Journal of the American Heart Association

ORIGINAL RESEARCH

External Validation of a Risk Score Model for Predicting Major Clinical Events in Adults After Atrial Switch

Mathieu Albertini, MD; Beatrice Santens, MD, PhD; Flavia Fusco, MD; Berardo Sarubbi, MD, PhD; Pastora Gallego, MD, PhD; Maria-Jose Rodriguez-Puras, MD, PhD; Katja Prokselj, MD, PhD; Robert Martijn Kauling, MD; Jolien Roos-Hesselink, MD, PhD; Fabien Labombarda, MD, PhD; Alexander Van De Bruaene, MD, PhD; Werner Budts, MD, PhD; Victor Waldmann, MD, PhD; Laurence Iserin, MD; Odilia Woudstra, MD; Berto Bouma, MD, PhD; Magalie Ladouceur, MD, PhD

BACKGROUND: A risk model has been proposed to provide a patient individualized estimation of risk for major clinical events (heart failure events, ventricular arrhythmia, all-cause mortality) in patients with transposition of the great arteries and atrial switch surgery. We aimed to externally validate the model.

METHODS AND RESULTS: A retrospective, multicentric, longitudinal cohort of 417 patients with transposition of the great arteries (median age, 24 years at baseline [interquartile range, 18–30]; 63% men) independent of the model development and internal validation cohort was studied. The performance of the prediction model in predicting risk at 5 years was assessed, and additional predictors of major clinical events were evaluated separately in our cohort. Twenty-five patients (5.9%) met the major clinical events end point within 5 years. Model validation showed good discrimination between high and low 5-year risk patients (Harrell C index of 0.73 [95% CI, 0.65–0.81]) but tended to overestimate this risk (calibration slope of 0.20 [95% CI, 0.03–0.36]). In our population, the strongest independent predictors of major clinical events were a history of heart failure and at least mild impairment of the subpulmonary left ventricle function.

CONCLUSIONS: We reported the first external validation of a major clinical events risk model in a large cohort of adults with transposition of the great arteries. The model allows for distinguishing patients at low risk from those at intermediate to high risk. Previous episode of heart failure and subpulmonary left ventricle dysfunction appear to be key markers in the prognosis of patients. Further optimizing risk models are needed to individualize risk predictions in patients with transposition of the great arteries.

Key Words: atrial switch ■ heart failure ■ risk score ■ transposition of the great arteries

The survival of patients with transposition of the great arteries (D-TGA) has improved dramatically after the introduction of the atrial switch (AtrS) procedures by Ake Senning and William Mustard from the mid-1960s to the mid-1980s, when the use of the AtrS procedure became commonplace. AtrS procedures involve the redirection of the blood flow in the atria; consequently, the morphological right ventricle supports the systemic circulation, whereas the left ventricle (LV) supports the pulmonary circulation. Although these procedures have significantly improved survival in the first 2 decades of life,[1] late complications

Correspondence to: Mathieu Albertini, MD, Adult Congenital Heart Disease Unit, Hôpital Européen Georges Pompidou, 20 rue Leblanc, 75015 Paris, France. Email: mathieu.albertini@aphp.fr

This article was sent to John L. Jefferies, MD, MPH, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Preprint posted on MedRxiv April 03, 2023. doi: https://doi.org/10.1101/2023.03.31.23286966.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.032174

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This is the first external validation of a risk model for major clinical events in patients with transposition of the great arteries after atrial switch, and the largest study emphasizing the importance of assessing subpulmonary left ventricle function in these patients.

What Are the Clinical Implications?

- This risk model helps determine the follow-up intensity and supports management decisions specifically for intermediate- and high-risk patients with a history of heart failure and at least mild subpulmonary left ventricle dysfunction, who have a poor prognosis and should be referred for consideration of advanced therapies.
- The subpulmonary left ventricle, which may be the forgotten chamber in these patients with a systemic right ventricle, should be carefully and regularly surveyed.

Nonstandard Abbreviations and Acronyms

AtrS	atrial switch
D-TGA	transposition of the great arteries
sRV	systemic right ventricular

are common, including systemic right ventricular (sRV) dysfunction, arrhythmias, heart failure (HF), and sudden cardiac death.[2–4] Survival at 40 years is estimated to be between 70% and 80%.[2,5,6] As a result, most patients today are approaching middle age and are at risk of serious cardiovascular complications. Assessing the prognosis of these patients has become essential to identify those at risk of major clinical events (HF, ventricular arrhythmias, death). This approach would allow a tailored risk prediction to support decisions on follow-up interval and therapeutic management. Patients in the high-risk category would likely benefit from referral to a quaternary center, where issues of cardiac support and heart transplantation would be discussed, given the poor evidence for the efficacy of medical therapy in congenital heart disease with sRV dysfunction.[7–9]

Recently, Woudstra et al provided a clinical risk model that estimates the risks of major events during the clinical course of patients with D-TGA and AtrS. The model provided a practical risk score based on 6 criteria (age >30 years, repair at >1 year of age, prior ventricular arrhythmia, moderate or greater right ventricular dysfunction, severe tricuspid regurgitation, and at least mild left ventricular dysfunction) stratifying patients into low-, intermediate-, and high-risk groups for HF, ventricular tachycardia, and death at 5 and 10 years.[10] Although this prediction model showed a good discriminatory ability in an internal validation analysis, an external validation in an independent population has not yet been performed. The aims of the current study were (1) to validate this prediction score in a large, independent, multicenter patient population and (2) to investigate new predictors of major clinical events, specifically death and heart transplantation.

METHODS

Population Study

Our study cohort comprised adult patients (>16 years of age) with D-TGA and AtrS from 7 participating European centers from the major adverse ventricular arrhythmias and related events (MAREs) registry (NCT03833843)[4] (Hôpital Européen Georges Pompidou, Paris; Erasmus Medical Center, Rotterdam; University Hospital Leuven, Leuven; Monaldi Hospital, Naples; Hospital Virgen del Rocio, Seville; University Medical Center Ljubljana, Ljubljana; Centre Hospitalo-Universitaire de Caen, Caen). This study adhered to the tenets of the Declaration of Helsinki. Local ethics approval was obtained from each collaborating center using a waiver of informed consent for retrospective, anonymized data (NCT03833843). The data will not be made available to other researchers to reproduce the results or replicate the procedures.

The included patients were evaluated between January 2000 and December 2018. We excluded patients with missing data from the calculation of the major clinical event score and those with <3 years of follow-up.[10] This cohort was independent of the major clinical event score of the development cohort.[10]

Patients were followed from their first visit to the hospital until December 2019 or the date of the primary outcome. Patient medical records were reviewed to collect demographic information and medical and surgical details.

The potential risk factors for clinical events with D-TGA after AtrS corresponded to those identified in the risk prediction score developed by Woudstra et al[10] and are listed in Table 1. Moreover, additional predictors selected from a literature review were assessed (Table S1).[2,4,6,10–26] Complex D-TGA was defined as D-TGA associated with ventricular septal defect, left ventricular outflow tract obstruction, and/or aortic coarctation. Associated pulmonary arterial hypertension was noted in the presence of Eisenmenger syndrome or when precapillary pulmonary hypertension was invasively confirmed according to the European Society of Cardiology (ESC) guidelines (mean pulmonary arterial

Table 1. Major Clinical Event Score Developed by Woudstra et al[10]

Criteria	Score points
Age >30 y	1
Repair at >1 y	1.5
Prior ventricular arrhythmia	1
≥Moderate RV dysfunction	1
Severe tricuspid regurgitation	1.5
≥Mild LV dysfunction	1.5

A risk score between 0 and 2 corresponded to the low-risk group, with a predicted 5-year risk <5%, a score between 2.5 and 3.5 to the intermediate-risk group with a predicted risk of 5–20%, and a score between 4 and 7.5 to the high-risk group with a predicted risk >20%.

LV indicates left ventricle; and RV, right ventricle.

pressure >20 mm Hg, pulmonary artery wedge pressure ≤15 mm Hg, and pulmonary vascular resistance ≥3 Wood units (WU)).[27] The history of supraventricular arrhythmias encompassed all the types of supraventricular arrhythmias, including ectopic atrial tachycardia, atrioventricular nodal re-entry tachycardia, atrioventricular reciprocating tachycardia, intra-atrial re-entry tachycardia, atrial flutter, and atrial fibrillation. Rhythm abnormalities recorded by Holter ECG or pacemaker/implantable cardioverter-defibrillator monitoring immediately before or at baseline were classified as sustained (≥30 seconds) or nonsustained (<30 seconds) atrial or ventricular arrhythmias and conduction abnormalities with sinus nodal dysfunction and complete heart block.

The baseline was defined as the first visit to the adult congenital heart disease center during the study period, which included a clinical examination and 12-lead electrocardiography. An echocardiography was considered if it was performed by an experienced operator within 1 year before or after the baseline visit. Echocardiographic sRV function was visually graded by cardiologists at each participating center as normal, or mildly, moderately, or severely impaired.[28] The severity of tricuspid regurgitation was graded from absent/trivial to severe tricuspid regurgitation according to European guidelines.[28,29] Left ventricular outflow tract obstruction was considered to be moderate if the maximum left ventricular outflow tract gradient was >36 mm Hg or the maximum Doppler velocity was >3 m/s. The function of the morphological LV, positioned beneath the pulmonary artery in D-TGA, was assessed using multiple parameters (visually estimated left ventricular ejection fraction, fractional area change, and mitral annular excursion plane (MAPSE)) and divided into 4 groups (normal, mildly, moderately, or severely impaired) based on at least 2 parameters.[19] Brain natriuretic peptide (BNP) was considered if within 3 years before or after the date of inclusion. Due to missing values, BNP was not assessed as a predictive factor. Data were collected independently at the participating centers, and data integrity was guaranteed by each participating author. Informed consent was not required due to the retrospective study design.

Study Outcome

The primary end points were major clinical events defined by Woudstra et al. These included (1) HF events defined as hospitalization for HF, heart transplantation, ventricular assist device implantation, or HF as the cause of death; (2) ventricular arrhythmias; and (3) all-cause mortality. Adjudication of ventricular arrhythmia events was previously described in the MAREs registry (Ladouceur et al). They included sustained ventricular tachycardia, appropriate implantable cardioverter-defibrillator therapy, and sudden death. Because nonsustained ventricular tachycardia may be missed during follow-up, we did not include this event in the definition of primary end point.

The most recent follow-up status was obtained by reviewing clinical medical records or by telephone contact or consultation with the patient. Patients lost to follow-up were excluded from the study population.

Statistical Analysis

Variables were described as the mean±SD, median (interquartile range [IQR]), and numbers or percentages, as appropriate. Group comparisons were performed using a Student *t* test, Mann-Whitney test, or χ^2 test, as appropriate. Follow-up time was calculated as the time from baseline evaluation to the time of reaching the study end point. The Kaplan-Meier method was used to estimate the incidence of reaching the study's end point.

Missing Data

Predictive variables used in the risk score model were all available. The data were not missing >1% of the expected values, except for BNP, which was not evaluated as a predictor.

Validation of the Risk Prediction Score for Major Clinical Events

Follow-up was censored at 5 years, and the estimated 5-year risk of major events was calculated for each individual patient using the following equation:

$$P\,(5-\text{years major clinical events}) = 1-0.96559^{\exp\,(\text{prognostic index})}$$

where the prognostic index=score×0.9841.

The Harrell C index was used to measure how well the model discriminated between high-, intermediate- and low-risk patients (a value of 1 indicates perfect discrimination, whereas a value of 0.5 indicates no discrimination).[30,31] Bootstrapping was used to calculate

confidence intervals. The calibration slope was used to assess the degree of agreement between the observed and predicted risks for major clinical events (a value close to 1 indicates good overall agreement).[32] Model calibration was described graphically by stratifying patients into the 3 risk groups identified in the study by Woudstra et al.[10]

The association of the predictors with the composite primary outcome and individually with death and heart transplantation during the entire study period was further assessed using Cox proportional hazards. The proportionality of hazards was confirmed in each case by assessing the correlation between the scaled Schoenfeld residuals and time. All predictors with a univariate value <0.05 were included in the multivariate model, after which stepwise backward selection based on the Akaike information criterion allowed the determination of the best-fitting model. A separate analysis was performed to characterize patients with a reduced anatomic LV function. A *P* value<0.05 was considered statistically significant. Analyses were performed with SAS statistical software version 9.4 (SAS Institute, Cary, NC) and MedCalc (MedCalc Software, Ostend, Belgium).

RESULTS

Baseline Clinical Characteristics

Among 512 adult patients with AtrS, 417 fulfilled inclusion criteria and constituted our study population (Figure 1). Baseline characteristics are shown in Table 2. Compared with the Woudstra et al cohort, the European cohort was younger at baseline evaluation (median age, 24 years [IQR, 18–30] versus 28 [IQR, 24–36]; *P*<0.01), patients were more frequently operated on before 1 year of age (72% versus 47%, *P*<0.01), and sRV function was more commonly impaired (49% versus 23%, *P*<0.01). Differences in baseline characteristics are summarized in Table 2.

Clinical Outcomes During the Study Period

The median follow-up in this validation cohort was 11 years (IQR, 8–16; range, 3–19 years). Seventy-three (17.5%) patients reached the primary end point during the study period: 53 (13%) patients developed HF, 10 (2%) underwent heart transplantation, 21 (5%) experienced ventricular arrhythmia, and 15 (4%) died. No patients were implanted with a ventricular assist device as destination therapy. Causes of death were HF (7), sudden cardiac death (4), noncardiac death (2), and unknown (2). Median event-free survival of event-naive patients surviving into adulthood was 50 years (95% CI, 48–52), and median survival until death or heart transplantation of adults with D-TGA after atrial switch was 53 years (95% CI, 51–54). The 1-year and 5-year freedom from major clinical events was 96.8% (95% CI, 97.6–99.8) and 94.0% (95% CI, 91.7–96.3), respectively (Figure 2A).

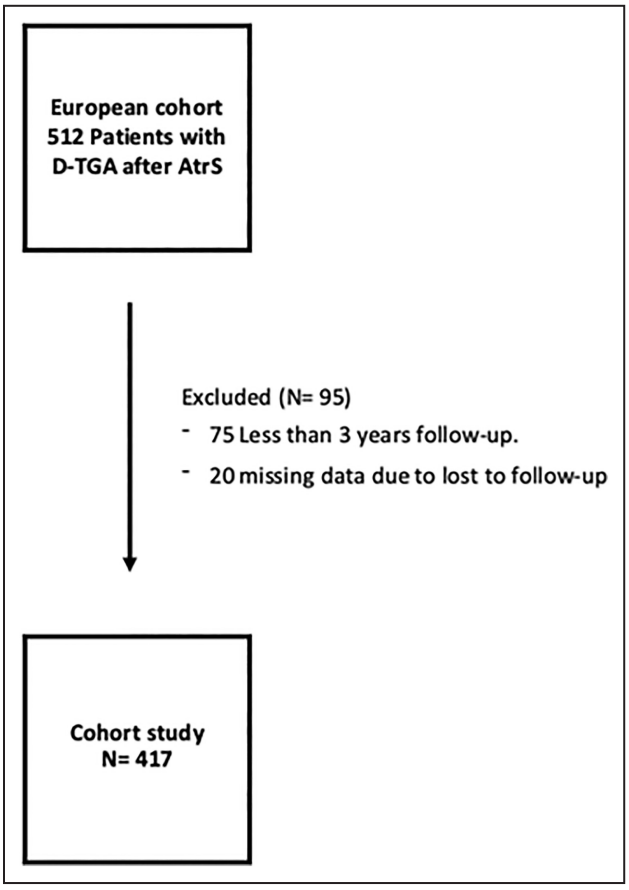

Figure 1. Flowchart of the study.
AtrS indicates atrial switch; and D-TGA, transposition of the great arteries.

According to the risk prediction model (Table 1), 298 (71%) patients had a low, 92 (22%) had an intermediate, and 27 (6%) had a high risk of a major clinical events. Baseline characteristics split by risk category are shown in Table S2. Figure 2B displays the Kaplan-Meier event-free survival plotted by years of follow and compared among low-, intermediate-, and high-risk group. Kaplan-Meier curves plotted by age are illustrated in Figure S1. Freedom from major clinical event survival was significantly reduced in the high- and intermediate-risk group compared with the low-risk group (log rank test, *P*<0.001). A 95% CI overlap was observed between the survival of the intermediate and high-risk group, and the risk of major clinical events was not significantly different between these 2 groups in the external validation population (Figures 2B and 3).

Table 2. Baseline Characteristics and Comparison With the Woudstra Cohort

Characteristics	Validation cohort (N=417)	Woudstra cohort (N=167)	*P* value
Age, y, median (IQR)	24 (18–29)	28 (24–36)	<0.01*
Age >30 y	102 (24%)	74 (44%)	<0.01*
Sex, men	261 (63%)	104 (62%)	0.86
Senning procedure	212 (51%)	66 (40%)	0.12
Complex D-TGA	112 (27%)	51 (31%)	0.60
Repair >1 y	115 (28%)	89 (53%)	<0.01*
Prior supraventricular tachycardia	140 (36%)	58 (35%)	0.88
Complete pregnancy	73 (18%)	NA	NA
Pulmonary arterial hypertension	26 (6%)	NA	NA
Prior heart failure	72 (17%)	8 (5%)	0.38
Prior ventricular arrhythmia	38 (9%)	13 (8%)	0.91
NYHA I	304 (73%)	123 (76%) (N=162)	0.39
NYHA ≥ II	112 (27%)	39 (24%) (N=162)	0.80
Moderate or greater RV dysfunction	205 (49%)	38 (24%) (N=157)	<0.01*
Severe tricuspid regurgitation	22 (5%)	12 (8%) (N=159)	0.73
Impairment of LV function	35 (8%)	8 (5%) (N=162)	0.77
Severe mitral regurgitation	1 (0,2%)	NA	NA
Moderate pulmonary stenosis	55 (13%)	NA	NA
Cardiac treatment	155 (37%)	NA	NA
β-Blockers	74 (18%)	28 (17%)	0.91
Diuretics	31 (7%)	14 (8%)	0.91
ACEi/ARA 2	107 (26%)	45 (27%)	0.90
Pacemaker	93 (22%)	41 (25%)	0.70
ICD for primary prevention	29 (7%)	5 (3%)	0.74

*Statistically significant. ACEi indicates angiotensin-converting enzyme inhibitor; ARA 2, angiotensin II receptor antagonist; D-TGA, transposition of the great arteries; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LV, left ventricle; NA, not available; NYHA, New York Heart Association; and RV, right ventricle.

Major Clinical Event Score Model Validation

The performance of the major clinical event score model in predicting risk at 5 years was assessed in 417 patients, with 25 events within 5 years of follow-up (Figure 4). Harrell C index was 0.73 (95% CI, 0.65–0.81). The calibration slope was 0.20 (95% CI, 0.03–0.36). Figure 4 illustrates the agreement between the predicted and observed 5-year cumulative proportion of major clinical events for each group of predicted risk.

Predictors of Major Clinical Events

We conducted a separate evaluation of predictors of major clinical events during the entire study follow-up period. Predictors independently associated with major clinical events are shown in Table 3. Those with a significant (*P*<0.05) univariate association with the primary outcome were fitted into a multivariate model. After stepwise backward selection based on AIC, the 7 factors included in the model were age at baseline, repair after 1 year of age, history of atrial arrhythmia, history of hospitalization for HF, New York Heart Association class ≥II, at least moderately sRV dysfunction, and at least mild subpulmonary LV dysfunction. History of hospitalization for HF (hazard ratio [HR], 29.9 [95% CI, 14.9–56.18]; *P*<0.01) and at least mildly impaired subpulmonary LV function (HR, 2.61 [95% CI, 1.46–4.65]; *P*<0.01) remained the strongest predictors of major clinical events in patients with D-TGA and AtrS. The absence of a history of HF and the absence of subpulmonary LV dysfunction were significantly associated with a low risk of major clinical events (HR, 0.038 [95% CI, 0.021–0.071]; *P*<0.01). The 5-year event-free survival was estimated to be 97.8% in this category of patients, allowing the identification of patients at low risk of adverse events (Figure S2). Conversely, the presence of a history of HF or even mild subpulmonary LV dysfunction significantly increased the risk of adverse events (HR, 25.90 [95% CI, 14.17–47.35]; *P*<0.01).

Assessment of predictors for all-cause death and heart transplantation are shown in Table S3.

Patients with subpulmonary LV dysfunction were characterized by a more severe sRV dysfunction compared with patients without LV dysfunction (odds ratio, 8.45 [95% CI, 3.38–20.63]; *P*<0.01). Moreover, symptoms, elevated BNP, and pulmonary hypertension

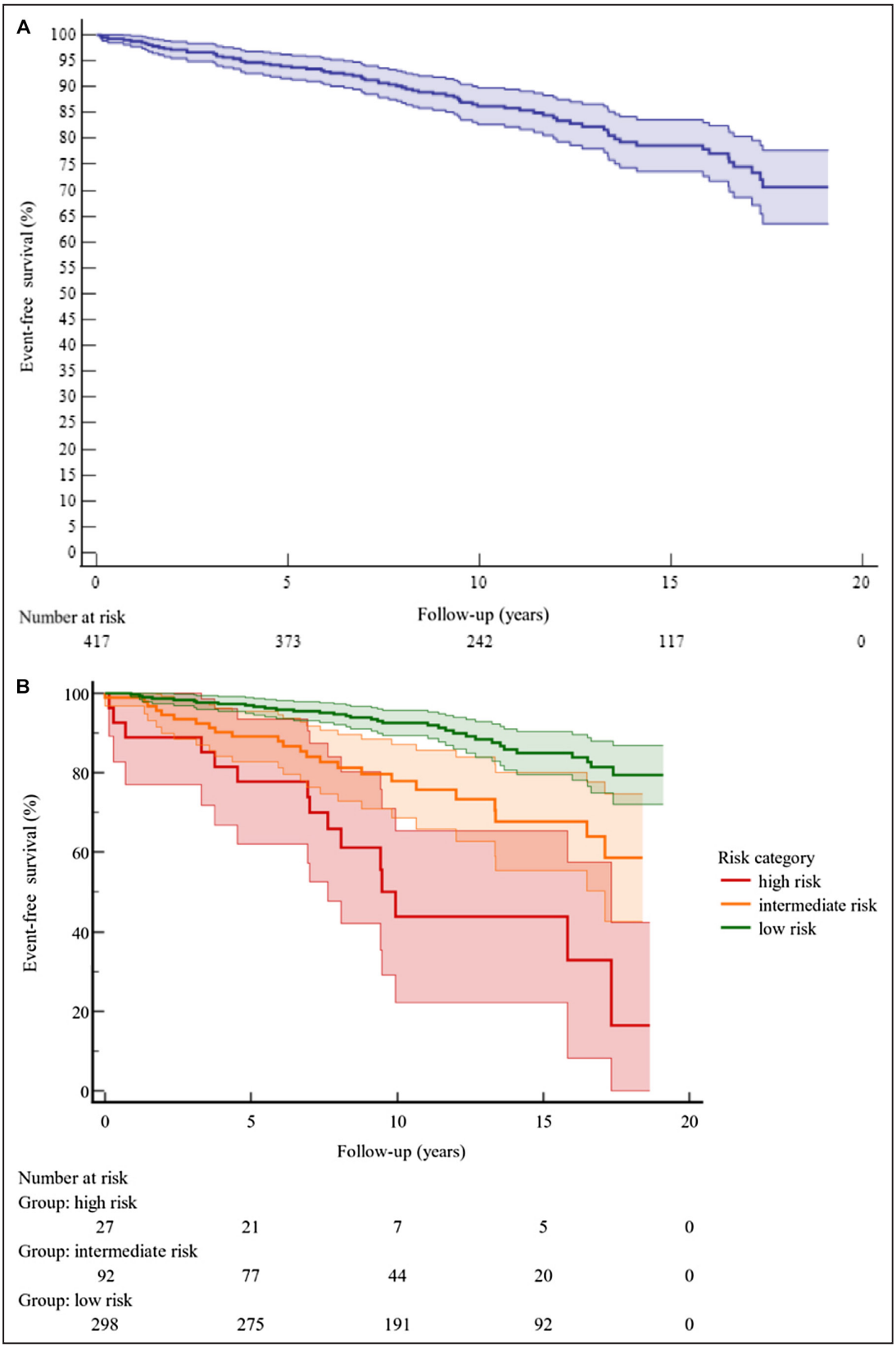

Figure 2. Observed event-free survival.
A, Kaplan-Meier curve showing survival free of major clinical events in the external validation cohort. Shaded area corresponds to 95% CIs. **B**, Kaplan-Meier curve showing survival free of major clinical events of the external validation cohort by risk category. Shaded areas correspond to 95% CIs.

were significantly more common in patients with subpulmonary LV dysfunction ($P<0.01$) (Table 4).

DISCUSSION

This is the first study to report the external validation of a risk score for major clinical events in patients followed after AtrS surgery from a large, multicenter, independent European cohort. This score, developed by Woudstra et al in 2021,[10] allowed stratification of risk for composite outcomes including HF, ventricular arrhythmias, sudden death, and death. This information on individual absolute risk could help determine the intensity of follow-up, and support management decisions on prevention and treatment of the prevailing complications. From our externally validated cohort, we showed that this score discriminated well between high-/intermediate- and low-risk patients at 5 years but tended to overestimate the absolute risk of major events. This indicates that the score demonstrates a high degree of sensitivity, enabling the identification of patients who are at low risk but still require regular clinical follow-up. Finally, such as in the study by Woudstra et al,[10] our results underscore the strong prognostic value of subpulmonary LV function in patients with sRV dysfunction.

Fewer major clinical events were observed in our cohort compared with the Woudstra et al study.[10] This may be explained by significant differences between our 2 populations. In our cohort, most patients underwent surgery before 1 year of age, and patients were younger at study entry, which may explain our lower rate of major clinical events. Although the incidence of HF did not differ between the 2 populations (14% in the European registry versus 18% in the Woudstra study), moderate to severe sRV dysfunction at baseline was more prevalent in the external validation population. These results should be interpreted with caution, because sRV function was assessed qualitatively by echocardiography, which is known to have a poor interobserver reproducibility.[28,33]

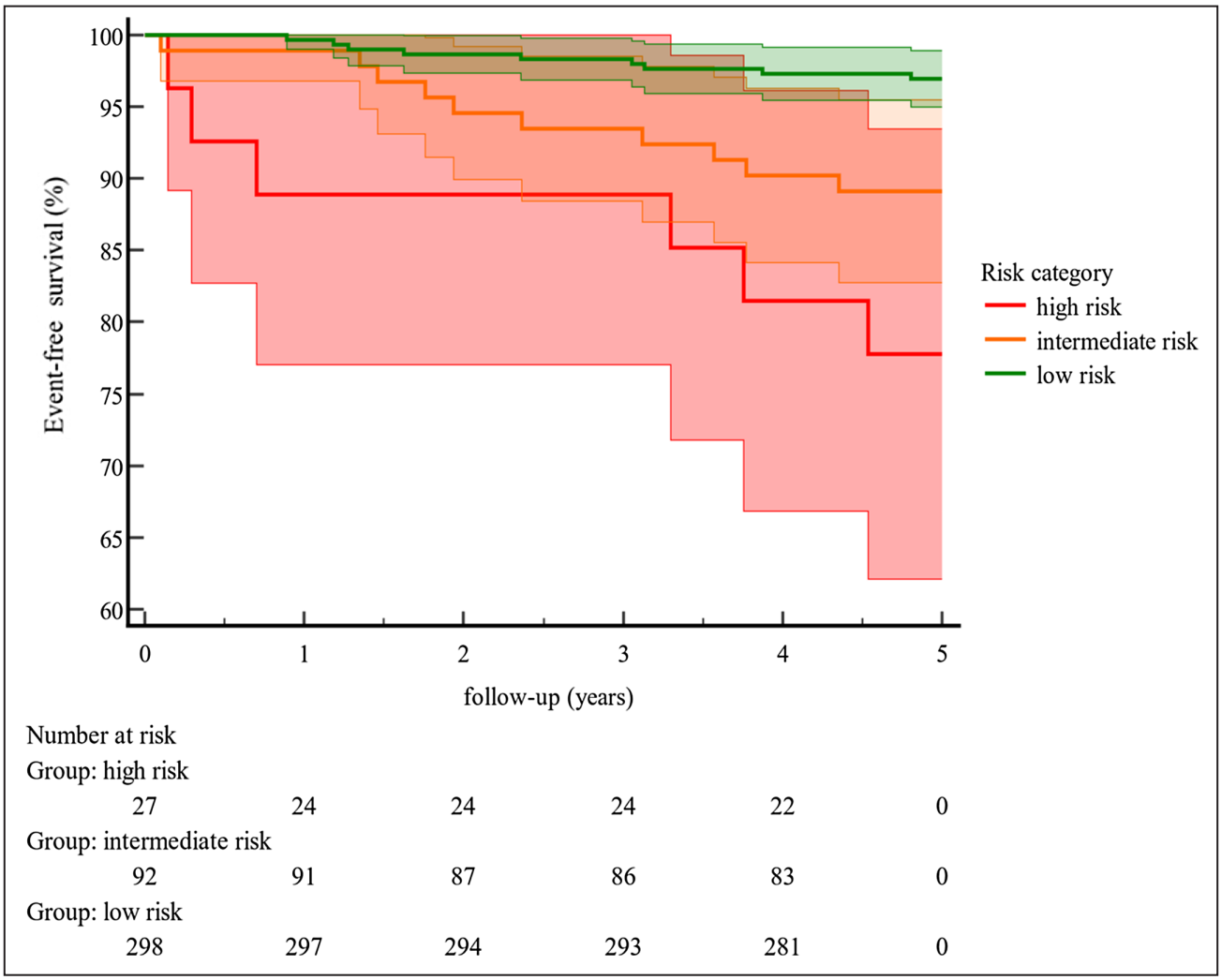

Figure 3. Kaplan-Meier curves showing survival free of major clinical events by risk category at 5 years.
Shaded areas correspond to 95% CIs.

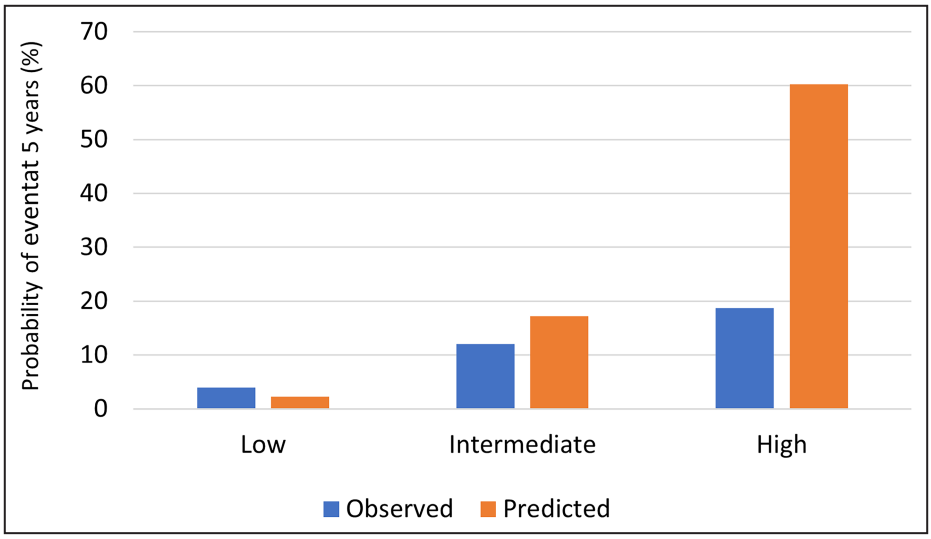

Figure 4. Comparison of observed and predicted 5-year risk of major clinical outcomes stratified by risk group.
Vertical bars represent model-based predicted (orange) and observed (blue) probability of events at 5 years (in percentages). The low-risk group corresponds to a predicted 5-year risk <5%, the intermediate-risk group to a predicted risk of 5% to 20%, and the high-risk group to a predicted risk >20%.

However, all echocardiographic examinations were performed by experienced cardiologists specialized in adult congenital heart disease, and the multicenter aspect of our study may have averaged the variability in the assessment of sRV function. Moreover, the rate of sRV dysfunction was similar to that previously reported in a large cohort of 1168 patients with AtrS surgery for D-TGA.[11] It seems that unlike LV dysfunction in acquired heart disease, sRV dysfunction is far from sufficient to predict the unfavorable evolution of patient with D-TGA and AtrS. A large number of patients have sRV dysfunction for several years without an episode of HF.[34]

Table 3. Baseline Characteristics of Patients With and Without Major Clinical Events

Clinical characteristic	Major clinical event (n=73)	No major clinical event (n=344)	Hazard ratio (95% CI)	*P* value
Age, y, median (IQR)	27 (20–32)	23 (18–29)	1.09 (1.05–1.12)	<0.01*
Sex, men	46 (63%)	215 (62%)	1.00 (0.62–1.61)	0.96
Aged >30 y	25 (34%)	77 (22%)	2.58 (1.57–4.23)	<0.01*
Age >1 y at AtrS	33 (45%)	82 (24%)	2.41 (1.52–3.82)	<0.01*
Mustard procedure	44 (60%)	161 (46%)	1.22 (0.86–1.96)	0.40
Complex anatomy	32 (44%)	80 (23%)	0.92 (0.49–1.72)	0.81
Symptoms (NYHA ≥ II)	30 (41%)	83 (24%)	2.71 (1.68–4.34)	<0.01*
Prior HF	56 (77%)	16 (5%)	30.51 (17.40–53.30)	<0.01*
Prior ventricular arrhythmia	12 (16%)	26 (8%)	1.76 (0.94–3.26)	0.07
Prior supraventricular tachycardia	46 (63%)	94 (27%)	3.52 (2.18–5.66)	<0.01*
PAH	13 (18%)	13 (4%)	3.43 (1.88–6.26)	<0.01*
Pacemaker	31 (42%)	62 (18%)	2.94 (1.84–4.68)	<0.01*
Moderate or greater RV dysfunction	49 (67%)	156 (45%)	2.05 (1.26–3,35)	<0.01*
Severe tricuspid regurgitation	11 (15%)	11 (3%)	3.47 (1.83–6.61)	<0.01*
LVOT obstruction	16 (22%)	39 (11%)	1.71 (0.98–2.97)	0.06
Impairment of LV function	18 (25%)	17 (5%)	4.88 (2.85–8.33)	<0.001*
Moderate or greater mitral regurgitation	3 (4%)	2 (0.6%)	4.78 (1.15–19.86)	0.03*

*Statistically significant. AtrS indicates atrial switch; HF, heart failure; IQR, interquartile range; LV, left ventricle; LVOT, left ventricular outflow tract; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; and RV, right ventricle.

Table 4. Comparison in Univariate Analysis of Patients With and Without Subpulmonary Left Ventricle Dysfunction

Variable	Patients with impairment of LV function (N=35)	Patients without LV dysfunction (N=382)	Odds ratio (95% CI)	*P* value
Normal RV function	0	46 (12%)	0.21 (0.01–1.32)	0.210
Mild impairment of sRV function	12 (34%)	154 (40%)	0.77 (0.34–1.67)	0.589
Moderate impairment of sRV function	11 (31%)	160 (42%)	0.64 (0.27–1.40)	0.282
Severe impairment of sRV function	12 (34%)	22 (6%)	8.45 (3.38–20.63)	<0.01*
PAH	10 (29%)	16 (4%)	9.05 (3.32–23.90)	<0.01*
NYHA ≥ II	18 (51%)	94 (25%)	3.23 (1.50–6.98)	<0.01*
BNP (N=265)	1584 (659.25–7278)	139.8 (78–259)	1.00 (1.00–1.00)	0.012*

*statistically significant. BNP indicates brain natriuretic peptide; LV, left ventricle; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; RV, right ventricle; and sRV, systemic right ventricular.

We found that the prognostic factors most associated with the occurrence of major clinical events were history of HF and subpulmonary LV dysfunction. Our findings underscore the value of considering the absence of both a history of HF and subpulmonary normal ventricular systolic function as robust indicators for identifying patients at low risk of adverse events.

Recently, several studies have demonstrated that adverse subpulmonary LV remodeling and systolic dysfunction are associated with worse clinical outcome in patients with sRV dysfunction.[19,22] Subpulmonary LV dysfunction is relatively common in patients with AtrS and severe systemic right ventricular dysfunction; in our cohort, one-third of patients with severe systemic right ventricle dysfunction had subpulmonary LV dysfunction. Our results suggest that LV dysfunction is a sensitive sign of failing sRV circulation and underscores the importance of its assessment in the routine evaluation of patients with sRVdysfunction.[19] Biventricular dysfunction in a patient with a sRV dysfunction is an important factor for heart transplant teams to consider in terms of time to listing.

The most obvious causes for subpulmonary LV dysfunction appear to be right ventricle/LV interdependence and pulmonary arterial hypertension (Table 4). Precapillary pulmonary hypertension appears to be a cause of subpulmonary LV dysfunction and is a recognized complication after AtrS, with an estimated prevalence of 6% to 7%.[35] Postcapillary pulmonary hypertension is related to atrial stiffness and dysfunction secondary to AtrS, tricuspid regurgitation, and sRV failure.[36] Particular attention should be paid to the subpulmonary LV after AtrS.

Our findings are complementary to those of the study by Woudstra et al.[10] The risk model allows identifying patients at high risk of major adverse events who require a close monitoring in tertiary centers offering therapeutic options for advanced HF such as mechanical circulatory support and heart transplantation. This approach should mainly concern patients with an intermediate- or high-risk score, and even more so if a history of HF or at least mildly impaired subpulmonary LV function is reported. The use of prognostic scores seems essential to stratify the risk of events, especially HF. Depending on the risk of HF, these patients may benefit from regular monitoring, cardiac rehabilitation programs, early detection and treatment of supraventricular rhythm disorders, and early HF treatment when the patient starts to be symptomatic.[22] Although medical therapy has failed to show preventive efficacy against HF events and death in several studies, screening of high-risk patients may allow future trials to show some benefit in this cohort.[7,8] However, current score models evaluate a composite end point, and predictors may vary depending on the event assessed, even if several factors overlap the risk of HF and sudden cardiac death in patients with sRV dysfunction. Recently, a sudden death prediction score for sRV (D-TGA after AtrS and congenitally corrected transposition) was developed, based on several criteria: age, HF, syncope, severe right ventricular dysfunction, moderate pulmonary stenosis, and QRS width.[4] Currently, there is no specific prognostic score for HF in this population, although it is the leading cause of death in adults with D-TGA and AtrS.[12]

The main limitation of our study is the retrospective design, supported by the low incidence of events in a rare cardiac condition. Notably, 20 (4%) patients were lost to follow-up, which may lead to selection bias. By conducting a large multicenter study, the bias inherent in the retrospective design could be more easily addressed. No predictors included in the risk prediction model were missing in the external validation data set. However, some factors known to be strong prognostic markers for clinical outcomes in sRV, such as BNP, cardiac magnetic resonance imaging, or maximun oxygen uptake (VO2 max) measurements, were missing in >25% of cases and were not assessed as predictive factors. Moreover, the major clinical event score developed by Woudstra et al[10] did not include risk factors such as a history of atrial arrhythmia, hospitalization for HF, or New York Heart Association class ≥II, which were determined from the separate evaluation of the MAREs population. Although sRV function was not retained in

the multivariate analysis, measurements of sRV function using cardiac magnetic resonance imaging may reveal a stronger relationship with adverse outcomes. These results may explain the overlapping confidence intervals between the intermediate-risk and high-risk groups in terms of the risk of major clinical events. The sensitivity of the risk model used may not have accurately differentiated between these groups, because of unaccounted for factors known to influence major clinical events. Further risk prediction models need to be developed by incorporating these markers.

CONCLUSIONS

We report the first external validation of a major clinical events risk model in a large patient population with D-TGA. The model discriminates well between patients at low 5-year risk of major clinical events and those at intermediate to high risk. Although it tends to overestimate the risk, it allows to identify patients who do not require active management. HF remains associated with poor outcome in D-TGA after AtrS. In patients with D-TGA after AtrS, subaortic right ventricle but also subpulmonary LV dysfunction are important prognostic markers. The development or optimization of new risk models is required, particularly to predict HF and individualize the management of subgroups of patients with D-TGA after AtrS.

ARTICLE INFORMATION

Received August 11, 2023; accepted March 27, 2024.

Affiliations

Université Paris Cité, Inserm, PARCC, France (M.A., V.W., L.I., M.L.); Centre de Référence des Malformations Cardiaques Congénitales Complexes, M3C, Paris, France (M.A., V.W., L.I., M.L.); Adult Congenital Heart Disease Unit, Hôpital Européen Georges Pompidou, APHP, Paris, France (M.A., V.W., L.I., M.L.); Division of Congenital and Structural Cardiology, University Hospitals Leuven, Leuven, Belgium (B.S., A.V.D.B, W.B.); Department of Cardiovascular Sciences, Catholic University Leuven, Leuven, Belgium (B.S., A.V.D., W.B.); Adult Congenital Heart Disease Unit, AORN dei Colli—Monaldi Hospital, Naples, Italy (F.F., B.S.); Adult Congenital Heart Disease Unit, Hospital Universitario Virgin del Rocio, Seville, Spain (P.G., M-J.R-P.); European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD Heart, Seville, Spain (P.G., M-J.R-P.); Department of Cardiology, University Medical Centre Ljubljana, Ljubljana, Slovenia (K.P.); Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia (K.P.); Department of Cardiology, Thoraxcenter, ErasmusMC, University Medical Center Rotterdam, Rotterdam, the Netherlands (R.M.K., J.R-H.); European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart-ERN GUARD Heart, Rotterdam, the Netherlands (R.M.K., J.R-H.); Department of Cardiology, CHU de Caen, Caen, France (F.L.); UNICAEN, UR PSIR 4650, Caen, France (F.L.); Department of Clinical and Experimental Cardiology, Heart Center, Amsterdam Cardiovascular Sciences, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, the Netherlands (O.W., B.B.); and Division of Cardiology, University Hospital Geneva, Geneva, Switzerland (M.L.).

Acknowledgments

The authors thank A. Boubrit, a French research technician from the Reference Center of Complex Congenital Heart Disease M3C, who helped with recording of data from Paris.

Sources of Funding

This work was supported by the Fédération Française de Cardiologie and the Assistance Publique des Hôpitaux de Paris.

Disclosures

None.

Supplemental Material

Data S1

REFERENCES

1. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, McGhie J, Bos E, Bogers AJ, Simoons ML. Decline in ventricular function and clinical condition after mustard repair for transposition of the great arteries (a prospective study of 22-29 years)*1. *Eur Heart J*. 2004;25:1264–1270. doi: 10.1016/j.ehj.2004.03.009
2. Cuypers JA, Eindhoven JA, Slager MA, Opić P, Utens EM, Helbing WA, Witsenburg M, van den Bosch AE, Ouhlous M, van Domburg RT, et al. The natural and unnatural history of the mustard procedure: long-term outcome up to 40 years. *Eur Heart J*. 2014;35:1666–1674. doi: 10.1093/eurheartj/ehu102
3. Vejlstrup N, Sørensen K, Mattsson E, Thilén U, Kvidal P, Johansson B, Iversen K, Søndergaard L, Dellborg M, Eriksson P. Long-term outcome of mustard/Senning correction for transposition of the great arteries in Sweden and Denmark. *Circulation*. 2015;132:633–638. doi: 10.1161/CIRCULATIONAHA.114.010770
4. Ladouceur M, Van De Bruaene A, Kauling R, Budts W, Roos-Hesselink J, Albert SV, Perez IS, Sarubbi B, Fusco F, Gallego P, et al. A new score for life-threatening ventricular arrhythmias and sudden cardiac death in adults with transposition of the great arteries and a systemic right ventricle. *Eur Heart J*. 2022;43:2685–2694. doi: 10.1093/eurheartj/ehac288
5. Couperus LE, Vliegen HW, Zandstra TE, Kiès P, Jongbloed MRM, Holman ER, Zeppenfeld K, Hazekamp MG, Schalij MJ, Scherptong RWC. Long-term outcome after atrial correction for transposition of the great arteries. *Heart*. 2019;105:790–796. doi: 10.1136/heartjnl-2018-313647
6. Dennis M, Kotchetkova I, Cordina R, Celermajer DS. Long-term follow-up of adults following the atrial switch operation for transposition of the great arteries – a contemporary cohort. *Heart Lung Circ*. 2018;27:1011–1017. doi: 10.1016/j.hlc.2017.10.008
7. Ladouceur M, Segura de la Cal T, Gaye B, Valentin E, Ly R, Iserin L, Legendre A, Mousseaux E, Li W, Rafiq I, et al. Effect of medical treatment on heart failure incidence in patients with a systemic right ventricle. *Heart*. 2021;107:1384–1389. doi: 10.1136/heartjnl-2020-318787
8. Zaragoza-Macias E, Zaidi AN, Dendukuri N, Marelli A. Medical therapy for systemic right ventricles: a systematic review (part 1) for the 2018 AHA/ACC guideline for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;139:e801–e813. doi: 10.1161/CIR.0000000000000604
9. VanderPluym CJ, Cedars A, Eghtesady P, Maxwell BG, Gelow JM, Burchill LJ, Maltais S, Koehl DA, Cantor RS, Blume ED. Outcomes following implantation of mechanical circulatory support in adults with congenital heart disease: an analysis of the interagency registry for mechanically assisted circulatory support (INTERMACS). *J Heart Lung Transplant*. 2018;37:89–99. doi: 10.1016/j.healun.2017.03.005
10. Woudstra OI, Zandstra TE, Vogel RF, van Dijk APJ, Vliegen HW, Kiès P, Jongbloed MRM, Egorova AD, Doevendans PAFM, Konings TC, et al. Clinical course long after atrial switch: a novel risk score for major clinical events. *J Am Heart Assoc*. 2021;10:e018565. doi: 10.1161/JAHA.120.018565
11. Broberg CS, van Dissel A, Minnier J, Aboulhosn J, Kauling RM, Ginde S, Krieger EV, Rodriguez F 3rd, Gupta T, Shah S, et al. Long-term outcomes after atrial switch operation for transposition of the great arteries. *J Am Coll Cardiol*. 2022;80:951–963. doi: 10.1016/j.jacc.2022.06.020
12. Jensen AS, Jørgensen TH, Christersson C, Nagy E, Sinisalo J, Furenäs E, Gjesdal O, Eriksson P, Vejlstrup N, Johansson B, et al. Cause-specific mortality in patients during long-term follow-up after atrial switch for transposition of the great arteries. *J Am Heart Assoc*. 2022;11:e023921. doi: 10.1161/JAHA.121.023921
13. Venkatesh P, Evans AT, Maw AM, Pashun RA, Patel A, Kim L, Feldman D, Minutello R, Wong SC, Stribling JC, et al. Predictors of late mortality

in D-transposition of the great arteries after atrial switch repair: systematic review and meta-analysis. *J Am Heart Assoc*. 2019;8:e012932. doi: 10.1161/JAHA.119.012932
14. Schwerzmann M, Salehian O, Harris L, Siu SC, Williams WG, Webb GD, Colman JM, Redington A, Silversides CK. Ventricular arrhythmias and sudden death in adults after a mustard operation for transposition of the great arteries. *Eur Heart J*. 2009;30:1873–1879. doi: 10.1093/eurheartj/ehp179
15. Wheeler M, Grigg L, Zentner D. Can we predict sudden cardiac death in long-term survivors of atrial switch surgery for transposition of the great arteries? *Congenit Heart Dis*. 2014;9:326–332. doi: 10.1111/chd.12145
16. Kammeraad JA, van Deurzen CH, Sreeram N, Bink-Boelkens MT, Ottenkamp J, Helbing WA, Lam J, Sobotka-Plojhar MA, Daniels O, Balaji S. Predictors of sudden cardiac death after mustard or Senning repair for transposition of the great arteries. *J Am Coll Cardiol*. 2004;44:1095–1102. doi: 10.1016/j.jacc.2004.05.073
17. McCombe A, Touma F, Jackson D, Canniffe C, Choudhary P, Pressley L, Tanous D, Robinson PJ, Celermajer D. Sudden cardiac death in adults with congenitally corrected transposition of the great arteries. *Open Heart*. 2016;3:e000407. doi: 10.1136/openhrt-2016-000407
18. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier LA, Viswanathan S, Chetaille P, Gordon E, Dore A, et al. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. *Circ Arrhythm Electrophysiol*. 2008;1:250–257. doi: 10.1161/CIRCEP.108.776120
19. Surkova E, Segura T, Dimopoulos K, Bispo D, Flick C, West C, Babu-Narayan SV, Senior R, Gatzoulis MA, Li W. Systolic dysfunction of the subpulmonary left ventricle is associated with the severity of heart failure in patients with a systemic right ventricle. *Int J Cardiol*. 2021;324:66–71. doi: 10.1016/j.ijcard.2020.09.051
20. Lewis MJ, Van Dissel A, Kochav J, DiLorenzo MP, Ginns J, Zemer-Wassercug N, Groenink M, Mulder B, Rosenbaum M. Cardiac MRI predictors of adverse outcomes in adults with a systemic right ventricle. *ESC Heart Fail*. 2022;9:834–841. doi: 10.1002/ehf2.13745
21. van der Bom T, Winter MM, Groenink M, Vliegen HW, Pieper PG, van Dijk AP, Sieswerda GT, Roos-Hesselink JW, Zwinderman AH, Mulder BJ, et al. Right ventricular end-diastolic volume combined with peak systolic blood pressure during exercise identifies patients at risk for complications in adults with a systemic right ventricle. *J Am Coll Cardiol*. 2013;62:926–936. doi: 10.1016/j.jacc.2013.06.026
22. Santens B, Helsen F, Van De Bruaene A, De Meester P, Budts AL, Troost E, Moons P, Claus P, Rega F, Bogaert J, et al. Adverse functional remodelling of the subpulmonary left ventricle in patients with a systemic right ventricle is associated with clinical outcome. *Eur Heart J Cardiovasc Imaging*. 2022;23:680–688. doi: 10.1093/ehjci/jeab086
23. Babu-Narayan SV, Goktekin O, Moon JC, Broberg CS, Pantely GA, Pennell DJ, Gatzoulis MA, Kilner PJ. Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries. *Circulation*. 2005;111:2091–2098. doi: 10.1161/01.CIR.0000162463.61626.3B
24. Rydman R, Gatzoulis MA, Ho SY, Ernst S, Swan L, Li W, Wong T, Sheppard M, McCarthy KP, Roughton M, et al. Systemic right ventricular fibrosis detected by cardiovascular magnetic resonance is associated with clinical outcome, mainly new-onset atrial arrhythmia, in patients after atrial redirection surgery for transposition of the great arteries. *Circ Cardiovasc Imaging*. 2015;8:e002628. doi: 10.1161/CIRCIMAGING.114.002628
25. Geenen LW, van Grootel RWJ, Akman K, Baggen VJM, Menting ME, Eindhoven JA, Cuypers JAAE, Boersma E, van den Bosch AE, Roos-Hesselink JW. Exploring the prognostic value of novel markers in adults with a systemic right ventricle. *J Am Heart Assoc*. 2019;8:e013745. doi: 10.1161/JAHA.119.013745
26. Haberger S, Hauser M, Braun SL, Schuster T, Ewert P, Nagdyman N, Hess J, Kaemmerer H. Prognostic value of plasma B-type natriuretic peptide in the long-term follow-up of patients with transposition of the great arteries with morphologic right systemic ventricle after atrial switch operation. *Circ J off J Jpn Circ Soc*. 2015;79:2677–2681. doi: 10.1253/circj.CJ-15-0348
27. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, Lung B, Kluin J, Lang IM, Meijboom F, et al. 2020 ESC guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42:563–645. doi: 10.1093/eurheartj/ehaa554
28. Li W, West C, McGhie J, van den Bosch AE, Babu-Narayan SV, Meijboom F, Mongeon FP, Khairy P, Kimball TR, Beauchesne LM, et al. Consensus recommendations for echocardiography in adults with congenital heart defects from the International Society of Adult Congenital Heart Disease (ISACHD). *Int J Cardiol*. 2018;272:77–83. doi: 10.1016/j.ijcard.2018.07.058
29. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713. doi: 10.1016/j.echo.2010.05.010
30. Rahman MS, Ambler G, Choodari-Oskooei B, Omar RZ. Review and evaluation of performance measures for survival prediction models in external validation settings. *BMC Med Res Methodol*. 2017;17:60. doi: 10.1186/s12874-017-0336-2
31. Harrell FE, Califf RM, Pryor DB, Lee KL, Rosati RA. Evaluating the yield of medical tests. *JAMA*. 1982;247:2543–2546. doi: 10.1001/jama.1982.03320430047030
32. Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. *Eur Heart J*. 2014;35:1925–1931. doi: 10.1093/eurheartj/ehu207
33. Chaix MA, Dore A, Marcotte F, Shohoudi A, Labombarda F, Mercier LA, Proietti A, Ibrahim R, Asgar AW, Mondésert B, et al. Variability in the echocardiographic evaluation of the systemic right ventricle. *Can J Cardiol*. 2019;35:178–184. doi: 10.1016/j.cjca.2018.11.021
34. Andrade L, Carazo M, Wu F, Kim Y, Wilson W. Mechanisms for heart failure in systemic right ventricle. *Heart Fail Rev*. 2020;25:599–607. doi: 10.1007/s10741-019-09902-1
35. Ebenroth ES, Hurwitz RA, Cordes TM. Late onset of pulmonary hypertension after successful mustard surgery for d-transposition of the great arteries. *Am J Cardiol*. 2000;85:127–130. doi: 10.1016/S0002-9149(99)00625-6
36. Chaix MA, Dore A, Mercier LA, Mongeon FP, Marcotte F, Ibrahim R, Asgar AW, Shohoudi A, Labombarda F, Mondésert B, et al. Late onset postcapillary pulmonary hypertension in patients with transposition of the great arteries and mustard or senning baffles. *J Am Heart Assoc*. 2017;6:e006481. doi: 10.1161/JAHA.117.006481