Physical Activity, Measured with Implanted Devices, Predicts Patient Outcome in Chronic Heart Failure

Conraads et al: Physical Activity and Outcome in Heart Failure

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Abstract

Background—Physical activity (PA) predicts cardiovascular mortality in the population at large. Less is known about its prognostic value in chronic heart failure (CHF) patients (pts).

Methods and Results—Data from 836 patients with implanted defibrillators without (ICD) or with cardiac resynchronization therapy (CRT-D) enrolled in the Sensitivity of the InSync Sentry OptiVol feature for the prediction of Heart Failure (SENSE-HF) Study and the Diagnostic Outcome Trial in Heart Failure (DOT-HF) were pooled. Devices continuously measured and stored total daily active time (single-axis accelerometer). Early PA (average daily activity over the earliest 30-day study period), was studied as a predictor of time to death or HF related hospital admission (primary endpoint). Data from 781 pts were analyzed (65±10 years, 85% men, left ventricular ejection fraction: 26±7%). Older age, shorter height, ischemic aetiology, peripheral artery disease, atrial fibrillation, diabetes, rales, peripheral oedema, higher New York Heart Association class, lower diastolic blood pressure and no angiotensin II receptor blockers/angiotensin converting enzyme inhibitor use were associated with reduced early PA. The primary endpoint occurred in 135 pts (15±7 months follow-up). In multivariable analysis including baseline variables, early PA predicted death or HF hospitalization, with a 4% reduction in risk for each 10 minutes/day additional activity (hazard ratio, HR=0.96; confidence interval, CI:0.94-0.98; p=0.0002 compared to a model with the same baseline variables but without PA). PA also predicted death (HR=0.93, CI:0.90-0.96, p<0.0001) and HF hospitalization (HR=0.97, CI:0.95-0.99, p=0.011).

Conclusions—Early PA, averaged over a 30-day window early after ICD or CRT-D implant in CHF pts, predicted death or HF hospitalization, as well as mortality and HF hospitalization separately, accounting for baseline HF severity.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00400985, NCT00480077.

Key Words: heart failure, physical activity, mortality, implantable devices, outcome prediction.
Despite significant improvements in the treatment of chronic heart failure (CHF), mortality remains as high as 20-30% after 3 years.\textsuperscript{1-3} The costs for heart failure (HF) care approach 2% of the total health care expenditure in Western countries, primarily due to hospitalization for decompensation.\textsuperscript{4} As a result, the past decade has witnessed a surge in finding reliable markers to identify patients at risk of early death and impending decompensation. Physical fitness predicts cardiovascular mortality in the population at large.\textsuperscript{5-7} The collection of multiple parameters derived during cardiorespiratory exercise testing, in particular the minute ventilation/carbon dioxide production relationship (the VE/VCO\textsubscript{2} slope) in conjunction with peak oxygen uptake, allows prognostic stratification in patients with CHF.\textsuperscript{8} However, repetitive cardiopulmonary exercise testing, which may be required for a dynamic condition such as CHF, is demanding in clinical practice.\textsuperscript{9}

Daily physical activity has been shown to predict outcome in various chronic diseases.\textsuperscript{10-12} However, data for the CHF population are scarce and are often based on qualitative subjective patient and physician reports or questionnaires or short-term measurement with pedometers and accelerometers.\textsuperscript{13-15} Continuous recording of physical activity, through accelerometers incorporated in implanted devices, may more accurately address the question whether physical activity merely reflects disease severity\textsuperscript{16} or whether it is an independent prognostic marker.

The Sensitivity of the InSync Sentry OptiVol feature for the prediction of Heart Failure (SENSE-HF) Study\textsuperscript{1} and the Diagnostic Outcome Trial in Heart Failure (DOT-HF)\textsuperscript{17} are recent prospective trials conducted to evaluate the utility of intrathoracic impedance measurement, incorporated as a diagnostic feature in implanted defibrillators without (ICD) or with cardiac resynchronization therapy (CRT-D). These devices also measured and stored total daily active time. We analyzed
the pooled patient data from SENSE-HF and DOT-HF to determine whether and to what extent
daily life physical activity as measured by implanted devices is related to patient outcome.

Methods

Patient population

Detailed descriptions of design and results of SENSE-HF and DOT-HF have been published
previously. Briefly, SENSE-HF\textsuperscript{1}\textsuperscript{,18} enrolled 501 patients within 34 days after implantation of
an ICD or CRT-D with the OptiVol\textsuperscript{®} feature (Medtronic Inc., Minneapolis, MN, USA), which
measures intrathoracic impedance. After a waiting period of 34 days to ensure correct
measurement of intrathoracic impedance, patients were followed-up for 6 months to determine
the sensitivity and the positive predictive value of OptiVol intrathoracic fluid monitoring for the
detection of HF-related hospitalizations (Phase I, blinded). Phase I was followed by maximally
18 months with full access to device data. Physical activity was recorded and stored during the
entire study period, starting at day 35 post-implant.

DOT-HF\textsuperscript{17,19} tested whether physician access to device-based diagnostic information, including
audible patient alerts for decreasing intrathoracic impedance, would improve outcome in HF
patients. In total, 335 patients were randomized to an access versus a control arm between 35
days and 6 months after implantation with an ICD or CRT-D. Patients were followed-up for 15
months, during which physical activity was continuously measured and stored.

The Supplemental Table describes endpoints and the major inclusion and exclusion criteria for
both studies. Both studies were approved by the local ethics committees, and written informed
consent was obtained from all patients. Given similarities in patient population and treatment,
and since all devices in SENSE-HF and DOT-HF recorded and stored physical activity during
daily life on a continuous basis, it was decided to pool and analyze patient data from both trials. The authors had full access to study data.

**Study endpoints**

The primary endpoint of the present analysis was time to death or HF related hospital admission. Time to death and time to first HF related hospital admission were analyzed as secondary endpoints. HF hospitalizations were adjudicated by study-specific independent blinded Adverse Event Advisory Committees.\(^{18, 19}\)

**Device measurement of daily life physical activity**

The activity measurement in the devices is designed to capture normal daily activities in HF patients, including walking at a slow pace. A single-axis accelerometer is used to capture patient motion as an electrical signal. The number of minutes a patient is active per day is counted, where a minute is considered active if a threshold is reached that incorporates both number and magnitude of the deflections in the accelerometer signal. The devices store the number of active minutes for the most recent 425 days (Figure 1) and this information was retrieved from device memory for this analysis. The sensor provides a quantification of patient activity that due to the specifics of the algorithm may numerically differ from measurements obtained from other devices such as pedometers or external accelerometers.

**Analyses methods**

We defined “early physical activity” as the average daily activity over the earliest 30-day period in the study (the “activity window”). For patients in SENSE-HF this window started 35 days
after implant and continued until day 64. For patients in DOT-HF the activity window started after randomization, which was between day 35 and day 183 post-implant. We averaged 30 daily values in order to account for within-patient variability. Patients were excluded from analysis if they died or had a HF hospitalization during or before the 30-day activity window, or if there were less than 7 days with valid activity data in the window.

Since lower activity was expected to be associated with a generally worse condition of patients, we have investigated the relation of early activity with baseline characteristics. The relation of early physical activity and outcome as well as the incremental value of activity as risk marker when added to known risk factors was assessed in line with the AHA scientific statement on evaluation of novel markers of cardiovascular risk.20 As measures of known risk, we have determined the best predictive model based on baseline patient characteristics and we have used the CHARM risk score, a validated score for risk of all-cause death in HF patients.21 For both approaches, time to event models including and excluding early activity are compared to determine incremental predictive value.

Statistical analyses

Results are reported with mean and standard deviation for continuous, and counts and percentages for categorical variables. The relation between baseline characteristics and early physical activity was analyzed with t-test for dichotomous, and linear regression for ordinal and continuous characteristics. Reported effect sizes (Table 1) are observed differences for dichotomous characteristics, and regression coefficients otherwise. Multivariable linear regression with backward variable elimination was used to assess joint association with early activity.
For calculation of the CHARM risk score, coefficients were taken from the paper by Pocock et al.\textsuperscript{21} Multiple imputation was used to account for missing values, using the multivariate normal specification. For categorical variables, the imputed value has been rounded to the nearest coded category value. Ten completed datasets were generated. The CHARM risk score was calculated for each completion separately. Finally, Rubin’s rule was used to determine a single risk score value per patient.

Cox proportional hazards regression was used to analyze the relation between events and early physical activity, which was included as a continuous variable. Patients were considered at risk starting at the end of the activity window (time zero). Hazard Ratio (HR) with associated 95% Confidence Interval (CI) is reported for 10 min/day incremental activity. Incidence of endpoints is illustrated with Kaplan-Meier graphs with patients divided into two or three equal-sized groups using medians or tertiles as cut points. Multivariable proportional hazards models using model reduction with backward selection are used to define predictive models based on baseline characteristics. To assess incremental predictive value of early activity, multivariable models including and excluding early activity are compared using likelihood ratio (LR) tests. Predictive ability of models is quantified using the Harrell c-index, which extends the area under the receiver operating characteristic curve to the context of time to event data with censoring.\textsuperscript{22}

All analyses were done using SAS (version 9.3, SAS Institute Inc., Cary, NC, USA) or R (version 3.0.1, the R project for statistical computing, www.r-project.org) and p-values <0.05 are considered significant. No correction for multiple testing was applied.
Results

Patients

SENSE-HF and DOT-HF together enrolled 836 patients between 2005 and 2009 in 100 centers across Europe (91% of patients), the Middle East and Asia. Fifty-five patients were removed from analysis because they experienced events before the end of the activity window (35 patients; 11 deaths and 28 HF hospital admissions), early study exit (5 patients) or because device data were not available for analysis (15 patients).

Demographic and clinical characteristics are presented in Table 1. At enrolment, the majority of patients was in NYHA class II/III, with severely impaired left ventricular ejection fraction (26±7%) and implanted with a CRT-D (80%).

Correlates of early physical activity

Early physical activity was 199±106 min/day, and was comparable between studies (SENSE-HF: 199 min/day, DOT-HF: 198 min/day; p=0.90; see Supplemental Figure). As a result of the design of both studies, the activity window started 35 days after implantation in all SENSE-HF patients, and on average 86 days after implantation in DOT-HF patients. Time between implant and start of the activity window did not affect early activity (linear regression, p=0.83) nor its prognostic value for DOT-HF patients.

Table 1 illustrates the relation between early physical activity and baseline characteristics. Multivariable analysis identified older age, shorter height, ischemic aetiology, peripheral artery disease, atrial fibrillation, diabetes, rales, peripheral oedema, higher NYHA class, lower diastolic blood pressure and absence of ARB/ACE inhibitor therapy as jointly associated with reduced early physical activity.
Patient outcome and early physical activity

During follow-up (15±7 months), 65 deaths and 141 HF hospitalizations were recorded in 100 patients. The primary endpoint of death or HF hospitalization occurred in 135 patients. Early physical activity was significantly associated with the primary endpoint, with 5% relative reduction of risk for each 10 minutes/day additional activity (HR=0.95 [CI:0.94-0.97], p<0.0001). There were also significant associations with death (HR=0.92 [CI:0.89-0.95], p<0.0001) and HF hospitalization (HR=0.97 [CI:0.95-0.99], p=0.0011). Figure 2 shows event incidence with patients stratified into 3 equal-sized groups according to early physical activity. The cut points are 235 min/day between high and medium activity and 146 min/day between medium and low activity. Incidence of the primary endpoint at 18 months is 12.5% for high activity, 17.5% for medium activity and 30.0% for low activity. Mortality is 2.5%, 9.9%, and 18.2%, respectively. Incidence of HF hospitalization is 11.7%, 10.2%, and 22.0%.

Outcome and early physical activity, accounting for disease severity

To assess the incremental value of early physical activity as risk marker for clinical events when added to other risk factors, two approaches were used. First, baseline characteristics were tested for their relation with patient outcome. Fourteen characteristics were significantly related to the primary endpoint (age, height, weight, underweight, Left Bundle Branch Block, diabetes, dyspnea, systolic blood pressure (SBP), diastolic blood pressure, QRS duration, QRS≥120ms, QRS≥150ms, ARB/ACE inhibitor, daily diuretic dosage). Additionally, peripheral oedema was predictive of mortality. These 15 variables were included in multivariable models, from which non-significant parameters were iteratively removed. In the final multivariable model for death or HF hospitalization, age (p=0.0011), SBP
(p=0.0001), daily diuretic dosage (p=0.0004), and absence of ARB/ACE inhibitor (p=0.04) were retained as joint predictors of outcome. The c-index for this model was 0.66 (CI:0.61-0.71).

Addition of early physical activity to the model significantly improved the predictive ability (LR p=0.0002). The model with activity has a c-index of 0.68 (CI:0.63-0.73). Accounting for the effect of the other factors, there was a 4% reduction in risk for each 10 minutes/day additional activity (HR=0.96 [CI:0.94-0.98]). These results are summarized in Table 2, which also includes results for mortality and HF hospitalization separately.

Next, we determined the predictive value of the validated CHARM risk score, on the current patient cohort. On its own, the score was significantly associated with the incidence of death or HF hospitalization (p<0.0001; c-index 0.61 [CI:0.56-0.66]) (Table 2). Figure 3 illustrates event incidence with patients stratified into low, medium and high risk groups. The CHARM score and early physical activity were significantly correlated (r=-0.33, p<0.0001).

Adding early physical activity to the model significantly improved the predictive ability (LR p-value p<0.0001), establishing lower activity as a predictor of increased event rates when accounting for baseline risk. The c-index increased to 0.65 (CI:0.60-0.70). With CHARM score in the model, there was a 4% reduction in risk of death or HF hospitalization for each 10 minutes/day additional activity (HR=0.96 [CI:0.94-0.98]). Figure 4 illustrates these findings by showing incidence of death or HF hospitalization for patients stratified by the CHARM score and early physical activity. For both parameters patients are classified as above or below the median value, creating four groups. Table 2 shows that also for death and HF hospitalization separately, early activity significantly improved the predictive value when added to the CHARM score in time to event models.
Discussion

The main finding of the present study is that “early physical activity”, measured by the accelerometer sensor of implanted ICD and CRT-D devices, strongly predicts outcome in CHF patients. Early physical activity was defined as the average activity over a 30-day window, measured either starting 35 days after implant for SENSE-HF patients or after randomization, between 35 days and 6 months after implant, for DOT-HF patients. Despite the expected significant relation between early physical activity and HF severity, low early physical activity was a significant predictor of the combined primary endpoint of death and HF hospitalization, as well as of both components separately, when correcting for HF severity.

Population-based studies show that physical activity and a high level of cardiorespiratory fitness predict longevity. Literature on the prognostic impact of daily life physical activity in HF patients is scarce and almost exclusively based on subjective evaluation of patients’ reports, or data gathered by intermittent application of pedometers and external accelerometers.

Continuous measurement of daily physical activity with accelerometers incorporated in implanted devices excludes non-adherence and avoids bias of deliberate changes in patients’ habits at the time of planned assessments. Surprisingly, few studies have investigated the clinical utility of continuous measurements and have mainly concentrated on short-term prediction of acute decompensated heart failure. The Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients With Heart Failure (PARTNERS-HF) demonstrated that a combination of device-measured parameters, including activity, predicted a 5.5 fold higher HF hospitalization risk in CRT-D patients, but results for activity are not reported separately. Only Shoemaker and co-workers retrospectively related physical activity recordings in 102 ICD or CRT-D patients to long-term outcome. They found a moderate
correlation between mean daily activity, calculated for a two week period, and estimated short and long-term outcome, based on the Seattle Heart Failure Score. Results of the present study support the notion that daily physical activity reflects disease severity, measured by means of a validated HF risk score. However, the fact that “early physical activity” predicted outcome, taking well-recognized traditional risk factors into account, is novel and may be of use in the management of patients with CHF.

As shown by a sub-analysis of the HF-ACTION trial, improved patient outcome, as well as increased exercise capacity depends on exercise volume. Our data support a similar dose-response effect with regard to daily life physical activity. The patients in the lowest tertile for early activity (< 146min/day), had a 2.3 times higher risk for the combined endpoint (HR=2.3) compared to those in the highest tertile (> 235min/day), and even a five-fold risk for mortality (HR=5.0). The advice provided to patients by SENSE-HF and DOT-HF physicians based upon the stored physical activity data was not part of the study protocols. Therefore, a prospective study is necessary to confirm current findings and to establish clinical recommendations.

In this study, several patient and disease characteristics, as well as comorbidities were associated with early physical activity. A significant effect of age and NYHA functional class on 6 min walking distances and cardiorespiratory fitness as well as a detrimental effect of raised jugular venous pressure on physical activity has been described. The decline of cardiorespiratory fitness with age likely increases exercise-induced symptoms of fatigue and dyspnea in HF patients. These effects may hamper the motivation and ability of HF patients to engage in daily life physical activity. A similar argument may explain lower levels of physical activity in patients presenting with higher NYHA functional class, rales and peripheral edema.
After multivariable analysis height was retained as a predictor of physical activity. Without providing a physiological justification, Witham et al\textsuperscript{30} described a significant effect of height on accelerometry-based quantification of physical activity in HF patients in univariate analysis. One plausible explanation may involve the larger excursion of the body during movements in taller people, which may be sensed by the accelerometer.

The fact that atrial fibrillation significantly determined low levels of physical activity may be related to lower cardiac output during exertion due to poorly controlled ventricular rate and atrioventricular dyssynchrony. The functional substudy of the AFFIRM trial\textsuperscript{33} demonstrated a significantly larger increase in functional status, assessed with the 6 min walk test, in HF patients with atrial fibrillation allocated to the rhythm versus the rate control group. Similar findings were reported in the PIAF trial up through 2 years follow-up.\textsuperscript{34} Recently, Izawa et al\textsuperscript{35} described a significantly reduced step count and estimated daily physical activity energy expenditure obtained with uniaxial accelerometers in diabetic versus non-diabetic HF patients. Skeletal muscle wasting as well as bioenergetic changes at the level of the peripheral skeletal musculature are plausible mechanisms.\textsuperscript{36}

Exercise induced pain and significant lower limb ischemia change gait pattern and lead to lower walking performance as well as poor daily physical activity.\textsuperscript{37} Heart failure patients with PAD have lower exercise capacity and a lower response to exercise training intervention.\textsuperscript{38} Patients with ischemic etiology, compared with those with non-ischemic etiology, demonstrate lower peak oxygen uptake and a steeper VE/VCO\textsubscript{2} slope.\textsuperscript{31} Impaired physical activity may result from chronotrophic incompetence, exercise induced myocardial ischemia and mitral regurgitation.\textsuperscript{39} Treatment with an ACE-inhibitor improves exercise duration,\textsuperscript{40} as well as peak aerobic capacity.\textsuperscript{41} Besides the direct benefit on cardiac performance through the inhibition of the renin-
angiotensin-aldosterone system, facilitated alveolar-capillary gas transfer, as well as restoration of peripheral endothelial function have been described.

Limitations

For this post-hoc analysis we pooled data from two studies with different design. As a result the 30-day “activity window” was collected in a period between 35 and 183 days. Nevertheless, prognostic information derived from this pooled dataset remains strong and seems not affected by this approach.

The devices used all had the same specific type of accelerometer, and it is not known if results can be extrapolated to other activity sensors. Literature on validation of the device’s activity sensor is limited. Gulati et al. found that the six-minute walk test and daily activity measured within the preceding or subsequent 24 hours were correlated \((r = 0.42\) and \(0.49\), respectively). A similar relation was found in a subset of 83 patients enrolled in SENSE-HF, in whom a six-minute walk test was conducted \((r=0.43, p<0.0001)\). Braunschweig et al. calculated weekly means of physical activity in a group of 56 patients after the novo device implant using the same accelerometer. There was a steady increase in weekly physical activity, that was clearly related to NYHA functional class with absolute values after 4 weeks that were well within the range of the current observations \((283\pm97, 206\pm132, 186\pm53\) min/day for NYHA II, III, IV respectively).

The CHARM risk score was developed from a large number of non-device patients across a broad spectrum of HF. Nevertheless, the risk score strongly predicted outcome for the currently analyzed cohort of patients, characterized by broad QRS complexes, impaired systolic left ventricular function and implanted with either an ICD or a CRT-D.
The present studies did not enroll patients in the US. Therefore, clinical recommendations for daily life physical activity, derived from the present analyses may not be applicable to the American HF population. Finally, >30 tests were done to assess the relation between activity and baseline characteristics so that some of the significant findings may be spurious.

Conclusions

Early physical activity, averaged over a 30-day window early after ICD or CRT-D implant in patients with CHF, predicted death or HF hospitalization, as well as mortality and HF hospitalization separately, also corrected for disease severity. These findings underscore the validity of spontaneous physical activity as clinical status marker. Whether regular follow-up of physical activity, provided by accelerometers in implanted devices, may aid physicians in modifying patients’ lifestyle and whether this will improve outcome, needs to be prospectively studied.

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Disclosures

Drs Borggrefe, Braunschweig, Conraads, Cowie, van Veldhuisen and Tavazzi received consultancy fees or research grants from Medtronic and from other device companies. Drs. Conraads, Cowie and Tavazzi served on the Steering Committee of the SENSE-HF study. Drs. Borggrefe, Braunschweig, Conraads, Cowie, and van Veldhuisen served on the Steering Committee for DOT-HF. Drs. Hill, Jacobs and Gerritse are employees of Medtronic. Dr. Gerritse reports having equity in Medtronic. Dr. Spruit reports no conflict of interest.

References


Table 1. Baseline characteristics and relation to early physical activity

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Analysis Cohort (n=781)</th>
<th>Effect size</th>
<th>Univariable P-value</th>
<th>Multivariable P-value</th>
<th>Reduced Multivariable P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>65±10</td>
<td>-3.19</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender, male</td>
<td>661(85%)</td>
<td>16.01</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body height, cm</td>
<td>171±8</td>
<td>1.40</td>
<td>0.002</td>
<td>0.012</td>
<td>0.003</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80±16</td>
<td>0.29</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>27±5</td>
<td>-0.32</td>
<td>0.70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underweight (BMI ≤ 21 kg/m²)</td>
<td>47(6%)</td>
<td>6.99</td>
<td>0.56</td>
<td></td>
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<tr>
<td>HF hospitalization prior 6 months*</td>
<td>406(87%)</td>
<td>7.39</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HF hospitalization prior 12 months</td>
<td>774(99%)</td>
<td>40.36</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic aetiology</td>
<td>445(57%)</td>
<td>-37.61</td>
<td>&lt;0.0001</td>
<td>0.032</td>
<td>0.002</td>
</tr>
<tr>
<td>Previous Myocardial Infarction</td>
<td>364(47%)</td>
<td>-30.20</td>
<td>&lt;0.0001</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td>360(46%)</td>
<td>3.60</td>
<td>0.64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Artery Disease</td>
<td>45(6%)</td>
<td>-41.23</td>
<td>0.011</td>
<td>0.055</td>
<td>0.020</td>
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<tr>
<td>Left Bundle Branch Block</td>
<td>418(54%)</td>
<td>-1.95</td>
<td>0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td>Analysis Cohort (n=781)</td>
<td>Effect size</td>
<td>Univariable P-value</td>
<td>P-value from multivariable model</td>
<td>P-value from reduced multivariable model</td>
</tr>
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</tr>
<tr>
<td>History of Atrial Fibrillation</td>
<td>292(37%)</td>
<td>-31.26</td>
<td>&lt;0.0001</td>
<td>0.025</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes</td>
<td>232(30%)</td>
<td>-35.86</td>
<td>&lt;0.0001</td>
<td>0.09</td>
<td>0.015</td>
</tr>
<tr>
<td>Diabetes (Type I)</td>
<td>27(3%)</td>
<td>-63.78</td>
<td>&lt;0.001</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>552(71%)</td>
<td>-33.08</td>
<td>&lt;0.0001</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Dyspnea at rest</td>
<td>8(1%)</td>
<td>-45.11</td>
<td>0.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rales</td>
<td>48(6%)</td>
<td>-54.21</td>
<td>&lt;0.001</td>
<td>0.033</td>
<td>0.043</td>
</tr>
<tr>
<td>Peripheral Oedema</td>
<td>119(15%)</td>
<td>-43.19</td>
<td>&lt;0.0001</td>
<td>0.008</td>
<td>0.007</td>
</tr>
<tr>
<td>Pulmonary Oedema</td>
<td>64(8%)</td>
<td>-31.87</td>
<td>&lt;0.001</td>
<td>0.021</td>
<td>0.12</td>
</tr>
<tr>
<td>NYHA Classification</td>
<td></td>
<td>-32.96</td>
<td>&lt;0.0001</td>
<td>0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Class I</td>
<td></td>
<td>38(5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td></td>
<td>381(49%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td></td>
<td>346(44%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td></td>
<td>15(2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td>72±12</td>
<td>-0.21</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td></td>
<td>117±18</td>
<td>0.39</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td></td>
<td>71±11</td>
<td>1.42</td>
<td>&lt;0.0001</td>
<td>0.033</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td>Analysis Cohort (n=781)</td>
<td>Univariable P-value</td>
<td>P-value from multivariable model</td>
<td>P-value from reduced multivariable model</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------------------------</td>
<td>---------------------</td>
<td>----------------------------------</td>
<td>----------------------------------------</td>
<td></td>
</tr>
<tr>
<td>LVEF, %</td>
<td>26±7</td>
<td>0.23</td>
<td>0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrinsic QRS duration, ms</td>
<td>146±36</td>
<td>-0.12</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLHF score, points</td>
<td>36±23</td>
<td>-0.52</td>
<td>0.002</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>Current Smoker</td>
<td>48(6%)</td>
<td>3.05</td>
<td>0.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRT-D</td>
<td>621(80%)</td>
<td>10.20</td>
<td>0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>689(88%)</td>
<td>16.99</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>682(87%)</td>
<td>24.90</td>
<td>0.029</td>
<td>0.005</td>
<td>0.027</td>
</tr>
<tr>
<td>Total Diuretics Dose, mg/kg</td>
<td>0.88±1.02</td>
<td>-10.98</td>
<td>0.003</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

Characteristics were taken at baseline, which could be up to 6 months after device implantation. Effect size is the average difference in early physical activity for patients with characteristic versus without (dichotomous) or the average change in activity per unit increase (ordinal, continuous).

* Data not collected in DOT-HF so that denominator is 469, the number of SENSE-HF patients in the Analysis Cohort.

Abbreviations: ACE=Angiotensin Converting Enzyme; ARB=Angiotensin Receptor Blocker; BMI=Body Mass Index; CRT=Cardiac Resynchronization Therapy; CRT-D=Defibrillator with CRT therapy; HF=Heart Failure; NYHA=New York Heart Association; LVEF=Left Ventricular Ejection Fraction; MLHF=Minnesota Living with Heart Failure questionnaire
Table 2. Incremental value of Early Physical Activity as risk marker

<table>
<thead>
<tr>
<th>death and HF hospitalization</th>
<th>risk model based on study data without activity</th>
<th>risk model with CHARM risk score without activity</th>
<th>risk model with CHARM risk score with activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>variables in model</td>
<td>age SBP diuretic dose ARB/ACE absence</td>
<td>age SBP diuretic dose ARB/ACE absence</td>
<td>age SBP diuretic dose ARB/ACE absence</td>
</tr>
<tr>
<td>Hazard Ratio, activity increase by 10 min/day</td>
<td>0.96 (0.94–0.98)</td>
<td>0.96 (0.94–0.98)</td>
<td>0.96 (0.94–0.98)</td>
</tr>
<tr>
<td>Harrell c-index</td>
<td>0.6585 (0.6064–0.7106)</td>
<td>0.6803 (0.6282–0.7324)</td>
<td>0.6114 (0.5601–0.6627)</td>
</tr>
<tr>
<td>p-value comparing models</td>
<td>p=0.0002</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>death</th>
<th>risk model based on study data without activity</th>
<th>risk model with CHARM risk score without activity</th>
<th>risk model with CHARM risk score with activity</th>
</tr>
</thead>
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<tr>
<td>variables in model</td>
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<td>age SBP diuretic dose ARB/ACE absence</td>
</tr>
<tr>
<td>Hazard Ratio, activity increase by 10 min/day</td>
<td>0.93 (0.90–0.96)</td>
<td>0.93 (0.90–0.96)</td>
<td>0.93 (0.90–0.96)</td>
</tr>
<tr>
<td>Harrell c-index</td>
<td>0.7123 (0.6350–0.7897)</td>
<td>0.7535 (0.6762–0.8309)</td>
<td>0.6108 (0.5348–0.6869)</td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------</td>
<td>------------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>p-value comparing models</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td>p=0.011</td>
</tr>
</tbody>
</table>

**HF hospitalization**

| Hazard Ratio, activity increase by 10 min/day | 0.97 (0.95–0.99) | 0.97 (0.95–1.00) |
| variables in model | weight | weight | CHARM | CHARM |
| | SBP | SBP | early activity | early activity |
| Harrell c-index | 0.6246 (0.5643–0.6849) | 0.6450 (0.5847–0.7053) | 0.6031 (0.5441–0.6621) | 0.6226 (0.5636–0.6816) |
| p-value comparing models | p=0.011 | p=0.013 |

Cox proportional hazards models were used to assess the relation of baseline risk markers and early physical activity with outcome. The first two data columns report on predictive models derived from the study data, comparing the model with only baseline risk factors to the model with these risk factors and early activity added. Reported p-values are from likelihood ratio tests. Similarly, the last two columns compare a model with only the CHARM risk score to a model with CHARM score and early physical activity.
Figure Legends

Figure 1. Illustration of device based activity measurement. Panel A: a stable and relatively active patient. Panel B: a patient with 2 HF hospitalizations. Panel C: a patient who died.

Figure 2. Kaplan-Meier estimates for the incidence of clinical events. Panel A: all-cause death or HF hospitalization (primary endpoint). Panel B: all-cause death. Panel C: HF hospitalization. Patients are stratified in 3 equal-sized groups based on their early activity with cut-points 145.6 and 235.0 minutes/day (tertiles). Events are counted after the activity window used to determine early activity.

Figure 3. Kaplan-Meier estimates for the incidence of death or HF hospitalization. Patients are stratified in 3 equal-sized groups based on their baseline CHARM risk score value with cut-points 2.0 and 8.0 (tertiles).

Figure 4. Kaplan-Meier estimates for the incidence of death or HF hospitalization. Patients are stratified in 4 groups based on the combination of early activity and CHARM risk score. For both parameters the median value (188 minutes/day and 4.8 points, respectively) is used to group patients in the ‘low’ or ‘high’ category.
Physical Activity, Measured with Implanted Devices, Predicts Patient Outcome in Chronic Heart Failure

Viviane M. Conraads, Martijn A. Spruit, Frieder Braunschweig, Martin R. Cowie, Luigi Tavazzi, Martin Borggrefe, Michael R.S. Hill, Sandra Jacobs, Bart Gerritse and Dirk J. van Veldhuisen

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SUPPLEMENTAL MATERIAL

Physical activity, measured with implanted devices,
predicts patient outcome in Chronic Heart Failure.

Viviane M Conraads, MD¹, Martijn A Spruit, PhD²,³, Frieder Braunschweig, MD⁴, Martin R Cowie, MD⁵, Luigi Tavazzi, MD⁶, Martin Borggrefe, MD⁷, Michael RS Hill, PhD⁸, Sandra Jacobs, PhD⁹, Bart Gerritse, PhD⁹, Dirk J van Veldhuisen, MD¹⁰

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⁹Medtronic Bakken Research Center, Maastricht, The Netherlands

¹⁰Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
**Methods**

The table below (eTable 1) provides additional details of the designs of SENSE-HF and DOT-HF. Investigators may have influenced patient behavior based on physical activity records, which were accessible after Phase I for SENSE-HF (unblinding after Phase I) and for patients in the access arm of DOT-HF. We therefore investigated the interaction effect between access to device diagnostic data and early physical activity. Both studies were approved by the local ethics committees, and written informed consent was obtained from all patients. The authors had full access to study data.

To evaluate the possible confounding effect of a positive response to CRT, in terms of exercise tolerance, as well as outcome, we compared patients implanted with an ICD only to those with an implanted CRT-D device.

Influences of access to diagnostics and CRT were assessed from interaction terms.

**Results:**

The average early physical activity is 199 minutes per day, with a standard deviation of 106 min/day. Further descriptive statistics are: range: 3-579 min/day; and quartiles 120 and 259 min/day. eFigure 1 provides the frequency distribution.

Access to device diagnostic data for patients enrolled in DOT-HF did not influence the relation between early activity and the primary endpoint (HR=0.96 in patients with, and HR=0.95 in patients without access, interaction p=0.58). Patients with ICD and CRT-D were comparable with respect to early activity (p=0.32) and incidence of primary endpoints (p=0.17). The association between early activity and primary endpoints did also not differ significantly (HR=0.92 in ICD patients and HR=0.96 in CRT-D patients, interaction p=0.15).
**eTable 1. Design of SENSE-HF and DOT-HF**

<table>
<thead>
<tr>
<th></th>
<th>SENSE-HF</th>
<th>DOT-HF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial registration</strong></td>
<td>NCT00400985</td>
<td>NCT00480077</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>single arm randomized parallel two arm</td>
<td>ICD/CRT-D device</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>ICD/CRT-D device</td>
<td>ICD/CRT-D device</td>
</tr>
<tr>
<td><strong>Main inclusion criteria</strong></td>
<td>chronic heart failure with impaired LVEF (≤ 35%) despite OMT, HF hospitalization in last 12 months, recent implant (≤ 34 days) of ICD or CRT-D with OptiVol</td>
<td>chronic heart failure with impaired LVEF (≤ 35%) despite OMT, HF hospitalization in last 12 months, recent implant (≤ 6 months) of ICD or CRT-D with OptiVol</td>
</tr>
<tr>
<td><strong>Main exclusion criteria</strong></td>
<td>post heart transplant or on waiting list, COPD, pulmonary hypertension, dialysis</td>
<td>post heart transplant or on waiting list, COPD, pulmonary hypertension, dialysis, cardiac surgery in last 90 days</td>
</tr>
<tr>
<td><strong>Access to device data</strong></td>
<td>phase I: 6 months, no access phase II/III: 18 months, full access</td>
<td>control arm: no access access arm: full access</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>phase I: sensitivity and PPV of OptiVol threshold crossing for detection of HF hospitalization phase II/III: PPV of first detected OptiVol alert for worsening HF</td>
<td>all-cause death and HF hospitalization</td>
</tr>
</tbody>
</table>

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; CRT=Cardiac Resynchronization Therapy; CRT-D=Defibrillator with CRT; HF=Heart Failure; ICD=Implantable Cardioverter Defibrillator; LVEF=Left Ventricular Ejection Fraction; OMT=Optimal Medical Therapy; PPV=Positive Predictive Value
eFigure 1. Histogram for early physical activity.

Histogram of early physical activity

Early Physical Activity (min/day)