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The Renal Effects of Neprilysin Inhibition in Heart Failure and Hypertension

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Abstract

Cardiovascular disease is one of the major causes of mortality throughout the world. Renin Angiotensin blockers are well known for their beneficial effects in patients with heart failure. New emerging medications like neprilysin inhibitors have shown trend towards positive benefit in patients with heart failure. Data on the effect on renal function is still limited. Through this article, we are reviewing multiple randomized clinical trials involving Neprilysin and summarize the renal effects of the medicine.

Keywords: Neprilysin; heart failure; hypertension; creatinine

Abbreviations: NEPi: Neprilysin inhibitors; HF: Heart failure; ACE: Angiotensin converting enzyme; ARB: Angiotensin receptor blocker HFREF: Heart Failure with Reduced Ejection Fraction

Introduction

Neprilysin inhibitors (NEPi) represent an emerging therapeutic option for treatment of congestion in heart failure (HF) as well as hypertension (HTN). While these agents have shown promising results regarding HF events, lowering blood pressure, and mortality, their impact on the kidney remains largely unknown. The aim of this study is to evaluate the currently available evidence on the effect of NEPi use on kidney-related parameters in patients with HF or HTN.

Methods

A search of articles cited in PubMed database using key words "neprilysin or neutal endopeptidase", "heart failure" and "hypertension" was performed. Animal studies were excluded. Only those studies containing kidney-related parameters such as serum creatinine or estimated glomerular filtration rate were selected. Relevant data including changes in renal function, blood pressure and mortality were extracted and compared.

Discussion

A total of 43,368 patients from 13 randomized controlled trials with data pertaining to NEPi use (4 studies used LCZ696, 3 used Omapatrilat, 2 used Sampatrilat, 1 used Daglutril, 1 used Sacubitril and 1 used GW660511X) in HF (5 studies) and HTN (8 studies) were included in this study (Table 1). 8 studies used ACE-I while 4 used ARBS as control. The mean age of the patients was 59.19 years with a mean baseline systolic blood pressure of 118 to 162 mm Hg. The follow up periods were between 7 days and 27 months. Concerning the reduction in BP, 11 studies reported better or similar BP lowering effect of NEPi compared to control drugs (ACE-I, ARBs or placebo).

Table 1: Review of randomized controlled trials showing renal effects of Neprilysin inhibitors.

First Author/ Year/ Reference	No of patients and HTN vs Heart failure study	Age	Baseline crea-tinine	Baseline systolic blood pressure	Agent used, action	ACEI or ARBs	Follow up	Change in renal fx	Change in BP	Weight reduction/ Mortality benefit	Major findings/ comments
Velazquez, 2019 Randomized double blind [1]	881, Heart failure	63	1.27	118	Sacubitril-Valsartan NEPi/ ARBNEPi/ ARB	Enalapril	8 weeks	Worsening renal function in 13.6% in study drug group vs 14.7 in Enalapril group	Symptomatic hypotension 15% in study drug group vs 12.7% in Enalapril group	NA, 2.3% deaths in study drug group vs 3.4% in Enalapril group. Hazard ratio 0.66 (0.30 to 1.48)	Significantly greater reduction in the NT-proBNP concentration in study drug group than enalapril group
McMurray, 2014, Randomized double blind [2]	8442, Heart failure	63.8	1.13	121.5	LCZ696 NEPi/ AT-1 blocker	Enalapril	27 months (median)	Elevated creatinine >/= 2.5 : 3.3% in the study drug group vs 4.5% in Enalapril group (Significant) but there was no significant difference in serum crt from baseline at 8 months btw groups	Mean systolic blood pressure at 8 months was 3.2±0.4 mm Hg lower in the LCZ696 group than in the enalapril group (P<0.001)	NA, LCZ696 was superior to ACE inhibition alone in reducing the risks of death and of hospitalization	LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. The trial was stopped early, according to prespecified rules because the boundary for an overwhelming benefit with LCZ696 had been crossed. Significantly fewer patients in the LCZ696 group than in the enalapril group stopped their study medication
Packer, 2002, randomized control trial [3]	5770, Heart failure	63.4	NA (excluded patients with crt more than 2.5)	123.5	Omapatrilat NEPi/ACE	Enalapril	14.5 months (Mean)	Impairment of renal function was seen in 10.1% patients in Enalapril group and 6.8% in study drug group	When measured before the next scheduled dose, SBP decreased more in the enalapril group throughout the uptitration period (-5.2 versus -3.6 mm Hg at end of uptitration). However, during the maintenance phase of the study, the decline in systolic blood pressures at trough was similar in the two groups.	NA, Omapatrilat reduces the risk of death and hospitalization in chronic heart failure	The omapatrilat group had a 9% lower risk of cardiovascular death or hospitalization (P_0.024)

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Rouleau, 2000, randomized double [4]	573, Heart failure	63.95	1.16	126.2	Omapatrilat NEPi/ACE	Lisinopril	24 weeks	Incidence of elevated creatinine in Omipatrilat group was 1.8% and Lisinopril was 6.1% which is significant, but plasma creatinine concentration was not significant.	Incidence of hypotension in omapatrilat was 10% and Lisinopril was 6%. (no data on change in BP)	Weight 'gain' is seen in 10% pts treated with Omapatrialt and 11% of Lisinopril group, No significant difference in mortality.	significant benefit of omapatrilat in the composite of death, admission, or discontinuation of study treatment for worsening heart failure
Solomon, 2012, randomized [5]	301, Heart failure	71	Mean GFR 65.5	Median 136/79	LCZ696 NEPi/AT-1 blocker	Valsartan	36 weeks	Incidence of renal dysfunction was not different but eGFR decreased to a greater extent in the valsartan group (LCZ696, −1.6 mL/min vs valsartan, −5.2 mL/min p=0 007	At 36 weeks, blood pressure was reduced by 7·5/5·1 in the LCZ696 group versus 1·5/0·34 in the valsartan group	No significant difference in mortality	LCZ696 reduced NT-proBNP to a greater extent than did valsartan and was significant at 12 weeks but not at 36 weeks
Kario, 2014, randomized [6]	389, HTN	51.6	0.89	155/99.9	LCZ696 NEPi/AT-1 blocker	none	8 weeks	NS change in renal function (0.01 vs 0.02)	Mean differences in clinic DBP were −7.84, −7.29, and −8.76 mm Hg for LCZ696 100, 200, and 400 mg, (all P<0.0001). mean differences in clinic SBP were −11.86, −12.57, and −15.38 mm Hg for LCZ696 100, 200, and 400 mg, (all P<0.0001).	The mean change in body weight from baseline at end point was small and similar for all treatment groups (−0.2 to 0.7kg), No cases of death were reported, no data on mortality	

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Kostis, 2004, randomized controlled [7]	25,302, HTN	56.9	616 patients have CKD at baseline	155.25/93.7	Omapatrilat NEPi/ACE	Enalapril	24 weeks	NA	Omapatrilat reduced systolic BP 3.6 mm Hg more than enalapril at week 8 and was associated with less use of adjunctive antihypertensive therapy by week 24 (19% v 27%; P 0.001 for both comparisons).	NA, death or hospitalization for cardiovascular causes occurred less frequently in subjects treated with omapatrilat	Angioedema was more frequent with omapatrilat than enalapril (2.17% v 0.68%). Target BP was achieved in 58.2% of subjects who received omapatrilat and 49.6% of those who received enalapril.
Norton, 1999, randomized [8]	58, HTN	50	NA	NA	Sampatrilat NEPi/ACE	Lisinopril	56 days	NA	Sampatrilat produced a sustained decrease in mean ABP over the 56-day treatment period (day 28: SBP -7.3, DBP -5.2; P < .01: day 56: SBP -7.8; DBP -5.2; P < 0.01). Lisinopril was significant at 24 day but not at 56	NA, No data on mortality	Black hypertensives
Ruilope, 2010, randomized controlled [9]	1328, HTN	53	NA	155.7/99.7	LCZ696 NEPi/AT-1 blocker	Valsartan	13 weeks	NA	Significantly greater reductions with LCZ696 vs valsartan (mean reduction: –2·17 mm Hg; p<0·0001	No significant changes in bodyweight were recorded in any group during the study, No data on mortality	Microalbumin-creatinine ratio decreased in all LCZ696 and valsartan groups during treatment. Changes were significantly different from that of the placebo group, in which the ratio increased
Wallis, 1998, randomized [10]	124, HTN	51	NA	162/102	Sampatrilat NEPi/ACE	Lisinopril	4-week placebo run-in period followed by 10 days (38 days)	N/A	After 10 days, lisinopril lowered clinic blood pressure 24 hours after dosing by 8/6 mm Hg compared with placebo. Sampatrilat also significantly decreased the BP by max of 8/7	NA, No data on mortality	

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Parvanova, randomized controlled, 2013 [11]	45, HTN	63.9	eGFR: 80.2	24 hours: 131.6/75.8	Daglutril NEPi/ECE	Placebo (all patient was taking losartan)	8+4+8+4: 24 weeks	GFR, renal plasma flow, filtration fraction, and renal vascular resistance did not change significantly before and after each treatment period	24-hour systolic BP significantly decreased by 3 mm hg with Daglutril 8 weeks	Daglutril did not affect haematocrit or haemoglobin concentration, body-mass index, No data on mortality	24-h urinary albumin excretion did not change signifi cantly throughout each treatment period
Johnson, randomized double blind, 2006 [12]	123, HTN	51	NA	NA	GW660511X NEPi/ACE	Placebo	20 days	NA	GW660511X 200mg significantly lowered mean cuff SBP (-8.00mm Hg) and DBP (-5.38mm Hg), 24 hours systolic -5.25 and diastolic -2.81 mmHg lower with study drug (significant)	NA, No data on mortality	GW660511X is a novel potent and selective dual inhibitor of ACE and NEP both in vitro and ex vivo
Regamey, randomized, 2002 [13]	32, HTN	25, Male only	NA	118/70	Omapatrilat NEPi/ACE	Fosinopril/HCTZ	7 days	No significant change in GFR	significant fall in baseline blood pressure from Omapatrilat	NA, No data on mortality	
Total: 13 studies	43,368 (5 heart failure studies and 8 HTN studies)	59.19		118 to 162 mmHg	4 LCZ696, 4 Omapatrilat, 2 Sampatrilat, 1 Daglutril, 1 sacubitril, 1 GW660511X	8 ACEI, 3 ARBs	7 days to 27 months	5 studies showed decreased renal dysfunction, 5 studies not available and 3 did not show any changes	Better or similar decrease in BP compared to control drug in 11 studies. 1 showed symptomatic hypotension 15% in study drug group vs 12.7% in Enalapril group. NA in 1	Not significant weight change, 6 showed better or no change in mortality	

One study reported symptomatic hypotension in 15% in study drug (Sacubitril/Valsartan) group vs 12.7% in Enalapril group. BP data was unavailable in 1 study. Although the data regarding renal dysfunction was unavailable in 5 out of 13 studies, 4 reported less renal dysfunction with NEPi, 3 did not show any significant change compared to the control drug and 1 showed less frequent worsening renal function (13.6%) in study drug group (Sacubitril/Valsartan) vs Enalapril group (14.7%). 6 studies showed better or at least no change in mortality (unavailable in 7).

Conclusion

Current evidence suggests that the novel angiotensin receptor-NEPi can lower HF events and mortality in patients with HF while having a modest impact on lowering their blood pressure. Although it is mechanistically conceivable that these medications portend favorable effects on the kidneys, so far studies have not shown any evidence of improvement in kidney-related parameters in these patients. There is one more randomized controlled trial "EntrestoTM (LCZ696) In Advanced Heart Failure (LIFE Study - NCT02816736) which is currently enrolling patients with advanced HFrEF and will assess the safety, tolerability, and efficacy of ARNI. Hopefully we will have more data from this upcoming study.

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