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Comparison of Cardiopulmonary Exercise Test Variables to Predict Adverse Events in Patients with Heart Failure

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ABSTRACT

KROESEN, S. H., J. A. SNOEK, R. R. J. VAN KIMMENADE, J. MOLINGER, C. G. ARAÚJO, M. T. E. HOPMAN, T. M. H. EIJSVOGELS, and E. A. BAKKER. Comparison of Cardiopulmonary Exercise Test Variables to Predict Adverse Events in Patients with Heart Failure. *Med. Sci. Sports Exerc.*, Vol. 56, No. 12, pp. 2394–2403, 2024. **Purpose:** Given the rising burden of heart failure (HF), stratification of patients at increased risk for adverse events is critical. We aimed to compare the predictive value of various maximal and submaximal cardiopulmonary exercise test (CPET) variables for adverse events in patients with HF. **Methods:** A total of 237 patients with HF (66 (58–73) yr, 30% women, 70% HF with reduced ejection fraction) completed a CPET and had 5 yr of follow-up. Baseline characteristics and clinical outcomes (all-cause mortality, major adverse cardiovascular events, and cardiovascular-related hospitalization) were extracted from electronic patient files. Receiver operating characteristics curves for maximal (e.g., peak $\dot{V}O_2$) and submaximal CPET variables (e.g., VE/$\dot{V}CO_2$ slope, cardiorespiratory optimal point (COP), $\dot{V}O_2$ at anaerobic threshold) were compared using the Akaike Information Criterion (AIC) method, whereas their calibration was assessed. **Results:** One hundred three participants (43%) reached the composite endpoint, and 55 (23%) died. Percent predicted peak $\dot{V}O_2$ was the best predictor for adverse outcomes (AIC: 302.6) followed by COP (AIC: 304.3) and relative peak $\dot{V}O_2$ (mL·(kg·min)$^{-1}$, AIC: 304.4). Relative peak $\dot{V}O_2$ (AIC: 217.1) and COP (AIC: 224.4) were also among the three best predictors for mortality, together with absolute peak $\dot{V}O_2$ (mL·min^{-1}, AIC: 220.5). A good calibration between observed and predicted event rate was observed for these variables. **Conclusions:** Percent predicated and relative peak $\dot{V}O_2$ had the best predictive accuracy for adverse events and mortality, but the submaximal COP had a noninferior predictive accuracy for adverse events in patients with HF. These findings highlight the potential of submaximal exercise testing in patients with HF. **Key Words:** VENTILATORY EFFICACY, CARDIORESPIRATORY OPTIMAL POINT, PHYSICAL FITNESS, RISK STRATIFICATION, MORTALITY

The global burden of heart failure (HF) is increasing given the aging population, with an estimated rise in the prevalence from 2.4% in 2012 to 3.0% in 2030 in the US population (1). HF is characterized by a high risk for morbidity and mortality as 50% of patients are readmitted to the hospital within 1 yr (2), and 50% of patients with HF die within 5 yr after diagnosis (3). However, the risk for morbidity and mortality differs for HF phenotypes (2). Therefore, stratification of patients with HF with an increased risk for adverse events is essential for optimal personalized treatment and resources allocation, for example, by a more rapid transition to advanced HF therapies (cardiac transplantation, left ventricular assist device) for high-risk patients (4).

Maximal cardiopulmonary exercise testing (CPET) is a powerful tool for acquiring information about disease severity and

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guiding clinical management strategies such as the timing of advanced HF therapies as recommended in international guidelines for patients with HF (classes 1–C) (4,5). Peak oxygen uptake (peak $\dot{V}O_2$) is a strong predictor for adverse events as it assesses multiple systems (6,7). In contrast, indices of ventilatory efficiency, including the ventilation/carbon dioxide production (VE/$\dot{V}CO_2$) slope, the oxygen uptake efficiency slope until maximal effort (OUES), and peak partial pressure of end-tidal CO_2 ($PetCO_2$) during exercise are increasingly recognized as alternative risk stratification variables (6,8). Submaximal-derived variants assessing multiple systems ($\dot{V}O_2$ at the anaerobic threshold (AT)) or ventilatory efficiency (VE/$\dot{V}CO_2$ slope until the AT) were previously also associated with mortality (6,8,9). Moreover, submaximal ventilatory efficiency indexes that do not require AT determination, which minimizes the intraobserver variation (10,11), are promising. The cardiorespiratory optimal point (COP) is defined as the lowest minute value of VE/$\dot{V}O_2$ and is reached at 44%–51% of peak $\dot{V}O_2$ (10,12). The COP has predictive potential as higher values are associated with an increased risk of unplanned hospitalization and mortality in patients with HF (12). In addition, the submaximal-derived OUES has risk stratification potential as the OUES values obtained at 50% and 75% of exercise are correlated to maximal OUES values (13). Studies examining which CPET variable is the best predictor for adverse events in HF are scarce and contradictory, do not provide a complete overview of (sub)maximal CPET variables (8,14–17) or only assess a specific type of HF (15).

Therefore, we compared the predictive value of maximal and submaximal CPET variables for major adverse clinical outcomes in patients with HF. We hypothesized that peak $\dot{V}O_2$ is the best predictor, whereas submaximal alternatives, including the $\dot{V}O_2$ at AT, submaximal VE/$\dot{V}CO_2$ slope, COP, and submaximal derived OUES, may have a comparable predictive value.

METHODS

Study Design and Population

Patients registered in the *HArtfalen Registratie Project* (HARP) database (18) were eligible for this retrospective cohort study. All patients with HF who performed a CPET before cardiac rehabilitation at the Isala clinic (Zwolle, the Netherlands) between October 2009 and January 2018 were included. Before CR participation, patients with HF were stable and on optimal medical therapy. Exclusion criteria were a follow-up <5 yr and incomplete CPET data. Participants provided informed consent before registration in the HARP database. The study complies with the Declaration of Helsinki, and the local medical ethics committee approved the study protocol (No. 2021-13378).

Patient and Disease Characteristics

Electronic patient files were used to collect 1) patient characteristics including age, sex, body mass index, smoking status, presence of diabetes mellitus, and/or chronic obstructive pulmonary disease, and 2) HF characteristics, including left ventricular ejection fraction (LVEF), type of HF, HF etiology (ischemic, idiopathic, valvular or other), New York Heart Association (NYHA) class, resting diastolic and systole blood pressure, medical device implementation (implantable cardioverter–defibrillator, pacemaker, or cardiac resynchronization therapy), cardiac comorbidities (atrial tachycardia, atrial fibrillation, percutaneous transluminal coronary angioplasty, coronary artery bypass graft, or heart transplantation), cardiovascular (CV) medication use (angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker, aldosterone receptor antagonist, β-blocker, diuretics, and statins), and selected laboratory values (N-terminal prohormone brain natriuretic peptide (NT-proBNP), modification of diet in renal disease (MDRD), creatinine, hemoglobin, and serum sodium).

CPET

After body weight assessment with sports cloths and without shoes, a symptom-limited maximal CPET on a cycle ergometer (Lode Corival, Lode, Groningen, the Netherlands) was performed. O_2 and CO_2 partial pressures were continuously sampled by a mass spectrometer (MetaMax IIIb, Cortex, Leipzig, Germany) and calibrated before every test by ambient air and daily by a fixed known gas mixture. $\dot{V}O_2$, VE, and $\dot{V}CO_2$ were computed by breath-by-breath analysis (19), and heart rate (HR) was measured continuously by electrocardiography. Capillary blood lactate concentrations were obtained from the ear lobe following a standardized procedure consisting of pricking the ear lobe, wiping the pricking location without alcohol, squeezing out a droplet, and analyzing the droplet with the Lactate Pro 2 (Axon Lab AG, Baden-Dätwill, Germany). Measurements were performed before the start of the test on the bike in sitting position and immediately after its end. A personalized ramp protocol was planned with a targeted CPET duration of 8–12 min. The protocol consisted of 1) 2-min rest measurement, 2) 3-min warm-up at 0 W, 3) gradual increase of the workload until the participant reached exhaustion or could not maintain a minimum of 60 rpm, and 4) 3-min cool-down. All participants were verbally encouraged throughout the CPET to reach maximum effort.

CPET Variables

Maximal values. Absolute peak $\dot{V}O_2$ was defined as the highest 30-s average value that was reached during the exercise protocol ($mL \cdot min^{-1}$) and consequently adjusted for body weight (relative peak $\dot{V}O_2$, $mL \cdot (kg \cdot min)^{-1}$). Other peak variables were obtained for HR (bpm), workload (W), ventilation (VE; $L \cdot min^{-1}$), respiratory exchange ratio (RER), and $PetCO_2$ (mm Hg). Peak O_2 pulse ($mL \cdot beat^{-1}$) was calculated as peak $\dot{V}O_2$/peak HR (20). Percentage predicted peak $\dot{V}O_2$ was calculated using the Hansen/Wasserman equations to predict peak $\dot{V}O_2$, which is suggested to have the highest predictive accuracy across several percent predicted models in patients with HF (21–23). Percentage predicted peak HR was calculated using $208 - 0.7 \times$ age to acquire the predicted peak HR (24).

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The VE/$\dot{V}CO_2$ slope was calculated from the start until peak exercise (6,21). The maximal oxygen uptake efficiency slope (OUES100) was calculated by taking the slope of $\dot{V}O_2$ and the log transformation of VE from the start of the exercise until the end of the exercise (25). The $\dot{V}O_2$/workload slope (mL·(min·W)$^{-1}$) was defined as the increase in $\dot{V}O_2$ (peak $\dot{V}O_2$ − resting $\dot{V}O_2$) during the CPET divided by the increase in workload during the test.

Submaximal values. At rest, HR (bpm) was obtained. An experienced exercise physiologist determined the AT by the V-slope method (26) using special software (MetaSoft® Studio, Cortex, Leipzig, Germany). In addition to the V-slope method, the $PetCO_2$, $PetO_2$, VE/$\dot{V}O_2$ and VE/$\dot{V}CO_2$ were used to verify the AT. The following variables at AT were obtained: absolute $\dot{V}O_2$ (mL·min^{-1}), relative $\dot{V}O_2$ (mL·(kg·min)$^{-1}$), $\dot{V}O_2$ as a percentage of peak $\dot{V}O_2$ (% of peak), HR (bpm), workload (W), O_2 pulse (mL·beat^{-1}) calculated as $\dot{V}O_2$ at AT/HR at AT, and $PetCO_2$ (mm Hg). The COP, a dimensionless variable, was calculated by obtaining the lowest VE/$\dot{V}O_2$ value in a given minute (10) using the raw CPET data. The VE/$\dot{V}CO_2$ slope until AT was calculated from the start of the exercise until AT (21). The submaximal oxygen uptake efficiency slope was calculated from the start of exercise until 75% peak exercise (OUES75) and 50% peak exercise (OUES50) (25).

Multicomponent values. The Metabolic Exercise data combined with Cardiac and Kidney Indexes (MECKI) score was calculated based on LVEF, percent predicted peak $\dot{V}O_2$ (using the equation peak $\dot{V}O_2$ predicted = (Height − Age) × 20 if male, peak $\dot{V}O_2$ predicted = (Height − Age) × 14 if female), VE/$\dot{V}CO_2$ slope, levels of hemoglobin, serum sodium, and MDRD using the earlier published equation (15).

Mortality, MACE, and Unplanned Hospitalization

The survival status of study participants was assessed using the Dutch National Death Registry. The incidence of major adverse CV events (MACE; defined as acute coronary syndrome, percutaneous coronary intervention, coronary artery bypass graft, cardiac arrest, cerebral vascular accident, and CV mortality) and CV-related unplanned hospitalization due to HF (including urgent heart transplantation and left ventricular assistant device implementation), acute coronary syndrome, rhythm or conduction abnormalities, valvular abnormalities, infectious disease affecting the heart, and cerebrovascular accidents (i.e., transient ischemic attack or stroke) were extracted from the electronic patient files. The primary composite endpoint at 5-yr follow-up consisted of all-cause mortality, MACE, and CV-related unplanned hospitalization (14,27). The secondary endpoint was 5-yr all-cause mortality.

Statistical Analysis

All statistical tests were performed using R version 4.2.1 with packages "pROC," "lme4," "AICcmodavg," and "rms." All tests were two-sided, and $P < 0.05$ was considered statistically significant. Continuous normally distributed data are presented as mean ± SD, continuous not-normally distributed data as median (interquartile range (IQR)) and categorical variables as number (%). All data were visually inspected for normality, and the Shapiro–Wilk test was performed. To assess the discriminative power of the different CPET variables and known risk factors, receiver operating characteristic (ROC) curves were made based on logistic regression models, and areas under the curve (AUC) were calculated for the composite endpoint and all-cause mortality. The optimal threshold for risk prediction for every CPET variable was determined using the Youden index method (28), and this threshold was used to obtain characteristics of the prediction models (e.g., sensitivity, specificity, positive predictive value, negative predictive value, and odds ratio). To compare the predictive accuracy across the different CPET variables, the Akaike Information Criterion (AIC) method (29) was used for the composite endpoint and all-cause mortality. The model with the lowest AIC had the best predictive accuracy. In contrast, models with AIC differences ($\Delta AIC = AIC_{model} - AIC_{best\ model}$) ≤2 had substantial support, $4 \leq \Delta AIC \leq 7$ had considerably less support and $\Delta AIC > 10$ had essentially no support (30). To assess the calibration, calibration plots were visually inspected to compare the predicted and actual probability for the three CPET variables with the best predictive accuracy. A sensitivity analysis was performed by including participants reaching maximal effort based on an RER ≥1.1 (31).

RESULTS

Cohort characteristics. The HARP database consisted of 280 patients with HF, of which 43 were excluded based on missing CPET variables or a follow-up <5 yr, yielding an analytical cohort of 237 (85%) patients (Fig. 1). Patients were 66 (58–73) yr old and had a body mass index of 29 ± 5 kg·m^{-2}, and 30% was female. Most participants had HF with reduced ejection fraction (72%) and an NYHA class of 2 (49%) or 3 (40%) (Table 1). Median relative peak $\dot{V}O_2$ was 13.9 (10.7–17.3) mL·(kg·min)$^{-1}$, which was 67% ± 19% of the predicted value (Table 2). In total, 103 participants (43%) reached the composite endpoint (first event in order of importance: mortality: $n = 19$, MACE: $n = 19$, and CV-related hospitalization: $n = 65$), and 55 participants (23%) died within 5 yr.

Discrimination and calibration. The CPET AUC values of the composite endpoint ranged from 0.56 (95% confidence interval (CI), 0.49–0.64) for the $\dot{V}O_2$/workload slope to 0.70 (95% CI, 0.63–0.77) for percent predicted peak $\dot{V}O_2$. The AUC values of other CV risk factors ranged from 0.49 (95% CI, 0.42–0.65) for serum sodium to 0.62 (95% CI, 0.55–0.69) for age. All AUCs values of all-cause mortality were higher compared with AUC values of the composite endpoint, except for $\dot{V}O_2$/workload slope (Fig. 2). ROC curves are depicted in Supplemental Figures 1 and 2 (Supplemental Digital Content, ROC curves of different CPET variables and other well-known predictors for the composite endpoint and for all-cause mortality, http://links.lww.com/MSS/D72). Characteristics of the prediction model are shown in

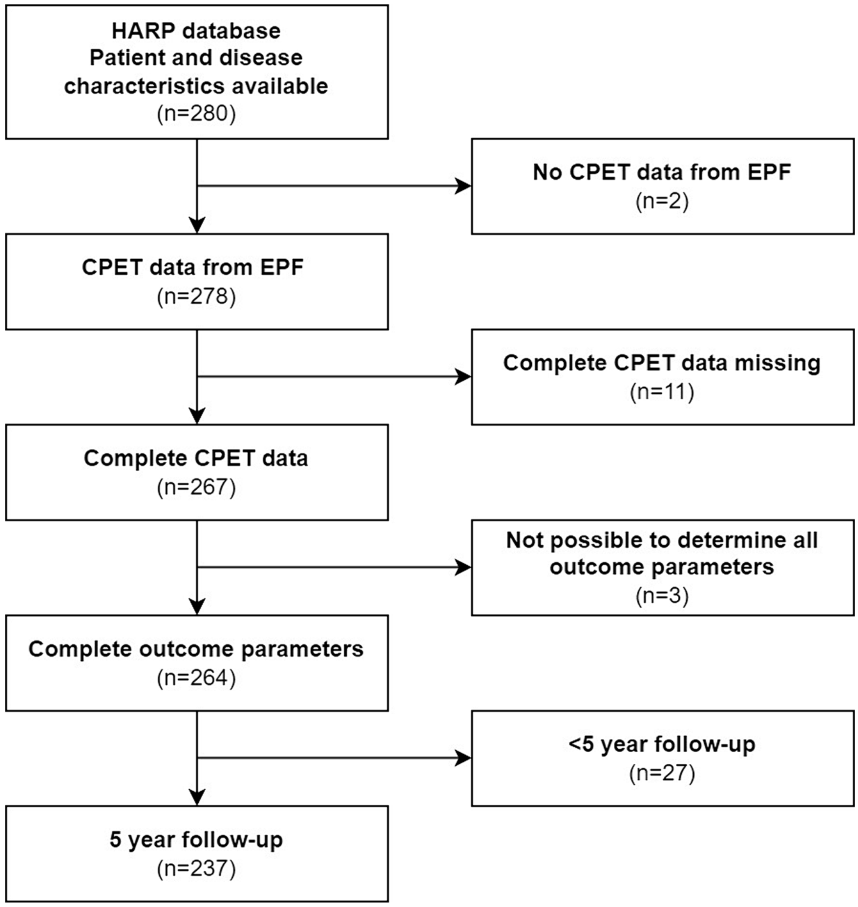

FIGURE 1—Flowchart of the study. Patient and disease characteristics were available of 280 participants. A total of 43 (15%) participants were excluded, leading to an analytical cohort of 237 (85%) patients. CPET, cardiopulmonary exercise test; EPF, electronic patient file.

Supplemental Tables 1 and 2 (Supplemental Digital Content, Characteristics of the prediction models for different maximal, submaximal and multicomponent CPET variables and the composite endpoint, and for all-cause mortality, at 5-yr of follow-up, http://links.lww.com/MSS/D72). Percent predicted peak $\dot{V}O_2$ had the highest predictive accuracy for the incidence of adverse events (AIC: 302.6), whereas the COP (ΔAIC: 1.7) and relative peak $\dot{V}O_2$ (ΔAIC: 1.8) had substantial support, and the VE/$\dot{V}CO_2$ slope until AT (ΔAIC: 4.3) had considerably less support for an equal model fit (Table 3). For all-cause mortality, relative peak $\dot{V}O_2$ had the highest predictive accuracy (AIC: 217.1), whereas the absolute peak $\dot{V}O_2$ (ΔAIC: 3.4) had considerably less-to-substantial support, and the COP had considerably less-to-essentially no support (ΔAIC: 7.3; Table 3). The calibration plots showed a good agreement between the actual and predicted probability for the three best-performing CPET variables for both the composite endpoint and all-cause mortality (Fig. 3).

Sensitivity analysis. A total of 134 participants (57%) reached maximal effort (with RER > 1.1), of which 61 (46%) experienced the composite endpoint and 28 (21%) died within 5 yr. As for the total cohort, COP (highest predictive accuracy, AIC: 168) and percent predicted peak $\dot{V}O_2$ (ΔAIC: 0.1) had the highest predictive accuracies for the composite end point in participants reaching maximal effort. Besides, VE/$\dot{V}CO_2$ until the AT had substantial support for an equal model fit (ΔAIC: 1.6; Supplemental Table 3, Supplemental Digital Content, Characteristics of the prediction models for different CPET variables and adverse events for participants reaching maximal effort, http://links.lww.com/MSS/D72). For all-cause mortality, relative peak $\dot{V}O_2$ had the highest predictive accuracy (AIC: 110.6) in participants reaching maximal effort, which was the same as for the total group. However, there was substantial support for an equal model fit for VE/$\dot{V}CO_2$ slope using all exercise data (ΔAIC: 1.7) and COP (ΔAIC: 1.9) in the maximal effort subgroup (Supplemental Table 3, Supplemental Digital Content, http://links.lww.com/MSS/D72).

DISCUSSION

This study compared the predictive capacity of different maximal and submaximal ventilatory CPET variables in patients with HF. Percent predicted peak $\dot{V}O_2$ had the highest predictive accuracy for major adverse events, whereas COP and relative peak $\dot{V}O_2$ had similar discriminative power. Relative peak $\dot{V}O_2$ had the highest predictive accuracy for all-cause mortality, with considerably less-to-substantial support

TABLE 1. Patient and disease-related characteristics of the total study cohort (n = 237).

	Total Population (n = 237)
Patient characteristics	
Age (yr)	66 (58–73)
Sex (women)	72 (30%)
Body mass index (kg·m^{-2})	29 ± 5
Current smoker	29 (12%)
Diabetes mellitus	59 (25%)
COPD, n (%)	30 (13%)
HF characteristics	
LVEF (%)	33 (20–42)
Type of HF	
HFrEF	167 (70%)
HFmrEF	41 (17%)
HFpEF	29 (13%)
HF etiology	
Ischemic	104 (44%)
Idiopathic	69 (29%)
Other	48 (20%)
Valvular	16 (7%)
NYHA class	
Class 1	24 (10%)
Class 2	116 (49%)
Class 3	94 (40%)
Class 4	3 (1%)
Diastolic blood pressure (mm Hg)	75 ± 11
Systolic blood pressure (mm Hg)	123 ± 21
Medical devices	
ICD	108 (46%)
Biventricular	39 (36%)
Pacemaker	54 (23%)
CRT	45 (19%)
Cardiac comorbidities	
Atrial tachycardia	197 (83%)
Atrial fibrillation	114 (48%)
PTCA	60 (25%)
CABG	44 (19%)
Heart transplantation	0 (0%)
Medication	
ACEI or ARB	215 (91%)
Aldosterone receptor antagonist	155 (65%)
β-Blocker	222 (94%)
Diuretic	215 (91%)
Statin	146 (61%)
Laboratory values	
NT-proBNP (ng·L^{-1}) (n = 222)	884 (424–1843)
MDRD (mL·min^{-1}·1.73 m^{-2})	59 (45–67)
Creatinine (μmol·L^{-1})	105 (86–128)
Hemoglobin (mmol·L^{-1})	8.4 ± 1.0
Na$^+$ (mmol·L^{-1})	139 (138–141)

Data are presented as n (%), mean ± SD, or median (IQR).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; HFmrEF, heart failure with midrange ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with restricted ejection fraction; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MDRD, modification of diet in renal disease; NT-proBNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; PTCA, percutaneous transluminal coronary angioplasty.

for an equal model fit for absolute peak $\dot{V}O_2$ and considerably less-to-essentially no support for COP. These findings were reinforced by our sensitivity analysis in participants reaching maximal effort. All models showed an excellent calibration between predicted and actual probabilities. Our findings suggest that the COP can be used as a submaximal alternative for peak $\dot{V}O_2$-derived CPET variables to stratify the risk for adverse events in patients with HF. In contrast, relative peak $\dot{V}O_2$ solely remains the best predictor for mortality.

Adverse clinical outcomes. The clinical relevance of CPET variables to predict adverse outcomes in patients with HF is broadly recognized. Still, studies examining the best predictor among a wide variety of CPET-derived variables are scarce. We found that the percent predicted peak $\dot{V}O_2$ was the best predictor for adverse clinical outcomes, which aligns with previous work (15). Combined with the finding that relative peak $\dot{V}O_2$ had substantial support for an equal model fit, this highlights the importance of peak $\dot{V}O_2$ to assess the risk for adverse clinical outcomes in patients with HF.

The novel submaximal ventilatory variable COP had the second highest predictive accuracy and performed better than other classic maximal, submaximal, and multicomponent variables. As COP had substantial support of an equal model fit compared with the percent predicted peak $\dot{V}O_2$, COP might be used as an alternative for peak $\dot{V}O_2$.

Some studies also identified the (submaximal) VE/$\dot{V}CO_2$ slope as an independent predictor of adverse outcomes (8,14,15), but this variable had considerably less support for an equal model fit compared with the best-performing variable in the total cohort (ΔAIC: 4.2). However, when assessing the subgroup reaching maximal effort, there was substantial support for the VE/$\dot{V}CO_2$ slope until AT (ΔAIC: 1.2) and VE/$\dot{V}CO_2$ slope during full exercise (ΔAIC: 2.2). There are

TABLE 2. CPET results of the total study cohort (n = 237).

	Total Population (n = 237)
Rest variables	
Rest HR (bpm)	74 (65–82)
Rest lactate (mmol·L^{-1}) (n = 236)	2.1 ± 0.7
Submaximal variables	
VE/$\dot{V}CO_2$ slope until AT	33.2 (29.4–38.7)
COP	28 (25–32)
$\dot{V}O_2$ at AT	
Absolute (mL·min^{-1})	819 ± 253
Relative (mL·(kg·min)$^{-1}$	9.5 ± 2.5
Percent peak (%)	66 ± 13
OUES	
OUES75	1.36 (1.08–1.65)
OUES50	1.17 (0.99–1.45)
HR at AT (bpm)	91 ± 17
Workload at AT (W) (n = 235)	37 (24–58)
O_2 pulse at AT (mL·bpm^{-1})	9.1 ± 2.6
PetCO_2 at AT (mm Hg) (n = 235)	34.6 (31.8–37.7)
Maximal variables	
Peak $\dot{V}O_2$	
Absolute (mL·min^{-1})	1186 (903–1541)
Relative (mL·(kg·min)$^{-1}$	13.9 (10.7–17.3)
Percent predicted (%)	67 ± 19
VE/$\dot{V}CO_2$ slope	35.6 (31.5–39.1)
Peak HR	
Absolute (bpm)	116 (97–139)
Percent predicted (%)	73 ± 15
Peak workload (W)	89 (61–128)
Peak O_2 pulse (mL·bpm^{-1})	10.0 (7.9–12.5)
Peak VE (L·min^{-1}) (n = 235)	54 (42–72)
Peak RER (n = 236)	1.1 ± 0.1
Peak PetCO_2 (mm Hg)	40.7 ± 5.1
Lactate (mmol·L^{-1}) (n = 227)	3.7 (2.8–4.7)
OUES100	1.39 (1.07–1.77)
$\dot{V}O_2$/W (mL·(min·W)$^{-1}$)	9.1 (7.7–10.3)
Multicomponent variables	
MECKI score	5 (2–11)

Data are presented as mean ± SD or median (IQR).
AT, anaerobic threshold; COP, cardiorespiratory optimal point; HR, heart rate; MECKI score, Metabolic Exercise Cardiac Kidney Indexes; OUES50/75/100, oxygen uptake efficiency slope with 50% of maximal data, 75% of maximal data, and 100% of maximal data; PetCO_2, partial pressure of end-tidal carbon dioxide; RER, respiratory exchange ratio; VE: ventilation; $\dot{V}O_2$/W slope, $\dot{V}O_2$/workload slope.

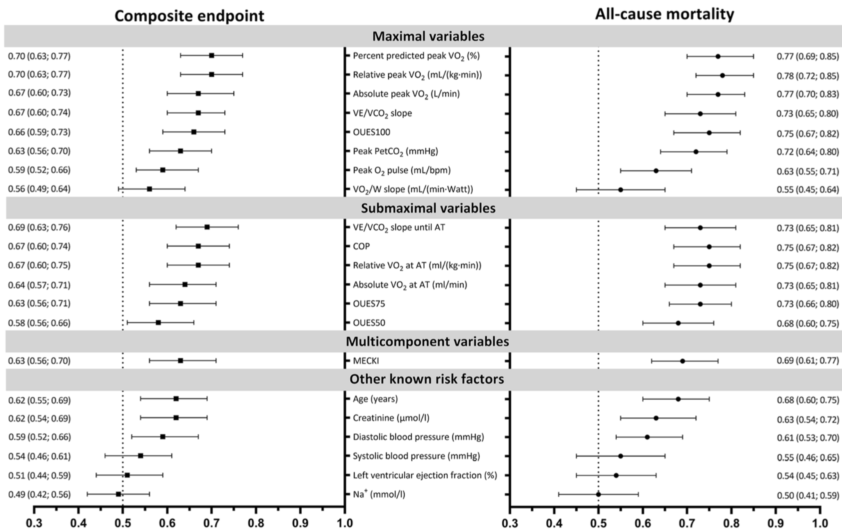

FIGURE 2—AUC of different CPET variables. AUCs were based on the ROC curves of different maximal, submaximal and multicomponent CPET variables as well as known CV risk factors and 5-yr event rate defined as a composite endpoint (left panel) and all-cause mortality (right panel). Composite endpoint consisted of CV-related unplanned hospitalization, major adverse CV events, and all-cause mortality. AT, anaerobic threshold; COP, cardiorespiratory optimal point; MECKI score, Metabolic Exercise Cardiac Kidney Indexes; OUES50/75/100, oxygen uptake efficiency slope with 50% of maximal data, 75% of maximal data, and 100% of maximal data; $PetCO_2$, partial pressure of end-tidal carbon dioxide; VE, ventilation; $\dot{V}O_2$/W slope, $\dot{V}O_2$/Workload slope.

several explanations for this discrepant finding. First, other studies included only patients who were considered to have reached maximal effort (15) or a larger proportion of participants (69%) who reached maximal effort (15). Second, they reported on hazard ratios of multivariable cox regression models or only AUC values, but did not use a comparing method to directly compare the different CPET variables such as the AIC method (32). Third, a study assessing the effect of RER on the discriminative power of the VE/$\dot{V}CO_2$ slope suggested that low RER values (RER ≤0.95) lead to poorer discriminative power (AUC of 0.53), where the AUC of peak $\dot{V}O_2$ was still 0.60 (16). Finally, several methods to calculate the VE/$\dot{V}CO_2$ slope are used in clinical practice, which greatly influences the slope (±4 units) (6,33), and therefore, we included two calculation methods. A standardized calculation method seems needed to explore the prognostic value in submaximal and maximal exercise testing further (33). Surprisingly, the multicomponent MECKI score, which combines CPET variables with cardiac and metabolic indexes, was not among the best predictors. To our knowledge, the score was earlier internally and externally validated in HFrEF (15,34,35), but we are the first to assess the predictive accuracy in comparison to other CPET variables in an external cohort consisting of different HF types. Taken together, we showed that percent predicted $\dot{V}O_2$, COP, and relative peak $\dot{V}O_2$ are predictive for adverse events, whereas other (classic) maximal, submaximal, and multicomponent CPET variables had considerably less to essentially no discriminative power.

Mortality. Relative peak $\dot{V}O_2$ was clearly the best predictor for all-cause mortality, followed by absolute peak $\dot{V}O_2$ and COP. As for the composite end point, the high predictive accuracy of (relative) peak $\dot{V}O_2$ for mortality was supported by other studies (16,36,37), but we found only a high predictive accuracy of the VE/$\dot{V}CO_2$ slope when assessing the subgroup reaching maximal effort (36,37). The higher predictive accuracy of relative $\dot{V}O_2$ compared with COP is supported by a study in the general population (38), although other studies reported it to be slightly worse (39) and not different in males compared with COP (40). A possible explanation for the

TABLE 3. Characteristics of the prediction models for different CPET variables and adverse events.

	Composite Endpoint		All-Cause Mortality	
	AIC	ΔAIC	AIC	ΔAIC
Maximal variables				
Peak $\dot{V}O_2$				
Percent predicted (%)	302.6	REF	225.5	8.4
Relative (mL·(kg·min)$^{-1}$	304.4	1.8	217.1	REF
Absolute (mL·min^{-1})	310.5	8.0	220.5	3.4
VE/$\dot{V}CO_2$ slope	311.2	8.7	234.7	17.6
OUES100	311.2	8.6	226.3	9.2
Peak $PetCO_2$ (mm Hg)	316.8	14.3	235.3	18.2
Peak O_2 pulse (mL·bpm^{-1})	323.4	20.8	252.0	34.9
$\dot{V}O_2$/W (mL·(min·W)$^{-1}$)	328.1	25.5	260.6	43.5
Submaximal variables				
VE/$\dot{V}CO_2$ slope until AT	306.9	4.3	233.5	15.4
COP	304.3	1.7	224.4	7.3
$\dot{V}O_2$ at AT				
Relative (mL·(kg·min)$^{-1}$	313.9	11.3	231.5	14.4
Absolute (mL·min^{-1})	320.7	18.1	233.6	16.5
OUES				
OUES75	316.4	13.8	230.9	13.8
OUES50	323.0	20.4	241.5	24.4
Multicomponent variables				
MECKI	321.5	18.9	250.5	33.4

AIC of the prediction models for different maximal, submaximal, and multicomponent CPET variables and the composite end point (left) and all-cause mortality (right) at 5-yr of follow-up. The composite outcomes contain all-cause mortality, major adverse CV event, and CV-related unplanned hospitalization.

95% CI, 95% confidence interval; AIC, Akaike Information Criterion; AT, anaerobic threshold; COP, cardiorespiratory optimal point; MECKI score, Metabolic Exercise Cardiac Kidney Indexes; OUES50/75/100, oxygen uptake efficiency slope with 50% of maximal data, 75% of maximal data, and 100% of maximal data; $PetCO_2$, partial pressure of end-tidal carbon dioxide; VE, ventilation; $\dot{V}O_2$/W slope, $\dot{V}O_2$/workload slope.

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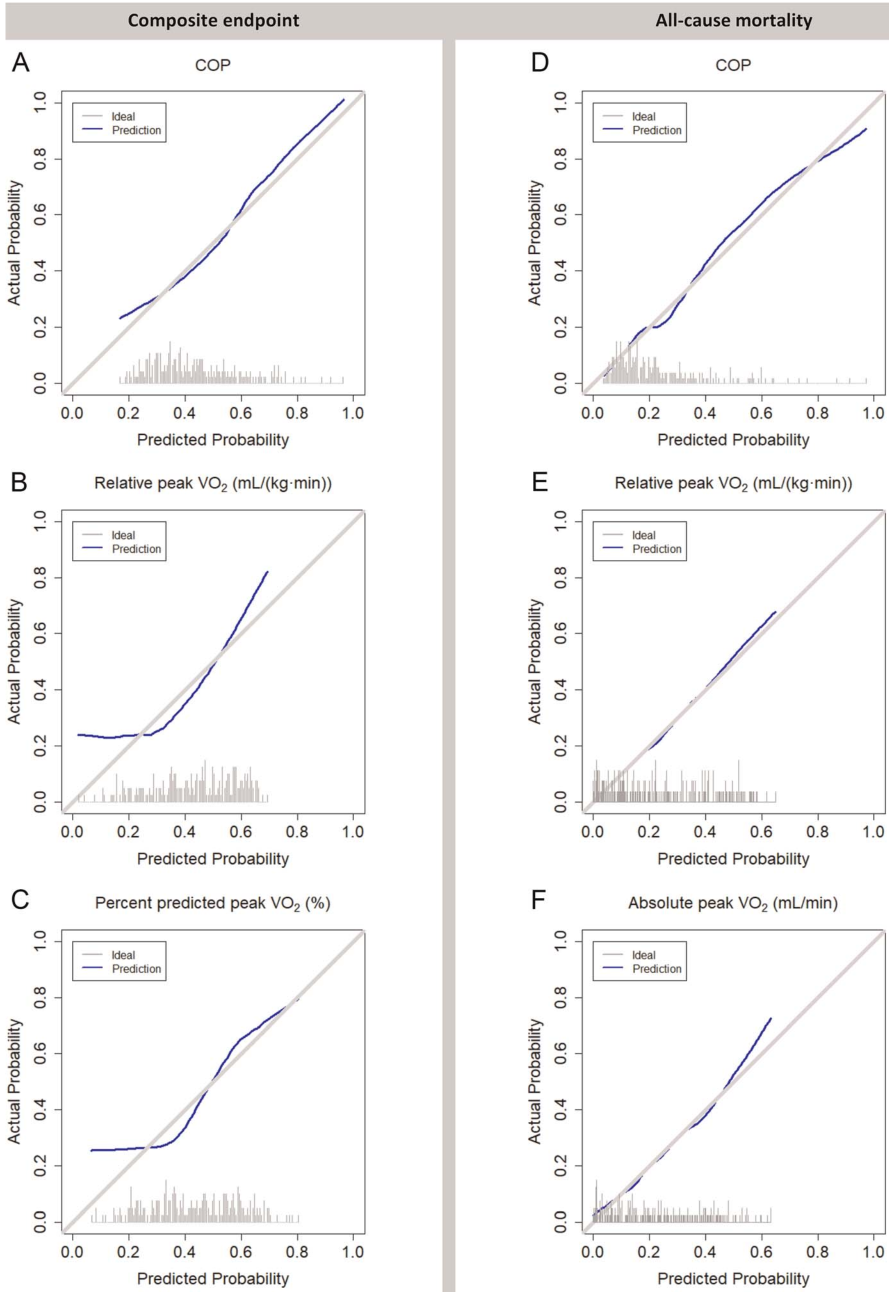

FIGURE 3—Calibration plots of the best-performing prediction models. Calibration plots of the three best-performing prediction models of CPET variables and the composite endpoint (left panel) and all-cause mortality (right panel) at 5-yr of follow-up. Dashed blue curve: prediction of the model. Gray line: ideal perfect calibration. The histogram above the *x* axis summarizes the relative prevalence of the specific predicted probability. COP, cardiorespiratory optimal point.

difference in predictive accuracy for mortality is that relative peak $\dot{V}O_2$ is a measure of functional capacity, and low values can reflect problems in a broad range of (organ)systems (41). COP is a measure of ventilatory efficiency (39), and abnormal values likely reflect a more significant CV dysfunction (i.e., abnormal pulmonary hemodynamics, exaggerated chemoreceptor and ergoreceptor sensitivity, and HR variability) leading to inefficient breathing (31), which might explain the lower predictive accuracy for all-cause mortality compared with MACE and CV-related hospitalizations. More research on the predictive accuracy of both COP and peak $\dot{V}O_2$ and their working mechanisms is warranted.

Based on the AUC values, CPET ventilatory variables seem to have a higher discriminative mortality capacity than the composite endpoint. Higher AUC values for mortality compared with HF hospitalization were earlier reported in a systematic review assessing a wide variety of predictors (42,43). It was suggested that a complex interplay of factors causes HF hospitalization and that nonmedical factors also play a large role (43). The finding that the AUC values of the best-performing

CPET variables were higher than the AUC values of the best-performing other well-known CV risk factors indicates that performing an exercise test delivers valuable information for the risk stratification in HF.

Clinical implications. The observation that the submaximal variable COP had substantial support for an equal model fit for adverse outcomes compared with peak $\dot{V}O_2$ variables may have significant clinical consequences. As the COP is typically reached at 44%–51% of peak $\dot{V}O_2$ (10,12), it can potentially be obtained by a submaximal incremental exercise test such as the incremental shuttle walk test that is already used in the context of cardiac rehabilitation programs (44). Submaximal exercise tests are cheaper, easier to perform or repeat for observing changes in clinical status or treatment options, and less burdensome for patients compared with maximal exercise tests (31). Besides, novel and cheaper wearables make it possible to measure gas exchange during the incremental shuttle walk test (45). This might increase the use of cardiorespiratory fitness assessment as it remains significantly underutilized in clinical settings (5). Other advantages of submaximal testing include that reaching maximal effort, which is difficult to obtain in patient with HF (31), is not necessary and that the intensity of the test represents the effort required for daily activities. We have previously shown that the COP is modifiable by enrollment in cardiac rehabilitation (12), which offers possibilities to monitor the effects of an intervention, such as supervised exercise training or other therapeutic options. Given the high hospital readmission rates in patients with HF, submaximal exercise test variables that are easy to obtain and hold good predictive value, such as the COP, offer new possibilities for risk stratification and treatment monitoring.

Study strengths and limitations. The strength of the current study includes the wide variety of examined ventilatory CPET variables ranging from (novel) submaximal, maximal, and multicomponent variables for risk stratification in patients with HF and the systemic approach to compare the CPET variables using discrimination and calibration. Besides, our models used continuous CPET variables instead of a binary approach in our models. This prevents the loss of information (46) and the subjective determination for the optimal threshold (47), as the clinical utility depends on the aim of the prediction and resulting desired balance between sensitivity and specificity. Future studies should examine clinically relevant thresholds for CPET variables considering the prediction's objective with desired balance between sensitivity and specificity. However, there were also some limitations. First, our sample size was moderate (n = 237 patients) and with diversity in the HF profile, but all patients were followed for 5 yr, and the event rate was high (n = 103 patients, 43%), ensuring sufficient statistical power. Nevertheless, external validation in a large sample is warranted to explore the generalizability of our findings. Second, the small number of women (30%) and patients with different subtypes or severities of HF made it impossible to perform stratified analysis across those subgroups. Third, the mortality rate in our cohort was lower than expected. This may possibly be explained by the lower age (48), relative low rate of ischemic HF causes (49), and the participation in CR, which is linked to better clinical outcomes (50). How the relative low mortality rate in our sample and ongoing advances in HF therapy (51) affect our findings should be further explored. Finally, some ventilatory CPET variables that were earlier reported to predict adverse events in patients with HF such as exercise oscillatory ventilation pattern, and resting $PetCO_2$ and $PetCO_2$ differences during exercise were unavailable for our cohort (14,52) and should be added to future federated analyses.

CONCLUSIONS

Percent predicted and relative peak $\dot{V}O_2$ had the highest predictive accuracy for adverse CV events and mortality in patients with HF, whereas the submaximal COP had comparable predictive accuracy for adverse events. These findings offer novel possibilities for submaximal exercise testing in patients with HF, as such tests are more accessible and more comfortable for the patients than maximal exercise tests, which might lead to a more convenient way of exercise-based risk stratification and disease monitoring in patients with HF.

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Authors' Contributions: S. K., T. E., M. H., and J. S. were involved in the conception of the study design and protocol. S. K., J. S., and T. E. were involved in the data collection. S. K. and E. B. analyzed the data. S. K., J. S., J. M., C. A., M. H., R. v. K., T. E., and E. B. interpreted the data. S. K. was responsible for initial writing and drafting of the article. J. S., J. M., C. A., M. H., R. v. K., T. E., and E. B. critically revised the manuscript. The final manuscript was approved by all authors.

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