Circulation

AHA SCIENTIFIC STATEMENT

Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective–An Update

A Scientific Statement From the American Heart Association

Endorsed by the American College of Sports Medicine and American Association of Cardiovascular and Pulmonary Rehabilitation

ABSTRACT: Epidemiological and biological plausibility studies support a cause-and-effect relationship between increased levels of physical activity or cardiorespiratory fitness and reduced coronary heart disease events. These data, plus the well-documented anti-aging effects of exercise, have likely contributed to the escalating numbers of adults who have embraced the notion that "more exercise is better." As a result, worldwide participation in endurance training, competitive long distance endurance events, and high-intensity interval training has increased markedly since the previous American Heart Association statement on exercise risk. On the other hand, vigorous physical activity, particularly when performed by unfit individuals, can acutely increase the risk of sudden cardiac death and acute myocardial infarction in susceptible people. Recent studies have also shown that large exercise volumes and vigorous intensities are both associated with potential cardiac maladaptations, including accelerated coronary artery calcification, exercise-induced cardiac biomarker release, myocardial fibrosis, and atrial fibrillation. The relationship between these maladaptive responses and physical activity often forms a U- or reverse J-shaped dose-response curve. This scientific statement discusses the cardiovascular and health implications for moderate to vigorous physical activity, as well as high-volume, high-intensity exercise regimens, based on current understanding of the associated risks and benefits. The goal is to provide healthcare professionals with updated information to advise patients on appropriate preparticipation screening and the benefits and risks of physical activity or physical exertion in varied environments and during competitive events.

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Substantial epidemiological, clinical, and basic science evidence suggests that regular physical activity (PA), higher cardiorespiratory fitness (CRF), or both, delay the development of atherosclerotic cardiovascular disease (CVD) and reduce the incidence of coronary heart disease (CHD) events.[1–3] PA is defined as any bodily movement resulting from the contraction of skeletal muscle that increases energy expenditure above the basal level. A systematic review and meta-analysis of 33 PA studies (n=883 372 participants) reported risk reductions of 30% to 50% for cardiovascular mortality and 20% to 50% for all-cause mortality with increasing volumes of PA.[4] More recently, researchers from the Nurses' Health Study (n=78 865) and the Health Professionals Follow-up Study (n=44 354) estimated the impact of 5 lifestyle factors, including ≥30 min/d of moderate to vigorous PA, on life expectancy in the US population.[5] During up to 34 years of follow-up, the most physically active cohorts of men and women demonstrated 7- to 8-year gains in life expectancy.

Exercise training, as a subcategory of PA, is defined as any planned and structured intervention with the objective of improving or maintaining CRF or health, achieving athletic goals, or both. Aerobic capacity or CRF can be directly measured during cardiopulmonary exercise testing via gas-exchange measurements or estimated from the attained treadmill speed, percent grade, and duration (minutes) or the cycle ergometer workload, expressed as kilogram meters per minute. After a 12-week exercise-based cardiac rehabilitation program in a cohort of >5600 patients with known CVD, each 1-metabolic equivalent (MET; 1 MET=3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) improvement in estimated CRF (CRFe) was associated with a 13% overall reduced risk of all-cause mortality and, in the least fit patient cohort (<5 MET capacity), a 30% reduction in mortality.[6] These risk reductions compare favorably with the survival benefit conferred by commonly prescribed cardioprotective medications, including statins.[7] In US veterans, the incidence of major CVD events was 16% lower for every 1-MET increase in CRFe. Compared with the least fit veterans, the risk of CVD events was ≈70% lower for individuals in the highest fitness category.[8] A prospective cohort study of >120 000 consecutive patients who underwent maximal treadmill testing and 1.1 million person-years of observation reported no upper limit for the protective effect of higher CRFe on all-cause mortality. Compared with the lowest performers (<25th percentile), elite CRFe (>97.7th percentile) was associated with an 80% reduction in mortality risk. Remarkably, the effect of low CRFe on all-cause mortality was comparable to or greater than that of traditional risk factors such as smoking and diabetes mellitus for coronary artery disease (CAD).[9] A study from the UK Biobank (n=502 635) showed inverse associations between CRFe and CHD (hazard ratio [HR], 0.51 [95% CI, 0.38–0.69]) and CRFe and atrial fibrillation (AF; HR, 0.40 [95% CI, 0.30–0.55]) among individuals at high genetic risk for these diseases.[10] Others have reported that highly fit individuals, regardless of their risk factor profile, have an ≈50% lower 30-year CVD mortality than their counterparts with low fitness.[11] Similarly, men with subclinical CAD (coronary artery calcium [CAC] score ≥100) whose CRFe was ≥10 METs have an age-adjusted HR for CHD events of 0.26 (95% CI, 0.15–0.45) compared with men whose CRFe is <10 METs.[12] More recently, compared with the least fit men, CVD events were shown to be progressively reduced with increasing fitness levels, and the effect was more prominent in individuals with the highest levels of CAC.[13] Collectively, these epidemiological analyses, combined with evidence of biological plausibility (Figure 1),[14,15] support a cause-and-effect relationship between increased levels of PA and CRF and reduced CVD mortality[16–18] and suggest that being unfit is an independent risk factor for CHD (Figure 2).[1,19]

Higher levels of PA or CRF (>5 METs) before hospitalization for acute coronary syndromes (ACS) and surgical procedures are associated with better short-term outcomes,[20,21] possibly because of exercise-induced ischemic preconditioning.[22] An investigation of 2172 patients hospitalized for ACS evaluated the effect of preadmission PA on in-hospital and 1-month post-discharge CVD health outcomes.[23] Patients were categorized as physically inactive (reference category), minimally active, and highly active. Multivariate analysis revealed that compared with the inactive cohort, minimal or high activity was associated with a 44% (95% CI, 10%–68%) reduction of in-hospital mortality and a 20% (95% CI, 1%–50%) lower risk of a CVD event within the first month of hospital discharge.[23] Complications after elective or emergent surgical procedures, including bariatric surgery[24] and coronary artery bypass grafting,[25] are also increased in those with reduced preoperative levels of PA or CRF (Figure 3).[26]

The favorable risk factor profiles and superior cardiac performance of long-distance runners and the observation that vigorous PA and high levels of CRF are associated with reduced use of diabetic, hypertensive, and hypercholesterolemia medications[27] suggest that high-volume and high-intensity endurance training regimens, including high-intensity interval training (HIIT),[28] are cardioprotective in individuals with and without CHD. These data have likely contributed to increasing numbers of middle-aged and older adults concluding that "more exercise is better."[29] As a result, worldwide participation in half- and full-marathon races, triathlon events, and HIIT has increased markedly since the American Heart Association's (AHA's) previous statement on exercise risk.[30] Nevertheless, prolonged exercise increases cardiac biomarkers[31–33] and postexercise transient myocardial dysfunction, and endurance athletes >35 years of age have increased myocardial late

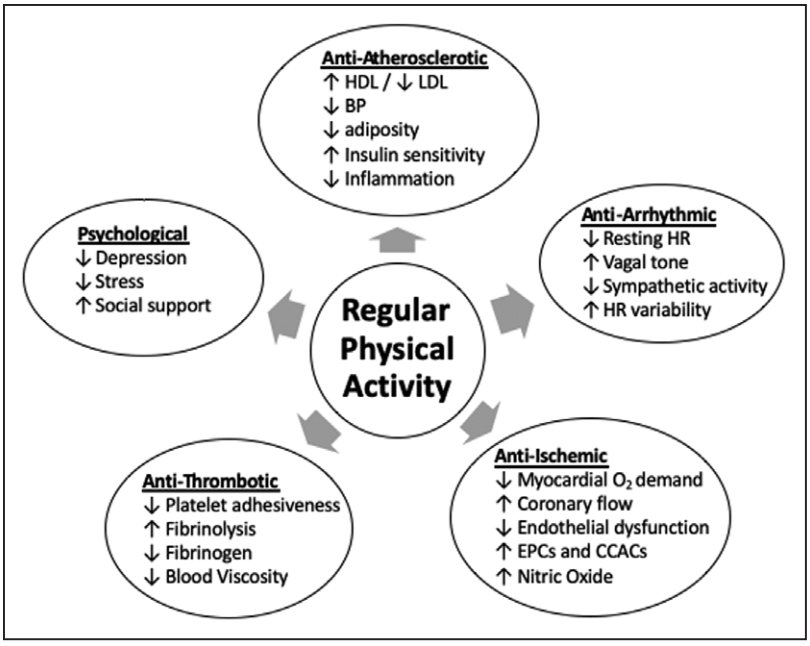

Figure 1. Cardioprotective effects of regular physical activity.
There are multiple mechanisms by which moderate to vigorous exercise training can decrease the risk of cardiovascular events. ↑ indicates increase; ↓, decrease; BP, blood pressure; CCACs, cultured/circulating angiogenic cells; EPCs, endothelial progenitor cells; HDL, high-density lipoprotein; HR, heart rate; and LDL, low-density lipoprotein.

gadolinium enhancement (LGE) suggesting fibrosis, elevated CAC scores,[34,35] and a greater incidence of AF.[36] Collectively, these studies suggest that high-volume, high-intensity training regimens may, at least in some individuals, create a substrate for adverse cardiovascular adaptations and the potential for exercise-related acute cardiac events.[37]

Although vigorous PA (usually defined as ≥60% functional capacity) appears to be superior to moderate-intensity exercise (40%–59% functional capacity) in eliciting cardiovascular adaptations and better outcomes,[28,38] including CRF,[39] even if the total energy expenditure is held constant,[40] the relative risk of acute cardiovascular events increases during vigorous- to high-intensity PA compared with the risk at other times.[41] This is particularly true among habitually sedentary individuals with known or occult CVD performing unaccustomed strenuous PA.[41] Although an absolute exercise intensity ≥6 METs has been suggested as vigorous PA in some population-based applications, it does not account for the fact that the cardiac demand of any PA is determined not by the specific metabolic level but by the metabolic demand relative to the individual's functional capacity. Consequently, lower MET requirements can still place considerable stress on the cardiovascular system of unfit, older individuals and those with established CVD.[30]

In people with a diseased or susceptible heart, there is the potential for a plateau or even a decline in benefit at more extreme levels of exercise (ie, in a reverse J-curve or U-curve pattern), with a leveling off of protection or possibly an increased risk in some individuals for deterioration in cardiovascular function, acute cardiac events, or sudden cardiac death (SCD).[36,37] It is important to address the risks associated with vigorous- to high-intensity endurance training and competition, because more people are engaged in this activity.[42]

This scientific statement seeks to update the benefits and risks of exercise based on current understanding of exercise-related SCD, conditions that can increase

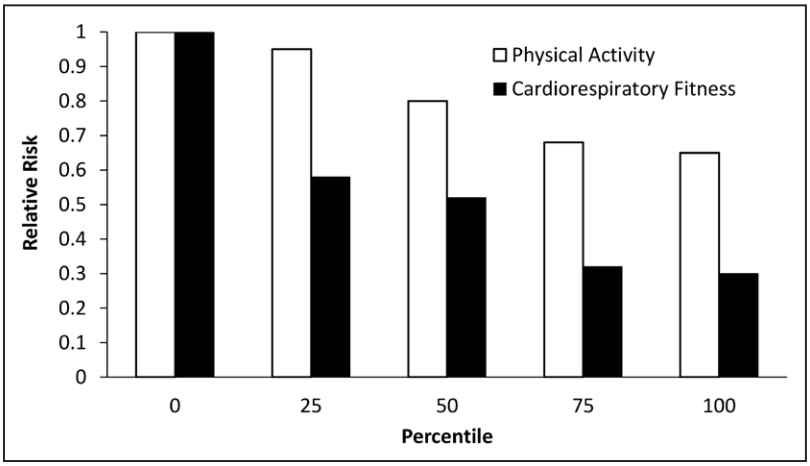

Figure 2. Physical activity, cardiorespiratory fitness, and risk of coronary heart disease and cardiovascular disease.
The risks of coronary heart disease and cardiovascular disease decrease linearly in association with increasing percentiles of physical activity. In contrast, there is a precipitous decrease in risk when the lowest is compared with the next-lowest category of cardiorespiratory fitness. Beyond this demarcation, the reductions in risk parallel those observed with increasing physical activity but are essentially twice as great for cardiorespiratory fitness. Adapted from Williams[19] with permission from Wolters Kluwer Health, Inc. Copyright © 2001, the American College of Sports Medicine.

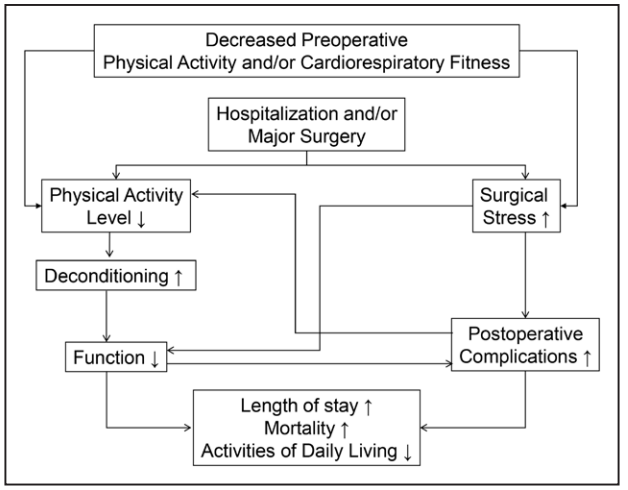

Figure 3. Possible impact of decreased preoperative physical activity or cardiorespiratory fitness on hospitalized patients undergoing emergent or elective surgery with specific reference to short-term outcomes.

↑ indicates increase; and ↓, decrease. Adapted from Hoogeboom et al[26] with permission. Copyright © 2014, Wolters Kluwer Health | Lippincott Williams & Wilkins. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 3.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

exercise risk, and the possibility that excessive exercise can increase markers of adverse cardiovascular outcomes. Additionally, this AHA scientific statement reviews common activities associated with acute cardiac events and provides strategies to potentially reduce these complications. The goal is to provide healthcare professionals with updated information to advise athletes and patients on the benefits and risks of moderate to vigorous PA.

CARDIOVASCULAR RISKS OF EXERCISE

Most studies,[43–46] but not all,[47,48] have reported a decrease in cardiovascular events with increasing regular PA. Despite these long-term benefits, the risk of SCD and myocardial infarction (MI) is increased during and shortly after bouts of vigorous physical exertion.

The relationship between physical exertion and SCD has been widely studied, both in general populations and in athletes. The proportion of SCDs related to physical exertion in the general population varies widely,[43,45,48–54] from 3%[45] to 26%,[53] depending on age, sex, and ethnic/racial characteristics of the population. The proportion of SCDs that occur during physical exertion is higher in younger age groups.[53,54] In a recent community-wide study, sports-related sudden cardiac arrest (SCA) accounted for 39% of SCAs in individuals <18 years old, 13% in those between 19 and 25 years old, and 7% between the ages of 25 and 34.[53] The proportion of deaths that occur during physical exertion in competitive athletes <35 years of age is much higher than in nonathletes in the general population.[53] In the most recent registries from the United States[55] and the United Kingdom,[56] 61% to 80% of the SCDs in athletes occurred during or just after physical exertion. Although the incidence of SCDs related to acute exertion is higher in competitive athletes, the absolute numbers of SCDs are greater during recreational sports,[51] and most of these exertion-related SCD events occurred in adults >35 years of age.[51] However, even in younger age groups, the majority of exercise-related cardiac arrests occur in those not engaged in organized competitive sports.[57,58] Therefore, despite the high profile of sports-related SCD, the majority of exercise-related SCDs occur during recreational exercise.

Acute MI (AMI) also occurs with a higher than expected frequency during or soon after physical exertion. SCD and AMI overlap among men >30 years of age, in whom exertion-related SCDs are often associated with underlying CHD or acute plaque rupture.[59] The proportion of AMIs associated with exertion ranges from 4.4%[41] to 13.6%.[41,60–63] Exercise is also a trigger for acute type A aortic dissection, which has been reported in alpine skiers[64] and weight lifters.[65,66] Sudden death caused by aortic dissection or rupture of an aortic aneurysm is found on autopsy in only ≈2% to 3% of SCDs in athletes[51,57,67] and ≈4% of exertion-related SCDs in broader populations.[58] The relative versus absolute risks of exercise and PA are summarized below.

Short-Term Relative Risks

Several studies have estimated the relative risk (RR) of SCD and MI during and up to 1 hour after exercise using case-crossover and case-control study designs. These studies have consistently reported that the RR of SCD or MI is transiently elevated during and immediately after physical exertion compared with other activities or rest, but the magnitude of the short-term RR varied across studies.[41,43,45,48,60,63]

Sudden Cardiac Death

Several studies of differing designs, primarily of men, have estimated the RR of SCA and SCD during vigorous exertion compared with rest or more moderate PA.[43,48,68,69] In a prospective case-crossover analysis of men in the US Physician's Health Study, the risk of SCD was transiently elevated ≈17-fold in the period during and up to 30 minutes after vigorous exertion.[48] On the other hand, only a 3-fold increase in risk was reported during and up to an hour after vigorous exercise in a retrospective case-crossover study involving men and women from Slovenia.[68] In all studies, regular participation in vigorous exercise decreased the magnitude of the increased SCD risk associated with vigorous exertion,[43,48,68] such that the highest risks were observed in the least active individuals. Men with the lowest level of habitual PA had marked elevations in the short-term

risk of SCD during vigorous exercise (RR=50[68] to 74[48]) compared with those who exercised regularly (RR=2[68] to 11[48]).[43] However, in 2 of these studies, the risk of SCD remained elevated during exertion even among the most habitually active men.[43,48]

There are limited data regarding whether more moderate levels of exercise might trigger SCD. One prospective case-crossover study among middle-aged nurses reported the RR of SCD associated with combined exposure to both moderate and vigorous levels of exertion.[45] Because of the small number of exercise-associated SCDs in women, the risk of moderate versus vigorous exercise could not be analyzed separately. The RR of SCD was modestly but significantly elevated during and 30 minutes after moderate and vigorous exercise, with an estimated RR of 2.4 (95% CI, 1.2–4.6; *P*=0.01). This transient increase in risk was again reduced by regular exercise participation, with the highest risks observed among women who reported <2 hours per week of moderate to vigorous exertion (RR, 9.0 [95% CI, 3.3–24.3]). In contrast to prior studies that examined vigorous exercise in men,[43,48] this transient elevation in risk was no longer significant among the most habitually active women. Women who reported participating in moderate to vigorous exercise ≥2 hours per week had an RR of 1.5 (95% CI, 0.61–3.61).

Myocardial Infarction

Several studies using differing designs have also demonstrated significant 2- to 10-fold elevations in the likelihood of experiencing an AMI within 1 hour of participating in vigorous exertion,[41,60–63,70,71] with 1 study demonstrating risk elevations persisting to 2 hours.[62] When the available data from 7 studies (n=5503 patients) were combined using meta-analysis, the summary RR of MI associated with bouts of physical exertion was 3.45 (95% CI, 2.33–5.13), with substantial between-study heterogeneity that was not explained by study size or the year the study was conducted.[72] Effect sizes for the association of episodic PA did not appear to change significantly over time. Again, as is the case for SCD, the magnitude of association between PA as a trigger of MI was greater in individuals with the lowest habitual activity. In these 7 studies, estimates of the RR associated with a bout of vigorous exertion in the least habitually active individuals ranged from 4.5[71] to 107[41] for MI. In comparison, RR estimates of MI in the setting of exertion were much more modest (0.88–3.3) in those with the highest levels of habitual PA.[72] In a meta-regression analysis, the RR of MI associated with episodic PA was decreased by ≈45% for each additional time per week a person habitually exercised.[72]

Since this meta-analysis was published in 2011, the INTERHEART Study has reported results from a retrospective case-crossover design performed in the largest population to date, including 12 461 patients with first MI in 262 centers across 52 countries.[63] Participation in heavy physical exertion was reported by 13.6% of participants within the 1 hour before MI compared with 9.1% at the same hour on a previous day (control period). Compared with the control period, the adjusted RR of AMI within 1 hour of physical exertion was estimated to be 2.3 (95% CI, 2.0–2.7), corresponding to a population attributable risk of 7.7% (95% CI, 6.3%–8.8%). Unlike prior studies, this study did not demonstrate evidence of effect modification by baseline PA level. However, the latter analysis only stratified by overall participation in categories of PA by intensity (sedentary, mild, moderate, or strenuous) and not by frequency of participation.

Compared with vigorous exercise, the data on whether moderate exercise also acutely elevates the risk of MI are much more limited. One case-crossover study within the Myocardial Infarction Registry in Augsburg, Germany, reported a modest increase in the risk of MI within 2 hours of participation in moderate exertion (METs=5; RR, 1.6 [95% CI, 1.2–2.1]).[71] However, a prior study from the same region in Germany found no elevation in the risk of MI associated with moderate physical exertion.[60] Both studies demonstrated no association between lighter levels of exertion and AMI.

Absolute Risks

Although there is a heightened RR of acute cardiac events with unaccustomed vigorous PA, it is important to recognize that the absolute risk of experiencing SCD or MI during physical exertion is very small. For example, in the Physicians' Health Study, marked elevations in the RR of SCD during and after a bout of vigorous physical exertion translated into an absolute risk of only 1 SCD for every 1.51 million episodes.[48] This absolute risk is even lower in middle-aged women, among whom 1 SCD occurred for every 36.5 million person-hours of participation in moderate to vigorous exercise.[45] Retrospective multicenter data from fitness facilities also report low absolute rates of adverse CVD events: 1 per 1 124 200 and 1 per 887 526 person-hours for nonfatal and fatal cardiovascular events, respectively.[73] In patients with established heart disease in supervised cardiac rehabilitation facilities, the absolute CVD event rate is higher (1 event per 58 000 patient-hours), but still low.[74]

Given that even the most avid exercisers do not spend the majority of their time exercising, these low absolute risks translate into extremely low incident rates of exertion-related SCD in the general population. Reported annual incidence rates of exertion-related SCD in the population at large and across various subgroups are shown in Table 1. Population-based estimates of the frequency of exercise-related out-of-hospital cardiac arrest and SCD range from 2.1 per 100 000 person-years in the Netherlands,[49] to 0.46 per 100 000 person-years

Table 1. Estimated Annual Incidence Rates of Exertion- or Sports-Related SCD According to Population Subgroups

Study Population	Estimated Annual Incidence Rates of Exertion-Associated SCD*
Overall	0.31–2.1[49,50,51,75]
Age	
<35 y of age	0.3[49]
>35 y	3.0[49]
Athletes	
Competitive	0.4–0.9[51,55,57]
Noncompetitive	0.2[51]
Sex	
Women	0.04–0.3[49,76]
Men	0.5–5.5[49,76]

SCD indicates sudden cardiac death.

*Rates are reported per 100 000 individuals. For comparison, annual incidence rates of SCD not related to exertion are estimated to be 43 to 55 per 100 000 individuals.[50,75]

in France,[51] and 0.31 per 100 000 person-years in Japan.[75] In the Dutch study,[49] survival after exercise-related out-of-hospital cardiac arrest was better than after non–exercise-related out-of-hospital cardiac arrest (46.2% versus 17.2%). Although rates of exertion-related SCA are somewhat lower in Japan, the overall incidence rate of exercise-related out-of-hospital cardiac arrest increased from 0.18 to 0.43 per 100 000 person-years from 2005 to 2012.[75] A population-based study in Oregon of adults 35 to 65 years of age found a similar estimate of sports-related SCA as in the Netherland's population (2.1 per 100 000 person-years).[50] To place these absolute rates of sports-related SCA into perspective, the absolute rate of SCA in other settings is much higher because of the greater absolute time spent in sedentary activities. In the Oregon and Japan studies, the absolute incidence of nonsports SCA was estimated to be 55.5 and 43.5 per 100 000 person-years, respectively.[50,75] Fewer estimates exist for exercise-associated MI, but a Swedish population-based study suggested that the absolute incidence of exercise-associated MI was 0.75 per 100 000 person-years.[70]

Impact of Age and Sex on Exertion-Related CVD Risk

Impact of Age

Few data are available as to whether age modifies the RR of SCD during exertion; however, according to a population-based study from Germany, older individuals had a higher RR of MI during and after exertion.[71] In contrast, the larger INTERHEART study did not find higher RRs of MI in older individuals.[63] The absolute incidence of exertion-related SCD and MI increases over 35 years of age,[51,70] with the greatest numbers of exertion-related SCDs reported between 40 and 64 years of age.[51] In the Netherlands, the incidence of exercise-related SCA was 10-fold higher in individuals >35 years old (3.0 per 100 000 person-years) than among those <35 years old (0.3 per 100 000 person-years).[49] In France, the absolute incidence of sports-associated SCD increased with age in men but not women. The absolute risk in men ranged from 0.4 per year per 100 000 in those 15 to 24 years of age to 17.5 per 100 000 in those 55 to 64 years of age.[76]

Absolute Risks in Athletes

Although incidence rates of exertion-related SCD are lower in younger age groups, rates of exercise-associated SCD or SCA are ≈4.5-fold higher in competitive athletes than in recreational athletes of similar age (10–35 years old).[51] Highly fit competitive athletes spend a significant proportion of time in both training and competition, and the intensity of exercise is likely greater, both of which could contribute to the higher incidence of exercise-related acute cardiac events. In France, the incidence rate was estimated at 0.9 per 100 000 per year in young competitive athletes compared with 0.2 per 100 000 among young noncompetitive athletes.[51] In series from the United States and the Veneto region of Italy, estimates of sports-related SCD were slightly lower at 0.61 per 100 000 person-years[55] and 0.4 per 100 000 person-years,[77] respectively. Although the incidence rates of exertion-related SCD are proportionally higher in competitive athletes, most exertion-related SCDs in those <35 years of age occur in noncompetitive sports participants, primarily because of the larger size of the source population.[57]

Impact of Sex

The incidence of exertion-related SCD is much lower in women than men. In multiple populations, the risk of SCD in association with exercise is 15- to 20-fold higher in men.[49,50,76] This sex difference in exercise risk is much more pronounced than the baseline 2- to 3-fold higher overall incidence of SCD observed in men versus women in epidemiological studies not focusing on exercise alone.[49–51] The estimated incidence of sports-related SCD in women ranges from 0.04 to 0.3 per 100 000 person-years compared with 0.5 to 5.8 per 100 000 person-years in men.[49,76] The sex difference in the incidence of sports-related SCD is most marked in the 45- to 55-year-old age range, in which the RR for women has been estimated to be only 3% (95% CI, 1.5%–7.5%) of that in similarly aged men.[76] Sex differences in participation in vigorous athletic activity might contribute to part of the lower incidence of exertion-related SCD among women, but likely not all. Indeed, rates of exertion-related SCD are higher among male than female college athletes[78] and adult athletes participating in the same sporting activity.[79,80] For example, the incidence of SCA during full and half marathons is higher in men than in women (0.9 versus 0.16 per

100 000 person-years, respectively).[80] Cardiovascular causes of death in athletes also vary by sex, with hypertrophic cardiomyopathy (HCM) more common in men and coronary anomalies, arrhythmogenic right ventricular cardiomyopathy (ARVC), and long-QT syndrome (LQTS) predominating in women.[67]

The absolute incidence of exercise-associated AMI is also slightly higher in men versus women, 0.046 versus 0.015 per 100 000 person-hours, respectively, but the magnitude of the sex difference is smaller,[61] and the majority of studies have not found a sex difference in the RR of MI during physical exertion.[41,70,71] A study of 1048 patients with AMI referred for primary angiography found that men had a higher RR of experiencing AMI during physical exertion and that these men were more likely to be classified as having very low or low levels of habitual PA.[61] Increasing amounts of regular moderate PA have generally been associated with decreased rates of CVD events in women,[45,46,81] but a recent prospective study of >1 million women in the United Kingdom raised the possibility that the relationship might not be similar for vigorous exercise.[82] In this study, women reporting daily strenuous PA were at higher risk of CHD, cerebrovascular disease, and venous thromboembolism than women reporting strenuous PA 2 to 3 times per week.[82]

Impact of Known CHD

Although CHD is responsible for a significant proportion of sports-related SCD in adults,[50] individuals experiencing SCD during exercise are less likely to have known heart disease than those who experience SCD during other activities. In Oregon, only 15% of those 35 to 65 years old who experienced SCA during sports were known to have heart disease, compared with 30% who experienced SCA during other activities or at rest.[50] In France, only 7% of women had a history of heart disease or 1 cardiovascular risk factor before their sports-related SCD.[51] Similarly, the majority of exercise-associated AMIs occur in patients without a prior history of CHD or AMI.[41,60] Although the incidence of exercise-induced CVD events appears to be somewhat higher in patients with established CVD, paradoxically, the risk of AMI during exertion has been reported to be higher in patients without established angina or CHD in some[41,60,71] but not all studies.[63] Overall, increasing habitual PA is not associated with elevated risks of AMI or stroke and appears to confer lower total CVD and non-CVD mortality in patients with stable CHD.[83] Because epidemiological studies indicate that low CRFe in middle age is the strongest predictor of future heart failure with a preserved ejection fraction,[84,85] exercise training could be helpful in attenuating or reversing this condition by preventing the associated increase in left ventricular stiffness attributable to sedentary aging.[86]

EXERCISE-RELATED CERVICAL ARTERIAL DISSECTION

Cervical artery dissection, which can occur in the extracranial carotid or vertebral arteries, is an important cause of stroke in young patients[87–91] and can result in significant morbidity and mortality.[87,92] The multicenter Cervical Artery Dissection and Ischemic Stroke Patients study group found that cervical trauma during sports was more common in stroke patients with cervical artery dissection than in age-, sex-, and country-matched control participants with stroke not associated with arterial dissection.[93] Although the available evidence supports an association between sports, exercise, and cervical artery dissection, few data are available regarding preventive strategies for patients who participate in sporting activities. Nevertheless, clinicians should be aware of the potential risk and presenting symptoms of exercise-related cervical artery dissections so that patients can be referred for appropriate diagnostic imaging and treatment.

COMMON ACTIVITIES ASSOCIATED WITH ACUTE CARDIAC EVENTS

Few systematic studies have identified activities associated with a heightened RR of cardiac events. This is likely because of the rarity of such events and the difficulty in comparing activities with different and unknown participation rates, as well as different participant characteristics. The cardiovascular stress of vigorous PA is determined by the individual's CRF, because identical physical tasks evoke lower cardiac demands in fit compared with unfit subjects.[30] Moreover, for individuals who already exercise vigorously, the more frequently vigorous exercise is performed, the lower the RR of each exercise bout (Figure 4).[41,94] Additional modulators of so-called high-risk activities include superimposed physical, cognitive, and environmental stresses, as well as competition, all of which can accentuate the cardiorespiratory and hemodynamic responses and thus heighten the risk of exertion-related acute cardiovascular events.

Strenuous PA, especially when sudden, unaccustomed, or involving high levels of anaerobic metabolism, increases the risk for AMI and SCD. For example, racquet sports,[95] downhill skiing,[96] marathon running,[80] triathlon participation,[79] and high-intensity sports activities (eg, basketball)[97] may be associated with a greater incidence of acute cardiovascular events than other activities. For certain individuals (predominantly men), mountaineering activities, including mountain hiking and cross country or downhill skiing, are associated with a heightened risk of SCD.[98] At-risk individuals are generally characterized by multiple risk factors (especially older age), and in particular, patients with heart failure or prior MI with left ventricular dysfunction (ejection fraction <40%) are at greatest risk for SCD.[99,100]

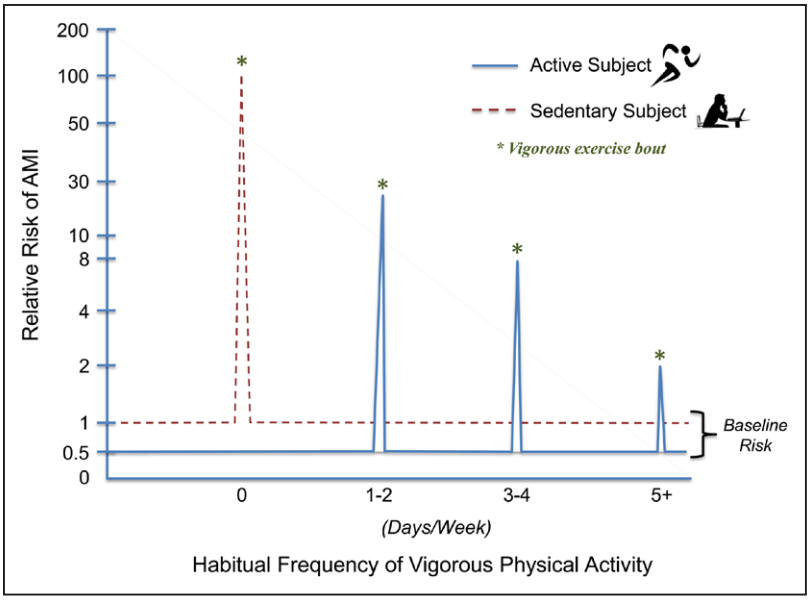

Figure 4. Relative AMI risk with vigorous physical activity vs sedentary behavior.
The relative risk of AMI at rest and during vigorous physical exertion (≥6 metabolic equivalents) is lower in those who engage in more frequent exercise sessions per week compared with sedentary subjects. AMI indicates acute myocardial infarction. Adapted from Mittleman et al[41] with permission from Massachusetts Medical Society. Copyright © 1993, Massachusetts Medical Society.

Although the risk of SCD in the mountains is similar to that reported for joggers at sea level[69] (1 SCD per 2 940 000 mountain-hours versus 1 death per 3 000 000 jogging-hours), the risk is higher if all cardiovascular events are included (1 cardiac event, including ACS, per 957 000 mountain-hours). Unusual physical exertion on the first day at altitude, acute hypoxia, or both, may represent the most potent triggers.[98] However, this risk can be reduced markedly (by >5-fold) by spending at least 1 night acclimatizing at altitudes above 1300 m before attempting strenuous exertion in the mountains.[101] In addition, the excitement of competition may increase sympathetic activity and catecholamine levels and lower the threshold for ventricular fibrillation.[102] Other activities that are associated with excessive cardiac demands and a greater incidence of acute cardiovascular events include deer hunting[103] and snow removal.[104,105]

Snow shoveling has repeatedly been associated with increased cardiovascular events soon after major snowstorms,[105–107] probably because it can elicit higher rate-pressure products than maximal treadmill testing[108] and is often performed by unfit individuals with known or occult CAD. Also, some cardiac patients develop angina at lower rate-pressure products during exercise in cold temperatures,[109] possibly because of cold-induced vasospasm. Ventricular arrhythmias, coronary plaque rupture and ST-segment–elevation MI,[110] and subacute stent thrombosis[111] have also been reported with snow shoveling.

Cardiovascular Risk of Marathon Running and Triathlon Participation

Cardiac events during amateur athletic events attract media attention and generate concern about the risks of such activity. To address this concern, the RACER study (Race Associated Cardiac Arrest Event Registry) estimated the risk of SCA for marathon and half-marathon races among 10.9 million individuals participating in US marathons from January 1, 2000, to May 31, 2010.[80] There were 59 cases of SCA in individuals 42±13 years of age, including 51 men, and 42 (71%) were fatal, yielding an SCA incidence rate of 0.39 per 100 000 participants. The rate was higher among men than women (0.90 versus 0.16 per 100 000) and among full-marathon versus half-marathon participants (1.01 versus 0.27 per 100 000). This corresponds to 1 SCA and 1 death per 184 000 and 259 000 participants, respectively. The incidence of SCA among male marathon runners increased significantly between the years 2000 to 2004 and 2005 to 2010, from 0.71 to 2.03 per 100 000, which suggests that these events have, over time, attracted more high-risk men with known or occult CVD.

These results demonstrated that the risk of SCA during full and half-marathons is low. The final mile accounted for almost 50% of the SCDs. The strongest predictors of survival of SCA were early initiation of bystander-administered cardiopulmonary resuscitation, use of automated defibrillators, and an underlying diagnosis other than HCM. Postmortem data were available to determine the likely cause of SCA in 31 of the 59 cases (53%). Definite or possible HCM (50.4%) and CHD (16.1%) accounted for the majority of SCAs.

The frequency of SCD and SCA has also been reported in >9 million triathlon participants >30 years of age.[79] There were 135 SCDs, or 1.74 per 100 000 participants. This rate was higher than previous estimates of triathlon SCDs[112] and exceeded the incidence reported for marathon running (1.01 per 100 000).[80] Women comprised only 15% of the study population, and their incidence of SCD was 3.5-fold less than in men. Most SCDs occurred during the swim (n=90; 67%), followed by the bicycle

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(n=22; 16%), run (n=15; 11%), and postrace (n=8; 6%) periods. Race experience was known for 68 participants, of whom 26 (38%) were competing in their first triathlon. Autopsies were performed on 61 victims, of whom only 27 (44%) had relevant cardiovascular abnormalities, including atherosclerotic CAD and cardiomyopathy.

These data suggest that SCA and SCD during marathon running and triathlon participation are rare. Clinicians should be aware of the risks associated with underlying myocardial disease and atherosclerotic CAD in patients contemplating such competition and of the increased risk among first-time participants. The latter suggests that inadequate preparation or poor training contributed to the exertion-related fatalities.[29,34] The higher death rate during the swim portion of the triathlon raises the possibility that factors associated with swimming, such as increased central volume from immersion,[113] panic attacks leading to drowning,[114] adverse environmental conditions (eg, large waves or cool temperatures), collisions among swimmers, and the added challenges of water rescue could contribute to the fatal events.[79] Competitors at risk for cardiac events should be encouraged to maintain their pace throughout the race, because sprinting during the final miles has been associated with a heightened risk of acute cardiac events.[115] Other race-related disorders, including hyponatremia and hyperthermia, are uncommon causes of competitor's deaths.[80]

CHANGING CONCEPTS OF EXERCISE–RELATED CARDIOVASCULAR EVENTS

Predominant Causes of Exercise-Related SCD in the Young

The previous AHA statement noted that hereditary or congenital cardiovascular abnormalities such as HCM and coronary artery anomalies were the most common causes of PA-related SCDs in young individuals <30 to 40 years old.[30] Many studies, primarily from the United States, identified HCM as the most common cause. More recent studies have questioned this conclusion and suggested that most cases of exercise-related SCD in high school or collegiate athletes have no cause identifiable at autopsy and are classified as either a sudden arrhythmic death[56] or SCD with a structurally normal heart (SNH).[116]

In a meta-analysis examining SCD in individuals <35 years of age that included 4605 subjects, HCM was responsible for 10.3% of all deaths, whereas 26.7% had SNHs.[116] There were 608 athletes included in this analysis of 34 studies published between 1990 and 2014; 13.6% of the deaths were attributed to HCM, whereas 18.1% were attributed to SNH. Differences in attributed causes appeared to depend on the geographic origin of the study. Among North American athletes, 27.0% and 10.0% of the deaths were attributed to HCM and SNH, respectively, whereas 5.7% and 23.1% of the deaths in European athletes were attributed to HCM and SNH. Genetic studies can identify some of these victims with SNH. An investigation of all SCDs in individuals 1 to 35 years of age in New Zealand and Australia identified 490 total cases of SCD, 40% of which were unexplained.[117] Genetic testing in 113 cases with SNH identified a clinically definable genetic mutation for conditions such as cardiomyopathy or cardiac arrhythmia in 27% of the samples.

It remains difficult to determine with certainty the prevalence of the causes and the incidence of exercise-related SCD in the young. Individual studies, including those examining a geographically defined population, often include a small number of subjects because of the rarity of exercise-related SCD. A prospectively collected emergency services cardiac arrest database in Toronto, Canada, identified SCAs during sports participation in individuals 12 to 45 years of age from 2009 to 2014.[118] There were only 16 SCAs during competition and 58 SCAs during noncompetitive athletic activity during 18.5 million hours of observation. This yields an annual incidence in competitive athletes of only 0.76 SCA per 100 000 individuals, an estimate that can vary widely with the addition or subtraction of only a few cases. Consequently, the prevalence of any causative condition and the incidence of SCD are highly variable depending on the number of deaths. Even large meta-analyses can be highly affected by the individual studies that comprise them. For example, some studies of SCD in athletes included only deaths during PA,[118] whereas others included deaths both during PA and at other times.[119]

The reasons for the apparent change in the prevalence of conditions causing SCD between the previous[30] and present document are probably multifactorial. Case-collection bias in earlier studies is possible, because the largest US studies originated from centers with expertise in HCM management.[120] Support for this possibility comes from the observed difference in causes of SCD between European and North American studies.[116] It is also possible that the wider appreciation of HCM as a cause of SCD has led to alterations in medical management or to more effective screening and restriction of vigorous sports participation in individuals with HCM.

Increased Appreciation of Nonacute Coronary Lesions as a Cause of Exercise-Related SCD in Adults

The previous AHA scientific statement noted that both ACS caused by plaque rupture or erosion and exercised-induced cardiac ischemia could precipitate exercise-related AMI and SCD.[30] It was assumed, but not directly stated, that ACS was primarily responsible for

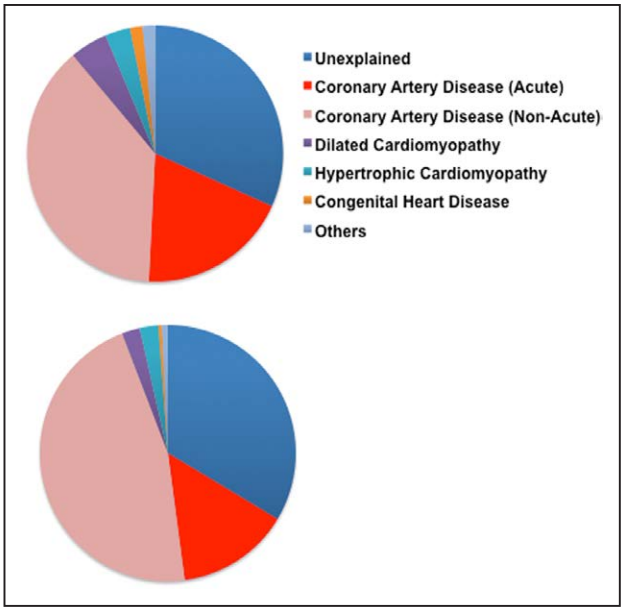

Figure 5. Sudden cardiac arrest during sports and nonsports activities. **Top,** Sudden cardiac arrest during sports (n=63). **Bottom,** Sudden cardiac arrest during nonsports activities (n=1184). Reprinted from Marijon et al.[50] Copyright © 2015, American Heart Association, Inc.

exercise-related cardiac events in previously asymptomatic individuals, whereas exercise-induced ischemia was most common in those with established CHD. Both historical[121] and more recent case series[61,122] support the notion that acute plaque disruption causes most exercise-related AMIs. However, recent evidence suggests that nonacute coronary disease and exercise-induced myocardial ischemia are the cause of most exercise-related SCDs in middle-aged adults and that acute plaque disruption is the second most common cause (Figure 5).[50] Although a 12-year prospective, population-based study of SCAs in individuals 35 to 65 years of age identified 1247 events, only 63 of the SCAs (5%) occurred during or within 1 hour of cessation of sporting activity.[50] Sports were defined as jogging, basketball, cycling, golf, volleyball, tennis, soccer, and other gymnasium activities. SCAs at rest or during physical exertion not in the setting of sports (eg, domestic chores, gardening, sexual intercourse) were classified as nonsports. ACS was identified in 33% of the sports-related and 24% of non–sports-related cardiac arrests, whereas 60% of the sports and 76% of the nonsports SCAs were associated with nonacute coronary disease. A history of known heart disease was less common among the sports-related SCAs (16%) than the non–sports-related SCAs (30%).

The Possibility That Exercise Accelerates Disease Progression in Inherited Cardiomyopathies

The previous AHA scientific statement raised the possibility that exercise could increase the progression of CVD in patients with inherited cardiac conditions.[30] This was speculative at that time but has subsequently been shown to occur in ARVC, which is caused by genetic abnormalities that affect desmosomal proteins. Desmosomes are structures that provide mechanical and electrical connections between the myocytes. Defects in desmosomal proteins make these myocyte connections vulnerable to disruption, with subsequent fibrosis and fatty infiltration leading to the cardiomyopathy. Penetrance of these genetic defects is variable, possibly because of environmental factors. It has long been known that prolonged endurance exercise acutely increases right ventricular volume,[123] which would stress these abnormal desmosomal junctions. Exercise also elicits a larger increase in right ventricular than in left ventricular wall stress relative to rest.[124] A series of human and animal studies have documented that exercise is an environmental factor that accelerates ARVC presentation and progression. Among 87 desmosomal defect gene carriers, endurance athletes and those with the most exercise participation were more likely to meet diagnostic criteria for ARVC.[125] The prognosis was also worse in desmosomal gene defect carriers who were athletes. Similar findings have been documented by others who demonstrated an increased risk of ventricular tachyarrhythmias and death in ARVC probands who participated in competitive sports before and after their diagnosis.[126] Participation in recreational as opposed to competitive sports did not increase risk.[126] Deleterious effects of exercise training have also been demonstrated in genetically modified murine models of ARVC, with defective genes encoding for the desmosomal proteins plakoglobin,[127] plakophilin-2,[128] and desmoplakin.[129]

Despite the absence of absolute proof from randomized controlled clinical trials, the deleterious effect of exercise training on ARVC is now well accepted, and recent guidelines recommend avoidance of intense exercise in patients with a clinical diagnosis of ARVC.[130] Whether high-volume, high-intensity endurance exercise training could induce similar negative effects on other genetic cardiac conditions is unknown, although exercise training might be deleterious in other inherited disorders of cardiac structural proteins such as lamin A/C mutations.[131]

LQTS is produced by defects in genes encoding for cardiac ion channels. Most patients with LQTS have defects in *KCNQ1*, *KCNH2*, and *SCN5A*.[132] Defects in *KCNQ1* are most common, affect the I_{Ks} potassium channel, and produce LQTS-1. Vigorous exercise and accompanying abrupt increases in sympathetic tone can acutely trigger syncope or SCA in patients with LQT1. There are also data to suggest that increased vagal tone can increase cardiac arrhythmias in LQTS-1 patients.[133] In one study, LQTS-1 patients who demonstrated the greatest reduction in heart rate immediately after exercise, a marker of vagal tone, were more likely to have

experienced ≥1 arrhythmogenic event.[134] Additional data are needed to determine whether the autonomic and cardiac adaptations elicited by exercise training affect the presentation and prognosis of other inherited conditions such as LQTS, HCM, and Brugada syndrome.

EXERCISE PREPARTICIPATION AND SCREENING PROCEDURES

Professional organizations, including the AHA, have traditionally promoted cost-effective screening procedures (eg, survey questionnaires) to identify at-risk individuals who should be medically evaluated before initiating an exercise program. Using data from 6785 adults (51% of whom were women) ≥40 years of age collected in the 2001 to 2004 National Health and Nutrition Examination Survey, it was estimated that 95.5% of women and 93.5% of men would be advised to consult a physician before starting an exercise program if they followed the AHA/American College of Sports Medicine (ACSM) Preparticipation Questionnaire referral criteria.[135] Such results highlight the limitations of this self-screening tool. The investigators concluded that in its present form, increasing use of the questionnaire would result in escalating medical referrals and create yet another barrier for many sedentary adults to become more physically active.

The value of routine medical screening procedures, including physician evaluation and exercise testing, as a preface to moderate- to vigorous-intensity exercise training remains controversial. The most recent ACSM preparticipation health screening recommendations emphasize the important public health message of habitual PA for all and the need to eliminate barriers to adopting and maintaining a regular exercise program.[136] In these updated recommendations for exercise preparticipation screening, which were reiterated in the latest ACSM guidelines,[137] age cutoffs, risk factor profiling, and risk stratification terminology (ie, low, moderate, high) were eliminated. The new algorithm focused primarily on 4 major variables: (1) the individual's current level of PA; (2) known cardiovascular, metabolic, or renal disease (CMRD); (3) the presence of signs or symptoms suggestive of CVD; and (4) the desired or anticipated exercise intensity (Table 2).[138] These characteristics, as well as the potential hazards of unaccustomed, vigorous PA, were identified as important modulators of exercise-related acute cardiovascular events. The term *medical clearance* replaced specific recommendations for a medical/physical examination, with or without exercise testing, because it was thought these evaluations should be at the clinician's discretion. Moreover, patients with pulmonary disease are no longer automatically referred for medical evaluation to exercise, perhaps with the exception of those with chronic obstructive pulmonary disease, which in current or former smokers often serves as an independent predictor of cardiovascular risk.[139] The new recommendations can be summarized by the following 4 points[136]:

- Physically active asymptomatic individuals without known CMRD may continue their usual moderate or vigorous exercise and progress gradually as tolerated, according to contemporary ACSM guidelines.[137] Those who develop signs or symptoms of CMRD should immediately discontinue exercise and seek guidance from a medical professional before resuming exercise of any intensity.
- Physically active asymptomatic individuals with known CMRD who have been medically evaluated within 12 months may continue a moderate-intensity exercise program unless they develop signs or symptoms, which requires immediate cessation of exercise and medical reassessment.
- Physically inactive individuals without known CMRD may begin light- to moderate-intensity exercise without medical guidance and, provided

Table 2. Potential Risk Modulators of Exercise-Related Acute Cardiovascular Events

Risk Modulator Category
Individual's current level of activity
"Active," defined as performing planned, structured moderate- to vigorous-intensity physical activity ≥30 min at least 3 d/wk, defined as 40%–59% or ≥60% functional capacity, respectively
Presence of signs and symptoms suggestive of CVD
Pain or discomfort at rest or with physical exertion in the chest, neck, jaw, arms, or other areas that could result from myocardial ischemia
Unusual shortness of breath
Lightheadedness
Ankle swelling
Awareness of a rapid or irregular heartbeat
Burning or cramping sensations in the lower extremities when walking short distances
Known CVD, metabolic, or renal disease
Diabetes (type 1 and type 2 diabetes mellitus)
Renal disease
CVD including angina pectoris, previous myocardial infarction, coronary revascularization, heart surgery, pacemaker, valve disease, heart failure, structural heart disease, or combinations thereof
Desired exercise intensity
Light: an intensity that evokes slight increases in heart rate and breathing (2 to 2.9 METs) or <40% FC
Moderate: an intensity that evokes noticeable increases in heart rate and breathing (3 to 5.9 METs) or 40%–59% FC
Vigorous: an intensity that evokes substantial increases in heart rate and breathing (≥6 METs) or ≥60% FC

CVD indicates cardiovascular disease; FC, functional capacity; and METs, metabolic equivalents (1 MET=3.5 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$).

Adapted from Armstrong et al[138] with permission. Copyright © 2018, by the American College of Sports Medicine.

they remain asymptomatic, progress gradually in intensity as recommended by current ACSM guidelines.[137]

- Physically inactive individuals with known CMRD or signs/symptoms that are suggestive of these diseases should seek medical guidance before starting an exercise program, regardless of the intensity.

In summary, engaging in regular moderate- to vigorous-intensity PA improves CRF and confers health benefits among middle-aged and older individuals with and without occult or documented atherosclerotic CVD. Although the exercise-related health benefits clearly outweigh the associated cardiovascular risks, any patient who was previously physically active and asymptomatic but who becomes symptomatic during exercise should immediately discontinue such activity and seek medical evaluation before resuming PA.[136,137] Increased assessment of patients' habitual PA levels and symptomatology in healthcare settings, with tools such as the PA vital sign, constitutes an important step in facilitating the implementation of the latest ACSM exercise preparticipation and screening recommendations. In contrast, vigorous- to high-intensity PA in individuals with congenital or structural cardiovascular abnormalities (eg, Marfan syndrome, inherited cardiomyopathies, and arrhythmic syndromes) should be undertaken with caution and with guidance from specialists in the management of these conditions. Such individuals should be discouraged from participating in highly competitive or strenuous endurance exercise without careful consultation but encouraged to engage in leisure-time, low- to moderate-intensity PA.[29]

Screening Exercise Testing

The US Preventive Services Task Force 2018 recommendations advised against screening with resting or exercise electrocardiography in low-risk asymptomatic adults to prevent cardiovascular events.[140] The companion US Preventive Services Task Force review of randomized controlled trials of screening with exercise ECGs found no improvement in health outcomes, despite focusing on higher-risk populations with diabetes mellitus.[141] The American College of Physicians, as part of the "Choosing Wisely" initiative, also recommends avoiding screening exercise electrocardiographic testing in asymptomatic individuals at low risk for CHD.[142] Similarly, a previous systematic review of the benefits and risks of structured exercise in people >75 years of age argued that mandatory preparticipation exercise testing, in addition to being expensive and of unproven benefit, could deter older people from exercising and cause more harm than good.[143] These findings, coupled with the extremely low incidence of exercise-related cardiovascular complications in physically active asymptomatic people, the high rate of false-positive exercise test responses in an ostensibly healthy population, the costs of exercise testing and to evaluate abnormal results, and the uncertainties associated with exercise-induced ST-segment depression in asymptomatic people with a low pretest risk of CHD,[94] further substantiate these recommendations.[140–142]

Exercise testing can be helpful for assessing selected cardiovascular disorders in patients at risk. Peak or symptom-limited exercise testing should be considered in high-risk middle-aged or older individuals, particularly inactive men with diabetes mellitus, who wish to pursue high-intensity endurance sports.[29] Exercisers with abnormal findings during auscultation or on the resting ECG should also be considered for an echocardiogram. Other asymptomatic patients who might benefit from exercise testing before beginning an exercise program include habitually sedentary individuals with multiple risk factors, an elevated CAC score,[144] or a family history of premature CHD who plan to start a vigorous exercise program, those whom the clinician suspects may be ignoring symptoms or not giving an accurate history, patients with critical aortic stenosis or to guide the management of those with valvular disease, patients with atypical chest pain, and those who complain of palpitations. A comparative study of exercise testing only versus exercise testing with concomitant myocardial perfusion imaging in symptomatic women with suspected CHD found similar 2-year posttest outcomes, highlighting the cost-effectiveness of the less expensive conventional treadmill test.[145]

Exercise testing is used in Wolff-Parkinson-White syndrome to risk stratify patients and specifically to determine whether there is a sudden, complete disappearance of accessary pathway conduction, which is a favorable prognostic sign. Treadmill or cycle ergometer testing can also be helpful in diagnosing exercise-induced catecholaminergic polymorphic ventricular tachycardia and to evaluate the effectiveness of β-adrenergic blockade or flecainide therapy in treating this arrhythmia.[146] In contrast, exercise testing has a limited role in diagnosing both LQTS and Brugada syndrome and in assessing the risk of exercise in patients with these electrocardiographic abnormalities. Failure of the QT interval to shorten during exercise supports the diagnosis of LQTS, and exercise can also evoke the classic Brugada pattern, usually during recovery when vagal tone is increased.[147]

Cardiac Screening of Young People Before Participation in Sports

There is insufficient evidence to justify routine cardiovascular screening to prevent sports-related acute cardiac events in young athletes. Nevertheless, this practice is common and typically includes a personal/family medical history and physical examination, with or without a

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12-lead resting ECG.[49,51,118,148–151] Adding a resting ECG to screening can enhance the detection of disorders associated with a heightened risk of SCD but increases false-positive results, with costly follow-up noninvasive/invasive studies and possible associated downstream psychological harm.[152] Consequently, a relevant AHA/American College of Cardiology scientific statement concluded that the available data do not support a significant public health benefit from using the 12-lead ECG as a universal screening tool for athletes.[153] This contrasts with recommendations from the European Society of Cardiology.[154]

There are multiple issues with routine cardiovascular screening in asymptomatic athletes. The true incidence of sports-related SCA is unknown. This has been generally estimated at ≈1 per 200 000 annually,[155] but studies in accomplished athletes, including National Collegiate Athletic Association basketball players[119] and English youth soccer players,[156] have reported annualized rates of 1 per 5200 and 1 per 14 794, respectively. It is also not clear how truly asymptomatic athletes with a cardiac condition should be managed. Others emphasize that preparticipation screening of large groups of asymptomatic athletes without known CVD will inevitably result in many false-positive responses, unnecessarily restricting PA among athletes who are free from CVD, while simultaneously providing a false sense of security to those with unremarkable findings.[151]

Other options are available to reduce exercise-related cardiac events. Coaches and athletes should be educated about possible warning signs/symptoms (eg, syncope, lightheadedness, perceived palpitations or arrhythmias) that could be harbingers of acute cardiac events. The Sudden Unexplained Death Study reported that of 3775 SCAs in all age groups in the Portland, OR, metropolitan area between 2002 and 2015, 186 (5%) occurred in the young (mean±SD age 25.9±6.8 years; 67% male), and the prevalence of warning signs before SCA was 29%. Moreover, 26 of the 186 (14%) were associated with sports as a trigger.[53] Such symptoms mandate the immediate cessation of training/competition and medical review. Regular emergency drills, bystander cardiopulmonary resuscitation, and the use of automated external defibrillators have increased survival rates in the general[157] and athletic[158] population. This writing group maintains that if cardiovascular preparticipation screening is offered to young athletes, it should be voluntary and conducted by highly experienced clinicians, but we recognize that the ability to alter survival by removal from sports participation or by other interventions has not been proven.[156,159]

CAN EXTREME EXERCISE HARM THE HEART?

Long-term exercise training alters cardiac structure and function. The athlete's heart is characterized by (1) enlargement of all cardiac chambers,[160] (2) improvement of cardiac function[161] and compliance,[162] and (3) electrical remodeling, such as sinus bradycardia, sinus arrhythmia, and first-degree atrioventricular block.[163] These exercise training–induced adaptations are believed to be benign. Emerging evidence, however, suggests that over time, high-volume, high-intensity exercise training can induce cardiac maladaptations such as an increased risk for AF, coronary artery calcification, and myocardial fibrosis.[164] Hence, there is debate as to whether intensive exercise can be harmful to the heart, especially in some individuals.[165–167]

Atrial Fibrillation

AF is characterized by chaotic electrical activity that replaces normal sinus rhythm and eliminates the contribution of atrial contraction to left ventricular filling. AF is the most common arrhythmia in the general population,[168] and the risk of AF depends on subject characteristics (age, race, height), health status (weight, blood pressure, [para]sympathetic tone, diabetes mellitus, a history of MI or heart failure), lifestyle factors (alcohol use, smoking, PA), obstructive sleep apnea,[169] and cardiac characteristics (left atrial size and pressure).[170,171] AF is associated with an increased risk for stroke,[172] MI,[173] heart failure,[174] and a multitude of adverse clinical consequences.[175]

The relation between exercise and incident AF is complicated. Low levels of CRFe (<6 METs) are associated with a higher risk for AF, and individuals with higher levels of CRFe (7.9±1.0 and 9.3±1.2 METs) have a dose-dependent decrease in AF risk.[176,177] Similarly, fit AF patients have a lower risk for AF recurrences during follow-up than their unfit counterparts.[178] AF burden and symptom severity decreased significantly in patients with AF who increased their fitness during an exercise training program versus those who failed to improve[178] and among patients with AF randomized to aerobic interval training in a small clinical trial.[179] Although these observations suggest that fitter individuals have the lowest AF risk, there is substantial evidence that the risk for AF is higher in athletes than in control subjects. High-intensity exercise training[180] and faster finishing times[181] were associated with an increase of AF in physically active older adults and long-distance cross-country skiers, respectively. In the US Physician's Health Study, men who jogged 5 to 7 times per week had a 50% higher risk of AF than men who did not exercise vigorously, even after adjustment for multiple cardiovascular risk factors.[182] Three meta-analyses found that AF risk was 2- to 10-fold higher in endurance athletes than in control participants.[170,183,184] Furthermore, long-term volume of vigorous endurance exercise (ie, ≥2000 hours of training[169] or ≥20 years of training[185]) was strongly associated with an increased risk for lone AF. These data

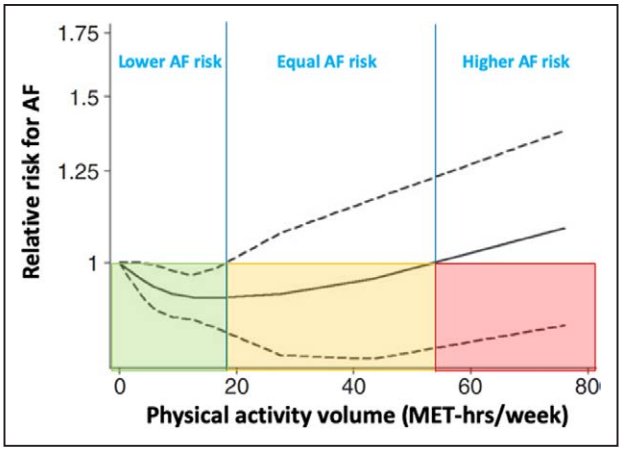

Figure 6. Dose–response association between physical activity volume and AF risk.
Individuals performing physical activity for 5 to 20 MET-h/wk demonstrate a significant risk reduction for AF, whereas higher exercise volumes do not appear to attenuate AF risk. A trend toward increased AF risk is apparent among individuals reporting >55 MET-h/wk. AF indicates atrial fibrillation; and MET-hrs/week, metabolic equivalents of task hours per week. Adapted from Ricci et al[186] by permission of SAGE Publications, Ltd. Copyright © 2018, by the European Society of Cardiology.

suggest that both low and very high volumes of exercise training are associated with an increased risk for AF, whereas moderate exercise volumes appear to reduce risk. Indeed, a nonlinear meta-regression analysis including data from 19 studies and 29 855 AF cases found a J-shaped association between PA volumes and risk for AF.[186] Individuals performing 5 to 20 MET-hours of PA per week had a significantly lower risk for AF, whereas physically inactive or highly active individuals (20–55 MET-h/wk) had similar relative risks for AF (Figure 6). A trend toward increased AF risk is apparent among individuals reporting >55 MET-h/wk, equaling >9.5 hours of vigorous exercise training per week.

The underlying mechanisms responsible for the increased prevalence of AF among athletes are unknown, but several pathways have been proposed (Figure 7). A prolonged (2 year) training study incorporating high-intensity training sessions showed that although left ventricular remodeling appears to plateau when training load plateaus, left atrial remodeling continues, even when the training dose is stable.[187] This finding suggests that the atria are especially prone to dilation and remodeling in individuals who have trained at a high level for many years. Interindividual genetic variability could also put some athletes at a higher risk of pathological remodeling leading to lone AF.[188–190] Furthermore, increased parasympathetic tone[191] in combination with left atrial enlargement[192] is likely to contribute to the increased AF risk, but exercise-induced sympathetic stimulation,[193] sustained hemodynamic stress,[194] and inflammation and oxidative stress[195] could also contribute to the development of AF in the most active exercisers.

In summary, the reported negative impact of high-volume, high-intensity exercise on maladaptive responses, specifically AF, varies considerably, according to the quality of evidence available. Indeed, differences in study methodology have led to varying estimates regarding the magnitude of risk, ranging from an ≈20% increase to a >10-fold risk of incident AF.[196] And, for obvious reasons, there may never be randomized, controlled quality evidence addressing the potential for an "alternative hypothesis" or U-shaped relation between exercise and AF.

Coronary Artery Atherosclerosis

Atherosclerotic CAD is the main contributor to cardiovascular morbidity and mortality in both men and women.[197] Atherosclerotic plaques have 2 common phenotypes: stable versus unstable plaques.[198] Stable (calcified) plaques are characterized by a small lipid pool, low concentrations of inflammatory cells, and a thick fibrous cap that reduces vulnerability to plaque rupture and subsequent ACS, including AMI.[199] Unstable (mixed) plaques are characterized by a large lipid pool, high inflammatory activity, and a thin fibrous cap, which makes them more vulnerable to rupture and trigger ACS.[200] Both stable and unstable coronary plaque development and progression take decades, and the presence of plaques does not necessarily cause clinical symptoms.[200]

Exercise training reduces the risk for symptomatic atherosclerotic CAD[201] and its clinical sequelae.[202] Nevertheless, several studies have found accelerated

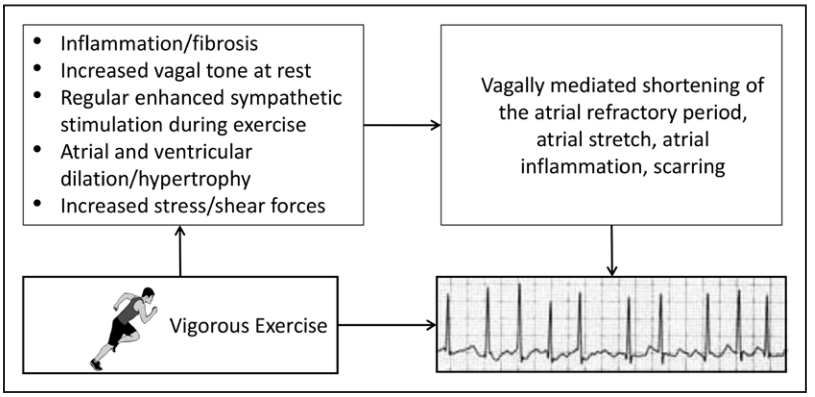

Figure 7. Potential mechanisms and associated sequelae for atrial fibrillation induced by strenuous endurance exercise.
The combination of autonomic, structural, and hemodynamic effects of high-volume, high-intensity aerobic exercise, repeated over time, likely impart some of the increased risk for atrial fibrillation. Adapted from Eijsvogels et al.[37]

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coronary artery atherosclerosis among veteran athletes. Möhlenkamp et al[203] were the first to demonstrate that German marathon runners had a higher prevalence of CAC scores ≥100 Agatston units compared with an age- and risk factor–matched control group from the general population (36% versus 22%, *P*=0.02). Aengevaeren et al[34] reported an increased CAC prevalence across progressive tertiles of PA volumes, 43%, 50%, and 68% (*P*=0.005), respectively, among Dutch male amateur athletes. More importantly, the most active athletes had a lower prevalence of unstable mixed plaques (48% versus 69%; OR, 0.35 [95% CI, 0.15–0.85]) and more often had only stable calcified plaques (38% versus 16%; OR, 3.57 [95% CI, 1.28–9.97]) compared with the least active athletes.[34] Merghani et al[35] reported similar findings in a cohort of British male master endurance athletes and sedentary control participants. The athletes had a higher prevalence of atherosclerotic stable plaques with any degree of luminal stenosis compared with control participants (44.3% versus 22.2%, *P*<0.001). Athletes demonstrated predominantly stable calcified plaques (73% versus 31%, *P*<0.001) and fewer vulnerable mixed plaques (23% versus 62%).[35] These observations demonstrated an increased prevalence of stable plaques among highly active middle-aged endurance athletes.

Only 2 small studies (n=46[35] and n=26[204]) assessed atherosclerotic characteristics among female athletes. There were no differences in CAC and plaque prevalence between female athletes and control participants in a British cohort.[35] In contrast, among American women undergoing computed tomography angiography to evaluate CAD, athletes had lower coronary plaque prevalence and calcific plaque volumes than comparison women.[204] Because the reference group had a significantly higher prevalence of hypertension, hyperlipidemia, smoking, and family history of CAD, the decreased plaque prevalence in the athletes could be more related to their low atherosclerotic risk profile than their exercise behavior.

The clinical relevance of accelerated coronary artery atherosclerosis in athletes performing very high-volume, high-intensity exercise is unknown. In clinical populations, any CAC or plaque presence represents a higher cardiovascular risk.[205,206] On the other hand, coronary artery size and dilating capacity are increased among athletes compared with control subjects,[207] which could offset the apparently negative adaptation of a higher CAC. Elevated CAC scores in athletes might also indicate increased cardiovascular risk, but definite data to evaluate this hypothesis are lacking.[208] Traditional CAC risk predictions might not be applicable to athletes, because physically active individuals have a lower risk for adverse cardiovascular outcomes than less active individuals with similar CAC scores.[209] The hypothesis that athletes are at reduced risk despite their higher CAC scores is supported by the observation that the most active athletes had fewer unstable "mixed" plaques and more stable "calcified" plaques.[34,35] Mixed plaques are associated with a high risk of cardiovascular events, whereas calcified plaques are associated with a lower risk.[199] Very high volumes of exercise training can therefore produce calcified stabilized plaques, similar to the observation that statins can increase CAC scores although they reduce atheroma volume and acute cardiovascular events.[13,210] In a large cohort of men (n=21 758) with more than a decade of follow-up in the Cooper Clinic Longitudinal study, adjusted risk of CAC score ≥100 was greater among individuals with very high levels of PA (n=432; ≥3000 MET-min/wk) compared with those with lower activity levels. Nevertheless, their risk for all-cause and cardiovascular mortality was not higher than that for those exercising at more moderate levels, and it was lower than the least active cohort with similar CAC scores. These findings refute the notion that high-volume endurance activity (>1 h/d) increases mortality risk, regardless of CAC level.[211]

Several mechanisms have been proposed to explain increased CAC after long-term, high-intensity exercise training. Exercise-related changes in calcium metabolism might contribute to the higher CAC score in athletes. Vitamin D levels are lower in athletes,[212] and low vitamin D levels are associated with increased CAC in the general population.[213] In contrast, exercise acutely increases parathyroid hormone,[214] which is associated with increased arterial calcification.[215] Alternatively, vigorous-intensity exercise can increase mechanical stress on the coronary wall, causing disrupted flow patterns,[216] elevate blood pressure, and cause shear stress, each of which is associated with accelerated atherosclerosis.[217,218] Regular high-intensity exercise training also transiently increases other nontraditional atherosclerotic risk factors, including oxidative free radicals,[219] dicarbonyl stress,[220] and systemic inflammation.[221]

Myocardial Fibrosis

Myocardial fibrosis is characterized by collagen infiltration in the myocardial extracellular matrix and can develop after injury from myocardial ischemia (hypoxia), inflammation, hypertensive overload, or combinations thereof.[222] It is associated with increased myocardial stiffness,[223] a higher incidence of ventricular arrhythmias,[224,225] and adverse cardiac outcomes.[226] Myocardial fibrosis is determined noninvasively using cardiac magnetic resonance imaging with gadolinium to determine LGE, a marker for myocardial fibrosis. The development of myocardial fibrosis generally occurs with cardiac remodeling secondary to diseases such as heart failure, hypertension, and valvular dysfunction,[227] but several studies have found evidence of LGE in apparently healthy athletes.[228] The prevalence of LGE in endurance

Table 3. Overview of Studies Comparing Prevalence of LGE Between Male Athletes and Control Subjects

Study	Athlete Cohort	Control Group	LGE Prevalence in Athletes, n (%)	LGE Prevalence in Control Subjects, n (%)
Abdullah et al[231]	21 competitive master athletes (68 [66–70] y of age), performing 6 or 7 exercise sessions per week for 25 y	25 healthy seniors (69 [65–71] y of age) performing <1 exercise session per week for 25 y	0/21 (0)	0/25 (0)
Bohm et al[232]	33 competitive elite male master endurance athletes (47±8 y of age) with a training history of 29±8 y	33 individuals exercising ≤3 h/wk	1/33 (3)	0/33 (0)
Breuckmann et al[233]	102 marathon runners (57±6 y of age) with a history of ≥5 marathons in ≤3 y	102 individuals (57±6 y of age) without exceptional endurance sports activity	12/102 (12)	4/102 (4)
Merghani et al[35]	106 masters athletes (55±9 y of age) with a training history 31±13 y	54 individuals (53±8 y of age) engaged in habitual physical activity (ie, walking, jogging, or swimming) according to WHO recommendations (150 min/wk)	15/106 (14)	0/54 (0)
Tahir et al[234]	54 male competitive triathletes (44±10 y of age), training >10 h/wk 29 female competitive triathletes (42±10 y of age), training >10 h/wk	22 sedentary controls (40±12 y of age), exercising ≤3 h/wk 14 sedentary controls (45±12 y of age), exercising ≤3 h/wk	9/54 (17) 0/29 (0)	0/22 (0) 0/14 (0)
Wilson et al[230]	12 veteran endurance athletes (57±6 y of age) with a training history of 43±6 y	20 sedentary controls (60±5 y of age)	6/12 (50)	0/20 (0)
Total	357 competitive endurance athletes	270 controls performing physical activity at or below WHO recommendations*	43/357 (12.0)	4/270 (1.5)

LGE indicates late gadolinium enhancement; and WHO, World Health Organization.
*WHO recommendation: 150 minutes of moderate intensity physical activity, 75 minutes of vigorous, or an equivalent combination per week.

athletes has ranged from 0%[229] to 50%.[230] A systematic review of 19 studies reported LGE in 5.9% of the 509 athletes.[228] Only 6 studies[35,230–234] directly compared LGE prevalence between athletes and control subjects (Table 3). Five found a higher LGE prevalence in athletes, and 1 study found no difference between athletes and control subjects, but the prevalence of LGE varied widely across studies, probably because of sample size differences. Overall, competitive endurance athletes had a substantially higher LGE prevalence than control subjects performing PA at or below World Health Organization recommendations (12% versus 1.5%).

Several studies have attempted to identify factors associated with the presence of LGE. Long-term exercise dose quantified as years of training[230,235] and number of completed foot races ≥42 km[203,230] was consistently found as a strong predictor for LGE, which suggests that high-volume, high-intensity exercise training may increase the risk of myocardial fibrosis. Alternatively, LGE may also represent edema,[236] inflammation,[237] or myocardial disarray[238] rather than scar tissue. LGE in athletes is often located where the right ventricle inserts into the ventricular septum. Indeed, 48% of athletes with LGE had LGE in the septum or right ventricular insertion points.[228] Short-term and prolonged exposure to high cardiac strain can also cause edema-induced LGE.[236] Vigorous exercise elicits a greater relative increase in pulmonic than aortic systolic pressure, estimated as an increase in wall stress of 125% versus 4% for the right and left ventricles, respectively.[124] This greater relative increase in wall stress imposed on the thinner right ventricular wall may contribute to edema and cardiomyocyte damage in the septum and right ventricular septal insertion points. An animal study found higher levels of myocardial fibrosis in the right but not left ventricle in rats running 60 min/d for 16 weeks compared with sedentary controls.[237] The amount of fibrosis was time dependent and accompanied by myofiber disarray, leukocyte infiltration, and expression of proinflammation factors (IL-1β [interleukin-1β] and MCP-1 [monocyte chemoattractant protein-1]), which suggests that exercise can induce deleterious remodeling.[237] It is unknown how these findings translate to humans, and future studies are needed to determine the nature and cause of LGE in athletes and whether edema-induced LGE will regress, remain unchanged, or progress to scar tissue over time.

There is little information about the clinical consequences of LGE in athletes. Coronary revascularization was more common in one study of athletes with versus without LGE (25% versus 1%, $P<0.001$) during 21±3 months of follow-up, but it is unclear how knowledge of the fibrosis influenced clinical decisions.[233] Also, nonsustained ventricular arrhythmias, symptomatic ventricular tachycardia, and progressive left ventricular dysfunction were found in a case series of athletes with subepicardial fibrosis.[239] Although overall systolic and diastolic cardiac function is usually normal in athletes with LGE, one study found wall motion abnormalities in myocardial segments with LGE.[240] However, masters athletes have more compliant hearts and blood vessels than matched healthy, sedentary individuals or

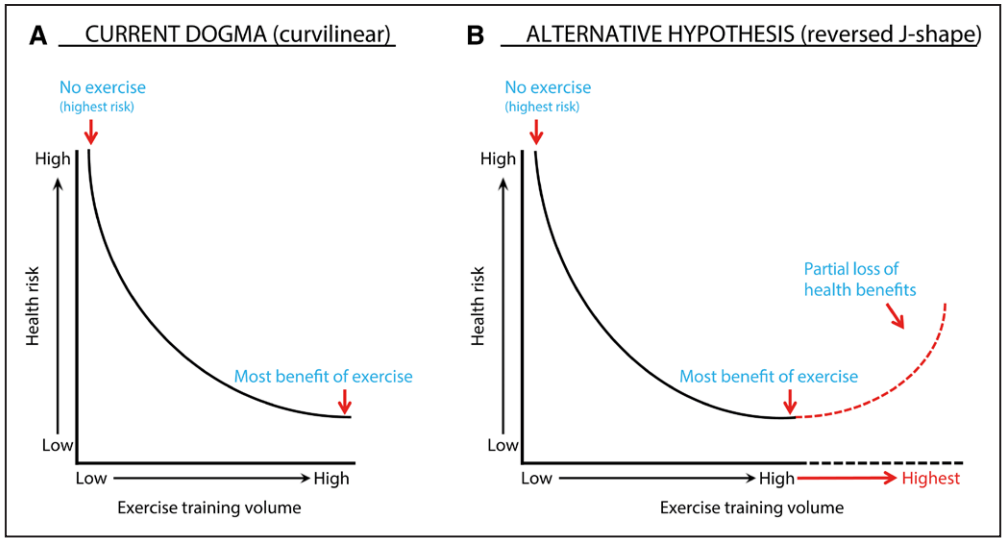

Figure 8. Conceptual overview of dose-response association between physical activity volume and cardiovascular health outcomes.
Conceptual overview of dose-response association between physical activity volume and cardiovascular health outcomes in line with (**A**) the current dogma and (**B**) an alternative hypothesis. There is currently no compelling evidence to reject the curvilinear association (**A**) between exercise volumes and cardiovascular health outcomes, with atrial fibrillation as a possible exception. Adapted from Eijsvogels et al.[37]

individuals who perform lower amounts of regular exercise.[162,241] Because the clinical course and consequences of LGE in endurance athletes are unclear, these athletes require additional follow-up to determine the significance of this finding.

Curvilinear Versus U-Shaped Associations

There is debate regarding the dose-response relationship between the volume of PA or exercise training and cardiovascular health outcomes. The prevailing dogma suggests a curvilinear relationship between exercise volume and cardiovascular health risks (Figure 8A), which indicates that individuals performing none to very low volumes of exercise training have the highest risk for adverse outcomes, whereas individuals who exercise the most have the lowest risk. Epidemiological evidence strongly supports this relationship.[38,242,243] Wen et al[38] found that 92 minutes per week of moderate- to vigorous-intensity PA was associated with a 19% risk reduction for CVD mortality (HR, 0.81 [95% CI, 0.71–0.93]) and a 14% risk reduction for all-cause mortality (HR, 0.86 [95% CI, 0.81–0.91]). Larger exercise volumes yielded greater health benefits, with a maximal risk reduction of 45% for CVD mortality (HR, 0.55 [95% CI, 0.46–0.66]) and 35% for all-cause mortality (HR, 0.65 [95% CI, 0.60–0.70]) in individuals performing 523 minutes of exercise per week. This exercise volume equals 3.5 to 4 times the amount of PA recommended in the 2018 Federal Physical Activity Guidelines,[244] but an increasing number of athletes are exceeding this exercise volume during their training. Arem et al[242] investigated the health benefits of a physically active lifestyle in individuals performing up to 10 times the World Health Organization–recommended exercise dose. Maximal mortality risk reduction (HR, 0.61 [95% CI, 0.59–0.62]) occurred at an exercise volume equaling 3 to 5 times the recommendations. Although the most active individuals (≥10 times the recommendations) had a lower mortality risk (HR, 0.69 [95% CI, 0.59–0.78]) compared with inactive control subjects, their risk reduction was not as large as the group with optimal exercise volume. Similar findings with large CIs for risk estimates among the most active exercisers were observed in other studies[38,82,242,243,245–247] (Table 4) and may be explained by the relatively small sample sizes of the most active subgroups (typically <5% of the total cohort).

The observation that very high volumes of PA may yield lower risk reductions than moderate- to high-activity volumes resulted in the extreme exercise hypothesis,[37,248] which postulates a U-shaped relationship between PA volumes and health outcomes (Figure 8B) and is characterized by partial loss of exercise-induced health benefits among the most active individuals. However, only limited data are available to support this hypothesis. Schnohr et al[246] found an increased mortality risk for strenuous versus light joggers (Table 4), but there were few individuals in the most active group (n=36) and only 2 deaths (no cause of death identified), resulting in an unusually large CI (0.48–8.14) and discussion about its interpretation.[249] Similarly, Lear et al[245] reported less mortality reduction from recreational PA in the most active exercisers (Table 4), but this effect disappeared when recreational and nonrecreational physical activities were combined. Armstrong et al[82] showed a higher risk ratio of cerebrovascular disease

Table 4. All-Cause Mortality (Unshaded Columns) and Incident Cardiovascular Diseases (Shaded Columns) Between the Optimal and Most Active Groups From Epidemiological Studies

	Study						
	Arem et al[242]	Lear et al[245]	Lee et al[243]	Schnohr et al[246]	Wen et al[38]	Armstrong et al[82]	Maessen et al[247]
Sample size							
Total cohort	661 137 (100%)	130 843 (100%)	55 137 (100%)	1252 (100%)	416 175 (100%)	1 094 327 (100%)	12 440 (100%)
Reference group	52 848 (8%)	N/A*	42 121 (76%)	394 (31%)	226 493 (54%)	516 035 (47%)	417 (4%)
Optimal group	124 446 (18.8%)	94 893 (72%)	2584 (5%)	570 (46%)	20 390 (5%)†	34 967 (3%)	2127 (19%)
Most active group	4077 (0.6%)	3597 (3%)	2570 (5%)	36 (3%)	20 390 (5%)†	34 947 (3%)	2130 (19%)
Exercise type and volume	MVPA	Recreational PA	Running time	Jogging	MVPA	Strenuous activity	MVPA
Reference group	0 MET-h/wk	N/A*	0 min/wk	Nonjoggers	0 MET-h/wk	0 times/wk	0 MET-h/wk
Optimal group	22.5–40 MET-h/wk	0–10 MET-h/wk	51–80 min/wk	Light jogger	41±14 MET-h/wk†	4–6 times/wk	12.8–18.2 MET-h/wk
Most active group	≥75 MET-h/wk	≥50 MET-h/wk	≥176 min/wk	Strenuous jogger	41±14 MET-h/wk†	7 times/wk	>29.5 MET-h/wk
Health risks	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	RR (95% CI)	OR (95% CI)
Optimal group	0.61 (0.59–0.62)	0.89 (0.82–0.95)	0.67 (0.55–0.80)	0.22 (0.10–0.47)	0.65 (0.60–0.70)†	0.80 (0.76–0.85)	0.31 (0.20–0.48)
Most active group	0.69 (0.59–0.78)	0.98 (0.91–1.06)	0.77 (0.63–0.92)	1.97 (0.48–8.14)	0.65 (0.60–0.70)†	0.89 (0.84–0.93)	0.43 (0.28–0.65)

HR indicates hazard ratio; MET, metabolic equivalents; MVPA, moderate to vigorous intensity physical activity; N/A, not applicable; PA, physical activity; OR, odds ratio; and RR, relative risk.

*A cubic spline regression analyses was performed; thus, no dedicated reference group was created.

†The most active group was the optimal group in the study of Wen et al[38]; thus, presented data are from the same subgroup.

and venous thromboembolism in women performing strenuous activities daily (RR, 0.96 [95% CI, 0.89–1.04] and RR, 1.08 [95% CI, 0.99–1.17], respectively) compared with women performing 2 to 3 sessions of strenuous activities per week (RR, 0.81 [95% CI, 0.78–0.84] and RR, 0.83 [95% CI, 0.79–0.87], respectively). The higher prevalence of smoking (25.6% versus 13.3%) and lower socioeconomic status (20.1% versus 13.1%) among daily strenuous exercisers compared with conventional exercisers might explain this finding in part and suggests that daily exercisers had a different lifestyle than the typical endurance athlete. In aggregate, there is currently no evidence to reject the curvilinear association (Figure 8A) between exercise volumes and cardiovascular health outcomes, with AF as a possible exception.

The health benefits of long-term, high-volume, high-intensity exercise training are supported by data comparing life expectancy in elite athletes with control populations. Kettunen et al[250] reported that endurance athletes (n=437; HR, 0.70 [95% CI, 0.61–0.79]) and team sports athletes (n=1046; HR, 0.80 [95% CI, 0.72–0.89]) had a lower all-cause mortality rate than control subjects (n=1712), whereas no difference was found in life expectancy between power sports athletes (n=941; HR, 0.93 [95% CI, 0.85–1.03]), including power lifters, short-distance runners, and jumpers, and control subjects, in part because of a high number of non-natural causes of death (ie, suicide/homicide) in the former. Similar data were found in a meta-analysis of cohort studies among elite athletes. The standardized mortality ratio was significantly lower in elite athletes (n=42 807) for all-cause mortality (standardized mortality ratio, 0.67 [95% CI, 0.55–0.81]), cardiovascular mortality (standardized mortality ratio, 0.73 [95% CI, 0.65–0.82]), and cancer mortality (standardized mortality ratio, 0.60 [95% CI, 0.38–0.94]).[251] On average, elite athletes lived 3 to 6 years longer than the general population.[250,252,253] An important limitation of these observational data is the inability to differentiate cause and effect, because some traits of elite athletes (eg, genetics, socioeconomic status, other lifestyle habits) unrelated to PA can also affect longevity. A Finnish study sought to minimize biological and behavioral confounders by comparing life expectancy between Finnish elite athletes (n=900) and their brothers (n=900).[254] Elite athletes had a more active lifestyle, smoked less, and lived ≈3 years longer than their brothers. These data suggest that both exercise training and a healthy lifestyle contributed to the athletes' increased longevity.

Strenuous Exercise in Cardiac Patients

Supervised exercise training and habitual PA are a class 1 recommendation for cardiac patients[255–257] because there is strong evidence that higher CRF[258] and higher PA volumes[259] are associated with a lower risk for adverse outcomes. Some have suggested using HIIT with cardiac patients,[260] because HIIT elicits greater increases in fitness than moderate-intensity continuous training (MICT) in healthy young to middle-aged adults.[261] There are conflicting reports on the benefits of HIIT versus MICT in cardiac rehabilitation. A meta-analysis including CHD patients engaging in HIIT (n=218) or MICT (n=254) found a 1.78 $mL \cdot kg^{-1} \cdot min^{-1}$ (95% CI, 0.45–3.1 $mL \cdot kg^{-1} \cdot min^{-1}$) greater increase in CRF with HIIT.[262] Other meta-analyses including

594 CHD patients[263] and 411 patients with heart failure and reduced ejection fraction[264] found a 1.3 mL·kg^{-1}·min^{-1} (95% CI, 0.6–1.9 mL·kg^{-1}·min^{-1}) and a 1.4 mL·kg^{-1}·min^{-1} (95% CI, 0.1–2.6 mL·kg^{-1}·min^{-1}) greater increase in CRF with HIIT versus MICT for both groups, respectively, but these effects disappeared after HIIT and MICT were matched for energy expenditure.[263,264] Furthermore, MICT was associated with greater reductions in body mass (–0.48 kg [95% CI, 0.15–0.81 kg]) and resting heart rate (–1.8 bpm [95% CI, 0.71–2.89 bpm) compared with HIIT,[261] and there were no differences in quality of life outcomes between the training modalities.[263,264] These findings suggest that the exercise-induced health benefits of HIIT and MICT in cardiac patients are comparable.

A major concern in using HIIT in cardiac patients is the increased risk for acute coronary events.[265] Data on the safety of HIIT in clinical populations are scarce. A systematic review reported an adverse event rate of 8% using HIIT in patients with cardiometabolic diseases.[266] Adverse responses included vasovagal reaction, nausea, ventricular bigeminy, atrial tachycardia, transient cerebral ischemia, and myocardial ischemia. Another study compared the cardiovascular event rates during HIIT and MICT in 4846 coronary patients participating in cardiac rehabilitation.[267] The absolute risk was low for HIIT (1 event per 23 182 patient-hours) and MICT (1 event per 129 456 patient-hours) but 5.6 times higher in the HIIT group. Although HIIT is a purported time-saving alternative to MICT, additional long-term studies assessing the safety, compliance, and morbidity and mortality after HIIT are needed before it can be widely adopted in patients with known or suspected CAD, especially in unsupervised, nonmedical settings.[268]

Several studies have explored the effects of high-intensity or high-volume PA on all-cause and cardiovascular mortality in cardiac patients outside of formal cardiac rehabilitation programs. Williams and Thompson[269] reported a gradual risk reduction (–15% per MET-h/d) of cardiovascular mortality in heart attack survivors (n=2377) running or walking up to 7.2 MET-h/d. However, patients running ≥7.2 MET-h/d had a mortality risk similar to inactive patients (HR, 0.88 [95% CI, 0.45–1.58]). Other studies have also reported a partial loss of the health benefits of PA among the most active cardiac patients. Keteyian et al[270] found the largest risk reduction for major adverse cardiovascular outcomes among patients with heart failure (n=959) exercising 3 to 5 MET-h/wk (–37%), but no risk reduction in patients performing ≥7 MET-h/wk. Wannamethee et al[271] reported a lower mortality risk for patients with CHD (n=772) performing light (RR, 0.42 [95% CI, 0.25–0.71]) or moderate (RR, 0.47 [95% CI, 0.24–0.92]) activities but a nonsignificant reduction in events in patients performing vigorous activities (RR, 0.63 [95% CI, 0.39–1.03]). Mons et al[272] demonstrated that patients with CHD (n=1038) who performed vigorous exercise 2 to 4 times weekly had the lowest all-cause mortality (7.6 per 1000 person-years), but that patients performing either no exercise (HR, 3.81 [95% CI, 2.17–6.70]) or 7 sessions/week (HR, 1.77 [95% CI, 0.90–3.47]) had an increased mortality risk. These findings suggest a U-shaped relationship between exercise volumes and health outcomes in cardiac patients; however, other studies suggest a curvilinear relationship. Stewart et al[83] demonstrated a graded risk reduction for all-cause mortality with increasing PA volumes among a large sample of CHD patients (n=15 486). The largest risk reductions were observed in patients performing any vigorous-intensity PA, irrespective of the PA volume. Similarly, Moholdt et al[273] found the lowest mortality risk in the most active (≥4 sessions/wk) CHD patients (n=3504; HR, 0.77 [95% CI, 0.66–0.89]). The conflicting outcomes on the association between high-intensity, high-volume PA and all-cause and cardiovascular mortality warrant further exploration. Nevertheless, all studies demonstrated that inactive patients have the highest mortality risk. Such results emphasize the importance of regular PA for cardiac patients, ideally via traditional medically supervised center- or home-based cardiac rehabilitation programs,[274] as well as the importance of prescribing exercise volumes according to current AHA/American College of Cardiology recommendations (Table 5).

Population Attributable Risk of Excessive Exercise/PA

The population attributable fraction is the proportion (fraction) of all cases in the population that can be attributed to an exposure, whereas the population attributable risk is the proportion of the incidence of a disease-related event in the population (exposed and unexposed) that is attributable to exposure. Nawrot et al[278] identified studies of specific triggers of nonfatal MI, including vigorous physical exertion (≥6 METs; 6 reports, n=5208), to calculate the corresponding population attributable fractions. Physical exertion was associated with increased odds of AMI (OR, 4.25 [95% CI, 3.17–5.68]), with a population attributable fraction of 6.16% (95% CI, 4.20%–8.64%). In INTERHEART (n=12 461), a case-control study of first AMI in 52 countries, investigators used a case-crossover approach to estimate ORs for AMI occurring within 1 hour of triggers.[63] Population attributable risk was calculated from the proportion of participants with exposure to physical exertion in the case and control periods. Any PA in the case period was associated with an OR of 2.31 (99% CI, 1.96–2.72), with a population attributable risk of 7.7% (99% CI, 6.3%–8.8%). However, moderate to strenuous exercise was associated with a population attributable risk of

Table 5. Physical Activity and Exercise Recommendations for Cardiac Patient Populations

Recommendations for Cardiac Patient Populations	Class of Recommendation	Level of Evidence
Chronic heart failure[257]		
Exercise training (or regular physical activity) is recommended as safe and effective for patients with heart failure who are able to participate, to improve functional status.	I	A
Cardiac rehabilitation can be useful in clinically stable patients with heart failure to increase functional capacity, exercise tolerance, and health-related quality of life and decrease mortality.	IIa	B
Congenital heart disease[275]		
Clinicians should assess activity levels at regular intervals and counsel patients with congenital heart disease about the types and intensity of exercise appropriate to their clinical status.	I	C
Cardiopulmonary exercise testing can be useful to guide activity recommendations for patients with congenital heart disease.	IIa	C
Cardiac rehabilitation can be useful to increase exercise capacity in patients with congenital heart disease.	IIa	B
Coronary and other atherosclerotic vascular disease[276]		
For all patients, the clinician should encourage 30 to 60 min of moderate-intensity aerobic activity, such as brisk walking, at least 5 d and preferably 7 d per week, supplemented by an increase in daily lifestyle activities (eg, walking breaks at work, gardening, household work) to improve cardiorespiratory fitness and move patients out of the least fit, least active high-risk cohort (bottom 20%).	I	B
For all patients, risk assessment with a physical activity history and/or an exercise test is recommended to guide prognosis and prescription.	I	B
The clinician should counsel patients to report and be evaluated for symptoms related to exercise.	I	C
It is reasonable for the clinician to recommend complementary resistance training at least 2 d per week.	IIa	C
Non-STEMI[255]		
All eligible patients with non–ST-segment–elevation acute coronary syndromes should be referred to a comprehensive cardiovascular rehabilitation program either before hospital discharge or during the first outpatient visit.	I	B
STEMI[256]		
Exercise-based cardiac rehabilitation/secondary prevention programs are recommended for patients with STEMI.	I	B
A clear, detailed, and evidence-based plan of care that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities, and compliance with interventions for secondary prevention should be provided to patients with STEMI.	I	C
Stable angina[277]		
Physical activity of 30 to 60 min, 7 d per week (minimum 5 d per week) is recommended. All patients should be encouraged to obtain 30 to 60 min of moderate-intensity aerobic activity, such as brisk walking, on most, preferably all, days of the week, supplemented by an increase in daily activities (such as walking breaks at work, gardening, or household work).	I	B
The patient's risk should be assessed with a physical activity history. Where appropriate, an exercise test is useful to guide the exercise prescription.	I	B
Medically supervised programs (cardiac rehabilitation) are recommended for at-risk patients (eg, recent acute coronary syndrome, revascularization, or heart failure).	I	B
Expanding physical activity to include resistance training on 2 d per week may be reasonable.	IIb	C

Classification of recommendations: Class I: Conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective. Class II: Conditions for which there is conflicting evidence, a divergence of opinion, or both about the usefulness/efficacy of a procedure or treatment. Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy. Class IIb: Usefulness/efficacy is less well established by evidence/opinion. Levels of evidence: Level of Evidence A: Data derived from multiple randomized clinical trials. Level of Evidence B: Data derived from a single randomized trial or nonrandomized studies. Level of Evidence C: Consensus opinion of experts. STEMI indicates ST-segment–elevation myocardial infarction.

14.3% (99% CI, 9.9%–18.7%). Nevertheless, it remains unclear whether and at which level there is a threshold dose to classify "excessive exercise/PA." Also, the cutoff of such a threshold dose is likely to be dependent on the outcome and may vary accordingly for coronary artery atherosclerosis, myocardial fibrosis, and AF. For these reasons, and because participation rates for endurance events such as half- and full-marathon running, triathlon, and long-distance cycling have skyrocketed over the past 2 decades, population risk estimates for excessive exercise/PA are likely to be tenuous, at best.

RECOMMENDING PRUDENT EXERCISE PROGRAMS

Inactive patients with and without CVD should be encouraged to develop gradually progressive exercise

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regimens. Because the least active, least fit individuals are at greatest risk for exercise-related acute cardiac events, novice exercisers should follow a gradual increase in exercise intensity to increase CRF without greatly increasing their cardiovascular risk by starting with vigorous exercise (Figure 4).[41,94] Although most cardiac patients initiate exercise-based rehabilitation programs at ≈2 to 3 METs, uptitration of training intensities over time is often suboptimal, especially when direct early outpatient medical supervision and continuous electrocardiographic monitoring have ceased.[279] Such patients should be counseled to gradually increase walking speed or grade over time to a moderate intensity (40%–59% functional capacity or 3.0–5.9 METs), provided they remain asymptomatic[136] This approach is prudent because these intensities are below the vigorous PA level (≥60% functional capacity or ≥6 METs) that is commonly associated with the triggering of exercise-related acute cardiovascular events.[41]

Patients should be counseled to include a warm-up and cool-down period during exercise training sessions to reduce the likelihood of inducing cardiac ischemia with sudden, intense physical effort[280,281] and to avoid the decrease in central blood volume that can occur with abrupt cessation of PA. Previously inactive patients with or without known CVD should also be advised to avoid unaccustomed, vigorous physical exertion and highly strenuous activities (eg, racquet sports,[95] snow removal[106]), to recognize potential exertion-related warning signs and symptoms (eg, chest pain or pressure, lightheadedness, palpitations or arrhythmias) that require cessation of exercise and medical evaluation, and to adapt the exercise to the environment. Because exercise in hot, humid environments requires an increased heart rate response to handle the associated thermal load,[282] patients should be advised to reduce the intensity of exercise under hot, humid conditions. Increased altitude reduces oxygen availability and further augments the cardiorespiratory and hemodynamic responses to a given submaximal work rate, thereby increasing cardiac demands. Accordingly, individuals exercising at altitudes of >1500 m should limit the intensity of their exercise until acclimated.[101,137,283] Patients with CVD who are interested in participating in competitive sports should be evaluated and advised in accordance with the AHA/American College of Cardiology eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities.[284–286]

Prophylactic Use of Cardioprotective Medications Before Exercise

Although some authors have suggested that individuals at risk for CAD may benefit from taking aspirin or β-blockers shortly before competitive exercise,[287–289] there are no definitive data that these medications prevent exercise-related acute cardiac events. The rationale for low-dose, uncoated aspirin to reduce the elevated, transient risk for exertion-related atherothrombosis is based on aspirin's ability to inhibit epinephrine-induced platelet aggregation, the observation that distance runners often show elevated inflammatory and hemostatic markers during races,[290–292] the finding that aspirin discontinuation is associated with an increase in acute cardiovascular events,[293] and the fact that aspirin use would preemptively provide athletes with the only medication with a class 1A recommendation for prehospital administration to treat ACS.[287,288] Nevertheless, in the TIMI II study (Thrombolysis in Myocardial Infarction phase II), aspirin use did not significantly reduce the likelihood of AMI during physical exertion.[289] Similarly, in the Myocardial Infarction Onset Study, aspirin use did not alter the RR of triggering AMI by heavy physical exertion.[41] In the RACER study, Kim et al[80] also concluded that taking aspirin before endurance running events would have limited efficacy, because acute plaque rupture and thrombosis were not found in any of the 5 runners who were discovered to have died with CHD.

Taking short-acting β-blockers before strenuous exercise has also been suggested,[294] despite their potential to reduce exercise tolerance.[295–297] Tofler et al[294] reported that peak and average heart rates during standardized bouts of physical exertion were significantly lower 30 minutes after ingestion of a β-blocker and aspirin than during a control period. Similarly, Kokkinos et al[298] concluded that β-blocker therapy could protect against excessive and repetitive elevations in blood pressure in hypertensive patients engaged in vigorous activities such as basketball, tennis, and racquetball. Analysis of the TIMI II database suggested that β-blockers provide the most compelling evidence for protection against physical exertion.[289] In contrast, the Myocardial Infarction Onset Study found that β-blockers did not significantly reduce the likelihood of AMI with heavy physical exertion, although the RR was slightly lower in users (RR, 4.2 [95% CI, 1.8–9.9]) than nonusers (RR, 6.2 [95% CI, 4.7–8.2]).[41]

Collectively, these data and more recent reports[63] suggest there is insufficient evidence to recommend the routine use of either aspirin or β-blockers before strenuous PA or sports participation. Decisions to recommend these prophylactic agents requires assessment of the individual patient's risk and a discussion with the patient of potential risks and benefits.

CONCLUSIONS AND PERSPECTIVES

There is abundant evidence that the amount of habitual PA and the level of CRF are inversely related to the risk of cardiovascular morbidity and mortality.[299]

Cardiovascular risk is reduced 30% and 64% in the most active and fit individuals (Figure 2), respectively,[19] and elite CRF is associated with an 80% reduction in all-cause mortality.[9] Life expectancy at 50 years of age is 7 to 8 years greater in the most physically active individuals.[5] The benefits of exercise are not limited to healthy individuals, because regular PA reduces recurrent events in patients with diagnosed CVD.[2,300] Lower event rates and higher survival rates have been reported in more active and more fit patients undergoing elective or emergent surgery[24,25] or hospitalized for ACS.[23] Vigorous-intensity exercise appears to provide greater health benefits for primary and secondary prevention than moderate-intensity exercise at a similar volume.[38,40] Hence, the number of individuals performing high-volume, high-intensity exercise training has increased appreciably in recent decades, and participation rates have skyrocketed for endurance exercise events such as half and full running marathons, triathlons, and long-distance cycling.[42] In this statement, we discussed the immediate and long-term risks of exercise in healthy and diseased populations.

Exercise is known to acutely, albeit transiently, increase the RR for SCD and MI. Risks appear to be highest in men unaccustomed to exercise, with substantially lower risks in regular exercisers and women. When expressed as an absolute risk, acute events are very rare, with only 0.31 to 2.1 SCDs per 100 000 person-years.[49,75] The most common cause of exercise-related SCD in middle-aged and older adults is atherosclerotic CAD. The most common cause in young individuals is controversial, but recent studies suggest that SCD with an SNH, and not HCM, could be the most common cause.[116]

Long-term exercise training induces cardiac remodeling, and limited evidence suggests that this may be maladaptive in some very active athletes. A J-shaped association is present between PA volumes and risk for AF.[186] Coronary artery atherosclerosis may be more prevalent in middle-aged athletes than in inactive individuals,[35] with the highest plaque prevalence in the most active athletes.[34] Calcified plaques, presumably more stable plaques, were more frequent in the most active athletes, but this finding is not associated with increased cardiovascular events.[211] Collectively, these data suggest that athletes with CAC are at higher risk for mortality and acute cardiac events than athletes without CAC; however, the risk for adverse cardiovascular outcomes is lower in physically active people than their inactive counterparts with the same CAC score. Myocardial fibrosis also appears to be more common in adult competitive athletes, and long-term exercise dose is the best predictor for LGE on cardiac magnetic resonance imaging.[228] Relative to cardiovascular outcomes, the clinical significance of accelerated coronary atherosclerosis and the presence of myocardial fibrosis in presumably healthy athletes requires additional study.

Most epidemiological studies report a decline in health risks with increasing PA volumes, with a plateauing of the reduction at the highest exercise volumes, although some have suggested that the relationship is U-shaped, with an increase in risk at the highest exercise volumes. Longevity data argue against the U-shaped relationship. Elite endurance athletes, for example, live 3 to 6 years longer than the general population.[250–253] A large prospective cohort study also observed no upper limit for the reduced risk of all-cause mortality with increasing CRF.[9] These findings might not be applicable to cardiac patients, because high-intensity, high-volume PA may increase all-cause mortality among these patients.[164,269–272] Also, exercise is known to accelerate disease development and severity in patients with ARVC, and possibly with lamin A/C mutations, but it is unclear whether exercise training can accelerate genotype to phenotype expression in other genetic cardiac diseases such as HCM and LQTS.

Despite such caveats, the benefits associated with long-term exercise training outweigh the risks for the majority of the population. Physical inactivity and sedentary behavior are a worldwide concern.[3] Interventions are needed to increase population levels of PA. To promote and maintain health, moderate-intensity aerobic (endurance) PA for a minimum of 30 minutes on 5 days each week, or vigorous-intensity aerobic PA for a minimum of 20 minutes on 3 days each week, or combinations thereof, is recommended.[301] Ostensibly healthy, inactive individuals starting to exercise should begin slowly, generally with a walking program, and increase the intensity and duration of exercise as their tolerance permits. Patients with CVD seeking to greatly increase their PA intensity or volume should be evaluated and advised in accordance with AHA/American College of Cardiology and related guidelines.[284–286]

Recommendations for exercise testing and prescription in those with concomitant AF have been published recently.[302]

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

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