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ORIGINAL ARTICLE

High Exercise Capacity Attenuates the Risk of Early Mortality After a First Myocardial Infarction: The Henry Ford Exercise Testing (FIT) Project

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Abstract

Objective: To examine the effect of objectively measured exercise capacity (EC) on early mortality (EM) after a first myocardial infarction (MI).

Patients and Methods: This retrospective cohort study included 2061 patients without a history of MI (mean age, 62±12 years; 38% [n=790] women; 56% [n=1153] white) who underwent clinical treadmill stress testing in the Henry Ford Health System from January 1, 1991, through May 31, 2009, and suffered MI during follow-up (MI event proportion, 3.4%; mean time from the exercise test to MI, 6.1±4.3 years). Exercise capacity was categorized on the basis of peak metabolic equivalents (METs) achieved: less than 6, 6 to 9, 10 to 11, and 12 or more METs. *Early mortality* was defined as all-cause mortality within 28, 90, or 365 days of MI. Multivariable logistic regression models were used to assess the effect of EC on the risk of mortality at each time point post-MI adjusting for baseline demographic characteristics, cardiovascular risk factors, medication use, indication for stress testing, and year of MI.

Results: The 28-day EM rate was 10.6% overall, and 13.9%, 10.7%, 6.9%, and 6.0% in the less than 6, 6 to 9, 10 to 11, and 12 or more METs categories, respectively ($P<.001$). Patients who died were more likely to be older, be less fit, be nonobese, have treated hypertension, and have a longer duration from baseline to incident MI ($P<.05$). Adjusted regression analyses revealed a decreased risk of EM with increasing EC categories. A 1-MET higher EC was associated with an 8% to 10% lower risk of mortality across all time points (28 days: odds ratio [OR], 0.92; 95% CI, 0.87-0.98; $P=.006$; 90 days: OR, 0.90; 95% CI, 0.86-0.95; $P<.001$; 365 days: OR, 0.91; 95% CI, 0.87-0.94; $P<.001$).

Conclusion: Higher baseline EC was independently associated with a lower risk of early death after a first MI.

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The relationship between low exercise capacity (EC) and all-cause and cardiovascular mortality and morbidity has been established in a wide range of patient populations; however, nearly all studies have assessed adverse outcomes over long-term follow-up.[1-8] Little is known about the effect of EC on early mortality (EM), particularly death after another medical illness such as myocardial infarction (MI). A protective effect of high EC in this setting may reasonably be posited, given association with various favorable physiological effects including increased cardiac stroke volume and cardiac reserve, enhanced autonomic stability, and advantageous changes in thrombogenic and fibrinolytic factors.[9-12] Empirically, participation in cardiac rehabilitative programs after acute MI can increase EC and has been shown to protect against all-cause and cardiovascular mortality over long-term follow-up.[13-15] Despite the wealth of literature identifying increased EC as a protective factor against adverse long-term outcomes in both primary and secondary prevention, whether higher antecedent EC affects EM after a first MI has not been established.[16] Such results would have important and actionable implications

For editorial comment, see page 125; for related articles, see pages 140 and 149

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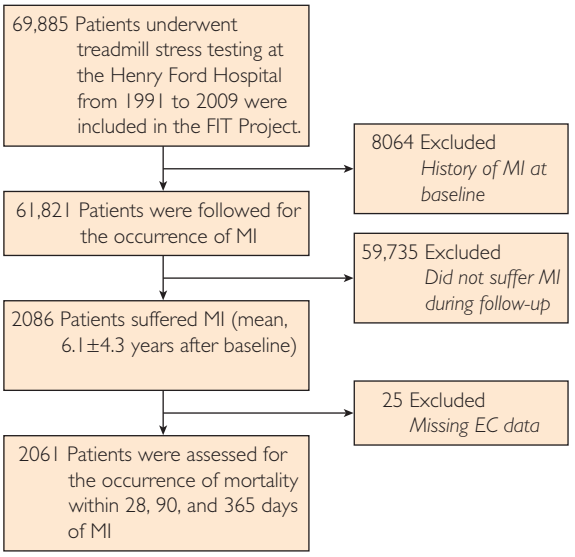

FIGURE 1. Study population selection and timeline. EC = exercise capacity; MI = myocardial infarction.

for recommendations in the primary prevention of cardiovascular death.

Accordingly, we sought to assess the effect of EC on EM after a first MI in a multiethnic cohort of clinically referred patients. We hypothesized that EC, measured remotely before the index MI, would be associated with a lower likelihood of near-term death after MI.

PATIENTS AND METHODS

Study Design

This study was based on data from the Henry Ford Exercise Testing Project (the FIT Project), a retrospective cohort study aimed at investigating the implications of EC on cardiovascular outcomes and total mortality.[17]

The FIT Project population is a registry of 69,885 consecutive patients who underwent physician-referred treadmill exercise testing at the Henry Ford Health System in metropolitan Detroit, Michigan, between 1991 and 2009. Treadmill, medical history, and medication data were collected by clinical exercise physiologists and nurses at the time of testing and entered into a common clinical reporting tool used to generate clinical reports and to directly populate the electronic medical record (EMR). Supporting clinical data and follow-up for cardiovascular outcomes were derived from the EMR and administrative databases shared in common across Henry Ford–affiliated subsidiaries. The FIT Project was approved by the Henry Ford Hospital Institutional Review Board.

In the present study, we included 2086 patients from the FIT Project who had no history of MI at the baseline examination and subsequently suffered a first MI during the follow-up period. Patients missing EC data (n=25) were excluded, leaving 2061 patients for analysis (Figure 1). The mean age at baseline was 62 years and ranged from 18 to 93 years. The mean time from the treadmill exercise test to MI was 6.1±4.3 years in the study population.

EC Testing

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

In accordance with clinical guidelines,[19] treadmill testing was terminated at the discretion of the supervising clinician for reasons that included marked arrhythmias, abnormal hemodynamic responses, diagnostic ST-segment changes, exercise-limiting symptoms such as chest pain or shortness of breath, or the patient's unwillingness or inability to continue. Resting heart rate and blood pressure were measured before exercise testing. The treadmill speed was set initially at 2.7 km/h and then increased to 4.0, 5.4, 6.7, 8.0, and 8.8 km/h at minute 3, 6, 9, 12, and 15, respectively. In the first 3 minutes, the grade was set at 10%, followed by a 2% increase every 3 minutes. The patient exercised for 3 minutes in each stage. If necessary to complete the test, patients were allowed to hold on to the handrail for support and balance. Exercise capacity, expressed in estimated metabolic equivalents (METs), was calculated with the treadmill controller system (Q-Stress, Quinton Instruments) using achieved speed and elevation and was categorized into 4 groups: less

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than 6, 6 to 9, 10 to 11, and 12 or greater METs.

Medical History and Medication Use

A medical history, including age, sex, race, indication for stress test, risk factor burden, existing comorbidities, and active medication use, was obtained by trained nurses and/or clinical exercise physiologists immediately before the exercise test. Race was defined exclusively by self-report. Obesity was defined by self-report and/or assessment by the clinician historian. Smoking was defined as self-reported active smoking at the time of the stress test. Indication for exercise testing was extracted from the test requisition provided by the referring physician and subsequently categorized into common indications.

Scores estimating 10-year risk of all-cause mortality and adverse atherosclerotic cardiovascular disease events were calculated using the FIT treadmill score equation[20] and American College of Cardiology/American Heart Association pooled cohort equations,[21] respectively.

Other risk factors were gathered by self-report at the time of the test and then supplemented and verified by a retrospective search of the EMR and administrative databases. A database-verified diagnosis was considered present when the appropriate *International Classification of Diseases, Ninth Revision* code was present on 3 or more separate encounters in the Henry Ford Health System. Diabetes mellitus, dyslipidemia, and hypertension were defined by either a previous clinical or database-verified diagnosis or use of medications for the respective medical conditions. The baseline use of β-blockers was considered separately from other antihypertensive medications for this analysis.

Established coronary artery disease was defined by baseline history of percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) procedures, or documented obstructive stenosis, as defined by the operating clinician on a previous angiogram. Previous heart failure and atrial fibrillation were defined as a previous clinical diagnosis of systolic or diastolic heart failure or at least paroxysmal atrial fibrillation, respectively. Risk factors were considered absent when they were not reported as present at the time of stress testing or did not meet criteria for a database-verified diagnosis.

Medication use history was gathered by self-report at the time of the stress test and categorized into common indications (eg, antihypertensive and lipid-lowering). In cases of missing data, medication use was supplemented and verified by a retrospective search of the EMR as well as pharmacy claims files from enrollees in the integrated health plan. The use of inhalers was considered to be a marker of chronic lung disease.

Follow-Up and EM Ascertainment

Myocardial infarctions and subsequent revascularizations were ascertained through May 2010 through linkage with administrative claims files from services delivered by the affiliated group practice and/or reimbursed by the health plan. Peri-MI PCI and CABG were defined as administration of each procedure within 28 days of incident MI. Linkage was performed using appropriate *International Classification of Diseases, Ninth Revision* and Current Procedural Terminology codes for MI, PCI, and CABG. To limit bias associated with loss to follow-up, patients were censored for nonmortality outcomes at their last contact with the integrated Henry Ford Health System group practice or when ongoing coverage with the health plan could no longer be confirmed.

In the FIT Project, mortality was ascertained in April 2013[22] via an algorithmic search of the Social Security Death Index Death Master File using social security number, first name, last name, and date of birth data. A complete algorithmic search was possible in more than 99.5% of patients.

For this analysis, EM was defined in separate analyses as all-cause mortality within 28, 90, and 365 days of incident MI.

Statistical Analyses

Baseline categorical and continuous variables were compared between patients surviving and those suffering EM within 28 days of MI by using the chi-square test and analysis of variance, where appropriate. Proportions suffering EM were calculated and displayed graphically across increasing MET groups.

Multivariable logistic regression models were used to estimate the odds ratio (OR) and 95% CI of EM at 28, 90, and 365 days post-MI in separate analyses. Models were adjusted for age at the time of MI, sex, race, and baseline

TABLE 1. Baseline Characteristics of the Study Population Stratified by 28-D Survival Status After MI[a,b]

Variable	Total cohort (N=2061)	No EM (n=1842)	EM (n=219)	*P* value
Demographic data				
Age (y)	62±12	61±12	66±13	<.001
Sex: female	790 (38)	701 (38)	89 (41)	.46
Race: white	1153 (56)	1025 (56)	128 (58)	.72
Medical history				
Obesity[c]	360 (18)	332 (18)	28 (13)	.05
Current smoker	969 (47)	867 (47)	102 (47)	.94
Hypertension	1686 (82)	1490 (81)	196 (90)	.002
Hyperlipidemia	906 (44)	819 (44)	87 (40)	.18
Diabetes mellitus	660 (32)	599 (33)	61 (28)	.17
Stable coronary artery disease	217 (11)	197 (11)	20 (9)	.48
Atrial fibrillation	98 (5)	85 (5)	13 (6)	.39
Aspirin	557 (27)	500 (27)	57 (26)	.73
Antihypertensive medication	1375 (67)	1214 (66)	161 (74)	.02
β-Blocker	569 (28)	499 (27)	70 (32)	.13
Statin	444 (22)	399 (22)	45 (21)	.71
COPD medication	177 (9)	161 (9)	16 (7)	.47
MI characteristics				
Time to MI from baseline (y)	6.1±4.3	6.0±4.3	6.7±4.2	.02
Year of MI				
1997-2001	595 (29)	536 (29)	59 (27)	.78
2002-2006	818 (40)	730 (40)	88 (40)	
2007-2010	648 (31)	576 (31)	72 (33)	
Peri-MI PCI	338 (16)	304 (17)	34 (16)	.71
Peri-MI CABG	111 (5)	104 (6)	7 (3)	.13
Stress test indication				
Evaluate ischemia/risk stratification	842 (41)	760 (41)	82 (37)	.05
Chest pain	858 (42)	776 (42)	82 (37)	
Shortness of breath	247 (12)	216 (12)	31 (14)	
Preoperative	114 (6)	90 (5)	24 (11)	
Stress testing data				
METs achieved	7.0±3.1	7.1±3.1	6.1±3.0	<.001
Distribution of MET categories				
<6	754 (37)	649 (35)	105 (48)	<.001
6-9	673 (33)	601 (33)	72 (33)	
10-11	467 (23)	435 (24)	32 (15)	
≥12	167 (8)	157 (9)	10 (5)	
Risk scores				
ASCVD risk estimation (%)[d]	24±17	23±17	28±18	<.001
FIT treadmill score[e]	−54±76	−51±75	−84±76	<.001

[a]ASCVD = adverse atherosclerotic cardiovascular disease; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; EM = early mortality; MET = metabolic equivalent; MI = myocardial infarction; PCI = percutaneous coronary intervention.

[b]Data are presented as mean ± SD or as No. (percentage).

[c]16 patients missing obesity data.

[d]24 patients missing ASCVD risk estimation data.

[e]363 patients missing FIT treadmill score data.

history of smoking, obesity, hypertension, hyperlipidemia, established history of coronary artery disease, diabetes mellitus, atrial fibrillation, use of aspirin, antihypertensive medications, β-blockers, statins, chronic obstructive pulmonary disease medications, year of MI, and indication for stress testing. Year of MI was included in the models to account for cohort effects and temporal changes in the treatment of MI over the time span of the FIT Project.

Supplemental analyses were performed using multivariable logistic regression models (1) adjusting for attempted peri-MI PCI and

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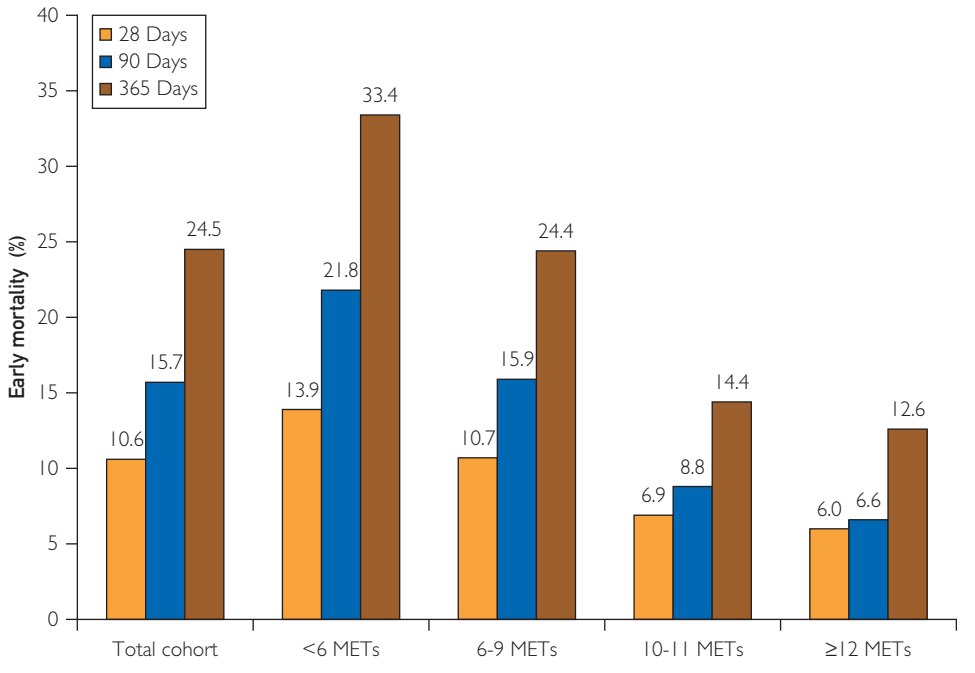

FIGURE 2. Proportion of patients suffering early mortality within 28, 90, and 365 days of myocardial infarction in the total cohort and stratified by exercise capacity category. $P<.001$ for all early mortality time points. MET = metabolic equivalent.

peri-MI CABG as surrogates for MI severity, (2) adjusting for potential interaction of age and EC, (3) excluding patients with a history of stable coronary artery disease, and (4) adjusting for PCI and CABG in the interval between stress test and incident MI.

All statistical analyses were performed using SPSS version 22.0 (IBM Corp). A *P* value less than .05 was considered significant.

An a priori statistical analysis plan was reviewed and approved by an internal FIT Project 4-member committee before analysis. A copy of this plan is available on request.

RESULTS

Baseline Characteristics

The baseline characteristics of the total cohort (n=2061) and those suffering 28-day EM vs MI survivors are described in Table 1. Those who suffered 28-day EM (n=219) were more likely to be older, have lower baseline EC, have less favorable baseline prognostic risk scores, have a history of hypertension or antihypertensive medication use, and have a longer duration of time between the date of the stress test and incident MI ($P<.05$). MI survivors at 28 days were more likely to report a history of obesity ($P<.05$).

EM Risk

The proportion of patients suffering 28-, 90-, and 365-day EM was 10.6%, 15.7%, and 24.5%, respectively. The unadjusted incidence of EM declined consecutively with increasing EC categories at each EM time point (Figure 2).

Odds ratios of EM in each EC category calculated using fully adjusted multiple logistic regression analyses are displayed in Figure 3. At each time point after MI, there were reduced odds of EM with increasing EC categories relative to the least fit EC category ($P<.001$ for trend). Compared with <6 METs, the OR was statistically significant in the 10- to 11-MET group for 28-day EM and in the 10- to 11-MET and ≥12-MET groups for both 90- and 365-day EM. When analyzing EC as a continuous variable, each additional 1-MET increment was associated with an 8% to 10% reduction in risk of EM

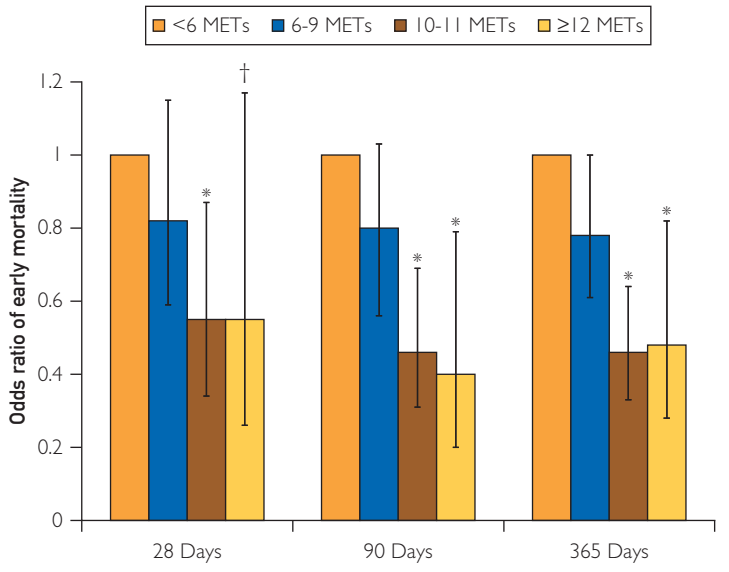

FIGURE 3. Effect of exercise capacity on odds ratio of early mortality within 28, 90, and 365 days of incident myocardial infarction. *$P<.05$. †10 fatal events out of 167 individuals. MET = metabolic equivalent.

across all time points (28 days: OR, 0.92; 95% CI, 0.87-0.98; $P=.006$; 90 days: OR, 0.90; 95% CI, 0.86-0.95; $P<.001$; 365 days: OR, 0.91; 95% CI, 0.87-0.94; $P<.001$).

Table 2 depicts ORs (95% CIs) for all statistically significant predictors of 28-, 90-, and 365-day EM in the fully adjusted models. Covariates not reaching statistical significance are listed in the table footnote. Significant non–fitness-related predictors of 28-day EM included age at MI and history of hypertension. Predictors of 90-day EM included age at MI. Predictors of 365-day EM included age at MI, history of antihypertensive medication use, and an inverse association with a history of statin use.

Supplemental Analyses

Supplemental analyses were conducted (1) adjusting for attempted peri-MI PCI and peri-MI CABG as surrogates for MI severity, (2) adjusting for potential interaction of age and EC, (3) excluding patients with a history of coronary artery disease, and (4) adjusting for PCI and CABG in the interval between stress test and incident MI, with results described in Supplemental Tables 1 to 4, respectively (available online at http://www.mayoclinicproceedings.org). These analyses yielded no major differences from our main results in the association between EC and EM, and overall conclusions remained unchanged.

DISCUSSION

In this multiethnic population of patients who were clinically referred for treadmill exercise testing, higher levels of baseline EC measured approximately 6 years before MI were independently associated with a lower risk of EM after a first MI, confirming our research hypothesis. This protective effect was present at 28 days and was further observed to persist at 365 days after a first MI. Each 1-MET increment in EC was associated with an 8% to 10% reduction in risk of EM after a first MI. To our knowledge, this is the first study to assess the effect of objectively measured antecedent EC on EM after a first MI. These findings suggest that high EC should be promoted as an important protective factor against the incidence of EM after a first MI.

Multiple mechanisms have been proposed to elucidate the protective effect of higher EC and physical activity on adverse outcomes. Several studies have found high levels of physical activity and EC to be associated with improved cardiovascular risk markers including favorable lipid profiles and lower body weight, blood pressure, insulin resistance, systemic inflammation, autonomic dysfunction, thrombogenic factors, and measures of atherosclerotic burden.[9,11,23,24]

Proposed protective molecular mechanisms include induction of myocardial heat shock proteins, increased myocardial cyclooxygenase 2 activity, elevated endoplasmic reticulum stress proteins, increased nitric oxide production, improved function of mitochondrial and/or sarcolemmal adenosine triphosphate–sensitive potassium channels, and increased myocardial antioxidant capacity.[25,26] These exercise-induced factors have been found in animal and human models to mediate adverse outcomes including myocardial stunning, infarction, and cardiac arrhythmias in response to myocardial ischemia and reperfusion injury.[25-27]

EC and EM Post-MI

Strengths of our study include the objective estimate of antecedent EC, a large number of MI episodes during follow-up, with ascertainment

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of subsequent mortality in all patients suffering from MI and comprehensive adjustment for pertinent risk factors. Previous studies analyzing the effect of EC on fatal cardiovascular outcomes use heterogeneous methods for ascertaining and categorizing EC and were largely targeted toward long-term outcomes. In addition, the populations previously studied reflect varying degrees of comorbidity burden and severity, which further limits comparison with the results of the present study. Nonetheless, our findings are similar to those of the previous literature citing all-cause mortality risk reductions per 1-MET increment in EC ranging from 9% to 26% in high-risk populations with advanced age,[28,29] hypertension,[7,30-32] dyslipidemia,[6] diabetes,[33,34] and established cardiovascular disease.[35,36]

We observed mostly consistent results indicating that higher levels of EC were independently associated with a lower risk of EM after a first MI in fully adjusted models. However, in the 28-day EM model, EC in the highest categorical group (≥12 METs) did not reach statistical significance as a predictor of mortality. This was likely due to the low number of patients in this EC category (n=167) and the relatively low number of fatal outcomes in this group (n=10). Extending EM to include fatal outcomes within 90 and 365 days of MI captured more fatal events and provided additional power to our analyses, yielding statistically significant results in the highest EC category.

Graded risk reductions in EM after a first MI were observed in higher EC groups in the 28- and 90-day analyses. Notably, the highest differences in relative and absolute EM risks were observed in those with lower levels of EC (<12 METs), a phenomenon observed in previous studies assessing long-term outcomes.[33,37,38] Our results indicate that individuals with the lowest EC may stand to benefit greatly from modest increases in EC, which may be achievable with increased physical activity and structured exercise training.[39,40] There was attenuation of the incremental benefit in mortality risk, increasing from the 10- to 11-METs group to the 12 or greater-METs EC group in the 365-day model. This finding in the extended EM time frame likely reflects attenuation by competing risks rather than a threshold effect in the benefits of EC.[41]

TABLE 2. ORs (95% CIs) for Significant Early Mortality Predictors Within 28, 90, and 365 Days of MI in the Fully Adjusted Models[a,b]

Covariate	OR (95% CI)		
	28 d	90 d	365 d
Age at MI (per year)	1.03 (1.01-1.04)[c]	1.03 (1.02-1.04)[c]	1.03 (1.02-1.04)[c]
History of			
Hypertension	1.83 (1.05-3.22)[c]	1.32 (0.81-2.14)	1.12 (0.75-1.69)
Antihypertensive medication	0.97 (0.63-1.48)	1.29 (0.86-1.89)	1.45 (1.04-2.03)[c]
Statin medication	0.94 (0.65-1.36)	0.74 (0.53-1.03)	0.65 (0.49-0.86)[c]
MET category (reference <6)			
6-9	0.82 (0.59-1.15)	0.80 (0.60-1.06)	0.78 (0.61-1.00)
10-11	0.55 (0.35-0.87)[c]	0.46 (0.31-0.68)[c]	0.46 (0.33-0.64)[c]
≥12	0.55 (0.26-1.16)	0.40 (0.20-0.80)[c]	0.48 (0.28-0.82)[c]
METs achieved (continuous)	0.92 (0.87-0.98)[c]	0.90 (0.86-0.95)[c]	0.91 (0.87-0.94)[c]

[a]Covariates included in the model not reaching statistical significance: sex, race, and stress test indication; baseline smoking status, history of coronary artery disease, diabetes, obesity, and atrial fibrillation; baseline use of aspirin, β-blockers, and chronic obstructive pulmonary disease medication; year of MI.

[b]MET = metabolic equivalent; MI = myocardial infarction; OR = odds ratio.

[c]$P<.05$.

Predictors of EM

Although EC was a powerful predictor of EM, several other factors substantially affected EM risk (Table 2). Age at the time of incident MI is a well-established negative prognostic indicator, which was confirmed by our findings of consistently increased EM risk up to 365 days post-MI. Baseline history of hypertension was a significant predictor of 28-day EM (OR, 1.83; 95% CI, 1.05-3.22), though there was a loss of statistical significance in extended EM analyses. This finding is consistent with previous studies identifying antecedent hypertension as a strong independent predictor of adverse outcomes shortly after acute MI, including heart failure, stroke, cardiac arrest, and cardiovascular and all-cause mortality.[42-44] Although hypertension appears to be a potent prognostic factor in the setting of acute myocardial injury, EC emerged as a progressively influential predictor of EM in the extended time periods.

Clinical Implications

The findings of the present study indicate that low EC may contribute more to risk of EM after a first MI than do other traditionally assessed cardiovascular risk factors such as

sex, smoking status, hypertension, hyperlipidemia, diabetes, and obesity.[45] In addition, risk reductions in EM were most pronounced with increases in EC to greater than 9 METs, suggesting that those with a relatively low EC may stand to benefit most from EC improvement. Fortunately, EC is amenable to clinically meaningful improvement, and we encourage clinicians to routinely counsel their patients to engage in regular moderate (ie, ≥150 min/wk) to vigorous (ie, ≥75 min/wk) intensity physical activity.[40,45]

Increases in EC up to 16% with moderate-intensity exercise training and up to 46% with high-intensity exercise training have been observed with the most pronounced improvements seen in relatively sedentary individuals.[23,39,46-49] Correspondingly, the results of the present study may inform comprehensive treatment approaches for primary prevention in high-risk populations by emphasizing the multifaceted benefits of improved EC, both in preventing incidence of MI and in guarding against subsequent fatal outcomes.

Study Limitations

The present study has several limitations. The study population was assessed at a single geographic region and included only those who could undergo maximal treadmill exercise stress testing, leading to potential selection bias. In addition, precise intensities of exposures for certain variables could not be ascertained, because our data did not include medication use duration or dosage.

Certain aspects of our exercise testing methodology may have led to overestimation of EC. Patients were able to use a handrail for support and balance during testing, which may have caused discrepancies between predicted and true EC.[50] In addition, EC estimation from achieved speed and elevation after the Bruce protocol may overestimate EC.[50-52] Although handrail use has been found to affect testing performance, this is a practice that is common to many laboratories outside of controlled research settings; thus, our results may be more generally applicable to data ascertained in the typical clinical setting. In addition, the uniformity of potential error associated with assessment methodology would be unlikely to have affected our results, which persistently indicate relative risk reductions across categories of EC.

Given recognized reductions in EC with increasing age,[53] the prognostic value of estimated EC may reasonably vary according to age; however, formal interactions between age and the prognostic value of EC have not been conclusively described. Various age-adjusted reference standards for EC have been developed to guide prognostic interpretation of EC data,[54-56] though the cohorts from which these standards were derived vary in demographic characteristics and clinical settings, limiting application to the current diverse and clinically referred cohort. Accordingly, we chose to report categories of absolute METs with additional adjustment for the interaction of age and EC, to allow for comparison to the previous literature with similarly derived cut points, and to facilitate interpretation in the common clinical setting.

Our results cannot be exclusively interpreted as the effect of previous exercise on EC and EM after MI, and data on physical activity were not available to include in our analysis. Protection may indeed be mediated by physiological adaptations to exercise training, which are reasonably presumed to increase objective fitness levels; however, up to 49% of the variance in this adaptive response may be significantly altered by genetic factors or other unaccounted for variables independent of an individual's history of physical activity and exercise.[57]

MI occurred, on average, approximately 6 years after exercise stress testing. This fact may limit the clinical application of our results, given the potential for significant improvement or reduction in EC during this time interval. Importantly, however, interval changes in EC toward the mean (less fit patients becoming more fit or more fit patients becoming less fit) would bias toward the null hypothesis. To address this potential limitation, we conducted additional sensitivity analyses excluding patients with an interval of more than 3 years between stress test and MI. These analyses again revealed a statistically significant and even more powerful negative association between EC and EM. Accordingly, our results indicate that EC ascertained by routine clinically referred exercise stress testing yields clinically

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meaningful and actionable prognostic information, as remotely as 6 years antecedent to incident MI, whereas more proximally ascertained EC data, when available, may further characterize EM risk status.

In our study, incident MI was identified, according to the review of administrative claims files, from services delivered by the affiliated group practice and/or reimbursed by the health plan. Data allowing further characterization of MI according to consensus definition, etiology, size, anatomy, or clinical severity were not available. In designing our analyses, we sought to assess whether the protective effects associated with high EC were mediated by reduced severity of MI versus improved resilience to the myocardial injury or arrhythmia after MI. However, in the absence of precise clinical data characterizing MI severity (ie, serum cardiac troponin curves, time from chest pain to acute presentation, or exact cardiac catheterization results), this distinction could not be evaluated with certainty.

In our analysis, we adjusted for peri-MI revascularization decisions (subsequent peri-MI medical therapy vs PCI vs CABG) as a surrogate for severity in our sensitivity analysis without change in our results, perhaps suggesting improved physiologic reserve in the setting of acute myocardial injury. However, given the inherent limitations of our data, we suggest future research seek to more directly elucidate the relationship between EC, MI severity versus resilience to myocardial injury, and the effect of these on EM.

CONCLUSION

We conclude that high baseline EC was independently associated with a significantly decreased risk of mortality at 28, 90, and 365 days after a first MI in this multiethnic cohort of patients clinically referred for antecedent stress testing. These data lend further evidence to the strategy that clinicians promote adequate physical activity as a means to improve EC in their high-risk patients and as an important protective factor against both the incidence of MI and survival after a first MI episode.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CABG** = coronary artery bypass graft; **EC** = exercise capacity; **EM** = early mortality; **EMR** = electronic medical record; **MET** = metabolic equivalent; **MI** = myocardial infarction; **OR** = odds ratio; **PCI** = percutaneous coronary intervention

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