World Journal of Diabetes

Submit a Manuscript: https://www.f6publishing.com

*World J Diabetes* 2024 May 15; 15(5): 867-875

DOI: 10.4239/wjd.v15.i5.867

ISSN 1948-9358 (online)

*MINIREVIEWS*

# Role of angiotensin receptor-neprilysin inhibitor in diabetic complications

Ying Liu, Cun-Yu Lu, Yi Zheng, Yu-Min Zhang, Ling-Ling Qian, Ku-Lin Li, Gary Tse, Ru-Xing Wang, Tong Liu

**Specialty type:** Endocrinology and metabolism

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): A
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

**P-Reviewer:** Ghannam WM, Egypt; Islam MS, South Africa; Nayak S, Trinidad and Tobago; Tziomalos K, Greece

**Received:** October 8, 2023
**Peer-review started:** October 8, 2023
**First decision:** December 18, 2023
**Revised:** December 31, 2023
**Accepted:** March 25, 2024
**Article in press:** March 25, 2024
**Published online:** May 15, 2024

**Ying Liu, Yi Zheng, Gary Tse, Tong Liu,** Department of Cardiology, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, Tianjin 300211, China

**Cun-Yu Lu,** Department of Cardiology, Xuzhou No. 1 Peoples Hospital, Xuzhou 221005, Jiangsu Province, China

**Yu-Min Zhang,** Department of Cardiology, Wuxi 9th People's Hospital Affiliated to Soochow University, Wuxi 214062, Jiangsu Province, China

**Ling-Ling Qian, Ku-Lin Li, Ru-Xing Wang,** Department of Cardiology, Wuxi People's Hospital Affiliated to Nanjing Medical University, Wuxi 214023, Jiangsu Province, China

**Gary Tse,** School of Nursing and Health Studies, Metropolitan University, Hong Kong 999077, China

**Gary Tse,** Kent and Medway Medical School, Kent CT2 7NT, Canterbury, United Kingdom

**Corresponding author:** Tong Liu, PhD, Professor, Department of Cardiology, Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Tianjin Institute of Cardiology, Second Hospital of Tianjin Medical University, No. 23 Pingjiang Road, Hexi District, Tianjin 300211, China. liutongdoc@126.com

## 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.

**Citation:** Liu Y, Lu CY, Zheng Y, Zhang YM, Qian LL, Li KL, Tse G, Wang RX, Liu T. Role of angiotensin receptor-neprilysin inhibitor in diabetic complications. *World J Diabetes* 2024; 15(5): 867-875
**URL:** https://www.wjgnet.com/1948-9358/full/v15/i5/867.htm
**DOI:** https://dx.doi.org/10.4239/wjd.v15.i5.867

## 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].

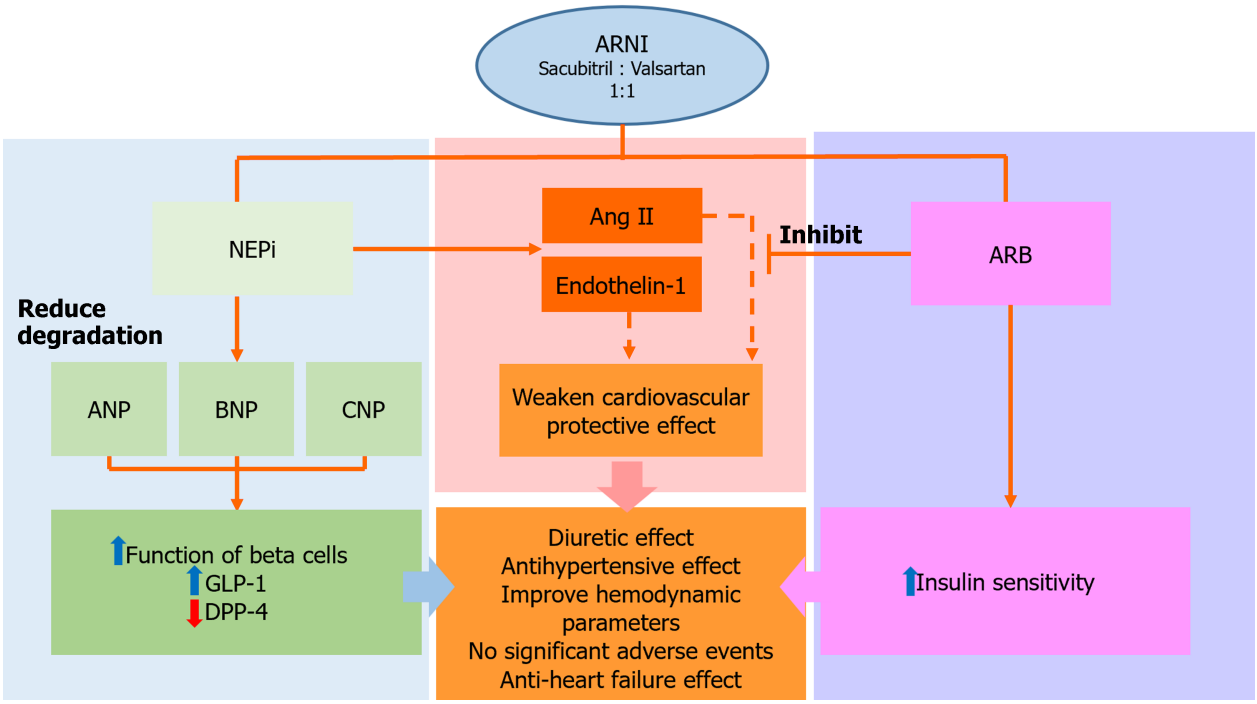


**Figure 1 Mechanisms of angiotensin receptor-neprilysin inhibitor in diabetes.** Angiotensin receptor-neprilysin inhibitor, a 1:1 combination of valsartan and sacubitril, reduces the damage due to diabetes mainly by reducing the degradation of natriuretic peptides and inhibiting the effect of Ang II 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

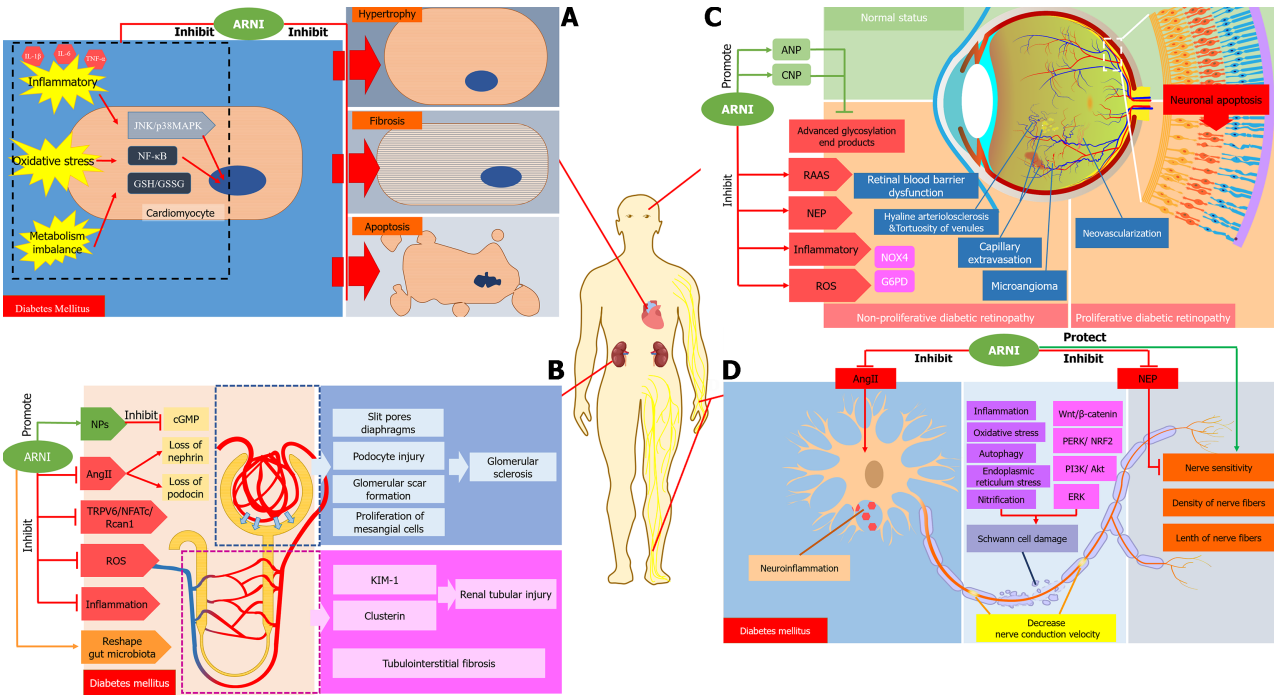


**Figure 2 Role and mechanisms of angiotensin receptor-neprilysin inhibitor in diabetic complications.** A: Angiotensin receptor-neprilysin inhibitor (ARNI) has protective effects on diabetic myocardial tissue through anti-apoptosis, anti-fibrosis, anti-inflammation, anti-oxidative stress activities 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.

**Author contributions:** Liu Y and Qian LL contributed to the conceptualization of this review; Zhang YM and Li KL performed the literature search; Liu Y, Lu CY, and Zheng Y drafted the work and finally; Tse G, Wang RX, and Liu T critically revised the work; and all authors have read and approved the final manuscript; Wang RX and Liu T contributed equally to this paper.

**Supported by** Tianjin Key Medical Discipline (Specialty) Construction Project, No. TJYXZDXK-029A; and the National Natural Science Foundation of China, No. 82370342.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.



**Country/Territory of origin:** China

**ORCID number:** Ru-Xing Wang 0000-0001-7355-5048; Tong Liu 0000-0003-0482-0738.

**S-Editor:** Wang JJ
**L-Editor:** Webster JR
**P-Editor:** Cai YX

## REFERENCES

1 **Zheng Y**, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018; **14**: 88-98 [PMID: 29219149 DOI: 10.1038/nrendo.2017.151]
2 **International Diabetes Federation**. IDF Diabetes Atlas. 2021. [cited 20 February 2024]. Available from: https://diabetesatlas.org/
3 **Lee S**, Zhou J, Guo CL, Wong WT, Liu T, Wong ICK, Jeevaratnam K, Zhang Q, Tse G. Predictive scores for identifying patients with type 2 diabetes mellitus at risk of acute myocardial infarction and sudden cardiac death. *Endocrinol Diabetes Metab* 2021; **4**: e00240 [PMID: 34277965 DOI: 10.1002/edm2.240]
4 **Lee S**, Zhou J, Wong WT, Liu T, Wu WKK, Wong ICK, Zhang Q, Tse G. Glycemic and lipid variability for predicting complications and mortality in diabetes mellitus using machine learning. *BMC Endocr Disord* 2021; **21**: 94 [PMID: 33947391 DOI: 10.1186/s12902-021-00751-4]
5 **Lee S**, Zhou J, Leung KSK, Wu WKK, Wong WT, Liu T, Wong ICK, Jeevaratnam K, Zhang Q, Tse G. Development of a predictive risk model for all-cause mortality in patients with diabetes in Hong Kong. *BMJ Open Diabetes Res Care* 2021; **9** [PMID: 34117050 DOI: 10.1136/bmjdrc-2020-001950]
6 **McMurray JJ**, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014; **371**: 993-1004 [PMID: 25176015 DOI: 10.1056/NEJMoa1409077]
7 **Jaffuel D**, Molinari N, Berdague P, Pathak A, Galinier M, Dupuis M, Ricci JE, Mallet JP, Bourdin A, Roubille F. Impact of sacubitril-valsartan combination in patients with chronic heart failure and sleep apnoea syndrome: the ENTRESTO-SAS study design. *ESC Heart Fail* 2018; **5**: 222-230 [PMID: 29469206 DOI: 10.1002/ehf2.12270]
8 **Dec GW**. LCZ696 (sacubitril/valsartan): can we predict who will benefit? *J Am Coll Cardiol* 2015; **66**: 2072-2074 [PMID: 26541916 DOI:

10.1016/j.jacc.2015.08.877]

9 **Solomon SD**, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ; Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. *Lancet* 2012; **380**: 1387-1395 [PMID: 22932717 DOI: 10.1016/S0140-6736(12)61227-6]

10 **Sun Y**, Song S, Zhang Y, Mo W, Zhang X, Wang N, Xia Y, Tse G, Liu Y. Effect of angiotensin receptor neprilysin inhibitors on left atrial remodeling and prognosis in heart failure. *ESC Heart Fail* 2022; **9**: 667-675 [PMID: 34779134 DOI: 10.1002/ehf2.13691]

11 **Malek V**, Gaikwad AB. Telmisartan and thiorphan combination treatment attenuates fibrosis and apoptosis in preventing diabetic cardiomyopathy. *Cardiovasc Res* 2019; **115**: 373-384 [PMID: 30184174 DOI: 10.1093/cvr/cvy226]

12 **Suematsu Y**, Jing W, Nunes A, Kashyap ML, Khazaeli M, Vaziri ND, Moradi H. LCZ696 (Sacubitril/Valsartan), an Angiotensin-Receptor Neprilysin Inhibitor, Attenuates Cardiac Hypertrophy, Fibrosis, and Vasculopathy in a Rat Model of Chronic Kidney Disease. *J Card Fail* 2018; **24**: 266-275 [PMID: 29325796 DOI: 10.1016/j.cardfail.2017.12.010]

13 **Li Y**, Kang L, Rong K, Zhang Y, Suo Y, Yuan M, Bao Q, Shao S, Tse G, Li R, Liu T, Li G. Renal protective effects and mechanisms of the angiotensin receptor-neprilysin inhibitor LCZ696 in mice with cardiorenal syndrome. *Life Sci* 2021; **280**: 119692 [PMID: 34102189 DOI: 10.1016/j.lfs.2021.119692]

14 **Wang Y**, Tse G, Roever L, Liu T. Sacubitril/valsartan in the treatment of cancer therapy-related cardiac dysfunction. *Int J Cardiol* 2020; **318**: 130 [PMID: 32610154 DOI: 10.1016/j.ijcard.2020.06.041]

15 **Liu X**, Huang L, Tse G, Liu T, Che J. Effects of sacubitril-valsartan in the treatment of chronic heart failure patients with end-stage renal disease undergoing dialysis. *Clin Cardiol* 2023; **46**: 930-936 [PMID: 37381644 DOI: 10.1002/clc.24075]

16 **Seferovic JP**, Claggett B, Seidelmann SB, Seely EW, Packer M, Zile MR, Rouleau JL, Swedberg K, Lefkowitz M, Shi VC, Desai AS, McMurray JJV, Solomon SD. Effect of sacubitril/valsartan versus enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial. *Lancet Diabetes Endocrinol* 2017; **5**: 333-340 [PMID: 28330649 DOI: 10.1016/S2213-8587(17)30087-6]

17 **Cloro C**, Zaffina I, Sacchetta L, Arturi F, Clausi C, Lucà S, Pelle MC, Giofrè F, Armentaro G, Forte V, De Rosa FM, Sciacqua A. Effects of sacubitril/valsartan on both metabolic parameters and insulin resistance in prediabetic non-obese patients with heart failure and reduced ejection fraction. *Front Endocrinol (Lausanne)* 2022; **13**: 940654 [PMID: 36034421 DOI: 10.3389/fendo.2022.940654]

18 **Willard JR**, Barrow BM, Zraika S. Improved glycaemia in high-fat-fed neprilysin-deficient mice is associated with reduced DPP-4 activity and increased active GLP-1 levels. *Diabetologia* 2017; **60**: 701-708 [PMID: 27933334 DOI: 10.1007/s00125-016-4172-4]

19 **Ge Q**, Zhao L, Ren XM, Ye P, Hu ZY. LCZ696, an angiotensin receptor-neprilysin inhibitor, ameliorates diabetic cardiomyopathy by inhibiting inflammation, oxidative stress and apoptosis. *Exp Biol Med (Maywood)* 2019; **244**: 1028-1039 [PMID: 31262190 DOI: 10.1177/1535370219861283]

20 **Díez J**. Chronic heart failure as a state of reduced effectiveness of the natriuretic peptide system: implications for therapy. *Eur J Heart Fail* 2017; **19**: 167-176 [PMID: 27766748 DOI: 10.1002/ejhf.656]

21 **Northridge DB**, Newby DE, Rooney E, Norrie J, Dargie HJ. Comparison of the short-term effects of candoxatril, an orally active neutral endopeptidase inhibitor, and frusemide in the treatment of patients with chronic heart failure. *Am Heart J* 1999; **138**: 1149-1157 [PMID: 10577447 DOI: 10.1016/S0002-8703(99)70082-7]

22 **Rouleau JL**, Pfeffer MA, Stewart DJ, Isaac D, Sestier F, Kerut EK, Porter CB, Proulx G, Qian C, Block AJ. Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure: IMPRESS randomised trial. *Lancet* 2000; **356**: 615-620 [PMID: 10968433 DOI: 10.1016/S0140-6736(00)02602-7]

23 **Malek V**, Gaikwad AB. Neprilysin inhibitors: A new hope to halt the diabetic cardiovascular and renal complications? *Biomed Pharmacother* 2017; **90**: 752-759 [PMID: 28419972 DOI: 10.1016/j.biopha.2017.04.024]

24 **Solomon SD**, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N Engl J Med* 2019; **381**: 1609-1620 [PMID: 31475794 DOI: 10.1056/NEJMoa1908655]

25 **Suzuki K**, Claggett B, Minamisawa M, Nochioka K, Mitchell GF, Anand IS, Zannad F, Shah SJ, Lefkowitz M, Shi V, Pfeffer MA, McMurray JJV, Solomon SD. Pulse Pressure, Prognosis, and Influence of Sacubitril/Valsartan in Heart Failure With Preserved Ejection Fraction. *Hypertension* 2021; **77**: 546-556 [PMID: 33356401 DOI: 10.1161/HYPERTENSIONAHA.120.16277]

26 **Skali H**, Shah A, Gupta DK, Cheng S, Claggett B, Liu J, Bello N, Aguilar D, Vardeny O, Matsushita K, Selvin E, Solomon S. Cardiac structure and function across the glycemic spectrum in elderly men and women free of prevalent heart disease: the Atherosclerosis Risk In the Community study. *Circ Heart Fail* 2015; **8**: 448-454 [PMID: 25759458 DOI: 10.1161/CIRCHEARTFAILURE.114.001990]

27 **Sun DK**, Zhang N, Liu Y, Qiu JC, Tse G, Li GP, Roever L, Liu T. Dysglycemia and arrhythmias. *World J Diabetes* 2023; **14**: 1163-1177 [PMID: 37664481 DOI: 10.4239/wjd.v14.i8.1163]

28 **Anker SD**, Butler J, Filippatos G, Khan MS, Marx N, Lam CSP, Schnaidt S, Ofstad AP, Brueckmann M, Jamal W, Bocchi EA, Ponikowski P, Perrone SV, Januzzi JL, Verma S, Böhm M, Ferreira JP, Pocock SJ, Zannad F, Packer M. Effect of Empagliflozin on Cardiovascular and Renal Outcomes in Patients With Heart Failure by Baseline Diabetes Status: Results From the EMPEROR-Reduced Trial. *Circulation* 2021; **143**: 337-349 [PMID: 33175585 DOI: 10.1161/CIRCULATIONAHA.120.051824]

29 **Kristensen SL**, Preiss D, Jhund PS, Squire I, Cardoso JS, Merkely B, Martinez F, Starling RC, Desai AS, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, McMurray JJ, Packer M; PARADIGM-HF Investigators and Committees. Risk Related to Pre-Diabetes Mellitus and Diabetes Mellitus in Heart Failure With Reduced Ejection Fraction: Insights From Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial. *Circ Heart Fail* 2016; **9** [PMID: 26754626 DOI: 10.1161/CIRCHEARTFAILURE.115.002560]

30 **Vaduganathan M**, Fonarow GC, Greene SJ, DeVore AD, Kavati A, Sikirica S, Albert NM, Duffy CI, Hill CL, Patterson JH, Spertus JA, Thomas LE, Williams FB, Hernandez AF, Butler J. Contemporary Treatment Patterns and Clinical Outcomes of Comorbid Diabetes Mellitus and HFrEF: The CHAMP-HF Registry. *JACC Heart Fail* 2020; **8**: 469-480 [PMID: 32387066 DOI: 10.1016/j.jchf.2019.12.015]

31 **Garcia MJ**, McNamara PM, Gordon T, Kannel WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up study. *Diabetes* 1974; **23**: 105-111 [PMID: 4359625 DOI: 10.2337/diab.23.2.105]

32 **Witte KK**, Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Fonseca C, Lonn E, Noè A, Schwende H, Butylin D, Chiang Y,

Pascual-Figal D; TRANSITION investigators. Influence of diabetes on sacubitril/valsartan titration and clinical outcomes in patients hospitalized for heart failure. *ESC Heart Fail* 2023; **10**: 80-89 [PMID: 36125177 DOI: 10.1002/ehf2.14166]

33 **El-Battrawy I**, Demmer J, Abumayyaleh M, Crack C, Pilsinger C, Zhou X, Mügge A, Akin I, Aweimer A. The impact of sacubitril/valsartan on outcome in patients suffering from heart failure with a concomitant diabetes mellitus. *ESC Heart Fail* 2023; **10**: 943-954 [PMID: 36479630 DOI: 10.1002/ehf2.14239]

34 **Wijkman MO**, Claggett B, Vaduganathan M, Cunningham JW, Rørth R, Jackson A, Packer M, Zile M, Rouleau J, Swedberg K, Lefkowitz M, Shah SJ, Pfeffer MA, McMurray JJV, Solomon SD. Effects of sacubitril/valsartan on glycemia in patients with diabetes and heart failure: the PARAGON-HF and PARADIGM-HF trials. *Cardiovasc Diabetol* 2022; **21**: 110 [PMID: 35717169 DOI: 10.1186/s12933-022-01545-1]

35 **Suematsu Y**, Miura S, Goto M, Matsuo Y, Arimura T, Kuwano T, Imaizumi S, Iwata A, Yahiro E, Saku K. LCZ696, an angiotensin receptor-neprilysin inhibitor, improves cardiac function with the attenuation of fibrosis in heart failure with reduced ejection fraction in streptozotocin-induced diabetic mice. *Eur J Heart Fail* 2016; **18**: 386-393 [PMID: 26749570 DOI: 10.1002/ejhf.474]

36 **El-Battrawy I**, Borggrefe M, Akin I. The Risk for Sudden Cardiac Death and Effect of Treatment With Sacubitril/Valsartan in Heart Failure. *JACC Heart Fail* 2019; **7**: 999 [PMID: 31672315 DOI: 10.1016/j.jchf.2019.05.010]

37 **Abo-Khookh AM**, Ghoneim HA, Abdelaziz RR, Nader MA, Shawky NM. The dual inhibitor Sacubitril-valsartan ameliorate high-fat high-fructose-induced metabolic disorders in rats superiorly compared to valsartan only. *J Pharm Pharmacol* 2023; **75**: 846-858 [PMID: 36966365 DOI: 10.1093/jpp/rgad012]

38 **Vila G**, Grimm G, Resl M, Heinisch B, Einwallner E, Esterbauer H, Dieplinger B, Mueller T, Luger A, Clodi M. B-type natriuretic peptide modulates ghrelin, hunger, and satiety in healthy men. *Diabetes* 2012; **61**: 2592-2596 [PMID: 22698919 DOI: 10.2337/db11-1466]

39 **Liu Y**, Fan Y, Li J, Chen M, Chen A, Yang D, Guan X, Cao Y. Combination of LCZ696 and ACEI further improves heart failure and myocardial fibrosis after acute myocardial infarction in mice. *Biomed Pharmacother* 2021; **133**: 110824 [PMID: 33378988 DOI: 10.1016/j.biopha.2020.110824]

40 **Maqbool M**, Cooper ME, Jandeleit-Dahm KAM. Cardiovascular Disease and Diabetic Kidney Disease. *Semin Nephrol* 2018; **38**: 217-232 [PMID: 29753399 DOI: 10.1016/j.semnephrol.2018.02.003]

41 **Fouli GE**, Gnudi L. The Future: Experimental Therapies for Renal Disease in Diabetes. *Nephron* 2019; **143**: 3-7 [PMID: 30257247 DOI: 10.1159/000492825]

42 **Whaley-Connell A**, Sowers JR. Obesity and kidney disease: from population to basic science and the search for new therapeutic targets. *Kidney Int* 2017; **92**: 313-323 [PMID: 28341271 DOI: 10.1016/j.kint.2016.12.034]

43 **Packer M**, Claggett B, Lefkowitz MP, McMurray JJV, Rouleau JL, Solomon SD, Zile MR. Effect of neprilysin inhibition on renal function in patients with type 2 diabetes and chronic heart failure who are receiving target doses of inhibitors of the renin-angiotensin system: a secondary analysis of the PARADIGM-HF trial. *Lancet Diabetes Endocrinol* 2018; **6**: 547-554 [PMID: 29661699 DOI: 10.1016/S2213-8587(18)30100-1]

44 **Palmer SC**, Mavridis D, Navarese E, Craig JC, Tonelli M, Salanti G, Wiebe N, Ruospo M, Wheeler DC, Strippoli GF. Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis. *Lancet* 2015; **385**: 2047-2056 [PMID: 26009228 DOI: 10.1016/S0140-6736(14)62459-4]

45 **Damman K**, Gori M, Claggett B, Jhund PS, Senni M, Lefkowitz MP, Prescott MF, Shi VC, Rouleau JL, Swedberg K, Zile MR, Packer M, Desai AS, Solomon SD, McMurray JJV. Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure. *JACC Heart Fail* 2018; **6**: 489-498 [PMID: 29655829 DOI: 10.1016/j.jchf.2018.02.004]

46 **Zhang X**, Zhou Y, Ma R. Potential effects and application prospect of angiotensin receptor-neprilysin inhibitor in diabetic kidney disease. *J Diabetes Complications* 2022; **36**: 108056 [PMID: 34893426 DOI: 10.1016/j.jdiacomp.2021.108056]

47 **Furukawa S**, Suzuki H, Fujihara K, Kobayashi K, Iwasaki H, Sugano Y, Yatoh S, Sekiya M, Yahagi N, Shimano H. Malondialdehyde-modified LDL-related variables are associated with diabetic kidney disease in type 2 diabetes. *Diabetes Res Clin Pract* 2018; **141**: 237-243 [PMID: 29775676 DOI: 10.1016/j.diabres.2018.05.019]

48 **Habibi J**, Aroor AR, Das NA, Manrique-Acevedo CM, Johnson MS, Hayden MR, Nistala R, Wiedmeyer C, Chandrasekar B, DeMarco VG. The combination of a neprilysin inhibitor (sacubitril) and angiotensin-II receptor blocker (valsartan) attenuates glomerular and tubular injury in the Zucker Obese rat. *Cardiovasc Diabetol* 2019; **18**: 40 [PMID: 30909895 DOI: 10.1186/s12933-019-0847-8]

49 **Jing W**, Vaziri ND, Nunes A, Suematsu Y, Farzaneh T, Khazaeli M, Moradi H. LCZ696 (Sacubitril/valsartan) ameliorates oxidative stress, inflammation, fibrosis and improves renal function beyond angiotensin receptor blockade in CKD. *Am J Transl Res* 2017; **9**: 5473-5484 [PMID: 29312499]

50 **Uijl E**, 't Hart DC, Roksnoer LCW, Groningen MCC, van Veghel R, Garrelds IM, de Vries R, van der Vlag J, Zietse R, Nijenhuis T, Joles JA, Hoorn EJ, Danser AHJ. Angiotensin-neprilysin inhibition confers renoprotection in rats with diabetes and hypertension by limiting podocyte injury. *J Hypertens* 2020; **38**: 755-764 [PMID: 31790054 DOI: 10.1097/HJH.0000000000002326]

51 **Roksnoer LC**, van Veghel R, Clahsen-van Groningen MC, de Vries R, Garrelds IM, Bhaggoe UM, van Gool JM, Friesema EC, Leijten FP, Hoorn EJ, Danser AH, Batenburg WW. Blood pressure-independent renoprotection in diabetic rats treated with AT1 receptor-neprilysin inhibition compared with AT1 receptor blockade alone. *Clin Sci (Lond)* 2016; **130**: 1209-1220 [PMID: 27129187 DOI: 10.1042/CS20160197]

52 **Rahman A**, Sherajee SJ, Rafiq K, Kobara H, Masaki T, Nakano D, Morikawa T, Konishi Y, Imanishi M, Nishiyama A. The angiotensin II receptor-neprilysin inhibitor LCZ696 attenuates the progression of proteinuria in type 2 diabetic rats. *J Pharmacol Sci* 2020; **142**: 124-126 [PMID: 31924408 DOI: 10.1016/j.jphs.2019.09.014]

53 **Eid S**, Sas KM, Abcouwer SF, Feldman EL, Gardner TW, Pennathur S, Fort PE. New insights into the mechanisms of diabetic complications: role of lipids and lipid metabolism. *Diabetologia* 2019; **62**: 1539-1549 [PMID: 31346658 DOI: 10.1007/s00125-019-4959-1]

54 **Undank S**, Kaiser J, Sikimic J, Düfer M, Krippeit-Drews P, Drews G. Atrial Natriuretic Peptide Affects Stimulus-Secretion Coupling of Pancreatic β-Cells. *Diabetes* 2017; **66**: 2840-2848 [PMID: 28864549 DOI: 10.2337/db17-0392]

55 **Judge P**, Haynes R, Landray MJ, Baigent C. Neprilysin inhibition in chronic kidney disease. *Nephrol Dial Transplant* 2015; **30**: 738-743 [PMID: 25140014 DOI: 10.1093/ndt/gfu269]

56 **Ogawa Y**, Mukoyama M, Yokoi H, Kasahara M, Mori K, Kato Y, Kuwabara T, Imamaki H, Kawanishi T, Koga K, Ishii A, Tokudome T, Kishimoto I, Sugawara A, Nakao K. Natriuretic peptide receptor guanylyl cyclase-A protects podocytes from aldosterone-induced glomerular injury. *J Am Soc Nephrol* 2012; **23**: 1198-1209 [PMID: 22652704 DOI: 10.1681/ASN.2011100985]

57 **Wang P**, Guo R, Bai X, Cui W, Zhang Y, Li H, Shang J, Zhao Z. Sacubitril/Valsartan contributes to improving the diabetic kidney disease and regulating the gut microbiota in mice. *Front Endocrinol (Lausanne)* 2022; **13**: 1034818 [PMID: 36589853 DOI: 10.3389/fendo.2022.1034818]

58 **Motz CT**, Chesler KC, Allen RS, Bales KL, Mees LM, Feola AJ, Maa AY, Olson DE, Thule PM, Iuvone PM, Hendrick AM, Pardue MT. Novel Detection and Restorative Levodopa Treatment for Preclinical Diabetic Retinopathy. *Diabetes* 2020; **69**: 1518-1527 [PMID: 32051147 DOI: 10.2337/db19-0869]

59 **Wong TY**, Cheung CM, Larsen M, Sharma S, Simó R. Diabetic retinopathy. *Nat Rev Dis Primers* 2016; **2**: 16012 [PMID: 27159554 DOI: 10.1038/nrdp.2016.12]

60 **Mrugacz M**, Bryl A, Zorena K. Retinal Vascular Endothelial Cell Dysfunction and Neuroretinal Degeneration in Diabetic Patients. *J Clin Med* 2021; **10** [PMID: 33504108 DOI: 10.3390/jcm10030458]

61 **Prasad T**, Roksnoer LC, Zhu P, Verma A, Li Y, Batenburg WW, de Vries R, Danser AH, Li Q. Beneficial Effects of Combined AT1 Receptor/Neprilysin Inhibition (ARNI) Versus AT1 Receptor Blockade Alone in the Diabetic Eye. *Invest Ophthalmol Vis Sci* 2016; **57**: 6722-6730 [PMID: 27951594 DOI: 10.1167/iovs.16-20289]

62 **Yamagata R**, Nemoto W, Nakagawasai O, Takahashi K, Tan-No K. Downregulation of spinal angiotensin converting enzyme 2 is involved in neuropathic pain associated with type 2 diabetes mellitus in mice. *Biochem Pharmacol* 2020; **174**: 113825 [PMID: 31987854 DOI: 10.1016/j.bcp.2020.113825]

63 **Wilkinson-Berka JL**, Tan G, Jaworski K, Harbig J, Miller AG. Identification of a retinal aldosterone system and the protective effects of mineralocorticoid receptor antagonism on retinal vascular pathology. *Circ Res* 2009; **104**: 124-133 [PMID: 19038868 DOI: 10.1161/CIRCRESAHA.108.176008]

64 **Li B**, Li N, Guo S, Zhang M, Li J, Zhai N, Wang H, Zhang Y. The changing features of serum adropin, copeptin, neprilysin and chitotriosidase which are associated with vascular endothelial function in type 2 diabetic retinopathy patients. *J Diabetes Complications* 2020; **34**: 107686 [PMID: 32768333 DOI: 10.1016/j.jdiacomp.2020.107686]

65 **Dahrouj M**, Alsarraf O, Liu Y, Crosson CE, Ablonczy Z. C-type natriuretic peptide protects the retinal pigment epithelium against advanced glycation end product-induced barrier dysfunction. *J Pharmacol Exp Ther* 2013; **344**: 96-102 [PMID: 23086231 DOI: 10.1124/jpet.112.199307]

66 **Kang Q**, Yang C. Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. *Redox Biol* 2020; **37**: 101799 [PMID: 33248932 DOI: 10.1016/j.redox.2020.101799]

67 **Feldman EL**, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, Bril V, Russell JW, Viswanathan V. Diabetic neuropathy. *Nat Rev Dis Primers* 2019; **5**: 41 [PMID: 31197153 DOI: 10.1038/s41572-019-0092-1]

68 **Hicks CW**, Selvin E. Epidemiology of Peripheral Neuropathy and Lower Extremity Disease in Diabetes. *Curr Diab Rep* 2019; **19**: 86 [PMID: 31456118 DOI: 10.1007/s11892-019-1212-8]

69 **Tang HY**, Jiang AJ, Ma JL, Wang FJ, Shen GM. Understanding the Signaling Pathways Related to the Mechanism and Treatment of Diabetic Peripheral Neuropathy. *Endocrinology* 2019; **160**: 2119-2127 [PMID: 31318414 DOI: 10.1210/en.2019-00311]

70 **Ogata Y**, Nemoto W, Nakagawasai O, Yamagata R, Tadano T, Tan-No K. Involvement of Spinal Angiotensin II System in Streptozotocin-Induced Diabetic Neuropathic Pain in Mice. *Mol Pharmacol* 2016; **90**: 205-213 [PMID: 27401876 DOI: 10.1124/mol.116.104133]

71 **Davidson EP**, Coppey LJ, Shevalye H, Obrosov A, Yorek MA. Vascular and Neural Complications in Type 2 Diabetic Rats: Improvement by Sacubitril/Valsartan Greater Than Valsartan Alone. *Diabetes* 2018; **67**: 1616-1626 [PMID: 29941448 DOI: 10.2337/db18-0062]

72 **Dewanjee S**, Das S, Das AK, Bhattacharjee N, Dihingia A, Dua TK, Kalita J, Manna P. Molecular mechanism of diabetic neuropathy and its pharmacotherapeutic targets. *Eur J Pharmacol* 2018; **833**: 472-523 [PMID: 29966615 DOI: 10.1016/j.ejphar.2018.06.034]

73 **Chen X**, Graham J, Dabbah MA, Petropoulos IN, Ponirakis G, Asghar O, Alam U, Marshall A, Fadavi H, Ferdousi M, Azmi S, Tavakoli M, Efron N, Jeziorska M, Malik RA. Small nerve fiber quantification in the diagnosis of diabetic sensorimotor polyneuropathy: comparing corneal confocal microscopy with intraepidermal nerve fiber density. *Diabetes Care* 2015; **38**: 1138-1144 [PMID: 25795415 DOI: 10.2337/dc14-2422]

74 **Davidson EP**, Coppey LJ, Holmes A, Yorek MA. Effect of inhibition of angiotensin converting enzyme and/or neutral endopeptidase on vascular and neural complications in high fat fed/low dose streptozotocin-diabetic rats. *Eur J Pharmacol* 2012; **677**: 180-187 [PMID: 22198047 DOI: 10.1016/j.ejphar.2011.12.003]

75 **Yorek MS**, Obrosov A, Lu B, Gerard C, Kardon RH, Yorek MA. Effect of Inhibition or Deletion of Neutral Endopeptidase on Neuropathic Endpoints in High Fat Fed/Low Dose Streptozotocin-Treated Mice. *J Neuropathol Exp Neurol* 2016; **75**: 1072-1080 [PMID: 27634964 DOI: 10.1093/jnen/nlw083]

76 **Davidson EP**, Coppey LJ, Yorek MA. Early loss of innervation of cornea epithelium in streptozotocin-induced type 1 diabetic rats: improvement with ilepatril treatment. *Invest Ophthalmol Vis Sci* 2012; **53**: 8067-8074 [PMID: 23169880 DOI: 10.1167/iovs.12-10826]

77 **Xi C**, Zhang Y, Yan M, Lv Q, Lu H, Zhou J, Wang Y, Li J. Exogenous neuritin treatment improves survivability and functions of Schwann cells with improved outgrowth of neurons in rat diabetic neuropathy. *J Cell Mol Med* 2020; **24**: 10166-10176 [PMID: 32667138 DOI: 10.1111/jcmm.15627]

78 **Liu YP**, Shao SJ, Guo HD. Schwann cells apoptosis is induced by high glucose in diabetic peripheral neuropathy. *Life Sci* 2020; **248**: 117459 [PMID: 32092332 DOI: 10.1016/j.lfs.2020.117459]

79 **Chung AM**. Calcitonin gene-related peptide (CGRP): role in peripheral nerve regeneration. *Rev Neurosci* 2018; **29**: 369-376 [PMID: 29216010 DOI: 10.1515/revneuro-2017-0060]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
**Telephone:** +1-925-3991568
**E-mail:** office@baishideng.com
**Help Desk:** https://www.f6publishing.com/helpdesk
https://www.wjgnet.com