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## ROLE OF ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR IN ESSENTIAL HYPERTENSION, HEART FAILURE WITH REDUCED EJECTION FRACTION AND CHRONIC KIDNEY DISEASE

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### ABSTRACT

This Hypertension is the potential risk factor and the most common co-morbidity in heart failure and chronic kidney disease. The interdependence that exists between heart and kidney disorders (cardiorenal syndrome) is associated with hypertension. Inhibition of renin Aldosterone Angiotensin system (RAAS) and Sympathetic nervous system is the cornerstone in the management of hypertension, heart failure with reduced ejection fraction and chronic kidney disease. Angiotensin receptor-neprilysin inhibitor (ARNI) is the novel drug, carries dual-acting inhibition, as it inhibits both RAAS and the Natriuretic Peptide System (NPS). (ARNI) has shown to be effective by reducing cardiovascular mortality by 20% as compared to RAAS inhibition monotherapy in patients with chronic heart failure with reduced ejection fraction. Hence, this agent is suitable for the management of above diseases. Despite of potential benefits, the uptake of ARNI in real world has remained to be low and there is paucity of data of treatment with ARNI in people with chronic heart failure with reduced ejection fraction especially in concomitant with hypertension or chronic kidney disease. This review summarizes the reported evidences regarding the use of ARNI in the treatment of hypertension, chronic heart failure with reduced ejection fraction and chronic kidney disease.

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## INTRODUCTION

Hypertension is both the risk factor, and the most prevalent co-morbidity in heart failure (HF) and chronic kidney disease (CKD). The interdependence that exists between heart and kidney disorders (cardiorenal syndrome) is associated with hypertension. Nearly, 60% of patients with heart failure have moderate to severe chronic kidney disease, with reduction in glomerular filtration rate being the predictor of morbidity and mortality in patients with co-existence of heart failure and chronic kidney disease. Inhibition of Renin-Angiotensin-Aldosterone system (RAAS) and Sympathetic nervous system is the cornerstone of the treatment of hypertension, heart failure and chronic kidney disease. Angiotensin receptor-neprilysin inhibitor (ARNI) is a novel drug which has shown to reduce cardiovascular mortality by 20% in patients with chronic heart failure with reduced ejection fraction. ARNI carries dual-acting inhibition, as it inhibits both RAAS and the Natriuretic Peptide System (NPS). Hence, this agent is suitable for the management of above diseases. Despite of potential benefits, the uptake of ARNI in the medical community is low since 2015 when this drug was included in heart failure guideline along with the insufficient of data in cardiorenal syndrome. Therefore, in this review, we have summarized the reported evidences regarding the use of ARNI in the treatment of hypertension, chronic heart failure with reduced ejection fraction and chronic kidney disease.

**Primary efforts in The augmentation of the role of the natriuretic Peptide System:** Neprilysin (NEP) is an enzyme responsible for the breaking down of endogenous natriuretic peptides (NP). Neprilysin inhibition represents a mechanism which potentiates the activity of endogenous natriuretic peptides (atrial natriuretic peptide-ANP, brain natriuretic peptide-BNP, C-type natriuretic peptide-CNP) hence providing natriuretic, diuretic, antifibrotic, antihypertrophic, vasodilation and sympatholytic effects [Fig1]. In the early nineties, pharmaceuticals innovated lone NEP inhibitors (NEPIs). NEPIs were hypothesized to be effective in treating hypertension and heart failure. Surprisingly, studies of lone NEPIs from 1992 to 2000 did not show significant clinical benefit in patients with hypertension or chronic heart failure (1-4). In continuous efforts, the pharmaceuticals innovated the intravenous (IV) NP infusions, represented by nesiritide (BNP). Initially, in small clinical studies IV nesiritide infusion showed positive clinical findings, whereas in the further larger randomized clinical studies failed to show consistency in reduction of markers of HF, mortality and rehospitalisation (5-9). Similar disappointing results were observed with ularitide, an A-type NP (ANP) in the later clinical trials from 2005 to 2017 (10-12). In the year 2000, efforts were directed towards combination of angiotensin converting enzyme inhibitor (ACEi) with neprilysin inhibitor (NEPI) to form ACEi-NEPI (13). Omapatrilat was the first member in the group. The idea of omapatrilat was meaningful in a way that NEPI augments endogenous natriuretic peptides whereas ACEi blocks the activated potential vasoconstrictors (angiotensin I, angiotensin II) made available from NEP inhibition (13,14). Clinical trials in chronic

HF patients, treatment with the dual-acting ACEi-NEPis (omapatrilat) showed significant reduction in cardiovascular mortality and cardiac failure related readmissions compared with the enalapril (15). However, due to higher incidence of angioedema in omapatrilat group compared with the enalapril, further development of omapatrilat was discontinued in 2004 (16). Angioedema was due to excessive serum bradykinin level. Nepriylsin, angiotensin converting enzyme and aminopeptidase P, each degrades bradykinin. The use of omapatrilat, simultaneously blocks NEP and ACE, leaving free undegraded bradykinin to accumulate, thus excessive bradykinin mediates angioedema. To avoid angioedema which was the major concern, and to ensure safety, pharmaceuticals designed a new approach whereby a NEPi was combined with ARB instead, to form a new molecule, named LCZ696 (currently known as sacubitril/valsartan), is the first ARNI member-in a group. With dual-acting inhibition of LCZ696, ARB blocks RAAS without blocking ACE whereas nepriylsin inhibition augments the natriuretic peptide system, thereby free and available ACE degrade endogenous bradykinin hence lowering the risk of angioedema (16). The new approach proved to be effective in 2015, LCZ696 was titled a "game changer" or "a breakthrough drug" due to overwhelming evidence from PARADIGM-HF (Prospective Comparison of Arni With an Angiotensin Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, where this agent demonstrated to be safe and remarkably reduced cardiovascular mortality and morbidity compared to enalapril in HFrEF. Initial clinical trials to augment natriuretic peptide system conclusively demonstrated that in chronic heart failure and hypertension, stand alone NEPi, ANP or BNP are not effective, so is dual-acting ACEi-NEPi due to safety concern of angioedema and finally established ARNI as safe and effective drug of choice in this population.

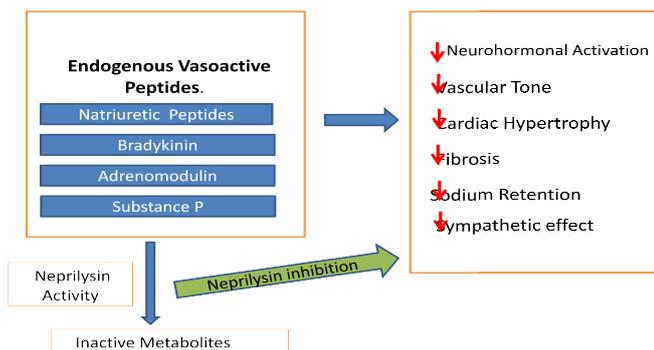


Figure 1. Nepriylsin Inhibition Enhances Actions Of Endogenous Vasoactive Peptides That Counter Maladaptive Mechanisms In Hypertension, Heart Failure and chronic kidney Disease

**Arni in Heart Failure with Reduced Ejection Fraction:** Nearly half of patients with heart failure have a left ventricular ejection fraction (LVEF) less than 40 percent (HFrEF), and nearly half have a LVEF above 50 percent (HF with preserved LVEF or HFpEF). LCZ696 has shown beneficial clinical findings in HFrEF as summarized in table 1. When LCZ696 in PARADIGM-HF trial which enrolled 8440 patients with chronic heart failure (HFrEF) of NYHA class II-IV was compared with enalapril, after 27 months, LCZ696 reduced cardiovascular mortality and rehospitalization by 20% and overall mortality by 3.7% compared to enalapril (17). These findings marked a milestone in the treatment of chronic HF over the past ten years since CONSENSUS and SOVLD trials by enalapril (18,19). Furthermore, Subjects randomized to ARNI therapy were also at reduced risk of 30 and 60-day all-cause and HF-related readmission (20). Benefits of ARNI therapy were rapid, with a reduction of HF hospitalization evident within the first 30 days post-randomization (21), and had higher health-related quality of life as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) (22), including the physical and social domains (23). In the sub analysis of data of PARADIGM-HF, LCZ696 revealed favorable clinical outcomes than enalapril. Compared to enalapril, treatment with LCZ696, significantly reduced cardiac markers of HF (NT-pro-BNP) (24), significantly reduced cardiovascular mortality irrespective of baseline Systolic Blood Pressure (SBP) (25) and was similarly

effective irrespective of glycemic status (26). Also analysis found no evidence of association of LCZ696 use and incidence of dementia (27). In the same year 2015, Dasai and colleagues conducted analysis comparing Sacubitril-valsartan versus enalapril on mode of deaths in patients with HFrEF. Sacubitril-valsartan reduced the risk of death from both progressive HF and sudden cardiac death compared to enalapril (28). Furthermore, in 2019 PIONEER-HF trial showed similar findings. When 881 patients with hospitalization for acute HFrEF were randomly assigned to take either Sacubitril-valsartan or enalapril, and followed for 8 weeks, Sacubitril-valsartan demonstrated greater reduction in markers of HF (NT-proBNP) and rehospitalization compared to enalapril. Amazingly, that greater reduction in NT-proBNP level was detected as early as first week post-randomisation (29). Also, in small retrospective study in Poland, patients with HFrEF, treatment with sacubitril/valsartan showed efficacy and safety and significant clinical improvement after 30 days (30). Similar findings were observed in the most recently published trial in 2019, which double-blindly randomized 540 patients with HFrEF to two up titration regimens of Sacubitril-valsartan for 12 weeks. 76 percent tolerated and maintain sacubitril-valsartan 200mg twice daily in both regimens over 12 weeks without dose interruption or down titration (31). Tolerability profile of Sacubitril-valsartan did not differ from other HF-guideline recommended treatments. Also, promising findings were shown by two different meta-analyses included the randomized controlled trials published between 1987 and 2017, authors described as 30 years of clinical experience of effects of drug therapy in chronic heart failure with reduced ejection fraction. The first meta-analysis included 57 randomized controlled trials (RCTs), including between 28 and 8399 patients with a mean follow-up duration ranging from 8 weeks to 4 years. The greatest reduction in all cause of mortality was found in combination of ARNI+BB+MRA (32). Furthermore, a sensitivity analysis suggested ARNI monotherapy was more effective than ACEi or ARB monotherapy. Similar findings were suggested in the another meta-analysis published in 2018, with 58 relevant randomized controlled trials, with follow-up period between 8 weeks to 3.5 years (33). The study with lowest number of patients included 641, the study with the highest number of patients included 8399 patients, combination of ARNI+BB+MRA was superior to ACEi+BB+MRA in reduction in all cause of mortality in patients with HFrEF. In general from all studies, treatment period ranges from 8 weeks to 4 years, ARNI has shown to be efficacious, safe and tolerable including in patients with low systolic blood pressure (100-110) and in prediabetes and diabetes this agent was effective disregarding glycemic status.

**Arni in Essential Hypertension:** Hypertension is a risk factor for cardiovascular diseases and chronic kidney disease. Appropriate control of hypertension improves rates of mortality, morbidity and survival and slow down the progression of these disease. ARB alone is effective antihypertensive agent by number of studies (34-36), addition of vasodilatation and sympatholytic effects to ARBs from nepriylsin inhibition, results into additional antihypertensive effect, also interpreted as synergism (1+1=3). The beneficial findings of ARNI in essential hypertension is summarized in table 2. In 2010, 1328 patients with mild to moderate hypertension were randomly assigned to 8 weeks treatments in either LCZ696 or valsartan group. After 8 weeks, greater BP lowering capacity was observed in LCZ696 group compared with stand alone valsartan. LCZ696 was well tolerated with no cases of angioedema (37). Another randomized, double-blind trial in 389 Asians with mild to moderate hypertension assigned to receive either sacubitril/valsartan or olmesartan for 8 weeks. Sacubitril/valsartan demonstrated significant reduction in office and 24 hour ambulatory blood pressure compared to olmesartan after 8 weeks of treatment. Sacubitril/valsartan was safe and tolerable (38). Moreover, in similar designed study, in 341 Asians with hypertension, treatment period was extended to 52 weeks, sacubitril/valsartan had greater BP reduction when acting alone or in combination with amlodipine or hydrochlorothiazide than olmesartan alone (39). Also, Kario and colleagues, evaluated the effects of LCZ696 in 35 Japanese patients with severe hypertension (mean baseline SBP 173 mmHg, DBP 112 mmHg) for 8 weeks. At the end of 8 weeks, LCZ696 400 monotherapy or in combination with other drugs (except ACEi or ARBs)

## Beneficial findings of ARNI in HF rEF

Authors	study	design	outcomes
Desai (20)	PARADIGM-HF substudy on effects of LCZ696 on 30-day readmission after HF-hospitalization	Secondary analysis PARADIGM-HF	Reduced the risk of 30 and 60 day and all cause of HF-related readmissions
Packer (21)	PARADIGM-HF substudy comparing lcz696 vs enalapril on the risk of progression of HF rEF in surviving patients	Post hoc analysis	Lcz696 prevents deterioration of surviving patients with HF significantly than ACEI.
Chandra (22)	PARADIGM-HF secondary analysis, to determine effects of LCZ696 on physical and social activity limitations	Using KCCQ at randomisation,4-month,8month and annual visits	LCZ696 group had significant higher health related quality of life than enalapril group.
Lewis (23)	PARADIGM-HF substudy of effect of LCZ696 on healthy related quality of life	Using KCCQ at randomisation,4-month,8month and annual visits	Sacubitril/valsartan group had more improved health related quality of life than enalapril group through 36 months
Zile (24)	PARADIGM-HF substudy, to determine effect of LCZ696 according to baseline N-Terminal pro B-type natriuretic peptide	Post hoc analysis	LCZ696 significant reduced NT-proBNP ,improved mortality and HF-readmission compared with enalapril
Bohm M(25)	PARADIGM-HF substudy	Post hoc analysis	Greater reduction in cardiovascular mortality in LCZ696 group than enalapril group was independent of baseline SBP
Kristensen (26)	PARADIGM-HF substudy of efficacy of LCZ696 across glycemic spectrum	Post hoc analysis	LCZ696was similarly effective, irrespective of glycemic status
Cannon (27)	PARADIGM-HF substudy, to determine whether the use of LCZ696 relate to the incidence of dementia	PARADIGM-HF substudy	No evidence found that LCZ696,compared to enalapril increases risk of dementia .
Desai et al(21)	PARADIGM-HF substudy, effects of LCZ696 versus enalapril on mode of deaths in HF rEF	Secondary analysis PARADIGM-HF	Compared to enalapril,lcz696 was superior in reducing both sudden cardiac death and cardiac death due to deterioration in HF
Velazquez (29)	To determine efficacy of LCZ696 in hospitalized acute decompensated HF patients	880 patient randomized to lcz696l or enalapril for 8-wks	Lcz696 was more efficacious, reduced mortality and readmission for HF compared to enalapril.
Marta (30)	Retrospective analysis to determine efficacy and safety of lcz 696l in HF rEF in Poland	follow up ,in outpatient basis for 3 months	-lcz 696l was safe and effective with improved HF-rehospitalization in 28days after initiation.
Senni (31)	TITRATION study,240randomized trialto evaluate safety of lcz696compared to enalapril in patients with HF rEF and SBP >100 for 12 weeks	Multicentre, randomized trial	Majority achieved LCZ696 200 mg with gradual up-titration than rapid up-titration. The benefit of LCZ696 200 over enalapril was consistent across all baseline SBP. LCZ696 is safe and effective in low SBP (100-110mmgh)
Burnett (32)	A network-metaanalysis to evaluate efficacy of drug therapy (RAAS inhibitors,ARNI,beta blockers and mineral corticoids receptor antagonists)on patients with HF rEF	Included 57 randomized clinical trials between1987 and 2015, follow up period ranged from 8wks to 4 years	-greatest reduction in mortality and HF-readmission were shown by combination of ARNI+BB+MRA -ARNi was superior to ACEi or ARB alone.
komajda(33)	Metaanalysis of randomized controlled trials to evaluate efficacy of drug therapy (RAAS inhibitors,ARNI,beta blockers and mineral corticoids receptor antagonists ) on patients with HF rEF	Included 58 randomized clinical trials published from 1987 to 2017, 30 years ago of clinical practice. Median follow up period of the included studieswas between 8weeks and 3.5 years.	-Combination therapy led to improvement in mortality and readmission. -Best reduction in mortality and rehospitalization rates was associated with combination of ARNI+BB+MRA

demonstrated significant BP lowering capacity(40). Furthermore, sacubitril/valsartan was studied in a small group of Japanese with hypertension and chronic kidney disease [eGFR 15-60ml/min/1.73m<sup>2</sup>]. After 8 weeks, mean sitting systolic/diastolic BP was reduced by 20.5+-11.38/8.3+-6.3mmhg from baseline. There was a 15%reduction in albuminuria (41). Findings provide evidence of safety of sacubitril/valsatan in patients with hypertension with chronic kidney disease. However, In the recent randomized study of 414 patients with chronic kidney disease assigned to either sacubitril/valsatan 97/103 (207 patients) or irbesaltan 300 (207 patients) for 52 weeks.177 patients had baseline SBP≥140 <160mmgh and 76 patients had SBP≥160mmghwhile 126had DBP≥80to<90mmgh and 87 had DBP≥90mmhg. Sacubitril/valsatan reduced BP significantly further than irbersaltan alone (42). Both drugs were similarly safe. These findings cementing the evidence of safety of sacubitril/valsartan essential hypertension in concomitant with chronic kidney disease. In 2016,a clinical trial was designed to determine effects of sacubitril/valsatan in salt sensitive hypertension [SSH], whereby 72 Asian patients with SSH randomized to receive either sacubitril/valsatan 400mg or valsartan 320 once a day daily for 4 weeks. sacubitril/valsatan was more efficacious in treating salt sensitive related-hypertension compared with valsartan monotherapy with significant increase in natriuresis on day 1and greater reductions

in office and ambulatory BP on day 28(43).In comparing with western data, sacubitril/valsatan showed better BP-reductions in Asian population. Moreover, in recent randomized trial of 371 patients with systolic hypertension unresponsive toamlodipine,at 8-week,the combination with sacubitril/valsatan and amlodipine (200mg/5mg) had greater reductions of 24hour-ambulatory BP and pulse pressure than stand alone amlodipine (5mg) (44). Also, findings of PARAMETER trial(Prospective Comparison an Angiotensin-Receptor Blocker Measuring Arterial Stiffness In The Elderly) lcz 696 showed favorable clinical outcomes.454 patients with hypertension and pulse pressure >60mmhg(indicating arterial stiffness) were randomized to receive lcz696 200 or olmesartan 20,uptitred to 400mg or 40 mg respectively as required and followed for 12 to 52 weeks. Amlodipine (5-10mg) or hydrochlorothiazide (6.25-25mg) were added on patients failed to achieve blood pressure target (<140/90).lcz696 demonstrated efficacy ,at 12 weeks reduced central aortic systolic pressure by 3.7mmhg more than olmesartan. At 52 week, the brachial BP, central aortic BP and pulse pressure were similarly reduced by both drug regimens with more subjects in olmesartan group required addition of amlodipine or hydrochlorothiazide.Lcz696 decreases central aortic pressure means it improves hemodynamic and adds therapeutic benefit in BP-lowering beyond RAAS inhibition alone(45).

## Beneficial findings of ARNI in essential hypertension

Clinical trial and intervention	Mean age of participants(y)	Number of participants	Follow-up period(wks)	Mean baseline SBP(mm Hg)	Change in SBP	Mean baseline DBP	Change in DBP
Ruilope(37)							
LCZ696 100	53	156	8	155	-3.2	100	-4.7
LCZ696 200	54	169	8	157	-11.0	100	-6.1
LCZ696 400	53	172	8	155	-12.5	100	-6.9
Valsartan 80	53	163	8	155	-4.7	100	-2.4
Valsartan 160	53	166	8	155	-5.7	100	-3.2
Valsartan 320	53	164	8	156	-12.5	100	-4.2
Kario 2014(38)							
LCZ696 100	3	100	8	156	-11.5	100	-4.7
LCZ696 200	52	101	8	156	-11.0	100	-6.5
LCZ696 400	51	96	8	154	-12.5	100	-7.8
plc	50.9	92	8	155	-4.97	100	-3.69
Supasyndh(39)							
LCZ696 200	52	295	10	154	-22.71	99.7	-8.58
Olmesartan 20	52	291	10	154	-16.11	99.7	-6.49
Kario 2016(40)							
LCZ696 200	51	35	4	173	-23.1	112	-14
LCZ696 400	51	32	8	173	-35.1	112	-22.1
Ito (41)							
LCZ696 100	66	32	4	152	-13.4	87	-5.2
LCZ696200	66	16	6	152	-19.4	87	-7.8
LCZ696 400	66	18	8	152	-20.7	87	-8.4
Haynes 2018(42)							
LCZ696	62	207	52	146	-5.1	82	-2.1
Irbarsartan	63	207	52	146		80	
Wang TD 2017(43)							
LCZ696 400	56	36	8	147	-13.3	90	-6.2
valsartan 320	59	36	8	148	-5.8	90	-4.2
Wang JG 2017(44)							
LCZ696 200+amlodipine5	55	123	8	138	-13.9	86	-0.8
amlodipine 5	55	128	8	140	-8.0	86	-0.3
Williams e(45)							
LCZ696 400	68	207	12	158	-13.7	87	-5.9
olmesartan 40	67	206	12	159	-9.9	90	-4.9
Izzo (46)							
Sacvalsartan400	60	142	8	159	-21.8	90	-9.6
Sac400,valsart320	62	144	8	160	-20.9	90	-8.5
Sac200,va320	62	145	8	160	-23.6	90	-9.8
Sac 100,vals320	61	141	8	159	-21.3	90	-8.0
Sac50 valsar320	61	134	8	159	-19.3	89	-7.2
Valsartan alone	61	143	8	159	-16.1	90	-7.3
placebo	61	57	8	159	-7.0	90	-3.4
Cheung (2018)(47)							
LCZ696	57	188	8	157	-4.5	90	-2.3
200	58	188	8	157	-1.1	91	-0.3
Olmesartan 20							

Also in the trial published in 2018, 852 patients with systolic blood pressure were assigned randomly to LCZ696 400mg once daily or valsartan 320mg alone or with free sacubitril-in dose increasing manner as placebo (50,100,200, or 400mg once daily) to determine safety and efficacy. At 8-week, LCZ696 400mg reduced systolic blood pressure further than valsartan 320 alone and had similar efficacy to combination of valsartan 320mg plus free sacubitril 200mg. Moreover, LCZ696 400mg was safe and well tolerated and suggested to be the optimal combination dose for lowering systolic BP(46). Furthermore, in 2018, in 376 patient with unresponsive systolic hypertension to olmesartan 20mg, were assigned to receive either LCZ696 200mg or olmesartan 20mg for 8-week therapy. At the end of 8 week, LCZ696 200mg showed greater BP reduction than olmesartan alone, and was safe and tolerable(47). Similar findings were demonstrated in the most recent meta-analyses in 2019. The first meta-analysis included 9 randomized controlled trials, with follow up period between 8wks and 52 wks, compared the effects and safety between LCZ 696 and angiotensin receptor antagonists in hypertension. LCZ 696 was more efficacious than ARB alone and there was no statistical difference found between LCZ696 and ARB group in any adverse events (48), implying LCZ 696B was as safe as standard care (ARB). Similar findings were found in another similar meta-analysis designed to compare the effects and safety between LCZ 696 and comparator (ARB) in elderly hypertensive patients

(age>55years). Included 5 randomized controlled trials with total of 1513 patients, mean follow up period between 8wks and 52 weeks. LCZ 696 was more superior antihypertensive compared to ARB monotherapy (49).

**Arni in Chronic Kidney Disease:** Chronic kidney disease patients usually face two major risks; cardiovascular death and risk of progression to end stage renal disease. Unfortunately the known drugs to prevent these risks including RAAS inhibitors are limited to low and moderate dosage usually under close surveillance especially in advanced chronic kidney disease. It was hypothesized that combination of neprilysin inhibitor and angiotensin-receptor blocker could carry potential renal benefits. These renal benefits shown in summary of randomized clinical trials in Table 4. A number of studies in using dual-acting NEP-RAAS inhibitors in animal models of HF have previously demonstrated relative preservation of renal function, including increases in glomerular filtration rate and natriuresis (50–53). Further, animal studies reported that atrial natriuretic peptides play a role in dilating afferent arterioles and in constricting efferent arterioles, thus they preserving glomerular filtration rate even when cardiac output is reduced. Moreover, compared with ARB alone, NEP-RAAS inhibitor demonstrated more renoprotective effect in diabetic rats (53). Recent reports from randomized controlled trials have demonstrated clinical benefits of dual-acting NEP-RAAS inhibitors in chronic kidney disease. In

randomized trial of 8,399 patients, 2,745 patients (33%) had chronic kidney disease with  $eGFR \geq 30$  ml/min/m<sup>2</sup>. Despite causing early and stable increase in urine albumin creatinine ratio (UACR), patients randomized to sacubitril-valsartan showed slower rate of decrease in the  $eGFR$  and significant improvement in cardiovascular outcomes than patients in enalapril group (54). In substudy on data of PARADIGM-HF trial by Gori, to evaluate effects of LCZ696 on urine albumin excretion, compared to enalapril, patients in LCZ696 group had better preserved renal functions despite of stable, early and fair increase in albuminuria (55). In 2015, LCZ696 was studied in 76 Japanese patients with Hypertension and chronic kidney disease [ $eGFR$  15-60 ml/min/1.73m<sup>2</sup>]. After 8 weeks, LCZ696 has shown 15% reduction in albuminuria without any significant changes in serum creatinine, potassium, blood urea nitrogen, and estimated glomerular filtration rate ( $eGFR$ ) (41). In contrast with previous studies (54,55), in this study there was no increase in albuminuria instead there was 15% reduction in albuminuria observed after 8 weeks. These findings cemented the evidence of safety and efficacy of sacubitril/valsartan in patients with chronic kidney disease. Moreover, in another randomized trial of 301 patients, with HF and mean  $eGFR$  between 40-85 ml/min/1.73m<sup>2</sup> (2) were randomized to receive lcz696 or valsartan for 36 weeks. At the end of 36 weeks LCZ696 associated with lesser GFR decline compared to valsartan (-1.5 vs. -5.2 ml/min per 1.73m<sup>2</sup>;  $P = 0.002$ ). lcz696 preserved renal function significantly more than valsartan (55). Further evidence was demonstrated by NEP-RAAS (LCZ696) in metaanalysis of 15,043 HF-patients with baseline  $eGFR \geq 30$  ml/min/m<sup>2</sup>.

The dual-acting inhibition appeared to preserve renal function more than RAAS inhibition alone. Further analysis showed NEP inhibition provides potential diuretic effect without affecting serum levels of potassium and uric acid (56). The most recent trial in 2019, The UK HARP-III which measured short-term effects of sacubitril/valsartan versus irbesartan in 404 patients with chronic kidney disease, baseline  $GFR \geq 20$  ml/min/m<sup>2</sup> (ckd I-IV). Patients were assigned to receive sacubitril/valsartan or valsartan in 52-weeks treatment, sacubitril/valsartan reduced albuminuria, systolic BP and markers of heart failure than valsartan alone. Albuminuria reduction was greater in sacubitril/valsartan group than in irbesartan group, though did not amount to statistical significance. In contrast with PARADIGM-HF trial, increase in UACR was not observed with sacubitril/valsartan in this trial instead there was reduction in albuminuria. This agent was safe and tolerable even in advanced ckd  $\geq 20$  ml/min/m<sup>2</sup> (ckd IV). These findings strengthen further the evidence of safety of sacubitril/valsartan in CKD (42). Also, in the most recent findings in 2019, a report of randomized clinical trial by Chang and coworkers to evaluate real world experience of dual acting-inhibition in 932 patients with HFrEF, among them 39% had ckd ( $eGFR < 60$  ml/min/m<sup>2</sup>), 10% with ckd stage IV and V while 17% had hypotension (SBP < 100 mmHg). sacubitril/valsartan demonstrated significant effectiveness compared to standard HF treatment. In different stages of CKD, sacubitril/valsartan group, had favorable clinical outcomes including in CKD stage IV and V, compared to standard care, however there was no significant difference in hypotensive patients with dual inhibition compared to standard of care (57).

#### Beneficial findings of ARNI in chronic kidney disease.

Authors	Study	Design	Intervention (LCZ696 vs comparator)	Included CKD ( $eGFR$ in ml/min/1.73m <sup>2</sup> ) [ $*CKD = eGFR < 60$ ml/min/1.73m <sup>2</sup> ]	Outcomes
Itoh (41)	To determine effect of lcz696 on HTN, renal function in Japanese patients	Patients randomized to lcz696 100, 200, 400 for 4-6-8 wks respectively	Lcz 696 100 Lcz696 200 Lcz696 400	15 – 60 CKD IIIa-b, and IV	- LCZ696 Preserve renal function (delays ckd progression) than placebo - greater BP reduction than placebo
Damman (54)	PARADIGM-HF substudy on LCZ696 and renal function	Post hoc analysis	LCZ696 Valsartan	$\geq 30$ (2,745 patients had ckd II-III)	LCZ696 delays GFR progression with better cardiovascular outcomes than enalapril.
Gori	PARADIGM-HF substudy on LCZ696 and UACR	Post hoc analysis	LCZ696 Valsartan	$\geq 30$ CKD IIIa-b	Compared to enalapril, LCZ696 led to modest, early and stable albuminuria increase with better clinical outcomes.
Voors (55)	PARAMOUNT trial substudy on LCZ696 and renal effect in patients with HFpEF	36wks-Randomized controlled trial of 301 patient, $eGFR$ 40-85 ml/min per 1.73m <sup>2</sup>	LCZ696 vs Valsartan	$\geq 30$ CKD IIIa-b	LCZ696 preserve GFR, reduced incidence of worsening of renal function and alleviated serum creatinine than valsartan.
F. Bodey (56)	Metaanalysis to evaluate whether neprilysin inhibitors preserve renal function in HF	Included 4 randomized controlled trials (with PARADIGM-HF data)	In 4 trials intervention was: 1. Omapatrilat vs lisinopril, 2. omapatrilat vs enalapril, 3. sac/val vs valsartan, 4. sac/vals vs enalapril	$\geq 30$ CKD IIIa,b	NEPi-RAAS inhibition preserves renal function than RAAS inhibition monotherapy.
Packer et al (2018) (58)	PARADIGM-HF substudy to evaluate effects of lcz696 on renal functions in concomitant diabetes and HFrEF patients	Post hoc analysis	Lcz696 vs Enalapril	$\geq 30$ CKD IIIa,b	LCZ696 group had slower decline in renal function than enalapril group.
Haynes et al (2018) (42)	UK HARP III trial on safety and efficacy of LCZ696 ckd [ $eGFR$ 20-60 ml/min/1.73m <sup>2</sup> ]	52 wks-randomized – multicentre-double blinded trial of 414 protenuric patients	LCZ696 vs Irbesartan	20 - 60 CKD III-IV (37.7% -156 patients had CKD IV)	-LCZ696 reduced albuminuria further than irbesartan - LCZ696 reduced BP significantly further than irbesartan - Both LCZ696 and Irbesartan were similar in safety and tolerability.
H-Y. Chang et al (2019) (57)	to determine effects of sac/val in HFrEF with ckd and hypotensive	15 months-randomised 932 patients to receive sac/val or other standard HF therapy	Sacubitril/valsartan vs Standard care	CKD III, IV and V CKD III (28%) CKD IV-V (11%)	-sac/val was more effective than standard care in all stages of ckd, -however in hypotensive patients there was no difference compared to standard care.

In general studies primarily dedicated for renal outcomes treatment period was between 8 weeks to 15 months (Itoh, Voors, Haynes and H-Y chang et al) ARNI was safe and tolerable similar to comparator with superior renal outcomes to comparator except in Haynes et al whereby albuminuria in ARNI group was greater than in irbesartan but was not of statistical significance. In substudies of PARADIGM-HF, where by renal outcomes were evaluated as secondary endpoints, follow-up period was 2.3 years renal outcomes of ARNI were superior to enalapril (Damman and Gori et al).

**Limitations and gaps of ARNI in clinical practice:** Despite of overwhelming benefits, ARNI carry potential limitations which medical community deserves to know. Patients with NYHA class IV were underrepresented in PARADIGM-HF trial, were only 33(0.8%) (17), hence the use of ARNI in this group, physicians need to select patients carefully with close surveillance afterwards. Also, despite of overwhelming evidence of superiority by ARNI over RAAS inhibition alone, the current guidelines-recommended therapy doesn't identify ARNI as first line in the treatment of HFrEF, instead is used as therapeutic option in patients tolerating ACEi or ARB. Moreover, HF-guideline is unclear about the inpatient use of ARNI in stabilized HF patients prior to discharge, despite of substantial beneficial outcome of PIONEER-HF trial(29). Despite of ARNI being safer than ACEi-NEPi (omapatrilat) regarding incidences of angioedema but still ARNI has been associating with more angioedema compared to the standard care(17)(21). This is still one of the reasons why clinicians hesitate to favor this novel agent as therapeutic option. Furthermore, medical community needs to be reminded that, ARNI may cause symptomatic hypotension, hyperkalemia, renal impairment and persistent dry cough. Symptomatic hypotension and hyperkalemia worsen in concurrent use with other potassium sparing diuretics. ARNI use has been linked with incidences of Alzheimer's disease due to amyloid- $\beta$  peptides accumulation in the brain, enhanced by neprilysin inhibition, these peptides cause neurotoxic plaques which are related to the pathology and development of Alzheimer's disease (59–61). Further reports emphasized that neprilysin inhibition favors Alzheimer's disease in patients at risk including genetics, cardiovascular diseases and cognitive impairment (62,63). This is another reason explaining why medical community to date does not prioritize ARNI, instead has been continuing to favor ACEi or ARB.

The cost of LCZ696 is significant higher compared with the first line guideline recommended therapy, this is the major obstacle of this novel drug to widespread adoption in medical community. Report show switching from generic ARB/ACEi to ARNI will lead to eight-fold increase in medication cost alone (64). Also, due to teratogenicity and oligohydramnios from RAAS inhibition, ARNI is strongly contraindicated in women expecting to conceive and in pregnancy. It is clear by now that in real world, the fear of adverse effects, high cost of medication, unclear linkage between ARNI and Alzheimer's disease and lack of knowledge and experience among physicians are the major reasons limiting the widespread of ARNI and its adoption within the medical community, despite of having overwhelming clinical benefits. The screening of evidences identified several gaps bringing up the need to conduct large scale research in particular areas. Efficacy of LCZ696 in treating secondary hypertension is still unclear, furthermore, there is no enough data demonstrating the long-term efficacy and safety of ARNI in severe hypertension (> 180/110), leaving the medical community at dilemma. However, to date, there is no clinical trial underway to test ARNI in severe hypertension. LCZ696 carries renoprotective effects established by numerous short-term studies (41,54,55) whereby renal outcomes were not primary end-points. The medical community lacks evidence of renoprotective effect of this novel agent in long-term by studies primarily dedicated for renal outcomes (58). Unfortunately, to date, there is no such studies underway leaving medical community with curiosity. Diabetic nephropathy is still a major cause of end stage renal disease. With previously established ARNi favorable renal outcomes and ARB antiproteinuric effects, there by the medical community cannot help to hypothesize whether ARNi could slower the decline in renal function in diabetic nephropathy especially in

long-term designed studies. In addition to that, the current proven renoprotective antidiabetic drugs (empagliflozin, canagliflozin) both used RAAS inhibition as background therapy in EMPA-REG and CREDENCE trials. Coupling SGLT-2 inhibitors to ARNI could bring a breakthrough in the therapy of diabetic nephropathy. In my knowledge to date, there is no trial underway or in the near future designed to determine effects of ARNI in diabetic nephropathy. ARNI could be used to control resistant hypertension. Resistant hypertension is still a major barrier in hypertension therapy with incidence of 5-10% in general population and up to 40% in CKD. Hidden fluid overload frequently associates with pathology of resistant hypertension. Adding hydrochlorothiazide to ARNI, the combination could bring improvement in treatment of resistant hypertension. Unfortunately there is no clinical trial under designing or underway by ARNI for hypertension patients.

**Clinical Perspectives:** Evidence have pointed out safety and efficacy of ARNI (sacubitril/valsartan) in hypertension and chronic heart failure with reduced ejection fraction [HFrEF]. Recent evidences have shown that ARNI reduces the two major risks in CKD, reduces cardiovascular morbidity and mortality and preserves renal functions along with being effective and tolerable in CKD including stage IV and V. ARNI could be the precious therapeutic option in essential hypertension, chronic heart failure with reduced ejection fraction and moderate chronic kidney disease. With ARNI treatment, physicians need to choose patients carefully especially those with ckd stage IV or V and HF NYHA class IV. This population needs close monitoring afterwards. The evidence gap, warrants a large-scale randomized clinical trial to study ARNI in coexistence of essential hypertension, chronic heart failure with reduced ejection fraction and chronic kidney disease.

## CONCLUSION

ARNI could be suitable treatment for reduction of cardiovascular risk, prevention of progression of disease as well as being effective in patients with hypertension, chronic heart failure with reduced ejection fraction and chronic kidney disease.

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