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Physical Activity and Depression Predict Event-Free Survival in Heart Transplant Candidates

Heike Spaderna
University of Wuppertal

Claus Vögele
University of Luxembourg

Markus J. Barten
Heart Center, Leipzig, Germany

Jacqueline M. A. Smits
Eurotransplant International Foundation, Leiden, The Netherlands

Vina Bunyamin
Johannes Gutenberg University

Gerdi Weidner
San Francisco State University

Objective: This study prospectively evaluated the relationship of physical activity (PA), depression, and anxiety to event-free survival during waiting time for heart transplantation in ambulatory patients enrolled in the Waiting for a New Heart Study. ***Method:*** Data from 227 ambulatory patients newly listed for heart transplantation were analyzed. Everyday PA (number of activities, caloric expenditure), depression, and anxiety at time of listing were assessed via questionnaires. Events were defined as death, high-urgency transplantation, delisting due to clinical deterioration, and mechanical circulatory support device implantation. Associations of PA scores, depression, and anxiety with event-free survival were analyzed using Cox proportional hazards models. Covariates included age, sex, body mass index, and objective indicators of disease severity. ***Results:*** After a median follow-up of 478 days (6–1,849 days), 132 events occurred (46 deaths, 20 mechanical circulatory support device implantations, 54 high-urgency transplantations, 12 delistings). A higher number of activities was significantly associated with a reduced hazard ratio (HR) to experience an event (HR = 0.88, 95% CI [0.81, 0.96]), and depression increased this risk (HR = 1.64, 95% CI [1.16, 2.32]). Both effects remained significant in multivariate analyses (HR = 0.91, 95% CI [0.83, 0.99]; HR = 1.60, 95% CI [1.12, 2.29], *ps* < .02). No significant interactions between PA scores and emotions were observed and anxiety was unrelated to survival. ***Conclusion:*** Both everyday PA and the absence of depression prolonged event-free survival in ambulatory heart transplant candidates. These findings were independent of objective measures of disease severity. Patients waiting for cardiac transplantation may benefit from interventions focused on increasing their everyday PA and reducing depressive symptoms.

Keywords: heart failure, depression, anxiety, physical activity, heart transplant waiting list

Heart failure (HF) affects 5.7 million people in the United States (Roger et al., 2011) and 15 million people in Europe (Dickstein et al., 2008). Because of an ageing population and better survival of patients with coronary events, the number of patients with advanced HF (Stage D) is increasing, but their prognosis remains poor (Metra et al., 2007).

Recommendations for the treatment of HF incorporate physical activity for stable patients (Heart Failure Society of America,

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Heike Spaderna, Department of Health Psychology and Applied Psychological Assessment, University of Wuppertal, Germany; Claus Vögele, Unité de recherche INSIDE, Université du Luxembourg, Luxembourg; Markus J. Barten, Heart Center Leipzig, Germany; Vina Bunyamin, Johannes Gutenberg University, Mainz, Germany; Jacqueline M. A. Smits, Eurotransplant International Foundation, Leiden, The Netherlands; Gerdi Weidner, Department of Biology, San Francisco State University.

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Correspondence concerning this article should be addressed to Heike Spaderna, Gesundheitspsychologie und Angewandte Diagnostik, University of Wuppertal, Gaußstraße 20, 42119 Wuppertal, Germany. E-mail: spaderna@uni-wuppertal.de; Gerdi Weidner, Department of Biology, Romberg Tiburon Center, San Francisco State University, 3250 Paradise Drive, Tiburon, CA 94965. E-mail: gweidner@sfsu.edu

2010), even for patients with advanced disease listed for heart transplantation (HTx; Jessup et al., 2006; Piña et al., 2003). Physical activity has been shown to improve health status in these patients in various domains, such as quality of life (Davies et al., 2010; Downing & Balady, 2011), peak oxygen consumption (peakVO_2), central hemodynamic function, autonomic nervous system function, endothelial function, skeletal muscles, and inflammatory markers (Downing & Balady, 2011). Even patients with advanced disease (i.e., <25% left ventricular ejection fraction) have been shown to benefit from exercise training (Erbs et al., 2010; Hollriegel et al., 2012).

Clearly, physical activity has beneficial effects on several health indicators among patients with advanced HF. Whether physical activity also influences hard outcomes, such as improved survival, remains elusive. Contrary to an earlier meta-analysis of the effects of exercise training in HF showing reduced mortality in patients of the intervention group compared with patients in the control group (Piepoli, Davos, Francis, & Coats, 2004), a recent Cochrane meta-analysis of exercise trials for patients with HF found no effect on mortality associated with participation in exercise interventions (Davies et al., 2010). This latter analysis included results from a large multicenter trial (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) that randomized 2,331 outpatients to either an exercise training group or a usual care group (O'Connor et al., 2009). Patients exercised on a treadmill or stationary bike during 36 supervised sessions in the first 3 months (target duration of 90 min/week), followed by home-based training with a target training regimen of five times per week for 40 min. However, after a median follow-up of 30 months, there was no group difference in mortality (16% vs. 17%; O'Connor et al., 2009). Importantly, adherence to the exercise regimen was rather low in the intervention group. At several time points, only 30% of the patients exercised at the prescribed target level, and some participants from the usual care group also reported engaging in physical activities, for example, walking (O'Connor et al., 2009).

These results suggest that it may be difficult to implement intensive exercise programs into the daily routine of patients with HF. In the Waiting for a New Heart Study (Spaderna, Zahn, et al., 2010), the percentage of patients reporting regular physical exercise (e.g., cycling on an ergometer, cardiac training) was also quite low (fewer than 7%). However, the percentage of patients engaging in regular household activities was high (41%), and 26% reported taking leisure walks (Spaderna, Zahn, et al., 2010).

There is some indication that engaging in simple everyday physical activity, such as walking, may improve the prognosis of patients with advanced HF awaiting HTx (Stevenson et al., 1995). In this uncontrolled study of 107 ambulatory HTx candidates, patients were instructed to go for 20- to 30-min walks at least four times per week. After 6 months, 38 patients showed peakVO_2 improvements, and 31 were removed from the waiting list. After 21 months, 28 of these patients were still alive without HTx (Stevenson et al., 1995). Thus, everyday physical activities, such as going for walks, housework, or gardening, in addition to physical activities patients already engage in, deserve more attention as an easily accessible alternative to structured exercise programs.

In the context of physical activity, it is also important to consider patients' emotional status, that is, depression and anxiety. Depression and depressive symptoms have been linked cross-sectionally to lower levels of physical activity in adults (Lindwall, Larsman, & Hagger, 2011; Trost, Owen, Bauman, Sallis, & Brown, 2002), patients with coronary heart disease (Petter, Blanchard, Kemp, Mazoff, & Ferrier, 2009), and HTx candidates, independent of their disease severity (Spaderna, Zahn, et al., 2010). Depression shows a mean prevalence rate of 21.5% in patients with HF (Gnanasekaran, 2011; Spaderna, Smits, Rahmel, & Weidner, 2007) and is associated with increased mortality in these patients (Freedland, Carney, & Rich, 2011), although not consistently (Madan et al., 2012; Pelle et al., 2010). In the Waiting for a New Heart Study, depression reduced chances for event-free survival (Weidner & Spaderna, 2012) and contributed to deterioration of health status as indicated by implantation of mechanical circulatory support devices (MCSDs) and by receiving high-urgency transplantation, independent of objectively measured disease severity (Spaderna et al., 2012).

In studies that considered both physical activity and depression, physical inactivity was found to mediate the relationship between depression and cardiovascular events (including mortality) in outpatients with stable coronary heart disease (Whooley et al., 2008) and between depression and cardiovascular mortality in elderly ambulatory, noninstitutionalized adults (Win et al., 2011), suggesting that physical inactivity is one of the mechanisms leading to deterioration of health. As depression was not assessed in the Stevenson et al. (1995) early physical activity study with HTx candidates, it remains to be examined whether everyday physical activity contributes to prognosis in patients with advanced HF listed for HTx independent of depression.

Anxiety has also been associated with reduced physical activity in patients with HF (Ingle et al., 2006), because patients might be anxious that being physically active could increase their symptoms and further impair their condition (Tierney et al., 2011). However, studies relating measures of anxiety to physical activity in this population are scarce. Moreover, the association of anxiety with survival in patients with HF remains elusive (Pelle, Gidron, Szabo, & Denollet, 2008; Spaderna et al., 2007).

The main aim of the present study was to prospectively evaluate the association of everyday physical activity with event-free survival in ambulatory patients enrolled in the Waiting for a New Heart Study, while considering objectively assessed medical risk, depression, and anxiety. Specifically, the association of everyday physical activity reported at wait listing with time until the occurrence of events indicating a decline in health status, including MCSD implantation, high-urgency transplantation, delisting due to clinical deterioration, and death, was analyzed. The following hypotheses were investigated: (1) Ambulatory patients who are more physically active at time of wait listing have better event-free survival, that is, have a lower risk of experiencing an event than patients who are less physically active, independent of disease severity. (2) Ambulatory patients with high depression scores indicating clinically relevant symptoms (or anxiety, respectively) have worse event-free survival during waiting time than those with no or few symptoms. (3) Physical activity is associated with event-free survival even after adjusting for the effects of depression or anxiety. Interactive effects of PA with negative emotions on event-free survival were also explored.

Method

Procedure and Participants

The Waiting for a New Heart Study is an ongoing prospective multisite observational study of patients newly listed for HTx in 17 hospitals (16 in Germany, one in Austria). It aims to identify psychological, social, and behavioral predictors of pretransplant outcomes. For the present report, waiting list outcomes were considered until March 31, 2010. The study procedures have been described previously (Spaderna, Mendell, et al., 2010; Spaderna, Weidner, Zahn, & Smits, 2009). Briefly, between April 2005 and December 2006, written informed consent was obtained from consecutive adult patients who were newly registered for HTx with the Eurotransplant International Foundation. Exclusion criteria were age younger than 18 years, listed for combined heart–lung transplantation or retransplantation, not fluent in German, and being too severely ill to participate, as rated by their primary physician. Of 479 newly listed patients, 380 met inclusion criteria. Questionnaires were mailed to 340 patients who consented and were completed by 318 patients (Spaderna et al., 2009).

Given the focus on everyday physical activity, the present report is restricted to 227 patients who were ambulatory and MCSD-free at time of listing. Changes in waiting list status to determine study endpoints were obtained from Eurotransplant. Comparisons of nonparticipants with participating patients have been reported previously (Spaderna, Mendell, et al., 2010; Spaderna et al., 2009). The nonparticipants were comparable to the participating patients in terms of age and percentage of women. However, nonparticipants were more likely to have severe HF as suggested by New York Heart Association Class IV (i.e., HF symptoms even at rest) than participants (Spaderna et al., 2009). These more severely ill patients would have been less likely to be included in the present sample because of their nonambulatory status. The study was approved by local ethics committees and carried out in accordance with the American Psychological Association's Ethical Principles of Psychologists and Code of Conduct and the Declaration of Helsinki.

Measures

Questionnaire variables. Everyday physical activity was assessed by a modified version of the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire (Stewart et al., 2001). Our adaptation (Spaderna, Zahn, et al., 2010) lists 15 activities of light to moderate intensity, that is, with metabolic equivalents of task values (MET; 1 MET = a metabolic rate at rest consuming 3.5 ml of oxygen per kilogram of body weight per minute) ≥ 2.5 and < 6 according to the compendium of physical activities (Ainsworth et al., 2000). Items include activities such as light gardening, riding a bike, walking to do errands, or stretching. Participants were asked whether or not they engaged in each activity, referring to a typical week during the past 4 weeks (yes or no). If the answer was yes, participants reported the frequency per week and how many hours/week they engaged in the activity, the latter providing an estimate of duration for each activity (6-point scale from *<1 hour* to *9 or more hours*, recoded to 0.5 to 9.75 hr/week; Stewart et al., 2001). An additional item, climbing stairs, was added to the CHAMPS activities. This was considered relevant because, in Europe, many buildings including private residences often do not have elevators. This item was assessed as an activity (yes or no) without an estimated duration or MET value.

Based on these data, we computed two sum scores: (a) number of physical activities engaged in, including all 15 activities with a MET value ≥ 2.5 (Ainsworth et al., 2000) plus climbing stairs, which yielded a score between 0 and 16; (b) caloric expenditure per week was calculated according to Stewart et al. (2001), that is, based on the duration of the 15 physical activities (excluding stair climbing) in which a patient had engaged. Each item value was weighted by the respective activity's MET value and multiplied by $3.5 \times 60 \times$ (weight in kg/200). These caloric expenditure values were summed, yielding the total amount of kilocalories/week spent in these activities (Spaderna, Zahn, et al., 2010; Stewart et al., 2001). In cross-sectional analyses of data from all Waiting for a New Heart Study participants, both number of physical activities and caloric expenditure were significantly positively correlated with objectively assessed peakVO_2, a measure of physical fitness (Spaderna, Zahn, et al., 2010). The original CHAMPS questionnaire has also been successfully validated using accelerometers (Pruitt et al., 2008) and showed acceptable reliability (Giles & Marshall, 2009).

Depression and anxiety were assessed using the German translation of the Hospital Anxiety and Depression Scale (HADS; Herrmann-Lingen, Buss, & Snaith, 2005). This scale comprises seven depression and seven anxiety items, excluding somatic symptoms that could be confounded with physical symptoms of heart disease. Responses range from 0 to 3, yielding total scores between 0 and 21 for each scale. Scores ≥ 9 on the Depression subscale and scores ≥ 11 on the Anxiety subscale suggest symptoms indicative of clinically relevant disorders (Herrmann-Lingen et al., 2005). Both the English and the German versions of the HADS have been extensively validated (Bambauer, Locke, Aupont, Mullan, & McLaughlin, 2005). Internal consistencies (Cronbach's alpha) of the Anxiety and Depression subscales were .80 and .81, respectively, in the German norm sample (Herrmann-Lingen et al., 2005) and acceptable in our entire sample of 318 patients with $\alpha = .79$ for anxiety and $\alpha = .77$ for depression (Spaderna et al., 2009).

Clinical variables at time of listing. Eurotransplant provided medical information at time of listing including anthropometric variables; medications; hemodynamic parameters such as left ventricular ejection fraction, cardiac index, and pulmonary capillary wedge pressure (PCWP); functional parameters such as peakVO_2; and laboratory parameters such as serum creatinine and sodium. The Heart Failure Survival Score was computed, a medical risk score consisting of seven parameters (see Table 1). This score was derived from ambulatory patients with HF awaiting HTx (Aaronson et al., 1997). Lower scores denote an increased medical risk. The score has acceptable prognostic performance (Goda, Lund, & Mancini, 2011) and was associated with death on the waiting list, high-urgency HTx, and need for an MCSD in the Waiting for a New Heart Study (Spaderna et al., 2012; Zahn et al., 2010). Demographic variables and ambulatory status were assessed via questionnaire.

Event-free survival. Event-free survival was expressed as time (number of days) until first event since entering the waiting list. Events were defined as death on the waiting list, delisting due to clinical deterioration, MCSD implantation, and high-urgency

Table 1
Baseline Characteristics of 227 Ambulatory Patients Newly Listed for Heart Transplantation

Variable	Mean SD	Median	IQR
Women, *n* (%)	42 (18.5)		
Age (years)	53.3 (10.3)	54	47–62
Currently living alone, *n* (%)	36 (15.9)		
Currently working, *n* (%)	23 (10.1)		
Education 9 years or less, *n* (%)	150 (66.1)		
Body mass index (kg/m^2)	26.3 (4.0)	26.1	23.7–28.9
Ischemic diagnosis, *n* (%)[a]	90 (39.6)		
QRS complex > 0.12 s, *n* (%)[a]	118 (52.0)		
Peak oxygen uptake (ml/min/kg)[a]	11.3 (2.7)	11.4	10.0–12.7
Left ventricular ejection fraction (%)[a]	24.2 (10.0)	23.0	18.5–29.0
Systolic blood pressure (mmHg)[a]	107.0 (16.4)	107.0	95.0–117.3
Diastolic blood pressure (mmHg)[a]	64.7 (12.0)	64.0	56.8–71.0
Heart frequency (bpm)[a]	75.1 (15.6)	73.0	65.0–84.3
Cardiac index (ml/min/m^2)	2.2 (0.6)	2.0	1.7–2.3
PCWP (mmHg)	19.7 (8.4)	19.0	14.0–25.0
Sodium (mmol/l)[a]	137.5 (4.0)	138.0	135.0–140.0
Serum creatinine (mg/dl)	1.4 (0.5)	1.3	1.1–1.5
Heart Failure Survival Score	7.9 (0.9)	7.8	5.8–11.2
Beta-blockers (*n* = 226), *n* (%)	192 (84.6)		
ACE inhibitors, AT$_1$ blockers (*n* = 225), *n* (%)	168 (74.0)		
Diuretics (*n* = 226), *n* (%)	196 (85.7)		
Digitalis (*n* = 226), *n* (%)	116 (50.2)		
Aldosterone antagonists (*n* = 226), *n* (%)	143 (63.0)		
Antiarrhythmics (*n* = 218), *n* (%)	57 (25.1)		
Anticoagulation drugs (*n* = 218), *n* (%)	167 (73.6)		
Antidepressants (*n* = 205), *n* (%)	17 (8.3)		
Previous heart surgery (*n* = 217), *n* (%)	66 (30.4)		
Diabetes mellitus (*n* = 208), *n* (%)	62 (29.8)		
Peripheral artery disease (*n* = 199), *n* (%)	10 (5.0)		
ICD (*n* = 207), *n* (%)	130 (57.3)		
Number of physical activities (0–16)	4.0 (2.2)	4	3–5
Caloric expenditure (kcal/week)	1,981.7 (1,680.5)	1,607	538–3,171
HADS Depression score ≥ 9, *n* (%)	84 (37.0)		
HADS Depression score (0–21)	7.60 (3.67)	7	5–10
HADS Anxiety score ≥ 11, *n* (%)	39 (17.2)		
HADS Anxiety score (0–21)	6.67 (3.77)	6	4–9

Note. IQR = interquartile range; PCWP = pulmonary capillary wedge pressure; ACE inhibitors = angiotensin converting enzyme inhibitors; ICD = implanted cardioverter defibrillator; HADS = Hospital Anxiety and Depression Scale.
[a] Included in the Heart Failure Survival Score. Lower scores denote a higher medical risk.

HTx, that is, HTx while upgraded to high-urgency status (a temporary status applied to patients in intensive care units with cardiac index < 2.2 l/m^2/min and mixed venous oxygen saturation < 55%, while on inotropic therapy for at least 48 hr and beginning secondary organ failure; Haneya et al., 2011). Date of MCSD implantation was provided by hospitals; dates of death, delistings, and transplantations together with patients' urgency status were provided by Eurotransplant. Events were combined into a composite endpoint, that is, the first occurrence of one of the events determined survival time. Elective HTx and delistings due to other reasons (clinical improvement, withdrawing of consent for transplantation, noncompliance) were censored at their time of occurrence. Patients who were still on the waiting list by the end of follow-up were administratively censored.

Data Analyses

Analyses were conducted using SPSS 19.0 and R 2.12.0 including the package Survival. In self-reported variables, less than 3% of observations were missing, which were substituted according to questionnaire manuals (Gerhardt, Weidner, Grassmann, & Spaderna, in press). In medical baseline parameters central to this investigation, less than 4% of values were missing, except for cardiac index, PCWP, and peakVO$_2$, with up to 18.6% of missing values. According to Eurotransplant policy, we used median values of the entire sample to substitute missing values. The percentage of patients engaging in each one of the physical activities was calculated. Continuous variables were described with means and standard deviations, categorical variables with number and percentage. Patient groups (depressed/not depressed, anxious/not anxious) were compared using *t* tests and chi-square tests as appropriate. Bivariate associations between baseline variables were evaluated applying Pearson correlations.

Cox proportional hazards models were used to evaluate associations of variables with event-free survival. The use of a composite endpoint was considered justified because the associations of physical activity scores with each of the single events separately were of the same direction and magnitude for each event. The same was true for the psychological variables. First, the associations of study variables (physical activity scores, depression and anxiety [both as continuously measured and categorically measured variables], demographic and medical variables) with the composite endpoint were evaluated in univariate analyses.

These analyses were followed by two sets of multivariate hierarchical models that were computed to test whether both conceptualizations of physical activity contributed to event-free survival. The physical activity score was entered in the third step after controlling for age, sex, and body mass index (Step 1) and medical indicators of disease severity significantly associated with the composite endpoint (Step 2). Depression was entered in the fourth step, and the interaction of the physical activity score with depression status was entered in the fifth step. As depression and anxiety were significantly correlated, these models were rerun with anxiety entered instead of depression. The contribution of variables to event-free survival was determined via reductions of the −2 log likelihood, expressed as change of chi square, hazard ratios (HRs), and 95% confidence intervals associated with potential predictor variables. The HR depicts the change in the hazard to experience an event per unit change in the predictor variable. Caloric expenditure values were rescaled (divided by 100), so that a 1-unit increase equates to 100 kcal/week.

Model fit of the multivariate Cox models was checked according to Fox (2002). Scaled Schoenfeld residuals were used to test the proportional hazard assumption (Therneau & Grambsch, 2000) and to plot residuals against time. There was no evidence of nonproportional hazards for any of the predictor variables. Checks for the influence of potential outliers by examining changes in HRs resulting from removal of each case from the analysis (dfbeta values) were also inconspicuous. Plots of Martingale residuals against predictor variables (Therneau & Grambsch, 2000) revealed no indication of nonlinearity. All statistical tests were two-tailed and the level of significance was set at $p < .05$.

Results

Everyday Physical Activity, Depression, and Anxiety at Baseline

Patient characteristics at time of wait listing are displayed in Table 1. In this subsample of ambulatory patients without MCSDs at time of listing, 91.2% of the participants reported that they still climbed stairs, and 32.6% to 76.7% still engaged in everyday physical activities such as housework, walking to do errands, or light gardening (see Figure 1). During a typical week, patients engaged on average in four different activities and spent a mean of 1,982 (SD = 1,681) kcal/week. Both number of physical activities and caloric expenditure correlated positively with peakVO_2 (r = .23, $p < .01$, and r = .16, $p < .05$, respectively).

Depression and anxiety correlated with $r(227) = .58$, $p < .0001$. Thus, their associations with physical activity and survival were analyzed separately. Patients with a HADS Depression score indicating clinically relevant depression (n = 84) engaged in fewer physical activities per week than the 143 nondepressed patients (M = 3.56, SD = 1.97 vs. M = 4.20, SD = 2.35), $t(225) = 2.11$, p = .036. Weekly caloric expenditure in depressed patients was also slightly lower, but not statistically different from that of nondepressed patients (M = 1,864, SD = 1,564 vs. M = 2,051, SD = 1,747), $t(225) = 0.81$, p = .419. Depressed and nondepressed patients did not differ in age, body mass index, or medical parameters ($ps > .15$; data not shown). Anxiety status was unrelated to number of physical activities (M = 4.10, SD = 2.50 vs. M = 4.00, SD = 2.18), $t(225) = -0.27$, p = .791, and caloric expenditure (M = 2,169, SD = 1,802 vs. M = 1,943, SD = 1,657), $t(225) = -0.67$, p = .446. Also, anxious and nonanxious patients did not differ in age, body mass index, or medical parameters ($ps > .33$; data not shown).

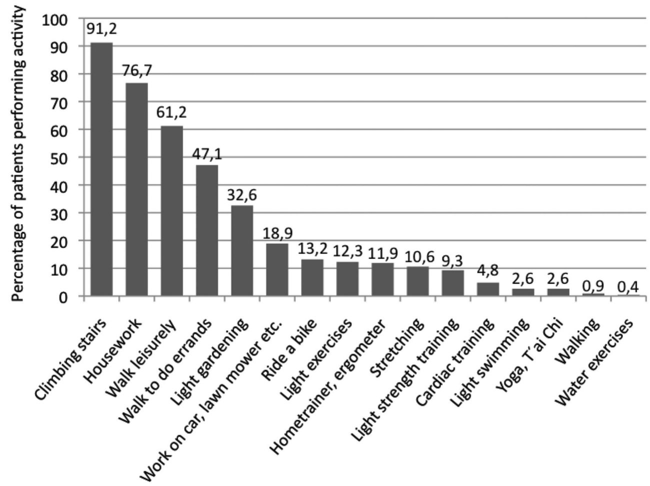

Figure 1. Percentage of patients engaging in different types of everyday physical activities at least once a week. Five patients (2.2%) engaged in none of the specified activities.

Event-Free Survival

After a median follow-up of 478 days (range 6–1,849 days), 132 events had occurred among the 227 MCSD-free ambulatory participants: 46 patients had died, 20 had received an MCSD, 54 were high-urgently transplanted, and 12 were delisted due to clinical deterioration. Ninety-five patients were censored (41 electively transplanted, 30 delisted due to clinical improvement, six due to other reasons such as declining consent for transplantation, 18 were still on the waiting list).

Table 2 shows univariate associations of patient characteristics with time until the composite endpoint. As expected, an increased medical risk indicated by lower Heart Failure Survival Score, lower cardiac index, higher PCWP, and higher creatinine values was related to an increased risk for experiencing an event. A higher number of physical activities was significantly associated with a reduced risk to experience an event. A similar trend emerged for higher weekly caloric expenditure. Being depressed (HADS Depression score ≥9) was related to an increased risk to experience an event. Anxiety was unrelated to the endpoint and not considered further.

In multivariate models controlling for age, sex, body mass index, and medical indicators of disease severity (Heart Failure Survival Score, PCWP, cardiac index, creatinine), a higher number of physical activities was independently related to prolonged event-free survival (see Table 3). The HR associated with each additional physical activity was 0.90, 95% CI [0.83, 0.98]. This

Table 2
Univariate Associations of Patient Characteristics With the Composite Endpoint in 227 Ambulatory Heart Transplant Candidates

Variable	Hazard ratio	95% CI	*p*
Age	1.01	[0.99, 1.02]	.555
Male sex	0.82	[0.53, 1.27]	.382
Currently living alone	1.14	[0.72, 1.78]	.586
Currently working	1.22	[0.73, 2.03]	.454
Education 9 years or less	1.06	[0.74, 1.53]	.741
Body mass index (kg/m^2)	1.00	[0.95, 1.04]	.851
HFSS	0.65	[0.53, 0.81]	<.0001
Cardiac index (ml/min/m^2)	0.59	[0.40, 0.86]	.004
PCWP (mmHg)	1.05	[1.03, 1.07]	<.0001
Creatinine (mg/dl)	2.48	[1.77, 3.49]	<.0001
Beta-blockers	0.72	[0.46, 1.12]	.158
ACE inhibitors, AT$_1$ blocker	0.68	[0.47, 0.98]	.047
Diuretics	0.89	[0.56, 1.44]	.651
Digitalis	0.97	[0.69, 1.37]	.878
Aldosterone antagonists	0.98	[0.69, 1.39]	.913
Antiarrhythmics	1.16	[0.78, 1.74]	.460
Antidepressants[a]	1.15	[0.60, 2.21]	.670
Previous heart surgery	0.87	[0.59, 1.28]	.466
Diabetes mellitus	0.98	[0.65, 1.47]	.912
Peripheral artery disease	0.60	[0.19, 1.89]	.343
ICD	1.09	[0.75, 1.59]	.646
Number of physical activities	0.88	[0.81, 0.96]	.001
Caloric expenditure (kcal/week)	0.99	[0.98, 1.00]	.109
Depressed (HADS-D ≥ 9)	1.64	[1.16, 2.32]	.005
HADS Depression score (range 0–21)	1.05	[1.00, 1.10]	.060
Anxious (HADS-A ≥ 11)	1.03	[0.65, 1.63]	.890
HADS Anxiety score (range 0–21)	1.00	[0.96, 1.05]	.912

Note. $N = 227$. BMI = body mass index; HFSS = Heart Failure Survival Score; PCWP = pulmonary capillary wedge pressure; ACE inhibitors = angiotensin converting enzyme inhibitors; ICD = implanted cardioverter defibrillator; HADS-D = Hospital Anxiety and Depression Scale Depression score; HADS-A = Hospital Anxiety and Depression Scale Anxiety score.
[a] Data on antidepressant medication at time of listing were available for 205 patients.

beneficial effect of physical activities on event-free survival was maintained when depression status was also entered into the model (see Table 3). Not being depressed significantly added to event-free survival (see Table 3). The interaction term of number of physical activities with depression status was not statistically significant, $\Delta\chi^2(1) = 0.68$, $p = .409$.

Physical activity in terms of caloric expenditure based on the original 15 activities was not associated with the endpoint (after controlling for covariates: HR = 0.996, 95% CI [0.986, 1.007], $p = .503$; and after including depression status: HR = 0.997, 95% CI [0.99, 1.01], $p = .588$). In this model, being depressed remained significant (HR = 1.63, 95% CI [1.14, 2.32], $p = .008$), whereas the interaction term Caloric Expenditure × Depression Status was not statistically significant, $\Delta\chi^2(1) = 0.42$, $p = .518$.

These results were maintained when continuous scores of depression and anxiety were used.

Post Hoc Analysis

To explore whether climbing stairs, which was added to the score "number of activities" but was not included in the caloric expenditure (specification of duration and MET values of stair climbing was not feasible), contributed to event-free survival, we ran post hoc analyses using an additional score computed from three items ("How often did you climb the following during the last 4 weeks? A few steps, one flight of stairs, several flights of stairs?"). Responses (*daily* = 2, *once a week* = 1, and *less frequently* = 0) were summed across the three items, yielding sum scores between 0 and 6. For participants who did not climb any stairs, this score was set to zero. Adding climbing stairs in the fifth step of the Cox model including caloric expenditure yielded a trend for climbing stairs to contribute to event-free survival: HR = 0.93, 95% CI [0.85, 1.01], $\Delta\chi^2(1) = 3.10$, $p = .078$.

Discussion

Ambulatory patients with advanced HF enrolled in the Waiting for a New Heart Study engaged in a wide range of everyday physical activities at the time of entering the waiting list. Activities such as housework, walking (both leisurely and to do errands), and light gardening were much more common than engaging in regular exercise regimens. More than 90% patients also reported climbing stairs. Prospective evaluation of the relationship of physical activity at time of listing to outcomes experienced while waiting for a donor heart supported the notion that engaging in everyday physical activities was associated with improved event-free survival, even after controlling for medical indicators of disease severity and depression status.

As expected, the least severely ill patients, as defined by medical parameters, were significantly less likely to die while on the waiting list, to become delisted due to clinical deterioration, or to receive an MCSD or a HTx in high-urgency status. Most important, engaging in everyday physical activities accounted for a moderate but statistically significant additional risk reduction in these patients. This latter finding supports the observation from an earlier study that reported beneficial effects of walking in HTx candidates (Stevenson et al., 1995).

It could be argued that engaging in more everyday physical activities is a proxy for being not depressed. Indeed, patients with elevated depression scores in the clinically significant range reported significantly fewer physical activities during a typical week compared with patients without depressive symptoms. Our findings suggest that both everyday physical activities and the absence of depression contributed independently to improved event-free survival.

These findings are in line with results from patients with coronary heart disease enrolled in INTERHEART, a case–control study including more than 10,000 cases of first myocardial infarction and 14,000 controls from 52 countries (Held et al., 2012). Independent of depression and stress, both walking and mild leisure-time activity were associated with reduced risks of myocardial infarction (Held et al., 2012). Physical activity was also linked to reduced mortality after controlling for positive and negative affect in the German Ageing Survey, a representative cohort of older adults (Wiest, Schuz, Webster, & Wurm, 2011). Thus, maintaining a physically active everyday life appears to benefit patients with HF regardless of whether they are depressed or not.

However, these results cannot tell whether physical activity reduced depressive symptoms over time or vice versa, as both predictors were assessed only at time of listing. Considering that

Table 3
Associations of Number of Physical Activities and Depression Status With the Composite Endpoint in 227 Ambulatory Heart Transplant Candidates After Controlling for Covariates

Variable	Hazard ratio	95% CI	$\Delta\chi^2$	*df*	*p*
Step 1			1.23	3	.747
Age	1.00	[0.98, 1.02]			
Male sex	0.76	[0.48, 1.20]			
Body mass index	0.97	[0.92, 1.01]			
Step 2			52.10	4	< .0001
HFSS	0.80*	[0.65, 0.99]			
Cardiac index	0.76	[0.51, 1.12]			
PCWP	1.04**	[1.02, 1.06]			
Creatinine	2.34***	[1.61, 3.39]			
Step 3			6.20	1	.013
Number of physical activities	0.91*	[0.83, 0.99]			
Step 4			6.42	1	.011
Depressed[a]	1.60*	[1.12, 2.29]			

Note. Hazard ratios and confidence intervals of all variables pertain to the final model. HFSS = Heart Failure Survival Score, lower values denote higher medical risk; PCWP = pulmonary capillary wedge pressure.
[a] If anxiety status was entered together with depression status in Step 4, number of activities and being depressed remained significantly associated with the endpoint, whereas anxiety status had no significant impact on event-free survival (hazard ratio = 0.95, 95% CI [0.56, 1.60]).
* $p < .05$. ** $p < .01$. *** $p < .0001$.

depression might increase with continuing waiting time (Zipfel et al., 1998), and that depressed persons are less physically active than nondepressed persons (Lindwall et al., 2011; Trost et al., 2002), depression might affect health via reducing physical activity over time (Roshanaei-Moghaddam, Katon, & Russo, 2009; Win et al., 2011). It is also conceivable that more physically active patients were able to prevent detrimental increases in depression or to reduce existing symptoms of depression. However, Blumenthal and colleagues (2004) found no support for the notion that changes in depression mediated the effect of exercise on mortality in patients after myocardial infarction. Lindwall et al. (2011) reported in their cross-lagged panel study of older adults that the association of physical activity with reduced depressive symptoms 2 years later was stronger than the alternative association of depressive symptoms with reduced future physical activity. Interestingly, their data were explained best by a model of reciprocal prospective relationships of physical activity and depressive symptoms, supporting the notion that both pathways might exist together (Lindwall et al., 2011). Future studies should address this issue by applying repeated measurements of depression and physical activity in patients with HF.

Although higher caloric expenditure also showed a trend for better event-free survival in univariate analysis, this effect was not maintained after controlling for covariates. However, this score might underestimate patients' real physical activity level, as it is only based on the 15 physical activities included in the modified CHAMPS questionnaire, which does not include climbing stairs. Interestingly, post hoc analysis revealed that climbing stairs constitutes an important part of everyday physical activities for patients with advanced HF. Everyday activities including stair climbing clearly deserve more attention in future studies.

Regarding the impact of negative emotions on mortality in HF, our study corroborates results linking depression to poor outcomes in this patient group (Freedland et al., 2011) and showing no impact of anxiety on survival (Jiang et al., 2004). Interestingly, anxiety was also unrelated to physical activity in our study. Similarly, changes in depression but not in HADS Anxiety scores were associated with adherence to exercise and other health-related behaviors (Bauer et al., 2012). It should be noted that anxiety as measured in the HADS is rather unspecific. Considering qualitative patient reports, a more specific assessment of fears associated with physical activity, for example, fear of worsening symptoms and of adverse events (Tierney et al., 2011) together with threat appraisals (cf. Vögele, Christ, & Spaderna, 2012), may provide further insight into the role of anxiety in physical activity in this patient population.

Our study has several limitations. First, it relied on self-reports of physical activity that might either be biased or underestimate real activity levels. Also, clinical diagnoses of depression and generalized anxiety disorder would have been preferable over self-reports. However, HADS cutoff scores were used that are considered indicative of clinical depression and anxiety (Bjelland, Dahl, Haug, & Neckelmann, 2002). Second, the fact that predictors were assessed only at time of listing precludes an evaluation of the impact of changes in these predictors on disease progression and outcomes, specifically causes of death, which were also not available. Finally, the observational nature of our study precludes causal conclusions. Nevertheless, our results from a multisite sample showing associations of everyday physical activity and depressive symptoms with important hard outcomes in patients with HF support the notion that maintaining and increasing everyday physical activities may provide an important option to improve prognosis of patients with HF, even among those with advanced disease who are eligible for HTx. In light of the fact that adherence to physical activity is also low for patients after HTx (Evangelista, Dracup, Doering, Moser, & Kobashigawa, 2005), behavioral interventions to help patients stay physically active during their daily life early in the course of HF management and HTx are needed.

To conclude, in ambulatory patients with advanced HF awaiting HTx, engagement in everyday physical activities including climbing stairs contributed to improved event-free survival, even after adjusting for medical risk factors and depression. Considering the multiple beneficial effects of physical activity in heart failure and the difficulties of adherence to exercise recommendations in this population (Downing & Balady, 2011), everyday activities provide a reasonable starting point to increase physical activity levels in this population.

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