Cardiorespiratory fitness attenuates risk for major adverse cardiac events in hyperlipidemic men and women independent of statin therapy: The Henry Ford ExercIse Testing Project

Rupert K. Hung, BA,[a] Mouaz H. Al-Mallah, MD, MSc,[a,b] Mohamud A. Qadi, BS,[a] Gabriel E. Shaya, BA,[a,c] Roger S. Blumenthal, MD,[a] Khurram Nasir, MD, MPH,[a,d] Clinton A. Brawner, PhD,[e] Steven J. Keteyian, PhD,[e] and Michael J. Blaha, MD, MPH[a]
Baltimore, MD; Riyadh, Saudi Arabia; Miami, FL; and Detroit, MI

Aims We sought to evaluate the effect of cardiorespiratory fitness (CRF) in predicting mortality, myocardial infarction (MI), and revascularization in patients with hyperlipidemia after stratification by gender and statin therapy.

Methods and results This retrospective cohort study included 33,204 patients with hyperlipidemia (57 ± 12 years old, 56% men, 25% black) who underwent physician-referred treadmill stress testing at the Henry Ford Health System from 1991 to 2009. Patients were stratified by gender, baseline statin therapy, and estimated metabolic equivalents from stress testing. We computed hazard ratios using Cox regression models after adjusting for demographics, cardiac risk factors, comorbidities, pertinent medications, interaction terms, and indication for stress testing.

Results There were 4,851 deaths, 1,962 MIs, and 2,686 revascularizations over a median follow-up of 10.3 years. In men and women not on statin therapy and men and women on statin therapy, each 1-metabolic equivalent increment in CRF was associated with hazard ratios of 0.86 (95% CI 0.85-0.88), 0.83 (95% CI 0.81-0.85), 0.85 (95% CI 0.83-0.87), and 0.84 (95% CI 0.81-0.87) for mortality; 0.93 (95% CI 0.90-0.96), 0.87 (95% CI 0.83-0.91), 0.89 (95% CI 0.86-0.92), and 0.90 (95% CI 0.86-0.95) for MI; and 0.91 (95% CI 0.88-0.93), 0.87 (95% CI 0.83-0.91), 0.89 (95% CI 0.87-0.92), and 0.90 (95% CI 0.86-0.94) for revascularization, respectively. No significant interactions were observed between CRF and statin therapy ($P > .23$).

Conclusion Higher CRF attenuated risk for mortality, MI, and revascularization independent of gender and statin therapy in patients with hyperlipidemia. These results reinforce the prognostic value of CRF and support greater promotion of CRF in this patient population. (Am Heart J 2015;170:390-399.e6.)

Higher cardiorespiratory fitness (CRF) has been shown to protect against mortality in both healthy individuals[1-4] and in those with chronic diseases such as coronary artery disease (CAD),[5-11] diabetes mellitus,[12-16] and hypertension,[17-22] in addition to modulating the relationship between obesity and mortality.[23-25] Cardiorespiratory fitness has also been associated with lower risk for mortality in patients with hyperlipidemia,[26-30] but little is known about the prognostic value of CRF on nonfatal cardiovascular outcomes in this patient population.

Management of hyperlipidemia uses multiple modalities including lifestyle modifications comprising physical activity, diet and weight loss, and medications such as statin therapies.[31-36] Notably, the high prevalence of obesity and physical inactivity in developed countries are often linked with hyperlipidemia and increased prescription of statin therapy. Furthermore, statins have well-known effects on skeletal muscle and, in some studies, have been associated with lower levels of physical activity and an attenuation in the response of CRF to exercise training.[35,37-40] However, statin therapy did not diminish the prognostic importance of CRF on mortality

From the [a]Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, MD, [b]King Abdul-Aziz Cardiac Center, Riyadh, Saudi Arabia, [c]University of Miami Miller School of Medicine, Miami, FL, [d]Baptist Health South Florida, Miami, FL, and [e]Henry Ford Health System, Detroit, MI.

None of the authors have any relevant relations to industry to disclose. The present study was conducted in accordance with the Declaration of Helsinki and was approved by the Henry Ford Health System Institutional Review Board. An oral presentation of this study was presented at the American College of Cardiology Scientific Sessions in Washington, DC, on March 30, 2014. Poster presentations of this study were presented at Cardiovascular Disease Prevention International Symposium in Miami, FL, on February 6, 2014, and at the Johns Hopkins Heart and Vascular Institute's Cardiovascular Research Retreat in Baltimore, MD, on May 30, 2014.

Submitted January 21, 2015; accepted April 15, 2015.

Reprint requests: Michael J. Blaha, MD, MPH, Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, 600 N Wolfe St, Carnegie 565A, Baltimore, MD 21287.
E-mail: mblaha1@jhmi.edu

0002-8703

http://dx.doi.org/10.1016/j.ahj.2015.04.030

risk in male veterans with hyperlipidemia,[41] suggesting that CRF may continue to be an important consideration even among those on statin therapy.

In addition, previous literature has been mixed on the effect of CRF on mortality between men and women[1,42-44] and between veteran and nonveteran cohorts.[6,45] Specifically, whether previous findings in male veterans with hyperlipidemia can be generalized to both men and women with hyperlipidemia seen in routine clinical practice remains an important area of uncertainty, especially given anticipated increases in statin therapy in response to the new cholesterol treatment guidelines.[46]

We sought to assess the prognostic value of CRF on risks for all-cause mortality, myocardial infarction (MI), and revascularization in a multiethnic, clinically referred cohort of patients with hyperlipidemia, stratified by gender and statin therapy.

Methods

Study design

This study is based on data from the Henry Ford ExercIse Testing Project (The FIT Project), a retrospective cohort study aimed at investigating the long-term implications of exercise capacity on cardiovascular outcomes and total mortality.[47]

The FIT Project is unique in its combined use of (1) directly measured exercise data, (2) retrospective collection of medical history and medication treatment data taken at the time of the stress test, (3) retrospective supplementation of supporting clinical data using the electronic medical record (EMR) and administrative databases, and (4) epidemiologic follow-up for all-cause mortality and select nonfatal outcomes via linkage with the death registry and medical claims files, respectively.

The FIT Project population is a registry of 69,885 consecutive patients who underwent physician-referred treadmill stress testing at Henry Ford Health System in metropolitan Detroit, MI, between 1991 and 2009. These medical centers are part of a large, vertically integrated organization that provides health care and offers a managed care insurance plan. Data from the exercise test, medical history, and medications were collected by exercise physiologists and nurses and entered at the time of testing into a common clinical reporting tool that directly populated the EMR. Supporting clinical data and follow-up for cardiovascular outcomes were derived from the EMR and administrative databases shared across Henry Ford Health System. The FIT Project was approved by the Henry Ford Health System Institutional Review Board.

Study population

We initially included all patients from The FIT Project who had established hyperlipidemia at the time of stress testing (n = 34,081). *Hyperlipidemia* was defined as self-reported diagnosis, an EMR problem list-based diagnosis, low-density lipoprotein cholesterol >160 mg/dL on laboratory testing closest to the date of the stress test, or use of medications for hyperlipidemia. Patients missing covariates of interest were excluded (n = 887), leaving 33,204 patients with hyperlipidemia for analysis. Patients were subsequently categorized according to both gender and baseline statin therapy: men not on statin therapy (n = 10,210), men on statin therapy (n = 8,220), women not on statin therapy (n = 8,650), and women on statin therapy (n = 6,124).

Exercise testing

All patients underwent routine, clinically referred, symptom-limited treadmill stress testing following the standard Bruce protocol.[48] For individuals with repeat stress testing, only the results from the first test were considered in the registry. Patients <18 years old at the time of stress testing and patients undergoing modified Bruce and non-Bruce protocol tests were not included in the registry.

In accordance with clinical guidelines,[49] treadmill testing was terminated at the discretion of the supervising clinician for reasons that included significant arrhythmias, abnormal hemodynamic responses, diagnostic ST-segment changes, exercise-limiting symptoms such as chest pain or shortness of breath, or if the patient was unwilling or unable to continue.

Resting heart rate and blood pressure were taken before stress testing by clinical personnel. Target heart rate was calculated as 85% of the age-predicted maximal heart rate determined by the formula: 220 − age. Cardiorespiratory fitness, expressed in estimated metabolic equivalents (METs), was calculated by the treadmill controller system (Q-Stress; Quinton Instruments, Bothell, WA) based on achieved speed and elevation and was further categorized into 4 groups (<6, 6-10, 10-12, or >12 METs) for select analyses.

Medical history and medication use

A medical history including age, gender, race, indication for testing, risk factor burden, active medication use, and medical history was obtained by trained nurses and/or exercise physiologists immediately before the stress test. Race and smoking were defined exclusively by self-report. Obesity was defined by self-report and/or assessment by the clinician historian. Family history of coronary artery disease was defined as compatible history in a first degree relative. Indication for stress testing was extracted from the stress test requisition provided by the referring physician and subsequently categorized into common indications (ischemia evaluation/risk stratification, chest pain, shortness of breath, preoperative evaluation, etc).

Medication use and medical history were gathered by self-report at the time of testing and then supplemented by a retrospective verification using the EMR, administrative databases, and/or pharmacy claims files from enrollees in the integrated health plan. A database-verified diagnosis was considered present when the appropriate *International*