THE INFLUENCE OF EXERCISE TRAINING ON CARDIOVASCULAR HEALTH OUTCOMES IN ADULTS WITH CARDIAC IMPLANTABLE ELECTRONIC DEVICES

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I have dedicated my life, as evidenced by my relocation to three different countries, to pursuing my academic goals. This dissertation reflects a journey made possible by a passion for science, and the support of mentors, colleagues, family, and friends around the world.

Almost five years ago, I was writing the acknowledgement section of my master's thesis in Brazil. That acknowledgment revisited my journey as a basketball athlete, my bachelor's degree, accreditation in cardiovascular rehabilitation, and master's training including two international internships. Writing another acknowledgement section today, in another language and in Canada, reveals the beauty of academia: a world rich in opportunity, history, and resilience. In times when science is often questioned, I begin this section by expressing my gratitude to science and the global research community for its perseverance and commitment to knowledge.

I thank the mentors and colleagues who guided the early stages of my academic journey. At the Dante Pazzanese Institute of Cardiology in São Paulo, I thank the cardiac rehab team, where I was first introduced to the world of cardiac devices. I am also grateful to the Exercise and Chronic Disease Laboratory at São Paulo State University in Brazil, and to my master's supervisor, Dr. Emmanuel Ciolac, and lab colleagues, where my research training began. I further extend my sincere thanks to the Research Group for Cardiovascular Rehabilitation at the University of Leuven and to Dr. Véronique Cornelissen, who provided me with an invaluable international research experience in Belgium during challenging times. Each of you has contributed, in your own way, to this journey, and I carry these lessons with me moving forward.

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PREFACE TO THIS DISSERTATION

This dissertation contains data from four original studies: two observational retrospective studies, one systematic review and meta-analysis, and one prospective randomized pilot trial. The studies were designed and conducted by the trainee (Isabela R. Marçal, PhD) with guidance from the supervisors Dr. Jennifer Reed and Dr. Kristi Adamo.

The retrospective studies of this dissertation (Study 1 and Study 2) were submitted and approved under the same ethical application within the University of Ottawa Heart Institute. Specifically, Study 1 was a two-site project with data collected from two large national cardiovascular rehabilitation centres. The protocol was approved by the University of Calgary Conjoint Health Research Ethics Board (protocol #: REB19-0588_REN4) and the Ottawa Health Science Network Research Ethics Board (protocol #:20240036-01H). I was responsible for multi-site coordination, including ethics submissions, delegated Research Ethics Board processes, and data-sharing agreements between the Total Cardiology Network, University of Calgary, and the University of Ottawa Heart Institute. Processes were supported by Research Manager of the Exercise Physiology and Cardiovascular Health Lab at the University of Ottawa Heart Institute, and Chair of the TotalCardiology Research Network, Calgary.

There is limited sex-disaggregated evidence in exercise trials among patients with CIEDs. The Sex and Gender Equity in Research (SAGER) guidelines suggest pooling sex-specific data of studies for performing meta-analyses. To address this gap, I led a systematic review and meta-analysis (Study 3) examining changes in cardiovascular health outcomes following exercise training in individuals with CIEDs. I contacted more than 50 study authors to obtain individual participant data. Despite challenges with data, I conducted a sex-based examination of the existing literature and completed a hypothesis-generating meta-analysis on cardiorespiratory fitness, adhering to best practices in evidence synthesis (e.g., librarian-supported search strategy, screening in peers, and formal risk-of-bias assessment).

The systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42024498519).

This dissertation contains original data from a randomized pilot trial, which leveraged the design and infrastructure of the *"Exercise Training in Women with Heart Disease"* - EXCEED trial, funded by the Canadian Institute of Health Research. I contributed to administrate tasks (e.g., standard of operating procedures, ethics, meetings), screening and recruitment, data collection and management (e.g., leading patient appointments including cardiopulmonary exercise tests and sessions, administrating questionnaires), data analysis (e.g., preliminary analysis of results), and manuscript preparation of the EXCEED. I conceived the idea of the *"The Effects of Exercise Training on Physical and Mental Health in Women with Cardiac Implantable Electronic Devices: A Pilot Randomized Clinical Trial'* CIEDEX study together with Dr. Jennifer Reed. I was selected and was awarded the CANet Discovery competition from the Cardiovascular Network of Canada, this competition allows trainees to be the principal investigator on an original work, to support operational funding. I led the CIEDEX trial from inception including research ethics board application, screening and recruitment efforts, coordination of administrative requirements, staff and volunteers (e.g., co-investigators, patient-partner). and patients, data collection (e.g., cardiopulmonary exercise tests, exercise sessions, scored questionnaires, collected baseline and follow-up health measures, accelerometer delivery and returns, CIEDs interrogation reports), knowledge dissemination (e.g., manuscript preparation, reports provided to patients with study data). The protocol was approved by the Ottawa Health Science Network Research Ethics Board (protocol number: 20230095-01H) and registered with ClinicalTrials.gov (protocol number: NCT05946304).

During my PhD, I was supported by several funding sources, including the Admission Scholarship and the Doctoral International Scholarship from the University of Ottawa, the CHEO Research Institute Joint Physical Activity and Health Initiative Doctoral Fellowship, the Ontario Graduate Scholarship Program, and the Canadian Heart Function Alliance Trainee Award.

DISSERTATION ABSTRACT

Aims and Methods: The overall purpose of this dissertation was to examine the influence of exercise training on cardiovascular health outcomes in patients with cardiac implantable electronic devices (CIEDs). Study 1 retrospectively examined the changes in physical (e.g., cardiorespiratory fitness [CRF]), and mental health (e.g., anxiety levels) outcomes in patients with CIEDs completing an exercise-based cardiovascular rehabilitation (CR) program. Study 2 retrospectively assessed the associations of CR on major adverse cardiovascular events (MACE) among adults with CIEDs. Study 3 investigated, through a systematic review and meta-analysis, sex differences in CRF changes following exercise training in women and men with CIEDs. Study 4 tested the feasibility of a pilot randomized controlled trial comparing a 12-week virtual program of high-intensity interval training (HIIT) and moderate-to-vigorous intensity continuous training (MICT) in women with CIEDs.

Results: Study 1 showed that patients with CIEDs (n = 252, 26% females) completing CR improved CRF and reduced anxiety and depression levels in patients with CIEDs. Study 2 found that CR was not associated with lower 5-year risk of MACE comparing propensity score-matched CIED patients with and without CR (n = 344, 23% females), whereas women derived greater benefit from CR. Study 3 demonstrated no sex differences in CRF following exercise among patients with CIEDs (n = 365, 22% women). Study 4 revealed that, among women with CIEDs (n = 20), a 12-week virtual HIIT intervention was feasible, whereas virtual MICT was not.

Conclusions: Findings of this dissertation highlight (i) the importance of CR to improve CRF, a strong predictor of mortality, in individuals with CIEDs, (ii) the need of large-scale studies to understand the impact of CR on MACE in patients with CIEDs, (iii) a call to action to advance sex-specific inclusion and reporting practices in exercise trials with CIEDs, and (iv) remote HIIT is a feasible and safe exercise alternative to women with CIEDs, where results on key cardiovascular data can inform future trials.

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LIST OF ABBREVIATIONS

BMI: Body Mass Index

CACPR: Canadian Association of Cardiovascular Prevention and Rehabilitation

CI: Confidence Interval

CIED: Cardiac Implantable Electronic Device

CPET: Cardiopulmonary Exercise Testing

CR: Cardiovascular Rehabilitation

CRT: Cardiac Resynchronization Therapy

CVD: Cardiovascular disease

GAD-7: Generalized Anxiety Disorder Disorder 7-Item Scale

HADS: Hospital Anxiety and Depression Scale

HF: Heart Failure

HIIT: High-intensity Interval Training

HR: Heart Rate

ICD: Implantable Cardioverter Defibrillator

LVEF: Left Ventricular Ejection Fraction

MCID: Minimal Clinically Important Difference

MCS: Mental Component Summary

MET: Metabolic Equivalent of Task

MICT: Moderate to Vigorous Intensity Continuous Training

MVPA: Moderate to Vigorous Intensity Physical Activity

PCS: Physical Component Summary

PPM: Permanent Pacemaker

Qol: Quality of Life

RPE: Ratings Of Perceived Exertion

SAGER: Sex And Gender Equity in Research

SD: Standard Deviation

SF-36: Medical Outcomes Short-Form 36

UOHI: University Of Ottawa Heart Institute

$\dot{V}O_2$peak: Peak Oxygen Consumption

1.1 CHAPTER 1. BACKGROUND AND LITERATURE REVIEW

1.1.1 Introduction to cardiac implantable electronic devices

1.1.2 Overview of the electrical system of the heart

The adult human heart beats approximately 70-85 times per minute, with an average heart rate (HR) of 70-72 beats per minute (bpm) in men and 78-82 bpm in women.[1] A heart beats result from the coordinated movement of ions (i.e., sodium, calcium, and potassium) across the heart muscle cells, also known as myocytes, which produces changes in the action potential that cause depolarization (i.e., less negatively charged compared to its external) and repolarization (i.e., return to resting potential).[2] The cardiac action potential consists of 5 phases: (i) phase 0 is the upstroke or rapid depolarization, (ii) phase 1 is the early rapid repolarization, (iii) phase 2 is the plateau, (iv) phase 3 is the final rapid repolarization, and (v) phase 4 is the resting membrane potential and diastolic depolarization.[3] The amplitude and duration of the action potentials vary across different regions of the heart because of variations in ion channel composition **(Figure 1.1)**. These changes in the electrical properties of the cardiac cells occur via the specialized myocytes that constitute the cardiac conduction system axis.[2]

The conduction system initiates and regulates the electrical impulse resulting in synchronized contraction of the cardiac myocytes, and thus the atria and ventricles. The main components of the cardiac conduction system include the sinus node and the atrioventricular conduction axis.[4] The sinoatrial node or 'pacemaker' cells have the ability to spontaneously depolarize (i.e., intrinsic automaticity) eliciting atrial contraction.[5] The electrical signal then moves towards the atrioventricular node, a slow-conducting structure that introduces a delay in the propagation of the impulse (allowing the ventricles to completely fill with blood following atrial contraction before their contraction). Subsequently, the impulse travels atrioventricular bundle of His, before it rapidly conducts through the left and right bundle branches that run down the interventricular septum. A network of Purkinje fibers

within the subendocardium continue the rapid propagation of the electrical impulse, triggering ventricular contraction in a coordinated fashion **(Figure 1.1)**.[5] Any disturbance in impulse generation and/or propagation may result in interatrial, atrioventricular, or interventricular dyssynchrony.[4] Progressive alteration of cardiac conduction may result in or exacerbate existing cardiovascular diseases (CVD), which are responsible for 32% of all global deaths.[6]

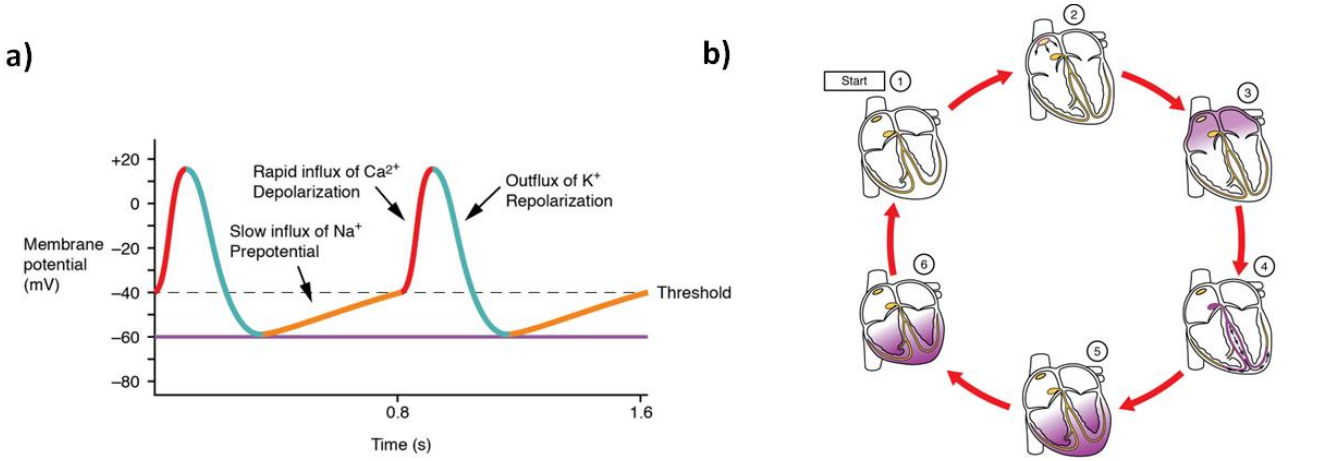

Figure 1.1 Action potential and conduction system. (a) Action potential at the sinoatrial (SA) node. (b) Simplified sequence of cardiac conduction: the SA node initiates the impulse, which spreads through the atria, pauses briefly at the AV node, then travels through the AV bundle, bundle branches, and Purkinje fibers to depolarize the ventricles. Adapted from "19.2 Cardiac Muscle and Electrical Activity," in Douglas College Human Anatomy and Physiology I (1st ed.), licensed under CC BY 4.0. Source: Pressbooks, https://pressbooks.bccampus.ca/dcbiol11031109/chapter/19-2-cardiac-muscle-and-electrical-activity/ (accessed September 15, 2024).

1.1.3 Pathology of the Cardiac Conduction System

The pathophysiology of CVDs involves highly interrelated electrical, structural, and functional processes.[7] Cardiac rhythm disorders are considered abnormal or a disruption in the heart's normal sinus rhythm.[8] These electrical disorders can arise from multiple underlying pathological factors such as genetic conditions and aging-related structural changes, which impair impulse generation or conduction of the heart.[9] Examples of cardiac rhythm disorders associated with a slow HR (i.e., bradycardia) are sinus node dysfunction (i.e., degenerative fibrosis of the sinus nodal tissue, sinus rate of ≤50 bpm), complete atrioventricular block (i.e., no evidence of atrioventricular conduction), and conduction tissue disease (i.e., complete right bundle-branch block with a QRS duration ≥120 ms).[10] In contrast to these bradyarrhythmias, other rhythm disorders involve abnormally rapid electrical activity. The most common cardiac arrhythmia is atrial fibrillation, a supraventricular tachyarrhythmia with uncoordinated atrial activation and ineffective atrial contraction.[11] While atrial fibrillation originates in the atria, more severe disturbances can arise within the ventricles. Ventricular arrhythmias are categorized in ventricular tachycardia (i.e., ≥3 consecutive complexes originating in the ventricles at a rate >100 bpm) and ventricular fibrillation (i.e., rapid, grossly irregular electrical activity with marked variability in electrocardiographic waveform, ventricular rate usually >300 bpm).[12] Electrical disorders are considered one of the most dangerous cardiovascular conditions due to its propensity to deteriorate into life-threatening arrhythmias, which may lead to sudden cardiac arrest (i.e., sudden cessation of cardiac activity, no normal breathing and no signs of circulation) or death.[8]

Cardiac arrhythmias can be associated with other structural and functional CVDs. Coronary heart disease, characterized as an inflammation and the buildup of and fatty deposits along the innermost layer of the coronary arteries, may directly damage critical areas of the conduction system through a myocardial infarction.[13] Cardiomyopathies are a heterogeneous group of heart muscle diseases that can also alter the distribution and function of conduction tissue, including dilated

cardiomyopathy (i.e., ventricular dilation and depressed myocardial performance),[5] hypertrophic cardiomyopathy (i.e., increased left ventricular wall thickness),[6] and infiltrative cardiomyopathy (i.e., cardiac sarcoidosis), and non-classified cardiomyopathies that frequently present as the syndrome of heart failure.[14,15] Heart failure, a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood, is also associated with electrical and structural remodeling. [16] There are three distinct phenotypes of heart failure based on the measurement of left ventricular ejection fraction (LVEF) - <40% LVEF: heart failure with reduced EF (HFrEF); 40-49% LVEF: heart failure mildly reduced EF (HFmrEF); and, ≥50% LVEF, heart failure with preserved EF (HFpEF).[17] HF symptoms are described using the New York Heart Association (NYHA) functional class I-IV, which measures a patient's overall heart function and severity of symptoms such as limitations during physical activity. CVDs can create a vicious deleterious cycle: hypertrophic cardiomyopathy leads to left atrial enlargement, which predisposes to AF; AF reduces the efficiency of ventricular filling, which in turn exacerbates heart failure symptoms.[18] These cardiovascular conditions, isolated or combined, compromise the heart's ability to maintain an appropriate rhythm and rate. As a result, they often necessitate specific interventions to restore and maintain a regular heart rhythm.[10] In many cases, this involves the use of cardiac implantable electronic devices (CIEDs, **Figure 1.2**), including permanent pacemakers (PPMs), implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy devices (CRTs).[19]

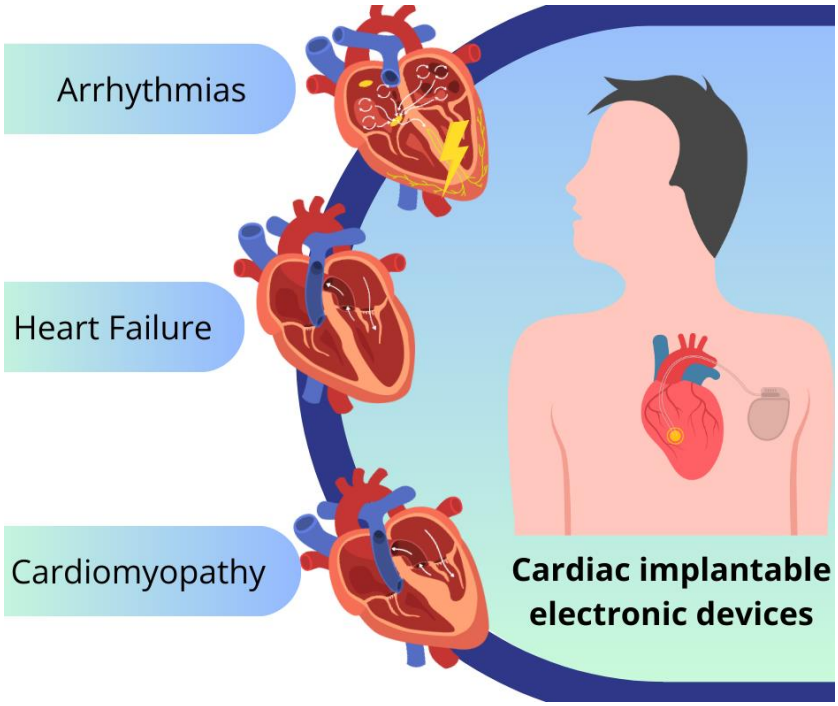

Figure 1.2. Common cardiovascular conditions treated with cardiac implantable electronic devices. Arrhythmias, heart failure, and cardiomyopathies may disrupt normal cardiac electrical conduction and mechanical function, for which device therapies are indicated. Source: author's own creation.

1.1.4 Structural components and programming

CIEDs comprise two main components - a pulse generator and one or more intracardiac leads. The pulse generator contains a battery, voltage capacitors, rhythm-sensing components, and software. The type and number of leads connected to the generator depend on the indication and type of device **(Figure 1.3)**.[20] CIEDs can be single-chambered (one lead, e.g., one placed into the right atrium or the right ventricle), dual-chambered (two leads, e.g., one placed in the right atrium and one in the right ventricle), and biventricular (three leads, e.g., one in the right atrium, one in the right ventricle, and one

in the coronary sinus).[21] In response to a sensed intracardiac signal, a CIED may inhibit output, trigger output, or pace in a different chamber after a timed delay.[22] This function is governed by the programmed pacing mode. An international system code based on 4 letters is used to describe the device's programming: (i) chamber(s) paced (i.e., O = none, A = atrium, V = ventricle, D = dual (A+V), (ii) chamber(s) sensed (same as number 'i'), (iii) response to sensing (i.e., O = none, T = Triggered/Tracked, I = Inhibited, D = dual (T+I), and (iv) rate modulation (O = none, R = rate adaptive).[23] For example, a VVIR code means: (a) the ventricle is paced (V) and sensed (V); (b) when the device senses a normal ventricular contraction, it is inhibited (I); and (c) the pulse generator is rate responsive (R).[23] The latest, rate response, is important to detect physical activity and increase the lower rate (shortens the cycle length) for pacing.[24] The lower rate limit indicates the rate below which pacing occurs (i.e., lowest rate allowed by the device), while an upper rate limit indicates the fastest rate at which the CIED will pace.[24] Regarding ICDs, a monitor zone and up to 3 programmable detection zones are individually programmed with independent rates and durations to detect and treat ventricular tachycardia.[22] The beat-by-beat behaviour of a CIED in response to intrinsic and paced activity is determined as 'timing cycles' and it may be terminated or reset (starts over again) by intrinsic cardiac events.[23] All programmable features of CIEDs are customized by the electrophysiologist according to the individual needs of each patient and are available in the device's interrogation report.[23]

1.1.5 Definition and epidemiology of CIEDs

The main function of CIEDs is to sense intrinsic electrical activity and pace the heart as necessary.[25] The main clinical indications for CIED implantation are outlined in **Table 1.1 and Figure 1.3**. PPM is indicated for cardiovascular conditions causing bradycardia.[23] PPMs have been in use the longest among CIEDs, with the first implantation occurring in 1960, and they served as the foundation

for the development of more advanced pacing technologies such as ICDs and CRTs.[26] New generation of PPMs capable of sensing and pacing in both chambers were invented in the 1980s, reflecting manufacturers' improvements to manage any form of bradycardia.[26] The DANPACE trial (n = 1384, 64% women) compared two different PPM modes (i.e., atrial lead vs. atrial and ventricular leads) and found similar effectiveness in reducing mortality among individuals with sick sinus syndrome 9 years after the PPM implantation (adjusted hazard ratio [HR]: 1.03, 95% confidence interval [CI]: 0.90-1.19, P = 0.65). In the past 50 years, research has demonstrated that PPMs decreased mortality (e.g., 61% in older adults),[27] and with a cost-effectiveness (i.e., total healthcare expenses associated with the intervention compared to usual care) of $6,800 per quality-adjusted life year gained over a patient's lifetime.[28]

ICD is used in the primary and secondary prevention of sudden cardiac arrest by treating potential fatal arrhythmias.[23] ICDs are indicated for primary prevention - those who have not previously had cardiac arrest or sustained ventricular tachycardia but have a severe family history of early mortality from a cardiac event - or secondary prevention – those who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia after evaluation to define the cause of the event and to exclude any completely reversible causes.[24,29] An ICD recognizes and promptly treats malignant ventricular arrhythmias by delivering antitachycardia pacing (i.e., electrical impulses to the heart to disrupt the abnormal electrical activity) or implementing high-energy shocks for defibrillation (i.e., cardioversion, appropriate shocks).[12] The algorithm of the device may also treat non–life-threatening arrhythmias, which is defined as inappropriate shocks (i.e., high-voltage discharge for a reason other than a ventricular arrhythmia). Either shock therapy has a strong impact on patients with ICDs, and it has been previously described as "an earthquake" or "being hit by a truck."[30] ICDs have been shown to reduce mortality (e.g., 54%) in those with coronary disease

and nonsustained ventricular tachycardia (MADIT trial, n = 1820), with a cost-effectiveness ratio of $27,000 per life-year added when compared to conventional medical therapies.[31,32]

CRT aims to restore or preserve ventricular synchrony using left ventricular stimulation at appropriately timed right ventricular sensing or stimulation, which is also referred to as biventricular pacing.[24] CRT is recommended for individuals with prolonged QRS intervals (e.g., ≥130ms) and heart failure with reduced LVEF.[33 87] The COMPANION and CARE-HF trials (n = 1738) showed that CRTs reduce mortality (e.g., 68%), and are highly cost-effective (e.g., $8,840 per quality-adjusted life year gained) in patients with mild heart failure (RESERVE trial, n = 610).[34–36] CRT devices can be equipped with an additional ICD component (CRT-D), as most of these patients also have the indication for an ICD. Therefore, there are ICD and CRT-D systems protecting against life-threatening arrhythmias with CRT-D systems most possibly improving left ventricular function.[37]

It is important to note that CIEDs implantation may also impact other physical and mental cardiovascular outcomes and quality of life of patients, which will be discussed later in this chapter. Over the past 60 years, the use of CIEDs has risen substantially.[38 39] To date, 1.2–1.4 million CIEDs are implanted annually worldwide, where 57% of patients receiving a CIED are men.[38] In Canada, 25,000 PPMs and 7,000 ICDs are implanted annually, and approximately 120,000 Canadians live with a CIED.[39] The likelihood of implantation of a CIED increases with age.[40,41] A rise in the prevalence of CIEDs is expected with a higher life expectancy and an aging population.

Table 1.1 Indications for cardiac implantable electronic devices.

Cardiac implantable electronic device	Indication Class I*
Pacemaker	Sinus Node Dysfunction Atrioventricular Block Acute Phase of Myocardial Infarction
Implantable cardioverter defibrillators	Indicated in patients who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable sustained ventricular tachycardia after evaluation to define the cause of the event and to exclude any completely reversible causes
Cardiac resynchronization therapy	Indicated for patients who have left ventricular ejection fraction (LVEF) ≤35%, sinus rhythm; left bundle branch block (LBBB) with a QRS duration ≥150 msec; New York Heart Association Functional Classification (NYHA) class II, Ill, or ambulatory IV (significant heart failure symptoms (shortness of breath, fatigue) despite optimal medical treatment).

*Strength of the recommendation based on the assessment of the magnitude and certainty of the benefits in proportion to the risks (Class I: Benefits >>> Risk).

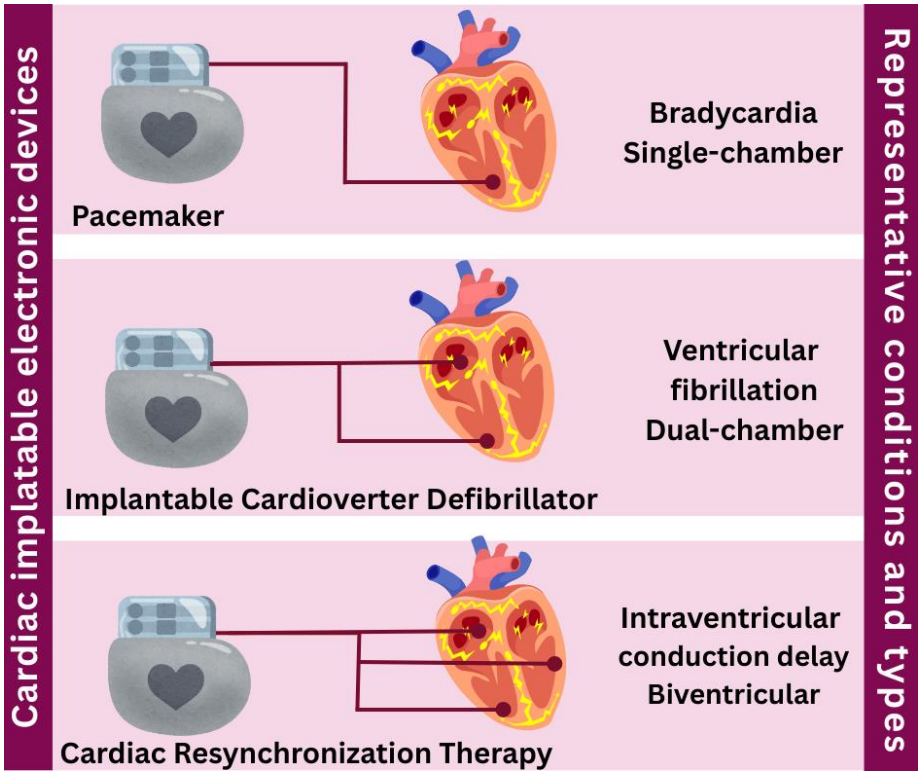

Figure 1.3. Representative cardiac implantable electronic devices and their primary clinical indications. Source: author's own creation.

CIEDs are continuously evolving and are now smaller, with longer battery life and improved functionality compared to previous devices.[42] Remote monitoring has become a class 1A recommendation to examine patients' cardiac rhythm from a distance, transmitting data from the device to healthcare professionals.[43] Built-in accelerometers have enabled rate-responsive pacing (e.g., HR for an increased demand of oxygen), also allowing the automatic collection and storage of the device-measured physical activity[44] CIED's technology associated with modern wearable devices such as smartwatches and smartphones may be an adjunct therapy to provide more accessible and valuable information to patients and healthcare providers.[45] The combination of these technologies allows electrocardiogram recording, activity monitoring, sleep tracking, fall detection, and medication reminders. Some of these functions may be an allied to support safe health-related behaviours such as monitoring exercise intensity using HR data or tracking daily/weekly physical activity levels.[45] Advancements in this field also include new implant sites and type of devices (e.g., leadless PPM, subcutaneous ICD),[46] however, conventional transvenous CIEDs (e.g., PPM, ICD, CRT) remain the highest level of evidence for patients (i.e., data derived from large randomized clinical trials),[24] and therefore, the primary focus of this dissertation.

1.1.6 Clinical management of patients living with CIEDs

Cardiovascular risk factors are highly prevalent in patients with CIEDs and are associated with poorer prognosis of their underlying cardiovascular condition.[15,47,48] Common cardiovascular risk factors include poor dietary choices, physical inactivity, dyslipidemia, hyperglycemia, hypertension, obesity, smoking, kidney dysfunction, genetics, psychosocial factors, all with considerations of select populations (e.g., older age, race/ethnicity, and sex differences).[49,50] Patients with CIEDs often report persistent and limiting symptoms such as palpitations, fatigue, dyspnea, and exercise intolerance.[51] Therefore, lifestyle interventions aimed at modifying these cardiovascular disease risk factors are

essential in the comprehensive management of individuals with CIEDs, which are described later in this chapter.

Most CIED-related guidelines primarily comprise implantation indications and procedures.[24] Guidelines highlight shared decision-making and clear communication with both patients and healthcare professionals.[17] This includes supporting informed choices about implantation, ensuring understanding of therapy expectations and follow-up, and recognizing complications such as inappropriate defibrillator shocks. Healthcare providers should offer educational information such as biophysiological (e.g., implantation process), social (e.g., available peer-support groups), and practical (e.g., follow-up routines), discuss lifestyle implications (e.g., driving restrictions), and address scenarios where device deactivation or removal may be necessary, all while involving patients and caregivers in ongoing decision-making.[17]

A CIED implantation represents an invasive, device-based intervention, and is typically accompanied by pharmacological therapies (e.g., antiplatelet agents, statins, beta- blockers, angiotensin converting enzyme inhibitors, antiarrhythmics, calcium channel blockers) depending on the CVD diagnosis.[10] A CIED implantation can also be accompanied by physical and psychological distress.[52] Patients have expressed daily challenges of living with a CIED (e.g., preventing damage), physical sequelae of CIED implantation (e.g., pain-related complications), psychological conditions of living with a CIED (e.g., posttraumatic stress disorder), and negative experiences related to health care while living with a CIED (e.g., costs, lead replacement).[53] In addition, patients and families received activity and care instructions before, during, and after the CIED implantation – this is important to prevent lead dislodgement and support safe return to activity. Examples of these guides include the American Heart Association, MyHealth Alberta, and the University of Ottawa Heart Institute (see hyperlinks). For instance, patients are advised to progressively increase movement while avoiding activities that may dislodge leads during the initial recovery period after an ICD implantation **(Table 1.2).**

Table 1.2. Summary of post-implant activity precautions for patients with ICDs.

Timeline	Activities to avoid	Activities permitted
First 24 hours	Limit shoulder movement on the side of the device implantation.	Gentle elbow movement is permitted.
First 2 weeks	Avoid lifting the affected arm above shoulder height.	After 24 hours, gradual arm movement below shoulder level is encouraged.
First 4 weeks	Do not lift items heavier than 10 lbs (5 kg). Refrain from vigorous or repetitive activities (e.g., golf, swimming,sweeping).	After approximately 2 weeks, most daily activities can be resumed as tolerated.
First 8 weeks	Avoid strenuous upper-body tasks such as shoveling.	After 4 weeks, patients may gradually return to all usual activities if cleared by their care team.

*Adapted from the University of Ottawa Heart Institute (2014). *ICDs: Implantable Cardioverter Defibrillators — A Guide for Patients and Families.**

Patients with CIEDs may face additional restrictions and lifestyle adjustments. Common limitations include restrictions on driving, sports participation, and exposure to potential sources of electromagnetic interference (e.g., mobile phones, microwaves, and security doors in airports).[54] Patients with CIEDs also report constant worries about the functionality of the device including fear of malfunctioning, inappropriate shock, or the need of battery replacement.[55] Such concerns may lead to avoidance or change lifestyle behaviours – for example, reduction in recreational activities, sleep disturbances, or altered sexual activity - which can ultimately diminish their physical activity and exercise participation.[8,13] Although CIEDs are used to treat and improve clinical outcomes, they represent a major life-changing experience for recipients. Thus, comprehensive strategies to manage and improve physical and mental health, and quality of life of those with CIEDs are needed. [56–58]

1.2 Exercise therapy in the context of CIED patients

1.2.1 Introduction to exercise-based cardiovascular rehabilitation

Cardiovascular rehabilitation (CR) is a class 1A recommendation for the management of CVD.24,25 CR is a multidisciplinary, systematic, and personalized approach to providing evidence-based secondary prevention therapies for individuals with CVD.[61] Clinical practice guidelines recommend CR for patients with stable angina, stable heart failure with a reduced ejection fraction, and for patients after myocardial infarction, coronary artery revascularization, heart transplant or peripheral artery disease.[62] CR models include three main phases: inpatient (Phase I, acute rehabilitation during hospital stay), outpatient (Phase II, structured and supervised CR), and maintenance (Phase III, long-term, often unsupervised, self-managed exercise to support sustainability).[63] The pathway and core components of a comprehensive of a CR program are highlighted in **Figure 1.4**.[61]

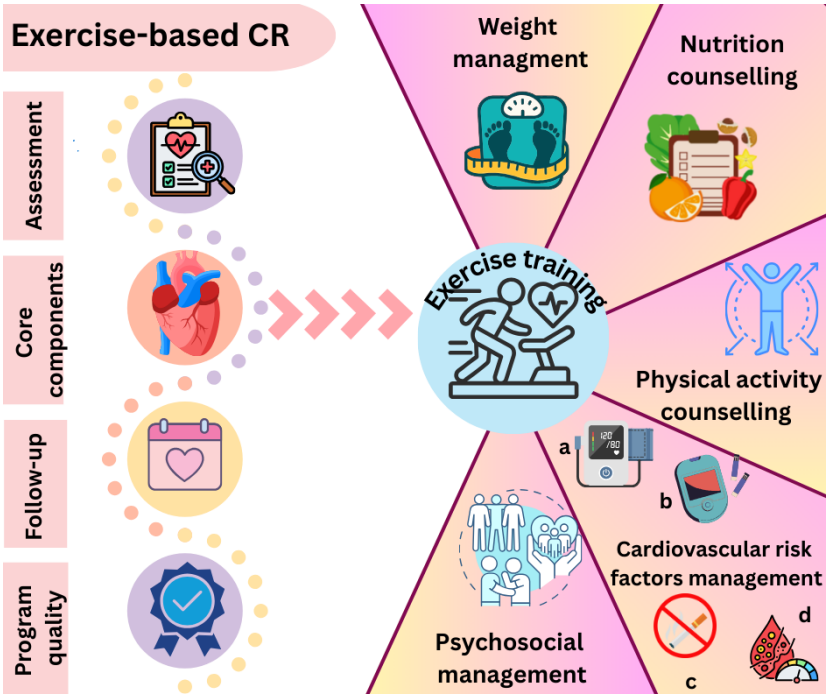

Figure 1.4. Pathway and core components of a comprehensive CR program. Cardiovascular risk factor management (a) blood pressure management, (b) diabetes management, (c) tobacco cessation, (d) lipid management. Source: author's own creation.

Participating in CR has been shown to improve several cardiovascular health outcomes including cardiorespiratory fitness (CRF, +1.05 METs), total cholesterol (−1.20 mmol/L), LDL cholesterol (−1.10 mmol/L), triglycerides (−0.31 mmol/L), BMI (−0.29 kg/m²), waist circumference (−1.4 cm), and anxiety (−0.75) and depression (−0.56) scores, along with a reduction in current smoking prevalence (from 22.3% to 19.9%).[64] Importantly, participation in CR was also associated with a 50% lower risk of all-cause mortality over a median follow-up of 5 years, and demonstrated cost-effectiveness (e.g., range across19 CR studies worldwide: $1,065 to $71,755 per quality-adjusted life-year) among individuals with CVD.[65,66]

Physical activity counseling is a key component of CR.[67] Physical activity refers to any bodily movement produced by skeletal muscles that results in energy expenditure, whereas exercise is a planned, structured, and repetitive form of physical activity performed to improve or maintain fitness.[67] The goal for patients participating in CR to achieve at least150 minutes per week moderate-intensity or 75 minutes vigorous activity, consistent with national and international guidelines such as the Canadian 24-Hour Movement Guidelines and the World Health Organization Guidelines.[68,69] Exercise training is safe and effective for most patients with CVD, and exercise testing is recommended for the development of a safe and optimized exercise prescription.[63] In this dissertation, the term "exercise-based CR" is used to refer to CR programming with a focus on exercise while exercise training is used for exercise interventions delivered alone, without incorporating other core elements (i.e., cardiovascular and risk factor, and psychosocial management, weight management, and body composition, nutrition and physical activity counseling).[67] Overall recommendations for an exercise program in CR include a combination of aerobic and strength training.[70–73] Guidelines-based exercise prescription for patients with CVD is presented in **Table 1.3,** following the Canadian Guidelines for Cardiac Rehabilitation and Cardiovascular Disease Prevention: Translating Knowledge into Action published by Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR).[63]

Table 1.3. Exercise training recommendations in cardiovascular rehabilitation.

Exercise prescription	Description
Aerobic exercise training	
Frequency	3-5d/wk
Intensity	Moderate intensity: 40%–59% of heart rate reserve or rating of perceived exertion of 12 or 13 on 6–20 Borg Scale Vigorous intensity: 60%–89% of heart rate reserve or rating of perceived exertion of 14–17 on 6–20 Borg Scale
Time	20–60 min, including warm-up and cool-down
Type	Treadmill, cycling, elliptical, rowing, stair climbing, arm/leg ergometry, recumbent stepper, and other modalities allowing continuous or interval aerobic training
Strength training	
Frequency	2–3 nonconsecutive d/wk
Intensity	10–15 repetitions 40%–60% of 1 repetition maximum Rating of perceived exertion of 11–13 on 6–20 Borg scale
Time	1–3 sets; 8–10 different exercises focused on major muscle groups
Type	Equipment that is safe and comfortable for the individual to use

1.2.2 Exercise recommendations in patients with CIEDs

There are important considerations for exercise testing and prescription to patients with CIEDs.[15,23] Patients with CIEDs need to wait between 2 weeks and 6 months following implantation before starting an exercise program.[74,75] In addition, strength training and specific movements such as abduction of the shoulder (above 90°) are not recommended during the first 4–6 weeks post-implantation for all CIEDs, as this may dislodge the newly implanted leads.[24] A symptom-limited exercise test, preferably a cardiopulmonary exercise test (CPET), should be performed before the start of an exercise program.[76] CPETs have been shown to be a useful tool to evaluate the safety of exercise

as well as for the evaluation of CIEDs technology, particularly rate-responsive pacing.[77] In addition, CPETs are recommended to examine HR zones (e.g., upper rate limit), programmed PPM and CRT modes, and ICD rhythm detection thresholds prior to an exercise program.[78] In patients with ICDs, HR should be maintained 10-15 bpm below the programmed HR threshold for defibrillation during exercise test and training.[79] Patients with CIEDs may also report unique challenges during an exercise training session such as (i) the presence of exercise-induced arrhythmias, (ii) chronotropic incompetence (i.e., inability of the sinus node to respond appropriately to varying metabolic demands)[80], or (iii) they may fear shock therapy during the session.[81–83] Thus, these patients may present with unique physiological and psychological factors compared to other CVD populations when it comes to exercise training.

1.2.3 Safety

One of the main concerns regarding exercise in patients with CIEDs is the risk of arrhythmias.[84] This paradox has emerged due to the increase in sympathetic activity during exercise, which directly influences HR control and may potentially trigger arrhythmias.[85] [76] A meta-analysis (n = 6 studies) demonstrated that exercise training was associated with a significantly lower likelihood of ICD shock (pooled odds ratios: 0.47, 95% CI = 0.24-0.91; I^2 = 57.1%) than the control group.[86] Similar effects were observed in patients with PPMs and CRTs, whereas a later meta-analysis (n = 3 studies) showed that no difference in serious adverse events between the exercise and control groups (fixed-effect RR: 0.85, 95% CI: 0.57-1.28, P = 0.43).[87] These data support the endorsement of CR in patients with CIEDs, demonstrating that exercise is safe and does not increase adverse events.[85]

1.3 Summary of current evidence

Evidence from studies of exercise-based CR in patients with CIEDs is sparse, and detailed clinical practice guidelines are lacking.[85] Whether an isolated CIED implantation is an indication for referral to exercise-based CR is conflicting in literature, which may limit the access to exercise programming in those with devices.[79,88] The abovementioned CACPR guidelines include comprehensive sections addressing patients with CIEDs.[78] However, these patients were defined as "special populations" that may benefit from exercise-based CR, recommendations were based in limited trials, and it was suggested that exercise prescription in those with CIEDs follow the guidelines of the underlying CVD (e.g., CRT recipients should follow heart failure guidelines as those with CRT are heart failure patients with a pacemaker).[78] A recent systematic review evaluated the available evidence related to exercise in patients with CIEDs, including risk screening, monitoring, and exercise prescription. [89] Among the 16 publications included, five were clinical guidelines; yet none offered specific recommendations for exercise training in individuals with CIEDs. One of the most comprehensive expert consensuses in exercise-based CR in patients with CIEDs was published in 2021, aiming to provide practical recommendations to enhance the safety, implementation, and efficacy of CR in patients with CIEDs.[88] Most of the evidence available in literature was related to patients with ICD with few data available in patients with PPM/CRT, and no definitive conclusions were made regarding key outcomes such as all-cause mortality and quality of life given limited data, emphasizing the need for more robust research to inform clinical practice. [88]

From 2017-2024, 7 systematic reviews and meta-analyses were performed in the field of exercise-based CR in patients with CIEDs **(Table 1.4**). The systematic reviews and meta-analyses included a range of 6 to 16 studies, with most reviews incorporating 6–8 studies and two reviews reaching 16 studies. These were mostly conducted in individuals with CRT devices (n = 4) followed by ICD populations (n = 2) or mixed CIED samples (n= 2). Across included trials, age range was 52 to 69

years, and the proportion of women varied from 5% to 53%, with lower proportions in ICD trials (5%–17%) and higher variability in CRT trials (10–53%). Exercise interventions ranged from 2 to 7 days per week, typically over 8 to 24 weeks, with some CRT trials with a long follow-up (~4 years). Intensity was prescribed at moderate to vigorous levels, most commonly 60%–95% of HR peak or $\dot{V}O_2$peak, or 60%–80% of 1 repetition maximum for resistance training. Time per session varied from 10 to 60 minutes, with most interventions delivering 30-60 minutes of exercise training. Type of exercise included mostly CR programs (i.e., combining aerobic training and resistance training), with additional components such as stretching, psychoeducational counseling, and some studies offered home-based settings. The main outcomes included CRF, quality of life, and psychosocial outcomes, which will be discussed in further detail in the following sections. Overall, main findings emphasize significant improvements in $\dot{V}O_2$peak, functional capacity and there is evidence of improved cardiac and quality of life following CR. In contrast, clinical outcomes such as mortality and serious adverse events showed no consistent effect, with most reviews reporting inconclusive results. The lack of clarity reflects the small number of trials evaluating different clinical endpoints and the heterogeneity in reporting across studies. In fact, **Table 1.5** shows that over the years (2003-2021), a total of 24 studies investigating exercise and CR in people with CIEDs were published and included in systematic reviews and meta-analysis, where 17 (71%) were assessed in more than one review. The overlap of studies included in reviews may suggest a heterogeneity of the CIED sample, suboptimal methodology, considerable redundancy across reviews, or emphasize the scarcity of primary trials in the field of CR and devices.[90]

Table 1.4. Systematic reviews and meta-analyses on exercise in individuals with CIEDs.

Details	Inclusion	Aim	Sample	Outcomes	Conclusions
Chen[91] et al., 2019, China	7 studies: RCTs (n = 7)	To evaluate the effects of CR on exercise tolerance and cardiac function in heart failure patients undergoing CRT	Intervention: n = 80 Control: n = 77 Total: n = 157 Women: NR Age: NR	$\dot{V}O_2$peak: ↑ (WMD = 2.17 ml/kg/min, 95% CI: 1.42, 2.92), P < 0.001) LVEF: ↑ (WMD = 4.75%, 95% CI (1.53, 7.97), P = 0.004)	CR can improve exercise tolerance and cardiac function in heart failure patients with CRT.
Grosman-Rimon[92] et al 2021, Canada	7 studies: RCTs (n = 6); observational (n = 1)	To evaluate the totality of evidence on the effect of aerobic exercise training on clinical outcomes in CRT recipients	Intervention: n = 332 Control: n = 534 Total: n = 866 Women: 21.6% in the exercise group; 20.4% control group Age intervention: 60.5 ± 6.5 y Age control: 62.5 ± 7.8 y	$\dot{V}O_2$peak: ↑ (MD: 2.26 ml/kg/min, 95% CI 1.38–3.13) $\dot{V}O_2$: ↑ (MD: 3.96, 95% CI 2.68–5.24 L/min) O_2 pulse, VE/VO_2, LV parameters, resting HR, HRpeak, quality of life and mortality: ↔	$\dot{V}$O2peak and AT-$\dot{V}$O2 are increased with aerobic exercise in CRT recipients, demonstrating a significant improvement in functional capacity.
Guo[93] et al., 2021, China	6 studies: RCTs (n = 6); Randomized prospective observation (n = 1);	To systematically review the current published literature on the impact of exercise training (ET) in chronic heart failure (CHF) patients who were conducted CRT	Intervention: n = 120 Control: n = 115 Total: n = 235	$\dot{V}O_2$peak: ↑ (MD: 3.05ml/kg/min, 95% CI: 2.53 – .56; P < 0.001) Maximal workload: ↑	Compared with no exercise or routine care control, the $\dot{V}$O2peak, LVEF, HR, and QoL in CHF patients with CRT were statistically improved with light to moderate intensity

	Retrospective case-control study (n = 1)		Women: NR Age: NR	(MD 26.32W, 95% CI 19.41–33.23; P < 0.001) Exercise duration: ↑ (MD: 68.95s, 95% CI 15.41–122.48; P = 0.01) LVEF: ↑ (MD: 4.97%, 95% CI1.44–8.49 P = 0.006) Health-related quality of life: ↑ (MD: 19.96, 95% CI21.57 to 18.34; P < 0.001) NYHA class: ↔ (MD: 0.75, 95% CI1.60 to 0.11; P = 0.09)	training, but there seemed no difference of above endpoints in the HIT group during short-term follow-up (up to 6 months).
Kaddoura et al 2024	16 RCTs	To discuss efficacy and safety of exercise-based CR in participants with CIED	Intervention: n = 1076 Control: n = 997 Total: n = 2053 Women: NR Age: 54-69 y	Combined ICD/CRT: ↑ $\dot{V}O_2$ (MD 2.17 ml/kg/min; 95% CI: 1.67–2.67 ml/kg/min, P < 0.0001; I2 = 99%) 6-min walk test in ICD group (MD 41.51 m; 95 % CI: 15.19–67.82 m, P = 0.002; I^2 = 95 %). LVEF: ↔ (MD 0.68; 95 % CI: -- 2.48 – 3.84, P = < 0.00; I^2 = 98 %).	Exercise-based CR programmes appear to be safe when enrolling participants with CIEDs and leading to favourable functional outcomes.
Nielsen[94] et al., 2019, Denmark	8 studies: RCTs (n = 8)	To assess the benefits and harms of exercise-based CR compared with control in adults with an ICD	Intervention: n = NR Control: n = NR	All-cause mortality: ↔ (RR: 1.96, 95% CI: 0.18 to 21.26)	Due to a lack of evidence, the impact of exercise-based cardiac rehabilitation on all-cause mortality, serious

			Total n = 1.730 Age: 54 to 65 y Women: NR Age: 54-65 y	Serious adverse events: ↔ (RR 1.05, 95% CI: 0.77 to 1.44) $\dot{V}O_2$peak: ↑ (MD: 0.91 mL/kg/min, 95% CI 0.60- 1.21) Risk of requiring antitachycardia pacing: ↔ (RR 1.26, 95% CI 0.84-1.90) Appropriate shock: ↔ (RR 0.56, 95% CI 0.20-1.58) Inappropriate shock: ↔ (RR 0.60, 95% CI 0.10-3.51) Quality of life: not possible to pooled data	adverse events and health-related quality of life in adults with an ICD were not completely assessed. Findings do provide very low-quality evidence that patients following exercise-based cardiac rehabilitation experience a higher exercise capacity compared with the no exercise control.
Pandey[86] et al., 2017, USA	6 studies: RCTs (n = 5); non RCT (n = 1)	To assess the efficacy and safety of exercise training in HF patients with ICD	Intervention: n = 858 Control: n = 745 Total: n = 1.603 Women (%): 5.2 % ICD + CRT n = 73.7 % Age: 54 – 66 y	$\dot{V}O_2$peak: ↑ (WMD: 1.98 ml/kg/min; 95% CI: 0.58-3.38) ICD shocks: ↓ (OR: 0.47; 95% CI: 0.24-0.91) HRpeak: ↔ (WMD: 3.15 beats/min; 95% CI: −4.25-10.54).	Exercise training was associated with significant improvement in CRF and lower likelihood of ICD shocks.
Steinhaus[95] et al., 2019, USA	8 studies: RCTs (n = 8); single-arm trials (n = 5); observatio	To evaluate exercise interventions in patients with ICDs and CRTs to characterize study design, safety, and effectiveness of	Intervention: n = 1215 Control: n = 1332	Safety: ICD shocks ↓ (15.2% vs 20.1%, OR: 0.70; 95% CI, 0.53-0.92, P = .013,	Exercise training in patients with ICDs and CRT appears safe and effective based on our review of the relatively scant available literature.

	nal cohort (n = 2); randomized cross-over trial (n = 1)	exercise in affected patients.	Total: n = 2547 Women: 17 % Age: 52-69 y	$\dot{V}O_2$peak: ↑ (1.98 vs 0.36 mL/kg/min, P < 0.001)	
Ye[87] et al., 2020, China	7 studies: RCTs (n = 7)	To assess the effects of exercise rehabilitation in HF patients with a CRT	Intervention: n = 332 Control: n = 355 Total: n = 687 Women: 10-53% Age: 55-67 y	All-cause mortality: ↔ (RR: 0.57, 95% CI: 0.19-1.73; P = 0.32) Serious adverse events: ↔ (RR: 0.85, 95% CI: 0.57-1.28; P = 0.43) $\dot{V}O_2$peak: ↑ (WMD: 2.02 ml/kg/min, 95% CI 0.62-3.41, P = 0.005) Exercise duration: ↑ (WMD = 102.34s, 95% CI 67.06-137.62, P < 0.001) LVEF: ↑ (WMD: 3.89%, 95% CI 1.50 to 6.28; P = 0.001) QoL: ↑ (WMD: -5.34, 95% CI: 10.12 - −0.56; P = 0.028)	Exercise rehabilitation may restore exercise capacity and cardiac function in HF patients with a CRT device. Furthermore, exercise training was associated with better health-related quality of life on follow-up.

Abbreviations: CI, confident intervals; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator, HF, heart failure; HR, heart rate; LVEF, left ventricular ejection fraction; NR, not reported; MD, mean difference; OR, odds ratio; PM, pacemaker; QoL, quality of life; RCT, randomized controlled trial; RR, risk ratio; $\dot{V}O_2$peak, peak oxygen updake; WMD, weighted mean difference. ↑ significant increase or ↓ decreased, ↔ = no significant change.

Table 1.5. Existing literature included across systematic reviews and meta-analyses to date.

Studies included	Systematic reviews and meta-analyses							
	Chen et al 2019[91]	**Grosman-Rimon et al 2021[92]**	**Guo et al 2021[93]**	**Kaddoura et al 2024[96]**	**Nielsen et al 2019[94]**	**Pandey et al 2017[86]**	**Steinhaus et al 2019[95]**	**Ye et al 2020[87]**
Prospective / Randomized trials								
Ahn et al 2021[97]				✓				
Belardinelli et al 2006[98]	✓	✓	✓	✓	✓	✓	✓	✓
Berg et al 2015[99]				✓	✓	✓		
Conraads et al 2007[100]		✓	✓	✓			✓	✓
Dougherty et al 2015[101]				✓	✓		✓	
Fitchet et al 2003[102]				✓				
Frizelle et al 2004[103]				✓	✓	✓	✓	
Isaksen et al 2015[104]				✓	✓	✓	✓	
Nobre et al 2016[105]	✓	✓		✓		✓	✓	
Patwala et al 2009[106]	✓	✓	✓	✓		✓	✓	
Piccini et al 2013[107]					✓		✓	
Piotrowicz et al 2015[108]				✓	✓			✓
Rakhshan et al 2017[109]				✓			✓	✓
Santa-Clara et al 2019[110]		✓	✓	✓				
Smialek et al 2013[111]								
Smolis-bak et al 2015[112]	✓	✓	✓		✓		✓	
Smolis-bak et al 2017[113]				✓	✓		✓	
Spee et al 2020[114]			✓	✓			✓	
Single-arm design								
Dougherty et al 2008[115]							✓	

Kamke et al 2003[116]								✓
Vanhees et al 2001[117]							✓	
Vanhees et al 2004[118]							✓	
Observational design								
Davids et al 2005[119]						✓	✓	
Martens et al 2018[120]		✓	✓				✓	✓

Note. Summary of existing prospective and randomized trials included across published systematic reviews and meta-analyses to date. Checkmarks indicate inclusion of individual studies within each review.

1.4 Physical health

1.4.1 Cardiorespiratory fitness

CRF refers to the capacity of the circulatory and respiratory systems to supply oxygen to skeletal muscle mitochondria for energy production needed during exercise.[121] Specifically, this process is dependent on the cardiovascular (e.g., systolic and diastolic function), respiratory (e.g., gas exchange), musculoskeletal (e.g., extract and use oxygen), and nervous (e.g., regulation of blood flow) systems.[122] CRF can be measured directly, expressed as peak oxygen uptake ($\dot{V}O_2$peak), which is the highest value of oxygen consumption during an exercise test, and the gold standard measure of CRF in clinical populations.[79] It can also be estimated, using the peak work rate achieved on a treadmill or a cycle ergometer or from non-exercise algorithms, expressed as metabolic equivalents (METs) - where 1 MET which is equal to 3.5 mL O_2/kg/min at resting state. Since there is a continuum of energy expenditure across the many forms of movement, occupational and leisure-time activities, exercise can range from light (e.g., < 3 METs) to high (e.g., > 9 METs) intensities.[123]

$\dot{V}O_2$peak is a strong independent predictor of mortality; every 1 mL/min/kg increase in $\dot{V}O_2$peak is associated with 31% and 26% reductions in the odds of cardiovascular and all-cause mortality in a predominantly male sample (17%), respectively, and a 10% reduction in mortality among women only.[64,124] $\dot{V}O_2$peak is the product of maximum cardiac output and arteriovenous oxygen difference, as explained by the Fick principle.[125,126] This is possible given central (i.e., cardiac output - the product of heart rate and stroke volume) and peripheral (e.g., changes in oxygen extraction and utilization) adaptations.[126] Aerobic training is the most effective form of increasing CRF. [121] A one unit increase in METs (or 3.5 mL/kg/min $\dot{V}O_2$peak) can be used as a minimum clinically important difference (MCID) when evaluating changes following exercise training in individuals with coronary artery disease who participated in CR.[97,103] In HF-ACTION trial, patients with heart failure (n = 120) demonstrated that even a modest 6% increase in $\dot{V}O_2$peak after three months of exercise training was

associated with a 7% lower risk of all-cause mortality (HR: 0.93, 95% CI: 0.90-0.97, P < 0.001) and an 8% lower risk of cardiovascular mortality or heart failure hospitalization (HR 0.92, 95% CI 0.88–0.96, P < 0.001).[127]

Patient with CIEDs report poor physical health (e.g., fatigue, exercise intolerance),[52] and decreased functional capacity (e.g., 47% NYHA class III, marked limitation of physical activity).[128] Lower levels of CRF have been observed in individuals with CIEDs compared to other CVD populations such as those with heart failure (~-27%).[129] Participating in exercise training has shown to improve CRF in patients with CIEDs.[96] Considering all CIED types, one meta-analysis showed that exercise training resulted in an average increase in peak $\dot{V}O_2$peak of 2.6 mL/kg/min, (range: 2.2-3.2) compared to a control group or usual care (i.e., no exercise training or CR intervention).[57] When assessing the effects of exercise training on CRF in patients with ICDs, two meta-analyses (n = 14 studies included; n = 3,333 participants) revealed improvements from 0.91 to 1.98 ml/kg/min in $\dot{V}O_2$peak.[86,94] In patients with CRT, four meta-analyses (n = 27 studies; n = 1,965 participants) demonstrated $\dot{V}O_2$peak improvements ranging from 2.02 to 3.05 ml/kg/min.[87,91,92,130] In patients with combined therapies (i.e., ICD + CRT), one meta-analysis (n = 16 studies; n = 2,547 participants) comparing exercise intervention and a control group (usual care) reported an increase in $\dot{V}O_2$peak (1.98 vs. 0.36 ml/kg/min).[95]

1.4.2 Physical activity

Physical activity is predictive of cardiovascular outcomes in patients with CIEDs, yet it is not regularly assessed in clinical practice in those with CIEDs.[131] Low levels of physical activity have been previously associated with a higher risk of major adverse cardiovascular events (MACE) in individuals with CIEDs.[132] Using internal device-measured physical activity data, a retrospective observational study in patients with ICDs (n = 41,731) revealed that participating in exercise-based CR increased physical activity levels in this group (+9.7 ± 57.8 min/d vs. control -1.0 ± 59.7 min/d, P < 0.001).[131,133]

Importantly, a retrospective analysis has shown a strong intra-individual correlation ($r > 0.7$) between ICD/CRT activity sensors (237 ± 105 min/d; range 28–575), and external accelerometers (276 ± 85 min/d, range 72–462), supporting the potential use of both methods as complementary tools for quantifying physical activity in individuals with CIEDs.[134] However, research in physical activity levels in patients with CIEDs is scarce, and CIEDs-measured physical activity present with limitations (e.g., different signal processing between manufactures).[131] More research is needed to measure physical activity levels using different methods and test the accuracy of physical activity data measured by CIEDs.

1.4.3 Exercise behaviour

Psychological theories behind exercise behaviour have been investigated in order to understand and modify exercise patterns across the lifespan.[135,136] Exercise behaviour is complex and marked by three distinct stages: adherence, adoption, and maintenance.[137] The ultimate goal is that individuals meet global exercise recommendations (i.e., ≥150 min/wk of moderate-to-vigorous intensity physical activity), [138] which has been associated with widespread health benefits.[139] Exercise behaviour is complex and crucial for designing effective interventions and support systems to promote lifelong exercise.[140] Understanding the determinants of change may enhance tailored interventions from the input (i.e., which behaviour change strategy to choose) to output (i.e., what the person can adhere to and sustain).[141]

Adherence indicates consistent involvement in a prescribed/planned exercise routine.[142] Exercise adherence has been inconsistently measured as (1) completion: number of weeks exercising, (2) attendance: average of exercise sessions attended per week/program, (3) duration: number of minutes exercising/weekly, and (4) intensity: meeting the exercise prescription.[143–145] Randomized controlled trials have defined successful adherence rates as completing 50%-70% of the number of exercise sessions per protocol.[146,147] Adherence has been used as an important metric in feasibility pilot

studies to assess the potential for successful implementation of a proposed intervention and to reduce risks to the validity of these studies.[148]

Self-efficacy and motivation are significant mediators of adherence to exercise.[149] Based on the self-efficacy theory, confidence has been identified as an important construct in exercise motivation. Confidence to participate, overcome barriers, and organize time (i.e., task, barrier, and scheduling self-efficacy, respectively) in the exercise context.[150] Motivation, which is based on the self-determination theory, proposes that all individuals have a natural drive toward growth, integration and overall well-being. [151–153] Connecting concepts, the affective experience during exercise - how good or bad a person feels - can significantly shape both self-efficacy and motivation. [169,174–176171–173] Positive affective response experienced during exercise may lead to greater enjoyment (i.e., enjoyment can be the first reason a person chooses to participate in exercise)[154] of the exercise session, promote a positive memory of the exercise experience, and may ultimately play a significant role in predicting exercise adherence.[155,156] In this sense, understanding whether an individual feels good or bad during exercise might be an important outcome of interest when trying to determine the association with continued exercise behaviour.[177] Qualitative research design may enhance the understanding of factors influencing exercise adherence and their association with improvements on quantitative outcomes.[157] Qualitative interviews (n = 10) following a 12-week exercise program in patients with ICDs revealed that patients gained knowledge (e.g., *"I was glad I participated in exercise training because I learned something new*") and physical capacity *("We could take one more stairway every time"*), by the end of the intervention. In addition, questionnaires evaluating patients' experiences with the exercise program can be useful to assess acceptance and satisfaction. A study examined the effects of 12-week telemonitoring home-based exercise in individuals with CRTs and found that approximately 90% of participants reported no difficulties coordinating exercises with study devices (i.e., mobile phone app, remote blood pressure and electrocardiogram monitoring) and felt safer during telemonitored training

compared to exercising unsupervised at home.[108] Altogether, such findings highlight the importance of integrating patients' perspectives to better understand determinants of exercise adherence and to inform the design and implementation of future research trials and CR programs.[150]

1.4.4 Cardiometabolic health

Adverse cardiometabolic health indicators are also prevalent among individuals with CIEDs, including elevated blood pressure and increased body mass index (BMI).[55,57,107] Such metabolic abnormalities may accelerate atherosclerosis and eventually lead to new cardiac events such as acute myocardial infarction.[158,159] Comprehensive secondary prevention programs for patients with CVD includes the management of cardiovascular disease risk factors (e.g., obesity, dyslipidemias, hypertension, and diabetes mellitus).[160] Few studies (n = 4) have demonstrated that exercise training reduces peak pulse pressure,[110] blood pressure,[100] and body weight[161] but no changes in HR[111] in patients with CIEDs. In patients with fixed-rate settings (i.e., stimulation of the heart at a regular rate independent of the intrinsic HR), target HR zones may be not applicable in exercise prescription, and therefore, perceived exertion - often assessed via Borg Scale[162] - is a reliable and valid method of exercise prescription in CIEDs.[63]

1.5 Mental health

Cardiovascular diseases can induce significant mental health conditions.[163] Mental health disorders refer to mental health states characterized by a clinically significant disturbance in an individual's cognition, emotional regulation, or behaviour.[164] Depression and anxiety are the most common mental health conditions in people with CVD. Depression involves a depressed mood or loss of pleasure or interest in activities, accompanied by symptoms ranging from mild to severe - such as sadness, loss of appetite, fatigue, psychomotor retardation, and suicidal ideation, lasting for at least two weeks. It affects 5% of adults (4% among men and 6% among women), and 5.7% of adults older than

60 years worldwide.[165] Depression is associated with a significantly increased risk of myocardial infarction (RR: 1.30, 95% CI: 1.22–1.40) and coronary heart disease (RR: 1.30, 95% CI: 1.22–1.40).[166] Anxiety is often characterized by 'future-oriented' fear and worry (i.e., perceived/ anticipated threats) that are both intense and excessive, common symptoms are restlessness, fatigue, poor concentration, and sleep disturbance.[167] Anxiety affects 301 million people globally[168]Anxiety is associated with a significantly elevated risk of coronary heart disease (RR: 1.41, 95% CI: 1.23-1.61), heart failure (RR: 1.35, 95% CI: 1.11-1.64), and cardiovascular mortality (RR: 1.41, 95% CI: 1.13-1.76).[169] The relationship between CVD and depression and anxiety has been defined as bidirectional – while CVD is associated with a higher incidence of these mental health conditions, patients diagnosed with depression or anxiety are also at increased risk of developing CVD and experiencing adverse cardiovascular outcomes.[167]

Depression and anxiety result from a complex interaction of biological and psychological factors.[170] The psychological distress caused by depression and anxiety leads to activation of the hypothalamic-pituitary-adrenal axis, resulting in dysregulation of the autonomic nervous system.[164] This may increase myocardial oxygen demand, precipitate myocardial ischemia, increase the risk of arrhythmia, and accelerate atherosclerosis.[163] In addition, depression and anxiety are also associated with lower levels of physical activity, smoking, poorer diet quality, and obesity.[171] These lifestyle factors are all causally linked to an increased risk of the development of CVD.[164] Guidelines have recognized psychosocial risk factors including depression and anxiety and their risk of developing CVD and the worsening of clinical course and prognosis of CVD.[172] This recognition is important, as depression and anxiety may impact health behaviour adherence in patients. Depression at the start of exercise-based CR was significantly associated with lower improvement in CRF, and anxiety was associated with lower participation in CR. Hence, addressing depression and anxiety in CR is vital to optimize health-related outcomes and adherence.

There is strong evidence demonstrating the benefits of exercise training in anxiety and depression symptoms in clinical populations.[173–175] A systematic review and network meta-analysis of randomized controlled trials (n = 218 studies, n = 495 arms and n = 14,170 adults with depression were included) demonstrated that exercise showed moderate effects on depression compared with active controls (e.g., usual care, placebo tablet), either alone or in combination with other established treatments such as cognitive behaviour therapy.[173] Interestingly, the most effective exercise modalities were walking or jogging (n = 1,210, Hedges' g -0.62, 95% CI -0.80 to -0.45), yoga (n = 1,047, g -0.55, 95% CI: -0.73 to -0.36), strength training (n = 643, g -0.49, 95% CI: -0.69 to -0.29), and mixed aerobic exercises (n = 1,286, g -0.43, 95% CI: -0.61 to -0.24).[173] Another systematic review demonstrated that physical activity had medium effects on depression (median effect size = -0.43, interquartile range [IQR] = −0.66 to –0.27), anxiety (median effect size = −0.42, IQR = -0.66 to -0.26) and psychological distress (effect size = -0.60, 95% CI -0.78 to -0.42), compared with usual care across all people with diagnosed mental health disorders and people with chronic disease.[175] Specifically, a systematic review and meta-analysis in patients with cancer (n = 27 randomized controlled trials, with 1,929 participants) observed exercise was associated with a significant reduction in depression (standardized mean difference [SMD] = −0.53; 95% CI, −0.79 to −0.28) and anxiety (SMD = −0.39; 95% CI, -0.66 to −0.12) levels and improvements in overall health-related quality of life (SMD = 0.63; 95% CI, 0.10 to 1.17).[174] Overall, the evidence supports exercise training and physical activity as key components in the management of depression and anxiety.

Approximately 20% of individuals with CIED report depression and anxiety disorders.[176] There is evidence demonstrating post-implantation shifts in depression and anxiety levels in individuals receiving a CIED.[177] A systematic review demonstrated that, between 0-6 months post-implant, the prevalence of symptoms of depression ranged from 8% to 38% (n = 10 studies) and symptoms of anxiety ranged from 13% to 50% (n = 12 studies) in patients with CIEDs.[178] A large meta-analysis (n =

109 studies, 39 954 participants) found clinically relevant increases in depression (15.4%, 95% CI: 11.9%–18.9%) and anxiety (23%, 95% CI: 18.3%–27.0%) among individuals following ICD implantation.155,156 In individuals with ICDs, depression and anxiety were predictors of mortality (OR: 1.81, OR: 4.17, respectively).[99] While some earlier studies reported comparable levels of depression and anxiety across CIED types,[179] accumulating evidence suggests a higher prevalence of clinically relevant depression, anxiety, and post-traumatic stress disorder in individuals with ICDs.[119,177,180,181] Collectively, these findings underscore the importance of incorporating psychosocial assessment and management within CR programs for patients with CIEDs.

Few studies have evaluated the impact of exercise and CR on mental health outcomes in individuals with CIEDs.[102,182,183] A previous study in individuals with ICDs (n = 16, 12% women) demonstrated reductions in depression (from 9.9 ± 3.4 to 6.7 ± 2.9 points) and anxiety (from 8.1 ± 3.6 to 3.4 ± 3.6 points) levels, as measured by the Hospital Anxiety and Depression Scale (HADS) questionnaire, following 12 weeks of exercise-based CR, while the control group (i.e., no intervention) increased anxiety and depression levels over time.[102] The Anti-Arrhythmic Effects of Exercise after an ICD Trial found significant decreases in depression (PHQ, Physician Health Questionnaire-9: 1.5 ± 0.9 to 1.3 ± 0.6) severity after a 8-week program of home walking, and anxiety (STAI, State-Trait Anxiety Inventory: 30.6 ± 10.4 to 29.5 ± 10.3) in patients who attended at least 80% of the exercise sessions.[184] A randomized controlled trial (n = 46, 21% women) observed significant reductions on shock anxiety (FSAS, Florida Shock Anxiety Scale: -1.2 ± 3.8) and increase self-compassion (SCS, Self-Compassion Scale: 0.2 ± 0.5) in ICD recipients following an 8-week yoga intervention.[182] As such, exercise training may be a therapeutic option to improve mental health among those with CIEDs,[75] although more studies are needed considering different devices.

1.6 Quality of life

Beyond secondary prevention and enhancing cardiovascular outcomes, CR also emphasizes promoting patient wellbeing and improving health-related quality of life.[66] Quality of life, well-being, and vitality are terms often used interchangeably in health and physical activity research.[185] According to Guérin et al (2012), vitality is the narrowest construct, referring to a psychological sense of aliveness, enthusiasm, or energy. Well-being is a broader construct, a multidimensional theoretical model encompassing emotional, psychological, and social dimensions.[185] Quality of life is multifaceted, defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. Health-related quality of life (i.e., one component of quality of life), most used in clinical populations, is defined as a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.[186] One of the best-known measures of health-related quality of life is the Short-Form (SF-36) Health Survey of the Medical Outcomes Study.[187] The 8 subscales (dimensions) of this instrument help to clarify the definition of health-related quality of life and distinguish it from other constructs, capturing elements of well-being such as vitality but also adding health-specific functions and perceptions.[188] Health-related quality of life measurements provide a comprehensive, patient-centered measure. For example, poor health-related quality of life was strongly associated with increased CVD risk (adjusted HR: 1.46; 95% CI: 1.24–1.70), adjusting for demographics, comorbidities, and CVD risk factors.[189]

Previous studies investigated the impact of receiving a CIED on quality of life. A systematic synthesis of 14 previous systematic reviews evaluated pre- and post-implantation changes in quality of life in patients with CIEDs.[177] Findings showed that patients reported an improved quality of life following implantation compared to their pre-implantation levels, except for the ICD group when compared to control groups post-implantation; this may be attributed by the fact that receiving shocks

from an ICD can negatively affect quality of life and increase the risk of psychological distress.[177] Indeed, another study demonstrated that history of ICD shock, negative ICD experience, higher levels of ICD-related concerns are associated with worse quality of life in these patients – in addition to other multi-morbidity burden, female sex, not working outside the home, and the presence of anxiety, depression, or Type D personality. 156

While there is evidence of the positive impact of exercise training in patients with CVD,[191–193] evidence in individuals with CIED is limited. In patients with PPM, significant improvements in self-reported SF-36 scores in the subscales of vitality (42.1 ± 15.9 to 57.2 ± 15.4, P = 0.04) and mental health (50.3 ± 18.3 to 68.2 ± 22.4, P = 0.04) were observed following a 8-week CR program.[97 11693]A prospective non-randomized trial demonstrated significant improvements in several SF-36 subscales following 12 weeks of aerobic interval training in patients with ICDs – as demonstrated by increased scores in general health (69.1 to 78.1), vitality (52.1 to. 63.7), social functioning (85.5 to 92.1), role-emotional (91.7 to 95.8), and mental health (81.1 to 86.9).[183] No meta-analysis, however, have assessed the effects of exercise training on quality of life in patients with ICDs [94] Two recent meta-analyses by Ye and colleagues (2020; n = 7 studies; n = 687) and Guo and collaborators (2021; n = 6 studies; n = 235) showed significant improvements in quality of life following exercise rehabilitation in patients with CRT (from -5.34, 95% CI: 10.12 to −0.56; P = 0.02[87] and 19.96, 95% CI: 21.57 to 18.34, P < 0.001[130] respectively). Whether these conflicting results depend on the type of device or exercise FITT characteristics requires further examination. Existing Cochrane systematic reviews and meta-analyses (i.e., rigorous methodological requirements and inclusion of only randomized controlled trials) assessing the effects of exercise on quality of life in CVD were defined as low-quality evidence.[66] Hereby, conduction and reporting of high-quality randomized controlled trials including health-related quality of life measurements are necessary to improve the certainty of the evidence base for exercise trials in the future.

1.7 Major adverse cardiovascular events

Numerous studies have demonstrated the significant impact of exercise on MACE in those with CVD.[194,195] MACE may encompass up to five-point events, including myocardial infarction, stroke, cardiovascular mortality, hospitalization for unstable angina or revascularization procedures, and heart failure.[196] In patients with CIEDs, a recent retrospective observational study demonstrated a reduction in re-hospitalization (40.6% vs. 44.9%, HR: 0.83, 95% CI: 0.78–0.87) and all-cause mortality (7.1% vs. 10.8%, HR: 0.63, 95% CI: 0.56–0.71) in favour of patients with CIEDs who completed CR when compared to non-completers.[197] When analyzing only randomized trials, one systematic review and meta-analysis (n = 3 studies; 160 participants) found no significant differences in all-cause mortality when comparing patients with a CRT following exercise-based CR vs. no intervention in the control group (RR: 0.57, 95% CI: 0.19-1.73; P = 0.32).[91] Another systematic review compared patients with and without ICDs, however, the meta-analysis was based on one single randomized controlled trial due to the lack of research, showing no significant effects in all-cause mortality (RR: 1.96, 95% CI: 0.18-21.26).[198] Given that only one study to date has specifically examined MACE as an outcome in individuals with CIEDs, further research is warranted to clarify the effects of CR on MACE. Understanding this relationship may provide valuable insights to optimize CR referral practices and improve clinical outcomes among patients with CIEDs.

1.8 Sex-and-gender based science and women's cardiovascular health

Sex refers to the systematic classification as male, female or intersex assigned at birth based on visual anatomy assessment. Sex includes several biological processes related to external morphology, including reproductive organs, genes, hormones, gonads, chromosomes, secondary sex characteristics, and the brain.[199] Gender refers to sociocultural factors that shape the identities, attitudes, behaviours, bodily appearances, and habits of women, men, and gender-diverse individuals.[200] Gender also

intersects with other sociocultural categories, such as (i) gender norms: legislated and both spoken and unspoken cultural rules produced through social institutions, (ii) gender-related traits: aspects of a person's gender identity not captured by self-reported categories (e.g., man, woman, non-binary, and gender-queer) and concern how individuals or groups perceive and present themselves in relation to gender norms, and (iii) gender relations: power relations, economic relations, affective relations, and symbolic relations (e.g., speech and writing) between individuals of different gender identities as these relate to gender norms.[201] Using 'sex' and 'gender' interchangeably leads to inaccurate scientific reporting of two important constructs that have different implications for population health.[199] In this dissertation, the terms female and male are used when referring to biological systems (e.g., sex-differences in physiological factors), whereas women and men are used when addressing gender-related behavioural norms that influence health and well-being.

CVD is the leading cause of death in women worldwide,[202] and the predominant reason of mortality in Canadian women.[203] Women experience unique sex-specific biological (e.g., monthly hormones changes), and gender-related factors (e.g., household responsibilities) that impact their heart health across the lifespan (e.g., pre/peri/post menopause, increased caregiving demands).[204] The influence of traditional CVD risk factors (e.g., physical inactivity, hypertension, diabetes, obesity, high depression levels), are greater in women when compared to men - they report more CVD symptoms (e.g., dyspnea, fatigue, palpitations), and worse outcomes (e.g., lower quality of life)[205,206] Thus, strategies to optimize secondary prevention, such as exercise, are essential to improve the care of women with CVD.

Growing research has demonstrated sex differences in patients with CIEDs.[204] Women are less likely than men to receive ICD (8.6% vs. 32.3% primary prevention) and CRT (29% vs. 71%) therapies,[207,208] although there is evidence that they may derive similar or greater responses from receiving a CIED compared with men (e.g., greater improvements in LVEF in patients with CRT).[209]

Women report lower risks of long-term all-cause mortality rate after CRT compared with men (HR: 1.50, 95% CI: 1.38-1.63, P < 0.001).[210] Women with ICDs are at higher risk of being affected psychologically by the device implantation;[211] they are more likely to experience body image issues and less likely to adjust their caregiving responsibilities after receiving an ICD,[179] and present greater levels of anxiety and depression than men recipients.[212] Studies have shown that women with CIEDs report lower physical activity levels and quality of life compared to men with CIEDs.[213,214] The COPE-ICD trial in a posterior sex-based analysis revealed that women (n = 20) reported lower improvements than men (n = 79) in $\dot{V}O_2$peak (21.7 ± 6.4 vs. 23.4 ± 9.5), total exercise time (494.6 ± 97.7 vs. 526.9 ± 105.2), and mental health (52.2 ± 8.6 vs. 54.8 ± 7.1) following a 6-month exercise-based CR program.[215]

Women are under-represented in research.[216] They represent <40% of participants included in trials across 3 to 6 major Sports and Exercise Medicine journals (2014: n = 2,366,9, 39% women vs. 61% of men; 2021: n = 12,511,386, 34% women vs. 66% men).[217,218] Our research group recently conducted a rapid review investigating sex-specific inclusion of patients with CVD in exercise research in Canada. [219] We found that women with CVD represented 34% of patients with CVD included in Canadian exercise-based trials, and their participation has not increased over the previous 10 years. Results also showed that sex-disaggregated reporting across different phases of trials and gender-related factors were poorly observed in these studies (<40% and 13%, respectively). In patients with CIEDs, women represented less than 20% (n=651) of participants included in the most recent European consensus of CR in CIEDs.[88] In addition, no previous study has investigated whether there are sex differences following CR in women with CIEDs.[220] Findings highlight the continued inequity regarding women participants in exercise-based trials across Canada, despite evidence-informed recommendations to address this issue, and the urgent need for best practices in exercise-based trials.[219]

1.9 Barriers to accessing CR and potential solutions in women

The barriers for women in CR are well-established and include multiple levels.[221] Individual level factors include age, comorbidities, language barriers, and the perception of exercise as being unpleasant.[221,222] Provider-level factors involve supportive endorsement of CR by a health care professional, for example, women are less likely than men to receive a physician recommendation, which is a strong predictor of CR attendance.[223,224] Social/environmental-level factors encompass work-related conflicts, transportation issues, household responsibilities, and lack of social support from family and friends.[225] Indeed, specific feminine gender characteristics (i.e., family obligations, caregiving responsibilities) have shown to contribute to the higher dropout rates in CR.[225] Program- and system-level barriers include privacy concerns related to group sessions, preference for alternative forms of exercise (e.g., community- or home-based), dissatisfaction with program length or frequency, scheduling inflexibility for sessions, and limited exercise variety (e.g., treadmill/cycle only exercise.[226] Consequently, women continue to be significantly less likely than men to be referred to (i.e., 39.6% vs. 49.4%),[227] enroll in (i.e., 38.5% vs. 45.0%),[228] and adhere in CR (i.e., 64.2% vs. 68.6% of prescribed sessions [229,230] and 18.9 vs 7.9% drop-out rates). [231,232]

In the past decade, growing efforts have focused on overcoming the persistent underutilization of exercise-based CR, including in women with CVD. [231,233] CR programs are encouraged to implement women-focused delivery models, including offering women-only exercise sessions - where virtual formats may help address limited in-person resources - and providing individually tailored exercise prescriptions.[225,231] Further, high-intensity interval training (HIIT), have emerged as an time efficient alternative to women in CR.[234] HIIT consists of repeated high-intensity bursts of activity interspersed with low intensity active periods of recovery.[234,235] HIIT, when compared to traditional moderate-to-vigorous intensity continuous training (MICT, sustained period of continuous aerobic exercise) have shown superior in improving key cardiovascular health outcomes in women with CVDs.[236–238] A

randomized trial (n = 56 women) found that HIIT was superior to MICT in improving $\dot{V}O_2$peak in women with coronary artery disease following 12 weeks of CR.[239] A matched case control study (n = 60) showed clinically significant improvements in levels of anxiety (≥1.7 points) and waist circumference (high [>90 cm] to low [70–89 cm]) health risk) following 12-weeks of HIIT vs. MICT in women with CVD.[240] Beyond physiological benefits, HIIT has been associated with shorter session durations and greater enjoyment compared with MICT, potentially addressing persistent barriers to CR participation such as lack of time and motivation, particularly among women.[241–243]

It is important to note, however, that evidence on HIIT in CR remains limited and somewhat conflicting. For instance, HIIT can also be perceived as challenging and difficult to sustain as a long-term behaviour change.[244,245] Moreover, few studies have evaluated HIIT across diverse CVD populations or underrepresented groups. To date, 3 trials have assessed HIIT in patients with CIEDs (n = 38 ICDs, n = 58 CRTs).[104,110,114] Although these studies deemed HIIT as feasible and safe (i.e., no-exercise related adverse events) and effective (i.e., significantly increase CRF), fewer than 24% of participants were women across the three trials. A systematic review and meta-analysis showed significantly smaller improvements in CRF (MD: −1.10, 95% CI: −2.08 to −0.12 mL·kg−1·min−1, P = 0.03); body mass index (MD: −0.25, 95% CI: −0.03 to −0.47 kg/m^2, P = 0.02) and fasting blood glucose (MD: −0.38, 95% CI: −0.05 to −0.72, P = 0.03) in women compared to men with coronary artery disease following at least 3 weeks of a HIIT intervention.[246] Whether these results extend to patients with CIEDs is unclear, as no other previous study has investigated sex differences following exercise training between women and men with CIEDs. While HIIT represents a promising and time-efficient exercise alternative that may enhance women's participation in CR, evidence remains scarce in women with CIEDs. Further research is needed to establish the feasibility and efficacy of HIIT across diverse CVD population, with sex and gender as key considerations.

Virtual programs have also been reported as a promising solution to bridge the gap in the delivery of CR. In-person delivery can create logistical and structural barriers to attendance such as travel, cost, and caregiving responsibilities, making virtual CR a more accessible option, especially for women and other underserved groups.[247–249] Virtual CR is defined as programs using synchronous real-time audiovisual communication where the patient, who is usually at home, is not in the same physical location as the CR-PR professional, but the 2 interact in real-time throughout the full duration of the session.[250] Compared to centre-based CR, virtual CR programs demonstrate similar improvements in CRF (SMD: -0.10, 95% CI: -0.24-0.04), quality of life (SMD: 0.11, 95% CI: -0.01 to 0.23), and mortality (RR: 1.19, 95% CI: 0.65- 2.16) among those with CVD.[61,251] In line with the evidence on HIIT, literature investigating virtual CR in women-only program remains scarce. Previous studies have shown that remote programs (i.e., delivered asynchronously without real-time audiovisual communication) were feasible and effective in patients with CIEDs. There was a significantly increase in CRF ($\dot{V}O_2$peak: 16.1 ± 4.0 vs. 18.4 ±4.1 ml/kg/min) and functional capacity (6-minute walking test: 428 ± 93 vs. 480 ± 87 m) in individuals with CRTs (n = 107, 8% women) following a home-based Nordic Walking program (i.e., MICT), with no adverse events reported.[108] Similarly, a significant increase in CRF ($\dot{V}O_2$peak: 24.6 ± 5.7 to 26.7 ± 7.0 ml/kg/min) was observed following an 8-week remote walking intervention (i.e., MICT) in those with ICDs (n = 160, 22% women), with no significant adverse events (i.e., ICD shocks, hospitalizations or deaths) observed.[101] Importantly, while these studies provide promising evidence for remote MICT, no study to date has examined the feasibility or efficacy of virtual HIIT in people with CIEDs. [101,108,112] Collectively, the exercise alternatives (i.e., women programs, HIIT, virtual) discussed in this chapter may offer promising approaches to enhance participation and outcomes in exercise-based CR, particularly among a women-only sample of patients with CVD.

1.10 Overview of evidence

In summary, growing evidence has shown that CR is safe and beneficial in the management of patients with CIEDs.[70,86,87] Participation in exercise may be a great opportunity to optimize the benefits of a device implantation.[106] However, despite the benefits of exercise training for those with CIEDs, referral to CR for a device alone is not yet established and part of their routine care.[40] In this sense, many limitations in the current evidence in literature are observed such as underreporting of patients with CIEDs in CVD specific trials, small sample sizes, heterogeneity within exercise prescription and methods of measurements, and underrepresentation of women with CIEDs. Consequently, the effects of exercise on physical and mental health, quality of life, and MACE in patients with CIEDs remain understudied.[88] These disparities are further reflected in the under-representation of women in CIED research. Although efforts have been made to address the persistent underutilization of CR among women, evidence evaluating the feasibility and effectiveness of alternative exercise modalities and delivery settings tailored to their needs remains limited. Hence, studies investigating the impact of exercise training and CR on cardiovascular health outcomes in patients with CIEDs are needed, while integrating sex and gender considerations, to enhance the quality of evidence supporting guideline-based exercise recommendations in patients with CIEDs.[63,88]

1.11 Research aims of this dissertation

The overall aim of this dissertation was to examine the effects of CR and exercise training on physical and mental health, quality of life, and MACE outcomes in patients with CIEDs. The main aims were separated into four research articles and are presented below:

1. A retrospective pre-post cohort study examining the effects of exercise-based CR on CRF and mental health outcomes in individuals with CIEDs. It was hypothesized that completing an exercise-based CR program would increase the CRF of patients with CIEDs.[94]

2. A propensity score-matched retrospective cohort study assessing the effects of exercise-based CR on MACE in patients with CIEDs. It was hypothesized that enrollment in CR would be associated with a reduced risk of MACE when compared to a non-CR control group.[197]

3. A systematic review and meta-analysis investigating sex differences in CRF changes and additional physical and mental health outcomes following exercise training in women and men with CIEDs. It was hypothesized that women would experience smaller improvements in CRF than men.[215]

4. A pilot randomized trial measuring the feasibility of 12-week virtual HIIT and MICT programs in women with CIEDs. This was a hypothesis generating study, and, therefore, no hypothesis was provided. [252,253]

Secondary and tertiary aims focused on CIED subtypes and/or sex- and gender-based analyses and are reported in the studies.

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CHAPTER 2

Study 1. Changes in physical and mental health in patients with cardiac implantable electronic devices following a cardiac rehabilitation program.

2.1 Abstract

Background: Patients with cardiac implantable electronic devices (CIEDs), including pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy, often experience diminished cardiorespiratory fitness (CRF), a strong predictor of mortality, alongside elevated rates of anxiety and depression. Females with CIEDs often experience poorer outcomes than males. Exercise-based cardiac rehabilitation (CR) has been shown to improve CRF and mental health outcomes in cardiovascular populations, however, evidence in individuals with CIEDs, including per CIEDs subtypes and sex-specific responses, remains limited. We aimed to assess the associations of exercise-based CR on CRF and mental health outcomes in adults with CIEDs.

Methods: This was a retrospective pre-post cohort study using the University of Ottawa Heart Institute and Total Cardiology Rehabilitation CR databases. Patients with CIEDs were included if they completed a 12-week exercise program and had baseline and follow-up measurements. A graded exercise test was performed to assess CRF, as measured by peak metabolic equivalents (METs), and self-reported questionnaires (Generalized Anxiety Disorder-7, GAD-7; Patient Health Questionnaire-9, PHQ-9; and Hospital Anxiety and Depression Scale, HADs) were used to assess anxiety and depression symptoms.

Results: A total of 252 patients were included (mean ± SD: 69 ± 12 years, 26% females, 46% implantable cardioverter defibrillators). A significant increase in METs was observed following exercise-based CR completion in all patients with CIEDs (6.0 ±1.8 to 6.9 ± 2.0 METs, $P < 0.001$). Significant reductions were observed in anxiety (3.5 ± 3.9 to 2.8 ± 3.9 points, $P = 0.04$) and depression levels (2.1 ± 3.9 to 1.2 ± 2.8 points, $P < 0.001$) over time. No significant differences were observed across CIED types or between sexes in cardiorespiratory fitness and anxiety and depression levels.

Conclusion: Completing an exercise-based CR program resulted in clinically meaningful improvements in CRF and reduced anxiety and depression levels in patients with CIEDs. Findings emphasize the importance of exercise-based CR in the management of individuals with CIEDs.

2.2 Introduction

Cardiac implantable electronic devices (CIEDs) such as permanent pacemakers (PPMs), implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy devices (CRTs) are established treatments to restore a normal heart rhythm.[1] According to the Canadian Institute for Health Information, approximately 120,000 Canadians live with one type of CIED.[2,3] Between 2018 and 2019, 18,597 PPMs (median age: 8 years [range: 70-84], 42% females) and 4,173 ICDs (median age: 66 years [range: 57-74], 23% females) were implanted in Canada.[3] Patients with these devices have a poor cardiovascular risk profile.[4,5] Along with their cardiovascular condition requiring device therapy (e.g., heart rhythm disorders, heart failure), they present with multi-comorbidities including hypertension (58%), diabetes (34%), and high body mass index (average: 30 kg/m^2).[6] Patients with CIEDs often also demonstrate poor cardiorespiratory fitness (CRF, ~15- 40% lower compared to other cardiovascular disease groups),[7] which is a strong predictor of physical and mental health, and mortality in individuals with cardiovascular diseases.[8,9] Strategies to manage and improve key cardiovascular health outcomes in those with CIEDs are needed.

Exercise-based cardiac rehabilitation (CR) is a class 1 standing for the management of cardiovascular diseases.[10,11] Whether CR is indicated for referral after a CIED implantation is conflicting in literature.[12–14] In practice, these patients are often seen in CR based on the referral of their main underlying cardiovascular condition (e.g., coronary artery disease, heart failure) .[15–17] However, patients may differ from other cardiovascular disease populations in CR settings given their unique needs (e.g., pre-determined heart rate thresholds, rate-adaptive pacing).[13] The first consensus document providing clinical practice CR guidelines for those with CIEDs was published in 2021. It highlighted the importance of exercise-based CR not only for enhancing physical health but also for improving mental health in those with CIEDs – mental health is a known predictor of worse outcomes

in these patients.[13] Despite advances in CR recommendations, a more thorough understanding of the effects of exercise-based CR among those with CIEDs is required.[13]

The limited existing studies examining physical health outcomes have shown that participating in exercise-based CR improves CRF in patients with CIEDs.[18–20] Most of the studies have focused on ICDs, given the greater severity of the cardiovascular condition (e.g., potentially life-threatening ventricular tachyarrhythmia) and worse clinical outcomes (e.g., 20% report clinically significant psychological distress).[21] A Cochrane review showed that exercise-based CR increased CRF as assessed by a cardiopulmonary exercise test (CPET, mean difference $\dot{V}O_2$peak : 0.91 mL/kg/min, 95% confidence interval [CI]: 0.60 - 1.21) in individuals with ICDs.[22] These findings were based on 7 randomized controlled trials (n =1,485 participants); but, the evidence generated from these trials were classified as very low quality due to substantial heterogeneity (I^2 = 78%). Further, these results showed that participants did not reach the suggested minimal clinically importance difference (MCID) which is equivalent to 1 metabolic equivalent of task (METs) – or 3.5 mL/kg/min $\dot{V}O_2$peak - from baseline to completing a CR program.[23] An MCID is defined as patient derived scores that reflect changes in a clinical intervention that are meaningful for the patient.[24] These values are thus essential for interpreting the clinical significance of observed changes, both at individuals level and when comparing outcomes across intervention arms or between different patient subgroups.

Less is known about the mental health outcomes of those with devices. Patients with CIEDs often experience significant psychological concerns, which can result in behavioural including avoidance of exercise.[25,26] One randomized trial study showed that 12 weeks of exercise-based CR significantly reduced anxiety levels (13.4 ± 3.6 to 8.1 ± 3.6 points) and depression (9.9 ± 3.4 to 6.70 ± 2.90 pointed, as measured by the Hospital Anxiety and Depression [HADS]) in individuals with ICDs.[27] Concerningly, there is growing evidence demonstrating that females with CIEDs report higher anxiety and depression levels compared to men with CIEDs (10.5 ± 8.2 vs. 7.0 ± 6.8 points) at the time

of CIED implantation.[28] Yet, fewer females with CIEDs have been included in exercise trials (≤20% of participants included),[13] which limits evidence-based conclusions. No previous systematic reviews and meta-analyses have included mental health outcomes given the lack of data to pool for such analyses in patients with CIEDs.[29–31] It is important to examine not only the physical effects of exercise-based CR, but also mental health outcomes, particularly among individuals with CIEDs, while considering potential sex differences between females and males.

Altogether, limited reporting of physical and mental health outcomes, lacking sex as key consideration, have resulted in sparse evidence to guide best practices in patients with CIEDs.[12,13] An improved understanding of the effects of exercise-based CR could inform and enhance exercise recommendations for this patient population. We aimed to perform a pre-post retrospective cohort study using administrative data from two large Canadian CR centres. Our primary aim was to assess the associations of exercise-based CR on changes in CRF in patients with CIEDs. We hypothesized that completing an exercise-based CR program would increase the CRF of patients with CIEDs.[22] The secondary aim was to examine the changes in mental health (e.g., anxiety and depression levels) following exercise-based CR in patients with CIEDs. The tertiary aims were to explore changes in CRF and mental health outcomes by CIED type and between sexes following exercise-based CR.

2.3 Methods

Study design

This was a retrospective cohort study using clinical databases from two large CR programs in Canada: Total Cardiology Network, University of Calgary, Calgary, Alberta and the University of Ottawa Heart Institute, Ottawa, Ontario, Canada. This study was described following The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement checklist.[32] The protocol was approved by the University of Calgary Conjoint Health Research Ethics

Board (protocol #: REB19-0588_REN4) and the Ottawa Health Science Network Research Ethics Board (protocol #:20240036-01H), through which a waiver of consent was granted.

Participants

This study included patients who: (1) had a CIED; (2) completed an exercise-based CR program, and (3) had baseline and follow-up exercise-based CR health measures assessments reported in the databases. Given the retrospective study design and limited availability of gender-related variables, the terms "females" and "males" are used throughout to reflect data analyses between sexes.

Data sources

Data used in this study were collected as part of standard care at TotalCardiology Rehabilitation and the Cardiac Rehabilitation Program at the University of Ottawa Heart Institute. Reports with eligible participants' demographic (e.g., age, sex) and CR (e.g., CR data) data relevant to this study were generated and the data from both centres were merged into a single database. Data were retrieved between January 2022 and December 2023.

Intervention

Patients completed an exercise-based CR program following CR guidelines.[33] Supervised exercise sessions were offered once to twice weekly, 60 minutes in duration, for 8-12 weeks. Sessions included 5-10 minutes of warm-up, 30 minutes of continuous aerobic conditioning at moderate-to-vigorous intensity (e.g., walking or jogging, cycling, elliptical, rowing), and 10-15 minutes cool-down of strengthening and stretching exercises.[34] Patients were offered nutrition, stress management, and smoking cessation education classes, with referral to dietitians, social worker, vocational counsellor, and clinical psychologists as needed. Patients completed baseline and follow-up measures following the exercise-based CR program.

Outcomes

Cardiorespiratory fitness

The primary outcome was CRF, as assessed using direct measurement or self-administered questionnaire and expressed as METs. Indirect measurement included patients performing a symptom-limited graded exercise test (GXT) on a treadmill using the Bruce or Modified Bruce protocol. Peak METs were calculated using established equations ($\dot{V}O_2peak$ = [peak speed (m/min) × 0.1] + [peak grade (decimal) × peak speed (m/min) × 1.8] + 3.5).[34,35] The self-administered questionnaire included the Duke Activity Status Index (DASI); a 12-item questionnaire that evaluates (through yes or no responses) an individual's ability to perform activities of daily living.[36] Each activity has a weighted score that represents the required metabolic demand to perform the task. All "yes" responses are summed to provide a DASI score, where greater weighted DASI scores represent a higher CRF. An equation, aerobic power (mL/kg/min) = (0.43 x DASI) + 9.6, was used to estimate CRF. The DASI is an internationally recognized and validated tool,[36] and has acceptable test-retest reliability for estimating CRF in adults with cardiovascular disease (intraclass correlation coefficient = 0.90, $p < 0.01$).[37,38] The suggested MCID for CRF is a change of at least 1 MET.[23]

Mental health

Secondary outcomes included anxiety and depression levels, assessed by three validated patient-reported questionnaires: Generalized Anxiety Disorder-7 (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9); both used by the University of Ottawa Heart Institute, and the HADS, used by the TotalCardiology Research Network.

The GAD-7 is a self-report scale that yields anxiety levels (7 items). Participants rate statements regarding symptoms of anxiety on a 4-point scale (0 = not at all to 4 = nearly every day), and items are then summed to obtain a score ranging from 0 to 21. Scores of 0-4, 5-9, 10-14, and 15-21 on the GAD-

7 are considered as minimal, mild, moderate, and severe.[39] The GAD-7 is a valid and efficient tool for assessing anxiety severity in clinical practice and research, with high internal consistency (Cronbach's $\alpha = 0.92$) and good test-retest reliability (intraclass correlation = 0.83).[40] The suggested MCID for GAD-7 is a change of at least 4.0 points, based on a sample of participants with chronic depression.[41,42]

The PHQ-9 consists of nine items adapted from the 4th Edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depression.[43] Each item is scored on a 4-point scale (0 = not at all to 4 = nearly every day), and the total score ranges from 0 to 27. Scores of 0-4, 5-9, 10-14, 15-19, and 20-27 on the PHQ-9 are considered as minimal, mild, moderate, severe, and very severe symptoms, respectively. A PHQ-9 score of ≥ 10 has a sensitivity of 88% and a specificity of 88% for major depression.[43] The PHQ-9 has been recommended for screening depression in patients with coronary heart disease due to its high sensitivity and adaptability to multiple languages. The MCID for PHQ-9 is a change of at least 3.0 points, based on a study conducted on a primary care sample.[44,45]

The HADS is a 14-item self-report scale that yields separate anxiety and depression levels (7 items each). Each item is rated on a 4-point scale (0-3 points). Subscale scores range from 0 to 21, and scores above 7 are considered elevated.[46] The HADS is a validated and reliable instrument, with high internal consistency for anxiety (Cronbach's $\alpha = 0.86$) and depression (Cronbach's $\alpha = 0.82$) in patients with cardiovascular disease.[47] It has been approved for use in the American Association of Cardiovascular and Pulmonary Rehabilitation performance measures.[48] The suggested MCID for the HADS is a change of at least 1.7 points, based on a CR study in patients with cardiovascular disease.[47]

Statistical analysis

Demographic and medical information were retrieved from clinical databases. Statistical analyses were conducted with SPSS, version 28 (IBM SPSS Statistics, IBMCorp, Armonk, New York,

US). All outcome variables were tested for normality using Shapiro-Wilk tests and visual assessments. A two-step approach for transforming continuous non-normalized variables to normal was applied to baseline and or follow-up METs, PHQ-9, GAD-7, and HADS.[49] Bland Altman analyses were performed to compare METs assessed by DASI and GXT, and linear regression was used to test for proportional bias.[50] A two-way analysis of variance (ANOVA) was used to examine the main effect of time (baseline and follow-up), CIED types, and sex (females and males), and their interaction on METs, anxiety and depression scores. Post-hoc comparisons were performed using Bonferroni when significant main or interaction effects were observed. Binomial and chi-squared analyses ($\chi 2$) were used to compare the proportion of patients meeting the MCID for each outcome and per sex.[53] $P < 0.05$ was considered significant.

Sample size was estimated *a priori* using G*Power 3.1.9.2 (Universität Kiel) for a repeated-measures ANOVA (test family: F tests; statistical test: ANOVA, repeated measures within factors), with time (baseline vs follow-up) as the within-subject factor. The primary effect of interest was the main effect of time on METs. Based on a previous prospective controlled, non-randomized, single-centre study in patients with CIEDs (91% ICDs), an assumed correlation of 0.50 between repeated measurements, a small ANOVA effect size ($f = 0.10$) was specified.[51] Using a two-sided alpha level of 0.05, statistical power (1-β) of 0.80, and a nonsphericity correction of 1.0, a total sample size of 200 participants was needed to detect this effect.[53]

2.4 Results

Patient characteristics are presented in **Table 2.1.** A total of 252 patients (mean age 69 ± 12 years, 26% females) were included in this study. Of the total participants, 111 had a PM (74 ± 10 years, 28% females), 115 an ICD (63 ± 12 years, 20% females), and 26 an CRT (69 ± 12 years, 42% females). The most common reason for CR referral was coronary artery disease (26%). Frequently

prescribed medications were statins (38%), β-blockers (34%), anti-hypertensives (27%), anti-platelets (24%), and anticoagulants (23%).

Table 2.1. Patient characteristics.

Variable	Total	Females	Males
Demographic characteristics			
Age, years	69 ± 12	67 ± 13	69 ± 11
Sex (%)	-	65 (26%)	187 (74%)
Physical health[a]			
Height, cm	172 ± 10	163 ± 7	175 ± 9
Body mass, kg	84 ± 16	73 ± 18	87 ± 14
Body mass index, kg/m²	27 ± 4	27 ± 7	27 ± 4
Waist circumference, cm	101 ± 13	95 ±1 4	102 ± 12
Systolic blood pressure, mmHg	111 ± 17	111 ± 18	111 ± 17
Diastolic blood pressure, mmHg	68 ± 9	70 ± 9	68 ± 9
Resting heart rate, beats/min	70 ± 13	69 ± 15	70 ± 13
Cardiovascular conditions[b]			
Atrio-ventricular block	36 (14%)	-	36 (14%)
Coronary artery disease	65 (26%)	37 (60%)	25 (15%)
Cardiomyopathy	24 (9.5%)	-	24 (13%)
Heart failure	9 (4%)	1 (1.5%)	8 (4%)
Sinus node dysfunction	15 (6%)	-	14 (7.5%)

Data is presented in mean ± SD.[a]Indicate data received from the Total Cardiology Research Network. [b]Indicate data received from the University of Ottawa Heart Institute.

Cardiorespiratory fitness

Of 252 participants included in the METs analysis, 192 (74%) were males and 66 (26%) were females. There were no significant differences between measurements **(Figure 2.1)** obtained using the DASI and GXT at baseline (P = 0.709) or follow-up (P = 0.670).

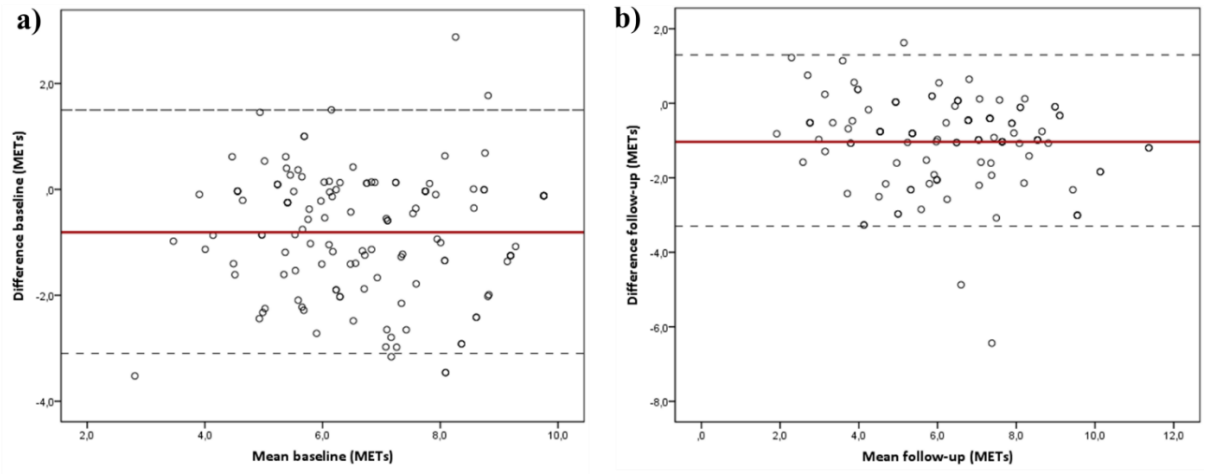

Figure 2.1. Bland-Altman plots comparing METs (n = 252) measured by the Duke Activity Status Index (DASI) and symptom-limited graded exercise test (GXT) at (a) baseline and (b) follow-up. Each plot displays the difference between DASI and GXT METs (DASI − GXT) against their mean for the corresponding time point. The solid red line represents the mean difference, and the dashed lines represent the limits of agreement (mean difference ± 1.96 standard deviation).

A significant main effect of time was observed (F = 77.233, P < 0.001, η^2 = 0.240), indicating improvements in METs over time **(Table 2.2)**. No significant interaction effects were found for time x CIED types (F = 1.042, P = 0.354, η^2 = 0.008), and time × sex (F = 1.303, P = 0.255, η^2 = 0.005). A total of 119 (47%) patients with CIEDs achieved the MCID (i.e., ≥1.0 METs); significant differences in these proportions were observed (P = 0.004). A total of 25 females (38%) and 78 (42%) males achieved the MCID in METs; no significant differences were observed between sexes (χ^2 = 0.646, P = 0.664).

Table 2.2. Participants' METs at baseline and follow-up.

	Baseline	Follow-up	Change
METs			
Total	6.0 ±1.8	6.9 ± 2.0	0.9 ± 1.1*
Per device			
PM	5.9 ± 2.1	6.7 ± 2.1	0.8 ± 1.1
ICD	6.2 ± 1.8	7.2 ± 1.9	1.00 ± 1.2
CRT	5.4 ± 1.0	6.3 ± 1.3	0.91 ± 0.9
Per sex			
Females	5.6 ± 1.9	6.4± 1.8	0.7 ± 1.3
Males	6.1 ± 1.8	7.1 ± 2.0	0.9 ± 1.1

Values are presented as mean ± standard deviation. Values are presented by device type for descriptive purposes.*denotes significant difference ($P < 0.001$) within-subject difference (baseline vs follow-up).

Mental health

A total of 216 patients (mean age 70 ± 12 years, 34% females) were included in the PHQ-9 and GAD-7 analyses, of which 102 patients had a PM (38% females), 74 an ICD (26% females), and 41 an CRT (39% females). A total of 66 patients were included in the HADS analyses (mean age 66 ± 11, 18% females), of which 31 participants had a PM (26% females) and 35 an ICD (11% females). No patients with CRT were included in the HADS analyses.

Anxiety levels (GAD-7 and HADS) scores and categories

Main effects of time demonstrated reductions in symptoms of anxiety using GAD-7 ($F = 4.287$, $P = 0.040$, $\eta^2 = 0.020$). No significant interaction for time × CIED type ($F = 0.205$, $P = 0.815$, $\eta^2 = 0.002$) and time × sex ($F = 0.108$, $P = 0.743$, $\eta^2 = 0.001$) was observed. A total of 19 (9%) patients with CIEDs achieved the MCID for the GAD-7 (i.e., ≥ 4 points) when compared to 198 patients (91%) non-achievers; significant differences in these proportions were observed ($P < 0.001$). A total of 7 females

(9.5%) and 12 (8%) males achieved the MCID for the GAD-7; no significant differences were found between sexes ($\chi^2 = 0.324$, P = 0.56).

No significant differences were observed in symptoms of anxiety over time using HADS (F = 0.443, P = 0.508, $\eta^2 = 0.007$) **(see Table 2.3)**. There were no significant interactions between time × CIED type (F = 0.001, P = 0.980, $\eta^2 = 0.001$) and time × sex (F = 1.509, P = 0.308, $\eta^2 = 0.017$). A total of 15 (23%) patients with CIEDs achieved the MCID for the HADS anxiety (i.e., 1.7 score) compared to 51 (77%) non-achievers; significant differences in these proportions were observed (P < 0.001). A total of 4 females (33%) and 11 (20%) males achieved the MCID in HADs anxiety scores; no significant differences were found between sexes ($\chi^2 = 0.939$, P = 0.33).

Depression levels (PHQ-9 and HADS) scores and categories

Significant main effects of time showed reductions in symptoms of depression using the PHQ-9 (F = 13.916, P < 0.001, $\eta^2 = 0.062$) **(see Table 2.3)**. No significant interaction effects were found for time × CIED type (F = 0.418, P = 0.659, $\eta^2 = 0.004$) and time × sex (F = 2.308, P = 0.569, $\eta^2 = 0.003$). A total of 6 (3%) patients with CIEDs achieved the MCID for the PHQ-9 (i.e., ≥3 points) compared to 211 patients (97%) non-achievers; significant differences in these proportions were observed (P < 0.001). No females (0%) and A 6 (4%) males achieved the MCID in PHQ-9; no significant differences were observed between sexes ($\chi 2 = 3.193$, P = 0.07).

No significant differences were observed in symptoms of depression over time using HADS depression (F = 0.262, P = 0.611, $\eta^2 = 0.004$) **(see Table 2.3)**. No significant interaction between time × CIED type (F = 0.037, P = 0.848, $\eta^2 = 0.001$) and time × sex (F = 0.396, P = 0.531, $\eta^2 = 0.006$) was observed. A total of 10 (15%) patients with CIEDs achieved the MCID for HADS depression (i.e., 1.7 score) vs. 56 (85%) non-achievers; significant differences were observed between proportions (P <

0.001). A total of 2 females (17%) and 8 (15%) males achieved the MCID for HADS depression scores; no significant differences were observed between sexes ($\chi 2 = 0.02$, $P = 0.87$).

Table 2.3. Mental health scores based on self-reported questionnaires.

	Pre	**Post**	**Change**
GAD-7			
Total	3.5 ± 3.9	2.8 ± 3.9	-0.6 ± 3.9*
Per device			
PM	3.7 ± 3.9	3.1 ± 4.0	-0.5 ± 4.0
ICD	3.2 ± 3.7	1.8 ± 2.9	-1.2 ± 3.4
CRT	3.6 ± 4.3	3.7 ± 4.8	0.0 ± 4.3
Per sex			
Females	1.9 ± 3.8	1.2 ± 2.7	-0.6 ± 2.7
Males	2.1 ± 3.9	1.30 ± 2.90	-0.6 ± 4.4
PHQ-9			
Total	2.1 ± 3.9	1.29 ± 2.84	-0.8 ± 3.6*
Per device			
PM	2.2 ± 3.9	1.3 ± 3.3	-0.6 ± 3.5
ICD	2.04± 3.6	0.8 ± 1.9	-1.1 ± 2.8
CRT	1.8 ± 4.3	1.2 ± 2.9	-0.6 ± 5.1
Per sex			
Females	1.9 ± 3.8	1.27 ± 2.7	-0.7 ± 2.2
Males	2.19 ± 3.97	1.3 ± 2.9	-0.0 ± 4.2
HADS anxiety			
Total	5.4 ± 3.6	5.3 ± 3.6	-0.0 ± 2.5
Per device			
PM	5.45± 4.1	5.9 ± 4.0	0.5 ± 2.9
ICD	5.4 ± 3.2	4.8 ± 3.2	-0.6 ± 2.1
Per sex			
Females	9.0 ± 3.6	9.0 ± 3.2	0.0 ± 3.4
Males	4.61 ± 3.15	4.54 ± 3.24	0.07 ± 3.20
HADS depression			
Total	4.1 ± 3.7	3.7 ± 3.1	-0.3 ± 1.9
Per device			
PM	4.6 ± 3.3	4.4 ± 3.6	-0.2 ± 1.8
ICD	3.6 ± 2.1	3.1 ± 2.5	-0.4 ± 2.0
Per sex			
Females	6.2 ± 3.3	5.5 ± 4.0	-0.0 ± 3.6

Males	3.6 ± 2.4	3.3 ± 2.8	-0.0 ± 2.3

Values are presented as mean ± standard deviation. *denotes significant difference (P < 0.001) within-subject difference (baseline vs follow-up).

2.5 Discussion

The evidence regarding the benefits of exercise-based CR in patients CIEDs is limited, and sex differences remains understudied.[52] This retrospective cohort study examined the association of exercise-based CR programs in improving CRF, anxiety, and depression outcomes in patients with CIEDs, with sex as key consideration. Consistent with our hypothesis, a significant increase in CRF was observed following an exercise-based CR completion in patients with CIEDs, and 47% achieved the suggested MCID for METs. Significant reductions were observed in anxiety and depression levels over time. No significant differences in CRF and anxiety and depression levels were observed by type of CIED or between females and males with CIEDs.

Cardiorespiratory fitness

Our findings showed that participants achieved improvements in CRF following CR. While our study had a pre-post design, findings are supported by a previous meta-analysis in patients with ICD and CRT (n = 2,547, 17.3 % females, age range: 52-69 years) showing greater improvements in $\dot{V}O_2$peak in patients with CIEDs compared to a control group (1.98 vs. 0.36 mL/kg/min, P[5353]. It has been previously postulated that exercise could maximize the benefits of CIEDs i[31,5431,54]. For instance, Patwala and colleagues (2009) showed that CRT implantation alone improved CRF ($\dot{V}O_2$peak: 16.12 ± 3.44 to 18.41 ± 3.56 mL/min/kg, P < 0.001) and subsequent exercise training for 12 weeks resulted in further improvements in CRF (18.74 ± 3.40 to 20.10 ± 3.84 ml/kg/min, P < 0.001)[5454]. Both CRT (biventricular CIEDs) and exercise training can improve central cardiovascular responses, particularly [5555]. Improvements in CRF due to [5656][5757]. however, are not universal; some individuals are identified as 'non responders'. In fact, 20% of patients enrolled in CR fail to improve $\dot{V}O_2$peak (i.e., reduced or

no significant increase in CRF after exercise[58,59,60] It is therefore possible that exercise training enhances other health parameters (e.g., submaximal exercise capacity, muscular strengthperipheral oxygen extraction) linked to exercise tolerance and functional capacity, even in the absence of measurable gains in CRF. The relationship between changes in CRF influenced by device therapy and exercise training is yet to be elucidated. CIED-specific analyses revealed no significant differences; however, interpretation is limited by the unequal distribution of devices types within the sample. Future adequately powered studies are needed to determine whether improvements in CRF differ by device indication. Nevertheless, the overall improvements in CRF observed in this cohort support the benefits of exercise-based CR in individuals with CIEDs.

Almost 50% of patients with CIEDs achieved the MCID for METs. Evidence from large cohorts demonstrates that each 1- MET increase in CRF is associated with a 11%–17% reduction in all-cause mortality.[61] Previous studies suggested that even smaller improvements (i.e., 6% of CRF) may carry prognostic significance.[62] This could also have significant implications in females with cardiovascular disease, as they have previously demonstrated small improvements in CRF (i.e., less than 1-MET) following 12 weeks of CR.[63] Our results showed no sex differences between females and males with CIEDs in CRF following exercise-based CR over time, as well as no significant differences in the proportion meeting this MCID. Of note, analyses between females and males were exploratory, reflecting the limited representation of females in the sample. A previous meta-analysis (n = 19 studies, 350 participants, 33% females) performed by our group has shown smaller improvements in CRF in females with atrial fibrillation following exercise training ($\dot{V}O_2$peak, mean difference = 0.15, 95% CI: −1.08 to 1.38 mL O_2/kg/min, P = 0.81, I^2 = 27). Anatomical and physiological differences may limit their CRF response to exercise when compared to males.[64,65] Females have smaller body size and mass, higher body fat, and lower muscle mass compared to men.[63,65] Females can also experience smaller increases in left ventricular mass and size, expansions in blood volume, and vascular changes (e.g.,

lower nitric oxide availability in post-menopausal females may limit their exercise-induced vasodilation) following exercise.[64] Further, females with cardiovascular disease face more barriers (e.g., caregiver responsibilities) and remain under-represented in both exercise-based CR programs[66] and CIEDs[67] trials. While the observed improvements in CRF emphasize clinically meaningful impact of exercise in patients with CIEDs, our findings underscore the need for sex-specific and tailored exercise interventions in these patients.

Mental health

Patients with CIEDs are at higher risk of developing depression (15%) and anxiety (23%).[68] Mckenzie et al (2022, n = 268 patients, 73% males) showed that participation in a CR program was associated with fewer depressive symptoms, particularly among patients presenting with greater depressive symptom severity at baseline..[69] Although most of our sample (≥70%) reported normal levels of anxiety and depression at baseline, we still observed improvements in these symptoms over time with exercise-based CR. Our results are supported by previous studies in patients with cardiovascular diseases, demonstrating that exercise-based CR reduced symptoms of anxiety and depression, while also lowering the risk of recurrent coronary events.[70,71] Notably, significant differences were observed for the GAD-7 and PHQ-9 but not the HADS. Differences observed across anxiety and depression measures are not unexpected.[72] Although all instruments demonstrate excellent internal consistency, with strong intercorrelations, they assess similar yet distinct symptom domains.[72,73] The GAD-7 and PHQ-9 both measure a heterogeneous spectrum of symptoms in anxiety and depressive disorders, respectively, while the HADS focuses more on the emotional aspects of anxiety and depression and does not contain items that measure somatic symptoms, which may contribute to the observed differences.[74] Overall, findings emphasize the positive impact of exercise-based CR on mental health in patients with CIEDs, while also highlighting differences in standardized psychological assessment tools and responses in individuals with CIEDs.

Limited evidence exists regarding clinically meaningful improvements in mental health outcomes in patients with CIEDs.[75] In a broader cardiovascular cohort of patients with coronary artery disease (n = 591, 26% females), a 12-week exercise-based CR program resulted in clinically meaningful improvements, with 40% achieving the MCID on the HADS-anxiety subscale (n = 234) and 32% on the HADS-depression subscale (n = 188).[47] Similarly in patients with heart failure (n = 852, 28% females), PHQ-9 scores have been shown to significantly predicted all-cause mortality risk (hazard ratio: 1.07, 95% CI: 1.04-1.09, P < 0.001), and rehospitalization (hazard ratio: 1.03; 95% CI: 1.01-1.04; P = 0.001).[76] With so few patients achieving the suggested MCID thresholds across GAD-7, PHQ-9, HADS measures (≤23%), important questions arise regarding the applicability of these cut-offs in patients with CIEDs. For instance, the MCID for the HADS were derived from a general CR cohort, and it is unclear whether patients with CIEDs were included in the sample.[47] Consequently, these values may not reflect changes most meaningful to individuals living with CIEDs, highlighting the need to explore complementary assessments and establish CIED-specific MCID estimates. Further, in contrast with previous literature, we did not find sex differences in anxiety and depression symptoms. O'Neill et al. (2022) showed that females entering CR exhibited greater anxiety than men, particularly younger adults, who also had the highest dropout rates.[77] Although our sample primarily comprised older adults, it is important to recognize that CIED implantation may occur earlier in life (i.e., for primary prevention) and these patients may subsequently be referred to CR.[78] Emerging evidence suggests that different types of exercise modality (i.e., high-intensity interval training) may yield greater reductions in anxiety (-1.6 ± 3.2 points), and depression (-0.9 ± 2.7 points), as measured by HADs, among females participating in exercise-based CR.[79] Given the high prevalence of psychosocial distress in females with cardiovascular disease, systematic screening for anxiety and depression is essential. The Screening and Triage for Anxiety and Depression (STAD) protocol offers an efficient approach to identifying and managing psychosocial needs in a CR setting. In a cohort of 1,504 patients (24% females), 19% presented with elevated HADS scores (≥16) and were referred to psychosocial

resources. After reassessment at week four, nearly half no longer required intervention, while the remainder were appropriately referred to psychology or social work services. This approach reduced unnecessary referrals, minimized patient burden, and optimized clinical time within the CR program.[80] Collectively, these findings highlight the need for future research to examine mental health outcomes and clinically meaningful changes in patients with CIEDs, with particular attention to sex- and perhaps age-related differences that may influence CR participation and benefits.

Limitations and strengths

The results of this study should be interpreted with caution given the following limitations. Frist, this was a retrospective cohort design without a control group; inclusion of a control group would have enabled comparison of key outcomes, such as CRF, to better isolate the effects of CR participation from other non-CR factors and strengthen casual effects. Although our sample size exceeded the estimate for the primary analysis (i.e., CRF), which was based on an ICD-focused trial,[51] analyses by CIED type were performed as exploratory due to unequal CIEDs distribution. Future adequately powered trials should stratify by CIED type to determine whether responses to exercise-based CR differ according to device indication. The cohort was drawn from two centres, which may have introduced variability in exercise-based CR delivery and measurement procedures. Females were not specifically targeted to match the proportion of males. While females were under-represented (26%), the inclusion rate was consistent with recent Canadian studies of exercise training in patients with cardiovascular disease.[66] Finally, while pre-post study designs have limited generalizability, our study is the first to combine data from two large CR centres in Canada, which may enhance external validity.

2.6 Conclusions

Exercise-based CR was effective in improving CRF and reducing symptoms of depression and anxiety in patients with CIEDs. The improvements observed in CRF were clinically meaningful, emphasizing the importance of exercise-based CR in the comprehensive management of individuals with CIEDs. Future prospective studies are needed to confirm findings, strengthening the evidence base for CR in patients with CIEDs.

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CHAPTER 3

Study 2. The association of exercise-based cardiovascular rehabilitation with major adverse cardiovascular events in patients with cardiac implantable electronic devices.

3.1 Abstract

Background: Cardiac implantable electronic devices (CIEDs) are established treatments to regulate heart rhythm disturbances. Exercise-based cardiovascular rehabilitation (CR) is part of CIED management, yet its long-term impact on major adverse cardiovascular events (MACE) in adults with CIEDs remains unclear. We aimed to examine the association between CR and the risk of MACE in patients with CIEDs up to five years after a CIED implantation.

Methods: This was a single-centre retrospective cohort study. Administrative data were obtained from visits at the University of Ottawa Heart Institute, between January 1st, 2002, and April 30st, 2025. Patients without a record of CR were compared with those who had attended at least one CR-related appointment. MACE was defined as mortality or any admission for heart failure, myocardial infarction, stroke, and cardiovascular procedures (i.e., percutaneous coronary intervention, or coronary artery bypass graft). Groups were matched on propensity score using nearest neighbour matching with caliper restriction. Outcomes were measured from the index event (i.e., CIED implantation) in both groups, up to five years. Kaplan-Meier survival curves were also produced with log-rank P-values. Cox proportional hazards models were used to evaluate the association between CR participation and MACE.

Results: A total of 344 patients were included in this analysis, with 172 in the CR group (77.0 ± 13.0 y, 47% pacemakers; 31% females). There was no significant difference in the reduction of MACE hazard over the 5-year follow-up period when comparing patients with a record of CR to propensity score-matched controls (hazard ratio [HR]: 0.99, 95% confidence interval [CI]: 0.708–1.408, P = 0.99). No significant aassociations were observed in subgroup analyses per type of device. CR was associated with a 42% reduction in MACE hazard among women (HR: 0.58, 95% CI: 0.389–0.892, P = 0.01).

Conclusion: CR is not associated with significantly lower 5-year risk of MACE when compared to propensity score-matched CIED patients without CR. Females with CIEDs may derive greater benefit from CR than males. Results should be considered hypothesis-generating and not interpreted as evidence of causation. Larger studies are needed to further understand the influence of CR in patients with CIEDs.

3.2 Introduction

Cardiac implantable electronic devices (CIEDs) are widely used in the management of cardiovascular disease to regulate heart rate and rhythm disturbances.[1] Over the past 50 years, device therapy has played an increasingly critical role in managing life-threatening heart rhythm disorders and heart failure in patients.[2] Permanent pacemakers (PPMs) treat slow heart rhythms, implantable cardioverter defibrillators (ICDs) terminate potentially fatal arrhythmias, and cardiac resynchronization therapy devices (CRTs) improve ventricular synchrony and contraction.[3] In Canada, the incidence of initial implantation procedures for PPMs and ICDs has substantially risen from 7 per 100,000 persons in 2003 to 70 per 100,000 persons in 2019 - a tenfold increase over this period.[4] CIEDs rank among the ten most frequently implanted medical devices globally, with over 1.5 million implantations each year.[5,6]

Landmark clinical trials have demonstrated that CIEDs significantly improve survival rates.[7–9] The Canadian Trial of Physiological Pacing (CTOPP, n = 2,568, 3-year follow-up) showed that PPMs reduced the annual rate of stroke or cardiovascular death in patients with symptomatic bradycardia, with similar outcomes observed between atrial (4.9%) and ventricular pacing (5.5%) modes (relative risk reduction: 9.4%, 95% confidence interval [CI]: –10.5 to 25.7, P = 0.33), suggesting a benefit of pacing independent of mode.[8] The Multi-center Autonomic Defibrillator Implantation Trial II (MADIT-II trial, n = 1,232, 20-month follow-up) showed a superiority of ICDs compared to conventional medical therapy (hazard ratio [HR]: 0.69, 95% CI: 0.51-0.93, P = 0.02) in individuals with prior myocardial infarction.[9] The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure trial (COMPANION, n = 1520, 14-month follow-up) revealed a reduction in all-cause mortality for CRTs with a pacemaker (HR: 0.81, 95% CI: 0.69-0.96, P = 0.02), and CRTs with a defibrillator (HR: 0.80, 95% CI: 0.68-0.95, P = 0.01) compared to medical therapy alone in individuals

with heart failure.[7] These trials underscore the life-saving potential of device therapy across diverse cardiovascular conditions, reinforcing its established role in clinical practice.

Despite CIEDs conferring significant survival benefits, patients with CIEDs remain at an increased risk of major adverse cardiovascular events (MACE).[10] MACE is a composite endpoint encompassing clinical events such as heart failure, myocardial infarction, and all-cause mortality.[11] Higher rates of MACE observed among patients with CIEDs are largely attributable to the severity of the underlying cardiac conditions, requiring device therapy.[12] For instance, incident atrial fibrillation has been associated with higher risks of stroke (3.8–11.4-fold), admission for heart failure (2.6–10.5-fold), all-cause hospitalization (2.4–2.7-fold), and all-cause mortality (4.1–5.0-fold) in patients with CIEDs.[13] Further, patients with these devices frequently present with poor cardiovascular risk factor profiles, including low physical activity levels.[14] Individuals with CIEDs who engage in low physical activity have a 2.02-fold higher risk of mortality (95% CI: 1.21–3.38, P = 0.007).[15] Further, device-derived data show that all-cause mortality is significantly associated with physically active time. Patients with PPMs averaging less than one hour per day had a nearly 7.5-fold increased risk of death over 10 years compared to those active for more than three hours daily (odds ratio: 7.44, 95% CI: 1.88-29.43; P = 0.007).[16] These findings highlight the importance of optimizing cardiovascular risk factors – particularly physical activity - to reduce secondary cardiovascular events in the CIED population.

Exercise-based cardiovascular rehabilitation (CR) is a cornerstone of comprehensive cardiovascular management guidelines.[17] CR has been shown to improve key cardiovascular health outcomes including physical activity levels (5 trials; weighted mean difference: 1423, 95%CI: 757.07-2089.43, P < 0.001)[18] and to reduce cardiovascular mortality by ~25% (27 trials; risk ratio: 0.74, 95% CI: 0.64-0.86) and rehospitalizations by ~18% (15 trials, risk ratio: 0.82, 95% CI: 0.70-0.96) in patients with coronary heart disease.[19] Although a considerable proportion of CR participants have CIEDs,

evidence on the long-term impact of CR in those with devices is sparse.[20] Existing systematic reviews and meta-analyses of randomized controlled trials report no significant mortality benefit of exercise-based CR compared to usual care among patients with ICDs (risk ratio: 1.96, 95% CI: 0.18-21.26)[21] or CRTs (fixed-effect relative risk: 0.57, 95% CI: 0.19-1.73).[22] In contrast, a retrospective observational study found lower all-cause mortality in patients with CIEDs who completed one year of exercise-based CR when compared to non-completers.[23] Current evidence likely reflects limitations of the existing trials, including small sample sizes and short follow-up periods in observational studies, affecting the ability to detect differences in outcomes such as mortality or MACE. Given no study has examined long-term (i.e., ≥ 5 years) MACE outcomes following CR in individuals with CIEDs, further research is needed in this field.

Beyond the limited primary data evaluating the impact of exercise-based CR on MACE in patients with CIEDs, females with CIEDs remain under-represented in clinical trials (~33%).[24,25] In the broader cardiovascular population, females are less likely to be referred to and participate in CR programs,[26,27] but CR has shown equal or greater mortality benefits in females when compared with males.[28–30] For instance, a large Canadian retrospective cohort study (n = 25,958 participants, 24.6% females) showed the greatest mortality reduction among females completing CR (HR: 0.36, 95% CI: 0.28-0.45), exceeding the benefit observed in males (HR: 0.51, 95% CI: 0.46-0.56).[31] Females entering CR are older, have more comorbidities, and poorer cardiovascular risk factor management (e.g., lower cardiorespiratory fitness, higher body mass index) than males, yet it remains unclear how these factors influence CR outcomes.[32,33] The limited evidence regarding the sex-specific effects of exercise-based CR is also evident in patients with CIEDs, emphasizing the need for targeted analyses to address this critical evidence gap.

Understanding the relationship between exercise-based CR and MACE is essential for informing evidence-based strategies for secondary prevention in patients with CIEDs. We aimed to examine the associations of CR on 5-year MACE risk in patients with CIEDs**.** We hypothesized that enrollment in CR would be associated with a reduced risk of MACE when compared to a non-CR control group.[23] Secondary aims examined the differences in MACE risk across CIEDs subtypes and assessed whether these risks differ between females and males with these devices, considering the distinct underlying diseases, indications associated with each CIED type,[34] and prior evidence of sex differences in cardiovascular disease, CR outcomes and MACE risk.[35]

3.3 Methods

Study design

This was a propensity score-matched retrospective single centre cohort study using clinical databases from the University of Ottawa Heart Institute (Ottawa - Ontario, Canada). This study was reported in accordance with the latest Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[36] Ethical approval was obtained from the Ottawa Health Science Network Research Ethics Board (protocol: 20240036-01H), through which a waiver of consent was granted. Given the retrospective study design and limited availability of gender-related variables, the terms “females” and “males” are used throughout to reflect sub-group analyses between females and males.

Settings

A data request was submitted for records between January 1, 2011, and April 30, 2025, with patients followed for up to five years. Data were obtained through health records and departmental patient lists from three sources: (i) PaceArt (i.e., database that manages patients’ cardiac device data;

January 2011 - December 2022), (ii) Cardiac Rehabilitation (i.e., clinical database; October 2015 - August 2019), and (iii) EPIC (i.e., electronic health record system; June 2019 - April 2025).

Participants

Patients were included if they: (1) were at least 18 years of age; (2) had a CIED; and (3) had a minimum follow-up period of 5 years from the time of their CIED implantation.

Exposure

The exposure of interest was exercise-based CR which was defined as a minimum of one CR-related appointment in the Cardiac Rehabilitation Program in the Division of Cardiac Prevention and Rehabilitation at the University of Ottawa Heart Institute. Exposure information was obtained from the CR database. The CR outpatient program supports participants in developing the knowledge and skills necessary to adopt and sustain a heart-healthy lifestyle, facilitating their return to daily life activities following a cardiac event.[37–40] Patients are offered one or two weekly exercise sessions, ≤60 minutes in duration, for 8-12 weeks. Sessions include 5-10 minutes of warm-up, 30 minutes of continuous aerobic conditioning at moderate-to-vigorous intensity (e.g., walking or jogging, cycling, elliptical, rowing), and 10-15 minutes cool-down of strengthening and stretching exercises.[34] Patients are also offered nutrition, stress management, and smoking cessation education classes, with referrals to dietitians, social workers, vocational counsellors, and clinical psychologists as needed.

Primary outcome

The primary outcome was MACE, defined as death or any nonfatal admission of myocardial infarction, heart failure, or stroke. MACE also included any admission for coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting) or severe arrhythmias.

Covariates

Several sociodemographic and medical variables were collected, including age, sex, type of CIED, admission and discharge dates, medications, and cardiovascular comorbidities (e.g., atrial fibrillation, hypertension). These variables were chosen as covariates because they are established risk factors for MACE.[41–43]

Statistical analysis

Baseline characteristics were summarized as mean (SD) for continuous variables and as frequency (percentage) for categorical variables. Between-group comparisons for categorical variables were performed using Chi-squared tests, and continuous variables using independent t-tests. CR patients were propensity score-matched 1:1 with controls based on age, sex, CIED type (i.e., PPM, ICD, CRT), and cardiovascular history. These variables were selected for their established association with cardiovascular outcomes and mortality.[44] After matching, standardized mean differences were substantially reduced across all covariates, with most falling within the threshold for imbalance (≤1.0), indicating improved comparability between groups. The standardized mean differences for the logit of the propensity score approached zero after matching, confirming appropriate matching performance. Kaplan–Meier survival curves were produced with log-rank tests for group comparisons. Crude and multivariable Cox proportional hazards models were used to estimate hazard ratios with 95% CI for MACE occurring up to 5 years following exercise-based CR, compared with matched controls.[23] Sub-group analyses were performed assessing differences by CIED subtype and sex.[34,35] Statistical significance was set at $P < 0.05$ for all tests. Analyses were conducted using SAS On Demand (SAS Institute, Cary, NC).

Sample size calculation

Sample size calculations estimated that approximately 163 events were required to detect a hazard ratio of 1.6 with 80% power and a two-sided alpha of 0.05.[45] This corresponded to a total sample of 912 participants (i.e., 456 participants per group), assuming event rates of 10.8% in the non-CR group and 7.1% in the CR group, based on previous literature. [46]

3.4 Results

Data from 14,120 patients were obtained from EPIC between January 2002, and April 2025. CIED implantation was defined as the admission visit documented within the specified date range in the medical chart. Covariate data included age at baseline, sex, CIED type, and cardiovascular history for all patients matched in the cohort. **Figure 3.1** shows the data linkage process and final analytical sample. After linkage, 832 patients were excluded (see **Figure 3.1** for reasons), resulting in a total of 344 individuals with CIEDs included in the analysis.

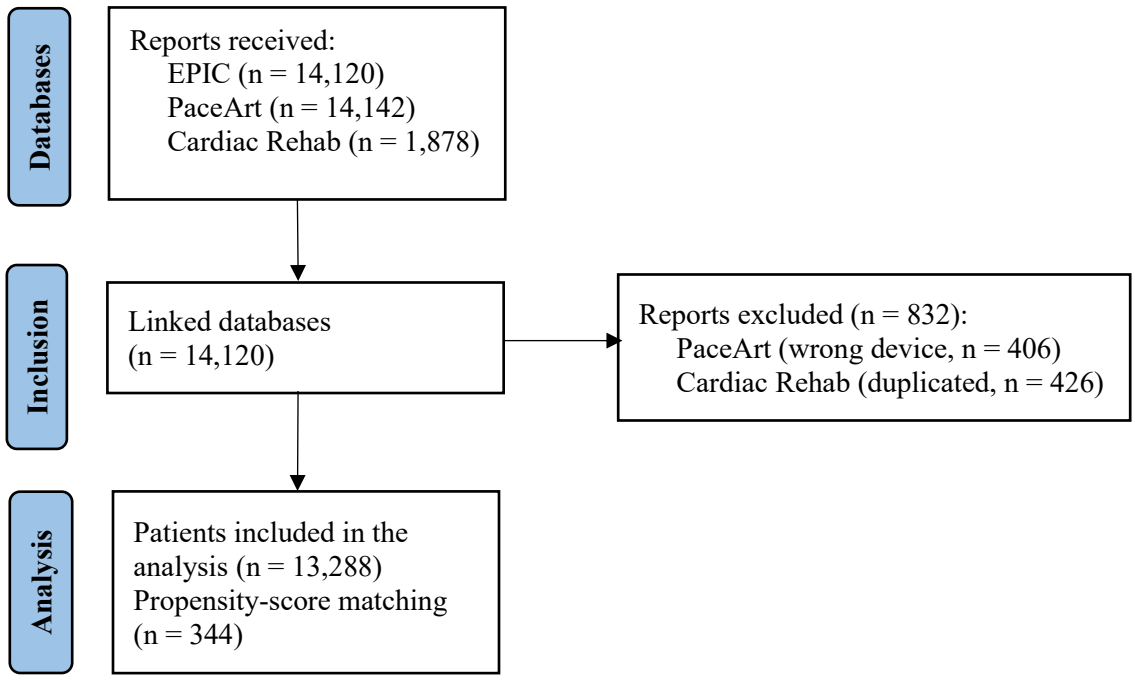

Figure 3.1. Flowchart depicting linked databases with the number of individuals at each stage.

Patient characteristics

After propensity score matching, 172 patients were retained in each group, resulting in a final analytic sample size of 344. **Figure 3.2** illustrates the standardized mean differences before and after matching, and **Table 3.1** summarizes baseline and post matching cohort characteristics.

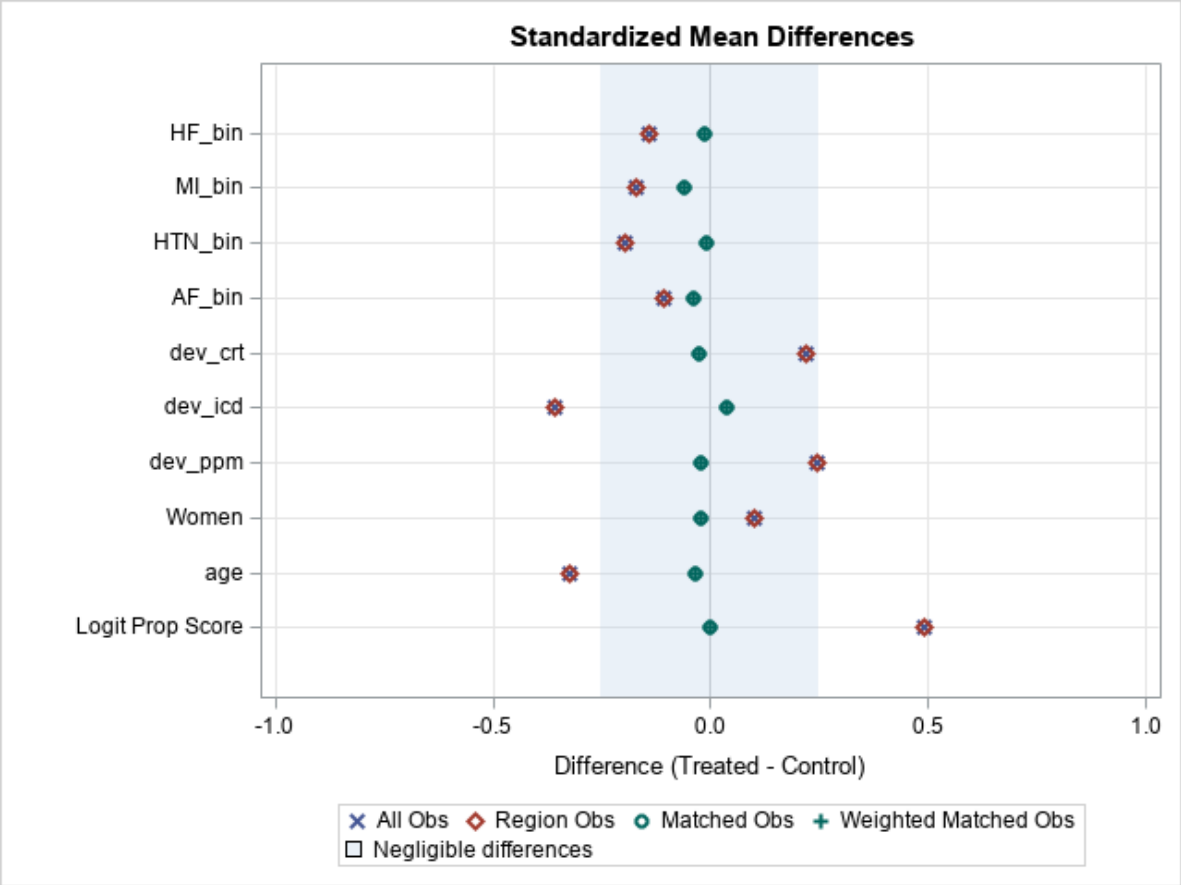

Figure 3.2. Standardized mean differences plot comparing baseline covariates between the non-CR and CR cohorts before and after propensity score matching. Per order: HF, heart failure; MI, myocardial infarction; HTN, hypertension; AF, atrial fibrillation; dev_crt, cardiac resynchronization therapy; dev_icd, implantable cardioverter defibrillator; dev_ppm, permanent pacemaker.

Table 3.1. Baseline characteristics for the CIED populations with and without exercise-based CR, before and after propensity score matching.

	Original population	**Propensity score matched population**			**Standardized mean difference**
	Non-CR (n = 13,288)	**CR (n = 172)**	**Non-CR (n = 172)**	**CR (n = 172)**	
Demographic data					
Age (y) at baseline; mean ± SD	81.3 ± 14.1	77.0 ± 12.1	77.0 ± 13.0	77.0 ± 12.1	-0.44767
Females, n (%)	4,805 (36%)	57 (31%)	54 (31%)	57 (31%)	-0.01163
CIED type, n (%)					
PPM	8,763 (66%)	93 (45%)	95 (55%)	93 (45%)	-0.01163
ICD	3,485 (26%)	74 (43%)	73 (42%)	74 (43%)	0.01744
CRT	1,040 (8%)	5 (7%)	4 (1%)	5 (7%)	-0.00581
Cardiovascular conditions, n (%)					
Atrial fibrillation	3,226 (24%)	50 (29%)	45 (26%)	50 (29%)	-0.01744
Heart failure	3,685 (28%)	59 (34%)	61 (35%)	59 (34%)	-0.00581
Hypertension	6,273 (24%)	98 (56%)	94 (55%)	98 (56%)	-0.00581
Myocardial infarction	1,986 (15%)	37 (21.5%)	29 (17%)	37 (22%)	-0.02326

Abbreviations. CR, cardiovascular rehabilitation. PPM: Permanent pacemaker. ICD, implantable cardioverter defibrillator. CRT, cardiac resynchronization therapy.

Additional baseline characteristics for the matched samples are shown in **Table 3.2**. Body mass index data were available for a limited number of patients, n = 101 in the non-CR group and n = 96 in the CR group. Similarly, New York Heart Association (NYHA) classification was recorded for 46 patients in the non-CR group and 32 in the CR group. The NYHA is a four-class system used to assess the severity of heart failure based on physical activity limitations, ranging from class I (no limitation) to class IV (severe limitation).

Table 3.2. Patient characteristics of the CIED cohort retained in the final analysis.

	Non-CR group (n = 172)	**CR group (n = 172)**	**P-value**
Body mass index (kg/m²)	27.2 ± 4.4	25.9 ± 4.5	0.03
NYHA functional class			
Class I	19 (41%)	23 (72%)	0.31
Class II	13 (28%)	3 (9%)	0.01
Class III	11 (24%)	5 (16%)	0.12
Class IV	3 (6.5%)	1 (3%)	0.31
Cardiovascular history			
Catheterization	38 (22%)	26 (15%)	0.09
Chronic obstructive pulmonary disease	22 (13%)	22 (13%)	0.61
Dyslipidemia	64 (37%)	71 (41%)	0.43
Diabetes mellitus	44 (26%)	48 (28%)	0.62
Heart failure	61 (35.5%)	59 (34%)	0.82
Hypertension	98 (57%)	98 (57%)	0.66
Myocardial infarction	29 (17%)	37 (21.5%)	0.27
Peripheral artery disease	7 (4%)	6 (3.5%)	0.77
Prior PCI	2 (1%)	1 (0.6%)	0.56
Stroke	1 (0.6%)	10 (6%)	0.01
Unstable angina	10 (6%)	7 (4%)	0.45
Ventricular tachycardia	19 (11%)	20 (12%)	0.86
Valvular disease	10 (6%)	20 (12%)	1.00
Medications			
ACE inhibitor	24 (14%)	22 (13%)	0.87
Antiarrhythmic	20 (12%)	13 (8%)	0.27
Anticoagulant	45 (26%)	30 (17%)	0.06
Antidepressant	21 (12%)	26 (15%)	0.53
Antiplatelet	29 (17%)	34 (20%)	0.57
ARB	25 (14.5%)	26 (15%)	1.00
β-Blocker	60 (35%)	62 (36%)	0.91
CCB	14 (8%)	13 (8%)	1.00
Nitrate	10 (6%)	9 (5%)	1.00
Statin	56 (33%)	57 (31%)	1.00

Abbreviations. ACE, angiotensin-converting enzyme inhibitor. ARB, angiotensin II receptor blocker. CCB, calcium-channel blockers. NYHA, New York Heart Association. PCI, percutaneous coronary intervention.

Primary outcome, MACE

The mean interval between device implantation and the first follow-up appointment was approximately 3 months (median: 93.5, 95% CI: 65-186 days) in the CR group. **Figure 3.3** illustrates Kaplan-Meier survival curves comparing the CR to non-CR group during the 5-year follow-up period. The log-rank test revealed no significant difference in MACE-free survival between groups (P = 0.60). The median follow-up duration for the non-CR group was 1,974 days (95% CI: 1875–2073 days) compared to 2,399 days (95% CI: 2329–2440 days) in the CR-group (P = 0.04).

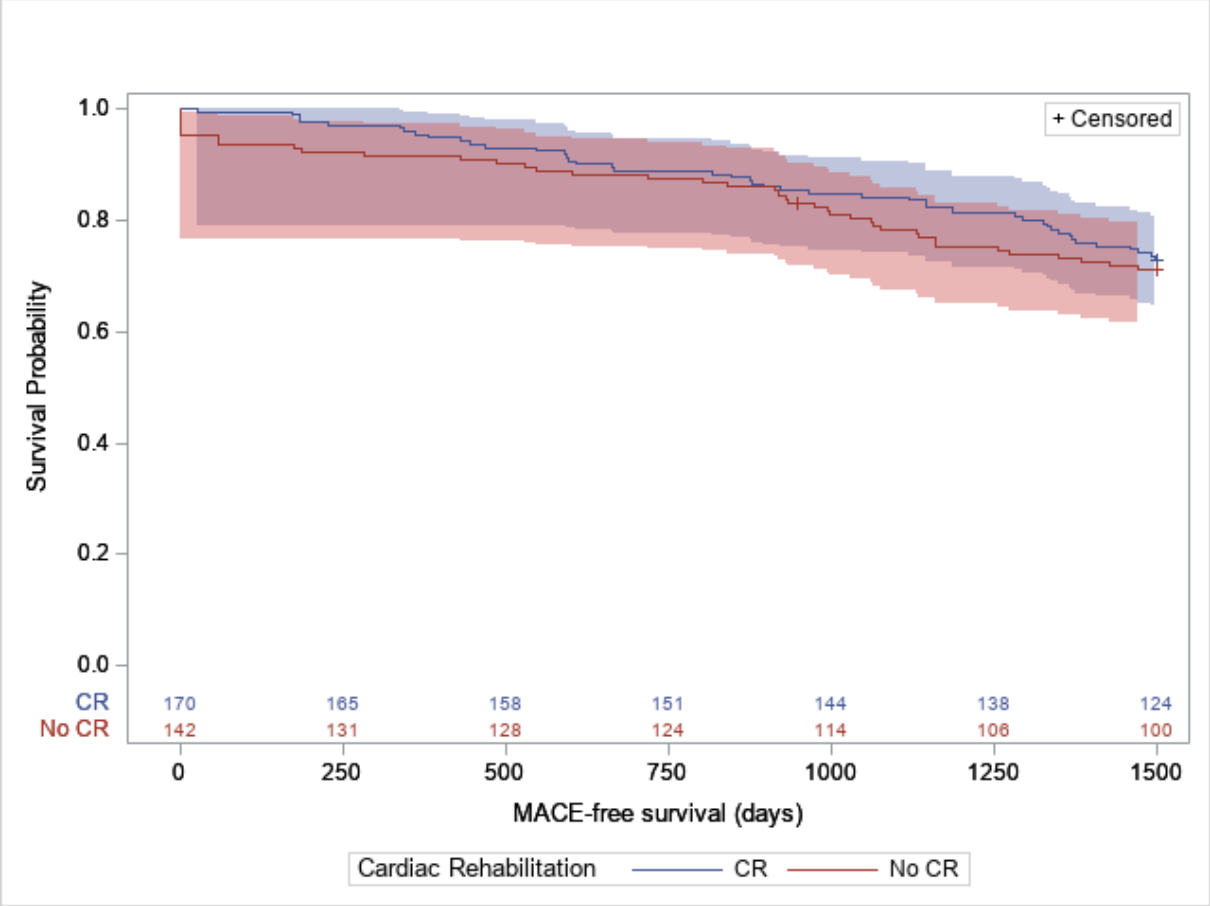

Figure 3.3. Kaplan-Meier curve of cumulative incidence of MACE in the non-CR and CR groups, with 95% confidence limits and number of participants at risk. MACE, major adverse cardiovascular events.

Table 3.3 shows the mean time in days to each MACE type in the matched cohort. Overall, most events occurred earlier in the non-CR group than the CR group. Heart failure was the most frequent event, followed by myocardial infarction and PCI. Few stroke events were observed (n = 1 in non-CR; n = 4 in CR), and estimates are unstable due to small number of events. No CABG or deaths were recorded in either groups.

Table 3.3. Average time in days to each MACE between patients in the non-CR and CR groups.

	Non-CR group (n = 172)			**CR group (n = 172)**		
MACE	**N**	**Days**	**95% CI**	**N**	**Days**	**95% CI**
Heart failure	29	547	484-873	34	1,007	851-1,191
Myocardial infarction	12	1,062	347-1,334	24	1,233	926-1,328
Stroke	1	59	-	1	408	-
PCI	15	981	484-873	8	2,460	-
CABG	0	-	-	0	-	-

Abbreviations. CABG, coronary artery bypass graft. CI, confident interval. CR, cardiovascular rehabilitation. PCI, percutaneous coronary intervention.

Multivariable models were adjusted for covariates associated with risk of MACE and CR, including age, sex, CIED type, and cardiovascular history. CR was modeled as a time-dependent variable. No significant differences were observed in crude or adjustment models for MACE at one, two, three, four, or five years **(Table 3.4).**

Table 3.4. Crude and adjusted hazard ratios with 95% confidence intervals comparing CR and non-CR groups for MACE at 1-, 2-, 3-, 4- and 5-year follow-up.

	Unadjusted			**Adjusted**		
	HR	**95% CI**	***P-v*alue**	**HR**	**95% CI**	***P-v*alue**
1-year MACE	0.88	0.37-2.09	0.77	1.06	0.44-2.57	0.89
2-year MACE	1.09	0.62-1.90	0.75	1.32	0.74-2.33	0.34
3-year MACE	0.95	0.59-1.52	0.84	1.13	0.70-1.83	0.59
4-year MACE	1.02	0.69-1.50	0.92	1.17	0.79-1.74	0.42
5-year MACE	0.99	0.70-1.40	0.99	1.12	0.79-1.59	0.50

Abbreviations. CI, confidence interval. HR, hazard ratio. MACE, major adverse cardiovascular events.

Figure 3.4 shows no significant differences observed in subgroup analyses by type of CIED. Subgroup analyses for CRTs were not performed because of the small sample in the cohort (7%). The sex-specific analysis revealed that CR was significantly associated with a lower 5-year hazard of MACE among women (adjusted HR: 0.58, 95% CI: 0.389-0.892, P = 0.01).

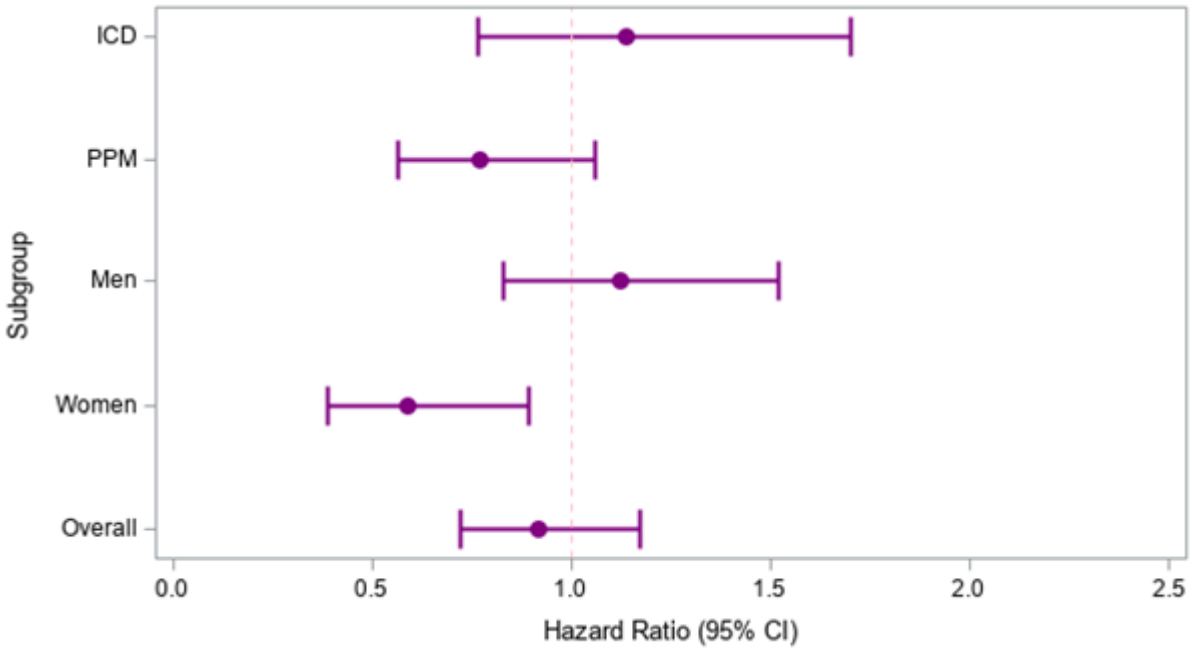

Figure 3.4 Forest plot of subgroup analyses comparing the hazard of MACE between patients with a record of CR to those without any record of CR.

3.5 Discussion

CR has been associated with reductions in MACE in broader cardiovascular populations.[47] Its association with long-term MACE risk in patients CIEDs, however, is not well established. This is the first study to investigate the impact of CR on the 5-year risk of MACE in patients with CIEDs. Contrary to our hypothesis, participation in CR was not associated with a reduced 5-year hazard of MACE in patients with CIEDs. However, our findings are inconclusive given the small sample size that limited statistical power - approximately 163 events (912 participants) would be required to detect a hazard ratio of 1.6. Interestingly, subgroup analyses indicated a potential sex-specific benefit, with women who attended CR having a significantly lower 5-year MACE hazard, whereas no such effect was observed in men. Our findings align with emerging literature reinforcing the importance of considering sex in CR programs.

A prior observational study provided the main evidence on CR in individuals with CIEDs. In a large retrospective cohort study (n = 12,016; 30% females), Buckley et al. (2021) demonstrated a reduction in all-cause mortality (7.1% vs. 10.8%, HR: 0.63, 95% CI: 0.56–0.71, $P < 0.001$) and re-hospitalization (40.6% vs. 44.9%, HR: 0.83, 95% CI: 0.78–0.87, $p < 0.001$) in favour of patients with CIEDs who completed CR, with outcomes assessed over a one-year follow-up period, compared to non-completers.[23] These findings suggest an early protective effect of CR (i.e., within 1 year) among those with CIEDs. However, when CR was defined as time-dependent variable in our Cox models, no significant association was observed at the 1-year timepoint or across five consecutive yearly timepoints. Our sample size calculation was based on the Buckley et al. study's, assuming that longer follow-up would yield more events and thus require a smaller sample size.[45] Considering that the University of Ottawa Heart Institute is Canada's largest CR centre (i.e., approximately 4,500 patients referred and 2,500 patients enrolled annually) and maintains extensive administrative records, a sample size of 912 seemed feasible. Surprisingly, only a small number of patients with CIEDs were referred to

CR over four years, highlighting a considerable care gap. The final cohort of 344 participants and the limited events count (i.e., 124) represent a major limitation of this study, leading to inconclusive results and reinforcing the need for larger studies among those with devices.

Robust evidence supports the long-term benefits of CR on MACE in other cardiovascular populations, which often represent underlying diseases requiring device therapy.[29,43,48] In one cohort study of 3,453 patients with CIEDs, approximately 75% and 70% of patients had atrial fibrillation and heart failure, respectively, highlighting the interplay between CIED and those cardiovascular conditions.[47,48] In a retrospective cohort of 7,815 patients with atrial fibrillation, CR was associated with a 40% reduction in MACE risk over three years (HR = 0.604: 95% CI, 0.387-0.945) when compared to propensity score–matched controls.[49] [51]In another retrospective cohort study of 40,364 individuals with heart failure, CR was associated with 42% lower odds of all-cause mortality (odds ratio: 0.58, 95% CI: 0.54–0.62), 26% lower odds of hospitalization (0.74, 95% CI 0.71–0.77), and 53% lower odds of incident atrial fibrillation (0.47, 95% CI 0.4–0.55) compared to propensity-score matching controls.[29] Collectively, these data demonstrate the long-term benefits of CR in individuals with cardiovascular disease, many of whom may also require CIED implantation; therefore, similar benefits could potentially extend to those with devices. Nonetheless, only large-scale evaluation can determine whether CR confers meaningful reductions in MACE and/or mortality rates in individuals with CIEDs.

There has been an ongoing debate regarding whether CR continues to improve patient survival in the modern era for specific cardiovascular diseases such as heart failure.[50] Recent RCTs have reported a diminished mortality benefit of CR, supporting the hypothesis that CR may no longer confer mortality benefits in the context of contemporary usual care.[51] This shift is often attributed to substantial advances in post-event management, including effective surgical interventions (e.g., percutaneous revascularization) and optimized pharmacological therapy (e.g., dual antiplatelet

therapy).[52] Similar considerations apply to patients with CIEDs, as device therapy reduces mortality and hospitalization, while CR serves as a complementary intervention that may enhance these benefits.[50] With continuing advancements in CIED technology and device programming, it is plausible that the incremental effects of CR on MACE may be attenuated. Another possibility is the lack of innovation in CR delivery. Redfern et al. (2022) highlighted in a historical overview article that most CR programs remain structured to those of 50 years ago, rendering them increasingly incongruent with modern healthcare and the digital era.[53] Timely CR opportunities exist to modernize CR for patients with CIEDs such as: (1) immediate CR initiation through automatic referral leveraging same-day discharge post-implantation; (2) comprehensive risk-factor management beyond exercise, including psychosocial support considering the high early anxiety burden;[54] (3) integrating of device-derived data (e.g., rhythm monitoring, physical activity behaviour) to personalize exercise prescriptions; and (4) remote delivery models integrated to CIED systems to promote engagement and individualized care.[55] In this context, CIEDs represent an opportunity to modernize CR while evaluating its impact on long-term outcomes such as MACE in those with devices.[56]

The impact of CR on MACE appears to be influenced by the timing of CR initiation and program characteristics. CR is most beneficial when delivered within one to three weeks after cardiac diagnosis (e.g., coronary artery disease, valvular heart disease), whereas delayed enrollment is directly associated with poorer patient outcomes.[57] For instance, in patients with dilated cardiomyopathy and symptomatic heart failure (n = 30,296; 29% females), early CR start (i.e., within 3 days of admission) was associated with significantly lower 90-day mortality compared to delayed or no CR (odds ratio: 0.70, 95% CI: 0.53–0.93; p = 0.01).[58] In our cohort, CR began, on average, three months after CIED implantation. Currently, there is no clear consensus on the optimal timing for resuming exercise after CIED implantation.[59,60] A randomized pilot study (n = 27, 70% females) in individuals with PPM revealed that CR participation starting 4 weeks after PPM implantation significantly improved health-

related quality of life (vitality: 42.1 ± 15.9 to 57.2 ± 15.4 points; mental health: 50.3 ± 18.3 to 68.2 ± 22.4 points), without increasing the risk of procedure-related complications such as lead dislodgement or changes in PPM parameters. Automatic referrals after a device implantation could optimize CR access (e.g., inpatient) and benefit the CIED population.[47] Notably, we were unable to retrieve detailed data of the CR program offered to patients with CIEDs. Characterizing the exercise intervention (e.g., frequency, volume) is important, as it may influence MACE outcomes. A retrospective study in heart transplant recipients (n = 140, 29% females) completing at least 23 sessions was associated with a ~60% reduction in MACE risk (HR: 0.42, 95% CI: 0.19-0.94).[48] [53]Thus, the absence of CR dosage in our study represents a limitation, and future research should examine dose–response relationships between CR participation and MACE in individuals with CIEDs.

Differences in underlying cardiac conditions and implantation indications are likely to impact MACE outcomes following CR across CIED types. For example, after receiving a PPM, survival rates were significantly higher in patients with sick-sinus-syndrome compared to those with high degree AV-block and atrial fibrillation.[61] Exercise may further modify prognosis in this subgroup; in a large cohort of patients with PPM (n = 13,542; 55% females), individuals engaging in at least five days of moderate-intensity exercise or at least three days of vigorous-intensity exercise per week demonstrated a significantly lower risk of MACE compared to non-exercisers (adjusted HR: 0.74, 95% CI: 0.66-0.89) during a median 2.5-year follow-up.[62] Among patients with ICDs, appropriate ICD shocks for ventricular arrhythmia are associated with an approximately two-fold increase of death for primary prevention patients and a 46% increase for secondary prevention patients.[63] Exercise-based interventions may mitigate this risk, as demonstrated in a meta-analysis of adults with ICDs (5 trials; n = 1,603; 8-22% females), where exercise training was associated with a lower likelihood of ICD shocks compared to control (pooled odds ratio: 0.47; 95% CI: 0.24 - 0.91).[64] In individuals with CRT, nonischemic cardiomyopathy was associated with improved survival (time ratio: 1.92; $P < 0.001$)

compared with ischemic cardiomyopathy over a 10-year follow-up.[65] Yet, a systematic review and meta-analysis (7 studies; n = 661 participants; 8-53% females range) revealed no significant difference in all-cause mortality (fixed-effect relative risk 0.57, 95% CI 0.19 to 1.73; P = 0.32; I^2 = 0%) or serious adverse events (fixed-effect relative risk 0.85, 95% CI 0.57-1.28; P = 0.43; I^2 = 0%) following CR in individuals with CRTs.[22] Taken together, these findings suggest that baseline prognosis and response to exercise differ across CIED subtypes and may moderate the effects of CR.

The abovementioned study conducted by Buckley was unable to examine the association between CR and outcomes by CIED subtype due to small subgroup sizes and overlapping electronic medical record codes,[23] highlighting an important evidence gap. In our cohort, device type was included as a covariate in the propensity score-matching given these distinct clinical characteristics. CR participants comprised individuals with PPMs (45%), followed by ICDs (43%) and CRTs (7%). MACE outcomes in the matched sample were stratified using CIED subgroup; however, subgroup analyses were limited by small numbers, precluding statistical inference regarding potential differences between device types. Females are underrepresented in studies with CIEDs. A systematic review and meta-analysis of 16 studies among adults with CIEDs noted a low female inclusion (17%).[66] Female sex is a known predictor of non-participation in CR.[69] A systematic review and meta-analysis showed that females are less likely to be enrolled in CR compared to males (odds ratio, 0.64, 95% CI: 0.57-0.72; P < 0.0001).[67] This is clinically relevant because CR participation is associated with a 61% reduction in all-cause mortality among females with atrial fibrillation (n = 23,894; 29% females).[43 7172]Notably, we observed a greater protective effect of CR in women compared to men with CIEDs - a significant 41% reduction in 5-year MACE risk with CR participation. This finding is promising, as prior evidence suggests that females with CIEDs experience poorer improvements in cardiovascular outcomes following CR compared with males;[68] yet, existing studies have been limited and underpowered. To

our knowledge, this is the first study indicating that women with CIEDs may derive greater benefit from CR than men, though confirmation in larger cohorts is needed.

Limitations

Given the observational nature of the study, several limitations warrant mention. First, this study was a single-centre retrospective cohort, which restricted variable selection to data previously collected in clinical records. Second, selection bias may be present, as missing data are often more common among individuals who experience barriers to care. Third, data quality concerns may apply because administrative health data are typically not documented with the same precision or completeness as prospectively collected research data.[69] In addition, participants who attended CR program or experienced cardiac outcomes outside of the University of Ottawa Heart Institute were not captured, reducing generalizability to the broader Canadian population. Fourth, due to the small number of CR appointments and the propensity score matching process, only 172 patients with a history of CR were included. The reduction in sample size may have limited the statistical power of the Cox proportional hazard models and further subgroup analyses, such as by CIED type. Finally, detailed information on CR program characteristics (e.g., frequency, intensity, type) was unavailable, preventing evaluation of how program-specific factors may have influenced observed outcomes.

3.6 Conclusion

In this single-center retrospective cohort of 344 patients with CIEDs, CR was not associated with lower 5-year risk of MACE compared to propensity score-matched CIED patients who did not attend CR. Interestingly, subgroup analysis indicated that women with CIEDs may derive greater benefit from CR than men, with a lower risk of MACE observed across time. This retrospective cohort study adds to the small body of evidence investigating the long-term benefits of CR in patients with

CIEDs. however, given the observational design and inherent limitations, results should be considered hypothesis-generating rather than causal. Further research – including large-scale cohort studies and prospective studies such as randomized controlled trials – is needed to confirm these findings and ascertain the impact and mechanisms by which CR may influence outcomes in patients with CIEDs.

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CHAPTER 4

Study 3. A sex-based examination of exercise training in patients with cardiac implantable electronic devices: a systematic review and meta-analysis.

4.1 Abstract

Background: Growing evidence suggests that women with cardiac implantable electronic devices (CIEDs) report smaller improvements in physical and mental health following exercise-based cardiovascular rehabilitation (CR). Yet, no investigation to date has summarized the sex differences following CR among individuals with CIEDs. This systematic review aimed to examine changes in cardiorespiratory fitness (CRF), anxiety and depression levels, quality of life, and additional physical health outcomes between women and men with CIEDs completing an exercise-focused CR program.

Methods: Three bibliographic databases: (1) MEDLINE (OvidSP), (2) Embase (OvidSP), and (3) Cochrane Library (Wiley) were searched to identify prospective clinical trials implementing exercise training (≥4 weeks) in patients with CIEDs. The primary outcome was CRF. Secondary outcomes included anxiety and depression levels, quality of life, and additional physical health outcomes (e.g., blood pressure, physical activity levels). Authors were contacted (up to 3 attempts) to obtain sex-specific data. Covidence was used for data management, and meta-analysis (using mean differences and random-effects models) were conducted in RevMan.

Results: We identified 22 eligible studies investigating exercise training or CR in patients with CIEDs. Sex-disaggregated data were available from two eligible studies, allowing analysis of sex differences in CRF only. The initial planned analysis of secondary outcomes (i.e., mental health, quality of life, additional health outcomes) was not feasible due to limited data. Instead, we examined sex-specific inclusion in CIED exercise trials, including proportion of participants enrolled, sex-reporting across phases of trials (e.g., enrollment, intervention allocation, follow-up, and data analysis), and gender-related factors. A total of 2,205 participants were included in the sex-based examination. Fewer women than men were included in these exercise studies (18% vs. 82%, $P < 0.001$), with no significant temporal changes over time (2003-2022). Across trials, sex-specific reporting was poor, and gender-related factors were rarely addressed. Meta-analysis revealed no significant difference in changes in

CRF between sexes (mean difference in $\dot{V}O_2$peak = 0.21: 95% CI, −1.70 to 2.12 mL/kg/min; P = 0.83). Separate meta-analyses compared exercise versus control within each sex showed no significant changes in women, while men showed significant improvements.

Conclusion: Women represented 18% of participants in exercise and CIED trials. Our findings highlight the need for improved sex-specific inclusion and reporting practices to guide future CIED exercise research. No sex differences were observed in CRF following CR among patients with CIEDs; however, these results should be interpreted with caution given the limited sample size and small number of available trials.

4.2 Introduction

Cardiac implantable electronic devices (CIEDs), including permanent pacemakers (PPMs), implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRTs), are well-established treatments to restore or maintain cardiac rate and rhythm.[1] Over a 30-year period, the annual implantation rates of CIEDs in women was 57.3 per 100,000 and 116.3 per 100,000 in men.[2] Growing research has shown sex-differences in indications, prognosis, and access to care across all types of CIEDs.[3] Among PPMs recipients, women are more likely to present with sinus node disease or atrial fibrillation as the primary cause of bradyarrhythmia, whereas high-degree atrioventricular block is more frequently observed in men.[4,5] For ICDs, women may experience a lower rate of appropriate ICD therapies, higher complication rates, and potentially reduced mortality benefit.[6,7] Women are more likely to derive clinical benefit from CRT possibly due to shorter QRS durations, yet current guidelines do not account for sex-specific differences, revealing a gap in sex-based research to device-based therapies.[6,8]

Sex disparities in CIEDs extend to cardiovascular disease management, particularly for health-related outcomes in women and men with CIEDs.[9,10] Sub-analyses of the HF-ACTION study revealed that women (n = 661, 14% paced) compared to men (n = 1,670, 20% paced) had lower cardiorespiratory fitness (CRF) measured in peak oxygen uptake ($\dot{V}O_2$peak, median: 13.4 vs. 14.9 ml/kg/min, respectively, $P < 0.001$).[11] Higher CRF levels are strongly associated with lower cardiovascular mortality risk among those with cardiovascular diseases (hazard ratio [HR] = 0.27, 95% confident interval [CI]: 0.16-0.48).[12] Women with CIEDs have also demonstrated lower moderate-to-vigorous physical activity levels as (60 vs. 120 min/wk),[13,14] poorer health-related quality of life (22.1 vs. 23.8 scores, $P = 0.014$),[15] and greater levels of anxiety (5.5 vs 3.7 points, $P < 0.001$) and depression (3.8 vs. 2.8 points, $P <0.001$) compared to their male counterparts.[16] These findings emphasize the need

for targeted interventions to optimize physical and mental health in those with CIEDs, with sex as a key consideration.

Exercise training is a key component in the treatment and management of patients with CIEDs.[17] Exercise training alone or combined with other strategies (e.g., nutrition counseling, risk factor management, psychosocial support), referred to as exercise-based cardiovascular rehabilitation (CR), has been shown to improve CRF, psychosocial health, and quality of life in individuals with cardiac devices.[18] A previous systematic review and meta-analysis (n = 6 studies, 1,603 participants, <20% women) in patients with ICDs demonstrated that participating in exercise training significantly improved CRF compared with those who received usual care (weighted mean difference: 1.98 ml/kg/min, 95% CI: 0.58-3.38, I^2 = 68.8%) and CRTs (n = 5 studies, weighted mean difference: 2.03 ml/kg/min, 95% CI: 0.47-3.60, I^2 = 74.6%).[19] Further, a randomized trial found that women with CIEDs (ICDs: n = 20) compared to men (ICDs, n = 79) achieved smaller gains in $\dot{V}O_2$peak (21.7 ± 6.4 vs. 23.4 ± 9.5 ml/kg/min) following a 6-month CR program.[15] They also reported lower total exercise time (8.2 ± 1.6 min vs. 8.8 ± 1.8 min), and improvements in mental health scores (52.2 ± 8.6 vs. 54.8 ± 7.1 points).[15] Yet, no other study has examined sex-differences in CRF and other health-related outcomes following exercise training in individuals with CIEDs, highlighting the need for further research.

There is a rising recognition of the under-representation of women with cardiovascular disease in exercise-based trials. Women are significantly less likely than men to be referred to (i.e., 39.6% vs. 49.4%),[11] enroll in (i.e., 38.5% vs. 45.0%),[12] and adhere to (i.e., 64.2% vs. 68.6% of prescribed sessions and 18.9 vs. 7.9% drop-out rates)[13,14] exercise-based CR programs.[20,21] Recently, our group found that women with cardiovascular diseases represented 34% of patients included in Canadian exercise-based trials, and their participation has not increased over the previous 10 years.[22] We also found that gender-related factors (e.g., socially constructed roles) such as educational and income

levels were poorly reported across studies (13%),[22] which is important given their influence on lifestyle behaviour.[23] Existing literature emphasize that sex- and gender-specific reporting in cardiovascular exercise trials is limited, a gap that also extends to the CIED population.[25]

We aimed to conduct a systematic review and meta-analysis investigating the impact of exercise training on CRF in women and men with CIEDs. We hypothesized that women would experience smaller improvements in CRF than men.[15] Secondary outcomes aimed to examine changes in mental health (e.g., anxiety and depressive symptoms), quality of life, and additional physical health outcomes (e.g., functional capacity, physical activity levels) between sexes following exercise training alone or CR.

4.3 Methods

Design

This systematic review protocol was designed in accordance with the Cochrane Handbook for Systematic Reviews, and follows the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)-P checklist for reporting.[24] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42024498519). The systematic review adheres to the most updated reporting guidelines of the PRISMA statement,[24] the Sex and Gender Equity in Research (SAGER) guidelines,[25] and followed the criteria outlined in the checklist A Measurement Tool to Assess Systematic Reviews (AMSTAR).[26]

Study eligibility criteria

Prospective experimental designs (randomized controlled trials, quasi-experimental, pre-post, and case-control studies) were eligible. Studies were included if the sample was comprised of adults (≥18 years old) with a CIED. There were no restrictions on the underlying cardiovascular condition (e.g., atrial fibrillation, heart failure) or health co-morbidities (e.g., hypertension, diabetes).

Intervention

Eligible studies comprising exercise training of any form with a duration of at least 4 weeks were included. Exercise training could include aerobic training (e.g., moderate intensity continuous training, high-intensity interval training), resistance training (e.g., machine-based resistance training, isometric exercises), and Yoga. Multi-component interventions, which are typical of CR programs, were eligible if they included a structured exercise program. There were no restrictions on the mode of delivery (e.g., in-person, virtual) or setting (e.g., hospital- community-based, individual, group) of the intervention or the control groups (e.g., usual care, stress management, nutritional counseling).

Search strategy and publication status

A systematic search was performed using three electronic databases: (1) MEDLINE (OvidSP), (2) Embase (OvidSP), and (3) Cochrane Library (Wiley), which were searched from inception to January 14, 2025. The search strategy used for each database is provided in the Supplemental Material (Table S1). Published peer-reviewed journal articles were included. No language restrictions were imposed on the search.

Outcomes

Eligible studies reported a baseline and follow-up measure for at least one primary or secondary outcome. The primary outcome of interest was the change in CRF following exercise training, as estimated or directly measured peak oxygen uptake ($\dot{V}O_2$peak) in L/min, mL/kg/min, or metabolic equivalent of task (METs).[27] If studies included both sexes but failed to report outcomes by sex, authors were contacted via email to obtain sex-specific data, after 3 unanswered email attempts they were considered as 'no response'. We initially planned to examine additional physical and mental health outcomes (i.e., functional capacity, resting heart rate and blood pressure, body mass index, anxiety and depressive symptoms, and physical activity levels), and quality of life.[28] However, sex-disaggregated

data were insufficient for further analyses in outcomes given the lack of data. Instead, we performed an examination of the number and proportion of women and men with CIEDs enrolled in randomized clinical trials investigating exercise training program in individuals with CIEDs. Randomised trials are considered the highest quality evidence in evaluating healthcare interventions. Critical appraisal of the quality of randomized trials is possible only if their design, conduct, analysis, and results are thoroughly and accurately reported.[29] We assessed sex-specific reporting across phases of trials (e.g., eligibility, allocation, analysis), and considerations of sex and gender-related factors throughout the trials. Eligible studies included randomized controlled trials across a range of intervention development stages as per the Obesity-Related Behavioral Intervention Trials (ORBIT) model, corresponding to preliminary (Phase II), efficacy (Phase III), and effectiveness (Phase IV) trials, as conceptualized within established trial phase frameworks (e.g., ORBIT and related models).[30] As such, all randomized trials meeting inclusion criteria were considered regardless of trial phase, provided they adhered to an randomized trial design.

Another important clarification is the sex and gender terminology used in this study. Sex refers primarily to biological factors (e.g., observed physiological and anatomical sex traits), while gender closely aligns with social norms and roles (e.g., social norms and roles based on what a society deems appropriate for individuals based on their sex assigned at birth). Gender is a multidimensional construct comprising four key dimensions: gender identity, relations, roles, and institutionalized gender. A gender-related variable may fall under any of these domains. A gender-related variable is a non-biological variable which differs in terms of magnitude, prevalence, and/or impact between people of different genders. Given that exercise training is a behavioural intervention, and that we assessed both physiological outcomes (e.g., changes in cardiorespiratory fitness) and gender-related factors reported in the included studies, the terms ‘women’ and ‘men’ are used throughout this article.[23,25]

Data management and extraction

Citations were imported into Covidence Systematic Review software (Veritas Health Innovation, Melbourne, Australia) where duplicate studies were removed. Two of three (IRM, AMV, LL) reviewers independently screened each titles and abstracts, followed by full-text review of potentially eligible studies. Authors were not blinded to the study authors or journal titles when screening. Any disagreements were resolved by discussion with a fourth reviewer (JLR).

Data from eligible studies were extracted using Microsoft Excel (Microsoft, Redmond, WA, USA). Extracted data included information about study (i.e., authors, title, year of publication, journal, and study design) and population (total sample size, number of women and men, demographic characteristics, gender-related factors). The FITT principle: frequency of exercise time (i.e., sessions per week), intensity (i.e., percentage of V̇O2peak, percentage of peak heart rate [HR], and rating of perceived exertion), duration of sessions (minutes/session), and type of activity (e.g., cycling, walking, running) was used to collect data information on exercise interventions. The primary outcome was retrieved using the mean difference in CRF between women and men with CIEDs following exercise training, and measure of variance around this outcome (e.g., V̇O2peak – mean, standard deviation [SD], 95% CI). The mean difference was determined by calculating the difference in the mean outcome per sex and dividing by the SD of the outcome among participants.[31] The means and SD of the primary outcome measured at baseline and following exercise were extracted by a reviewer and verified by a second (IRM, AVM).

Risk of bias and GRADE assessment

Only studies containing sex-disaggregated CRF data were assessed for risk of bias. For the sex-based examination, studies were not formally assessed for quality given they were reported descriptively. Two reviewers (IRM, AVM) independently assessed the risk of bias and GRADE

assessment, and any disagreements in scores were resolved by discussion with a third reviewer (JLR). The methodological quality of each study was assessed by using the "Tool for the assEssment of Study qualiTy and reporting in EXercise" (TESTEX) given the focus on exercise trials.[32] The TESTEX scale uses 12 criteria for a maximum score of 15 points, 5 pertain to study quality: (1) eligibility criteria specified, (2) randomization specified, (3) allocation concealment, (4) groups similar at baseline and (5) blinding of assessor for the primary outcome; and 7 pertain to study reporting: (1) outcome measures assessed in 85% of patients, (2) intention-to-treat analysis, (3) between-group statistical comparisons reported, (4) point measures and measures of variability for all reported outcome measures, (5) activity monitoring in control groups, (6) relative exercise intensity remained constant and (7) exercise volume and energy expenditure. As per best practices, the overall quality of the evidence was also assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[33] GRADE classifies the evidence as high, moderate, low, or very low depending on: (a) risk of bias within individual studies, (b) inconsistency of results between studies, (c) indirectness of evidence, (d) imprecision, and (e) publication bias.[33] Randomized clinical trials started with a high quality of evidence and were rated downward in the presence of study limitations such as risk of bias, indirectness of evidence, heterogeneity, imprecision, or publication bias. Inconsistency was assessed by considering the heterogeneity of the studies using the I^2 statistic (25%, 50% and 75% was classified as low, moderate, and high heterogeneity, respectively).[34] Visual inspection was used to determine the presence of bias along with Egger's test ($P < 0.10$).[35]

Data synthesis

Sex-specific inclusion and reporting are presented descriptively. Sex reporting was based on the CONSORT (Consolidated Standards of Reporting Trials) statement, designed to improve the quality of reporting and provides a set of items to be included in a report of a randomized trial (i.e., enrollment, intervention allocation, follow-up, and data analysis).[29] Trials phase II (i.e., preliminary testing) III

(i.e., efficacy), or IV (e.g., effectiveness) were included. When multiple sub-studies reported on the same sample, only the main trial was included to avoid duplication in the reported number of women and men with CIEDs. The proportion of women and men with CIEDs included in trials were analyzed using chi-square (χ^2). Temporal changes in the proportion of male and female participants were evaluated using a simple linear regression, with year as the independent variable and sex-specific proportions as the dependent variables. Statistical significance was set at $P < 0.05$. Meta-analyses were completed using Review Manager 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) to compare mean differences and standardized mean differences (SMDs) in CRF between women and men. Where possible, pooled estimates were also calculated in each sex separately for the changes in CRF following exercise training when compared to a non-exercise control group. Random-effect models (women vs. men) were used to determine effect sizes with significance set at $P < 0.05$ (two-tailed). Pooled effects are reported as mean weighted difference and its 95% CIs.

4.4 Results

Study selection

The search **(Table S4.1** Supplemental Material**)** identified 4,413 relevant studies. After duplicate record removal, 3,679 articles were screened by title and abstract, from which 122 studies were then assessed for eligibility at the full-text level. In total, 22 were deemed eligible for data extraction **(Figure 4.1).** A total of 21 authors were contacted via e-mail with a request to provide sex-disaggregated data **(see Figure 4.1)**. Sex-specific data were obtained from two eligible studies; one article reported outcomes segregated by sex,[15] and one provided raw data by sex.[36]

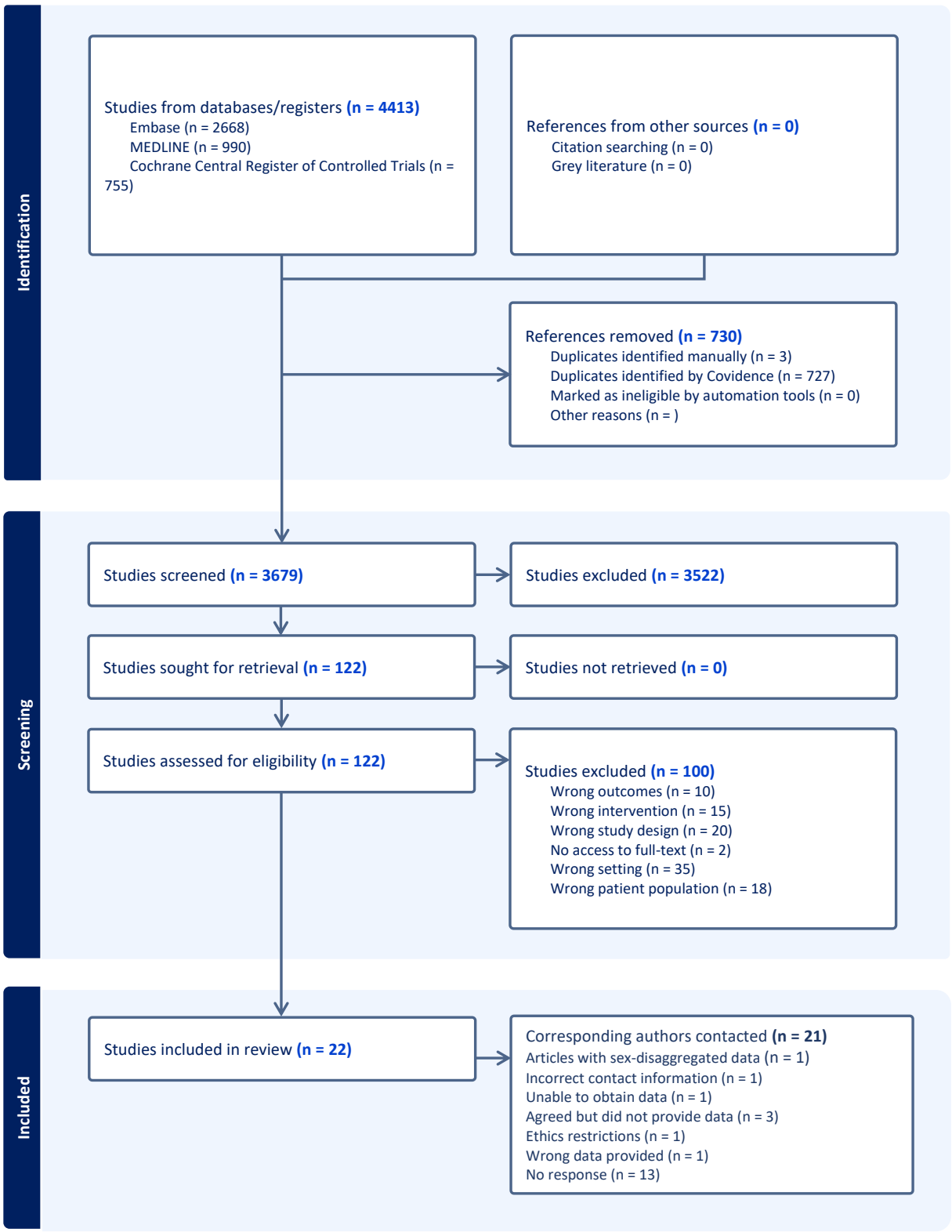

Figure 4.1.PRISMA flow diagram.

Study, participant and intervention characteristics

Table 4.1 shows an overview of participant characteristics and studies. Studies were published between 2003 to 2022 and were single-centre trials. Most of studies were conducted in Europe, followed by the United States, Asia, and South America. Sample sizes ranged from 10 to 1053 participants, and most of studies were performed in patients with ICDs. Exercise interventions were performed 1-7 days per week, from 4 weeks to 6 months of duration. Exercise prescription included a variety of aerobic training (e.g., moderate-to-vigorous intensity training, high-intensity interval training) or combined aerobic and resistance programs - often observed in CR settings. Studies conducted in outpatient CR settings, with additional interventions delivered in home-based or inpatient environments. Overall, findings highlight improvements in CRF, functional capacity, and quality of life, with no increase in exercise-related adverse events. All included studies were published in English.

Table 4.1. Prospective trial characteristics of the studies included in the systematic review.

Author, year, country	Participants, type of device	Exercise intervention	Main findings
Ahn et al 2021, Republic of Korea[37]	Total n = 27 Men n = 8 (30%) Women n = 19 (70%) PPM (100%)	**F:** 1-3x/wk for 4wks (8 sessions) **I:** 55%-70% HR reserve / 3 sets of 12–15 repetitions **T:** 60min **T:** Combined aerobic, resistance, flexibility **S:** Hospital (outpatient CR)	Improved 6-minute walk test distance, quality of life, $\dot{V}O_2$peak in both groups but no significant between groups.
Akdal et al 2021, Turkey[38]	Total n = 24 Men n = 20 (83%) Women n = 4 (17%) ICD (100%)	**F:** 5x/wk for 6wks (30 sessions) **I:** 70-80% $\dot{V}O_2$peak (leg endurance training group and combined arm-leg endurance training) + 60% of peak Watts (combined arm-leg endurance training group) **T:** 40 + 20 min **T:** Aerobic **S:** Hospital (outpatient CR)	Combined arm-leg endurance training improved cardiopulmonary fitness and test duration. No shocks or ventricular arrhythmias were recorded.
Belardinelli et al 2006, United States[39]	Total n = 52 Men n = 52 (100%) Women n = 0 (0%) CRT (100%)	**F:** 3x/wk for 8x/wks **I:** 60% of peak $\dot{V}O_2$peak **T:** 60min **T:** Aerobic **S:** Hospital (outpatient CR)	Improved $\dot{V}O_2$peak, quality of life, endothelial function. No adverse events in the exercise group.
Berg et al 2015,[15,40] / Christensen et al 2015 (sub-study), Denmark	Total n = 196 Men n = 155 (79%) Women n = 41 (21%) ICD (100% - primary indication 66%)	**F:** 2x/wk for 12wks **I:** 50-80% HR peak + 60-80% one-repetition maximum **T:** 60 min **T:** Aerobic and resistance **S:** Hospital (outpatient CR)	Improved $\dot{V}O_2$ peak, general and mental health. No difference in ICD shocks or anti-tachycardia pacing therapy.
Conraads et al 2007, Belgium[41]	Total n = 17 Men n = 8 (47%) Women n = 9 (53%) CRT (100%)	**F:** 3x/wk for 5 months **I:** 90% HR at ventilatory threshold **T:** 60min **T:** Aerobic **S:** Hospital (inpatient CR)	Improved $\dot{V}O_2$peak, maximal workload and circulatory power ($\dot{V}O_2$peak, systolic blood pressure at peak exercise).
Dougherty et al 2008, United States[42]	Total n = 10 Men n = 9 (90%) Women n = 1 (10%) ICD (100%)	**F:** 3x/wk for 8wks (24 sessions) + 2h home walking for 8/wks **I:** 60−80% HR peak **T:** 60min + 60min **T:** Aerobic	Improved cardiopulmonary fitness (exercise time, $\dot{V}O_2$peak, METs), heart rate variability, quality of life, and physical activity levels.

		S: Non-clinical; Home-based	
Dougherty et al 2015, United States[36]	Total n = 160 Men n = 124 (78%) Women n = 36 (22%) ICD (100%, secondary indication 67%)	**F:** 5x/wk for 8wks + 150 min/wk for 16wk **I:** 60-85% of HR reserve + 80% HR reserve **T:** 60min + 150min **T:** Aerobic, resistance + home walking **S:** Non-clinical; Home-based	Improved $\dot{V}O_2$peak, without shocks/hospitalizations recorded.
Fitchet et al 2003, United Kingdom[43]	Total n = 16 Men n = 14 (88%) Women n = 2 (12%) ICD (100%)	**F:** 2x/wk for 12wks **I:** 60–75% HR peak **T:** 60 min **T:** Aerobic, resistance **S:** Hospital (outpatient CR)	Improved exercise time and decreased scores for anxiety and depression. No ventricular arrhythmias or ICD discharges occurred during the exercise component.
Kamal et al 2021, Egypt[44]	Total n = 20 Men n = 18 (90%) Women n = 2 (10%) CRT (100%)	**F:** 3x/wk for 4 months **I:** 40-70% HR reserve **T:** NR **T:** Aerobic, flexibility, breathing exercises **S:** Hospital (outpatient CR)	Improved quality of life, NYHA functional class, $\dot{V}O_2$peak, and left ventricular ejection fraction.
Katayıfc et al 2022, Turkey[45]	Total n = 36 Men n = 25 (69%) Women n = 7 (19%) CIEDs (ICD 84%, CRT 16%)	**F:** 7x/wk for 8wks **I:** 50% maximal inspiratory pressure + endurance training at 30% maximal inspiratory pressure **T:** 30 min/day **T:** Inspiratory muscle strength training **S:** Hospital	Improved functional exercise capacity, respiratory and peripheral muscle strength, respiratory muscle endurance, quality of life, physical activity level. No arrhythmia, shock, or syncope during sessions.
Kato et al 2017, Japan[46]	Total n = 50 Men n = 39 (78%) Women n = 11 (22%) CIEDs (CRT-D (74%, ICD 26%).	**F:** 3-5 x/wk for 6 months **I:** NR **T:** 60 min **T:** Combined aerobic and resistance **S**: Hospital and home-based	Improved vascular endothelial dysfunction through attenuation of oxidative stress.
Koike et al 2022, Japan[47]	Total n = 18 Men n = 13 (72%) Women n = 5 (28%) CRT (100%, CRT-D 89%)	**F:** 3–5x/wk, for 12 wks **I:** 12–14 Borg scale **T:** 30 min **T:** Aerobic, flexibility **S:** Hospital (outpatient CR)	No heart failure hospitalizations, ventricular tachyarrhythmias, or death. Improved quality of life and physical activity levels.
Nobre et al 2016, Brazil[48]	Total n = 30 Men n = 16 (53%)	**F:** 3x/wk, for 4 months **I:** NR **T:** 60 min **T:** Aerobic, flexibility	Improved exercise tolerance (exercise duration and $\dot{V}O_2$peak) and neurovascular control and alters Ca^{2+}

	Women n = 14 (47%) CRT (100%)	**S:** Hospital (outpatient CR)	handling gene expression in the skeletal muscle.
Patwala et al 2009, United Kingdom[49]	Total n = 50 Men n = 46 (92%) Women n = 4 (8%) CRT (100%)	**F:** 3x/wk for 6 months **I:** 80-90% HR peak **T:** 30min **T:** Aerobic **S:** University	Improvements in all functional, exercise hemodynamic, and echocardiographic measures.
Piccini et al 2013, United States[50]	Total n = 1053 Men n = 831 (79%) Women n = 222 (21%) ICD (100%)	**Phase 1:** **F:** 3x/wk for 12x/wks (36 sessions) **I:** 60-70% HR peak **T:** 15-35min **T:** Aerobic, resistance training **Phase 2:** Continuous aerobic maintenance component (5x/wk) up to 4 years **S:** Hospital (outpatient CR) and home-based	Exercise therapy is not associated with an increase in all-cause ICD shocks. Ventricular arrhythmias induced during exercise testing are associated with ICD shocks.
Piotrowicz et al 2015, Poland[51]	Total n = 107 Men n = 95 (89%) Women n = 12 (11%) CIEDs (67% ICD)	**F:** 5x/wk for 8wks **I:** 40-70% HR reserve **T:** 60min **T:** Aerobic (Nordic Walking) **S:** Home-based	Improved $\dot{V}O_2$peak, 6-minute walking test distance, quality of life. No deaths or hospitalizations recorded.
Rakhshan et al 2022, Iran[52]	Total n = 100 Men n = 59 (59%) Women n = 41 (41%)	**F:** 16 sessions for 8wks **I:** NR **T:** 120 min **T:** CR **S:** Hospital and home-based	Improved adjustment and body image.
Santa-Clara et al 2019, Portugal[53]	Total n = 37 Men n = 28 (76%) Women n = 9 (24%) CRT (100%)	**F:** 2x/wk for 24wks **I:** 4x4 high-intensity interval training periods (high intensity: 90–95% of HR peak) with 3 lower-intensity active periods (moderate intensity: 60–70% of HR peak) **T:** 60 min **T:** Aerobic **S:** Hospital (outpatient CR)	Improved exercise performance (test duration). No further improvements in functional capacity and health-related quality of life, and left ventricular structure and function, compared to CRT alone.
Smolis-bak et al 2015[54]	Total n = 52 Men n = 47 (90%) Women n = 5 (10%)	**F:** 5x/week for 8wk **I:** Low intensity **T:** 60 min **T:** Aerobic, resistance	Improved directly physical fitness ($\dot{V}O_2$peak and test duration) and quality of life. No adverse events.

	CRT (100%)	Followed by a 3-month home-based exercise program. **S:** Home-based	
Smolis-bak et al 2017[55]	Total n = 84 Men n = 76 (90%) Women n = 8 (10%) ICD (100%)	**F:** 3×/week for 6 months **I:** 55-64 revolutions per minute + 50% muscle strength **T:** 30-60 min **T:** Aerobic, resistance training **S:** Hospital (outpatient CR)	Improved exercise tolerance and capacity ($\dot{V}O_2$peak, power output, METs, 6-minute walking test distance) and left ventricular ejection fraction. No exercise-related ICD shocks.
Spee et al 2020, Netherlands[56]	Total n = 24 Men n = 19 (79%) Women n = 5 (21%) CRT (100%)	**F:** 3x/week for 12wks (36 sessions) **I:** 4x4 high-intensity interval training (high intensity: 85–95% of $\dot{V}O_2$peak) with lower-intensity active periods. **T:** 35min **T:** Aerobic **S:** Hospital (outpatient CR)	Improved exercise capacity ($\dot{V}O_2$peak recovery kinetics and peak workload).
Toise et al 2014, United States[57]	Total n = 46 Men n = 36 (78%) Women n = 10 (22%) ICD (100%)	**F:** 1x/wk for 8 wks **I:** NR **T:** 80 min **T:** Yoga **S:** Home-based	Decreased shock anxiety, greater overall self-compassion and mindfulness, lower risk of experiencing device-related firings.

Abbreviations. CR: cardiovascular rehabilitation: CIED = cardiac implantable electronic device. CRT: cardiac resynchronization therapy (CRT-D, with defibrillation). HR: heart rate. ICD = implantable cardioverter-defibrillator. MET: metabolic equivalent of task. NYHA: New York Heart Association functional class. PPM: permanent pacemaker. RPE: rating of perceived exertion. VO_2: oxygen uptake. FITT principles. F: frequency. I = intensity. T: time. T: type. S: study setting.

Sex-specific inclusion and reporting

A total of 2,205 participants were included in the sex-inclusion analysis, retrieved from 22 prospective experimental trials **(Table 4.1)**. Most patients had ICDs (59%), followed by CRTs (36%) and PPMs (5%). Fewer women than men were included in these exercise studies (n = 467 [18%] vs. n = 1738 [82%], $\chi^2 = 75.780$, $P < 0.001$). There were no significant changes over time in the inclusion of women ($\beta = 0.87$, $P = 0.19$) or men ($\beta = -0.87$, $P = 0.19$) **(Figure 4.2)**.

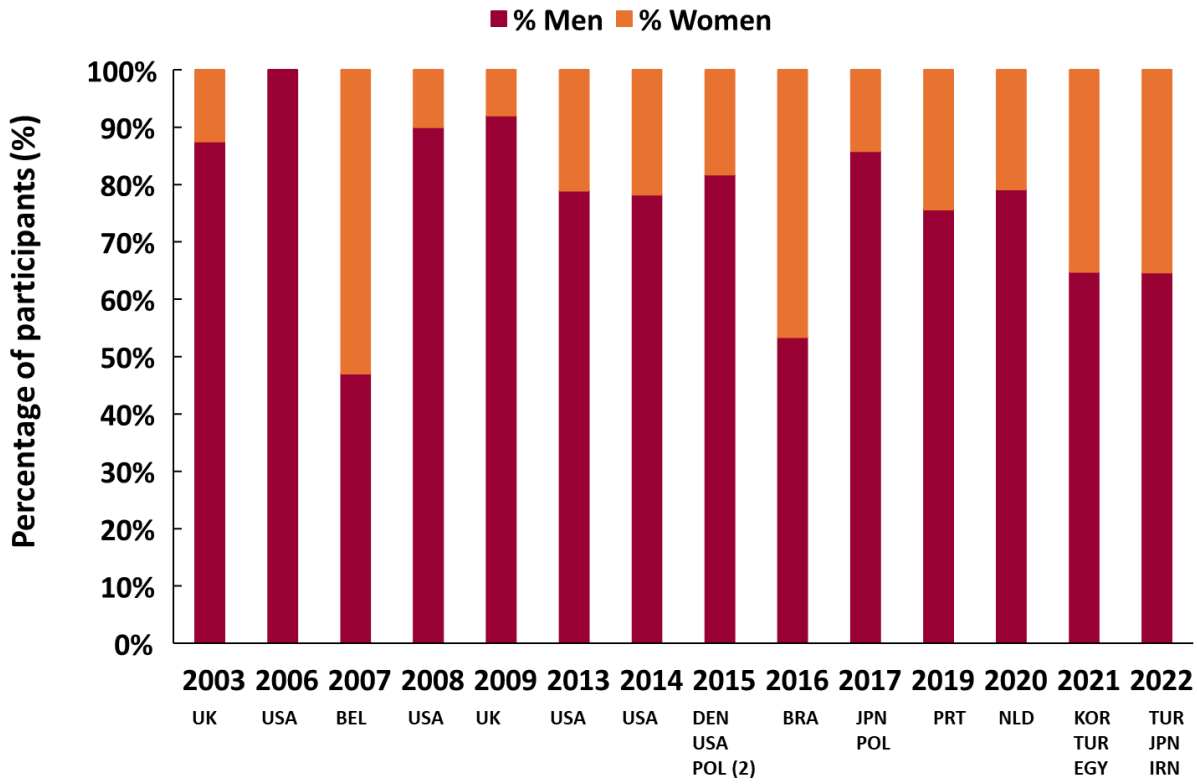

Figure 4.2. Sex-specific inclusion of patients with cardiac implantable electronic devices in exercise trials. Red bars represent men; Orange bars represent women.

Sex-disaggregated reporting across trial phases was limited (**Figure 4.3**). No study reported sex-based recruitment strategies, provided any sex-based inclusion and exclusion criteria, or reported

sex-specific enrollment and randomization data. Sex-based allocation data were reported in 7 (32%) studies (21% women), and 8 (36%) reported follow-up by sex (17% women). Most studies reported sex-disaggregated data in the final analysis phase (95%) for the exercise group (21% women) and control group (22% women). One study (6%) considered implications of sex in the discussion section, and 3 studies (14%) reported sex as a limitation.

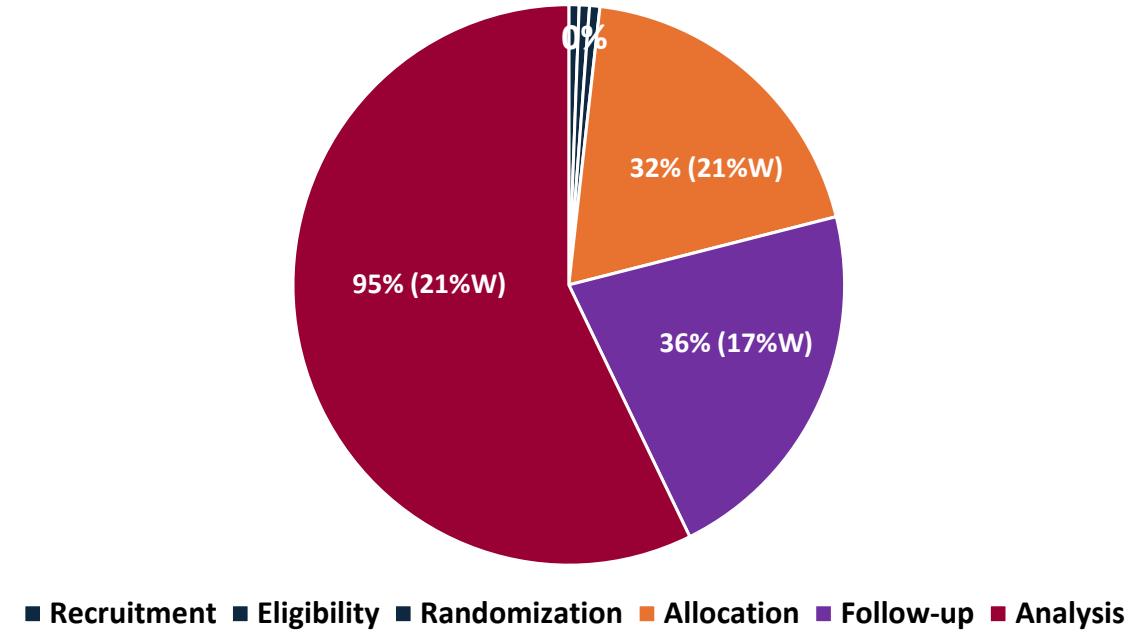

Figure 4.3. Sex-disaggregated reporting across different phases of trials. Percentage of studies reporting sex, and percentage of women included at each stage of the trial process.

Representative quotes are presented below in the Discussion and Limitations sections, respectively: (i) *"However, we only randomised about one-third of potential eligible patients and this may represent bias. The literature reports female gender, age, co-morbidity, socioeconomic burden, distance and disbelief in the beneficial effect as the most important barriers to participation in cardiac rehabilitation."* and *(ii) "Small number of women compared to men in the study and therefore there is an apparent risk of type 2 error." (iii) "Rather few women were included in the study, though the sex is*

known to determine the rehabilitation effectiveness. Therefore these results cannot be fully extrapolated to the female population." (iv) "All females (5) were randomized to the control group by chance."

Gender-related factors were reported in 8 (36%) of the studies. One study provided gender-specific data, and no differences were observed in marital and employment status in women and men with ICDs.[15] Four studies reported race/ethnicity where patients with CIEDs (n = 1429) were predominantly informed as white (range: 54-100%), followed by black participants (range: 5-40%) of the total sample in the included studies.[58–60] Two studies demonstrated that participants with CIEDs (n = 146) were mostly married (range: 55-78%), followed by single (range: 5%-8%), divorced (range: 21-36%) and widowed as marital status (range: 12-22%).[52,59] Three studies showed that these patients (n = 306) had no formal education (range: 35-55%), had a high school diploma or less (range: 20-31%), some college or a college diploma (range: 19-30%), or completed college or had education above a diploma (range: 9-24%).[52,58,59] Two studies revealed that participants (n = 206) reported household incomes below $50,000 per year (range: 44-47%), between $50,000 and $90,000 (range: 53- 56%), and higher incomes between $75,000 and $124,000 (range: 19-38%).[58,59] Four studies described patients with CIEDs (n=126) as active smokers, (range: 0-36%) and non-smokers (range: 17-42%).[38,44,59,61] Two studies reported employment status in patients (n = 206) as employed (range: 1-51%) or unemployed (range: 42-49%).[58,59]

Primary outcome: cardiorespiratory fitness

Sex-disaggregated data were available in two randomized trials evaluating exercise interventions in patients with CIEDs, mostly in patients with ICDs. **Table 2** shows the demographic characteristics of participants, disaggregated by sex, included in the following two studies. In Christensen et al., 196 patients were randomized to usual care (n = 97) or exercise (n = 99); 52 participants were lost to follow-up (n = 26 exercise group; n = 26 control group).[15] The program was

delivered twice weekly for 12 weeks in an exercise-based CR setting, including individualized aerobic and resistance training either in hospital or at home. As described by the authors in the abovementioned study, participants in the control group did not receive any intervention. In Dougherty et al. (2015), 160 patients were randomized to usual care (n = 76) or exercise (n = 84); 18 were lost to follow-up (n = 8 exercise group; n = 10 control group).[58] The intervention consistent of an 8-week walking program performed five days per week, followed by 16 weeks of home-based walking totaling 150 minutes per week. Exercise intensity was progressively increased from 60–65% to 80–85% of HR reserve. Weekly telephone support was provided, and the control group was requested not to start a new exercise program or change their exercise patterns for the duration of the study.

Table 4.2. Participants characteristics retrieved from studies included in the meta-analysis.

Variable, n (%)	**Men (n = 279)**	**Women (n = 77)**
Type of device		
ICD	269 (76%)	75 (21%)
Primary indication ICD	111 (31%)	23 (6%)
CRT	10 (3%)	2 (1%)
Clinical characteristics		
Age (years), mean ± SD	60 ± 12	51 ± 13
BMI, mean ± SD	30 ± 5	27.3 ± 6
BMI ≥ 30 (kg/m²), n (%)	31 (40%)	12 (60%)
Ejection fraction (%)	31 (9%)	41 (11%)
Diabetes	45 (13%)	3 (1%)
Arrthythmia	73 (21%)	14 (4%)
Heart failure	133 (37%)	28 (8%)
Hypertension	85 (24%)	8 (2%)
Ischemic heart disease	107 (30%)	12 (3%)
Myocardial infarction	84 (24%)	8 (2%)

Data is presented descriptively, as number and percentage (%) of the total sample.

Two randomized controlled trials with 156 participants (n = 34 women [22%]) enrolled in exercise training were included in the meta-analysis assessing sex differences in changes in CRF

between women and men with CIEDs. No sex differences were identified for changes in CRF **(Figure 4.4)** (mean difference $\dot{V}O_2$peak = 0.21: 95% CI, −1.70 to 2.12 mL mL/kg/min; P = 0.83) following exercise training; low, nonsignificant heterogeneity was observed (I^2 = 14%, P = 0.28).

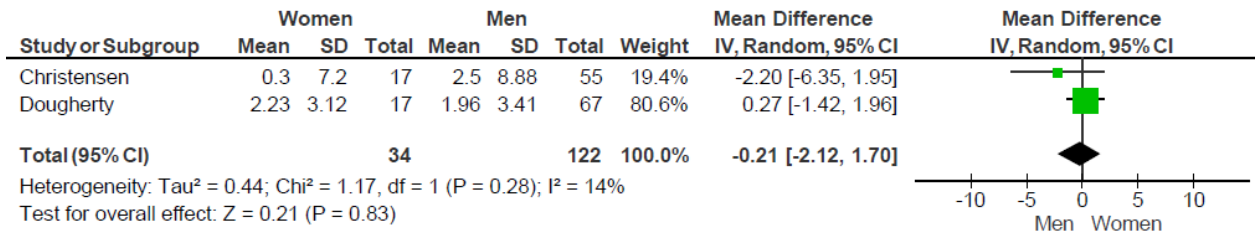

Figure 4.4. Meta-analysis comparing changes in CRF following exercise training between women and men with CIEDs.

Meta-analyses were conducted separately for each sex to compare the effects of exercise training with a non-exercise control group (i.e., same sex) on CRF (**see Figure 4.5**). Among women (n = 34 [49%] in the exercise group) no significant differences were observed between the exercise training and control groups (mean difference $\dot{V}O_2$peak = 1.36, 95% CI, −0.70 to 3.43 mL mL/kg/min; P = 0.20); low, nonsignificant heterogeneity was observed (I^2 = 0%, P = 0.49).

Among men (n = 122 [52%] in the exercise group) significant differences were found between the exercise training and control group (mean difference $\dot{V}O_2$peak = 1.75, 95% CI, 0.72 to 2.79 mL mL/kg/min; P < 0.001); low, nonsignificant heterogeneity was observed (I^2 = 0%, P = 0.50).

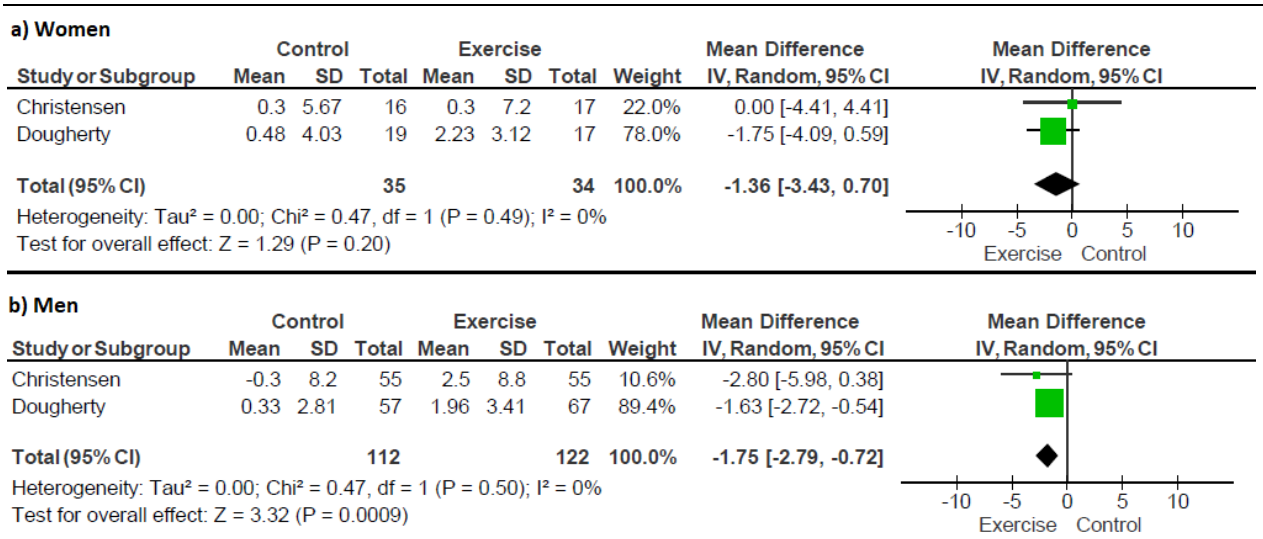

Figure 4.5. Meta-analysis comparing changes in CRF between exercise training and control groups in (a) women and (b) men with CIEDs.

Risk of bias, quality of the evidence, and publication bias

Risk of bias was assessed for the 2 included randomized controlled trials. Results from TESTEX and GRADE are presented in Supplemental Material (**Table S4.2, Table S4.3**).Christensen et al. scored 14/15, fulfilling nearly all criteria, except incomplete between-group outcome reporting for all other outcomes.[15] Similarly, Dougherty et al. scored 13/15, with one additional point lost for not assessor blinding, but meeting most of the same standards.[36] Overall, the quality of the evidence (i.e., GRADE) was low. For outcomes with only two studies, funnel plots are presented descriptively (see supplemental material **Figure S4.4**) but formal testing for asymmetry (e.g., Egger's test) was not conducted, following best methodological practices.

4.5 Discussion

This is the first systematic review to compare changes in CRF following exercise training between women and men with CIEDs. Contrary to our hypothesis, the meta-analysis did not identify a

significant sex difference in CRF improvements following exercise training. Women did not show significant improvement in $\dot{V}O_2$peak compared with controls, whereas men demonstrated significant gains. Our systematic review also highlights the persistent under-representation (18%) and limited sex-disaggregated reporting in clinical exercise research; reporting was minimal in early phases (0–36%) and became consistent only at final analysis (95%). The small number of studies and limited sex-specific data for the meta-analysis may have constrained the ability to detect sex-based differences. These findings should be considered hypothesis-generating and underscore the need for adequately powered trials with balanced sex representation and standardized sex-disaggregated reporting.

Cardiorespiratory fitness

There are no other studies comparing changes in CRF following exercise training between women and men with CIEDs, making direct comparison with existing evidence difficult. A quantitative synthesis of the limited available evidence offered an exploratory approach to help contextualize existing findings. Indeed, two studies can be a sufficient number to perform a meta-analysis, provided that those two studies can be meaningfully pooled and provided their results are sufficiently 'similar'.[62] A previous Cochrane review of exercise-based CR for patients with ICDs performed a meta-analysis of two trials (n = 136 participants) reporting $\dot{V}O_2$peak) at 12 months of follow-up.[27] Considering our comparable pooled sample (n = 303) and a higher proportion of women than those represented in ICD trials (25% vs. 12%), conducting a quantitative synthesis was both appropriate and justified. [63,64] Yet, given the small overall sample size and the heterogeneity across CIED groups, future sex-based individual studies and meta-analyses are warranted.

No sex differences were observed in CRF improvements in patients with CIEDs. Similarly, a recent systematic review and meta-analysis of 19 studies in patients with atrial fibrillation (n = 886, 29% women) revealed no sex differences in $\dot{V}O_2$peak improvements following exercise training (MD: 0.15, 95% CI, −1.08- 1.38 mL ml/kg/min; P = .81; I^2 = 27%), and no sex-specific effects compared

with controls. In our study, women did not experience significant increases in $\dot{V}O_2$peak (range: 1-8%; 0.1-0.6 METs) compared with controls, while men showed significant improvements (range: 8-12%; 0.5-0.7 METs) over time. Strong evidence shows that every 1- MET (or 3.5 ml/kg/min $\dot{V}O_2$peak) increase in CRF is associated with a 10%–17% reduction in all-cause mortality.[12,65] The large HF-ACTION trial (n = 2,331; 36% with CIEDs), found that exercise training improved $\dot{V}O_2$peak relative to usual care (0.6 vs. 0.2 ml/kg/min) in patients with heart failure.[66] This 6% increase in $\dot{V}O_2$peak was associated with an 8% lower risk of the cardiovascular mortality or rehospitalization in individuals with heart failure.[67] In a sex-based analysis of the HF-ACTION trial, women showed larger but not statistically significant increases in $\dot{V}O_2$peak than men (0.88 ± 2.2 vs. 0.77 ± 2.7 ml/kg/min). These gains in women were associated with a 26% lower risk of death, whereas no benefit was observed in men (HR: 0.74 vs. 0.99, respectively, P = 0.027).[11] These findings suggest that even modest increases in CRF confer clinically meaningful benefits for both sexes and may extend to patients with devices, although further investigations in CIED-focused populations are warranted.

The type of CIED and device programming modes influence CRF. In our meta-analysis, more than 90% of participants were ICD recipients and evidence on sex differences among patients with other CIEDs remains limited. In patients with PPMs, pacing programming mode (dual chamber) was an independent predictor of CRF estimated by METs in men (r = 0.51, P = 0.014), but not in women (r = 0.08, P = 0.76).[68] Sex has also been shown to independently predict CRT effectiveness, with proposed underlying mechanisms including sex-differences in body size and QRS duration.[69–71] CRTs can further increase $\dot{V}O_2$peak after implantation, attributed to improvements in central and peripheral hemodynamics.[72] Taken together with established sex differences in cardiac structure and vascular function (e.g., smaller left ventricular mass and size, reduced nitric oxide availability in women),[73–75] it is possible to speculate sex-differences may extend to CRF in PPM and CRT recipients, supporting the need for more research.

Sex-examination and gender-related factors

The lack of clarity regarding sex differences may be attributable to the historical underrepresentation of women in cardiovascular research.[76] A recent large study (n = 1,396,104 participants, 41% women) reported low participation-prevalence ratio in women with heart failure (0.51) and coronary artery disease (0.39) - conditions that frequently require device procedures.[77] A large retrospective cohort (n = 1,291, 258 patients with cardiovascular admissions) found that women had lower implantation rates for all three major cardiac devices (PPMs, ICDs, and CRTs) compared to men, across nearly all indications (e.g., heart block and cardiac arrest), even after adjustment for age and comorbidities, raising concerns for underuse of CIEDs in women.[64] Landmark trials in patients with CIEDs have historically included less than 33% of women with CIEDs, yet these studies continue to serve as the basis for guideline recommendations.[8,78] The low proportion of women enrolled can not be explained solely by disease prevalence. Across studies of ICDs, 12% of patients were women with a participation to prevalence ratio of 0.41 (i.e., <0.8 participation-prevalence ratio denotes significant under-representation), indicating significant under-representation compared to the disease population.[63,64] Our findings show that women with CIEDs represented 26% of patients included in exercise trials. The small number of women included may have limited our statistical power and constrained sex-based analyses of CRF. More-inclusive recruitment practices including tailored exercise prescriptions that consider women's preferences for exercise modalities and settings have been suggested and may enhance their participation in exercise and exercise-based CR settings.[79]

Insufficient sex-stratified reporting persists in cardiovascular research. A recent systematic review of 1,079 registered cardiovascular trials (2017–2023) found that fewer than one-third of phase 3 trial publications reported sex-stratified outcomes.[77] Our results reveal that most randomized trials reported sex-disaggregated data in the final analyses (95%), yet fewer than 36% of studies presented such data during trial phases as per CONSORT guidelines (e.g., enrollment, intervention allocation,

follow-up, and data analysis). Dewidar and colleagues (2022) assessed 253 cohort studies reporting clinical or safety outcomes among heart failure patients treated with CRT over the past two decades.[80] They found that 14% considered sex in the study design, 17% presented outcome data disaggregated by sex, and 13% conducted sex-stratified analyses. Their temporal analysis (2000-2020) showed an increase in sex-disaggregated reporting, which does not fully explain the limited change in our study.[80] The Sex and Gender Equity in Research (SAGER) checklist remains highly recommended to improving the reporting of sex and gender variables in trials and has been increasingly recognized within the cardiovascular field.[25,81] Expanding the use of the SAGER guidelines across all stages of conducting randomized exercise trials can enhance transparency and promote equitable, evidence-based care.

Fewer studies reported gender-related variables (36%). Gender may influence how women perceive themselves and how they respond to exercise.[23] Women with atrial fibrillation are often described as widowed and having lower levels of education, income, and employment compare with men.[82,83] These factors have been associated with lower physical activity levels.[22,84] Investigating gender-related factors may help tailor exercise interventions; for example, women with low income may prefer cost-effective, community-based group exercise classes.[85] Findings showed that most trials reported gender-related factors as demographic variables, without using validated tools to assess gender scores. Instruments such as the Traditional Masculinity and Femininity scale (TMF) provide self-reported measures of masculine and feminine traits.[86,87] To date, no study has measured gender scores in patients with CIEDs, highlighting an important gap.

Limitations and strengths

Of the 22 eligible studies, sex-specific data were available from only two studies, limiting our sample size and ability to assess sex differences in the initially proposed outcomes. Several authors did not respond to requests for sex-disaggregated data or were unreachable. Nevertheless, we conducted

the first systematic review and meta-analysis assessing the effects of exercise training in patients with CIEDs from a sex-examination perspective, using rigorous quality methodologies (e.g., PRISMA, TESTEX, and GRADE). Another strength is that our meta-analysis included 22% women, which is above the sex-specific inclusion typically observed in previous exercise and cardiovascular studies.[22,88] Larger sample sizes are needed to generate more definitive evidence regarding CRF, and further studies should confirm these findings and explore underlying mechanisms, as well as other key cardiovascular outcomes in patients with CIEDs. The use of data repositories can facilitate data sharing across organizations and enable more robust analyses, consistent with the ongoing efforts of open science in cardiology toward reproducible and publicly accessible research, which is essential for advancing sex- and gender-based science.

4.6 Conclusion

This review addressed the lack of sex-based analyses in previous exercise studies involving patients with CIEDs - a critical first step toward developing evidence-based exercise recommendations for both sexes. While no sex differences in CRF were observed overall, women showed a smaller increase in $\dot{V}O_2$peak compared to women in control groups, whereas men demonstrated significant improvements. As our sample consisted predominantly of ICD recipients, further research is needed in patients with other CIED subtypes. Our sex-based analysis also highlighted the underrepresentation of women in exercise and CIED trials (18%) and the limited reporting of sex-specific data across randomized trials. Findings aim to enhance the sex-specific evidence base and inform future research in this area.

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Supplementary material

Table S4.1. Search strategies for all databases used for the systematic review.

Embase Classic+Embase
1 exp cardiac implantable electronic device/ 2 implantable cardioverter defibrillator/ or biventricular implantable cardioverter defibrillator/ or cardiac resynchronization therapy defibrillator/ or dual chamber implantable cardioverter defibrillator/ or implantable atrial defibrillator/ or single chamber implantable cardioverter defibrillator/ 3 exp cardiac resynchronization therapy/ 4 exp cardiac rhythm management device/ 5 pacemaker.mp. 6 or/1-5 7 exp exercise/ 8 exp heart rehabilitation/ 9 exp kinesiotherapy/ 10 exp sport/ 11 exp muscle strength/ 12 exp resistance training/ 13 exp fitness/ 14 exp physical activity/ 15 (sport* or walk* or gym? or running or jog? or jogging or pilates or yoga or bicycl* or cycling or spinning or bike* or biking or swim* or swimming or rollerblad* or kickbox* or stair climb* or rowing or elliptical* or treadmill*).ti,ab,kf. 16 (exercise* or exert* or train* or conditioning or strength* or isokinet* or isomet* or resistance* or fitness or aerobic* or weight lift* or dumbbell* or kettlebell or kettle-bell or (physical* adj1 (activ* or fit*))).ti,ab,kf. 17 ((functional* or combin* or anaerob* or circuit or weight* or bodyweight* or muscl* or muscul* or bone*) adj2 program*).ti,ab,kf. 18 or/7-14 19 6 and 18 20 exp randomized controlled trial/ 21 exp controlled clinical trial/ 22 exp randomization/ 23 intermethod comparison/ 24 placebo.ti,ab. 25 (compare or compared or comparison).ti,ab. 26 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 27 (open adj label).ti,ab. 28 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 29 double blind procedure/ 30 parallel group$1.ti,ab. 31 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or

intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
32 (assigned or allocated).ti,ab.
33 (controlled adj7 (study or design or trial)).ti,ab.
34 (volunteer or volunteers).ti,ab.
35 exp clinical trial/
36 trial.ti.
37 exp human experiment/
38 or/20-37
39 19 and 38

Ovid MEDLINE(R)

1 (CIED or (Cardiac adj2 implant* adj2 electronic* adj2 device?)).ti,ab.
2 defibrillators, implantable/ or exp pacemaker, artificial/
3 ((biventricular adj2 pacemaker*) or pace-maker*).ti,ab.
4 ((resynch* or re-synch*) adj3 (cardiac or therap* or treatment* or device*)).ti,ab.
5 (cardioconver* or (cardio adj conver*)).ti,ab.
6 1 or 2 or 3 or 4 or 5
7 exp exercise/ or exp exercise therapy/ or exp sports/ or muscle strength/ or exp physical endurance/ or physical exertion/ or physical fitness/
8 (exercise* or exert* or train* or conditioning or strength* or isokinet* or isomet* or resistance* or fitness or aerobic* or weight lift* or dumbbell* or kettlebell or kettle-bell or (physical* adj1 (activ* or fit*))).ti,ab,kf.
9 (sport* or walk* or gym? or running or jog? or jogging or pilates or yoga or bicycl* or cycling or spinning or bike* or biking or swim* or swimming or rollerblad* or kickbox* or stair climb* or rowing or elliptical* or treadmill*).ti,ab,kf.
10 ((functional* or combin* or anaerob* or circuit or weight* or bodyweight* or muscl* or muscul* or bone*) adj2 program*).ti,ab,kf.
11 or/7-10
12 6 and 11
13 randomized controlled trial.pt.
14 controlled clinical trial.pt.
15 randomized.ab.
16 placebo.ab.
17 drug therapy.fs.
18 randomly.ab.
19 trial.ab.
20 groups.ab.
21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 exp animals/ not humans.sh.
23 21 not 22
24 12 and 23

Cochrane Central Register of Controlled Trials

1 CIED.mp. or (Cardiac adj2 implant* adj2 electronic* adj2 device?).ti,ab. [mp=title, original title, abstract, floating sub-heading word, mesh headings, heading words, keyword]

2 defibrillators, implantable/ or exp pacemaker, artificial/

3 ((biventricular adj2 pacemaker*) or pace-maker*).ti,ab.

4 ((resynch* or re-synch*) adj3 (cardiac or therap* or treatment* or device*)).ti,ab.

5 (cardioconver* or (cardio adj conver*)).ti,ab.

6 1 or 2 or 3 or 4 or 5

7 exp exercise/ or exp exercise therapy/ or exp sports/ or muscle strength/ or exp physical endurance/ or physical exertion/ or physical fitness/

8 (exercise* or exert* or train* or conditioning or strength* or isokinet* or isomet* or resistance* or fitness or aerobic* or weight lift* or dumbbell* or kettlebell or kettle-bell or (physical* adj1 (activ* or fit*))).ti,ab,kw.

9 (sport* or walk* or gym? or running or jog? or jogging or pilates or yoga or bicycl* or cycling or spinning or bike* or biking or swim* or swimming or rollerblad* or kickbox* or stair climb* or rowing or elliptical* or treadmill*).ti,ab,kw.

10 ((functional* or combin* or anaerob* or circuit or weight* or bodyweight* or muscl* or muscul* or bone*) adj2 program*).ti,ab,kw.

11 or/7-10

12 6 and 11

Table S4.3. Assessment of study quality and reporting of randomized controlled trials included in the systematic review.

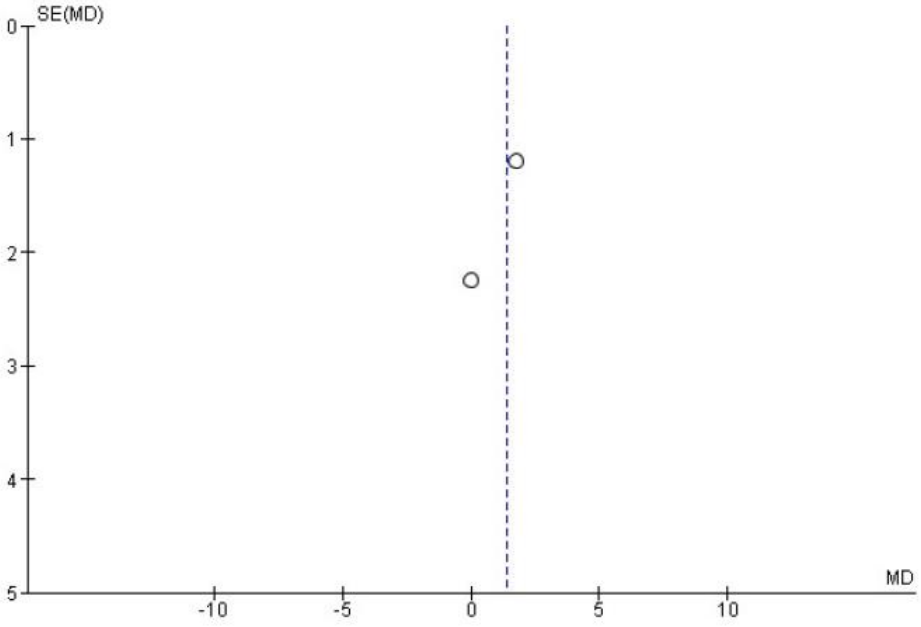
	Study quality					Study reporting							
Author	**Eligibility**	**Randomization**	**Allocation**	**Groups similarity**	**Blinding**	**Measures assessed 85% of patients**	**Intention-to-treat analysis**	**Between group comparisons****	**Endpoint and variability**	**Activity in control**	**Constant intensity**	**Exercise prescription**	**Total**
Christensen	**1**	**1**	**1**	**1**	**1**	**2**	**1**	**2**	**1**	**1**	**1**	**1**	**14**
Dougherty	**1**	**0**	**1**	**1**	**1**	**3**	**1**	**2**	**1**	**0**	**1**	**1**	**13**

Measured using the tool for the assessment of study quality and reporting in exercise (TESTEX) scale. *Three points possible: 1 if adherence >85%, 1 if adverse events reported, 1 if exercise attendance reported. **Two points possible: 1 if primary outcome is reported, 1 if all other outcomes are reported.

Table S4.4. Grading of Recommendations Assessment, Development and Evaluation (GRADE) of the most relevant outcomes of the review.

Certainty assessment						№ of patients		Effect (change in Women vs. Men)	Certainty
№ of studies	**Study design (a)**	**Risk of bias (b)**	**Inconsistency (c)**	**Indirectness (d)**	**Imprecision (e)**	**Women**	**Men**	**Mean difference (95% CI)**	
CRF (follow up range: 12 - 24 weeks; assessed with direct measurements in 2 studies)									
2	2 trials	not serious	not serious	serious	serious	77	279	-0.21 mL/kg/min (-2.12 to 1.70)	⨁⨁◯◯ LOW

Figure S4.4. Funnel plot of comparison: sex differences in CRF.



CHAPTER 5

Study 4. The effects of exercise training on physical and mental health in women with cardiac implantable electronic devices: a pilot randomized clinical trial.

5.1 Abstract

Background: Cardiac implantable electronic devices (CIEDs) are established treatments for cardiovascular diseases. Women with CIEDs report poorer physical and mental health compared to men. Growing evidence demonstrates the importance of exercise-based cardiovascular rehabilitation (CR) in improving cardiovascular health outcomes in women; however, evidence for women with CIEDs remains limited. We aimed to assess the feasibility of virtual exercise programs in women with CIEDs.

Methods: This was a pilot randomized clinical trial. Twenty women with CIEDs were randomly assigned to twice weekly virtual dance-based high-intensity interval training (HIIT) and moderate-to-vigorous intensity training (MICT) for 12 weeks. Patients completed either HIIT (45 minutes: 4x4 minutes alternating high-intensity intervals at 85%-95% of peak heart rate [HR] interspersed with 3x3 minutes low-intensity intervals at 60%-70% peak HR) or MICT (60 minutes: continuous aerobic conditioning within 70%-85% of peak HR. Feasibility was assessed by attendance, compliance, safety, and patient experience. Secondary outcomes comprised cardiorespiratory fitness (CRF), mental health, quality of life, and determinants of exercise behaviour (motivation, self-efficacy, enjoyment). Descriptive statistics were used to report the means and their variations.

Results: Of the 20 patients (62 ± 12 years, 60% with implantable cardioverter defibrillators) who consented, 14 (70%) completed the exercise interventions. In the HIIT group (n = 10), participants attended 21 ± 2 classes (out of 24 classes), with 100% adherence. Most patients met (37%) or exceeded (46%) the target HR ranges for the high-intensity intervals (average HR: 131 ± 15 bpm), with met (17%) or exceeded (53%) the HR low-intervals (average HR: 110 ± 14 bpm). Four patients completed the MICT program (two dropped out before, and four after the program started, due to: did not enjoy the exercise format, medical reasons, and caregiving responsibilities). Of the 4 completers in the MICT group, patients attended 23 ± 1 classes and met (68%) or exceeded (32%) the target HR ranges, respectively (average HR: 111 ± 7 bpm). Less than 1% of adverse events were reported across

programs. Participants reported positive experiences with the virtual programs. Changes in secondary outcomes were provided descriptively to inform the design of a larger efficacy trial.

Conclusion: Virtual HIIT was feasible in women with CIEDs, whereas MICT was not. This pilot study provides recommendations for a future efficacy trial examining virtual exercise in women with cardiac devices.

5.2 Introduction

Cardiovascular disease is the leading cause of death in women in Canada and across the globe.[1] Cardiac implantable electronic devices (CIEDs) are established treatments for cardiovascular diseases, such as arrhythmias and heart failure.[2] CIEDs encompass permanent pacemakers (PMs), indicated for symptomatic bradyarrhythmias,[3] implantable cardioverter defibrillators (ICDs), recommended in the primary and secondary prevention of sudden cardiac arrest, and cardiac resynchronization therapy (CRT), used to treat chronic heart failure. [4] Despite evidence indicating women experience similar or superior clinical benefits from CIEDs compared to men, they are less likely to receive a CIED (57.3 vs. 116.3 per 100,000 between 1988 and 2018).[5] Women also represent less than 30% of participants in CIED trials (<30%),[6] highlighting sex-disparities that may negatively impact clinical care.

Women with CIEDs experience a multifaceted cardiovascular burden.[8–11 8] Women with CIEDs present with traditional cardiovascular risk factors such as hypertension, diabetes, high anxiety and depression levels, and reduced quality of life.[7–11] Women with CIEDs also demonstrate low CRF (peak oxygen uptake, $\dot{V}O_2$peak: ~13.4ml/kg/min), which is a strong predictor of mortality.[12] Indeed, both sex-specific biological factors (e.g., hormones influence, reproductive events) and gender-related factors (e.g., caregiving and household responsibilities) impact women's heart health across the lifespan.[3] Sex refers to biological traits while gender encompass socially constructed roles, behaviours, expressions, and identities – both are important determinants of cardiovascular health.[13] The intersection of clinical, biological, and psychosocial factors influence the cardiovascular health trajectory of women with CIEDs, emphasizing the importance of tailored secondary prevention strategies.

Exercise-based cardiovascular rehabilitation (CR) is part of the management of patients with CIEDs.[14,15] A Cochrane review in patients with ICDs (n = 1,730 participants) demonstrated that exercise-based CR programs (exercise-based interventions alone or in combination with psychoeducational components) improved $\dot{V}O_2$peak compared to control (mean difference: 0.91

mL/kg/min, 95% confiden interval [CI]: 0.60-1.21; participants = 1,485; trials = 7; quality of evidence: very low). Yet, authors were unable to definitively assess the impact of exercise-based CR on all-cause mortality, serious adverse events, and health-related quality of life due to insufficient evidence.[15] A recent EAPC–EHRA consensus statement concluded that, despite sparse literature, CR offers an important opportunity to optimize medical care, enhance functional and psychological well-being, monitor device function, and support safe exercise in those living with CIEDs.[16] Current literature emphasizes the lack of formal clinical CR guidelines for patients with CIEDs – a gap that is even more pronounced in underserved communities.

Considerable sex and gender disparities exist in CR.[17] Women have less access to CR than men and are less likely to complete the program.[18,19] CR barriers are multifactorial, from health system and patient levels.[20] A global survey (n = 2,163 patients from 16 countries) elucidated the top barriers among referred but not enrolled women, including lack of knowledge about CR, not being contacted by the program, cost, and perceptions that exercise is tiring or painful.[21] Among enrolled women, the greatest barriers to adherence were distance, transportation, family responsibilities, and lack of motivation and enjoyment. [21] Traditional CR programs often fail to address these barriers adequately, contributing to poor participation and completion rates among eligible women. [17] These factors also affect subgroups of women in CR, such as those with CIEDs. While exercise-based CR has demonstrated beneficial effects on cardiovascular outcomes among patients with CIEDs, women represented fewer than 20% of participants included in these studies.[16] Given their higher cardiovascular risk profile, women with CIEDs may have greater needs for comprehensive CR, including exercise training - an essential component of standard care.[22] Addressing this gap is necessary to understanding the role of CR in women with CIEDs and promoting equitable access to evidence-based secondary prevention strategies.

In recent years, recommendations have increasingly focused on addressing women's needs in

CR.[23] Virtual or home-based exercise programs have been shown to improve CR attendance and completion rates in women.[24,25] A systematic review and meta-analysis (23 trials, n = 2,890 participants) demonstrated that home- and centre-based forms of CR had similar effectiveness in improving clinical and health-related quality of life outcomes in adults with cardiovascular diseases, supporting the continued expansion of evidence-based, home-based cardiac rehabilitation programs.[26] Alternative time-efficient exercise modalities such as high-intensity interval training (HIIT: e.g., interspersed periods of high- and low-intensity exercise) have emerged, eliciting similar or superior improvements in physical (e.g., CRF, cardiometabolic health indicators)[27,28] and mental health (e.g., anxiety levels)[29] compared to traditional moderate-to-vigorous intensity continuous training (MICT) in women participating in CR.[30] Dance-based MICT programs have proven be safe and effective (e.g., increased functional capacity and endothelial function) within CR settings, broadening the range of exercise formats (e.g., against traditional treadmill/cycle) suitable for those with cardiovascular disease.[29,31,32] Improving women's participation requires modernizing program delivery to better address frequently reported barriers, such as time constraints, transportation challenges, and limited flexibility associated with traditional hospital-based settings.[24] Alternative and virtual exercise models may help mitigate these barriers and enhance accessibility and participation among women.

How women experience exercise-based CR matters. Consistent with social cognitive theories, self-efficacy, motivation, and enjoyment are key determinants of exercise participation and long-term adherence.[33–35] For instance, in low active adults (n = 47; 87% women), participation in a 12-week home-based HIIT program led to higher self-efficacy, enjoyment, and positive engagement levels compared to control, suggesting the feasibility and favorable psychosocial responses to home-based HIIT among predominantly women participants.[36] Further, there is evidence that HIIT using dance-based programs are perceived as more fun, enjoyable, and motivating compared to traditional aerobic exercise.[24,29,37] In contrast, higher exercise intensities have also been associated with more negative

affective responses (i.e., how one feels during exercise). In inactive adults (n = 44, 28% women), HIIT was reported to be less pleasurable than MICT both during and following an exercise session, highlighting a practical paradox for HIIT, and the need for longer-term studies to better understand these affective responses.[38,39] Additionally, gender may influence exercise behaviour.[40] Masculine gender traits are associated with higher exercise self-efficacy and greater participation, whereas individuals endorsing more feminine traits may enter CR with lower functional capacity.[41,42] Understanding how exercise-based CR influences psychological and gender-related factors is essential to supporting women's exercise experiences and, ultimately, sustained exercise behaviour.

Promising CR approaches for women have emerged with the potential to advance women's cardiovascular care. However, the applicability of these new exercise alternatives to women with CIEDs has not been evaluated, highlighting the need for further investigation. A necessary first step is to generate evidence on the feasibility and safety of virtual exercise interventions in women with CIEDs. As per ORBIT model[43] recommendations, the primary aim of this study was to assess the feasibility of a pilot randomized clinical trial comparing a 12-week program of virtual HIIT and MICT in women with CIEDs. The secondary aims were to evaluate the effects of a 12-week program of virtual HIIT and MICT on CRF, mental health, quality of life, cardiometabolic health indicators, and exercise behaviour determinants.[45,46]

5.3 Methodology

Study Design

This single-centre, open-label, parallel group, pilot randomized clinical trial was conducted at the University of Ottawa Heart Institute, a tertiary care cardiovascular care centre in Ottawa, Ontario,Canada. The protocol was approved by the Ottawa Health Science Network Research Ethics Board (protocol number: 20230095-01H) and registered with ClinicalTrials.gov (protocol number:

NCT05946304). This study is described in accordance with the Consolidated Standards of Reporting Trials (CONSORT): Extension to randomised pilot and feasibility trials, and template for intervention description and replication (TIDieR) checklist.[44,45] All patients provided written informed consent; there was no financial compensation.

Recruitment and Screening

Patients were recruited between January 2024 and April 2025; the trial was completed in August 2025. Research staff reviewed the cardiac device clinical database and electronic medical records (using EPIC) weekly to identify patients who consented to be contacted for research purposes. Study staff documented patients' age, sex, and medical information (e.g., diagnosis, type of CIED). The research coordinator subsequently contacted potential patients via phone to provide them with information regarding the study, determine their interest, confirm eligibility, and schedule a baseline visit. Recruitment also included advertisements via posters in public areas of the University of Ottawa Heart Institute.

Participants

Participants were included if they (1) were women with CIEDs (i.e., female sex assigned at birth) receiving optimal medical therapy (e.g., standard of care) with functioning CIEDs (e.g., no troubleshooting documented); (2) were able to perform a symptom-limited cardiopulmonary exercise test (CPET, being essential to determine peak HR for exercise prescription); (3) were able to read and understand English or French; (4) had internet connection and a mobile device with camera and speakers; and (5) agreed to sign an informed consent. Sex refers to biological attributes, whereas gender encompasses socially constructed roles and norms. As both dimensions were considered in this study, the terms 'women' and 'men' are used throughout.

Patients were excluded if they (1) were participating in routine exercise training (>2x/week); (2)

had documented unstable angina; or established diagnosis of chronic obstructive pulmonary disease, severe mitral or aortic stenosis, or hypertrophic obstructive cardiomyopathy; (3) had no internet connection; (4) were pregnant during the 12-week intervention phase; or (5) were unable to provide written informed consent or return for a follow-up visit at 12 weeks.

Baseline

Demographic and medical information were retrieved from clinical databases. For the baseline visit, patients were asked to (1) fast for 4h prior to the visit, (2) take any medication as prescribed (3) refrain from moderate-to-vigorous intensity exercise, and alcohol/caffeine consumption 12h prior to the appointment, and (4) wear comfortable exercise clothes. During the baseline visit, study staff measured patients' resting blood pressure and heart rate (HR) and body composition. Subsequently, participants underwent a symptom-limited CPET. A modified Balke protocol, developed for patients with ICD, was used to determine the peak HR for the exercise prescription. [46] The Gellish equation (207 – [0.7 x age]) was used to estimate HR max, with a subtraction of 30 bpm for individuals taking beta-blockers.[47] Peak HR achieved during the CPET was used to prescribe exercise. For patients with ICDs or CRT with defibrillator (CRT-D), peak HR was set 10 bpm under the zone for anti-tachycardia pacing or shock therapy for both CPET and exercise prescription.[48,49] Each participant was then fitted with a 7-day accelerometer to measure physical activity levels and received a wrist-worn Polar HR monitor and elastic band.

Randomization

After the baseline visit, patients were randomized in a simple 1:1 ratio to HIIT or MICT using a computer-generated sequence provided by the University of Ottawa Heart Institute Cardiovascular Research Methods Centre via REDCap. Patients received an online REDCap survey with self-reported questionnaires assessing anxiety and depression severity, quality of life, motivation, and gender scores,

to be completed on the same day.[53]

Intervention

All patients participated in supervised virtual exercise training sessions (i.e., HIIT or MICT) twice weekly for 12 weeks using Zoom for Healthcare. The HIIT and MICT sessions were led by different staff to avoid bias between groups. HIIT and MICT were performed individually or in groups when possible. Pre-recorded dance-based exercise videos developed with our Cardiac Rehabilitation Centre were used for the exercise program. Patients were asked to keep their camera on during the exercise sessions. HR and ratings of perceived exertion (RPE) were collected during the sessions to monitor exercise intensity and perceived exertion (e.g., via Polar watch and Borg Scale, respectively), and the one-Item Feeling Scale was used to assess affective responses to exercise at the beginning and end of sessions. The one-Item Feeling Scale was used to assess affective responses to exercise at the beginning and end of sessions. After each exercise session, patients were offered a 5–10-minute question and answer period, and educational components on patient-preferred topics (e.g., healthy eating, sleep, stress management) were delivered at weeks 4, 8, and 12, using exercise-based CR materials. Two weeks into the intervention, patients received another online link to complete self-efficacy and physical activity enjoyment questionnaires. Because target HR zones may require adjustment during the training period, patients returned for an in-person visit after 6 weeks to complete another CPET to optimize exercise prescription for the remaining sessions.[50]

High-intensity interval training

Each HIIT session was 45 minutes in duration and followed a modified Norwegian[51] aerobic protocol (dance-based movements) which consisted of: (i) a 10-minute warm-up at 60%-70% peak HR; (ii) 4 × 4 minutes of high-intensity work periods at 85–95% peak HR interspersed with 3 minutes of low-intensity work periods at 60%-70% peak HR (totaling 28 min); and, (iii) a 10- minute cool-down at 60%–70%

peak HR with strength and stretching exercises. The intensity gradually increased by 5% after every other session until patients were able to exercise at 85%-95% of their peak HR throughout an exercise training session. RPE (6–20 scale) values of 15–17 (hard to very hard) during the high-intensity work periods and 11–13 (light to somewhat hard) during the low-intensity work periods were also encouraged.

Moderate-to-vigorous intensity continuous training

The MICT sessions was 60 minutes in duration and followed CR guidelines, including (i) a 10-minute warm-up at 60%-70% peak HR; (ii) 35-minute of continuous aerobic conditioning (dance-based) at 75%-85% peak HR; and (iii) a 15-minute cool-down of strengthening and stretching exercises at 60%-70% peak HR. Patients were encouraged to maintain a perceived exertion between 12 and 16 (somewhat hard to hard) on the RPE scale.

Follow-up

After 12 weeks, patients returned for the follow-up visit within approximately 1 week of their last exercise session. The baseline measures were repeated at follow-up.

Primary outcome

Feasibility

To assess the feasibility of virtual HIIT and MICT, exercise adherence, compliance, safety, and patients' experiences were examined at follow-up, based on previous studies assessing the feasibility of HIIT in CR settings.[52,53] Exercise adherence was assessed by the number of exercise classes participants attended (out of 24 sessions offered). High attendance to the programs was defined as attending ≥70% of the sessions.[52,53] Exercise compliance was assessed by the number of participants who achieved the

prescribed exercise intensity HR targets (i.e., HIIT or MICT). The HR across individual HIIT or MICT sessions were averaged and compared to the target prescription. Average HRs were coded as 'does not comply', 'complies', or 'exceeds'.[52,54] Given RPE is a widely used tool to monitor exercise intensity in CR, compliance to RPE targets were also examined. RPE, measured by the Borg scale, is a validated method for monitoring exercise intensity in patients with cardiovascular disease, where patients self-report their perceived effort of exercise on a scale of 6 (no exertion at all) to 20 (very, very hard).[50,55]

Safety was assessed by the number of adverse events (e.g., symptoms) during the study. Patients were asked to complete a feedback questionnaire, which comprised 15 questions regarding their experience with the intervention. The questionnaire was developed by scientists and clinicians involved with the CR program at the University of Ottawa Heart Institute. The questionnaire assessed participants' experiences with the online exercise platform, including ease of use, technical support, safety, and usefulness of communication features. It also evaluated changes in motivation, knowledge, and confidence to exercise, as well as overall satisfaction and willingness to recommend the virtual exercise program. Questions were scored using a 5-point Likert scale with '0' being 'strongly disagree' to '5' being 'strongly agree'. Open-ended questions captured enjoyable aspects, barriers, and suggestions for improvement, providing a comprehensive view of the patient's experience.

Secondary outcomes

Cardiorespiratory fitness

Change in CRF from baseline to follow-up was measured using a gold-standard symptom-limited CPET on a treadmill, with gas exchange, HR, and blood pressure continuously monitored during the test (i.e., metabolic cart [Parvo Medics TrueOne® 2400, Salt Lake City, UT], 4-lead electrocardiogram (Nasiff CardioCard®, Central Square, NY), blood pressure measurements [SunTech Tango M2, Morrisville, NC]).[49,50] The protocol included a 2-minute resting, and the test started at 0%

grade and 0.5 mph, increasing each minute to 3.3 mph by minute 6. Thereafter, grades increased by 1% per minute while speed remained at 3.3 mph until maximal effort was reached. Participants completed a cool-down stage with 5 minutes of walking at 1.5 mph and 0% grade. [46] Oxygen consumption ($\dot{V}O_2$) was collected every 20 seconds, and the average of three values during the last minute of the CPET represented $\dot{V}O_2$peak, an objective measure of CRF. $\dot{V}O_2$peak, METs, total duration, RPE, and HR peak were also assessed during the test. The suggested minimal clinically important difference (MCID) in CRF is 1-MET, equivalent to 3.5 mL O_2/kg/min.[56]

Mental health

Changes in anxiety and depression levels from baseline to follow-up were measured using the Generalized Anxiety Disorder-7 (GAD-7) and the Patient Health Questionnaire-9 (PHQ-9) questionnaires. The GAD-7 scores range from 0-21, categorized as mild (0-5), moderate (10-14), and severe (≥15) anxiety.[57] The suggested MCID for the GAD-7 is ≥ 4.0 points established from a multisite trial in participants with chronic depression.[58,59] The PHQ-9 score ranges from 0-27, categorized as minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27) depression. [60] The MCID for the PHQ-9 is ≥3.0 points, based on findings from a longitudinal study conducted in a primary care population.[61,62]

General quality of life

Changes in general quality of life was measured using the Short Form 36 (SF-36) version 1.0. The SF-36 yields 8 domains of functional health and well-being scores (i.e., physical functioning; role limitations due to physical problems; bodily pain; general health perceptions; energy/vitality; social functioning; role limitations due to emotional problems; and mental health) as well as psychometrically-based Physical Component Summary and Mental Component Summary scores. The SF-36 is validated

in cardiovascular disease populations and has shown good internal consistency (Cronbach's $\alpha \geq 0.80$).[63] The suggested MCID for the Physical Component Summary and Mental Component Summary is ≥5 points for clinical populations.[64]

Additional physical health outcomes

Cardiometabolic health indicators

Cardiometabolic health indicators were measured following standardized recommendations.[65] Resting blood pressure and HR were measured with the patient in a seated position after a 5-minute rest period using an automated blood-pressure monitor (Spot Vital Signs,
Welch Allyn, Skaneateles Falls, NY, USA).[66,67] Height (cm) and body mass (kg) were measured using standardized procedures to compute body mass index (kg/m^2). Waist circumference (cm) was measured using a tape. Blood pressure, height, and waist circumference were taken in triplicate and the averages were calculated and used for descriptive statistics.[65] Fat mass (kg) and fat-free mass (kg) were measured using bioelectrical impedance (Omron Karada Scan®, Model HBF-510, China), these measurements have been shown to be safe in patients with CIEDs.[68,69] Menstrual status were also collected using the Stages of Reproductive Aging Workshop (STRAW) criteria.[70]

Physical activity levels

Physical activity levels were measured using the wGT3X-BT accelerometer (ActiGraph, Pensacola, Florida), over 7 days at baseline and follow-up. A valid day was defined as 10 hours of wear time, and participants were required to have a minimum of 4 valid days in total to be retained in the analyses.[71] Triaxial Sasaki cut points were used to define light (150-2689 cpm), moderate (2690-6166 cpm), and vigorous (≥6167 cpm) intensity physical activity.[72] Weekly total minutes of moderate-to-vigorous physical activity were used to quantify whether patients were meeting the Canadian 24-hour Movement Guidelines (≥150 min/wk).[73]

Exercise affective response, motivation, confidence, and enjoyment

The one-Item Feeling Scale was used to assess affective responses to exercise by rating feelings of pleasure and displeasure from very good (+5) to very bad (−5) with neutral feeling anchored to 0. [74,75]Self-determined motivation for exercise was measured using the 24-item Behavioural Regulation in Exercise questionnaire (BREQ-3), which yields an overall Relative Autonomy Index (RAI) score, representing overall self-determined motivation. A Relative Autonomy Index (RAI) was calculated to provide a single indicator of self-determined motivation by applying weighted values to each subscale score and summing the results. The weighting system was as follows: −3 × Amotivation, −2 × External regulation, −1 × Introjected regulation, +1 × Identified regulation, +2 × Integrated regulation, and +3 × Intrinsic regulation. The resulting RAI ranges from −24 to +20 (0–4 Likert scale), with higher scores indicating greater self-determined motivation for exercise.[76] Exercise self-efficacy was assessed using the 9-item Multidimensional Self-Efficacy for Exercise Scale (MSES-R), yielding an overall self-efficacy for exercise score reflecting scheduling, task, and coping self-efficacy, on a 100% confidence scale (0-100) - higher values indicating greater self-efficacy.[77] Physical activity enjoyment was measured using the 18-item Physical Activity Enjoyment Scale (PACES) which assesses the extent (on a 7-point Likert scale) to which participants enjoy doing physical activity.[78] PACES scores range from 18 to 126, with higher scores indicating greater enjoyment. These scores are calculated by summing the 18 responses on a 7-point Likert scale, with some items requiring reverse scoring.

Gender

Given that gender may influence how women perceive themselves and how they respond to an exercise program, we explored gender scores using the Traditional Masculinity-Femininity (TMF) scale, a 6-item measure of gender-role adoption, gender-role preference, and gender-role identity. The TMF scores range from 1 (not at all feminine) to 7 (totally feminine).[79]

Statistical analysis

A pilot study is a feasibility study designed to test various aspects of the methods planned for a larger, more rigorous, or confirmatory investigation.[52,80,81] Pilot studies have been used to estimate the effect sizes and determine the sample size needed for a larger scale randomized controlled trial.[82,83] Following guidelines to determine the sample size for pilot studies and to incorporate sex based analyses, the total recruitment target was 20 participants (10HIIT/10MICT).[84,85] As per best research practices, we did not test a hypothesis to assess efficacy of secondary outcomes. [86,87] Testing hypotheses in feasibility pilot trials have been criticized because estimation is poor due to the small sample size, and therefore, this was a hypothesis generating study.[86,87]

The University of Ottawa Heart Institute REDCap was used to collect questionnaire responses of consented participants and then manage the study data. All outcome variables were tested for normality using Shapiro-Wilk tests in SPSS for Windows (Version 26; IBM Corp, Armonk, NY, USA). Descriptive statistics were used for the primary outcome and secondary outcomes and are presented using raw mean ± standard deviation (SD). Results of the normality test and median and 95% CIs are presented in **Table S5.1**, **Supplemental Material**.

5.4 Results

Of the 538 patients screened, a total of 20 women were randomized to HIIT or MICT **(Figure 5.1)**. A total of 6 (30%) patients dropped out of the trial; all of these patients who dropped out were randomized to the MICT group. Two participants (ICD, 48y; PPM, 78y) dropped out prior to beginning the intervention due to CPET-related reasons (i.e., did not feel comfortable wearing the gas analyzer mask), while the other participant reported medical issues. Four participants dropped out after starting the MICT program. The following reasons were documented: (i) did not enjoy providing HR and RPE measures throughout the sessions (primary prevention ICD, 68y), (ii) did not enjoy the exercise intensity (primary prevention ICD, 30y), (iii) experienced pain in her hip replacement and was scared to proceed

with sessions (PPM, 71y), (iv) had death in the family and caregiving responsibilities and discontinued the program (CRT-Pacemaker, 68y).

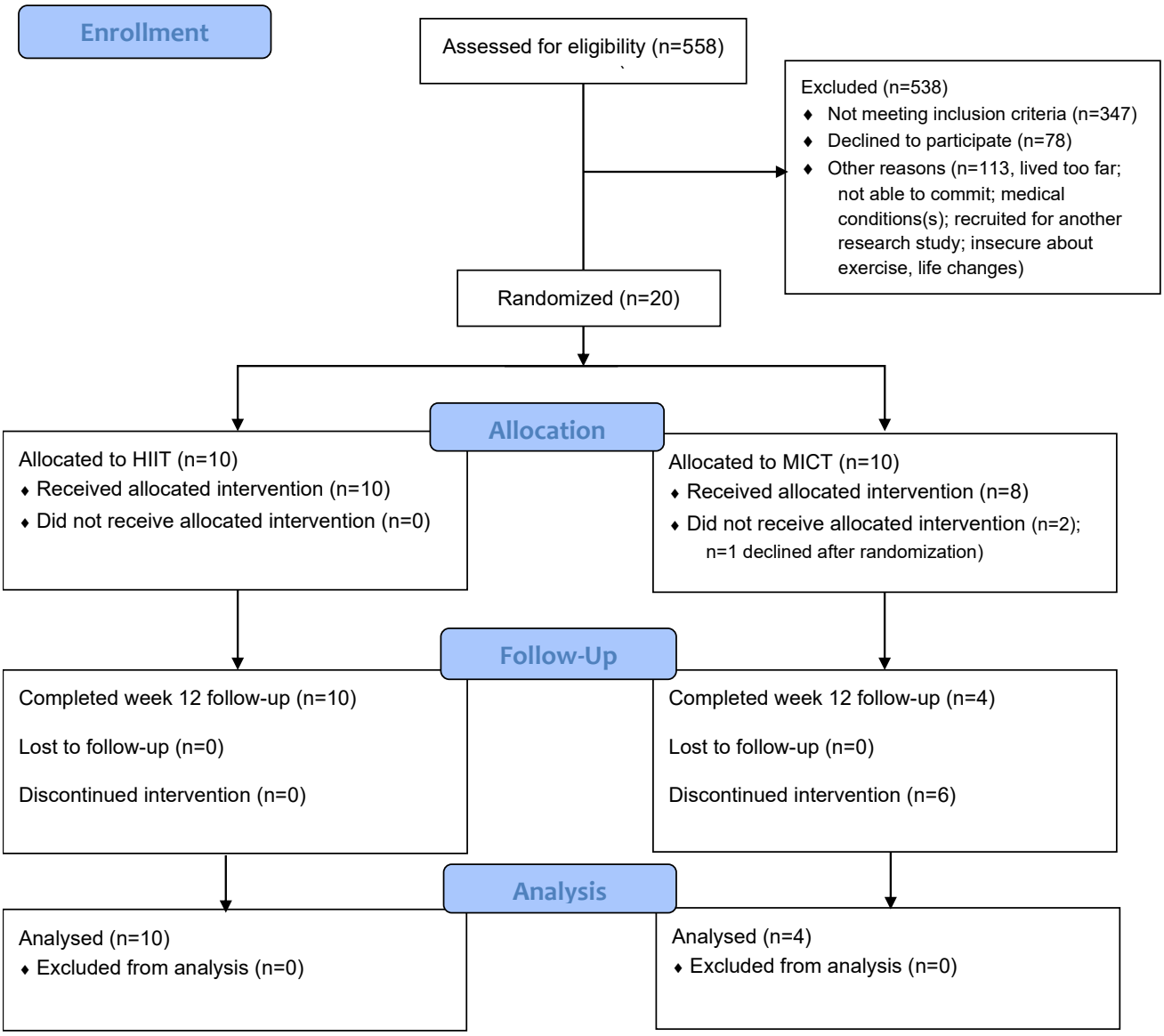


Figure 5.1. CONSORT flow diagram of participants recruited for the CIED-EX study. CONSORT, = Consolidated Standards of Reporting Trials.

All participants self-identified as cisgender, corresponding with their sex assigned at birth. Patients' demographic characteristics, gender-related factors, anthropometrics, medical conditions, and medications are presented in **Table 5.1.** Aside from those who were retired (n = 12), participants' occupations included lawyer, executive assistant, elementary teacher, and paramedic in the HIIT group, and a registered nurse in the MICT group. Most participants (80%) reported English as their first language, while 4 participants (20%) identified French as their primary language. All visits and exercise sessions were conducted in English, except one appointment conducted in French as per patient preference.

Table 5.1. Participants' sociodemographic and gender-related factors at baseline.

	Total (n=20)	**HIIT (n=10)**	**MICT (n=10)**
Demographics			
Age (years)	62 ± 12	60 ± 10	64 ± 13
Type of device			
Pacemaker	7 (35%)	2 (20%)	5 (50%)
Implantable cardioverter defibrillator (secondary prevention)	8 (40%)	4 (40%)	4 (40%)
Cardiac resynchronization therapy	5 (25%)	4 (40%)[a]	1 (10%)[b]
Time since implantation (years)	4.3 ± 3.4	5.5 ± 4.3	3.1 ± 1.3
Gender-related characteristics*			
Citizenship (n, % Canadian)	18 (90%)	9 (90%)	9 (90%)
Race/Ethnicity (n, %)			
White (Caucasian)	17 (85%)	8 (80%)	9 (90%)
Black (African, Nigerian, Somali)	2 (10%)	1 (10%)	1 (10%)
South Asian (Bangladeshi, Punjabi, Sri Lankan)	1 (5%)	1 (10%)	0 (0%)
Marital status (n, %)			
Single	5 (25%)	4 (40%)	1 (10%)
Married	14 (70%)	6 (60%)	8 (80%)
Divorced	1 (5%)	0 (0%)	1 (10%)
Education (n, %)			
Trade certificate	1 (5%)	0 (0%)	1 (10%)
College certificate or diploma	6 (30%)	2 (20%)	4 (40%)
Completed University	11 (55%)	8 (80%)	3 (30%)
Prefer not to answer	2 (10%)	0 (0%)	2 (10%)
Employment (n, %)			

Student	1 (5%)	0 (0%)	1 (10%)
Unemployed	2 (10%)	1 (10%)	1 (10%)
Currently working	5 (25%)	4 (40%)	1 (10%)
Retired	12 (60%)	5 (50%)	7 (70%)
Personal income (n, %)			
Less than $15,000	2 (10%)	1 (10%)	1 (10%)
$30,000 to $49,999	3 (15%)	2 (20%)	1 (10%)
$50,000 to $69,999	2 (10%)	1 (10%)	1 (10%)
$70,000 to $99,999	2 (10%)	1 (10%)	1 (10%)
$100,000 and greater	6 (30%)	4 (40%)	2 (20%)
Prefer not to answer	5 (25%)	1 (10%)	4 (40%)
Housework responsibility (n, %)	15 (75%)	9 (90%)	6 (60%)
Anthropometrics and hemodynamics			
Height (cm)	158.2 ± 7.4	157.7 ± 9.7	160.8 ± 3.9
Body mass (kg)	77.8 ± 20.5	82.8 ± 22.3	86.2 ± 20.9
Body mass index (kg/m^2)	30.8 ± 6.9	32.9 ± 6.8	28.7 ± 6.3
Free fat mass (%)	43.7 ± 9.5	46.5 ± 8.9	40.8 ± 9.3
Free lean mass (%)	23.8 ± 4.1	22.7 ± 4.0	24.8 ± 3.9
Waist circumference, cm	95.9 ± 17.4	102.2 ± 17.9	89.6 ± 14.2
Resting systolic blood pressure (mmHg)	126 ± 19	119 ± 10	134 ± 23
Resting diastolic blood pressure (mmHg)	74 ± 5	74 ± 5	74 ± 6
Resting heart rate (bpm)	65 ± 8	67 ± 8	64 ± 5
Menstrual status (n, %)			
Perimenopausal stage -2	1 (5%)	1 (10%)	0 (0%)
3-6 years postmenopausal	3 (15%)	2 (20%)	1 (10%)
Late menopause	12 (60%)	6 (60%)	6 (60%)
Medications, n (%)			
Anticoagulant	4 (20%)	3 (30%)	1 (10%)
β-Blocker	11 (55%)	7 (70%)	4 (40%)
Statin	11 (55%)	6 (60%)	5 (50%)
Calcium antagonist	2 (10%)	1 (10%)	1 (10%)
ACE inhibitor	4 (20%)	3 (30%)	1 (10%)
Diuretic	5 (25%)	2 (20%)	3 (30%)
Aspirin	4 (20%)	2 (20%)	2 (20%)
Antidepressant	5 (25%)	3 (30%)	2 (20%)
Medical conditions, n (%)			
Hypertension	8 (40%)	4 (40%)	4 (40%)
Angina	1 (5%)	0 (0%)	1 (10%)
Prediabetes	2 (10%)	1 (10%)	1 (10%)
Type 2 diabetes	3 (15%)	2 (20%)	1 (10%)
Overweight/obese	10 (50%)	5 (50%)	5 (50%)
Heart failure	7 (35%)	4 (40%)	3 (30%)
Hypercholesterolemia	2 (10%)	2 (20%)	0 (0%)
Cardiomyopathy	9 (45%)	5 (50%)	4 (40%)

Heart block	9 (45%)	3 (30%)	7 (70%)
Coronary heart disease	3 (15%)	2 (20%)	1 (10%)
Valvular heart disease	3 (15%)	2 (20%)	1 (10%)
Anxiety	4 (20%)	2 (20%)	2 (20%)
Depression	6 (30%)	3 (30%)	3 (30%)
Sleep apnea	5 (50%)	2 (20%)	3 (30%)
Arrhythmias	12 (60%)	6 (60%)	6 (60%)

*Gender-based framework (GENESIS-PRAXY).[88,89] Abbreviations: ACE, angiotensin-converting enzyme; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training. [a] Indicates cardiac resynchronization therapy with defibrillator, [b] represents cardiac resynchronization therapy with pacemaker.

Feasibility outcomes

Exercise attendance and compliance

The exercise HRs and RPE at which the HIIT and MICT groups exercised throughout the interventions are presented in **Figure 5.2 and Figure 5.3**, respectively. All patients randomized to the HIIT group completed the exercise program. Most sessions were conducted individually (80%). On average, participants attended 21 ± 2 HIIT sessions (out of 24 sessions), with all patients (100%) completing ≥ 70% of the sessions. The mean HR at high-intensity intervals (target: 85%-95% peak HR) was 131 ± 15 bpm (range: 98-171 bpm), with a mean RPE of 'somewhat hard', 15 ± 2 (range: 11-17 points). Participants were able to meet (37%) or exceed (46%) the target HR ranges for the high-intensity intervals, while only a few participants met (36%) or exceeded (4%) the RPE targets. The mean HR at low-intensity intervals (target: 60%-70% peak HR) was 110 ± 14 bpm (range: 72-142 bpm), with a mean RPE of 'very light', 10 ± 2 points (range: 7-14 points). Participants met (17%, 53%) or exceeded (77%, 9%) the HR and RPE targets during the low intervals, respectively. On average, the feeling scale before starting the session was 'good', 3 ± 1 (range: fairly bad [-1], to very good [5]) and 'very good', 4 ± 1 (range: neutral [0] to very good [5]) at the end of the sessions.

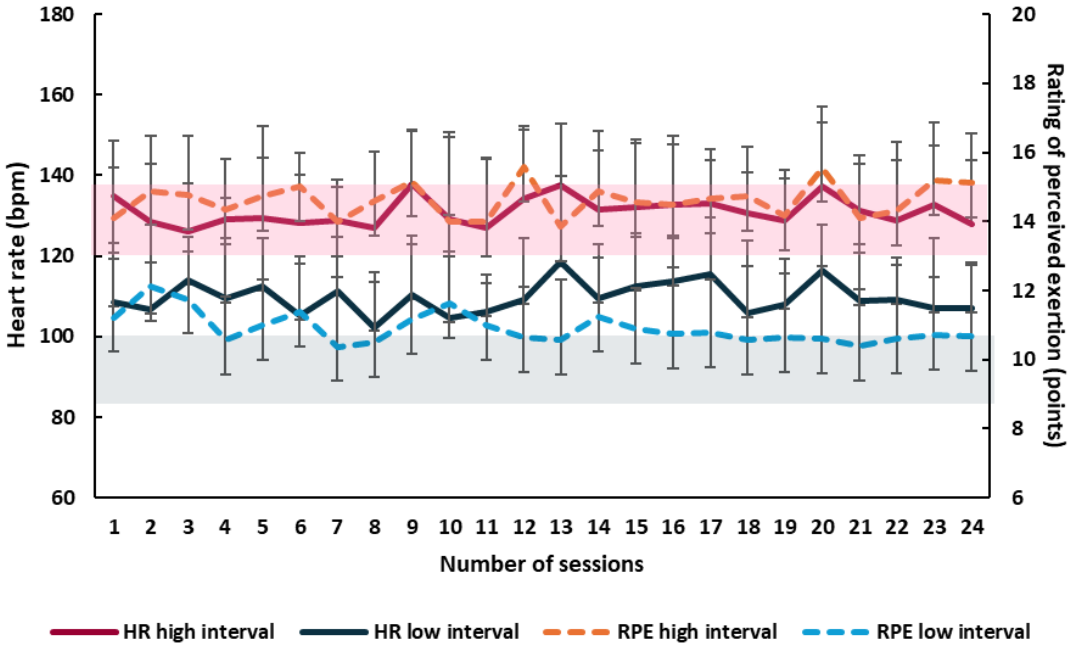


Figure 5.2. Heart rate (HR) and ratings of perceived exertion (RPE) during high-intensity and low-intensity intervals during high-intensity interval training (HIIT) across the 12-week training program (24 sessions). Values are plotted as means and standard deviations. The highlighted ranges in the figure represent the prescribed 85–95% (top) and 60-70% (bottom) of peak heart rate. Bpm, beats per minute.

Four participants randomized to the MICT group completed the intervention. Most sessions were performed individually (80%). On average, participants who completed the MICT program (n = 4) attended 23 ± 1 classes (out of 24 classes), with all (100%) patients completing ≥70% of the classes. Considering the completers (n = 4) and patients who dropped out after starting the intervention (n = 4), participants attended 15 ± 9 MICT classes (out of 24 classes), with a few patients (40%) completing ≥70% of the classes. Most participants met (68%, 76%) or exceeded (32%, 16%) the target HR and RPE ranges, respectively. The peak HR (target: 60%-70% peak HR) was 111 ± 7 bpm (range: 85-129 bpm), with a mean RPE of 'somewhat hard', 14 ± 2 points (range: 7-16). On average, the feeling scale at rest was around 'very good', 4 ± 1 (range: 'fairly bad' [-1], to 'very good' [5]) and 'very good', 5 ± 1 (range:

'fairly good' [1] to 'very good' [5]) at the end of the sessions.

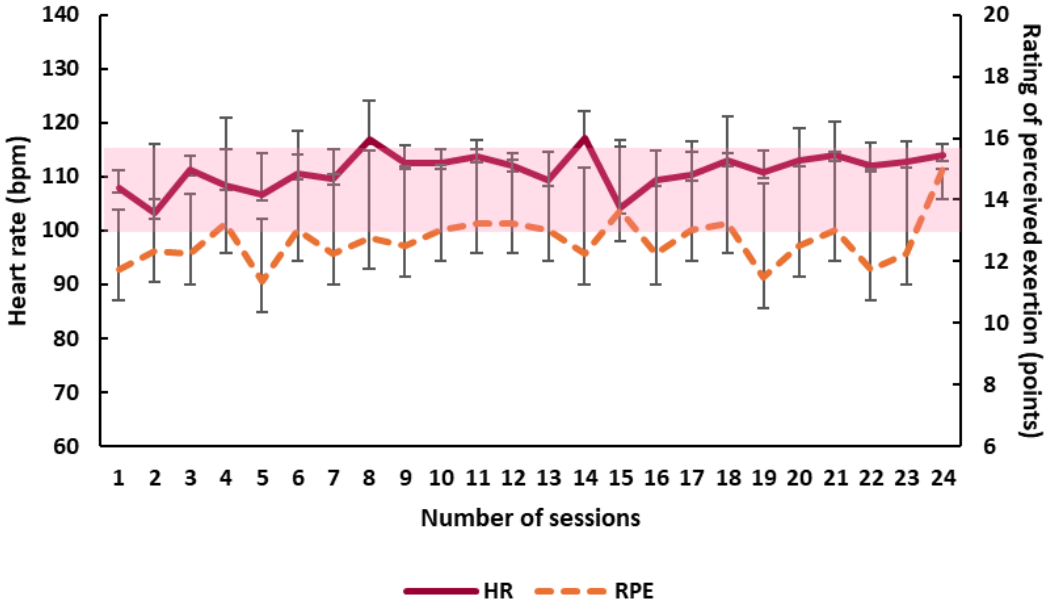


Figure 5.3. Heart rate (HR) and ratings of perceived exertion (RPE) during moderate-intensity continuous training (MICT) across the 12-week training program (24 sessions). The highlighted range in the figure represents the prescribed average of 70-85% of the peak heart rate. Values are plotted as means and standard deviations. Bpm, beats per minute.

Safety

No adverse events were observed during the CPETs. A total of 2 (0.95%) exercise-related adverse events (i.e., dizziness, hip replacement related) occurred during the 211 HIIT sessions vs. 1 (0.85%) in the 117 MICT sessions. No exercise shock therapy was observed in patients with ICDs during measurements or the interventions.

Patient experience

Descriptive data from the feedback questionnaire is presented in **Table S5.2** and responses from the open-ended questions are shown in **Table S5.3** in the **Supplemental Material**. In the HIIT group, the majority (80%) agreed or strongly agreed that the platform was easy to navigate (80%), and they felt safe exercising at home (80%). Most (75%) also perceived it as a convenient method to exercise and manage physical activity goals, and 70% indicated they would recommend it to others. Participants emphasized the supportive and interactive nature of the sessions - *"the interaction with the session moderator who provided ongoing feedback"* - and several reported gains in fitness and motivation, noting *"I feel that my fitness level did improve"* and *"I realized that I can accomplish it after my workdays."* Minor challenges included connectivity issues or losing the Zoom link (<10%) and suggestions for *"more variety in workouts"* and *"more engaging music."* In the MICT group, participants expressed positive perceptions of the online exercise platform. Most found it safe (70%), easy to navigate (75%), and convenient (70%), with 65% reporting that communication with instructors was helpful and supportive. Approximately 50% felt more motivated, confident, and knowledgeable about exercise after participation. Participants particularly appreciated the program's flexibility - *"I was impressed with the flexibility for the time and date the sessions could be without too much trouble"* - and the comfort of home-based training - *"So nice to be able to get everything out of the sessions, in my own home."* No major barriers were reported, though some suggested *"more upbeat music"* and *"more variety changes weekly."*

Secondary outcomes

Cardiorespiratory fitness

Changes in patients' $\dot{V}O_2$peak levels per individual and group (or device) are shown in **Figure 5.4**. Baseline and follow-up data were available for 10 patients in the HIIT group and 4 in the MICT group. For the HIIT group (n = 10), $\dot{V}O_2$peak at baseline, 6 weeks, and follow-up was 16.4 ± 4.0

(baseline), 16.4 ± 4.8 (week 6), and 16.9 ± 4.7 (follow-up) mL/kg/min, respectively. The change score between baseline and follow-up was 0.5 ± 2.0 mL/kg/min. Four participants (40%) met the MCID of 1.0 MET following HIIT. In absolute terms, $\dot{V}O_2$peak was 1.31 ± 0.3 (baseline), 1.35 ± 0.2 (week 6), and 1.35 ± 0.3 (follow-up) L/min, respectively. METs, total exercise duration, peak RPE, and peak HR at baseline, 6 weeks, and follow-up were 4.7 ± 1.1 (baseline), 4.7 ± 1.2 (week 6), and 4.3 ± 1.6 (follow-up) points; 10:15 ± 4:21 (baseline), 11:00 ± 4:09 (week 6), and 11:48 ± 4:27 (follow-up) min; 15.8 ± 1.8 (baseline), 17.5 ± 2.7 (week 6), and 16.6 ± 2.0 (follow-up) points; and 139.5 ± 16.4 (baseline), 139.9 ± 17.7 (week 6), and 140.6 ± 18.6 (follow-up) bpm, respectively.

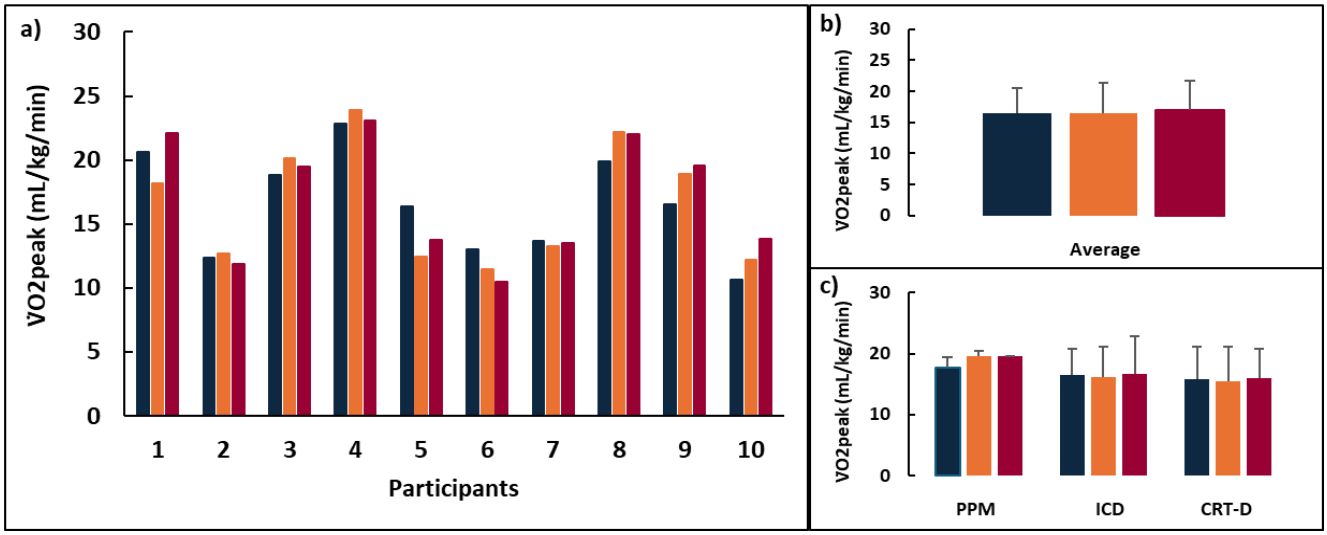


Figure 5.4. Peak oxygen volume ($\dot{V}O_2$peak) changes following high-intensity interval training. Values are plotted as means and standard deviations when possible. (a) Descriptive data are shown for each individual participant (n = 10). (b) Descriptive data are presented as the average across all participants. (c) Descriptive data are presented as the average by device type. PPM: permanent pacemaker. ICD: implantable cardioverter defibrillator. CRT: cardiac resynchronization therapy. Baseline, 6-week, and follow-up assessments are illustrated using blue, orange, and red bars, respectively.

For the MICT group, $\dot{V}O_2$peak at baseline (n = 10), 6 weeks (n = 5), and follow-up (n = 4) was 16.6 ± 4.4, 15.9 ± 2.1, and 16.9 ± 12.9 mL/kg/min, respectively. When considering only participants who completed the MICT intervention (n = 4), $\dot{V}O_2$peak at baseline, 6 weeks and follow-up was 14.6 ± 4.3 (baseline), 18.2 ± 4.7 (Week 6), and 16.9 ± 2.9 (follow-up) mL/kg/min, respectively. The change score between baseline and follow-up was 2.2 ± 2.7 mL/kg/min. Three patients (33%) met the MICD (1.0 MET) following MICT. In absolute terms, $\dot{V}O_2$peak was 1.17 ± 0.2 (baseline), 1.2 ± 0.2 (week 6), and 1.4 ± 0.3 (follow-up) L/min, respectively. METs, total exercise duration, peak HR, and peak RPE at baseline, 6 weeks, and follow-up were 4.3 ± 1.5 (baseline), 4.5 ± 0.6 (week 6), and 4.8 ± 0.8 (follow-up) points; 10:43 ± 4:31 (baseline), 10:13 ± 3:25 (week 6), and 11:00 ± 3:39 (follow-up) min; 18.8 ± 1.7 (baseline), 16.8 ± 0.8 (week 6), and 18.0 ± 1.4 (follow-up) points; and 130.4 ± 17.7 (baseline), 133.0 ± 15.6 (week 6), and 133.2 ± 17.6 (follow-up) bpm, respectively.

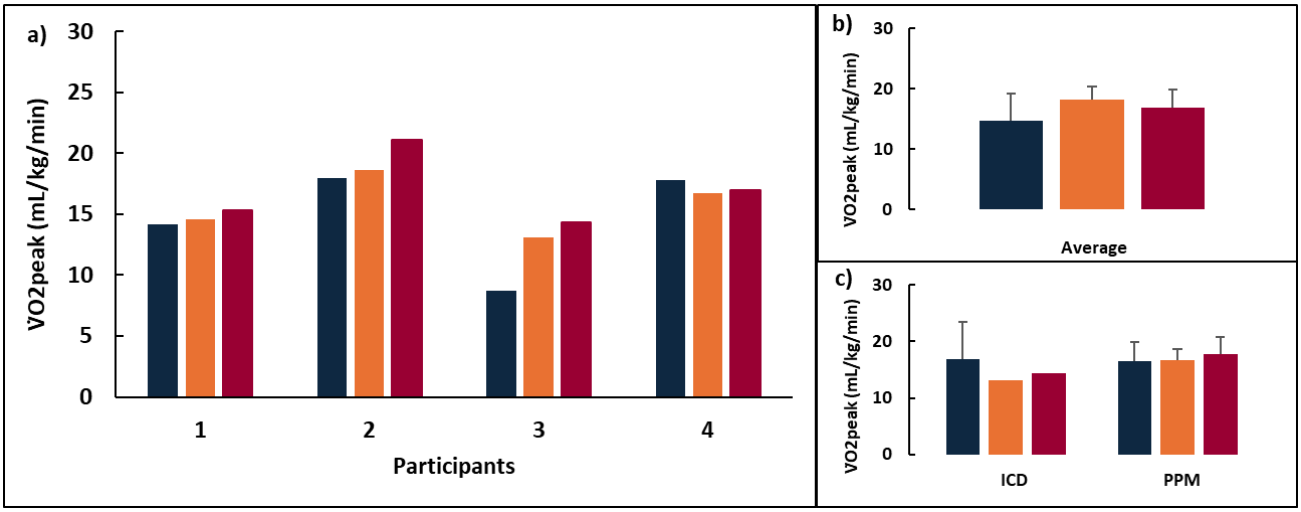


Figure 5.5. Peak oxygen volume ($\dot{V}O_2$peak) changes following moderate-intensity continuous training. Values are plotted as means and standard deviations when possible. (a) Descriptive data are presented as the individual data per participant (n = 4). (b) Descriptive data are presented as the average across all participants. (c) Descriptive data are presented as the average per type of device. PPM: permanent pacemaker. ICD: implantable cardioverter defibrillator. Baseline, 6-week, and follow-up assessments are illustrated using blue, orange, and red bars, respectively.

Additional secondary outcomes

Changes in patients' mental health, general quality of life, cardiometabolic health indicators, physical activity levels, exercise motivation, confidence and enjoyment, and gender scores are shown in **Table 5.2**. In the HIIT group, 3 (30%) participants achieved the MCID for anxiety and 4 (40%) for depression, whereas no participants in the MICT group reached these thresholds. Two (20%) participants in the HIIT group and 3 (33%) in the MICT group reached the MCID for the Physical Component Summary, whereas 2 (20%) in the HIIT group and one (25%) in the MICT group reached the MCID for the Mental Component Summary. Four (40%) participants in HIIT and 4 (40%) in MICT met the Canadian 24-hour Movement Guidelines[73] of ≥150 min/wk at baseline, and 4 patients (40%) in the HIIT group and one (25%) at follow-up.

Table 5.2. Participants' physical and mental health at baseline and follow-up.

	HIIT			MICT		
	Baseline (n=10)	**Follow-up (n=10)**	**Change**	**Baseline (n =10)**	**Follow-up (n=4)**	**Change**
Mental health						
Anxiety, points (GAD-7)	4.0 ± 2.4	2.6 ± 2.3	-1.4 ± 2.6	2.7 ± 2.8	0.5 ± 1.0	-0.2 ± 0.5
Depression, points (PHQ-9)	7.0 ± 3.9	4.9 ± 4.0	-2.3 ± 3.2	1.5 ± 1.7	2.0 ± 2.4	1.0 ± 1.4
General quality of life (SF-36)						
Physical functioning, points	46.7 ± 7.8	48.2 ± 7.8	1.3 ± 4.9	48.7 ± 3.1	53.4 ± 3.7	5.4 ± 2.8
RL–physical health, points	42.9 ± 12.6	46.6 ± 12.9	2.2 ± 19.1	48.9 ± 7.8	46.3 ± 14.0	7.4 ± 8.5
Bodily pain, points	38.0 ± 6.5	32.7 ± 5.2	-5.0 ± 9.0	37.1 ± 8.6	37.3 ± 4.6	2.4 ± 10.2
General health, points	38.4 ± 8.2	35.7 ± 8.9	-3.9 ± 7.9	34.3 ± 12.0	38.9 ± 12.1	6.2 ± 6.5
Vitality, points	46.6 ± 7.4	45.6 ± 10.1	-2.6 ± 8.7	48.7 ± 9.4	55.4 ± 6.9	7.1 ± 10.8
Social functioning, points	47.8 ± 10.9	43.9 ± 11.8	-4.4 ± 10.7	49.8 ± 9.7	55.4 ± 6.9	1.4 ± 5.3
RL–emotional problems, points	46.5 ± 13.3	43.5 ± 12.4	0.0 ± 12.5	47.8 ± 13.1	48.0 ± 9.6	-5.0 ± 5.8
Mental health, points	47.0 ± 9.4	46.6 ± 12.2	-0.6 ± 5.4	48.4 ± 13.4	59.5 ± 5.4	0.0 ± 10.8
Physical Component Summary, points	41.2 ± 5.2	40.9 ± 7.9	-1.1 ± 8.1	40.1 ± 4.9	41.8 ± 8.3	8.4 ± 4.9
Mental Component Summary, points	47.3 ± 12.0	45.6 ± 14.5	-2.1 ± 8.8	58.7 ± 3.9	56.9 ± 5.6	-2.6 ± 7.5
Cardiometabolic health indicators						
Body mass index (kg/m^2)	32.9 ± 6.8	32.9 ± 6.5	0.0 ± 1.0	28.7 ± 6.3	32.3 ± 6.2	-0.8 ± 0.8
Free fat mass (%)	46.5 ± 8.9	47.0 ± 7.9	0.7 ± 1.7	40.8 ± 9.3	45.1 ± 6.5	-1.4 ± 2.1
Free lean mass (%)	22.4 ± 4.0	22.3 ± 3.2	-0.4 ± 1.2	24.8 ± 3.9	23.2 ± 1.8	0.4 ± 1.4

Waist circumference, cm	102.2 ± 17.9	101.2 ± 17.3	0.1 ± 3.7	89.6 ± 14.2	96.0 ± 8.5	0.1 ± 5.1
Resting systolic blood pressure (mmHg)	119 ± 10	118 ± 9	-1.0 ± 12	134 ± 23	148 ± 9	-15.4 ± 7.2
Resting diastolic blood pressure (mmHg)	74 ± 5	73 ± 6	-0.07 ± 5.5	74 ± 6	75 ± 10	-1.9 ± 8.2
Resting heart rate (bpm)	67 ± 8	65 ± 5	-2.2 ± 4.3	64 ± 5	65 ± 6	0.8 ± 4.7
Physical activity levels						
Light (min/wk)	1,725.9 ± 784.7	1,696.7 ± 779.4	-29.2 ± 312.6	1,852.1 ± 405.3	1,930.5 ± 212.8	-307.0 ± 302.5
Moderate (min/wk)	159.1 ± 150	164.1 ± 167.5	5.0 ± 101.1	162.3 ± 98.4	103.2 ± 42.9	-61.5 ± 54.6
Vigorous (min/wk)	4.2 ± 6.6	8.4 ± 18.9	2.1 ± 6.3	0.5 ± 0.9	2.0 ± 2.3	0.88 ± 1.24
MVPA (min/wk)	163.3 ± 155.7	172.5 ± 179.5	9.2 ± 104.1	162.8 ± 98.5	105.2 ± 43.2	-51.0 ± 58.3
Exercise behaviour						
Motivation (BREQ-3, score: −24-20)	12.2 ± 6.8	10.6 ± 5.2	-1.5 ± 6.3	14.4 ± 7.5	16.1 ± 5.7	-2.4 ± 6.1
Self-efficacy (MSES, score: 0-100%)	76.2 ± 16.1	71.3 ± 20.3	-4.8 ± 13.3	80.3 ± 7.3	82.9 ± 6.7	0.8 ± 7.8
Enjoyment (PACES, score: 18-126)	62.0 ± 6.3	61.8 ± 9.0	-0.2 ± 8.9	61.1 ± 7.9	58.2 ± 5.0	-1.0 ± 4.5
Gender scores (TMF, score: 1-7)	5.6 ± 0.7	5.5 ± 0.9	-0.1 ± 0.7	5.9 ± 0.8	6.5 ± 0.8	0.5 ± 0.8

Data presented in mean ± standard deviation. Abbreviations: RL, role limitations. BREQ-3: Behavioral Regulation in Exercise Questionnaire; GAD-7: Generalized Anxiety Disorder; MSES: Multidimensional Self-Efficacy for Exercise Scale; PACES: Physical Activity Enjoyment Scale; PHQ-9: Patient Health Questionnaire; TMF: Traditional Masculinity–Femininity Scale.

5.5 Discussion

This is the first study to assess the feasibility as defined by exercise adherence, compliance, safety, and patients' experiences of virtually delivered and supervised HIIT and MICT in women with CIEDs. Virtual HIIT was feasible for women with CIEDs; all participants completed the intervention. Caution is needed for virtual MICT, as only 40% of patients completed the program, and therefore, MICT was not feasible in women with CIEDs. Importantly, less than 1% of adverse events occurred in HIIT and MICT. Participants felt safe and reported positive experiences with both exercise programs. Changes in secondary outcomes (i.e., CRF, mental health, quality of life, physical activity levels, exercise behaviour, gender) were provided descriptively, to inform the design of a larger efficacy trial.

Feasibility

In this women-focused study, the HIIT program was proved feasible for those with different types of CIEDs, with no serious adverse events reported and overall positive feedback. Most participants achieved the target HR but did not fully return to the prescribed HR during recovery periods. Elevated hemodynamic responses during recovery periods in HIIT is explained by a lag in $\dot{V}O_2$ and HR responses given the continue stress on the cardiovascular system, where HR during recovery can still reflect the preceding high-intensity bout.[90,91] It is also possible that peak HR achieved during CPET did not reflect patient's true maximal effort, resulting in patients exercising at a higher intensity during sessions than prescribed. CPET has limitations as patients may present fear or discomfort with the treadmill, early peripheral fatigue, chronotropic incompetence, or reach the CIED safety zones, which may affect the accuracy of peak HR-based exercise prescription.[51] For these reasons, a combination of objective (i.e., HR) and subjective (i.e., RPE) measures are recommended to prescribe and monitor exercise intensity during HIIT in the cardiac population.[50] We prioritized meeting HR zones, as RPE is subjective and may be perceived differently by patients. RPE is a recommended tool to support exercise prescription in patients with heart failure and arrhythmias, including those who alternate between sinus rhythm and atrial fibrillation, which

can be similarly applied to individuals with CIEDs.[65] Most participants did not reach RPE targets during high-intensity and low-intensity intervals. Possible reasons for the low RPE compliance include exercising at a lower intensity than prescribed, not fully comprehending the RPE scale, and perceiving HIIT as challenging.[52] Overall, our results are supported by Way et al (2020) demonstrating that women with coronary artery disease (n = 50) exceeded HR targets at high (29%) and low-intervals (40%) intervals, and did not comply with RPE prescription at high-intensity intervals (58%) and low-intensity (66%) in HIIT.[52] Most of these women perceived HIIT as difficult and the sessions as challenging, while also reporting high satisfaction with the intervention. Understanding participants' experiences with HIIT may represent an important next step for patients with CIEDs, as it could help explain observed physiological responses to HR and RPE targets. However, given the feasibility design of the present study, we prioritized evaluating participants' experiences with the online platform. Notably, 45% of participants reported feeling safe at all times while exercising at home, and 80% strongly agreed that the trainer's presence was helpful. These findings suggests that synchronous, supervised HIIT delivered remotely is feasible and safe within CR settings for women with CIEDs.[92]

The feasibility of virtual MICT in women with CIEDs requires further examination prior to a larger trial, given the lack of feasibility. Two participants randomized to MICT withdrew before the intervention began. Their withdrawal cannot therefore not be entirely attributed to the characteristics of the exercise intervention. The reasons for dropout during the MICT intervention (i.e., burden with study measurements, dislike of program settings, pain during sessions) aligns with previous findings in CR among women with cardiovascular disease, where common barriers such as program characteristics, exercise component, family responsibilities, and comorbidities.[93,94] Specifically, one participant who withdrew was young (30y) and found the program 'boring', while an older adult (68y) experienced hip pain during the sessions. Younger patients report higher dropout rates compared to older individuals following CR and may prefer more challenging activities.[24,95,96] On the contrary, older adults have more comorbidities, with musculoskeletal issues

disproportionately affecting women.[97] In addition, we observed that approximately a third of women exceeded (32%) the target HR ranges for MICT program, indicating that participants exercised at a higher HR zone. Similar results were observed in the SAINTEX-CAD trial, where the 12-week MICT program in patients with coronary artery disease (n = 200; 10% women) exceeded the intended 70%–75% peak HR, limiting conclusive comparisons with HIIT. [98] Taken together, these results highlight opportunities for refinement to the MICT intervention and study procedures.

Lessons learned from MICT can help to optimize future research designs. Exercise sessions can be adapted to the target population, including tailored video-based content and movements adapted to participants' age range and comorbidities. Incorporating an educational component at baseline may also reduce dropout by clarifying study procedures (e.g., HR monitoring), setting expectations for the exercise format (e.g., video-based delivery), and addressing potential challenges (e.g., musculoskeletal concerns) without introducing bias to programs. Moreover, staff close monitoring and consistent feedback is important, ensuring participants stay within their prescribed intensity zones. Recommendations should preserve the program's supportive elements, as participants reported positive perceptions of safety (70%), ease of navigation (75%), and convenience (70%), and helpful communication with instructors (65%). Findings underscore the challenges associated with the feasibility MICT, which remains the standard of care in CR.

The present study may help to inform sample size calculations for future trials based on our secondary outcomes. We observed a more pronounced change in $\dot{V}O_2$peak following MICT, while a greater change in the total duration of the CPET was observed following HIIT. A direct comparison between these modalities has never been investigated in patients with CIEDs. Previous studies have shown that both exercise modalities were effective in improving $\dot{V}O_2$peak in predominantly male samples of patients with ICDs and CRT-Ds (MICT: 14.8± 2.5 to 18.9 ±2.7; HIIT: 17.4 ± 4.6 to 18.4 ± 5.3).[99,100] In contrast, two randomized trials (≤25% women) showed that HIIT did not significantly improve $\dot{V}O_2$peak but increased total CPET duration (372 ± 56 to 548 ± 50s) and peak workload (109 ± 45 to 118 ± 44 W) among adults with CRTs.[48,101] It is possible that

HIIT enhanced exercise performance variables rather than $\dot{V}O_2$peak alone. Studies investigating sex-differences in CRF have shown that women demonstrated lower hemodynamic responses (e.g., stroke volume, cardiac output, and hemoglobin concentration), but greater peripheral (e.g., increased mitochondrial enzyme activity, capillary density) and metabolic adaptations to HIIT (e.g., delayed lactate accumulation, greater fat oxidation, enhanced resynthesis of ATP).[102–104] These adaptations may improvement anaerobic pathways and exercise tolerance even when maximal aerobic capacity remains unchanged. Current evidence is, however, largely based on healthy adults, and studies in women with cardiovascular disease who may present unique physiological considerations (e.g., chronotropic incompetence, beta-blockers medications) remain scarce, highlighting the need for more research to understand HIIT mechanisms.

The changes in mental health, quality of life, and cardiometabolic health indicators were modest between groups. Patients reported mild levels of anxiety and depression at baseline and follow-up in both groups, with only a few patients in HIIT reaching clinically meaningful improvements and none in MICT. Patients in the HIIT group had higher levels of anxiety and depression at baseline, which could be explained by the greater number of patients with ICDs randomized to HIIT - women with defibrillator therapy are known for higher levels of anxiety and depression.[8] Further, the HIIT group presented with lower quality of life scores compared to the MICT group at follow-up. The COPE-ICD trial (n = 196 patients with ICDs; 21% women) revealed no significant differences among women in the physical (36.3 ± 9.9 to 46.8 ± 12.1 points) and mental (46.2 ± 11.9 to 52.2 ± 8.6 points) component summary scores of the SF-36 following a 12-week CR (MICT) program.[12] In a matched case-control study of 60 women with cardiovascular disease, Reed et al (2019) found that a 10-week dance-based HIIT and MICT program improved anxiety (HIIT: -1.8 ± 3.5; MICT: -1.5 ± 3.0 points, $P < 0.001$) and depression (HIIT: -0.7 ± 3.0; MICT: -1.1 ± 2.3 points, $P= 0.003$) scores, with no significant differences between these exercise modalities.[29] Additional significant reductions in body mass index (HIIT -0.4 ± 1.2; MICT: -0.2 ± 0.7 kg/m^2) and waist circumference (HIIT: -4.4 ± 7.4; MICT: -2.3 ± 4.7 cm, $P = 0.001$) were also

observed, which contrasts with the direction of changes observed in this study. Participants in this study were classified as obese at baseline and follow-up in both groups and were mostly postmenopausal. Obesity is a complex condition associated with poorer psychosocial health, greater cardiometabolic burden, and smaller gains in perceived physical health.[105] In addition, postmenopausal women have a lower resting metabolic rate, decrease in total energy expenditure, and reduced fat oxidation during exercise.[106] More intensive weight management strategies in CR have been suggested, including HIIT.[107] A meta-analysis assessing the effects of HIIT in body composition in women (n = 38 trials, 959 women) showed that HIIT interventions lasting ≥8 weeks and comprising three sessions per week reduced total and intra-abdominal fat mass in postmenopausal women, raising the question of whether higher exercise frequencies may be required to achieve comparable benefits in women with CIEDs.[108] As conclusions cannot be drawn from secondary outcomes, we emphasize the importance of integrating educational CR components into exercise-based interventions to support more patient-centred, comprehensive care.

Approximately 40% of participants across the HIIT and MICT groups reported high moderate-to-vigorous physical levels at baseline; this proportion is comparable with a recent observational study demonstrating that 38% of Canadian women with cardiovascular disease (n = 173) met the national moderate-to-vigorous physical levels (accelerometer-measured) recommendations of ≥150 min/wk.[109] Although our eligibility criteria excluded patients enrolled in structured exercise twice a week, it is possible that women were relatively fit at baseline, given their physically demanding full-time job positions (e.g., paramedic), or presented with volunteer bias (i.e., misrepresented baseline physical activity levels) to participate in an exercise trial.[110,111] An active sample at baseline may blunt changes in outcomes, and a sub-analysis by fitness categories would be appropriate in outcomes of interest in future trials. In addition, we did not restrict any activities outside the program, it is possible that some participants engaged in other physical activities throughout the intervention. The abovementioned factors may influence intervention effects and should be carefully considered in the design and interpretation of future exercise trials in

women with CIEDs.

Literature examining theoretical constructs in patients with CIEDs is scarce, making it difficult to contrast with our results. Participants reported generally positive affective responses before and after each session - ranging from “good” to “very good” on the Feeling Scale. Motivation and self-efficacy seemed to decrease in HIIT and increase in MICT at follow-up, while enjoyment slightly decreased across time for both groups. Evidence suggests that the greater perceived challenge of HIIT may reduce participants’ confidence in sustaining exercise intensity, whereas the more manageable nature of MICT may reinforce self-efficacy.[33] Conversely, other studies have shown that completing the repeated bouts of HIIT is associated with improvements in self-efficacy,[52] emphasizing the need for additional research in this field. Furthermore, patients’ feedback also highlighted the need for greater variety in exercise sessions. Reduced novelty and engagement over time contribute to the decline in enjoyment, a phenomenon frequently observed in structured exercise programs.[112] Importantly, despite the opportunities for question and answer period after sessions, individual sessions and virtual format limited opportunities for social interactions, which are known to enhance motivation, enjoyment, and perceived competence in CR.[20] Blanchard and colleagues (2007) found that women improved self-efficacy (3.69 ± 1.36 to 4.24 ± 1.35 points) during CR participation, though its association with physical activity levels weakened post CR, suggesting that confidence to overcome barriers may decline over time.[113] Thus, longer-term interventions may be needed to sustain psychological adaptation. Finally, a small shift toward more traditionally masculine self-perceptions was observed in the MICT group, indicating enhanced feelings of competence, control, and mastery, while the HIIT group remained stable. These subtle changes suggest that experiences in MICT may have strengthened confidence and autonomy - key mediators of motivation and long-term exercise adherence.[114] Taken together, these findings suggest that HIIT and MICT may differentially influence self-efficacy, motivation, enjoyment, and gender traits, and should be considered in the design of studies in women with CIEDs.

Limitations

This study has limitations. The open-label design may have introduced performance and detection bias due to lack of blinding, however, this is a challenge of non-pharmaceutical trial including participative interventions.[115] To support a robust intervention delivery, we used methods to reduce selection (e.g., randomization), performance (e.g., separate groups and trainers), detection (e.g., objective and validate assessments), attrition (e.g., standardize timepoints, participant completion packages), and reporting (e.g., predefined outcomes in the protocol) bias in the study.[116] Participants were recruited from a single-centre, and were mostly white and well-educated, which may not represent the broader population of women living with CIEDs. Another limitation is the heterogeneity of the sample, as participants had different types of CIEDs and underlying indications for device implantation, which may have introduced variability in responses to the intervention. Because some MICT participants exercised at the higher end of their 70%- 85% peak HR exercise prescription range, this may have affected change scores in physical and mental health outcomes between the HIIT and MICT groups, which could diminish the ability to detect group differences in efficacy trials. The effects of additional interventions cannot be excluded, as some participants may have engaged in other forms of exercise outside the prescribed program during the intervention period. The absence of a control group limits the understanding of the differences between exercise modalities and standard care which typically includes optimal medical therapy without a structured exercise intervention in CIED trials.[48] However, because MICT is an established component of traditional CR for individuals with cardiovascular disease, we considered that it would be unethical to not offer standard care due to its well-known benefits.

Future directions

Overall, continued recruitment in this pilot study to a target sample of 40 women (20 per group; consistent with recommendations for pilot study sample sizes of 20–40), would allow refinement of feasibility outcomes (i.e., current MICT limitations were mostly attributed to non-intervention related factors), improve precision of secondary outcome estimates, and inform

progression to a fully powered efficacy trial.[84] Specifically, future trials could consider (1) efforts to ensure a diverse sample (e.g., accessible and multilingual recruitment material); (2) a complementary functional exercise capacity test (e.g., incremental shuttle walk test, 6-minute walk test) addressing CPET limitations observed;[117,118] (3) stratified randomization by CIED type; (4) implement strategies to monitor and control for additional exercise participation (e.g., weekly/monthly activity logs) to minimize potential contamination with the program, and, (5) offering more variety in dance-based routines and flexibility with scheduling appointments and sessions. Finally, replication of this study at other sites is needed to confirm our feasibility findings.

5.6 Conclusions

The findings from this pilot randomized clinical trial reveal that 12-week virtual HIIT was well attended and safe in women with CIEDs, while MICT was not feasible given high drop-out rates. We provided recommendations for future trials exploring dance-based virtual formats, as well as descriptive data on a comprehensive array of secondary outcomes investigating physical and mental health, quality of life, and determinants of exercise behaviour in women with CIEDs. These results provide essential parameters for powering and implementing a future full-scale efficacy trial examining virtually delivered exercise in women with cardiac CIEDs.

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Table S5.1. Secondary outcomes at baseline and follow-up.

	HIIT		MICT	
	Baseline (n = 10)	**Follow-up (n = 10)**	**Baseline (n = 10)**	**Follow-up (n = 4)**
Cardiorespiratory fitness				
$\dot{V}O_2$peak (ml/kg/min)	16.4 (13.0-19.9)	16.6 (13.5-22.0)	15.9 (8.7-17.9)	16.1 (14.3-21.0)
VO_2peak (L/O_2/min)	1.3 (0.9-1.5)	1.4 (1.1-1.6)	1.2 (0.8-1.5)	1.4 (0.9-1.7)
METs	4.7(3.7-5.7)	4.0 (3.2-5.6)	4.5 (2.5-5.1)	4.6(4.1-6.0)
Total time duration (min)	9.0 (6.0-14.0)	13.0 (7.0-14.0)	9.0 (5.0-15.0)	11.0 (7.0-15.0)
RPE peak (points)	15.0 (14.0-17.0)	16.0 15.0-18.0)	16.0 (15.0-17.0)	17.5 (17.0-20.0)
HR peak (bpm)	140.0 (130.0-150.0)	137.5 (127.0-154.0)	134.0 (120.0-150.0)	132.0 (113.0-156.0)
Mental health				
Anxiety, points (GAD-7)	1.0 (0.0-4.5)*	0 (0.0-2.5)*	3.0 (1.0-5.0)	3 (1.0-5.0)
Depression, points (PHQ-9)	3.0 (1.0-7.0)	2.0 (0.0-5.5)	6.0 (4.0-12.0)	4.0 (3.0-7.0)*
General quality of life (SF-36)				
Physical functioning	43.7 (38.2-54.6)	45.8 (40.4-56.8)	51.3 (45.8-52.4)	54.6 (48.0-56.8)
RL–physical health	40.8 (29.7-55.6)*	55.6 (26.0-55.6)*	51.9 (40.8-55.6)	51.9 (26.0-55.6)
Bodily pain	35.4 (33.7-44.7)*	32.4 (27.3-35.4)	33.6 (27.3-39.6)*	35.2 (34.9-44.3)
General health	39.0 (26.7-45.2)	34.0 (27.9-46.4)	38.9 (29.1-48.9)	41.5 (24.1-48.9)
Vitality	44.7 (38.7-53.1)	39.9 (36.3-54.3)	54.3 (49.5-61.5)	55.5 (47.1-63.9)
Social functioning	51.7 (35.1-57.3)*	40.6 (35.0-57.3)	57.3 (46.2-57.3)*	54.5 (46.2-57.3)
RL–emotional problems	35.5 (25.4-55.7)*	45.6 (25.4-55.7)	55.7 (45.6-55.7)*	50.7 (35.5-55.7)
Mental health	50.6 (35.2-55.1)	44.0 (32.9-59.5)	59.5 (44.0-64.0)	60.7 (52.9-64.0)
Physical Component Summary	40.2 (35.6-47.1)	43.8 (30.2-45.4)	40.9 (34.3-44.5)*	45.9 (29.3-46.3)
Mental Component Summary	53.9 (27.9-56.4)	48.3 (32.2-62.2)*	58.9 (54.1-63.1)	56.7 (50.9-63.7)
Cardiometabolic health indicators				
Body mass index (kg/m^2)	31.3 (28.4-39.9)	30.9 (28.6-39.4)	34.8 (23.4-39.3)	34.2 (22.6-38.1)
Free fat mass (%)	48.7 (43.2-54.2)	49.0 (43.6-54.4)	49.6 (35.2-52.0)	45.9 (36.0-52.8)

Free lean mass (%)	21.2 (19.7-24.0)	20.6 (19.6-23.8)	22.2 (20.8-26.1)	23.4 (20.5-25.5)
Waist circumference, cm	96.4 (91.3-127.3)	98.0 (88.5-128.8)	99.1 (75.0-110.3)	98.1 (83.0-105.1)
Resting systolic blood pressure (mmHg)	117.7 (113.3-132.0)	114.3 (111.0-125.0)*	152.0 (101.0-177.3)	150.5 (134.0-158.7)
Resting diastolic blood pressure (mmHg)	77.3 (72.0-79.0)*	74.3 (68.7-78.0)	78.5 (74.3-80.0)	75.2 (62.3-91.0)
Resting heart rate (bpm)	65.0 (60.5-75.2)	63.7 (60.3-70.5)	64.7 (57.0-70.7)	62.5 (59/7-75.7)
Physical activity levels				
Light (min/wk)	2,090.0 (453.0-3,165.0)	2,006.0 (621.0-2,950.0)	1,950.0 (1196.0-2,584.0)	1,562.0 (909.0-2,766.0)
Moderate(min/wk)	37.0 (24.0-378.0)	56.0 (36.0-430.0)	213.0 (25.0-385.0)	147.0 (31.0-533.0)
Vigorous (min/wk)	1.0 (1.0-22.0)*	0.0 (0.0-44.0)*	2.0 (1.0-11.0)*	2.0 (1.0-10.0)*
MVPA (min/wk)	380.0 (250.0-400.0)	56.0 (36.0-492.0)	157.0 (47.0-260.0)	149.0 (32.0-541.0)
Exercise behaviour				
Motivation (BREQ-3, score: −24-20)	15.0 (9.0-21.0)	10.0 (4.0-13.0)	14.0 (4.0-17.5)	16.0 (10.0-21.0)
Self-efficacy (MSES, score: 0-100%)	78 (66.7-82.4)	88.0 (72.0-91.0)	82.0 (72.0-94.0)	61.0 (52.0-92.0)
Enjoyment (PACES, score: 18-126)	58.0 (54.0-63.0)	55.0 (54.0-64.0)*	63.0 (59.0-69.0)	64.0 (56.0-68.0)
Gender (TMF, score: 1-7)	6.0 (5.0-7.0)*	7.0 (5.0-7.0)*	6.0 (5.0-6.0)*	6.0 (5.0-6.0)*

Data is presented in median and 95% confidence interval.* indicates non-parametric data.

Table S5.2. Feedback questionnaire.

	Total (n=20)	**HIIT (n=10)**	**MICT (n=4)**
If/when I had questions related to navigating the online platform I was able to get them answered.	Strongly disagree: 2 (10%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 3 (15%) Strongly agree: 9 (45%) Prefer not to answer: 0 (0%)	Strongly disagree: 2 (20%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 2 (20%) Strongly agree: 6 (60%) Prefer not to answer: 0 (0%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 2 (20%) Strongly agree: 2 (20%) Prefer not to answer: 0 0(%)
I found the online platform easy to navigate.	Strongly disagree: 2 (10%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 4 (20%) Strongly agree: 8 (40%) Prefer not to answer: 0 (0%)	Strongly disagree: 2 (20%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 2 (20%) Strongly agree: 6 (60%) Prefer not to answer: 1 (5%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 2 (20%) Strongly agree: 2 (20%) Prefer not to answer: 0 (0%)
The online platform provides a convenient method for me to exercise, understand my heart health, and manage my physical activity goals.	Strongly disagree: 2 (10%) Disagree: 0 (0%) Neutral: 1 (5%) Agree: 3 (15%) Strongly agree: 8 (40%) Prefer not to answer: 0 (0%)	Strongly disagree: 2 (20%) Disagree: 0 (0%) Neutral: 1 (10%) Agree: 2 (20%) Strongly agree: 5 (50%) Prefer not to answer: 0 (0%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 1 (10%) Strongly agree: 3 (30%) Prefer not to answer: 0 (0%)
I felt safe at all times while exercising at home when participating in the online platform.	Strongly disagree: 2 (10%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 3 (15%) Strongly agree: 9 (45%) Prefer not to answer: 0 (0%)	Strongly disagree: 2 (20%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 2 (20%) Strongly agree: 6 (60%) Prefer not to answer: 0 (0%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 1 (10%) Strongly agree: 3 (30%) Prefer not to answer: 0 (0%)
I found the following features on the online platform to be useful in supporting me to exercise and manage my physical activity goals:			
Private chats.	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 2 (10%) Agree: 3 (15%) Strongly agree: 8 (40%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 1 (10%) Agree: 2 (20%) Strongly agree: 6 (60%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 1 (10%) Agree: 1 (10%) Strongly agree: 2 (%) Prefer not to answer: 0

	Prefer not to answer: 1 (5%)	Prefer not to answer: 0 (0%)	(0%)
Ability to communicate with the instructor(s) following each session.	Strongly disagree: 0 (%) Disagree: (0%) Neutral: 1 (5%) Agree: 3 (15%) Strongly agree: 10 (50%) Prefer not to answer: 0 (0%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 2 (20%) Strongly agree: 8 (80%) Prefer not to answer: 0 (0%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 1 (10%) Agree: 1 (10%) Strongly agree: 2 (20%) Prefer not to answer: 0 (0%)
Ability to communicate with other patients following each session.	Strongly disagree: 1 (5%) Disagree: 0 (0%) Neutral: 8 (40%) Agree: 1 (5%) Strongly agree: 1 (5%) Prefer not to answer: 3 (15%)	Strongly disagree: 1 (10%) Disagree: 0 (0%) Neutral: 5 (50%) Agree: 1 (10%) Strongly agree: 1 (10%) Prefer not to answer: 0 (0%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 3 (30%) Agree: 0 (%) Strongly agree: 0 (%0) Prefer not to answer: 1 (10%)
I feel more motivated to exercise after engaging in the online platform for exercise training.	Strongly disagree: 1 (5%) Disagree: 0 (0%) Neutral: 3 (15%) Agree: 4 (20%) Strongly agree: 5 (25%) Prefer not to answer: 0 (0%)	Strongly disagree: 1 (10%) Disagree: 0 (0%) Neutral: 1 (10%) Agree: 5 (50%) Strongly agree: 3 (30%) Prefer not to answer: 0 (0%)	Strongly disagree: 0 (10%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 3 (30%) Strongly agree: 1 (10%) Prefer not to answer: 0 (0%)
I feel more knowledgeable about physical activity after engaging in the online platform for exercise training.	Strongly disagree: 1 (5%) Disagree: 1 (5%) Neutral: 3 (15%) Agree: 4 (20%) Strongly agree: 5 (25%) Prefer not to answer: 0 (0%)	Strongly disagree: 1 (10%) Disagree: 1 (10%) Neutral: 2 (20%) Agree: 2 (20%) Strongly agree: 2 (20%) Prefer not to answer: 4 (40%)	Strongly disagree: 0 (0%) Disagree: 0 (0%) Neutral: 1 (10%) Agree: 2 (20%) Strongly agree: 1 (10%) Prefer not to answer: 0 (0%)
I feel more confident in my ability to exercise after engaging in the online platform for exercise training.	Strongly disagree: 1 (5%) Disagree: 1 (5%) Neutral: 1 (5%) Agree: 6 (30%) Strongly agree: 5 (25%) Prefer not to answer: 0 (0%)	Strongly disagree: 1 (10%) Disagree: 0 (0%) Neutral: 1 (%) Agree: 5 (50%) Strongly agree: 3 (30%) Prefer not to answer: 0 (0%)	Strongly disagree: 0 (0%) Disagree: 1 (10%) Neutral: 0 (0%) Agree: 1 (%) Strongly agree: 2 (20%) Prefer not to answer: 0 (0%)

I would recommend this online platform for exercise training to others who may benefit.	Strongly disagree: 1 (5%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 3 (15%) Strongly agree: 10 (50%) Prefer not to answer: 0 (0%)	Strongly disagree: 1 (10%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 2 (20%) Strongly agree: 7 (70%) Prefer not to answer: 0 (0%)	Strongly disagree: 1 (10%) Disagree: 0 (0%) Neutral: 0 (0%) Agree: 0 (0%) Strongly agree: 3 (30%) Prefer not to answer: 0 (0%)

Table S5.3. Open-ended questions and responses feedback questionnaire.

Question	HIIT (n=10)	MICT (n=4)
"Please include any suggestions you may have that would help us to improve the online platform"	"From the perspective of a young mom, the exercises were very repetitive and got boring about halfway through. The instructor could have been more motivating. The program seemed more geared toward the older generation." "I like the way it is." "More variety in workouts; more engaging/energizing music." · "No suggestions." "Having a heart rate check after the last high session and after the band stretches." "The program worked well for me." "No suggestions to make." "I feel it was very well done. I cannot think of anything that could make it better." "It worked well for me." "The time should be more flexible."	"The soft music is counterintuitive. Should be more upbeat and louder. Better countdown from instructor when changing to another movement." "Can't really think of anything, all went perfectly." "This program seems adequate for the purpose it was designed to achieve, however the music could be more upbeat." "More variety changes weekly. Not the same thing every week."
"Please describe what you enjoyed most about the online platform"	"Ease of engaging in the program." "Talking with the instructor and feeling I was doing it the right way." "Convenience." "The interaction with the session moderator who provided ongoing feedback." "Friendly facilitator, encouragement, my questions answered, able to do movements I couldn't before such as squats and side-to-side movements." "I liked the schedule-it kept me on board by participating regularly." "Not exercising alone; if I fell or had a problem, someone was watching."	"No travel time." · "Impressed with the flexibility for time and date of sessions, time to ask questions and chat after sessions, never felt rushed." · "I enjoyed the variation of the exercises; this ensured I was engaged and less likely to be distracted." · "Flexible, could travel, having a fitness routine."

	"It was very convenient. I enjoyed the challenge and The trainer was very supportive." "The motivation to exercise and the interaction with people monitoring the program." "I enjoyed every part of the exercise."	
"Please describe any barriers you experienced related to accessing/using the online platform"	"N/A." "None." "None." "None." "Timing of exercises, as my work is very exhausting." "A few technical glitches but the program continued." "Sometimes lost the Zoom link and had to scroll to find it." "Occasional internet connection issues due to lower-level service." "No real barriers; program adapted to my needs." "None."	"None." "None at all." "No barrier I can recall that prevented me accessing the online platform." "None."
"Please include any additional comments or suggestions regarding the online nature of the program"	"N/A." "No comment." "N/A." "The virtual classes provided an easy way to participate in a research study and include a wide variety of participants." "I learned that my attitude impacts my exercise program and that I can accomplish it after workdays - thank you for ongoing support!" "Online nature of the program did not require me to drive to another location and made it easy to do. No special equipment required." "I enjoyed participating and would do so again; online nature was a benefit as I didn't have to travel."	"None." "In the beginning I was apprehensive about the online sessions, but the instructor made it easy to relax and get comfortable. So nice to get everything from my own home." "It was a very pleasant experience. I do hope my participation helps to further the research." "Provide exercise program for after the study period."

	“Very interesting and informative process; grateful for this experience.” “It worked well.” “It is a very good program, keep it up.”

CHAPTER 6. DISCUSSION AND CONCLUSION

6.1 Final discussion

Managing patients with CIEDs is increasingly complicated with expanding prevalence and evolving technologies.[1] Over the past two decades, CIEDs have become the cornerstone of management for patients with brady- or tachyarrhythmias and heart failure.[2] Widespread adoption of CIEDs have been accompanied by a rising number of patients with different cardiovascular diseases treated with CIEDs; PPMs, ICDs and CRTs.[2] The expansion of CIED use has also generated ongoing debates about device indications (e.g., 24% of patients with indication for CRT have never received the device, and gender and sex disparities in ICD placements), further demonstrating the complexity of these therapies.[3,4] Meanwhile, CIED technology continues to advance in efforts to enhance clinical care, yet these modern features can also introduce uncertainty in clinical implementation and data interpretation.[5] Studies have reported heterogeneity in care management ranging from remote monitoring approaches to the methodology behind device-measured physical activity, highlighting the challenges of managing a heterogeneous patient group with increasingly modern devices.[6,7] While scientific and technological progress continues to "move the needle," secondary prevention strategies, particularly exercise-based CR, have not evolved at the same pace. Consequently, despite their unique needs and growing numbers, individuals with CIEDs appear to be a forgotten population within CR.

Exercise recommendations for individuals with CIEDs remain largely based on expert consensus.[8] Current guidelines encourage those with CIEDs to follow exercise prescriptions pertaining to the underlying disease.[9] As a result, clinical practice relies on a small number of CIED-focused studies.[8] This dissertation exposes a critical stagnation in the evidence base: no new trials have been conducted in the past five years. The sole Cochrane review focused on ICDs reported low quality evidence and inconclusive results. Existing studies are small, methodologically heterogeneous, and often report inconsistent outcomes. These findings underscore the urgent need to expand the current

evidence base and modernize CR approaches tailored to their unique clinical needs. Across four studies, this dissertation contributes important evidence on CR among adults with CIEDs.

The overall aim of this dissertation was to examine the effects of exercise training on physical and mental health, quality of life, and major adverse cardiovascular events (MACE) in patients with CIEDs. A summary of findings for the four original studies is shown in **Table 6.1.**

Table 6.1. Summary of findings from the four studies included in this dissertation.

Research aims	**Findings**
Study 1 Retrospective pre-post cohort study Primary aim: To examine the effects of exercise-based cardiovascular rehabilitation (CR) on cardiorespiratory fitness in individuals with cardiac implantable electronic devices (CIEDs). Secondary aim: To assess the effects of exercise-based CR on mental health outcomes in individuals with CIEDs. Tertiary aim: To evaluate CIED type and between females and males in cardiorespiratory fitness and mental health outcomes following exercise-based CR between females and males with CIEDs.	Participation in exercise-based CR in individuals with CIEDs (n = 252, 69 ± 12 y, 26% females): • Significantly improved cardiorespiratory fitness (metabolic equivalents of task [METs]: 6.0 ± 1.8 to 6.9 ± 2.0, P < 0.001). • Significantly reduced anxiety levels (3.5 ± 3.9 to 2.8 ± 3.9 scores, P = 0.04). • Significantly reduced depression levels (2.1 ± 3.9 to 1.2 ± 2.8 scores, P < 0.001). Sub-analysis per CIED type and between females and males: • No significant interactions were observed for time x CIED type and time x sex in METs and anxiety and depression levels.

Study 2 Propensity score-matched retrospective cohort study Primary aim: To assess the effects of exercise-based CR on major adverse cardiovascular events (MACE, primary) in patients with CIEDs. Secondary aims: To investigate the differences in MACE risk across CIEDs subtypes and between females and males with these devices.	Patients with CIEDs enrolled in CR (n = 172, 77.0 ± 13.0 y, 31% females) • No significant difference in the reduction of MACE hazard over the 5-year follow-up period when comparing patients with a record of CR to propensity score-matched controls (hazard ratio [HR]: 0.998, 95% confidence interval [CI]: 0.708–1.408, P = 0.99). • No significant differences observed in subgroup analyses by type of CIED (PPMs, HR: 0.77, 95% CI: 0.56-1.05, P = 0.10; ICDs, HR: 1.13, 95% CI: 0.76-1.69, P = 0.52). • CR was associated with a 42% reduction in MACE hazard among females (HR: 0.58, 95%CI: 0.38–0.89, P = 0.01).
Study 3 Systematic review and meta-analysis Primary aim: To investigate sex differences in changes in cardiorespiratory fitness following exercise training in women and men with CIEDs. Secondary aims: To examine additional physical (e.g., physical activity levels) and mental health outcomes following exercise	Sex-based examination and gender-related factors (22 studies included in the systematic review) • Fewer women than men were included in exercise and CIED studies (22 studies, 18% vs. 82%, p < 0.001) • No significant temporal changes over the years (2003-2022) in trials. • Variable sex-disaggregated reporting across different phases of trials: 0% in recruitment, eligibility and randomization, 32% in

training in women and men with CIEDs. Revised secondary aims: Sex-disaggregated data were insufficient for analyses in secondary outcomes. A sex-based examination was performed including the proportion of women and men with CIEDs enrolled in exercise trials, sex-specific reporting (e.g., eligibility, allocation, analysis), and considerations of sex and gender-related factors throughout the trials.	allocation, 36% in follow-up, and 95% in the final analysis. • Gender-related factors were reported in 8 (36%) of the 22 studies: most participants were white (range: 54%-100%), married (range: 55-78%), had no formal education (range: 35-55%), and had annual household incomes below $50,000 (range: 44-47%). Meta-analysis between women and men with CIEDS (2 studies, n = 156 participants, 22% women) • No significant changes in cardiorespiratory fitness between sexes: mean difference in V̇O2peak = 0.21: 95% CI, −1.70 to 2.12 mL/kg/min; P = 0.83). • Significant differences in peak oxygen uptake (V̇O2peak) following exercise training in men compared to their same-sex control group: mean difference V̇O2peak = 1.75, 95% CI, 0.72-2.79 mL/kg/min; P < 0.001). • No significant differences in V̇O2peak following exercise training in women compared to their same-sex control group: mean difference V̇O2peak = 1.36, 95% CI, −0.70-3.43 mL/kg/min; P = 0.20).

Study 4 A pilot randomized trial Primary aim: To assess the feasibility of 12-week virtual high-intensity interval training (HIIT) and moderate-to-vigorous intensity training (MICT) programs in women with CIEDs. Secondary aims: To evaluate the effects of a 12-week program of virtual HIIT and MICT on cardiorespiratory fitness, mental health, quality of life, cardiometabolic health indicators, and exercise behaviour determinants.	Women with CIEDs (n = 20, 62 ± 12 y) HIIT • Adherence: 100% completed the program. • Attendance: 21 ± 2 / 24 sessions. • Compliance: 37% met and 46% exceeded the target heart rate (HR) ranges for the high-intensity intervals (average HR: 131 ± 15 bpm); 17% met and 53% exceeded the HR targets for the low-intensity intervals (average HR: 110 ± 14 bpm). • Adverse events: 2 (0.95%) / 211 sessions. MICT • Adherence: 40% completed the program. • Attendance: 23 ± 1 / 24 sessions. • Compliance: 68% met and 32% exceeded the target HR ranges for MICT (average HR: 111 ± 7 bpm). • Adverse events: 1 (0.85%) / 117 sessions.

The first objective of this dissertation was to investigate the effects of CR on cardiovascular outcomes in those with CIEDs. Study 1 was a retrospective pre-post cohort study examining the associations of exercise-based cardiovascular rehabilitation (CR) on cardiorespiratory fitness (CRF) and mental health outcomes, with sex as key consideration in females and males with CIEDs. Findings from Study 1 demonstrated that participating in exercise-based CR improved METs and reduced anxiety and depression levels in individuals with CIEDs. A strong methodological approach was used, representing the first two-site retrospective study in the CIED population. This design enabled the largest Canadian retrospective observational study to date, comparable with previous CIED-focused studies in the United States (n = 82) in ICDs and Europe (n = 656) in CRTs.[10,11] Despite this strength, questions remain regarding the optimal dose, delivery, and duration of CR. For instance, more than 50% of the sample did not achieve the suggested MCID for several outcome measures (i.e., CRF, anxiety and depression levels). In addition, the specific characteristics of the CR interventions (i.e., FITT principles) delivered at the centres are not fully delineated, nor is the impact of COVID-19 pandemic on programs.[12,13] These limitations can be addressed by further data collection and expansion of the dataset in future studies.

The second objective was to investigate the effects of exercise-based CR on MACE in patients with CIEDs. Study 2 was a propensity score-matched retrospective cohort study assessing the associations of exercise-based CR on MACE in patients with CIEDs, whereas secondary aims examined the differences in MACE risk across CIEDs subtypes and between females and males with these devices. Findings from Study 2 showed no significant difference in MACE hazard reduction over the 5-year follow-up among all patients who enrolled in CR, whereas a significant 42% reduction in MACE risk was observed among women. Prior research has demonstrated the short-term (e.g., 1 year) impact of CR in reducing mortality and rehospitalization among those with CIEDs.[14] Hence, it was plausible to hypothesize that CR would confer sustained benefits in individuals with CIEDs over the

longer term. However, because the study did not reach its planned sample size, the finding of no significant difference in 5-year MACE risk between those who enrolled in CR and those who did not remain inconclusive and may reflect limited statistical power. Yet, the sex-specific analysis revealed a significant reduction in MACE risk in females, suggesting that they may derive greater benefit from CR participation. In light of these limitations with the sample size, expanding this project across more centres/provinces in Canada would enable a more comprehensive examination of CR programs and their impact on MACE in those with CIEDs.

The evaluation of women with cardiovascular disorders must be done through a sex- and gender-specific lens.[15] Following best practices in research, this dissertation reported sex-disaggregated data and performed sub-analyses per sex for all outcomes across Studies 1-3.[16] Specifically, Study 3 was a sex-based examination (via systematic review and meta-analysis) of exercise trials in women and men with CIEDs. Findings from Study 3 demonstrated that 18% women were enrolled in exercise and CIED research. The findings highlighted the need for continued efforts to increase enrollment of women into clinical trials. Major challenges were faced to retrieve sex-specific data from authors, despite our efforts with several contact attempts and offered collaboration on the project. Such limitations demonstrate the importance of implementing openness and transparency in not only cardiology research, but all fields of study.[17] Data sharing typically occur through two methods: investigators may share trial data on their own terms in response to individual requests, or by depositing data in a repository.[18] Yet, clinical trial investigators and funders have raised several concerns about data sharing due to associated financial costs, the possibility for inappropriate data use (e.g., misleading secondary analyses), and because sharing may foster competition.[18] The FAIR Principles have been suggested to provide guidance on data management for producers and publishers through four foundational principles (i.e., Findability, Accessibility, Interoperability, and Reusability).[19]

Open science in cardiology continue to evolve toward rigorous, reproducible, transparent, and publicly accessible research[17] - conditions that are essential for advancing sex- and gender-based science.

The fourth objective of this dissertation was to assess the feasibility and changes in cardiovascular health outcomes following 12 weeks of virtual exercise programs in women with CIEDs. Study 4 demonstrated that HIIT is a feasible and safe exercise alternative to MICT for women with CIEDs. Results from Study 4 address a pressing evidence gap in the field. A recent American Heart Association Scientific Statement of women in CR highlighted several urgent priorities for future research, including (1) enhancing accessibility through flexible CR schedules and hybrid CR models, which may overcome barriers with work, caregiving, and transportation; (2) promoting research innovation by exploring nontraditional CR models with a focus on safety and effectiveness for women; (3) developing and testing protocols tailored to women's unique needs, including targeted exercise regimens; (4) ensuring adequate female representation in CR trials; and (5) determining optimal strategies to improve CRF in women with CVD.[20] In this context, findings from the CIEDEX trial offer a timely contribution that aligns with emerging priorities for exercise options in women with CIEDs and adhere to best practices in early-phase intervention development (e.g., ORBIT model), thereby allowing the continuation of the pilot study as well as informing the design of future larger trials.

6.2 Overall limitations and strengths of this dissertation

Additional key general limitations and strengths should also be acknowledged. First, the retrospective cohort nature of Study 1 (i.e., pre-post) and Study 2 (i.e., MACE) with insufficient information on CR interventions and sample size limitations. In Study 3 (i.e., systematic review and meta-analysis), the small number of trials and heterogeneous reporting across outcomes limits the certainty of the evidence. Across Studies 1, 2 and 3, sex representation was unequal, and the samples lacked diversity (i.e., most participants in all studies were Caucasian), limiting the applicability of our

results. Study 4 (i.e., pilot trial) did not integrate mixed-methods or qualitative approaches to more thoroughly understand patients' experiences - an important gap in a feasibility study, given that patients are the most important stakeholders in the healthcare system.[21]

Major strengths of this dissertation include its multi-study designs, which enabled a comprehensive examination of key evidence gaps in exercise-based CR for individuals with CIEDs. Together, the retrospective cohort studies, systematic review and meta-analysis, and pilot randomized clinical trial provide a comprehensive examination of long-term outcomes, existing evidence, and feasibility of a virtual exercise intervention tailored to women with CIEDs. This dissertation places emphasis on subgroup data across all studies, providing device-specific evidence that accounts for unique clinical characteristics. These analyses also advance sex-specific inclusion and reporting practices in cardiovascular research. Taken together, these strengths highlight the dissertation's contribution to advancing evidence-based, sex-informed, and modern approaches to CR among adults living with cardiac devices.

6.3 Future directions

Future directions highlight opportunities for greater integration and modernization of CR delivery for individuals with CIEDs. One example is the TELEREH-HF trial, a multicenter randomized clinical trial in patients with heart failure (n = 850), which tested a 9-week hybrid telerehabilitation program (1 week hospital-based followed by 8 weeks home-based, 5 days/week).[22] This trial found significant improvements in $V\dot{O}_2$peak (0.95 [95% CI: 0.65-1.26] mL/kg/min vs 0.00 [95% CI: −0.31-0.30] mL/kg/min, P < .001) and quality of life (SF-36 questionnaire score, 1.58 [95% CI: 0.74-2.42] vs 0.00 [95% CI: −0.84-0.84]; P = 0.008) compared to controls. Most importantly, a total of 335 participants (79%) in the exercise group had a CIED, and the device technology was used to enhance the home-based program. Automatic transmission of data from the implant to a web-based monitoring platform enabled real-time alerts on device integrity (e.g., battery status), programming issues (e.g.,

antitachycardia pacing therapy), and clinical indicators (e.g., arrhythmias, lung fluid accumulation). This example emphasized the potential of leveraging CIED-derived data to support modern CR models and research.

Another example includes the adaptation of traditional peer-based support programs that leverage digital innovations to enhance patient-centered care for individuals with CIEDs. For instance, ICD support groups offer patients the opportunity to discuss challenges with their devices, collaboratively problem-solve issues, and access educational resources, all while receiving emotional support from others who share similar experiences. Sears et al. (2025) reviewed the long-standing ICD support group in Calgary, Alberta, which has operated for over 35 years, and highlighted persistent challenges with enrollment.[23] Despite over 1,100 ICD patients in the region, only about 2% actively participate in the support group. Strategies to modernize program delivery and improve engagement are ongoing, including hybrid meeting formats, transitioning to email communications, and developing subgroups tailored to specific populations, such as younger ICD patients.[23] These support programs also offer accessible resources, as many are no-cost or community-run services.[23] Together, these examples abovementioned illustrate how modernization can incorporate device-specific considerations into research and clinical care and address both the physical and psychosocial needs of individuals with CIEDs, inspiring future research to integrate innovative strategies into contemporary CR models

This dissertation will inform ongoing clinical trials and systematic reviews examining exercise-based CR in individuals with CIEDs. For example, the ongoing *Effectiveness of Exercise After an ICD (E-ICD)* trial (ClinicalTrials.gov identifier: NCT03544489) is a pragmatic randomized mixed-methods study evaluating a 12-week home-based walking intervention compared with usual care in patients with ICDs, guided by the RE-AIM framework and with completion anticipated in 2029. Further, the systematic reviews underway include studies examining the efficacy and safety of exercise therapies in patients with CIEDs (PROSPERO #: CRD42024593085, China, 2024, ongoing status), a network

meta-analysis evaluating the effects of exercise intensity in heart failure patients with CRTs (PROSPERO #: CRD42024568351, China, 2024, ongoing status), and an updated systematic review and meta-analysis of CR in patients with ICDs (PROSPERO #: CRD420251163872, Romania, 2025, ongoing status). Finally, Canadian Cardiovascular Society (CCS) guideline updates are currently in development, including the planned CCS-CHRS Guideline on Cardiac Implantable Electronic Device Therapy, expected in 2025 but not released yet. This forthcoming guideline represents a formal update to device-specific recommendations that were last issued in 2016.[24] Related CCS guidelines in cardiovascular areas such as atrial fibrillation and heart failure (i.e., common clinical conditions underlying CIED implantation) are also scheduled for updates between 2025 and 2027. Findings from this dissertation will be shared with relevant CCS guideline committees to support the integration of emerging evidence into future recommendations.

.6.4 Expanding the scope of this dissertation

Looking ahead, several emerging areas involving patients with CIEDs may have important implications for future research and clinical practice. While this dissertation focused on secondary prevention, research has shown the importance of preventive measures for individuals already manifesting electrocardiogram conduction abnormalities that may progress to more severe conduction disease requiring pacemakers. A retrospective observational study (n = 112,160, 53% women) demonstrated that optimizing all components of the 'Life's Essential 8' score (i.e., healthy diet, participation in physical activity, avoidance of nicotine, healthy sleep, healthy weight, and healthy levels of blood lipids, blood glucose, and blood pressure) could prevent up to 50% (hazard ratio [HR]: 0.48, 95% CI: 0.40–0.56) of all new cases of conduction disease and nearly 40% (HR: 0.63, 95% CI: 0.51–0.78) of clinically relevant conduction blocks.[25] Yet, current guidelines do not address primary prevention CR in cardiac electrophysiology conditions. Similarly, evidence for CIEDs in pregnancy is relatively limited and rare.[26] In a large cohort of pregnancy-related hospitalizations (n = 23,611,200), a

total of 11,220 (0.05%) women had a history of CIED implantation. Among these women, ICDs had a higher risk of cardiogenic shock (odds ratio: 3.06, 95% CI: 2.17–4.30) and need for mechanical circulatory support (odds ratio: 2.37, 95% CI: 1.48–3.80) compared to women without CIEDs, while women with PPM were generally comparable to those without CIEDs.[27] Little is known about the effects of virtual exercise, mainly HIIT, in pregnant women with CIEDs. In healthy pregnant women, research has shown that HIIT can be safe and effective in improving blood pressure and CRF following an 8-week program.[28] Continued advancements in this field have the potential to generate evidence and enhance care for clinical populations.

Beyond HIIT in clinical settings, there is an ongoing debate around patients with CIEDs participating in highly competitive sports. Until recently, guidelines have recommended against all competitive and high-intensity sports except light sports such as bowling, due to uncertainty about safety and efficacy during competition and concerns about risk.[29] For this reason, the ICD Sports Safety Registry (Clinicaltrials.gov #: NCT05754138) was established as an international multicenter registry collecting sports participation-related adverse events in individuals with ICDs. Results from this database showed that athletes with ICDs engaging in vigorous competitive sports (e.g., basketball, soccer) did not sustain physical injury or failure to terminate arrhythmia, despite occasional inappropriate and appropriate shocks.[30] Lampert et al (2019) emphasized that while shocks may occur during sports, whether discontinuing sports reduces their likelihood remains unknown.[30] Furthermore, while there have been no adverse events described in the 440 patients in the ICD Sports Registry over four years, the sample size remains insufficient to conclude that the risk is zero.[31] The central consideration for sports competition should be the athlete's preferences and priorities alongside with their family, using a shared decision-making approach.[30]

The basic design of CIEDs has remained relatively unchanged over the past 50 years. Because of inherent limitations in their design, conventional (transvenous) CIEDs are prone to multiple potential

complications (e.g., infection, lead failures).[32] Since 2012, leadless pacemaker technologies have evolved with longer-lasting batteries, smaller low-power designs, improved communication systems, and safer catheter-based implantation.[33] Leadless pacemakers for bradycardia are already clinically available, while other leadless pacing, defibrillation, and resynchronization technologies are currently under investigation and rapidly evolving.[33] Ongoing innovation in leadless technologies will continue to transform cardiac electrophysiology. As device therapies evolve, multidisciplinary care remain essential in providing physical (e.g., re-engaging in daily and physical activities) and psychosocial support (e.g., device acceptance).[34] Beyond the need to optimize care for those with conventional CIEDs demonstrated in this dissertation, the future also calls for continued advancements in exercise-based CR to keep pace with emerging device technologies and better support individuals living with cardiac devices.

6.5 Conclusions

These four studies provide novel insights on the role of exercise training on cardiovascular health outcomes in patients with CIEDs. This dissertation shows: (i) the importance of exercise-based CR in improving physical and mental health in individuals with CIEDs; (ii) the need of large-scale studies to further ascertain the mechanisms and impact of CR on MACE in patients with CIEDs; (iii) a call to action to advance sex-specific inclusion and reporting practices in exercise trials with CIEDs - future studies must ensure adequate representation of women (e.g., aligned with disease prevalence); and (iv) remote HIIT is a feasible and safe exercise alternative to standard care MICT in women with CIEDs, with promising cardiovascular outcomes that support the expansion of the pilot study and inform a future full-scale efficacy trial.

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