REVIEW

Exercise as a Therapeutic Intervention in Patients with Stable Ischemic Heart Disease: An Underfilled Prescription

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ABSTRACT

Treatment for stable ischemic heart disease may include guideline-directed pharmacologic therapy, coronary revascularization, and lifestyle and behavioral changes, including structured exercise. Of these, regular exercise is arguably one of the most cost-effective yet underused interventions. Most patients with stable ischemic heart disease are eligible for secondary prevention programs, which should include exercise training regimens, but participation in such programs remains suboptimal. This review emphasizes the importance of education for both patients and providers to enhance participation in lifestyle physical activity, structured exercise, or both.

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Of the more than 16 million Americans with coronary heart disease, approximately 9 million have chronic angina and stable ischemic heart disease (myocardial ischemia).[1] Treatment for myocardial ischemia imposes significant clinical and economic burdens, with annual direct and indirect costs

estimated at tens of billions of dollars.[2] By optimizing guideline-directed medical therapy, the prognosis for long-term survival continues to improve. However, many patients with myocardial ischemia may not be benefiting from structured exercise—a widely available, inexpensive, and critically important therapeutic intervention with relative risk reductions that rival or exceed those commonly achieved with medications used for secondary prevention.

PHYSICAL ACTIVITY AS AN ANTIANGINAL THERAPEUTIC INTERVENTION

Although some patients with coronary heart disease may be asymptomatic, individuals with myocardial ischemia often have angina pectoris, characterized by chest discomfort, which is typically substernal but also may radiate to the neck, jaw, or epigastrium.[2,3] Anginal symptoms also can manifest as shortness of breath or unusual fatigue. Frequent episodes of angina may diminish quality of life[4] and productivity and result in premature retirement.[5]

The mechanism responsible for anginal symptoms reflects a physiologic imbalance between myocardial oxygen

supply and demand. Obstructive coronary disease decreases myocardial oxygen delivery, whereas associated elevations in heart rate and systolic blood pressure increase myocardial demand. When hypoxemia disrupts oxidative metabolic pathways, cellular anaerobic pathways and mediators are activated, evoking the characteristic symptoms of angina.[6]

Endothelial dysfunction is also a key modulator of myocardial ischemia. Nitric oxide released by the normal vascular endothelium is responsible for endothelium-dependent vasodilation. With myocardial ischemia, nitric oxide production is reduced, and vasodilation is compromised. In addition to coronary heart disease, anginal symptoms can occur in patients with valvular heart disease, hypertrophic cardiomyopathy, or uncontrolled hypertension.[2]

The goals of therapy for all patients with coronary heart disease are 3-fold: (1) to reduce morbidity and mortality, (2) to alleviate associated anginal symptoms, and (3) to improve quality of life. Commonly, patients with myocardial ischemia are treated with multiple medications, which may include beta-blockers (particularly in patients with a history of myocardial infarction), inhibitors of the renin-angiotensin system (particularly in patients with left ventricular systolic dysfunction), and lipid-lowering and antiplatelet agents. Nitrates, calcium-channel blockers, and ranolazine also may be used to reduce symptoms.[2,7,8] In addition, depending on patients' risk of coronary events and symptomatology, physicians may recommend percutaneous coronary intervention or coronary artery bypass graft surgery.

CLINICAL TRIALS SUPPORTING BENEFITS OF OPTIMAL MEDICAL THERAPY

In the late 1990s, investigators in the Clinical Outcomes Utilizing Revascularization and Aggressive drug Evaluation (COURAGE) trial evaluated whether elective percutaneous coronary intervention provided incremental clinical benefit beyond medical management in patients with objective evidence of myocardial ischemia. In COURAGE, 2287 eligible patients were treated with optimal medical therapy and lifestyle modification with or without percutaneous coronary intervention. Optimal medical therapy is a broad treatment approach reflecting not only the use of guideline-directed medical therapy but also lifestyle interventions aimed at reducing cardiovascular risk associated with poor diet and physical inactivity, as well as abnormal lipids or blood pressure, diabetes, and smoking. The results of COURAGE, published in 2007,[9] demonstrated that during a 7-year follow-up, angina symptoms were reduced in both

> ### CLINICAL SIGNIFICANCE
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> - Risk factor modification is a key component of the treatment of patients with stable ischemic heart disease.
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> - Benefits of exercise programs for patients with stable ischemic heart disease include increasing functional capacity, decreasing anginal symptoms, and improving endothelial function.
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> - Despite the benefits of secondary prevention programs in stable ischemic heart disease, rates of referral and participation remain unacceptably low in eligible patients.

the intervention group and the no intervention group (ie, medical therapy alone). Of note, percutaneous coronary intervention added to optimal medical therapy did not reduce the primary composite end point of death and nonfatal myocardial infarction or reduce major cardiovascular events compared with optimal medical therapy alone.[9]

COURAGE showed that optimal medical therapy without percutaneous coronary intervention can be implemented safely in most patients with myocardial ischemia and that aggressive modification of coronary risk factors can improve clinical outcomes.[9] Moreover, whereas the cost of optimal medical therapy and lifestyle modification was modest, the incremental cost-effectiveness ratio (ie, the additional cost of percutaneous coronary intervention divided by the quality-adjusted life years gained) exceeded $200,000.[10]

The Bypass Angioplasty Revascularization Investigation type 2 Diabetes trial replicated the COURAGE methodology in 2368 patients with diabetes and concomitant myocardial ischemia. Patients were randomized to guideline-directed medical therapy alone or to early revascularization (coronary artery bypass graft or percutaneous coronary intervention). After a mean 5-year follow-up, there was no significant difference in rates of death and major cardiovascular events between the 2 strategies.[11] The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches trial will evaluate an invasive or conservative management strategy in 8000 hospitalized patients with moderate to severe myocardial ischemia.

IMPORTANCE OF RISK FACTOR INTERVENTION AND SECONDARY PREVENTION

According to a 2007 report, between 1980 and 2000, mortality from coronary heart disease decreased by more than 40%.[12] By using a sophisticated mathematic model, the investigators found that only approximately 5% of the reduction in cardiovascular mortality during this 20-year interval was attributable to coronary revascularization. The primary decrease in US mortality was due to reductions in major cardiac risk factors and improved medical treatments. Despite these findings, many low-risk patients are still referred for elective coronary revascularization. The costs of these interventions are substantial: According to a 2006 US report, some $60 billion was spent that year for percutaneous coronary intervention and more than $44 billion for coronary artery bypass grafting.[13]

Lifestyle modifications are multidimensional and include improved dietary practices, achieving optimal body weight,

smoking cessation, compliance with prescribed medications, stress management, and increased physical activity or structured exercise.[14] Although each of these plays an important role, the benefits of exercise/physical activity in the treatment of patients with symptomatic or asymptomatic myocardial ischemia are often underappreciated.

PIVOTAL ROLE OF INCREASED PHYSICAL ACTIVITY AND STRUCTURED EXERCISE

Frequently, myocardial ischemia is associated with exercise intolerance, which limits patients' activities of daily living.[15] Regular moderate-to-vigorous physical activity has been shown to promote salutary antiatherosclerotic, anti-thrombotic, anti-ischemic, and antiarrhythmic effects and is associated with beneficial psychologic effects (**Figure 1**).[16] Specific anti-ischemic effects include reducing myocardial oxygen demand by lowering heart rate and systolic blood pressure at rest and during any given submaximal workload, as well as increasing the period of diastole, during which coronary perfusion predominates. Additional physiologic benefits include improved coronary blood flow and endothelial function,[17] as well as the production of endothelial progenitor cells and increased nitric oxide delivery.[18,19] Thus, exercise exerts cardioprotective effects in the entire arterial bed.[18]

For patients with myocardial ischemia, contemporary guidelines recommend 30 to 60 minutes of moderate-intensity aerobic activity at least 5 days per week, supplemented by an increase in daily lifestyle activities. Complementary resistance training at least 2 days per week also is strongly recommended.[20] Aerobic training augments maximum or peak oxygen uptake and favorably modifies selected cardiovascular risk factors.[21] Muscular strengthening activities promote the maintenance or enhancement of metabolically active lean muscle mass, which improves glucose metabolism and helps maintain basal metabolic rate.[22,23] Resistance training also attenuates the exercise-induced rate-pressure product when any given load is lifted, which may further decrease cardiac demands during activities of daily living.[21]

A "shorthand" method for estimating somatic aerobic requirements or energy expenditure is the use of metabolic equivalents (METs). One MET is equivalent to 3.5 mL O_2 per kilogram of body weight per minute and approximates a person's energy expenditure while sitting quietly.[23] Each 1-MET increase in performance during peak or symptom-limited treadmill testing is associated with an 8% to 35% (median 16%) reduction in mortality.[24] Vigorous-intensity physical activities (>6 METs) generate a greater energy expenditure than moderate-intensity physical activities (3.0-6.0 METs) undertaken for the same duration and frequency.[23] The American College of Sports Medicine now recommends ≥500 to 1000 MET-minutes per week, beyond activities of daily living.[25]

ROLE OF CARDIAC REHABILITATION AND STRUCTURED EXERCISE PROGRAMS

Cardiac rehabilitation programs are medically directed, multidisciplinary interventions designed to assist patients with coronary heart disease to achieve and maintain adherence to healthy lifestyle behaviors.[26] Exercise training is a central focus of these programs. Physically trained patients with myocardial ischemia who would otherwise experience ischemic symptoms during physical exertion can achieve a higher-intensity level before reaching their anginal or ischemic electrocardiographic threshold.[19]

Most patients with myocardial ischemia are eligible for cardiac rehabilitation programs. Such programs have been shown to reduce total mortality by ≥20%, cardiac mortality by ≥26%, and nonfatal myocardial infarction by ≥21%.[19,27-30] The primary beneficiaries are individuals at the bottom 20% of the fitness/activity continuum,[31] that is, the least fit, least active cohort.

For patients with coronary heart disease, regular exercise is cardioprotective; conversely, failure to exercise is tantamount to leaving an important prescription unfilled. Of all
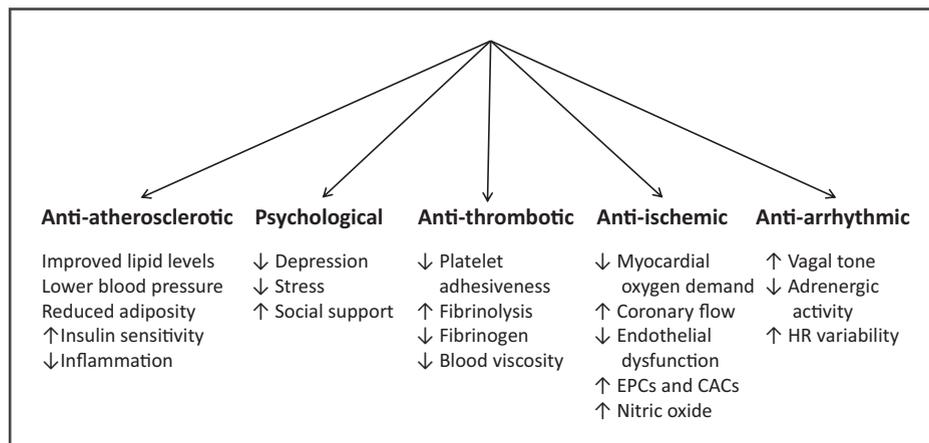
Figure 1   Potential cardioprotective effects of regular physical activity.[16] CAC = cultured/circulating angiogenic cell; EPC = endothelial progenitor cell; HR = heart rate.

patients eligible for cardiac rehabilitation/exercise training regimens, less than 20% to 30% are referred to such programs.[32-34] Of those referred, only approximately 40% actually participate, and fewer still persist for the recommended duration of the program.[33,35]

IDENTIFYING AND REMOVING BARRIERS TO EXERCISE TRAINING REGIMENS

Factors associated with limited referral and enrollment in cardiac rehabilitation programs include female sex, older age, racial/ethnic minority group, lack of or limited health insurance, low socioeconomic status, poor self-efficacy, decreased health literacy, inadequate understanding of the disease and its treatment, lack of perceived need, language barriers, cultural beliefs, work-related conflicts, limited social support, home or spousal caregiving responsibilities, and multiple comorbidities, including depression and musculoskeletal conditions.[26]

Among Americans aged 40 to 74 years, the age-adjusted prevalence of angina is higher among women than men. It is also greater in African American women and in Mexican Americans of both sexes.[1] Nevertheless, although angina has a less favorable prognosis in women,[36] women are less likely than men to be referred to or attend a cardiac rehabilitation program, particularly if they are elderly or nonwhite.[37,38] Individuals aged more than 65 years make up greater than 50% of the eligible population but are less likely to be referred to and participate in exercise-based cardiac rehabilitation programs than their younger counterparts,[39-41] despite deriving greater benefit from increased physical activity than younger patients.[28,42]

Reasons for the poor use of guideline-recommended cardiac rehabilitation/exercise training regimens are generally known. The most significant reason for the poor use of cardiac rehabilitation is failure to refer,[26] despite the fact that referral of hospitalized patients to a cardiac rehabilitation program is included in performance measures.[43] For patients with stable ischemic heart disease, physicians may be unaware of the frequency of their patients' anginal pain or its effect on their quality of life. In the Coronary Artery Disease in General Practice study, physicians reported that angina was optimally controlled in 80% of their patients and that 61% had minimal angina-related impediments during physical activity. In contrast, interviews with patients revealed that only 52% described themselves as angina-free, and only 47% thought that angina did not adversely affect their quality of life.[44] Accordingly, physicians' underestimation of their patients' level of symptom control may negatively influence referral to cardiac rehabilitation programs.

Other factors, in addition to low rates of referral, include limited facilitation of enrollment for those who are referred, the quality of the relationship between the patient and the primary care provider, and whether that provider strongly endorses the program. The availability and characteristics of the program also may affect enrollment, for example, limited programs in rural and low-income areas,[45] distance to the facility from the patient's home, hours of operation, poor access via public transportation, lack of racial or ethnic diversity among the staff of the program, and gender-dominated programs.[26] For older patients, reasons for lack of participation, in addition to physician failure to refer, include lack of awareness of cardiac rehabilitation programs, a perception that they can self-manage their condition, or the fear that exercise may exacerbate symptoms or trigger recurrent cardiovascular events.[41]

Fortunately, these barriers are surmountable. For example, hospital discharge plans for patients with myocardial ischemia should include a referral to an outpatient cardiac rehabilitation program and vigilant attention to follow-up appointments.[46,47] Whenever possible, nonhospitalized patients should be referred by their physician's office. Details regarding cardiac rehabilitation programs should be made available in multiple languages, with interpreters provided, as required.[26,48] The unavailability of a baseline exercise test[49] should not preclude participation in a moderate-intensity physical activity program. Alternative forms of functional screening include the Physical Activity Readiness Questionnaire,[50] the 6-minute walk test,[49] or the Duke Activity Status Index.[51]

Traditional exercise programs that allow for direct medical supervision and group support remain the gold standard. However, many patients have real-life work, caregiving, or transportation barriers to attendance. In addition, some women may be reluctant to participate in mixed-gender programs or may be self-conscious about exercising in public.[26] Accordingly, options should be extended so that low-risk patients with myocardial ischemia can enroll in a home-based program. Such programs have been shown to be as effective as center-based programs and may encourage better adherence, particularly in older patients and those who do not have easy access to structured programs,[35,52-55] or if there is an extended duration between hospital discharge and initiation of an outpatient program, when insurance coverage may no longer apply.[56] Home-based programs added to cardiac rehabilitation programs increase exercise frequency. They may also help transition patients from center-based cardiac rehabilitation programs to self-care.

Web-based technologies, such as video conferencing, and devices, such as mobile phones and blood pressure, glucose, and heart-rate monitors, provide education and ongoing feedback to patients who participate in secondary prevention programs in their homes, as well as to practitioners.[57,58] Although further research is warranted, these modalities are cost-effective and have great promise in patients with ischemic heart disease.[26]

MOTIVATIONAL TOOLS FOR THE PATIENT WITH STABLE ISCHEMIC HEART DISEASE

Patient motivation is an important factor for both enrollment in and adherence to an exercise training regimen. Patients

may not be motivated to participate in an exercise-based cardiac rehabilitation program if they believe that their disease is not severe or, conversely, that the disease is uncontrollable regardless of their lifestyle practices. They may not know where medically based exercise resources are available, may lack the time, or may simply be uncomfortable exercising. Some patients also fear triggering a cardiac event or anginal symptoms by overexertion.[59]

New tools are available to educate and motivate patients. For example, Exerscript is an American College of Sports Medicine guideline–compliant exercise prescription form that is designed to help patients with cardiac disease and their healthcare providers set realistic and achievable physical activity goals. The components include frequency, intensity, time, and type of activity. Another innovative tool, Exerscore, is a wheel calculator that patients can use to tally their exercise activity points each week and track their achievements. Exerscore enables patients to translate the guideline-driven minimum recommendation (500 MET-minutes per week)[25] into achievable goals by quantifying incremental exercise in a simple formula: METs per activity × no. of minutes = no. of Exerscore points for recommended 500 MET-minutes per week.

As an example, 10 minutes of 3 mph walking (3.5 METs) = 35 divided by 500 = 7% (0.07 times the weekly goal and intensity) = 7 Exerscore points. Another example: 20 minutes of 5 mph jogging (8 METs) 3 days/week = approximately 480 MET-minutes per week (160 × 3), or approximately 96 points. This calculator is available in both paper and electronic formats.

For many patients with symptomatic or asymptomatic myocardial ischemia, guideline-directed recommendations of 30 to 60 minutes of aerobic exercise at least 5 days per week, with complementary resistance training twice per week, may be perceived as unrealistic. Yet, because even modest amounts of exercise are cardioprotective,[60] reluctant patients should be encouraged to do what they can, because moving out of the least fit, least active cohort (the bottom 20%) is associated with the greatest mortality reduction.[31] Patients with reduced exercise capacity can begin to increase their activity by 5 to 10 minutes per day by increasing the length of time for each exercise bout or the number of short bouts each day.

Symptomatic patients with myocardial ischemia should be reassured that a moderate-intensity exercise regimen can help treat their anginal symptoms and, with appropriate use of preemptive medical therapy, actually increase the anginal threshold by attenuating their heart rate and blood pressure responses to physical exertion. Both exercise and nitroglycerin are Class I American Heart Association/American College of Cardiology Foundation recommendations. These can be administered as an integrated therapeutic approach that empowers patients to preemptively manage their symptoms. Patients have reported a marked increase in exercise duration after taking prophylactic short-acting nitroglycerin before beginning their physical activity.[61] However, studies have consistently shown that many patients are unaware of the fact that they can often prevent anginal symptoms to enhance exercise capacity.[59,62-64] Informing patients that the prophylactic use of sublingual nitroglycerin spray or tablets can help prevent exercise-induced angina is reassuring, and providers should appropriately educate patients about this preemptive strategy.

Caregivers should be cognizant of their patients' commitment to exercise and monitor and reinforce their progress. The knowledge that their caregivers are partnering with them in their rehabilitation and in preventing future cardiovascular events is highly therapeutic for coronary patients with and without angina symptoms.

PHYSICAL INACTIVITY AS A MODIFIABLE RISK FACTOR: CALL TO ACTION

All healthcare providers who come in contact with patients with cardiac disease should, at every opportunity, reinforce the message that exercise is an integral part of their therapy. Most important, patients should understand that physical inactivity is an important, modifiable cardiovascular risk factor.[23,65] Clinicians should advise patients that the time spent exercising is just as important as treating their elevated low-density lipoprotein cholesterol or blood pressure.

CONCLUSIONS

For apparently healthy persons, exercise is an effective intervention in the primary prevention armamentarium. For those with a history of stable ischemic heart disease, regular physical activity or structured exercise is an integral component of a comprehensive therapeutic program. Physicians and allied health professionals involved with patient care should embrace the importance of this message and ensure that this prescription is optimally filled.

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References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation.* 2012;125:e2-20.
2. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation.* 2003;107:149-158.
3. Wei J, Wu T, Yang Q, Chen M, Ni J, Huang D. Nitrates for stable angina: a systematic review and meta-analysis of randomized clinical trials. *Int J Cardiol.* 2011;146:4-12.
4. Brorsson B, Bernstein SJ, Brook RH, Werko L. Quality of life in patients with chronic stable angina before and four years after coronary revascularisation compared with a normal population. *Heart.* 2002;87:140-145.

5. Furze G, Cox H, Morton V, et al. Randomized controlled trial of a lay-facilitated angina management programme. *J Adv Nurs*. 2012;68: 2267-2279.

6. DeJongste MJ, Tio RA, Foreman RD. Chronic therapeutically refractory angina pectoris. *Heart*. 2004;90:225-230.

7. Conti CR. Re-thinking angina. *Clin Cardiol*. 2007;30(Suppl I):I-1-I-3.

8. Fox K, Garcia MAA, Ardissino D, et al. Guidelines on the management of stable angina pectoris: executive summary. *Eur Heart J*. 2006;27: 1341-1381.

9. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503-1516.

10. Weintraub WS, Boden WE, Zhang Z, et al. Cost effectiveness of percutaneous coronary intervention in optimally treated stable coronary patients. *Circ Cardiovasc Qual Outcomes*. 2008;1:12-20.

11. Frye RL, August P, Brooks MM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503-2515.

12. Ford ES, Ajani UA, Croft JB, et al. Explaining the decrease in US deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356: 2388-2398.

13. Chopra D, Ornish D, Roy R. "Alternative" medicine is mainstream. *Wall Street Journal*. September 1, 2009:A13.

14. Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 Chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task force on Practice Guidelines Writing Group. *Circulation*. 2007;116: 2762-2772.

15. Gardner AW, Montgomery PS, Ritti-Dias RM, Thadani U. Exercise performance, physical activity, and health-related quality of life in participants with stable angina. *Angiology*. 2011;62:461-466.

16. Franklin BA, Lavie CJ. Triggers of acute cardiovascular events and potential preventive strategies: prophylactic role of regular exercise. *Phys Sportsmed*. 2011;39:11-21.

17. Niebauer J, Cooke JP. Cardiovascular effects of exercise: role of endothelial shear stress. *J Am Coll Cardiol*. 1996;28:1652-1660.

18. Green DJ, O'Driscoll G, Joyner MJ, Cable NT. Exercise and cardiovascular risk reduction: time to update the rationale for exercise? *J Appl Physiol*. 2008;105:766-768.

19. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease. An American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation*. 2005;111:369-376.

20. Smith SC Jr, Benjamin EJ, Bonow RO, et al. Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease. 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124:2458-2473.

21. Pollock ML, Franklin BA, Balady GJ, et al. Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: an advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association: position paper endorsed by the American College of Sports Medicine. *Circulation*. 2000;101:828-833.

22. Williams MA, Haskell WL, Ades PA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2007;116:572-584.

23. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116:1081-1093.

24. Boden WE, Franklin BA, Wenger NK. Physical activity and structured exercise for patients with stable ischemic heart disease. *JAMA*. 2013;309:143-144.

25. Garber CE, Blissmer B, Deschenes MR, et al. American College of Sports Medicine Position Stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc*. 2011;43:1334-1359.

26. Balady GJ, Ades PA, Bittner VA, et al. Referral, enrollment, and delivery of cardiac rehabilitation/secondary prevention programs at clinical centers and beyond: a presidential advisory from the American Heart Association. *Circulation*. 2011;124:2951-2960.

27. Lavie CJ, Milani RV. Cardiac rehabilitation and exercise training in secondary coronary heart disease prevention. *Prog Cardiovasc Dis*. 2011;53:397-403.

28. Suaya JA, Stason WB, Ades PA, Normand SL, Shepard DS. Cardiac rehabilitation and survival in older coronary patients. *J Am Coll Cardiol*. 2009;54:25-33.

29. Nocon M, Hiemann T, Muller-Riemanschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prev Rehabil*. 2008;15:239-246.

30. Heran BS, Chen JM, Ebrahim S, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database Syst Rev*. 2011;7:CD001800.

31. Franklin BA, Lavie CJ, Squires RW, Milani RV. Exercise-based cardiac rehabilitation and improvements in cardiorespiratory fitness: implications regarding patient benefit. *Mayo Clin Proc*. 2013;88: 431-437.

32. Blackburn GG, Foody JM, Sprecher DL, Park E, Apperson-Hansen C, Pashkow FJ. Cardiac rehabilitation participation patterns in a large, tertiary care center: evidence for selection bias. *J Cardiopulm Rehabil*. 2000;20:189-195.

33. Mazzini MJ, Stevens GR, Whalen D, Oronoff A, Balady GJ. Effect of an American Heart Association Get With the Guidelines program-based clinical pathway on referral and enrollment into cardiac rehabilitation after acute myocardial infarction. *Am J Cardiol*. 2008;101:1084-1087.

34. Ades PA. Cardiac rehabilitation and secondary prevention of coronary heart disease. *N Engl J Med*. 2001;345:892-902.

35. Jolly K, Lip GY, Taylor RS, et al. The Birmingham Rehabilitation Uptake Maximisation study (BRUM): a randomised controlled trial comparing home-based with centre-based cardiac rehabilitation. *Heart*. 2009;95:36-42.

36. Daly C, Clemens F, Lopez-Sendon JL, et al. Gender differences in the management and clinical outcome of stable angina. *Circulation*. 2006;113:490-498.

37. Suaya JA, Shepard DS, Normand SL, Ades PA, Prottas J, Stason WB. Use of cardiac rehabilitation by Medicare beneficiaries after myocardial infarction or coronary bypass surgery. *Circulation*. 2007;116:1653-1662.

38. Mochari H, Lee JR, Kligfield P, Mosca L. Ethnic differences in barriers and referral to cardiac rehabilitation among women hospitalized with coronary heart disease. *Prev Cardiol*. 2006;9:8-13.

39. Witt BJ, Jacobsen SJ, Weston SA, et al. Cardiac rehabilitation after myocardial infarction in the community. *J Am Coll Cardiol*. 2004;44: 988-996.

40. Pasquali SK, Alexander KP, Peterson ED. Cardiac rehabilitation in the elderly. *Am Heart J*. 2001;142:748-755.

41. Grace SL, Shanmugasegaram S, Gravely-Witte S, Brual J, Suskin N, Stewart DE. Barriers to cardiac rehabilitation: does age make a difference? *J Cardiopulm Rehabil*. 2009;29:183-187.

42. Lavie CJ, Milani RV. Effects of cardiac rehabilitation and exercise training programs in patients > or = 75 years of age. *Am J Cardiol*. 1996;78:675-677.

43. Thomas RJ, King M, Lui K, Oldridge N, Pina IL, Spertus J. AACVPR/ ACCF/AHA 2010 update: performance measures on cardiac rehabilitation for referral to cardiac rehabilitation/secondary prevention services: a report of the American Association of Cardiovascular and Pulmonary Rehabilitation and the American College of Cardiology

Foundation/American Heart Association Task Force on Performance Measures. *Circulation*. 2010;122:1342-1350.

44. Beltrame JF, Weekes AJ, Morgan C, Tavella R, Spertus JA. The prevalence of weekly angina among patients with chronic stable angina in primary care practices: the Coronary Artery Disease in General Practice (CADENCE) study. *Arch Intern Med*. 2009;169:1491-1499.

45. De Angelis C, Bunker S, Schoo A. Exploring the barriers and enablers to attendance at rural cardiac rehabilitation programs. *Aust J Rural Health*. 2008;16:137-142.

46. Gravely-Witte S, Leung YW, Nariani R, et al. Effects of cardiac rehabilitation referral strategies on referral and enrollment rates. *Nat Rev Cardiol*. 2010;7:87-96.

47. Smith KM, Harkness K, Arthur HM. Predicting cardiac rehabilitation enrollment: the role of automatic physician referral. *Eur J Cardiovasc Prev Rehabil*. 2006;13:60-66.

48. Krantz MJ, Havranet EP, Mehler PS, Haynes DK, Long CS. Impact of a cardiac risk reduction program on vulnerable patients hospitalized with coronary artery disease. *Pharmacotherapy*. 2004;24: 768-775.

49. Beatty AL, Schiller NB, Whooley MA. Six-minute walk test as a prognostic tool in stable coronary heart disease: data from the Heart and Soul study. *Arch Intern Med*. 2012;172:1096-1102.

50. Thomas S, Reading J, Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). *Can J Sport Sci*. 1992;17: 338-345.

51. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). *Am J Cardiol*. 1989;64:651-654.

52. Miller NJ, Haskell WL, Berra K, DeBusk RF. Home vs group exercise training for increasing functional capacity after myocardial infarction. *Circulation*. 1984;70:645-649.

53. Gossard D, Haskell WLO, Taylor CB, et al. Effects of low- and high-intensity exercise training on functional capacity in healthy middle-aged men. *Am J Cardiol*. 1986;57:446-449.

54. Dalal HM, Zawada A, Jolly K, Moxham T, Taylor RS. Home-based versus centre-based cardiac rehabilitation: Cochrane systematic review and meta-analysis. *BMJ*. 2010;340:b5631.

55. Grace SL, McDonald J, Fishman D, Caruso V. Patient preferences for home-based versus hospital-based cardiac rehabilitation. *J Cardiopulm Rehabil*. 2005;25:24-29.

56. Arena R, Williams M, Forman DE, et al. Increasing referral and participation rates to outpatient cardiac rehabilitation: the valuable role of healthcare professionals in the inpatient and home health settings: a science advisory from the American Heart Association. *Circulation*. 2012;125:1321-1329.

57. Neubeck L, Redfern J, Fernandez R, Briffa T, Bauman A, Freedman B. Telehealth interventions for the secondary prevention of coronary heart disease: a systematic review. *Eur Cardiovasc Prev Rehabil*. 2009;16: 281-289.

58. Vandelanotte C, Dwyer T, Van Itallie A, Hanley C, Mummery WK. The development of an Internet-based outpatient cardiac rehabilitation intervention: a Delphi study. *BMC Cardiovasc Disord*. 2010;10:1-8.

59. Kolenda K-D. Value of glyceryl trinitrate in exercise therapy. Prophylactic use in patients with coronary heart disease and stable angina pectoris. *Forttschr Med*. 1998;116:65-70.

60. Glazer NL, Lyass A, Esliger DW, et al. Sustained and shorter bouts of physical activity are related to cardiovascular health. *Med Sci Sports Exerc*. 2013;45:109-115.

61. Thadani U, Wittig T. A randomized, double-blind, placebo-controlled, crossover, dose-ranging multicenter study to determine the effect of sublingual nitroglycerin spray on exercise capacity in patients with chronic stable angina. *Clin Med Insights: Cardiol*. 2012;6:87-95.

62. Ingram S, Love J. Cardiac patients' perceived education and use of sub-lingual glyceryl trinitrate on commencement of outpatient cardiac rehabilitation. *Coronary Health Care*. 1999;3:128-134.

63. Kimble LP, Kunic CL. Knowledge and use of sublingual nitroglycerin and cardiac-related quality of life in patients with chronic stable angina. *J Pain Sympt Manag*. 2000;19:109-117.

64. Nichols N, Oldford D, Duke SNURSE. Nitroglycerin Use: Revisiting Strategies for Efficacy. *Can J Cardiovasc Nurs*. 2007;17:31-38.

65. Thijssen DH, Maiorana AJ, O'Driscoll G, Cable NT, Hopman MT, Green DJ. Impact of inactivity and exercise on the vasculature in humans. *Eur J Appl Physiol*. 2010;108:845-875.