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Review Article

Sacubitril/valsartan: A novel angiotensin receptor-neprilysin inhibitor

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ABSTRACT

Objective: To describe the efficacy, superiority and safety profile of the first-in-class angiotensin receptor-neprilysin inhibitor "Sacubitril/Valsartan" as compared to angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blocker (ARB) in heart failure (HF) patients, reviewing data available from both clinical and pre-clinical studies. Evidences on health care utilization outcomes such as hospitalizations and emergency department visits were also evaluated.

Material (data source): **Sources**: Medical literature on 'Sacubitril/Valsartan' and 'Angiotensin Receptor-Neprilysin Inhibitor' was identified by searching databases (including, but not limited to, PubMed, Embase and HighWire) for articles published since 1991, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the companies developing the drug.

Search Strategy: We conducted separate searches for each of the interventions of interest. The timeframe for both searches spanned the period from January 1991 to the most recently published data available and focused on PubMed, Embase and HighWire indexed articles. The search strategies included a combination of indexing terms as well as free-text terms included separately in 'Keywords' section. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analysis. Searches were last updated on 12th July 2017.

Selection: Studies in patients with hypertension who received sacubitril/valsartan combination drug were included. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well-controlled trials with appropriate statistical methodology was preferred. Relevant pharmacodynamics and pharmacokinetics data was also included.

Data evaluation: Many clinical trials have been conducted comparing the efficacy of sacubitril/valsartan with other anti-hypertensives. The trials have shown sacubitril/valsartan to be more effective in improving symptoms and physical limitations, reducing the risk of cardiovascular (CV) death, HF hospitalization, and the overall mortality and morbidity compared to its counterparts.

Conclusion: Effective reduction of blood pressure to accepted goals is the key to reduce the risk of CV events and stroke. Dual inhibition of neprilysin and the angiotensin receptor with sacubitril/valsartan may represent an attractive and serendipitous therapeutic approach for a range of CV diseases, including hypertension and HF, in which vasoconstriction, volume overload and neuro-hormonal activation play a part in pathophysiology. Sacubitril/Valsartan appears to be more efficacious in reducing blood pressure than currently available ACEi and ARBs with a similar safety and tolerability profile. Besides, pleiotropic benefits like HbA_{1c} reduction, better eGFR progression and a greater decrease in blood pressure and serum creatinine levels make this drug a novel addition to the current hypertension armamentarium.

1. Introduction

Heart failure (HF) is a major and growing health challenge in India and the developing countries. It is one of the most important causes of morbidity and mortality in the industrialized world. The

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incidence and prevalence estimates of HF are unreliable in India because of the lack of surveillance systems to adequately capture these data. Regardless of this, the prevalence of HF in India is possibly on the rise as India remains doubly burdened by the rise in the risk factors of traditional cardiovascular (CV) disease and by the persistence of pre-transitional diseases such as rheumatic heart diseases, endomyocardial fibrosis, tuberculous pericardial disease and anaemia. Burden of HF in India due to hypertension is extrapolated to be 3.5–7 million (estimate of about 4–5 million) and HF due to myocardial infarction is 2.1 million to 8.4 million (estimate of about 4–5 million) while an annual mortality due to HF around 0.1–0.16 million.[1–3]

With resources like cardiac resynchronization therapy and the heart transplant program available on a limited basis, pharmacotherapy still remains the primary treatment option. The latest results from SPRINT trial indicate that intensive blood pressure lowering to a target <120 mmHg is superior to routine management with a target of <140 mmHg in high-risk non-diabetic hypertensives, including elderly patients. An intensive strategy resulted in lower rates of fatal and nonfatal major CV events and death from any cause, although significantly higher rates of some adverse events were observed in the intensive-treatment group.[4,5]

Sacubitril/Valsartan is a first-in-class angiotensin receptor-neprilysin inhibitor (ARNi) approved for the treatment of HF. It consists of the angiotensin receptor blocker (ARB) 'valsartan' and the neprilysin inhibitor 'sacubitril', in a 1:1 mixture by molecule count. The combination is thereby marketed as an "Angiotensin Receptor-Neprilysin Inhibitor".[6]

Currently, sacubitril/valsartan combination has been approved in more than 57 countries including India. The U.S. Food and Drug Administration approved sacubitril/valsartan combination in July 2015 for the treatment of patients with New York Heart Association (NYHA) class II through IV HF symptoms and a reduced ejection fraction (HFrEF) based on the results of the PARADIGM-HF trial.[6,7] It has now been included as a Class I B recommendation by the 2016 ESC and ACC/AHA/HFSA guidelines.[8–10]

2. Mechanism of action

Neprilysin, also known as membrane metallo-endopeptidase (MME), neutral endopeptidase (NEP), cluster of differentiation 10 (CD10), and common acute lymphoblastic leukemia antigen (CALLA), is an enzyme that in humans is encoded by the *MME* gene. It is found in many tissues, particularly in kidney on the brush border of proximal tubules and on glomerular epithelium. It is the principal enzyme for degradation of multiple vasoactive peptides (VAP) including natriuretic peptides, angiotensin, endothelin 1, adrenomedullin, opiods and amyloid-β peptide (Aβ). It cleaves peptides at the amino side of hydrophobic residues and inactivates several peptide hormones including glucagon, enkephalins, substance P, neurotensin, oxytocin, and bradykinin.[11,12]

Sacubitril (AHU-377), neprilysin inhibitor, is a prodrug that is activated to the active metabolite 'Sacubitrilat' (LBQ657) by de-ethylation via esterases. Sacubitril, thus, increases the levels of these peptides, promoting natriuresis, vasodilation and reduction of ECF volume via sodium excretion; eventually reducing preload and ventricular remodeling.[13,14]

Valsartan inhibits the effects of angiotensin-II by selectively blocking the receptor type-1 (AT_1), and concomitantly inhibiting angiotensin-II-dependent aldosterone release. Blockade of AT_1 thus reduces vasoconstriction, sodium and water retention and myocardial hypertrophy. In experimental studies, sacubitril/valsartan have shown to attenuate angiotensin-II-mediated cardio-renal fibrosis and cardiac remodeling and dysfunction after experimental myocardial infarction; attributed to superior inhibition by sacubitril/valsartan on cardiac fibrosis and cardiac hypertrophy than either stand-alone neprilysin inhibitor or ARB.[15,16]

In summary, the CV and renal benefits of sacubitril/valsartan in HF patients are attributed to the increased levels of peptides that are degraded by neprilysin and the simultaneous inhibition of the effects of AT_1 receptor by valsartan (Fig. 1).

3. Physical and chemical properties

Sacubitril/Valsartan complex comprises of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. A single complex consists of 6 valsartan anions, 6 sacubitril anions, 18 sodium cations, and 15 molecules of water, resulting in the molecular formula $C_{288}H_{330}N_{36}Na_{18}O_{48}\cdot 15H_2O$ and a molecular mass of 5748.03 g/mol.[6,13]

The substance is a white powder consisting of thin hexagonal plates. It is stable in solid form as well as in aqueous (watery) solution with a pH of 5 to 7, and a melting point of about 138 °C (280 °F)[6,13] (Fig. 2).

4. Pharmacokinetics

4.1. Absorption

Following oral administration, sacubitril/valsartan dissociates into individual components with plasma concentrations of sacubitril, sacubitrilat, and valsartan achieving peaks in 0.5 h, 2 h, and 1.5 h, respectively. The oral absolute bioavailability of sacubitril is estimated to be ≥60%. Following BID dosing, steady state levels of sacubitril, sacubitrilat, and valsartan are reached in 3 days. Administration with food has no clinically significant effect on sacubitril, sacubitrilat or valsartan.[6,13]

4.2. Distribution

Sacubitril, sacubitrilat and valsartan are highly bound to plasma proteins (94%–97%) with average apparent volumes of distribution of valsartan and sacubitril around 75 L and 103 L, respectively.[6,13]

4.3. Metabolism

Sacubitril is readily converted to sacubitrilat by esterases which is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite can be identified in plasma at low concentrations (<10%).[6,13]

4.4. Elimination

Following oral administration, 52% to 68% of sacubitril (primarily as sacubitrilat) and ~13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as sacubitrilat), and 86% of valsartan and its metabolites are excreted in feces. Sacubitril, sacubitrilat, and valsartan are eliminated from plasma with a mean elimination half-life ($T_{1/2}$) of approximately 1.4 h, 11.5 h, and 9.9 h, respectively. Sacubitril/valsartan is unlikely to be removed from systemic circulation by hemodialysis because of high protein binding.[6,13]

5. Pharmacodynamics

In a 7-day valsartan-controlled study in heart failure with reduced ejection fraction (HFrEF) patients, administration of sacubitril/valsartan resulted in a significant non-sustained

increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to valsartan.[13]

In a 21-day study in patients with HFrEF, sacubitril/valsartan significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. It also blocked the AT_1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations.[13,17]

In PARADIGM-HF, sacubitril/valsartan decreased plasma NT-proBNP (not a neprilysin substrate) and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril.[7,18]

In a thorough QTc clinical study in healthy male subjects, single doses of 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan had no effect on cardiac repolarization.

Administration of sacubitril/valsartan for 2 weeks to healthy subjects was associated with an increase in CSF $A\beta_{1-38}$ with no changes in concentrations of CSF $A\beta_{1-40}$ or CSF $A\beta_{1-42}$. Notably, though sacubitrilat crosses blood–brain barrier (BBB), no corresponding increase in amyloid-β levels or amyloid-β accumulation were noted in the brain tissues of cynomolgus monkeys.[7,18]

Addition of a 50 mg single dose of sildenafil to sacubitril/valsartan at steady state (194 mg sacubitril/206 mg valsartan OD for 5 days) in patients with hypertension was associated with additional blood pressure reduction (~5/4 mmHg, systolic/diastolic blood pressure) compared to administration of sacubitril/valsartan alone.

Co-administration did not significantly alter the blood pressure effect of intravenous nitroglycerin.[19]

6. Clinical trials

6.1. PARADIGM-HF trial

The PARADIGM-HF trial (Kindly modify it to: PARADIGM-HF trial**P**rospective comparison of **AR**Ni with **A**CE-I to **D**etermine

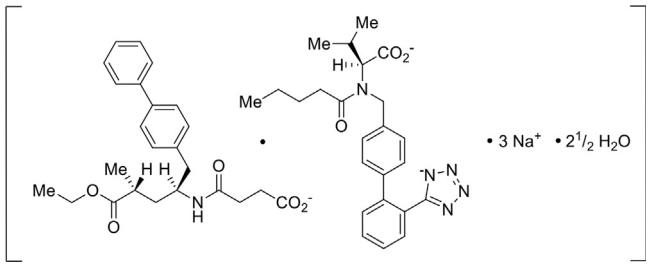

Fig. 2. Molecular Structure of Sacubitril/valsartan(LCZ696).

Impact on **G**lobal **M**ortality and morbidity in **HF**) was the largest clinical trial ever conducted in heart failure. It was a multinational (47 countries), randomized, double-blind trial comparing sacubitril/valsartan and enalapril in 8442 adult patients with symptomatic chronic HF (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤40%). Patients were randomized to receive either sacubitril/valsartan (n = 4209) or enalapril (n = 4233). In both arms patients were treated with evidence-based therapies, including beta-blockers (94%), diuretics (82%), and mineralocorticoid receptor antagonists (58%).[7,20–22]

Prior to study enrolment, patients were required to have a plasma B-type natriuretic peptide (BNP) ≥ 150 pg/mL or *N*-terminal pro-BNP (NT-proBNP) ≥ 600 pg/mL, or, if they had been hospitalized for heart failure in the last 12 months, a BNP ≥ 100 pg/mL or a NT-proBNP ≥ 400 pg/mL. Patients had to have been on an ACEi or ARB at a dose equivalent to at least 10 mg of enalapril daily for at least four weeks prior to screening, and on maximally tolerated doses of beta-blockers.[7,20–22]

Patients with symptomatic hypotension, or having a systolic blood pressure of <100 mmHg at screening were excluded. Patients with severe hepatic impairment, eGFR <30 mL/min/

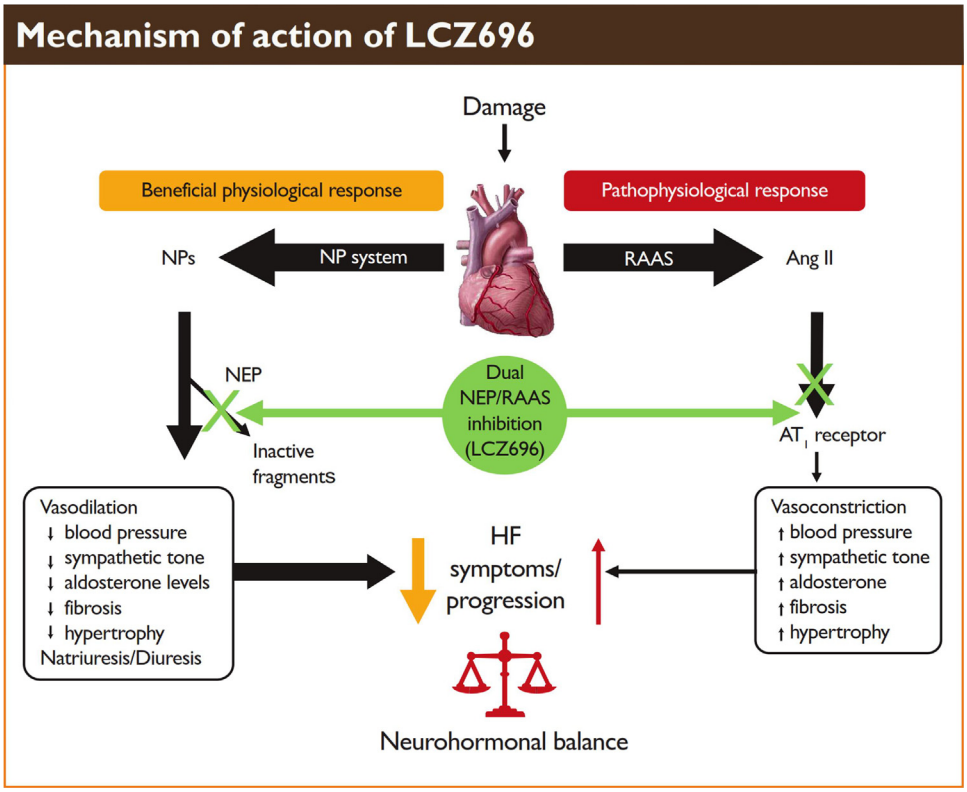

Fig. 1. Schematic representation of the mechanism of action of sacubitril/valsartan (LCZ696).

1.73 m^2 or serum potassium ≥5.2 mmol/L at baseline, or those with any history of angioedema were also excluded. The primary endpoint was the composite of CV death or hospitalization for HF.[7,20–22]

Prior to study participation, patients were well treated with standard of care therapy which included ACEi/ARBs (>99%), beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (83%). The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

The population was 66% Caucasian, 18% Asian, and 5% Black; the mean age was 64 years (19% of patients were 75 years or older); and 78% were male. At randomization, 70% of patients were NYHA Class II, 24% were NYHA Class III, and 0.7% were NYHA Class IV. The mean left ventricular ejection fraction was 29%.[7,20–22]

6.1.1. Results

PARADIGM-HF demonstrated that sacubitril/valsartan combination was superior to RAAS inhibitor (enalapril), in reducing the risk of CV death or HF hospitalizations by 20% (hazard ratio (HR): 0.80, 95% CI [0.73; 0.87], 1-sided $p < 0.0001$). The absolute risk reduction was 4.69%. A statistically significant reduction for CV death and first HF hospitalization was observed (CV death, RRR 20%, HR 0.80; 95% CI [0.71, 0.89]; and hospitalization for HF RRR 21%; HR 0.79; 95% CI [0.71, 0.89]).[7,20–22]

Sudden death accounted for 45% of CV deaths and was reduced by 20% in sacubitril/valsartan treated patients compared to enalapril treated patients (HR 0.80). Pump failure accounted for 26% of CV deaths and was reduced by 21% in sacubitril/valsartan treated patients compared to enalapril treated patients (HR 0.79).

This risk reduction was consistent across subgroups including: age, gender, race, geography, NYHA class, ejection fraction, renal function, history of diabetes or hypertension, prior heart failure therapy, and atrial fibrillation. Sacubitril/valsartan also significantly reduced all-cause mortality by 16% compared with enalapril (RRR 16%, HR 0.84; 95% CI [0.76 to 0.93], 1-sided $p = 0.0005$). The absolute risk reduction was 2.84%.[7,20–22]

Overall, there were fewer all cause hospital admissions in patients treated with sacubitril/valsartan compared to enalapril, including a 12% relative risk reduction for the first hospitalization (HR 0.88 [95% CI: 0.82, 0.94], $p < 0.001$), and a 16% relative rate reduction for total number of hospitalizations (RR 0.84 [95% CI: 0.78, 0.91], $p < 0.001$)][7,20–22] (Fig. 3A–C).

6.1.2. Conclusion

In summary, sacubitril/valsartan was more effective than enalapril in reducing the risk of CV death by 20%, HF hospitalization by 21%, all-cause mortality by 16% and reducing overall symptoms with much better tolerability.[7,20–22]

6.1.3. Note

Post hoc analyses of the PARADIGM-HF trial have revealed additional pleiotropic benefits of sacubitril/valsartan, which are discussed in the later part of the review.

6.2. PARAMOUNT trial

The PARAMOUNT trial (**P**rospective comparison of **AR**Ni with **A**RB on **M**anagement **O**f HF with preserved ejectio**N** fraction **T**rial) was a randomized, multinational (13 countries) double-blind, parallel group, active control trial which tested the safety and efficacy of sacubitril/valsartan in 301 heart failure with preserved ejection fraction (HFpEF) patients. Patients were selected to have NYHA Class II–III HF with left ventricular ejection fraction (LVEF) ≥45%, *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) >400 pg/mL at screening, be on diuretic therapy, and have a systolic blood pressure <140 or ≤160 mmHg, or less if on ≥3 blood pressure drugs at randomization, having an eGFR of at least 30 mL/min/1.73 m2 at screening, and a potassium concentration of no >5.2 mmol/L. The primary endpoint was change in NT-proBNP, a marker of left ventricular wall stress, from baseline to 12 weeks. The trial showed a significant reduction in NT-proBNP at 12 weeks and significant improvement in left atrial size and NYHA class in patients randomized to sacubitril/valsartan compared to valsartan alone at 36 weeks. Sacubitril/valsartan reduced the levels of NT-proBNP by 23% compared with valsartan ($p = 0.005$).[23–25]

6.2.1. Conclusions

The angiotensin receptor-neprilysin inhibitor sacubitril/valsartan reduced NTproBNP to a greater extent than valsartan after 12 weeks of therapy, in association with reduction in left atrial size and improvement in NYHA class. These are all measures that have been associated with worse prognosis in patients with HFpEF.

Overall sacubitril/valsartan was well tolerated with fewer serious and overall adverse events than the comparator valsartan. Findings were encouraging and suggestive that sacubitril/valsartan may have beneficial effects in patients with HFpEF and that further testing of this compound may be warranted in patients with this condition[23–25] (Fig. 4).

6.3. PARAGON-HF trial

The PARAGON-HF trial (**P**rospective comparison of **AR**Ni with **A**RB **G**lobal **O**utcomes in HF with preserved ejectio**N** fraction) will assess the effect of sacubitril/valsartan on outcomes (CV death and total – first and recurrent – HF hospitalizations) in patients with HFpEF.[26]

6.3.1. Primary and secondary objectives

6.3.1.1. Primary. The primary objective of this trial is to compare sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of CV death and total (first and recurrent) HF hospitalizations, in HFpEF patients (NYHA Class II–IV) (left ventricular ejection fraction [LVEF] ≥45%).[26]

6.3.1.2. Secondary.

- To compare sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of CV death, total HF hospitalizations, total non-fatal strokes, and total non-fatal myocardial infarctions. Total is defined as the first and all recurrent events.
- To compare sacubitril/valsartan to valsartan in improving NYHA functional classification at 8 months.
- To compare sacubitril/valsartan to valsartan in delaying the time to new onset AF in patients with no history of AF and without AF on electrocardiogram (ECG) at baseline.
- To compare sacubitril/valsartan to valsartan in delaying the time to all-cause mortality.[26]

Estimated completion date of trial is 2019.[26]

6.4. PARAMETER trial

The PARAMETER study (**P**rospective comparison of **A**ngiotensin **R**eceptor neprilysin inhibitor with **A**ngiotensin receptor blocker **ME**asuring arterial s**T**iffness in the Eld**ER**ly) was a multicenter, double-blind, randomized controlled trial conducted to determine the effects of sacubitril/valsartan versus olmesartan on central aortic pressures, in elderly patients (aged ≥60 years) with systolic hypertension and pulse pressure >60 mmHg, indicative of arterial stiffness. Total number of patients enrolled n = 454 with mean age = 67.7 years, mean seated systolic blood pressure = 158.6 mmHg and mean seated pulse pressure = 69.7 mmHg. The study

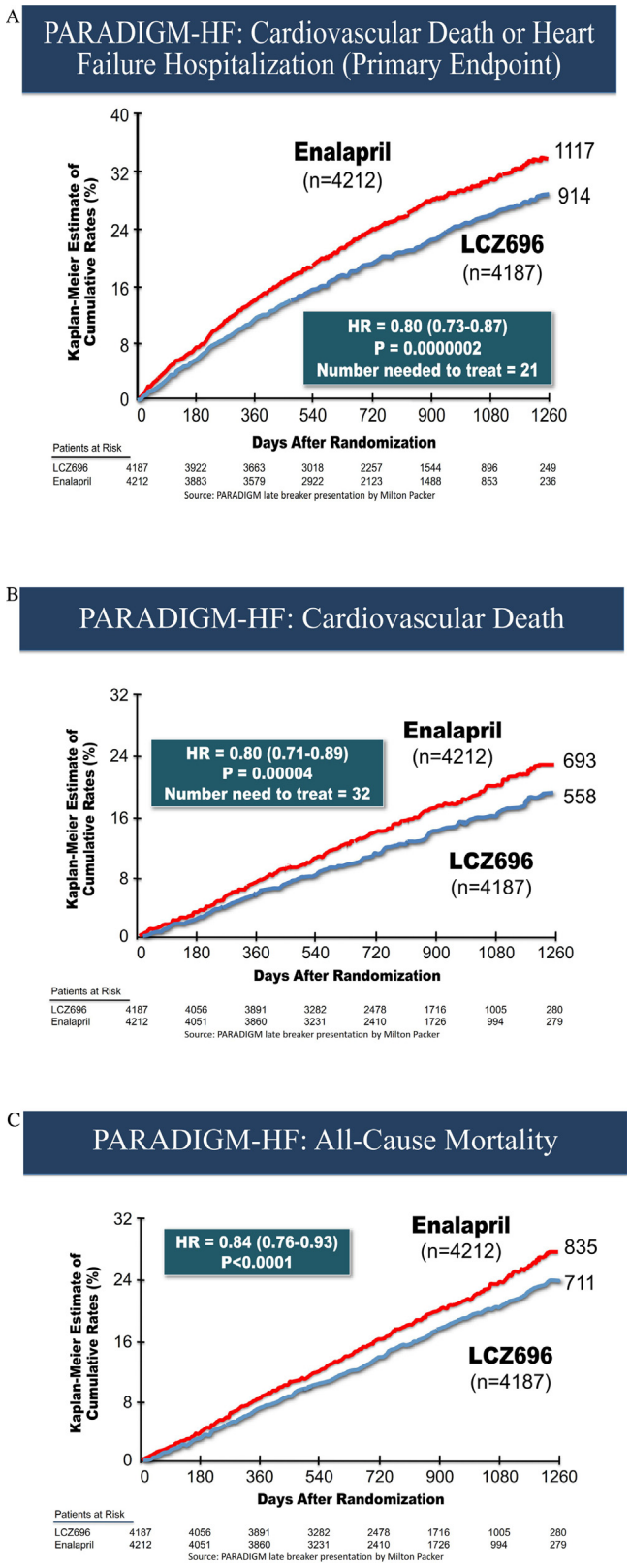

Fig. 3. Kaplan-Meier curves showing estimates of the probability of the primary composite end point (death from CV causes or first hospitalization for HF) (A), death from CV causes (B), and death from any cause (C).

extended double-blind treatment for 12 to 52 weeks, during which amlodipine (2.5–5 mg) and subsequently hydrochlorothiazide (6.25–25 mg) were added-on for patients not achieving blood pressure target (<140/90).[27]

6.4.1. Results

At week 12, sacubitril/valsartan reduced central aortic systolic pressure (primary assessment) greater than olmesartan by −3.7 mmHg (p = 0.010), further corroborated by secondary assessments at week 52 (central aortic pulse pressure, −2.4 mmHg, $P < 0.012$; mean 24-h ambulatory brachial systolic blood pressure and central aortic systolic pressure, −4.1 mmHg and −3.6 mmHg, respectively, both $p < 0.001$). Differences in 24-h ambulatory pressures were pronounced during sleep. After 52 weeks, blood pressure parameters were similar between treatments ($p < 0.002$); however, more patients required add-on antihypertensive therapy with olmesartan (47%) versus sacubitril/valsartan (32%; $p < 0.002$). Both treatments were equally well tolerated.[27]

6.4.2. Conclusion

THE PARAMETER trial demonstrated superiority of sacubitril/valsartan versus olmesartan in reducing clinic and ambulatory central aortic and brachial pressures in elderly patients with systolic hypertension and stiff arteries.[27]

Other trials planned by Novartis with regards to sacubitril/valsartan include:

- PARADISE-MI trial: testing the hypothesis that sacubitril/valsartan can reduce CV death, HF hospitalizations and new onset heart failure in patients at high risk for HF after a myocardial infarction, expected study completion in 2020.
- TRANSITION trial: comparing in-hospital initiation of sacubitril/valsartan to initiation after hospital discharge in heart failure patients with reduced ejection fraction (HFrEF) who have recently been hospitalised for acute decompensation, expected study completion in 2018.
- PIONEER trial: investigating the effect of in-hospital initiation of sacubitril/valsartan on changes in NT-proBNP (compared to enalapril) in patients with HFrEF following an acute decompensation, expected study completion in 2018.

More details can be found on the official website of Novartis AG at https://www.novartis.com/news/media-releases/novartis-announces-investment-fortihfy-clinical-program-entrestor-and-heart.

7. Omapatrilat vs sacubitril/valsartan

Though Omapatrilat, an investigational vasopeptidase inhibitor (VPi), too have shown sustained, favourable, haemodynamic and neurohumoral actions in past, it failed to beat enalapril 10 mg BID in a head-to-head comparison in patients with chronic HFrEF in the OVERTURE (**O**mapatrilat **V**ersus **E**nalapril **R**andomized **T**rial of **U**tility in **R**educing **E**vents) trial.[28–29] The results weren't encouraging for the other two trials namely OPERA (Omapatrilat in Persons With Enhanced Risk of Atherosclerotic Events)[30] and OCTAVE (**O**mapatrilat **C**ardiovascular **T**reatment **A**ssessment **V**ersus **E**nalapril).[31] Omapatrilat angioedema was attributed to its dual mechanism of action i.e., inhibiting both angiotensin-converting enzyme and neprilysin. Both of these enzymes are responsible for the metabolism of bradykinin which causes vasodilation, angioedema, and airway obstruction. Omapatrilat was not approved by USFDA due to angioedema safety concerns. The final vote from the Committee was 5-1 against approval.[32,33]

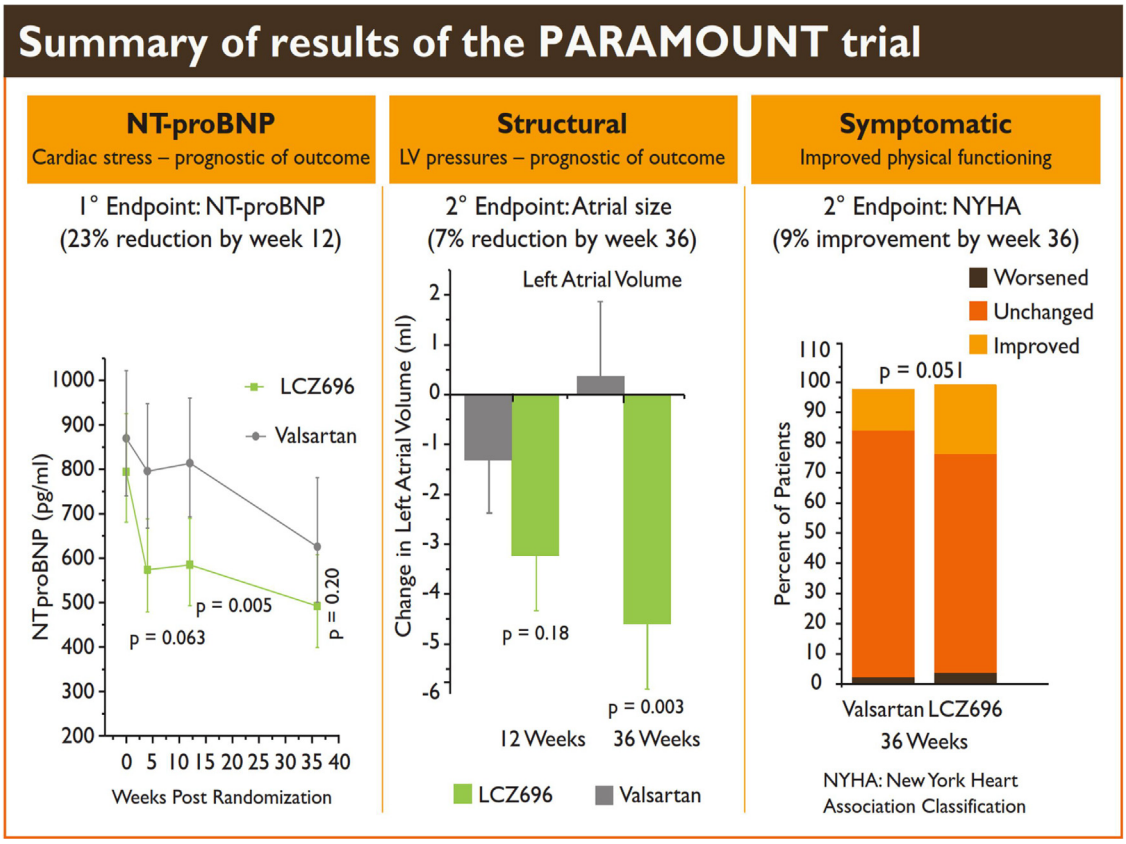

Fig. 4. Summary of results of the PARAMOUNT triaL.

8. Dosage and administration

ARNIs have been recently approved for patients with symptomatic HFrEF and it is intended to be substituted for ACE inhibitors or ARBs and should replace ACE or ARBs when stable patients with mild-to-moderate HF on these agents have an adequate blood pressure and are otherwise tolerating standard therapies.[8–10,13]

Starting dose of 24/26 mg BID is recommended for patients not currently taking an ACEi or an ARB, patients previously taking low doses of these agents, patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) and patients with moderate hepatic impairment (Child-Pugh classification Class B, 7–9 points score). Dose can be doubled every 2–4 weeks to the target maintenance dose of 97/103 mg BID, as tolerated by the patient.[8–10,13]

No starting dose adjustment is needed for mild or moderate renal impairment and mild hepatic impairment (Child-Pugh A classification) though use in patients with severe hepatic impairment (Child-Pugh classification Class C, 10–15 points score) is not recommended.[8–10,13]

9. Drug interaction & adverse reactions

Because CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, co-administration with drugs that impact CYP450 enzymes is not expected to affect the pharmacokinetics of sacubitril/valsartan. Dedicated drug interaction studies demonstrated that co-administration of furosemide, warfarin, digoxin, carvedilol, a combination of levonorgestrel/ethinyl estradiol, amlodipine, omeprazole, hydrochlorothiazide, metformin, atorvastatin, and sildenafil, did not alter the systemic exposure to sacubitril, sacubitrilat or valsartan.[8–10,13]

Use with an ACE inhibitor is contraindicated due to increased risk of angioedema. Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increase in serum potassium concentrations. In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible though periodic monitoring of renal function should be performed.

Concomitant administration with lithium may result in an increase in serum lithium concentration and lithium toxicity.[8–10,13]

Clinically significant ADR include hypotension (18%), hyperkalemia (12%), cough (9%), dizziness (6%), orthostasis (2.1%), angioedema (<1%), impaired renal function *(reversible)*, dementia risk *(theoretical)*.[8–10,13]

10. Contraindications

Sacubitril/valsartan is contraindicated:

- in pregnancy & lactation
- in patients with hypersensitivity to any component
- in patients with severe renal (eGFR <30 mL/min/1.73 m2) or hepatic impairment (Child-Pugh classification Class B and C, >7 points score)
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy
- with concomitant use of ACEi. Do not administer within 36 h of switching from or to an ACEi
- with concomitant use of aliskiren in patients with diabetes.[8–10,13]

11. Other pleiotropic benefits of ARNi

11.1. Hypertension

The antihypertensive benefits of sacubitril/valsartan were demonstrated in the PARAMETER trial discussed earlier. In another study by Wang et al 266 patients (mean age 55.4 years; 24 h SBP/DBP 139.0/86.1 mmHg at baseline) who did not respond to 4-week treatment with amlodipine 5 mg/day were randomized. At week 8, sacubitril/valsartan in combination with amlodipine provided greater reductions in 24 h systolic blood pressure compared with amlodipine monotherapy from baseline (−13.9 versus −0.8 mmHg, $p < 0.001$). Besides, all the secondary efficacy assessments were significantly ($p < 0.001$) in favor of sacubitril/valsartan plus amlodipine, for instance, 24-h PP (-5.8 versus −0.6 mmHg). Overall, the incidence of adverse events was 20.0% with LCZ696/amlodipine and 21.3% with amlodipine. The study concluded that sacubitril/valsartan + amlodipine combination could be an effective treatment for patients with systolic hypertension uncontrolled with amlodipine.[34,35]

11.2. Post myocardial infarction

The risk for further fatal and non-fatal ischemic events continues to increase following an event of myocardial infarction. In an article published, Von Lueder et al demonstrated lower cardiac weight and reduced fibrosis in the *peri*-infarct and remote myocardium in the sacubitril/valsartan group compared with a placebo group. The sacubitril/valsartan group also had a lower left ventricular end-diastolic diameter, a higher LVEF, and higher circular and diastolic wall strain, confirming improved left ventricular function 4 weeks after treatment.[15,34]

11.3. Renal impairment

A multicenter open-label, 8-week clinical trial assessing the safety and efficacy of sacubitril/valsartan in patients with hypertension and renal dysfunction by administering sacubitril/valsartan (100 mg) with an optional titration to 200 and 400 mg in a sequential manner found no clinically significant changes in creatinine, potassium, blood urea nitrogen and eGFR of the patients. Besides, the geometric mean reduction in the urinary albumin-to-creatinine ratio (UACR) was 15.1% and the decrease was greater in patients with microalbuminuria than in those with normoalbuminuria. Moreover, re-analysis of the data from the PARAMOUNT study revealed better eGFR progression, a greater decrease in BP and serum creatinine levels in patients on sacubitril-valsartan when compared to valsartan.[23,36]

11.4. Diabetes

In a post hoc analysis of the PARADIGM-HF trial, 3778 patients with HFrEF and known diabetes or $HbA_{1c} \geq 6.5\%$ at screening who were randomly assigned to treatment with sacubitril/valsartan or enalapril, found that during the first year of follow-up, HbA_{1c} concentrations decreased by 0.16% (SD 1.40) in the enalapril group and 0.26% (SD 1.25) in the sacubitril/valsartan group. The HbA_{1c} concentrations were persistently lower in the sacubitril/valsartan group than in the enalapril group over the 3-year follow-up.

Those on sacubitril/valsartan were also less likely to start taking insulin or other meds for glycaemic control and showed better improvements in HDL cholesterol. The significant improvement in HbA_{1c} levels ($p = 0.0055$) over 3 years in the sacubitril/valsartan group vs enalapril implies that heart-failure patients with diabetes who take the drug might benefit from and even require lower doses of any antidiabetic agents they may be taking.[37,38]

12. Discussion

Dementia and cognition-related adverse effects were not increased by sacubitril/valsartan in PARADIGM-HF, and the beneficial CV actions of angiotensin receptor-neprilysin inhibition might prevent cognitive decline in other ways. However, as a precaution, serial cognitive function testing was planned in the recently initiated PARAGON-HF trial which builds upon the promising 'proof-of-concept' findings in the PARAMOUNT trial.

Concern has been raised that neprilysin inhibition might lead to accumulation of amyloid-beta peptides in the brain as this enzyme is one of the clearance mechanisms for neurotoxins which are implicated in the development of Alzheimer's disease. It should be noted that as multiple other enzymatic pathways (possibly as many as 20) and transport proteins are involved in the clearance of amyloid-beta peptides in the brain, it is not known whether long-term neprilysin inhibition might have a significant effect on accumulation of these peptides.[39]

A secondary analysis of the PARADIGM-HF trial revealed that among patients who newly started taking mineralocorticoid receptor antagonists (MRA) during the PARADIGM-HF trial, severe hyperkalemia remained more common in those randomly assigned to enalapril than to those randomly assigned to sacubitril/valsartan (3.3 vs 2.3 per 100 patient-years; HR, 1.43 [95%CI, 1.13–1.81]; $p = 0.003$). These data suggest that neprilysin inhibition attenuates the risk of hyperkalemia when MRAs are combined with other inhibitors of the renin-angiotensin aldosterone system in patients with HF.[40]

13. Conclusion

Effective reduction of blood pressure to accepted goals is the key to reduce the risk of CV events and stroke. The FDA approval of sacubitril/valsartan made available a novel, oral treatment option for patients with heart failure. Sacubitril/valsartan is a first-in-class ARNi providing systemic exposure to sacubitril, a neprilysin inhibitor, and valsartan, an ARB. It demonstrated a significant mortality benefit in patients with HFrEF in the PARADIGM-HF trial and a similar positive and encouraging results were demonstrated in subsequent clinical trials as well.

Sacubitril/valsartan is unique in simultaneously blocking the renin angiotensin system while augmenting the body's intrinsic natriuretic peptide system through neprilysin inhibition which may represent an attractive and serendipitous therapeutic approach for a range of CV diseases, including hypertension and HF, in which vasoconstriction, volume overload and neurohormonal activation play a part in pathophysiology. The potential clinical benefits from neutral endopeptidase inhibition however can only be leveraged if the renin–angiotensin–aldosterone system (RAAS) is inhibited concomitantly.

The recent evidence-based ESC and AHA/ACC guidelines have recommended ARNi as an important therapeutic for the management of heart failure and prevention of sudden cardiac deaths. Although ACEi and a beta-blocker, with a diuretic therapy for symptom relief, are considered as the first line of therapy for HFrEF patients, sacubitril/valsartan have demonstrated significant improvement in patient outcomes and must be considered in the current practices for HF management and prevention of sudden cardiac death.

The mechanisms of action of sacubitril/valsartan suggest that it may have an impact on the pathophysiology of HFpEF, in which it is believed that excessive fibrosis and myocyte hypertrophy lead to abnormal left ventricular relaxation and filling, impaired diastolic

distensibility and/or increased vascular stiffness, with consequent elevated cardiac filling pressures. Pleiotropic effects shown in anti-hypertensives, post-myocardial infarction, renal impairment and diabetes are remunerative, propitious and warrants ancillary impetus to the therapeutic acceptance of the combination as an entity. Sacubitril/valsartan is considered 'investigational' in patients under the age of 18 years and in patients with all other indications.

With over 40 (active or planned) clinical studies planned by Novartis in 5 years under its FortiHFy *(***Forti***fying* **H***eart* **F***ailure clinical evidence and patient quality of life)* umbrella clinical program there's a lot that's awaiting to be discovered about this new, unique and first-in-class combination, sacubitril/valsartan. Though the results of various trials and numerous post hoc analyses currently being studied are way encouraging, sacubitril/valsartan was quick enough to draw the attention and viewpoint of the medical fraternity. Undoubtedly, sacubitril/valsartan opens a wide horizon for research and development in the direction of ARNi, an altogether different approach in combating hypertension, CV disorders and HF.

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Conflict of interest

None.

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