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 Cardiac Rehabilitation and Adverse Events Among Adult Patients with Simple Congenital Heart Disease and Heart Failure

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Article

1 **Cardiac Rehabilitation and Adverse Events Among Adult Patients with Simple**

2 **Congenital Heart Disease and Heart Failure**

3 Running title: Cardiac Rehabilitation in Adult Simple Congenital Heart Disease

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25

26 Abstract

27 **Aims.** Improved care has resulted in prolonged survival of patients with congenital heart disease

28 (ConHD), increasing age-related cardiovascular comorbidities. Although cardiovascular rehabilitation

29 (CR) represents evidence-based care for heart failure (HF), the clinical impact of CR in patients with

30 ConHD who developed HF during adulthood is unclear. We investigated 12-month mortality and

31 morbidity in patients with simple ConHD diagnosed with HF with CR versus without CR.

32 **Methods.** A retrospective cohort study was conducted for the time period February 2004 - February

33 2024. Utilizing TriNetX, a global federated health research network, a real-world dataset of simple

34 ConHD patients was acquired to compare patients with vs. without (controls) prescription for exercise-

35 based CR. Patients were propensity-score matched for age, sex, ethnicity, comorbidities, procedures,

36 and medication. The primary outcome was a composite of all-cause mortality, ischemic stroke, and acute

37 coronary syndrome (major adverse cardiovascular events; MACE) within 12 months.

38 **Results.** Following propensity score matching, the total cohort consisted of 6,866 simple ConHD

39 patients with HF. CR was associated with significantly lower odds for MACE (odds ratio (OR) 0.61

40 [95% confidence interval (CI): 0.54–0.69]) and its individual components all-cause mortality (OR 0.40

41 [95% CI 0.33–0.47]) and ischemic stroke (OR 0.75 [95% CI 0.64–0.88]), but not acute coronary

42 syndrome (OR 1.24 [95% CI 0.91–1.69]).

43 **Conclusion.** CR was associated with significantly lower 12-month MACE in patients with simple

44 ConHD with concomitant HF compared to usual care.

45

46 Key Learning Points

47 What is already known?

48   1. Improved care has resulted in prolonged survival of patients with congenital heart disease

49   2. Cardiovascular Rehabilitation represents evidence-based care for heart failure, however patients
50   with congenital heart disease are often excluded from trials investigating long-term clinical
51   outcome.

52   3. Cardiac rehabilitation programs are capable to improve exercise tolerance in congenital heart
53   disease.

54 What this study adds?

55   1. This study using a global health research network suggests that cardiac rehabilitation for heart
56   failure improves clinical outcomes in patients with congenital heart disease.

57   2. The association seems comparable for different types of heart failure.

58   3. Given the limitations of this study design, more research is required to explore the causal
59   relationship between cardiac rehabilitation and clinical outcome.

60 *Key words:* Simple congenital heart disease – Exercise-based cardiac rehabilitation – Secondary
61 Prevention – Heart Failure

62

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

90 syndrome, and ischemic stroke). Given the challenges of performing randomized-controlled trials in

91 patients with simple ConHD, we performed a propensity matched cohort study using a real-world global

92 federated database to explore the potential of CR in patients with ConHD and concomitant HF. We

93 hypothesized that CR is associated with lower MACE in patients with simple ConHD.

94

Methods

95 **Methods**

96 **Study design and Population**

97 Using anonymized data within TriNetX, a global federated health research network with access to

98 electronical medical records (EMRs) from participating healthcare organizations, a retrospective

99 observational study was conducted. The participating organizations are predominantly located in the

100 USA, including academic medical centers, specialty physician practices, and community hospitals.

101 Simple ConHD was defined in line with guidelines and previous work [16], i.e., atrial septal defect (ASD),

102 ventricular septal defect (VSD), patent ductus arteriosus (PDA), or isolated Pulmonary Valve Stenosis

103 (PVS). These were identified using International Classification of Diseases, Ninth and Tenth Revisions,

104 Clinical Modification (ICD-10-CM) codes in patient EMRs. ASD: Q21.1, VSD: Q21.0, PDA: Q25.0,

105 PVS: I37.0. Cardiac Rehabilitation was identified from procedural codes: SNOMED (313395003,

106 395698004, 395699007) HCPCS (S9472, G0422), and CPT (93797, 93798, 1013171) and was

107 prescribed in adulthood within 6 months of HF diagnosis (ICD-10-EM: I50). This study is reported in

108 line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

109 guidelines (Supplementary file).[16] Ethical approval was not required for research studies using the

110 TriNetX research network, since no patient identifiable information is received.

111

112 **Data Collection**

113 On February 8th, 2024, the TriNetX network was searched from February 2004 to February 2024,

114 acquiring an online real-world dataset of patients aged 18 years or older with simple ConHD. For the

115   cohorts, patients with simple ConHD receiving CR within 6 months of HF diagnosis were identified

116   from at least 12 months prior to the search date to ensure a minimum follow-up of 1 year after

117   diagnosis/CR. At the time of the search, 78 participating healthcare organizations had data available for

118   patients meeting the inclusion criteria.

119

120   **Clinical outcomes**

121   The primary composite endpoint, i.e., MACE, included all-cause mortality, acute coronary syndrome,

122   and ischemic stroke. Secondary endpoints included the individual MACE components and atrial

123   fibrillation. All endpoints were assessed during the 12-month follow-up period. Endpoints occurring

124   during the first month of follow-up after the prescription date of CR were excluded, since these were

125   deemed unlikely to be affected by CR and/or timings of events may have been misclassified.

126

127   **Statistical Analysis**

128   All analyses were performed on the TriNetX online platform. Continuous variables at baseline were

129   compared using an independent-sample t-tests, categorical variables were compared using chi-squared

130   test. Exercise-based CR is typically prescribed following an acute coronary syndrome, HF, or after a

131   revascularization procedure either planned or unplanned. Therefore, propensity score matching (PSM)

132   was used to adjust for these indications. The patients with versus without CR prescription were 1:1

133   matched using logistic regression for age, sex, ethnicity, cardiovascular diseases (e.g., ischemic heart

134   disease, hypertension), and cardiovascular medications (e.g., calcium channel blockers, beta-blockers,

135   lipid lowering agents). These characteristics were selected for PSM since they are known cardiovascular

136   risk factors. Additionally, characteristics significantly different between groups at baseline were added.

137   PSM on the TriNetX platform uses a greedy nearest-neighbor matching with a caliper of 0.1 standard

138   deviations of the samples estimated propensity scores. Only complete cases were analyzed. After PSM,

139   incidence of MACE, individual components, and AF were analyzed at 12-months follow-up using

140   logistic regression, producing odds ratios (ORs) with 95% confidence intervals (CI). A sub-group

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).

Results

Before PSM, the cohort consisted of 107,377 patients with simple ConHD and concomitant HF. From

this study population, 3,643 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 6,866 patients with CR (n=3,433) and without CR

(n=3,433) (**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.

Cardiac Rehabilitation: Clinical outcomes.

After PSM, MACE at 12 months occurred in 16% of patients with CR (539 of 3,433 patients) and in

23% of patients without CR (805 out of 3,433, P<0.001). A significant association with MACE was

165 observed for those receiving CR compared to those without CR (OR 0.61 [95% CI: 0.54 – 0.69)] (**Figure**

166 **1**).

167 When investigating individual elements of MACE, odds of all-cause mortality and ischemic stroke were

168 lower in patients with CR *versus* without CR (0.40 [95% CI: 0.33 – 0.47] and 0.75 [95% CI: 0.64 –

169 0.88], respectively). We found no significant associations between CR and acute coronary syndrome

170 (OR 1.24 [95% CI: 0.91 – 1.69]) nor incident AF (OR 0.87 [95% CI 0.63 – 1.19]) compared to matched

171 controls.

172 Sub-group analysis showed comparable odds ratios for MACE versus the original pooled analysis for

173 both HFrEF (OR 0.61 [95%CI 0.52-0.72]) and HFpEF (OR 0.59 [95% CI 0.50 – 0.69]) (Supplemental

174 Figure S1).

175 The sensitivity analysis including only patients who had a correction procedure (n=1,076 following

176 propensity score matching) showed comparable odds ratios for MACE versus the original pooled

177 analysis (OR 0.62 [95%CI 0.44, 0.87]).

178 **Discussion**

179 The principal observation from this study suggests that prescription of CR was associated with a lower

180 12-month MACE, consisting of all-cause mortality, acute coronary syndrome, and ischemic stroke

181 compared to patients without CR prescription. This finding seems mainly driven by lower odds for all-

182 cause mortality and ischemic stroke.

183 Although clinical studies in patients with ConHD are highly challenging and scarce, recent literature

184 showed CR programs are capable to improve exercise tolerance in patients with ConHD. [17] Sheng et al.

185 found an increase in peak VO_2 of 2.5 ml/kg per minute (i.e., ±12% improvement from baseline) in people

186 with ConHD. This increase is in line with previous studies examining CR in heart failure,[18] and

187 highlights the efficacy of CR in patients with ConHD to improve physical fitness levels. To put this

188 effect size into perspective, a 1-metabolic equivalent (MET; 3.5 ml O_2 per kg per minute) higher level

189 of cardiorespiratory fitness has previously been associated with a 13% risk reduction for all-cause

190 mortality and CHD/CVD events in healthy individuals. [19] Whilst this suggests that CR could impact all-

191 cause mortality and cardiovascular events, clinical studies on CR have typically excluded patients with

192 ConHD. Moreover, follow-up data on clinical events in ConHD and CR is lacking. Additionally, since

193 CR programs should by definition be comprehensive and consists of multiple modalities and core

194 components[20], it remains unclear whether a specific component, such as exercise, a combination of

195 multiple components, or a more general improvement in a patients integrated and holistic care

196 contributes to our observations. To the best of our knowledge, our data provide the first suggestion that

197 prescription of CR is associated with lower MACE in patients with ConHD (39% lower odds of MACE

198 with CR versus controls).

199 Currently, CR for HF is part of international HF guidelines [21], with studies showing lower HF related

200 hospitalization and improved quality of life following exercise-based CR. [22] Despite these benefits, a

201 Cochrane systematic review found no clear risk reduction (relative risk 0.89 [95% CI 0.66 – 1.21]) for

202 all-cause mortality within 1 year following CR. [10] In contrast, we observed that CR was associated with

203 significantly lower all-cause mortality in patients with simple ConHD and HF. Additionally, the odds

204 for ischemic stroke are lower for CR *versus* no CR. A possible explanation for these conflicting findings

205 regarding all-cause mortality may be related to study design (i.e., randomized controlled trials versus

206 database). Observational studies have inherent biases that need to be considered when interpreting the

207 results, particularly selection bias, as patients were not randomized. It is possible less severely affected

208 patients may have been referred for CR in this database study. Although speculative, another explanation

209 for the potential mortality benefit of CR relates to a priori low physical activity levels in our cohort,[23,24]

210 since lower physical activity levels prior to CR may allow more potential for improvement of fitness [25]

211 and consequently clinical outcomes. [26] At the very least, our data highlight a potential benefit of CR in

212 patients with simple ConHD, although the underlying mechanisms remain to be investigated.

213 Further exploring the association of CR and MACE, lower odds were also observed for ischemic stroke

214 in patients who were prescribed CR *versus* without CR. The potential benefit of CR in relation to

215 ischemic stroke is of interest. Physical activity has numerous health benefits in multiple (chronic)

216 conditions including hypertension and diabetes, [27] and is associated with reduced ischemic stroke

217   incidence specifically. [28] Moreover, patients with simple ConHD seem to have an excess lifetime risk

218   for ischemic stroke. [6] The relation between simple ConHD and an increased risk for ischemic stroke

219   may be related to structural changes, such as venous to arterial shunt lesions and increased rate of atrial

220   arrhythmias. [6] [29] One should consider that etiology of ischemic stroke can be multiple (e.g.,

221   thromboembolic, atherosclerotic) and is unknown in our cohort. The possible underlying mechanism

222   remains speculative and could be related to thromboembolic risk, arrhythmias and/or improved vascular

223   health and could be subject for future research.

224   In contrast with our hypothesis, we found no significant association between CR and ACS or incident

225   AF. Although previous studies showed that physical activity was associated with lower AF incidence in

226   adults, [30-33] the impact of CR in relation to AF was mainly assessed in patients with a history of AF. [34-

227   37] Similarly, whilst studies have often examined the effects of CR following ACS, not many studies

228   specifically explored the effects of CR on ACS occurrence which was also included. Importantly, we

229   should be careful in our interpretation given the relatively low incidence of both ACS (2.7% versus

230   2.2% in patients with and without CR, respectively) and AF (5.6% versus 6.4% in patients with and

231   without CR, respectively). Altogether, these factors made it difficult to evaluate the association of CR

232   and AF within this population.

233   In a sub-group analysis, we compared the observed associations for CR between ConHD patients with

234   HFrEF and HFpEF. In line with previous work reporting a similar distribution of HFpEF and HFrEF [21],

235   we found stratifying by HFrEF (n=1,819) and HFpEF (n=1,739) resulted in comparably sized groups

236   (Supplemental Table S1). Confirming our initial analysis, similar odds for MACE were observed in

237   patients with simple ConHD and HFrEF or HFpEF, as well as in the sensitivity analysis including only

238   patients who had received correction procedures (n=1,076), whilst no association was found for incident

239   AF (Supplemental Figure S1).

240

241   *Limitations.* Although this study design allows for the investigation of CR in simple ConHD patients

242   with HF, we acknowledge some limitations related to e.g., heterogeneity of disease and CR intervention,

243 and selection bias. First, details of certain disease characteristics were not included in the analysis, for

244 example information on the congenital heart defect (e.g., shunt size), detailed information on (surgical)

245 corrections, and information pertaining to HF severity, thus hampering matching of groups based on

246 disease severity. Additionally, the detail of data on clinical characteristics is limited, for example

247 pertaining to comorbidity severity or anthropometrics. Although PSM effectively removed most *a priori*

248 differences between groups, residual confounding might impact our results, including medical history

249 and age. Second, we cannot exclude bias for CR prescription based on subject or disease characteristics,

250 potentially affecting our results through selection bias by selecting the healthy patients, the patients

251 possibly more receptive to lifestyle changes, or even patients with a healthier lifestyle a priori. Third,

252 information on the CR program content (i.e., frequency, duration, intensity) and adherence was lacking,

253 making it difficult to identify the optimal program for patients with ConHD and limiting generalizability.

254 Finally, information on adverse events is based on EMRs and therefore events could be missed.

255

256 **Conclusion**

257 Taken together, prescription of CR after diagnosis of HF in patients with simple ConHD was associated

258 with lower odds of MACE, mainly pertaining to all-cause mortality and ischemic stroke, at 12-months

259 follow-up. Given the limitations, our observations warrant further studies to directly evaluate the effects

260 of exercise-based CR in the management of this patient group. Indeed, these findings suggest a potential

261 for exercise-based CR for clinical benefits in this relatively rare, but growing, patient population. Our

262 observations are especially of interest since patients with ConHD seem at higher lifetime risk of

263 cardiovascular disease, for which CR might be a non-pharmacological treatment option targeting

264 multiple comorbidities. Additional studies to investigate the causality between CR and clinical events

265 in this population are warranted.

266

272   **Conflicts of interest**

273   TK, MF, and DT: none declared. BJRB has received research funding from Bristol Myers Squibb

274   (BMS)/Pfizer, Public Health England, MS Society, and NIHR. GYHL: Consultant and speaker for

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277   which has received funding from the European Union's Horizon 2020 research and innovation

278   programme under grant agreement No 899871.

279

280   **Author Contributions**

281   BB, TK, DT, GL were involved in conceptualization and design. BB and MFR conducted all statistical

282   analyses. TK and DT drafted the manuscript. All authors reviewed the results, revised it critically,

283   approved the final version of the manuscript and agreed to be accountable for all aspects of this work.

284

285   **Data availability**

286   A request can be made to TriNetX (https://live.trinetx.com) to access data in the research network, costs

287   may be applied, a data sharing agreement is necessary, and no patient identifiable information can be

288   provided.

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Figure legends

Figure 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 (CR-) prescription. MACE, major adverse cardiac events; CI,

confidence interval.

Supplemental Figure S1. Forest plot for the association of cardiac rehabilitation and endpoints and

incidence of occurrence per group and per type of heart failure. Odds ratio presented for the group with

cardiac rehabilitation (CR+) versus without cardiac rehabilitation (CR-) prescription. MACE, major

427   adverse cardiac events; HFrEF, Heart Failure with reduced Ejection Fraction; Heart Failure with

428   preserved Ejection Fraction; CI, confidence interval.

429

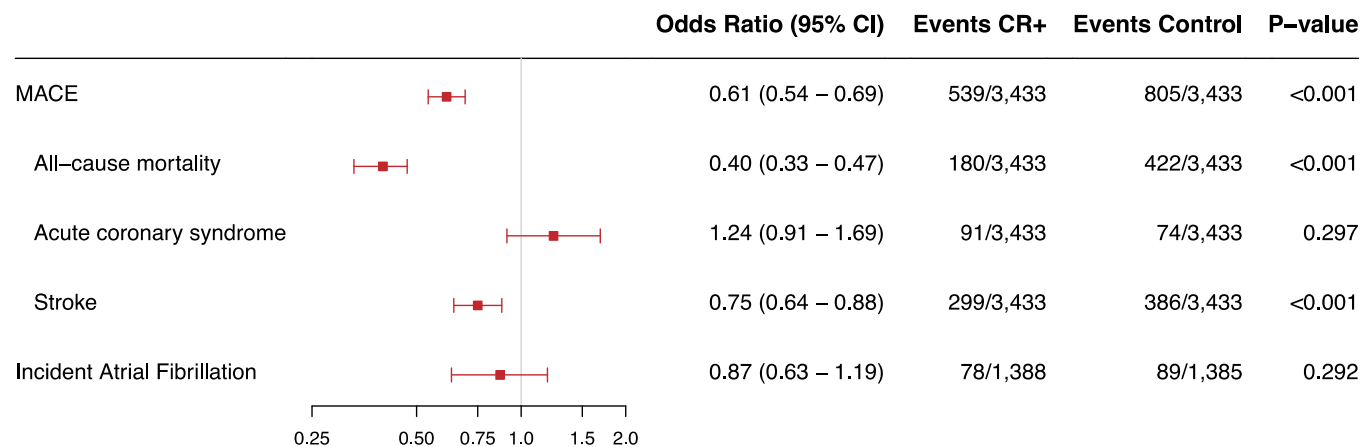Table 1. Characteristics of included cohort of simple ConHD patients, before and after propensity score matching.

	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	3,605	100,130		3,433	3,433	
Age	64.1 +/- 15.1	52.9 +/- 28.3	<0.001	64.1 +/- 15.2	64.9 +/- 17.9	0.03
Sex						
Male	2,199 (61.0%)	49,743 (49.70%)	<0.001	2,064 (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	2,773 (76.90%)	647,05 (64.60%)	<0.001	2,620 (76.30%)	2,588 (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	3,186 (88.40%)	58,765 (58.70%)	<0.001	3,025 (88.10%)	30,68 (89.40%)	0.101
Ischemic Heart Disease	30,77 (85.40%)	39,569 (39.50%)	<0.001	2,906 (84.60%)	2,946 (85.80%)	0.174
Cerebrovascular Disease	1,489 (41.30%)	24,087 (24.10%)	<0.001	1,415 (41.20%)	1,432 (41.70%)	0.677
Pulmonary Heart Disease/diseases of Pulmonary Circulation	1,681 (46.60%)	19,719 (19.70%)	<0.001	1,560 (45.40%)	1,575 (41.70%)	0.677
Diseases of Nervous System	3,003 (83.30%)	50,684 (50.60%)	<0.001	2,845 (82.90%)	2,876 (83.80%)	0.316
Congenital Malformations, deformations, and chromosomal abnormalities	2,791 (77.40%)	42,475 (42.40%)	<0.001	2,619 (76.30%)	2,620 (76.30%)	0.977
Neoplasms	1,820 (50.50%)	30,106 (30.10%)	<0.001	1,718 (50.0%)	1,779 (51.80%)	0.141
Heart Failure	3,564 (98.90%)	3,9481 (39.40%)	<0.001	3,392 (98.80%)	3,396 (98.90%)	0.649
Diabetes Mellitus	1,651 (45.50%)	27,256 (27.20%)	<0.001	1,559 (45.40%)	1,593 (46.40%)	0.41

Acute kidney failure and CKD	1,935 (53.70%)	28,102 (28.10%)	<0.001	1,842 (53.70%)	1,865 (54.30%)	0.578
Cardiovascular Procedures	3,593 (88.40%)	58,765 (58.70%)	<0.001	3,421 (99.70%)	3,414 (99.40%)	0.208
Correction Procedures*	600 (16.64%)	7,450 (7.44%)				
Medication						
Antiarrhythmics	3,185 (88.30%)	45,755 (45.70%)	<0.001	3,013 (87.80%)	3,001 (87.40%)	0.66
Beta blockers	3,201 (88.80%)	49,512 (49.40%)	<0.001	3,034 (88.40%)	3,058 (89.10%)	0.36
Diuretics	3,222 (89.40%)	52,613 (52.50%)	<0.001	3,052 (89.90%)	3,026 (88.10%)	0.325
Antilipemic	2,889 (80.10%)	40,801 (40.70%)	<0.001	2,722 (79.30%)	2,720 (79.20%)	0.953
Antianginals	2,439 (67.70%)	23,116 (23.10%)	<0.001	2,271 (66.20%)	2,290 (66.70%)	0.627
Calcium channel blockers	2,349 (65.20%)	31,486 (31.40%)	<0.001	2,202 (64.10%)	2,200 (64.10%)	0.96
ACE-inhibitors	2,127 (59.0%)	33,118 (33.10%)	<0.001	2,028 (59.10%)	2,042 (59.50%)	0.731
Antihypertensives	1,882 (52.20%)	23,327 (23.30%)	<0.001	1,770 (51.60%)	1,774 (51.70%)	0.923
Angiotensin Receptor Blockers	1,311 (36.40%)	17,144 (17.10%)	<0.001	1,227 (35.70%)	1,218 (35.50%)	0.821

431 ConHD, congenital heart disease; CR, cardiac rehabilitation; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; Cardiovascular procedures

432 include echocardiography, catheterization, cardiac devices, and electrophysiological procedures. *Due to multiple procedure codes for a relatively small sample

433 size, propensity score matching was unable to be performed for correction procedures.

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435

	Odds Ratio (95% CI)	Events CR+	Events Control	P–value
MACE	0.61 (0.54 – 0.69)	539/3,433	805/3,433	<0.001
All–cause mortality	0.40 (0.33 – 0.47)	180/3,433	422/3,433	<0.001
Acute coronary syndrome	1.24 (0.91 – 1.69)	91/3,433	74/3,433	0.297
Stroke	0.75 (0.64 – 0.88)	299/3,433	386/3,433	<0.001
Incident Atrial Fibrillation	0.87 (0.63 – 1.19)	78/1,388	89/1,385	0.292

0.25   0.50   0.75   1.0   1.5   2.0

436

Figure 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.

439

Supplemental Table S1. Characteristics of included cohort of simple ConHD patients for sub-analysis after propensity-score matching

	HFrEF			HFpEF		
	Simple ConHD + CR	Simple ConHD - CR	P-value	Simple ConHD + CR	Simple ConHD - CR	P-value
Patients	1,819	1,819		1,739	1,739	
Age	63.1 ± 14.8	63.4 ± 18.7	0.645	67.2 ± 13.9	67.4 ± 16.5	0.704
Sex						
Male	1,165 (64.0%)	1,140 (62.7%)	0.390	975 (56.1%)	991 (57.0%)	0.584
Ethnicity						
Black or African American	278 (15.3%)	276 (15.2%)	0.926	190 (10.9%)	193 (11.1%)	0.871
American Indian/Alaska Native	13 (0.7%)	19 (1.0%)	0.287	10 (0.6%)	10 (0.6%)	1.000
White	1,326 (72.9%)	1,320 (72.6%)	0.823	1,362 (78.3%)	1,361 (78.3%)	0.967
Asian	42 (2.3%)	43 (2.4%)	0.913	28 (1.6%)	19 (1.1%)	0.186
Other	45 (2.5%)	42 (2.3%)	0.745	28 (1.6%)	27 (1.6%)	0.892
Medical History						
Hypertensive Disease	1,620 (89.1%)	1,619 (89.0%)	0.958	1,593 (91.6%)	1,590 (91.4%)	0.855
Ischemic Heart Disease	1,574 (86.5%)	1,567 (86.1%)	0.735	1,526 (87.8%)	1,531 (88.0%)	0.795
Cerebrovascular Disease	743 (40.8%)	759 (41.7%)	0.590	826 (47.5%)	824 (47.4%)	0.946
Pulmonary Heart Disease/diseases of Pulmonary Circulation	931 (51.2%)	916 (50.4%)	0.619	931 (53.5%)	928 (53.4%)	0.919
Diseases of Nervous System	1,494 (82.1%)	1,522 (83.7%)	0.218	1,536 (88.3%)	1,548 (89.0%)	0.521
Congenital Malformations, deformations, and chromosomal abnormalities	1,350 (74.2%)	1,360 (74.8%)	0.704	1,391 (80.0%)	1,413 (81.3%)	0.345
Neoplasms	875 (48.1%)	927 (51.0%)	0.085	1,008 (58.0%)	1,028 (59.1%)	0.491
Heart Failure	1,810 (99.5%)	1,810 (99.5%)	1.000	1,726 (99.3%)	1,723 (99.1%)	0.576
Diabetes Mellitus	890 (48.9%)	895 (49.2%)	0.868	854 (49.1%)	851 (48.9%)	0.919
Acute kidney failure and CKD	1,139 (62.6%)	1,154 (63.4%)	0.606	1,048 (60.3%)	1,051 (60.4%)	0.917

Cardiovascular Procedures	1,810 (99.8%)	1,810 (99.8%)	1.000	1,735 (99.8%)	1,732 (99.6%)	0.365
Medication						
Antiarrhythmics	1,610 (88.5%)	1,615 (88.8%)	0.794	1,612 (92.7%)	1,612 (92.7%)	1.000
Beta blockers	1,638 (90.0%)	1,649 (90.7%)	0.537	1,615 (92.9%)	1,618 (93.0%)	0.842
Diuretics	1,676 (92.1%)	1,676 (92.1%)	1.000	1,622 (93.3%)	1,614 (92.8%)	0.594
Antilipemic	1,445 (76904)	1,439 (79.1%)	0.806	1,467 (84.4%)	1,470 (84.5%)	0.888
Antianginals	1,196 (64.7%)	1,166 (64.1%)	0.729	1,266 (72.8%)	1,239 (71.2%)	0.308
Calcium channel blockers	1,122 (61.7%)	1,082 (59.5%)	0.175	1,266 (72.8%)	1,225 (70.4%)	0.123
ACE-inhibitors	1,185 (65.1%)	1,212 (66.6%)	0.345	1,060 (61.0%)	1,067 (61.4%)	0.808
Antihypertensives	956 (52.6%)	949 (52.2%)	0.816	1,005 (57.8%)	1,009 (58.0%)	0.891
Angiotensin Receptor Blockers	715 (39.3%)	693 (38.1%)	0.454	693 (39.9%)	669 (35.5%)	0.404

441 ConHD, congenital heart disease; CR, cardiac rehabilitation; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; Cardiovascular procedures

442 include echocardiography, catheterization, cardiac devices, and electrophysiological procedures.
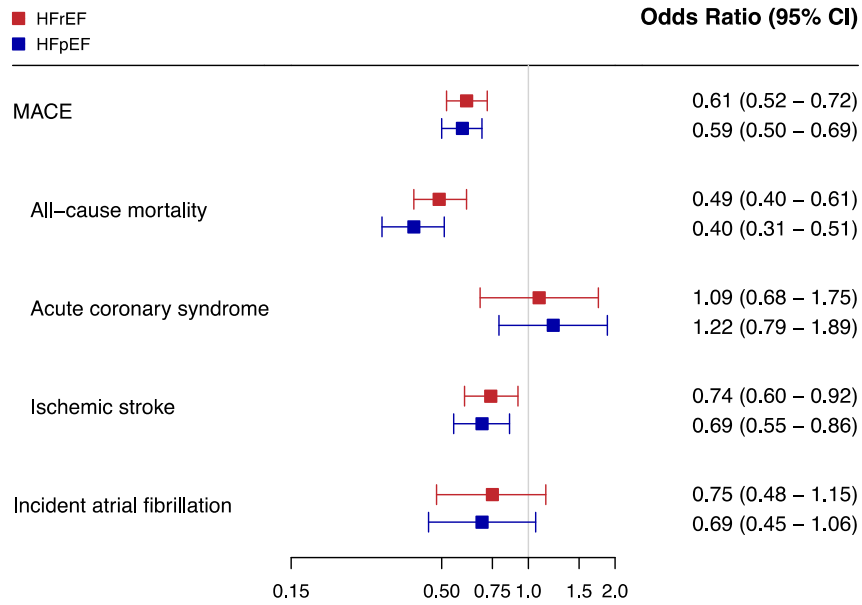
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444   Supplemental Table S2. CPT codes and prevalence of correction procedures for sensitivity analysis.

CPT Code	Simple ConHD + CR; % (n)	Simple ConHD – CR; % (n)
PDA Closure		
93582	0 (0)	3.94 (293)
33824	1.67 (10)	0.14 (10)
ASD closure codes		
33641	81.67 (490)	52.70 (3916)
33645	2 (12)	2.52 (187)
33660	1.67 (10)	1.88 (140)
VSD defect repairs		
33681	6.17 (37)	18.45 (1371)
33684	0 (0)	1.05 (78)
33688	0 (0)	0.58 (43)
33675	0 (0)	0.98 (73)
33676	0 (0)	0.24 (18)
33677	0 (0)	0.28 (21)
Procedures on the Pulmonary Valve		
33471	0 (0)	0.14 (10)
33474	1.67 (10)	2.22 (165)
33475	7.17 (43)	8.09 (601)
33476	1.67 (10)	3.90 (290)
33477	2.83 (17)	4.28 (318)
33478	1.83 (11)	3.55 (264)
Endovascular Repair of Congenital Heart and Vascular Defects		
33894	1.67 (10)	0.14 (10)
33895	0 (0)	0.15 (11)
33897	0 (0)	0.35 (26)
Cardiac Catheterization for Congenital Defects		
93593	1.67 (10)	1.67 (124)
93594	1.67 (10)	2.64 (196)
93595	1.67 (10)	0.36 (27)
93596	1.67 (10)	3.19 (237)
93597	1.67 (10)	9.74 (724)

445   ConHD, congenital heart disease; CR, cardiac rehabilitation.

446

447

	Odds Ratio (95% CI)
■ HFrEF	
■ HFpEF	
MACE	0.61 (0.52 – 0.72)
	0.59 (0.50 – 0.69)
All–cause mortality	0.49 (0.40 – 0.61)
	0.40 (0.31 – 0.51)
Acute coronary syndrome	1.09 (0.68 – 1.75)
	1.22 (0.79 – 1.89)
Ischemic stroke	0.74 (0.60 – 0.92)
	0.69 (0.55 – 0.86)
Incident atrial fibrillation	0.75 (0.48 – 1.15)
	0.69 (0.45 – 1.06)

448

449 **Supplemental Figure S1.** Forest plot for the association of cardiac rehabilitation and endpoints and

450 incidence of occurrence per group and per type of heart failure. Odds ratio presented for the group with

451 cardiac rehabilitation versus without cardiac rehabilitation prescription. MACE, major adverse cardiac

452 events; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced

453 Ejection Fraction; CI, confidence interval.