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Long-Term Mortality Risk According to Cardiorespiratory Fitness in Patients Undergoing Coronary Artery Bypass Graft Surgery

Gregory Trachiotis MD[1,2*]

[1]Division of Cardiothoracic Surgery and Heart Center, Washington DC Veterans Affairs Medical Center, Washington DC, USA
[2]Division of Cardiothoracic Surgery, The George Washington University Medical Center, Washington DC, USA

***Correspondence:** Gregory Trachiotis MD, Chief, Division of Cardiothoracic Surgery and Heart Center, Washington DC Veterans Affairs Medical Center, 50 Irving St NW, Washington DC 20422

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Key words: CABG, cardiorespiratory fitness, coronary artery disease

1. Abstract:

Objective: To evaluate the association between cardiorespiratory fitness (CRF) and long-term survival in United States (US) Veterans undergoing CABG.

Methods: We identified 14,550 US Veterans who underwent CABG at least six months after completing a symptom-limited exercise treadmill test (ETT) with no evidence of cardiovascular disease. During a mean follow-up period of 10.0 ±5.4 years, 6,502 (43.0%) died. To assess the association between CRF and risk of mortality, we formed the following five fitness categories based on peak workload achieved (metabolic equivalents; METs) prior to CABG: Least-Fit: 4.3±1.0 METs (n=4,722); Low-Fit: 6.8±0.9 METs (n=3,788), Moderate-Fit: 8.3±1.1 METs (n=2,608), Fit: 10.2±0.8 METs (n=2,613) and High-Fit: 13.0±1.5 METs (n=819). Cox proportional hazard models were used to calculate risk across CRF categories. Models were adjusted for age, body mass index, race, cardiovascular disease, percutaneous coronary intervention prior to ETT, cardiovascular medications, and cardiovascular disease risk factors. P-values <0.05 using two sided tests were considered statistically significant.

Results: The association between cardiorespiratory fitness and mortality was inverse and graded. For every 1-MET increase in exercise capacity the mortality risk was 11% lower (HR=0.89; CI: 0.88-0.90; p<0.001). When compared to the Least-Fit category (referent), mortality risk was 22% lower in Low-fit individuals (HR=0.78; CI: 0.73-0.82; p<0.001), 31% lower in Moderate -Fit (HR=0.69; CI: 0.64-0.74; p<0.001), 52% lower in Fit (HR=0.48; CI: 0.44-0.52; p<0.001), and 66% lower in High-Fit individuals (HR=0.34; CI: 0.29-0.40; p<0.001).

Conclusions: Cardiorespiratory fitness is inversely and independently associated with long-term mortality after CABG in Veterans referred for exercise testing.

Central Message: In this retrospective cohort study of 14,550 Veterans, the association between pre-operative cardiorespiratory fitness and mortality was inverse and

graded. For every 1-MET increase in exercise capacity, mortality risk was 11% lower. Long term mortality risk was 67% lower for the most fit individuals in comparison to the least fit.

2. Introduction

Coronary artery disease (CAD) is the leading cause of death in the United States (US) and represents a tremendous burden to the US healthcare system [1]. The quantity of years of life lost due to premature mortality from CAD is greater than the sum of lung cancer, colon cancer, breast cancer, and prostate cancer [2]. The incidence of CAD and death from CAD are expected to continue to rise in the coming decades [3]. For many patients, coronary artery bypass grafting (CABG) provides long term survival benefits far in excess of what is achievable via medical management or percutaneous intervention [4, 5]. Tremendous progress has been made in the medical and surgical management of CAD over the past several decades leading to excellent short-term and long-term mortality after CABG. Risk factors associated with 30-day mortality after CABG have been well studied and accurately modeled in the Society of Thoracic Surgeons (STS) Risk Calculator, however patient factors associated with long-term mortality have not been as well defined [6-8]. Though many comorbidities such as chronic kidney disease, diabetes mellitus, obesity, and smoking have been investigated as risk factors for late mortality after CABG, pre-operative cardiorespiratory fitness (CRF) has not been adequately studied [9, 10].

Cardiorespiratory fitness is widely recognized as a powerful predictor of all-cause mortality in patients with and without cardiovascular disease (CVD) [11,12]. CRF has also been noted to have an inverse and graded association with the development of many adverse health conditions, including CAD, CVD events including myocardial infarction, and heart failure [11, 13-17]. A study using the STS database found a significant association between low fitness and 30-day mortality after CABG, however the association between CRF and long-term outcomes after CABG has not been inadequately studied [18]. To date, the only study to investigate the relationship between CRF and survival after CABG relied on patient reports of physical activity to estimate fitness levels, and did not include direct objective measures of CRF such as treadmill exercise tolerance testing [19].

The demonstration of an inverse relationship between CRF and long-term mortality after CABG would provide clinicians with more evidence to promote exercise and physical fitness to their patients and to the public. Considering the immense impact of CAD on the health of the US population, as well as the tremendous health expenditures associated with CAD treatment including revascularization, illuminating the relationship between CRF and survival after CABG would provide additional prognostic information about long-term risk and benefit of CABG, thereby assisting patients, surgeons, and other clinicians in shared decision-making regarding optimal management of CAD. The aim of the present study was to investigate the association between pre-operative CRF and long-term survival in United States Veterans undergoing CABG.

3. Methods

3.1 Study Population

The cohort was derived from the Exercise Testing and Health Outcomes Study (ETHOS) based at the Veterans Affairs Medical Center in Washington DC (DCVAMC). The ETHOS study was initiated in April of 2016 and evolved as data mining tools became available and more powerful. The main aim of the study was to investigate associations between CRF and health outcomes. Accordingly, any clinical assessments and data we extracted before the study initiation date will be considered retrospective, while data captured post the study initiation date would be considered prospective. We identified 822,995 US Veterans who underwent an ETT performed within Veterans Affairs hospitals across the USA between October 1, 1999, to September 3, 2020, using the Bruce protocol. The reason for referral for ETT is not known. The goals of ETT with the Bruce protocol are not to determine the presence or absence of cardiac ischemia but rather to quantify aerobic capacity. Exercise tolerance testing is terminated at the development of signs or symptoms of cardiac ischemia; any such test would be considered incomplete and was not included in our study. Figure 1 illustrates how the study population was selected. We excluded 72,693 subjects who met the following criteria: 1) individuals <30 years of age at the time of the ETT (n=1,962); 2) individuals who did not achieve a maximal effort, (ETT was deemed incomplete as stated in the medical notes), achieved <2.0 METs, (n=24,014), or MET values that exceeded physiologic criteria (n=18,641); 3) those with body mass index (BMI) <18.5 g/m^2; or missing BMI (n=5,587); and 4) those with a follow-up period <6 months (n=5,701). To lower the likelihood of including individuals with overt heart disease, we also excluded those who met the following conditions within 6 months post-ETT: 1) those who underwent coronary artery bypass grafting (CABG; n=2,296); 2) percutaneous coronary

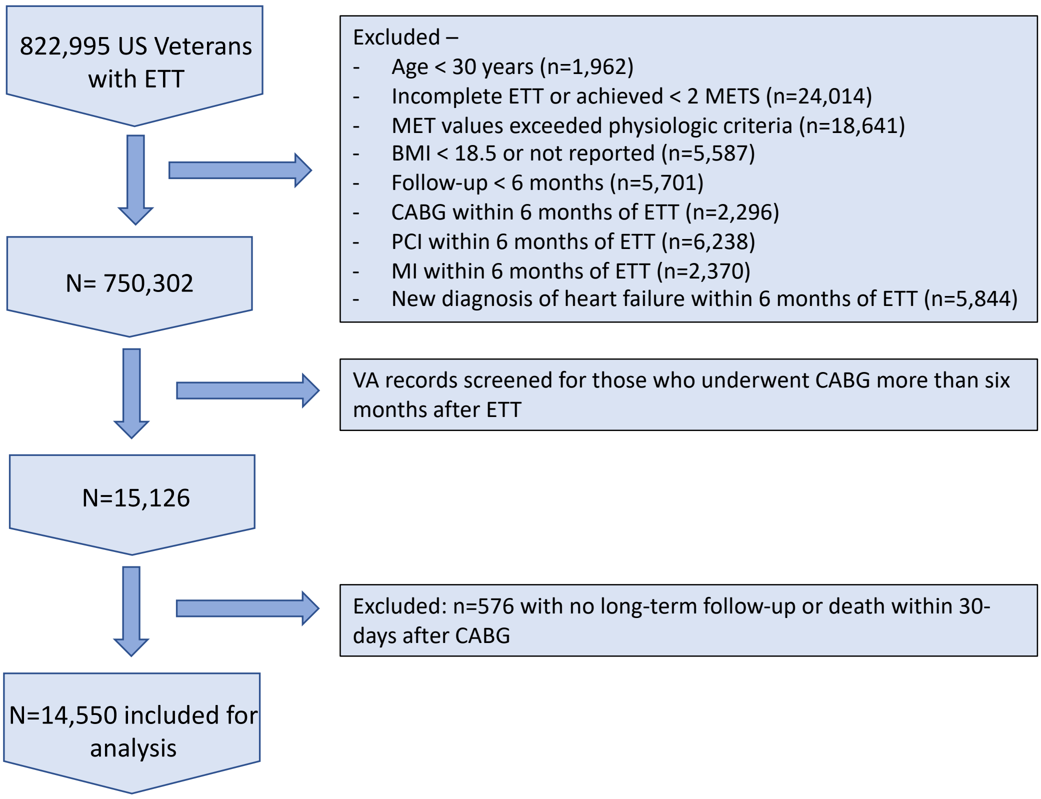


Figure 1: Flow chart of study population selection with exclusion criteria. US = United States; ETT = Exercise Tolerance Test; METS = Metabolic Equivalents; BMI = Body Mass Index; CABG = Coronary Artery Bypass Grafting; PCI = Percutaneous Coronary Intervention; MI = Myocardial Infarction; VA = Veterans Affairs;

intervention (PCI; n=6,238); 3) myocardial infarction (MI; n=2,370) or a diagnosis of chronic heart failure (CHF; n=5,884). After these exclusions, the final cohort consisted of 750,302 subjects (705,163 men and 45,139 women). Of those, 552,922 (73.7%) were white, 142,798 (19.0%) African-American, 35,197 (4.7%) Hispanic, 16,050 (2.1%) Native-American, Asian, or Hawaiian, and 3,335 (0.4%) declined to report. This study was conducted under the supervision of the Washington DC Veterans Affairs Medical Center IRB, IRBNet ID 1584919-3, initially approved 12/2/2011.

Detailed information on relevant demographic, clinical and medication information, risk factors and co-morbidities as defined by ICD9 and ICD10 coding, with at least two recordings at least 6 months apart, were obtained for all participants from the VA Computerized Patient Record System at the time of the ETT. The VA records have high sensitivity for incidence of chronic conditions [20, 21]. Historical information included onset of previous myocardial infarction, cardiac procedures, heart failure, hypertension, diabetes mellitus, hypercholesterolemia, cancer (all), renal disease, stroke, smoking status (current and past), aspirin and use of cardiac/antihypertensive medications. Data and analyses are presented in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies [22].

3.2 MET Extraction

We randomly selected 3,000 samples of physician clinical notes on exercise capacity from the dataset and identified METs manually. This annotated dataset was further preprocessed and then used to train Natural Language Processing models. In the preprocessing phase, we removed special characters ($, &, etc.) and restricted the note to 30 characters before and after the words METs or MET. These words were then replaced with a special character to identify their location within the notes. Spacy software was then used to convert the resulting string into word tokens and then to vector of numbers. The corresponding labels were created such that 1 meant that the corresponding token contained the MET value and 0 if it did not. We used a two-layer convolutional neural network using the Tensorflow software library to predict the probable location of METs in the note. The model was trained over 100 epochs. Once METs were extracted the MET data were randomly and manually checked for errors. The model accuracy on the test dataset was 97%.

3.3 CABG and Mortality

Participants were cross-referenced with the VA Informatics and Computing Infrastructure (VINCI) database for incidence of CABG using standard CPT codes. Patients who underwent CABG less than six months after ETT were excluded to further ensure all ETTs were limited by exercise capacity and not by cardiac ischemia. We identified 15,126 patients who underwent CABG. 576 (3.8%) did not have long-term follow-up data available and were excluded from survival analysis. Patients who died in the perioperative period, defined as within 30-days of surgery, were excluded from long-term mortality analysis. We identified 6502 patients who died in the follow-up period, representing 43.0% of the total cohort. Date of death was determined via the VINCI database, which is linked with Veterans Health Administration vital status files, Social Security Administration, Center for Medicare and Medicaid Services, and the National Cemetery Administration. Follow-up was completed through September 30, 2021, and is reported as mean +/- standard deviation, determined from the date of ETT to date of death or last reported medical visit.

3.4 CRF Categories

Peak MET levels were calculated for each participant by standardized American College of Sports Medicine equations based on treadmill speed and grade [23]. To determine the age-specific CRF categories, we stratified the cohort into five age groups (30-49, 50-59, 60-69, 70-79, and 80-95 years) and established five CRF categories within each age group using methods described in our previous work [24]. We identified subjects with exercise performance less than 20%, 21-40%, 41-60%, 61-80%, and greater than 80% of predicted CRF within their respective age group. The following five fitness quintiles were formed: Least-Fit: 4.3±1.0 METs (n=4,722); Low-Fit: 6.8±0.9 METs (n=3,788), Moderate-Fit: 8.3±1.1 METs (n=2,608), Fit: 10.2±0.8 METs (n=2,613) and High-Fit: 13.0±1.5 METs (n=819).

Cox proportional hazard models were used to calculate mortality risk for each CRF category. The models were adjusted for age, body mass index, race, cardiovascular disease including stroke and peripheral vascular disease, percutaneous transluminal coronary angioplasty prior to ETT, cardiovascular medications, time from ETT to CABG, and cardiovascular disease risk factors including hypertension, diabetes, chronic kidney disease, smoking, and dyslipidemia. Using the least-fit group as a reference, relative risk of mortality was assessed across the five CRF categories. Comparisons between categorical variables were evaluated by chi-squared test and continuous variables were assessed with one-way ANOVA tests. All statistical analyses were performed using SPSS software version 26 (IBM SPSS Statistics for Windows, Version 26; IBM Corp, Armonk, NY).

4. Results

Clinical and demographic data at the time of ETT are presented in Table 1. Patients in the lower CRF quintiles tended to be older, have higher body weight and body mass index (BMI), and more frequently had chronic medical conditions such as diabetes mellitus, hypertension, and chronic kidney disease. The amount of time from ETT to

Table 1: Clinical and Demographic Patient Characteristics at the Time of Exercise Tolerance Test by Fitness Group.

Patient Characteristic	Least Fit (n=4722)	Low Fit (n=3788)	Moderate Fit (n=2608)	Fit (n=2613)	High Fit (n=819)	Significance (p-value)
Age at ETT (years)	64.2 ± 8.2	63.3 ± 8.2	65.0 ± 9.0	62.0 ± 7.2	62.5 ± 8.5	< 0.001
BMI (kg/m^2)	30.6 ± 5.7	30.2 ± 5.1	29.4 ± 4.5	29.0 ± 4.3	27.9 ± 4.0	< 0.001
Bodyweight (kg)	95.7 ± 19.3	94.5 ± 17.9	91.7 ± 15.9	90.4 ± 15.2	86.4 ± 14.0	< 0.001
Atrial Fibrillation or Flutter	464 (9.8%)	248 (6.5%)	179 (6.9%)	123 (4.7%)	29 (3.5%)	<0.001
Chronic Kidney Disease	691 (14.6%	368 (9.7%)	222 (8.5%)	164 (6.3%	29 (3.5%)	<0.001
Diabetes Mellitus	1810 (38.3%)	1158 (30.6%)	663 (25.4%)	477 (18.3%	100 (12.2%)	<0.001
Cardiac / Hypertension Medications	4171 (88.3%)	3181 (84.0%)	2161 (82.9%)	1968 (75.3%)	562 (68.6%)	<0.001
CVD including CAD	2878 (60.9%)	2117 (55.9%)	1401 (53.7%)	1267 (48.5%)	349 (42.6%)	<0.001
Smoking	1386 (29.4%)	959 (25.3%	516 (19.8%	629 (24.1%)	176 (21.5%)	< 0.001
History of Stroke	69 (1.5%)	28 (0.7%)	28 (1.1%)	10 (0.4%)	5 (0.6%)	<0.001
Hypertension	3960 (83.9%)	2989 (78.9%)	2032 (77.9%)	1866 (71.4%)	514 (62.8%)	<0.001
Statin Use	2948 (36.6%)	2125 (56.1%)	1360 (52.1%)	1253 (48.0%)	361 (44.1%%)	< 0.001
ETT = Exercise Tolerance Test; BMI = Body Mass Index; CVD = Cardiovascular Disease; CAD = Coronary Artery Disease						

CABG differed slightly among the CRF quintiles: Least Fit 4.7 ± 3.6 years, Low Fit 5.2 ± 3.5 years, Moderate Fit 5.4 ± 3.6 years, Fit 5.4 ± 3.5 years, High Fit 5.9 ± 3.6 years. The mean follow-up time after CABG was 10.0 ± 5.4 years.

Patient factors that had a significant association with mortality risk after CABG are presented in Table 3. Notably, patient characteristics associated with improved survival included history of PCI (HR 0.83, 95% confidence interval 0.75-0.93, p=0.001), and statin use at the time of ETT (HR 0.93, 95% confidence interval 0.89-0.99, p=0.012).

The association between CRF and mortality after CABG was inverse and graded. There was improved survival with increased CRF across the spectrum of fitness levels. Each 1-MET increase in CRF was associated with an 11% lower mortality risk. Hazard ratios for mortality for each of the five fitness categories are presented in Table 2. Hazard ratios were similar for patients who had a prior diagnosis of cardiovascular disease in comparison to those who did not. Time from CABG to death varied significantly between CRF quintiles: Least Fit 7.1 ± 4.2 years, Low Fit 7.8 ± 4.1 years, Moderate Fit 8.0 ± 4.2 years, Fit 8.6 ± 3.9 years, High Fit 9.1 ± 3.9 years. The cumulative hazard for mortality risk across CRF categories are illustrated by survival curves in Figure 2.

Table 2: Mortality Risk According to Cardiorespiratory Fitness Quintile.

Cardiorespiratory Fitness Quintile	Hazard Ratio	95% Confidence Interval	P-value
Entire Cohort (n = 14,550)			
Least Fit (referent)	1.00	--	--
Low Fit	0.76	0.72-0.81	<0.001
Moderate Fit	0.66	0.62-0.71	<0.001
Fit	0.47	0.44-0.51	<0.001
High Fit	0.33	0.29 – 0.38	<0.001
No Known CVD (n = 6,538)			
Least Fit (referent)	1.00	--	--
Low Fit	0.76	0.69-0.83	<0.001
Moderate Fit	0.63	0.56-0.7	<0.001
Fit	0.45	0.40-0.51	<0.001
High Fit	0.33	0.27-0.41	<0.001
Known CVD (n = 8,012)			
Least Fit (referent)	1.00	--	--
Low Fit	0.77	0.71-0.82	<0.001
Moderate Fit	0.69	0.63-0.75	<0.001
Fit	0.49	0.45-0.54	<0.001
High Fit	0.34	0.28-0.41	<0.001
ETT = Exercise Tolerance Testing			

Table 3: Notable Clinical and Demographic Variables and Their Association with Long-Term Mortality after CABG.

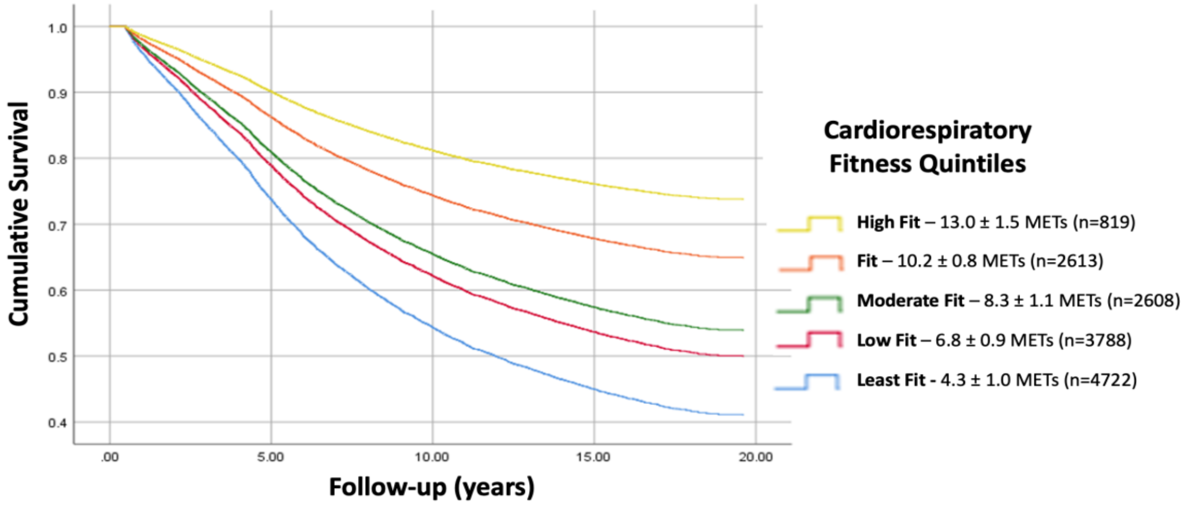
Patient Characteristic	Hazard Ratio	95% Confidence Interval	P-value
Atrial Fibrillation or Flutter	1.60	1.52-1.69	<0.001
Chronic Kidney Disease	1.53	1.42 - 1.64	<0.001
Diabetes Mellitus	1.44	1.37 - 1.52	<0.001
Cardiac / Hypertension Medications	1.27	1.16 - 1.39	<0.001
CVD including CAD	1.21	1.15 - 1.27	<0.001
Smoking	1.14	1.08 - 1.21	<0.001
History of Stroke	1.14	0.92 -1.42	0.243
Age	1.04	1.04 - 1.05	<0.001
Hypertension	1.03	0.95 - 1.10	0.519
BMI	0.97	0.97 - 0.98	<0.001
Statin Use	0.93	0.89 - 0.99	0.012
History of PCI	0.83	0.75 - 0.93	0.001
CABG = Coronary Artery Bypass Graft; CVD = Cardiovascular Disease; CAD = Coronary Artery Disease' BMI = Body Mass Index			

5. Discussion

Cardiorespiratory fitness has long been established as a significant factor influencing all-cause mortality, the development of CAD, and the incidence of CVD events such as MI. The major new finding in the present study is the graded inverse relationship between fitness and long-term mortality after CABG. This is the first study to assess the relationship between directly measured CRF and long-term survival after CABG.

These data demonstrate increased survival with higher fitness across the spectrum of fitness levels. The long-term mortality difference between the least fit and low fit groups, for instance, is similar to the long-term mortality difference between fit and high fit groups. Every 1-MET increase in exercise capacity decreased the mortality risk by 11% (HR=0.89; CI:0.88-0.90; p<0.001). This finding suggests that even slight improvements in CRF, regardless of baseline fitness level, could potentially lead to improved long-term outcomes after CABG. There is a significant survival advantage for a relatively modest CRF level that most adults can likely attain by adhering to national physical activity guidelines [25, 26].

It has been debated in the literature whether it is the amount of physical activity or the resultant increased aerobic power capacity that is protective against the development of cardiovascular disease [27]. Moderate to high levels of physical activity and physical fitness both produce long-term health benefits [28]. To date, national guidelines on the role of exercise in the prevention of CVD limit their recommendations to physical activity duration and



	Number at Risk				
Least Fit (referent)	4722	3218	1040	220	6
Low Fit	3788	2904	1022	240	22
Moderate Fit	2608	2008	730	150	0
Fit	2613	2242	804	195	13
High Fit	819	746	281	75	0

Figure 2: The cumulative hazard for mortality risk across CRF categories are illustrated by survival curves. At the mean follow-up, ten years after surgery, more than 80% of High-Fit patients are alive compared to approximately 55% of patients in the Least-Fit category. CABG = Coronary Artery Bypass Grafting.

intensity, with little mention of specific performance goals or parameters [25, 26]. Our study does not include any data points on patient's physical activity patterns, a notable limitation. However, our findings demonstrate a durable survival advantage for high level of fitness at a single point in time years prior to the need for surgical revascularization.

It has been noted in some studies and suggested by some authors that high amounts of strenuous physical activity and resultant high level of CRF can be detrimental to cardiovascular health [29, 30]. In the present study the highest quintile of CRF was associated with the lowest long-term mortality after surgery. Our data therefore do not support an upper limit of benefit for increased cardiorespiratory fitness.

Recently, Smenes and the other investigators in the HUNT study demonstrated an inverse and graded relationship between physical activity and survival after CABG similar to our own findings, noting a mortality improvement of 15% for each one MET increase in estimated CRF [19]. An important distinction between this study and our own is the manner in which CRF was determined. In the present study CRF was objectively measured via exercise tolerance testing, whereas Smenes et al estimated CRF based primarily upon the number of hours patients reported performing light and high intensity physical exercise on a weekly basis. It may therefore be appropriate to understand the HUNT study as an analysis of physical activity, and the current study as an analysis of CRF. As noted, both studies demonstrated improved survival after CABG.

Smith et al recently demonstrated improved short-term survival after CABG in a high-fit group in comparison to a low-fit group using outcome data from the STS database [18]. Similar to our own study, these investigators used a measured CRF level attained via maximum capacity exercise tolerance testing on a treadmill. Unlike our own study, follow-up was limited to perioperative and 30-day outcomes, and the sample size only allowed for stratification into two groups. Taken together, these studies suggest that CRF is independently associated with improved short and long-term survival after CABG.

It is important to note that while participants whose ETT was limited by angina or had EKG evidence of ischemia during ETT were excluded from our study, 55% of the patients in our cohort (8019/14550) had an established diagnosis of CVD and 5.9% (862/14550) had undergone previous PCI. It is well established that aerobic exercise is beneficial after diagnosis of CAD and after a CAD event such as MI, and participation in structured cardiac rehabilitation is strongly supported by national guidelines [31-34]. Our data add additional support to the benefit of CRF for CVD patients as well as patients who are free of CVD. The strong relationship between CRF and survival suggests a potential mortality benefit of an exercise program aimed at increasing CRF. Such a program would best be prescribed by an exercise physiologist and supervised and encouraged by a primary care physician or preventative cardiologist. It is not currently the authors' practice to prescribe exercise regimens or make routine referrals to an exercise physiologist for patients referred for CABG.

Age is an important covariate to consider in any study investigating mortality as an end-point. In the present study, the Least-fit individuals were approximate 2 years older than the younger group (Fit), however they were approximately one year younger than the oldest group in our cohort (Moderate-fit), who had a 31% lower risk of mortality in comparison to least fit. The models were adjusted for age in addition to other covariates. Thus, it is unlikely that 1 to 2 years of age difference across the CRF groups will be responsible for the graded decline in risk.

6. Limitations

This study has several notable limitations. First the conclusions of this study may not be applicable to the general population since the study population is limited to primarily male Veterans. It has been demonstrated that the progression of CAD and the factors influencing outcomes after CABG differ between men and women [4, 35]. Secondly, the association between fitness and survival, while compelling, does not indicate causality. Third, since this study includes only a single exercise tolerance test for each subject, we cannot conclude that an intervention to increased CRF such as an exercise program would necessarily lead to changes in survival after CABG. Fourth, we have no data on the physical activity of our subjects. Neither do we have data on the development of chronic medical conditions after exercise testing. Lastly, the cause of death of our subjects is not known, so it is not possible to delineate cardiac versus noncardiac death.

7. Strengths

This study has several notable strengths. With over 14,000 patients included in the study, the sample size is quite large in comparison to other studies of fitness and outcomes after CABG, allowing for stratification into distinct fitness quintiles. CRF was objectively measured using validated exercise tolerance tests rather than estimated. Follow-up of study participants after surgery averaged ten years, providing excellent long-term mortality data.

8. Conclusions

CRF is inversely and independently associated with long-term mortality after CABG in Veterans referred for exercise testing. This association was present at all levels of fitness. CRF is a significant prognostic factor for long-term mortality after CABG. A high level of fitness at a single point in time, even when measured months or years prior to CABG, is associated with improved long-term survival after CABG. Interventions aimed at improving CRF may improve long-term survival after CABG, but more research is necessary in this area. Cardiothoracic surgeons should add their voice to the national call for increased physical activity and CRF for the public.

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