

## Exercise and Physical Activity in the Prevention and Treatment of Atherosclerotic Cardiovascular Disease

### A Statement From the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)

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*This statement was reviewed by and has received the endorsement of the American College of Sports Medicine.*

Regular physical activity using large muscle groups, such as walking, running, or swimming, produces cardiovascular adaptations that increase exercise capacity, endurance, and skeletal muscle strength. Habitual physical activity also prevents the development of coronary artery disease (CAD) and reduces symptoms in patients with established cardiovascular disease. There is also evidence that exercise reduces the risk of other chronic diseases, including type 2 diabetes,<sup>1</sup> osteoporosis,<sup>2</sup> obesity,<sup>3</sup> depression,<sup>4</sup> and cancer of the breast<sup>5</sup> and colon.<sup>6</sup> This American Heart Association (AHA) Scientific Statement for health professionals summarizes the evidence for the benefits of physical activity in the prevention and treatment of cardiovascular disease, provides suggestions to healthcare professionals for implementing physical activity programs for their patients, and identifies areas for future investigation. This statement focuses on aerobic physical activity and does not directly evaluate resistance exercises, such as weight lifting, because most of the research linking physical activity and cardiovascular disease has evaluated aerobic activity. Whenever possible, the writing group has cited summary articles or meta-analyses to support conclusions and recommendations. This evidence supports the recommendation from the Centers for Disease Control and Prevention (CDC) and the American College of Sports Medicine (ACSM) that individuals should engage in 30 minutes or more of moderate-intensity physical activity on most (preferably all) days of the week.<sup>7</sup>

#### Definition of Terms

*Physical activity* is defined as any bodily movement produced by skeletal muscles that results in energy expenditure beyond resting expenditure. *Exercise* is a subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that improvement or maintenance of physical fitness is the objective. *Physical fitness* includes cardiorespiratory fitness, muscle strength, body composition, and flexibility, comprising a set of attributes that people have or achieve that relates to the ability to perform physical activity. When defining the amount of physical activity or exercise, an important interrelationship exists between the total dose of activity and the intensity at which the activity is performed. *Dose* refers to the total amount of energy expended in physical activity, whereas *intensity* reflects the rate of energy expenditure during such activity.<sup>7</sup> Intensity can be defined in absolute or relative terms. Absolute intensity reflects the rate of energy expenditure during exercise and is usually expressed in metabolic equivalents or METs, where 1 MET equals the resting metabolic rate of  $\approx 3.5 \text{ mL O}_2 \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Relative intensity refers to the percent of aerobic power utilized during exercise and is expressed as percent of maximal heart rate or percent of  $\dot{V}\text{O}_2\text{max}$ . Moderate-intensity activities are those performed at a relative intensity of 40% to 60% of  $\dot{V}\text{O}_2\text{max}$  (or absolute intensity of 4 to 6 METs). Vigorous-intensity activities are those performed at a relative intensity of >60% of  $\dot{V}\text{O}_2\text{max}$  (or absolute intensity of >6

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This statement was approved by the American Heart Association Science Advisory and Coordinating Committee in February 2003. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0249. To purchase additional reprints: up to 999 copies, call 800-611-6083 (US only) or fax 413-665-2671; 1000 or more copies, call 410-528-4426, fax 410-528-4264, or e-mail [klbradle@lww.com](mailto:klbradle@lww.com). To make photocopies for personal or educational use, call the Copyright Clearance Center, 978-750-8400.

(*Circulation*. 2003;107:3109-3116.)

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*Circulation* is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000075572.40158.77

METs). For example, brisk walking at  $4.8 \text{ km} \cdot \text{h}^{-1}$  (3 miles  $\cdot \text{h}^{-1}$ ) has an absolute intensity of  $\approx 4$  METs. In relative terms, this intensity is considered light for a 20-year-old healthy person but represents a vigorous intensity for an 80-year-old person.<sup>8</sup>

### Prevention of Atherosclerotic Vascular Disease

During the past half-century, prospective epidemiological studies of occupational and leisure-time physical activity have consistently documented a reduced incidence of CAD events in the more physically active<sup>9</sup> and fit<sup>10</sup> subjects. More recent studies have provided similar data by using measures of exercise capacity such as treadmill performance as an indicator of habitual physical activity. The data satisfy the criteria required to infer a causal relationship from epidemiological evidence.<sup>11,12</sup> The results are strong, with the most physically active subjects generally demonstrating CAD rates half those of the most sedentary group. The data demonstrate a graded relationship of decreasing CAD rates with increasing levels of activity. Multiple studies were prospective and thereby demonstrate appropriate sequencing because the lower physical activity levels preceded the development of CAD rather than resulted from the disease itself. The results are consistent with all published studies documenting lower CAD rates in the more active subjects, although the relationship did not reach statistical significance in some individual reports. In many studies, the lower frequency of CAD was independent of other known atherosclerotic risk factors. The results are also plausible and coherent with evidence demonstrating beneficial effects of exercise on atherosclerotic risk factors, myocardial function, coronary artery size and vasodilatory capacity, vascular tone, and vulnerability to ventricular fibrillation. Available data do not provide clear evidence that withdrawal of physical activity increases CAD risk, although results from the Harvard Alumni Study suggest that college athletic activity is not protective in later years without lifelong physical activity.<sup>13</sup> Studies using the best designs and measurement instruments tend to show the strongest relationships between physical activity and decreased CAD events, probably because superior assessment techniques limit inaccuracies in categorizing physical activity levels.<sup>10</sup> For example, studies on cardiorespiratory fitness, measured as treadmill performance times, and CAD show stronger associations than are seen in activity studies, probably because of the better classification by objective measures of fitness in comparison to the relatively imprecise assessments of self-reported physical activity.<sup>10</sup> These epidemiological studies, combined with studies providing biological plausibility, provide conclusive evidence that physical activity reduces the incidence of CAD.

### Reduction of Atherosclerotic Risk Factors

Physical activity both prevents and helps treat many established atherosclerotic risk factors, including elevated blood pressure, insulin resistance and glucose intolerance, elevated triglyceride concentrations, low high-density lipoprotein cholesterol (HDL-C) concentrations, and obesity. Exercise in combination with weight reduction can decrease low-density lipoprotein cholesterol (LDL-C) concentrations and limit the

reduction in HDL-C that often occurs with a reduction in dietary saturated fat.<sup>14</sup>

The magnitude of the exercise effect is influenced by characteristics of the exercise intervention, individual variation, and whether exercise produces concomitant reductions in body weight. The effect on atherosclerotic risk factors can be large in some individuals and obviate the need for other interventions. In general, the effect of exercise on atherosclerotic risk factors is substantially less than that achieved by pharmacological therapies, although the exercise effect can be significantly magnified by other lifestyle changes such as changes in dietary composition and weight loss.

A meta-analysis of 52 exercise training trials of  $>12$  weeks' duration including 4700 subjects demonstrated an average increase in HDL-C levels of 4.6% and reductions in triglyceride and LDL-C concentrations of 3.7% and 5.0%, respectively.<sup>15,16</sup> The largest and most carefully controlled exercise trial, the HEalth, RiSk factors, exercise Training, And GENetics (HERITAGE) study, included 675 normolipidemic subjects who participated in 5 months of exercise training.<sup>17</sup> HDL-C increased 1.1 mg/dL (3%) among the 299 men studied, whereas triglycerides and LDL-C decreased 5.9 and 0.9 mg/dL or 2.7% and 0.8%, respectively. HDL-C among the 376 women increased 1.4 mg/dL (3%), and triglycerides and LDL-C decreased 0.6 and 4.4 mg/dL or 0.6% and 4%, respectively. Greater increases in HDL-C may occur in individuals with baseline hypertriglyceridemia,<sup>18</sup> but few studies have addressed the effect of exercise in subjects with lipid disorders.

At least 44 randomized controlled trials including 2674 participants have studied the effect of exercise training on resting blood pressure.<sup>19</sup> The average reduction in systolic and diastolic blood pressure was 3.4 and 2.4 mm Hg, respectively. Baseline blood pressure was an important determinant of the exercise effect. Average systolic and diastolic blood pressures decreased 2.6 and 1.8 mm Hg in normotensive subjects and 7.4 and 5.8 mm Hg in hypertensive subjects, respectively, suggesting that exercise may serve as the only therapy required in some mildly hypertensive subjects. There was no relationship between the weekly training frequency, time per session, or intensity of exercise training and the magnitude of the blood pressure reduction, which suggests that the dose-response curve for exercise and blood pressure is flat.

Physical activity also reduces insulin resistance and glucose intolerance, postprandial hyperglycemia, and possibly hepatic glucose output.<sup>20</sup> A review of 9 trials examining the effect of exercise training in 337 patients with type II diabetes reported an average reduction of hemoglobin (Hgb) A1c of 0.5% to 1%.<sup>20</sup> These findings may underestimate the absolute decrease in Hgb A1C because of concomitant reductions in diabetic medications. The Diabetes Prevention Program demonstrated the powerful effect that physical activity and weight loss can exert in preventing the onset of type II diabetes in individuals at high risk for this disease.<sup>1</sup> Compared with usual care, there was a 58% reduction in the onset of type II diabetes over 2.8 years among individuals randomized to a lifestyle intervention that produced an average 4-kg decrease in body weight and an 8-MET-h/wk increase in physical

**Effect of Exercise-Based Cardiac Rehabilitation on Cardiac Events**

Outcome	Mean Difference	95% CI	Statistically Significant?
<b>Exercise-only intervention</b>			
Total mortality	-27%	-2% to -40%	Yes
Cardiac mortality	-31%	-6% to -49%	Yes
Nonfatal myocardial infarction	-4%	-31% to +35%	No
<b>Comprehensive rehabilitation</b>			
Total mortality	-13%	-29% to +5%	No
Cardiac mortality	-26%	-4% to -43%	Yes
Nonfatal myocardial infarction	-12%	-30% to +12%	No

CI indicates confidence intervals. CIs not including zero are statistically significant. Data are derived from Jolliffe et al.<sup>25</sup>

activity. The latter corresponds to an additional 593 kcal of energy expenditure weekly or  $\approx$ 6 miles of walking for a 70-kg individual. The lifestyle intervention was also significantly more powerful than metformin (850 mg BID), which reduced the onset of type II diabetes by 31%.

Physical activity is also an important adjunct to diet for achieving and maintaining weight loss. The National Weight Control Registry enrolled 3000 individuals who lost >10% of their body weight and maintained this weight loss for at least 1 year.<sup>3</sup> The average weight loss of 30 kg was maintained for an average of 5.5 years. Eighty-one percent of the registrants reported increased physical activity. Women and men, respectively, reported expending 2445 and 3298 kcal weekly in such activities as walking, cycling, weight lifting, aerobics, running, and stair climbing.

At least 8 studies have examined the adjunctive effect of exercise on smoking cessation, but most trials were small and the results not subjected to meta-analysis.<sup>21</sup> One larger trial randomly assigned 281 healthy women to a 12-week behavior modification program and thrice-weekly sessions of supervised vigorous exercise or to an identical behavioral program with thrice-weekly health education sessions.<sup>22</sup> Of the exercisers, 19.4% achieved at least 2 months of continuous abstinence at the end of the 12-week intervention, compared with 10.2% of the controls. At 12-month follow-up, 11.9% of the exercisers and 5.4% of the controls remained continuously abstinent. Such results are preliminary, but they suggest that physical activity facilitates long-term smoking cessation by increasing the initial quit rate.

Some of the effect of physical activity on cardiovascular risk factors is an acute effect of recent exercise and is not dependent on prolonged exercise training or improvement in fitness.<sup>20</sup> Serum triglycerides are reduced by vigorous exercise for up to 72 hours.<sup>20</sup> HDL-C is also transiently increased by exercise.<sup>20</sup> Vigorous exercise also acutely reduces systolic blood pressure, and this effect may persist for up to 12 hours.<sup>20</sup> Exercise also has favorable acute effects on glucose homeostasis.<sup>20</sup> These acute effects provide additional support for the recommendations from the CDC and the ACSM that adults should participate in moderate-intensity physical activity on most, if not all, days of the week.<sup>7</sup>

**Treatment for Patients With Diagnosed CAD**

Several meta-analyses have concluded that comprehensive, exercise-based cardiac rehabilitation reduces mortality rates

in patients after myocardial infarction.<sup>23,24</sup> The most recent and comprehensive meta-analysis identified 51 randomized controlled trials of exercise-based cardiac rehabilitation.<sup>25</sup> All studies were published before January 1, 1999, and included 8440 patients who were primarily middle-aged, low-risk men. Patients were included if they had sustained a myocardial infarction, had undergone coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, had angina pectoris, or had CAD identified by angiography. Supervised exercise training in these programs was generally of 2 to 6 months' duration followed by unsupervised exercise.<sup>23,24</sup> The mean follow-up was 2.4 years.<sup>25</sup> Results were analyzed according to whether the cardiac rehabilitation program consisted of exercise only or also included psychosocial and/or educational interventions.<sup>25</sup> Total mortality was reduced 27% ( $P<0.05$ ) with the exercise-only intervention and 13% ( $P=NS$ ) with comprehensive rehabilitation (Table). Cardiac mortality was reduced 31% ( $P<0.05$ ) and 26% ( $P<0.05$ ) for the exercise-only and comprehensive programs, respectively. Neither the exercise-only program nor the comprehensive intervention significantly reduced the rate of nonfatal myocardial infarction. Additionally, rates of sudden cardiac death were not reduced, although only 4 exercise-only and 14 comprehensive rehabilitation trials analyzed this outcome. Similarly, only 5 exercise-only trials and 10 comprehensive trials examined the rate of coronary artery bypass grafting.

This review<sup>25</sup> adds  $\approx$ 4000 patients to the prior, widely cited meta-analyses of cardiac rehabilitation<sup>23,24</sup> and confirms that exercise-based cardiac rehabilitation reduces cardiac mortality but does not reduce the risk of recurrent myocardial infarction. In contrast to the prior analyses, however, these recent results suggest that the exercise component is a critical aspect of the rehabilitation process. The reduction in death without a reduction in nonfatal reinfarction raises the possibility that exercise training enhanced electrical stability and reduced ventricular fibrillation<sup>26</sup> or reduced myocardial damage directly or via such factors as ischemic preconditioning.<sup>27</sup> Many of the studies in this meta-analysis preceded most of the present treatments for CAD patients, including widespread use of acute thrombolytic therapy, primary angioplasty, aggressive revascularization,  $\beta$ -adrenergic blockers, aggressive lipid management, and angiotensin-converting

enzyme inhibitors. The smaller effect of comprehensive cardiac rehabilitation in this review may also reflect the absence of more powerful interventions to lower cardiovascular risk, such as newer lipid-lowering agents. Thus, it is not clear that exercise therapy after myocardial infarction would have as great an impact on mortality rates in the present era of cardiovascular disease management. Similarly, the effects of medical treatment may be overestimated in medical intervention trials not involving exercise.

Exercise training is also useful for patients with angina pectoris who are not candidates for revascularization therapy because of disease not amenable to intervention, angiographically noncritical stenoses, or patient preference. Early studies demonstrated that the symptomatic improvement in exercise tolerance after exercise training was due primarily to a reduction in the heart rate and systolic blood pressure or rate-pressure product (RPP) at submaximal workloads with no change in the RPP at the onset of angina.<sup>28</sup> Some subsequent reports also demonstrated an increase in the RPP at the onset of angina as well as a reduction in the ischemic response measured as angina, ST-segment depression,<sup>29</sup> or nuclear and positron-emission tomography scanning perfusion defects<sup>30,31</sup> at a given RPP, which suggests that exercise training improved myocardial oxygen delivery. In one study, the increase in RPP at the onset of angina occurred only during exercise,<sup>32</sup> whereas the RPP at the onset of angina with ventricular pacing was unchanged. These findings suggest that exercise training altered the coronary vasomotor response to exercise.<sup>32</sup> This hypothesis is supported by recent angiographic studies documenting that exercise training reduces the abnormal vasoconstrictive response to acetylcholine in patients with CAD and documented endothelial dysfunction.<sup>33</sup>

The aforementioned studies support the use of physical activity to improve exercise capacity after coronary revascularization procedures, including coronary bypass surgery and percutaneous interventions. No large studies have directly addressed the utility of exercise in this group, although there are encouraging data. The Exercise Training Intervention after Coronary Angioplasty (ETICA) trial<sup>34</sup> randomized 118 consecutive patients to 6 months of exercise training or control. Angiographic restenosis was not affected by exercise training, but trained patients demonstrated significant increases in peak  $\dot{V}O_2$  (26%) and quality-of-life parameters (27%). Furthermore, during  $33 \pm 7$  months of follow-up, the exercise-trained patients had fewer cardiac events (11.9% versus 32.2%) and hospital readmissions (18.6% versus 46%) than subjects assigned to usual care. Residual coronary stenosis and recurrent cardiac events were reduced by 30% and 29%, respectively, in the trained subjects.

### Treatment for Patients With Heart Failure

Activity restriction was recommended for heart failure (HF) patients until the late 1970s and 1980s, when it was recognized that exercise capacity in patients with left ventricular dysfunction could not be predicted by such parameters as intracardiac filling pressures and left ventricular ejection fraction. Numerous trials have demonstrated that both exercise testing and training of patients with HF appear to be safe.

A detailed discussion of exercise and HF is presented in the AHA Statement on Exercise and Heart Failure.<sup>35</sup> Exercise training benefits HF in several ways. The mean increase in peak  $\dot{V}O_2$  in 15 randomized controlled trials of exercise training that included 426 HF patients was 20.5%. The frequency, duration, and intensity varied among the trials, but all showed an increase in the average peak  $\dot{V}O_2$  between 12% and 31%.<sup>35</sup> In addition to improving exercise capacity, exercise training in HF patients has been shown to improve cardiac output at maximal workloads,<sup>36</sup> improve mitochondrial size and density,<sup>37</sup> increase skeletal muscle oxidative enzymes, reduce endothelial dysfunction,<sup>38</sup> and decrease circulating catecholamines.<sup>39</sup> Exercise training has also been shown to improve quality of life in both men and women with moderate, chronic HF.<sup>40</sup> Whether these physiological adaptations will ultimately reduce mortality and morbidity is yet to be determined by a large prospective trial, although there is at least one small trial which showed a reduction in hospitalizations and improved 1-year survival.<sup>41</sup> A prospective large randomized trial, Heart Failure—A Controlled Trial Investigating Outcomes of exercise training (HF-ACTION), has been funded by the National Institutes of Health. This trial proposes to randomize HF patients to a formal exercise-training program or usual care with the primary end points of all-cause mortality and all-cause hospitalizations.

### Treatment for Patients With Peripheral Arterial Disease and Claudication

Progressive physical activity is an effective treatment for improving walking distance in patients with peripheral arterial disease and exercise-induced claudication. Supervised exercise may serve as a primary therapy for many individuals with claudication if such a program is available and if claudication is the primary functional limitation. A meta-analysis of 21 exercise programs for patients with claudication demonstrated that, after exercise training, average walking distance to pain onset increased 179% or 225 m, and average distance to maximal tolerated pain increased 122% or 397 m.<sup>42</sup> Although there are few direct comparisons of therapeutic exercise programs versus pharmacological or surgical interventions, these increases in walking distance are greater than those reported for the most widely used agents for claudication, pentoxifylline and cilostazol. The greatest improvement with exercise training for claudication occurred with training to maximal tolerated pain, when training lasted at least 6 months, and when walking was the primary mode of exercise.<sup>42</sup> A review of randomized controlled trials suggests that the evidence favoring exercise training outweighs that for peripheral angioplasty in improving exercise tolerance in claudication patients.<sup>43</sup> In contrast, a direct comparison of invasive treatment and supervised exercise training found improvement at 1 year only in the invasively treated patients,<sup>44</sup> so the issue remains controversial. In addition, no trials have examined the effect of exercise training on the need for revascularization or on subsequent cardiovascular events or mortality in patients with claudication.

### Exercise Training for Older Patients With CAD

Older patients constitute a high percentage of those with diagnosed CAD and are at high risk for disability after a

coronary event. Studies of exercise rehabilitation in patients >65 years of age have evaluated outcomes in the elderly patients with coronary disease. Older patients with CAD have exercise trainability comparable to that of younger patients participating in similar exercise rehabilitation, with elderly male and female patients showing comparable improvement.<sup>45–47</sup> However, referral to and participation in exercise rehabilitation is less frequent for older patients, especially for older women.<sup>48</sup> No significant complications or adverse outcomes of exercise training in older patients have been described in any study. Consequently, older patients of both genders should be strongly encouraged to participate in exercise-based cardiac rehabilitation.

Whether exercise training is associated with a reduction of morbidity or mortality in the elderly CAD patient is controversial, although in the British Regional Heart Study, men with CAD and a mean age of 63 years who engaged in light-to-moderate physical activity had a significantly lower all-cause mortality over the 5-year follow-up than did their sedentary counterparts.<sup>49</sup>

### Risks of Physical Activity

Physical activity and exercise training have risks that must be considered when recommending regular physical activity for the general population and for individuals with cardiovascular disease. Fortunately, several strategies are recognized as effective at reducing risk when recommending physical activity. Overall, available information suggests that physical activity in the range recommended by recent public health guidelines, such as the CDC/ACSM guideline,<sup>7</sup> has quite an acceptable risk-to-benefit ratio. The most common risk of physical activity in adults is musculoskeletal injury.<sup>50,51</sup> The incidence of injury can be as high as 55% in 8 weeks among women undergoing US Army basic training.<sup>52</sup> In contrast, injuries are rare in research studies of supervised exercise training among older adults when individuals at high risk of injury are excluded.<sup>53</sup> In a cohort study of community adults aged 20 to 85 years with above-average activity levels, ≈25% reported a musculoskeletal injury over 1 year,<sup>50</sup> and one third of injured adults stopped exercising. Several factors affecting injury risk are modifiable and offer opportunities for risk management. Risk of injury increases with obesity,<sup>51</sup> volume of exercise,<sup>50</sup> and participation in vigorous exercise such as competitive sports,<sup>54</sup> whereas higher fitness,<sup>50</sup> supervision, stretching exercises, protective equipment such as bike helmets, and well-designed environments protect against injury. The general principle that the volume of physical activity should be increased gradually over time is widely regarded as critical for reducing injury risk.<sup>7</sup> Walking, the most popular activity and the standard example of a moderate-intensity activity, is a low-risk activity. One study reported that increasing the duration of walking did not result in any increase in injury risk.<sup>50</sup> In some situations, regular physical activity actually reduces injury risk, as indicated by a recent consensus statement that physical activity is recommended to reduce the risk of fall injuries in older adults.<sup>55</sup>

Vigorous physical activity acutely increases the risk of sudden cardiac death<sup>56,57</sup> and myocardial infarction<sup>58,59</sup> among individuals with both diagnosed and occult heart

disease. A variety of congenital and acquired conditions such as hypertrophic cardiomyopathy, coronary artery anomalies, aortic stenosis, and cardiomyopathies are associated with sudden death during vigorous activity in children and young adults.<sup>60,61</sup> Recommendations for athletic screening and participation for these conditions have been presented in the AHA Statement on Cardiovascular Preparticipation Screening of Competitive Athletes.<sup>62</sup> The incidence of sudden death during exercise is not well defined in this age group. Among high school and college athletes, an estimated 1 death per year occurs during or within an hour after athletic activity for every 133 333 male and 769 230 female participants.<sup>60</sup> Atherosclerotic CAD is the overwhelming cause of exercise-related deaths in adults.<sup>56,57</sup> The incidence has been estimated to be 1 exertion-related death per year for every 15 000<sup>56</sup> to 18 000<sup>57</sup> ostensibly healthy men. These incidence rates are based on only 10<sup>56</sup> and 9<sup>57</sup> exercise-related deaths, which gives these figures wide confidence limits. A preliminary report from a 3-million-member national fitness facility noted 61 male and 10 female deaths over 2 years and calculated incidence rate of 1 death per 82 000 members per year or 2.6 million workouts.<sup>63</sup> Although the absolute incidence of sudden death associated with exercise is quite low, exercise does acutely increase the rate of sudden death compared with more leisurely activities.<sup>56,57</sup> Exercise also transiently increases the risk of acute myocardial infarction.<sup>58,59</sup> Approximately 5% to 10% of myocardial infarctions are associated with vigorous physical activity. The relative risk of both exercise-related myocardial infarction and sudden death is greatest in individuals who are the least physically active and who were performing unaccustomed vigorous physical activity.<sup>57–59</sup>

Sedentary adults should avoid isolated bouts of unaccustomed vigorous physical activity and should follow the standard recommendation to increase physical activity levels gradually over time. The possible value of this strategy is supported by the observation that the risk of exercise-related cardiac events is greatest in the least active individuals.<sup>57,59</sup>

Because atherosclerotic CAD is the most frequent cause of exercise-related events, the incidence of such events is higher among patients with known atherosclerotic coronary disease. Among participants in cardiac rehabilitation programs, the average incidence of cardiac arrest, nonfatal myocardial infarction, and death is ≈1 for every 117 000, 220 000, and 750 000 patient-hours of participation,<sup>64</sup> respectively. The low ratio of cardiac arrest to death is due to the availability of acute medical care.

### Recommendations

The evidence summarized above and more extensively presented in the 1996 Surgeon General's Report<sup>65</sup> attests to the value of exercise and physical activity in reducing the incidence of coronary heart disease. Indeed, the original AHA Statement on Exercise in 1992<sup>66</sup> was among the first documents to conclude that physical inactivity is a major CAD risk factor. Because atherosclerotic vascular disease remains the major cause of death in many countries, it is important that healthcare providers support the implementation and maintenance of exercise programs for their patients across the lifespan.

Health professionals should personally engage in an active lifestyle to familiarize themselves with the issues involved in maintaining lifelong physical activity and to set a positive example for patients and the public. This may increase the likelihood that healthcare providers will recommend physical activity to their patients. Healthcare providers should use their influence as parents and community members to encourage schools to provide physical education programs that teach the importance of, and the skills necessary for, developing and maintaining physically active lifestyles. There is growing recognition of the contribution of social support and the value of integrating behavioral changes into daily routines to sustain improvements in physical activity levels. For this reason, healthcare providers should advocate changes in organizational practices within work sites and civic and recreational settings that encourage active living. Health professionals should also encourage their communities to make facilities for physical activity available to the public and to engineer environments conducive to safe physical activity. Such environmental engineering efforts should allow purposeful physical activities, such as walking to work and climbing stairs, to be used in lieu of labor-saving devices. Health professionals should support public health efforts that encourage these active lifestyles.

The importance of physical activity for health and the use of exercise training in managing selected disease states should be incorporated into the education of physicians and other medical professionals. A physical activity history is an important component of the health history, and healthcare providers should include the patient's habitual physical activity as part of the medical record. Healthcare providers should identify for patients the importance of physical activity as primary or adjunctive therapy for such medical conditions as hypertension, hypertriglyceridemia, glucose intolerance, and obesity.

Health professionals should prescribe physical activity programs commensurate with those recommended by the CDC and the ACSM, ie, 30 minutes or more of moderate-intensity physical activity such as brisk walking on most, and preferably all, days of the week.<sup>7</sup> Patients should be encouraged to engage in a variety of physical activities and to progressively increase their activity as tolerated. Detailed guidelines for prescribing exercise in patients with and without cardiovascular disease are provided in the AHA Exercise Standards for Testing and Training.<sup>8</sup> Recommendations are also available for the incorporation of resistance and flexibility exercise training.<sup>67</sup> Healthcare professionals should provide an exercise prescription to patients and should familiarize themselves with behavioral change material available from the Provider-Based Assessment and Counseling for Exercise Program (PACE)<sup>68</sup> and the Activity Counseling Trial (ACT).<sup>69</sup>

It is not necessary that all individuals beginning a moderate-intensity and moderately progressive exercise program undergo an exercise stress test, although this issue remains controversial. A Consensus Group from the AHA and the American College of Cardiology<sup>70</sup> considered routine exercise stress testing before the initiation of a *vigorous* exercise program in healthy men >45 and women >55 years

of age as a Class IIb Recommendation—ie, a condition in which the usefulness and efficacy is not well established. Selected exercise testing should be performed at the discretion of the physician before vigorous exercise in patients with known cardiovascular problems.

Healthcare providers caring for patients with diagnosed cardiovascular disease should support the development of exercise programs to manage these patients and make appropriate referrals for treatment. There are also effective strategies to promote active lifestyles for whole communities that complement those designed for individuals. The Task Force on Community Preventive Services has completed an evidence-based review of these community strategies.<sup>71</sup> The 6 strategies deemed effective were: (1) large-scale, intense, highly visible, community-wide campaigns; (2) point-of-decision prompts that encourage people to use the stairs instead of elevators or escalators; (3) physical education programs in schools; (4) social support programs (such as buddy systems and walking groups); (5) individually adapted behavior change programs; and (6) enhanced access to places for physical activity. For example, 12 studies have studied increasing access to places for physical activity, with a median effect size of a 26% increase in persons exercising at least 3 days per week.

### Areas for Future Investigation

Although there is sufficient evidence to encourage increased physical activity for the public and most patient groups, multiple aspects of physical activity and health warrant additional investigation. Foremost is research into behavioral strategies and techniques to increase physical activity levels among children and adolescents and to maintain increased activity over their lifespans. Similar information on factors influencing the adoption and maintenance of physical activity is required for adults. In particular, there is a need to focus on physical activity promotion efforts via organizational (eg, work sites and communities) and legislative policy changes, rather than just on the individual level. Additionally, the message that incremental change in physical activity behavior is important has to be emphasized so that patients do not see physical activity participation as an all-or-none behavior, like cigarette smoking. Much has been learned in the past decade about how to use behavioral interventions to help sedentary adults become more active in individual and small-group settings. There is a need to evaluate the efficacy of disseminating these interventions with modern technology, such as the Internet. Additional physiological and basic research is necessary to provide the scientific rationale supporting the importance of physical activity. Such research should address the mechanisms by which exercise reduces CAD risk as well as explore other medical conditions effectively managed by exercise training. The contribution of physical inactivity to the development of the present obesity epidemic warrants additional investigation, as does the role of physical activity in the treatment of obesity. It is important to develop information on the minimal and optimal amounts of exercise and physical activity required to produce specific beneficial outcomes and to understand individual differences that may augment or impede the beneficial effects of physical training.

More attention also needs to be given to assessing the health benefits from physical activity when intensity is measured relative to the individual's fitness and not as an absolute value. Additional studies are needed on the value of physical activity programs superimposed on contemporary therapy for CAD patients because most data forming our knowledge base were obtained more than a decade ago when CAD mortality rates were substantially higher than at present. Additional studies are also needed on the risks of exercise because the benefits of exercise for patients with diagnosed or occult CAD can be maximized only if the risks are as low as possible. Finally, cost-effectiveness studies are needed to evaluate the role of physical activity relative to other interventions on healthcare costs.

### Summary of Key Points

- (1) Physical activity and exercise training have important roles in:
  - A. Preventing atherosclerotic CAD;
  - B. Managing selected CAD risk factors, including elevated triglyceride levels, low HDL-C, hypertension, glucose intolerance, hypertension, obesity, and possibly cigarette use;
  - C. Treating patients with CAD, HF, and claudication.
- (2) Healthcare professionals should:
  - A. Engage in an active lifestyle;
  - B. Encourage schools to teach skills required for physically active lifestyles and communities to develop programs and facilities conducive to physical activity;
  - C. Be educated about exercise as a therapeutic modality and the importance of lifelong physical activity in their patients;
  - D. Routinely prescribe exercise and increased physical activity to their patients in accordance with recommendations provided by the CDC/ACSM<sup>7</sup> and the AHA<sup>8</sup>;
  - E. Perform exercise testing before vigorous exercise in selected patients with cardiovascular disease and other patients with symptoms or those at high risk.
- (3) Additional research should:
  - A. Address behavioral strategies to increase and maintain physical activity over the lifespan;
  - B. Increase the scientific rationale supporting the importance of physical activity by examining the amount of exercise required to alter CAD risk, the effect of exercise on morbidity and mortality, and its cost-effectiveness.

### References

1. Knowler WC, Barrett-Connor E, Fowler SE, et al, for the Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346:393–403.
2. Vuori IM. Dose-response of physical activity and low back pain, osteoarthritis, and osteoporosis. *Med Sci Sports Exerc*. 2001;33(6 suppl):S551–S586.
3. Wing RR, Hill JO. Successful weight loss maintenance. *Annu Rev Nutr*. 2001;21:323–341.
4. Pollock KM. Exercise in treating depression: broadening the psychotherapist's role. *J Clin Psychol*. 2001;57:1289–1300.
5. Breslow RA, Ballard-Barbash R, Munoz K, et al. Long-term recreational physical activity and breast cancer in the National Health and Nutrition Examination Survey I epidemiologic follow-up study. *Cancer Epidemiol Biomarkers Prev*. 2001;10:805–808.
6. Slattery ML, Potter JD. Physical activity and colon cancer: confounding or interaction? *Med Sci Sports Exerc*. 2002;34:913–919.
7. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273:402–407.
8. Fletcher GF, Balady GJ, Amsterdam EA, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation*. 2001;104:1694–1740.
9. Lee IM, Paffenbarger RS Jr, Hennekens CH. Physical activity, physical fitness and longevity. *Aging (Milano)*. 1997;9:2–11.
10. Blair SN, Jackson AS. Physical fitness and activity as separate heart disease risk factors: a meta-analysis. *Med Sci Sports Exerc*. 2001;33:762–764.
11. US Department of Health, Education, and Welfare. *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. Washington, DC: US Department of Health, Education, and Welfare, Public Health Service; 1964. PHS Publication No. 1103. Available at: [http://www.cdc.gov/tobacco/sgr/sgr\\_1964/sgr64.htm](http://www.cdc.gov/tobacco/sgr/sgr_1964/sgr64.htm). Accessed May 9, 2003.
12. Powell KE, Thompson PD, Caspersen CJ, et al. Physical activity and the incidence of coronary heart disease. *Annu Rev Public Health*. 1987;8:253–287.
13. Paffenbarger RS Jr, Hyde RT, Wing AL, et al. A natural history of athleticism and cardiovascular health. *JAMA*. 1984;252:491–495.
14. Stefanick ML, Mackey S, Sheehan M, et al. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. *N Engl J Med*. 1998;339:12–20.
15. Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc*. 2001;33(6 suppl):S502–S515.
16. Leon AS, Sanchez O. Meta-analysis of the effects of aerobic exercise training on blood lipids. *Circulation*. 2001;104(suppl II):II-414–II-415. Abstract.
17. Leon AS, Rice T, Mandel S, et al. Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the HERITAGE Family Study. *Metabolism*. 2000;49:513–520.
18. Couillard C, Despres JP, Lamarche B, et al. Effects of endurance exercise training on plasma HDL cholesterol levels depend on levels of triglycerides: evidence from men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. *Arterioscler Thromb Vasc Biol*. 2001;21:1226–1232.
19. Fagard RH. Exercise characteristics and the blood pressure response to dynamic physical training. *Med Sci Sports Exerc*. 2001;33(6 suppl):S484–S492.
20. Thompson PD, Crouse SF, Goodpaster B, et al. The acute versus the chronic response to exercise. *Med Sci Sports Exerc*. 2001;33(6 suppl):S438–S445.
21. Ussher MH, West R, Taylor AH, et al. Exercise interventions for smoking cessation. *Cochrane Database Syst Rev*. 2000;(3):CD002295.
22. Marcus BH, Albrecht AE, King TK, et al. The efficacy of exercise as an aid for smoking cessation in women: a randomized controlled trial. *Arch Intern Med*. 1999;159:1229–1234.
23. O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation*. 1989;80:234–244.
24. Oldridge NB, Guyatt GH, Fischer ME, et al. Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. *JAMA*. 1988;260:945–950.
25. Jolliffe JA, Rees K, Taylor RS, et al. Exercise-based rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2001;(1):CD001800.
26. Billman GE. Aerobic exercise conditioning: a nonpharmacological antiarrhythmic intervention. *J Appl Physiol*. 2002;92:446–454.
27. Hamilton KL, Powers SK, Sugiura T, et al. Short-term exercise training can improve myocardial tolerance to I/R without elevation in heat shock proteins. *Am J Physiol Heart Circ Physiol*. 2001;281:H1346–H1352.
28. Clausen JP, Trap-Jensen J. Heart rate and arterial blood pressure during exercise in patients with angina pectoris: effects of training and of nitroglycerin. *Circulation*. 1976;53:436–442.
29. Ehsani AA, Martin WH 3rd, Heath GW, et al. Cardiac effects of prolonged and intense exercise training in patients with coronary artery disease. *Am J Cardiol*. 1982;50:246–254.
30. Niebauer J, Hambrecht R, Velich T, et al. Attenuated progression of coronary artery disease after 6 years of multifactorial risk intervention: role of physical exercise. *Circulation*. 1997;96:2534–2541.
31. Gould KL, Ornish D, Kirkeide R, et al. Improved stenosis geometry by quantitative coronary arteriography after vigorous risk factor modification. *Am J Cardiol*. 1992;69:845–853.

32. Sim DN, Neill WA. Investigation of the physiological basis for increased exercise threshold for angina pectoris after physical conditioning. *J Clin Invest.* 1974;54:763–770.
33. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. *N Engl J Med.* 2000;342:454–460.
34. Belardinelli R, Paolini I, Cianci G, et al. Exercise training intervention after coronary angioplasty: the ETICA trial. *J Am Coll Cardiol.* 2001;37:1891–1900.
35. Piña IL, Apstein CS, Balady GJ, et al. Exercise and heart failure: a statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention. *Circulation.* 2003;107:1210–1225.
36. Cheetham C, Green D, Collis J, et al. Effect of aerobic and resistance exercise on central hemodynamic responses in severe chronic heart failure. *J Appl Physiol.* 2002;93:175–180.
37. Hambrecht R, Fiehn E, Yu J, et al. Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol.* 1997;29:1067–1073.
38. Gielen S, Erbs S, Schuler G, et al. Exercise training and endothelial dysfunction in coronary artery disease and chronic heart failure: from molecular biology to clinical benefits. *Minerva Cardioangiol.* 2002;50:95–106.
39. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure: a randomized trial. *JAMA.* 2000;283:3095–3101.
40. Tyni-Lenne R, Gordon A, Europe E, et al. Exercise-based rehabilitation improves skeletal muscle capacity, exercise tolerance, and quality of life in both women and men with chronic heart failure. *J Card Fail.* 1998;4:9–17.
41. Belardinelli R, Georgiou D, Cianci G, et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. *Circulation.* 1999;99:1173–1182.
42. Gardner AW, Poehlman ET. Exercise rehabilitation programs for the treatment of claudication pain: a meta-analysis. *JAMA.* 1995;274:975–980.
43. Whyman MR, Ruckley CV. Should claudicants receive angioplasty or just exercise training? *Cardiovasc Surg.* 1998;6:226–231.
44. Gelin J, Jivegard L, Taft C, et al. Treatment efficacy of intermittent claudication by surgical intervention, supervised physical exercise training compared to no treatment in unselected randomised patients: I. one year results of functional and physiological improvements. *Eur J Vasc Endovasc Surg.* 2001;22:107–113.
45. Lavie CJ, Milani RV, Littman AB. Benefits of cardiac rehabilitation and exercise training in secondary coronary prevention in the elderly. *J Am Coll Cardiol.* 1993;22:678–683.
46. Williams MA, Maresh CM, Esterbrooks DJ, et al. Early exercise training in patients older than age 65 years compared with that in younger patients after acute myocardial infarction or coronary artery bypass grafting. *Am J Cardiol.* 1985;55:263–266.
47. Ades PA, Waldmann ML, Gillespie C. A controlled trial of exercise training in older coronary patients. *J Gerontol A Biol Sci Med Sci.* 1995;50A:M7–M11.
48. Ades PA, Waldmann ML, Polk DM, et al. Referral patterns and exercise response in the rehabilitation of female coronary patients aged greater than or equal to 62 years. *Am J Cardiol.* 1992;69:1422–1425.
49. Wannamethee SG, Shaper AG, Walker M. Physical activity and mortality in older men with diagnosed coronary heart disease. *Circulation.* 2000;102:1358–1363.
50. Hootman JM, Macera CA, Ainsworth BE, et al. Epidemiology of musculoskeletal injuries among sedentary and physically active adults. *Med Sci Sports Exerc.* 2002;34:838–844.
51. Sutton AJ, Muir KR, Mockett S, et al. A case-control study to investigate the relation between low and moderate levels of physical activity and osteoarthritis of the knee using data collected as part of the Allied Dunbar National Fitness Survey. *Ann Rheum Dis.* 2001;60:756–764.
52. Jones BH, Knapik JJ. Physical training and exercise-related injuries: surveillance, research and injury prevention in military populations. *Sports Med.* 1999;27:111–125.
53. Buchner DM, Coleman EA. Exercise considerations in older adults: intensity, fall prevention and safety. *Phys Med Rehabil Clin N Am.* 1994;5:357–375.
54. Nicholl JP, Coleman P, Williams BT. The epidemiology of sports and exercise related injury in the United Kingdom. *Br J Sports Med.* 1995;29:232–238.
55. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. *J Am Geriatr Soc.* 2001;49:664–672.
56. Thompson PD, Funk EJ, Carleton RA, et al. Incidence of death during jogging in Rhode Island from 1975 through 1980. *JAMA.* 1982;247:2535–2538.
57. Siscovick DS, Weiss NS, Fletcher RH, et al. The incidence of primary cardiac arrest during vigorous exercise. *N Engl J Med.* 1984;311:874–877.
58. Mittleman MA, Maclure M, Tofler GH, et al. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of Myocardial Infarction Onset Study Investigators. *N Engl J Med.* 1993;329:1677–1683.
59. Giri S, Thompson PD, Kiernan FJ, et al. Clinical and angiographic characteristics of exertion-related acute myocardial infarction. *JAMA.* 1999;282:1731–1736.
60. Van Camp SP, Bloor CM, Mueller FO, et al. Nontraumatic sports death in high school and college athletes. *Med Sci Sports Exerc.* 1995;27:641–647.
61. Maron BJ, Shirani J, Poliac LC, et al. Sudden death in young competitive athletes: clinical, demographic, and pathological profiles. *JAMA.* 1996;276:199–204.
62. Maron BJ, Thompson PD, Puffer JC, et al. Cardiovascular preparticipation screening of competitive athletes: a statement for health professionals from the Sudden Death Committee (Clinical Cardiology) and Congenital Cardiac Defects Committee (Cardiovascular Disease in the Young), American Heart Association. *Circulation.* 1996;94:850–856.
63. Franklin BA, Conviser JM, Stewart B, et al. Sporadic exercise: a trigger for acute cardiovascular events? *Circulation.* 2000;102(suppl II):II-612. Abstract.
64. Franklin BA, Bonzheim K, Gordon S, et al. Safety of medically supervised outpatient cardiac rehabilitation exercise therapy: a 16-year follow-up. *Chest.* 1998;114:902–906.
65. US Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General.* Atlanta, Ga: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996. Available at: <http://www.cdc.gov/nccdphp/sgr/sgr.htm>. Accessed May 30, 2003.
66. Fletcher GF, Balady G, Blair SN, et al. Statement on exercise: benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation.* 1996;94:857–862.
67. Pollock ML, Franklin BA, Balady GJ, et al. AHA Science Advisory. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation.* 2000;101:828–833.
68. Calfas KJ, Long BJ, Sallis JF, et al. A controlled trial of physician counseling to promote the adoption of physical activity. *Prev Med.* 1996;25:225–233.
69. King AC, Sallis JF, Dunn AL, et al. Overview of the Activity Counseling Trial (ACT) intervention for promoting physical activity in primary health care settings. Activity Counseling Trial Research Group. *Med Sci Sports Exerc.* 1998;30:1086–1096.
70. Gibbons RJ, Balady GJ, Beasley JW, et al. ACC/AHA Guidelines for Exercise Testing. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol.* 1997;30:260–311.
71. Increasing physical activity: a report on recommendations of the Task Force on Community Preventive Services. *MMWR Recomm Rep.* October 26, 2001;50(RR-18):1–14.

KEY WORDS: AHA Scientific Statements ■ exercise ■ prevention ■ cardiovascular disease



**Exercise and Physical Activity in the Prevention and Treatment of Atherosclerotic Cardiovascular Disease: A Statement From the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity)**

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*Circulation*. 2003;107:3109-3116

doi: 10.1161/01.CIR.0000075572.40158.77

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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