

Current insights into exercise-based cardiac rehabilitation in patients with CHD and CHF

NICHOLS, Simon <http://orcid.org/0000-0003-0377-6982>, MCGREGOR, Gordon, BRECKON, John and INGLE, Lee

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Abstract:

Cardiac rehabilitation is a package of lifestyle secondary prevention strategies designed for patients with coronary heart disease and chronic heart failure. A community-based cardiac rehabilitation programme provides patients with a structured exercise training intervention alongside educational support and psychological counselling. This review provides an update regarding the clinical benefits of community-based cardiac rehabilitation from a psycho-physiological perspective, and also focuses on the latest epidemiological evidence regarding potential survival benefits. Behaviour change is key to long-term adoption of a healthy and active lifestyle following a cardiac event. In order for lifestyle interventions such as structured exercise interventions to be adopted by patients, practitioners need to ensure that behaviour change programmes are mapped against patient's priorities and values, and adapted to their level of readiness and intention to engage with the target behaviour. We review the evidence regarding behaviour change strategies for cardiac patients and provide practitioners with the latest guidance. The "dose" of exercise training delivered to patients attending exercise-based cardiac rehabilitation is an important consideration because an improvement in peak oxygen uptake requires an adequate physiological stimulus to invoke positive physiological adaptation. We conclude by critically reviewing the latest evidence regarding exercise dose for cardiac patients including the role of traditional and more contemporary training interventions including high intensity interval training.

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Keywords: cardiac, behaviour change, high intensity interval training, exercise dose.

A brief history of cardiac rehabilitation

Exercise training has been used to induce weight loss, increase muscular strength and mass, manage diabetes, and reduce the 'incidence of disease' for more than 2,500 years [1]. However, accounts of exercise training being used to improve the health of someone with coronary heart disease (CHD) did not emerge until the 18th century [2]. Despite this early observation, bedrest, rather than exercise, remained the most common treatment for patients with CHD until the 1940's when early mobilisation was shown to prevent complications caused by prolonged bedrest [3]. In 1964, the World Health Organisation acknowledged the important role of 'reconditioning' patients with heart disease [4] and, in 1993, recommended that exercise training become a key component of cardiac rehabilitation (CR) [5]. Exercise training is now considered a core component of a comprehensive CR programme [6] and is thought to improve patient survival [7] and quality of life [8]. However, despite the wide application of exercise training in CR, controversy relating to best practice remains.

Scope of the review

The term 'heart disease' refers to all diseases of the coronary arteries, electrical system or and/or mechanical function of the heart [9]. The benefits of participating in exercise-based CR can vary depending on the type of heart disease being treated and for simplicity, this review will focus on the benefits of exercise-based CR in patients with CHD and chronic heart failure (CHF). The term 'exercise' will be applied in line with WHO definitions, where physical activity is 'any bodily movement produced by skeletal muscles that requires energy expenditure' and exercise is physical activity that is 'planned, structured, repetitive, and purposeful' [5].

Coronary heart disease is caused by atherosclerotic plaques that develop in one or more coronary arteries which can restrict the blood supply to the myocardium and cause angina, or rupture and cause a myocardial infarction (MI) [9]. Although CHD is the leading cause of CHF [10], CHF is fundamentally different, and has other causes which include cardiomyopathies and cardiac valve

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disease [10]. Regardless of aetiology, CHF is characterised by structural and/or functional cardiac abnormalities, reduced cardiac output and/or elevated intracardiac pressures which cause patients to experience severe breathlessness, ankle swelling and/or fatigue [11]. Whilst patients with CHD and CHF can both benefit from exercise-based CR, the benefits of exercise-based CR may differ. This review was conducted ethically in accordance with the requirements of the journal [12].

Clinical benefit of cardiac rehabilitation

Although the effects of exercise training in patients with angina are under reported [13], systematic reviews and meta-analyses conducted in 2011 and 2016 have reported that exercise-based CR reduces cardiovascular mortality and hospital admissions by up to 26% and 18% respectively, over 12 months in patients with CHD [7, 14]. Nevertheless, the effect of exercise-based CR in the era of contemporary medical care has been brought in to question by a recent systematic review and meta-analysis of trials conducted after the year 2000 [15]. Powell et al. [14] found that exercisebased CR did not reduce all-cause (risk difference [RD] 0.00; 95% confidence interval [CI] -0.02 to 0.01, P=0.38) or cardiovascular mortality (RD -0.01; 95% CI -0.02 to 0.01, P=0.25) in patients with CHD. These findings are supported by data from sequential Cochrane reviews which report ever smaller reductions in all-cause and cardiovascular mortality following exercise-based CR for patients with CHD [7, 14, 16]. It is likely that this reflects the beneficial effect that contemporary revascularisation techniques [17, 18] and potent medical management have on shorter and longterm patient survival. In contrast to data recorded in patients with CHD however, exercise-based CR has not historically been considered to improve all-cause mortality in patients with CHF (relative risk [RR] 0.88; 95% CI 0.75 to 1.02) [8, 19]. In addition to the physiological impact, evidence suggests enhanced psychological functioning and emotional regulation reducing both stress and anxiety and increasing the perception of autonomy (self-determination) and control [20].

Despite exercise-based CR having limited impact on patient survival [8, 15], patients with CHD (RD -0.05; 95% CI -0.10 to -0.00; *P*=0.05) [15] and CHF may still benefit from fewer hospital admissions (RR 0.70; 95% CI 0.60 to 0.83) [8]. Furthermore, exercise-based CR may improve patients' health-related quality of life [8, 21] and improve cardiometabolic risk factors [22, 23] which could allow patients to reduce the number and/or dose of secondary prevention medications, although further research is needed to confirm this assertion. In light of these findings, practitioners should continue to explore ways of optimising exercise-based CR.

Modifiable cardiovascular risk factors

Clinical trials and systematic reviews have shown that exercise-based CR can reduce the severity of cardiovascular risk factors associated with the progression of CHD or CHF (Table 1). These include a reduction in low-density lipoprotein (LDL) cholesterol [23, 24], triglycerides, fasting blood glucose, obesity [25], inflammatory markers such as C-reactive protein (CRP) [25], resting blood pressure [24], and end-diastolic volume [26]. Conversely, exercise training can increase high-density lipoprotein (HDL) cholesterol [22, 25] and improve endothelial function [27]. Limited evidence indicates that exercise training could limit myocardial remodelling [28] and attenuate the progression of atherosclerosis [29], although participation for between six and twelve months respectively, may be needed to achieve this outcome.

Clinical trials have shown that aerobic fitness, a key cardiovascular risk factor, may also be improved following exercise-based CR [22, 25, 26, 28-30]. However, data from 950 patients [31] indicated that aerobic fitness improvements following routine exercise-based CR may be small (~0.5 metabolic equivalents; METs) when compared to the effects noted in clinical trials (~1.5 METs) [32]. This may indicate that the dose of exercise delivered in routine healthcare is insufficient [33, 34] and recent data from 332 exercise sessions conducted in a routine exercise-based CR setting supports this

observation [35]. The mean exercise training intensity during a routine exercise-based CR session was reportedly 37% ± 10% of heart rate reserve [HRR], despite practitioners prescribing exercise at 40-70% [35]. This suggests that patients are not being adequately supported to engage in exercisebased CR, a finding emphasised by recent data from the pan-European research project, EUROASPIRE V [36]. EUROAPSIRE V reported that only 34% (n=2,809) of 8,261 patients with CHD were taking part in 30 minutes of exercise on five or more days per week, and that 42% (n=3,470) of patients had no intention of changing their exercise behaviour [36]. Furthermore, 46% (n=3,800) of patients did not receive advice to increase their exercise levels. A similar pattern was evident in relation to weight management [36], and recent findings indicate that obesity may increase following participation in some exercise-based CR programmes [37]. Increasing participation in exercise and reducing levels of obesity and overweight are core objectives of exercise-based CR. A failure to support patients to modify these risk factors could explain why exercise-based CR delivered in routine clinical practice may not improve survival [38]. Exercise-based CR can only be expected to improve cardiovascular risk factors and survival if patients meaningfully engage in the intervention. There is a clear need for researchers, policy makers and practitioners to re-examine the evidence for exercise-based CR to allow the translation of established benefits identified from clinical trials to be integrated into clinical practice. A focus of support from CR programme teams should be to assist patients in making positive lifestyle choices which help improve aerobic fitness and cardiometabolic health.

Behaviour change strategies

While the benefits of structured exercise regimens are unequivocal for those CR patients, practitioners and rehabilitation teams cannot assume that the patient will initiate and maintain recommended rehabilitation programmes just because it is a clinical recommendation. Indeed, evidence suggests that those patients that do adopt lifestyle behaviour change (e.g. diet, PA,

smoking, alcohol and medication adherence) are highly likely to relapse, with programmes suffering from around 75% dropout within 12 weeks of their start [39]. For several years, evidence has highlighted the limits of the long-term effectiveness of exercise for sedentary individuals (which typically reflects these individuals' level of activity) [40] with an over-emphasis by practitioners on exercise initiation, neglecting long term-behaviour change strategies [41]. This action planning approach has typically relied on passive information exchange (e.g. leaflets and signposting to guidelines) which has demonstrated little impact on patient's long-term behaviour change and lifestyle modification. That is not to say that information and knowledge exchange does not have a role to play, but rather that it should not be the only tool in the practitioner's toolbox. To increase impact, an appreciation of effective exercise prescription and other lifestyle intervention components and strategies for the maintenance of such changes, are required [42].

In order for lifestyle interventions such as structured exercise interventions to be adopted by patients, practitioners need to ensure that behaviour change programmes are mapped against the individual's priorities and values [43] and adapted to their level of readiness [and intention] to engage with the target behaviour [e.g. exercise and dietary modification] [44]. An understanding of the patients' intention to change (an individual's desire to perform a given behaviour) is a facet of their likelihood to maintain change and has been highlighted as fundamental by numerous theories. These include: The Theory of Planned Behaviour (TPB) [45], Theory of Reasoned Action (TRA) [46], and Health Action Process Approach (HAPA) [47], all of which place intention as the proximal determinant of behaviour separating motivation and action. The support required for patients in exercise programming and lifestyle change is therefore multifaceted and requires any combination of resilience development, autonomy building, identifying flexible rather than rigid change goals, agenda mapping and environmental support in the form of peers and family members. Evidence has suggested that exercise interventions should also include clearly identifiable Behaviour Change Techniques (BCTs) to increase a patients' autonomy and intention toward change. Examples of BCT

(behaviour)' or 'behavioural practice/rehearsal', all of which have been recommended as key ingredients to promoting long-term change [48]. These approaches increase an individual's perception of self-control and sense of autonomy toward their own change, fundamental aspects when trying to build and maintain motivation.

Patient lifestyle behaviour change is complex and often difficult to achieve. Practitioners should consider utilising the clients experience and raised awareness of their own resource in order to build their engagement in the planning, initiation and maintenance phases [44]. While BCTs have been cited as important ingredients toward supporting patient change, it is important that interventions are evidence-based and practitioners be aware of both the *what* to change as well as the *how* to facilitate this [49].

The role of aerobic fitness

Peak oxygen uptake (\dot{VO}_{2peak}) is determined during a maximal cardiopulmonary exercise test (CPET) and can be summarised by the Fick Equation [50]:

$\dot{V}O_2 = \dot{Q} \times a - vO_2 diff$

Peak oxygen uptake therefore reflects the functional reserve of the heart (cardiac output; \dot{Q}) and muscles (*a-vO_{2 diff}*) when responding to meet the metabolic demands of severe physical stress. The functional reserve of patients with CHD and CHF may be limited, as evidenced by a low \dot{VO}_{2peak} [51-53]. Multiple factors may contribute to a patient having a low \dot{VO}_{2peak} . For example, chronotropic incompetence caused by poor sympathetic and parasympathetic tone, may limit a rise in heart rate during exercise and thus limits \dot{Q} [54]. Similarly, exercise may induce left ventricular dysfunction which can also limit peak stroke volume and therefore, \dot{Q} [55]. These factors may impede the delivery of oxygenated blood to the exercising muscle [56,57] where adverse changes to skeletal muscle physiology including low muscle mass [58,59], poor perfusion and matching of the capillaries and muscle fibres, as well as reduced muscle oxidative capacity [56], may reduce $a-vO_2 d_{iff}$ and aerobic synthesis of adenosine triphosphate [55]. A low \dot{Q} and $a-vO_2 d_{iff}$ causes a marked reduction in $\dot{V}O_{2peak}$ such that the $\dot{V}O_{2peak}$ of men (20.2 ml·kg⁻¹·min⁻¹) [51] and women (15.1 ml·kg⁻¹·min⁻¹) [52] with heart disease who are aged between 50 and 59 years is typically half of that found in healthy men (42.1 ml·kg⁻¹·min⁻¹) and women (33.7 ml·kg⁻¹·min⁻¹) of a similar age [60]. This is concerning because individuals with a low $\dot{V}O_{2peak}$ also have a higher risk of death [61] and disability [62] when compared to those with a higher $\dot{V}O_{2peak}$.

The importance of maintaining aerobic fitness in to older age can be demonstrated by data which suggests that men and women with a $\dot{V}O_{2peak}$ below 18 and 15 ml'kg⁻¹min⁻¹ respectively, may struggle to maintain physical independence [62]. Furthermore, men with a $\dot{V}O_{2peak}$ <14.9 ml'kg⁻¹min⁻¹ have significantly greater risk of death (HR 15.15; 95% CI 7.68 to 29.88) when compared to men with a $\dot{V}O_{2peak}$ <22.8 ml'kg⁻¹min⁻¹. Similar, data are reported for women with a $\dot{V}O_{2peak}$ <11.9 ml'kg⁻¹min⁻¹ (HR 5.87; 95% CI 2.60 to 13.10) when compared to women with a $\dot{V}O_{2peak}$ <16.6 ml'kg⁻¹min⁻¹ [60]. The reasons for this are not fully understood, however patients with a low $\dot{V}O_{2peak}$ typically have more risk factors including advanced age, poor sympathetic and parasympathetic tone indicated by a slower post-exercise heart rate recovery [63], higher markers of cardiac stress (N-terminal pro-brain natriuretic peptide) and inflammation (hs-CRP), higher non-fasting blood glucose levels, more severe atherosclerosis, and lower haemoglobin and haematocrit [63]. Importantly however, increasing a patient's $\dot{V}O_{2peak}$ may improve survival and quality of life.

In 1995, Vanhees and colleagues [64] demonstrated that a 1% improvement in \dot{VO}_{2peak} conferred a 2% reduction in mortality over 5-years, following exercise-based CR in patients with CHD. More recent evidence suggests that a 3.5 ml·kg⁻¹·min⁻¹ improvement in \dot{VO}_{2peak} following exercise training reduces mortality by 25%, if improvements are maintained for more than one year [65]. Exercise-based CR has the potential to increase a patients \dot{VO}_{2peak} by 5.4 ml·kg⁻¹·min⁻¹ (95% CI 4.2-6.6 ml·kg⁻¹·min⁻¹) [32]

suggesting that long-term adherence to accurately prescribed exercise-based CR should be capable of improving survival and quality of life.

We have recently investigated the effects of a routine, twice weekly, exercise-based CR programme for eight weeks (intervention group) compared with abstention from supervised exercise training [control group] in patients with coronary heart disease [66]. The primary outcome was $\dot{V}O_{2peak}$ measured using criterion methods. In 70 patients (age 63.1 ± 10.0 years; 86% male; n = 48intervention; n = 22 controls), $\dot{V}O_{2peak}$ was 23·3 ml·kg⁻¹·min⁻¹ at baseline, and there were no changes in $\dot{V}O_{2peak}$ between groups at any time point. Based on our findings, routine CR does not lead to an increase in $\dot{V}O_{2peak}$ and is unlikely to improve long-term physiological outcomes. One of the key reasons for this lack of improvement in peak oxygen uptake may relate to how we prescribe exercise in this patient group.

Exercise prescription strategies

Exercise prescription recommendations for CR have been highlighted in national and international guidelines (Table 2) [6, 67]. Exercise prescription should first take account of the needs and goals of the individual, including their clinical status and readiness to change behaviour. Furthermore, exercise must be accessible to improve adherence and facilitate sustainable long-term change. Accordingly, exercise-based CR is delivered in numerous settings, either in supervised centre-based programmes, or at home, facilitated by manuals and online platforms. Every individual is different, thus a personalised programme taking account of these factors is likely to be the most successful approach. Unfortunately, in different healthcare settings around the world, it is common for prescription to be dictated by convention and resource, rather than preference or evidence-based best practice [68].

Supervised, centre-based CR is by far the most common delivery model, particularly in the UK [69]. Indeed, the accumulated evidence of the benefits of CR is based almost exclusively on studies adopting this approach either in the 'laboratory' or in pragmatic trials. However, recent evidence from the REACH HF study [21] has definitively demonstrated that a home-based CR intervention, that includes a progressive exercise training programme, can improve quality of life in patients with CHF. Patients in the intervention group reported a 5.7 point reduction in the Minnesota Living with Heart Failure Score after four months (95% confidence interval -10.6 to -0.7; P=0.025), indicating a significant improvement in quality of life. This was maintained after 12 months (Minnesota Living with Heart Failure Score –3.2; 95% CI –5.7 to –0.6; P=0.016). Whilst the intervention did not increase estimated aerobic fitness, historical data from patients with coronary artery bypass grafts indicates that patients engaging in home-based CR are more likely to sustain improvements in aerobic fitness after 12 months, when compared to patients enrolling on centre-based CR [70]. The reasons for these conflicting findings are likely to be multifaceted, but could include factors such as patients with CHF typically experiencing faster disease progression than patients with coronary artery bypass graft, differences in intervention compliance, or exercise stimulus. Nonetheless, self-facilitated or home-based exercise-based CR is significantly underutilised and under researched, despite it showing great potential as an effective alternative to traditional centre-based CR. With countries currently in lockdown due to the outbreak of Covid-19, home-based exercise is, and should, benefit from increased interest amongst healthcare professionals and researchers. Whilst this will benefit patients, practitioners, and healthcare services, it would be easy to lose sight of the longer-term goal of widening access to exercise-based CR and improving the outcomes of patients who attend. Instead of exclusively focusing on the use of home-based CR during the Covid-19 crisis, researchers and practitioners should identify opportunities to incorporate high quality home-based CR in to future standard practice and research projects.

A common aim of exercise-based cardiac CR studies is to improve aerobic capacity, both as a means to enhance quality of life, and as a proxy for improved survival [71,72]. Likewise, improvements in

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muscular strength, endurance and flexibility are considered important to improve the cardiometabolic risk profile and maintain functional independence into older age [73]. To achieve this, guidelines promote comprehensive and holistic exercise assessment and prescription [74]. Perhaps the most contentious issue is that of exercise intensity. The lower and upper safe and effective limits are still debated, as is assessment and prescription in practice. Guidelines vary; Europe, North America and Canada, for example, advocate higher intensity exercise than the UK [67]. Higher intensity exercise results in greater improvements in cardiorespiratory fitness [75] but, for some patients, may be associated with an increased risk of cardiac events [76] or may not be personally acceptable and/or sustainable. With individually tailored exercise prescription, there is a delicate balance to be achieved between optimal intensity, acceptability and safety.

In the context of contemporary pharmacological and interventional management of CHD and CHF, evidence increasingly supports the safety and efficacy of higher intensity exercise-based CR. In metaanalyses, aerobic interval or high intensity interval training (HIIT) have been consistently shown to improve aerobic capacity more than conventional moderate intensity continuous training (MICT) [77-80]. Short bouts (1 to 4 min) of higher intensity (>85% VO_{2 peak}) exercise interspersed with low intensity recovery allow patients to accumulate a greater overall 'dose' of exercise. Benefits appear consistent, regardless of which HIIT protocol is adopted (i.e. 4 x 4 min or 10 x 1 min models) [81]. Historically, there has been a reluctance to deviate from conservative CR exercise intensity guidelines, but large datasets now confirm the safety of HIIT [82,83] and, importantly, patient acceptability [81]. However, two pragmatic multi-centre trials (SAINTEX-CAD [84] and SMARTEX-CHF [85]) did not report the superiority of HIIT using the 4 x 4 model in CHD and CHF. Both studies highlighted issues relating to compliance with the prescribed exercise intensity. In both cases, it was observed that there was little difference between the training intensities in the HIIT or MICT groups due to under achievement in the HIIT groups and over achievement in the MICT groups. This raises issues of compliance with HIIT which are likely multi-factorial, potentially relating to discomfort experienced when exercising above the ventilatory anaerobic threshold (VAT) in addition to logistics

and implementation [81]. Nevertheless, with appropriate medical approval, pre-screening, supervision and monitoring, HIIT can be prescribed safely and effectively in the CR setting for people with CHD and CHF [86, 87]. It should be considered an alternative to, but not replacement for MICT, rather an additional tool available to CR practitioners.

Exercise intensity in CR is commonly determined using predictive equations such as 40-70% heart rate reserve, derived from an estimated maximal heart rate with or without a sub-maximal exercise assessment [67]. This range equates to an RPE of 11-14, eliciting an exercise training intensity that straddles the VAT and is known to be effective at improving cardiorespiratory fitness [88]. In lieu of formal assessment of aerobic capacity using CPET, this approach provides a guide with which exercise can be prescribed and subsequently adjusted. However, recent studies have highlighted the inherent inaccuracy of such calculations, leading to exercise intensities that are consistently lower or higher than the intended optimal thresholds [88, 89]. This may contribute to reports of the diminishing efficacy of CR for some patients and of poor adherence and compliance for others [15, 69]. Whilst CPET can enable precision in exercise prescription, it is not routinely available, particularly in the UK, and is an expensive resource compared to commonly used submaximal 'field tests' such as the six-minute walk test, the incremental shuttle walk test (ISWT), and step tests. Field-tests may provide a useful indication of a patients' aerobic fitness, the presence of a 'normal response' to exercise, and provide information that can be used to inform exercise prescription. However, estimating VO_{2peak} may be inaccurate, particularly when measuring *changes* in VO_{2peak} after exercise-based CR [90]. Maximal cycle ergometry data from patients with CHD, collected by our group, showed that estimating changes in $\dot{V}O_{2peak}$ resulted in significant measurement error, when compared to directly determined VO_{2peak} (limits or agreement -4.7 to 5.9 ml·kg¹·min). Measurement error was such that estimated changes in VO_{2peak} significantly increase following exercise-based CR (1.3 ml kg¹ min; 95% CI 0.4 to 2.2 ml kg¹ min; P=0.006), whilst directly determined changes in \dot{VO}_{2neak} did not (0.5 mlkg¹ min; 95% CI 0.6 to 1.8 mlkg¹ min; P=0.332). We recently observed similar findings in a study of patients attending CR where estimated changes in VO_{2peak} following treadmill work significantly increased, but directly determined $\dot{V}O_{2peak}$ did not [66]. This may have important implications for the way we interpret data from studies that have only estimated $\dot{V}O_{2peak,}$. At the very least, this should encourage caution when discussing whether individual patients had an increase in $\dot{V}O_{2peak}$ after completing exercise-based CR. However, further research is needed to confirm whether other field tests have similar levels of measurement error. Whilst the use of CPET should be encouraged as widely as possible, it is likely that the adoption of CPET prescribed exercise intensity in CR will be dictated by resource implications rather than the potential to confer additional benefit to the patient with CHD or CHF.

One area of exercise prescription in CR that still requires investigation relates to the consistently observed inter-individual difference in training effects. Up to one third of CR patients appear to gain only minimal [or no] improvement in aerobic capacity despite apparent compliance and adherence with their exercise prescription [92]. The reasons for this are not well understood but are likely to include genetic, epigenetic, environmental, nutritional and medical factors, all of which may have a significant impact on exercise prescription for individuals with CHD and CHF [93]. Optimised prescription to maximise outcome may need to take account of these factors, as has personalised medicine in the treatment of disease. Identifying individuals who are the most or least likely to benefit from CR, and how best to optimise exercise prescription, will be the focus of ongoing translation research investigating the determinants and mechanisms of improved exercise capacity in CR [93].

In conclusion, CR is a key treatment vehicle for a broad spectrum of patients with heart disease. Its delivery format has evolved based on a robust body of evidence demonstrating improvements in psychological wellbeing and quality of life. However, CR appears to be underutilised by many clinicians which inevitably has a negative impact on patient outcomes. Further refinements to CR interventions may be required as current evidence indicates that there is a failure to improve peak oxygen uptake following CR, and longer-term survival benefits may be open to question. The "dose"

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of exercise provided by community-based CR teams may not be of sufficient stimulus to drive physiological adaptation required to invoke positive changes in aerobic fitness and ultimately improve long-term mortality outcomes. Adopting effective behaviour change strategies are key to maintaining positive lifestyle changes in the longer-term, and strategies adopted must be individually tailored to meet specific patient requirements.

Table legends

Table 1. Favourable impact of exercise on physical and psychological aspects of health.

Table 2. Exercise prescription guidelines for the cardiac patient. Based on guidance from the BACPR[6].

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