Research Letter

Exercise-based cardiac rehabilitation for cardiac implantable electronic device recipients

Benjamin J.R. Buckley, PhD[1,2*], Stephanie L. Harrison, PhD[1,2], Paula Underhill[3], David J. Wright, MD[1], Dick H.J. Thijssen, PhD,[4,5], Gregory Y.H. Lip, MD[1,2,4,6]

[1]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

[2]Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, United Kingdom

[3]TriNetX LLC., London, United Kingdom

[4]Liverpool Centre for Cardiovascular Science, Liverpool John Moores University, Liverpool, United Kingdom

[5]Research Institute for Health Science, Department of Physiology, Radboud university medical centerum, Nijmegen, The Netherlands

[6]Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Manuscript word count 986

***Corresponding author**

Dr Benjamin Buckley, Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, Liverpool, L7 8TX United Kingdom

Email: Benjamin.Buckley@liverpool.ac.uk.

Phone: +44 (0)151 794 2000

Exercise-based cardiac rehabilitation (CR) promotes secondary prevention of cardiovascular disease and is an essential component of routine care for patients with acute coronary syndrome, heart failure, and those undergoing revascularisation (e.g., coronary artery bypass graft or percutaneous coronary intervention).[1, 2]

Currently, millions of people in Europe live with a cardiac implantable electronic device (CIED) and the prevalence is increasing by hundreds of thousands every year. For example, according to the 2017 European Heart Rhythm Association (EHRA) report, 547,586 pacemakers, 105,730 implantable cardioverter-defibrillators (ICDs), and 87,654 cardiac resynchronization therapy (CRT) devices were implanted in 2016 alone.[3] Patients with CIEDs are also eligible for exercise-based CR and therefore form a large subset of patients who participate in such interventions.[2] However, evidence in support of exercise-based CR for patients with CIEDs is sparse.[4, 5]

The aim of the present study was to compare 1-year all-cause mortality, hospitalisation, atrial fibrillation (AF)/flutter and ventricular arrythmias (ventricular tachycardia/fibrillation or cardiac arrest) requiring hospital attendance, amongst patients with CIEDs and an electronic medical record (EMR) of exercise-based CR compared to propensity score matched patients with CIEDs and no EMR of CR.

For this retrospective observational study, searches were conducted on 2 April 2021, with anonymised data analysed within TriNetX, a global federated health research network with access to EMRs from participating academic medical centres, specialty physician practices, and community hospitals, predominantly in the United States. Patients with a CIED were identified via Centers for Disease Control and Prevention (CDC) coding using ICD-10-CM codes, or Current Procedural Terminology (CPT) codes: Z95.0 (presence of cardiac pacemaker), Z95.810 (presence of automatic implantable cardiac defibrillator), C171; C172; C1882 (Cardioverter defibrillator), 0JH607Z; 0JH637Z; 0JH639Z (Insertion of cardiac resynchronisation defibrillator), or 1006075 (Pacemaker or implantable defibrillator procedures).

All patients were aged ≥18 years with a CIED procedure recorded in EMRs between 2002-2020 with at least 18-months follow-up (1-year from CR). Exercise-based CR was identified from ICD-10-CM codes Z71.82 (Exercise counselling), Healthcare Common Procedure Coding System (HCPCS) S9472 (CR program, non-physician provider, per diem), G0422 (Intensive cardiac rehabilitation), or CPT codes 93797/93798/1013171/ (Physician or other qualified health care professional services for outpatient CR). Correspondingly, these CR and exercise programme codes were excluded in the propensity score-matched controls. At the time of the search, 47 participating healthcare organisations had patient

data available meeting the study inclusion criteria. Thus, following propensity score matching, the cohort consisted of patients with a CIED who either were referred for exercise-based CR within 6-months of the CIED procedure (intervention) or were not referred to CR (control).

Baseline characteristics were compared using chi-squared tests or independent-sample t-tests. Using logistic regression, CR patients were 1:1 propensity score-matched with controls for age, sex, race, ischaemic heart disease, heart failure, hypertensive disease, diabetes mellitus, chronic kidney disease, cerebrovascular disease, cardiovascular procedures (e.g. cardiography, echocardiography, cardiac catheterisation, cardiac devices, electrophysiological procedures), and cardiovascular medications (e.g. beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, ACE inhibitors). These variables were chosen because they are important factors for cardiovascular disease and mortality or were significantly different between the two cohorts. Logistic regression models produced odds ratios (OR) with 95% confidence intervals (CI) for all-cause mortality, hospitalisation, AF/flutter, and severe ventricular arrhythmias (ventricular tachycardia/fibrillation or cardiac arrest) at 18-months following CIED procedure (1-year following CR), comparing exercise-based CR with propensity score-matched controls. Hazard ratios and Kaplan-Meier survival curves were also produced with Log-Rank. Statistical significance was set at $P<0.05$.

In total, 461,044 patients with a CIED met the inclusion criteria for the control group and 4,607 patients received exercise-based CR within 6-months of a CIED procedure. Compared to controls, the CR cohort were generally younger, had less females, and more cardiovascular comorbidities (**Table 1**). Following propensity score-matching, cohorts were well balanced for age, race, sex, comorbidities, cardiovascular medications and cardiovascular procedures (4,600 patients in each cohort; **Table 1**).

Using the propensity score-matched cohort, 1-year mortality was proportionally lower with 5.9% (n=270 of 4,588 patients) in the CR cohort compared to 10.3% (n=470 of 4,569 patients) in the controls (OR 0.55, 95% CI 0.47-0.64). Re-hospitalisations were also proportionally lower with 31.5% (n=1,448 out of 4,600 patients) in the CR cohort compared to 44.0% (n=2,022 out of 4,600 patients) in the controls (OR 0.59, 95% CI 0.54-0.64). Hazard Ratios were consistent with the ORs (**Figure 1**).

Kaplan-Meier analyses show 1-year survival probability was significantly higher and re-hospitalisation probability significantly lower in CIED patients who received CR (Log-Rank tests $P<0.0001$; **Figure 1**). No significant differences were found for AF/flutter (OR 0.97, 95% CI 0.82-1.13), or severe ventricular arrythmias (OR 0.96, 95% CI 0.83-1.11).

The present study of 9,200 patients with a CIED suggests that exercise-based CR associates with significantly lower odds of mortality and re-hospitalisation at 1-year from CR, when compared to propensity score-matched CIED patients without CR. Also, exercise-based CR was not associated with an increase in the incidence of atrial or ventricular arrhythmias requiring hospitalisation, which is promising for CR as an adjunct preventative strategy for patients with CIEDs. The provision of exercise-based CR for patients with a CIED warrants further, prospective investigation.

Several limitations are noteworthy. First, the characterisation of CIEDs, health conditions, and CR were based on ICD codes from EMRs, and reporting of conditions with ICD codes may vary by patient and healthcare organisation.[6] We did not look at the association of CR and outcomes in subtypes of CIEDs (pacemakers, ICDs, and CRT devices) or the severity of cardiovascular comorbidity, which may moderate CR effects. The incidence of non-hospitalised arrythmia during CR also warrants further investigation. Another important caveat is we do not know precise details of the CR interventions, including whether they were comprehensive/multicomponent or exercise-only. Further, an EMR of CR does not necessarily provide information as to whether a patient attended or intervention adherence. We could also not determine the influence of attending different healthcare organizations due to data privacy restrictions. Finally, although we were able to match patients for important co-morbidities and demographic factors, residual confounding may be present.

Disclosures

Benjamin JR Buckley has received funding from Bristol-Myers Squibb (BMS)/Pfizer. Stephanie L Harrison has received funding from BMS. Elnara Fazio-Eynullayeva and Paula Underhill are employees of TriNetX LLC. Gregory YH Lip: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

Funding

No specific funding was received for this study. TriNetX LLC. funded the acquisition of the data used.

Authorship

BJRB contributed to the conception or design of the work. BJRB contributed to the acquisition, analysis, and interpretation of data for the work. BJRB drafted the manuscript. SLH, EFE, PU, DHJT, and GYHL critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

References

1. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? European Journal of Preventive Cardiology 2016;**23**(16):1715-1733.
2. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RF, Schmid JP, Vigorito C, Voller H, Wilhelm M, Piepoli MF, Bjarnason-Wehrens B, Berger T, Cohen-Solal A, Cornelissen V, Dendale P, Doehner W, Gaita D, Gevaert AB, Kemps H, Kraenkel N, Laukkanen J, Mendes M, Niebauer J, Simonenko M, Zwisler AO. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol 2020:2047487320913379.
3. Raatikainen MJP, Arnar DO, Merkely B, Nielsen JC, Hindricks G, Heidbuchel H, Camm J. A Decade of Information on the Use of Cardiac Implantable Electronic Devices and Interventional Electrophysiological Procedures in the European Society of Cardiology Countries: 2017 Report from the European Heart Rhythm Association. Europace 2017;**19**(suppl_2):ii1-ii90.
4. Pedretti RFE, Iliou MC, Israel CW, Abreu A, Miljoen H, Corrà U, Stellbrink C, Gevaert AB, Theuns DA, Piepoli MF, Reibis R, Schmid JP, Wilhelm M, Heidbuchel H, Völler H. Comprehensive multicomponent cardiac rehabilitation in cardiac implantable electronic devices recipients: a consensus document from the European Association of Preventive Cardiology (EAPC; Secondary prevention and rehabilitation section) and European Heart Rhythm Association (EHRA). Europace 2021.
5. Zeitler EP, Piccini JP, Hellkamp AS, Whellan DJ, Jackson KP, Ellis SJ, Kraus WE, Keteyian SJ, Kitzman DW, Ewald GA, Fleg JL, Piña IL, O'Connor CM. Exercise training and pacing status in patients with heart failure: results from HF-ACTION. J Card Fail 2015;**21**(1):60-7.
6. Chong WF, Ding YY, Heng BH. A comparison of comorbidities obtained from hospital administrative data and medical charts in older patients with pneumonia. BMC health services research 2011;**11**:105-105.

Table 1. Baseline characteristics %(*n*)* for the CIED populations with and without exercise-based CR, before and after propensity score matching.

	Initial populations			Propensity score matched populations		
	CIED without CR (n=461,044)	CIED with CR (n=4,607)	*P*-value	CIED without CR (n=4,600)	CIED with CR (n=4,600)	*P*-value
Age in years at Index (SD)	70.0 (14.6)	65.7 (14.0)	<0.0001	66.1 (13.6)	65.8 (14.0)	0.23
Sex						
Male	59.5 (269,642)	69.5 (3,204)	<0.0001	70.1 (3,223)	69.5 (3,197)	0.55
Female	40.5 (183,384)	30.5 (1,403)	<0.0001	29.9 (1,376)	30.5 (1,403)	0.54
Race						
White	75.8 (343,478)	75.3 (3,470)	0.4445	76.2 (3,506)	75.4 (3,469)	0.37
Black or African American	11.8 (53,375)	16.9 (778)	<0.0001	17.3 (797)	16.8 (773)	0.51
Unknown Race	11.0 (49,626)	5.9 (270)	<0.0001	5.0 (232)	5.9 (270)	0.08
Comorbidity						
Ischemic heart diseases						
Hypertensive diseases	22.6 (102,465)	78.7 (3,626)	<0.0001	79.1 (3,637)	78.7 (3,619)	0.65
Heart failure	31.3 (141,630)	77.2 (3,558)	<0.0001	78.5 (3,610)	77.2 (3,551)	0.14
Diabetes mellitus	19.9 (90,169)	65.9 (3,038)	<0.0001	65.1 (2,994)	65.9 (3,031)	0.42
Chronic kidney disease	14.4 (65,398)	38.1 (1,753)	<0.0001	38.2 (1,755)	38.1 (1,751)	0.93
Cerebrovascular diseases	8.8 (39,907)	28.9 (1,332)	<0.0001	28.7 (1,322)	28.8 (1,325)	0.94
Cardiovascular care	6.5 (29,303)	20.0 (920)	<0.0001	19.5 (899)	19.9 (917)	0.64
Cardiovascular Procedures[b]	36.9 (166,971)	91.1 (4,198)	<0.0001	90.9 (4,181)	91.1 (4,191)	0.72
Cardiovascular Medications[b]	42.9 (194,278)	89.7 (4,133)	<0.0001	90.0 (4,138)	89.7 (4,126)	0.68

*Values are % (n) unless otherwise stated. Baseline characteristics were compared using a chi-squared test for categorical variables and an independent-sample t-test for continuous variables. [a]Data are taken from structured fields in the electronic medical record systems of the participating healthcare organizations, therefore, there may be regional or country-specific differences in how race categories are defined. [b]Cardiovascular procedures include cardiography, echocardiography, catheterization, cardiac devices, electrophysiological procedures. [c]Cardiovascular medications include beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, ACE inhibitors. CIED; cardiac implantable electronic device, CR; cardiac rehabilitation and exercise programmes, SD; standard deviation.

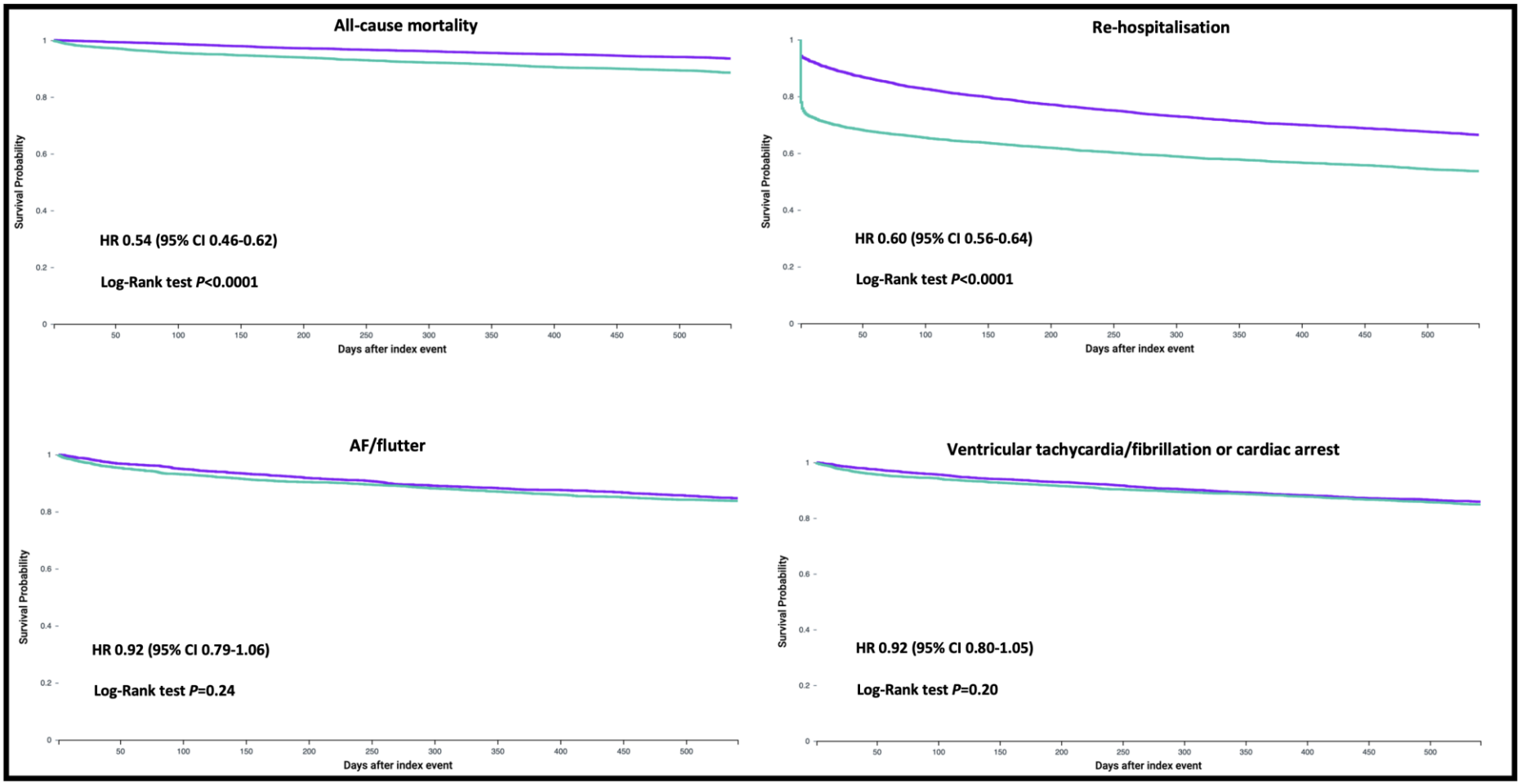

Figure 1. Kaplan-Meier survival curves for all-cause mortality, re-hospitalisation, AF/flutter, and ventricular tachycardia/fibrillation or cardiac arrest, following propensity score matching patients with CIED and exercise-based CR (purple) and without exercise-based CR (green).

HR; hazard ratio and Log-Rank *P*-value presented for each outcome.