

# Angiotensin Receptor and Nephylisin Inhibitor: A new drug in pediatric cardiologist's armamentarium

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## ABSTRACT

Heart failure due to congenital heart disease and cardiomyopathies is a significant burden in the pediatric population. Pharmacological strategies for the management of pediatric heart failure are largely based on the extrapolation of adult data and Delphi process based on expert opinion. There are differences in the etiology, clinical course, and outcome of pediatric heart failure as compared to adult, thus the results of adult heart failure trials cannot be simply extrapolated to pediatric patients. There have been a lot of newer drugs for adults with heart failure, but there is a void for pediatric population with heart failure due to many reasons. Early results of multi-centric randomized control PANORAMA HF Trial and subsequent Food and Drug Administration approval for Angiotensin Receptor and Nephylisin Inhibitor (Sacubitril / Valsartan) for pediatric patients have tried to fill in this void and paved the way for a newer class of drugs for heart failure with proven benefits in pediatric patients.

**Keywords:** ARNI, heart failure, pediatric, sacubitril-valsartan

## BACKGROUND

Heart failure due to congenital heart disease and cardiomyopathies is a significant burden in the pediatric population.<sup>[1]</sup> Pharmacological strategies for the management of pediatric heart failure are largely based on extrapolation of adult data and Delphi process based on expert opinion.<sup>[2]</sup> With limited evidence and difficulty in conducting trials in the pediatric population, the insights of experts provide a valuable contribution to the decision-making but also leads to prescribing of old age drugs such as digoxin and other unlicensed and off-label drugs.<sup>[3]</sup> The current clinical management and drugs used for pediatric heart failure are based on evidence extrapolated from adult heart failure clinical trials. None of these pharmacotherapies to date have demonstrated the outcome benefits in children with heart failure in clinical trials.<sup>[4]</sup>

## INTRODUCTION

There are differences in the etiology clinical course and outcome of pediatric heart failure as compared to adult, thus the results of adult heart failure trials cannot be simply extrapolated to pediatric patients. Among these differences and void for newer agents for pediatric heart failure, only one pediatric randomized control trial was completed under the auspices of Food and Drug Administration (FDA)-issued written request. This study examined the effects of carvedilol in children and adolescents with congestive heart failure.<sup>[5]</sup> This trial demonstrated no difference in heart failure symptoms between carvedilol and placebo treated patients and also discouraged many from undertaking trials of drugs which were found useful in the adult population. However, still there is an unmet need for newer and better pharmacological agents which target the different pathways of heart failure<sup>[6]</sup> considering

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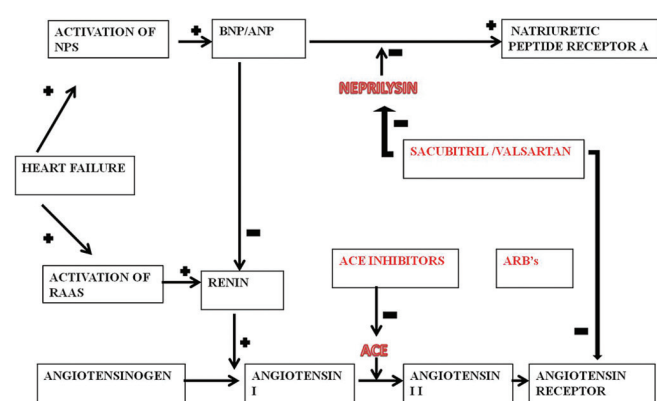
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the significant morbidity and mortality associated with pediatric heart failure.

### Drug: Angiotensin receptor and neprilysin Inhibitor (ARNI)

Based on the results of PARADIGM-HF trial, ARNI have been approved for use in adults with heart failure with reduced ejection fraction.<sup>[7]</sup> Results of another multicenter trial (PARAGON-HF trial) in adult patients with heart failure and preserved ejection fraction are awaited. Early results of multi-centric randomized control PANORAMA HF Trial and subsequent FDA approval for ARNI in children have paved the way for a newer class of drugs for heart failure with proven benefits in pediatric patients.

ARNI has recently been approved by FDA for the treatment of children with heart failure with specific indications, i.e., symptomatic heart failure (New York Heart Association/Ross class II-IV) with systemic left ventricular systolic dysfunction (left ventricular ejection fraction  $\leq 40\%$ ) in pediatric patients aged 1–18 years.<sup>[8]</sup> This approval is based on initial 12-week follow-up of total 52 weeks follow-up planned during part 2 of study. The endpoint was the difference in the change in plasma NT-pro-BNP from baseline to 12 weeks. The reduction from baseline in NT-pro-BNP was 44% and 33% in the ARNI versus enalapril group, respectively. While the difference was not statistically significant, the reductions for ARNI and enalapril were similar to or larger than what was seen in adults. Because ARNI improved outcomes and reduced NT-pro-BNP in PARADIGM-HF trial, the effect on NT-pro-BNP was considered a reasonable basis to infer improved cardiovascular outcomes in pediatric patients. The details of the design trial can be assessed online at [clinicaltrials.gov](http://clinicaltrials.gov) (Identifier-NCT02678312).<sup>[9]</sup>



**Figure 1: Systems activated in heart failure and pathways blocked by angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, and neprilysin inhibitors. (sympathetic nervous system activation pathway is not shown in the figure). ANP: Atrial natriuretic peptide, BNP: B-type natriuretic peptide, NPS: Natriuretic peptide system, RAAS: Renin angiotensin aldosterone system**

### Mechanism of action: Why a combination? Why combination with a angiotensin receptor blocker and not an angiotensin-converting enzyme inhibitor

Drugs for heart failure are targeted on the different pathways which are activated due to heart failure [Figure 1]. Neprilysin inhibitors were initially used for hypertension patients. Initial attempts at inhibiting neprilysin using candoxatril were successful in promoting natriuresis, but further studies showed that reduction in blood pressure was not sustained on chronic use.<sup>[10]</sup> This might be explained by the finding that neprilysin also breaks down angiotensin II.<sup>[11]</sup> Therefore, inhibiting neprilysin alone, while raising natriuretic peptides levels, also increases angiotensin II levels. The solution to the problem was thought of as a combination with an angiotensin-converting enzyme (ACE) inhibitor. The combined ACE and neprilysin inhibitor omapatrilat was studied in a large randomized controlled trial against enalapril. Although the study suggested a benefit with omapatrilat, the rate of angioedema was much higher in the omapatrilat group.<sup>[12]</sup> Both ACE and neprilysin break down bradykinin and omapatrilat also inhibits aminopeptidase P which also catabolizes bradykinin. Therefore, due to excessive levels of bradykinin and resultant high rates of serious angioedema drug was discontinued. Combining an angiotensin receptor blocker (ARB) and a neprilysin inhibitor was the next logical step as a potential solution to the problem encountered with omapatrilat. The angiotensin receptor neprilysin inhibitor (ARNI) Sacubitril/Valsartan was designed with the aim of inhibiting neprilysin while blocking the adverse effects of rennin angiotensin aldosterone system and reducing bradykinin potentiation. Sacubitrilat (active metabolite of sacubitril) does not inhibit aminopeptidase P, so the risk of angioedema was expected to be lower than with omapatrilat. The cardiovascular and renal effects of ARNI in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by sacubitrilat (active metabolite of sacubitril) and the simultaneous inhibition of the effects of angiotensin II by Valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

**Table 1: Recommended dose (twice daily)**

	Starting	Second	Final
Pediatric patients <40 kg** (mg/kg)	1.6	2.3	3.1
Pediatric patients at least 40 kg, <50 kg (mg)	24/26	49/51	72/78 <sup>†</sup>
Pediatric patients at least 50 kg (mg)	49/51	72/78 <sup>†</sup>	97/103

Available as 24/26, 49/51 and 97/103 mg tablets, where first drug is sacubitril and second drug is valsartan. <sup>†</sup>Doses of 72/78 mg can be achieved using three 24/26 mg tablets, Titration - titrate dose every 2 weeks and target final dose, <sup>\*\*</sup>An oral suspension can be substituted at the recommended tablet dosage in patients unable to swallow tablets

## Administration

### Dosage

Dosage-recommended dose [Table 1]. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient.

### General considerations

- ARNI is contraindicated with concomitant use of an ACE inhibitor. If switching from an ACE inhibitor to ARNI allow a washout period of 36 h between the two drugs
- In patients not currently taking an ACE inhibitor or an ARB and for patients previously taking low doses of these agents, start ARNI at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter
- Dose manipulations needed in severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m<sup>2</sup>) and moderate hepatic failure (Child Pugh B)
- Not indicated in severe hepatic impairment.

### Contraindications and side effects

#### Contraindications

- Hypersensitivity to any component
- History of angioedema related to previous ace inhibitor or ARB therapy
- Breastfeeding

Adverse effects (based on PARADIGM-HF trial)

- Angioedema (0.5% vs. 0.2% in ARNI and enalapril group)
- Hypotension
- Impaired renal function
- Hyperkalemia
- Fetal toxicity.

### Future prospects

With trials underway for utility of this novel drug combination in adults with congenital heart diseases with systemic right ventricle and univentricular hearts,<sup>[13,14]</sup> these indications might well be studied for pediatric age group in near future.

## CONCLUSION

This newer class of drug having a different mechanism of action and proven efficacy in adults and initial promising results in pediatric heart failure study (PANORAMA-HF) and FDA approval of ARNI for pediatric patients with systolic dysfunction of systemic left ventricle may prove boon for a large number of pediatric patients suffering from chronic heart failure. However, in India, we might have to wait a bit longer, till central drug standards control organization approves the drug in India for the pediatric use.

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## Conflicts of interest

There are no conflicts of interest.

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