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Cardiac rehabilitation and adverse events among adult patients with simple congenital heart disease and heart failure

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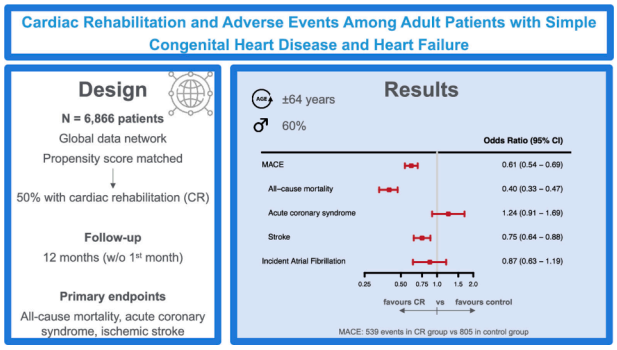
GRAPHICAL ABSTRACT



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ABSTRACT

Aims: Improved care has resulted in prolonged survival of patients with congenital heart disease (ConHD), increasing age-related cardiovascular comorbidities. Although cardiovascular rehabilitation (CR) represents evidence-based care for heart failure (HF), the clinical impact of CR in patients with ConHD who developed HF during adulthood is unclear. We investigated 12-month mortality and morbidity in patients with simple ConHD diagnosed with HF with CR versus without CR.

Methods: A retrospective cohort study was conducted for the time period February 2004 - February 2024. Utilizing TriNetX, a global federated health research network, a real-world dataset of simple ConHD patients was acquired to compare patients with vs. without (controls) prescription for exercise-based CR. Patients were propensity-score matched for age, sex, ethnicity, comorbidities, procedures, and medication. The primary

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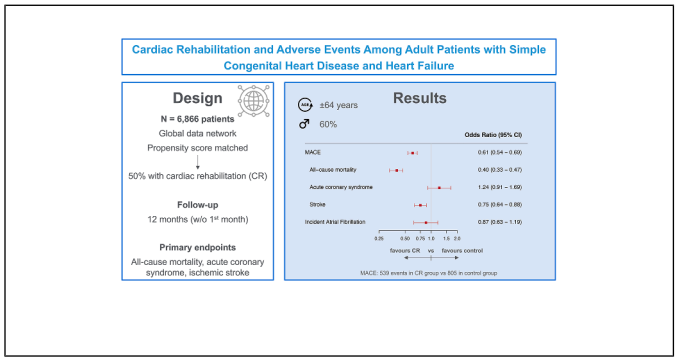
outcome was a composite of all-cause mortality, ischemic stroke, and acute coronary syndrome (major adverse cardiovascular events; MACE) within 12 months.
Results: Following propensity score matching, the total cohort consisted of 6,866 simple ConHD patients with HF. CR was associated with significantly lower odds for MACE (odds ratio (OR) 0.61 [95 % confidence interval (CI): 0.54–0.69]) and its individual components all-cause mortality (OR 0.40 [95 % CI 0.33–0.47]) and ischemic stroke (OR 0.75 [95 % CI 0.64–0.88]), but not acute coronary syndrome (OR 1.24 [95 % CI 0.91–1.69]).
Conclusion: CR was associated with significantly lower 12-month MACE in patients with simple ConHD with concomitant HF compared to usual care.



1. Introduction

Congenital Heart Disease (ConHD) consists of developmental abnormalities of the heart, potentially combined with abnormalities of the (intrathoracic) vessels, leading to a wide variety in conditions and concomitant pathophysiologic and clinical complexity [1]. Due to significant improvements in clinical care over the last decades, mortality rate for ConHD has decreased substantially [2]. Consequently, characteristics of the population of patients with ConHD have changed. First, without substantial changes in incidence, the prevalence of patients with ConHD has increased. [2,3] Second, due to improvements in survival, the mean age of this population has increased. Third, because of the higher age, ConHD patients increasingly experience age-related cardiovascular comorbidities, in addition to already being susceptible to heart failure (HF). [4–8] Altogether, these changes pose new challenges for ConHD patients during adulthood in the prevention and treatment of cardiovascular comorbidities.

There is substantial evidence for clinical benefit of exercise-based cardiac rehabilitation (CR) in the management of cardiovascular diseases, such as coronary heart disease (CHD) and HF. [9–11] Beyond exercise alone, contemporary cardiac rehabilitation includes an integrated 'cardiovascular health' rehabilitation approach [12,13]. Research showed that CR reduces all-cause mortality in patients with CHD, and reduces hospital admissions and improvements in health-related quality of life in HF. [9,14] Patients with ConHD are typically excluded from these trials investigating CR. Additionally the heterogeneity in ConHD make it challenging to perform randomized trials to evaluate the effects of CR in this population specifically. Although physicians have been conservative in their advice regarding physical activity for patients with ConHD, moderate-intensity exercise training is demonstrated to be safe and efficacious to improve physical fitness in this population. [1,15] To date, studies have not evaluated the effects of exercise-based CR on clinical endpoints in patients with ConHD. [3]

Given the increasing number of cardiovascular comorbidities in ConHD and the effectiveness of exercise-based CR in non-ConHD patients, [10] this study aimed to investigate the association between CR prescription and 12-month major adverse cardiac events (MACE; all-cause mortality, acute coronary syndrome, and ischemic stroke). Given the challenges of performing randomized-controlled trials in patients with simple ConHD, we performed a propensity matched cohort study using a real-world global federated database to explore the potential of CR in patients with ConHD and concomitant HF. We hypothesized that CR is associated with lower MACE in patients with simple ConHD.

2. Methods

2.1. Study design and population

Using anonymized data within TriNetX, a global federated health research network with access to electronical medical records (EMRs) from participating healthcare organizations, a retrospective observational study was conducted. The participating organizations are predominantly located in the USA, including academic medical centers, specialty physician practices, and community hospitals.

Simple ConHD was defined in line with guidelines and previous work [1,6], i.e., atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA), or isolated Pulmonary Valve Stenosis (PVS). These were identified using International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-10-CM) codes in patient EMRs. ASD: Q21.1, VSD: Q21.0, PDA: Q25.0, PVS: I37.0. Cardiac Rehabilitation was identified from procedural codes: SNOMED (313395003, 395698004, 395699007) HCPCS (S9472, G0422), and CPT (93797, 93798, 1013171) and was prescribed in adulthood within 6 months of HF diagnosis (ICD-10-EM: I50). This study is reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary file) [16]. Ethical approval was not required for research studies using the TriNetX research network, since no patient identifiable information is received.

2.2. Data collection

On February 8th, 2024, the TriNetX network was searched from February 2004 to February 2024, acquiring an online real-world dataset of patients aged 18 years or older with simple ConHD. For the cohorts, patients with simple ConHD receiving CR within 6 months of HF diagnosis were identified from at least 12 months prior to the search date to ensure a minimum follow-up of 1 year after diagnosis/CR. At the time of the search, 78 participating healthcare organizations had data available for patients meeting the inclusion criteria.

2.3. Clinical outcomes

The primary composite endpoint, i.e., MACE, included all-cause mortality, acute coronary syndrome, and ischemic stroke. Secondary endpoints included the individual MACE components and atrial fibrillation. All endpoints were assessed during the 12-month follow-up period. Endpoints occurring during the first month of follow-up after the prescription date of CR were excluded, since these were deemed unlikely to be affected by CR and/or timings of events may have been misclassified.

2.4. Statistical analysis

All analyses were performed on the TriNetX online platform. Continuous variables at baseline were compared using an independent-sample *t*-tests, categorical variables were compared using chi-squared test. Exercise-based CR is typically prescribed following an acute coronary syndrome, HF, or after a revascularization procedure either planned or unplanned. Therefore, propensity score matching (PSM) was used to adjust for these indications. The patients with versus without CR prescription were 1:1 matched using logistic regression for age, sex, ethnicity, cardiovascular diseases (e.g., ischemic heart disease, hypertension), and cardiovascular medications (e.g., calcium channel blockers, beta-blockers, lipid lowering agents). These characteristics were selected for PSM since they are known cardiovascular risk factors. Additionally, characteristics significantly different between groups at baseline were added. PSM on the TriNetX platform uses a greedy nearest-neighbor matching with a caliper of 0.1 standard deviations of the samples estimated propensity scores. Only complete cases were analyzed. After PSM, incidence of MACE, individual components, and AF were analyzed at 12-months follow-up using logistic regression, producing odds ratios (ORs) with 95 % confidence intervals (CI). A subgroup analysis we analyzed patients with HF with reduced Ejection Fraction (ICD I50.2) and patients with Heart Failure with preserved Ejection Fraction (HFpEF) (ICD I50.3) separately. A sensitivity analysis examining the incidence of MACE was performed in patients who had a correction procedure (codes reported in supplemental table S2), $P < 0.05$ was considered significant. The entire cohort had an electronic medical record of HF; however, this is presented as 98 % in the baseline characteristics table as these present characteristics up to one day prior to the index event (i.e. when a patient meets all eligibility criteria).

3. Results

Before PSM, the cohort consisted of 107,377 patients with simple ConHD and concomitant HF. From this study population, 3643 patients were prescribed CR within 6 months following HF diagnosis (Table 1). ConHD patients with CR were older (64.1 ± 15.1 vs 52.9 ± 28.3, $p < 0.001$), the group showed a higher proportion of white ethnicity (76.9% vs 64.6 %, $p < 0.001$), and reported more health conditions, cardiovascular procedures, and medication use than ConHD patients without CR (Table 1).

Following PSM, the total cohort consisted of 6866 patients with CR ($n = 3433$) and without CR ($n = 3433$) (Table 1). Although age remained significantly different (CR: 64.1 ± 15.2 vs no CR: 64.9 ± 17.9, $p = 0.03$), no differences between groups were observed for cardiovascular comorbidities, including hypertensive disease, ischemic heart disease, and diabetes mellitus nor for prescription of antiarrhythmics or HF medications, such as ACE-inhibitors. (Table 1) Overall, the cohorts were deemed to be well matched.

3.1. Cardiac rehabilitation: clinical outcomes

After PSM, MACE at 12 months occurred in 16 % of patients with CR (539 of 3433 patients) and in 23 % of patients without CR (805 out of

Table 1
Characteristics of included cohort of simple ConHD patients, before and after propensity score matching.

	Initial Populations			Propensity-score matched populations		
	Simple ConHD and HF + CR	Simple ConHD and HF - CR	P-value	Simple ConHD and HF + CR	Simple ConHD and HF - CR	P-value
Patients	3605	100,130		3433	3433	
Age	64.1 +/- 15.1	52.9 +/- 28.3	<0.001	64.1 +/- 15.2	64.9 +/- 17.9	0.03
Sex						
Male	2199 (61.0 %)	49,743 (49.70 %)	<0.001	2064 (60.10 %)	20,38 (59.40 %)	0.522
Ethnicity						
Black or African American	431 (12.0 %)	15,440 (15.40 %)	<0.001	422 (12.30 %)	442 (12.90 %)	0.467
American Indian/Alaska Native	27 (0.70 %)	415 (0.40 %)	0.002	23 (0.70 %)	20 (0.60 %)	0.646
White	2773 (76.90 %)	647,05 (64.60 %)	<0.001	2620 (76.30 %)	2588 (75.40 %)	0.367
Asian	72 (2.0 %)	25,39 (2.50 %)	0.043	70 (2.0 %)	65 (1.90 %)	0.664
Other	68 (1.90 %)	26,82 (2.70 %)	0.004	64 (1.90 %)	68 (2.0 %)	0.725
Medical History						
Hypertensive Disease	3186 (88.40 %)	58,765 (58.70 %)	<0.001	3025 (88.10 %)	30,68 (89.40 %)	0.101
Ischemic Heart Disease	30,77 (85.40 %)	39,569 (39.50 %)	<0.001	2906 (84.60 %)	2946 (85.80 %)	0.174
Cerebrovascular Disease	1489 (41.30 %)	24,087 (24.10 %)	<0.001	1415 (41.20 %)	1432 (41.70 %)	0.677
Pulmonary Heart Disease/diseases of Pulmonary Circulation	1681 (46.60 %)	19,719 (19.70 %)	<0.001	1560 (45.40 %)	1575 (41.70 %)	0.677
Diseases of Nervous System	3003 (83.30 %)	50,684 (50.60 %)	<0.001	2845 (82.90 %)	2876 (83.80 %)	0.316
Congenital Malformations, deformations, and chromosomal abnormalities	2791 (77.40 %)	42,475 (42.40 %)	<0.001	2619 (76.30 %)	2620 (76.30 %)	0.977
Neoplasms	1820 (50.50 %)	30,106 (30.10 %)	<0.001	1718 (50.0 %)	1779 (51.80 %)	0.141
Heart Failure	3564 (98.90 %)	3,9481 (39.40 %)	<0.001	3392 (98.80 %)	3396 (98.90 %)	0.649
Diabetes Mellitus	1651 (45.50 %)	27,256 (27.20 %)	<0.001	1559 (45.40 %)	1593 (46.40 %)	0.41
Acute kidney failure and CKD	1935 (53.70 %)	28,102 (28.10 %)	<0.001	1842 (53.70 %)	1865 (54.30 %)	0.578
Cardiovascular Procedures	3593 (88.40 %)	58,765 (58.70 %)	<0.001	3421 (99.70 %)	3414 (99.40 %)	0.208
Correction Procedures*	600 (16.64 %)	7450 (7.44 %)				
Medication						
Antiarrhythmics	3185 (88.30 %)	45,755 (45.70 %)	<0.001	3013 (87.80 %)	3001 (87.40 %)	0.66
Beta blockers	3201 (88.80 %)	49,512 (49.40 %)	<0.001	3034 (88.40 %)	3058 (89.10 %)	0.36
Diuretics	3222 (89.40 %)	52,613 (52.50 %)	<0.001	3052 (89.90 %)	3026 (88.10 %)	0.325
Antilipemic	2889 (80.10 %)	40,801 (40.70 %)	<0.001	2722 (79.30 %)	2720 (79.20 %)	0.953
Antianginals	2439 (67.70 %)	23,116 (23.10 %)	<0.001	2271 (66.20 %)	2290 (66.70 %)	0.627
Calcium channel blockers	2349 (65.20 %)	31,486 (31.40 %)	<0.001	2202 (64.10 %)	2200 (64.10 %)	0.96
ACE-inhibitors	2127 (59.0 %)	33,118 (33.10 %)	<0.001	2028 (59.10 %)	2042 (59.50 %)	0.731
Antihypertensives	1882 (52.20 %)	23,327 (23.30 %)	<0.001	1770 (51.60 %)	1774 (51.70 %)	0.923
Angiotensin Receptor Blockers	1311 (36.40 %)	17,144 (17.10 %)	<0.001	1227 (35.70 %)	1218 (35.50 %)	0.821

ConHD, congenital heart disease; CR, cardiac rehabilitation; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; Cardiovascular procedures include echocardiography, catheterization, cardiac devices, and electrophysiological procedures.

* Due to multiple procedure codes for a relatively small sample size, propensity score matching was unable to be performed for correction procedures.

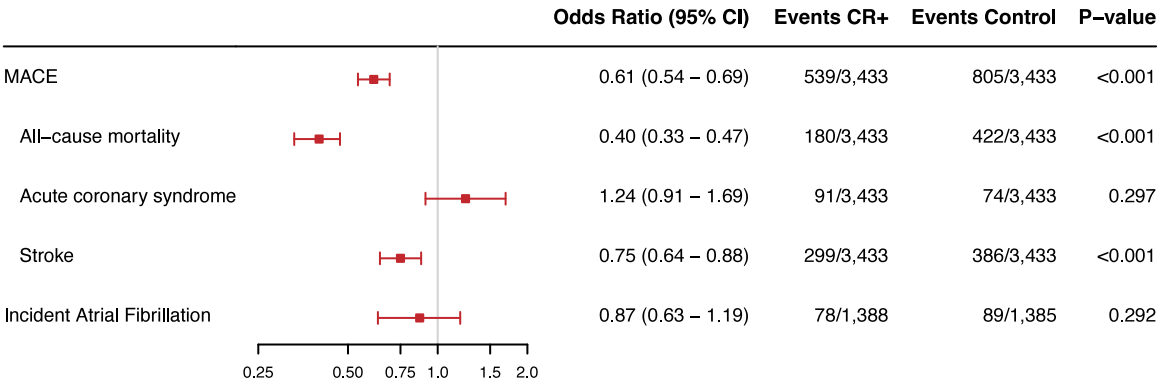


Fig. 1. Forest plot for the association of cardiac rehabilitation and endpoints and incidence of occurrence per group. Odds ratio presented for the group with cardiac rehabilitation (CR+) versus without cardiac rehabilitation (control) prescription. MACE, major adverse cardiac events; CI, confidence interval.

3433, $P < 0.001$). A significant association with MACE was observed for those receiving CR compared to those without CR (OR 0.61 [95 % CI: 0.54 – 0.69)] (Fig. 1).

When investigating individual elements of MACE, odds of all-cause mortality and ischemic stroke were lower in patients with CR versus without CR (0.40 [95 % CI: 0.33 – 0.47] and 0.75 [95 % CI: 0.64 – 0.88], respectively). We found no significant associations between CR and acute coronary syndrome (OR 1.24 [95 % CI: 0.91 – 1.69]) nor incident AF (OR 0.87 [95 % CI 0.63 – 1.19]) compared to matched controls.

Sub-group analysis showed comparable odds ratios for MACE versus the original pooled analysis for both HFrEF (OR 0.61 [95 %CI 0.52–0.72]) and HFpEF (OR 0.59 [95 % CI 0.50 – 0.69]) (**Supplemental Figure S1**).

The sensitivity analysis including only patients who had a correction procedure (n = 1076 following propensity score matching) showed comparable odds ratios for MACE versus the original pooled analysis (OR 0.62 [95 %CI 0.44, 0.87]).

4. Discussion

The principal observation from this study suggests that prescription of CR was associated with a lower 12-month MACE, consisting of all-cause mortality, acute coronary syndrome, and ischemic stroke compared to patients without CR prescription. This finding seems mainly driven by lower odds for all-cause mortality and ischemic stroke.

Although clinical studies in patients with ConHD are highly challenging and scarce, recent literature showed CR programs are capable to improve exercise tolerance in patients with ConHD. [17] Sheng et al. found an increase in peak VO_2 of 2.5 ml/kg per minute (i.e., ±12 % improvement from baseline) in people with ConHD. This increase is in line with previous studies examining CR in heart failure [18], and highlights the efficacy of CR in patients with ConHD to improve physical fitness levels. To put this effect size into perspective, a 1-metabolic equivalent (MET; 3.5 ml O_2 per kg per minute) higher level of cardiorespiratory fitness has previously been associated with a 13 % risk reduction for all-cause mortality and CHD/CVD events in healthy individuals. [19] Whilst this suggests that CR could impact all-cause mortality and cardiovascular events, clinical studies on CR have typically excluded patients with ConHD. Moreover, follow-up data on clinical events in ConHD and CR is lacking. Additionally, since CR programs should by definition be comprehensive and consists of multiple modalities and core components[20], it remains unclear whether a specific component, such as exercise, a combination of multiple components, or a more general improvement in a patients integrated and holistic care contributes to our observations. To the best of our knowledge, our data provide the first suggestion that prescription of CR is associated with lower MACE in patients with ConHD (39 % lower odds of MACE with CR versus controls).

Currently, CR for HF is part of international HF guidelines [21], with studies showing lower HF related hospitalization and improved quality of life following exercise-based CR. [22] Despite these benefits, a Cochrane systematic review found no clear risk reduction (relative risk 0.89 [95 % CI 0.66 – 1.21]) for all-cause mortality within 1 year following CR. [10] In contrast, we observed that CR was associated with significantly lower all-cause mortality in patients with simple ConHD and HF. Additionally, the odds for ischemic stroke are lower for CR versus no CR. A possible explanation for these conflicting findings regarding all-cause mortality may be related to study design (i.e., randomized controlled trials versus database). Observational studies have inherent biases that need to be considered when interpreting the results, particularly selection bias, as patients were not randomized. It is possible less severely affected patients may have been referred for CR in this database study. Although speculative, another explanation for the potential mortality benefit of CR relates to a priori low physical activity levels in our cohort [23,24], since lower physical activity levels prior to CR may allow more potential for improvement of fitness [25] and consequently clinical outcomes. [26] At the very least, our data highlight a potential benefit of CR in patients with simple ConHD, although the underlying mechanisms remain to be investigated.

Further exploring the association of CR and MACE, lower odds were also observed for ischemic stroke in patients who were prescribed CR versus without CR. The potential benefit of CR in relation to ischemic stroke is of interest. Physical activity has numerous health benefits in multiple (chronic) conditions including hypertension and diabetes, [27] and is associated with reduced ischemic stroke incidence specifically. [28] Moreover, patients with simple ConHD seem to have an excess lifetime risk for ischemic stroke. [6] The relation between simple ConHD and an increased risk for ischemic stroke may be related to structural changes, such as venous to arterial shunt lesions and increased rate of atrial arrhythmias. [6,29] One should consider that etiology of ischemic stroke can be multiple (e.g., thromboembolic, atherosclerotic) and is unknown in our cohort. The possible underlying mechanism remains speculative and could be related to thromboembolic risk, arrhythmias and/or improved vascular health and could be subject for future research.

In contrast with our hypothesis, we found no significant association between CR and ACS or incident AF. Although previous studies showed that physical activity was associated with lower AF incidence in adults, [30–33] the impact of CR in relation to AF was mainly assessed in patients with a history of AF. [34–37] Similarly, whilst studies have often examined the effects of CR following ACS, not many studies specifically explored the effects of CR on ACS occurrence which was also included. Importantly, we should be careful in our interpretation given the relatively low incidence of both ACS (2.7 % versus 2.2 % in patients with and without CR, respectively) and AF (5.6 % versus 6.4 % in patients with and without CR, respectively). Altogether, these factors made it

difficult to evaluate the association of CR and AF within this population.

In a sub-group analysis, we compared the observed associations for CR between ConHD patients with HFrEF and HFpEF. In line with previous work reporting a similar distribution of HFpEF and HFrEF [21], we found stratifying by HFrEF ($n = 1819$) and HFpEF ($n = 1739$) resulted in comparably sized groups (Supplemental Table S1). Confirming our initial analysis, similar odds for MACE were observed in patients with simple ConHD and HFrEF or HFpEF, as well as in the sensitivity analysis including only patients who had received correction procedures ($n = 1076$), whilst no association was found for incident AF (Supplemental Figure S1).

Limitations. Although this study design allows for the investigation of CR in simple ConHD patients with HF, we acknowledge some limitations related to e.g., heterogeneity of disease and CR intervention, and selection bias. First, details of certain disease characteristics were not included in the analysis, for example information on the congenital heart defect (e.g., shunt size), detailed information on (surgical) corrections, and information pertaining to HF severity, thus hampering matching of groups based on disease severity. Additionally, the detail of data on clinical characteristics is limited, for example pertaining to comorbidity severity or anthropometrics. Although PSM effectively removed most *a priori* differences between groups, residual confounding might impact our results, including medical history and age. Second, we cannot exclude bias for CR prescription based on subject or disease characteristics, potentially affecting our results through selection bias by selecting the healthy patients, the patients possibly more receptive to lifestyle changes, or even patients with a healthier lifestyle a priori. Third, information on the CR program content (i.e., frequency, duration, intensity) and adherence was lacking, making it difficult to identify the optimal program for patients with ConHD and limiting generalizability. Finally, information on adverse events is based on EMRs and therefore events could be missed.

5. Conclusion

Taken together, prescription of CR after diagnosis of HF in patients with simple ConHD was associated with lower odds of MACE, mainly pertaining to all-cause mortality and ischemic stroke, at 12-months follow-up. Given the limitations, our observations warrant further studies to directly evaluate the effects of exercise-based CR in the management of this patient group. Indeed, these findings suggest a potential for exercise-based CR for clinical benefits in this relatively rare, but growing, patient population. Our observations are especially of interest since patients with ConHD seem at higher lifetime risk of cardiovascular disease, for which CR might be a non-pharmacological treatment option targeting multiple comorbidities. Additional studies to investigate the causality between CR and clinical events in this population are warranted.

Data availability

A request can be made to TriNetX (https://live.trinetx.com) to access data in the research network, costs may be applied, a data sharing agreement is necessary, and no patient identifiable information can be provided.

Author declaration

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property. We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

Key learning points

What is already known?

1. Improved care has resulted in prolonged survival of patients with congenital heart disease
2. Cardiovascular Rehabilitation represents evidence-based care for heart failure, however patients with congenital heart disease are often excluded from trials investigating long-term clinical outcome.
3. Cardiac rehabilitation programs are capable to improve exercise tolerance in congenital heart disease.

What this study adds?

1. This study using a global health research network suggests that cardiac rehabilitation for heart failure improves clinical outcomes in patients with congenital heart disease.
2. The association seems comparable for different types of heart failure.
3. Given the limitations of this study design, more research is required to explore the causal relationship between cardiac rehabilitation and clinical outcome.

CRediT authorship contribution statement

Benjamin JR Buckley: Writing – review & editing, Formal analysis, Conceptualization. **Thijs P. Kerstens:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Madeleine France-Ratcliffe:** Writing – review & editing, Formal analysis. **Gregory Y.H. Lip:** Writing – review & editing, Methodology, Conceptualization. **Dick HJ Thijssen:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

Declaration of competing interest

TK, MF, and DT: none declared. BJRB has received research funding from Bristol Myers Squibb (BMS)/Pfizer, Public Health England, MS Society, and NIHR. GYHL: Consultant and speaker for Bristol Myers Squibb (BMS)/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is co-principal investogator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 899871.

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Supplementary materials

Supplementary material associated with this article can be found, in

the online version, at doi:10.1016/j.ajpc.2024.100677.

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