



Universiteit  
Leiden  
The Netherlands

## Effect of sodium-glucose cotransporter 2 inhibitors in adults with congenital heart disease

Neijenhuis, R.M.L.; Macdonald, S.T.; Zemrak, F.; Mertens, B.J.A.; Dinsdale, A.; Hunter, A.; ... ; Egorova, A.D.

### Citation

Neijenhuis, R. M. L., Macdonald, S. T., Zemrak, F., Mertens, B. J. A., Dinsdale, A., Hunter, A., ... Egorova, A. D. (2024). Effect of sodium-glucose cotransporter 2 inhibitors in adults with congenital heart disease. *Journal Of The American College Of Cardiology*, 83(15), 1403-1414. doi:10.1016/j.jacc.2024.02.017

Version: Publisher's Version

License: [Creative Commons CC BY-NC-ND 4.0 license](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Downloaded from: <https://hdl.handle.net/1887/4245569>

**Note:** To cite this publication please use the final published version (if applicable).



# Effect of Sodium-Glucose Cotransporter 2 Inhibitors in Adults With Congenital Heart Disease

Ralph M.L. Neijenhuis, MD,<sup>a,b</sup> Simon T. MacDonald, MD, DPHIL,<sup>c</sup> Filip Zemrak, MD, PhD,<sup>d,e</sup> Bart J.A. Mertens, PhD,<sup>f</sup> Anna Dinsdale, RN, BNURS,<sup>d</sup> Amanda Hunter, MBChB, MD,<sup>g</sup> Niki L. Walker, MBChB, PhD,<sup>g</sup> Lorna Swan, MBChB, MD,<sup>g</sup> Sushma Reddy, MD,<sup>h</sup> Joris I. Rotmans, MD, PhD,<sup>i</sup> J. Wouter Jukema, MD, PhD,<sup>b,j</sup> Monique R.M. Jongbloed, MD, PhD,<sup>a,b,k</sup> Gruschen R. Veldtman, MBChB,<sup>g,\*</sup> Anastasia D. Egorova, MD, PhD<sup>a,b,\*</sup>

## ABSTRACT

**BACKGROUND** Heart failure (HF) is the principal cause of morbidity and mortality in adults with congenital heart disease (ACHD). Robust evidence-based treatment options are lacking.

**OBJECTIVES** This study aims to evaluate the safety, tolerability, and short-term HF-related effects of sodium-glucose cotransporter 2 inhibitors (SGLT2i) in a real-world ACHD population.

**METHODS** All patients with ACHD treated with SGLT2i in 4 European ACHD centers were included in this retrospective study. Data were collected from 1 year before starting SGLT2i to the most recent follow-up. Data on side effects, discontinuation, mortality, and hospitalizations were collected.

**RESULTS** In total, 174 patients with ACHD were treated with SGLT2i from April 2016 to July 2023. The mean age was  $48.7 \pm 15.3$  years, 72 (41.4%) were female, and 29 (16.7%) had type 2 diabetes mellitus. Ten (5.7%) patients had mild, 75 (43.1%) moderate, and 89 (51.1%) severe congenital heart disease. HF was the most frequent starting indication ( $n = 162$ , 93.1%), followed by type 2 diabetes ( $n = 11$ , 6.3%) and chronic kidney disease ( $n = 1$ , 0.6%). At median follow-up of 7.7 months (Q1-Q3: 3.9-13.2 months), 18 patients (10.3%) reported side effects, 12 (6.9%) permanently discontinued SGLT2i, and 4 (2.3%) died of SGLT2i-unrelated causes. A significant reduction in the HF hospitalization rate was observed from 6 months before to 6 months after starting SGLT2i (relative rate = 0.30; 95% CI: 0.14-0.62;  $P = 0.001$ ).

**CONCLUSIONS** SGLT2i generally seem safe, well-tolerated, and potentially beneficial in patients with ACHD. SGLT2i was associated with a 3-fold reduction in the 6-month HF hospitalization rate. These results warrant prospective randomized investigation of the potential benefits of SGLT2i for patients with ACHD. (J Am Coll Cardiol 2024;83:1403-1414)  
© 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Listen to this manuscript's  
audio summary by  
Editor-in-Chief  
Dr Valentin Fuster on  
[www.jacc.org/journal/jacc](http://www.jacc.org/journal/jacc).

From the <sup>a</sup>CAHAL, Center for Congenital Heart Disease Amsterdam-Leiden, location Leiden University Medical Center, Leiden, the Netherlands; <sup>b</sup>Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands; <sup>c</sup>Department of Cardiology, University Hospital of Wales, Cardiff, United Kingdom; <sup>d</sup>Barts Heart Centre, St Bartholomew's Hospital, Barts Health NHS Trust, London, United Kingdom; <sup>e</sup>Institute of Cardiovascular Science, University College London, London, United Kingdom; <sup>f</sup>Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands; <sup>g</sup>Scottish Adult Congenital Cardiac Service (SACCS), Golden Jubilee University National Hospital, Glasgow, United Kingdom; <sup>h</sup>Department of Pediatrics (Cardiology), Lucile Packard Children's Hospital, Cardiovascular Institute, Stanford University, Stanford, California, USA; <sup>i</sup>Department of Internal Medicine and Nephrology, Leiden University Medical Center, Leiden, the Netherlands; <sup>j</sup>Netherlands Heart Institute, Utrecht, the Netherlands; and the <sup>k</sup>Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, the Netherlands. \*Drs Veldtman and Egorova contributed equally to this work.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received December 4, 2023; revised manuscript received February 7, 2024, accepted February 8, 2024.

**ABBREVIATIONS  
AND ACRONYMS****ACEI** = angiotensin-converting  
enzyme inhibitor**ACHD** = adult congenital heart  
disease**ARB** = angiotensin receptor  
blocker**ARNI** = angiotensin receptor-  
neprilysin inhibitor**CHD** = congenital heart disease**HF** = heart failure**MRA** = mineralocorticoid  
receptor antagonist**NT-proBNP** = N-terminal pro-  
B-type natriuretic peptide**SGLT2i** = sodium-glucose  
cotransporter 2 inhibitor

In adults with congenital heart disease (ACHD), heart failure (HF) represents the principal cause of morbidity and mortality.<sup>1</sup> Compared to patients with ACHD without HF, patients with HF have an almost 5 times higher mortality rate.<sup>2</sup> Contrary to the “conventional” left ventricular HF population, the etiology of HF in patients with ACHD is heterogeneous. HF complicates the clinical course of these younger patients with a lifelong condition who are also increasingly affected by classical risk factors such as coronary artery disease, hypertension, or degenerative valvular pathology. There is limited evidence on the efficacy of conventional HF pharmacotherapies, and the existing evidence remains largely empirical based on relatively small studies with heterogeneous populations.<sup>3</sup> Consequently, the current ACHD guidelines do not provide evidence-based recommendations to address ACHD-related HF.<sup>4,5</sup>

SEE PAGE 1415

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a relatively new class of drugs shown to reduce the risk of worsening HF and cardiovascular-related death in patients with conventional HF. They have rapidly become a pillar in the treatment of HF.<sup>6,7</sup> Although the exact mechanisms of action are still largely to be elucidated, SGLT2i appear to combat HF by targeting numerous pathways. SGLT2i have a direct hemodynamic effect, promoting diuresis and natriuresis. Moreover, SGLT2i seem to improve cardiac function by reducing sympathetic nervous system overactivation, decreasing pressure overload-induced myocardial fibrosis, decreasing inflammation, and improving overall myocardial energetics, thereby leading to favorable cardiac remodeling.<sup>8</sup>

Despite the compelling evidence on the effectiveness of SGLT2i over a broad range of cardiac dysfunction, robust data supporting the use of SGLT2i in the treatment of ACHD-related HF is lacking to date. The growing burden of ACHD-related HF has nonetheless led to an “off-label” prescription of SGLT2i as part of compassionate care for selected patients with ACHD worldwide.<sup>9-13</sup> The current study aims to evaluate prescription patterns, safety and tolerability, and short-term HF-related efficacy of SGLT2i in a contemporary, real-world ACHD population.

**METHODS**

**STUDY DESIGN AND PARTICIPANTS.** This international, multicenter, retrospective cohort study was

conducted at the Center for Congenital Heart Disease Amsterdam-Leiden, location Leiden University Medical Center (LUMC, Leiden, the Netherlands), Scottish Adult Congenital Cardiac Service at the Golden Jubilee University National Hospital (Glasgow, United Kingdom), Barts Heart Centre (St Bartholomew’s Hospital, London, United Kingdom), and University Hospital of Wales (Cardiff, United Kingdom). All tests and procedures were performed as part of standard clinical care. The study was conducted in accordance with the ethical standards of the institutional and/or national research committees and with the 2013 Helsinki Declaration or comparable ethical standards. Appropriate approval with a waiver for written informed consent was obtained from the institutional medical ethical boards/clinical governance divisions of all participating centers (LUMC Medical Research Involving Human Subjects Act [WMO] committee division 1, protocol reference 2022-068). All patients with ACHD ( $\geq 18$  years of age) who were initiated on an SGLT2i in the period between April 2016 to July 2023 were included.

**DATA COLLECTION AND FOLLOW-UP.** Data were collected retrospectively from the electronic health records and included anatomical characteristics, medical history, complaints, hospitalization data, pharmacologic therapy, physical examination, 12-lead electrocardiogram recordings, exercise testing, transthoracic echocardiography, laboratory investigations, intervention data, and cardiac implantable electronic device interrogation when applicable. Systolic systemic and subpulmonary ventricular function were classified into 4 categories based on transthoracic echocardiography examination, including biplane (or 3-dimensional when available) assessment of the ejection fraction, global longitudinal strain analysis, fractional area change, and qualitative visual function assessment. Data were collected from 1 year before the initiation of the SGLT2i and at each subsequent outpatient visit and/or admission until the most recent follow-up. The closing date for follow-up was July 2023, the date of discontinuation of SGLT2i therapy, last outpatient visit, death, or admission for any catheter or surgical intervention influencing the hemodynamic status of the patient (ie, implantation or an upgrade to a cardiac resynchronization therapy device, severe valvular heart disease necessitating intervention, and heart transplantation).

**PRIMARY OUTCOME MEASURES.** The primary outcome measures were the safety and tolerability of SGLT2i in the contemporary ACHD population. This was evaluated by assessing side effects, discontinuation of

SGLT2i therapy, mortality, and short-term effects on safety indices from 2 weeks to 3 months after starting SGLT2i including weight, systolic and diastolic blood pressure, serum sodium, potassium, glucose, and creatinine.

**SECONDARY OUTCOME MEASURES.** The secondary outcome measures focused on HF-related efficacy of SGLT2i in patients who started SGLT2i due to HF. A diagnosis of HF was defined as a clinical syndrome with symptoms and/or signs of HF, combined with elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) and/or objective evidence of pulmonic or systemic congestion, in accordance with the universal definition of HF.<sup>14</sup> The principal secondary outcomes were the occurrence of HF hospitalizations and a comparison of HF hospitalization rates before and after starting SGLT2i. An HF hospitalization was defined as an unscheduled admission with a primary diagnosis of HF, with a duration of at least 24 hours or crossing a calendar day, in accordance with the Clinical Data Interchange Standards Consortium.<sup>15</sup>

Additional secondary outcome measures included clinical data on admissions for arrhythmia and (changes in) concomitant HF pharmacotherapy. HF pharmacotherapy (other than SGLT2i) was divided into 4 categories: 1) beta-blockers; 2) angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI); 3) mineralocorticoid receptor antagonists (MRA); and 4) diuretics.

**STATISTICAL ANALYSIS.** All statistical analyses were performed and figures were created in SPSS version 25 (IBM Corp), R (R Foundation for Statistical Computing), and GraphPad Prism version 9.3.1 (GraphPad Software). For the descriptive analyses at baseline, normally distributed continuous data were displayed as mean  $\pm$  SD and compared between systemic ventricle groups using a one-way analysis of variance. Non-normally distributed continuous data were presented as median (Q1-Q3) and compared using a Kruskal-Wallis test. Categorical data were presented as counts and percentages and compared using the chi-square test or Fisher exact test as appropriate. Paired Student's *t*-tests or Wilcoxon signed-rank tests were performed to assess the safety and tolerability effects of SGLT2i therapy on continuous variables from baseline to the short-term visit.

Kaplan-Meier survival analysis and log-rank tests were used to evaluate the occurrence of hospitalizations. Hospitalization rates before and after SGLT2i initiation were compared with a Poisson regression with random effect to account for within-person correlation. McNemar's tests were used to evaluate

changes in HF pharmacotherapy categories. A 2-sided  $P < 0.05$  was considered statistically significant.

## RESULTS

**PATIENT CHARACTERISTICS AND FOLLOW-UP.** In total, 174 patients with ACHD were treated with an SGLT2i and included at the 4 participating ACHD centers (Supplemental Figure 1). The mean age was  $48.7 \pm 15.3$  years, 72 (41.4%) were female, and 29 (16.7%) had type 2 diabetes mellitus. At inclusion, the median systolic and diastolic blood pressures were 113 mm Hg (Q1-Q3: 104-126 mm Hg) and 68 mm Hg (Q1-Q3: 61-75 mm Hg), respectively. The median estimated glomerular filtration rate was 60 mL/min/1.73 m<sup>2</sup> (Q1-Q3: 59-76 mL/min/1.73 m<sup>2</sup>). According to the European Society of Cardiology classification of congenital heart disease (CHD) complexity, 10 (5.7%) participants had mild, 75 (43.1%) had moderate, and 89 (51.1%) had severe CHD.<sup>4</sup> The majority ( $n = 162$ , 93.1%) had a biventricular circulation, and 12 (6.9%) participants had univentricular circulations. Seven cyanotic patients (4.0%) with a baseline oxygen saturation  $<90\%$  were included (Table 1, Supplemental Table 1).

The median follow-up duration was 7.7 months (Q1-Q3: 3.9-13.2 months). One patient was lost to follow-up (99.4% complete), and 4 patients (2.3%) died during follow-up. Causes of death were progressive congestive cardiac failure ( $n = 1$ ), sudden cardiac death ( $n = 1$ ), respiratory tract infection ( $n = 1$ ), and chronic gastrointestinal bleeding secondary to warfarin use for mechanical valve prostheses ( $n = 1$ ).

**PRESCRIPTION PATTERNS.** A clear temporal increase in SGLT2i prescription was observed in the ACHD population with a notable progression in the past 2 years (Figure 1). Most patients were started on dapagliflozin ( $n = 137$ , 78.7%) or empagliflozin ( $n = 36$ , 20.7%) at the standard dose of 10 mg once per day ( $n = 171$ , 98.3%). In 31 patients (17.8%), SGLT2i was initiated during a clinical admission. The most common starting indication was HF ( $n = 162$ , 93.1%) (Table 2).

**SAFETY AND TOLERABILITY.** Side effects were observed in 18 patients (10.3%), 9 of whom discontinued SGLT2i therapy. Overall, SGLT2i was permanently discontinued in 12 patients (6.9%). The side effects and reasons for discontinuing SGLT2i therapy are presented in Table 3. After 3 years, 1 patient developed Fournier's gangrene (necrotizing fasciitis) requiring surgical debridement and discontinuation of SGLT2i. The patient had a history of a

**TABLE 1 Patient Characteristics at Baseline (N = 174)**

|                                                             |                  |
|-------------------------------------------------------------|------------------|
| Female                                                      | 72 (41.4)        |
| Age, y                                                      | 48.7 ± 15.3      |
| Systemic ventricle                                          |                  |
| LV                                                          | 102 (58.6)       |
| RV                                                          | 60 (34.5)        |
| Univentricular circulation                                  | 12 (6.9)         |
| CHD complexity <sup>a</sup>                                 |                  |
| Mild                                                        | 10 (5.7)         |
| Moderate                                                    | 75 (43.1)        |
| Severe                                                      | 89 (51.1)        |
| No. of cardiac surgeries                                    | 1 (1-2)          |
| CIED                                                        | 84 (48.3)        |
| Pacemaker                                                   | 37 (21.3)        |
| Transvenous ICD (single and dual chamber)                   | 18 (10.3)        |
| S-ICD                                                       | 5 (2.9)          |
| CRT-P                                                       | 7 (4.0)          |
| CRT-D                                                       | 17 (9.8)         |
| Type 2 diabetes mellitus                                    | 29 (16.7)        |
| On oral therapy                                             | 26 (14.9)        |
| On insulin therapy                                          | 3 (1.7)          |
| Physical examination findings                               |                  |
| Systolic blood pressure, mm Hg (n = 123)                    | 113 (104-126)    |
| Diastolic blood pressure, mm Hg (n = 122)                   | 68 (61-75)       |
| Heart rate, beats/min (n = 137)                             | 69 (60-80)       |
| Weight, kg (n = 115)                                        | 72 (60-89)       |
| BMI, kg/m <sup>2</sup> (n = 110)                            | 26.6 (22.5-30.8) |
| Laboratory parameters                                       |                  |
| Hemoglobin, mmol/L (n = 147)                                | 8.7 ± 1.3        |
| Hematocrit, L/L (n = 146)                                   | 0.419 ± 0.060    |
| Creatinine, μmol/L (n = 165)                                | 85 (73-106)      |
| eGFR, mL/min/1.73 m <sup>2</sup> (n = 163)                  | 60 (59-76)       |
| Renal function (n = 161)                                    |                  |
| Normal (eGFR ≥60 mL/min/1.73 m <sup>2</sup> )               | 118 (73.3)       |
| Moderately reduced (eGFR 30-59 mL/min/1.73 m <sup>2</sup> ) | 38 (23.6)        |
| Severely reduced (eGFR 15-29 mL/min/1.73 m <sup>2</sup> )   | 5 (3.1)          |
| Renal failure (eGFR <15 mL/min/1.73 m <sup>2</sup> )        | 0 (0)            |
| Serum glucose, mmol/L (n = 43)                              | 5.6 (5.0-7.2)    |
| HbA1c, mmol/mol (n = 43)                                    | 43.9 (39.0-54.4) |

Values are n (%), mean ± SD, or median (Q1-Q3). <sup>a</sup>CHD complexity categorization adapted from the ESC classification.<sup>4</sup> Data were available for all 174 patients unless otherwise specified.

BMI = body mass index; CHD = congenital heart disease; CIED = cardiac implantable electronic device; CRT(-P/D) = cardiac resynchronization therapy (-pacemaker/defibrillator); eGFR = estimated glomerular filtration rate; ESC = European Society of Cardiology; HbA1c = hemoglobin A1c; ICD = implantable cardioverter-defibrillator; LV = left ventricle; RV = right ventricle; S-ICD = subcutaneous implantable cardioverter-defibrillator.

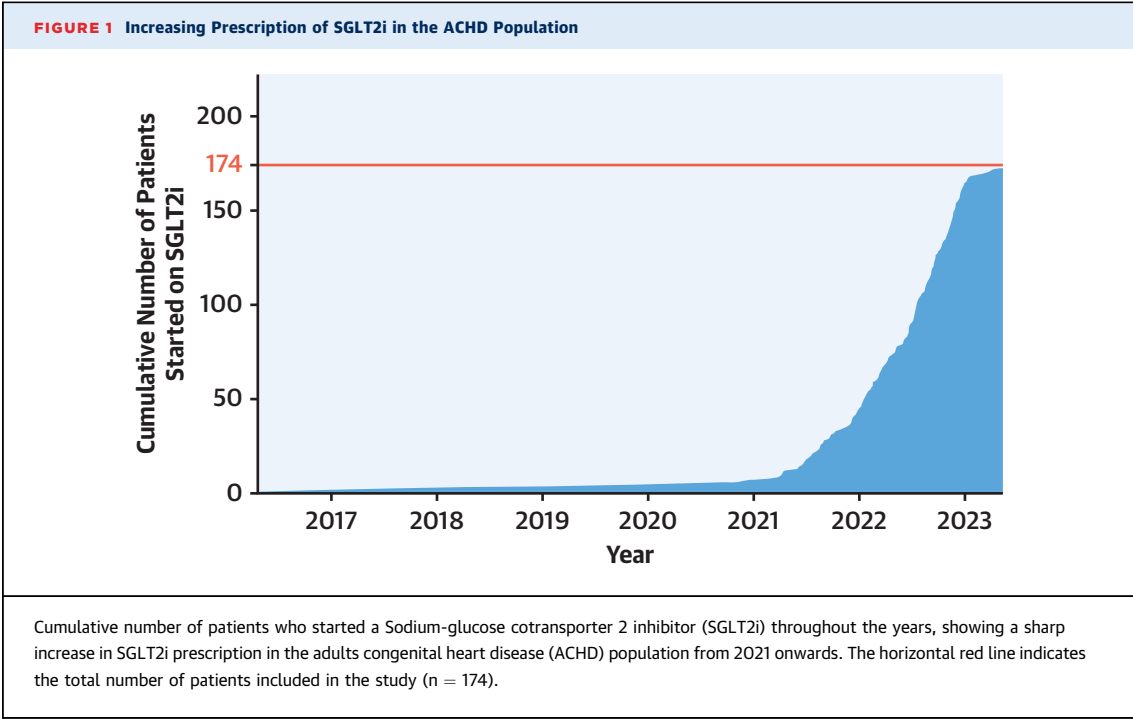
perineal abscess, noninsulin dependent type 2 diabetes mellitus with persistent high-serum glucose, and obesity. The patient survived and was doing well 10 months after surgery. Three patients (1.7%) experienced recurrent urinary tract infections which were treated successfully with oral antibiotics. In 2

patients, these recurrent urinary tract infections were associated with episodes of atrial fibrillation requiring electrical cardioversions. Of these 2 patients, 1 discontinued SGLT2i therapy. A rash developed after starting dapagliflozin in 3 patients (1.7%). One patient was switched to empagliflozin, after which the rash was resolved. The other 2 patients discontinued SGLT2i therapy. The side effects and reasons for discontinuing SGLT2i in the remaining patients resolved without issues.

In the first 3 months, no significant changes were observed in weight (73.7 ± 19.7 kg to 73.3 ± 20.1 kg,  $P = 0.525$ ), serum sodium (139 mmol/L [Q1-Q3: 137-141 mmol/L] to 139 mmol/L [Q1-Q3: 137-140 mmol/L];  $P = 0.765$ ), potassium (4.4 mmol/L [Q1-Q3: 4.0-4.6 mmol/L] to 4.4 mmol/L [Q1-Q3: 4.1-4.6 mmol/L];  $P = 0.974$ ), and glucose (5.5 mmol/L [Q1-Q3: 5.0-7.1 mmol/L] to 5.2 mmol/L [Q1-Q3: 4.5-6.6 mmol/L];  $P = 0.755$ ). Although diastolic blood pressure did not change significantly (68 mm Hg [Q1-Q3: 61-75 mm Hg] to 67 mm Hg [Q1-Q3: 58-72 mm Hg];  $P = 0.420$ ), there was a significant decrease in systolic blood pressure from 113 mm Hg (Q1-Q3: 104-126 mm Hg) to 108 mm Hg (Q1-Q3: 100-121 mm Hg) ( $P = 0.004$ ). A statistically significant creatinine increase (84 μmol/L [Q1-Q3: 73-106 μmol/L] to 93 μmol/L [Q1-Q3: 78-115 μmol/L];  $P < 0.001$ ) was observed compared to baseline, and SGLT2i was discontinued for this reason in 1 patient.

**SGLT2i in ACHD-RELATED HF.** HF was the indication for initiation of SGLT2i in 162 patients (93.1%); 93 patients had a systemic left ventricle (LV), 58 a systemic right ventricle (RV), and 11 a univentricular circulation. Systemic ventricular function was at least moderately reduced in 69.5%, and subpulmonary ventricular function was at least mildly reduced in 52.1%. In the year preceding SGLT2i therapy, 20.4% experienced at least 1 HF hospitalization, and the majority of patients were in NYHA functional class II (45.2%). Baseline HF-related characteristics are shown in [Table 4](#).

At baseline, there were significant differences in: 1) systemic ventricular function between circulation types, with more severe dysfunction in patients with a systemic RV or univentricular circulation compared to a systemic LV ( $P < 0.001$ ); 2) subpulmonary ventricular function, with more systemic LV patients with at least moderately reduced function ( $P < 0.001$ ); 3) systemic atrioventricular valve regurgitation, with at least moderate regurgitation being more prevalent in the systemic RV group ( $P = 0.045$ ); and 4) subpulmonary atrioventricular valve regurgitation, with



more systemic LV patients with at least mild regurgitation ( $P < 0.001$ ).

Most patients were on at least 3 HF drugs at baseline (68.8%). An ACEI, ARB, or ARNI was prescribed for 83.1% of patients. Details on baseline

pharmacotherapy are shown in [Figure 2](#). There were no significant changes in concomitant HF pharmacotherapy during follow-up ([Supplemental Table 2](#)). After a median follow-up of 7.5 months (Q1-Q3: 3.7-12.6 months) in the HF cohort, 28 (17.3%) patients reached end of follow-up due to having undergone an intervention with significant hemodynamic impact (n = 15, 9.3%), permanent discontinuation of SGLT2i (n = 11, 6.8%), or heart transplantation (n = 2, 1.2%).

**HF HOSPITALIZATIONS AND ARRHYTHMIA ADMISSIONS.**

In total, 60 HF hospitalizations occurred in 38 patients (23.5%); 42 (70%) in the 12 months preceding initiation of SGLT2i therapy, and 18 (30%) during follow-up. There was a significantly higher risk of HF hospitalization in patients with an HF hospitalization in the 12 months before SGLT2i initiation (n = 33) compared to patients without HF hospitalization in the previous year (n = 129) (log-rank  $P = 0.0024$ ) ([Figure 3](#)). Of the 11 individuals who experienced HF hospitalization(s) during follow-up, 6 had an HF hospitalization in the 12 months before start. There were no differences in HF hospitalizations when stratified for systemic ventricular morphology or CHD complexity subgroups (log-rank  $P = 0.43$  and  $P = 0.84$ , respectively) ([Supplemental Figures 2 and 3](#)). A significant reduction in HF hospitalization rate was observed during the 6 months after starting (n = 9) compared to the 6 months before starting SGLT2i

| TABLE 2 SGLT2i Prescription Details (N = 174)                                                                                                                                                                                                                   |            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| SGLT2i types                                                                                                                                                                                                                                                    |            |
| Dapagliflozin                                                                                                                                                                                                                                                   | 137 (78.7) |
| Empagliflozin                                                                                                                                                                                                                                                   | 36 (20.7)  |
| Canagliflozin                                                                                                                                                                                                                                                   | 1 (0.6)    |
| SGLT2i dose at start, OD                                                                                                                                                                                                                                        |            |
| 10 mg                                                                                                                                                                                                                                                           | 171 (98.3) |
| 5 mg (dapagliflozin reduced dose)                                                                                                                                                                                                                               | 1 (0.6)    |
| 25 mg (empagliflozin increased dose)                                                                                                                                                                                                                            | 1 (0.6)    |
| 100 mg (canagliflozin standard dose)                                                                                                                                                                                                                            | 1 (0.6)    |
| SGLT2i starting indication                                                                                                                                                                                                                                      |            |
| Heart failure                                                                                                                                                                                                                                                   | 162 (93.1) |
| HF <sub>r</sub> EF                                                                                                                                                                                                                                              | 159 (91.4) |
| Systemic RV failure                                                                                                                                                                                                                                             | 59 (33.9)  |
| Systemic LV failure                                                                                                                                                                                                                                             | 49 (28.2)  |
| Biventricular failure                                                                                                                                                                                                                                           | 25 (14.4)  |
| Subpulmonary RV failure                                                                                                                                                                                                                                         | 15 (8.6)   |
| Univentricular circulation failure                                                                                                                                                                                                                              | 11 (6.3)   |
| HF <sub>p</sub> EF                                                                                                                                                                                                                                              | 3 (1.7)    |
| Type 2 diabetes mellitus                                                                                                                                                                                                                                        | 11 (6.3)   |
| Chronic kidney disease                                                                                                                                                                                                                                          | 1 (0.6)    |
| Values are n (%). Data were available for all 174 patients.                                                                                                                                                                                                     |            |
| HF <sub>p</sub> EF = heart failure with preserved ejection fraction; HF <sub>r</sub> EF = heart failure with reduced ejection fraction; OD = once daily; SGLT2i = sodium-glucose cotransporter 2 inhibitor; other abbreviations as in <a href="#">Table 1</a> . |            |

**TABLE 3 Side Effects and Discontinuation of SGLT2i Therapy (N = 174)**

|                                                                                                      |           |
|------------------------------------------------------------------------------------------------------|-----------|
| Side effects                                                                                         | 18 (10.3) |
| Symptomatic (orthostatic) hypotension                                                                | 6 (3.4)   |
| Urinary tract infections                                                                             | 5 (2.9)   |
| Rash                                                                                                 | 3 (1.7)   |
| Fatigue                                                                                              | 2 (1.1)   |
| Dysuria                                                                                              | 1 (0.6)   |
| Fournier's gangrene                                                                                  | 1 (0.6)   |
| Permanent discontinuation of SGLT2i                                                                  | 12 (6.9)  |
| Fatigue                                                                                              | 2 (1.1)   |
| Rash                                                                                                 | 2 (1.1)   |
| Symptomatic (orthostatic) hypotension                                                                | 2 (1.1)   |
| Dysuria                                                                                              | 1 (0.6)   |
| Fournier's gangrene                                                                                  | 1 (0.6)   |
| No beneficial effects noticed                                                                        | 1 (0.6)   |
| Precautionary due to weight loss                                                                     | 1 (0.6)   |
| Significant increase in serum creatinine (started SGLT2i simultaneously with intravenous furosemide) | 1 (0.6)   |
| Urinary tract infections                                                                             | 1 (0.6)   |

Values are n (%) experiencing the respective side effects or discontinuing SGLT2i for the mentioned reasons. Data were available for all 174 patients.  
Abbreviation as in Table 2.

(n = 36) (relative hospitalization rate = 0.30; 95% CI: 0.14-0.62;  $P = 0.001$ ) (Central Illustration).

Sixty-eight arrhythmia admissions were observed in 33 patients (20.4%); 41 (60.3%) in the 12 months preceding SGLT2i initiation, and 27 (39.7%) during follow-up. There was no significant difference in arrhythmia admission rate in the 6 months before (n = 21) and after (n = 12) SGLT2i initiation (relative admission rate = 0.68; 95% CI: 0.33-1.39;  $P = 0.289$ ) (Central Illustration).

## DISCUSSION

The main findings of this study are that: 1) despite limited evidence, SGLT2i are prescribed with increased frequency in the heterogeneous ACHD population, with HF as the most frequently encountered indication; 2) SGLT2i are safe and generally well-tolerated, with comparable occurrence of side effects to the landmark trials in conventional HF patients; and 3) SGLT2i use was associated with a decreased 6-month HF-related hospitalization rate, suggesting a potential prognostic benefit for patients with ACHD with HF.

**SGLT2i PRESCRIPTION PATTERNS AND REAL-WORLD TREATMENT OF ACHD-RELATED HF.** The study reports on a heterogeneous ACHD cohort with varied anatomy and frequent concomitant defects including pulmonary hypertension and tricuspid regurgitation, in whom SGLT2i therapy was most frequently

initiated for HF with a reduced ejection fraction. HF with a preserved ejection fraction was the indication for starting SGLT2i in only 3 patients (1.7%). This might partly be explained by underdiagnosis of HF with a preserved ejection fraction in the ACHD population but also reflects that SGLT2i were only recently included as a Class 1 treatment for HF with a preserved ejection fraction in the updated European Society of Cardiology HF guidelines.<sup>7</sup>

In this contemporary, real-world ACHD setting, a steady increase in SGLT2i prescriptions was observed over time. This indicates a more prevalent prescription of SGLT2i for HF in patients with ACHD than the recently reported observational experience of 35 patients with ACHD treated with SGLT2i at a single center in the United States, where only 40.6% of patients had HF as the starting indication. More than 65% of the cohort reported in Saef et al<sup>11</sup> had diabetes mellitus, whereas this was only 16.7% in the current cohort. These differences might reflect the early prescription indications of SGLT2i as a treatment for diabetes regardless of the cardiorenal status, the higher prevalence of diabetes in the United States compared to Northern European countries, and the proactive treatment of ACHD-related HF by the centers participating in this study.

The proactive HF management strategy in our population is reflected by more than 80% of patients using an ACEI/ARB/ARNI, and 45% a combination of beta-blockers, ACEI/ARB/ARNI, and MRA. To show the disparity between centers when it comes to HF management in the ACHD population, pharmacotherapy has been evaluated in systemic RV patients—who make up more than one-third of our cohort—in the German National Register for Congenital Heart Defects. No patients used SGLT2i, and in patients with systemic RV dysfunction, a combination of beta-blockers, ACEI/ARB/ARNI, and MRA was prescribed in 26.7% whereas 13.6% did not use any cardiovascular drugs. The investigators concluded that there were signs of beneficial effects of pharmacotherapy for systemic RV failure.<sup>16</sup> In a recent Dutch evaluation of systemic RV patients, 52% used renin-angiotensin-aldosterone system inhibitors and 29% did not use any cardiovascular drugs. Symptomatic patients had a lower risk of mortality when using renin-angiotensin-aldosterone system inhibitors and beta-blockers. These findings indicate a potential beneficial effect of HF pharmacotherapy for systemic RV failure.<sup>17</sup> Patients with ACHD have a higher use of cardiovascular and noncardiovascular drugs, and a higher prevalence of polypharmacy ( $\geq 5$  drugs) compared to age- and sex-matched controls from the general population.<sup>18</sup> This highlights the

**TABLE 4 HF-Related Baseline Characteristics**

|                                                     | Total<br>(N = 162)    | Systemic LV<br>(n = 93) | Systemic RV<br>(n = 58) | Univentricular<br>(n = 11) | P Value |
|-----------------------------------------------------|-----------------------|-------------------------|-------------------------|----------------------------|---------|
| No. of HF hospitalizations in year preceding SGLT2i | 33 (20.4)             | 18 (19.8)               | 11 (18.3)               | 4 (36.4)                   | 0.287   |
| 1                                                   | 27 (16.7)             | 14 (15.4)               | 10 (16.7)               | 3 (27.3)                   |         |
| 2                                                   | 4 (2.5)               | 3 (3.3)                 | 0 (0)                   | 1 (9.1)                    |         |
| ≥3                                                  | 2 (1.2)               | 1 (1.1)                 | 1 (1.7)                 | 0 (0)                      |         |
| NYHA functional class (n = 62)                      |                       |                         |                         |                            | 0.658   |
| I                                                   | 5 (8.1)               | 4 (10.3)                | 1 (4.5)                 | 0                          |         |
| II                                                  | 28 (45.2)             | 19 (48.7)               | 8 (36.4)                | 1 (100)                    |         |
| III                                                 | 24 (38.7)             | 13 (33.3)               | 11 (50)                 | 0                          |         |
| IV                                                  | 5 (8.1)               | 3 (7.7)                 | 2 (9.1)                 | 0                          |         |
| NT-proBNP, ng/L (n = 112)                           | 924.1 (477.5-2,317.8) | 1,170 (479-2,748.5)     | 858 (518.7-1,184.8)     | 647.9 (220.8-2,259)        | 0.306   |
| Exercise capacity (n = 33)                          |                       |                         |                         |                            |         |
| VO <sub>2</sub> max, mL/kg/min                      | 15.4 ± 4.2            | 16.2 ± 3.5              | 14.6 ± 4.3              | 17.5 ± 5.6                 | 0.396   |
| % predicted VO <sub>2</sub> max                     | 53.4 ± 15.9           | 53.6 ± 21.9             | 53.6 ± 12.4             | 51.3 ± 16.0                | 0.974   |
| Transthoracic echocardiography (n = 146)            |                       |                         |                         |                            |         |
| Systemic ventricular function                       |                       |                         |                         |                            | <0.001  |
| Good                                                | 18 (12.8)             | 18 (21.7)               | 0 (0)                   | 0 (0)                      |         |
| Mildly reduced                                      | 25 (17.7)             | 16 (19.3)               | 6 (12)                  | 3 (37.5)                   |         |
| Moderately reduced                                  | 33 (23.4)             | 17 (20.5)               | 15 (30)                 | 1 (12.5)                   |         |
| Severely reduced                                    | 65 (46.1)             | 32 (38.6)               | 29 (58)                 | 4 (50)                     |         |
| Subpulmonary ventricular function                   |                       |                         |                         |                            | <0.001  |
| Good                                                | 56 (47.9)             | 20 (27.8)               | 36 (80)                 | —                          |         |
| Mildly reduced                                      | 31 (26.5)             | 23 (31.9)               | 8 (17.8)                | —                          |         |
| Moderately reduced                                  | 11 (9.4)              | 11 (15.3)               | 0 (0)                   | —                          |         |
| Severely reduced                                    | 19 (16.2)             | 18 (25)                 | 1 (2.2)                 | —                          |         |
| Systemic AV valve regurgitation                     |                       |                         |                         |                            | 0.045   |
| No                                                  | 20 (14.8)             | 15 (19.5)               | 5 (10.4)                | 0 (0)                      |         |
| Mild (grade 1-2)                                    | 95 (70.4)             | 55 (71.4)               | 30 (62.5)               | 10 (100)                   |         |
| Moderate (grade 3)                                  | 8 (5.9)               | 4 (5.2)                 | 4 (8.3)                 | 0 (0)                      |         |
| Severe (grade 4)                                    | 12 (8.9)              | 3 (4)                   | 9 (18.8)                | 0 (0)                      |         |
| Subpulmonary AV valve regurgitation                 |                       |                         |                         |                            | <0.001  |
| No                                                  | 24 (19.8)             | 5 (6.3)                 | 19 (46.3)               | —                          |         |
| Mild (grade 1-2)                                    | 75 (62)               | 55 (68.8)               | 20 (48.8)               | —                          |         |
| Moderate (grade 3)                                  | 9 (7.4)               | 8 (10)                  | 1 (2.4)                 | —                          |         |
| Severe (grade 4)                                    | 13 (10.7)             | 12 (15)                 | 1 (2.4)                 | —                          |         |

Values are n (%), median (Q1-Q3), or mean ± SD. Data were available for the 162 patients who started SGLT2i for heart failure, unless otherwise specified. For the comparison of categorical variables across systemic ventricle groups, the Fisher exact test was used. For the comparison of continuous variables, 1-way analysis of variance was used (Levene's test for equal variance  $P > 0.05$  in all cases).

AV = atrioventricular; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in [Tables 1 and 2](#).

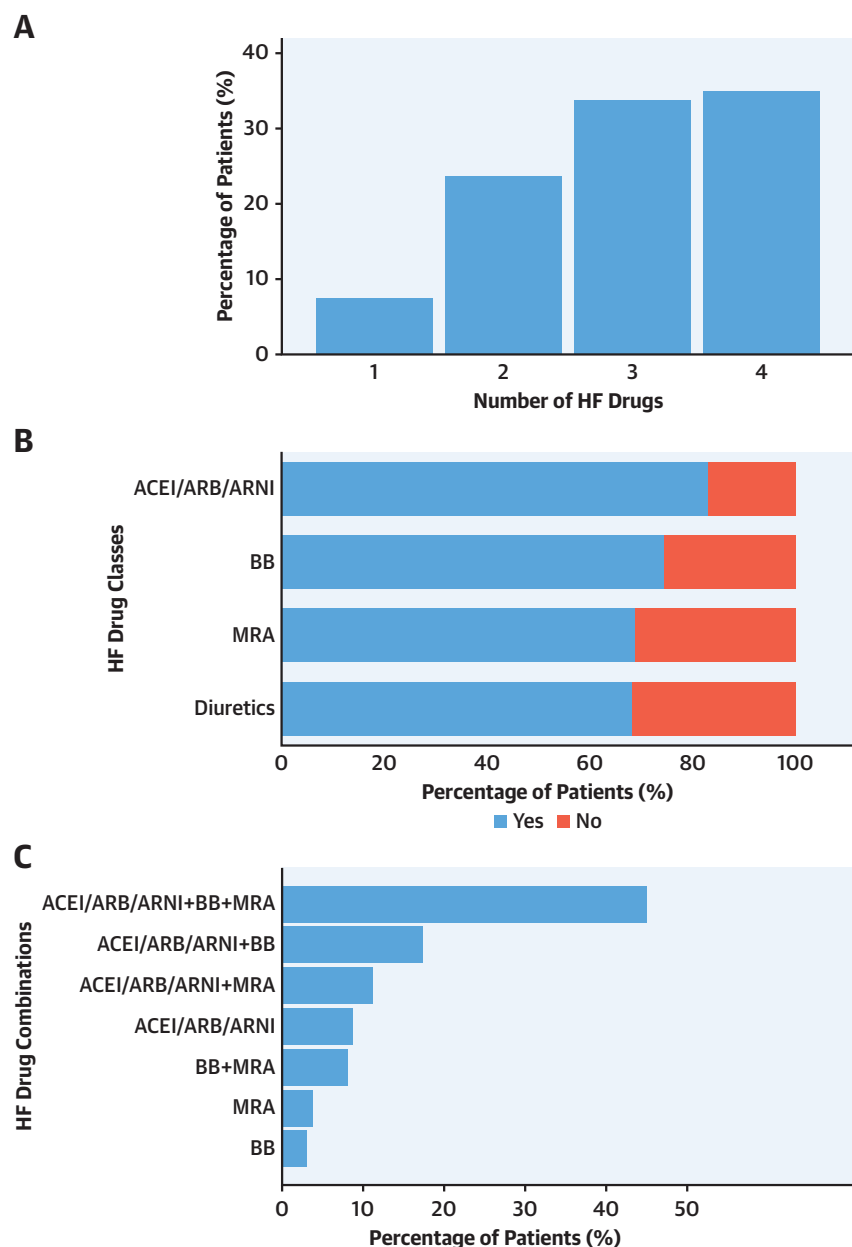
demographic differences between the non-ACHD and the ACHD patient, who is burdened with the consequences of a chronic condition from a much younger age.

**SAFETY AND TOLERABILITY.** In the current study, 10.3% reported side effects and 6.9% discontinued SGLT2i. In the landmark SGLT2i trials, discontinuation of SGLT2i therapy ranged from 10.5% to 23.2% and did not differ significantly from placebo.<sup>19-22</sup> Although direct comparison of side effect profiles is not possible due to different study designs, adverse event definitions and observation periods, no novel side effects were observed, and the occurrence of reported side effects seems comparable to the

literature.<sup>23</sup> This suggests that SGLT2i are generally well-tolerated and safe in patients with ACHD. During follow-up, 1 patient nonetheless developed Fournier's gangrene (necrotizing fasciitis) requiring surgical debridement. Retrospectively, this patient had several risk factors for developing Fournier's gangrene in addition to the SGLT2i therapy. This devastating side effect is very rare but, given the rapid progression and high associated morbidity and mortality, early recognition and action is imperative.<sup>24</sup>

Short-term effects on safety indices were evaluated from baseline to the first routine check within 2 weeks to 3 months after starting SGLT2i. Although

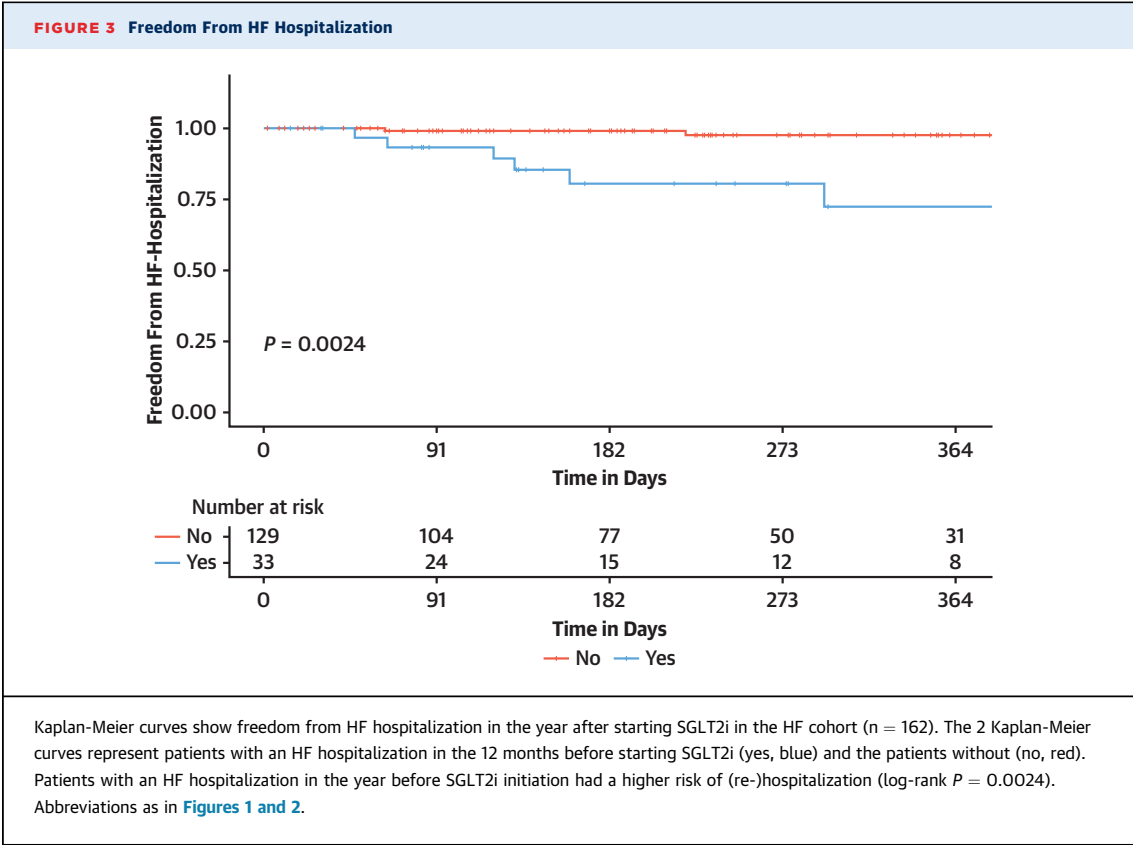
**FIGURE 2** HF Pharmacotherapy at Baseline



Details on heart failure (HF) pharmacotherapy at baseline in patients who were started on SGLT2i due to HF. Data were available for 160 of 162 patients (98.8%). (A) The number of HF drugs used at baseline. Most patients were on  $\geq 3$  HF drugs (68.8%), consisting of the following categories: 1) beta-blockers (BB); 2) angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI); 3) mineralocorticoid receptor antagonist (MRA); and 4) diuretics. (B) Percentage (%) of patients using specific classes of HF drugs at baseline. (C) The most frequently encountered combinations of HF drugs at baseline, excluding diuretics use.

most parameters remained unchanged, a statistically significant decrease in systolic blood pressure and an increase in creatinine were observed. Although these changes were statistically significant, their clinical relevance might be limited and related to the

mechanisms of action of SGLT2i. During follow-up, 6 patients (3.4%) reported symptomatic (orthostatic) hypotension (of whom only 2 discontinued treatment), and SGLT2i was discontinued in 1 patient due to an increase in creatinine. An initial "dip" in renal



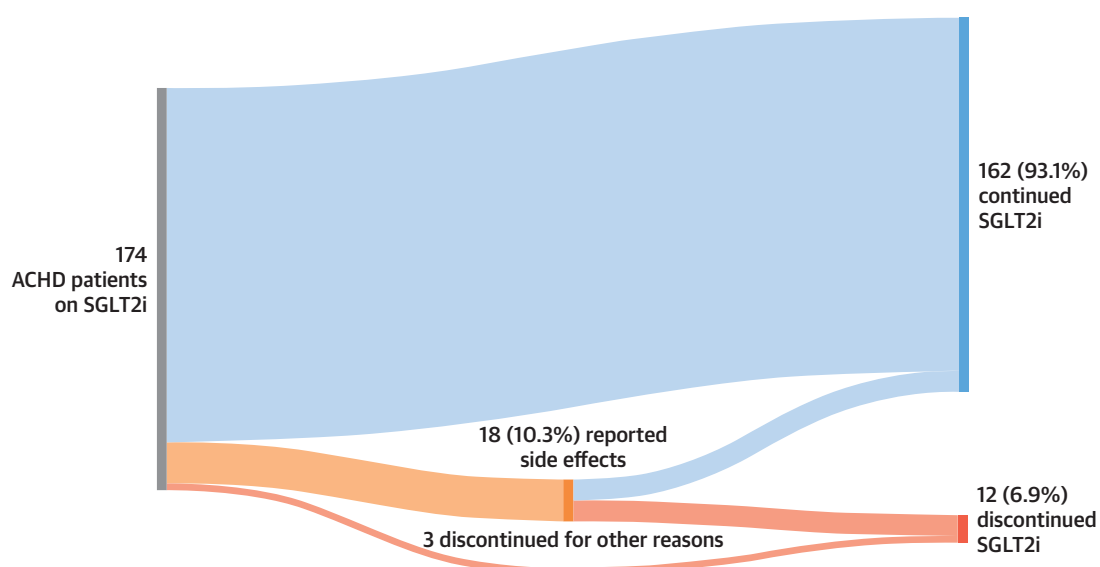
function after starting SGLT2i has now been widely reported in the literature and may be associated with renal protection in the long term.<sup>25</sup>

**VALUE OF NT-proBNP IN ACHD-RELATED HF.** NT-proBNP is a surrogate marker of clinical status in ACHD-related HF and provides prognostic information on the risk of cardiovascular events, including mortality and HF course.<sup>26,27</sup> Although a pilot study evaluating 10 patients with systemic RV failure on SGLT2i has shown a reduction in NT-proBNP after 6 months, longitudinal changes in NT-proBNP were not formally evaluated in this study.<sup>9</sup> While significant reductions in NT-proBNP have also been reported in the majority of the large SGLT2i trials,<sup>19,20,22</sup> the risk of HF events is reduced independently of baseline NT-proBNP levels.<sup>28</sup> Moreover, the observed reduction in NT-proBNP after SGLT2i initiation seems modest compared to other established HF therapies and not in line with the large clinical improvements. Thus, the role of NT-proBNP as a surrogate marker of the efficacy of SGLT2i remains to be investigated.<sup>29</sup>

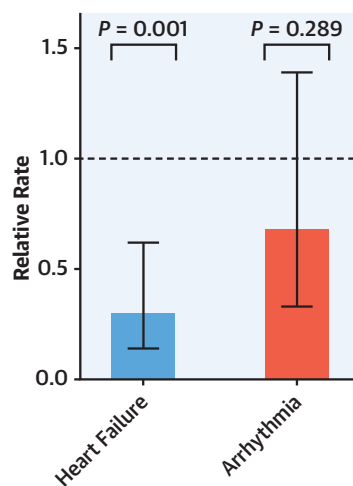
**HOSPITALIZATIONS.** In the ACHD population, HF hospitalizations have increased dramatically over the years, and are more complex and costly than in the

non-ACHD HF population.<sup>30</sup> HF hospitalizations severely impact prognosis and are associated with a substantially higher risk of death in ACHD patients, and it is imperative to closely monitor these patients.<sup>31,32</sup> Patients in our study with an HF hospitalization in the 12 months before SGLT2i initiation were at a higher risk of HF hospitalization during follow-up compared to patients without HF hospitalization in the year preceding SGLT2i initiation. This emphasizes the need for intensified follow-up regimens in high-risk ACHD HF patients who may be identified by recent HF hospitalization. Studies have shown that SGLT2i therapy consistently reduces HF hospitalizations in the conventional HF population, regardless of ejection fraction, hospitalization duration, or severity.<sup>33</sup> This study found no differences in HF hospitalizations after stratifying for systemic ventricular morphology or CHD complexity, despite markedly different ventricular function profiles at baseline. The 3-fold reduction in HF hospitalization rate that was observed from 6 months before to 6 months after SGLT2i initiation is a promising signal. Investigating a potential confounder of these results, no significant changes in the use of other HF drugs were observed from baseline to 6 months or most recent follow-up.

### CENTRAL ILLUSTRATION Sodium-Glucose Cotransporter 2 Inhibitors in Adults With Congenital Heart Disease



**3-Fold Reduction in Heart Failure Hospitalization Rate:**  
Relative Rate = 0.30 (95% CI: 0.14-0.62),  $P = 0.001$   
**No Significant Reduction in Arrhythmia Admission Rate**



Neijenhuis RML, et al. J Am Coll Cardiol. 2024;83(15):1403-1414.

In this multicenter retrospective cohort study, SGLT2i were safe, well-tolerated and potentially beneficial in 174 ACHD patients. Side effects were observed in 18 patients (10.3%), 9 of whom discontinued SGLT2i therapy. Overall, SGLT2i was permanently discontinued in 12 patients (6.9%). In a subset of 162 ACHD patients with heart failure, a 3-fold reduction in heart failure-hospitalization rate from the 6 months before to the 6 months after starting SGLT2i was observed ( $P = 0.001$ ). There was no significant reduction in arrhythmia admission rate ( $P = 0.289$ ). ACHD = adult congenital heart disease; SGLT2i = sodium-glucose cotransporter 2 inhibitor.

Finally, we observed no differences in the occurrence of arrhythmia admissions. We did not expect SGLT2i to have a direct effect on these admissions, nor do we see this as a robust marker for HF status. Supraventricular arrhythmias are common in ACHD-related HF and often related to scar tissue, especially in complex cohorts such as systemic RV patients.

**STUDY LIMITATIONS.** The decision to start SGLT2i therapy was at the discretion of the physician, introducing potential selection bias. There were no standardized follow-up protocols across the participating centers, which resulted in variable follow-up assessments. The heterogeneity of the ACHD population and relative overrepresentation of complex ACHD patients in the current study should be noted, as should the relatively limited follow-up duration. Although the study was not powered for “hard endpoints” such as mortality and HF hospitalizations, a promising reduction in HF hospitalization rate was observed. Keeping these limitations in mind, this study design allowed a real-world evaluation of SGLT2i in the ACHD population.

**FUTURE DIRECTIONS.** The positive results presented in this study provide a strong foundation to justify a prospective randomized trial to further elucidate the effects of SGLT2i on ACHD-related HF. Moreover, further follow-up is required to perform dedicated neurohormonal biomarker and imaging studies to evaluate the mechanistic effects of SGLT2i in the larger ACHD-related HF subgroups such as tetralogy of Fallot, univentricular circulation/Fontan, and systemic RV patients.

## CONCLUSIONS

This study is the largest to date to evaluate the use of SGLT2i in the ACHD population. SGLT2i were well-tolerated and safe in 174 patients with ACHD, with similar side effects and treatment discontinuation rates to the SGLT2i trials in conventional HF patients. In 162 patients who received SGLT2i for HF, SGLT2i therapy was associated with a 3-fold reduction in HF hospitalization rate during follow-up compared to before treatment. These positive results might

indicate a prognostic benefit and warrant further prospective randomized investigation of the potential benefits of SGLT2i for ACHD-related HF.

## FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Neijenhuis has received support from the Foundation “De Drie Lichten” (Hilversum, the Netherlands), AstraZeneca, and the Leiden University Medical Center research council Cardio-Vascular cluster Themes for Innovation funding. Dr Zemrak has received speaker fees from Abbott Laboratories. Dr Rotmans has received an unrestricted research grant from AstraZeneca. Dr Jongbloed has received support from the Leiden University Medical Center research council Cardio-Vascular cluster Themes for Innovation funding; and has received a personal grant from the NWO/ZonMw (The Hague, the Netherlands), the Bontius Foundation (Leiden, the Netherlands), and the Rembrandt Institute (Leiden, the Netherlands). Dr Egorova has received support from the Leiden University Medical Center research council Cardio-Vascular cluster Themes for Innovation funding; and has received consultancy and speaker fees from Boston Scientific Corporation and Medtronic Inc. The Department of Cardiology of the Leiden University Medical Center has received unrestricted research and educational grants from Boston Scientific Corporation, Medtronic, and Biotronik. The funders were not involved in study design, collection, analysis, interpretation of data, the writing of this paper, or the decision to submit it for publication. No artificial intelligence programs contributed to the compilation of the submitted manuscript. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

**ADDRESS FOR CORRESPONDENCE:** Dr Anastasia D. Egorova, Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands. E-mail: [a.egorova@lumc.nl](mailto:a.egorova@lumc.nl). [@LUMC\\_Leiden](mailto:@LUMC_Leiden).

## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL

**SKILLS:** SGLT2i are an established component of guideline-directed medical therapy for patients with HF. In clinical practice, SGLT2i generally seem safe, well-tolerated, and potentially beneficial in patients with ACHD.

**TRANSLATIONAL OUTLOOK:** HF is the principal cause of morbidity and mortality in patients with ACHD, but more research is required to expand evidence-based treatment options and develop structured protocols to guide therapy for patients with defined types of ACHD.

## REFERENCES

1. Brida M, Lovrić D, Griselli M, Riesgo Gil F, Gatzoulis MA. Heart failure in adults with congenital heart disease. *Int J Cardiol*. 2022;357:39–45.
2. 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;8:2940–2950.
3. Ladouceur M, Valdeolmillos E, Karsenty C, Hascoet S, Mocerit P, Le Gloan L. Cardiac drugs in ACHD cardiovascular medicine. *J Cardiovasc Dev Dis*. 2023;10:190.
4. Baumgartner H, De Backer J, Babu-Narayan SV, et al. 2020 ESC guidelines for the management of adult congenital heart disease. *Eur Heart J*. 2021;42:563–645.
5. Stout KK, Daniels CJ, Aboulhosn JA, et al. 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(12):e81-e192.
6. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599-3726.
  7. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2023;44:3627-3639.
  8. Lopuschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *J Am Coll Cardiol Basic Trans Science*. 2020;5:632-644.
  9. 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.
  10. Egorova AD, Nederend M, Tops LF, Vliegen HW, Jongbloed MRM, Kiës P. The first experience with sodium-glucose cotransporter 2 inhibitor for the treatment of systemic right ventricular failure. *ESC Heart Fail*. 2022;9:2007-2012.
  11. Saef J, Sundaravel S, Ortega-Legaspi J, Vaikunth S. Safety and treatment experience with sodium/glucose cotransporter-2 inhibitors in adult patients with congenital heart disease. *J Card Fail*. 2023;29:974-975.
  12. Muneuchi J, Sugitani Y, Kobayashi M, Ezaki H, Yamada H, Watanabe M. Feasibility and safety of sodium glucose cotransporter-2 inhibitors in adults with heart failure after the fontan procedure. *Case Rep Cardiol*. 2022;2022:5243594.
  13. Konduri A, West C, Lowery R, et al. Experience with SGLT2 inhibitors in patients with single ventricle congenital heart disease and fontan circulatory failure. *Pediatr Cardiol*. Published online November 2, 2023. <https://doi.org/10.1007/s00246-023-03332-5>
  14. Bozkurt B, Coats AJS, 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.
  15. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *Circulation*. 2018;137:961-972.
  16. Leberher C, Gerhardus M, Lammers AE, et al. Late outcome, therapy and systemic ventricular function in patients with a systemic right ventricle: data of the German National Register for Congenital Heart Defects. *Cardiol Young*. 2021;1-11.
  17. Woudstra OI, Kuijpers JM, Jongbloed MRM, et al. Medication in adults after atrial switch for transposition of the great arteries: clinical practice and recommendations. *Eur Heart J Cardiovasc Pharmacother*. 2022;8:77-84.
  18. Woudstra OI, Kuijpers JM, Meijboom FJ, et al. High burden of drug therapy in adult congenital heart disease: polypharmacy as marker of morbidity and mortality. *Eur Heart J Cardiovasc Pharmacother*. 2019;5:216-225.
  19. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995-2008.
  20. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413-1424.
  21. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387:1089-1098.
  22. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451-1461.
  23. Mascolo A, Di Napoli R, Balzano N, et al. Safety profile of sodium glucose co-transporter 2 (SGLT2) inhibitors: a brief summary. *Front Cardiovasc Med*. 2022;9:1010693.
  24. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier gangrene associated with sodium-glucose cotransporter-2 inhibitors: a review of spontaneous postmarketing cases. *Ann Intern Med*. 2019;170:764-769.
  25. Umanath K, Testani JM, Lewis JB. "Dip" in eGFR: stay the course with SGLT-2 inhibition. *Circulation*. 2022;146:463-465.
  26. Baggen VJ, van den Bosch AE, Eindhoven JA, et al. Prognostic value of N-terminal pro-B-type natriuretic peptide, troponin-T, and growth-differentiation factor 15 in adult congenital heart disease. *Circulation*. 2017;135:264-279.
  27. Popelová JR, Kotaška K, Tomková M, Tomek J. Usefulness of N-terminal pro-brain natriuretic peptide to predict mortality in adults with congenital heart disease. *Am J Cardiol*. 2015;116:1425-1430.
  28. Januzzi JL, Zannad F, Anker SD, et al. Prognostic importance of NT-proBNP and effect of empagliflozin in the EMPEROR-Reduced trial. *J Am Coll Cardiol*. 2021;78:1321-1332.
  29. Cunningham JW, Myhre PL. NT-proBNP response to heart failure therapies. *J Am Coll Cardiol*. 2021;78:1333-1336.
  30. Burchill LJ, Gao L, Kovacs AH, et al. Hospitalization trends and health resource use for adult congenital heart disease-related heart failure. *J Am Heart Assoc*. 2018;7:e008775.
  31. Lal S, Kotchetkova I, Cao J, Jackson D, Cordina R, Celermajer DS. Heart failure admissions and poor subsequent outcomes in adults with congenital heart disease. *Eur J Heart Fail*. 2018;20:812-815.
  32. Zomer AC, Vaartjes I, van der Velde ET, et al. Heart failure admissions in adults with congenital heart disease; risk factors and prognosis. *Int J Cardiol*. 2013;168:2487-2493.
  33. Chatur S, Kondo T, Claggett BL, et al. Effects of dapagliflozin on heart failure hospitalizations according to severity of inpatient course: insights from DELIVER and DAPA-HF. *Eur J Heart Fail*. 2023;25:1364-1371.

---

**KEY WORDS** congenital heart disease, heart failure, pharmacotherapy, sodium-glucose cotransporter 2 inhibitors

---

**APPENDIX** For supplemental tables and figures, please see the online version of this paper.