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ORIGINAL RESEARCH

Comparison of the FRIEND and Wasserman-Hansen Equations in Predicting Outcomes in Heart Failure

Jonathan Myers, PhD; Christina G. de Souza e Silva, PhD; Ross Arena, PhD, PT; Leonard Kaminsky, PhD; Jeffrey W. Christle, PhD; Vincent Busque, BA; Euan Ashley, MB, CHB, DPhil; Kegan Moneghetti, MBBS (hons), PhD

BACKGROUND: Percentage of age-predicted peak oxygen uptake (VO_2) achieved ($ppVO_2$) has been widely used to stratify risk in patients with heart failure. However, there are limitations to traditional normal standards. We compared the recently derived FRIEND (Fitness Registry and the Importance of Exercise: A National Data Base) equation to the widely used Wasserman-Hansen (WH) $ppVO_2$ equation to predict outcomes in patients with heart failure.

METHODS AND RESULTS: A subgroup of 4055 heart failure patients from the FRIEND registry (mean age 53±15 years) was followed for a mean of 28±16 months. The FRIEND and WH equations along with measured peak VO_2 expressed in mL/kg^{-1} per min^{-1} were compared for mortality and composite cardiovascular events. $ppVO_2$ was higher for the FRIEND versus the WH equation (66±30% versus 58±25%; $P<0.001$). The areas under the receiver operating characteristic curves were slightly but significantly higher for the FRIEND equation for mortality (0.74 versus 0.72; $P=0.03$) and cardiac events (0.70 versus 0.68; $P=0.008$). Area under the receiver operating characteristic curve for measured peak VO_2 was 0.70 ($P<0.001$) for mortality and 0.73 ($P<0.001$) for cardiovascular events. For each 1-SD higher $ppVO_2$ for the FRIEND equation, mortality was reduced by 18% (hazard ratio, 0.82; 95% CI, 0.69–0.97; $P<0.02$); for each 1-SD higher $ppVO_2$ for the WH equation, the mortality was reduced by 17% (hazard ratio, 0.83; 95% CI, 0.71–0.97; $P=0.02$). The corresponding reductions in risk per 1 SD for cardiovascular events for the FRIEND and WH equations were 23 and 21%, respectively (both $P<0.001$).

CONCLUSIONS: Peak VO_2 expressed as percentage of an age-predicted standard strongly predicts mortality and major cardiovascular events in patients with heart failure. The FRIEND registry equation exhibited test characteristics slightly superior to the commonly used WH equation.

Key Words: cardiorespiratory fitness ■ exercise testing ■ heart failure ■ outcomes ■ oxygen uptake

Exercise intolerance, frequently exhibited by fatigue or shortness of breath with a minimal degree of exertion, is a cardinal symptom of chronic heart failure (HF). In recent years, there has been growing recognition of the value of measuring exercise capacity, commonly termed cardiorespiratory fitness (CRF), in patients with HF.[1,2] Quantifying CRF has important implications for making decisions regarding therapy, the determination of disability, quality of life, prognosis, and the capacity to perform daily activities.[1–4] One of the principal goals of treatment in HF is therefore to improve CRF, and therapies designed to improve CRF are thus critical to improving outcomes in these patients.[4,5] Indeed, many pharmaceutical and device interventions in HF today are based on their impact on CRF more than any other clinical feature. In a rapidly expanding number of studies across the spectrum of health and chronic disease, an individual's level of CRF

Correspondence to: Jonathan Myers, PhD, VA Palo Alto Health Care System, Cardiology 111C, 3801 Miranda Ave, Palo Alto, CA 94304. E-mail: drj993@aol.com

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CLINICAL PERSPECTIVE

What Is New?

- Traditional equations for normal standards for peak oxygen uptake can be cumbersome to apply and do not always function well in particular populations.
- In this study, we observed that a new equation for predicted peak oxygen uptake based on a national fitness registry (FRIEND [Fitness Registry and the Importance of Exercise: A National Data Base]) exhibited test characteristics slightly superior to the commonly used Wasserman-Hansen equation for predicting mortality and a composite outcome of major cardiovascular events (death, hospitalization for worsening heart failure, left ventricular assist device implantation, or transplantation) in patients with heart failure.

What Are the Clinical Implications?

- While the traditional Wasserman-Hansen equation has been widely used for many decades for the purpose of determining predicted standards for peak oxygen uptake, the FRIEND equation is easier to apply and stratifies risk for adverse events similar to or slightly better than the Wasserman-Hansen equation.

Nonstandard Abbreviations and Acronyms

CPX	cardiopulmonary exercise test
CRF	cardiorespiratory fitness
FRIEND	Fitness Registry and the Importance of Exercise: A National Data Base
$ppVO_2$	peak predicted oxygen uptake
WH	Wasserman-Hansen

more powerfully predicts risk for adverse events than traditional risk factors.[6–8]

The benchmark expression of CRF in HF is peak oxygen uptake (VO_2) using ventilatory gas exchange techniques. This is because directly measured peak VO_2 is significantly more precise and reproducible than exercise capacity estimated from the external work rate on a treadmill or a cycle ergometer.[9,10] Because peak VO_2 declines with age and tends to be higher among men compared with women, it is frequently expressed in comparison to what is normal for a given individual if he or she were healthy for a given age and sex. This is commonly termed *percentage of age-predicted peak VO_2* ($ppVO_2$). Equations have been developed for the purpose of providing reference values for $ppVO_2$ based on age, sex, body mass, and other factors.[9–16] The most commonly used equations since their initial publication in 1984 are those of Wasserman-Hansen (WH).[16,17] In patients with HF, CRF expressed as $ppVO_2$ using the WH equations has been demonstrated in some studies to be superior to absolute peak VO_2 values in terms of estimating risk for adverse outcomes.[18–20] Because $ppVO_2$ achieved can influence clinical decisions including the efficacy of treatment, risk stratification, exercise prescription, and even whether a patient is listed for transplantation, it is critical to have an expression of peak VO_2 based on a reliable standard.

The need for better reference standards for peak VO_2 was recognized in a 2013 policy statement by the American Heart Association.[21] The FRIEND (Fitness Registry and the Importance of Exercise: A National Data Base)[22] was initiated in part to enhance the value of CRF across environments, including the clinical setting and workplace as well as the public, to better inform national policy efforts on physical fitness, physical activity, health, and well-being. Using data from the FRIEND registry, we recently improved upon commonly used traditional equations for determining $ppVO_2$ (termed the *FRIEND equation*). Using a broader data set than was available previously for both men and women, we observed greater stability in both sexes across a wide spectrum of age and body mass index when compared with traditional equations.[14,15] Moneghetti et al[23] recently compared the FRIEND equation with the long-established WH equation[17] and observed that while both were predictive of a composite outcome, the FRIEND equation elicited a higher $ppVO_2$. However, it remains unclear whether one equation is superior to another in terms of estimating risk for mortality or other HF-related adverse outcomes. Should the FRIEND equation provide superior prognostic power when compared with traditional equations, it would provide further validation of this new equation. The purpose of the current study was to compare the FRIEND $ppVO_2$ equation with the WH equation in terms of risk for mortality and composite cardiovascular events in patients with HF.

METHODS

The procedures used for acquiring and managing the data for the FRIEND registry have been previously reported.[21,22] In brief, laboratories determined by the FRIEND Advisory Board applying valid and reliable calibration and cardiopulmonary exercise test (CPX) procedures administered by experienced personnel were invited to be considered for inclusion in the FRIEND registry. Although there were some variations in laboratory equipment, protocols, and procedures defining peak VO_2, the characteristics of all participating laboratories are consistent with recommendations outlined in published guidelines.[9,24] Local institutional review board

approval for participation in the FRIEND registry was obtained by each participating CPX laboratory to submit deidentified, coded data to the coordinating center at Ball State University, which then forwarded these data to the core CPX laboratory housed at the University of Illinois at Chicago. Institutional review board approval for the core CPX laboratory was also obtained at the University of Illinois at Chicago. The CPX laboratories contributed their data to the FRIEND registry between April 2014 and May 2018. Data from each CPX laboratory were reviewed for uniformity and to ensure they were within expected normal ranges by both the coordinating center and the core laboratory before merging into the FRIEND database. A listing of the participating sites and the distribution of values for peak VO_2, $ppVO_2$, and exercise modes is presented in Table S1. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Sample

The study cohort included 4510 patients with HF; of these, 361 were missing weight, height, or age; 84 were <20 years old, and 10 were missing outcomes. The final sample thus included 4055 subjects (2809 men and 1246 women; mean, 53.1±15.3 years) from 9 participating CPX laboratories in the United States and Europe (see Acknowledgments). HF was defined by clinical history at the time of the test, including patients with reduced or preserved ejection fraction. For inclusion, subjects were required to be >20 years of age and undergo a symptom- or sign-limited maximal exercise test performed on a treadmill or cycle ergometer. The indications for the exercise tests were standard clinical evaluations and determination of exercise capacity before entry into an exercise program or a research study. The sample was independent from that which the FRIEND equation was developed.[15] The protocol was approved by the Stanford Panel on Human Subjects Research (protocol #7425), and all subjects signed an informed consent form.

Age-Predicted Equations

The equation for $ppVO_2$ was developed from the FRIEND registry among 7759 men and women[14] and then validated in a sample of 10 881 subjects[15] in which it was shown to provide a lower average error between measured and predicted peak VO_2 when compared with traditional equations. It was designed to consider men or women and exercise mode (cycle ergometer or treadmill) in a single equation. The equation is as follows:

$$\begin{aligned} VO_2\left(\mathrm{mL\cdot kg^{-1}\cdot min^{-1}}\right) &= 45.2 - 0.35\times \mathrm{Age} - 10.9 \\ &\times \mathrm{Sex\,(male=1;\ female=2)} \\ &- 0.15\times \mathrm{Weight\,(pounds)} + 0.68\times \mathrm{Height\,(inches)} \\ &- 0.46\times \mathrm{Exercise\ Mode\ \ (treadmill=1;\ bike=2)}. \end{aligned}$$

Age-predicted peak VO_2 was expressed as a percentage of normal using: (achieved peak VO_2/predicted peak VO_2×100). The WH equation was chosen as a standard for comparison because it has been widely applied since its publication in 1984,[16] has been recommended in CPX guidelines,[9] and has been shown to be superior to other equations in terms of prognostic power.[25] The FRIEND and WH equations were stratified by quintiles of equal numbers in each group (n=811/group). Peak VO_2 in ml/kg^{-1} per min^{-1} was similarly stratified into quintiles achieved, yielding the following mean values: quintile 1: 9.7±5.8 mL/kg^{-1} per min^{-1}; quintile 2: 13.8±2.3 mL/kg^{-1} per min^{-1}; quintile 3: 17.2±2.5 mL/kg^{-1} per min^{-1}; quintile 4: 21.7±4.5 mL/kg^{-1} per min^{-1}; and quintile 5: 33.5±29 mL/kg^{-1} per min^{-1}.

End Points

The primary end point was a composite of major cardiovascular events (death, hospitalization for worsening HF, left ventricular assist device implantation, or transplantation); all-cause mortality was a secondary end point. Time to event was defined as the time between the baseline CPX and death, composite cardiovascular event, or May 31, 2018.

Statistical Analysis

Comparisons of means for clinical, demographic, and CPX data between those experiencing an event and those not experiencing an event were performed using unpaired *t*-tests for continuous variables. Categorical data are reported as percentages, and chi-square tests were used to assess differences in the distribution of HF pathogenesis, sex, and exercise test mode between groups. Continuous and categorical Cox proportional hazard models were used to estimate hazard ratios and 95% CIs for all-cause mortality and composite events. For the latter analyses, increments in exercise capacity were expressed per SD and adjusted for sex, exercise mode (treadmill versus cycle ergometer), ejection fraction (< or ≥40%), respiratory exchange ratio achieved (< or ≥1.0), and body mass index (< or ≥30 kg/m^2). To account for random effects and unobserved heterogeneity between different participating CPX laboratories from the FRIEND registry, shared frailty models (with gamma distribution) were performed.[26] The predictive performances of each equation were quantified and compared on the basis of the Akaike information criterion (AIC) and the Bayesian information criterion, in which a lower Akaike information criterion and Bayesian information criterion indicate a more effective model in predicting outcomes.[27] The predictive accuracy of the 3 models was further evaluated using Harrell's concordance index, validated with 20 bootstrap samples. Receiver operating characteristic (ROC) curves were constructed for

the FRIEND and WH $ppVO_2$ values for both categorical and time-to-event outcomes, and *Z*-tests were used to assess differences between areas under the ROC curves. Kaplan-Meier curves using the log-rank test were constructed for quintiles of each equation for $ppVO_2$ and composite cardiovascular events. NCSS software (Kayesville, Utah) was used for all analyses. Test results with a *P* value <0.05 were considered statistically significant.

RESULTS

Among the sample of 4055 patients, 417 (10%) died and 596 (15%) had a major event during a mean follow-up of 28±16 months. Baseline characteristics of the total sample, those who were event free, those who died, and those who had a composite cardiovascular event are shown in Table 1. Those who died or had a cardiovascular event were older and had lower ejection fractions compared with those who were event free. CPX results are shown in Table 2. Mean $ppVO_2$ was higher for the FRIEND equation versus the WH equation (65.7±29.9% versus 58.3±25.2%; *P*<0.001). Compared with those who were event free, both those who died and those who experienced a composite event had lower values for peak VO_2, lower VO_2 at the ventilatory threshold, lower percentages of $ppVO_2$ by both the WH and FRIEND equations, and higher ventilation-to-carbon dioxide output slopes. $ppVO_2$ between the FRIEND and WH equations were significantly correlated (*r*=0.81; *P*<0.001). Table 3 shows exercise capacity by percentile (10th to 90th) for peak VO_2 and the FRIEND and WH $ppVO_2$ equations. The $ppVO_2$ values were slightly (5%–10%) higher for the FRIEND equation across the percentiles of exercise capacity.

Table 4 shows multivariate associations between CPX responses, mortality and cardiovascular events. Each 1-SD higher measured peak VO_2 was associated with a 21% reduction in mortality (*P*=0.01) and a 32% reduction in composite cardiac events (*P*<0.001). For each 1-SD higher $ppVO_2$ for the FRIEND equation, mortality was reduced by 18% (hazard ratio, 0.82; 95% CI, 0.69–0.97; *P*=0.02). For each 1-SD higher $ppVO_2$ for the WH equation, mortality was reduced by 17% (hazard ratio, 0.83; 95% CI, 0.71–0.97; *P*=0.02). The corresponding reductions in risk per 1-SD increment for cardiovascular events for the FRIEND and WH equations were 23% and 21%, respectively (both *P*<0.001). Each 1 mL/kg^{-1} per min^{-1} higher peak VO_2 was associated with a 3.3% reduction in mortality and a 5.0% reduction in cardiac events. Table 4 also shows Akaike information criterion, Bayesian information criterion, and concordance indexes for each $ppVO_2$ equation, showing similar results between the different models for both cardiovascular events and all-cause

Table 1. Subject Characteristics in the Total Sample, Those Who Were Event Free, Those Who Died, and Those Who Experienced a Major Cardiovascular Event

Characteristics	Total (n=4055)	Event free (n=3459)	Total mortality (n=417)	Cardiovascular events (n=596)
Age, y	53.1±15.3	52.5±15.5	59.0±13.1*	56.1±13.7*
Male, %	69.3	67.7	79.1*	78.5*
Weight, kg	83.4±19.4	83.6±19.5	81.2±18.7†	82.3±19.2
Height, cm	172.5±10.2	172.4±10.3	172.2±10.1	172.9±10.0
BMI, kg/m^{-2}	28.0±5.7	28.0±5.7	27.4±5.6†	27.5±5.7†
Ejection fraction	40.9±17.6	42.4±17.3	33.9±16.6*	32.4±16.7*
Heart failure pathogenesis				
Ischemic, %	23.9	21.9	39.1*	34.7*
Nonischemic, %	76.1	78.1	60.9*	65.3*
HFpEF, %	52.1	55.9	34.1*	30.8*
HFrEF, %	47.9	44.1	65.9*	69.2*
Medications				
β Blocker, %	57.3	56.1	61.4	64.6*3
ACE inhibitor, %	46.9	44.9	57.5*	58.2*
Diuretic, %	44.7	40.7	67.8*	69.1*
Resting HR, bpm	74.6±14.2	74.5±14.1	75.3±15.1	75.3±15.0
Resting SBP, mm Hg	120±20	121±20	114±22*	110±22*
Resting DBP, mm Hg	73±13	74±12	71±13†	70±13*

ACE indicates angiotensin-converting enzyme; BMI, body mass index; DBP, diastolic blood pressure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; and SBP, systolic blood pressure.

*$P<0.001$ vs those who were event free.

†$P<0.05$ vs those who were event-free.

Table 2. Cardiopulmonary Exercise Test Responses in the Total Sample, Those Who Were Event Free, Those Who Died, and Those Who Experienced a Major Cardiovascular Event

Characteristics	Total (n=4055)	Event free (n=3459)	Total mortality (n=417)	Cardiovascular events (n=596)
Exercise mode				
Treadmill, %	70.0	71.9	60.0*	59.4*
Cycle, %	30.0	28.1	40.0*	40.6*
Peak HR, bpm	131.5±28.2	134.1±27.8	116.7±25.4*	115.8±25.3*
Peak SBP, mm Hg	153±33	156±32	139±33*	133±32*
Peak DBP, mm Hg	77±15	78±15	74±14*	73±14*
Peak VO_2, mL/kg^{-1} per min^{-1}	19.2±8.9	20.1±9.0	14.3±6.1*	14.0±5.7*
% Age-predicted VO_2 max, FRIEND equation	65.7±29.9	68.8±30.0	50.0±22.3*	47.8±22.2*
% Age-predicted VO_2 max, Wasserman/Hansen equation	58.3±25.2	61.0±25.0	44.7±20.3*	42.5±19.7*
Ventilatory threshold, mL/kg^{-1} per min^{-1}	11.9±4.3	12.2±4.4	10.5±4.0*	10.1±3.7*
Peak respiratory exchange ratio	1.11±0.14	1.11±0.14	1.10±0.16	1.11±0.16
VE/VCO_2 slope	33.6±9.0	32.6±8.2	38.4±11.1*	39.3±11.1*

DBP indicates diastolic blood pressure; FRIEND, Fitness Registry and the Importance of Exercise: A National Data Base; HR, heart rate; SBP, systolic blood pressure; VE/VCO_2, ventilation-to-carbon dioxide output; and VO_2, oxygen uptake.

*P<0.001 vs those who were event free.

mortality. To further assess the potential impact that exercise mode (treadmill versus cycle ergometer) had on the ppVO_2 equations, we removed the cycle ergometer tests (29% of the sample) and repeated the analyses. The hazard ratios remained similar between the FRIEND and WH equations.

Kaplan-Meier curves showing all-cause mortality for the different percentages of age-predicted peak VO_2 for the FRIEND and WH equations are illustrated in Figure 1. There was a progressive decline in survival as ppVO_2 was lower, and the pattern was similar for the FRIEND and the WH equations. ROC curves comparing the FRIEND and WH peak VO_2 prediction equations for all-cause mortality and cardiovascular events are shown in Figure 2. The area under the ROC curve was significantly higher for the FRIEND equation versus the WH equation for mortality (0.70 [95% CI, 0.67–0.72] versus 0.68 [95% CI, 0.65–0.71]; P=0.02). Likewise, the area under the ROC curve was significantly higher for the FRIEND versus the WH equation for composite cardiovascular events (0.74 [95% CI, 0.72–0.76] versus 0.72 [95% CI, 0.70–0.74]; P=0.008). Area under the ROC curve for measured peak VO_2 was 0.70 (95% CI, 0.67–0.72; P<0.001) for mortality and 0.73 (95% CI, 0.71–0.75; P<0.001) for cardiovascular events. Table 5 shows estimated time-dependent areas under the curve for all-cause mortality and cardiovascular events across years 1, 3 and 5. Areas under the curve for the 3 methods of expressing peak VO_2 were similar across the follow-up period.

Figure 3 shows the relative risks for composite events for each quintile of peak VO_2 comparing the FRIEND and WH equations along with quintiles of peak VO_2 in mL/kg^{-1} per min^{-1}, with the least fit quintile as the referent (≈10 mL/kg^{-1} per min^{-1}). A sharp decline in the rate of events was observed as peak VO_2 was higher regardless of how it was expressed; the sharpest decline in risk occurred between the least-fit and the next-least-fit quintile. While the gradients for reduction in risk with higher CRF were similar, it is notable that the 2 fittest quintiles had roughly 90% reductions in risk for adverse events for both of the ppVO_2 equations.

Table 3. Exercise Capacity by Percentile for Peak VO_2 and the FRIEND and Wasserman/Hansen ppVO_2 Equations

Percentile of cohort	10th	20th	40th	60th	80th	90th
Peak VO_2, mL/kg^{-1} per min^{-1}	10.1	12.2	15.5	19.0	25.3	31.4
% Age-predicted VO_2 max, FRIEND equation	34.0	42.0	55.0	67.3	86.2	102.2
% Age-predicted VO_2 max, Wasserman/Hansen equation	29.1	36.6	48.6	61.0	77.6	92.6

FRIEND indicates Fitness Registry and the Importance of Exercise: A National Data Base; ppVO_2, peak predicted oxygen uptake; and VO_2, oxygen uptake.

Table 4. Multivariate Associations of CPX Responses to Composite Cardiovascular Events and All-Cause Mortality, Per SD*

	Hazard ratio	95% CI	*P* value	AIC	BIC	Concordance index†
All-cause mortality						
Peak VO_2	0.79	0.66–0.95	0.01	4606	4642	0.76
$ppVO_2$ FRIEND	0.82	0.69–0.97	0.02	4632	4669	0.77
$ppVO_2$ Wasserman/Hansen	0.83	0.71–0.97	0.02	4636	4673	0.77
Cardiovascular events						
Peak VO_2	0.68	0.59–0.79	<0.001	6610	6647	0.79
$ppVO_2$ FRIEND	0.77	0.67–0.88	<0.001	6624	6661	0.79
$ppVO_2$ Wasserman/Hansen	0.79	0.70–0.80	<0.001	6628	6665	0.79

AIC indicates Akaike information criterion; BIC, Bayesian information criterion; CPX, cardiopulmonary exercise test; FRIEND, Fitness Registry and the Importance of Exercise: A National Data Base; $ppVO_2$, peak predicted VO_2; and VO_2, oxygen uptake.

*Cox proportional hazards regression by shared frailty model.

†Harrell's concordance statistics index.

DISCUSSION

While the search for an optimal approach to estimating risk in HF remains the topic of a great deal of investigation,[12,28,29] peak VO_2 continues to have an integral place in the risk stratification paradigm.[1–3,9,30,31] For >30 years, peak VO_2 has been an important metric in numerous HF guidelines, particularly in the context of consideration for transplant listing.[1,2,9,31] Because peak VO_2 is strongly influenced by age, sex, exercise mode, body weight, and other factors, it is often preferable to express peak VO_2 as a percentage achieved relative to a normal standard. Normal reference values provide a comparative basis for addressing important clinical questions and can significantly impact the decision-making process in patients with HF. For example, in the International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates,[31] the percentage of age-predicted VO_2 is recommended for transplant listing rather than the conventional absolute value of ≤14 mL/kg^{-1} per min^{-1} among relatively young patients (<50 years) and women. In a recent European Society of Cardiology position paper on CPX,[32] an age-predicted peak VO_2 <50% was recommended as a cut point to stratify high- and low-risk patients with preserved ejection fraction. Accurate reference standards are therefore paramount in patients with HF, among whom critical decisions rely on these standards. In response to shortcomings associated with available standards for peak VO_2,[11,12,33,34] a call for improved standards across a broader spectrum of age and sex was recently made in a Scientific Statement by the American Heart Association.[21] We recently developed normal standards for peak VO_2 based on the FRIEND registry.[14,15] While these standards were demonstrated to have greater stability among both sexes and across a wide spectrum of age and body mass index when compared with traditional equations, additional studies on the utility of the FRIEND equations to stratify risk are needed to validate their application in patients with chronic disease.

The current results confirm the prognostic power of peak VO_2 expressed as a percentage of an age-predicted standard both in terms of overall mortality (Table 4) and a composite of cardiac events (Table 4, Figure 3). We observed that both the widely applied WH and the newer FRIEND equation for age-predicted peak VO_2 were significant predictors of mortality and adverse events in patients with HF. These observations have several clinical implications. First, in contrast to the recent observations of Moneghetti et al,[23] the FRIEND equation yielded a somewhat higher $ppVO_2$ compared with the WH equation (66% versus 58%; Table 2). Second, both equations showed gradients for marked reductions in survival as the percentage of peak VO_2 achieved was lower. Patients achieving >80% of their respective age-predicted values had survival rates >95% at 4 years. In contrast, those achieving <40% of their age-predicted value had survival rates <50% at 4 years. The 2 $ppVO_2$ equations were largely similar in terms of their ability to predict mortality and composite cardiovascular outcomes. This may be attributable in part to the homogeneity of age in the sample, and the results may differ in populations with a wider variation in age. Notably however, the FRIEND equation exhibited slightly but significantly higher areas under the ROC curves than the WH equation for all-cause mortality (0.70 versus 0.68; P=0.003) and for composite events (0.74 versus 0.72; P<0.001; Figure 2).

An additional notable finding was the confirmation that relatively small changes in measured peak VO_2 resulted in considerable outcome benefits, in terms of both overall mortality and major cardiac events. Each

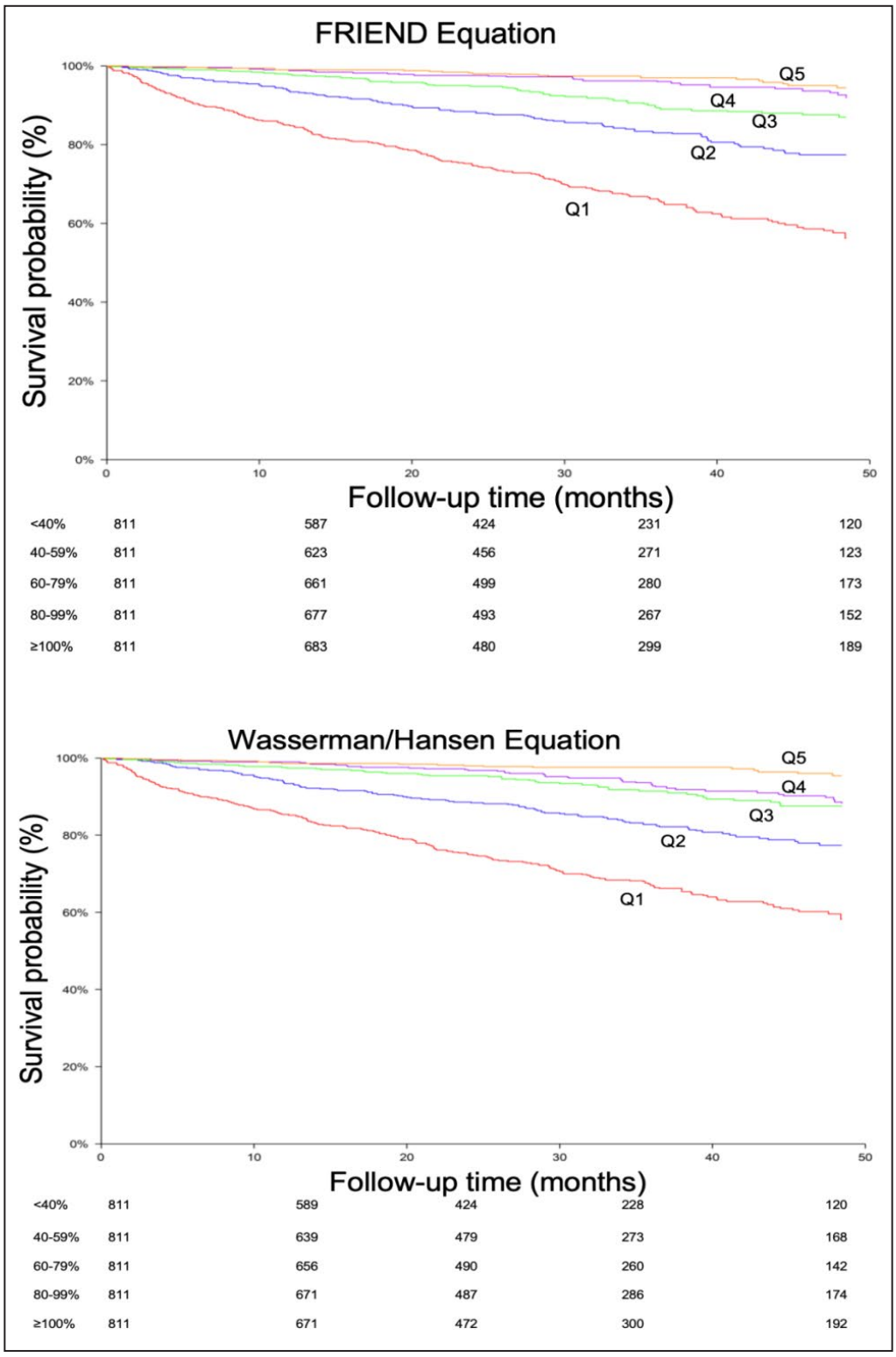

Figure 1. Kaplan-Meier survival curves for composite cardiovascular events using quintiles of percentage predicted VO_2 max from the FRIEND equation (top) and the Wasserman-Hansen equation (bottom).
Numbers of subjects at risk are shown for each 1-year interval. Log-rank $P<0.001$ for both curves. FRIEND indicates Fitness Registry and the Importance of Exercise: A National Data Base; and VO_2, oxygen uptake.

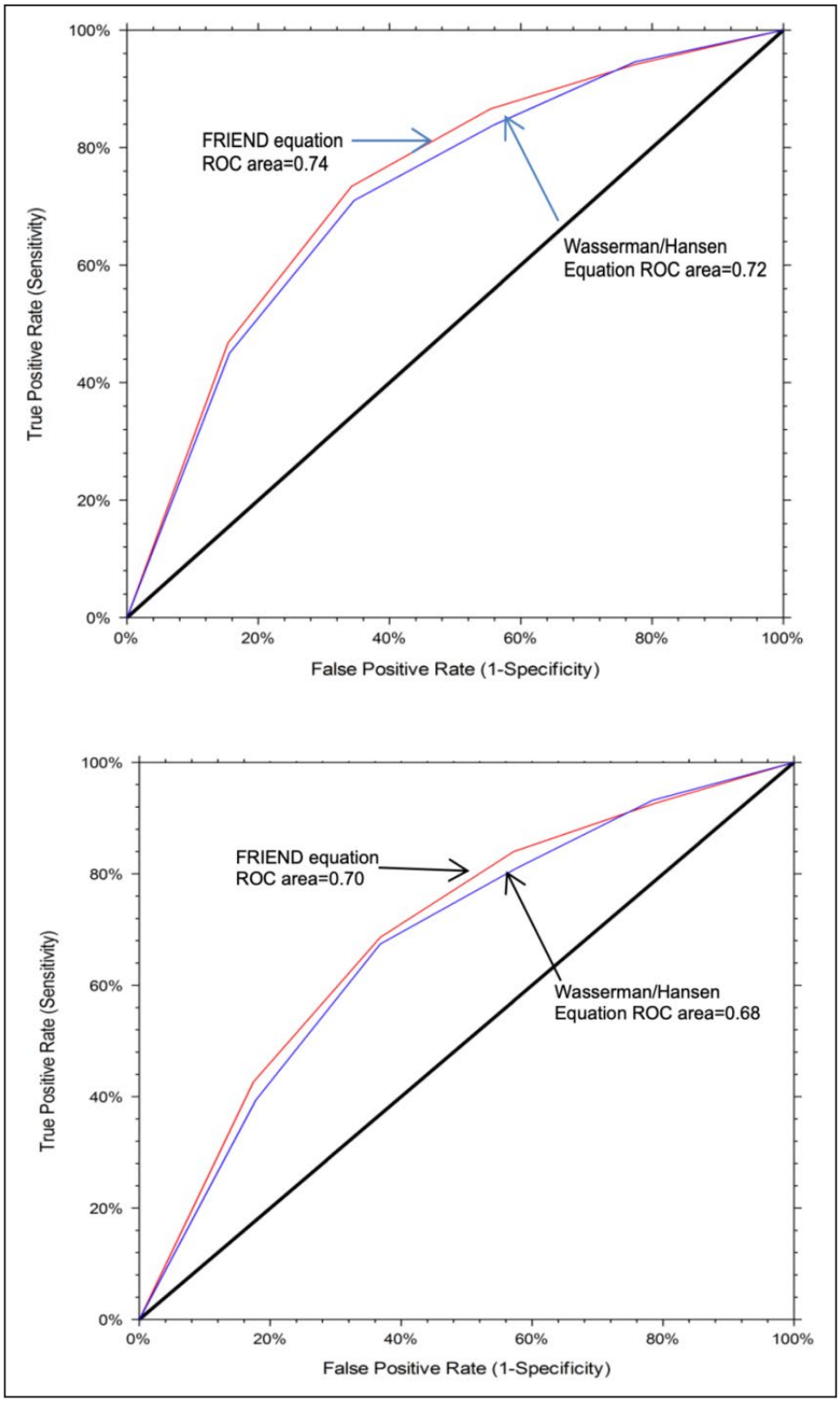

Figure 2. Receiver operating characteristic (ROC) curves for % predicted peak VO_2 achieved using the FRIEND and Wasserman-Hansen equations for cardiovascular events (top) and all-cause mortality (bottom).
The differences between curves were significant (*P*=0.008 for cardiovascular events and *P*=0.02 for all-cause mortality). FRIEND indicates Fitness Registry and the Importance of Exercise: A National Data Base; and VO_2, oxygen uptake.

Table 5. Estimated Time-Dependent AUCs for Years 1, 3, and 5 of the Follow-Up

All-cause mortality	AUC			
	Total	Year 1	Year 3	Year 5
Peak VO_2	0.70 (0.68–0.73)	0.75 (0.71–0.79)	0.74 (0.71–0.77)	0.72 (0.69–0.74)
$ppVO_2$ FRIEND	0.70 (0.67–0.72)	0.74 (0.70–0.79)	0.74 (0.71–0.77)	0.72 (0.69–0.75)
$ppVO_2$ Wasserman/Hansen	0.69 (0.66–0.71)	0.73 (0.68–0.77)	0.72 (0.69–0.75)	0.70 (0.68–0.73)
Cardiovascular events				
Peak VO_2	0.73 (0.71–0.75)	0.79 (0.76–0.82)	0.76 (0.74–0.78)	0.75 (0.72–0.77)
$ppVO_2$ FRIEND	0.75 (0.73–0.77)	0.79 (0.76–0.82)	0.77 (0.74–0.80)	0.76 (0.74–0.78)
$ppVO_2$ Wasserman/Hansen	0.73 (0.71–0.75)	0.78 (0.74–0.81)	0.76 (0.74–0.79)	0.74 (0.72–0.77)

AUC indicates area under the curve; FRIEND, Fitness Registry and the Importance of Exercise: A National Data Base; $ppVO_2$, peak predicted VO_2; and VO_2, oxygen uptake.

1-SD higher $ppVO_2$ was associated with ≈20% reductions in mortality and cardiovascular events (Table 4). Each 1 mL/kg^{-1} per min^{-1} improvement in peak VO_2 was associated with a 3.3% reduction in mortality and a 5% reduction in cardiac events. This is similar to results from the HF-ACTION (Heart Failure:A Controlled Trial Investigating Outcomes of Exercise Training) trial,[35] in which each 6% increase in peak VO_2 (≈1 mL/kg^{-1} per min^{-1}), adjusted for other significant predictors, was associated with a 5% lower risk of all-cause mortality or hospitalization. Other cohorts of patients with more severe HF than the current study (ejection fractions ≈20%–30% and peak VO_2 values 14–16 mL/kg^{-1} per min^{-1}) have reported a larger impact per unit change in peak VO_2, in the order of 11% to 15%.[36–38] Chiaranda et al[39] reported that after adjustment for confounders, each percentage increase in $ppVO_2$ using the FRIEND equation was associated with a 3% reduction in risk of hospital readmission following enrollment in a cardiac rehabilitation program. While the populations from

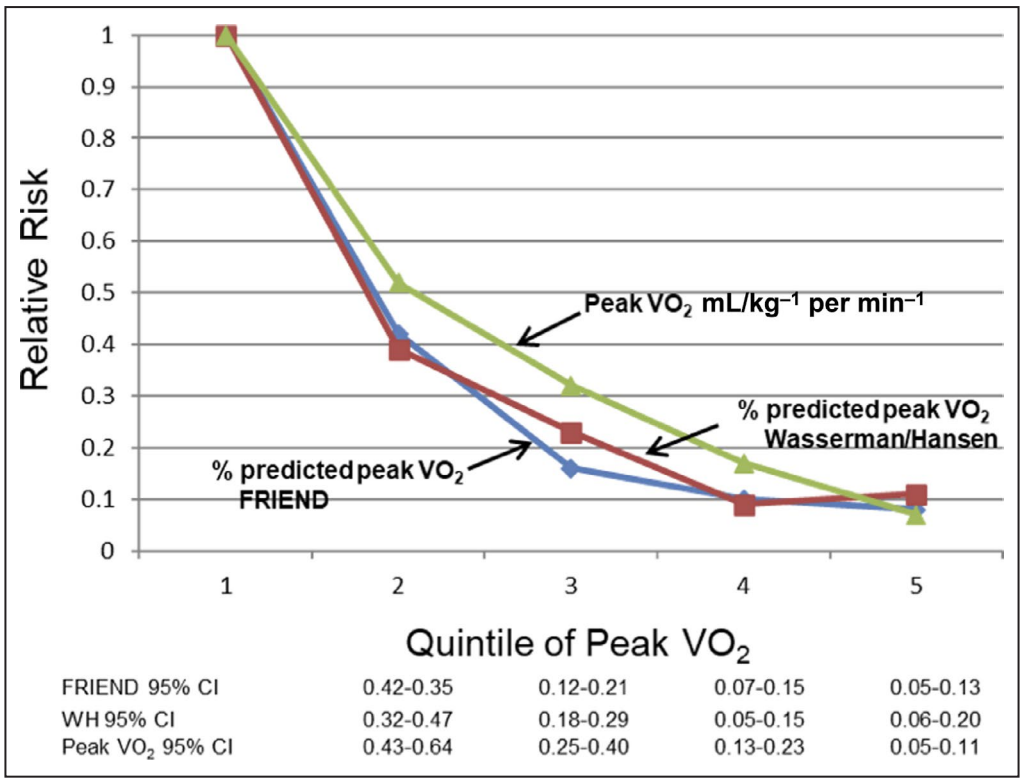

Figure 3. Relative risks for composite events for each quintile of peak VO_2 comparing the FRIEND and Wasserman/Hansen equations and quintiles of peak VO_2 in mL/kg^{-1} per min^{-1}.
Variance (95% CIs) for each of respective the quintiles are presented below the figure. FRIEND indicates Fitness Registry and the Importance of Exercise: A National Data Base; VO_2, oxygen uptake; and WH, Wasserman-Hansen.

these studies differ and are not directly comparable, collectively they underscore the importance of strategies (eg, exercise therapy) to achieve small improvements in CRF in patients with HF.

A related observation was that the largest impact on health outcomes occurred between the least fit category and the next-least-fit category (Figure 3). For both the prediction equations and measured VO_2 in mL/kg^{-1} per min^{-1}, subjects moving from the least-fit (reference) category (<40% of age-predicted VO_2, reflecting a mean of ≈10 mL/kg^{-1} per min^{-1}) and the next CRF category (mean of ≈14 mL/kg^{-1} per min^{-1}) had roughly 60% reductions in cardiovascular events. While the concept that the greatest reductions in risk occur at the low end of the fitness spectrum has become well established in recent years among healthy individuals and various chronic conditions,[6–8] the gradient in relative risk in the current study among patients with HF was particularly striking. It is also notable that the higher CRF categories (quintiles 4 or 5; ≈22 mL/kg^{-1} per min^{-1} or higher) were associated with minimal risk for adverse events (>80%–90% event free). The clinical implication of the latter finding is that it is unlikely that any intervention would improve risk in patients with HF with a peak VO_2 beyond 80% of their age-predicted standard or a measured peak VO_2 >22 mL/kg^{-1} per min^{-1}.

Previous normal standards for peak VO_2 have been criticized because they have tended to be population specific, are derived from populations that lack normal distribution, have lacked portability, are poorly represented by women, and can be cumbersome to apply.[11–14,33,34,40] For example, Papp and Takken[33] reviewed 16 studies on reference values for age-predicted VO_2 max encompassing ≈30 years and concluded that none of the studies fulfilled the 14 quality criteria established by the American Thoracic Society/American College of Chest Physicians Guidelines on CPX.[40] These criteria included adequate sample size, quality assurance of equipment and methodology, validation in populations other than those used to generate a given standard, and appropriate sampling of the data. The FRIEND equation was designed to improve upon previous efforts by addressing most of these criteria.[15] An additional advantage of the FRIEND equation is that a single equation was applied for men and women and exercise mode and that it was validated across a broad spectrum of age for both treadmill and cycle ergometer tests. While the differences between the FRIEND and WH equations were relatively small in the current study, the fact that the FRIEND equation generated a higher ROC area for both mortality and composite cardiac events (Figure 2) suggests a slightly superior predictive accuracy for the FRIEND equation.

While there have been a number of previous efforts to develop normal standards for peak VO_2, most have been descriptive, and few have applied them to outcomes in HF or other chronic conditions. Two recent studies applied the FRIEND equation to estimate risk in patients with cardiovascular disease. Moneghetti and colleagues[23] studied 1094 patients referred for evaluation of HF and followed them for major cardiac events for a median of 4.5 years. The FRIEND equation resulted in a slightly lower predicted VO_2 (71±31%) compared with the WH equation (74±29%). Both expressions of peak VO_2 were significant univariate predictors of outcomes with no significant differences between equations on the basis of ROC curves. However, when compared at a similar threshold of predicted VO_2, the event rate was significantly lower using the FRIEND registry equation versus the WH equation. Chiaranda et al[39] assessed the utility of ppVO_2 from the FRIEND equation to predict hospitalization up to 6 years following enrollment in an exercise-based secondary prevention program. Strong gradients for reduced hospitalization rates were observed with higher ppVO_2; those achieving ≤55% by the FRIEND equation had a rehospitalization rate 4 to 6 years after enrollment of 45%, roughly twice that of those achieving a value ≥82%. Before the development of the FRIEND equation, Arena et al[25] compared 5 commonly used equations among 1165 patients with HF and followed them for mortality and major cardiac events over 2 years. All equations were significant predictors of adverse events. The ppVO_2 value derived from the WH equation slightly outperformed other equations in predicting adverse outcomes.

Limitations

The cohort was derived from an international database, and we do not have details regarding the type and severity of HF; our sample of patients with HF was heterogeneous and the results may differ by pathogenesis of HF. The choice of treadmill protocols, equipment, and data collection procedures, although consistent with current guidelines,[2,9,24,32,40] was specific to each laboratory.

CONCLUSIONS

Peak VO_2 expressed as an age-predicted standard strongly predicts mortality and major cardiovascular events in patients with HF. Expressing CRF as a percentage of an age-specific reference value can facilitate both communication with patients regarding normalcy of function and the clinical decision-making process in patients with HF. The FRIEND registry equation exhibited test characteristics similar to or slightly better than the widely used WH equation.

ARTICLE INFORMATION

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Affiliations

Cardiology Division, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA (J.M.); Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, CA (J.M., J.W.C., V.B., E.A., K.M.); Healthy Living for Pandemic Event Protection (HL-PIVOT) Network, Chicago, IL (J.M., R.A., L.K., J.W.C.); Exercise Medicine Clinic - CLINIMEX, Rio de Janeiro, Brazil (C.G.d.S.e.S.); Heart Institute Edson Saad, Federal University of Rio de Janeiro, Brazil (C.G.d.S.e.S.); Department of Physical Therapy, College of Applied Health Sciences, University of Illinois at Chicago, IL (R.A.); and Fisher Institute of Health and Well-Being and Clinical Exercise Physiology Laboratory, Ball State University, Muncie, IN (L.K.).

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Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Data from individual centers in the cohort.

Site name	Sample size	Treadmill (%)	Peak VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	% age-predicted VO_{2max},FRIEND equation	% age-predicted VO_{2max},Wasserman/Hansen equation
Milan	314	0	14.7±4.5	51.5±16.5	50.4±18.9
VAPAHCS	1596	72.7	23.2±10.6	74.4±31.7	67.1±27.9
Stanford	570	97.7	20.3±7.4	72.2±27.4	60.2±22.8
BW	335	99.4	15.6±6.1	52.9±19.2	46.3±19.4
MC	658	76.0	15.3±5.6	58.9±31.6	49.6±19.5
Serbia	249	16.5	17.2±5.7	59.7±23.5	58.7±24.0
VCU	158	100	14.9±5.2	58.0±32.5	46.4±19.7
USP-PS	175	51.4	15.2±5.4	56.6±24.3	51.2±19.0

Milan - University of Milan, Italy
VAPAHCS – VA Palo Alto Health Care System, Palo Alto CA
Stanford - Stanford University Medical Center, Stanford, CA
BW - Brigham and Women's Hospital, Boston MA
MC - Moses Cone Hospital, Greensboro, NC
Serbia - University of Belgrade, Serbia
VCU - Virginia Commonwealth University, Richmond, VA
USP-PS - Federal University of Sao Carlos, Brazil; and Ribeirao Preto School of Medicine, University of Sao Paulo, Brazil.