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Narrative review

Physical exercise training and coronary artery disease

Robert Höllriegel [1], Norman Mangner [1], Gerhard Schuler [1], Sandra Erbs [1]

[1] *Heart Center Department of Internal Medicine/Cardiology, University of Leipzig, Germany*

Abstract

Coronary artery disease (CAD) is a leading cause of death worldwide, despite improvements in medical and interventional therapies. Based on many studies in large cohorts, regular physical exercise training plays a central and indispensable role in both the primary and secondary prevention of CAD. Exercise training was shown to improve blood pressure control, lipid profile, glucose control, and enhance weight loss in obese patients. Moreover, exercise training not only affects clinical symptoms, it reduces CAD mortality and morbidity in addition to dietary, pharmacological and interventional treatments. Different kinds of exercise training (aerobic, interval, resistance training) have been studied and all are feasible, well tolerated, and beneficial in patients with CAD. Therefore, exercise training has the highest recommendation class (I) and level of evidence (A) in the European guidelines for patients with coronary artery disease. Nonetheless, exercise training is underutilized in patients with cardiac diseases and only a minority of eligible patients is referred to a cardiac rehabilitation or structured exercise training program by their physician.

Keywords

Physical exercise training; Coronary artery disease; Cardiovascular risk factors

Corresponding author
Robert Höllriegel, MD
Heart Center Department of Internal Medicine/ Cardiology
University of Leipzig
Struempellstrasse 39 04289 Leipzig, Germany
e-mail: robert.hoellriegel@med.uni-leipzig.de

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Introduction

Coronary artery disease (CAD) is still a main cause of mortality worldwide. Based on many large cohort studies physical exercise training (ET) plays a central and indispensable role in both the primary and secondary prevention of CAD. Therefore, ET was given the highest recommendation class (I) and level of evidence (A) in the European guidelines for that issue [1]. However, despite the proven effects of ET, physical activity and structured exercise is underutilized in patients with CAD and only a minority of eligible patients are referred to a cardiac rehabilitation or ET program [2].
In this review, we describe effects of ET on CAD risk factors, impact on CAD morbidity and mortality, provide information about underlying mechanisms and discuss different kinds of ET.

Impact of ET on CAD risk factors

CAD results from atherosclerosis, with endothelial dysfunction as an early step in its development [3]. Several risk factors are well established to be associated with endothelial dysfunction and coronary artery disease (Figure 1). Therefore, a therapeutic intervention for CAD should be able to influence these risk factors.

Blood pressure

Arterial hypertension is associated with an increased incidence of all-cause and cardiovascular mortality. Especially in survivors of myocardial infarction elevated blood pressure is an independent predictor of subsequent morbidity and mortality [4]. Optimal blood pressure is usually achieved by pharmacological therapy, but also ET can contribute to blood pressure control. Resting blood pressure, ambulatory blood pressure and exercise blood pressure are reduced after regular aerobic exercise training [5]. Thereby, the improvement in blood pressure decrease seems to be more pronounced in hypertensive than in normotensive patients. In different meta-analyses, which included between 29 and 54 randomized controlled trials the average in training-mediated decreases of systolic and diastolic blood pressure was 4.7/3.1 mmHg, 3.4/2.4 mmHg, and 3.8/2.8 mmHg, respectively [6-8].

Blood lipids

Clearly, most patients with CAD are taking lipid medications, especially statins, because the importance of modifying increased levels of low-density lipoprotein cholesterol (LDL) and decreased levels of high-density lipoprotein cholesterol (HDL) is well established in secondary CAD prevention [9]. Already in 1989, Tran et al. performed a meta-analysis including 15 reports about the effects of ET on lipid and lipoprotein levels in patients after myocardial infarction. In this study they demonstrated significant reductions of total cholesterol, LDL, and triglycerides; and an increase in HDL with ET [10]. However, most following studies noted reductions in total cholesterol or LDL only in the setting of significant exercise-induced weight loss [11]. In contrast, effects of ET on

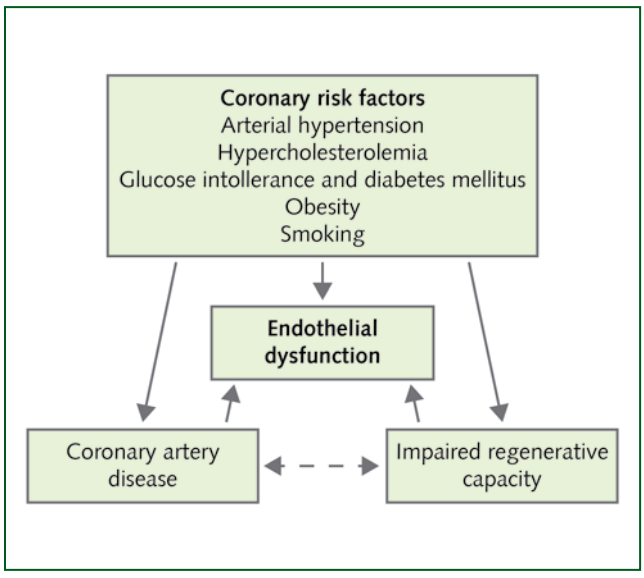

Figure 1. Causes of endothelial dysfunction and their interrelations

HDL and triglycerides seem to be independent of weight loss [12]. Moreover, Kokkinos et al. reported a dose-response relationship between the increase in HDL and miles run per week [13]. More recent data suggest the importance of functional properties of HDL beyond pure quantity as therapeutic target [14]. But so far, the influence of ET on HDL quality is still under investigation.

Glucose intolerance and diabetes mellitus

Diabetes mellitus is the sixth-leading cause of death, with nearly 70% of deaths attributed to cardiovascular diseases [15]. One of the most important studies on this to-date, a randomized, controlled trial in 251 patients with diabetes mellitus type 2, reported significant changes in absolute hemoglobin A1c values of -0.51 percentage point (95% CI: -0.87 to -0.14; p=0.007) after 6 months of aerobic training and -0.38 percentage point (CI: -0.72 to -0.22; p=0.038) after 6 months of resistance training in comparison to a control group [16]. Moreover, the combination of the two ET modalities resulted in an additional change in the hemoglobin A1c value of -0.46 percentage point (CI: -0.83 to -0.09; p=0.014) compared with aerobic training alone and -0.59 percentage point (CI: -0.95 to -0.23; p=0.001) compared with resistance training alone. In a meta-analysis of Snowling and Hopkins the overall beneficial effect of ET on hemoglobin A1c levels was an absolute reduction of −0.8% (90% CI: −1.3 to −0.2) [17]. However, these changes are similar to what is seen in an intensive pharmaceutical intervention. And even these small improvements have been reported to be clinically significant in terms of the effects on a diabetes-related endpoint (sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation (of at least one digit), vitreous haemorrhage, retinal photocoagulation, blindness in one eye, or cataract extraction) [18].

Potential mechanisms for a better glucose control due to regular physical ET include improved insulin sensitivity/resistance, effects on glucose transporters (eg. GLUT4), muscle hypertrophy and increased peripheral blood flow [19-23].

Obesity

Obesity is an independent risk factor for the development of CAD [24]. Moreover, obesity increases the risk for CAD indirectly through its association with insulin resistance, unfavourable lipid profiles, and hypertension [25]. Although there is an ongoing discussion about the "obesity paradox" in patients with CAD and other cardiovascular disorders (in which overweight and obese patients with established cardiovascular diseases seem to have better prognosis than do leaner patients), many studies have demonstrated the efficacy and safety of weight loss for CAD patients [26-30]. In a large study by Lavie et al. a purposeful weight loss and ET program in overweight/obese CAD patients was associated with significant improvements in obesity indices, exercise capacity, plasma lipids, and inflammation, as well as behavioral factors and quality of life. Moreover, a non-significant trend for lower mortality was detectable [29]. In a recent study by Sierra-Johnson et al. weight loss in cardiac rehabilitation led to a lower rate of mortality plus acute cardiovascular events, regardless of initial BMI [31].

Smoking

Cigarette smoking is a well established major risk factor for CAD, particularly sudden cardiac death. Due to a lack of sufficient trials there is no evidence that ET is able to help people quit smoking. So far, just one study showed a long-term benefit for ET versus control on abstinence of borderline significance after 12 months [32]. Most other trials were too small or included an exercise intervention which was insufficiently intense to achieve the desired level of exercise. Although a review by Ussher et al. support recommendation of ET as an aid for reducing tobacco withdrawal and cravings [33], there is no sufficient evidence to recommend exercise as a specific aid to smoking cessation.

Impact of ET on CAD morbidity and mortality

CAD with preserved left ventricular ejection fraction

Beside above mentioned positive effects of ET on CAD risk factors the most important question for our patients is: "Does ET reduce my risk for myocardial infarction or progression of CAD?". Several observational studies have reviewed the relation between participation in a cardiac rehabilitation (CR) program and the cardiovascular (CV) prognosis in post-myocardial infarction, post-coronary intervention, and elderly CAD patients [34-38]. Witt et al. examined the association between participation in a CR program and survival in 1,821 patients with incident myocardial infarction. And indeed, participation in CR was independently associated with improved survival (RR: 0.44; 95% CI: 0.36 to 0.54; p<0.001) and decreased risk for recurrent myocardial infarction (RR: 0.72, CI: 0.52 to 0.99, p=0.049) [34]. In another study an inverse dose-response relationship between the number of CR sessions and long-term outcomes was observed. Attending all recommended 36 sessions was associated with lower risks of death and myocardial infarction at 4 years compared with attending fewer sessions [35]. Likewise, CR completers with CAD have lower risk of death (HR: 0.59; 95% CI: 0.49-0.70), all-cause hospitalization (HR: 0.77; 95% CI: 0.71-0.84) and cardiac hospitalization (HR: 0.68; 95% CI: 0.55-0.83) in comparison to non-completers with CAD [36]. One of the largest studies with 601,099 U.S. Medicare beneficiaries (age ≥ 65 years) who were hospitalized for coronary conditions or cardiac revascularization procedures revealed a 21 to 34% lower mortality rate in CR users compared to non-users [38].

Moreover, there have been prospective randomized trials regarding ET in CAD patients. Hambrecht et al. compared PCI with a 12-months program of regular physical exercise in patients with stable coronary artery disease [39]. And indeed ET was associated with a higher event-free survival (88% versus 70% in the PCI group, p=0.023), notably owing to reduced re-hospitalizations and repeat revascularizations. These data are in accordance with the ETICA trial [40]. In this study 118 consecutive patients with CAD who underwent percutaneous intervention were randomized into an ET or control group for six months. At 33-months follow up patients of the ET group showed a significantly better cardiac event-free survival than patients in the non-exercise group.

One of the largest meta-analysis (48 trials with a total of 8,940 patients) regarding effects of ET on CAD morbidity and mortality was published by Taylor et al. [41]. They showed that exercise-based cardiac rehabilitation reduces both cardiac and total mortality but not the risk of recurrent myocardial infarction or revascularization. Moreover, the mortality effects of an ET therapy were consistent across a number of coronary heart disease groups (e.g., post-myocardial infarction, post-revascularization, angina). A subsequent meta-analysis was focused on the issue how much of the reduction in cardiac mortality in coronary heart disease patients with ET is the result of direct effects on the heart and coronary vasculature, or to indirect effects, via primary risk factors [42]. And indeed, approximately half of the 28% reduction in cardiac mortality achieved with exercise-based cardiac rehabilitation was attributable to reductions in major risk factors.

However, for our patients it doesn't matter if the positive impact of ET is driven by direct effects on the heart and coronary vasculature, or indirect effects. It is clear, that ET/physical activity reduces CAD mortality and morbidity in addition to dietary, pharmacological and interventional treatments.

CAD with reduced left ventricular ejection fraction

Patients with chronic heart failure (CHF) on basis of CAD are not only limited by a reduced left ventricular (LV) function. Several peripheral maladaptations involving an impaired peripheral perfusion secondary to endothelial dysfunction, intrinsic alterations of skeletal muscle, neurohumoral activation and impaired endogenous regenerative capacity are evident in the syndrome of CHF [43-46]. Regarding effects of ET on LV remodeling and LV ejection fraction (LVEF) so far published data are hete-

rogeneous and conflicting. Some studies were able to show an improved LVEF whereas other studies did not find changes in LV performance [47-51]. In a meta-analysis of Kaykowsky et al. aerobic but not combined aerobic and strength training was associated with improved LVEF as well as reduced LV end-diastolic and end-systolic volumes. In contrast to LV performance, several studies were able to demonstrate more homogeneous positive effects of regular physical ET on above mentioned peripheral alterations in both patients with stable CHF and patients with advanced CHF (NYHA IIIb) [52-55]. Moreover, the Exercise training meta-analysis of trials in patients with chronic heart failure (ExTra-MATCH) showed a significant reduction in the primary endpoint of mortality (HR: 0.65; 95% CI: 0.46-0.92, p<0.05) and in the secondary endpoint of death or hospitalization (HR: 0.72, 95% CI: 0.56-0.93, p=0.011) [56]. However, in a recent large randomized clinical trial (HF-ACTION) ET resulted in a non-significant reduction in the primary end point of all-cause mortality or hospitalization [57]. But after adjustment for highly prognostic predictors the primary end point became modest significant. This unexpected result may be attributable to an only modest training intensity and a low adherence rate to the ET program in the training group.

Mechanisms

Analysing the underlying mechanisms by which ET exerts its beneficial effects, the following adaptations were reported as possible key players:

1. Correction of generalized endothelial dysfunction;
2. Improvement of endogenous regenerative capacity;
3. Other pathways or mechanisms directly affecting the heart and its blood supply like the training-induced regression of atherosclerotic lesions or the formation of collaterals.

Correction of generalized endothelial dysfunction

Endothelial dysfunction can occur years before a makroangiopathy, e.g. CAD, becomes evident and has been identified as a general phenomenon independently predicting future cardiovascular events in patients with cardiovascular diseases or risk factors [58]. Suwaidi et al. measured endothelial function in the coronary vessel of 157 patients with moderate non-stenotic CAD and showed significantly increased cardiac events (myocardial infarction, percutaneous or surgical coronary revascularization, and/or cardiac death) in patients with severe endothelial dysfunction after an average follow up of 28 months [59]. Schächinger et al. found that impaired endothelial-dependent and endothelium-independent coronary vasoreactivity was associated with a significantly higher incidence of cardiovascular events over a 7.7-year period [60]. Moreover, impaired peripheral endothelial function independently predicts higher rates of in-stent re-stenosis and re-intervention following percutaneous coronary intervention [61]. The first prospective clinical trial, investigating the effect of ET on endothelium-dependent vasodilatation of coronary conduit and resistance vessels was published by Hambrecht et. al. [62]. Nineteen patients with coronary endothelial dysfunction, as documented by acetylcholine-induced coronary vasoconstriction, were prospectively randomized to a training group or a control group. After four weeks of intensive physical ET, acetylcholine-induced coronary artery constriction was significantly reduced by 54%. Coronary flow velocity increased by 142% in the target vessel during acetylcholine infusion, indicating a remarkable improvement of acetylcholine-induced endothelial nitric oxide release. Moreover, coronary flow reserve as an indicator of intra-myocardial resistance vessel function increased by 29% after four weeks of ET, whereas it remained virtually unchanged in the control group. But how can the above mentioned clinical observations and functional changes can be explained on the molecular level? In patients with CAD risk factors and cardiovascular diseases, coronary and peripheral endothelial dysfunction develops secondary to a reduced nitric oxide (NO) production and

early NO inactivation by reactive oxygen species (ROS), which are produced in excessive amounts [63]. The restoration of the equilibrium between NO production and inactivation by ROS appears to be the primary mechanism contributing to the exercise training-mediated improvement in perfusion in CAD. Human, animal and cell culture experiments suggest that a repetitive increase in shear stress during ET lead to an up-regulation of the endothelial nitric oxide synthase (eNOS), the main source of NO, due to a complex pattern of intracellular regulation like acetylation, phosphorylation, and translocation to the caveolae [64-69]. In addition, ET has an impact on the generation of ROS, scavenging NO. Extended periods of ET result in a reduced expression of NAD(P)H oxidase, the major source of ROS, and a stimulation of radical scavenging systems like copper-zinc containing superoxide dismutase (SOD), extracellular SOD, glutathione peroxidase, and glutathione levels [70-76].

Improvement of endogenous regenerative capacity

In patients with cardiovascular diseases an impaired NO synthesis in association with an increase in oxidative stress promotes the loss of endothelial cells by apoptosis and consequently harms the integrity of the vasculature. Additionally, during aging a proportion of endothelial cells lining the vasculature is lost, also due to apoptosis [77]. In the past, it was believed that the outgrowth of neighboring endothelial and smooth muscle cells represents the only way of repair in case of vascular damage. Recent data provide strong evidence that a subpopulation of bone marrow-derived stem cells – so-called endothelial progenitor cells (EPCs) – are able to promote vascular repair and the formation of entirely new vessels through "vasculogenesis" [78,79]. But in patients with atherosclerosis or cardiovascular risk factors, repair of endothelial damage by progenitor cells appears to be attenuated [80,81]. Beside an absolute reduction in number of EPCs, proliferation, migration and differentiation of EPCs were found to be attenuated in patients with atherosclerotic diseases, which is suggestive of an impaired regenerative capacity [80]. The underlying mechanisms contributing to EPC dysfunction and the reduction in EPC number in atherosclerotic diseases are not well defined yet. It has been proposed that continuous vascular damage in patients with cardiovascular risk factors contributes to an exhaustion of competent EPCs in the blood and the bone marrow [82]. Alternatively, an impaired mobilization of EPCs from the bone marrow might account for the limited EPCs-derived regenerative capacity.

Animal studies suggest that regular physical activity considerably increases the number of EPCs, since ET enhances the NO-mediated liberation from the bone-marrow and reduces the apoptosis of circulating EPCs. These EPCs enhance neoangiogenesis and attenuate neointima formation after vascular injury in exercise-trained animals [83]. The hypothesis of an exercise training-mediated increase in EPCs is supported by studies in humans, showing a 4-fold higher number of circulating EPCs in runners than in inactive healthy control subjects [84]. However, only little is known about the effects of ET on EPC release in patients with CAD and the existing data turned out to be controversial [83,85,86]. Laufs et al. reported that ET results in an increase in circulating EPCs in a mouse model and also in patients with CAD. At least in mice, this effect was NO-mediated [83]. In contrast, in a study by Sandri et. al, EPC levels were found to be unaltered in patients with CAD despite of the fact that the applied training below the ischemic threshold increased vascular NO synthesis. Nevertheless, the integrative capacity of EPCs was significantly improved as a result of the training intervention that might be involved in the regeneration of damaged endothelium [86]. However, when patients with CAD were subjected to one single bout of exercise that induced myocardial ischemia a significant increase in the amount of circulating EPC was detectable within 24 to 48 hours preceded by a rise in VEGF [85]. These data suggest that an enhanced exercise-mediated eNOS expression and NO production – in the absence of an ischemic stimulus – do not necessarily affect the number of circulating EPCs in humans. One might speculate that the exercise training-mediated modulation of EPC function, possibly in combination with an increase in circulating EPC count, rejuvenates the damaged endothelium of the coronary circulation thereby improving myocardial perfusion, but further studies are necessary to address this issue.

Regression of coronary stenosis and collateral formation

For a long time, it was believed that the training-mediated reduction in risk profile and correction of endothelial dysfunction might be associated with a regression of coronary stenosis. However, the exercise training-induced regression of coronary atherosclerosis was negligible in the majority of the trials and, therefore, most likely does not account for the relief in symptoms and the improvement of myocardial perfusion in patients with CAD undergoing exercise training [87-89]. Beside the regression of atherosclerosis, the formation of collaterals has been considered a mechanism explaining the increase in myocardial perfusion in response to ET in CAD. This anticipation was supported by animal studies, showing an enhanced exercise training-induced growth of collaterals, in particular in dogs [90]. However, studies in humans revealed conflicting results. The Heidelberg Regression Study failed to document collateral formation as determined by angiography after one year of regular physical activity in patients with significant CAD [91]. Due to the limitations of angiographic evaluation of coronary collaterals Belardinelli et al. used thallium uptake and reported a significant increase of collateral coronary blood flow in patients with ischemic cardiomyopathy after ET [92]. However, to clarify the importance of coronary collateral formation as a consequence of ET, we have to await the results of the upcoming EXCITE trial investigating the effects of intense physical activity on coronary collateral flow in patients with CAD [93].

Exercise program for patients with CAD

Upon the recommendation of current guidelines for primary and secondary prevention of cardiovascular diseases (CVD) all age groups should perform aerobic exercise, preferably for 30-60 minutes, 5-7 times a week [1,94,95]. These recommendations also point out that activities to increase muscular health and endurance, such as strengthening and flexibility exercises, and balance training to prevent falls are important.

Aerobic exercise

In general, regular aerobic physical activity, at intensity levels ranging between 40-85% of maximal oxygen consumption (VO2) or heart rate reserve, leads to an improved exercise performance, which depends on an increased ability to use oxygen to derive energy for work [96].

Aerobic physical activity in patients with known CAD is usually included into CR program. As already mentioned above, a lot of observational studies have been published regarding the relation between participation in a CR program and the CV prognosis in post-myocardial infarction, post-coronary intervention, and elderly CAD patients showing in particular an inverse dose-response relation between session attendance and mortality/cardiovascular risk [34-38].

In patients with CAD, exercise prescription needs to be tailored to the individual profile after adequate exercise-related risk stratification [1]. The most common modes of aerobic exercise include walking, jogging, cycling, swimming, rowing, stair climbing, or treadmill. Many approaches may be used to determine aerobic exercise intensity [97]. They include % of peak heart rate, heart rate reserve, or the Borg Perceived Exertion Scale. The most accurate assessment uses data derived from cardiopulmonary exercise test results, in which exercise intensity is determined by measuring the maximal oxygen consumption or the anaerobic threshold. An incremental cardiopulmonary exercise test is proposed as the gold standard for a physiologically comprehensive exercise intensity assessment and prescription [98].

In general, low-risk patients, e.g. after uncomplicated MI, should exercise with moderate to vigorous intensity for 3-5 sessions per week, each about 30 minutes [1]. Regardless of the total duration of aerobic exercise, each session should include a 5-minute warm up to decrease the risk of musculoskeletal or cardiovascular complications, and should be finished by a cool down to return heart rate and blood

pressure to near pre-exercise values [97]. In severely deconditioned individuals, accumulated bouts of exercises for 10 minutes can produce similar benefits than described for longer exercise sessions [99]. This finding may support the guideline's statement that some physical activity is better than none [100]. However, there is an on-going debate about the best way of aerobic exercise in CAD patients which can be either continuous or in intervals. Interval ET includes short periods of aerobic exercise at high intensity followed by intervals of low intensity. A recent meta-analysis revealed that this mode of ET is superior to continuous ET in improving aerobic capacity in patients with CAD [101]. Interval ET was shown to improve cardiorespiratory fitness, endothelial function, left ventricle morphology and function (e.g. ejection fraction) to a significantly greater extent when compared with conventional moderate-intensity continuous training. Although this review provides support for interval training, one should be extremely cautious. All reviewed trials are suffered from methodological limitations according to the current standards of reporting. The number of examined patients in each trial was small and selection of patients could be biased by choosing the fittest ones [101].

Resistance exercise

Strengthening exercises and resistance training improve muscle strength, bone density, coordination, balance, and metabolic parameters and thereby lead to a better quality of life and less frailty [102-104]. Adequate technique while performing resistance training using hand weights, elastic bands, weight machines or the person's own body weight is essential to reduce the risk of injuries. Valsalva manoeuvres during resistance exercise should be avoided to reduce the risk of uncontrolled blood pressure elevation [102]. The intensity of resistance training can be prescribed by measuring one repetition performed at maximal weight, the so called 1 RM. For initial training, 30-60% of 1 RM should be used performing one to three sets with 8-15 repetitions with the last repetition producing volitional fatigue. If muscle endurance is the objective, then 30-50% of 1 RM with 15-30 repetitions is considered. For significant strength gain, it is recommended to use 50-70% of 1 RM with 8-15 repetitions [97]. Two or three sessions per week, interrupted by a rest time of at least 48 hours to allow muscle recovery, are endorsed.

Combination of aerobic and resistance exercise training

The combination of both above described exercise modalities was examined in both CAD and CHF patients [105,106]. In post-myocardial infarction patients, the combination of endurance and resistance exercise is safe without a pronounced left ventricular remodelling in comparison to endurance exercise alone. Peak VO_2 and muscle strength increased significantly in both groups, but no difference between the groups was noticed [105]. Also in CHF, no safety concerns occurred and, in contrast to the before mentioned study, the combination of endurance and resistance training had a more pronounced effect on submaximal exercise capacity, muscle strength, and quality of life as endurance training alone in those patients [106]. But caution is necessary since the studies are small and underpowered. In this regard it is important to realize that, in particular in CHF patients, endurance exercise remains the mainstay and that resistance exercise or the combination of both can reasonably complement but not substitute [107].

Hospital-based vs. home-based secondary prevention programs

Programs provided in hospital settings are well established and use multidisciplinary health care teams to address the main modifiable risk factors [108]. But patients' attendance to them is low (~30%) and is even lower in patients with a greater need for risk reduction [109]. For this reason home-based programs have become more common and may be more accessible or preferable to some patients. A recent meta-analysis of 36 trials evaluated the benefits and costs of such a home-based secondary prevention program in CAD patients [110]. Clark et al. showed that home-based interventions improved the main CV risk factors and quality of life in comparison to usual care. Compared with usual care, home-based interventions improved quality of life (weighted mean difference: 0.23; 95% CI: 0.02-0.45),

systolic blood pressure (weighted mean difference: -4.36 mmHg; 95% CI: -6.50 to -2.22), smoking cessation (difference in proportion: 14%; 95% CI: 0.02-0.26), and total cholesterol (standardized mean difference: -0.33; 95% CI: -0.57 to -0.08). But effect sizes were small-to-moderate and the quality of the included trials was only low-to-moderate with high levels of heterogeneity. This was one reason why a robust comparison between hospital-based and home-based interventions was not possible. In the end, the authors conclude that a home-based program may offer a cost effective alternative for stable individuals less likely to access hospital-based cardiac rehabilitation (e.g. increased distance of residency from a cardiac rehabilitation center). Further high quality randomized trials have to clarify the relative effectiveness of home-based programs compared to the classical hospital-based CR programs.

Risk of exercise in CVD patients

In patients with an established cardiovascular disease, exercise is intensely determined by exercise related risk. Different risk stratification algorithms are available [111], and the safety of medically supervised programs is established [1]. The incidence of cardiovascular events while exercising in a CR program is low, even in long term exercise programs [112]. Major cardiovascular events may occur from 1 in 50,000 to 1 in 120,000 patient-hours of exercise. Fatal events are by far rare with 1 in 340,000 to 1 in 750,000 patient-hours of exercise [113,114]. It is true that a vigorous bout of exercise may increase the risk of a CV event by 2- or 3-fold for about 30-60 minutes following the bout, even in adopted exercisers. It is reported that ET induces a hypercoagulable state simultaneously with an increase in fibrinolytic capacity, especially during short-term strenuous exercise [115]. Conversely to a persistent activation of the coagulation cascade, the fibrinolytic activity falls relevantly during the recovery period. Moreover, strenuous ET seems to induce a transient increase in platelet counts, aggregation and adhesiveness. These changes in hemostasis and platelet reactivity have been thought to possibly cause acute cardiovascular events [115]. However, major cardiovascular events are reduced by 30% to 50% for the continuing 23-23.5 hours after ET, making the net effect of regular exercise obviously beneficial [116].

What is in the guidelines?

In relation to the before mentioned, both European and American guidelines for CVD prevention, describe recommendations for physical activity and CR participation in the means of primary and secondary prevention in independent sections [1,95]. Both primary and secondary prevention have the

	Recommendations	Level of evidence
ESC	Patients with previous acute myocardial infarction, CABG, PCO, stable angina pectoris, or should undergo moderate-to-vigorous intensity aerobic exercise training ≥ 3 times a week and a 30 min. per session. Sedentary patients should be strongly encouraged to start light-intensity exercise programmes after adequate exercise-related risk stratification (Class I)	A
AHA/ACCF	For all patients, the clinician should encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, at least 5 days and preferably 7 days per week, supplemented by an increased in daily lifestyle activities (e.g., walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least fit, least active high-risk-cohort (bottom 20%) (Class II)	B

Table I. Comparison of recommendations and level of evidence in ESC (European Society of Cardiology) and AHA/ACCF (American Heart Association/American College of Cardiology Foundation) guidelines [1,95]

Questions for further research

The knowledge about ET as a therapeutic intervention in patients with CAD is by no means complete, but evidence suggests it is well effective, especially in secondary prevention. An important open question that might influence future guidelines of ET in CAD is the dose-response relationship between the training intensity and the effects on coronary atherosclerosis. Is there a threshold of training intensity and/or duration that must be surmounted to achieve improvements in long-term survival and reduce cardiovascular events? Moreover, the question remains of how we can increase the prevalence of physical activity and adherence to exercise training programs. Can we solve the compliance problem by starting with prevention in children? Or might a more intensive school based physical education (e.g. daily physical exercise) prevent CAD? All these questions should be addressed in further studies to improve our understanding and optimise the therapy in our patients.

highest recommendation class (I) and level of evidence (A) in the European guidelines whereas the level of evidence is medium (B) in the American guidelines (Table I) [1,95]. Furthermore, the American guidelines recommend that it is reasonable for the clinician to recommend complementary resistance training at least 2 days per week (Class IIa, Level of Evidence C) [95]. Absolute contraindications are not mentioned but both guidelines emphasize adequate exercise-related risk stratification as discussed above [111].

The review in brief	
Clinical question	Aim of this review is to provide the reader with an up-to-date knowledge about exercise training in patients with CAD. Thereby, we focused on exercise-mediated effects on CAD risk factors, impact on CAD morbidity and mortality, underlying mechanisms and different kinds of ET.
Type of review	Narrative
Conclusions	Taken together, ET in patients with CAD is feasible, well tolerated, and beneficial. Beside its positive impact on CAD risk factors, ET improves cardiorespiratory fitness and is able to reduce CAD mortality and morbidity in addition to dietary, pharmacological and interventional treatments. Nonetheless, ET is widely underutilized in patients with CAD and new concepts are needed to improve prescription by physicians, as well as patient compliance to exercise training.
Limitations	As naturally given in a narrative review, there is a higher degree of bias involved in search of literature. Nevertheless, we provide a comprehensive overview of published information to-date.

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