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Impact of Cardiac Rehabilitation and Exercise Training Programs in Coronary Heart Disease

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Short Title: Impact of Exercise-Based Cardiac Rehabilitation

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Key Words:
Cardiac rehabilitation
Coronary heart disease
High-intensity interval exercise training
Abbreviations:
BP – Blood pressure
CABG – Coronary artery bypass graft
CHD – Coronary heart disease
CI – Confidence interval
CR – Cardiovascular rehabilitation
CRF – Cardio-respiratory fitness
CV – Cardiovascular
CVD – Cardiovascular disease
ET – Exercise training
HDL-C – High density lipoprotein cholesterol
HF – Heart failure
HIIT – High intensity interval training
HR – Heart rate
HRQoL – Health-related quality of life
LDL-C – Low density lipoprotein cholesterol
MICT – Moderate intensity continuous training
O₂ – Oxygen
PA – Physical activity
PSS – Psychosocial stress
RCT – Randomized controlled trial
VO₂ – Peak/Maximal oxygen uptake
Abstract

Cardiovascular rehabilitation (CR) is the process of developing and maintaining an optimal level of physical, social, and psychological well-being in order to promote recovery from cardiovascular (CV) illness. It is a multi-disciplinary approach encompassing supervised exercise training, patient counseling, education and nutritional guidance that may also enhance quality of life. Beneficial CV effects may include improving coronary heart disease risk factors; particularly exercise capacity, reversing cardiac remodeling, and favorably modifying metabolism and systemic oxygen transport. We review the historical basis for contemporary CR, the indications and critical components of CR, as well as the potential salutary physiological and clinical effects of exercise-based CR.

Introduction to Cardiac Rehabilitation (CR)

Cardiovascular (CV) disease (CVD) remains the leading cause of mortality worldwide with >17.3 million deaths annually. In the United States alone, CVD causes 800,000 deaths annually, of these 370,000 are attributable to coronary heart disease (CHD) – namely patients that have established atherosclerosis by invasive and non-invasive measures or those that have a myocardial infarction (MI), percutaneous coronary intervention, or require coronary artery bypass graft (CABG), and/or ischemic heart failure (HF). The incidence of MI is approximately 735,000 events annually; 525,000 are an initial event and ~210,000 recurrent MIs.

Major components of secondary prevention for CHD are formal CR and exercise training (ET) programs, which should be considered a vital intervention in the treatment of all CVD patients. Data from randomized controlled trials (RCTs) have shown that ET-based CR after both MI and HF is associated with lower rates of recurrent MI, favorable ventricular remodeling, and decreases in both CVD and all-cause mortality. Moreover, formal CR following MI appears to reduce hospital readmissions, which has gained recent interest in the era of bundled payments. Thus, enrollment in a CR program received a Class I recommendation for patients after an acute CHD event or coronary revascularization procedure in both the European and American College of Cardiology/American Heart Association guidelines.
CR is a supervised program intended to improve outcomes in patients with CHD through ET, dietary, and lifestyle changes (e.g., smoking cessation) that compliment adjunctive cardioprotective pharmacotherapies and address risk factors for CHD. Criteria for referral to CR include angina, MI, HF or a CV procedure, such as percutaneous coronary intervention, heart valve replacement, heart or lung transplant and CABG.

Despite significant benefits, CR continues to be underutilized in the United States, United Kingdom, and Canada, with only 13.9% post acute MI and 31% of post-CABG Medicare beneficiaries enrolled in CR, 29% post-MI enrollment according to a Canadian CHD registry, and 44% of eligible participants enrolled in the National Health System in 2013. Reasons for this include lack of referrals and support from physicians, limited hours of operation and number of facilities, inadequate insurance coverage, and/or patients’ home/work responsibilities. Moreover, availability of CR programs is limited in many countries around the world, thus hindering access for eligible patients. Here, we review current trends and advances in CR, as well as its role in the changing landscape of CHD therapies.

A Brief History of CR

One of the first recorded prescriptions of ET was by Susruta of India in 600 BCE, who advocated that ET “made the body stout, strong, firm, compact, and light, enhanced the growth of limbs and muscles, improved digestion and complexion, prevented inactivity, and reduced senility, [and absolutely] conducive to a better preservation of health.” The links between physical activity (PA)/ET and health were further promulgated through the work of Hippocrates in ancient Greece, as well as the early physicians of Rome and China.

By the time of the Renaissance and into the early 20th century, bedrest became the norm in recuperation from illness (possibly the result of infectious pandemics such as the Black Plague) so that by the 1930s, patients with acute CHD events were still prescribed 6 weeks of bedrest. In the 1940’s, however, the paradigm began to shift as complications from prolonged recumbence became evident. The introduction of “chair therapy” by Levine and Lown in 1951 was one of the first changes in this paradigm. Shortly thereafter, Morris and Heady linked sedentary behaviors to increased risks of CHD by finding higher rates of CHD events in London bus drivers when compared with conductors (the latter...
routinely climbed the stairs of London’s double-decker buses). Data supporting the relative benefits of PA continued to accumulate through the 1960s, and a concerted effort by Hellerstein and colleagues helped link exercise benefits to CHD outcomes and spurred the development of a multi-disciplinary approach to CR.

**Indications, Contraindications, and CR Utilization**

Most patients referred for CR are eligible to participate. Common contraindications to the ET-component are shown in Table 1. Other barriers to participation may include musculoskeletal problems, illnesses, co-morbid conditions, acute infectious and inflammatory states that limit ET, or combinations thereof.

The indications for CR are listed in Table 2; HF is a relatively new addition, as there were long-standing concerns that ET would exacerbate HF. However, more recent studies by Wisløff and others have shown that ET can elicit beneficial peripheral metabolic adaptations in patients with HF, resulting in a paradigm shift in favor of structured ET as an integral component of CR.

Despite favorable data and Class I recommendations, most eligible CHD patients do not enroll in CR. Likely reasons are that referrals for these programs are often not part of routine care for many physicians and access to facilities is difficult in rural areas. One reason for low referral rates may be the significant competition from advances in both medical and revascularization therapies, which have seen faster adoption by the cardiology community because of a combination of physician reimbursement and marketing by pharmaceutical companies and device manufacturers. However, given the impact of CHD as a major cause of morbidity and mortality, interest in conventional and alternative approaches to the delivery of CR has grown and adoption is increasing, spurred by programs such as the Million Hearts Initiative.

**Structure of CR**

The development of structured and physician-supervised CR programs evolved from concerns about the safety of unsupervised ET in patients with recent CVD events. To maximize the benefits of ET in CHD, Hellerstein and Ford pioneered the multi-disciplinary form of CR that is widely used today.
Most CR programs have three phases: inpatient enrollment, a supervised outpatient program, and individual maintenance. The goal is to combine education, ongoing medical management, dietary modifications, lifestyle changes and structured ET to optimize recovery and decrease subsequent CVD morbidity and mortality.

Inpatient enrollment, termed phase I, usually involves low-level ET to the point of performing activities of daily living through early mobilization, medical/lifestyle education, and transitions of care to outpatient CR facilities. These programs are not currently emphasized, as clinically stable patients are rapidly discharged from the hospital, and the accelerated inpatient stay is often used as a preface to the Phase II program.

The supervised ambulatory early outpatient program, phase II, commonly consists of up to 12 weeks of supervised ET and aggressive risk factor reduction. Cornerstones of CR treatment have remained similar to Hellerstein’s original methods, including medical evaluation, PA, lifestyle education, and ongoing medical surveillance and emergency support. Medical care includes patient assessment and aggressive risk factor management; the PA component consists of both education and supervision of a structured ET regimen with periodic reassessments.

Controlling modifiable CHD risk factors involves addressing common medical issues, such as diabetes mellitus, hypertension, and the lipid/lipoprotein profile. However, efficacy is further improved by utilizing therapeutic education to emphasize the importance of smoking cessation, cardioprotective lifestyle changes, dietary modification, and psychosocial stress (PSS) management. In comprehensive/multi-component CR centers, patients learn stress management and other self-control tools, which may favorably modify these risk factors. Support is provided through a multi-specialty care team that includes physicians, nurses, exercise physiologists, physical and occupational therapists, dietitians or nutritionists, mental health specialists and often a case manager, as recommended in guidelines released by the American Heart Association, the American College of Cardiology Foundation, and the American Association of Cardiovascular and Pulmonary Rehabilitation. Multi-specialty teams foster comprehensive lifestyle changes with the goal of long-term behavior modification through reinforcement during CR.
Phase 3 is the culmination of the first 2 phases, that is, inpatient (phase 1) and early outpatient (phase 2), where regular ET and healthy lifestyle habits are continued by patients outside of a supervised healthcare setting with the goal of improving CVD outcomes, health-related quality of life (HRQoL), and mortality. Patient compliance with Phase 2 is one indicator of long-term retention of CR-associated lifestyle modification and is suggested to have a direct association with mortality benefits.\textsuperscript{28}

Modes of Delivering ET

Given the low rate (i.e., 13%-30%) of CR referral and completion after an acute CVD event or revascularization procedure, alternative methods of delivering therapy and ways to optimize CR are being investigated. One of the goals of the Million Hearts initiative in preventing 1 million CVD events over 5 years is to achieve >70% participation in CR through a roadmap of increased referrals and enrollment and more flexible delivery of CR services.\textsuperscript{29}

RCT’s have been conducted to study home-based CR since 2002, especially among patients at low-risk for recurrent CVD events. In a cohort with ischemic CVD at moderate risk, one RCT found no significant differences between the traditional CR with mixed surveillance, and home-based tele-CR when it came to ET time, energy expenditure, and heart rate (HR) recovery in the first minute after exercise testing; however, HRQoL scores were higher in the conventional group.\textsuperscript{30} Hwang et al. enrolled 53 participants with HF into either home-based or conventional CR and found no significant difference with respect to the 6-minute-walk performance test.\textsuperscript{31} Similarly, Moholdt and colleagues evaluated differences in oxygen (O2) uptake and HRQoL between facility-based and home-based CR and found no difference between groups in either O2 uptake and HRQoL.\textsuperscript{32} A meta-analysis of 17 RCTs that included 2172 patients found no significant differences in mortality, major acute CVD events, exercise capacity, and most other markers of CV health when comparing home-based versus center-based CR. Significant differences were noted in center-based participants with respect to improvements in cholesterol and blood pressure. However, home based programs had higher completion rates with a significantly higher adherence (95% CI 1.01 to 1.07).\textsuperscript{33}
Hybrid CR consists of conventional therapy with a rapid transition to home-based/work-based/tele-CR as a means to improve compliance, especially in patients who are still working. One comparison of hybrid CR to center-based CR (n = 53) showed no significant differences in markers of cardiorespiratory fitness (CRF), a finding that was substantiated in another study that compared 195 patients enrolled in hybrid CR with tele-CR to 585 enrolled in conventional therapy.\textsuperscript{34,35} Adherence was evaluated for a hybrid CR model (with a tele-CR at home component) using 99 patients who demonstrated improvements in fitness as well as improved compliance and attendance, and 82.8\% of participants attended >80\% of sessions (higher than the ~60\% completion rate of CR in conventional therapies).\textsuperscript{36} Although data on hybrid CR programs are limited, preliminary findings suggest that they are associated with better adherence and comparable outcomes to center-based interventions, taken together with favorable adherence data from home-based programs, hybrid CR may represent a cost-effective option to conventional therapy.

Mobile health interventions have the potential to reach 91\% of adults in the United States, and the utilization of health information on mobile platforms has been shown to be more likely in minority than nonminority populations, with growing adoption by older adults.\textsuperscript{37} Few trials comparing mobile health initiatives to conventional CR have been conducted to date. In those that have, some results have been encouraging, with reported improvements in CRF and HRQoL.\textsuperscript{38} In the Heartcycle study, session adherence was high, but exercise time and early cessation of sessions were problematic, and completion of phase II was only 34\%.\textsuperscript{39} Nevertheless, interest by patients in mobile options is high\textsuperscript{40} and there are data that mobile health interventions in the form of text messaging improve compliance with existing CR programs.\textsuperscript{41} Currently, the effectiveness of these interventions is unclear and large RCTs are needed to validate this treatment approach. At least two related clinical trials are underway, EU-CaRE and eEduHeart I, the results of which will hopefully clarify both the advantages and limitations of mobile health therapies and their role in today’s CR landscape.

There are also efforts underway to optimize delivery of conventional CR therapies. The first focuses on improving social support through a Family-Centered Empowerment model. This model consists of using the patient/family unit to identify challenges, solve them, co-educate, and re-evaluate progress.\textsuperscript{42} This model was implemented through an
international consortium into a large RCT, with preliminary results demonstrating significant improvements in exercise tolerance, HRQoL, and PSS.\textsuperscript{43}

PREhabilitation is another novel approach to ET-based therapy that has been suggested to optimize post-CABG outcomes. The premise is to start CR pre-operatively, that is, before bypass surgery, to decrease post-CABG morbidity and mortality. In one report, implementing pre-operative ET yielded improved performance on a 6-minute walk test, a shorter hospital stay, fewer pulmonary complications, and a significantly lower incidence of post-operative atrial fibrillation.\textsuperscript{44}

Ades et al. developed a specific physical conditioning regimen called high-calorie-expenditure ET, which they compared with standard ET in cardiac patients who were overweight or obese. This program achieved much higher ET-related energy expenditure (3000-3500 kcal/week) using more frequent, lower intensity (50-60% VO\textsubscript{2}) workouts with longer durations. Using this high kcal regimen, the investigators reported a significantly greater weight loss with improvement in insulin sensitivity when compared with standard moderate intensity protocols.\textsuperscript{45}

Many recent innovations in ET protocols have included interval training, often with high intensity interval training (HIIT). The differentiating factors between HIIT and continuous moderate intensity continuous training (MICT; usual therapy) are that usual therapy involves continuous maintenance of workload at an intensity of 50%-65% of the peak, often measured as peak O\textsubscript{2} uptake (VO\textsubscript{2}) or peak HR. HIIT protocols consist of shorter high-intensity intervals (75%-95% of maximal effort) interrupted by periods of rest.\textsuperscript{46} The effects of ET intensity and interval training are elaborated below.

**Role of Exercise Intensity**

Weston and colleagues have studied ET intensity and in reviewing a collection of meta-analysis data encompassing 1468 patients enrolled in high versus moderate intensity protocols, and conclude that the benefits of HIIT in improving CRF exceed those gained from MICT protocols utilized as current standard of care for CR.\textsuperscript{47–50} In a similar comparative meta-analysis of 277 patients with CHD, Elliot and colleagues demonstrated
that HIIT was associated with a significantly higher VO$_2$, which is independently associated with reduced CVD mortality.$^{51}$

Larger national cohort studies across the globe support these findings in disease-free general populations. Shiroma and colleagues compared 150 minutes per week of moderate-intensity PA with 75 minutes per week of vigorous-intensity PA among 7,979 men (Harvard Alumni Health Study, 1988–2008) and 38,671 women (Women’s Health Study, 1992–2012) and reported benefits related to moderate-intensity ET in both sexes; however, additional modest reductions in all-cause mortality were associated with high intensity PA.$^{52}$ Similarly, Wisløff and colleagues found that a single weekly session of high-intensity ET reduced CVD mortality in 56,072 men and women enrolled in the HUNT study in Norway; and Wen et al reported a significantly lower all-cause mortality association in those with vigorous ET among 416,175 individuals in Taiwan.$^{53,54}$

In case control and cohort studies of CHD patients, high intensity ET has been shown to elicit higher aerobic capacity, improved endothelial function, and enhanced HRQoL.$^{55}$ In cohort studies of individuals with metabolic syndrome, HIIT improved fat oxidation and fasting glucose levels, as well as VO$_2$.$^{56,57}$

Interestingly, a randomized prospective trial of 200 CHD patients in Belgium comparing HIIT and moderate intensity continuous training protocols showed no significant differences in improvements in peak VO$_2$, endothelial function, and high-density lipoprotein (HDL-C) between the two training groups, although the trends were higher in the HIIT group. One possible explanation for this deviation from previously documented benefits is that average peak HR was relatively high in the MICT group compared with prior trials (80% of predicted).$^{58}$ Similarly, the SMARTEX Heart Failure Study, a multi-center RCT involving 261 patients, failed to find a benefit from HIIT in comparison to MICT.$^{59}$ However, control of ET intensity in different cohorts was imprecise; those in the ET cohort had only 15 out of 77 ET sessions at an intensity consistent with their HIIT protocol; and of 65 patients in the MICT group, 33 exercise at higher than prescribed intensity. This results in significant cross-over and decreases both the effect size and resulting statistical power of inter-group comparisons. In smaller studies, HIIT protocols have a clear benefit to MICT protocols.$^{3,32,60}$ In all three studies, O$_2$ uptake/aerobic capacity was significantly higher in the HIIT participant subgroups. Additionally Wisløff and colleagues found that HIIT was
associated with more reversal of LV remodeling than the lower intensity protocol. The major difference between the smaller and larger studies discussed above is the presence of strict controls on ET intensity, allowing a clearer separation in ET patterns of individuals enrolled into HIIT and MICT protocols. Collectively, these data suggest added benefits from higher intensity ET, especially when using HIIT protocols.

Along with ET intensity, frequency and optimal “dosing” of ET also plays an important role. Michaelides and colleagues found that 30 minutes of ET increased vascular elasticity and improved antioxidant balance; however, these benefits were lost when the ET duration was extended to 60 minutes. These and other recent data suggest that when applied to vigorous ET, more moderate amounts of ET may provide added benefits at reduced risk (<5 hours of ET per week). These physiologic findings appear to be supported by a cohort study of ~13,000 men and women conducted by Blair et al. In it, the authors noted a plateau in benefits above 9-10 metabolic equivalents above which adjusted all-cause mortality no longer improved. Similarly, increases above levels of moderate ET frequency in women were not associated with reductions in the risk of vascular diseases in a prospective study of women in the United Kingdom. These findings support the AHA recommendation.

Effects of ET on CV Physiology

Regular PA has multi-faceted effects on health throughout the body, including improved endothelial function, increased maximal aerobic capacity with better oxidative efficiency, and higher anti-oxidant activity. These physiological changes lead to improvements in both diastolic dysfunction and contractility, lower resting blood pressure (BP) and HR, increased muscle mass and even better cognitive performance.

Increased metabolic demands during ET cause upregulation of mitochondrial division and modify energy pathways within the organelles. Increased mitochondrial content in muscle promotes fat oxidation preferentially over carbohydrate oxidation. This adaptation decreases lactate as a byproduct and permits a longer duration of ET at increased aerobic capacity. In addition, ET favorably impacts cardiac remodeling and results in improvements in cardiac performance. One mechanism is through the reversal of metabolic decoupling processes and associated decreases in glucose uptake in patients.
with metabolic syndrome. Another mechanism is postulated to reflect angiogenesis in working muscles mediated by β-adrenergic stimulation of capillary growth by vascular endothelial growth factors and platelet-derived growth factors. These processes are both stimulated by insulin-like-growth-factor-1, expressed proportionally with ET, and have been shown to reverse adrenergic related cardiac remodeling in animal models. More recent studies have shown that ET-associated post-transcriptional gene regulation via micro-RNA reduces remodeling through interactions among metabolic, contractile and epigenetic genes.

Pathologic cardiac remodeling is closely related to neurohumoral activation resulting from increased sympathetic and decreased parasympathetic tone. Associated frequent ventricular arrhythmias are a risk factor for sudden cardiac death after acute MI. ET modifies sympathovagal signaling toward a persistent increase in parasympathetic tone, resulting in increased HR variability which confers a better prognosis. Accordingly, ET increases the threshold for ventricular ectopic activity, and controlled trials have shown that ectopic beats are less prevalent in trained than untrained post-MI patients.

An increase in CRF is associated with reduced HR and BP responses to ET through changes in angiotensinogen II modulation, with or without concomitant weight loss. This occurs via alterations in systemic vasoconstriction, sodium and water retention, and aldosterone production. Decreasing aldosterone lowers sympathetic tone, complementing the effect of other ET-induced modulators of parasympathetic activity. Another mechanism of regulating sympathetic tone is through the actions of plasma adrenomedullin and atrio/brain-natriuretic-peptides which are tied closely to aerobic consumption. These molecules attenuate BP by suppressing noradrenaline and endothelin-1, and improving endothelial responsiveness and function. ET also protects against oxidative stress, leading to lower nitric oxide scavenging by oxidation and higher nitric oxide bioavailability which have anti-hypertensive effects.

ET-induced improvements in managing oxidative stress help lower systemic inflammatory markers in physically active people with CHD. Ranković et al. reported that men and women participating in a 6-week ET program (a combination of center-based followed by home-based delivery) had C-reactive protein levels that declined by 23.7% (p
<0.001), and plasma vascular cell adhesion molecule-1 levels that decreased by 10.2% ($p$ <0.05) when compared to the sedentary cohort. In addition, for each incremental increase in moderate-to-vigorous PA, adjusted levels of adiponectin increased ($\beta=0.04$) and levels of leptin ($\beta=-0.06$), interleukin-6 ($\beta=-0.08$), and resistin ($\beta=-0.05$, $p$ <0.05 for all) decreased, independent of changes in adiposity. Similarly, in a small RCT of patients with HF, both local expression of tumor-necrosis factor-α, interleukin-1β, and interleukin-6 decreased with regular ET in comparison with the sedentary groups.

In addition to affecting cardiac performance, ET improves lipid profiles. In a meta-analysis ET-based CR was associated with significant decreases in total cholesterol level (-14.3 mg/dL; 95% CI: -24.3 to -4.2 mg/dL) and triglycerides (-20.4 mg/dL; 95% CI: -34.5 to -6.2 mg/dL). Controlled trials of ET-based CR have shown that CHD patients benefit from the lowering of total cholesterol and increasing HDL-C. Furthermore, ET as an intervention to facilitate weight loss has been shown to increase insulin sensitivity while decreasing severity of metabolic syndrome and mortality.

**Impact of CR on Mortality**

One of the initial objectives of CR was to help patients regain autonomy via regular PA. The positive impact of regular PA on mortality in CHD patients has been examined in observational and case-control studies; establishing PA as one of the principal modifiers of mortality risk. In the early era of CR, two pilot meta-analyses, which involved 10 to 22 randomized clinical trials and >4000 participants revealed that ET-based CR was associated with significant reductions in all-cause and CVD mortality of ~20%-25% as compared with usual care. However, these early studies primarily included smaller trials that involved mostly middle-aged male post-MI survivors. Women and elderly populations were largely absent from the analyses, which limited the generalizability of these reports.

In subsequent systematic reviews and meta-analyses, higher-risk patients and improved methodology and reporting were employed. These demonstrated a similar reduction in mortality rates associated with CR, as high as 13%-27% for all-cause mortality and 26%-36% for CVD mortality. Due to recent developments in
interventional and surgical revascularization procedures, and advances in medical therapies for CHD, including high intensity statins and dual anti-platelet therapy, some have questioned whether or not the beneficial effects of CR continue to persist in contemporary CVD patients. Several systematic reviews and meta-analyses have been conducted to address this query. A large meta-analysis of 25 randomized and non-randomized studies from 1995 onward evaluating 219,702 patients supported the benefit of CR in overall mortality reduction in patients who were post-acute coronary syndrome, post-CABG, and in mixed CHD populations. A trend in favor of CR in the reduction of major CVD and cerebrovascular events was also observed. In a recent Cochrane review and meta-analysis of 63 RCTs between 1970 and 2014, including 14,486 CHD patients, CR was associated with an absolute risk reduction for CVD mortality from 10.4% to 7.6%. However, no difference in all-cause mortality between CR and conventional care was observed. Subgroup analyses showed that a significant reduction in all-cause mortality was observed if studies before 1995 were included, but this effect was inconsistent among studies published after 1995. A meta-regression analysis from the same study confirmed this theory by demonstrating an overall gradual reduction in pooled total mortality over time, suggesting that optimal medical therapy and advances in interventions likely play a major role in mortality benefit. However, this effect could also have been confounded by a more comprehensive inclusion of women and older patients in later trials – groups that have historically had less robust benefits from CR. Another meta-analysis that only involved RCTs from 2010-2015 (18 trials, 7,691 patients) supported the impact of supervised ET programs on CVD mortality (Hazard risk 0.58, 95% CI 0.21-0.88), but also did not find a significant effect on all-cause mortality. Interestingly, the investigators also showed that a subgroup analysis of trials involving comprehensive CR programs (i.e., ET program along with close monitoring and management of major risk factors for CHD) both all-cause and CVD mortality were significantly decreased.

The impact of CR on all-cause and CVD mortality based on different categories of CHD (such as stable CHD/stable angina and acute coronary syndrome, including unstable angina, ST elevation MI and non-ST elevation MI, with or without revascularization) remains unclear. A limited number of RCT’s have focused on these subcategories of CHD, but due to the small number of studies, vague descriptions of the type of CHD involved, and
enrollment numbers that are too small to study mortality effects, benefits are unclear. Studying deconditioned and/or unfit patients, those with impaired left ventricular function, and patients with incomplete coronary revascularization will be important in determining optimal approaches for those at high risk of decompensation and death. In addition, most previous studies only followed patients for 12-36 months, which may not have allowed sufficient time to observe the associated mortality benefits from CR. Given the current environment of shrinking healthcare funding, it will be crucial to identify the types of patients most likely to benefit from CR, as this will improve resource utilization in long-term management of CVD patients.

**CR and Hospital Readmissions**

Only a few trials focused on hospital readmissions during the early studies of CR. Heran and colleagues demonstrated that total readmission rates were reduced in patients who underwent ET-based CR when compared with usual care in studies that followed patients for up to 12 months.\(^95\) In a large population-based surveillance study from the Mayo Clinic evaluating 2,991 patients with incident MI, CR participants had lower all-cause hospital readmissions (Hazard Risk 0.75, \(p < 0.001\)) as well as reductions in mortality (Hazard Risk 0.58, \(p < 0.001\)).\(^5\) A 2016 Cochrane review reported a reduced risk of hospital admissions with CR reducing risk of hospitalization from 30.7% to 26.1%.\(^97\) However, most RCTs included in this study did not specify whether the hospital admissions were recurrent hospitalizations or first-time admissions and the trend for improvement in hospital readmissions was inconsistent as other studies failed to observe any benefit of CR. This is especially true when more recent trials and observational studies were included,\(^96\) confirming the notion that optimal medical management and early intervention may have a major impact on reducing recurrent hospitalizations in CHD. In contrast, the benefit of CR in reducing hospitalization has been shown for HF patients, which is reviewed in another section.

**CR and Non-fatal MI**

Most early meta-analyses and systematic reviews did not demonstrate the benefit of CR on recurrent rates of non-fatal MI.\(^87,92-95\) Only two meta-analyses associated ET-based
CR with a reduction in non-fatal MI rates, including a 47% reduction in one review.\textsuperscript{2,98} A lack of benefit in the prevention of recurrent non-fatal MI in the CR group was reported by others.\textsuperscript{96,97} It was suggested that this was due to the conversion of fatal to non-fatal MIs, thereby decreasing mortality rates once CR was incorporated into routine cardiac care.

Van Halewijn et al. reported that MI rates were reduced by 30% in ET-based CR as compared with usual care, and that cerebrovascular events were decreased by 60%, with the number needed to treat being 45 and 82 for MI and cerebrovascular events, respectively.\textsuperscript{25} This study was the first to show a significant reduction in stroke rates in this population after CR; however, this may be attributed to more comprehensive CV care, medication optimization, and improvements in CVD risk factors, such as BP control, smoking cessation, and reduced cholesterol levels, rather than the effects of ET alone.

Revascularizations after CR

The impact of CR on revascularization rates has not been systematically evaluated for the need for subsequent CABG or percutaneous coronary intervention.\textsuperscript{87,95,97} However, revascularization rates were not the primary outcomes in the majority of these trials which largely included post-MI and/or post-CABG patients. Future research appears warranted to address the impact of CR on revascularization rates, especially in high-risk patients with incomplete revascularization or with coronary vasculature that is not amenable to percutaneous coronary intervention.

Health-Related Quality of Life and Psychosocial Stress in Cardiac Rehabilitation

The role of CR in enhancing patients’ well-being is directly related to restoring or improving functional capacity. This relates to both physical work capacity and cognitive function. The latter is important because ~25% of CVD events are associated with PSS, which has been independently shown to be associated with prolonged hospitalization, delayed return to work, and heightened mortality.\textsuperscript{99,100} The effects of PSS appear to be cumulative, and are inversely related to HRQoL.\textsuperscript{101}

In studies that have evaluated major dimensions of HRQoL on post-MI and post-CABG patients using disease-specific and general outcome measures, CR has been reported to enhance PSS profiles, and HRQoL scores.\textsuperscript{102–104} Patients in the CR cohort also
demonstrated a tendency to return to work sooner than those in the conventional care group. Although most trials reported improved HRQoL with CR, meta-analyses were generally unavailable due to heterogeneity in the outcome measures used and varied data reporting. Among patients with CHD, those who undergo percutaneous coronary intervention may experience higher HRQoL when compared with CABG over the short term, but the beneficial effects of CR for these patient subsets appear comparable at 2 years. Of note, women with CHD may have lower HRQoL scores when compared to their male counterparts. Additional gender-focused research is needed to address the impact of CR in enhancing HRQoL in women.

**Impact of CR on the CVD risk factor profile**

The favorable effects of ET on modifiable CVD risk factors have been demonstrated in some previous RCTs and meta-analyses, but in an inconsistent manner. In one meta-analysis of CHD patients, total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were significantly decreased in patients in the comprehensive CR intervention, but not the ET-only group. Another meta-analysis based on this population demonstrated reductions in total cholesterol and triglycerides, without improvements in LDL-C and HDL-C levels. Moreover, systolic but not diastolic BP was significantly reduced following CR. A trend toward an improved lipid profile and BP was reported in another CR systematic review and meta-analysis, but the differences were not statistically significant. Similarly, in RCTs that prescribed and modulated medications within preventive and rehabilitative ET programs, significant reductions in LDL-C and systolic BP were noted. However, this was not the case in the ET-only interventions. In addition, one RCT that addressed ≥6 CVD risk factors during CR demonstrated a reduction in overall mortality, but no differences in overall mortality were present in studies that addressed fewer risk factors. Based on these findings, the improvement in CHD risk factors observed with CR were likely associated with concomitant comprehensive medical management during the ET-based programs, suggesting a critical role of risk factor modification in the secondary prevention of CHD. The overall benefits of CR programs for CHD are summarized in Fig 1.

**CV Risks of ET**
Because strenuous physical exertion is a CV stressor, it has been linked with both non-fatal and fatal arrhythmias, especially in persons with known or occult CVD who undergo unaccustomed vigorous PA. The 2007 American Heart Association scientific statement on exercise and acute CVD events estimated that the risk of any major CV complication (sudden cardiac death, total mortality or MI) is one event in 60,000-80,000 patient-hours. In a study of >25,000 patients participating in 65 CR centers, there was one CVD event for every 8484 exercise tests performed, one CVD event for every 50,000 patient hours of ET, and 1.3 cardiac arrests for every million patient hours of ET. In a review of 4846 CHD patients enrolled in interval and continuous CR regimens in Norway, the difference in event rates were 1 in 129,456 hours of moderate ET and 1 in 23,182 hours of high intensity ET. Of such studies, Japan appears to have some of the lowest rates of adverse events, with only 1 life-threatening adverse event occurring in 383,096 patient-hours of ET. The most serious CVD complications of structured ET for CVD patients are acute MI and sudden cardiac death, usually from ventricular fibrillation which can be triggered by exercise-induced myocardial ischemia, especially in patients with left ventricular dysfunction.

In the elderly CHD population, Chahal et al. studied 97 patients after implantable cardioverter defibrillator implantation who had PA assessed by questionnaire preceding a shock event and found an increased risk of ventricular arrhythmia within 1 hour of ET (HR 5.3, 95% CI, 2.7-10.6), especially in previously inactive patients, with a relative risk of 52.8 (95% CI, 10.1-277).

Although the benefits of structured CR clearly outweigh the risks, additional data on risk stratification and prophylactic strategies (e.g., value of warm-up/cool-down, education of warning signs or symptoms) may help reduce the infrequent, ET-related CVD events. These efforts are already under-way with the development of the Physical Activity Intelligence score, a validated physiologic metric that predicts CVD and all-cause mortality based on aerobic capacity this is discussed further later in this issue.

Conclusions and Future directions

Considerable data now substantiate the molecular, physiological, and medical benefits of regular moderate-to-vigorous PA in the treatment of CHD. By combining this
intervention into a comprehensive treatment program, Hellerstein and others enabled the medical community to greatly improve outcomes after major CVD and cerebrovascular events, including survival, reduced recurrent CVD events, and an enhanced HRQoL. Recent advances in ET regimens and emphasis on comprehensive care in CR programs show promise in further improving the effectiveness of CR, while advances in electronic referrals and mobile delivery are likely to assist in adoption and adherence. Although considerable data now show the benefits of CR programs, the magnitude of benefit from each component of CR requires clarification. Optimizing therapies to maximize CVD outcomes and clarifying the magnitude of benefit from any given component may help to compartmentalize CR and allow for more individualized approaches with targeted therapeutic benefits.
Table 1 – Indications for CR

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<tr>
<th>Indications</th>
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<tbody>
<tr>
<td>Acute myocardial infarction</td>
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<tr>
<td>Stable angina pectoris</td>
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<tr>
<td>Coronary artery bypass graft surgery</td>
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<tr>
<td>Heart valve repair or replacement surgery</td>
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<tr>
<td>Percutaneous transluminal coronary angioplasty</td>
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<tr>
<td>Chronic congestive heart failure</td>
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<tr>
<td>Peripheral arterial disease</td>
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<tr>
<td>Heart transplantation</td>
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<td>Heart-lung transplantation</td>
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Table 2 – Contraindications for CR

<table>
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<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Unstable Angina</td>
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<tr>
<td>Severe or Symptomatic Aortic Stenosis</td>
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<tr>
<td>Decompensated HF</td>
</tr>
<tr>
<td>Severe Obstructive Cardiomyopathy</td>
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<tr>
<td>Acute Cardiac Mural Thrombus</td>
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<tr>
<td>Acute Deep Venous Thrombosis</td>
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<td>Pulmonary embolism</td>
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Fig 1 – Mechanisms by which moderate-to-vigorous exercise training may reduce the risk for nonfatal and fatal cardiovascular events. Abbreviations: BP = blood pressure; EPCs = endothelial progenitor cells; CACs = cultured/circulating angiogenic cells; ↑ = increased; ↓ = decreased; O₂ = oxygen. *Nitric oxide also has antithrombotic effects.
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