canagliflozin and dapagliflozin reduce renal dysfunction, and others showing that dapagliflozin and empagliflozin improve outcomes in HFrEF. Notably, these trials did not exclude patients with PH-LHD unless they required oxygen, while they did exclude patients with PAH.[89–92] Subsequent analysis of the canagliflozin cardiovascular outcomes trial (CANVAS) also showed a reduction in hospitalization and death in both the HFpEF and HFrEF subgroups.[93]

SGLT2 inhibitors have multiple effects that may be beneficial in patients with PH-LHD. They directly address insulin resistance and improve cardiac energy utilization by reducing glycolysis and increasing fatty acid oxidation.[94,95] They induce osmotic diuresis via glucosuria and have shown a primary benefit in improving outcomes in both the HFrEF and HFpEF populations.[91–93,96] Their role in reducing the progression of chronic kidney disease (CKD) might also be therapeutically important as CKD is associated with PAH and its presence worsens outcomes.[97,98] There is also growing evidence that SLGT2 inhibitors reduce inflammation and prevent cardiac remodeling, although further work is needed to determine if this is a direct effect on cardiomyocytes or secondary to improvement in the inflammatory dysmetabolic state.[95,99–104]

Evidence is accumulating of their potential efficacy in both PAH and PH-LHD. An ex-vivo study of pulmonary and coronary arteries in a diabetic mouse model showed that SGLT inhibition, using both a nonspecific SGLT inhibitor and the SGLT2 specific inhibitor canagliflozin, resulted in direct, specific vasodilation of the pulmonary arteries.[105] In a rat model of monocrotaline-induced PAH, empagliflozin treatment resulted in reduced mortality, hemodynamic, pulmonary vasculature and myocardial architecture alterations.[106] A randomized, controlled, open-label trial of 78 patients with a baseline normal EF, type 2 diabetes, hypertension, and/or stable ischemic in Japan showed that treatment with dapagliflozin attenuated the development of exercise-induced PH defined as an echocardiographic RV systolic pressure (RVSP) > 50 mmHg post-exercise. The trial excluded patients with advanced heart failure (New York Heart Association class 3 or 4, or any prior heart failure hospitalization), or with a resting RVSP > 50 mmHg.[107] EMBRACE-HF randomized 65 stable heart failure patients with preserved and reduced EF in a double-blind study of empagliflozin to study its effects on pulmonary artery (PA) pressures. All patients had implantable PA pressure monitors and the mean PA pressure of both groups on enrollment was 30 mmHg. Treatment with empagliflozin resulted in a reduction in PA diastolic pressure of 1.7 mmHg at 12 weeks. The secondary endpoints of decreased PA systolic and mean pressures were not significant, but the PA mean decrease trended towards significance ($p = 0.07$). The study was limited by the small sample size and significant differences in age, glomerular filtration rate, and mineralocorticoid receptor antagonist usage.[108] Both human studies, while methodologically limited, suggest that SGLT2 inhibitors may be effective in addressing both myocardial dysfunction and pulmonary vascular disease in patients with PAH and PH-LHD. Future work is needed to explore this possibility further with adequately powered clinical trials.

GLP1 receptor agonist therapy

Glucagon-like peptide-1 (GLP1) is an incretin hormone secreted by the intestinal L cells in response to nutrients

in the gut lumen.[109] GLP1 has pleiotropic effects with its major functions occurring at the pancreas to regulate insulin secretion, the gastrointestinal tract to coordinate digestion, adipose tissue to promote brown fat thermogenesis, and the hypothalamus to regulate satiety.[109,110] GLP1 is rapidly degraded by dipeptidyl-peptidase 4 (DPP4), with a half-life of only 1–2 min.[109] Given its beneficial effects to correct metabolic dysfunction, multiple agents were developed to target the GLP1 axis. Novel small-molecule inhibitors of DPP4 prevent degradation of endogenous GLP1.[111,112] Degradation-resistant GLP1 agonists activate the GLP1 receptor.[113,114] These agents are effective in lowering hemoglobin A1c and promote significant weight loss, with semaglutide generally showing superiority.[113–119] GLP1 agonists have also been studied for their outcomes in cardiovascular disease, with dulaglutide, liraglutide, and semaglutide showing significant improvement in MACE outcomes primarily driven by ischemic event reductions.[120–123]

The GLP1 receptor is expressed in multiple tissues, including the heart and the smooth muscle cells of the main pulmonary artery branches in primates.[124] GLP1 agonists reduce inflammatory signaling at a cellular level, and animal studies show GLP1 agonists reduce infarct size and improve outcomes in the setting of induced acute myocardial infarction (AMI), strongly suggestive of a cardioprotective role.[125–131] Following a small nonrandomized trial of 10 patients with AMI who received GLP1 agonist infusions peri-AMI and had significant improvement in post-AMI cardiac function, a larger randomized trial of GLP1 infusion in ST-elevation AMI showed a significant decrease in infarct size and increase in salvaged myocardium following coronary intervention as compared to ischemic area matched controls.[132,133] A cardioprotective effect has also been shown in non-AMI settings, with GLP1 agonists improving cardiac function in the setting of dobutamine-induced cardiac stress, and in patients undergoing elective coronary intervention requiring temporary coronary artery balloon occlusion.[134,135] A subsequent safety and efficacy study of higher dose GLP1 agonist in AMI showed safety but was underpowered to assay for cardioprotective effects.[136]

Outside the ischemic setting, GLP1 agonists and DDP4 inhibitors have been evaluated for their ability to improve cardiac function. In a small nonrandomized cohort of patients with symptomatic HFrEF, a GLP1 agonist infusion resulted in improved LV function and exercise capacity, however, subsequent randomized controlled trials demonstrated no difference in outcomes with GLP1 agonists in HFrEF patients.[137–140] Subsequent analysis of the EXSCEL trial showed that while exenatide had no overall benefit for patients with type 2 diabetes, in patients without heart failure it did reduce new heart failure hospitalizations and risk of death.[140,141]

Diabetic patients seem to benefit most from GLP1 agonist therapy, with a large retrospective cohort showing GLP1 agonist therapy in patients with diabetes was associated with reduced incidence of new heart failure.[142] A rat model of diabetes-induced cardiomyopathy showed the DPP4 inhibitor sitagliptin prevented myocardial remodeling and improve left ventricle (LV) function.[143] A small randomized, double-blind trial of liraglutide in diabetic patients showed improvement in LV function on cardiac MRI.[144] Another small randomized non-blinded trial of liraglutide versus metformin showed a significant improvement in the primary endpoint of echocardiographic strain imaging with GLP1 agonist therapy. The study additionally showed significant improvements in its secondary endpoints of reduced arterial stiffness and decreased oxidative stress as measured by serum oxidized lipids and proteins.[145] A nondiabetic rat model of aortic-band induced HFpEF showed that GLP1 agonist therapy improved LV function and survival, suggestive that GLP1 agonists can be beneficial in HFpEF and act directly on cardiomyocytes to prevent adverse remodeling.[146] Further work is needed but the animal models and clinical data suggest that GLP1 therapy could substantially reduce and possibly treat heart failure associated with metabolic dysfunction, potentially reducing the burden of PH-LHD.

The GLP1 axis is a promising target for PAH as well. In vitro studies show that GLP1 agonists reduce intracellular inflammatory signals, increase NO signaling, and prevent the EMT which is linked to abnormal lipid metabolism and a number of disease states including PAH.[147–149] While the precise mechanism is yet to be fully elucidated, in hepatocytes GLP1 agonists increase lipid efflux and restore cellular viability suggesting that the restoration of normal cellular lipid metabolism is key.[150] GLP1 agonist therapy in a rat model of bleomycin-induced idiopathic lung fibrosis (IPF) attenuated both the inflammatory and fibrotic phases of the model, improved lung architecture, and reduced RV hypertrophy.[151] Additional studies in rat PAH models induced by bleomycin, monocrotaline, and hypoxia have shown that DPP4 agonists protect against pulmonary vascular remodeling, that the effect is abolished by GLP1 antagonist therapy, and then rescued by GLP1 agonist therapy.[147,152] In these models, GLP1 activation reduced inflammatory signaling, reduced smooth muscle cell proliferation, and reversed TGFβ mediated EMT.[147,152] A murine hypoxia model of PAH showed GLP1 agonist therapy improved directly measured RVSP, decreased pulmonary arteriole thickening, and augmented intrinsic NO production.[153] An angiotensin-II induced model of

PAH in mice suggests these effects are mediated by endothelial cells, as an endothelial cell-specific GLP1 receptor knockout population showed no response to liraglutide.[154] Additional studies are needed to determine if these effects are seen in humans, but accumulating data is encouraging that GLP1 agonists may benefit PAH.

The endogenous natriuretic peptide system: A regulator of hemodynamic and metabolic homeostasis

B-natriuretic peptide (BNP) is an endogenous natriuretic peptide-hormone released primarily from ventricular cardiomyocytes in response to stretch.[155] Secreted Pro-BNP is cleaved to form BNP and the N-terminal fragment, NT-Pro-BNP, which is also released. BNP is cleared by binding to the natriuretic peptide clearance receptor (NPCR, also known as natriuretic peptide receptor [NPR] C) or degradation by neprilysin, an endopeptidase.[155] Atrial natriuretic peptide (ANP) is released from the atrial cardiomyocytes and functions similarly to BNP.[156]

The natriuretic system acts to reduce heart afterload by increasing natriuresis/diuresis, vasodilatation, and inhibition of the renin–angiotensin–aldosterone (RAA) and sympathetic axes.[157] If not cleared by NPCR, BNP binds NPR-A and B receptors which increase intracellular cyclic guafnosine monophosphate (cGMP) to trigger these effects.[156,158] In the endothelium, this results in vasodilation, reduced sodium reabsorption in the nephron, RAA antagonistic intracellular signaling, and diminished sympathetic outflow from the nervous system.[159–162] BNP also is a well-established biomarker of ventricular hemodynamic overload for both PAH and left heart failure.[163,164]

There is growing evidence that the natriuretic system is a modulator of metabolism and that its dysfunction seen in both PAH and PH-LHD might play a causative role. Increased natriuretic peptides have been shown to promote thermogenic browning of white adipose tissue in both human and mouse adipocytes.[165] Insulin resistance and especially obesity are associated with decreased circulating natriuretic peptides, which might represent a natriuretic peptide deficient state similar to that of insulin resistance.[166,167] Adipose-specific deletion of NPCR in mice has been shown to be protective against insulin resistance, obesity, and visceral fat accumulation, potentially by decreasing natriuretic peptide clearance and shunting the natriuretic peptides to the other natriuretic peptide receptors, NPR-A and -B.[168] Activation of NPR-A and -B receptors increases intracellular cGMP which promotes mitochondrial biogenesis, increases fat metabolism, prevents obesity, reduces insulin resistance, and attenuates inflammation.[169–171] Modulation of cGMP with PDE5 inhibitors such as sildenafil and tadalafil has also been shown to result in improved metabolic function in humans, suggesting another mechanism of these agents' action in PAH.[172,173] NRPA stimulation with natriuretic peptides is protective against hypoxia-induced PAH in a mouse model, with NRPA deletion resulting in increased RV and PA pressures, and RV and pulmonary vascular remodeling.[174]

The natriuretic system also plays a role in the regulation of the cellular architecture of the myocardium. Multiple animal studies have shown that NRPA activation and natriuretic peptides attenuate fibrosis and cardiomyocyte hypertrophy.[156] In preclinical models, natriuretic peptide signaling counteracts profibrotic TGFβ signaling, suppresses ET-1 expression, and acts on numerous other pathways to produce these beneficial effects.[156,175,176] A mouse model of HFD-induced HFpEF and PH-LHD found increased expression of the NPCR in the RV and that its overexpression in cardiomyocytes resulted in hypertrophy. This effect was attenuated by NPCR stimulation with a natriuretic peptide.[177]

Angiotensin receptor/neprilysin inhibitor therapy

The natriuretic peptide system, including both BNP and ANP, therefore, has numerous effects that may benefit patients with PAH, PH-LHD, heart failure, and/or metabolic syndrome. Both BNP and NT-Pro-BNP have been well studied as prognostic biomarkers for multiple cardiovascular conditions, including PAH, and have been targeted therapeutically.[178–185] Recombinant ANP was approved for decompensated heart failure in Japan in 1995.[156,186] Initial trials of synthetic BNP (nesiritide) and a neprilysin inhibitor (ecadotril) showed no effect in heart failure, however, when the neprilysin inhibitor sacubitril was combined with the angiotensin receptor blocker valsartan (termed angiotensin receptor/neprilysin inhibition or ARNI), a significant improvement in cardiovascular mortality was found in patients with HFrEF.[187–190] While ARNI therapy has not been shown to benefit mortality in a multinational population of patients with HFpEF, it is FDA-approved for all patients with HF as a posthoc analysis suggested a particular benefit in the postdecompensation setting.[191,192]

Correcting the relative deficiency of both BNP and ANP with ARNI therapy seeks to improve cardiac hemodynamics, metabolic homeostasis, and cellular function. The available data suggests testing ANRI therapy in patients with both PAH and PH-LHD is warranted. There

is evidence that ARNI therapy directly reduces hemodynamic alterations of PH, with case series of HFrEF patients with both PH-LHD and CPH treated with ARNI therapy showing significant reductions in PA pressures, to the point of reversal of some patients' PH.[193,194] A rat model of PAH induced by PA banding showed ARNI therapy improved hemodynamics and prevented myocardial architecture disruption.[195] A hypoxic model of PAH in rats also showed ARNI therapy improved hemodynamics, prevented RV remodeling, and reduced PA vascular wall thickness.[196] Combination of ANP therapy with a PDE5 inhibitor was shown in a rat model of hypoxia-induced PAH to enhance pulmonary vasculature dilation, resulting in reduced pressures and vascular remodeling beyond either agent alone.[197] A rat model of AMI showed that ARNI therapy reduced cardiomyocyte size, hypertrophic biomarkers, and prevented interstitial fibrosis.[198] Analysis of profibrotic serum biomarkers obtained from the participants in the PARADIGM-HF trial of ARNI therapy showed significant reductions of analytes associated with extracellular matrix fibrosis.[199] ARNI therapy is, therefore, a potentially efficacious therapy for both PAH and PH-LHD which deserves further investigation.

CONCLUSION

Metabolic dysfunction is a likely driver of both PH-LHD and PAH due to toxic effects on both the myocardium and pulmonary vasculature. Recently developed drug classes hold promise as potential future treatments based on animal and early clinical studies. The SGLT2 inhibitors improve metabolic dysfunction, improve hemodynamic measures, and may directly prevent cardiac remodeling in animal models. Small trials in humans have shown improvements in pulmonary artery pressures with therapy. The GLP1 agonists are highly efficacious agents to treat obesity, diabetes, and metabolic dysfunction, and might prevent the onset of heart failure in diabetics. Emerging evidence suggests they might be cardioprotective by reducing cardiac remodeling in the acute ischemic and chronic heart failure setting. Animal models also show they improve RV hemodynamics and pulmonary vascular remodeling in PAH. ARNI therapy enhances natriuretic peptide signaling and has been shown to result in improved RV hemodynamics in patients with PH and heart failure. Emerging evidence implicates natriuretic peptide deficiency in metabolic dysfunction and in adverse cardiac remodeling. These findings suggest SGLT2 inhibitors, GLP1 agonists, and ARNI therapy could provide significant therapeutic benefit in patients with PH due to PAH, PH-LDH, or CPH (Table 1). Further work is needed to elucidate the mechanisms of each agent's diverse actions and to determine if their promise translates into these highly morbid populations.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

Not applicable.

AUTHOR CONTRIBUTIONS

Nicholas E. King contributed to the drafting, preparation, and editing of the manuscript. Evan Brittain contributed to the drafting and editing of the manuscript.

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