

## Original article

## NT-proBNP in systemic right ventricles: a new cutoff level for risk stratification?



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## ABSTRACT

**Introduction and objectives:** The role of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in the risk prediction of patients with systemic right ventricles (sRV) is not well defined. The aim of this study was to analyze the prognostic value of NT-proBNP in patients with an sRV.

**Methods:** The prognostic value of NT-proBNP was assessed in 98 patients from the SERVE trial. We used an adjusted Cox proportional hazards model, survival analysis, and c-statistics. The composite primary outcome was the occurrence of clinically relevant arrhythmia, heart failure, or death. Correlations between baseline NT-proBNP values and biventricular volumes and function were assessed by adjusted linear regression models.

**Results:** The median age [interquartile range] at baseline was 39 [32–48] years and 32% were women. The median NT-proBNP was 238 [137–429] ng/L. Baseline NT-proBNP concentrations were significantly higher among the 20 (20%) patients developing the combined primary outcome compared with those who did not (816 [194–1094] vs 205 [122–357];  $P = .003$ ). In patients with NT-proBNP concentrations > 75th percentile (> 429 ng/L), we found an exponential increase in the sex- and age-adjusted hazard ratio for the primary outcome. The prognostic value of NT-proBNP was comparable to right ventricular ejection fraction and peak oxygen uptake on exercise testing (c-statistic: 0.71, 0.72, and 0.71, respectively).

**Conclusions:** In patients with sRVs, NT-proBNP concentrations correlate with sRV volumes and function and may serve as a simple tool for predicting adverse outcomes.

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## NT-proBNP en el ventrículo derecho sistémico, ¿un nuevo valor de corte para la estratificación del riesgo?

## RESUMEN

**Introducción y objetivos:** El objetivo de este estudio es analizar el valor pronóstico de la fracción aminoterminal del péptido natriurético cerebral (NT-proBNP) en pacientes con ventrículo derecho sistémico (VDs).

**Métodos:** El valor pronóstico del NT-proBNP se evaluó en 98 pacientes del ensayo clínico SERVE. Se empleó un modelo de riesgos proporcionales de Cox ajustado, análisis de supervivencia y estadístico c. El objetivo primario compuesto fue la ocurrencia de arritmia clínicamente relevante, insuficiencia cardíaca o muerte. Como objetivos secundarios se evaluaron las correlaciones entre los valores basales de NT-proBNP y los volúmenes y la función biventriculares mediante modelos de regresión lineal ajustados.

## Palabras clave:

Cardiopatías congénitas del adulto  
Transposición de las grandes arterias  
Biomarcadores  
Insuficiencia cardíaca

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◇ These authors contributed equally to the study design, data interpretation, and manuscript preparation.

**Resultados:** La mediana [intervalo intercuartílico] de edad al inicio fue de 39 [32–48] años y el 32% eran mujeres. La mediana de NT-proBNP fue de 238 [137–429] ng/l. Las cifras basales de NT-proBNP fueron significativamente más altas entre los 20 pacientes (20%) que cumplían el objetivo primario combinado (816 [194–1.094] frente a 205 [122–357];  $p = 0,003$ ). En pacientes con valores de NT-proBNP superiores al percentil 75 ( $> 429$  ng/l), se halló un aumento exponencial en la razón de riesgos ajustada por sexo y edad para el resultado primario. El valor pronóstico del NT-proBNP fue comparable al de la fracción de eyección del ventrículo derecho y al del consumo máximo de oxígeno en la prueba de esfuerzo (estadístico  $c$ , 0,71, 0,72 y 0,71 respectivamente).

**Conclusiones:** En pacientes con VD, los valores de NT-proBNP se correlacionan con los volúmenes y la función ventriculares y pueden ser un medio útil para la estratificación del riesgo.

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## Abbreviations

ACHD: adult congenital heart disease  
 ccTGA: congenitally corrected transposition of the great arteries  
 HS-cTnT: high-sensitivity cardiac Troponin T  
 NT-proBNP: N-terminal pro-B-type natriuretic peptide

## INTRODUCTION

The population of adults with congenital heart disease and a systemic right ventricle (sRV) with biventricular circulation consists of patients with congenitally corrected transposition of the great arteries (ccTGA) and patients with dextro-transposition of the great arteries (d-TGA) after an atrial switch operation.<sup>1,2</sup> Due to its embryological, morphological, and histological characteristics, the right ventricle is at increased risk for failure when exposed to systemic pressures. Thus, in adults with sRVs, ventricular dilatation and dysfunction are common, and there is a strong association between sRV dysfunction and cardiac complications (eg, arrhythmias and heart failure) and premature death.<sup>3–5</sup>

Natriuretic peptides such as B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are quantitative markers of hemodynamic cardiac stress and heart failure (HF) that have gained increasing importance in the diagnosis of left ventricular dysfunction and HF among patients with acquired cardiovascular diseases.<sup>6,7</sup> Moreover, the prognostic role of these biomarkers among patients with normal biventricular physiology is well-established.<sup>8–10</sup> Pilot studies have suggested that NT-proBNP may also play an important role in risk prediction among patients with congenital heart disease (CHD).<sup>11,12</sup> However, most of these studies included mixed cohorts of patients with CHD<sup>11,12</sup> or focused solely on those with d-TGA after an atrial switch operation.<sup>13</sup>

The SERVE trial is a multicenter, double-blind, randomized, placebo-controlled clinical trial aiming to assess the effects of tadalafil on sRV size and function, exercise capacity, and neurohormonal activation over time.<sup>14,15</sup> The present study is a substudy of the SERVE trial. We aimed to assess the determinants and the prognostic value of NT-proBNP in patients with an sRV from the SERVE trial.

## METHODS

### Ethics approval

This study used data from the SERVE trial. The responsible investigator at each site ensured that approval from an appropri-

ately constituted Competent Ethics Committee was sought for the clinical study. All changes in the research activity (including the case of planned or premature study end), all unanticipated problems involving risks to humans and the final report were reported to the ethics committee.

The study was carried out in accordance with the protocol and with the principles outlined in the current version of the Declaration of Helsinki. The ethics committee and regulatory authorities received annual safety and interim reports and were informed about study stop/end in agreement with local requirements.

### Study population

The study population consisted of participants from the SERVE trial with valid baseline NT-proBNP values. The detailed methodology of the study has already been published.<sup>14,15</sup> In short, the SERVE trial is a double-blind, randomized, placebo-controlled, multicenter trial comparing placebo vs tadalafil in a 1:1 ratio. All participants started on tadalafil 20 mg or placebo once daily, or both. At baseline, a clinical examination, a 12-lead electrocardiogram, and an echocardiogram were performed. Neurohormonal activation, detailed cardiac anatomy, biventricular volumes, and function, as well as exercise capacity and cardiopulmonary fitness were assessed by means of blood tests, cardiac magnetic resonance (CMR) or coronary multidetector computed tomography (CMDCT) if CMR was contraindicated, and a cardiopulmonary exercise test, respectively. These examinations were repeated after 1 year and at the end of the study follow-up 3 years later. For the purpose of this analysis, data on 98 patients with no missing NT-proBNP values at baseline from a total of 100 were analyzed.

### Assessment of neurohumoral activation

Concentrations of NT-proBNP (ng/L) were analyzed in a core lab with expertise in biomarker analysis: the Cardiovascular Research Institute Basel (CRIB) in Basel, Switzerland. An electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics, Switzerland) was used. Specific patient sets with plastic tubes and barcodes corresponding to the individual patient numbers and time points in the study were used. Samples were collected locally, followed by centrifugation, aliquoting, and initial storage at  $-80^{\circ}\text{C}$  at the participating centers. Routine sample collection at the local study sites and refrigerated transportation to the dedicated biobank at the CRIB were provided by the core lab. The data obtained from the analysis were then centrally entered into the electronic database of the SERVE trial.

## Primary and secondary outcomes of the current study

The combined primary outcome of the current study (from now on also referred to as cardiac complications) was defined as the occurrence of either clinically relevant arrhythmias (requiring hospitalization and/or therapeutic intervention), hospitalization for HF, or all-cause death.

Secondary outcomes investigated the pathophysiological determinants of NT-proBNP in patients with an sRV by assessing the correlations of this biomarker with baseline biventricular end-diastolic and end-systolic volumes, stroke volumes, and ejection fraction assessed by CMR/CMDCT.

## Statistical analysis

Continuous variables are presented as medians (interquartile range [IQR]), and categorical variables as counts (percentages). Baseline characteristics were stratified by NT-proBNP quartiles and compared using the Kruskal-Wallis test for continuous variables and the chi-square or Fisher exact test for categorical variables, as appropriate. Confidence intervals were computed as recommended.<sup>16</sup>

Friedman 2-way ANOVA was used for the comparison of dependent samples. Multivariable linear regression models (age-, sex-, and creatinine-adjusted) were fitted for each baseline CMR/CMDCT variable related to biventricular volumes and function. To avoid dichotomizing continuous variables and imposing linearity, continuous variables were modeled using restricted cubic splines. Three spline knots were placed at 0.1, 0.5, and 0.9 percentiles of each variable marginal distribution, following Harrell's recommendations.<sup>17</sup> Linear regression assumptions were checked using diagnostic plots. Consequently, the dependent variable (NT-proBNP) in each model was log-transformed to satisfy the assumption of homoscedasticity. To avoid dichotomizing our main variable of interest (NT-proBNP), another Cox proportional hazards model corrected for age and sex was fitted. NT-proBNP was then modeled with a restricted cubic spline function (3 knots) to take possible nonlinearity into consideration and to treat the main variable of our study continuously. Because NT-proBNP was modeled with a restricted cubic spline, we expressed its hazard ratio (HR) using the 75th percentile of our NT-proBNP values (429 ng/L) as the reference value. We calculated the HR of several levels of NT-proBNP compared with this specific reference value. The proportional hazard assumption was tested by means of the Schoenfeld residuals. The assumption was not violated (overall  $P = .73$ ; [figure 1 of the supplementary data](#)). In addition, to investigate the association of clinically relevant parameters with the occurrence of the primary outcome, an age- and sex-corrected Cox proportional hazards model was fitted for each of the following variables: New York Heart Association (NYHA) functional class > I, NT-proBNP, predicted peak oxygen uptake (predicted peak  $VO_2$  [%]), and right ventricular ejection fraction (RVEF), as %. To test the added value of NT-proBNP on top of RVEF and peak  $VO_2$ , a sequential modeling approach starting with RVEF, adding peak  $VO_2$ , and ending with NT-proBNP was performed. Due to the limited sample size, we were unable to adjust the base model for more prior information.

Survival analysis for the occurrence of the combined primary outcome of patients with NT-proBNP values lower vs higher than the cutoff value (> 429ng/L) was assessed using the Kaplan-Meier estimator. If a patient experienced multiple events, event-free survival time was calculated from the date of inclusion until the occurrence of the first event. The statistical significance for the difference between groups was assessed by means of the log-rank test. The individual prognostic accuracy of NT-proBNP and those of

other established markers for predicting the primary outcome was assessed by means of the concordance statistic (c-statistic). To compare the prognostic value of NT-proBNP, we built a model adjusted for age and sex and compared the c-statistic with adjusted models for RVEF and predicted peak  $VO_2$ .

All hypothesis testing was 2-tailed, and  $P$  values < .05 were considered statistically significant. There was 1 missing value for the variable "predicted peak  $VO_2$  (%)". This patient was excluded from the corresponding analysis. Data analysis was performed in R, version 4.1.3 (R Foundation for Statistical Computing, Austria).

## RESULTS

Baseline characteristics stratified by NT-proBNP quartiles are depicted in [table 1](#). The median age at baseline was 39 [32–48] years and 32% of the patients were female. There was no significant difference in NT-proBNP concentrations between men and women (220 [125–426] vs 259 [154–456];  $P = .504$ ). The median [IQR] of NT-proBNP was 238 [137–429] ng/L. Older patients had higher NT-proBNP concentrations. In 24 patients (24%), the NT-proBNP concentration was above the chosen cutoff value of > 429 ng/L (fourth quartile). Eighty-two (84%) patients were in functional NYHA class I and had lower NT-proBNP levels compared with patients in functional class II or III. The 3 patients with permanent atrial fibrillation/flutter were in the highest NT-proBNP quartile.

## Occurrence of the cardiac outcomes and the prognostic value of NT-proBNP

There were 24 primary outcome events in 20 (20%) patients. Specifically, there were 2 deaths, 5 hospitalizations due to HF, and 17 clinically relevant arrhythmias (15 supraventricular arrhythmias and 2 ventricular arrhythmias). The occurrence of the combined primary outcome increased significantly within the fourth quartile compared with quartiles 1–3 (for each of quartile 1–3: 3 events (12%), compared with 11 events in quartile 4 (46%);  $P = .012$ ). Levels of NT-proBNP were significantly higher among patients meeting the combined primary outcome (816 [194–1094] vs 205 [122–357];  $P = .003$ ). The median [IQR] of NT-proBNP levels for arrhythmia and HF were 322 [190–1095] and 1202 [928–3980], respectively. The 2 (male) patients who died had NT-proBNP levels of 773 and 932 ng/L, respectively. The occurrence of the primary outcome did not significantly differ among cardiac anatomy groups (6 [24%], 5 [22%], and 9 [17%];  $P = .768$  for ccTGA, d-TGA after Mustard operation, and d-TGA after Senning operation).

HRs with 95% confidence intervals (95%CI) for other established risk factors for increased risk of cardiovascular events during the 36-month follow-up are shown in [table 2](#). The association between NT-proBNP levels and the risk of 36-month complications (primary outcome) is depicted in [figure 1](#). A significant nonlinear dose-response association is shown. HRs (95%CI in gray) of NT-proBNP compared with the cutoff value of 429 ng/L for the occurrence of the primary outcome are also outlined in [figure 1](#). Event-free survival (median [IQR] follow-up duration = 37 [36–37]) was significantly higher in patients with NT-proBNP values below the cutoff value (429 ng/L) when compared with patients above this level ([figure 2](#)). The unadjusted c-statistic for NT-proBNP and other established markers for poor prognosis are depicted in [table 3](#). There was no difference in the prognostic performance of NT-proBNP, RVEF, NYHA class > I, and peak  $VO_2$  (predicted) for the occurrence of the primary outcome ([table 3](#)). When comparing Model I to Model II and Model III ([table 4](#)), there was no significant difference in their prognostic value ( $P = .815$  and  $.935$ , respectively). The base model with RVEF yielded a c-statistic of 0.69 (95%CI,

**Table 1**  
Baseline characteristics of the study population

Variable [IQR]	Overall NT-proBNP	Quartile 1 [56-136]	Quartile 2 [137-237.5]	Quartile 3 [237.6-429]	Quartile 4 [430-5778]	P
No.	98	25	24	25	24	
Age, y	39 [32,48]	32 [30-40]	36 [31-38]	41 [37-49]	52 [41-54]	< .001
Female sex	31 (32)	7 (28)	7 (29)	9 (36)	8 (33)	.946
Treatment with tadalafil	50 (51.0)	15 (60.0)	9 (37.5)	12 (48.0)	14 (58.3)	.379
Weight, kg	78.5 [70-86]	80 [72-88]	75 [70-86]	75 [63-85]	82 [72-85]	.573
BMI	25.5 [23-28]	26 [25-28]	24 [22.0-26]	26 [23-28]	27 [25-28]	.143
PM/ICD implantation	20 (20)	2 (8)	4 (17)	7 (28)	7 (29)	.189
Cardiac anatomy						.149
ccTGA	25 (26)	7 (28)	3 (13)	6 (24)	9 (38)	
d-TGA and Mustard	21 (21)	3 (12)	4 (17)	9 (36)	5 (21)	
d-TGA and Senning	52 (53)	15 (60)	17 (71)	10 (40)	10 (42)	
Additional lesion						.334
None	58 (59)	15 (60)	15 (62)	16 (64)	12 (50)	
VSD	11 (11)	3 (12)	3 (13)	1 (4)	4 (17)	
Pulmonary stenosis	8 (8.2)	4 (16)	2 (8)	0 (0)	2 (8)	
VSD and pulmonary stenosis	10 (10)	1 (4)	1 (4)	3 (12)	5 (21)	
Other	11 (11)	2 (8)	3 (13)	5 (20)	1 (4)	
NYHA classification						.001
I	82 (84)	23 (92)	23 (96)	23 (92)	13 (54)	
II	13 (13)	1 (4)	1 (4)	2 (8)	9 (38)	
III	3 (3)	1 (4)	0 (0)	0 (0)	2 (8)	
Rhythm (ECG)						.145
Junctional	12 (12.2)	1 (4.0)	2 (8.3)	6 (24.0)	3 (12.5)	
Sinus rhythm	66 (67.3)	21 (84.0)	19 (79.2)	13 (52.0)	13 (54.2)	
Atrial flutter	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	
Atrial fibrillation	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.2)	
Pacemaker	15 (15.3)	2 (8.0)	3 (12.5)	5 (20.0)	5 (20.8)	
Other	2 (2.0)	1 (4.0)	0 (0.0)	1 (4.0)	0 (0.0)	
TR severity						.584
None	8 (8.8)	3 (12.5)	1 (4.5)	2 (9.5)	2 (8.3)	
Mild	52 (57.1)	14 (58.3)	15 (68.2)	13 (61.9)	10 (41.7)	
Moderate	27 (29.7)	7 (29.2)	6 (27.3)	5 (23.8)	9 (37.5)	
Severe	4 (4.4)	0 (0.0)	0 (0.0)	1 (4.8)	3 (12.5)	
CMR/CMDCT <sup>a</sup>						
Indexed RVESV, mL	63.9 [51.7-82.9]	60.2 [49.4-68.9]	61.9 [49.5-69.1]	70.1 [53.1-89.5]	84.5 [55.8-108.6]	.012
Indexed RVEDV, mL	121.4 [103.6-140.1]	110.7 [98.4-122.8]	117.9 [101.0-128.2]	128.8 [105.6-157.5]	128.2 [113.6-161.3]	.022
Indexed RVSV, mL	53.9 [47.7-62.1]	52.8 [46.9-56.0]	52.9 [48.5-58.3]	63.2 [51.8-69.6]	50.8 [43.6-61.7]	.016
RVEF, %	45.6 [39.5-50.5]	46.1 [43.1-50.6]	47.5 [44.9-50.6]	46.0 [41.4-52.8]	35.3 [30.3-46.9]	.001
Indexed LVESV, mL	26.8 [21.3-38.2]	25.0 [20.9-33.5]	28.2 [20.8-33.8]	31.7 [23.4-41.6]	30.8 [22.2-39.4]	.377
Indexed LVEDV, mL	77.5 [62.8-88.5]	77.6 [62.4-84.7]	74.4 [64.6-84.5]	83.9 [72.2-97.8]	72.2 [62.5-90.7]	.375
Indexed LVSV, mL	48.1 [41.1-55.5]	50.2 [43.5-55.8]	45.8 [40.9-51.5]	51.9 [43.9-56.9]	42.5 [38.6-51.6]	.185
LVEF, %	63.5 [58.4-67.5]	66.3 [60.2-67.8]	64.2 [61.0-68.7]	63.0 [56.1-67.4]	62.2 [55.4-65.3]	.353
CPET <sup>b</sup>						
Peak VO <sub>2</sub> , mL/min/kg	25.3 [19.1-29.2]	29.1 [21.6-31.3]	27.0 [22.9-29.8]	25.1 [19.0-28.9]	18.3 [14.3-22.8]	< .001
Predicted peak VO <sub>2</sub> , %	76.0 [67.0-86.0]	81.0 [74.0-92.0]	77.0 [69.8-86.5]	82.0 [67.8-92.5]	67.0 [56.0-77.0]	.006
Laboratory parameters						
Creatinine, μmol/L	82 [73-93]	86 [81-96]	79 [74-85]	75 [71-78]	90 [79-99]	.007
Hs-cTnT, ng/L	7 [4-11]	5 [3-7]	6 [4-9]	7 [5-9]	14 [9-17]	< .001

BMI, body mass index (in kg/m<sup>2</sup>); ccTGA, congenitally corrected transposition of the great artery; CMR, cardiac magnetic resonance; d-TGA, dextro-transposition of the great arteries; hs-cTnT, high-sensitivity cardiac troponin T; ECG, electrocardiogram; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; VO<sub>2</sub> = oxygen uptake.

The data are expressed as median [interquartile range] or No. (%).

<sup>a</sup> 21 patients (21%) with CDMCT.

<sup>b</sup> 64 patients with RER ≥ 1.1.

**Table 2**  
Hazard ratios for the occurrence of the primary outcome

Variable	HR*	95%CI	P
NYHA class > I	3.098	1.109-8.651	.031
NT-proBNP > 429 ng/L	2.740	0.998-7.523	.051
RVEF, %	0.895	0.848-0.946	<.001
Predicted peak VO <sub>2</sub> , mL/min/kg	0.967	0.940-0.995	.021

95%CI, 95% confidence interval; HR, hazard ratio; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; predicted peak VO<sub>2</sub>, maximal oxygen uptake; RVEF, right ventricular ejection fraction.

\* Adjusted for age (years) and sex (male).

0.56-0.82). Incorporating peak VO<sub>2</sub> into the model resulted in a c-statistic of 0.7 (95%CI, 0.56-0.84). Finally, the addition of NT-proBNP to the model comprising RVEF and peak VO<sub>2</sub> increased the c-statistic to 0.71 (95%CI, 0.57-0.85). These results are depicted in table 5.

In a sensitivity analysis assuming linearity for the association between NT-proBNP and the outcome and for the association between NT-proBNP and the magnetic resonance imaging parameters, the results were comparable (figure 2 and 3 of the supplementary data).

**Determinants of NT-proBNP concentrations**

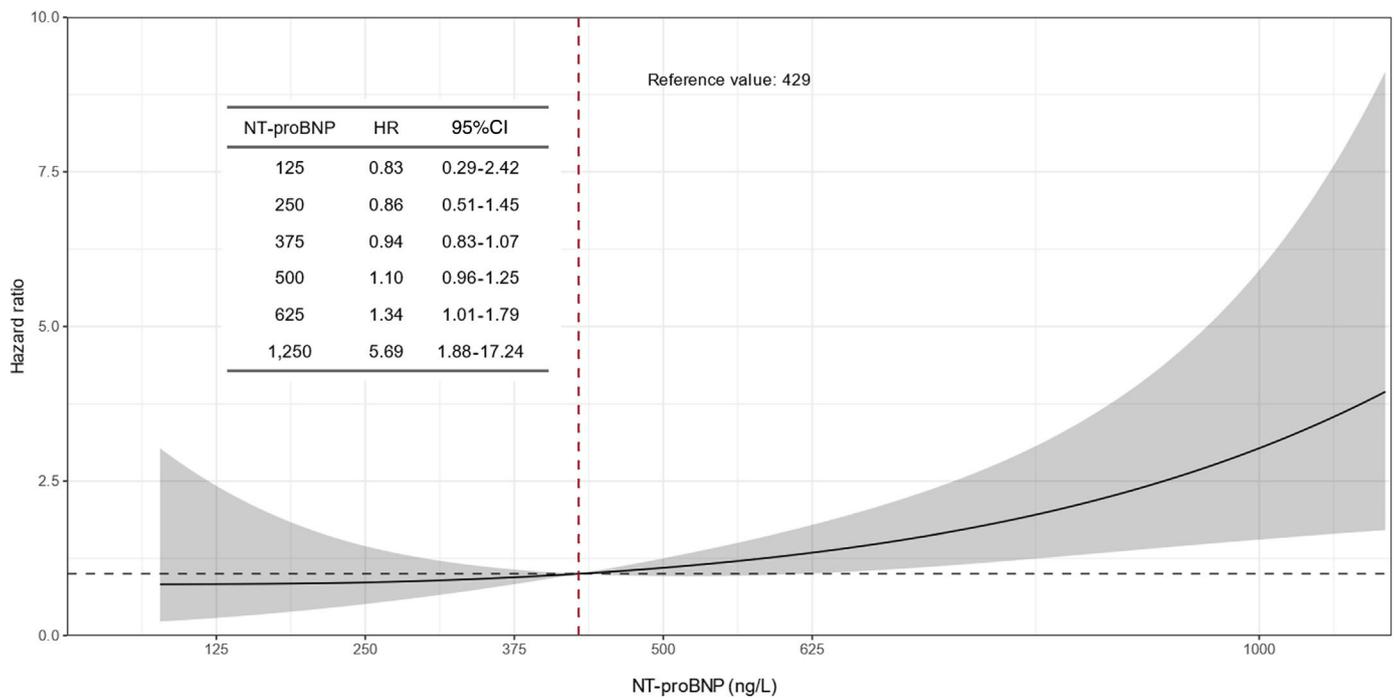
Measurements of biventricular volumes and function are shown in table 1. Systemic RV end-systolic and end-diastolic volumes, ejection fraction and stroke volume were significantly associated with NT-proBNP (P < .03 for all correlations).

A graphic representation of the multivariable linear regression models for the correlation of NT-proBNP levels with CMR- or CDMCT-derived biventricular indexed volumes and function are depicted in figure 3. A statistically significant positive correlation between NT-proBNP levels and right ventricular end-systolic and

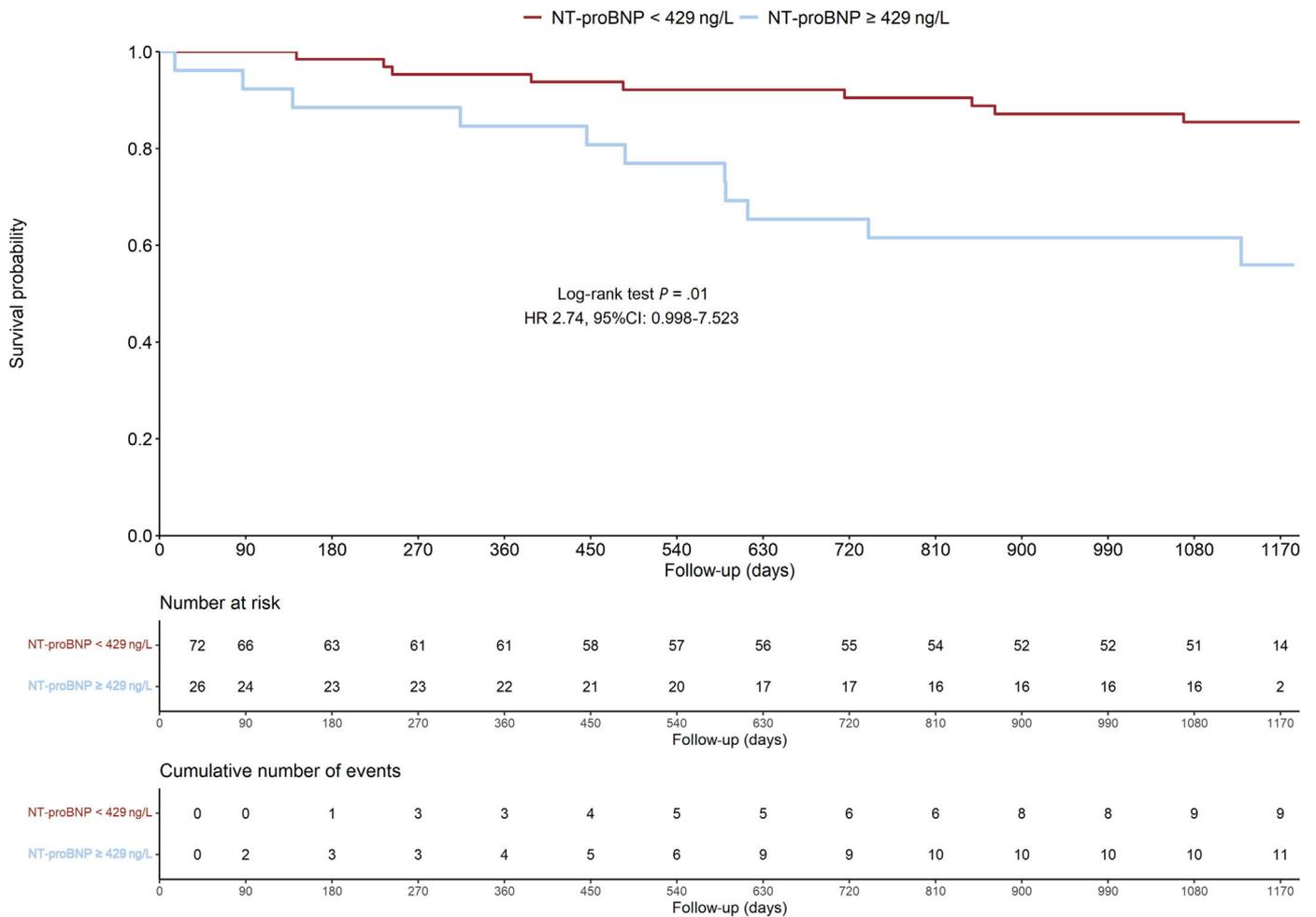
end-diastolic volume index was observed (coefficient of determination: +0.481; P < .001, and +0.427; P < .001 respectively). There was a statistically significant negative correlation between NT-proBNP levels and RVEF (coefficient of determination: -0.561; P < .001). For the remaining parameters, no statistically significant correlation with NT-proBNP was observed.

**DISCUSSION**

To our knowledge, this is the first prospective study investigating the prognostic value and determinants of NT-proBNP in a well-defined population of patients with an sRV (SERVE trial). Individuals meeting the primary outcome of adverse cardiovascular events (a composite endpoint of death, hospitalization for HF, and/or occurrence of clinically relevant arrhythmia) had significantly higher baseline NT-proBNP levels than those who remained event-free during follow-up. An NT-proBNP level > 429 ng/L seems to be a practical cutoff level indicating an increased risk of adverse events during mid-term follow-up. The prognostic accuracy of NT-proBNP was comparable to that of RVEF and predicted peak VO<sub>2</sub>. By comparing the prognostic value of NT-proBNP with RVEF and peak VO<sub>2</sub> in separate models, the study aimed to assess whether NT-proBNP could offer comparable prognostic performance to magnetic resonance imaging analysis or exercise stress tests, which are more resource-intensive, not widely accessible, and require specialized trained personnel. The similar prognostic performance underscores the potential value of NT-proBNP as a widely accessible prognostic biomarker. While the addition of NT-proBNP on top of RVEF and peak VO<sub>2</sub> increased prognostic discrimination, the improvement was modest. However, due to the wide confidence intervals (resulting from the small sample size), it is difficult to draw conclusions from this sequential approach. Higher NT-proBNP levels were associated with higher right ventricular end-systolic and end-diastolic volume index and lower



**Figure 1.** NT-proBNP and the occurrence of the primary outcome. This dose-response plot shows the association between NT-proBNP levels at baseline and the risk of complications at 36 months. We calculated age- and sex-adjusted hazard ratios (95%CI) for several levels of NT-proBNP and compared them to our reference value of 429ng/L. 95%CI, 95% confidence interval; HR, hazard ratio; NT pro-BNP, N-terminal pro-B-type natriuretic peptide.



**Figure 2.** Survival analysis stratified by a NT-proBNP level of 429ng/L. Kaplan-Meier curve showing the occurrence of the combined primary outcome in patients with NT-proBNP values above and below the median. There was a significantly higher occurrence in patients with levels at or above 429ng/L. 95%CI, 95% confidence interval; HR, hazard ratio; NT pro-BNP, N-terminal pro-B-type natriuretic peptide.

RVEF as measured by CMR or CMDCT. **Figure 4** depicts the findings as a central illustration.

**Our findings compared with the current literature**

Previous studies analyzing the prognostic impact of NT-proBNP were either performed in heterogeneous cohorts of patients with adult congenital heart disease or were retrospective in nature.

Popelovà et al.<sup>11</sup> investigated the prognostic value of NT-proBNP in 646 adults with various congenital heart lesions. These authors found a significant correlation between NT-proBNP and all-cause mortality. Of these, 84 patients (13%) had transposition of the great arteries after Mustard or Senning operation and

**Table 3**  
Prognostic performance of individual variables

Variable	c-statistic	95%CI
NYHA class > I	0.64	0.53-0.74
NT-proBNP, ng/L	0.70	0.57-0.83
RVEF, %	0.69	0.56-0.82
Predicted peak VO <sub>2</sub> , mL/min/kg	0.65	0.53-0.77

95%CI, 95% confidence interval; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; peak VO<sub>2</sub>, maximal predicted oxygen uptake; RVEF, right ventricular ejection fraction.

**Table 4**  
Prognostic performance of different variables adjusted for age and sex

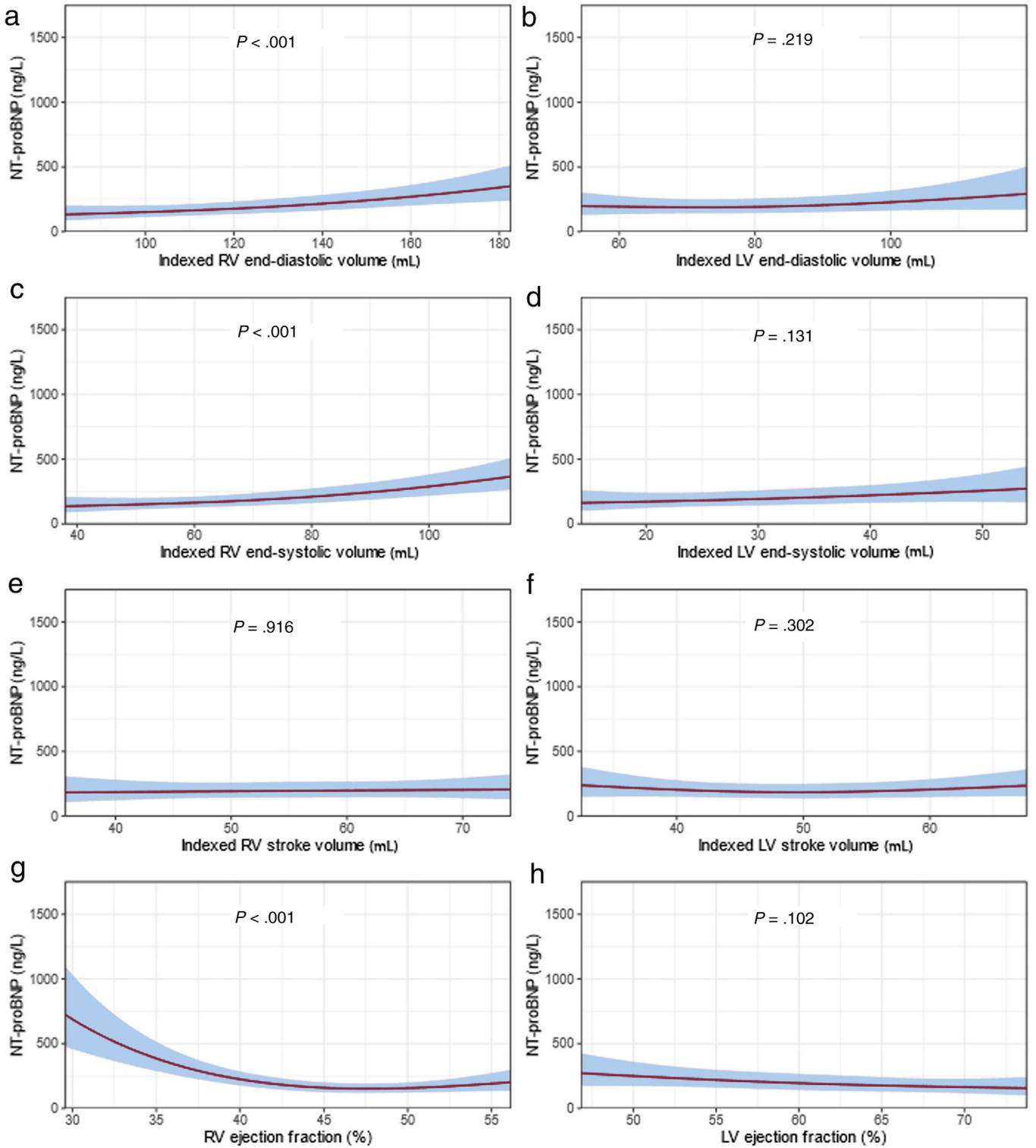
Model	c-statistic	95%CI
Model I NT-proBNP adjusted for age and sex	0.71	0.58-0.83
Model II RV EF adjusted for age and sex	0.72	0.59-0.84
Model III Predicted peak VO <sub>2</sub> adjusted for age and sex	0.71	0.59- 0.83

95%CI, 95% confidence interval; NYHA, New York Heart Association; peak VO<sub>2</sub>, maximal predicted oxygen uptake; RVEF, right ventricular ejection fraction.

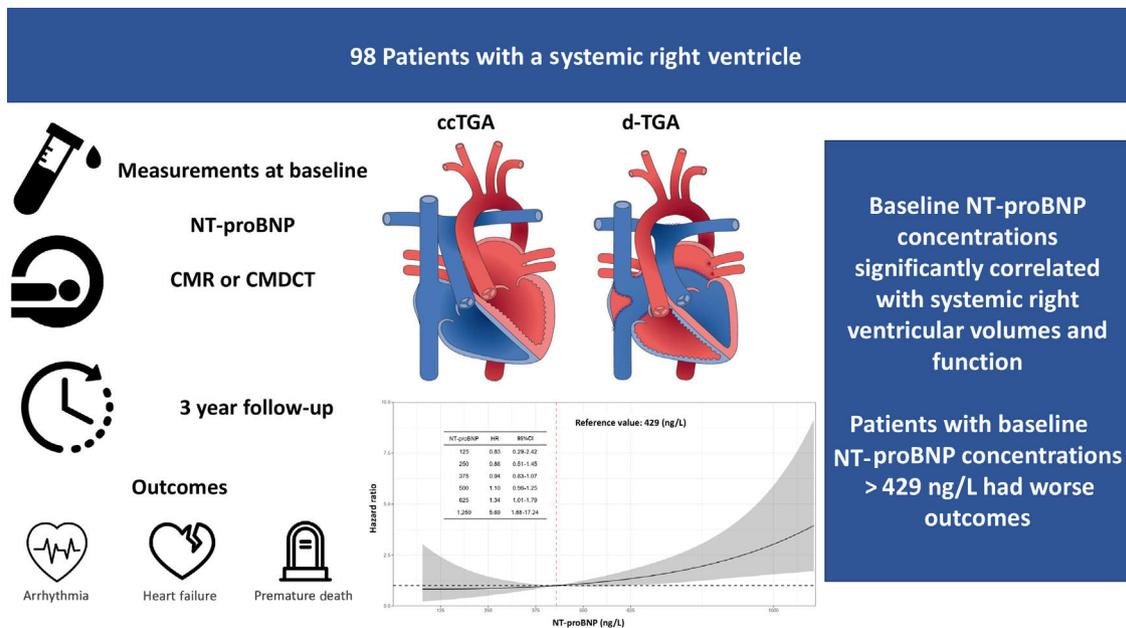
**Table 5**  
Added prognostic performance of different variables

Variables	c-statistic	95%CI
RVEF	0.69	0.56-0.82
RVEF + predicted peak VO <sub>2</sub>	0.70	0.56-0.84
RVEF + predicted peak VO <sub>2</sub> + NT-proBNP	0.71	0.57-0.85

95%CI, 95% confidence interval; NYHA, New York Heart Association; peak VO<sub>2</sub>, maximal predicted oxygen uptake; RVEF, right ventricular ejection fraction.



**Figure 3.** Correlation of NT-proBNP levels with variables regarding the right ventricular size and function. Multivariable linear regression models (age-, sex-, and creatinine adjusted) were fitted for baseline biventricular end-diastolic and end-systolic volumes, stroke volumes and ejection fraction assessed by either cardiac magnetic resonance or coronary multidetector computed tomography. There was a significant association between NT-proBNP levels and right ventricular volumes and function. LV, left ventricular; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular.



**Figure 4.** Central illustration. Analyzing NT-proBNP in patients with a systemic right ventricle. ccTGA, congenitally corrected transposition of the great arteries; d-TGA, dextro-transposition of the great arteries; 95%CI, 95% confidence interval; CMDCT, coronary multidetector computed tomography; CMR, cardiac magnetic resonance; HR, hazard ratio; NT pro-BNP, N-terminal pro-B-type natriuretic peptide.

22 patients (3%) had ccTGA.<sup>11</sup> Baggen et al.<sup>12</sup> also examined the prognostic value of serial NT-proBNP measurements in 602 ACHD patients, including 65 (11%) patients with d-TGA after atrial switch operation and 20 (3%) patients with ccTGA. They found an association between elevated NT-proBNP measurements and a combined endpoint of death, HF, hospital admission, arrhythmia, thromboembolic event, and cardiac intervention. However, neither study reported lesion-specific outcomes. A retrospective study of 87 patients after atrial switch operation found NT-proBNP to be the most reliable prognostic marker for mortality.<sup>18</sup> Another retrospective cohort study of 89 TGA patients with prior atrial switch operation showed that BNP had a high predictive value for distinguishing patients with and without critical cardiac events.<sup>13</sup>

The strength of our analysis is that measures of neurohormonal activation, ventricular volumes and function derived from CMR and CMDCT, as well as determinants of exercise capacity, were obtained from dedicated core labs, used in the SERVE trial.<sup>14,15</sup> While our analysis supports findings from previous studies regarding the prognostic value of NT-proBNP levels, the determined NT-proBNP cutoff > 429 ng/L derived from our data may serve as a clinical risk marker, although this should be confirmed in larger patient cohorts. Additionally, our data strongly support the prognostic importance of NT-proBNP levels, which are comparable to RVEF and peak oxygen uptake on exercise testing, and may therefore help in tailoring the frequency and type of follow-up studies in clinically stable patients.

### Clinical relevance of our findings

The role of NT-proBNP in patients with a systemic left ventricle has been thoroughly investigated, and its importance in the evaluation and management of these patients, for example in the setting of the emergency department, is undisputed.<sup>19</sup>

While the importance of NT-proBNP in predicting adverse events in ACHD is mentioned in the current guidelines, there is no specific recommendation for patients with an sRV.<sup>20</sup> Our study

showed that NT-proBNP may help to discriminate patients who are at risk of clinically relevant arrhythmia, HF, or death. Values of NT-proBNP > 429 ng/L may now be seen as a screening tool for closer follow-up or even as a turning point to consider starting HF medication in asymptomatic patients with an sRV. The correlations of NT-proBNP with sRV volumes and function points toward a comparable pathophysiological pathway to that seen in subaortic left ventricles. Furthermore, the prognostic accuracy of NT-proBNP alone was comparable to that of models using RVEF or predicted peak  $\text{VO}_2$ . Thus, this widely available and inexpensive biomarker may be seen as an alternative to other more costly, time-consuming, and less universally available tools.

### Limitations

Only 24 cardiac events occurred during our 3-year follow-up period. Of these, only 2 were deaths. Furthermore, the overall number of patients was low. Given the relatively small sample size of the cohort, the suggested cutpoint for NT-proBNP should be interpreted with caution. Studies with longer follow-ups and a larger number of patients are needed to assess the prognostic value of NT-proBNP with regard to mortality and to validate the cutpoint and assess its extrapolation and robustness. For the same reason, we were only able to adjust for some selected variables, and the effect of other variables on NT-proBNP levels and their prognostic value is still unknown. Additionally, Kaplan-Meier curves should be interpreted with caution due to potential residual confounding.

### CONCLUSIONS

Patients with higher concentrations of NT-proBNP were at a significantly higher risk of adverse events. The accuracy of NT-proBNP in predicting death, hospitalization for HF, and/or clinically relevant arrhythmia was comparable to that of the RVEF and

predicted peak  $VO_2$ . N-terminal natriuretic peptide significantly correlated with right ventricular volumes and function measured by CMR. NT-proBNP may be a reliable and widely available diagnostic tool for the risk stratification of patients with sRV. Our findings need to be validated with further studies including longer follow-up duration time.

#### WHAT IS KNOWN ABOUT THE TOPIC?

- NT-proBNP has gained increasing importance in the diagnosis of left ventricular dysfunction and HF among patients with acquired cardiovascular diseases.
- However, there is scarce evidence on the importance of NT-proBNP in risk prediction among patients with CHD and most published studies included mixed cohorts of patients with CHD or focused solely on patients with d-TGA after atrial switch operation.

#### WHAT DOES THIS STUDY ADD?

- This study shows that NT-proBNP may help discriminate patients with an sRV who are at risk for clinically relevant arrhythmia, HF, or death.
- Values of NT-proBNP > 429 ng/L may now be seen as a screening tool for closer follow-up or even as an indication to consider starting HF medication in asymptomatic patients with an sRV.
- The prognostic accuracy of NT-proBNP alone was comparable to that of models using RVEF or predicted peak  $VO_2$ .

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#### ETHICAL CONSIDERATIONS

This work was carried out in accordance with the protocol and the principles enunciated in the current version of the Declaration of Helsinki. All patients provided written informed consent. We did not specifically take possible sex/gender biases into consideration, as the effect/level of the biomarker should not be influenced by sex or gender.

#### STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

No artificial intelligence was used in the preparation of this paper.

#### AUTHORS' CONTRIBUTIONS

All authors meet the International Committee of Medical Journal Editors criteria for authorship of this article, take responsibility for the integrity of the work as a whole, were involved in drafting and critical review of the manuscript, and approved the final version for submission. All authors agree to be accountable for all aspects of the work and attest to the accuracy

and integrity of the work. F. Tran and F.J. Ruperti-Repilado (first authors) contributed equally to the study design, data interpretation, and manuscript preparation. C. Mueller and D. Tobler contributed to the drafting of the manuscript, the conception of the research, and the critical revision of the manuscript. F.J. Ruperti-Repilado, F. Tran, and P. Lopez Ayala contributed to the statistical analysis. M. Freese and K. Wustmann were responsible for biomarker and CMR analysis, respectively. J. Bouchardy, M. Greutmann and M. Scherzmann contributed to the conception and design of the study. J. Schwitter and C. Mueller were responsible for the core labs of CMR and biomarkers, respectively.

#### CONFLICTS OF INTEREST

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#### SUPPLEMENTARY DATA

Supplementary data associated with this article can be found in the online version, at <https://doi.org/10.1016/j.rec.2024.05.006>

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