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MINIREVIEWS

Role of angiotensin receptor-neprilysin inhibitor in diabetic complications

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Abstract

Diabetes mellitus is a prevalent disorder with multi-system manifestations, causing a significant burden in terms of disability and deaths globally. Angiotensin receptor-neprilysin inhibitor (ARNI) belongs to a class of medications for treating heart failure, with the benefits of reducing hospitalization rates and mortality. This review mainly focuses on the clinical and basic investigations related to ARNI and diabetic complications, discussing possible physiological and molecular mechanisms, with insights for future applications.

Key Words: Angiotensin receptor-neprilysin inhibitor; Diabetic mellitus; Complication

Core Tip: Diabetes mellitus is a prevalent disorder with multi-system manifestations, causing a significant burden in terms of disability and deaths globally. Angiotensin receptor-neprilysin inhibitor (ARNI) belongs to a class of medications for treating heart failure, with the benefits of reducing hospitalization rates and mortality. This review mainly focuses on the clinical and basic investigations related to ARNI and diabetic complications, discussing possible physiological and molecular mechanisms, with insights for future applications.

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INTRODUCTION

Over the past 30 years, the number of individuals suffering from diabetes mellitus (DM) has increased nearly 4-fold worldwide, with DM being the ninth leading cause of reduced life expectancy[1]. In 2021, approximately 537 million adults (20-79 years) are living with diabetes, and by 2045, International Diabetes Federation projections show that 1 in 8 adults, approximately 783 million, will be living with diabetes, an increase of 46%[2]. DM-related complications include neuropathy, retinopathy, nephropathy, dementia, osteoporosis, peripheral vascular disease, myocardial infarction, heart failure (HF) and sudden cardiac death[3,4], all of which are associated with higher morbidity and mortality[5]. Patients with severe diabetes-related complications have a poor prognosis, highlighting the need for more effective and early treatment.

LCZ696 is the first clinical application of an angiotensin receptor-neprilysin inhibitor (ARNI), a 1:1 combination of angiotensin receptor blocker (ARB, valsartan) and neprilysin inhibitor (NEPi, Sacubitril, AHU377)[6]. Previous clinical studies have shown that LCZ696 has significant benefits in reducing the rates of hospitalization, mortality and major cardiovascular events[7-9], which are likely attributable to improve cardiac remodeling[10]. Compared with ARB, LCZ696 has been reported to confer cardiovascular and renal protective effects in animal models[11-13].

With increasing recognition of better prognosis in HF patients receiving ARNI, recent studies have explored its possible benefits beyond HF, such as in DM, cancer and renal disease[13-15]. A post-hoc analysis of the PARADIGM-HF trial "Prospective comparison of ARNI with angiotensin-converting enzyme inhibitors (ACEI) to determine impact on global mortality and morbidity in heart failure" found that in patients with DM and HF, the hemoglobin A1c (HbA1c) level in the LCZ696 group was significantly lower than that in patients treated with enalapril over 1-3 years of follow-up [16]. These findings are consistent with the inverse correlation between blood glucose control and urinary atrial natriuretic peptide (ANP) levels. Initial insulin use was significantly lower in DM patients in the LCZ696 group [114 (7%) *vs* 153 (10%)]. Similarly, ARNI administration resulted in better insulin resistance and metabolic profiles in non-obese HF patients with reduced ejection fraction (HFrEF) and pre-diabetes[17]. In high-fat-fed neprilysin-deficient mice, improved beta cell function was accompanied by elevated active glucagon-like peptide 1 and reduced plasma dipeptidyl peptidase-4 activity[18]. Thus, ARNI plays an important role in the regulation of blood glucose and insulin in diabetic patients, indicating its potential clinical value in diabetes. This review summarizes the evidence supporting the beneficial effects of ARNI on diabetic complications, with discussion on the molecular mechanisms.

OVERVIEW OF ARNI

Due to the combined effects of valsartan and sacubitril, LCZ696 not only inhibits over-activation of the renin-angiotensin-aldosterone system (RAAS), but also reduces the over-degradation of NPs (Figure 1). NEPi inhibits the activation of RAAS, with cardiovascular protective effects[19]. NPs can regulate the diuretic, natriuretic and vasodilating functions, but also regulate the reduction of sympathetic drive and anti-proliferation. NEPi can reduce the degradation of NPs by inhibiting the effect of NEP and increasing the biological activity of the NP system, indirectly protecting cardiovascular function[20]. Candoxatril, a NEPi, has diuretic effects and showed a concentration-dependent increase of ANP in patients with mild HF[21]. The increase in angiotensin II and endothelin-1 by NEPi weakens its cardiovascular protective effect. Omapatrilat, a complex composed of ACEI and NEPi, has antihypertensive effects and can significantly improve hemodynamic parameters in patients with HF[22]. Despite its significant effectiveness in hypertension, the combined effects of NEPi and ACEI unfortunately lead to the frequent occurrence of angioedema, restricting their widespread clinical application[23]. By contrast, ARNI use is not associated with angioedema, with distinct anti-HF and hypotensive effects compared to valsartan and enalapril[24,25].

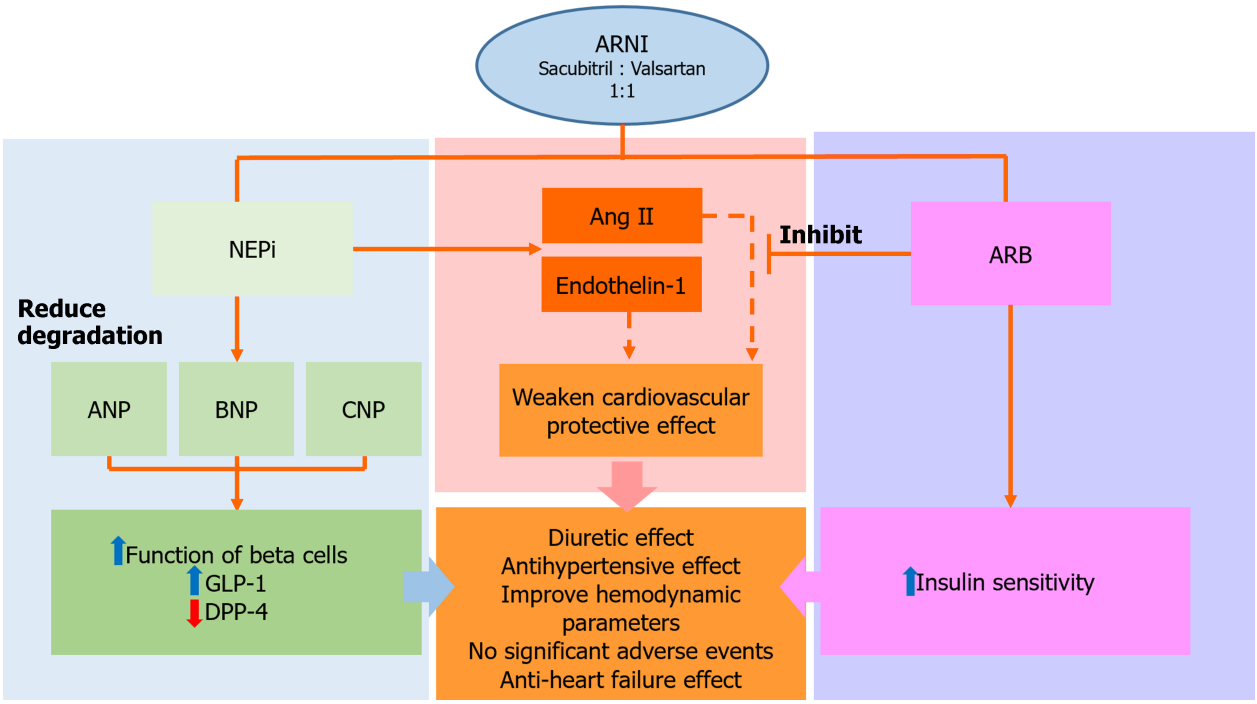

Figure 1 Mechanisms of angiotensin receptor-neprilysin inhibitor in diabetes. Angiotensin receptor-neprilysin inhibitor, a 1:1 combination of valsartan and sacubitril, reduces the damage due to diabetes mainly by reducing the degradation of natriuretic peptides and inhibiting the effect of Ang II and endothelin-1. ARNI: Angiotensin receptor-neprilysin inhibitor; NEPi: Neprilysin inhibitor; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; ANP: Atrial natriuretic peptide; CNP: C-type natriuretic peptide; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide 1.

ARNI IN DIABETIC COMPLICATIONS

ARNI in diabetic cardiomyopathy

Dysglycemia is often associated with structural and functional damage to the heart[26,27], and accordingly, DM increases the risk of hospitalization in patients with HF by more than 50%[28]. Studies have shown that compared to patients with normal HbA1c, patients with DM had lower left ventricular ejection fraction (LVEF) and significantly higher hospitalization rates due to HF and cardiovascular death[29,30]. Diabetic cardiomyopathy can significantly increase the risk of death in patients with DM[31]. It does not appear to be reversible, and hypoglycemic agents may have additional adverse effects on patients with HF.

LCZ696 has been demonstrated to reduce the risk of cardiovascular death and HF-related hospitalization in patients with DM or pre-diabetes compared with enalapril[29]. The mortality and HF rehospitalization rates were similar between HFrEF patients with and without DM after application of ARNI[32]. However, one study showed that all-cause mortality was higher in patients with diabetes than in those without diabetes (25% *vs* 8%)[33]. Furthermore, a pooled analysis of PARAGON-HF and PARADIGM-HF suggested that ARNI may increase the risk of hypoglycemia[34]. Compared with valsartan, ARNI can significantly reduce the level of N-terminal pro-brain NP (NT-proBNP) in diabetic rats[35]. Moreover, compared with non-diabetic patients, diabetic patients had a more pronounced decrease in LVEF, a higher degree of myocardial fibrosis, and a higher incidence of ischemic cardiomyopathy[36], which may lead to a higher incidence of ventricular arrhythmia in diabetic patients. Nevertheless, the incidence of ventricular tachyarrhythmia in diabetic patients was similar to that in non-diabetic patients[33], which demonstrates that to some extent, ARNI can reduce the risk of ventricular arrhythmias in diabetic patients.

This review mainly discusses the related mechanisms of ARNI in improving diabetic cardiomyopathy in relation to the following aspects: ARNI improves cardiac remodeling and cardiac function in patients with diabetic cardiomyopathy. In comparison with diabetic control rats, treatment with LCZ696 and valsartan significantly reduced the heart weight to body weight ratio and improved LVEF[35]. ARNI can reduce appetite, body weight and normalize insulin and glycosylated hemoglobin in rats fed high-fat high fructose diet-induced DM[37], this may be related to an increase in satiety and decrease in hunger and food intake by NPs through inhibition of the appetite-stimulating hormone ghrelin[38]. Secondly, ARNI reduces myocardial fibrosis and prevents myocardial apoptosis. Animal experiments found a reduction in apoptotic cells and myocardial fibrosis, and down-regulation of the expression level of related landmark proteins[19,39]. ARNI inhibits oxidative stress related indicators and inflammatory factors induced by high glucose or diabetes, including c-Jun N-terminal kinase/p38 mitogen-activated protein kinase, nuclear factor-κB nuclear translocation, glutathione (GSH) contents and GSH/GSH disulfide ratios, and interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α in the serum, *etc*[19]. Thiorphan monotherapy, which is a NEPi, decreased the expression of cardiac NEP proteins, telmisartan monotherapy significantly reduced the expression of heart-specific ANP, BNP and NEP proteins, and compared with control, ARNI significantly limited the expression of plasma and heart-specific NPs in diabetes [11,

35]. In conclusion, ARNI has protective effects on diabetic myocardial tissue through anti-apoptotic, anti-fibrotic, anti-inflammatory, and anti-oxidative actions, providing a theoretical basis for protection against cardiac dysfunction in diabetes (Figure 2A).

ARNI in diabetic nephropathy

Patients with abnormal glucose tolerance and insulin resistance are at high risk of developing chronic kidney disease (CKD). Of note, diabetic nephropathy is an important and independent risk factor for serious cardiovascular events of DM, and eventually develops into end-stage renal disease[40-42]. Compared with enalapril, ARNI has profound effects on protecting renal function in patients with diabetes and CKD[43], likely through a reduction in proteinuria and delayed progression of diabetic nephropathy from RAAS inhibition[44]. ARNI use is associated with better renal outcomes in patients with HFrEF, slowing the rate of estimated glomerular filtration rate (eGFR) reduction more effectively than enalapril[45]. In addition, the index of renal insufficiency was also significantly decreased, independent of the blood glucose status[29]. Whether ARNI is more effective than ARB in albuminuria (especially microalbuminuria) and glycemic control, which play important roles in the progression of diabetic kidney disease (DKD), is still unknown[46].

The mechanisms by which ARNI improves renal function in diabetic patients remain elusive. In the section below, we highlight some of the potential key mechanisms. Firstly, the occurrence of hyperlipidemia in diabetic patients is often associated with oxidized low-density lipoprotein and kidney damage[47]. Total plasma cholesterol in obese rats was significantly reduced after the administration of ARNI[48]. Thus, the improvement in renal function may be explained by improvement in total plasma cholesterol. ARNI improved renal function in rats after partial nephrectomy and in a model of diabetic kidney damage[49,50]. ARNI use is associated with improved renal function independent of blood pressure effects, characterized by reduced proteinuria and glomerulosclerosis[51]. In terms of glomerular filtration function, it mainly showed preservation of renal plasma flow and glomerular filtration rate, and the creatinine clearance rate was higher than that in the non-treated group[50]. Similarly, LCZ696 also restricts the increase in blood urea nitrogen and creatinine level, which indicated that it could maintain renal function in diabetic rats[52]. Importantly, diabetic nephropathy with increased proteinuria and decreased glomerular filtration is closely related to its pathological changes, including hypertrophy of glomerular and tubular components, glomerular and tubule basement membrane thickening, disappearance of podocytes, and eventually glomerular sclerosis and tubulointerstitial fibrosis[53]. Following treatment with ARNI, renal pathology scores, such as focal segmental glomerulosclerosis, glomerulosclerosis score and tubular injury score, were improved[51]. Whilst ARNI had a negative effect on the occurrence of glomerulosclerosis by reducing glomerular scar formation[52], ARNI can preserve the integrity of podocytes by inhibiting the expression of transient receptor potential cation channel, subfamily C, member 6 transient receptor potential-6 (TRPC6) or the role of its downstream Rcan1 promoter[50]. Rcan 1, which is positively related to the activation of TRPC6, was 50% suppressed by ARNI [52]. In addition, ANP reduces the number of TRPC6 channels by lowering blood glucose[50,54]. Furthermore, ARNI can prevent renal tubular injury, as reflected by reductions in the renal injury markers, clusterin and kidney injury molecule-1. ARNI, valsartan and hydralazine inhibited tissue interstitial fibrosis by 35%, 47%, and 19%, respectively[48]. The NP system could play a role in natriuretic, diuretic and vasodilation by reducing the synthesis of cyclic guanosine monophosphate (cGMP), and inhibit the proliferation of mesangial cells and renal fibrosis[55,56]. However, there was no significant change in cGMP in the plasma and urine of diabetic rats after treatment with ARNI[51]. ARNI can increase the gene expression of nephrin and podocin[48]. The renal protective effect of ARNI can be attributed to reduced oxidative stress response in the glomeruli or renal tubules[48]. Lastly, ARNI partially reshaped the composition of gut microbiota, reduced the abundance of some harmful bacteria and increased the abundance of beneficial bacteria. Functional prediction analysis suggested that ARNI can improve kidney function in DKD rats[57]. Thus, ARNI reduces hyperglycemia, proteinuria and inflammation, improves intestinal flora disorder, retains eGFR, and inhibits the TRPC6/NFATc/Rcan1 pathway, which may improve podocyte integrity, and protects glomerular and renal tubular function and structure (Figure 2B).

ARNI in diabetic retinopathy

Cardiovascular disease, HF, atherosclerosis and cerebrovascular events are mainly caused by dysfunction of the macrovascular system. Diabetic retinopathy is one of the most common diabetic microangiopathies, whose incidence is projected to reach 146 million people by 2050[58]. It is an important cause of acquired blindness in adults[59], and mainly consists of hyaline arteriolosclerosis, thickening of capillary basement membrane, formation of microangioma and tortuosity of venules. Further development may lead to changes such as retinal capillary extravasation and macular edema. Diabetic retinopathy is divided into two stages: Non-proliferative diabetic retinopathy and proliferative diabetic retinopathy[60]. Retinal and iris neovascularization is the hallmark of proliferative retinopathy.

Prasad *et al*[61] found that RAAS and NEP dual inhibition (irbesartan + thiorphan) could inhibit the further development of diabetic retinopathy more effectively than irbesartan alone. The protective mechanisms of ARNI on diabetic retinopathy are shown in Figure 2C. Diabetic retinopathy is associated with local RAAS activation in the eye vasculature, and its retinal angiotensin II level increases[62]. Angiotensin II blockade leads to anti-angiogenesis, anti-inflammatory and improving retinal function. Inhibiting the mineralocorticoid receptor and angiotensin II type 1 receptor, the oxygen-induced retinopathy could be significantly improved through inhibition of the aldosterone induced inflammatory pathway and regulation of factors such as glucose-6-phosphate dehydrogenase and Nicotinamide adenine dinucleotide phosphate NADPH oxidases 4[63]. The level of retinal NEP activity increased after streptozotocin induced diabetes in Ren2 rats[64]. Clinical studies have shown that the expression of NEP in the serum of patients with diabetic retinopathy was markedly higher than those without retinopathy. NEP expression gradually rises with worsening retinopathy[64]. Due to its effects on the RAAS as well as the NEP system, ARNI can significantly prevent or delay diabetic retinopathy [61]. ANP and CNP could reverse the retinal blood barrier dysfunction induced by advanced glycosylation end products

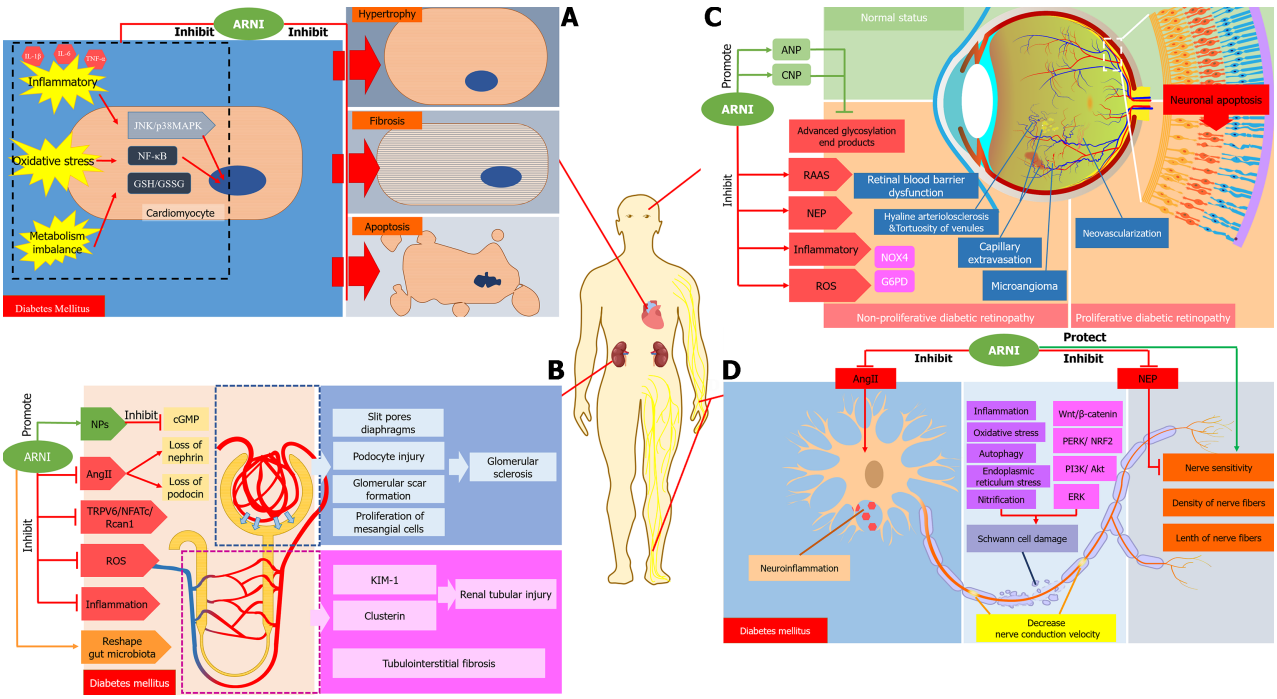

Figure 2 Role and mechanisms of angiotensin receptor-neprilysin inhibitor in diabetic complications. A: Angiotensin receptor-neprilysin inhibitor (ARNI) has protective effects on diabetic myocardial tissue through anti-apoptosis, anti-fibrosis, anti-inflammation, anti-oxidative stress activities and improving metabolism; B: ARNI reduces inflammation, Ang II, reactive oxygen species (ROS) and inhibits the transient receptor potential-6/NFATc/Rcan1 pathway, which may improve podocyte integrity, protects glomerular and renal tubular function and structure; C: ARNI alleviates diabetic retinopathy by the inhibiting renin-angiotensin-aldosterone system, ROS and inflammatory response and simultaneously increasing the protective effects of atrial natriuretic peptide and C-type natriuretic peptide; D: ARNI delays the development of diabetic peripheral neuropathy by reducing Ang II and inhibiting the effect of neprilysin, improving nerve conduction velocity and sensitivity and protecting Schwann cells. ARNI: Angiotensin receptor-neprilysin inhibitor; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; JNK: c-Jun N-terminal kinase; NF-κB: Nuclear factor-κB; GSH: Glutathione; GSSG: Glutathione/glutathione disulfide; NPs: Natriuretic peptide system; TRPV6: Transient receptor potential-6; ROS: Reactive oxygen species; cGMP: Cyclic guanosine monophosphate; KIM-1: Kidney injury molecule-1; ANP: Atrial natriuretic peptide; CNP: C-type natriuretic peptide; RAAS: Renin-angiotensin-aldosterone system; NEP: Neprilysin; NOX4: NADPH oxidases 4; ERK: Extracellular signal-regulated kinase; G6PD: Glucose-6-phosphate dehydrogenase; NRF2: Nuclear factor erythroid 2-related factor 2; p38MAPK: p38 mitogen-activated protein kinase; PERK: Protein kinase RNA-like endoplasmic reticulum kinase; PI3K: Phosphoinositide 3-kinase.

of retinal pigment epithelium; thus, inhibiting the activity of retinal NEP and increasing the level of NPs may be beneficial in the treatment of diabetic retinopathy[65]. Increased expression of inflammatory cytokines, excessive accumulation of ROS, loss of capillaries, glial cell proliferation and neuronal apoptotic cell death are all indicators of diabetic retinopathy[61,66]. Long-term treatment with ARNI significantly reduced the damage related to the above diabetic retinopathy in comparison with ARB[61].

ARNI in diabetic peripheral neuropathy

Diabetic peripheral neuropathy (DPN) affects the quality of life of approximately 50% of DM patients[67], due to increased pain and the risk of falls[67]. Approximately half of patients with diabetes develop foot ulcers, which can eventually lead to lower limb amputations[68]. At present, the treatments for DPN are very limited, and most patients only have symptomatic treatment, such as neurotrophic agents[69].

ACEI and ARB have benefits on peripheral neuropathy in diabetic rats[70], mainly manifested in improving neurological function and endoneurial blood flow in diabetic rats[71]. Hyperglycemia can increase the level of tissue angiotensin II, leading to endothelial injury, neuroinflammation and vascular dysfunction, and thus induce diabetic neuropathy. The development of diabetic neuropathy could be slowed by ACEI/ARB through inhibition of this pathway [72]. Clinical and preclinical studies showed that the sensory and motor nerve conduction velocity was significantly decreased in diabetes, while valsartan had no effect during early intervention, but ARNI can preserve the conduction velocity of action potentials through motor and sensory nerves. Measurements of sensory nerve density in the skin and cornea and the associated biosensitivity of these nerves have been promoted as possible alternative markers of peripheral neuropathy[73]. ARNI intervention can completely reverse the loss and heat sensitivity of skin sensory nerve fibers[71]. Similarly, NEPis can significantly improve nerve conduction velocity, improve thermal sensitivity, and protect the density of nerve fibers in the epidermis of diabetic sciatic nerve[74]. Calcitonin gene-related peptide promotes the regeneration and elongation of nerves. In NEP knockout mice, the expression of calcitonin gene-related peptide was markedly increased in the corneal nerve, which explains why NEP inhibitors increase the expression of calcitonin gene-related peptide to promote the regeneration of nerve cells, finally delaying the development of DPN[75]. By inhibiting the activity of neprilysin, corneal sensitivity of diabetic animals could be restored[76]. Schwann cells are glial cells in the peripheral nervous system and form the myelin sheath that protects axons, which play a crucial role in the pathogenesis

of DPN. Decreased Schwann cell activity leads to demyelination, which aggravates the development of DPN forming a vicious circle[77]. Apoptosis of Schwann cells increases in diabetes, mainly through inflammation, oxidative stress, autophagy, endoplasmic reticulum stress and nitrification, as well as signal pathways such as extracellular signal-regulated kinase, protein kinase RNA-like endoplasmic reticulum kinase/nuclear factor erythroid 2-related factor 2, phosphoinositide 3-kinase/Akt and Wnt/β-catenin[78]. Calcitonin gene-related peptide also plays an important role in peripheral nerve regeneration and Schwann cell proliferation[79]. NEP inhibitors can protect the calcitonin gene-related peptide. Taken together, these results show that ARNI can delay the development of DPN by reducing angiotensin II, improving nerve conduction velocity and sensitivity, and protecting Schwann cells (Figure 2D).

CONCLUSION

In conclusion, although ARNI is currently indicated for HF, it has demonstrated benefits in a number of diabetes-related complications such as cardiomyopathy, nephropathy, retinopathy and peripheral neuropathy. These data might encourage additional research into the beneficial metabolic properties of drugs of this class. More studies are needed to explore the potential benefits of ARNI in diabetes, especially in diabetic cardiomyopathy and diabetic nephropathy.

FOOTNOTES

Co-first authors: Ying Liu and Cun-Yu Lu.

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