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JACC FOCUS SEMINAR

Exercise for Primary and Secondary Prevention of Cardiovascular Disease

JACC Focus Seminar

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ABSTRACT

Regular exercise that meets or exceeds the current physical activity guidelines is associated with a reduced risk of cardiovascular disease (CVD) and mortality. Therefore, exercise training plays an important role in primary and secondary prevention of CVD. In this part 1 of a 4-part focus seminar series, we highlight the mechanisms and physiological adaptations responsible for the cardioprotective effects of exercise. This includes an increase in cardiorespiratory fitness secondary to cardiac, vascular, and skeletal muscle adaptations and an improvement in traditional and nontraditional CVD risk factors by exercise training. This extends to the role of exercise and its prescription in patients with CVDs (eg, coronary artery disease, chronic heart failure, peripheral artery disease, or atrial fibrillation) with special focus on the optimal mode, dosage, duration, and intensity of exercise to reduce CVD risk and improve clinical outcomes in these patients. (J Am Coll Cardiol 2022;■:■–■) © 2022 by the American College of Cardiology Foundation.

In 2013, physical inactivity was estimated to incur $67.5 billion in direct (health care expenditure) and indirect (productivity losses) costs worldwide.[1] Recent World Health Organization (WHO) estimates suggest that 27.5% of adults do not meet physical activity guidelines, defined as at least 150 minutes of moderate-intensity aerobic or 75 minutes of vigorous-intensity aerobic physical activity per week.[2,3] The consequences of a physically inactive lifestyle include low cardiorespiratory fitness (CRF), obesity, dyslipidemia, hypertension, insulin resistance, and hyperglycemia. Moreover, chronic physical inactivity is associated with increased risk of type 2 diabetes mellitus (T2DM),[4] coronary artery disease (CAD),[4] heart failure,[5] stroke, cardiovascular events,[6] and all-cause mortality.[6] Of note, a global examination of physical inactivity and major noncommunicable disease found that physical inactivity caused ~9% of premature deaths, or more than 5.3 million of the 57 million deaths that occurred worldwide in 2008.[7] As such, physical inactivity represents an important modifiable risk factor for

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ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CAD = coronary artery disease

CRF = cardiorespiratory fitness

CVD = cardiovascular disease

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HIIT = high-intensity interval training

HRR = heart rate reserve

MICT = moderate intensity continuous training

MET = metabolic equivalent of task

NO = nitric oxide

PAD = peripheral artery disease

Q = cardiac output

T2DM = type 2 diabetes mellitus

VO_2max = maximal oxygen consumption

VO_2peak = peak oxygen consumption

WHO = World Health Organization

primary prevention of cardiovascular disease (CVD). In contrast, regular exercise that meets or exceeds the current physical activity guidelines is associated with reduced risk of CAD, stroke, heart failure, CVD-related mortality, and all-cause mortality.

With this as the background, in this part 1 of a 4-part *JACC* Focus Seminar series, we set the stage for a "deep dive" on exercise, cardiology, the athlete's heart, heart failure with preserved ejection fraction (HFpEF), and other related issues. We discuss the physiological mechanisms and adaptations that occur in response to exercise and how these exercise-induced changes contribute to reduction in CVD risk. We will particularly focus on "exercise prescription," defining the optimal mode, dose, duration, and intensity of exercise to reduce CVD risk and improve outcomes for both primary and secondary prevention. For the purposes of this paper, we follow the definition of exercise as physical activity that is planned, structured, and repetitive with the main objective of improving CRF, reducing CVD risk, and reducing clinical outcomes in patients with CVD.[8]

Following this, the other 3 papers in this series cover the full range of aspects relevant to "Exercise, Cardiovascular Disease and The Athlete's Heart," including in part 2 the relationship between exercise and HFpEF, in part 3 the place of sports in the management of hypertrophic cardiomyopathy and other CVDs, and in part 4 the challenging issues and controversies related to the athlete's heart. Collectively, this Focus Seminar covers all the major aspects of this field and should serve as an important resource for clinicians, researchers and recreational and competitive athletes alike.

IMPROVEMENT IN CARDIORESPIRATORY FITNESS WITH EXERCISE TRAINING: ROLE OF CARDIAC, VASCULAR, AND SKELETAL MUSCLE ADAPTATIONS

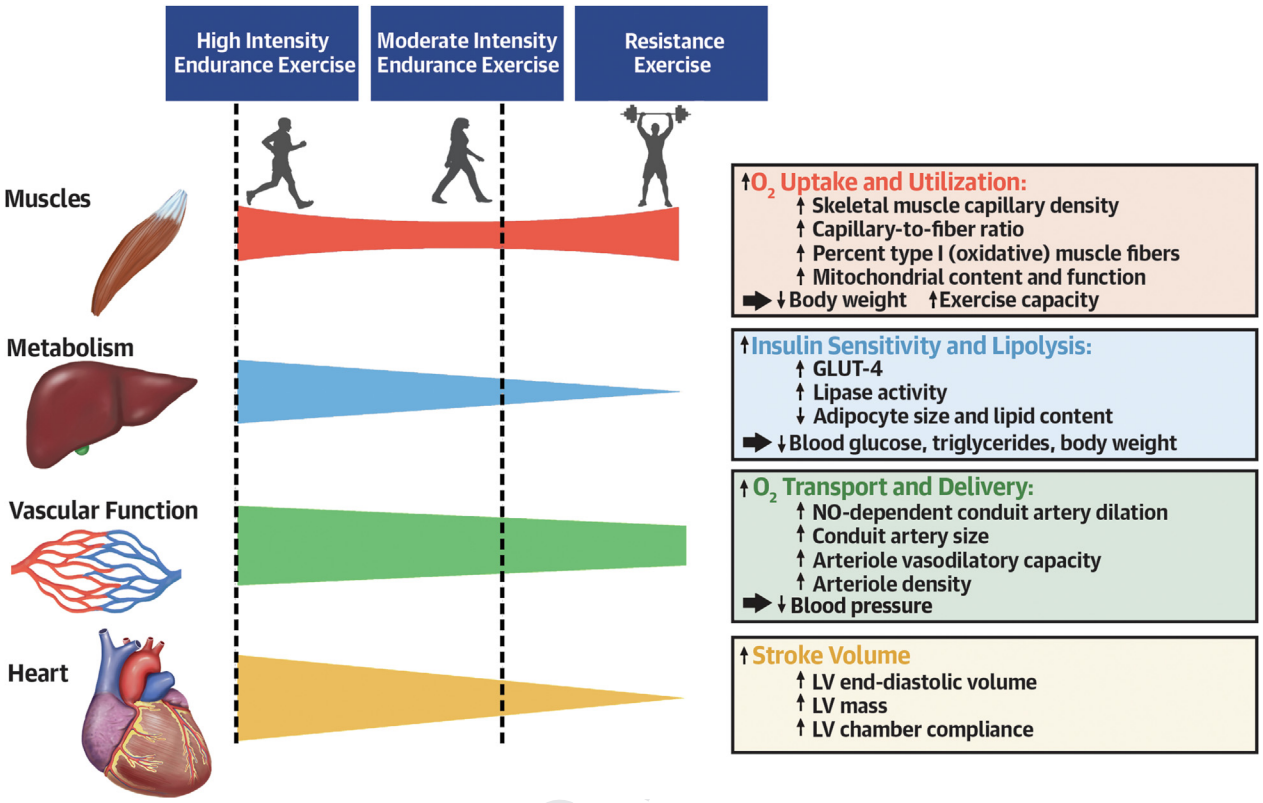
The cardioprotective effects of exercise are mediated by multiple mechanisms including adaptations that improve CVD risk factors.[6,9] However, the greatest benefits with exercise training can be attributed to improvements in CRF, which is a stronger predictor of prognosis than physical activity levels alone.[10] Low CRF is an independent risk factor for CVD and all-cause mortality.[6,11] The gold standard objective assessment of CRF remains the measurement of maximal oxygen consumption (VO_2max) during cardiopulmonary exercise testing. Although not the same as VO_2max, peak oxygen consumption (VO_2peak), measured as the highest VO_2 during an exercise test, is a related measure that is also often used to assess CRF. In at-risk populations such as the overweight or obese, or older adults, aerobic exercise training typically increases CRF (ie VO_2peak) by 3.78 to 3.82 mL/kg/min (~1.1 metabolic equivalent of task [MET]).[12,13] This magnitude of improvement is clinically meaningful, as each 1-MET improvement in CRF is associated with 13% and 15% reductions in all-cause mortality and CVD events, respectively.[6]

The Fick principle dictates that VO_2 = cardiac output (Q) × arterial-venous oxygen difference. Thus, improvements in CRF are the result of increased convective O_2 delivery (increased Q caused by cardiac and vascular adaptations) and O_2 utilization (increased arterial-venous oxygen difference caused by skeletal muscle adaptations), or a combination of both (**Central Illustration**). Long-term aerobic exercise training is associated with changes in cardiac morphology (increased end-diastolic volume, ventricular mass, and left ventricular chamber compliance) that result in a larger stroke volume and Q during maximal aerobic exercise.[14] Exercise training also increases circulating blood volume by approximately 20% to 25%. To accommodate this increase in convective O_2 delivery in response to exercise training, large conduit arteries and smaller

HIGHLIGHTS

- Regular exercise that meets or exceeds physical activity guidelines reduces cardiovascular risk and mortality and plays an important role in primary and secondary prevention.
- The cardioprotective effect of exercise is mediated by cardiorespiratory fitness and improvement in cardiovascular risk factors.
- In contrast to general recommendations on physical activity, exercise recommendations for patients with CVD are more specific, defining mode, intensity, and duration. Specific training plans typically begin with moderate aerobic training, followed by resistance training at increasing intensity.

CENTRAL ILLUSTRATION Differing Forms of Exercise Trigger Differing Physiological Adaptations



Tucker WJ, et al. J Am Coll Cardiol. 2022;■(■):■-■.

As shown, different modes of exercise and exercise intensity trigger different adaptations and effects on muscle energy metabolism, liver energy metabolism, endothelial function and myocardial function. LV = left ventric[illegible]an images from artist/shutterstock.com.

downstream arterioles undergo functional and structural adaptations to facilitate increased skeletal muscle blood flow and local O_2 transport. Specifically, short-term exercise training increases nitric oxide (NO) production and bioavailability for improved conduit artery peak vasodilation (functional adaptation), whereas extended training induces shear stress-mediated arterial remodeling (structural adaptation).[15] Further downstream, exercise training also leads to arteriolar adaptations including greater vasodilatory capacity (functional adaptation) and increased vascular density (structural adaptation) that accommodate increased skeletal muscle blood flow and increase tissue perfusion.[16] Finally, exercise training also elicits multiple skeletal muscle adaptations that increase O_2 uptake and utilization including increased capillary density, capillary-to-fiber ratio, percent type I (oxidative) muscle fibers,[17] and increases in mitochondrial content and function (driven by increases in oxidative enzyme capacity).[18]

In summary, aerobic exercise training elicits cardiac, vascular, and skeletal muscle adaptations that increase CRF secondary to greater convective O_2 delivery (primarily driven by greater maximal Q) and increased O_2 uptake and utilization (arterial-venous oxygen difference) by the exercising muscles (**Central Illustration**).

IMPROVEMENT IN TRADITIONAL CVD RISK FACTORS WITH EXERCISE TRAINING

As well as improving CRF, aerobic exercise training improves traditional CVD risk factors such as insulin resistance, hypertension, dyslipidemia, and obesity.[16,19] In overweight and obese individuals, aerobic exercise training enhances whole-body insulin sensitivity[20] and improves glycemic control,[21] independent of changes in body weight. During exercise, frequently contracting muscle exhibits greater glucose uptake via increased insulin-independent

TABLE 1 Examples of Moderate- and Vigorous-Intensity Aerobic Activities

2020 WHO Physical Activity Guidelines for Aerobic Exercise	Activity	Duration (min/wk)
150-300 min moderate-intensity aerobic exercise per week	Walking (2.5 miles/h, moderate pace)	150-300
	Ballroom dancing (slow pace)	150-300
	Gardening and yardwork	113-225
	Bicycling (light, <10 mph)	113-225
	Brisk walking (3.5 miles/h, fast pace)	105-209
75-150 min vigorous-intensity aerobic exercise per week	Jogging (4.0 miles/h)	75-150
	Swimming (leisure)	75-150
	Hiking	75-150
	Bicycling (moderate, 12-14 miles/h)	56-113
	Running (6 miles/h)	46-92

Examples listed in Table 1 meet the 2020 World Health Organization (WHO) Physical Activity Guidelines for health benefits. [a]Activity classification based on MET codes from 2011 Compendium of Physical Activities.[110]

translocation of GLUT-4 glucose transporters.[19] In addition, exercise-induced peripheral vascular adaptations such as increased arteriole and capillary density allow for increased blood flow that enhances glucose transport and uptake in skeletal muscle.[22] Exercise-induced peripheral vascular adaptations also decrease total peripheral resistance, which reduces arterial blood pressure (BP) and cardiac afterload. However, this is not the only mechanism whereby exercise training lowers BP. It also reduces sympathetic activity, prevents/reverses arterial stiffness, and lowers inflammation,[23] which together also contribute to a reduction in BP. Exercise training also has a favorable effect on the blood lipid profile.[24] Although the mechanisms responsible for this are still unclear, it is believed that exercise enhances the ability of skeletal muscle to utilize lipids as opposed to glycogen, thus reducing plasma lipid levels.[19] Finally, exercise training increases total daily energy expenditure and induces lipolysis, which may result in a modest reduction in body weight and fat mass.[25] The magnitude of improvement for traditional CVD risk factors with exercise training and the clinical significance of these improvements on CVD risk reduction are discussed in further detail in the following text.

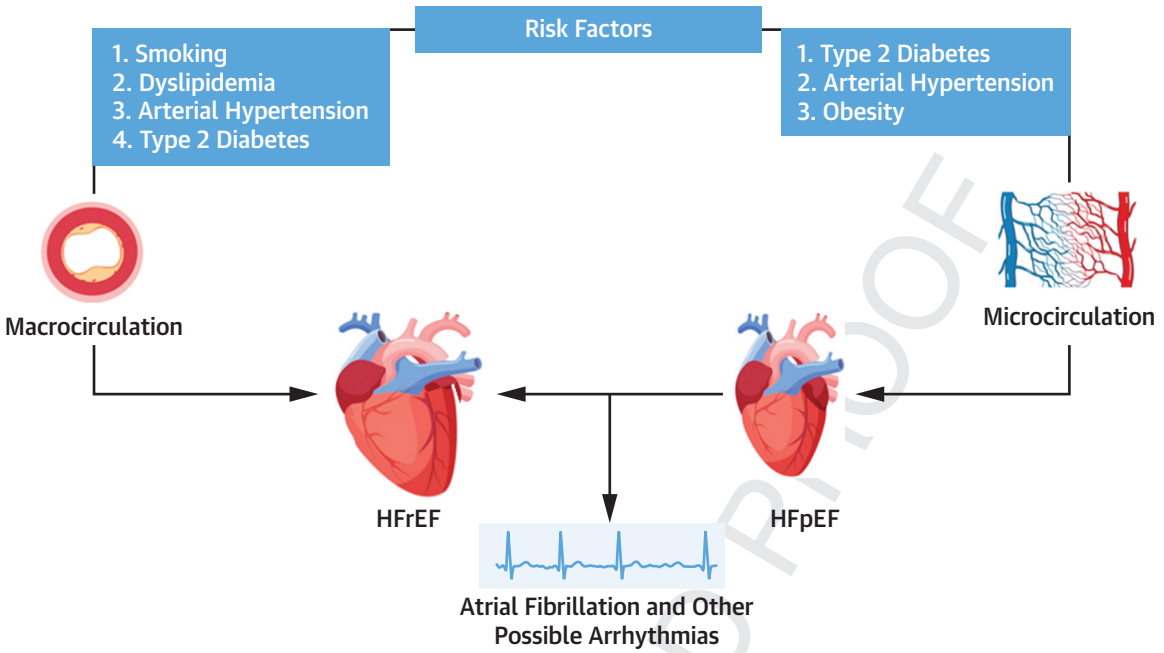
GLYCEMIC CONTROL. Aerobic and resistance exercise training reduce hemoglobin A_{1c} by 0.6% to 0.8% in patients with established T2DM.[26,27] In a 2006 Cochrane Review,[27] which included 14 randomized controlled trials with 377 patients with T2DM, exercise training interventions that typically lasted 8 to 10 months and included aerobic and/or resistance training led to a 0.6% improvement in hemoglobin A_{1c} without changes in body weight. By comparison, in the UK Prospective Diabetes Study,[28] intensive glycemic control using metformin resulted in a hemoglobin A_{1c} reduction of 0.6% and risk reductions of 32% for diabetes-related complications and 42% for diabetes-related mortality in patients with T2DM. As such, exercise training leads to clinically meaningful improvements in glycemic control[27] that may contribute to the reduced risk of cardiovascular events and CVD mortality observed with higher amounts of physical activity in patients with T2DM.[29]

Exercise training also improves insulin resistance and glycemic control in individuals with prediabetes and those who are at risk for T2DM.[20,30] In a recent network analysis[30] that included 13 randomized controlled trials with 567 participants with prediabetes, exercise training that typically lasted 12 weeks and included aerobic and/or resistance training led to a 0.67% improvement in hemoglobin A_{1c}. Furthermore, exercise training by itself[31] or as part of a lifestyle intervention that includes weight loss and dietary education[32] may prevent or delay the onset of T2DM in at-risk individuals. Of note, in the seminal Diabetes Prevention Program study,[32] a lifestyle intervention with the goal of 7% weight loss and at least 150 minutes of physical activity each week reduced the incidence of T2DM by 58% at 2.8-year follow-up in individuals with impaired glucose tolerance.

BLOOD PRESSURE. Both aerobic and resistance exercise training reduce systolic and diastolic BP by 2 to 5 mm Hg in normotensive adults and by 5 to 7 mm Hg in hypertensive adults.[33] Although these reductions are modest, they are clinically relevant and similar to reductions observed with antihypertensive medications.[34] Indeed, in a recent analysis of 48 randomized clinical trials that included 344,716 participants, a 5-mm Hg reduction of systolic BP reduced the risk of cardiovascular events by 10% in both normotensive and hypertensive adults.[35] Although exercise training by itself exerts clinically relevant reductions in BP,[33,36,37] the addition of diet and weight loss may further reduce BP and CVD risk. In the recently published TRIUMPH study,[38] a 4-month randomized clinical trial in patients with resistant hypertension, a lifestyle intervention that included dietary counseling, behavioral weight management, and structured aerobic exercise training reduced systolic BP by 12.5 mm Hg v a 7.3-mm Hg reduction in the standard of care group. Furthermore, the 4-month lifestyle intervention reduced 24-hour ambulatory systolic BP by an average of 7 mm Hg, whereas BP in standard of care group was unchanged.[38]

HYPERLIPIDEMIA. Exercise training has a beneficial effect on blood lipid profiles, independent of weight loss.[24] Meta-analyses indicate that exercise training increases high-density lipoprotein cholesterol by 2 to 5 mg/dL,[24,39] and reduces low-density lipoprotein

FIGURE 1 Pathophysiology of Coronary Artery Disease



The clinical phenotype of coronary artery disease involves differing cardiovascular risk factors that can impact the pathophysiology of the macrocirculation and microcirculation, as well as clinical outcomes like coronary heart disease, heart failure with preserved ejection fraction (HFpEF), heart failure with reduced ejection fraction (HFrEF), and atrial fibrillation. Organ images from artist/shutterstock.com.

cholesterol by 3 to 10 mg/dL[40] and fasting triglycerides by 5 to 25 mg/dL.[39] Although these changes are modest in comparison to drugs like statins, it should be noted that both statin therapy and exercise capacity significantly and independently reduce mortality risk in patients with hypercholesterolemia.[41] Although the majority of the additional survival benefit is most likely attributed to improved CRF and not to further improvements in blood lipids, exercise may directly impact the homeostasis of the arterial wall to antagonize the progression of atherosclerotic disease in patients with dyslipidemia.[16]

OBESITY. Long-term aerobic exercise training typically leads to modest reductions in body weight.[42,43] For example, in a 2011 meta-analysis,[43] aerobic exercise programs of 6 to 12 months were associated with a 1.6 to 1.7 kg weight loss. However, although exercise training does not result in major reductions in body weight, it does lead to significant reductions in harmful visceral and hepatic fat,[42] which are strongly linked to increased risk of CVD and T2DM.[44] Meta-analyses of aerobic exercise training in overweight or obese adults show that exercise significantly reduces visceral and hepatic fat, despite minimal overall weight loss.[45] This may explain why exercise training interventions are typically associated with improvements in cardio-metabolic risk profile with little, to no, weight loss.

EXERCISE INDUCES CARDIOVASCULAR BENEFIT BEYOND IMPROVEMENT IN TRADITIONAL CVD RISK FACTORS

The effects of exercise training on traditional CVD risk factors fail to fully account for the major CVD risk reduction observed with higher amounts of exercise.[46] Indeed, in a prospective study of 27,055 healthy middle-aged women,[47] a combination of traditional and novel CVD risk factors only explained 59% of the exercise-induced risk reduction in CVD and only 35% of the risk reduction in CAD. These data suggest that a large portion of the benefit of exercise (in terms of risk reduction for CVD) remains unaccounted for and cannot be explained by improvements in traditional risk factors alone. In the following section, we highlight some of the nontraditional mechanisms and adaptations that occur with exercise training and how they may contribute to CVD risk reduction.

TABLE 2 Exercise Mode and Intensity: Preferred Recommendation

	Optimal Effects and Preferred Recommendation of Mode and Exercise Intensity		
	High-Intensity Training	Moderate-Intensity Training	Resistance Training
Chronic coronary disease without heart failure	↑↑	↑↑	↑
Peripheral artery disease	↑↑	↑	(↑)
HFrEF	↑	↑↑	↑
HFpEF	↑↑	↑↑	↑
Atrial fibrillation	↑	↑↑	↑

HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

ANTIATHEROGENIC VASCULAR MECHANISMS AND ADAPTATIONS. Vascular endothelial dysfunction plays a key role in the pathogenesis of atherosclerosis. Exercise training opposes endothelial dysfunction via enhanced endothelial NO synthase and increased NO production and bioactivity, which improves NO-dependent vasodilation of large conduit vessels. As such, exercise training improves vascular endothelial function, independent of changes in traditional CVD risk factors.[46] Specifically, meta-analyses of exercise training studies demonstrate that exercise training is associated with an increase in brachial artery flow-mediated dilation (measure of endothelial function) of approximately 2% to 4%.[48] For context, it has previously been reported that a 1% increase in flow-mediated dilation is associated with a 13% reduction in future cardiovascular events.[49]

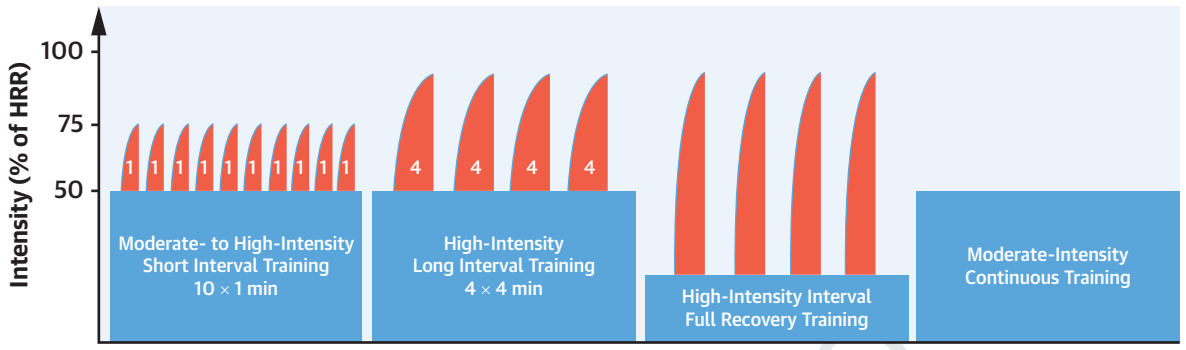
Long-term aerobic exercise training also induces shear stress-mediated arterial remodeling that results in larger conduit and peripheral artery sizes.[15] Evidence of this can be observed in athletes, who exhibit larger peripheral artery diameters than sedentary individuals even when accounting for body size. However, similar vascular remodeling is also seen in sedentary individuals who undergo 8 weeks of aerobic exercise training.[15] Exercise training also reduces the wall thickness of conduit arteries.[50] Together, these vascular structural adaptations markedly increase the luminal reserve of the vessel and reduce the probability of a flow-limiting stenosis.[46] Aerobic exercise training may also reduce arterial stiffness in at-risk populations such as individuals with metabolic syndrome and/or hypertension.[51] In a recent meta-analysis, aerobic exercise training (≥4 weeks duration) was associated with a significant reduction of 0.76 m/s for pulse wave velocity (measure of arterial stiffness).[51] For context, a 1 m/s increase in pulse wave velocity corresponds with an age-, sex-, and risk factor-adjusted risk increase of 15% in CVD and all-cause mortality in adults.[52]

ANTI-INFLAMMATORY EFFECTS OF EXERCISE TRAINING. Chronic systemic inflammation is implicated in the development and progression of atherosclerosis, CAD, and cardiovascular events.[53] Large cohort studies consistently demonstrate an inverse relationship between markers of systemic inflammation and physical activity levels.[53] Moreover, exercise produces beneficial anti-inflammatory effects that lower systemic inflammation by reducing proinflammatory cytokines, such as circulating C-reactive protein and interleukin-6.[46] The anti-inflammatory effects of exercise training are believed to be mediated in large part by myokines, which protect arteries against atherosclerosis and stenosis, and stabilize existing atherosclerotic plaques.[46] In addition, exercise training increases recruitment and mobilization of endothelial progenitor cells, which have the ability to promote endothelial repair, neovascularization and restoration of endothelial function.[54] Finally, exercise training is associated with lower oxidative stress and maintained NO bioavailability that contribute to preserved vascular endothelial function in older adults.[55]

BENEFITS OF EXERCISE ON STRESS AND DEPRESSION. Psychosocial stress and depression are known to be associated with increased CV risk.[56] This can range from an increase in rates of myocardial infarction after a major event, such as divorce or a major public event like earthquake, to longer-term effects arising from mild chronic stress or anxiety. Although the pathways are still being defined, activation of the sympathetic nervous system appears to be key aspect of this stress/depression-CVD axis. Moreover, acute and intense activation of the sympathetic nervous system is the major precipitating factor for acute left ventricular dysfunction in the form of takotsubo cardiomyopathy. Exercise has been shown to result in both a resetting of autonomic tone (evidenced by resting bradycardia, increased heart rate variability, and other effects), and additional benefits in terms of alleviating stress and anxiety mediated by acutely increased endorphin levels and other effects.[57]

EXERCISE PROTECTS AGAINST CVD VIA MULTIPLE DEPENDENT AND INDEPENDENT PATHWAYS. The preceding sections have highlighted how exercise protects against CVD via multiple dependent and independent pathways that include amelioration of traditional CVD risk factors (eg, glycemic control, blood pressure, obesity, lipid profile) and nontraditional risk factors such as attenuated inflammation, antiatherogenic mechanisms, and effects on stress and depression.[58] Among these factors, Mora et al[47] found that the most important effects of exercise on

FIGURE 2 Modes of Exercise Training



Different types of exercise training are shown and defined by basic training intensity **(blue)** and different forms of intervals **(red)** differing in duration and intensity. HRR = heart rate reserve.

reducing risk of CVD were through changes in inflammatory and hemostatic biomarkers, and also reductions in blood pressure. Other important changes brought about by exercise that contribute to reduced CVD risk that are discussed elsewhere in this *JACC* series include protection against HFpEF (part 2) and beneficial exercise-induced cardiac remodeling (part 4).

An important side issue that can dispelled at this point is that of potential reverse causation in the association of exercise and improved health. That is, individuals with preexisting or undiagnosed diseases who are at higher risk of subsequent morbidity or mortality may be more likely to be inactive,[59] and therefore, the perceived benefits of exercise may merely represent the absence of such concomitant disease. The multiple beneficial mechanisms presented in the previous text serve to prove the profound physiological benefits of exercise and to refute the possibility of mere reverse causality. In addition, from large clinical studies that have sought to tease out these effects, there is robust evidence that the degree of physical activity is inversely associated with mortality in a dose-responsive manner.[59]

OPTIMAL TYPE, AMOUNT, AND INTENSITY OF EXERCISE TO REDUCE CVD AND ALL-CAUSE MORTALITY RISK

The most recent WHO guidelines on physical activity for health benefits recommend that adults (age 18-64 years) perform at least 150 to 300 minutes of moderate-intensity (3-6 METs, 64%-76% maximum heart rate, 5-6 on a 0-10 scale) aerobic exercise, at least 75 to 150 minutes of vigorous-intensity (6-9 METs, 77%-93% maximum heart rate, 7-8 on a 0-10 scale) aerobic exercise, or an equivalent combination of moderate and vigorous-intensity exercise (eg, see Table 1).[3] Muscle strengthening exercises involving all major muscle groups should also be performed 2 d/wk at a moderate or greater intensity. Physical activity guidelines for individuals ≥65 years are similar, however multicomponent exercises that emphasize functional balance and strength training at a moderate or greater intensity should also be performed 3 d/wk. Finally, all adults should limit the amount of time spent being sedentary and aim to replace sedentary time with physical activity of any intensity.

Adherence to these WHO physical activity guidelines is associated with a 23% to 40% and 27% to 31% reduction in CVD[60-62] and all-cause mortality,[63,64] respectively. Moreover, there is an inverse curvilinear dose-response relationship between the amount of weekly physical activity and reduction of risk. The most significant relative benefit is changing from inactivity to 30 minutes of walking per day. Whether high volumes of aerobic exercise (such as those seen in endurance-trained athletes) lead to increased risk for cardiovascular events (sudden cardiac death) or CVD mortality is the topic of much debate.[9] That said, a recent meta-analysis showed that compared with the current physical activity guidelines, CVD and all-cause mortality risk was lower at physical activity levels exceeding the recommendations up until 5,000 MET min/wk (7-10 times the current guidelines).[65] These findings suggest that the cardiovascular and survival benefits associated with high-volume aerobic exercise training easily outweigh the risk of sudden cardiac death in this population.

Moderate- and vigorous-intensity aerobic exercise that meets or exceeds the current guidelines leads to major reductions in CVD and all-cause mortality risk.[9] However, there is some evidence that higher-intensity exercise may lead to additional cardiovascular benefit and risk reduction relative to moderate-intensity aerobic exercise.[66] In a prospective study of 204,542 middle-aged and older adults,[66] compared with those who reported no vigorous activity, individuals who reported some vigorous exercise (<30% of their total physical activity) or more vigorous exercise (>30% of their total physical activity) had a 9% and 13% lower risk of death, respectively. One popular and time-efficient form of vigorous exercise is high-intensity interval training (HIIT), which consists of brief intermittent bursts of vigorous activity (most commonly walking/running or cycling) interspersed with periods of active recovery. HIIT produces larger improvements in CRF compared with moderate-intensity continuous training,[67] which may contribute to the additional CVD risk reduction observed with higher amounts of vigorous exercise.

NOVEL APPROACHES TO INCREASE PARTICIPATION AND ADHERENCE TO EXERCISE GUIDELINES

Despite the proven benefits of exercise, adherence to current physical activity guidelines is poor.[68] In the United States, only 53% of adults currently meet the recommendations for aerobic exercise, and only 22% meet recommendations for combined aerobic and muscle strengthening exercises.[69] Moreover, 36% of U.S. adults currently report no leisure-time physical activity.

Important factors to consider when trying to increase participation in exercise include the many barriers that individuals may face. These include the economic costs of undertaking exercise, perceived and real hazards of acute exercise, and both psychological and sociodemographic barriers to exercise participation and adherence. These barriers often stem from particularly complex societal and demographic disparities that are beyond the scope of this paper and that may be challenging to address. Nevertheless, a keen awareness of these competing factors is paramount in addressing the potential barriers to exercise and for establishing an exercise program for any given individual.

Furthermore, at a minimum, patients should be encouraged to engage in *any* activity, because even a change from inactive to insufficiently active yields large reductions risk of CVD and mortality. There is strong evidence that increasing physical activity levels by modest amounts significantly lowers the risk of CVD and all-cause mortality in previously inactive adults.[61,64] In a pooled analysis of household-based surveillance studies, insufficiently active adults over the age of 40 years who reported only exercising 1 or 2 times/wk had a 40% lower risk of CVD mortality and 34% lower risk of all-cause mortality compared with inactive adults.[61] Indeed, the 2018 update to the U.S. Physical Activity Guidelines emphasized that any improvement in "moving more, sitting less" is beneficial.[70]

Physical activity interventions have small-to-moderate effects on behavior change and physical activity levels.[71,72] Certain behavior change strategies are more likely to promote significant and lasting changes in physical activity levels in inactive adults. These include behavioral goal setting, creating detailed plans, demonstration of the behavior, using biofeedback from objective monitoring, gradually increasing the volume and intensity of exercise, prompts/cues, and individuals rewarding themselves for progress.[71,72] Smart phone applications (apps) and physical activity trackers (Fitbit, Apple Watch, etc) are emerging tools that incorporate several of these behavior change strategies to increase physical activity. In a recent meta-analysis that evaluated physical activity interventions involving smartphone apps or physical activity trackers, Laranjo et al[72] showed a small-to-moderate positive effect on physical activity measures, which corresponded to an 1,850 increase in steps/d. For context, an increase of 1,000 steps/d is known to lower the risk of death by 12%.[73] As such, smartphone apps and physical activity trackers may facilitate clinically meaningful increases in physical activity that are associated with primary prevention of CVD.

EXERCISE AS A SECONDARY PREVENTIVE THERAPY IN CVD

In the second half of this paper, we turn our attention from primary to secondary prevention, where in addition to medical therapy, exercise is a key pillar of therapeutic intervention. Moreover, it should be noted that the benefits of exercise in patients with CVD are in addition to the effects of medication, and after careful evaluation, sports participation may be possible for a great number of these patients.[74] Data from a population-based cohort study including 131,558 subjects with CVD revealed a continuous decline of mortality with increasing exercise volume. This effect was even stronger than in those without CVD (n = 310,240). Every 500 MET-min/wk increase

of physical activity resulted in a 14% and 7% risk reduction in mortality in the secondary and primary prevention groups, respectively.[75]

EXERCISE IN CAD. Pathophysiology. The development of CAD is dependent on the burden of cardiovascular risk factors and can affect the macrocirculation (eg, single plaque in proximal coronary artery), the microcirculation (eg, small vessel disease), or both. Although all risk factors affect the macrocirculation and the microcirculation, large vessel atherosclerosis is primarily caused by hypercholesterolemia, hypertension, and smoking, whereas small vessel disease is primarily caused by T2DM and hypertension (Figure 1). The occlusion of the coronary macrocirculation may lead to myocardial infarction and potential development of heart failure with reduced ejection fraction (HFrEF), whereas the impairment of microcirculation is an important pathophysiological step in the development of HFpEF (Figure 1).

Effects of exercise on clinical endpoints. Exercise-based rehabilitation confers a 36% to 63% total mortality reduction for CAD patients.[76] Moreover, data from the STABILITY study including 15,486 patients with stable CAD revealed that exercise volume was stepwise and inversely related to the incidence of events at 36 months.[77] The effect of exercise reached significance beyond 10 MET•h/wk, which relates to 2 hours of brisk walking per week. In fact, 10-20 MET•h/wk reduced the CVD event rate by 50%. Interestingly those at high cardiovascular risk, eg, those who are older; who are smokers; or who have hypercholesterolemia, diabetes, peripheral artery disease (PAD), or elevated N-terminal pro-B-type natriuretic peptide or troponin T benefited most. Regarding exercise intensity, vigorous exercise limited by dyspnea was most effective.[77] Furthermore, in stable patients with significant coronary stenosis, compared with coronary lesion intervention, the exercise time of 20 min/d over a year was associated with improvement of maximal exercise capacity, a higher event-free survival, reduced rehospitalizations, and fewer repeat revascularizations.[78]

Mechanisms that explain these effects include reduction of plaque volume and stabilization of plaque morphology,[79] improved endothelial function,[80] and improved collateral blood flow.[81] These latter effects on the microcirculation and the dose-dependent effects of exercise intensity have been investigated in an exercise intervention trial (EXCITE [Impact of Intensive Exercise Training on Coronary Collateral Circulation in Patients With Stable Coronary Artery Disease]) randomizing 60 patients with significant CAD in a 1:1:1 fashion to high-intensity exercise, moderate-intensity exercise, or a control group. The primary end point was the change in coronary collateral flow index. After 4 weeks, collateral flow index increased significantly in both exercise groups compared with the control group. High-intensity exercise did not lead to a greater coronary collateral flow index than moderate-intensity training.[81]

Exercise prescription. Before starting an exercise program, CAD patients should be clinically stable, and significant ischemia should be excluded by exercise testing or other diagnostic tools. This is the basis for including higher intensities into the exercise program, because this seems to be safe and at the same time seems to have superior effects than moderate continuous endurance exercise.[82] Patients should be advised to aim for ≥20 min/d of mostly vigorous activity,[77] although less exercise seems to have some effect. This training schedule should be adapted according to disease severity, frailty, and baseline exercise capacity. Those at highest risk should not be excluded from this approach, as they benefit most from this exercise intervention. Structured exercise training may start early after acute coronary syndrome with PCI, eg, after 7 to 10 days in a supervised rehabilitation setting. Then moderate intensity continuous training (MICT) is the preferred exercise modality, which should first be increased in duration and thereafter in intensity. Several exercise sessions of shorter duration per day are an alternative for longer sessions, particularly at the beginning.

EXERCISE IN HFpEF. Pathophysiology. HFpEF is increasingly considered as a systemic and multiorgan disease.[83] Common risk factors for developing HFpEF include traditional CVD risks such as obesity, T2DM, hypertension, and sedentariness. Furthermore, HFpEF is prevalent in the elderly and is often associated with frailty, sarcopenia, and loss of mitochondrial and endothelial function.[83]

Effects of exercise on clinical endpoints. Exercise intolerance is a cardinal symptom of HFpEF and exercise training has been proposed as a treatment modality, as it is known to improve CRF. In a meta-analysis that included 276 patients from 6 randomized controlled trials, cardiopulmonary fitness assessed as VO_2peak and quality of life improved significantly with exercise training (VO_2peak: mean change 2.72 ml/kg/min). However, no improvements in diastolic function were observed.[83]

Defining the optimal exercise intensity for intervention, the OptimEx-CLIN trial randomized 180 patients (age 70 years, 67% women; 1:1:1) to either HIIT

(3 × 38 min/wk), MICT (5 × 40 min/wk), or usual care (exercise according to guidelines) for 12 months.[84] Change in VO_2peak after 3 months was +1.0 for HIIT and +1.6 mL/kg/min for MICT vs reduction of −0.6 mL/kg/min in the usual care group. Although this improvement was statistically significant, the predefined threshold of 2.5 mL/kg/min was not reached.[84] However, this change was higher than traditionally defined improvements of 1.0 mL/min/kg.[85] In this study, exercise intensity was not a determinant of response of VO_2peak during exercise intervention. Although prior smaller studies have indicated that diastolic function may change by HIIT, these changes could not be confirmed in the larger OptimEx trial.[84] However, data from the Reversing the Cardiac Effects of Sedentary Aging in Middle Age study, including healthy and sedentary patients (age 4 64 years)[86] revealed that left ventricular stiffness decreased significantly in the exercise group compared with the control group.[86] Hence, following this prolonged intervention of 2 years and the strong association of age with the development of HFpEF, reversing myocardial remodeling may be possible in younger patients with mild dysfunction.

Prescription of exercise in HFpEF. As in all CVD patients, cardiovascular risk factor management needs to be optimally adjusted. Exercise training should start with a combination of aerobic MICT (3-4/wk, at 50%-60% of heart rate reserve [HRR], which is the difference between the resting and maximal heart rate) and resistance training. This should be followed by HIIT training after 6 weeks (3×/wk, 10-min warm-up at 40%-50% of HRR, 4 × 1-min intervals at 80%-90% of HRR 3×/day, with 3 minutes of active recovery).[87] From our perspective, 4-minute intervals of submaximal intensity seem to be too long in deconditioned, sedentary, obese, and old individuals, but shorter intervals, eg, 1 minute with lower intensity of ∼75% to 85% HRR, are better tolerated. In general, variation in training mode and intensity may improve adherence.

HRR is the preferred method to be applied for prescribing exercise intensity when a cardiopulmonary exercise test cannot be performed to assess ventilatory thresholds. Percent values of maximal heart rate are not appropriate in cases of chronotropic incompetence.

EXERCISE TRAINING IN HFrEF. Pathophysiology. HFrEF is defined as heart failure with left ventricular ejection fraction <40%. Causes include ischemic heart disease or nonischemic causes such as hypertension, myocarditis, or valvular heart disease. Exercise capacity is often severely impaired in these patients because of reduced cardiac output accompanied by peripheral impairment, eg, vascular dysfunction and impaired muscle energy metabolism.

Exercise effects on clinical endpoints. In stable HFrEF patients, exercise training is recommended in addition to optimal medical therapy and device treatment. MICT combined with resistance training has the highest level of evidence.[88] These recommendations are mainly based on the largest trial in HFrEF, the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), which revealed a modest but statistically significant benefit of exercise training on the primary combined outcome of all-cause mortality or all-cause hospitalization after adjusting for relevant predictors.[89] A total of 2,331 patients were included in this trial with left ventricular ejection fraction <35% and New York Heart Association functional class II-IV, and the effects were independent of etiology of heart failure, ischemic or nonischemic. Furthermore, the recent REHAB-HF trial in elderly heart failure patients after decompensation revealed that physical performance can be improved significantly during short-term rehabilitation.[90]

In addition to MICT, HIIT has also been recognized as an additional modality in stable HFrEF patients. This is mainly based on the SMARTEX-HF (Study of MyocArdial Recovery afTer EXercise training in heart failure), which found superior improvements of left ventricular dimensions for HIIT over MICT and comparable improvements of maximal aerobic capacity for HIIT and MICT after 12 weeks of supervised exercise intervention compared with exercise recommendations only.[91]

Exercise recommendations. After optimization of guideline-directed medical therapy and consideration of defibrillator and/or resynchronization therapy as appropriate, patients are encouraged to actively increase general physical activity, eg, walking. Several split exercise sessions per day, eg, 3× 5 to 10 minutes each, seem to be particularly effective during the starting phase eventually reaching the goal of ≥20 minutes exercise per day. Intensity of endurance exercise should start as MICT, but should subsequently include short bouts of 30 to 60 seconds of HIIT at 70% to 80% HRR, which can thereafter be increased by intensity or duration depending on individual tolerance and capacity. Resistance and balance training should also be initiated in frail and elderly heart failure patients.[90]

EXERCISE IN PAD. Pathophysiology. PAD is caused by the limitation of blood flow to the periphery leading to a decrease in skeletal muscle volume and replacement by fat and fibrosis,[92] and also often to

impaired skeletal muscle mitochondrial function.[93,94] Vascular stenosis or occlusion is mainly caused by atherosclerosis and, depending on the extent, can lead to intermittent claudication, fatigue, and weakness of the lower extremity during exercise or even at rest. Similar to CAD, atherosclerosis in PAD is mainly caused by cardiovascular risk factors, with smoking and T2DM playing the most important role.[95] Even without claudication, patients with PAD exhibit a significant reduction of their functional status, which is exacerbated by sedentarism.

Effects of physical exercise on clinical endpoints. The framework of exercise in PAD addresses both the stabilization of the atherosclerosis by reduction of risk factors, and improving functional status, symptoms, and quality of life. During exercise an increased vascular resistance, as well as a low poststenotic pressure and endothelial dysfunction (including lower capillary density and impaired microcirculation), do not allow for a sufficient blood flow to meet higher demands. Regular exercise counteracts this pathophysiology by improving vascular function, muscle metabolism, mitochondrial function, and angiogenesis.[95]

Clinical data underlying the effects of exercise training in PAD come from a large number of randomized trials consistently showing an improvement in symptoms, walking distance, quality of life, and VO_2peak. In a systematic review, exercise was associated with an increase in both maximum walking distance (by 6 m increase) and pain-free walking distance (128 m increase).[96] Moreover, exercise is superior to interventional procedures. The CLEVER (Claudication: Exercise Versus Endoluminal Revascularization) study, including 111 patients randomized to optical medical therapy alone, optical medical therapy plus endoluminal revascularization, or optical medical therapy plus exercise, showed that exercise led to the greatest improvement in maximal walking distance after 6-month follow-up, compared with stenting and optimal medical therapy only. Interestingly, quality of life improved in both the exercise and revascularization groups, with the latter showing the best results.[97]

Training intensity may be an important factor in the approach to exercise in PAD, with high-intensity training having the greatest benefits (**Central Illustration, Table 2**). The recent LITE trial compared usual care vs unsupervised high-intensity (with moderate-severe symptoms of ischemia) vs low-intensity (with no ischemia) walking exercise (5×/wk, up to 50 min/session) in 305 patients with PAD. The change in 6-minute walking distance between baseline and 12 months increased from 338 to 371 minutes in the high-intensity group, whereas the distance remained unchanged in the low-intensity exercise and usual care groups.[98]

Prescription of exercise in PAD. High-intensity walking exercise inducing moderate to severe ischemia seems to be the best mode of exercise to improve pathophysiology and walking distance, although adherence is often lower compared with low-/moderate-intensity exercise.[98] In addition, resistance exercise is recommended to improve muscular function. General recommendations are 30 to 45 minutes of training/session, at least 3×/wk, reaching moderate to severe ischemia symptoms within 10 minutes. In contrast to training in CAD patients, electrocardiography monitoring is less recommended in patients with PAD, as most patients are primarily limited by peripheral ischemia.

EXERCISE IN ATRIAL FIBRILLATION. Pathophysiology. Besides increasing age and genetics, modifiable risk factors for atrial fibrillation (AF) include T2DM, hypertension, sedentary lifestyle, excessive alcohol consumption, obesity, and sleep apnea.[99] Mechanisms inducing the vulnerable substrate are manifold. For example, obesity and diabetes increase local inflammation (ie, by pericardial fat deposition), whereas hypertension increases wall stress by pressure overload in the left atrium, with all of these factors inducing left atrial remodeling, one of the key mechanisms for electrical atrial disarray.[100]

Effects of exercise on clinical endpoints. In addition to heart rate control and anticoagulation, the prevention of further AF after a first event focuses on reduction of risk factors, aiming to reverse the underlying pathophysiology. These measures include medications such as antihypertensive therapy, as well as lifestyle changes such as weight reduction, alcohol restriction, and exercise training.[101]

The majority of data on lifestyle intervention in AF originates from an Australian cohort, with several subanalyses having been published, eg, CARDIO-FIT,[102] LEGACY (Long-Term Effect of Goal Directed Weight Management on Atrial Fibrillation Cohort),[103] ARREST-AF[104] and REVERSE-AF.[105] In this data set, symptomatic AF patients (mean age 58 years, two-thirds women) were enrolled, who were characterized by a body mass index ≥27 kg/m^2 and ≥1 CVD risk factor (hypertension, glucose intolerance/T2DM, hyperlipidemia, sleep apnea, smoking, or alcohol excess).[104] On individual preference, patients chose to follow usual care or a multifactorial risk factor intervention program including nutritional and exercise counseling to reduce weight and improve exercise capacity as well as optimizing all other cardiovascular risk factors.[104]

Follow-up data on recurrence of AF was retrieved after 2 to 5 years.

The ARREST-AF cohort subanalysis revealed that aggressive risk factor management had significantly greater effect on weight, BP, glucose, and lipid profile after 2 years. Moreover, left atrial volume and left ventricular septal thickness decreased and diastolic function improved to a greater extent in the intervention arm. These changes were associated with reductions in AF frequency, duration, symptoms, and symptom severity.[104] These data were extended by the LEGACY subanalysis, which revealed that progressive weight loss had a dose-dependent effect on 5-year freedom from AF.[103] Specifically, in the group with weight loss <3%, 41% progressed from paroxysmal to persistent AF and 26% from persistent to paroxysmal or no AF, whereas in those who lost ≥10%, 3% progressed to persistent and 88% reversed from persistent to paroxysmal or no AF.[105] Increased weight loss was also associated with greater freedom from AF: 39% in the low weight loss group versus 86% in the high weight loss group. The CARDIO-FIT subanalysis analyzed exercise capacity,[102] which revealed a dose-response relationship between baseline cardiorespiratory fitness and AF burden, with a 20% reduction in the risk of AF recurrence for each MET increase in baseline cardiorespiratory fitness.[102] Importantly, an increase in cardiorespiratory fitness had an additive effect to weight loss in improving outcomes and freedom from AF.[102]

The only randomized controlled trial investigating the effects of 12 weeks of HIIT (51 sedentary patients with nonpermanent AF; age ~60 years, four-fifths men) compared with usual care showed a decrease in AF burden in the intervention group compared with the control group. Moreover, significant reductions were documented in body mass index and lipids, with concurrent improvements in VO_2peak, left ventricular ejection fraction, and active left atrial emptying fraction. These changes were associated with a decrease in AF symptom frequency and symptom severity, as well as an increase in quality of life.[106]

In other studies, in a cohort of 210 patients (age 59 years, 74% men) that were post-catheter ablation for AF who were randomized 1:1 to exercise intervention (12 weeks, 3 ×/wk) vs usual care, the primary endpoint of VO_2peak showed a significant increase, although quality of life (Short-Form 36) did not differ and clinical endpoints were not assessed.[107] Although in a study by McNamara et al[108] that was a subanalysis of the previously mentioned Reversing the Cardiac Effects of Sedentary Aging in Middle Age study,[86] 2 years of HIIT training was associated with greater left atrial mechanical remodeling than left ventricular mechanical remodeling, with no electrophysiological changes, suggesting that different thresholds may exist for electrophysiological vs mechanical changes in response to exercise training.[108]

Prescription of exercise in AF. The focus of exercise and lifestyle intervention for AF is on the reduction of body weight in obese individuals to reverse pathophysiology. MICT seems to be the preferred exercise modality, particularly in sedentary and obese individuals, with the goal of improving metabolism and vascular function. Resistance exercise should also be incorporated to improve vascular function. Moreover, resistance training generally improves body perception and underscores weight reduction programs by increasing basic energy expenditure. HIIT may be added after a period of 4 to 6 weeks depending on the rate of improvement and baseline exercise capacity, aiming first at short intervals, eg, 1 minute, and steadily increasing up to 3- to 4-minute intervals, eg, 1 min/mo. Also, intensity of intervals may increase from 70% to 80% of maximum heart rate, and even beyond. Exercise after catheter ablation for AF may potentially be started as early as 2 weeks postintervention, although general recommendations (without supporting data) advise on postponing HIIT for a 12 week "blanking period" postablation.

In general, all medication for risk factor control, heart rate control, and anticoagulation should be taken according to guidelines.[99] Hypertension should be carefully treated particularly in those with added HFpEF. In those taking antiarrhythmic drugs, vigorous exercise should not be performed while using class I antiarrhythmic medication as monotherapy without rate control. Similarly, intensive exercise should not be performed after ingestion of "pill-in-the pocket" flecainide or propafenone until 2 half-lives of the antiarrhythmic drug have elapsed. Bodily contact and other sports with potential for causing injury should be avoided in those receiving anticoagulation therapy.[74]

CLINICAL DIAGNOSTICS INCLUDING EXERCISE TESTING TO PRESCRIBE EXERCISE

Before exercise prescription, patients should ideally pass several safety gateways. First, optimal medical therapy for their specific heart disease, including all cardiovascular risk factors, is mandatory. This should be followed by a thorough cardiopulmonary evaluation, preferably including cardiopulmonary exercise testing. In some cases, stress echocardiography

and/or further cardiac imaging (eg, coronary tomography, cardiac magnetic resonance) may be appropriate.[74] Cardiopulmonary exercise testing can be combined with performance testing in terms of lactate measurements or spiroergometry (adding information about cardiopulmonary function), either on the bicycle ergometer or treadmill. BP during exercise should be closely monitored and treated, if necessary.

Generally, in exercise studies there are 3 training concepts that are used, being HIIT, MICT, and resistance training. In primary prevention, the percentage of VO_2peak and maximal heart rate are generally used for guiding exercise modes. In secondary prevention, the percentage of HRR or ventilatory thresholds are preferred. Often HIIT training is described with 4-minute intervals at 90% to 95% HRR with a gradual increase in heart rate during those intervals, and MICT at 50% to 70% HRR. Several gradations exist, such as high/moderate intensity interval training with 1-minute intervals up to 75% of HRR, HIIT with almost full recovery during interval, or moderate continuous training of different intensities (**Figure 2**).

Performance testing should be repeated after 3 months to assess and visualize exercise improvements and update exercise prescriptions, particularly regarding exercise intensity and corresponding heart rate corridors.

CONCLUSIONS

Regular exercise plays an important role in the prevention of CVD. The cardioprotective effects of exercise are mediated by increased CRF and improvements in traditional and nontraditional CVD risk factors. Exercise volumes that meet or exceed the current physical activity guidelines of 150 to 300 minutes of moderate-intensity or 75 to 150 minutes of vigorous-intensity aerobic exercise each week are associated with significant reductions in CVD and all-cause mortality. For secondary prevention, structured exercise training, including endurance and resistance training, has positive effects on disease pathophysiology, CVD risk factors, and clinical outcomes. In contrast to general recommendations on physical activity, exercise recommendations in those with CVD are more specific, defining mode, intensity, and duration (structured exercise program, "exercise prescription"). This approach is important in patients at high CVD risk or with established CVD, to optimize benefits while avoiding risks. Specific training plans in these patients mostly start with MICT, and then add resistance training, while progressively increasing intensity. General practitioners as well as cardiologists should be included in educational curricula on exercise prescription, an integral part of the cardiovascular armamentarium.[109]

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KEY WORDS **atrial fibrillation, cardiorespiratory fitness, cardiovascular disease, cardiovascular risk factors, heart failure, mortality, physical activity**

Exercise for Primary and Secondary Prevention of Cardiovascular Disease: *JACC* Focus Seminar

Wesley J. Tucker, Isabel Fegers-Wustrow, Martin Halle, Mark J. Haykowsky, Eugene H. Chung, Jason C. Kovacic

Exercise training plays an important role in primary and secondary prevention of cardiovascular disease (CVD), as it improves cardiovascular risk factors and reduces risk of CVD and CVD-related mortality. In this first of a 4-part focus seminar series, we highlight the mechanisms and physiological adaptations responsible for the cardioprotective effects of exercise and relate this to its prescription, focusing on the optimal mode, dosage, duration, and intensity of exercise to reduce CVD risk and improve clinical outcomes.

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 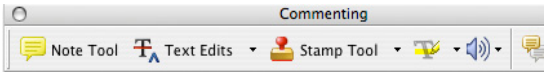

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 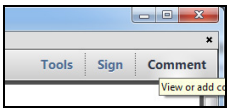

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 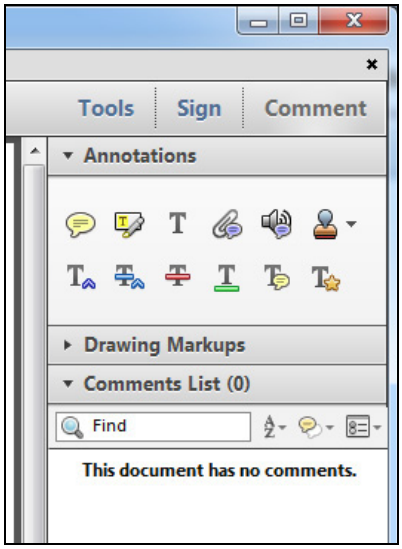
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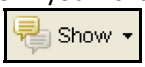
Review	To review your changes, click on the 'Show' button  on the Commenting tool bar. Choose 'Show Comments List'. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.	Your changes will appear automatically in a list below the Comment tool bar. Navigate by clicking on a correction in the list. Alternatively, double click on any mark-up to open the commenting box.
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