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Prognostic comparison of the FRIEND and Wasserman/Hansen peak VO2 equations applied to a submaximal walking test in outpatients with cardiovascular disease

--Manuscript Draft--

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Abstract:	Aims. To determine the ability to predict all-cause mortality using established percent-predicted (%PRED) equations for peak oxygen consumption (VO2peak) estimated by a submaximal walk test in outpatients with cardiovascular disease. Methods. 1491 male patients, aged 62±10 years at baseline, underwent a moderate and perceptually regulated (11-13 on the 6-20 Borg scale) one-km treadmill walking test (1k-TWT) to estimate VO2peak. %PRED was derived from the Fitness Registry and the Importance of Exercise: A National Data Base (FRIEND) and the Wasserman/Hansen equations. Results. There were 215 deaths during a median 9.4-year follow-up. The FRIEND prediction equation provided better prognostic information with receiver operating curve analysis showing significantly different areas under the curve (0.72 and 0.69 for the FRIEND and Wasserman/Hansen equations respectively, P=0.001). Overall mortality rate was higher across decreasing tertiles of %PRED using FRIEND, with 26%, 11%, and 5% for the least fit, intermediate, and high fit tertiles, respectively (P for trend<0.0001). Compared to the least fit tertile, the adjusted hazard ratios for the second and third tertiles were 0.54 (95%CI 0.34-0.87, P=0.01), and 0.45 (95%CI 0.25-

	0.81, P=0.008), respectively. Each 1% increase in %PRED conferred a 3% improvement in survival (P=0.0004). Conclusion. Low %PRED VO2peak in cardiac outpatients determined by the FRIEND equation was associated with a high mortality rate independent of traditional cardiovascular risk factors and clinical history. The FRIEND equation may provide a suitable normal standard when applied to clinically stable outpatients with cardiovascular disease.

Dear Editor-in-Chief,

On behalf of my co-authors, I submit for the publication on the European Journal of Preventive Cardiology after second revision the manuscript entitled:

“Prognostic comparison of the FRIEND and Wasserman/Hansen peak VO_2 prediction equations applied to a submaximal walking test in outpatients with cardiovascular disease”

We thanks Editor-in-chief and Reviewer #2 for additional suggestions and recommendations.

After having replied to the comments we believe that the paper has substantially further improved.

Looking forward to hearing from you.

Best regards,

Simona Mandini

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Reviewers' Comments

Reviewer #2

The authors have defended their manuscript almost sufficiently.

Comment #1

Methods: "If >1 cardiac diagnosis was recorded during that admission..." Why restrict to 1 diagnosis? It normal that patient has multiple diagnoses/procedures.

Reply

We agree. Patients with CVD often report acute coronary sindrome with or without myocardial infarction, PTCA, and CABG. However, as stated in the Methods, the study population consisted of patients referred between 1998 and 2015 (mostly between 2000 and 2010). At that time PTCA was less common than today, and patients with CABG were more commonly referred to an exercise-based cardiac rehab/secondary prevention program. CABG was, and is currently recommended as the standard of care for patients with complex multivessel coronary artery disease. Thus, if present, the diagnosis of CABG superseded other reasons for hospitalization. However, in accordance with this comment (and also with your related comment in Revision I) an additional limitation of the study has been added.

Comment #2

Author reply on Comment #2: "However, the aim of this study was to compare the prognostic accuracy of the two equations." Ok, then you may perform discrimination and reclassification analyses on them.

Reply

The FRIEND prediction equation provided better prognostic information, with receiver operating curve analysis showing significantly different areas under the curve (0.72 and 0.69 for the FRIEND and Wasserman/Hansen equations respectively, P=0.001). In accordance with your comment, this is better clarified in the Abstract.

Whether these results may have potential additional value to other clinical data in stratifying risk among patients undergoing exercise testing (i.e. reclassifcation analysis) is beyond the scope of this study. However, thank you for your suggestion, that will be considered in future studies on the application of these findings.

Reviewer #4

Thank you for your revised article.

TITLE PAGE

Prognostic comparison of the FRIEND and Wasserman/Hansen peak VO2 equations applied to a submaximal walking test in outpatients with cardiovascular disease

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ABSTRACT

Aims. To determine the ability to predict all-cause mortality using established percent-predicted (%PRED) equations for peak oxygen consumption (VO_2peak) estimated by a submaximal walk test in outpatients with cardiovascular disease.

Methods. 1491 male patients, aged 62±10 years at baseline, underwent a moderate and perceptually regulated (11-13 on the 6-20 Borg scale) one-km treadmill walking test (1k-TWT) to estimate VO_2peak. %PRED was derived from the Fitness Registry and the Importance of Exercise: A National Data Base (FRIEND) and the Wasserman/Hansen equations.

Results. There were 215 deaths during a median 9.4-year follow-up. The FRIEND prediction equation provided better prognostic information with receiver operating curve analysis showing significantly different areas under the curve (0.72 and 0.69 for the FRIEND and Wasserman/Hansen equations respectively, *P*=0.001). Overall mortality rate was higher across decreasing tertiles of %PRED using FRIEND, with 26%, 11%, and 5% for the least fit, intermediate, and high fit tertiles, respectively (*P* for trend<0.0001). Compared to the least fit tertile, the adjusted hazard ratios for the second and third tertiles were 0.54 (95%CI 0.34-0.87, *P*=0.01), and 0.45 (95%CI 0.25-0.81, *P*=0.008), respectively. Each 1% increase in %PRED conferred a 3% improvement in survival (*P*=0.0004).

Conclusion. Low %PRED VO_2peak in cardiac outpatients determined by the FRIEND equation was associated with a high mortality rate independent of traditional cardiovascular risk factors and clinical history. The FRIEND equation may provide a suitable normal standard when applied to clinically stable outpatients with cardiovascular disease.

Keywords: Exercise testing, peak oxygen consumption, normative equations, secondary prevention

INTRODUCTION

Directly measured peak oxygen consumption (VO_2peak) determined during maximal incremental cardiopulmonary exercise testing (CPET) is the gold standard objective measure of cardiorespiratory fitness (CRF).[1] The measurement of VO_2peak is used for evaluating disease severity, for predicting prognosis among patients with cardiovascular disease (CVD), and to assess the effectiveness of training programs for patients involved in cardiac rehabilitation and secondary prevention programs.[2] However, because of physical, financial and time limitations, direct CRF determination is often not routinely assessed in clinical settings. The interpretation of CPET results call for knowledge of a normal response, usually considered with respect to age and gender which are the most important variables affecting VO_2peak. Thus, it is useful to express VO_2peak as a percentage of an age- and gender-predicted value. Several equations to estimate normal VO_2peak are available.[3,4] However, these reference values have limitations that involve sample specificity, variation attributable to the exercise protocol, medications and the presence of disease. The most widely used equation as a normal standard to express CRF is the Wasserman/Hansen equation.[5-7] However, some limitations associated with the Wasserman/Hansen equation have been reported, including the fact that it was derived from a relatively small and homogeneous cohort.[5,6,8-10]

A small number of investigations have examined the prognostic value of percent-predicted VO_2peak. These studies have generally included short follow-up periods, and the results have been mixed. Superior prognostic impact of the percent-predicted VO_2peak compared with absolute values has been demonstrated in patients with severe chronic heart failure.[11] Myers et al observed that the prognostic power of absolute and percent age-predicted VO_2peak were similar in patients with CVD .[12] In contrast, Stelken et al reported that percent-predicted VO_2peak was superior to absolute VO_2peak for predicting mortality in patients with ischemic and dilated cardiomyopathy.[13] More recently, Arena et al demonstrated that percent-predicted VO_2peak provided similar or better predictive information compared to absolute VO_2peak value for estimating major cardiac events in a large heart failure cohort.[3]

Little is known about the association between exercise capacity assessed by submaximal exercise testing and clinical outcomes in patients with CVD. It has been demonstrated that a moderate and self-paced 1000m[14] or 500m[15-16] treadmill or outdoor[17] walking test is useful for estimating CRF and predicting survival[18-20] or hospitalization[21] in men and women with CVD, as well as those with and without[22] preserved left ventricular ejection fraction.

As the primary indication for exercise testing is usually clinical, the aim of the current study was to examine the association between percentage of age-predicted VO_2peak estimated using the 1-km treadmill-walking test (%PRED) and all-cause mortality in outpatients with CVD. Percentage predicted VO_2peak was determined on the basis of the widely-used Wasserman/Hansen equations, and a new equation using the Fitness Registry and the Importance of Exercise: A National Data Base (FRIEND) cohort, whose validity has been previously demostrated.[9,10,23] In addition, we determined the degree to which differences in %PRED might explain variations in survival. Given the recent call for the inclusion of "fitness as a vital sign"[24] this information may provide insight into improved risk stratification strategies in patients with CVD through the application of a simple, submaximal walking test. Such information could also facilitate discussions between physicians and their patients with regard to physical activity counseling.

METHODS

The study population consisted of 1491 men with CVD, aged 62±10 years at baseline, referred by their primary care physician or cardiologist to the exercise-based secondary prevention program at the Center for Biomedical Studies Applied to Sport at the University of Ferrara, Italy, between January 1st 1998 and December 31st 2015. The objective of the program was an improvement in CRF and functional capacity through a physically active lifestyle. A home program consisting of 30 to 60 minutes of moderate walking, at least 3 and preferably 7 days of the week, was recommended. In addition, patients were encouraged to adopt active lifestyle also by increasing daily activities, such as taking more walking breaks at work, gardening, or household work.

Patients were clinically stable, with no symptoms at rest and during light to moderate exercise intensities. Medical therapy was required to be stable for at least three months before testing. Subjects with comorbities that interfered with walking ability such as neurological, musculoskeletal, or peripheral vascular conditions were excluded. Before admission to the program, patients underwent a comprehensive clinical evaluation. Blood pressure (BP) was measured, and hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or use of antihypertensive agents. Blood chemistry analyses previously performed, and left ventricular ejection fraction derived from a prior echocardiographic evaluation were registered. The study was approved by the Ethics Committee of the University of Ferrara, no. 22-13, and all participants gave written informed consent.

VO_2peak was estimated for each patient at the baseline examination using the 1km treadmill-walking test (1k-TWT).[14] Briefly, the test was carried out as follows: the patients were instructed to select a pace that they could maintain for approximately 20 minutes at a moderate perceived exercise intensity . Patients began the test walking on the level at a walking speed of 2.0 km/h, with subsequent increases of 0.3 km/h every thirty seconds up to a walking speed corresponding to a perceived exertion of 11-13 on the 6-20 Rate of Perceived Exertion (RPE) Borg scale. The 1k-TWT then started and the RPE was assessed every two minutes, adjusting walking speed to maintain the selected moderate perceived intensity. Heart rate was monitored continuously during the test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland). VO_2peak was defined by the value obtained from entering age, height, weight, time to walk 1000-m, and heart rate into equations developed by the 1k-TWT.[14]

Patients unable to complete the 1k-TWT at walking speed ≥ 3.0 km/h performed the test over 500-m,[15,16] and the time to walk 500-m was multiplied by two.

The equations for estimating VO_2peak from the 1k-TWT was determined using a multivariate forward stepwise regression procedure. A coefficient of determination was calculated for each variable for the VO_2peak estimation. After removal of variables that were not significant, the model included age, BMI, walking speed and heart rate. The model was set as follows:

$$Y = \beta_0 - \beta_1 X_1 - \beta_2 X_2 - \beta_3 X3 - \beta_4 X_4$$

where Y = directly measured VO_2peak; β = regression coefficient for each of the independent variables; X_1 = mean walking speed in km/h; X_2 = BMI in weight/height^2; X_3 = age in years; and X_4 = heart rate in beats per minute (bpm). The resulting predictive equations were:

$$[33.42 + 2.79 \text{ (walking speed)} - 0.49 \text{ (BMI)} - 0.14 \text{ (age)}]$$

and

$$[46.11 + 4.41 \text{ (walking speed)} - 0.40 \text{ (BMI)} - 0.30 \text{ (age)} - 0.11 \text{ (heart rate)}]$$

for patients taking and not taking β-blockers, respectively.

Percent-predicted VO_2peak values were calculated according to normative values as defined by Wasserman/Hansen,[5,6] and the FRIEND[8-10] equations. Participants were followed for overall mortality from the date of their baseline examination for up to 10 years. Patients were flagged by the Health Service Registry of the Emilia-Romagna region, which provided the date of death where applicable, or by contacting relatives and personal physician to determine vital status. Time from baseline evaluation to death was calculated in months. The prognostic significance of %PRED values derived from the Wasserman/Hansen and FRIEND equations were determined.

At baseline, patient's CVD diagnosis was determined from the hospital discharge record. If >1 cardiac diagnosis was recorded during that admission, we defined the diagnosis as follows: Coronary Artery Bypass Graft (CABG) superseded other reasons for hospitalization such as myocardial infarction (MI) or valve replacement or repair. If the admitting diagnosis was MI and a subsequent Percutaneous Transluminal Coronary Angioplasty (PTCA) was or was not performed, it was coded as an MI. If a PTCA was performed in the absence of MI, it was coded as PTCA without MI.

Statistical analyses were performed using MedCalc 16.2.1 software (Ostende, Belgium). The participants were divided into tertiles on the basis of the %PRED values by the two equations. One way ANOVA was used to determine differences between tertiles in terms of age, BMI, left ventricular ejection fraction, total and HDL cholesterol, triglycerides, glycaemia, serum creatinine, and absolute estimated VO_2peak. Differences in categorical variables were assessed using the χ^2 test for trend. Overall mortality was used as the end point for survival analysis. Differences in survival across tertiles during the follow up period were assessed using Kaplan-Meier curves. Cox proportional hazard models were employed to determine the multivariable adjusted relative risk of mortality across tertiles. Demographic and clinical characteristics significantly associated with %PRED VO_2peak were included in the multivariable Cox regression model as potential confounders. Individuals in the lowest %PRED VO_2peak tertile were considered the reference group in the regression model. To assess the discriminatory accuracy of percent-predicted VO_2peak in estimating survival, receiver-operating-characteristic (ROC) curves were constructed and the corresponding areas under the curve were calculated. The level of statistical significance was set at $P < 0.05$.

RESULTS

The clinical characteristics of the 1491 patients included in the analysis are presented in Table 1. Average walking speed during the 1k-TWT was 4.2 ± 1.0 km/h. VO_2peak predicted from the 1k-TWT was 22.7 ± 5.6 ml/kg/min. Mean heart rate was 96 ± 14 bpm, representing 61% ± 9% of the age-predicted maximal heart rate (based on 220-age). During the median follow-up period of 9.4 years (interquartile range 6.1 to 10), there were 215 deaths from any cause with an average annual mortality of 1.4 percent.

The age-adjusted hazard ratios for death relative to exercise testing variables and other clinical predictors are presented in Supplemental Table 1. The best predictors of all-cause mortality were the absolute estimated VO_2peak, and age-predicted VO_2peak by both FRIEND and Wasserman/Hansen equations, with lower values associated with higher mortality.

ROC curve analyses for predicted VO_2peak showed that the two prognostic classification schemes were statistically significant for both the Wasserman/Hansen and FRIEND equations. However, the area under the ROC curve was higher for the FRIEND equation (0.72, 95% CI 0.70 to 0.74, P<0.0001) compared to the Wasserman/Hansen equation (0.69, 95%CI 0.67 to 0.71, P<0.0001) (Figure 1). The optimal threshold values were ≥66% and ≥81% for the FRIEND and Wasserman/Hansen equations, respectively. The area under the ROC curve was higher for the absolute VO_2peak (0.77, 95% CI 0.74 to 0.81, P<0.0001).

Based on the FRIEND %PRED VO_2peak, the patients were divided into tertiles, and demographic and clinical characteristics are presented in the Table 1. There were 130, 53, and 32 deaths from any cause among the first, second, and third tertiles respectively, corresponding to mortality rates of 26%, 11%, and 5% respectively (P for trend <0.0001). Kaplan-Meier survival analysis showed that the rate of mortality decreased across increasing tertiles of FRINED %PRED (Figure 2), as well as across increasing tertiles of estimated absolute VO_2peak and Wasserman/Hansen percentage of age-predicted VO_2peak (Supplemental Figure 1 and Supplemental Figure 2).

Comparisons between CRF categories revealed significant differences for the following variables; age, family history of CVD, BMI, LVEF, fasting glucose, serum creatinine, history of hypertension, CABG, PTCA, AMI, valvular repair/replacement, and use of ACE/ARB inhibitors, β-blockers, calcium antagonists, diuretics, statins, and number of medications; these variables were included in the Cox regression models as covariates. Compared to the lowest %PRED VO_2peak tertile (mean 55% ± 9%), the adjusted relative risk of mortality decreased for the second (70% ± 3%), and third (83% ± 7%) tertiles, with hazard ratios (HR) of 0.54 (95%CI 0.34-0.87, p=0.01), and 0.45 (95%CI 0.25-0.81, *P*=0.008) for the second and third tertiles respectively, compared to the first (p for trend <0.0001). When the %PRED value was assessed as a continuous variable in a Cox regression model fully adjusted for confounders, each 1% increase in %PRED was associated with a 3% lower risk of death (HR 0.97, 95%CI 0.96-0.99, p=0.0004).

DISCUSSION

We observed an inverse association between percent-predicted cardiorespiratory fitness estimated by the 1k-TWT in a large cohort of stable cardiac outpatients and all-cause mortality over a 10-year follow-up. Independent from clinical history and traditional cardiovascular risk factors, low age-predicted values were associated with a high mortality rate. %PRED VO_2peak values obtained by the Wasserman/Hansen and FRIEND equations estimated by the 1k-TWT differed from one another. In comparing the prognostic performance between equations, the FRIEND equation provided the best risk estimation. However, the prognostic performance was higher for absolute estimated VO_2peak. The prognostic power of %PRED from the FRIEND equation applied to the 1k-TWT is evidenced by the grade of risk represented by the Kaplan Meier curves (Figure 2) and by the 55% lower mortality observed among the fittest patients relative to the least fit.

The current findings are consistent with other recent investigations suggesting superior prognostic value of percent predicted VO_2peak using the FRIEND equation compared to other equations.[8] The percentage of age-predicted values derived from the FRIEND equation showed the highest univariate $\chi 2$ value, and were confirmed in the multivariate regression. Our results are also consistent with a previous study among 6213 US Veterans with and without CVD followed over a mean of 6.2 years.[12] The areas under the receiver-operating-characteristic curves obtained were 0.67 and 0.62 for estimated VO_2peak and percent-predicted values respectively,[12] slightly lower than the 0.72 (95% CI 0.70-0.74) value obtained in our study.
The capacity to estimate VO_2peak and predict mortality using a submaximal testing protocol is noteworthy. The association between VO_2peak and mortality are generally determined using incremental maximal

exercise testing. Submaximal exercise tests, in addition to being more practical, are safer and more cost-effective. Thus, they represent an opportunity to assess a patient's function when maximal testing is not available. One advantage of the 1k-TWT is the mode of exercise. Walking is the most frequently performed and one of the safest forms of physical activity.[27] This characteristic may make the 1k-TWT particularly appropriate for less fit patients or for those whom walking is their preferred form of physical activity. Another advantage is the use of moderate exercise intensity. The average percentage of age-predicted maximal heart rate during the 1k-TWT in the present study falls within current recommended limits (55% to 69%) for moderate intensity.[28] In this regard, the 1k-TWT provides the opportunity to provide an appropriate exercise intensity, and to facilitate the transition from a supervised to a self-guided exercise program. Finally, considering the strong effect of age on cardiorespiratory function, expressing CRF as a percentage of the age-predicted value can help health professionals seeking to make judgements about "normalcy" of their patients. In turn, this has the potential to enhance a patient's comprehension of their exercise capabilities.

Strengths of this study include the large sample size of patients across a wide range in age and exercise capacity. The ability to predict survival in patients with stable CVD by the percent-predicted VO_2peak determined with a simple walking test is also relevant. Since the protocol addresses physical activity, a modifiable risk factor for secondary prevention, the demonstration of the inverse association between %PRED and mortality makes it applicable for assessing treatment strategies. Given that every 1% increase in %PRED VO_2peak was associated with a 3% lower risk of mortality, repeated measurement of the 1k-TWT could be used as a simple tool to promote and monitor patients to achieve and maintain appropriate levels of physical activity. Finally, the simplicity of the 1k-TWT and its prognostic power in outpatients with CVD with non-restrictive inclusion criteria reflect real-world practice.

This study has several limitations. First, the sample comprised male participants only; thus, the results may not be generalized to women. Second, the results may not apply to patients with more impaired exercise capacity, such as those with chronic heart failure. Third, caution should be taken in using these findings among patients with PTCA or valvular repair/replacement, who had limited representation in the study. Fourth, we did not consider social, behavioral or psychological factors that have been independently associated with reduced walking ability.[29] Finally, a reverse causality effect, particularly related to dietary and physical activity habits, cannot be excluded.

Conclusion

Although direct determination of cardiorespiratory fitness remains the gold standard, variables obtained from a simple 1k-TWT provide useful prognostic information among outpatients with stable CVD. While many laboratories report cardiorespiratory fitness as a percentage of age-predicted VO_2peak values in their exercise test summary, they do not regularly consider its prognostic significance. The percent-predicted VO_2peak determined by the FRIEND equation applied to the 1k-TWT is inversely and significantly related to survival in cardiac outpatients, independent from clinical history. The results of the present study may have practical implications in the context of transitioning patients from clinically based and supervised programs to fitness facilities or self-guided exercise programs.

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AUTHORS' CONTRIBUTION: GG, GM, and GC designed data collection tools, monitored data collection, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. GG and GC are guarantors. GG, GC, JM, LK, and RA analysed the data, and drafted and revised the paper. BS, GP, SM monitored data collection, and analysed the data.

REFERENCES

1. Arena R, Myers J, Williams A, et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation* 2007; 116(3): 329–343
2. Ekelund LG, Haskell WL, Johnson JL, et al. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. The Lipid Research Clinics Mortality Follow-Up Study. *N Engl J Med* 1988; 319: 1379–1384
3. Arena R, Myers J, Abella J, et al. Determining the preferred percent-predicted equation for peak oxygen consumption in patients with heart failure. *Circ Heart Fail* 2009; 2:113-120
4. Evans HJL, Ferrara KE, Smith AE, et al. A systematic review of methods to predict maximal oxygen uptake from submaximal, open circuit spirometry in healthy adults. *J Sci Med Sport* 2015; 18:183–188

5. J.E. Hansen, D.Y. Sue, K. Wasserman, Predicted values for clinical exercise testing, *Am Rev Respir Dis* 1984; 129: S49–55
6. K. Wasserman, J.E. Hansen, D.Y. Sue, W.W. Stringer, B.J. Whipp, Principles of Exercise Testing and Interpretation, Indian Reprint, 2005:160-182
7. M. Guazzi, V. Adams, V. Conraads, et al. European Association for Cardiovascular Prevention & Rehabilitation, American Heart Association, EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations, *Circulation* 2012; 126: 2261–2274
8. Moneghetti KJ, Hock J, Kaminsky L. et al. Applying current normative data to prognosis in heart failure: The Fitness Registry and the Importance of Exercise National Database (FRIEND). *Int J Cardiol* 2018; 263: 75-79
9. Myers J, Kaminsky L, Lima R, et al. A reference equation for normal standards for VO2max: Analysis from the Fitness Registry and the Importance of Exercise Database (FRIEND Registry). *Progr Cardiovasc Dis* 2017; 60(1): 21-29. doi: 10.1016/j.pcad.2017.03.002. Epub 2017 Apr 1.
10. de Souza e Silva CG, Kaminsky LA, Arena R, et al. A reference equation for maximal aerobic power for treadmill and cycle ergometer exercise testing: Analysis from the FRIEND Registry. *Eur J Prev Cardiol* 2018; 25:742-750. doi: 10.1177/2047487318763958. Epub 2018 Mar 8.
11. Aaronson KD, Mancini DM. Is percentage of predicted maximal exercise oxygen consumption a better predictor of survival than peak exercise oxygen consumption for patients with severe heart failure? *J Heart Lung Transplant* 1995; 14: 981–989
12. Myers J, Prakash M, Froelicher V, et al. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002; 346: 793–801
13. Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. *J Am Coll Cardiol* 1996; 27: 345–352
14. Chiaranda G, Myers J, Mazzoni G, et al. Peak oxygen uptake prediction from a moderate, perceptually regulated, 1-km treadmill walk in male cardiac patients. *J Cardiopulm Rehabil Prev* 2012; 32: 262–269
15. Mazzoni G, Chiaranda G, Myers J, et al. 500-meter and 1000-meter moderate walks equally assess cardiorespiratory fitness in male outpatients with cardiovascular diseases. *J Sports Med Phys Fitness* 2018; 58(9): 1312-1317
16. Mazzoni G, Sassone B, Pasanisi G, et al. A moderate 500-m treadmill walk for estimating peak oxygen uptake in men with NYHA class I-II heart failure and reduced left ventricular ejection fraction. *BMC Cardiovasc Disord* 2018; 18(1): 67 doi: 10.1186/s12872-018-0801-9

17. Grazzi G, Chiaranda G, Myers J, et al. Outdoor reproducibility of a 1-km treadmill-walking test to predict peak oxygen consumption in cardiac outpatients. *J Cardiopulm Rehabil Prev* 2017; 37(5): 347-349
18. Chiaranda G, Bernardi E, Codecà L, et al. Treadmill walking speed and survival prediction in men with cardiovascular disease: a 10-year follow-up study. BMJ Open 2013;3:e003446. doi:10.1136/bmjopen-2013-003446
19. Grazzi G, Myers J, Bernardi E, et al. Association between VO_2peak estimated by a 1-km treadmill walk and mortality. A 10-year follow-up study in patients with cardiovascular disease. *Int J Cardiol* 2014; 173: 248–252
20. Grazzi G, Mazzoni G, Myers J, et al. Determining the best percent-predicted equation for estimated VO_2peak by a 1-km moderate perceptually-regulated treadmill walk to predict mortality in outpatients with cardiovascular disease. *J Sci Med Sport* 2018; 21(3): 307-311
21. Grazzi G, Mazzoni G, Myers J, et al. Improved walking speed is associated with lower hospitalization rates in patients in an exercise-based secondary prevention program. *Heart* 2016; 102(23): 1902-1908
22. Mandini S, Grazzi G, Mazzoni G, et al. A moderate 1-km treadmill walk predicts mortality in men with mid-range left ventricular dysfunction. *Eur J Prev Cardiol* 2017; 24(15): 1670-1672
23. Kaminsky LA, Arena R, Beckie T, et al. The importance of cardiorespiratory fitness in the U.S.: the need for a national registry: a policy statement from the American Heart Association. American Heart Association Advocacy Coordinating Committee, Council of Clinical Cardiology, and Council on Nutrition, Physical Activity and Metabolism. *Circulation* 2013; 127(5): 1-11
24. Ross R, Blair SN, Arena R, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign. A Scientific Statement From the American Heart Association. *Circulation* 2016; 134(24): e653-e699
25. Kokkinos P, Kaminsky LA, Arena R, et al. New generalized equation for predicting maximal oxygen uptake from the Fitness Registry and the Importance of Exercise National Data Base (FRIEND). *Am J Cardiol* 2017; 120: 688-692
26. Kokkinos P, Kaminsky LA, Arena R, et al. New generalized cycle ergometry equation for predicting maximal oxygen uptake from the Fitness Registry and the Importance of Exercise National Data Base (FRIEND). *Eur J Prev Cardiol* 2018; Jul;25(10):1077-1082. doi: 10.1177/2047487318772667. Epub 2018 Apr 25
27. Landi F, Russo A, Cesari M, et al. Walking one hour or more per day prevented mortality among older persons: results from ilSIRENTE study. *Prev Med*. 2008; 47(4): 422–6
28. Mezzani A, Hamm LF, Jones AM, et al. European Association for Cardiovascular Prevention and Rehabilitation, American Association of Cardiovascular and Pulmonary Rehabilitation, Canadian Association of Cardiac Rehabilitation. Aerobic exercise intensity assessment and prescription in

cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitation and the Canadian Association of Cardiac Rehabilitation. *Eur J Prev Cardiol* 2013; 20(3): 442-467

29. Tolea MI, Costa PT, Terracciano A, et al. Sex-specific correlates of walking speed in a wide age-ranged population. *J Gerontol B Psychol Sci Soc Sci* 2010; 65B(2): 174-184

APPENDICES: none

TABLES

Table 1. Baseline Demographics and Clinical Characteristics of the 1491 subjects by tertiles of %PRED VO_2peak.

Supplemental Table 1. Age-adjusted risk of death according to clinical and exercise testing variables.

FIGURES

Figure 1. Receiver operating characteristics curves for prediction of mortality over a 10 years follow-up by the two FRIEND and Wasserman/Hansen equations.

Figure 2. Survival curves according to the percentage of age-predicted VO_2peak using the FRIEND equation.

Supplemental Figure 1. Survival curves stratified according to estimated absolute VO2peak

Supplemental Figure 2. Survival curves stratified according to the Wasserman/Hansen percentage of age-predicted VO2peak.

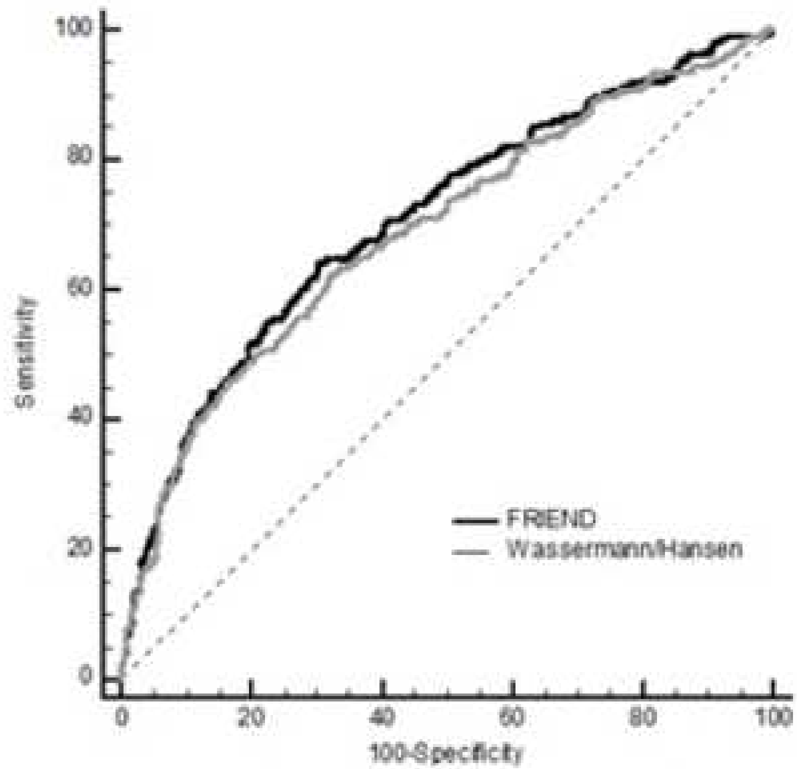
Table 1

Table 1. Baseline Demographics and Clinical Characteristics of the 1491 subjects by tertiles of %PRED VO_2peak.

Variable	Total (n=1491)	I Tertile (n=496)	II Tertile (n=498)	III Tertile (=497)	*P*-value
VO_2peak (FRIEND %PRED) Range	74 (6) 19-113	55 (9) 19-65	70 (3) 66-74	83 (7) 75-113	-
VO_2peak (W/H %PRED) Range	84 (15) 23-137	68 (11) 23-80	86 (3) 81-91	99 (7) 92-137	-
VO_2peak (mL/kg/min)	22.7 (5.6)	17.6 (4.4)	23.4 (3.2)	27.1 (4.2)	<0.001
Walking Speed (km/h)	4.2 (1.0)	3.1 (0.7)	4.3 (0.5)	5.1 (0.7)	<0.001
Demographics					
Age (y)	62 (10)	66 (10)	61 (10)	60 (9)	<0.001
BMI	27.8 (3.6)	28.3 (4.0)	27.4 (3.3)	27.5 (3.3)	<0.001
LV ejection fraction (%)	55 (10)	54 (10)	56 (10)	57 (9)	<0.001
Risk factor					
Current Smoking (%)	6	9	6	6	0.8
Hypertension (%)	58	64	55	55	0.002
Family history (%)	51	43	53	56	0.001
Fasting glucose (mg/dl)	110 (30)	113 (34)	109 (28)	107 (26)	0.009
Total cholesterol (mg/dl)	189 (38)	191 (40)	189 (38)	188 (37)	0.59
HDL cholesterol (mg/dl)	49 (13)	49 (14)	50(13)	49 (13)	0.73
Serum triglycerides (mg/dl)	142 (78)	144 (85)	144 (77)	139 (72)	0.57
Serum creatinine (mg/dl)	1.15 (0.50)	1.25 (0.66)	1.13 (0.47)	1.09 (0.27)	<0.001
Medical history (%)					
CABG	54.1	64.7	53.7	44.1	<0.0001
Myocardial infarction	24.6	18.1	27.6	28.0	0.0003
PTCA	7.6	3.2	6.2	13.3	<0.0001
Valvular repair/replacement	9.7	12.5	7.6	8.9	0.03
Medications (%)					
ACE inhibitor or ARB	54	59	51	53	0.03
Aspirin	74	72	75	74	0.4
β-blocker	57	49	72	50	<0.0001
Calcium antagonist	13	16	10	13	0.048
Diuretic	15	26	11	7	<0.0001
Statin	51	46	52	56	0.004
Number of medications	2.7 (1.2)	2.7 (1.2)	2.8 (1.2)	2.6 (1.3)	0.18

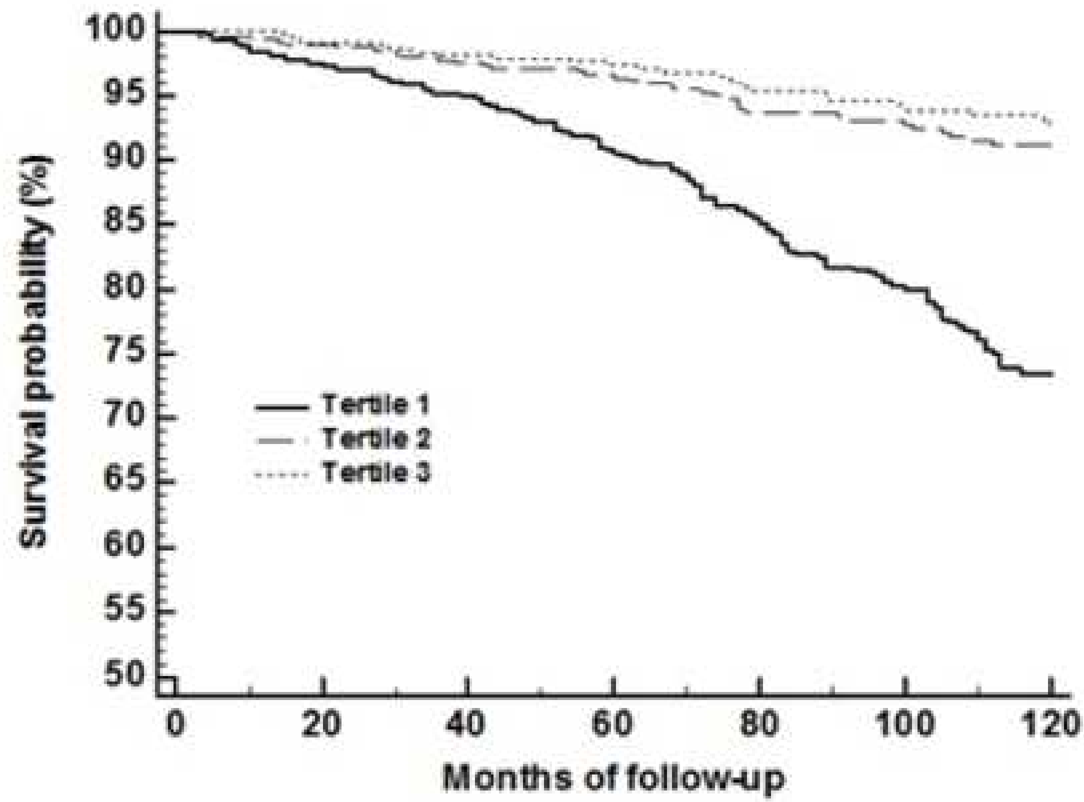
Values are presented as mean (standard deviation) or percentage. Abbreviations: BMI, Body Mass Index; LV, Left Ventricular; HDL, high-density lipoproteins; CABG, Coronary Artery Bypass Graft; PTCA, Percutaneous Transluminal Coronary Angioplasty, stenting or both; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Figure 1



100
80
60
40
20
0
Sensitivity
0
20
40
60
80
100
100-Specificity
FRIEND
Wassermann/Hansen

Figure 2 Click here to access/download;Figure;Figure 2.jpg



Supplemental table 1

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Supplemental Table 1.docx