Added value of exercise test findings beyond traditional risk factors for cardiovascular risk stratification

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A B S T R A C T

Background: Functional aerobic capacity (FAC) determined by treadmill exercise testing (TMET) is associated with cardiovascular (CV) disease mortality independent of traditional CV risk factors and is a potentially underutilized tool. The purpose of this study was to determine added prognostic value of reduced FAC and other exercise test abnormalities beyond CV risk factors for predicting total and CV mortality.
Methods: The TMET database was queried for Minnesota patients (≥30 years) without baseline CV disease from September 21, 1993, through December 20, 2010. Risk factors and exercise abnormalities including low FAC (<80% predicted), abnormal heart rate recovery (<13 bpm), and abnormal electrocardiogram (ST depression ≥1 mm regardless of baseline) were extracted. Mortality data were obtained through February 2016. Patients were divided into 9 groups by abnormality number (0, 1, or ≥2) and risk factors (0, 1, or ≥2). Cox regression was used to determine mortality risk according to exercise abnormalities/CV risk factors, adjusted for age and sex.
Results: 19,551 patients met inclusion criteria; 1271 (6.5%) died over 12.4 ± 5.0 years' follow-up (405 [32%] CV deaths). Exercise abnormalities significantly modified risk for every number of CV risk factors. Hazard ratios (95% CI) for total mortality (0 vs ≥2 abnormalities) were 2.4 (1.9–2.9; *P* < .001) for 0 CV risk factors; 2.7 (2.2–3.3; *P* < .001), 1 risk factor; and 6.1 (4.8–7.7; *P* < .001), ≥2 risk factors. Similar results were noted for CV disease mortality.
Conclusions: Exercise test abnormalities strongly predict mortality beyond traditional CV risk factors. Our results indicate that TMET should be considered for CV risk assessment.

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1. Background

A significant inverse relationship between cardiorespiratory fitness (CRF) and mortality is well documented in the literature [1–4]. Current guidelines from the American Heart Association (AHA) [5], American Diabetes Association, and US Department of Health and Human Services recommend regular physical activity to reduce the risk of cardiovascular (CV) disease [6,7]. Exercise testing is the primary tool used to assess CRF, and current studies have shown the ability of CRF to predict CV disease mortality independent of traditional CV risk factors, including

current smoking, hyperlipidemia, hypertension, and diabetes mellitus [2,8].

Despite substantial numbers of studies showing that CRF can predict mortality from CV disease, the 2013 American College of Cardiology (ACC)/AHA Guidelines on the Assessment of Cardiovascular Risk do not endorse CRF or include it in their risk prediction tool, making it a potentially underutilized tool in the decision-making process for CV disease risk stratification [9]. Specifically, exercise test abnormalities, such as low functional aerobic capacity ([FAC] <80%), abnormal heart rate recovery (>13 bpm [beats per minute]), and abnormal findings on electrocardiography (ECG) have shown prognostic value in patients with and without CVD [10–14]. Some exercise test abnormalities, such as low FAC and heart rate recovery, have additive risk, increasing mortality in patients with CV risk factors [10]. ST-segment deviation has also been described as part of the treadmill exercise score used for prediction of CV disease, and, in combination with the European Systematic Coronary Risk Evaluation (SCORE) [15], for 10-year risk prediction of CV events, including mortality [16]. In the ACC/AHA guidelines [9], however, only age, sex, and traditional risk factors such as diabetes mellitus, hypertension, systolic blood pressure, smoking, and total and high-density lipoprotein cholesterol levels are included in

the pooled-cohort risk prediction equation. Therefore, the purpose of this study was to evaluate the contribution of exercise test abnormalities beyond traditional CV risk factors in the prediction of total and CV mortality for patients without prior CV disease.

2. Methods

2.1. Study design

This was an observational, single-center, retrospective study approved by the Mayo Clinic Institutional Review Board. Informed consent was waived for those providing research authorization, and only patients who provided research authorization were included.

2.2. Study population

The Mayo Integrated Stress Center database was queried for patients who had nonimaging treadmill exercise testing (TMET) performed between September 21, 1993, and December 20, 2010. Patients were included in the study if they were ≥30 years and their tests were performed on a treadmill using the Bruce protocol [17]. Patients were excluded if they had known cardiovascular disease other than systemic hypertension (i.e., ischemic heart disease, heart failure, any cardiac surgery, valvular disease defined as native valve regurgitation or stenosis, valve procedures [repair or replacement], any other structural heart disease such as congenital disease, hypertrophic cardiomyopathy, arrhythmias including paroxysmal atrial fibrillation/flutter, >5 premature ventricular contractions on resting ECG, a pacemaker, or an implantable cardioverter defibrillator). When multiple qualifying tests were available for a patient, the first test chronologically was chosen to maximize follow-up.

2.3. Clinical data and traditional CV risk factors

All data, including demographic characteristics, were derived from the database, and the traditional CV risk factors were confirmed by the authors (M.I.B.-L., S.F.-G., A.R.B.), who reviewed each patient's record and interview at the time of the test for hypertension, hyperlipidemia, diabetes mellitus, overweight/obese, and current smoking (defined as a patient's lifetime smoking of at least 100 cigarettes and smoking within the past 12 months). Preliminary analysis showed that many patients with hyperlipidemia were taking statin therapy. Because hyperlipidemia was not a significant risk factor for mortality, it was not included in the model (hazard ratio [HR], 0.695 [95% CI, 0.419–1.152]). In addition, obesity/overweight was not associated with increased risk of CV mortality in this study. Because the only measure of obesity we had available was body mass index (BMI), which has substantial limitations as a measure of adiposity and CV risk [18], obesity/overweight were also excluded.

2.4. Exercise test protocol and variables

All studies were conducted as symptom-limited tests using the Bruce protocol, with fatigue as the primary reason for stopping. The laboratory protocol was to achieve a subjective maximum, with a rating of perceived exertion >17. Resting heart rate and blood pressure (BP) measurements were obtained with patients sitting, supine, and standing. Our goal was to investigate commonly accepted and easily determined findings and measure risk on the basis of the stress test and not to investigate all possible abnormal exercise responses and CV risk factors. Heart rate, BP, and ECG were monitored throughout testing and during 3 min of active and 3 min of passive recovery. Ratings of perceived exertion were recorded using the Borg scale [19]. Measurements extracted from the database included peak exercise HR, HR at 1 min of active recovery, total exercise time, and ECG abnormalities. Exercise variables used in the analysis included low FAC, defined as actual exercise time/predicted exercise time <80% [20]; abnormal HR recovery, defined as <13 bpm change from peak heart rate at 1 min of active recovery; and abnormal exercise ECG, defined as ST-segment depression ≥1 mm regardless of baseline ECG.

2.5. Mortality outcomes

Outcomes were determined from Mayo Clinic patient records and the Minnesota Death Index through February 2016 (the current status of the database). A CV-related death was defined as an outcome if the first 3 causes of death in the Minnesota Death Index identified a CV condition. Data for a CV death were classified by using the *International Classification of Diseases* (ICD), *9th Revision* (codes 391, 391.9, 394-398, 402, 404, 410-414, 415-417, 420-429, 430-438, 440-448, 451-454, 456-459) and ICD *10th Revision* (codes I101, I05-I09, I11, I13, I20-I25, I26-I28, I30-I52, I60-I69, I70-I79, I80-I89).

2.6. Statistical methods

The results are presented as number of exercise treadmill abnormalities, specifically low FAC, abnormal heart rate recovery, and abnormal exercise ECG, with categories of 0, 1, or ≥2 abnormalities vs the number of traditional CV risk factors (0, 1, or ≥2), including diabetes mellitus, hypertension, and current smoking. SAS Studio 2013, version 5 (SAS Institute Inc.) was used for a preliminary Cox proportional hazards regression analysis (PROC PHREG) to determine the independent effect on total and CV mortality of each variable, with adjustment for age and sex. Cox regression was also used to identify the HR associated with each

combination of exercise test abnormalities and traditional risk factors, using 0 for exercise test abnormalities and 0 for CV risk factors as the referents; these analyses were adjusted for age and sex. Kaplan-Meier survival curves were also generated with PROC LIFETEST (SAS Institute Inc.) to show survival rates for each exercise test abnormality/CV risk factor combination. The level of significance was set at *P* < .05.

3. Results

A total of 19,551 patients whose records were in the database met the inclusion criteria. The mean ± SD age of patients was 50.9 ± 10.4 years; 34.6% were women; and the average BMI was 28.66 ± 5.31 kg/m². The mean treadmill FAC was 94.95% ± 5.31%, and the mean heart rate recovery was 18.95 ± 8.20 bpm. The predominant symptom reported during testing was fatigue (95.4%) followed by dyspnea (20%), atypical chest pain (3%), orthopedic limitation (3%), typical angina (2%), and dizziness/lightheadedness (1.2%). CV risk factors included hypertension in 4281 (21.9%) patients, diabetes mellitus in 1075 (5.5%) patients, and current smoking for 2189 (11.2%) patients. Of the patients, 3284 (16.8%) had abnormal exercise ECGs, 4145 (21.2%) had abnormal heart rate recovery, and 4536 (23.2%) had low FAC. There were 1271 (6.5%) deaths during follow-up of 12.4 ± 5.0 years; 405 (32%) of those were CV-related deaths.

The results of Cox regression analysis, including age, sex, and all exercise test abnormalities and CV risk factors, are shown in Table 1. Of CV risk factors, current smoking had the highest HR (and χ^2 result) for predicting total mortality among the CV risk factors, followed by diabetes mellitus and hypertension. For CV mortality, diabetes mellitus was most predictive, followed by current smoking. Of the exercise test abnormalities, low FAC had the highest HR and χ^2 value for predicting both total and CV mortality, followed by abnormal heart rate recovery, which was significant (*P* < .001) and abnormal exercise ECG, which was not significant (*P* = .08) for CV mortality.

Table 2 presents the main findings for how exercise test abnormalities contribute to risk assessment beyond traditional CV risk factors. The HR for total mortality with 0 CV risk factors and 0 exercise test abnormalities (referent) increased when only 1 abnormality was added and increased 2.4-fold when 2 or more abnormalities were present. Even greater increases occurred with increased exercise test abnormalities for CV mortality. Similar results were shown for CV risk factors of 1 or ≥2. For each level of CV risk factors, adding ≥2 exercise test abnormalities increased risk of both total and CV mortality.

Figs. 1 and 2 show overall and CV survival vs each combination of CV risk factors and exercise test abnormalities. At 10 years, survival was 98% for 0 CV risk factors/0 exercise test abnormalities but decreased to 95% for 0 CV risk factors/≥2 abnormalities. The 20-year survival decreased from 92% for 0 CV risk factors/0 abnormalities to 87% for 0 CV risk factors/1 abnormality and to 70% for 0 CV risk factors/≥2 abnormalities. At the extreme end of the risk continuum, nearly 20% of patients with ≥2 CV risk factors/≥2 abnormalities died over 10 years of follow-up, while >55% had died at 20 years. The survival curves are similar for CV mortality.

4. Discussion

The principal results of this study showed that multiple exercise test abnormalities were associated with an increased risk of mortality, even in the absence of CV risk factors, and that exercise test abnormalities add significantly to mortality risk when CV risk factors are present. Low FAC was the most important determinant of mortality among the exercise test abnormalities. A similar risk was attributable to abnormal HR recovery. Abnormal exercise ECG was the least important statistically of the 3 abnormalities. Although the purpose of this study was not to compare the strength of exercise test abnormalities vs CV risk factors for predicting risk, adding an abnormality at each level of CV risk factors seemed to increase risk by a slightly greater amount than adding CV risk factors to any level of abnormalities. Although the CIs overlap, the differences in the HRs were not statistically significant.

Table 1
Total and cardiovascular death independent of risk and adjusted for all variables.

Variable	Total mortality			Cardiovascular mortality		
	Hazard ratio (95% CI)	χ^2	P value	Hazard ratio (95% CI)	χ^2	P value
Age	1.096 (1.089–1.102)	902	<.001	1.108 (1.096–1.120)	331	<.001
Female sex	0.697 (0.618–0.787)	34	<.001	0.822 (0.668–1.012)	3.4	.06
Cardiovascular risk factors						
Hypertension	1.170 (1.038–1.320)	6.6	.01	1.314 (1.067–1.617)	6.6	.01
Diabetes mellitus	1.611 (1.358–1.910)	29	<.001	2.091 (1.543–2.633)	26.4	<.001
Current smoker	1.845 (1.571–2.167)	55	<.001	2.083 (1.597–2.737)	25	<.001
Hyperlipidemia	0.906 (0.710–1.154)	0.64	.42	0.695 (0.419–1.152)	1.98	.16
Obesity/overweight	0.913 (0.807–1.033)	2.10	.15	0.833 (0.668–1.038)	2.64	.10
Exercise test abnormalities						
Low FAC	1.655 (1.456–1.882)	59	<.001	2.065 (1.655–2.576)	41.3	<.001
Abnormal exercise HRR	1.569 (1.392–1.769)	54	<.001	1.932 (1.560–2.392)	36.4	<.001
Abnormal exercise ECG	1.189 (1.010–1.399)	4.31	.04	1.274 (0.969–1.675)	3.02	.08

Abbreviations: ECG, electrocardiogram; FAC, functional aerobic capacity; HRR, heart rate recovery.

Numerous papers have reported that low FAC and abnormal heart rate recovery are independently associated with increased HRs for total and CV death [12,21–28], including studies from our institution [21,29,30]. Aijaz et al. [21] studied results for patients who had treadmill exercise tests between 1993 and 2003 and found that multiple exercise test abnormalities might constitute a "CV disease risk equivalent," with a long-term mortality rate equal to that of patients with CV disease without TMET abnormalities.

The idea that exercise test findings, particularly FAC, can modify the impact of traditional CV risk factors has also been reported previously. For example, current smokers who could exercise had 30% less total mortality than current smokers who were not fit [31]. Mortality has also been shown to be less for patients with diabetes mellitus or hypertension who exercise [31–33]. These studies described how exercise modifies outcomes of patients with 1 risk factor, whereas we studied the impact of multiple exercise test abnormalities and CV risk factors.

Abnormal exercise ECG was the weakest prognostic indicator of the 3 exercise test abnormalities that we studied, which has been reported by other investigators [22], although in clinical practice many physicians may still regard the exercise test as an *exercise ECG* and regard the ECG data obtained as the most important or only important information derived from the test [22,30]. Clearly, we have shown that this is not the case and that exercise capacity and heart rate recovery have a much more important role in establishing prognosis. Restricting the analysis only to patients who reported potential cardiac symptoms

Table 2
Age- and sex-adjusted mortality rates (%).

Mortality	CV risk factors	Exercise treadmill abnormalities		
		0	1	≥2
Total	0	294/8750 = 3.36% HR, 1[a] 95% CI (referent)	203/3344 = 6.07% 1.270 (1.061–1.521)	145/951 = 15.25% 2.431 (1.986–2.977)
CV		68/8750 = 0.78% HR, 1[a] 95% CI (referent)	55/3334 = 1.64% 1.419 (0.993–2.029)	58/951 = 6.10% 3.953 (2.768–5.645)
Total	1	154/2758 = 5.58% 1.188 (0.976–1.445)	164/1880 = 8.72% 1.775 (1.463–2.153)	158/875 = 18.06% 2.722 (2.234–3.315)
CV		45/2758 = 1.63% 1.457 (1.005–2.141)	53/1880 = 2.82% 2.369 (1.648–3.405)	65/875 = 7.43% 4.576 (3.235–6.472)
Total	≥2	22/310 = 7.10% 1.798 (1.165–2.774)	43/378 = 11.38% 2.542 (1.843–3.504)	89/305 = 29.18% 6.093 (4.789–7.752)
CV		8/310 = 2.58% 2.899 (1.392–6.035)	14/378 = 3.70% 3.405 (1.911–6.067)	39/305 = 12.79% 11.606 (7.773–17.328)

Abbreviations: CV, cardiovascular; HR, hazard ratio.
[a] HR adjusted for age and sex.
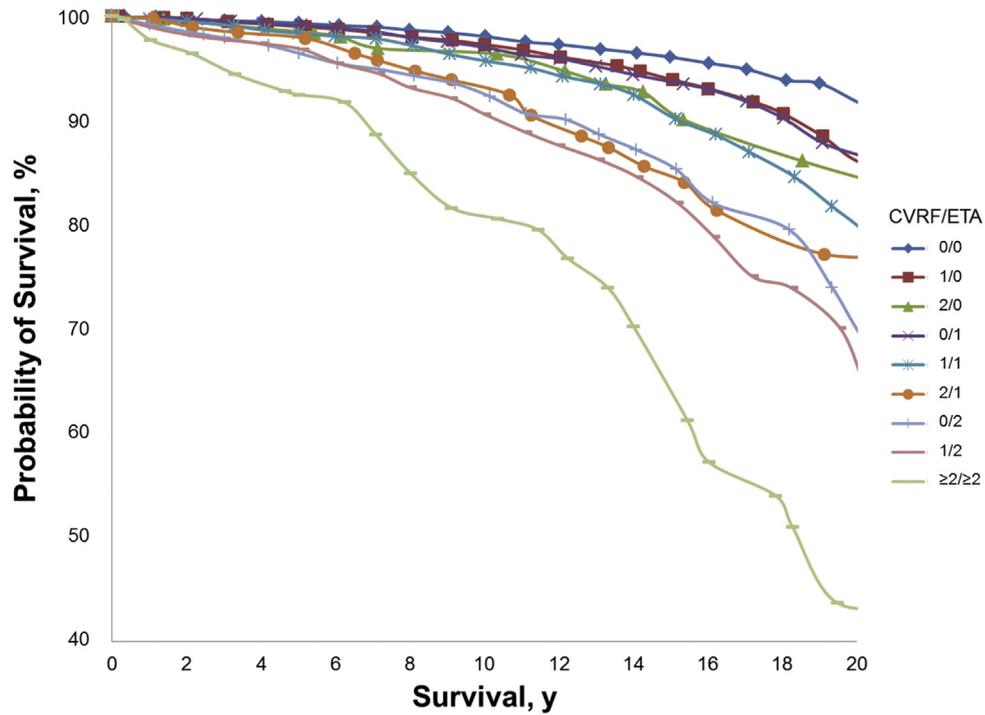
No. Surviving:	19,551	19,453	19,219	17,067	14,078	11,747	11,175	8,564	5,415	2,865	880
No. at Risk:											
0/0	8,750	8,722	8,258	6,044	5,975	4,961	4,750	3,587	2,250	1,101	410
1/0	3,344	3,330	3,303	3,042	2,760	2,211	2,078	1,613	1,025	445	144
2/0	951	932	921	833	760	667	624	501	247	98	30
0/1	2,758	2,750	2,740	2,369	1,950	1,779	1,599	1,223	808	434	111
1/1	1,880	1,866	1,838	1,708	1,388	1,121	1,060	846	482	243	126
2/1	875	856	851	772	670	579	533	375	224	112	28
0/2	310	307	283	268	253	175	147	111	88	23	0
1/2	378	373	372	312	295	187	172	155	101	73	0
≥2/≥2	305	292	288	249	179	164	139	106	50	17	6

Fig. 1. Kaplan-Meier survival curves for total mortality for combinations of number of Exercise Test Abnormalities (ETA) and Cardiovascular Risk Factors (CVRF).

before the test did not improve the HR for abnormal exercise ECG (data not shown).

We chose not to use a risk score, such as the Framingham heart score or pooled cohort risk score [9], because these scores are always dominated by age and sex (we adjusted for age and sex) [34], and we wanted to assess the impact of the traditional risk factors. We also did not have complete lipid data for our patients, which are needed for the pooled risk score, and our population is a referral group rather than a community cohort. In addition, the pooled cohort model predicts coronary events (heart attack and stroke), and we planned to analyze outcomes of total and CV mortality. Finally, the pooled cohort equation, which was first described in November 2013, was not being used during most of the period covered by this retrospective study.

The individual CV risk factors are less age dominated, although certainly risk of diabetes mellitus and hypertension do increase with age. However, the opposite is true of smoking, at least for our patients, where current smoking rates were inversely related to age. Among the exercise test abnormalities in our study, low FAC was independent of age and sex. A study from our institution previously showed that heart rate recovery is relatively constant until age 60 but then shows some decline with age [24]. Exercise test abnormalities increased in frequency with age and were slightly male-sex dominant. The Duke treadmill score [35], which is the most widely used prognostic index that includes multiple exercise abnormalities, is also strongly age dependent because aerobic capacity in absolute terms (metabolic

equivalents [METs]) rather than relative exercise capacity (FAC) is the primary driver in the Duke score. Therefore, older patients will perform shorter durations on exercise testing, resulting in a lower Duke score, and by virtue of their age, they also will be more likely to die during any follow-up interval, thus providing a somewhat biased positive association. That we were looking for a prognostic tool that was not age and sex dependent is yet another unique feature of the current study.

Our data confirmed a strong relationship between exercise test abnormalities and CV risk factors. Previous studies have shown that good physical fitness lowers the risk of CV disease by mechanisms such as decreased inflammation, improved metabolic biomarkers, and fewer traditional risk factors (such as hypertension and diabetes mellitus), as well as decreases mortality [31–33].

Having CV risk factors, such as diabetes mellitus and hypertension, can impair exercise capacity. Heart rate recovery response has been shown to be substantially impaired in patients who currently smoke and in patients with diabetes mellitus [36,37]. In patients with diabetes, the prevalence of cardiac autonomic neuropathy (CAN) is 20% to 70%, causing impaired parasympathetic function and concomitant impaired sympathetic function [38]. This leads to increased cardiac adrenergic sensitivity that portends risk for tachycardia and sudden death [38]. Additional consequences include depression of vagal activity, which leads to loss of heart rate variability during deep breathing and the loss of heart rate response to exercise, indicating nearly complete cardiac denervation [38]. The simple assessment of vagal response to
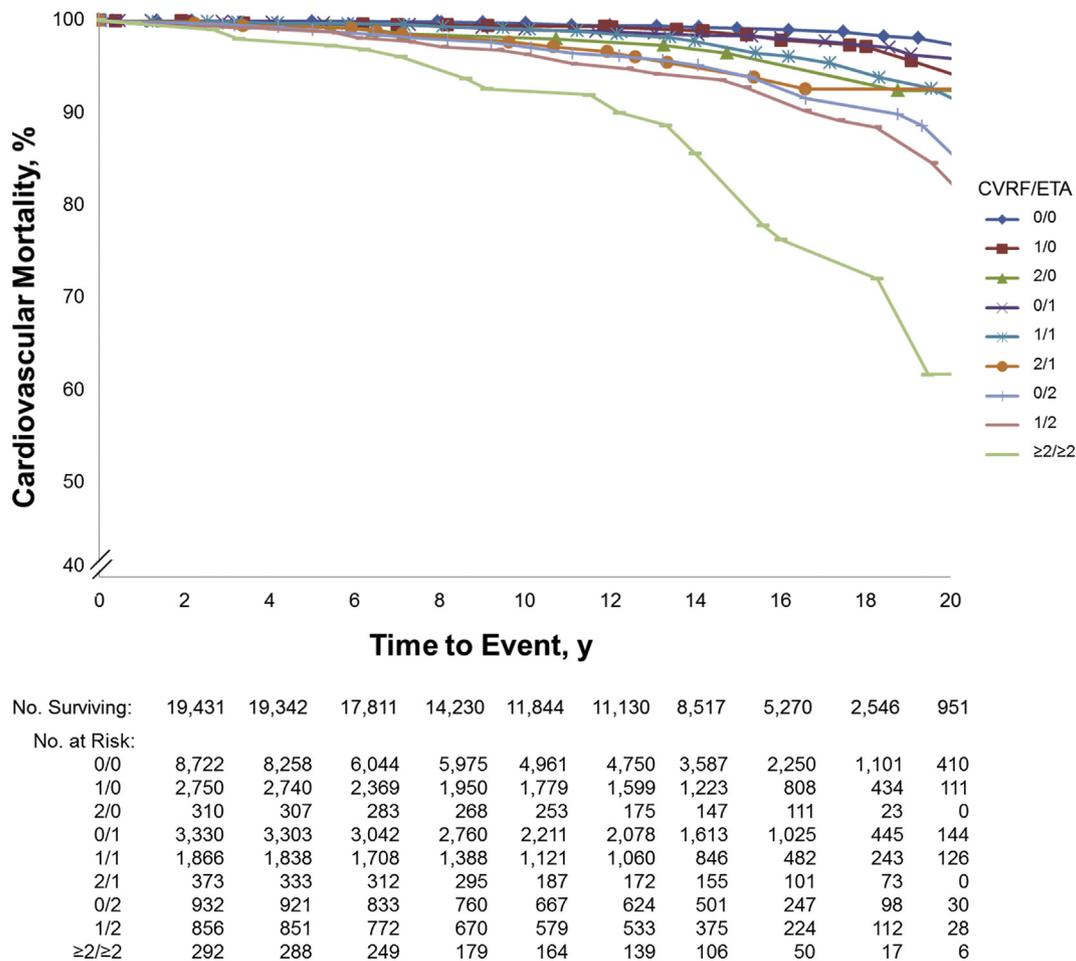
No. Surviving:	19,431	19,342	17,811	14,230	11,844	11,130	8,517	5,270	2,546	951
No. at Risk:										
0/0	8,722	8,258	6,044	5,975	4,961	4,750	3,587	2,250	1,101	410
1/0	2,750	2,740	2,369	1,950	1,779	1,599	1,223	808	434	111
2/0	310	307	283	268	253	175	147	111	23	0
0/1	3,330	3,303	3,042	2,760	2,211	2,078	1,613	1,025	445	144
1/1	1,866	1,838	1,708	1,388	1,121	1,060	846	482	243	126
2/1	373	333	312	295	187	172	155	101	73	0
0/2	932	921	833	760	667	624	501	247	98	30
1/2	856	851	772	670	579	533	375	224	112	28
≥2/≥2	292	288	249	179	164	139	106	50	17	6

Fig. 2. Kaplan-Meier survival curves for cardiovascular mortality for combinations of number of Exercise Test Abnormalities (ETA) and Cardiovascular Risk Factors (CVRF).

exercise in patients with diabetes is important because the presence of CAN is associated with increased risk of all-cause mortality, cardiovascular mortality, and cardiovascular events [39].

Results of a meta-analysis showed that improvement in CRF by 1 MET was comparable to a decrease of 7 cm in waist circumference, a 5-mm Hg decrease in systolic blood pressure, and a 1-mmol/L (18 mg/dL) decrease in fasting plasma glucose [2]. In addition to the known benefits of increasing FAC, as stated above, our findings suggest that the results of TMET could be integrated into prognostic tools, in addition to CV risk factors, to enhance risk prediction.

In general, a higher FAC is associated with lower CV disease mortality [33,35]. Mortality risk reduction has occurred with a 1-MET increase in exercise performance, equating to 13% lower risk of all-cause mortality and 15% lower risk of CV mortality [2,8,21]. Today, approximately 12% of all-cause mortality in the United States has been attributed to physical inactivity, yet FAC is still excluded from the pooled cohort equation, the most prominent risk prediction tool [26,40]. Our data clearly confirm that abnormalities on the exercise test add significantly to age- and sex-adjusted risk estimates beyond the traditional CV risk factors. The exercise test should be endorsed as a valuable tool for risk assessment —if interpreted from a prognostic perspective and not from a diagnostic perspective based solely on the interpretation of the exercise ECG.

4.1. Limitations

This is an observational, retrospective, single-center study. The study population consisted primarily of white patients living in Minnesota, so the result may not be generalizable to other populations because of the limitation of racial/ethnic diversity and the low CV death rates in

Minnesota. Nonetheless, the study focused on describing the use and potential of exercise test abnormalities observed during treadmill exercise testing as a tool for risk assessment and mortality prediction in patients without clinically apparent CV disease.

This study did not take into account lipid status (or use of a statin) or obesity, as described. Hyperlipidemia was not included for 2 reasons: first, lipid data was not available for all patients; second, most patients were being treated with a statin, thus negating the risk of hyperlipidemia. Hyperlipidemia and obesity had HRs <1.0, although neither was statistically significant in our preliminary model (Table 1). The presence of both multiple risk factors and reduced exercise capacity implied that patients likely had some degree of undiagnosed CV disease. However, this likelihood does not bias the findings that poor results on the stress test are additive to the presence of other risk factors.

5. Conclusion

The current study showed the usefulness of treadmill exercise testing, based on FAC and heart rate recovery, as a prognostic tool. Multiple exercise test abnormalities, in the absence of CV risk factors, are associated with an increased risk of mortality. When added to traditional CV risk factors, exercise test abnormalities are strong, independent predictors of mortality. Although a diagnostic exercise test is not recommended by current guidelines for asymptomatic patients without any traditional CV risk factors, our results show that even in these patients, the exercise test delivers important prognostic information and would be appropriate for risk assessment. Integration of exercise test findings into current prognostic calculators would enhance risk stratification for CV disease.

Conflict of interest

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