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CARDIOVASCULAR PROTECTION WITH FINERERNONE AND EMPAGLIFLOZIN IN A PRE-CLINICAL MODEL FOR HYPERTENSION-INDUCED END-ORGAN DAMAGE

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ABSTRACT Pronounced cardiac hypertrophy and abnormal collagen deposition leading to impaired ventricular function frequently complicate chronic hypertension. Despite remarkable advances in drug therapies, hypertension remains a severe medical problem. An unfavourable consequence of chronic hypertension is multiple end-organ damage that can progress to overt heart failure, renal failure, myocardial infarction, and stroke. Moreover, compared with untreated normotensive subjects, even optimally treated hypertensive individuals are at increased risk of adverse cardiovascular events. Thus, strategies that prevent the complications of hypertension and directly target end-organ damage, independent of blood pressure-lowering actions, are of interest for drug development. Clinical trials of Finerernone (FIGARO-DKD) and Empagliflozin (EMPA-REG OUTCOME) have shown cardioprotective effects with significantly reduced mortality. In addition, the combination of Finerernone and Empagliflozin has shown promising cardioprotective effects in a preclinical study. This paper will discuss the driving factors of end-organ damage in hypertension and the effect of the combination of Finerernone and Empagliflozin in preventing end-organ damage.

KEYWORDS :

INTRODUCTION

Hypertension is a multifactorial disease characterized by the elevation of arterial pressure. It can be complicated by damage and metabolic changes in the heart, blood vessels, brain, kidney, retina and other target organs. Reducing the incidence and mortality rates of heart and cerebrovascular disease in patients with hypertension is the ultimate goal of antihypertensive therapy. However, organ damage and abnormal metabolism may not be resolved entirely even when blood pressure is under control.[1]

An unfavourable consequence of chronic hypertension is multiple end-organ damage that can progress to overt heart failure (HF), renal failure, myocardial infarction, and stroke.[2] Increasing the arterial blood pressure leads to organ damage via hemodynamic load. In addition to this elevated pressure load, many pathogenetically relevant factors have been identified that affect the severity of hypertensive end-organ damage and are independent of the pressure load (blood pressure level). In classical terms, end-organ damage is defined as the presence of one or more of the following features: hypercalcemia, renal failure, anaemia, and lytic bone lesions (which can be diagnosed on bone radiographs). The classic manifestations of hypertensive end-organ damage include the following[3]:

- Vascular and hemorrhagic stroke,
- Retinopathy,
- Coronary heart disease/myocardial infarction
- Heart failure,
- Proteinuria and renal failure and in the vasculature,
- Atherosclerotic change including the development of stenoses and aneurysms

The early detection and severity of typical end-organ damage and secondary diseases are vital determinants of cardiovascular prognosis in patients suffering from arterial hypertension. Thus, there is a high unmet medical need for effective therapies for preventing complications associated with hypertension. To reduce the incidence of cardiovascular morbidity and mortality, such as heart failure, end-stage renal disease, stroke and premature death, ideally, one should strive to prevent the initial damaging stages of the cardiovascular continuum as early as possible.[4]

Strikingly, optimally-treated hypertensive individuals have also been found to be at increased risk of adverse cardiovascular events. Thus, strategies that prevent the complications of hypertension and directly target end-organ damage, independent of blood pressure-lowering actions, is of vital interest.[2]

Hypertension And End-organ Damage

The human heart produces many hormones involved in regulating cardiac structure, systemic blood pressure, and water homeostasis. However, in hypertension, the regulatory function of the heart is diminished for many reasons, including reduced gene expression, the accumulation of altered molecular forms with reduced biological value, and reflex activation of the sympathetic nervous system.

The renin-angiotensin-aldosterone system (RAAS) is one of the essential hormonal mechanisms in controlling hemodynamic stability by regulating blood pressure, fluid volume, and sodium-potassium balance. For that reason, an alteration in any molecules that compose RAAS contributes to developing hypertension.[5] Aldosterone is another effector molecule of the RAAS, whose synthesis and secretion are stimulated by Angiotensin II through the AT1-R in the adrenal cortex. Through specific actions on the distal nephron of the kidney, aldosterone promotes sodium reabsorption, water retention, and potassium and magnesium loss, thereby modulating extracellular space volume and blood pressure.[6]

Since blood pressure is finely tuned by the RAAS, and any unbalance in this system will produce arterial blood pressure alterations.[7] Also, it has been shown that high plasma levels of aldosterone can also induce structural and functional alterations in the heart, kidneys, and blood vessels, such as vascular inflammation, myocardial fibrosis, nephrosclerosis, and tissue remodelling.[7]

Kidneys are one of the organs affected during hypertension, resulting in functional and structural damage with consequent renal dysfunction, in turn inducing an exacerbated hypertension phenotype. Aldosterone can cause sustained renal damage characterized by proteinuria, collagen accumulation, and glomerular structural lesions. Aldosterone promotes fibrosis and target-organ dysfunction in hypertensive or diabetic patients in different ways, such as plasminogen activator inhibitor stimulation, TGF-β1 and ROS. Also, aldosterone promotes the loss of glomerular podocytes, decreasing the slit-pore membrane integrity, which leads to proteinuria. The Renin-angiotensin-system (RAAS) Gliflozins, including empagliflozin, dapagliflozin, and canagliflozin, are a novel class of antidiabetic agents used for the treatment of T2D that selectively inhibit the sodium-glucose cotransporter (SGLT)2 to prevent glucose reabsorption in the proximal renal tubule. In the cardiovascular EMPA-REG OUTCOME trial, including 7020 T2D patients with established CVD, empagliflozin reduced cardiovascular death by 38% and heart failure (HF) hospitalization by 35% also directly affect the progression of renal fibrosis. Ang II acts on vascular smooth muscle cells, causing afferent and efferent arterioles to vasoconstriction.

During hypertensive renal damage, the progressive impairment of renal function, or chronic kidney disease, is caused by replacing functional nephrons with fibrotic scar tissue, as triggered by hemodynamic and cellular factors. Immediate consequences include hypoperfusion of damaged nephrons, increased sodium retention, stimulation of RAAS, uremia, metabolic waste retention, and extensive proteinuria, among other effects. Chronic kidney disease is characterized by interstitial macrophage infiltration. These macrophages can synthesize and secrete several molecules related to fibrogenesis, such as fibroblast growth factors or cytokines (TGF-β, TNF-α, IFN-γ), enzymes (e.g., ACE, plasminogen activators, collagenases) and their inhibitors (like tissue inhibitors of metalloproteinase (TIMPs)), matrix proteins (e.g., collagen, fibronectin, thrombospondin), and many other complement proteins, bioactive lipids, ROS, etc. Chronic kidney disease has a rapid progression, and, generally, the patient dies before receiving a kidney transplant. Patients also suffer accelerated cardiovascular diseases, a condition known as a cardiorenal syndrome. The cardiorenal syndrome can be induced by hypertension, inflammation, oxidative stress, and vascular calcification, among other conditions.[7]

Modalities For Reducing The Occurrence Of End-organ Damage Using Finerernone And Empagliflozin

Although new therapeutic approaches to blood pressure control have been developed, there is a greater appreciation that many patients require combination therapy, ideally as a fixed-dose combination, to achieve a satisfactory reduction in blood pressure and help reduce side effects and maximize patient compliance. However, recent outcomes trials have demonstrated that prevention of target organ damage is not simply a matter of lowering blood pressure and that other pressure-independent, neurohormonal mechanisms are involved.[2] The use of mineralocorticoid receptor antagonism, ACE inhibitors, and AT-R antagonism as drugs used to control the blood pressure has shown promising benefits besides lowering blood pressure.[7]

Renin-angiotensin-system blockade, either with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, has been included in respective guidelines as an antihypertensive cornerstone therapy for heart failure with reduced ejection fraction (HFrEF) as well as for CKD with albuminuria (>300 mg/g/d) during the last three decades. At least two major pharmacological principles were investigated recently in heart failure and CKD clinical trials beyond blood pressure control by the renin-angiotensin-system blockade.[8] First, sodium-glucose cotransporter-2 inhibition (SGLT2i) was introduced as a novel treatment option for metabolic control in type 2 diabetes (T2D). Gliflozins, including empagliflozin, dapagliflozin, and canagliflozin, are novel antidiabetic agents used to treat type 2 diabetes selectively inhibits the sodium-glucose cotransporter (SGLT)2 to prevent glucose reabsorption in the proximal renal tubule. In the cardiovascular EMPA-REG OUTCOME trial, including 7020 type 2 diabetes patients with established CVD, empagliflozin reduced cardiovascular death by 38%. Heart failure (HF) hospitalization by 35%.9,10 SGLT2 inhibitor empagliflozin reduced the risk of major adverse cardiovascular (CV) events in patients with T2D at high risk for CV events. It was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than the placebo. Subsequent analysis of the EMPA-REG OUTCOME data indicated that the cardioprotective effect of empagliflozin appears to be independent of glycemic control, suggesting that mechanisms, in addition to glycemic control, are involved.[10]

The second study demonstrated that mineralocorticoid receptor (MR) antagonism has kidney- and cardioprotective effects. In animal studies, it was found that finerenone prevented organ damage to the heart and kidney in deoxycorticosterone acetate-/ salt-induced hypertensive rats and rats with chronic heart failure after coronary artery ligation. Notably, finerenone exerted cardiorenoprotective effects independent of its blood pressure reduction.[11,12] Finerenone has been shown to prevent tubular injury in a rat ischemic acute kidney injury model [ischemia/reperfusion (IR)]. In another study, the effects of finerenone on the progression of acute kidney injury (AKI) to CKD was evaluated at four months after IR. Finerenone significantly attenuated tubulointerstitial fibrosis and the TGF- expression by downregulating the oxidative stress in rats receiving IR.[13] Finerenone has also been shown to reduce oxidative stress by inhibiting Rac1 activation and the subsequent MR signalling pathway in vascular smooth muscle cells.[14] Myeloid MR plays an essential role in IR-mediated renal fibrosis. Phase 2 trials of finerenone have also been reported, including the mineralocorticoid receptor antagonist tolerability study (ARTS), ARTS-Heart Failure (ARTS-HF), and ARTS-Diabetic Nephropathy (ARTS-DN). ARTS is an RCT that assessed changes in the serum potassium levels by finerenone as a primary endpoint in patients with HFrEF and mild or moderate CKD. After a follow-up period of 28 days, finerenone at all doses was associated with significantly smaller increases in serum potassium levels and lower incidences of hyperkaliemia and eGFR decline than spironolactone 50 mg daily. Finerenone also decreased the levels of B-type natriuretic peptide (BNP), amino-terminal proBNP, and albuminuria at least as much as spironolactone.[15] Taken together, these findings suggest that finerenone (5 or 10 mg/day) was as efficient at lowering albuminuria and cardiac biomarkers as spironolactone (25 or 50 mg/day) with a smaller risk of hyperkalemia. The primary endpoint of ARTS-HF was the proportion of patients with a >30% decline in NT-proBNP from baseline.[16] Finerenone was well tolerated and induced a ≥30% decrease in NT-proBNP levels. In ARTS-DN, the reduction in albuminuria was not associated with changes in the blood pressure or eGFR, suggesting that renoprotection by finerenone was independent of the hemodynamic effects.[17] FIDELIO-DKD was performed to assess whether or not

finerenone slows CKD progression and reduces cardiovascular morbidity and mortality in patients with advanced CKD and T2D. The primary outcome was a composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline over a period of at least four weeks, or death from renal causes. The key secondary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure.[18] Finerenone in Reducing CV Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) was a trial that assessed the efficacy of finerenone on cardiovascular and renal outcomes and its safety in T2D patients with CKD.[19] The primary endpoint was the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalization for heart failure. Finerenone significantly reduced the risk of the composite CV outcome, which included the time to CV death, myocardial infarction, stroke, or hospitalization for HF in these patients with no significant interaction between patients with and without CVD.

Thus, combination therapy of Finerenone with Empagliflozin seems a promising therapeutic approach. A preclinical study in rats demonstrates that a combination of finerenone and empagliflozin confer pronounced cardiovascular protection in hypertension-induced cardiorenal disease. Combining these two drugs with independent modes of action at low dosages revealed an efficacious reduction in clinically meaningful parameters such as proteinuria, blood pressure, plasma creatinine, plasma uric acid, and mortality. A striking survival benefit from combination therapy in the hypertensive cardiorenal model was accompanied by significant effects on renal function as deduced from plasma creatinine, plasma uric acid, and urinary protein/creatinine ratio in the combination group. A dose-dependent reduction in histological lesions in both cardiac left ventricular and renal tissue with both compounds was found. Similarly, vascular, cardiac, and renal fibrosis were reduced by both modes of action with comparable efficacy at the higher dosages. Thus, a combination of finerenone and empagliflozin effectively reduces cardiac and renal lesions, proteinuria, and mortality in a nondiabetic hypertensive cardiorenal disease model, indicating a strong potential for combined clinical use in broad cardiorenal patient populations.[12]

CONCLUSION

Hypertension is a multifactorial disease that can be complicated by damage and metabolic changes in the heart, blood vessels, brain, kidney, retina and other target organs. Even optimally-treated hypertensive individuals have also been found to be at increased risk of adverse cardiovascular events leading to end-organ damage. Thus, there is a need for strategies that prevent the complications of hypertension and directly target end-organ damage, independent of blood pressure-lowering actions. Results from EMPA-REG OUTCOME data demonstrated the cardioprotective effect of empagliflozin independent of glycemic control. At the same time, FIGARO-DKD demonstrated that finerenone significantly reduced the risk of the composite CV outcome, which included the time to CV death, myocardial infarction, stroke, or hospitalization for HF in these patients with no significant interaction between patients with and without CVD. A combination of Finerenone with Empagliflozin was evaluated in the preclinical study for its efficacy in end-organ damage in hypertensive rats. The combination of finerenone and empagliflozin was found to effectively reduce cardiac and renal lesions, proteinuria, and mortality in a nondiabetic hypertensive cardiorenal disease model, indicating a strong potential for combined clinical use in broad cardiorenal patient populations. Thus, encouraging results from the preclinical study calls for a clinical trial to evaluate the efficacy of the combination of Finerenone with Empagliflozin to prevent end-organ damage in hypertensive patients. The combination of Finerenone with Empagliflozin has given new hope for effective therapeutic management to prevent end-organ damage in hypertensive patients.

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