1 *Research Letter*

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3 **Exercise-based cardiac rehabilitation for cardiac implantable electronic device recipients**

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30   Exercise-based cardiac rehabilitation (CR) promotes secondary prevention of cardiovascular disease

31   and is an essential component of routine care for patients with acute coronary syndrome, heart

32   failure, and those undergoing revascularisation (e.g., coronary artery bypass graft or percutaneous

33   coronary intervention).[1, 2]

34   Currently, millions of people in Europe live with a cardiac implantable electronic device (CIED) and the

35   prevalence is increasing by hundreds of thousands every year. For example, according to the 2017

36   European Heart Rhythm Association (EHRA) report, 547,586 pacemakers, 105,730 implantable

37   cardioverter-defibrillators (ICDs), and 87,654 cardiac resynchronization therapy (CRT) devices were

38   implanted in 2016 alone.[3] Patients with CIEDs are also eligible for exercise-based CR and therefore

39   form a large subset of patients who participate in such interventions.[2] However, evidence in support

40   of exercise-based CR for patients with CIEDs is sparse.[4, 5]

41   The aim of the present study was to compare 1-year all-cause mortality, hospitalisation, atrial

42   fibrillation (AF)/flutter and ventricular arrythmias (ventricular tachycardia/fibrillation or cardiac

43   arrest) requiring hospital attendance, amongst patients with CIEDs and an electronic medical record

44   (EMR) of exercise-based CR compared to propensity score matched patients with CIEDs and no EMR

45   of CR.

46   For this retrospective observational study, searches were conducted on 2 April 2021, with anonymised

47   data analysed within TriNetX, a global federated health research network with access to EMRs from

48   participating academic medical centres, specialty physician practices, and community hospitals,

49   predominantly in the United States. Patients with a CIED were identified via Centers for Disease

50   Control and Prevention (CDC) coding using ICD-10-CM codes, or Current Procedural Terminology (CPT)

51   codes: Z95.0 (presence of cardiac pacemaker), Z95.810 (presence of automatic implantable cardiac

52   defibrillator), C171; C172; C1882 (Cardioverter defibrillator), 0JH607Z; 0JH637Z; 0JH639Z (Insertion of

53   cardiac resynchronisation defibrillator), or 1006075 (Pacemaker or implantable defibrillator

54   procedures).

55

56   All patients were aged ≥18 years with a CIED procedure recorded in EMRs between 2002-2020 with at

57   least 18-months follow-up (1-year from CR). Exercise-based CR was identified from ICD-10-CM codes

58   Z71.82 (Exercise counselling), Healthcare Common Procedure Coding System (HCPCS) S9472 (CR

59   program, non-physician provider, per diem), G0422 (Intensive cardiac rehabilitation), or CPT codes

60   93797/93798/1013171/ (Physician or other qualified health care professional services for outpatient

61   CR). Correspondingly, these CR and exercise programme codes were excluded in the propensity score-

62   matched controls. At the time of the search, 47 participating healthcare organisations had patient

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63 data available meeting the study inclusion criteria. Thus, following propensity score matching, the

64 cohort consisted of patients with a CIED who either were referred for exercise-based CR within 6-

65 months of the CIED procedure (intervention) or were not referred to CR (control).

66

67 Baseline characteristics were compared using chi-squared tests or independent-sample t-tests. Using

68 logistic regression, CR patients were 1:1 propensity score-matched with controls for age, sex, race,

69 ischaemic heart disease, heart failure, hypertensive disease, diabetes mellitus, chronic kidney disease,

70 cerebrovascular disease, cardiovascular procedures (e.g. cardiography, echocardiography, cardiac

71 catheterisation, cardiac devices, electrophysiological procedures), and cardiovascular medications

72 (e.g. beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel

73 blockers, ACE inhibitors). These variables were chosen because they are important factors for

74 cardiovascular disease and mortality or were significantly different between the two cohorts. Logistic

75 regression models produced odds ratios (OR) with 95% confidence intervals (CI) for all-cause mortality,

76 hospitalisation, AF/flutter, and severe ventricular arrhythmias (ventricular tachycardia/fibrillation or

77 cardiac arrest) at 18-months following CIED procedure (1-year following CR), comparing exercise-

78 based CR with propensity score-matched controls. Hazard ratios and Kaplan-Meier survival curves

79 were also produced with Log-Rank. Statistical significance was set at $P<0.05$.

80

81 In total, 461,044 patients with a CIED met the inclusion criteria for the control group and 4,607

82 patients received exercise-based CR within 6-months of a CIED procedure. Compared to controls, the

83 CR cohort were generally younger, had less females, and more cardiovascular comorbidities (**Table 1**).

84 Following propensity score-matching, cohorts were well balanced for age, race, sex, comorbidities,

85 cardiovascular medications and cardiovascular procedures (4,600 patients in each cohort; **Table 1**).

86

87 Using the propensity score-matched cohort, 1-year mortality was proportionally lower with 5.9%

88 (n=270 of 4,588 patients) in the CR cohort compared to 10.3% (n=470 of 4,569 patients) in the controls

89 (OR 0.55, 95% CI 0.47-0.64). Re-hospitalisations were also proportionally lower with 31.5% (n=1,448

90 out of 4,600 patients) in the CR cohort compared to 44.0% (n=2,022 out of 4,600 patients) in the

91 controls (OR 0.59, 95% CI 0.54-0.64). Hazard Ratios were consistent with the ORs (**Figure 1**).

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93 Kaplan-Meier analyses show 1-year survival probability was significantly higher and re-hospitalisation

94 probability significantly lower in CIED patients who received CR (Log-Rank tests $P<0.0001$; **Figure 1**).

95 No significant differences were found for AF/flutter (OR 0.97, 95% CI 0.82-1.13), or severe ventricular

96 arrythmias (OR 0.96, 95% CI 0.83-1.11).

97

98   The present study of 9,200 patients with a CIED suggests that exercise-based CR associates with

99   significantly lower odds of mortality and re-hospitalisation at 1-year from CR, when compared to

100   propensity score-matched CIED patients without CR. Also, exercise-based CR was not associated with

101   an increase in the incidence of atrial or ventricular arrhythmias requiring hospitalisation, which is

102   promising for CR as an adjunct preventative strategy for patients with CIEDs. The provision of exercise-

103   based CR for patients with a CIED warrants further, prospective investigation.

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105   Several limitations are noteworthy. First, the characterisation of CIEDs, health conditions, and CR were

106   based on ICD codes from EMRs, and reporting of conditions with ICD codes may vary by patient and

107   healthcare organisation.[6] We did not look at the association of CR and outcomes in subtypes of CIEDs

108   (pacemakers, ICDs, and CRT devices) or the severity of cardiovascular comorbidity, which may

109   moderate CR effects. The incidence of non-hospitalised arrythmia during CR also warrants further

110   investigation. Another important caveat is we do not know precise details of the CR interventions,

111   including whether they were comprehensive/multicomponent or exercise-only. Further, an EMR of CR

112   does not necessarily provide information as to whether a patient attended or intervention adherence.

113   We could also not determine the influence of attending different healthcare organizations due to data

114   privacy restrictions. Finally, although we were able to match patients for important co-morbidities and

115   demographic factors, residual confounding may be present.

116

124 **Authorship**

125 BJRB contributed to the conception or design of the work. BJRB contributed to the acquisition,

126 analysis, and interpretation of data for the work. BJRB drafted the manuscript. SLH, EFE, PU, DHJT, and

127 GYHL critically revised the manuscript. All gave final approval and agree to be accountable for all

128 aspects of work ensuring integrity and accuracy.

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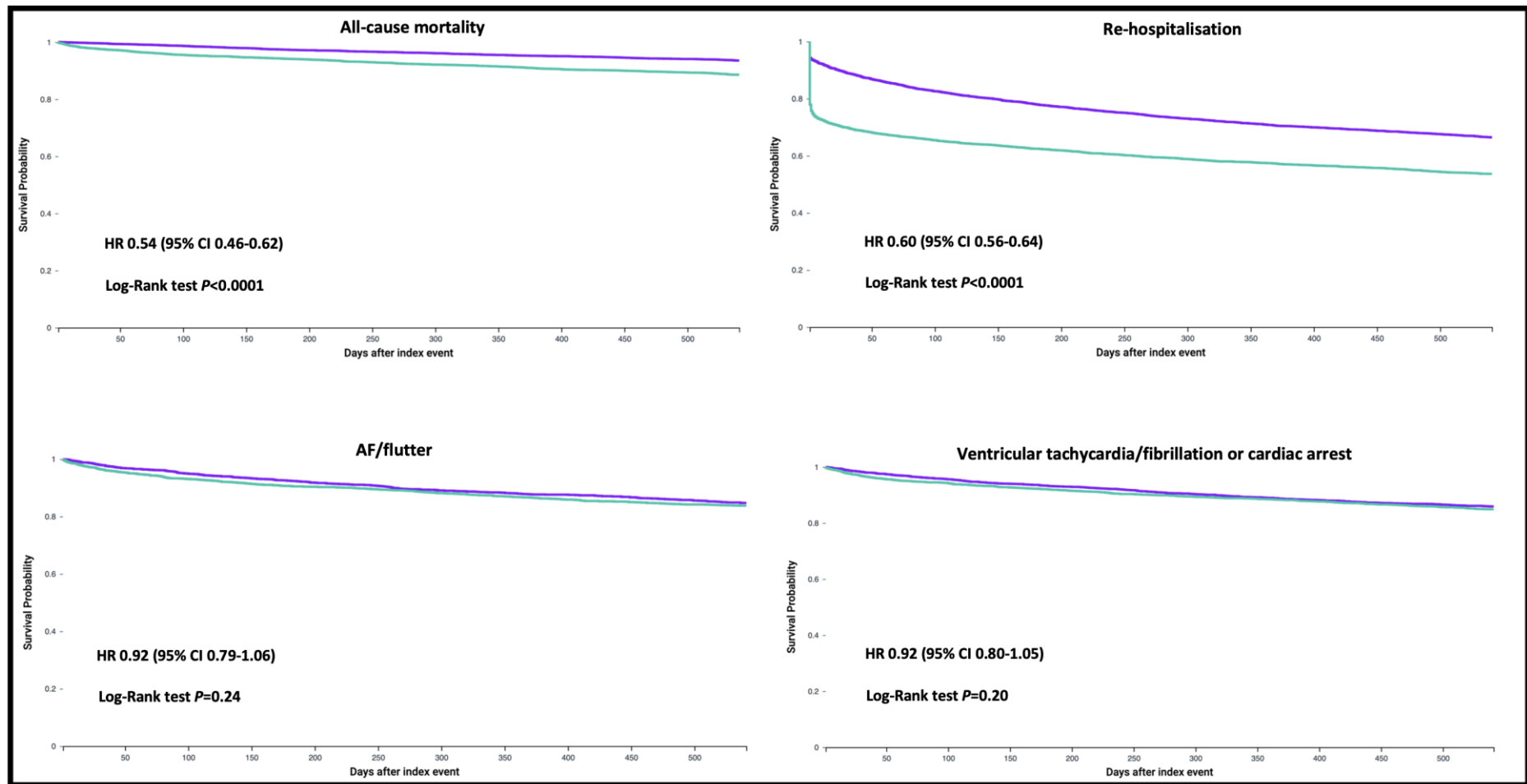
Figure 1. Kaplan-Meier survival curves for all-cause mortality, re-hospitalisation, AF/flutter, and ventricular tachycardia/fibrillation or cardiac arrest, following propensity score matching patients with CIED and exercise-based CR (purple) and without exercise-based CR (green).

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