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ABSTRACT

Background Systemic right ventricle (sRV) patients are at an increased risk of developing heart failure. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) could be a valuable treatment option. This study investigated the changes in ventricular function in sRV failure patients in the first year after starting SGLT2i.

Methods Adult sRV patients from the international, real-world ACHIEVE-SGLT2i registry were included if they had a clinical diagnosis of sRV failure, a transthoracic echocardiogram before starting SGLT2i, and at least one in the first year after starting available for analysis. The primary outcomes were changes in sRV global longitudinal strain (GLS) and fractional area change (FAC). Longitudinal changes were evaluated using linear mixed models.

Results Thirty-nine sRV failure patients (46±9.3 years old, 41% female) were included. Twenty-five (64%) had transposition of the great arteries after an atrial switch procedure and 14 (36%) had congenitally corrected transposition. sRV GLS improved significantly in the first 50 days (−1.4%-point per month, p<0.001) and stabilised afterwards (<0.1%-point per month, p=0.520). Though age had a significant overall negative effect on sRV GLS (0.1%-point per year of age, p=0.049), it did not influence the longitudinal changes after starting SGLT2i. sRV FAC also improved in the first 50 days (3.2%-point per month, p=0.002), after which sRV FAC deteriorated in patients with subpulmonary left ventricular pacing (−0.9%-point per month, p=0.012) while it stabilised in patients without pacing (0.1%-point per month, p=0.573). In the first 50 days, tricuspid annular plane systolic excursion also improved significantly in all patients (1.2 mm per month, p=0.006), and stabilised afterwards (p=0.721).

Conclusions SGLT2i therapy is associated with improvements in systolic ventricular function in sRV failure patients. Despite early improvement in sRV FAC, there was a negative longer term correlation with subpulmonary left ventricular pacing, potentially reflecting adverse effects of subpulmonary ventricular pacing on sRV function.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Systemic right ventricle (sRV) patients are at an increased risk of developing heart failure. There is a lack of evidence-based treatment options, but promising preliminary reports suggest that sodium-glucose cotransporter 2 inhibitors (SGLT2i) might be a valuable treatment option.

WHAT THIS STUDY ADDS

⇒ This real-world, international study demonstrates that SGLT2i treatment is associated with improvements in systolic ventricular function in sRV failure patients, with improvements in sRV global longitudinal strain and fractional area change.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study highlight the potential of SGLT2i for the treatment of sRV failure, although differences between patients emphasise the need for patient-tailored treatment strategies.

INTRODUCTION

Heart failure (HF) is the leading cause of morbidity and mortality in the adult congenital heart disease (ACHD) population, and there is a lack of robust evidence for pharmacological treatment options.[1–3] Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a novel group of drugs that substantially improve outcomes in conventional left ventricular HF across all ranges of ejection fraction, although the effects of SGLT2i on cardiac remodelling and ventricular function remain a topic of debate.[4]

Based on promising observational data, SGLT2i are increasingly considered a viable treatment option for patients with ACHD-related HF.[5] SGLT2i are safe and well-tolerated in ACHD patients, with early data suggesting that SGLT2i use is associated with reduced HF hospitalisation rates.[6] Systemic right ventricle (sRV) patients, including those with transposition of the great arteries (TGA) after an atrial switch procedure (Mustard or

Senning) and congenitally corrected TGA (ccTGA), have a morphological right ventricle (RV) in the subaortic position, exposed to systemic pressures. Due to lifelong pressure overload, sRV patients are at a particularly high risk of developing HF.[7 8] Evidence suggests that the RV shows a stronger fibrotic response than the left ventricle (LV) to volume overload, and a recent meta-analysis demonstrated that SGLT2i therapy reduces pulmonary artery pressure and improves RV performance in conventional HF patients with RV dysfunction.[9 10] The proposed antifibrotic effects of SGLT2i might be one of the mechanisms by which the pathologic remodelling seen in the sRV could be ameliorated.[11]

Literature on the efficacy of SGLT2i in the sRV failure population is scarce,[12–14] and the magnitude of benefit may vary depending on the unique morphological characteristics of sRV patients. This study investigates the longitudinal changes in biventricular function as assessed with transthoracic echocardiography (TTE) in sRV patients in the first year after initiation of SGLT2i.

METHODS

Study design and population

A retrospective cohort study was conducted in a subgroup of patients included in the international, real-world ACHIEVE-SGLT2i (Adult Congenital Heart disease International EValuation of the Effectiveness of SGLT2i) registry (NCT06932081). Adult sRV failure patients (≥18 years of age) with a biventricular circulation started on an SGLT2i were eligible for inclusion if they had a baseline TTE performed within 6 months before starting SGLT2i and at least one follow-up TTE between 6 weeks and 12 months after starting SGLT2i. Patients from the Center for Congenital Heart Disease Amsterdam-Leiden, location Leiden University Medical Center (LUMC, Leiden, the Netherlands) and the Scottish Adult Congenital Cardiac Service at the Golden Jubilee University National Hospital (GJNH, Glasgow, United Kingdom) were included, driven by the availability of raw TTE scans for reanalysis.

sRV failure was adjudicated based on the universal definition of HF, entailing a clinical syndrome with symptoms and/or signs of HF, combined with elevated baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) and/or objective evidence of pulmonic or systemic congestion.[15] The study was conducted in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[16]

Data collection and follow-up

All clinical data were retrieved retrospectively from the electronic patient files. TTEs obtained in an outpatient clinic setting as part of routine care, performed at varying intervals at physician's discretion, were included. TTEs obtained during hospitalisations or unplanned HF visits were excluded from analysis, as these were expected to reflect a state of (temporary) congestion, potentially introducing bias. All data were collected from the baseline visit and at each outpatient visit and/or hospitalisation until either: (1) 12-month follow-up, (2) the last date of data inclusion at the participating centre (if less than 12-month follow-up), (3) discontinuation of SGLT2i therapy, (4) any catheter or surgical intervention influencing the haemodynamic status, (5) loss to follow-up, or (6) death.

TTE analysis

All TTE exams were performed with commercially available ultrasound systems, and all images were retrieved for offline analysis with EchoPAC software (GE Healthcare, Chicago, Illinois, USA). RMLN performed the offline analyses, blinded to the patients' clinical status and supervised by two experienced European Association of Cardiovascular Imaging-certified ACHD imaging cardiologists (MVR and GRV). A dedicated comprehensive TTE analysis workflow was constructed as previously described, based on the consensus recommendations of the International Society of Adult Congenital Heart Disease.[17–19] The following parameters were evaluated: sRV global longitudinal strain (GLS, %), subpulmonary left ventricle (spLV) free wall strain (FWS, %), sRV and spLV fractional area change (FAC, %), tricuspid annular plane systolic excursion (TAPSE, mm), S' (cm/s), e' (cm/s), systemic atrioventricular valve (sAVV) inflow E and A velocity (cm/s), E/A ratio, E/e' ratio, and regurgitation grades. sRV GLS was measured with EchoPAC software, after manual delineation of the myocardium in the apical four-chamber view, including the interventricular septum. S' represented the peak systolic velocity, and e' the peak early diastolic velocity, both measured at the lateral tricuspid annulus of the sRV. Global systolic sRV and spLV function were classified into four categories based on GLS, FAC and qualitative visual function assessment.

Primary outcome measures

The primary outcome measures were the longitudinal changes in sRV GLS and FAC. The influence of the following covariates on the longitudinal changes in sRV GLS and FAC was investigated: age at start SGLT2i, sex (male or female), sRV anatomy, inclusion centre, presence of sinus rhythm, single-site spLV pacing, sAVV regurgitation grade (≤grade 2 vs ≥grade 3), systolic blood pressure, and escalation in HF pharmacotherapy. Escalation in HF pharmacotherapy was defined as the addition of one of the four pharmacological pillars or a switch from an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker to an angiotensin receptor-neprilysin inhibitor.

Secondary outcome measures

Longitudinal changes in TAPSE, S', spLV FWS, spLV FAC, E/e' ratio, and E/A ratio were assessed as secondary outcome measures. The influence of the prespecified covariates on these parameters was also evaluated.

Statistical analysis

All statistical analyses were performed with SPSS V.25 (IBM Corp, Armonk, New York, USA) and R Statistical Software (V.4.3.1; R Core Team 2023). Linear mixed models were constructed with the 'nlme' package (V.3.1.165; R Core Team 2024). For the descriptive analysis, normally distributed continuous data were displayed as mean (± SD), non-normally distributed continuous data were presented as median (Q1 to Q3), and categorical data were presented as numbers (%). Groups were compared with unpaired t-tests, Mann-Whitney U-tests, or Fisher's exact tests as appropriate.

Linear mixed models were used to evaluate the relation between the TTE parameters and time since start SGLT2i, as previously described.[20] Both linear and non-linear temporal relations were explored with random intercepts, random slopes, and piecewise linear splines to model non-linear changes. Different correlation and variance structures were tested. The best fitting models were selected based on the Akaike information criterion (AIC)/Bayesian information criterion (BIC) or the likelihood ratio test if appropriate. Preference was given to the BIC because model parsimony was prioritised over the ability to predict future observations. Categorical

Table 1 Baseline characteristics

	All (n=39)	ccTGA (n=14)	TGA atrial switch (n=25)	P value
Age, years	46.0±9.3	46.9±12.5	45.6±7.2	0.726
Sex, female	16 (41.0)	5 (35.7)	11 (44)	0.740
Inclusion centre, GJNH	22 (56.3)	7 (50)	15 (60)	0.738
sAVV replacement	7 (17.9)	5 (35.7)	2 (8)	0.075
Subpulmonary outflow tract obstruction	2 (5.1)	1 (7.1)	1 (4)	1.000
HF diagnosis				
Systolic sRV failure	35 (89.7)	13 (92.9)	22 (88)	1.000
Biventricular systolic failure	3 (7.7)	1 (7.1)	2 (8)	1.000
Preserved systolic function	1 (2.6)	0	1 (4)	1.000
HF hospitalisation in the year preceding SGLT2i	5 (12.8)	3 (21.4)	2 (8)	0.329
HF pharmacotherapy				
ACEi/ARNI/ARB	37 (94.9)	12 (85.7)	25 (100)	0.123
ARNI	30 (76.9)	12 (85.7)	18 (72)	0.455
MRA	23 (59.0)	10 (71.4)	13 (52)	0.317
Beta-blocker	22 (56.4)	6 (42.9)	16 (64)	0.314
Diuretics	20 (51.3)	6 (42.9)	14 (56)	0.514
Clinical parameters				
Body mass index, kg/m^2	25.4±4.4	24.2±3.8	26.1±4.7	0.327
Heart rate, bpm	65(60–75)	70(64–76)	65(60–72)	0.102
Heart rhythm				
Sinus rhythm	21 (53.8)	7 (50)	14 (56)	0.750
Atrial rhythm	1 (2.6)	0	1 (4)	1.000
Atrial fibrillation/flutter	6 (15.4)	5 (35.7)	1 (4)	0.016
Atrial pacing	11 (28.2)	2 (14.3)	9 (36)	0.266
Ventricular pacing	13 (33.3)	6 (42.9)	7 (28)	0.482
Biventricular pacing	2 (5.1)	1 (7.1)	1 (4)	1.000
Systolic blood pressure, mm Hg	114±14	117±13	112±15	0.362
Diastolic blood pressure, mm Hg	71±12	71±14	70±11	0.789
NT-proBNP, ng/L	726.6 [328.8–1139.5)	819.6 [295.2–1691.8)	714.2 [329.5–1129.0)	0.790

Values are n (%), mean±SD, or median (Q1–Q3). Groups were compared with unpaired t-tests, Mann-Whitney U-tests, or the Fisher's exact tests as appropriate.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor; ccTGA, congenitally corrected transposition of the great arteries; GJNH, Golden Jubilee University National Hospital; HF, heart failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro–B-type natriuretic peptide; sAVV, systemic atrioventricular valve; sRV, systemic right ventricle; TGA, transposition of the great arteries.

covariates were included if there were at least 10 observations per category, to avoid model overfitting on sparse data. Both interaction and fixed effects of the covariates were tested. Residual analyses were performed to evaluate model fit. The predicted fixed effects for the models were visualised with the corresponding 95% CIs for the fixed-effect variance, and coefficients were presented as change per month for ease of interpretation. A two-sided p value ≤0.05 was considered statistically significant.

RESULTS

Of 58 sRV patients included in the ACHIEVE-SGLT2i registry by the LUMC and GJNH, 39 sRV failure patients initiated on an SGLT2i between April 2021 and May 2024 met the inclusion criteria and were included. The mean age was 46±9.3 years, 16 (41%) were female, dapagliflozin was prescribed in 34 (87.2%) and empagliflozin in 5 (12.8%). Fourteen patients (35.9%) had ccTGA, and 25 (64.1%) had TGA after an atrial switch procedure (80% Mustard and 20% Senning). Eleven patients (28.2%) had

Table 2 TTE parameters at baseline

	All (n=39)	ccTGA (n=14)	TGA atrial switch (n=25)	P value
sRV function				0.895
Good	1 (2.6)	0	1 (4)	
Mildly reduced	3 (7.7)	1 (7.1)	2 (8)	
Moderately reduced	13 (33.3)	5 (35.7)	8 (32)	
Severely reduced	22 (56.4)	8 (57.1)	14 (56)	
spLV function				0.370
Good	22 (56.4)	9 (64.3)	13 (52)	
Mildly reduced	15 (38.5)	4 (28.6)	11 (44)	
Moderately reduced	1 (2.6)	1 (7.1)	0	
Severely reduced	1 (2.6)	0	1 (4)	
sAVV regurgitation grade				0.084
Grade 1 or less	15 (38.5)	7 (50)	8 (32)	
Grade 2	8 (20.5)	0	8 (32)	
Grade 3	7 (17.9)	4 (28.6)	3 (12)	
Grade 4	9 (23.1)	3 (21.4)	6 (24)	
spAVV regurgitation grade				0.244
Grade 1 or less	31 (81.6)	9 (64.3)	22 (91.7)	
Grade 2	3 (7.9)	2 (14.3)	1 (4.2)	
Grade 3	3 (7.9)	2 (14.3)	1 (4.2)	
Grade 4	1 (2.6)	1 (7.1)	0	
sRV function				
sRV GLS (%)	−10.4±3.8	−10.3±5.1	−10.4±2.9	0.932
sRV FAC (%)	20.6±7.5	21.1±8.7	20.3±7.0	0.741
TAPSE (mm)	10.2±3.2	10.9±3.8	9.7±2.9	0.246
S' (cm/s)	6(5–8)	8 (6.3–9)	5.5 (5–6.5)	0.025
Diastolic function				
E/A ratio	1.8±0.7	1.7±0.2	1.9±0.9	0.714
E/e' ratio	9.3±3.8	6.9±1.7	11.0±4.0	0.038
spLV function				
spLV FWS (%)	−20.1±7.3	−24.9±5.6	−17.3±6.7	0.001
spLV FAC (%)	46.1±11.8	47±9.9	45.6±12.9	0.750

Values are n (%), mean±SD, or median (Q1–Q3). Groups were compared with unpaired t-tests, Mann-Whitney U tests or the Fisher's exact tests as appropriate.
ccTGA, congenitally corrected transposition of the great arteries; FAC, fractional area change; FWS, free wall strain; GLS, global longitudinal strain; sAVV, systemic atrioventricular valve; spAVV, subpulmonary atrioventricular valve; spLV, subpulmonary left ventricle; sRV, systemic right ventricle; TAPSE, tricuspid annular plane systolic excursion; TGA, transposition of the great arteries.

single-site spLV pacing, and atrial fibrillation/flutter was more commonly present in ccTGA patients than in TGA atrial switch patients at baseline (35.7% vs 4%, p=0.016) (table 1).

In total, 97 TTEs were available for analysis. Patients had a median of 1 (1 to 2) follow-up TTEs over a median echocardiographic follow-up duration of 5.8 (3.2 to 11.0) months. There was no significant difference in follow-up duration between ccTGA and TGA atrial switch patients (5.7 (2.8 to 11.3) vs 5.9 (3.4 to 10.8) months, p=0.966). Patients with ccTGA had a significantly higher S' (8 (6.3 to 9) vs 5.5 (5 to 6.5) cm/s, p=0.025) and a better spLV FWS (−24.9±5.6% vs −17.3±6.7%, p=0.001) at baseline than TGA atrial switch patients (table 2).

Primary outcome measures

A non-linear relation between sRV GLS and time was observed. sRV GLS showed a significant improvement

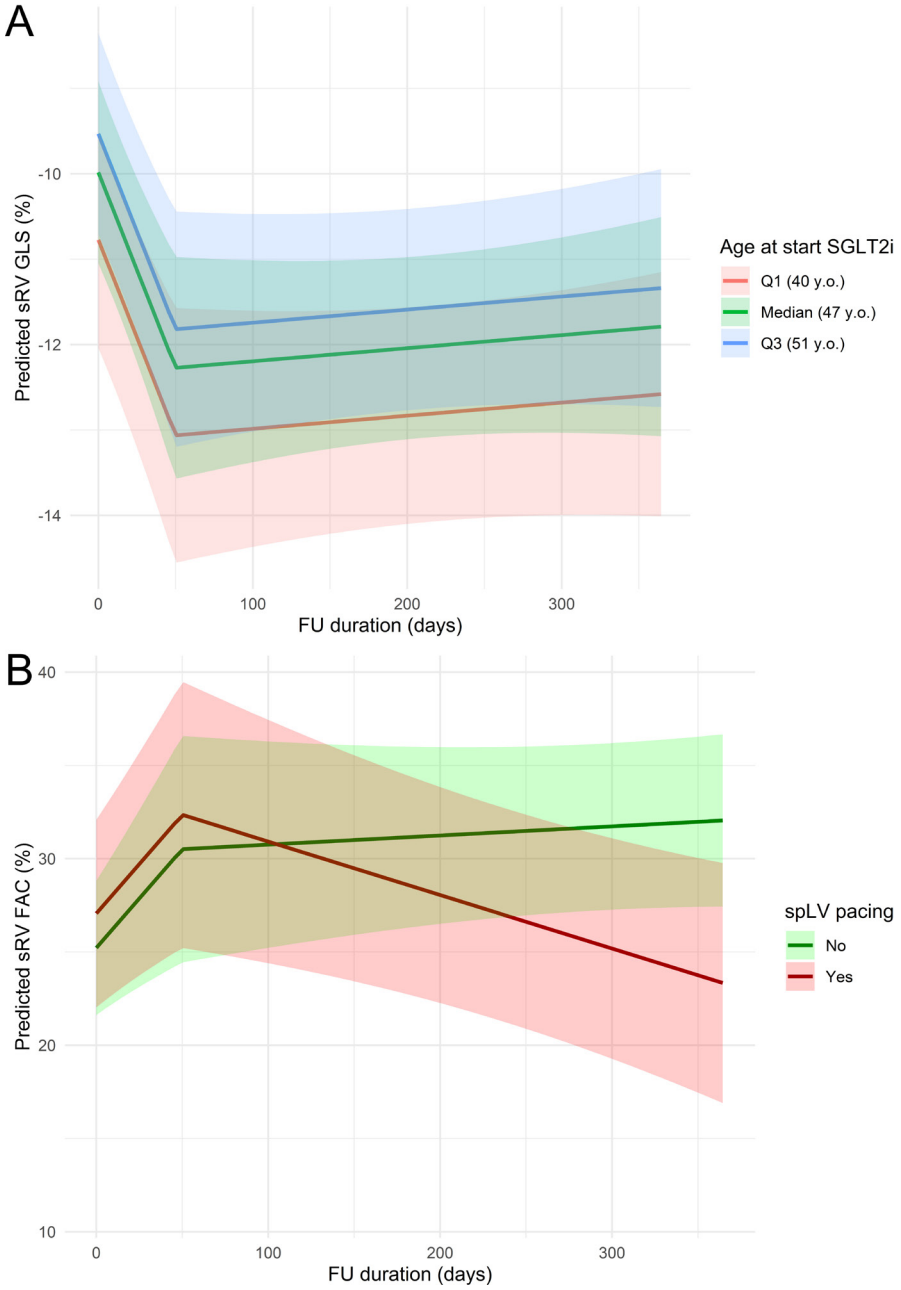

Figure 1 Changes in sRV GLS and FAC after starting SGLT2i. (A) Predicted longitudinal change in sRV GLS with 95% CIs. There is a significant improvement in the first 50 days after starting SGLT2i (−1.4%-point per month, p<0.001) and subsequent stabilisation (p=0.520). There was a significant negative effect of age (−0.1%-point per year of age, p=0.049), but age did not influence the temporal changes after starting SGLT2i. (B) Predicted longitudinal change in sRV FAC. There is a similar initial improvement in the first 50 days (3.2%-point per month, p=0.002), followed by a significant deterioration in patients with single-site spLV pacing (−0.9%-point per month, p=0.012). In contrast, patients without spLV pacing remained stable (p=0.573). FAC, fractional area change; FU, follow-up; GLS, global longitudinal strain; SGLT2i, sodium-glucose cotransporter 2 inhibitor; spLV, subpulmonary left ventricle; sRV, systemic right ventricle.

in the first 50 days after SGLT2i initiation (−1.4%-point per month, p<0.001) and stabilised afterward (p=0.520). Although older patients had a worse sRV GLS (intercept 0.1%-point per year of age, p=0.049), age at SGLT2i commencement did not influence the temporal changes (figure 1A).

A similar temporal effect was observed for sRV FAC, significantly improving in the first 50 days (3.2%-point per month, p=0.002). After this improvement, patients with single-site spLV pacing had a significant deterioration in sRV FAC (−0.9%-point per month, p=0.012). In contrast, patients without spLV pacing remained stable (p=0.573) (figure 1B). The other covariates did not significantly influence the sRV GLS and FAC changes after starting SGLT2i. Outputs and characteristics of all models are presented in online supplemental tables 1 and 2.

Secondary outcome measures

In the first 50 days, there was a significant improvement in TAPSE (1.2 mm per month, p=0.006), after

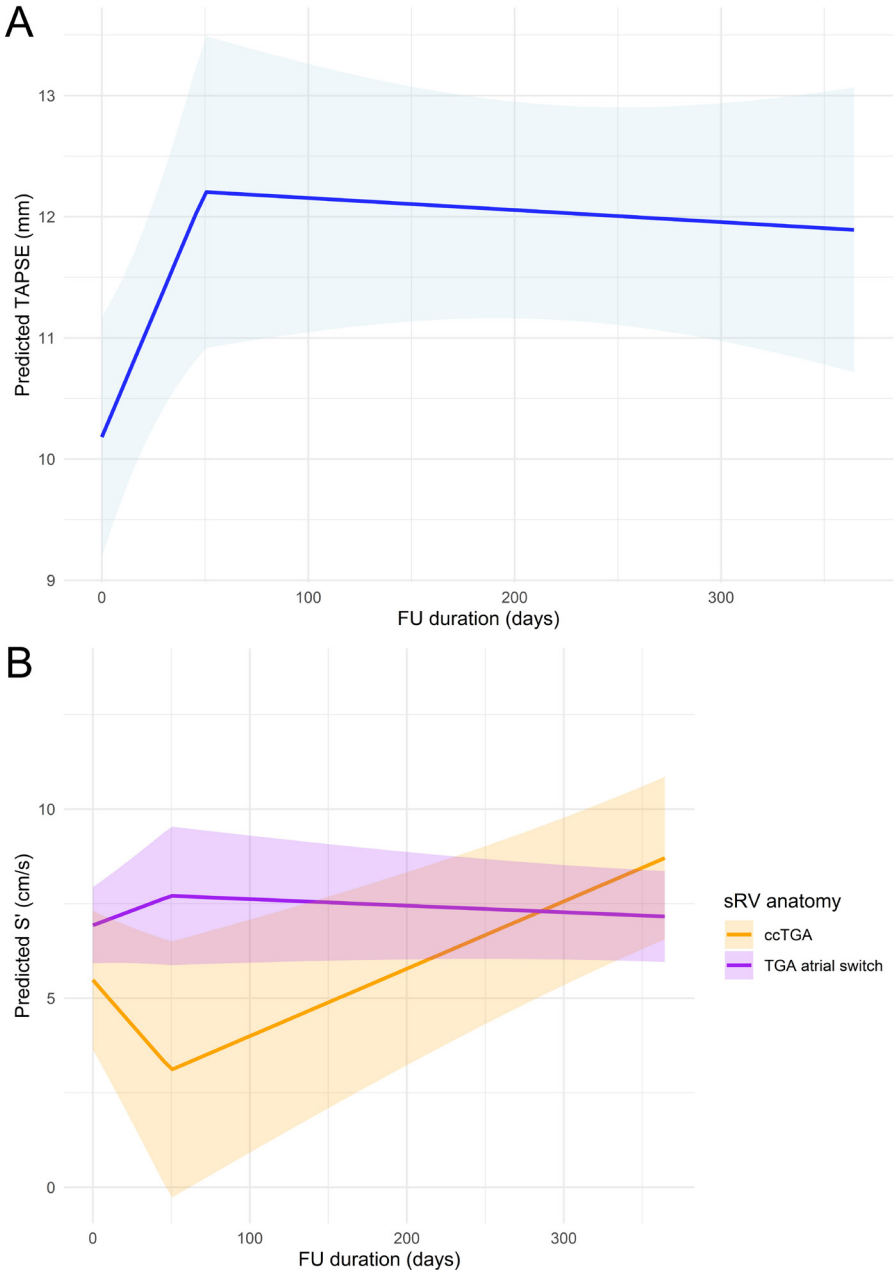

Figure 2 Changes in TAPSE and S' after starting SGLT2i. (A) Predicted longitudinal change in TAPSE with 95% CIs. A significant improvement can be appreciated in the first 50 days (1.2 mm per month, p=0.006). After 50 days, this was no longer significant (p=0.721). No covariates contributed significantly to the model. (B) Predicted change in S' over time. Patients with ccTGA had a significant decrease in S' in the first 50 days (−1.4 cm/s per month, p=0.014), followed by a significant improvement (0.5 cm/s per month, p<0.001). TGA atrial switch patients remained stable. (cc)TGA, (congenitally corrected) transposition of the great arteries; FU, follow-up; SGLT2i, sodium-glucose cotransporter 2 inhibitor; sRV, systemic right ventricle; TAPSE, tricuspid annular plane systolic excursion.

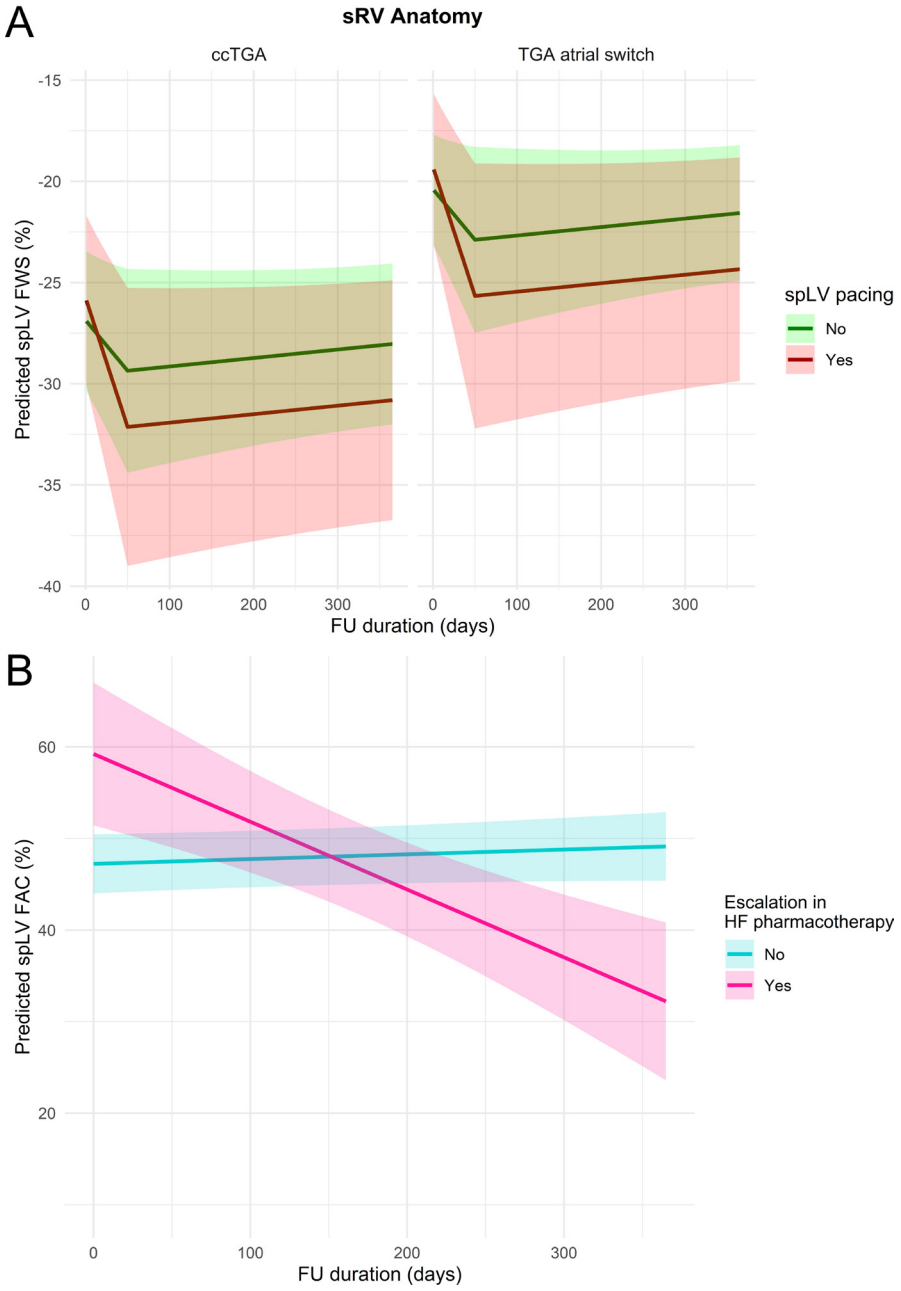

Figure 3 Changes in spLV FWS and FAC after starting SGLT2i. (A) Predicted longitudinal change in spLV FWS (%) with 95% CIs, faceted for sRV anatomical subgroups. There was a significant improvement in the first 50 days for patients without spLV pacing (–1.5%-point per month, p=0.048). This improvement was more pronounced in patients with spLV pacing (–3.9%-point per month, interaction p=0.046). After the first 50 days, there were no significant changes in both groups (p=0.368). Overall, ccTGA patients had a significantly better spLV FWS than TGA atrial switch patients (intercept 6.5%-point, p<0.001). (B) Predicted change in spLV FAC (%) over time. Patients with an escalation in HF pharmacotherapy during follow-up had a significantly higher spLV FAC at baseline (intercept 12.0%-point, p=0.003) and showed a significant deterioration (–2.3%-point per month, p<0.001) compared with patients without an escalation in pharmacotherapy (0.2%-point per month, p=0.237). (cc) TGA, (congenitally corrected) transposition of the great arteries; FAC, fractional area change; FU, follow-up; FWS, free-wall strain; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; spLV, subpulmonary left ventricle; sRV, systemic right ventricle.

which TAPSE stabilised (p=0.721) (figure 2A). There was a significant interaction between change in S' and sRV anatomical subgroups. S' decreased significantly in patients with ccTGA in the first 50 days (–1.4 cm/s per month, p=0.014), after which there was a significant improvement (0.5 cm/s per month, p<0.001). S' remained stable in TGA atrial switch patients (≤50 days; 0.5 cm/s per month, interaction p=0.005, >50 days; –0.1 cm/s, interaction p<0.001) (figure 2B).

Although TGA atrial switch patients had a significantly higher E/e' ratio than ccTGA patients at

baseline (6.9±1.7 vs 11.0±4.0, p=0.038), no significant temporal changes in diastolic function markers E/A or E/e' ratio were observed (online supplemental figures 1 and 2).

Patients with ccTGA had a significantly better overall spLV FWS than TGA atrial switch patients (intercept 6.5%-point, p<0.001) (figure 3A). spLV FWS improved significantly in the first 50 days in both groups. This improvement was more pronounced in patients with single-site spLV pacing (−3.9%-point per month, interaction p=0.046) than in patients without spLV pacing (−1.5%-point per month, p=0.048). After 50 days, the change in spLV FWS stabilised and a differential association with pacing status was no longer observed (p=0.368). Patients with an escalation in HF pharmacotherapy during follow-up had a significantly higher spLV FAC at baseline than patients who did not have an escalation in pharmacotherapy (intercept 12.0%, p=0.003) (figure 3B). Moreover, lack of escalation in HF pharmacotherapy after starting SGLT2i was associated with a stable spLV FAC over time (p=0.237), while an escalation in HF pharmacotherapy was associated with a deterioration of spLV FAC (−2.3%-point per month, p<0.001). A graphical abstract of the study is presented in figure 4.

DISCUSSION

This study demonstrates that SGLT2i therapy is associated with an improvement in systolic sRV and spLV function parameters in sRV failure patients during the first year of treatment.

sRV GLS improved significantly in the first 50 days after starting SGLT2i and remained stable afterwards. A relationship between age and sRV GLS has, to our knowledge, not been previously described, but lower LV GLS values have been reported with increasing age in the general population.[21] Our data indicate a similar relationship in the sRV cohort, with older patients having a worse overall sRV GLS, likely reflecting the cumulative detrimental effects of long-standing pressure overload on the morphological RV. This relationship might be more pronounced in sRV patients, who appear to suffer from premature multiorgan biological ageing processes compared with healthy peers.[22]

sRV FAC also improved significantly in the first 50 days, after which the change was modulated by the presence of single-site spLV pacing. Pacing-induced ventricular dysfunction is a well-documented phenomenon in sRV patients with chronic spLV pacing and has been associated with lower sRV FAC compared with non-paced controls.[23 24] The initial improvement in sRV FAC in both groups may be reflective of an early, beneficial diuretic effect of SGLT2i, while the following gradual deterioration seen in the spLV pacing group suggests that these patients do not have a similar beneficial response to SGLT2i over the longer term. These findings are in line with reports of pacing-induced sRV dyssynchrony contributing to sRV dysfunction and limiting the effects of therapeutic interventions, and this study reinforces the notion that we should remain critical of spLV pacing in sRV patients.[25] Cardiac resynchronisation therapy and conduction system pacing are gaining recognition as strategies to counter some of these adverse effects, and

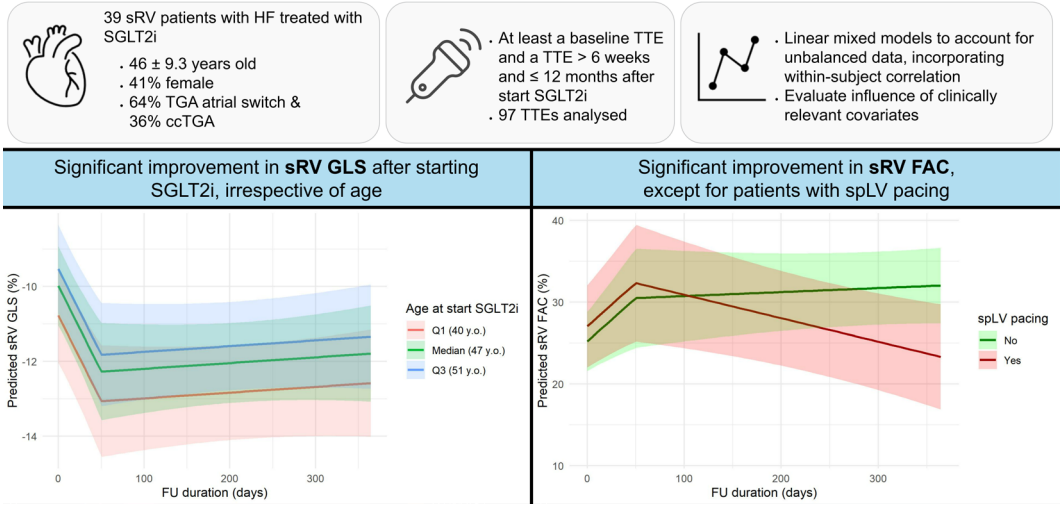

Figure 4 Effect of SGLT2i on ventricular function in sRV failure. This real-world evaluation of data from the ACHIEVE-SGLT2i registry demonstrated that SGLT2i are associated with improvements in systolic function in sRV failure patients. sRV GLS improved significantly in the first 50 days and stabilised afterwards. Age at start SGLT2i significantly influenced overall sRV GLS, as indicated by the separate lines for the first quartile (Q1), median and third quartile (Q3) of age. sRV FAC also improved significantly in the first 50 days. After 50 days, patients without spLV pacing remained stable, while patients with spLV pacing deteriorated. (cc)TGA, (congenitally corrected) transposition of the great arteries; FAC, fractional area change; FU, follow-up; GLS, global longitudinal strain; HF, heart failure; SGLT2i, sodium-glucose cotransporter 2 inhibitor; spLV, subpulmonary left ventricle; sRV, systemic right ventricle; TTE, transthoracic echocardiography.

while no patients received conduction system pacing, two patients received biventricular pacing in this study.[26]

Differences between ccTGA and TGA atrial switch patients

Baseline and temporal differences in S', E/e' ratio, and spLV FWS were found between ccTGA and TGA atrial switch patients, suggesting that atrial switch patients have worse systolic and diastolic function than ccTGA patients. The clinical implications of this remain uncertain.

Recent studies have revealed differences in the contraction patterns between ccTGA and TGA atrial switch patients.[27 28] While all contraction components contribute equally in ccTGA patients, atrial switch patients are most dependent on anteroposterior contraction, compensating for reduced longitudinal and radial contraction.[27 28] This might be due to embryological differences, and it is hypothesised that ccTGA patients are better equipped to handle the chronic sRV pressure overload as the RV functions in the systemic position immediately after birth, while atrial switch patients have to transition to an sRV circulation at a later stage with the atrial switch procedure creating rigid atrial baffles.[29] *Surkova et al* previously reported that the imbalance in contraction components in atrial switch patients might lead to an underestimation of sRV systolic function, as traditional TTE parameters focus on longitudinal contraction forces.[27] This could even be more pronounced in parameters assessed solely at the basal ventricular segment—such as S'—as relative basal hypokinesis has been described in TGA atrial switch compared with ccTGA patients.[28]

E/e' ratio, a marker of diastolic function, was significantly higher in atrial switch patients, suggesting worse diastolic function. While data on diastolic dysfunction in the sRV population are scarce and the value of 'E/e' is not well established in this population, these findings align with the hypothesis that the rigid atrial baffles in atrial switch patients contribute to reduced atrial function, exacerbating diastolic dysfunction.[30] Nonetheless, no temporal effect of SGLT2i on markers of diastolic function was observed. spLV FWS was improved in both groups but was consistently better in ccTGA patients, in line with previous work.[31]

These results should be interpreted cautiously as no significant differences between sRV anatomical subgroups were observed for our primary outcome measures. sRV GLS and FAC provide a more comprehensive evaluation of the myocardial contraction patterns. They have been extensively validated in the sRV population, correlate well with the gold standard cardiac magnetic resonance-derived sRV ejection fraction, and have a validated prognostic value.[19 32]

Concomitant HF medication changes

Patients who had an escalation in HF pharmacotherapy during follow-up showed a significant deterioration in spLV FAC over time compared with patients without intensification of their HF treatment, in whom the spLV FAC remained stable. Escalation in HF pharmacotherapy did not influence any of the other outcomes. The positive changes observed after starting SGLT2i are thus not likely to be attributable to the addition of other HF drugs during follow-up. The worsening in spLV FAC might be reflective of relative inertia of treatment initiation; therapeutic escalation was perhaps reactive instead of proactive in this patient cohort. This might at least in part be explained by the current ACHD guidelines, which do not provide specific recommendations for starting HF pharmacotherapy due to a lack of robust large-scale trials.[2 3] Importantly, a recent scientific statement from the American Heart Association does recommend careful consideration of initiating state-of-the-art medical therapy in children and adolescents with CHD from stage B HF onwards.[33] This is supported by a recent study demonstrating that ACHD patients on three or four HF drugs had better clinical outcomes and ventricular function than patients on just one or two, suggesting that a more proactive approach may be beneficial.[34]

SGLT2i for sRV failure in the current literature

Little is known about the effectiveness of SGLT2i for sRV failure. A recent study by *Fusco et al* is the only randomised study of SGLT2i in the sRV population to date.[12] Although not blinded nor placebo-controlled, 50 sRV patients were randomised to SGLT2i therapy or continuation of their present treatment. After 1 year, significant improvements in sRV FWS (+1.6%-point) and FAC (+3.5%-point) were reported in the SGLT2i group. Looking at population-level predictions of our sRV GLS model for a hypothetical 38-year-old patient (median age in *Fusco et al*), it predicts an improvement in sRV GLS of 1.8%-point from baseline to 1 year. In patients without spLV pacing, our sRV FAC model predicts an improvement of 6.8%-point from baseline to 1 year. This is more than the overall 3.5%-point improvement reported by *Fusco et al* but partially countered by the predicted 3.7%-point deterioration in patients with spLV pacing from baseline to 1 year in our study. It is important to acknowledge that in both studies, the vast majority were already receiving sacubitril/valsartan (92% in *Fusco et al*, 77% in our cohort), which has also been associated with significant improvements in systolic sRV function.[18 35] The optimal sequencing of these HF therapies and potential synergistic effects remain to be established. While these comparisons should be approached with caution, the effect sizes predicted by our models in a real-world setting seem to align with the randomised study results.

Limitations

This study is limited by the retrospective design, small sample size, and lack of a randomised control group. The study aimed to provide a comprehensive evaluation of the longitudinal echocardiographic changes in biventricular function after starting SGLT2i. Although the findings are in line with and provide

further mechanistic insight into the promising clinical findings reported for the sRV failure population, clinical outcomes and longitudinal biomarker surrogates such as natriuretic peptide levels were not included in this on-treatment analysis.[12 13 36] While escalation in HF pharmacotherapy was evaluated, detailed data on dose adjustments were unavailable. The influence of differences in HF pharmacotherapy at baseline on the changes after starting SGLT2i was also not evaluated. Intraobserver or interobserver variability was not evaluated given the previously published reproducibility of sRV strain, FAC, TAPSE and S' measurements in the sRV population by our study group and others.[12 19 37] ACHD research is often plagued by missing data, considerable individual-level variability, and a lack of well-structured prospective clinical trials. As such, follow-up intervals varied as they were scheduled at the discretion of the treating cardiologists. This study utilised mixed models to handle the unbalanced data effectively, and it provides a framework for real-world repeated measurements analysis in ACHD in the largest cohort of sRV patients on SGLT2i to date.

CONCLUSIONS

This real-world evaluation of data from the ACHIEVE-SGLT2i registry highlights the potential of SGLT2i therapy to improve systolic ventricular function in sRV failure patients in the first year of treatment. Significant improvement in sRV GLS was observed. Older patients exhibited worse overall sRV GLS but benefitted equally from treatment. A similar improvement was observed in sRV FAC, after which a differential effect based on chronic single-site spLV pacing was present, which might be reflective of the detrimental effects of spLV pacing on sRV function. These findings support the growing evidence for the use of SGLT2i in the sRV failure population, although the differences between patients emphasise the need for patient-tailored treatment strategies.

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REFERENCES

1 Brida M, Lovrić D, Griselli M, *et al*. Heart failure in adults with congenital heart disease. *Int J Cardiol* 2022;357:39–45.
2 Stout KK, Daniels CJ, Aboulhosn JA. Correction to: 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:e698–800.
3 Baumgartner H, De Backer J. The ESC Clinical Practice Guidelines for the Management of Adult Congenital Heart Disease 2020. *Eur Heart J* 2020;41:4153–4.
4 Vaduganathan M, Docherty KF, Claggett BL, *et al*. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet* 2022;400:757–67.
5 Das BB, Niu J. A Systematic Review and Meta-Analysis of the Safety and Efficacy of SGLT2 Inhibitors in Chronic Heart Failure in ACHD Patients. *Am J Cardiovasc Drugs* 2025;25:231–40.
6 Neijenhuis RML, MacDonald ST, Zemrak F, *et al*. Effect of Sodium-Glucose Cotransporter 2 Inhibitors in Adults With Congenital Heart Disease. *J Am Coll Cardiol* 2024;83:1403–14.
7 Arnaert S, De Meester P, Troost E, *et al*. Heart failure related to adult congenital heart disease: prevalence, outcome and risk factors. *ESC Heart Fail* 2021;8:2940–50.
8 Zaragoza-Macias E, Zaidi AN, Dendukuri N, *et al*. 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. *J Am Coll Cardiol* 2019;73:1564–78.
9 Das BB. Unlocking the Potential: Angiotensin Receptor Neprilysin and Sodium Glucose Co-Transporter 2 Inhibitors for Right Ventricle Dysfunction in Heart Failure. *Medicina (Kaunas)* 2024;60:1112.
10 Cinar T, Saylik F, Cicek V, *et al*. Effects of SGLT2 inhibitors on right ventricular function in heart failure patients: Updated meta-analysis of the current literature. *Kardiol Pol* 2024;82:416–22.
11 Lopaschuk GD, Verma S. Mechanisms of Cardiovascular Benefits of Sodium Glucose Co-Transporter 2 (SGLT2) Inhibitors: A State-of-the-Art Review. *JACC Basic Transl Sci* 2020;5:632–44.
12 Fusco F, Scognamiglio G, Abbate M, *et al*. Dapagliflozin in Patients With a Failing Systemic Right Ventricle: Results From the DAPA-SERVE Trial. *JACC Heart Fail* 2024;12:789–91.
13 Neijenhuis RML, Nederend M, Jongbloed MRM, *et al*. The potential of sodium-glucose cotransporter 2 inhibitors for the treatment of systemic right ventricular failure in adults with congenital heart disease. *Front Cardiovasc Med* 2023;10:1093201.
14 Egorova AD, Nederend M, Tops LF, *et al*. The first experience with sodium-glucose cotransporter 2 inhibitor for the treatment of systemic right ventricular failure. *ESC Heart Fail* 2022;9:2007–12.
15 Bozkurt B, Coats AJ, Tsutsui H, *et al*. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail* 2021;27:387–413.
16 Elm E von, Altman DG, Egger M, *et al*. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *BMJ* 2007;335:806–8.
17 Li W, West C, McGhie J, *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.
18 Nederend M, Kiès P, Regeer MV, *et al*. Tolerability and beneficial effects of sacubitril/valsartan on systemic right ventricular failure. *Heart* 2023;109:1525–32.
19 Zandstra TE, Jongbloed MRM, Widya RL, *et al*. Validation and Feasibility of Echocardiographic Assessment of Systemic Right Ventricular Function: Serial Correlation With MRI. *Front Cardiovasc Med* 2021;8:644193.
20 Neijenhuis RML, Regeer MV, Walker NL, *et al*. Echocardiographic Effects of Sodium-Glucose Cotransporter 2 Inhibitors in Single Ventricle Circulatory Failure. *International Journal of Cardiology Congenital Heart Disease* 2025;2025:100603.
21 Sugimoto T, Dulgheru R, Bernard A, *et al*. Echocardiographic reference ranges for normal left ventricular 2D strain: results from the EACVI NORRE study. *Eur Heart J Cardiovasc Imaging* 2017;18:833–40.
22 Tournoy TK, Moons P, Daelman B, *et al*. Biological Age in Congenital Heart Disease-Exploring the Ticking Clock. *J Cardiovasc Dev Dis* 2023;10:492.
23 Bevilacqua F, Pasqualin G, Ferrero P, *et al*. Overview of Long-Term Outcome in Adults with Systemic Right Ventricle and Transposition of the Great Arteries: A Review. *Diagnostics (Basel)* 2023;13:2205.
24 Yeo WT, Jarman JWE, Li W, *et al*. Adverse impact of chronic subpulmonary left ventricular pacing on systemic right ventricular function in patients with congenitally corrected transposition of the great arteries. *Int J Cardiol* 2014;171:184–91.
25 Nederend M, Jongbloed MRM, Kiès P, *et al*. Atrioventricular Block Necessitating Chronic Ventricular Pacing After Tricuspid Valve Surgery in Patients With a Systemic Right Ventricle: Long-Term Follow-Up. *Front Cardiovasc Med* 2022;9:870459.
26 Kharbanda RK, Moore JP, Taverne YJHJ, *et al*. Cardiac resynchronization therapy for the failing systemic right ventricle: A systematic review. *Int J Cardiol* 2020;318:74–81.
27 Surkova E, Kovács A, Lakatos BK, *et al*. Contraction patterns of the systemic right ventricle: a three-dimensional echocardiography study. *Eur Heart J Cardiovasc Imaging* 2022;23:1654–62.
28 Morcos M, Kilner PJ, Sahn DJ, *et al*. Comparison of systemic right ventricular function in transposition of the great arteries after atrial switch and congenitally corrected transposition of the great arteries. *Int J Cardiovasc Imaging* 2017;33:1993–2001.
29 Eindhoven JA, Menting ME, van den Bosch AE, *et al*. Quantitative assessment of systolic right ventricular function using myocardial deformation in patients with a systemic right ventricle. *Eur Heart J Cardiovasc Imaging* 2015;16:380–8.
30 Tan J-L, Prati D, Gatzoulis MA, *et al*. The right ventricular response to high afterload: comparison between atrial switch procedure, congenitally corrected transposition of the great arteries, and idiopathic pulmonary arterial hypertension. *Am Heart J* 2007;153:681–8.
31 Diller G-P, Radojevic J, Kempny A, *et al*. Systemic right ventricular longitudinal strain is reduced in adults with transposition of the great arteries, relates to subpulmonary ventricular function, and predicts adverse clinical outcome. *Am Heart J* 2012;163:859–66.
32 Woudstra OI, van Dissel AC, van der Bom T, *et al*. Myocardial Deformation in the Systemic Right Ventricle: Strain Imaging Improves Prediction of the Failing Heart. *Can J Cardiol* 2020;36:1525–33.
33 Amdani S, Conway J, George K, *et al*. Evaluation and Management of Chronic Heart Failure in Children and Adolescents With Congenital Heart Disease: A Scientific Statement From the American Heart Association. *Circulation* 2024;150:e33–50.
34 Bright C, Rizvi A, Ezekwueme F, *et al*. Impact of guideline directed medical therapy on myocardial function in adults with congenital heart disease. *Int J Cardiol* 2024;414:132413.
35 Fusco F, Scognamiglio G, Merola A, *et al*. Safety and Efficacy of Sacubitril/Valsartan in Patients With a Failing Systemic Right Ventricle: A Prospective Single-Center Study. *Circ Heart Fail* 2023;16:e009848.
36 Albertini M, Waldmann V, David P, *et al*. Safety and Efficacy of Dapagliflozin in Patients With Systemic Right Ventricular Dysfunction: DAPA-SRV Trial. *J Am Heart Assoc* 2025;14:e040302.
37 Pommier V, Bredy C, Abassi H, *et al*. Reliability of echocardiographic parameters of the systemic right ventricle systolic function: A prospective multicentre study. *International Journal of Cardiology Congenital Heart Disease* 2021;4:100139.