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ORIGINAL ARTICLE

Association between NT-proBNP changes and clinical outcomes in paediatric patients with heart failure: Insights from PANORAMA-HF and PARADIGM-HF

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Abstract

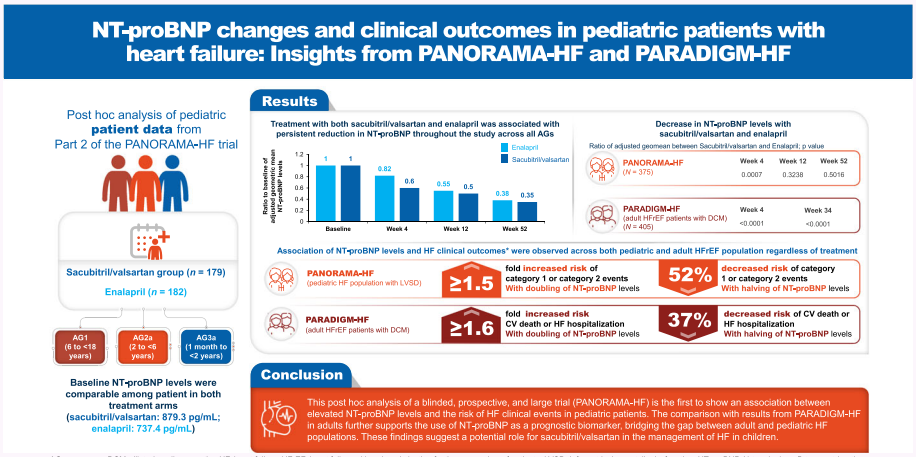
Aims The PANORAMA-HF trial demonstrated significant N-terminal pro-B-type natriuretic peptide (NT-proBNP) reductions in paediatric patients with left ventricular systolic dysfunction with sacubitril/valsartan or enalapril treatment over 52 weeks. This post hoc analysis aims to correlate changes in NT-proBNP levels with clinical outcomes in PANORAMA-HF patients receiving either sacubitril/valsartan or enalapril. Additionally, NT-proBNP reductions in the paediatric population were compared with a subset of adult heart failure with reduced ejection fraction (HFrEF) patients from the PARADIGM-HF trial.

Methods and results This post hoc analysis utilized data from Part 2 of the PANORAMA-HF trial. Associations between baseline NT-proBNP levels, changes post-baseline and the risk of HF clinical events in paediatric patients on sacubitril/valsartan or enalapril were assessed. The paediatric HF population from PANORAMA-HF was categorized into age groups (AG): AG1 (aged 6 to $<$18 years), AG2a (aged 2 to $<$6 years) and AG3a (aged 1 month to $<$2 years). The Cox proportional hazard model evaluated the relationship between NT-proBNP and clinical outcomes. Analysis of 361 paediatric patients (sacubitril/valsartan, n = 179; enalapril, n = 182) demonstrated overall higher baseline NT-proBNP levels in younger AGs. At Week 52, both treatment groups exhibited reduced NT-proBNP levels across all AGs. Reductions were comparable between sacubitril/valsartan and enalapril, with a numerically greater reduction observed in adult patients versus children. Strong associations between NT-proBNP levels and HF clinical outcomes were observed in paediatric populations in PANORAMA-HF and in adult DCM patients with HFrEF in PARADIGM-HF. Doubling of NT-proBNP levels was associated with a $\geq$1.7-fold increased risk of HF clinical events, while halving of the levels correlated with a 52% reduction in the risk of clinical events.

Conclusions This is the first prospective, randomized large-scale study to demonstrate a strong correlation between NT-proBNP levels and risks of HF clinical events in paediatric patients with HF.

Graphical Abstract

This post hoc analysis of the PANORAMA-HF paediatric heart failure trial evaluates the correlation of baseline and clinical changes in NT-proBNP and clinical outcomes in children with heart failure due to left ventricular systolic dysfunction. This is the first prospective, randomized large-scale study to demonstrate that changes in NT-proBNP levels are associated with the risk of heart failure clinical events in this patient population.



Keywords Left ventricular systolic dysfunction; NT-proBNP; Paediatric heart failure; Sacubitril/valsartan

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Introduction

Paediatric heart failure (HF) carries a significant burden of morbidity and mortality and is associated with frequent hospitalization and poor quality of life.[1,2] Prevalence estimates for HF in children range between 0.87 and 7.4 per 100 000 children.[1–4] The aetiologies and pathogenesis of HF differ among adult and paediatric patients.[5] However, it has been observed that there are common clinical features between paediatric patients with HF due to left ventricular systolic dysfunction (LVSD) and adult patients with HF with reduced ejection fraction (HFrEF) and dilated cardiomyopathy (DCM).[6] The major morphologic feature in DCM is dilatation of the left ventricle along with decreased cardiac output, resulting in compensatory activation of the sympathetic, renin-angiotensin-aldosterone (RAAS) and natriuretic peptide pathways. These pathophysiologic responses play a key role in the progression of HF due to chronic systolic ventricular dysfunction.[7,8]

Due to a paucity of clinical trials conducted in paediatric patients with HF, treatment recommendations for HF in children are frequently based on results from clinical trials in adults.[9] N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a proven biomarker in the diagnosis and prognosis of HF in adult patients, and its correlation with clinical outcomes is well established in clinical practice.[10–13] Results from the adult HF PARADIGM-HF trial demonstrated the superiority of sacubitril/valsartan (vs. enalapril) in reducing the risk of cardiovascular (CV) death and HF hospitalization among adult patients with chronic HFrEF. The treatment benefits of sacubitril/valsartan were correlated with a significant reduction in NT-proBNP.[13]

The PANORAMA-HF trial, the largest, randomized, double-blind, paediatric HF trial conducted to date, investigated sacubitril/valsartan versus enalapril for the treatment of paediatric HF with LVSD.[14,15] Based on the PANORAMA-HF study, sacubitril/valsartan received approval for the management of HF in children from the European Medicines Agency, the US Food and Drug Administration, the UK Medicines and Healthcare products Regulatory Agency, and SwissMedic. In PANORAMA-HF, NT-proBNP was recognized as a bridging or surrogate biomarker for extrapolating the treatment efficacy of sacubitril/valsartan from adults with HFrEF consistent with DCM to the paediatric population. Primary results from PANORAMA-HF have since demonstrated that NT-proBNP levels decreased substantially in paediatric patients with LVSD receiving sacubitril/valsartan and in those receiving enalapril over 52 weeks of follow-up.[14] A prespecified

exploratory analysis of the study also evaluated the change in NT-proBNP levels over the entire study period.[14]

The present study reports data from a post hoc analysis conducted to carefully assess the relationship between changes in NT-proBNP levels over time, and clinical outcomes in PANORAMA-HF patients receiving sacubitril/valsartan or enalapril. It also compares the trend in reduction in NT-proBNP between the paediatric patient population from PANORAMA-HF with those observed in a subpopulation of adult HFrEF patients with DCM from the PARADIGM-HF trial, with the aim to provide additional evidence for the adequacy of NT-proBNP as a prognostic biomarker for HF in the paediatric population.

Methods

Study design and participants

The design of the PANORAMA-HF study (NCT02678312) has been reported previously.[16] Briefly, the study comprised two parts: Part 1 was an open-label, single-dose pharmacokinetics and pharmacodynamics study and guided the dose selection for Part 2. Part 2 was a 52-week randomized, double-blind, parallel group, active-controlled, efficacy and safety study. Paediatric inpatients or outpatients with HF, aged 1 month to <18 years, with systemic LVSD were included. Eligible patients were stratified into different age groups (AGs) as follows: AG1 aged 6 to <18 years, AG2 aged 1 to <6 years, and AG3 aged 1 month to <1 year. As the enrolment of patients <1 years was less than expected, the age groups were subsequently modified for analysis based on the ICH E11 Guidelines on paediatric subsets to AG1 aged 6 to <18 years, AG2a aged 2 to <6 years, and AG3a aged 1 month to <2 years. Patients were randomly assigned (1:1) to receive either sacubitril/valsartan or enalapril. AG1 and AG2 were set a target dose of 3.1 mg/kg BID of sacubitril/valsartan or 0.2 mg/kg BID of enalapril, while AG3 received a target dose of 2.3 mg/kg BID of sacubitril/valsartan or 0.15 mg/kg BID of enalapril. Patients in AG3 who turned 1 year old during the study could be further uptitrated to a dose of 3.1 mg/kg BID of sacubitril/valsartan and 0.2 mg/kg BID of enalapril. The primary study endpoint was a novel global rank endpoint, a combination of clinical events, clinical evaluation of NYHA/Ross class and patient-reported outcomes. Secondary endpoints included time to first occurrence of clinical events. Change from baseline to 52 weeks in NT-proBNP was an exploratory endpoint.[14]

The design of the adult PARADIGM-HF (NCT01035255) study has also been previously reported.[17–19] Briefly, the study was a randomized, double-blind, parallel group, active-controlled, long-term efficacy and safety study. The primary study endpoint was a composite of death from CV causes or a first hospitalization for HF.[18,19]

Ethical considerations

The PANORAMA-HF and the PARADIGM-HF trials were conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 guideline for Good Clinical Practice, which has its origin from the Declaration of Helsinki. The study protocol and all amendments were approved by the independent ethics committee or institutional review board of all participating centres. All patients provided written informed consent.

Study analyses

The current post hoc analysis from Part 2 of PANORAMA-HF assessed association between NT-proBNP levels (at baseline and changes post-baseline at prespecified time intervals) and the risk of clinical events of Category 1 or Category 2 (Category 1 events: Death, urgent heart transplant listing, need for mechanical support for ventilation/circulation; Category 2 events: Worsening of HF with/without hospitalization with/without intensive care unit stay). This analysis also included

- A comparison of the trend observed in the reduction of NT-proBNP levels with sacubitril/valsartan versus enalapril and the association of NT-proBNP levels with clinical outcomes in PANORAMA-HF paediatric patients, and how these compare with the subpopulation of PARADIGM-HF which included adult HFrEF patients with DCM (referred to henceforth as 'DCM patients'). This adult DCM cohort was derived from the 8399 randomized patients in PARADIGM-HF, which included 5036 subjects with ischaemic heart disease and 3363 subjects with nonischaemic heart disease. Of the nonischaemic subjects, 1810 were classified as DCM, and 405 of these DCM subjects had complete biomarker data collected.
- An investigation ('responder analysis') into the proportions of patients in each treatment group in whom a reduction in NT-proBNP below their baseline, or 'reference' value, where the reference change value (RCV) reached a threshold of −22%, −33%, −46% and −61% below baseline in both PANORAMA-HF and PARADIGM-HF (DCM patients).
    - An RCV is based on the intraindividual biological variation, for example, NT-proBNP measurements in the same patient over time during a stable period, and can be defined as the percentage by which concentrations had to increase or decrease to be assessed as statistically different from the absolute previous measurement.[20] The RCVs used in the 'responder analysis' presented here are estimated from PARADIGM-HF (enalapril run-in dataset) and datasets from 8 published studies (*Table* S1). These studies showed an RCV range from

−16% to −61%, depending on the dataset with a 97.5% insurance level chosen against false-positive reduction. RCV thresholds were selected to cover the majority of RCVs from these previous studies. Here, the RCV cut-offs chosen were −22%, −33%, −46% and −61%. These values were derived based on the following selection rules: −22% and −61% were the largest and smallest estimated RCV cut-offs for the 97.5% probability insurance level; −46% was the smallest estimated RCV cut-off for the 90% probability insurance level; −16% was thought to be too small to reflect a clinically meaningful change; and finally, −33% was chosen as midpoint between −22% and −46%. For comparing the change in NT-proBNP levels, assessments were done at baseline and at Weeks 4, 12 and 52 in PANORAMA-HF, for all paediatric age groups (AGs) AG1: 6 to <18 years [subset 1: 12 to <18 years, and subset 2: 6 to <12 years]; AG2a: 2 to <6 years; AG3a: 1 month to <2 years).

To illustrate the association between reduction of NT-proBNP levels and risk of clinical outcomes in PANORAMA-HF and those associations observed in the PARADIGM-HF DCM patients, the overall paediatric HF population from PANORAMA-HF, regardless of treatment group was used. Clinical outcomes assessed were occurrence of Category 1 or Category 2 events (PANORAMA-HF) and occurrence of CV death or HF hospitalization (PARADIGM-HF). Analyses in both studies were performed only in those patients who had both a baseline and a post-randomization measurement of NT-proBNP at the specified time points.

Sample collection and analysis

In the PANORAMA-HF study, NT-proBNP was measured at baseline and at Weeks 4, 12 and 52 by two central laboratories (Clinical Reference Laboratory [CRL; Lenexa, KS, USA] from 3-Nov-2016 to 30-Nov-2020 and Q2 Solutions [Q2S; Valencia, CA, USA], from 11-Sep-2020 to 21-Apr-2022). Both laboratories analysed the plasma NT-proBNP samples using the same methodology (Elecys proBNP assay; Roche Diagnostics, Indianapolis, IN, USA). NT-proBNP sample collection was added to Week 4 (protocol Amendment 3, 1-Oct-2018), thus the number of patients that provided a sample at Week 4 was lower than the other weeks. Details on measurement of NT-proBNP in PARADIGM-HF have been previously published.[13] NT-proBNP was measured at five timepoints: at the baseline of the single-blind period before enalapril run-in, at baseline after enalapril run-in, at randomization, Week 4 and Week 34. Testing was performed at a central laboratory (Quintiles Laboratory, Atlanta, GA, USA) that used the same methodology used in PANORAMA-HF. The coefficients of variation for NT-proBNP measurement in PARADIGM-HF and PANORAMA-HF were 2.6% and <5.9%, respectively.

Statistical analysis

For paediatric patients in PANORAMA-HF, NT-proBNP change from baseline was analysed using mixed model for repeated measures (MMRM) which included change from baseline in log-transformed NT-proBNP as response, modified age group, NYHA/Ross class group at randomization, region, treatment (sacubitril/valsartan and enalapril), visit and treatment-by-visit interaction as fixed-effect factors; log baseline NT-proBNP and visit-by-log-baseline interaction are covariates. Results are presented as ratio to baseline and percentage change at Week 52. The percentage change was calculated by 1 − [ratio to baseline of adjusted geometric mean]*100.

For the DCM adult subpopulation in PARADIGM-HF, the MMRM model used change from baseline in $\log_2$ (NT-proBNP) at Weeks 4 and 34 as response and contained treatment, region, visit, treatment-by-visit interaction, log baseline NT-proBNP and visit-by-log-baseline interaction as explanatory variables assuming a common covariance for each treatment.

The association between NT-proBNP and clinical outcomes in the paediatric population was assessed using the Cox proportional hazard model. The adjusted hazard ratio (HR) and the *P*-values were stratified by modified age group and NYHA/Ross class group with treatment included as a fixed-effect factor, baseline log2 (NT-proBNP) as covariate, and change from baseline $\log_2$ (NT-proBNP) as time-dependent covariate. The association between NT-proBNP and clinical outcomes in the adult subpopulation was assessed using Cox regression. HRs and *P*-values were derived from the model containing treatment, region, baseline $\log_2$ (NT-proBNP) and time-dependent change from baseline in $\log_2$ (NT-proBNP) as explanatory variables.

For the responder analysis for RCV thresholds, the responders in the paediatric population refer to Week 52 in PANORAMA-HF, and the responders in the adult subpopulation refer to Week 34 in PARADIGM-HF. The analysis was performed using a logistic regression model with treatment, region and log baseline NT-proBNP for PARADIGM-HF and with treatment, region, modified age group, NHYA/Ross class group and $\log_2$ baseline NT-proBNP as covariates for PANORAMA-HF. Statistical testing was performed at the two-sided 0.05 significance level. There was no multiplicity adjustment.

Results

NT-proBNP levels at baseline in paediatric population

From a total population of 375 paediatric patients randomized in PANORAMA-HF, the current analysis included 361 patients who had NT-proBNP levels measured at baseline (sacubitril/valsartan, *n* = 179; enalapril, *n* = 182). The geometric means

Table 1 Baseline geometric mean NT-proBNP levels (pg/mL) in paediatric HF overall population with LVSD and by age groups

Groups	Baseline NT-proBNP levels (pg/mL)	
	Sacubitril/valsartan GM (95% CI)	Enalapril GM (95% CI)
Overall	*n* = 179 879.3 (693.9–1114.2)	*n* = 182 737.4 (586.4–927.3)
Age group 1: 6 y to <18 y	*n* = 105 637.3 (476.3–852.6)	*n* = 108 589.0 (439.4–789.7)
Subset 1: 12 y to <18 y	*n* = 60 501.3 (338.1–743.4)	*n* = 67 611.4 (410.2–911.2)
Subset 2: 6 y to <12 y	*n* = 45 877.6 (571.1–1348.8)	*n* = 41 554.3 (359.0–855.8)
Age group 2a: 2 y to <6 y	*n* = 44 1240.7 (786.2–1958.0)	*n* = 38 831.8 (470.3–1470.9)
Age group 3a: 1 m to <2 y	*n* = 30 1637.0 (821.8–3260.6)	*n* = 36 1274.2 (807.4–2010.9)

NT-proBNP assessment at baseline is the assessment at randomization or the last nonmissing assessment (scheduled or unscheduled) prior to or on the date of randomization and after last Part 1 dose date plus 5 days.
CI, confidence interval; GM, geometric mean; HF, heart failure; LVSD, left ventricular systolic dysfunction; m, month; NT-proBNP, N-terminal pro-B-type natriuretic peptide; n, number of patients in each group; y, year.

Table 2 Baseline characteristics of the populations from the PANORAMA-HF and the PARADIGM-HF studies

Variables	PANORAMA-HF overall (*N* = 375)[a]	PARADIGM-HF overall (*N* = 405)
Age, y, mean ± SD	8.1 ± 5.6	63.7 ± 11.1
Female, *n* (%)	193 (51.5)	87 (21.5)
LVEF at screening, mean ± SD	32.2 ± 7.7	29.2 ± 6.2
NYHA/Ross class, *n* (%)		
I	59 (15.7)	10 (2.5)
II	260 (69.3)	311 (76.8)
III	54 (14.4)	83 (20.5)
IV	2 (0.5)	1 (0.2)
NT-proBNP, pg/mL, GM (95% CI)	804.6 (682.8–948.2)	1598.7 (1464.3–1745.4)

CI, confidence interval; GM, geometric mean; HF, heart failure; LVEF, left ventricular ejection fraction; N, number of patients; NT-proBNP, N-terminal pro-B-type natriuretic peptide; m, month; SD, standard deviation; y, year.
[a]In this model-based analysis, baseline data for patients with missing information were imputed.

of NT-proBNP levels at baseline were comparable across patients in both treatment arms (sacubitril/valsartan: 879.3 pg/mL [95% CI: 693.9–1114.2]; enalapril: 737.4 pg/mL [95% CI: 586.4–927.3]). Patients in AG2a and AG3a had relatively higher baseline NT-proBNP levels compared with patients in AG1 in both treatment arms (*Table 1*). Detailed demographics and baseline characteristics of paediatric patients in PANORAMA-HF have been previously published.[14] Baseline characteristics of the population from the PANORAMA-HF and the PARADIGM-HF studies are listed in *Table 2*.

Reduction in NT-proBNP levels in paediatric and adult patients

In PANORAMA-HF, at Week 52, there was a decrease from baseline in NT-proBNP levels in both sacubitril/valsartan and enalapril groups, across all AGs (*Figure 1*). The ratio of the geometric mean of NT-proBNP levels at Week 52 to baseline was 0.35 (sacubitril/valsartan arm) and 0.38 (enalapril arm) in the overall paediatric population; 0.55 and 0.64, respectively, in AG1 subset 1; 0.36 and 0.35, respectively, in AG1 subset 2; 0.25 and 0.26, respectively, in AG2a, and 0.28 and 0.22, respectively, in AG3a. When describing this as percentage change, the reduction in NT-proBNP levels with sacubitril/valsartan from baseline to Week 52 was 65% in the overall paediatric population; 45% and 65% reduction in AG1 (subsets 1 and 2, respectively); and >70% reduction in both AG2a and AG3a. The decrease from baseline in NT-proBNP levels was not significantly different between sacubitril/valsartan and enalapril at Week 52 in the overall paediatric population, or any of the AGs.

In the PARADIGM-HF DCM cohort, there was a significantly greater decrease in NT-proBNP levels in the sacubitril/valsartan group, compared with the enalapril group (*Figure 2*). A significantly greater decrease in NT-proBNP levels was observed with sacubitril/valsartan compared with enalapril in both studies at Week 4, although this difference was not statistically significant at Weeks 12 or 52 in PANORAMA-HF.

Figure 1 Change from baseline to Week 52 in paediatric HF population with LVSD: Ratio to baseline of adjusted geometric mean levels of NT-proBNP. AG, age group; AGMR, adjusted geometric mean ratio (sac/val: ENA); ENA, enalapril; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sac/val, sacubitril/valsartan; y, years.

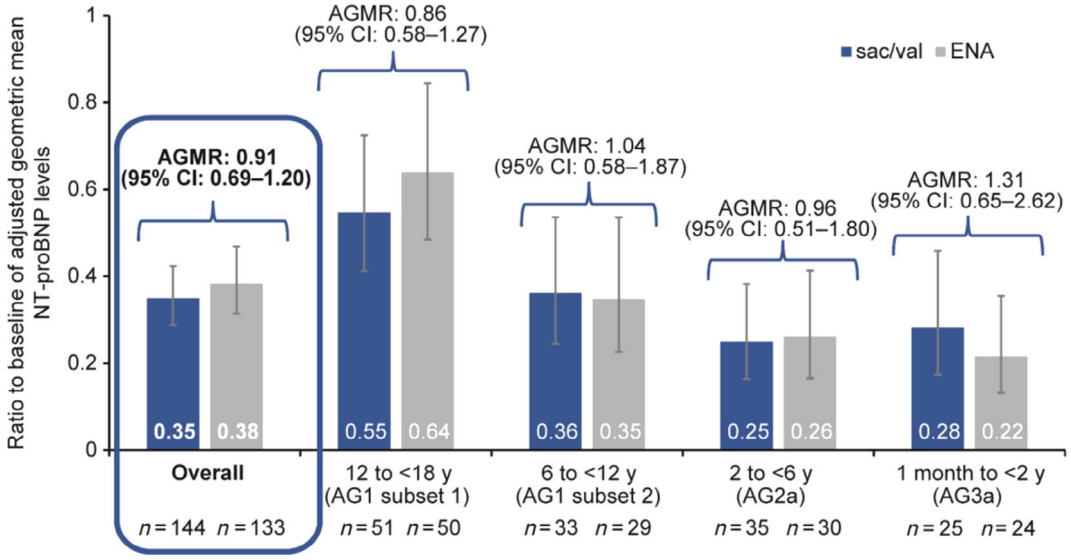
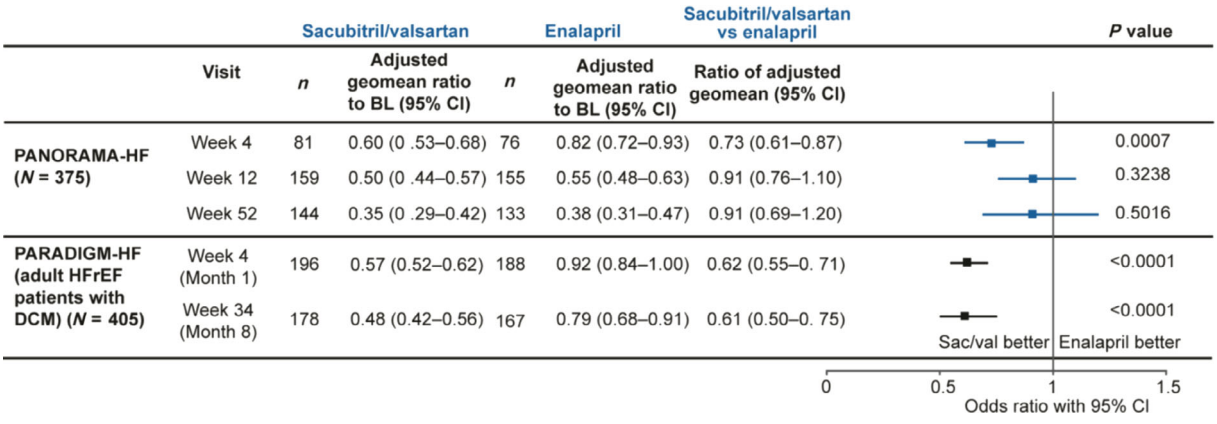


Figure 2 Reduction in NT-proBNP levels in paediatric HF population with LVSD and adult HFrEF patients with DCM receiving sacubitril/valsartan and enalapril. BL, baseline; CI, confidence interval; DCM, dilated cardiomyopathy; HFrEF, heart failure with reduced ejection fraction; LVSD, left ventricular systolic dysfunction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sac/val, sacubitril/valsartan.



Overall, a significant decrease in NT-proBNP levels was observed in both the sacubitril/valsartan and enalapril treatment groups in paediatric patients in PANORAMA-HF as well as with sacubitril/valsartan in the adult HF DCM patients in PARADIGM-HF.[13] The reduction in NT-proBNP in the paediatric population was comparable between sacubitril/valsartan and enalapril treatment groups, whereas the reduction in NT-proBNP was greater in adults treated with sacubitril/valsartan compared with enalapril. Direct comparison of the effect of sacubitril/valsartan on paediatric and adult patients with HF was feasible only at Week 4, as the NT-proBNP levels were discordant thereafter (*Figure 2*).

Association of NT-proBNP levels and clinical outcomes in paediatric and adult patients

As previously published, results from PANORAMA-HF revealed that both baseline values and the change from baseline to any post-baseline value in NT-proBNP were strongly associated with the risk of Category 1 or 2 events in paediatric patients with HF.[14] The present analysis shows that a similar pattern was observed in the adult DCM patients from PARADIGM-HF (*Table* 3). Using the mixed effects NT-proBNP model in the paediatric population, it was observed that a doubling of NT-proBNP levels at baseline or

Table 3 Association of NT-proBNP levels with category 1 or category 2 event in paediatric HF population with LVSD and adult HFrEF patients with DCM

	Sacubitril/valsartan (*n*/*N*)	Enalapril (*n*/*N*)	Baseline $\log_2$ (NT-proBNP)		Change from baseline $\log_2$ (NT-proBNP)	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
PANORAMA-HF (paediatric HF)						
Category 1 or 2 event	34/187	33/188	1.79 (1.55–2.06)	<0.0001	2.09 (1.52–2.87)	<0.0001
Category 1 event	13/187	20/188	1.71 (1.41–2.08)	<0.0001	2.09 (1.36–3.21)	0.0007
Category 2 event	31/187	27/188	1.81 (1.55–2.11)	<0.0001	2.37 (1.69–3.33)	<0.0001
PARADIGM-HF (adult HFrEF patients with DCM)						
Composite of CV death or HF hospitalization	32/213	41/192	1.61 (1.32–1.96)	<0.0001	1.49 (1.19–1.85)	0.0004

NT-proBNP change from baseline was analysed using mixed model for repeated measures (MMRM), which included change from baseline in log transformed NT-proBNP as response, modified age group, NYHA/Ross class group at randomization, region, treatment (sacubitril/valsartan and enalapril), visit, and treatment-by-visit interaction as fixed-effect factors; log baseline NT-proBNP and visit-by-log-baseline interaction as covariates. Imputation was done for missing data. PANORAMA-HF: Discontinuation was not treated as an event. n: the number of patients with at least one event. N: the number of patients included in the analysis: Category 1 events: Death, urgent heart transplant listing, need for mechanical support for ventilation/circulation; Category 2 events: Worsening of HF with/without hospitalization with/without intensive care unit stay.
CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVSD, left ventricular systolic dysfunction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

a doubling in the change in NT-proBNP at any post-baseline value was associated with a 1.8-fold and 2.1-fold increase of the risk of Category 1 or 2 events, respectively ($P < 0.0001$). Similarly, in adult patients from PARADIGM-HF, an approximately 1.6-fold and 1.5-fold increase in the risk of CV death or HF hospitalization, respectively, ($P = 0.0004$) was observed. Conversely, when we illustrate the reverse scenario, a halving of NT-proBNP post-baseline levels (i.e., ratio to baseline = 0.5) in the paediatric population was associated with a 52.2% decrease in risk for a Category 1 or 2 event and a 37.2% decrease in risk of CV death or HF hospitalization in the adult patients.

Responder analysis: Comparison of paediatric and adult patients reaching reference change value (RCV) thresholds

The proportion of patients achieving each RCV threshold for reduction in NT-proBNP showed a consistent pattern: numerically higher in the sacubitril/valsartan group compared with the enalapril group, in both paediatric and adult DCM patient populations. In these populations, the odds ratios for achievement of each RCV threshold for NT-proBNP reduction were all greater than 1.5 (sacubitril/valsartan vs. enalapril group) and were greater than 2 for RCVs of −33% and −46%, indicating that the odds of achieving a 33% or 46% reduction in NT-proBNP with sacubitril/valsartan was more than twice that with enalapril. In both the paediatric and adult DCM patients, the lower limit for the 95% CI was greater than 1 for RCVs of −33% (OR 2.04 [95% CI: 1.23–3.44] and OR 2.97 [95% CI: 1.88–4.68], respectively) and −46% (OR 2.12 [95% CI: 1.27–3.52] and OR 2.60 [95% CI: 1.64–4.14], respectively), indicating a significant difference between treatment groups (*Figure 3*).

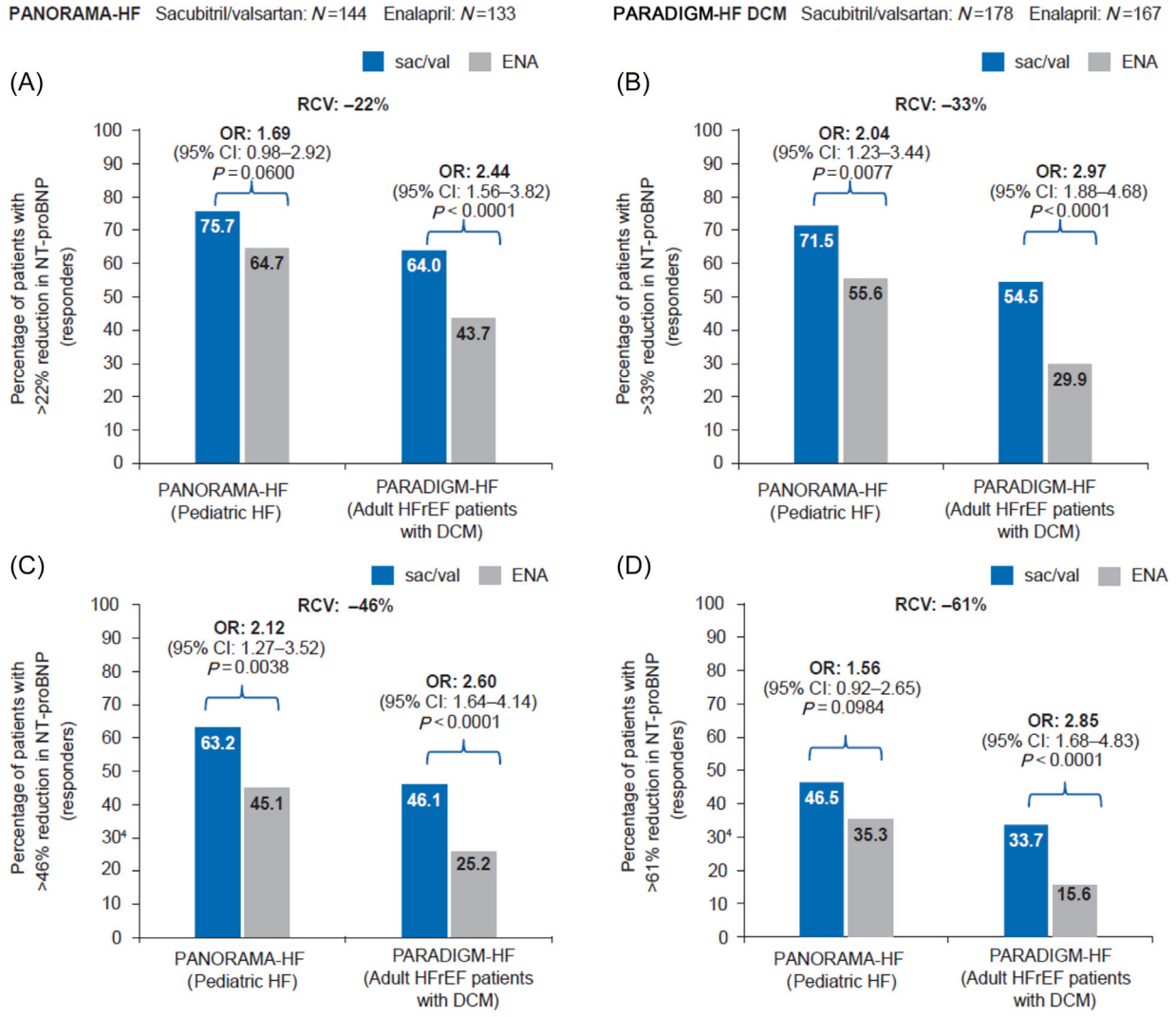
Discussion

The assessment of NT-proBNP serves as a valuable tool in predicting HF prognosis, as its levels are associated with the severity of the condition. Regular monitoring of NT-proBNP concentrations could be beneficial in tracking the response to medical interventions and the clinical advancement of patients.[21,22]

The current study analysed the relationship of NT-proBNP levels to clinical outcomes in paediatric HF patients from the PANORAMA-HF trial, the largest randomized, double-blind study in paediatric HF to date. The association of baseline NT-proBNP levels and change in those levels following treatment for HF was compared with clinical outcomes in adult HFrEF patients with DCM from the PARADIGM-HF trial. In both the paediatric and adult HFrEF patient populations, a strong association between NT-proBNP levels and clinical events was observed. In PANORAMA-HF, a doubling of NT-proBNP levels was associated with a ≥1.7-fold increased risk of HF clinical events (category 1 events were death, urgent heart transplant listing, need for mechanical support for ventilation/circulation and category 2 events were worsening of HF with/without hospitalization with/without intensive care unit stay), while halving of NT-proBNP levels demonstrated a reduction by around 52%. A similar pattern was also seen in adults in PARADIGM-HF[13], although the reductions in NT-proBNP in adults were greater with sacubitril/valsartan than with enalapril. This may represent a broader neurohormonal impact with sacubitril/valsartan in adults due to its dual acting mechanism of simultaneously inhibiting neprilysin and blocking the angiotensin II type-1 receptor. It is unclear why the reduction in NT-proBNP levels in PANORAMA-HF was not statistically different between those who received sacubitril/valsartan and those who received enalapril.

NT-proBNP reduction is known to indicate haemodynamic improvement and has been used as a surrogate or an inter-

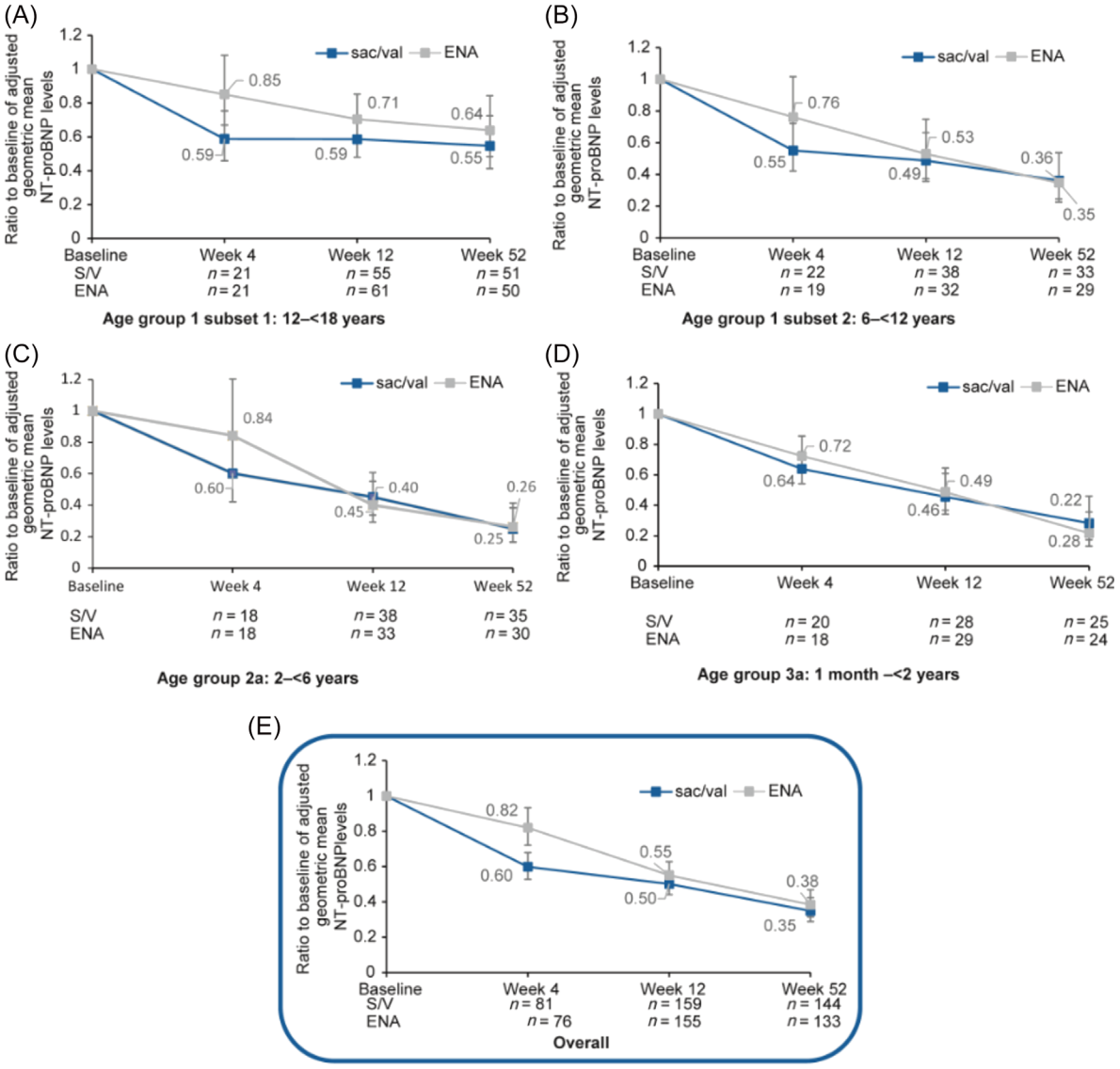
Figure 3 Proportion of paediatric and adult patients reaching Reference Change Value thresholds for reduction of NT-proBNP, sacubitril/valsartan versus enalapril. CI, confidence interval; DCM, dilated cardiomyopathy; HFrEF, heart failure with reduced ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; RCV, reference change value; sac/val, sacubitril/valsartan.



mediate endpoint in clinical trials in HF.[10–13] While the role of NT-proBNP as a prognostic cardiac biomarker is well established among adult patients with HF,[10,19,23,24] this is the first time that a large-scale prospective study with investigators blinded to NT-proBNP levels has demonstrated a predictive function of NT-proBNP in paediatric HF patients. The PANORAMA-HF study provides evidence that changes in NT-proBNP are associated with important clinical endpoints, providing major implications for future paediatric HF trials.

It was also observed that similar to adults in PARADIGM-HF, paediatric patients in PANORAMA-HF had elevated baseline NT-proBNP values. Although this was true for all paediatric age groups, the highest levels of NT-proBNP were observed among the youngest age groups (1 month to <6 years) compared with the older age group (6 years to <18 years). This finding is consistent with results from a previous study that demonstrated that neonates with significant heart disease had higher BNP levels compared with older children with heart disease.[25] However, it is noteworthy that BNP levels are usually elevated among normal newborns and decline within a few weeks of birth and that there is a significant and steady decrease in NT-proBNP levels during childhood in children with normal heart function, with higher cut-off values for younger children and lower cut-off levels for teenagers.[26–28] The higher baseline levels of NT-proBNP among the youngest age group in PANORAMA-HF may also be due to the fact that most of these patients (especially infants) would be more likely to have current symptoms of HF that correspond to elevated levels of NT-proBNP, unlike patients in relatively older age groups who were enrolled in

Figure 4 NT-proBNP ratio to baseline through Week 52 in paediatric HF population with LVSD. AG, age group; AGM, adjusted geometric mean; LVSD, left ventricular systolic dysfunction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sac/val, sacubitril/valsartan; S/V, sacubitril/valsartan.



the study due to current or previous HF symptoms. Moreover, diverse metabolic processes in early childhood lead to elevated levels of BNP and NT-proBNP in the initial days of life, followed by a significant decrease thereafter.[27,28]

The ratio to baseline of the adjusted geometric mean of NT-proBNP through Week 52 indicates that treatment with both sacubitril/valsartan and enalapril was associated with persistent reduction in NT-proBNP throughout the study across all AGs (*Figure 4*). The greatest reductions were seen in the younger age groups, while decreases similar to the adult DCM population were observed in the oldest age group. This finding could be partially explained by the previously described known reduction in BNP throughout childhood, but may also reflect the known greater propensity for younger children to recover from LVSD when compared with older children.[29]

Our comparison showed that more patients achieved reductions in NT-proBNP with sacubitril/valsartan compared with enalapril, consistent across adult DCM and paediatric populations. While geometric mean reductions were similar, greater numbers achieving reductions in RCV with sacubitril/valsartan suggest a possible therapeutic advantage, reinforced by a more rapid decline in NT-proBNP at 4 weeks. This supports potentially greater benefits of sacubitril/valsartan over enalapril in paediatric HF patients, consistent with observed superiority in adult HFrEF patients.[13] However, caution is needed as the decline in NT-proBNP at Week 4 did not sustain at Weeks 12 and 52.

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These findings provide support for the use of NT-proBNP as a therapeutic target in the clinical practice of paediatric HF as well as use as an endpoint for future paediatric trials due to its relationship with haemodynamic improvement, modification with treatment, and its possible clinical implications as a predictive marker for worsening and improving HF symptoms.

The current analyses has a few limitations that should be considered. Firstly, there is a small number of patients with available NT-proBNP values at Week 4 compared with the other weeks, which may affect the generalizability of the findings. Additionally, it is important to note that the direct comparison of the effect of sacubitril/valsartan on paediatric and adult patients with heart failure was only feasible at Week 4, so caution should be exercised when interpreting the data. Furthermore, the treatment effect of sacubitril/valsartan on NT-proBNP was an exploratory endpoint in both the PANORAMA-HF and PARADIGM-HF studies and therefore, the results related to NT-proBNP should be interpreted with caution. Lastly, it is important to consider that NT-proBNP concentrations are relatively high in neonates during the initial days after birth and then decline rapidly over the following months. This should be taken into account when interpreting NT-proBNP data in the context of this analysis.

Conclusions

This is the first prospective, randomized large-scale study to demonstrate that an increase in NT-proBNP levels is associated with an increased risk of HF clinical events in paediatric patients with HF. Data from this post hoc analysis of PANORAMA-HF, and comparison with results in adults with HF in PARADIGM-HF, provide evidence for the value of NT-proBNP as a prognostic biomarker for bridging between adult and paediatric HF populations.

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Conflict of interest

RS: Consultant for Novartis, American Regent Inc., CRI Biotech, and Rocket Pharmaceuticals. JG: Employee of Novartis Pharmaceuticals, East Hanover, New Jersey, USA. TG: Employee of Novartis Pharma AG, Basel, Switzerland and owns its shares. SSY: Employee of Novartis Pharmaceuticals Corporation, US, and owns stocks in Novartis Pharma AG, Basel, Switzerland. SZ: Employee of Novartis, Shanghai, China. MFP: Employee of Novartis Pharmaceuticals, East Hanover, New Jersey, USA. DB: Reports consulting fees from Novartis. PFK: Reports consulting fees from Novartis, Rocket Pharmaceuticals. MB: Member of Data Safety Monitoring Board and Advisory Board for this study. CM: Nothing to disclose. AC: Nothing to disclose. CC: Data and Safety Monitoring Board chairman at the Mayo Research Foundation and has participated in an advisory board for CareDx. YL: Nothing to disclose. GG: Nothing to disclose. JKW: Nothing to disclose. AJ: Nothing to disclose. JR: Reports receiving consulting fees from Bayer, Enzyvant, Merck, AskBio, American Regent, Bristol Myers Squibb.

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Data Availability Statement

Novartis is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Estimated RCVs from PARADIGM-HF and other HF clinical trials – RCVs were calculated with the lognormal distribution.

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