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High-Intensity Interval Training for Patients With Cardiovascular Disease—Is It Safe? A Systematic Review

Michael A. Wewege, BExPhys;* Dohee Ahn, BExPhys;* Jennifer Yu, MBBS; Kevin Liou, PhD; Andrew Keech, PhD

Background—Cardiac rehabilitation (CR) for patients with cardiovascular disease has traditionally involved low- to moderate-intensity continuous aerobic exercise training (MICT). There is growing and robust evidence that high-intensity interval training (HIIT) shows similar or greater efficacy compared with MICT across a range of cardiovascular and metabolic measures, in both healthy populations and populations with a chronic illness. However, there is understandable concern about the safety aspects of applying HIIT in CR settings. This systematic review analyzed safety data drawn from recent proof-of-concept studies of HIIT during CR among patients with cardiovascular disease.

Methods and Results—We included trials comparing HIIT with either MICT or usual care in patients with coronary artery disease or heart failure participating in tertiary care services, such as phase 2 (outpatient) CR. Adverse events occurring during or up to 4 hours after an exercise training session were collated. There were 23 studies included, which analyzed 1117 participants (HIIT=547; MICT=570). One major cardiovascular adverse event occurred in relation to an HIIT session, equating to 1 major cardiovascular event per 17 083 training sessions (11 333 training hours). One minor cardiovascular adverse events and 3 noncardiovascular adverse events (primarily musculoskeletal complaints) were also reported for HIIT. Two noncardiovascular events were reported in relation to MICT.

Conclusions—HIIT has shown a relatively low rate of major adverse cardiovascular events for patients with coronary artery disease or heart failure when applied within CR settings. **(*J Am Heart Assoc*. 2018;7:e009305. DOI: 10.1161/JAHA.118.009305.)**

Key Words: cardiac rehabilitation • exercise • exercise capacity • exercise training • safety

Cardiovascular disease (CVD), including heart failure (HF) and coronary artery disease (CAD), is currently the leading cause of death worldwide.[1] Cardiac rehabilitation (CR) is an important secondary prevention service after an acute cardiovascular event or hospitalization. Exercise-based CR typically involves patients engaging in low- to moderate-intensity continuous training (MICT), and it is effective for reducing cardiovascular mortality, all-cause mortality, and incidence of myocardial infarction (MI), and for improving quality of life.[2,3] However, outpatient CR uptake and adherence rates are less than optimal, with estimates of only 20% to 50% of eligible patients participating in CR and only a minority of participants completing a full exercise-training program within the CR setting.[4,5] Exercise interventions within CR that are optimized for the individual patient are an important priority.[6]

High-intensity interval training (HIIT) involves repeated intervals of high-intensity activity interspersed with rest or active lower-intensity recovery intervals. There is growing interest in HIIT because of robust and ever-increasing evidence of its efficacy for improving cardiovascular and metabolic function in both healthy populations and populations with a chronic illness.[7–10] HIIT has the additional benefit of being relatively time efficient compared with MICT, whereas preliminary data suggest many individuals report equal or greater enjoyment with HIIT and show at least similar overall training adherence compared with MICT within a laboratory or clinical environment.[11–14]

As such, numerous "proof-of-concept" studies have been conducted in recent years, applying HIIT within the CR setting for patients with CAD and HF. These preliminary studies have typically involved small samples of well-screened, clinically stable patients, although 2 large-scale, multicenter, randomized

From the Department of Exercise Physiology, School of Medical Sciences (M.A.W., D.A., A.K.), and Department of Cardiology, Prince of Wales Hospital and the Prince of Wales Clinical School (J.Y., K.L.), University of New South Wales, Sydney, Australia.

Accompanying Data S1 and Tables S1, S2 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009305

*Mr Wewege and Ms Ahn are co–first authors.

Correspondence to: Andrew Keech, PhD, Department of Exercise Physiology, School of Medical Sciences, University of New South Wales, Sydney, New South Wales 2052, Australia. E-mail: andrew.keech@unsw.edu.au

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Clinical Perspective

What Is New?

- High-intensity interval training appears to be relatively safe to conduct in patients with cardiovascular disease, including coronary artery disease and heart failure, within tertiary-care cardiac rehabilitation settings.

What Are the Clinical Implications?

- Considering the now robust evidence of high-intensity interval training efficacy for improving a range of cardiovascular-related health and fitness measures, the role of high-intensity interval training within cardiac rehabilitation settings can be further considered.

controlled trials (RCTs) have been completed recently.[15,16] To date, there have been generally positive findings about the efficacy of HIIT. Multiple recent meta-analyses have reported superior effectiveness of HIIT compared with traditional moderate-intensity exercise training within CR for improving cardiorespiratory fitness (maximal aerobic capacity),[17–22] an outcome measure predictive of mortality and cardiovascular event risk.[23–27] However, safety data from these training studies are yet to be systematically explored, a key area of interest considering the perceived increased risk of HIIT to patient safety is currently a major barrier toward its implementation within CR. This concern is based on the evidence that high-intensity physical activity acutely and transiently increases the risk of acute MI and sudden cardiac death, particularly among habitually sedentary individuals.[28]

To date, only 2 prominent studies have explored the safety profile of HIIT within the CR setting.[29] Rognmo et al conducted a retrospective analysis of cardiovascular adverse events (AEs) during HIIT and MICT sessions applied in 4846 patients with CAD across 3 CR sites in Norway.[29] Their data showed HIIT only induced a few AEs (HIIT, 2 nonfatal cardiac arrests and 1 event per 23 182 training hours; MICT, 1 fatal cardiac arrest and 1 event per 129 456 training hours). Although the relative risk of cardiovascular AEs was higher with HIIT than MICT, the absolute number of events overall was extremely low. A systematic review of all AEs, including non–exercise-related events, conducted recently by Hannan and colleagues, involving patients with CAD[17] (17 studies; 465 patients with HIIT; 488 patients with MICT), showed no deaths or major cardiac events (ie, requiring hospitalization) among participants with HIIT or MICT. More total AEs were reported for MICT interventions compared with HIIT interventions (HIIT, 9 AEs; MICT, 14 AEs).

The purpose of this systematic review was to establish the safety profile of HIIT for patients with CVD. The review includes a comparison of relative safety risk of HIIT to traditional MICT and covers only exercise-related AEs.

Methods

The data from each study are outlined in Table 1, and the R script for meta-analysis is supplied in Data S1, for purposes of reproducing the results.

Literature Search Strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[51] A systematic literature search was performed in 5 online bibliographic databases (Medline, Embase, Scopus, SPORTDiscus, and CINAHL) for studies published from database inception through August 17, 2017 (Table S1). After duplicate deletion, 2 researchers (D.A. and A.K.) independently screened articles via title/abstract. Full-text examination was performed in duplicate across 3 authors (D.A., A.K., and M.W.), with the third author moderating discrepancies. Reference lists of the included studies were cross-checked to ensure all available studies had been identified.

Inclusion and Exclusion Criteria

Studies were restricted to peer-reviewed trials with an English full-text article that included participants diagnosed with HF or CAD. CAD was defined as including patients having experienced an MI or undergone a percutaneous coronary intervention or coronary artery bypass graft. Studies needed to have included an HIIT group and a comparator group that undertook either usual care or a specific MICT intervention, and nonrandomized studies were included. Exercise interventions required a minimum training duration of 4 weeks, and sessions needed to be supervised in a specialized cardiology-based tertiary-care setting, such as a CR site or similar site (eg, heart failure clinic or cardiology department).

HIIT programs were limited to interval durations of up to 4 minutes, with the intensity classified as being ≥85% of heart rate (HR) peak or a surrogate physiological index (namely, ≥80% peak aerobic capacity [VO_{2peak}] or a rating of perceived exertion ≥15).[52] MICT programs included continuous aerobic exercise of intensity 60% to 75% of HR peak (or 50%–65% VO_{2peak}; 12–15 ratings of perceived exertion). Studies were included if adjunct exercise was applied (eg, supplemental resistance training), but it needed to be applied equally for both groups if the study involved an MICT comparison group rather than usual care.

Table 1. Participant Demographics and Study Characteristics

Study First Author	Year	Cardiac Population	Study Design; Population Details (Key CVD-Related Inclusion/Exclusion Criteria)	AE Reporting	HIIT				MICT or Usual Care				Lead-In Period/ Supplemental Intervention
					Sample Size	Sex, No. (%) Men	Age, y	BMI, kg/m^2	Sample Size	Sex, No. (%) Men)	Age, y	BMI, kg/m^2	
Angadi[30]	2015	HF	Randomized; NYHA classes II–III, preserved EF (mean, 65%); excluded unstable angina, MI within 4 wk	During sessions	9	8 (89)	69±6	29.8±5.1	6	4 (67)	72±12	29.3±2.8	
Cardozo[31]	2015	CAD	Randomized; history of CAD diagnosed by AHA guidelines; >3 mo MI or revascularization	During sessions	23	14 (61)	56±12	27.5±5.9	24	16 (67)	62±12	26.8±4.8	
Chrysohoou[32]	2015	HF	Randomized; patients with chronic, stable HF (NYHA classes I–III) attributable to left ventricular dysfunction (NYHA classes II–IV; EF, <50%)	During sessions	33	29 (88)	63±9	28.9±4.2	39	32 (82)	56±11	31.3±7	Supplemental RT (3 sets×8–10 repetitions, progressing from 30% 1RM to 90% 1 Repetition Maximum, 4 exercises, mixed muscle groups)
Conraads (SAINTEX-CAD)[15]	2015	CAD	Randomized; within 4–12 wk after MI, PCI, or CABG (EF >40%), receiving optimal medical treatment, stable symptoms, and	During sessions	85	81 (95)	57±9	28.0±4.4	89	80 (90)	60±9	28.5±4.3	

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Table 1. Continued

Study First Author	Year	Cardiac Population	Study Design; Population Details (Key CVD-Related Inclusion/Exclusion Criteria)	AE Reporting	HIIT				MICT or Usual Care				Lead-In Period/ Supplemental Intervention
					Sample Size	Sex, No. (%) Men	Age, y	BMI, kg/m^2	Sample Size	Sex, No. (%) Men)	Age, y	BMI, kg/m^2	
			medication for >4 wk										
Currie[33]	2013	CAD	Randomized; >2 mo after MI, PCI, or CABG, or stenosis >50% in at least 1 major coronary artery, or positive stress test result (mean start postevent HIIT, 136 d; MICT. 160 d)	During or immediately after sessions	11	11 (100)	62±11	27.9±4.9	11	11 (100)	68±8	27.3±4.2	
Currie[34]	2015	CAD	Randomized; >2 mo after MI, PCI, or CABG, or stenosis >50% in at least 1 major coronary artery, or positive stress test result (mean start postevent HIIT, 157 d; MICT, 163 d)	During or immediately after sessions	9	9 (100)	63±8	28.9±4.8	10	9 (90)	66±8	27.3±4	Supplemental RT (2 sets×10–12 repetitions; RPE, 11–15; mixed muscle groups; RT only included for final 3 mo of the 6-mo study)
Ellingsen (Study of Myocardial Recovery After Exercise Training in Heart Failure study)[16]	2017	HF	Randomized; chronic stable HF, NYHA classes II–III; EF <35%, optimal pharmacological treatment	During or within 3 h after sessions	77	63 (82)	65 (58–68)*	27.6 (26.3–28.7)*	65	53 (81)	60 (58–65)*	27.5 (26.6–29.7)*	
Freyssin[35]	2012	HF	Randomized; stable	NS	12	6 (50)	54±9	24.8±4.0	14	7 (50)	55±12	24.1±5.4	Supplemental assorted gymnastics

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Table 1. Continued

Study First Author	Year	Cardiac Population	Study Design; Population Details (Key CVD-Related Inclusion/Exclusion Criteria)	AE Reporting	HIIT				MICT or Usual Care				Lead-In Period/ Supplemental Intervention
					Sample Size	Sex, No. (%) Men	Age, y	BMI, kg/m^2	Sample Size	Sex, No. (%) Men	Age, y	BMI, kg/m^2	
			chronic HF, EF <40%										and water gymnastics exercises 7 h/wk
Huang[36]	2014	HF	Nonrandomized; clinically stable HF with reduced ejection fraction, ≥3 mo disease duration, EF ≤40%	NS	33	26 (79)	60±3	24.3	33	25 (76)	56±4	24.4	
Iellamo[37]	2014	HF secondary to CAD	Randomized; NYHA classes I–II, EF <40%, stable for >3 mo; excluded MI within 6 mo, unstable angina	During sessions	17	15 (88)	67±6	28.3±3	16	13 (82)	68±8	28.1±2	
Isaksen[38]	2015	HF (with ICD)	Nonrandomized; >2 mo after ICD insertion	During or within 12 h after sessions	24	21 (88)	65±9	27.8±4.0	11	11 (100)	69±9	27.3±4.2	Supplemental assorted RT and stretching for 15 min at end of session
Keteyian[39]	2014	CAD	Randomized; >3 wk after -MI or PCI, >4 wk after CABG, EF >40%	During or within 3 h after sessions	15	11 (73)	60±7	30.4±5.6	13	12 (92)	58±9	30.6±6.2	
Kim[40]	2015	CAD (with DES)	Randomized; acute MI with follow-up PCI and DES implantation (mean start post-MI HIIT,	NS	14	12 (86)	57±12	24.3±2.9	14	10 (71)	60±14	24.6±3.6	Lead-in period of minimum 1 wk (3 sessions) of MICT was

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Table 1. Continued

Study First Author	Year	Cardiac Population	Study Design; Population Details (Key CVD-Related Inclusion/Exclusion Criteria)	AE Reporting	HIIT				MICT or Usual Care				Lead-In Period/ Supplemental Intervention
					Sample Size	Sex, No. (%) Men	Age, y	BMI, kg/m^2	Sample Size	Sex, No. (%) Men)	Age, y	BMI, kg/m^2	
			17 d; MICT, 18 d)										usually applied
Koufaki[41]	2014	HF	Randomized; NYHA classes I–III, EF <45%; excluded <8 wk after MI	During or within 20 min after sessions	8	6 (75)	59±9	29.2±5.1	9	8 (89)	59±9	29.2±5.1	
Madssen[42]	2014	CAD	Randomized; ACS (non–ST-segment elevation) or AP treated with stent implantation	NS	15	14 (93)	56	27.3	21	15 (71)	61	26.3	
Mahmoud[43]	2016	CAD	Randomized; ischemic disease, stenosis of 1–2 CAD arteries; excluded <6 mo after MI	During sessions	20	20 (100)	54±3	32.3±0.8	20	20 (100)	54±3	32.3±0.7	
Moholdt[44]	2012	CAD	Randomized; 2–12 wk after MI (mean, 7 wk), EF >30%	NS	30	25 (83)	57±10	26.8±3.0	59	49 (83)	58±9	32.2±6.7	
Moholdt[45]	2009	CAD	Randomized; 4–16 wk after CABG; excluded HF	NS	28	24 (86)	60±7	26.0±6.2	31	24 (77)	62±8	28.1±3.5	Supplemental 45–60 min assorted exercises at end of each session
Spee[46]	2016	HF	Randomized; NYHA classes II–III, EF <40%, stable >3 mo; excluded unstable angina, <3 mo after MI	NS	12	10 (83)	58±8	27.1	14	13 (93)	66±9	28.4	
Tschentscher[47]	2016	CAD	Randomized; stable CAD with or	During sessions	20	15 (75)	62±10	28.3±4.6	20	15 (75)	63±11	28.7±4.7	

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Table 1. Continued

Study First Author	Year	Cardiac Population	Study Design; Population Details (Key CVD-Related Inclusion/Exclusion Criteria)	AE Reporting	HIIT				MICT or Usual Care				Lead-In Period/ Supplemental Intervention
					Sample Size	Sex, No. (%) Men	Age, y	BMI, kg/m^2	Sample Size	Sex, No. (%) Men	Age, y	BMI, kg/m^2	
			without MI, PCI, or CABG										
Villelabeitia Jaureguizar[48]	2016	CAD	Randomized; NYHA classes I–II with AP or MI; excluded HF	During sessions	36	28 (78)	58±11	29.6±4.4	36	33 (92)	58±11	29.5±4.1	Supplemental home-based walking on nontraining days (RPE, 11–13)
Warburton[49]	2005	CAD	Randomized; >6 mo after CABG or angioplasty, highly functional (VO_{2peak} >9 METs)	NS	7	7 (100)	55±7	26.0	7	7 (100)	57±8	28.7	Supplemental 3 additional d/wk MICT protocol
Wisløff[50]	2007	HF	Randomized; HF with >12 mo after MI, EF <40%; excluded unstable angina, uncompensated HF, <4 wk after MI	During sessions	9	7 (78)	77±9	24.5±3	8	6 (75)	74±12	24.7±3	

Age and BMI data are mean±SD. ACS indicates acute coronary syndrome; AE, adverse event; AHA, American Heart Association; AP, angina pectoris; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CVD, cardiovascular disease; DES, drug-eluting stent; EF, ejection fraction; HF, heart failure; HIIT, high-intensity interval training; ICD, implantable cardioverter-defibrillator; MET, metabolic equivalent; MI, myocardial infarction; MICT, moderate-intensity continuous training; NS, not specified; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RPE, rating of perceived exertion; RT, resistance training; SAINTEX-CAD, Study on Aerobic Interval Exercise Training in CAD Patients; and VO_{2peak}, peak value attained during maximal aerobic capacity test; SMARTEX, Study of Myocardial Recovery After Exercise Training in Heart Failure; 1RM, 1 Repetition Maximum.
*Age and BMI data are median (95% confidence interval).

In instances of multiple publications presenting different data from the same overall study, only the study presenting AE data was included. We excluded 1 study that presented data in only conference abstract form (no full-text version) but otherwise met our inclusion criteria for study inclusion,[53] after the authors informed us that a full-text version was not being planned.

Data Extraction and Analysis

Participant characteristics, intervention characteristics, and AE data were extracted from the included studies. An AE was defined as an event occurring during or up to 4 hours after an exercise session. If AE data were not specifically stated, or if the data were unclear in specific relation to exercise sessions, study authors were contacted for clarification. AE data were subdivided by the nature of the event (cardiovascular or noncardiovascular) and by the severity of the event (major or minor). Cardiovascular events included angina, arrhythmias, MI, and stroke. All other events were classified as noncardiovascular events, which primarily involved musculoskeletal complaints. Major events were defined as those that lead to an outcome of withdrawal from the study as a minimum consequence.

For each study, the total number of training sessions was calculated: total number of exercise sessions completed=sessions per week×study duration×participants who completed the study×adherence rates (if stated). Session attendance rates were not reported in 4 studies[31,32,36,43] and therefore, were imputed as the weighted mean attendance rate of other studies in the review (93%). Total number of training hours were also calculated: total number of exercise sessions×session duration. Supplementary interventions were not included in the calculations.

Quality Assessment

Study quality was assessed with the Physiotherapy Evidence Database score. Confirmed scores of 10 were obtained from http://www.PEDro.org.au for 19 studies. For 4 studies without confirmed scores,[36,38,40,43] 2 researchers (A.K. and M.W.) scored the studies independently and resolved discrepancies through discussion. All studies' assignments were open-label (blinding is seldom achievable in exercise training intervention studies) and, thus, a modified Physiotherapy Evidence Database score (of 8) was reported. Studies were considered higher quality if they scored ≥6 of 8 (75%).

Statistical Analysis

The "exactmeta" package for *R* (R Foundation for Statistical Computing, Vienna, Austria) was used to calculate risk difference (95% confidence intervals) for each of the 19 HIIT versus MICT studies across all AEs.[54] The "rmeta" package was used to calculate the overall risk difference between HIIT and MICT. The code for the analysis is supplied in Data S1. The threshold for significance was set to $P<0.05$.

Results

Studies Included in the Review

The search strategy returned a total of 1385 items, reduced to 663 after removal of duplicates (Figure). The initial screen removed a further 482 articles. Last, after the full-text screen, 155 studies were excluded, leaving 26 studies eligible for inclusion in the review (Figure). Nineteen studies provided safety data directly related to the exercise session within the publication. Safety data from 4 studies[33,34,36,41] were gathered by personal correspondence with the study authors because they were not clearly detailed in the publication or it was unclear if safety data pertained directly to the exercise sessions. Safety data could not be gathered from 3 studies[55–57] despite multiple attempts to contact study authors (70 participants; all studies involved patients with HF). Therefore, data from 23 included studies were reviewed.

Participants and Study Design

From 23 included studies, 1117 patients completed their respective exercise training intervention (or usual care) from the 1268 patients initially enrolled in the studies (12% dropout rate). Of the completers, 547 patients received HIIT and 570 patients received MICT or usual care (MICT, N=473; usual care, N=97). Dropout rates were similar ($P=0.55$) across groups (HIIT, 13±13% [range, 0%–50%]; MICT/usual care, 11±11% [range, 0%–47%]). Participant characteristics are outlined in Table 1, and intervention characteristics are outlined in Table 2. Nineteen trials randomly assigned participants to HIIT or MICT. Two trials randomly assigned participants to HIIT or usual care,[32,46] and 2 nonrandomized trials compared HIIT with usual care.[36,38] Of the 23 studies, 13 involved only patients with CAD (N=668 patients),* 9 involved only patients with HF (N=416 patients),† and 1 involved 33 patients with HF secondary to CAD.[37] The mean age across all the studies was 61±5 years (HIIT=61±5 years; MICT=62±5 years), 83% were men (84% for HIIT; 83% for MICT), and mean body mass index was 27.8±2.1 kg/m^2 (HIIT=27.7±2.0 kg/m^2; MICT=28.1±2.2 kg/m^2). The mean body mass index was 28.6 kg/m^2 for studies involving only

*References 15, 31, 33, 34, 39, 40, 42–45, 47–49.
†References 16, 30, 32, 35, 36, 38, 41, 46, 50, 57.

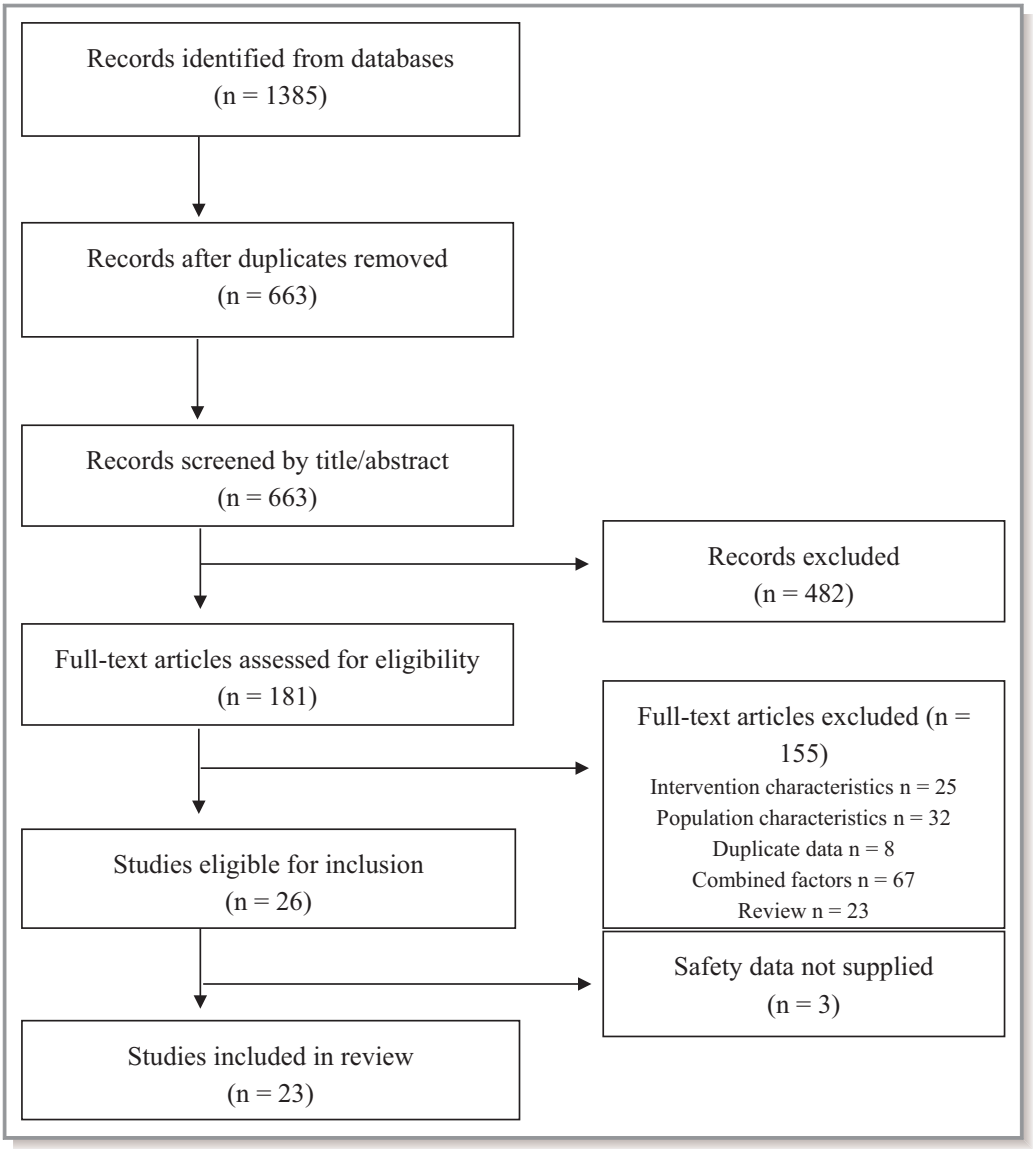

Figure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection.

patients with CAD and 27.4 kg/m^2 for studies involving patients with HF (including secondary to CAD).

All studies stated clear inclusion and exclusion criteria for CAD or HF classification; however, procedures on patient selection (all-comers versus volunteers) were generally not stated. Characteristics for the CVD pathological features of included patients (eg, severity of HF based on New York Heart Association [NYHA] classification guidelines) varied widely across studies; however, all studies included only patients with stable symptoms (Table 1). For studies involving patients with HF, most included patients with functional classification up to NYHA class III (moderate severity), and no studies included patients with severe pathological features (class IV). A calculation of the number of patients in each NYHA class within the HF studies was not possible because some studies did not provide a breakdown of patient pathological characteristics. Similarly, not all CAD studies provided a breakdown of patients across the MI, percutaneous coronary intervention, and coronary artery bypass graft categories. Most studies did not specifically screen for contraindicating musculoskeletal issues in the inclusion/exclusion criteria.

All studies applied a pretraining peak stress test with electrocardiography, usually including a direct measure of VO_{2peak}. All studies involved patient supervision during exercise sessions, typically stated as being CR staff, such as physical therapists, physiotherapists, exercise physiologists, and clinical nurses. Two studies[33,50] required participants to complete 1 session per week unsupervised at home, with the other sessions being performed at the CR site. Most studies explicitly stated if AEs occurred specifically during or immediately after

Table 2. Exercise Intervention Characteristics and AE Data

Study First Author	Exercise Training (Wk×D per Wk)/Modality	HIIT						MICT or Usual Care						Details of AEs
		Exercise Intervention	Total Training Sessions	Total Training Time, h	AE (Cardiovascular Related)	AE (Other)	Adherence	Exercise Intervention	Total Training Sessions	Total Training Time, h	AE (Cardiovascular Related)	AE (Other)	Adherence	
Angadi[30]	4×3/Treadmill	4×2 Min at 80%–85% HR_{peak}, 2 min at 50% HR_{peak}; progression to 4×4 min at 85%–90% HR_{peak}, 3 min at 50% HR_{peak}	107	71	0	0	9/9	15 Min at 60% HR_{peak}; progression to 30 min at 70% HR_{peak}	71	53	0	0	6/6	
Cardozo[31]	16×3/Treadmill	8×2 Min at 90% HR_{peak}, 2 min at 60% HR_{peak}	1022	681	0	0	23/23	30 Min at 70%–75% HR_{peak}	1071	714	0	0	24/24	
Chrysohoo[32]	12×3/Cycle	30 s at 80%–100% W_{peak}, 30 s rest, alternated for up to 45 min of exercise	1100	825	0	0	33/50	Usual care					39/50	
Conraads[15]	12×3/Cycle	4×4 Min at 90%–95% HR_{peak}, 3 min at 50%–70% HR_{peak} (actual mean interval, 88% HR_{peak} drawn from study data)	3029	1919	0	0	85/100	37 Min at 70%–75% HR_{peak} (actual mean, 80% HR_{peak} drawn from study data)	3172	2485	0	0	89/100	
Currie[33]	12×2/Cycle	10×1 Min at 89% W_{max}, 1 min at 10% W_{max}; progression to mean 110% W_{max}	209	104	0	0	11/15	30 Min at 58% W_{max}, progressed to 50 min by wk 9	243	202	0	0	11/15	
Currie[34]	26×2/Cycle	10×1 Min at 85% W_{max}, 1 min at 10% W_{max}; progression to mean 121% W_{max}	431	215	0	0	9/16	30 Min at mean 57% W_{max}; progression to 50 min at mean 78% W_{max}	468	390	0	0	10/12	

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Table 2. Continued

Study First Author	Exercise Training (Wk×D per Wk)/Modality	HIIT						MICT or Usual Care						Details of AEs
		Exercise Intervention	Total Training Sessions	Total Training Time, h	AE (Cardiovascular Related)	AE (Other)	Adherence	Exercise Intervention	Total Training Sessions	Total Training Time, h	AE (Cardiovascular Related)	AE (Other)	Adherence	
Ellingsen[16]	12×3/Cycle	4×4 Min at 90–95 HR_{max}, 3 min at moderate intensity	2689	1703	1	2	77/82	47 Min at 60%–70% HR_{max}	2270	1778	0	0	65/73	Cardiovascular: ventricular arrhythmia and cardiac arrest during exercise session in wk 1, requiring DC shock (withdrew from study); noncardiovascular: ICD discharge during exercise with no arrhythmia in wk 12 (withdrew from study); dizziness within 3 h after exercise session without any cardiovascular cause in wk 1 (continued in study)
Freyssin[35]	8×6/Treadmill	36×30 S at 50% maximum workload during SRT, 60 s rest; progression interval intensity to 80% workload for final 4 wk	576	269	0	0	12/12	45 Min at VT1	672	672	0	0	14/14	
Huang[36]	12×3/Cycle and treadmill	7×3 Min at 80% VO_2R, 3 min at 40% VO_2R (MICT lead-in for first 12 sessions)	1100	917	0	0	33/35	Usual care					33/33	
Iellamo[37]	12×3/Treadmill	4×4 Min at 75%–80% HRR, 3 min at 45%–50% HRR	539	404	0	0	17/18	30–45 Min at 45%–60% HRR	484	484	0	0	16/18	
Isaksen[38]	12×3/Cycle	4×4 Min at 85 HR_{max}, 3 min at 60%–70% HR_{max}	847	847	0	0	24/26	Usual care					11/12	

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Table 2. Continued

Study First Author	Exercise Training (Wk×D per Wk)/Modality	HIIT						MICT or Usual Care						Details of AEs
		Exercise Intervention	Total Training Sessions	Total Training Time, h	AE (Cardio-vascular Related)	AE (Other)	Adher-ence	Exercise Intervention	Total Training Sessions	Total Training Time, h	AE (Cardio-vascular Related)	AE (Other)	Adher-ence	
Keteyian[39]	10×3/Treadmill	4×4 Min at 80%–90% HRR, 3 min at 60%–70% HRR	437	291	0	1	15/21	60%–80% HRR	378	252	0	1	13/18	HIIT: knee pain (continued in study); MICT: limiting leg pain (withdrew from study)
Kim[40]	6×3/Treadmill	4×4 Min at 85%–95% HRR, 3 min at 50%–70% HRR	252	189	0	0	14/16	25 Min at 70%–85% HRR	252	189	0	0	14/16	
Koufaki[41]	24×3/Cycle	20×30 S at 50% maximum workload during SRT, 60 s active recovery	518	259	1	0	8/16	21–30 Min at 90% VT (≈40%–60% VO_{2peak}), progression to 40 min by final month	583	389	0	1	9/17	HIIT: syncope (continued in study); MICT: anxiety/panic attack (continued in study)
Madssen[42]	12×3/Treadmill	4×4 Min at 85%–95% HR_{max}, 3 min at 70% HR_{max}	486	308	0	0	15/19	46 Min at 70% HR_{max}	680	522	0	0	21/22	
Mahmoud[43]	12×3/Cycle	4×4 Min at 80%–85% HR_{peak}, 3 min at 50%–60% HR_{peak}	667	422	0	0	20/20	30 Min at 50%–60% HR_{max}	670	446	0	0	20/20	
Moholdt[44]	12×2/Treadmill	4×4 Min at 85%–90% HR_{max}, 3 min at 70% HR_{max}	598	378	0	0	30/35	35 Min assorted aerobic exercises, no specified i ntensity	1119	1119	0	0	59/72	
Moholdt[45]	4×5/Treadmill	4×4 Min at 90% HR_{max}, 3 min at 70% HR_{max} (mean interval, 92% HR_{max})	459	291	0	0	28/33	46 Min at 70% HR_{max} (mean, 74%)	521	399	0	0	31/36	

Continued

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Table 2. Continued

Study First Author	Exercise Training (Wk×D per Wk)/Modality	HIIT						MICT or Usual Care						Details of AEs
		Exercise Intervention	Total Training Sessions	Total Training Time, h	AE (Cardiovascular Related)	AE (Other)	Adherence	Exercise Intervention	Total Training Sessions	Total Training Time, h	AE (Cardiovascular Related)	AE (Other)	Adherence	
Spee[46]	12×3/Cycle	4×4 Min at 85%–95% VO_{2peak}, 3 min active recovery	346	202	0	0	12/16	Usual care					14/15	
Tschentscher[47]	6×3/Cycle	4×4 Min at 85%–95% HR_{peak}, 3 min at 60%–70% HR_{peak}	356	208	0	0	20/23	33 Min at 65%–85% HR_{peak}	356	285	0	0	20/22	
Villelabeitia Jaureguizar[48]	8×3/Treadmill	15×20 S at 50% maximum workload during SRT (104% W_{max}), 40 s at 10% maximum workload; progression to 30 repetitions and 134% W_{max} by wk 4	795	530	0	0	36/36	15 Min at VT1 (64% VO_{2peak}); progression to 30 min at VT1+10% (69% VO_{2peak}) by wk 5	760	507	0	0	36/36	
Warburton[49]	16×2/Treadmill	9×2 Min at 90% HHR/VO_2R, 2 min at 40% HHR/VO_2R	224	112	0	0	7/7	30 Min at 65% HRR/VO_2R	224	112	0	0	7/7	
Wisløff[50]	12×3/Treadmill	4×4 Min at 90%–95% HR_{peak}, 3 min at 50%–70% HR_{peak}	298	189	0	0	9/9	47 Min at 70%–75% HR_{peak}	274	214	0	0	8/9	
Total		HIIT	17 083	11 333	2	3	87%	MICT	14 268	11 213	0	2	89%	

Total training hours equals number of training sessions completed×training session duration (including warm-up and cool-down). AE indicates adverse event; DC, direct current (defibrillation); HIIT, high-intensity interval training; HR_{max}, heart rate maximum; HR_{peak}, heart rate peak; HRR, heart rate reserve; ICD, implantable cardioverter-defibrillator; MICT, moderate-intensity continuous training; SRT, Steep ramp test; VO_2, volume of oxygen consumption; VO_2R, VO_2 reserve; VT1, first ventilatory threshold (aerobic); W_{max}, workload at maximal aerobic capacity; Wpeak, workload at test termination during maximal effort exercise test.

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an exercise training session; other studies stated simply that no AEs occurred over the duration of the study.

Interventions

The most common HIIT protocol applied was the so-called Scandinavian HIIT model (4×4-minute intervals with 3-minute recovery intervals), which was applied in 14 studies.[15,16,30,37–40,42–47,50] Other HIIT protocols ranged in interval duration from 30 seconds to 3 minutes. MICT protocols ranged from 30 to 60 minutes per session. Exercise modalities used were either cycle ergometer (10 studies[‡]) or treadmill (12 studies[§]), with 1 study using both.[36] For the 4 studies that applied a comparator control group involving usual care, the description of what constituted usual care was variously that patients "were advised to remain physically active according to recommendations for physical activity"[46]; "received optimal medical treatment only"[36]; "were managed as usual by the admitting physician in the Heart Failure Unit, and no advice for any specific exercise protocol was given"[32]; or there was no description of the usual care provided.[38]

Across all HIIT studies, 17 083 training sessions were conducted, totaling 11 333 training hours. During MICT (applied in 19 of the 23 included studies), 14 268 sessions were conducted, totaling 11 213 hours.

Adverse Events

Seven AEs were reported across all studies; 5 occurred during or after HIIT, and 2 occurred during or after MICT (Table 2). Of the 7 AEs, 2 were cardiovascular, and both occurred in relation to HIIT. One could be classified as major and nonfatal (ventricular arrhythmia leading to cardiac arrest, treated with direct current cardioversion, and the patient was successfully resuscitated; occurred first week of training; participant withdrew from the study; the patient had refused cardioverter-defibrillator implantation before inclusion into the study)[16]; the other could be classified as minor (syncope during one training session; participant continued in the study).[41] Both cardiovascular events occurred in populations with HF; none were reported from populations with CAD. The major cardiovascular-related AE occurred in the largest of the included studies: the Study of Myocardial Recovery After Exercise Training in Heart Failure study, a multicenter (9 European centers) RCT.[16] The study applied HIIT sessions involving 4×4-minute intervals (with 3 minutes active recovery in between intervals) and applied a lower intensity (88% HR peak) than intended in the study design (90%–95% HR peak).

The other 5 AEs were classified as noncardiovascular. Two were lower-limb musculoskeletal complaints: HIIT=1 (knee pain in a patient with CAD who was evaluated and allowed to resume the HIIT protocol after a 2-week period[39]); MICT=1 (limiting leg pain in a patient with CAD that led to withdrawal from the study[39]). Both musculoskeletal complaints were reported from the same study[39] and occurred in patients with CAD undertaking treadmill exercise. One patient with HF experienced an inappropriate implantable cardioverter-defibrillator discharge unrelated to arrhythmia occurring during an exercise session in the final week of the HIIT and stopped the exercise program. One patient with HF experienced dizziness within 3 hours after a supervised HIIT session, with no detectable cardiovascular cause, and the participant continued with the training program without any reoccurrences. Both of those AEs occurred in the SMARTEX Heart Failure study for patients with HF.[16] One patient with HF performing MICT experienced an anxiety/panic attack during an exercise session and then continued with the training program.[41] We were unable to analyze the sex or ethnic characteristics of the patients with AEs because of lack of detail provided within the published articles.

On the basis of the available training and AE data, a major cardiovascular event occurred at a rate of 1 per 17 083 HIIT sessions (11 333 training hours), whereas the overall cardiovascular event rate for HIIT (including minor events) was 1 per 8541 sessions (5667 training hours). MICT did not induce any cardiovascular AEs. When considering only HF trials, a major cardiovascular event occurred at a rate of 1 per 8119 HIIT sessions (5685 training hours), with an overall cardiovascular event rate of 1 per 4059 sessions (2842 training hours).

The overall AE rate (all reported events) was 1 event per 3417 sessions (2227 training hours) for HIIT and 1 event per 7134 sessions (5606 training hours) for MICT. Overall, the risk difference for all AEs between HIIT and MICT (19 studies) was not observed to be significantly different (risk difference=−0.06 [−0.028 to 0.009]; P=0.70).

Study Quality

Studies were a moderate quality (5.0±1.0 of 8 using the modified Physiotherapy Evidence Database score, Table S2). Five studies were considered higher quality, whereas 2 studies were considered low quality (each scoring 3). No differences were noted between studies of CAD (5.2±1.1) and HF (4.8±0.7).

Discussion

The aim of this systematic review was to examine the safety profile of HIIT applied in CR sites for patients with CAD and HF. From 23 studies involving 547 participants completing

[‡]References 15, 16, 32–34, 38, 41, 43, 46, 47.
[§]References 30, 31, 35, 37, 39, 40, 42, 44, 45, 48–50.

HIIT across 17 083 training sessions (equivalent to 11 333 training hours), only 1 major (and nonfatal) cardiovascular AE was reported in direct relation to the exercise training sessions. The total number of AEs was low for both HIIT and MICT sessions, with musculoskeletal complaints being the most commonly reported AE.

The absolute incidence of major cardiovascular-related events among participants with HIIT was low (1 major cardiovascular event; 1 per 11 333 training hours). The only other comparable safety study to date, by Rognmo et al,[29] reported 2 major cardiovascular events in total from 4846 patients with CHD (1 per 23 182 training hours). Data from the study by Rognmo et al were not included in the current review because of its retrospective, observational study design (survey of 3 Norwegian CR sites). The other recent systematic review on this topic,[17] which covered all AEs, including non–exercise-related events from studies involving only patients with CAD, also reported no major cardiovascular events from HIIT interventions (the HIIT-related major cardiovascular event we reported occurred in an HF study).[16]

Recent contemporary data drawn from surveys from clinical practice have shown traditional MICT to be safe within CR.[29,58,59] For example, a French observational sample (survey of 65 CR sites, 25 420 patients) reported 1 event per 49 565 training hours,[58] the Norwegian sample by Rognmo et al reported 1 event per 129 456 training hours,[29] and a Japanese observational sample (survey of 136 CR sites) reported 1 event per 383 096 training hours.[59] It needs to be acknowledged that each MICT observational study only observed 1 major cardiovascular event in total, which makes the comparison of relative rate of events (per training hours) from HIIT and MICT somewhat misleading at this stage.

Therefore, although it appears that HIIT has been seen to be safe within CR service in terms of absolute number of major cardiovascular events (at least within research settings), there are some caveats limiting the generalizability of these findings at this stage. First, most studies to date have been relatively small proof-of-principle studies, with only 2 large, multicenter, RCTs completed.[15,16] Another large multicenter RCT is now underway in the United Kingdom.[60] The evidence in this area is rapidly advancing (20 of the 23 studies included in this review were published since 2012). Second, there was considerable heterogeneity across studies for patient characteristics (eg, age and CVD pathological features), although mean patient characteristics of the included studies (mean age, 60 years; body mass index, 27 kg/m^2) appear typical for a CR clientele. Also, it is a higher mean age than observed in the recent Cochrane review analyzing the efficacy of exercise interventions within CR (comprising 63 studies; mean age, 56 years).[61] Five of the included studies involved patients with HIIT with a mean (or median) age of ≥65 years,[16,30,37,38,50] with only 1 study (the Study of Myocardial Recovery After Exercise Training in Heart Failure study) reporting any AEs. No HF studies involved patients with severe pathological characteristics (NYHA class IV), and it is difficult to generalize the severity of pathological characteristics within the CAD studies. Third, many studies in this review did not specifically state key facets of the study design, especially the recruitment process (ie, whether participants were "all-comers" to the CR service, were volunteers, or were carefully selected patients hand-picked by the researchers) or the timing of commencement of the study in relation the patient's CAD event (MI, coronary artery bypass graft, or percutaneous coronary intervention).

HIIT Within CR: Weighing the Risk Versus Reward

So where should HIIT sit within CR exercise service? Is the evidence of "efficacy relative to safety risk" now strong enough to warrant recommending HIIT be implemented within CR services as an adjunct option to traditional MICT? HIIT is clearly more effective for improving peak aerobic fitness (VO_{2peak}) compared with MICT in patients with CVD, on the basis of consistently robust findings from several recent meta-analyses.[17–22] These studies each reported a greater magnitude of improvement in VO_{2peak} from HIIT compared with MICT, with overall estimates ranging from 1.15 to 1.78 mL O_2/kg per minute. The prognostic value of VO_{2peak} in predicting all-cause and cardiovascular-related mortality is strong; an improvement in fitness of 3.5 mL O_2/kg per minute (or 1 metabolic equivalent) equates to ≈8% to 17% reduction in all-cause and cardiovascular-related mortality.[23–27] The relative efficacy of HIIT for improving other health measures, such as insulin sensitivity and glucose control, body composition, and vascular function, is also robust, as detailed in recent meta-analyses.[7,9,10,62] As a counterpoint, the evidence for the efficacy of HIIT in relation to strong clinical end points, such as all-cause and cardiovascular-related mortality risk, or improvements in key direct measures of cardiac function, such as left ventricular mass and ejection fraction, is sparse at this stage.[16,45,63,64] In addition, the 2 large-scale multicenter RCTs to date have not clearly shown superior efficacy of HIIT compared with MICT within CR[15,16]; however, there have been methodological concerns over the application of HIIT within each of these studies that limit interpretation of their findings.[65]

So, at this point, the "rewards" of applying HIIT within CR are reasonably compelling, and the accumulated evidence of safety of HIIT within CR would suggest that HIIT could be considered an acceptable option within CR service, at least as an adjunct option to traditional MICT. This would be a component of an individualized service within CR, applying exercise programs designed specifically for the patient's needs and accounting for patients' individual safety risk

profile (eg, age, CVD pathological characteristics, and initial fitness levels) and factors that would affect training adherence and enjoyment, such as personal goals and preferences. Some leading CR societies in North America and Europe already recommend that patients progress from moderate- to vigorous-intensity aerobic endurance exercise over the course of the program; however, this is yet to become the consensus position worldwide.[66]

Perhaps the larger question now is more patient specific: is HIIT appropriate for all CR patients or only certain "lower-risk" patients? Risk of acute cardiovascular events during exercise is related to several factors: presence of CVD pathological characteristics (type and severity), stability of associated symptoms, patient age, presence of substantial comorbidity, baseline fitness levels, and exercise-history.[28] On the basis of this, it could be argued that HIIT would be most appropriate for those patients who are younger, have less complex CVD pathological characteristics (eg, percutaneous coronary intervention only or NYHA class I HF) and stable symptoms, are otherwise low cardiovascular risk (including normal body mass index and normotensive), have a relatively high baseline level of aerobic fitness, and have a recent history of performing regular vigorous physical activity. HIIT has yet to be applied in NYHA class IV patients with HF (severe), and without evidence of its safety within that cohort, it cannot yet be recommended for those patients. However, there is no evidence yet to suggest that HIIT is inherently unsafe for any other specific CVD patient characteristics (eg, older age).

To apply HIIT within a CR setting, we recommend the following practical steps to optimize the *risk versus reward* balance. First, a baseline maximal-effort stress test and a negative electrocardiographic result appears prudent. All studies in this review applied a baseline stress test. Ideally, the HIIT sessions should be designed on the basis of the data drawn from this test (ie, interval intensity calculated as a percentage of HR maximum or maximum workload achieved during the stress test). None of the studies included in this review applied a minimum fitness level as an inclusion or exclusion criterion. Second, regular monitoring of physiological responses (eg, HR, blood pressure, and rating of perceived exertion) during and immediately after an HIIT session is appropriate. Simple monitoring of rating of perceived exertion, as many CR services apply for moderate-intensity sessions typically conducted in group-based settings,[67] is not appropriate for HIIT sessions. It would also be prudent for the level of supervision to be higher for the "higher-risk" patients (eg, patients with class III HF) with 1-to-1 supervision recommended. Last, all exercise training programs should be graduated, and a "lead-in period" of moderate-intensity exercise would seem appropriate before commencement of HIIT for all patients starting at a CR service. Considering the only major cardiovascular-related AE occurred in the first week of training without any stated lead-in period of moderate-intensity exercise,[16] we believe this is a sensible step. The lead-in period may also act to minimize risk of musculoskeletal injuries.

Each of these recommendations has logistical implications for CR sites, with need for greater staffing and resources to implement HIIT safely and effectively. For instance, the application of a baseline stress test is not currently standard practice within normal CR service: although North American and European guidelines recommend electrocardiographic stress testing as standard procedure, the current UK, Australia, and New Zealand guidelines do not specifically recommend it[66] and instead tend toward less technical baseline functional capacity testing, such as the 6-minute walk test.[67]

Strength and Limitations

We reviewed only exercise-related AEs, defined as occurring either during a session or up to 4 hours after a session. Many studies reported AEs occurring at any time during the study. For example, Conraads et al[15] reported 3 cardiac events occurring in the MICT group; however, 1 event occurred 24 hours after an exercise session, and 2 others occurred during the postintervention stress test assessment. Other studies reported an assortment of clearly non–exercise-related AEs, such as gastroenteritis[44] and bronchitis[45] (Hannan et al provide a full list[17]).

We also applied strict parameters for study inclusion, which meant many recent randomized HIIT studies were excluded from data analysis (eg, those that were abstract only,[53] those that did not include an MICT or usual care comparison group [eg, applied a resistance training group as a comparator],[68,69] or those that did not specifically involve phase 2 [outpatient] CR).[70] Aamot et al[71] conducted a 1-year follow-up program involving home-based, unsupervised HIIT (often termed phase 3 CR) for patients who had already completed 12 weeks of HIIT within the phase 2 CR setting and reported no cardiovascular AEs in relation to the exercise sessions (the only AE was a broken clavicle). More phase 3 CR research is required to clearly determine the safety profile of unsupervised, home-based HIIT after outpatient CR.

Because this review focused specifically on HF and CAD, the findings are not generalizable for patients with other types of CVD, such as cardiac transplant or valvular heart disease. It was also beyond the scope of this review to analyze the timing of AEs during each study; it would be plausible that the risk of an AE is highest in the first few exercise sessions, while the cardiovascular system is still relatively fragile. Indeed, the only major cardiovascular AE reported in relation to HIIT (cardiac arrest) occurred during the first week of the training study.[16] We recommend that future exercise studies on this topic

report characteristics of the AEs more completely (eg, cardiovascular versus noncardiovascular AE; exercise related versus non–exercise related; timing of the event within the training intervention; and any distinguishing patient characteristics or CVD pathological features). Development of a risk screening tool that can accurately identify patients at risk of cardiac AEs during exercise sessions within CR is a priority, and the recently developed Risk of Activity Related Events score[72] may have promise in this regard. However, studies reporting more complete characterization of the safety profile of their exercise training interventions would aid in this process.

Conclusions

HIIT appears safe when applied to patients with CVD within a tertiary care service, on the basis of safety data from studies that applied appropriate patient screening and a baseline stress test with electrocardiography. Further estimates of safety are required to answer this question, using studies appropriately powered to measure AE differences.

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