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Abstract

Introduction-Aerobic interval training (AIT) has recently emerged as a more effective strategy than moderate intensity continuous exercise (MICE) for improving VO2peak in CAD patients. The primary purpose of this retrospective study was to describe the change in VO2peak, and CV risk profile characteristics (secondary outcomes) after progressive AIT practiced in the largest, outpatient cardiac rehabilitation (CR) program in North America compared to usual care CR involving MICE. ***Methods***- Electronic database records were retrieved from consecutively enrolled patients with CAD who attended the Toronto Rehabilitation Institute, between January 1, 2005 to December 31, 2015. Patients were then separated into two, age and sex propensity score matched groups: 772 patients were prescribed 26 weeks of MICE (60-80% of VO2peak, 5 times/week) as per usual care CR (56.0±9.2 years; 12% female/88% male; VO2peak: 20.8±5.9 $ml \cdot kg^{-1} \cdot min^{-1}$), and 772 patients were prescribed 26 weeks of progressive walk/jog intervals (15min/mile walking pace, 12min/mile jogging pace, 5 times/week) (55.9±9.3 years; 12% female/88% male; VO2peak: 24.8±5.7 $ml \cdot kg^{-1} \cdot min^{-1}$). Treatment effect analysis of AIT on VO2peak and CV risk profile characteristics was performed using multiple regression with baseline values as covariates. ***Results***- Treatment effect analysis revealed a 3.84 $ml \cdot kg^{-1} \cdot min^{-1}$ superior improvement in VO2peak in the AIT group compared to usual care MICE group ($p<0.001$). Furthermore, AIT significantly improved BMI, triglycerides, hip and abdominal girth, and depression score compared to MICE ($p<0.023$ for all). ***Conclusions***-Progressive AIT performed in a standard, outpatient CR program appears to be superior to usual care MICE for improving VO2peak, CV risk profile characteristics, and depression score in stable CAD patients. These findings may have important implications for exercise training guidelines in the rehabilitation setting, and in future studies.

Key Words: exercise; coronary artery disease; aerobic capacity; cardiovascular risk profile

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Introduction

Recently, aerobic interval training (AIT), otherwise more commonly known as high intensity interval training (HIIT), has emerged as a more effective strategy than moderate intensity continuous exercise (MICE) for increasing aerobic exercise capacity in individuals with stable Coronary Artery Disease (CAD) (1-4). AIT is characterized by intermittent bouts of exercise, typically ranging from 15 seconds to four (4) minutes, performed at approximately 85-95% of peak heart rate (HRpeak) (1, 5, 6), or 85-100% of maximal aerobic power (7-9), followed by periods of active or passive recovery. Aerobic exercise capacity, as measured by peak oxygen consumption (VO2peak), has been established as a powerful, independent predictor of cardiovascular (CV) and all-cause mortality in patients with CAD (10-12). Importantly, previous studies investigating this population have found that with every 1 $ml \cdot kg^{-1} \cdot min^{-1}$ improvement in VO2peak, there is an associated 9-15% reduction in cardiac mortality in both men and women (10-12). Therefore, exercise training-induced improvements in VO2peak in patients with CAD serve as an attractive therapeutic target that can be addressed in the cardiac rehabilitation (CR) setting with the primary objective of improving survival rates.

Notwithstanding the positive and encouraging superior improvements in aerobic exercise capacity observed in the AIT intervention groups compared to the MICE (control) groups, it would be remiss to overlook the limitations of the small, selective samples of predominantly male CAD patients used in these studies. In addition, most studies were of shorter duration (4-12 weeks), and used 4x4 minute intervals at an intensity of 85-95% of HRpeak, or 80%-90% of heart rate reserve (HRR), with 3 minutes of active recovery between these intervals at an intensity of ~50-70% of HRpeak, or 60%-70% of HRR, in 80% of those studies (1, 2, 4, 13). The generalizability of those findings were recently called into question when two of the largest,

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multicenter, randomized controlled trials (RCTs) investigating AIT versus MICE in 261 heart failure, and 200 CAD patients failed to show any significant differences in VO2peak after either of the two exercise programs (14, 15). The parameters of all of these studies may preclude the generalizability of these findings to the greater CAD population, especially in consideration of those patients who may be undergoing a 6-month, outpatient CR program and using a different AIT protocol. Therefore, we critically evaluate the effect of AIT in the largest, outpatient CR program in North America (University Health Network Cardiovascular Prevention and Rehabilitation Program). The purpose is to describe the effects that AIT has on health outcome measures, such as VO2peak, and to describe the feasibility of this prescription in a "genuine" clinical setting.

Therefore, the primary objective of this study is to describe the change in aerobic exercise capacity, as measured by VO2peak, after the progressive AIT CR program versus usual care CR program. Secondary objectives include comparing the demographics, CV risk profile, and characteristics between completers of the progressive AIT & usual care CR groups. In addition, we compare gender differences in the primary outcome measure of VO2peak between the groups as a secondary objective. Finally, we compare the feasibility of progressive AIT currently practiced in a 6-month, outpatient CR program versus usual care CR, as defined by program completion.

Methods

Electronic database records from an initial 7726 consecutively enrolled patients with documented CAD, who entered into the six- month, University Health Network (UHN) Cardiovascular Prevention and Rehabilitation program at the Toronto Rehabilitation Institute Rumsey Cardiac Centre, from January 1, 2005 to December 31, 2015 were retrospectively

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analyzed for this cohort study. This study was approved by the UHN Research Ethics Board (Approval # 16-5441). Patients received a physician referral to the CR program four to eight weeks (minimum) after a cardiac event or surgical intervention. Of the initial 7726 enrolled patients, 6554 patients were prescribed MICE (walking) at both their initial and final exercise prescriptions (Ex Rx), as per usual standard of care CR Ex Rx and progression (16). The remaining 1172 patients were prescribed MICE at their initial Ex Rx, but ended the 6-month program with a final Ex Rx of performing walk/jog intervals. A complete cardiopulmonary exercise assessment (CPA), anthropometric measurements, and Centre for Epidemiological Studies Depression Scale (CES-D) were administered to patients at baseline, after 3-months (mid-way), and 6-months post-CR program. Cardiovascular risk profile was assessed by standard blood requisition blood draw (performed off-site, at a lab according to patient preference) capturing lipid, cholesterol, and triglyceride levels, in addition to the manual measurement of anthropometrics, such as height, body mass, waist circumference, and systolic and diastolic blood pressure performed by qualified Cardiopulmonary Exercise Technicians (CPETs) at the time of CPA, as per standard practice at the Centre. Furthermore, patients were provided with the standard of care Cardiovascular Prevention & Rehabilitation Medical Health Questionnaire at the time of CPA, which included the self-administered, 20-item CES-D questionnaire.

Subsequently, a subgroup consisting of 772 patients who began with an initial Ex Rx of MICE, but ended with a final Ex Rx of performing walk/jog intervals, and who had completed both baseline and 6-month post-CR program assessments in their entirety (referred to as the AIT intervention group hereafter), were age and sex propensity score matched to a subgroup of 772 patients who had an initial and final Ex Rx of MICE (referred to as the MICE group hereafter). Propensity score matching was performed for the specific variables of age and sex, because they

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are the two most important factors that influence our primary outcome measure of VO2peak. Therefore, using the Centre's definition of a "Completer", which encompasses those patients who performed both baseline and 6-month post-program assessments, the intent of this retrospective study was to capture the treatment effect of the progressive AIT intervention versus usual care MICE in these specific subgroups of "Completers". Baseline characteristics of all remaining patients not included in these two subgroups are presented in Supplemental Table 1, and addressed briefly in the Results and Discussion, but otherwise not described in this retrospective study [see Table, Supplemental Digital Content 1, Baseline characteristics of remaining patients (n = 6182) excluded from the two subgroups (AIT and MICE) of 772 age and sex propensity score matched "completer" patients, http://links.lww.com/MSS/B160].

Cardiac Rehabilitation Exercise Program

The CR program was comprised of two exercise components: aerobic and resistance training (RT). Both components were carried out in a group environment, once per week for 6-months, under the supervision of cardiac rehabilitation supervisors (CRS) and with medical specialists in close proximity at all times. This 6-month CR program was free of cost to all patients, courtesy of government health care coverage. In addition to the weekly, supervised, exercise sessions conducted at the Centre, patients were expected to perform their exercise prescription at home on four other days for a total of five days of exercise per week, with two of those five days including RT. RT involved the use of resistance bands and dumbbells, which were available at the Centre, as well as for purchase for home sessions. Patients documented the duration, intensity, and frequency of their exercise sessions in weekly exercise diaries, which were closely monitored for adherence by the patient's specific CRS every week. In addition to

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the exercise components, weekly classes at the Centre also included education sessions, and access to allied health professionals, such as psychosocial support and nutritional/dietary counseling. The efficacy of this CR program has been established by our group previously (17).

Exercise Prescription Progression for Usual Care MICE (Control Group)

Initial Ex Rx involved walking approximately 1.6km at an intensity of 60% of a patient's VO2peak, based on initial CPA. VO2peak was measured directly via breath-by-breath gas exchange analysis captured by a metabolic cart (Vmax Encore, SensorMedics, Yorba Linda, CA), while a patient performed a symptom-limited CPA using a cycle ergometer (Ergoselect 200P, Ergoline, Bitz, Germany). The CPA protocol consisted of increasing workload by increments of 16.7 Watts every minute, while VO2 was continually recorded throughout the duration of the CPA as 20-second averages (18). VO2peak was recorded as the highest 20-second average obtained in the final minute of exercise, prior to exhaustion and/or CPA test termination, and normalized for body mass (reported as $ml \cdot kg^{-1} \cdot min^{-1}$). Ex Rx were judiciously progressed biweekly by the CRS or Case Manager for each patient in consultation with physicians/medical director, when necessary, to a maximum distance of 6.4km. Only when patients were able to achieve this distance was the intensity of exercise increased to a maximum of 80% of VO2peak. Ex Rx were monitored and progressed using a combination of HR and VO2 data obtained from patients' baseline and 3-month CPA results, in addition to achieving target walking speeds and/or distance (19), corresponding Metabolic Equivalents (METS) (20), and the Borg Scale of Rating of Perceived Exertion (RPE). The precise description of Ex Rx cannot be completely defined, as it is standard practice at the Centre to optimize and individualize prescriptions based on each patient's unique needs throughout the course of the program, in

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accordance with a patient-centered model of care (21). Ex Rx were contained to a maximum daily dose of 60 minutes.

Exercise Prescription Progression "A to F" for Walk/Jog Program (AIT Intervention Group)

As standard practice at the Rumsey Cardiac Centre, patients in the AIT intervention group similarly began with an initial Ex Rx involving walking approximately 1.6km, at an intensity of 60% of a patient's VO2peak based on initial CPA results. The walk/jog interval progressions beginning with Progression A, and ending with Progression F are listed below. Each of the progressions prescribed also included a 5-10 minute warm up and cool down period. All of the progressions were carried out at a 15min/mile walking pace, and a 12min/mile jogging pace, and no Ex Rx exceeded 6.4km or an hour in duration.

Progressions

A) Walk 700m @15min/mile pace, Jog 100m @12min/mile pace, and Repeat.

B) Walk 300m @15min/mile pace, Jog 100m @12min/mile pace, and Repeat.

C) Walk 100m @15min/mile pace, Jog 100m @12min/mile pace, and Repeat.

D) Walk 200m @15min/mile pace, Jog 200m @12min/mile pace, and Repeat.

E) Walk 100m @ 15min/mile pace, Jog 300m @12min/mile pace, and Repeat.

F) Jog @ 12min/mile pace

In an identical manner to the usual care MICE group, Ex Rx were monitored and judiciously progressed by the CRS using the same combination of factors outlined above. However, in contrast to the MICE group, upon CRS observation and recommendation of performing AIT,

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based on a combination of the aforementioned considerations above, and in particular, the guideline that a patient was considered to be capable of achieving and/or achieved a VO2peak in the range of ~22.0-25.0 $ml \cdot kg^{-1} \cdot min^{-1}$ upon CPA, that the patient agreed to perform progressive AIT, as suggested by the CRS. Although this approach introduces some self-selection bias in this study (as discussed in Study Limitations), this was considered to be the standard practice at the Centre. VO2peak cutoff values of ~22.0-25.0 $ml \cdot kg^{-1} \cdot min^{-1}$ correspond with the chosen jogging speed of 12min/mile pace, while a 15min/mile walking pace corresponds with a VO2 of ~18.0 $ml \cdot kg^{-1} \cdot min^{-1}$, as calculated and shown in ACSM guidelines (22). Furthermore, in accordance with the five-level classification of physical activity in terms of exercise intensity (23), the VO2peak cutoff values of ~22.0-25.0 $ml \cdot kg^{-1} \cdot min^{-1}$ fall under the classification of "heavy" exercise intensity, while a VO2 of ~18.0 $ml \cdot kg^{-1} \cdot min^{-1}$ falls under the classification of "moderate" exercise intensity. Notwithstanding the nuances in cutoff values arising from body weight and sex, this multi-factorial approach to prescribing walk/jog intervals and their progression are representative of AIT, and is considered standard practice for this outpatient CR program.

Data Analysis

All data are reported as the mean ± SD, or frequency. Propensity score matching using the nearest neighbor matching technique was performed on individuals in the AIT (treatment) group, with age and sex as the adjustment variables of interest. Completers of the AIT group were age and sex propensity score matched to completers in the Control group in R Programming (R Version 3.3.1, Package "MatchIt", available free of charge at www.R-project.org) (Vienna, Austria). Subsequently, paired t-tests were performed to determine

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significant differences in baseline and six-month, post-program cardiovascular risk profile characteristics, exercise-related health outcome variables, and gender differences between and within the AIT and Control groups. P-values correspond with the associated t-test for Equality of Means between or within a group of matched samples, or with the associated Wilcoxon Signed Rank Test to assess whether their population mean ranks differ between the two groups, with $p<0.05$ indicating statistical significance. In order to accurately determine the treatment effect of AIT on the primary outcome measure of VO2peak, and secondary supporting variables of cardiovascular risk profile, and exercise-related outcome measures, multiple regression using baseline values as covariates was employed. The decision to use this approach for determining the treatment effect of progressive AIT was based on the premise of enhanced accuracy by using baseline values of each variable of interest as covariates, in the event that baseline values were imbalanced or significantly different in the sample groups being compared, i.e. not controlled, which was pertinent in our study with respect to the majority of CV risk profile characteristics, and our primary outcome measure of VO2peak.

Results

Baseline Clinical and Cardiovascular Risk Profile Characteristics

Table 1 compares the characteristics of the two groups. There were no differences in sex or age as expected by matching. Overall, patients in the AIT group had a more favorable CV risk profile compared to the Control group, in addition to significantly lower depression scores, as measured by the CES-D (with scores ≥16 indicating clinical depression). The baseline characteristics for the remaining 6182 patients that were not included in the two AIT and MICE subgroups are presented in Supplemental Table S1 [see Table, Supplemental Digital Content 1,

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Baseline characteristics of remaining patients (n=6182) excluded from the two subgroups (AIT and MICE) of 772 age and sex propensity score matched "completer" patients, http://links.lww.com/MSS/B160]. Peak VO2 was lower in the excluded group compared to both subgroups, but overall, those excluded had a more similar CV risk profile to the MICE group compared to the AIT group.

Exercise-Related Outcome Variables

Figure 1 illustrates baseline and 6 month, post-program exercise-related outcome values for both MICE and AIT groups. Differences in all of these variables between the groups were not only evident at baseline (with $p<0.001$ for all comparisons), but they persisted at 6 months, post-program, with the exception of peak RER (1.16±0.094 vs 1.16±0.10, respectively, $p=0.65$) (Figure 1). Resting HR was significantly lower in the AIT group compared to the Control group at 6 months (66.7±12bpm vs 69.5±12bpm, respectively, $p<0.001$), while peak HR (148±18bpm vs 137±23bpm), Rx distance (3.25±0.52mi vs 2.69±0.77mi), Rx time (45.33±7.5 vs 44.71±18.8 min), peak workload achieved during CPA (932±212W vs 789±221W), and the primary outcome measure, VO2peak (33.0±6.4 ml/kg/min vs 26.0±8.1 ml/kg/min) were all significantly higher in the AIT group compared to the Control group ($p<0.001$ for all).

As shown in Figure 1, AIT had a significant Tx effect on lowering resting HR compared to Control (Tx effect=-1.37bpm, $p=0.005$). The AIT intervention significantly increased peak HR (Tx effect=5.95bpm, $p<0.001$), Rx distance (Tx effect=0.47mi, $p<0.001$), and the primary outcome measure of VO2peak (Tx effect=3.84 $ml \cdot kg^{-1} \cdot min^{-1}$, $p<0.001$).

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Gender Differences in VO2peak

Although aggregate data of both men (88% of sample) and women are presented with respect to all of the primary and secondary outcomes measures, the primary outcome measure of VO2peak is reported separately, as stratified by gender here (data not shown in Table or Figures). Women in the control group showed improvements in VO2peak from baseline to 6 months (17.0±3.4 $ml \cdot kg^{-1} \cdot min^{-1}$ to 20.0 ±2.6 $ml \cdot kg^{-1} \cdot min^{-1}$, $p<0.001$), as did the women in the AIT group (24.8±7.7 $ml \cdot kg^{-1} \cdot min^{-1}$ to 31.0 ±4.8 $ml \cdot kg^{-1} \cdot min^{-1}$, $p<0.001$). Group differences in VO2peak between the women existed at baseline and 6 months ($p<0.001$ for both comparisons). Similarly, men in the control and AIT groups demonstrated improvements in VO2peak from baseline to 6 months (19.7 ±4.8 $ml \cdot kg^{-1} \cdot min^{-1}$ to 24.2 ±4.2 $ml \cdot kg^{-1} \cdot min^{-1}$, $p<0.001$) and (24.8 ±9.2 ml/kg/min to 33.3 ±7.9 ml/kg/min, $p<0.001$), respectively. Additionally, between group differences for the men were observed at baseline and 6 months ($p<0.001$ for both comparisons). At baseline, the men and the women in the AIT group showed no significant differences in VO2peak (24.8±9.2 $ml \cdot kg^{-1} \cdot min^{-1}$ versus 24.8 ±7.7 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively, $p=0.99$), however, the men demonstrated significantly higher VO2peak values at 6 months compared to the women (33.3 ±7.9 $ml \cdot kg^{-1} \cdot min^{-1}$ versus 31.0 ±4.8 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively, $p<0.001$).

Post-Program Follow-Up of Clinical and Cardiovascular Risk Profile Characteristics

After 6 months of CR, patients in the AIT group continued to demonstrate a more favorable CV risk profile compared to the usual care Control group, with respect to body mass index (BMI) (26.1± 4.2kg/m^2 vs 28.5±6.3kg/m^2, respectively, $p<0.001$), hip girth (98.8±7.0cm vs 103.9±10.5cm, $p<0.001$), abdominal girth (90.9±10.3cm vs 98.3±14.0cm, $p<0.001$), triglycerides (1.01±0.55mmol/L vs 1.27±0.79mmol/L, $p<0.001$), and CES-D score (5.77±7.06 vs 8.44±9.44, $p<0.001$) (Figure 2). Moreover, BMI (Tx effect=-0.75kg/m^2, $p<0.001$), hip girth (Tx

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effect=-1.5cm, p<0.001), abdominal girth (Tx effect=-1.9cm, p<0.001), triglycerides (Tx effect=-.28mmol/L, p=0.004), and CES-D score (Tx effect=-0.92, p=0.023) were all shown to have a significant Tx effect favoring AIT compared to usual care MICE (Figure 2).

Feasibility

From the 1172 patients who were prescribed a final exercise prescription of performing walk/jog intervals, 772 patients completed the program, yielding a completion rate of 66%. From the 6554 patients who were prescribed usual care CR consisting of MICE (Control group) over the same time period, 4863 patients completed the program, giving a completion rate of 74%.

Discussion

The major finding of this retrospective study was that a structured, progressive program of AIT consisting of walk/jog intervals performed in a standard, 6-month, outpatient CR setting was superior to usual care CR involving MICE, with respect to improving VO2peak in stable CAD patients. Importantly, the treatment effect analysis revealed a 3.84 $ml \cdot kg^{-1} \cdot min^{-1}$ improvement in VO2peak in response to AIT that was conferred beyond the MICE group. Our findings present the results of the implementation of a more progressive version of AIT, where the emphasis does not rest on unwieldy (90%-95%) HRpeak or VO2 values that have recently been shown to be unfeasible in similar populations of heart failure patients (14), and CAD patients (15). Furthermore, this study is the first to use treatment effect analysis to demonstrate that progressive AIT was more beneficial in improving CV risk profile characteristics, and depression score, in this patient population.

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Generalizability of Formal versus Progressive AIT

Despite the small but growing number of RCTs investigating the potential superiority of formal AIT (most often using the 4x4min@85-95% of peak HR with 3min of active recovery protocol) over traditional MICE, the conclusions supporting the benefits of AIT remain limited in their generalizability to the greater population of CAD patients in a standard CR setting. This can be attributed to small (≤30 patients in the AIT groups), and selective samples that are not necessarily representative of this population (1-4). Recently, this concern over the lack of generalizability has meritoriously emerged, as multicenter RCTs investigating populations of heart failure (n=261), and CAD patients (n=200) have not been able to replicate these earlier findings of the superiority of AIT over MICE, in improving aerobic exercise capacity in these populations (14, 15).

Contrary to these smaller studies (1-4), AIT in the form of 4-minute intervals performed at 90% to 95% of maximal HR was found to be unfeasible in more than 50% of heart failure patients in Ellingson et al.'s 2017 study (14), and similarly found to be "hardly feasible" in the majority of CAD patients in the SAINTEX-CAD study (15). Both of these studies also found that patients randomized to the MICE group exercised above the target intensity, therefore minimizing the targeted difference in exercise intensity level between the AIT and MICE groups (14, 15). With both of these RCTs reporting only an approximate 10% difference in training intensity between the groups, this may largely account for no significant differences in improvement of VO2peak found between the groups in these studies (14, 15). Despite the retrospective limitation of being unable to precisely quantify exercise intensity relative to individual peak HR and VO2peak data for the AIT and MICE groups in our study, our findings are encouraging in suggesting that a rigid, "one size fits all", 4x4 minute interval training

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protocol may not be necessary to reap the greater improvements in VO2peak, compared to usual care MICE in this population.

A similar improvement in VO2peak of 46% in response to AIT, which is comparable to our absolute value of 3.84 $ml \cdot kg^{-1} \cdot min^{-1}$, has been shown previously in a population of heart failure patients (5). Interestingly, our progressive version of AIT, which is arguably more conservative than the 4x4 min protocol typically used in studies to date, exceeded the weighted mean difference of a 1.53 $ml \cdot kg^{-1} \cdot min^{-1}$ improvement in VO2peak, observed in a recent meta-analysis of RCTs examining the effectiveness of AIT versus MICE in stable CAD patients (24). Possible mechanisms attributing to the larger increase in peak VO2 observed in the AIT versus MICE group could be from the larger increase in cardiac contractility elicited by AIT, and a greater stimulus of shear stress on the endothelium, and the corollary of exercise-induced vasodilation, resulting in increased oxygen delivery (5). Additionally, at the peripheral level, AIT may also have a greater impact on the oxidative capacity (mitochondrial function) of skeletal muscle, which may lead to a greater enhancement in peak VO2 compared to MICE (5). It is important to note that our program is longer than most of the CR programs that are available globally (26 vs 12 weeks), and it is possible that the longer duration of performing progressive AIT contributed to the larger improvement in VO2peak observed in our study, compared to others (24). Therefore, we must remain cautious in generalizing our findings to shorter CR programs around the world, and we recognize the need to conduct future RCTs examining the benefits of progressive AIT versus MICE in potentially more representative, shorter duration rehabilitation programs worldwide.

Although other studies have designed their MICE protocols to be equal in training volume (as calculated by VO2peak) (2), or isocaloric (5) to their AIT regimens, which were

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eight and nine minutes shorter than their respective MICE protocols, we were unable to address whether shorter exercise prescriptions of AIT were more attractive to patients with respect to reduced time commitment, due to our retrospective limitation of study design. Our progressive AIT and MICE protocols were similar in duration, and thus it remains elusive as to whether the attractiveness of interval training would in part be attributed to savings in time commitment in this population, and therefore, warrants further exploration in future research.

Our data suggest for the first time that women who are capable of carrying out a progressive protocol of AIT in a standard, CR setting demonstrate greater improvements in peak VO2 compared to women performing usual care MICE, when propensity score matched for age. Although the women in the AIT group did not experience the same gain in VO2peak as their male, age-matched counterparts, their >6 $ml \cdot kg^{-1} \cdot min^{-1}$ increase is compelling in setting the stage for what is achievable for this population in future rehabilitation settings. Prospective, large-scale RCTs are necessary to confirm our findings in the relentless pursuit of determining what is best practice, and standard of care in future CR programs in this population, taking into consideration these important gender differences.

Although retrospective in nature, the strength of this present study lies in the large sample of CAD patients that were captured over a 10-year period, who participated in progressive AIT. Obtaining a matched sample size of almost 800 CAD patients (completers) in both the progressive AIT and MICE groups afforded us with the statistical power to detect differences between the groups, which was particularly relevant at 6 months post-program follow-up in determining the treatment effect of AIT. While it is recognized that this subgroup analysis of completers regrettably precludes the ability to comment on the feasibility of performing the AIT intervention in non-completers, and thus remains a limitation of this study, it would have been

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impossible to determine the treatment effect of AIT without complete 6-month, post-program data. Those patients not included in the subgroup analysis [see Table, Supplemental Digital Content 1, Baseline characteristics of remaining patients (n = 6182) excluded from the two subgroups (AIT and MICE) of 772 age and sex propensity score matched "completer" patients, http://links.lww.com/MSS/B160] were less fit, and overall less healthy compared to our AIT and MICE groups, but did more closely resemble the MICE group with respect to several characteristics. Therefore, we must remain cautious in generalizing our findings to the larger population of CAD patients referred to outpatient CR. Nevertheless, our data do corroborate the benefits of performing MICE, and the possibility of even greater benefits conferred by performing progressive AIT, especially if we are able to engage patients to complete a six-month program in its entirety.

Post-Program Follow-Up of Cardiovascular Risk Profile Characteristics and Exercise Outcome Variables

We found that only three other studies investigating the effects of AIT versus MICE in a CAD population reported HDL-C values (1, 13, 15), and similar to our findings, showed no statistically significant differences between the groups.

We showed that progressive AIT significantly improved depression scores more than MICE, which has not been reported previously in the literature pertaining to CAD patients. Only one study reported that anxiety and depression showed similar improvements with AIT and MICE in a population of heart failure patients (25). With the increasing prevalence of psychosocial comorbidities that patients with CAD have upon referral to CR (26), it is integral

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for future research to consider the most effective type of exercise that addresses the unique needs of a given rehabilitation population with chronic disease.

Limitations

This study was retrospective in nature and therefore has a number of limitations, with missing data being the primary barrier. Although we could discern that each patient in the progressive AIT group was prescribed the walk/jog progressions "A-F" during the CR program, we did not have the data to precisely quantify his or her exact progression over the 6-month period, nor did we have access to the exercise diaries that would have described detailed training intensities in terms of HR and RPE data. Furthermore, patients who were in the AIT group presented with a higher baseline VO2peak, and in general, had an overall CV risk profile that was more favorable compared to the MICE group at baseline. This may have contributed to a selection bias, and thus is another limitation of our study, as these patients would have likely been introduced by their CRS to perform interval training at an earlier point in the CR program than MICE group patients. This would have been based on their VO2peak and myriad factors discussed previously in progressing patients in this program, and they may have been more likely to self-select into performing the walk/jog intervals. On a positive note, however, this limitation has helped elucidate the profile of CAD patients who appear to have success in performing this intervention, and who have the potential to reap greater improvements in their health outcomes. This information may help to optimize exercise prescriptions in the future CR setting.

Despite having a large sample size of patients to compare between the groups in this study, the retrospective limitation precludes any generalizations with respect to the safety of this informal version of AIT. In regards to our more selective two subgroups of 772 patients in both the AIT and MICE groups, however, we can confidently state that there were no fatalities, and

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no major hospitalizations that occurred during the 6-month CR program. It would be our recommendation that future, large-scale RCTs examining the safety of AIT be conducted prospectively.

Conclusions

This present study suggests that a structured progression of AIT is superior to usual care MICE in improving aerobic exercise capacity performed in a standard, 6-month, outpatient, cardiac rehabilitation program. Moreover, this study also demonstrates that cardiovascular risk profile characteristics, such as BMI, abdominal and hip girth, and triglycerides, in addition to depression scores, show greater improvements in response to progressive AIT compared to usual care MICE. Taken together, these findings may have important implications for the way in which we approach exercise training in the rehabilitation setting, and in future, prospective RCTs. Notwithstanding these encouraging preliminary findings that favor AIT, we recognize the need for performing prospective, large-scale, multicenter RCTs examining the effects of AIT versus MICE in the rehabilitation setting in more representative programs, which are more likely to be 12 weeks in duration, in addition to more representative samples of CR populations, including older patients, women, and cardiac patients with comorbidities, etc., prior to adopting this exercise training modality into clinical guidelines and practice.

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This manuscript describes original work and is not under consideration by any other journal and has not been published elsewhere. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by ACSM. All authors approved the manuscript

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Figure Legends

Figure 1. Comparison of baseline and 6-month exercise-related outcome variables. Data are shown as Mean ± SD. Horizontal bars with an asterisk (*) shown between groups denote a statistically significant treatment effect ($p<0.05$), as assessed by multiple regression using baseline values as covariates. (‡) denotes within-group differences from baseline to 6 months ($p<0.05$), (†) denotes between-group differences at baseline ($p<0.05$). CPA=cardiopulmonary exercise assessment, HR=heart rate, Peak VO2=peak oxygen consumption, RER=respiratory exchange ratio Rx=exercise prescription

Figure 2. Comparison of baseline and 6-month cardiovascular risk profile characteristics. Data are shown as Mean ± SD. Horizontal bars with an asterisk (*) shown between groups denote a statistically significant treatment effect ($p<0.05$), as assessed by multiple regression using baseline values as covariates. (‡) denotes within-group differences from baseline to 6 months ($p<0.05$), (†) denotes between-group differences at baseline ($p<0.05$). BMI=body mass index, BP=blood pressure, CES-D=Centre for Epidemiologic Studies Depression Scale, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol

Supplemental Digital Content (SDC)

RWJ_Supplemental_Table_S1.docx—Baseline characteristics of remaining patients (n=6182) excluded from the two subgroups (AIT and MICE) of 772 age and sex propensity score matched "completer" patients

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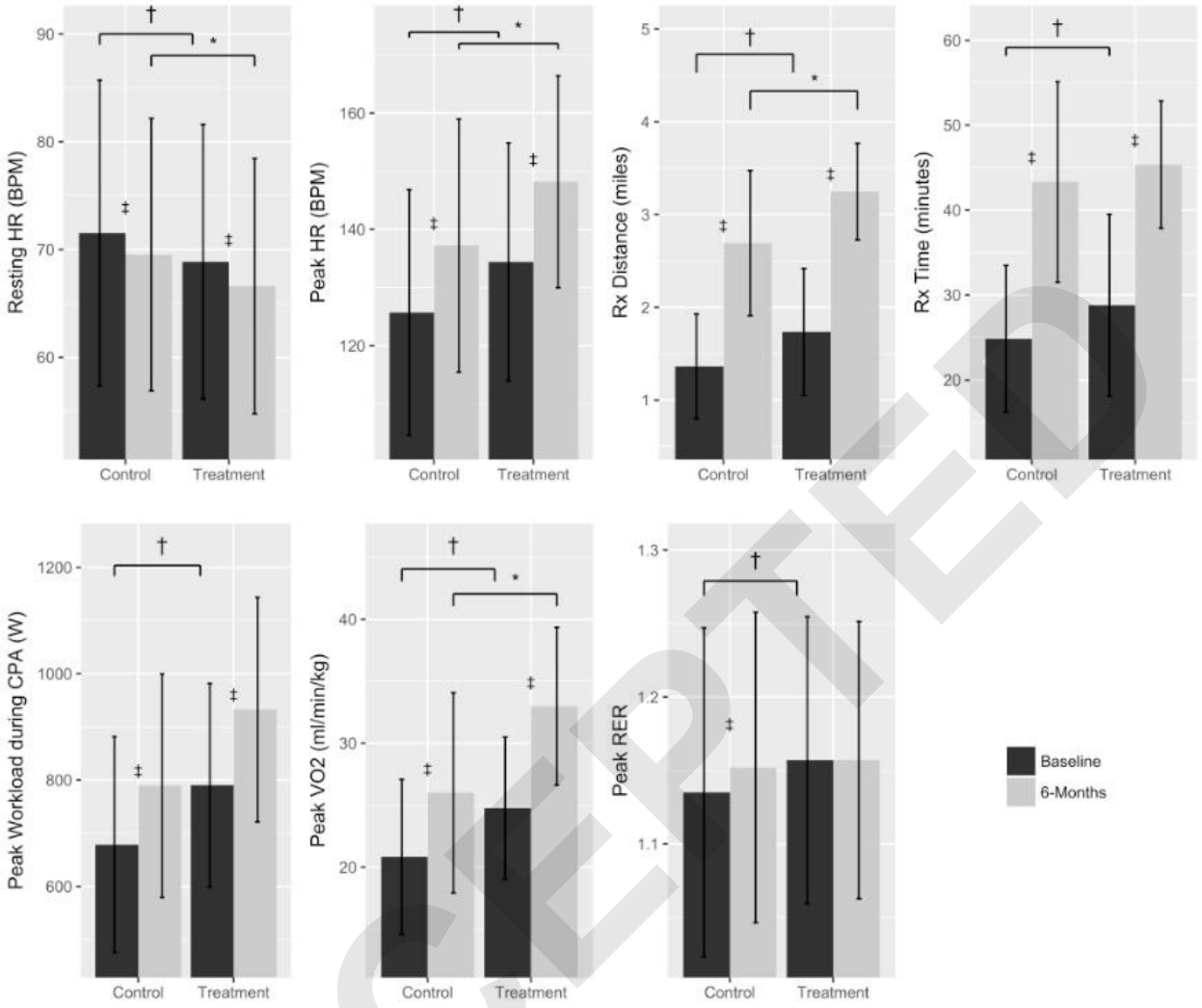

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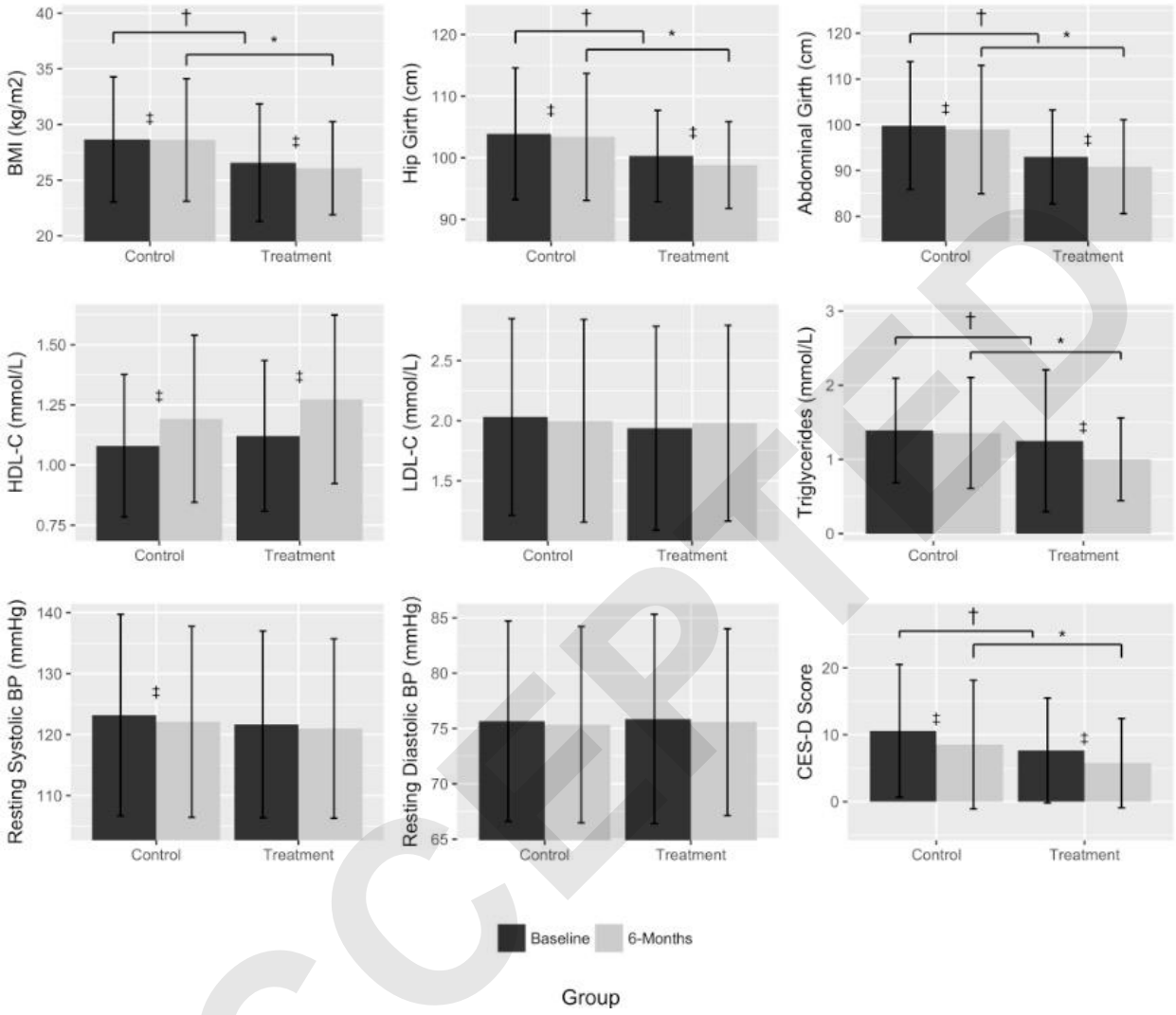

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Table 1: Comparison of baseline characteristics in 772 age and sex propensity matched patients

	AIT Group (Completers) Mean ± SD or frequency	**MICE Group (Completers) Mean ± SD or frequency**	**P-value**
Female/Male (n) (%)	93/679 (12%/88%)	92/680 (12%/88%)	0.94
Age (y)	55.89 ±9.3	55.99±9.2	0.93
BMI (kg/m^2)	26.57 ± 5.3	28.8 ± 6.4	<0.001
Hip Girth (cm)	100.3 ± 7.4	104.4 ± 11.1	<0.001
Abdominal Girth (cm)	92.97 ± 10.3	98.82 ± 14.0	<0.001
HDL-C (mmol/L)	1.12 ± 0.3	1.08 ± 0.3	0.069
LDL-C (mmol/L)	1.94 ± 0.9	1.99 ± 0.8	0.69
Triglycerides (mmol/L)	1.25 ± 1.0	1.41 ± 0.8	0.01
Resting Systolic BP (mmHg)	122 ± 15	124 ± 16	0.15
Resting Diastolic BP (mmHg)	76 ± 9.5	75 ± 9.2	0.64
CES-D score	7.66 ± 7.9	10.86 ±10.0	P<0.001
Cardiovascular Disease (%)	65	60	P=0.028
Percutaneous	49	45	0.13

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Intervention (%)			
Valve Repair (%)	6.1	7.6	0.76
Diabetes (Type 1 & 2)(%)	15	29	<0.001
Hypertension (%)	34	42	<0.001
Ischaemic Heart Disease (%)	4.8	6.1	0.19
Beta-blockers (%)	90	77	<0.001
ACE Inhibitors (%)	59	63	0.11
Statins (%)	83	82	0.67
Time Delay from Event to Exercise (d)	91±49	99±54	<0.001
Peak VO2 (ml/kg/min)	24.8±5.7	20.8±5.9	<0.001
RER	1.16±0.098	1.14±0.11	<0.001
Marital Status (% married)	86.5	85.2	0.55
Smoking Status (% smokers)	0.78	1.30	0.45

ACE=angiotensin converting enzyme, AIT=aerobic interval training, BMI=body mass index, BP=blood pressure, CES-D=Centre for Epidemiologic Studies Depression Scale, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, Peak VO2=maximal oxygen consumption, RER=respiratory exchange ratio

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Supplemental Table S1: Baseline characteristics of remaining patients (n=6182) excluded from the two subgroups (AIT and MICE) of 772 age and sex propensity score matched "completer" patients

	Excluded Group Mean ± SD or frequency	**P-value compared to AIT group**	**P-value compared to MICE group**
Age (y)	65.63 ±10.4	<0.001	<0.001
BMI (kg/m^2)	28.11 ± 5.6	<0.001	0.0071
Hip Girth (cm)	104.10 ± 10.9	<0.001	0.7
Abdominal Girth (cm)	96.82 ± 13.37	<0.001	<0.001
HDL-C (mmol/L)	1.22 ± 0.38	<0.001	<0.001
LDL-C (mmol/L)	2.02 ± 0.81	0.63	0.84
Triglycerides (mmol/L)	1.36 ± 1.9	<0.001	0.73
Resting Systolic BP (mmHg)	127 ± 17	<0.001	<0.001
Resting Diastolic BP (mmHg)	75 ± 9.6	0.003	0.03
CES-D score	9.36 ± 9.0	P<0.001	0.08
Cardiovascular Disease (%)	55	<0.001	0.04
Percutaneous	36	<0.001	<0.001

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Intervention (%)			
Valve Repair (%)	11	<0.001	<0.001
Diabetes (Type 1 & 2)(%)	27	<0.001	0.38
Hypertension (%)	48	<0.001	<0.001
Ischaemic Heart Disease (%)	7.6	0.014	0.42
Beta-blockers (%)	92	0.13	<0.001
ACE Inhibitors (%)	61	0.34	0.55
Statins (%)	89	0.18	0.62
Time Delay from Event to Exercise (d)	100±57	<0.001	0.092
Peak VO2 (ml/kg/min)	18.5±5.5	<0.001	<0.001
RER	1.12±0.19	<0.001	0.10

ACE=angiotensin converting enzyme, AIT=aerobic interval training, BMI=body mass index, BP=blood pressure, CES-D=Centre for Epidemiologic Studies Depression Scale, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, MICE=moderate intensity continuous exercise, Peak VO2=maximal oxygen consumption, RER=respiratory exchange ratio

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