STUDY REPORT SYNOPSIS

A non-interventional, cross-sectional study for evaluating factors relating to daily step counts and physical activity in Japanese patients with COPD: STEP-COPD

Background/rationale:

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow obstruction[1] and is a preventable and treatable disease, but with its high morbidity and mortality rates, rank COPD fourth for cause of death globally.[2] In 2016, COPD was ranked eighth in Japan for cause of death among males.[3] According to an epidemiological survey, the estimated prevalence of COPD is 8.6% in those aged at least 40 years.[4]

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure and is a complex behavior characterized by type, intensity, and duration of activities, patterns, and symptom experience.[5] People with COPD have been reported to have a decreased level of physical activity compared with healthy adults, even at an early stage of the disease.[6] The decreased level of physical activity itself is related increased risks of exacerbation, and related to death due to COPD.[7,8] Indeed, level of physical activity and daily step counts assessed by accelerometers were the strongest predictive factors for death. Furthermore, a longitudinal study reported that the risk of death increased in a group with decreased levels of physical activity.[9] This suggests that maintenance of physical activities is important to the prognosis of COPD. However, interventions that increase the level of physical activity have not been established yet, and prognostic factors of levels of physical activity have not been fully elucidated.[5,8] The level of physical activity in patients with COPD is suggested to be influenced by various factors such as respiratory function, exercise tolerance capacity, self-efficacy, and motivation.[5,10] It is also reported to be influenced by sociodemographic and environmental factors.[5,6]
In Japan, factors that influence levels of physical activity in people with COPD have been reported only in a few nationwide surveys.[11] There is, therefore, an unmet need to identify levels of physical activity in the COPD population. Thus, this study was planned as a multicenter, cross-sectional study to elucidate the status of physical activity in patients with COPD in Japan and explore factors related to levels of physical activity.Objectives:

The purpose of this study was to elucidate the actual status of levels of physical activity in patients with COPD in Japan and explore factors related to levels of physical activity in a multicenter cross-sectional study in an actual clinical setting.

Primary Objectives

- To describe the physical activity pattern of patients with COPD in Japan. For this objective, the following primary endpoints were defined:
    a. Daily step counts of patients with COPD (primary endpoint 1).

b. Activity time measured in minutes of each group of activity intensity, defined by metabolic equivalents (METs) in patients with COPD (primary endpoint 2).

- To determine if any correlation exists between levels of physical activity and selected demographic factors in patients with COPD.

a. Correlation between daily steps counts and a group of selected demographic factors (primary endpoint 3.1).

Correlation between total activity time of each intensity group by METs count and demographic factors (primary endpoint 3.2).

Secondary Objectives

- To compare patients in whom the level of physical activity and the respiratory function correlate with other patients for any difference in demographic factors (secondary endpoint 1).
- To investigate the actual status of levels of physical activity (step counts, METs, energy expenditure, inactivity time) by demography in patients with COPD (secondary endpoint 2).
- To examine the degree of influence of demographic factors that correlate with levels of physical activity in patients with COPD (secondary endpoint 3).

To assess the relationship between prescription status of medications (by class) and levels of physical activity (secondary endpoint 4).

Study design:

This was a multicenter, non-interventional, cross-sectional study conducted in Japan. COPD outpatients in follow-up, who met the study selection (inclusion and exclusion) criteria, were continuously enrolled by a central registration method to avoid selection bias. This was performed by Linical Co., Ltd. by request of AstraZeneca K.K.

Investigators provided verbal and in writing explanation of the study details (by the PIS), including aims, methods, anticipated benefits, and potential hazards of the study, for all eligible patients. Patients had to provide written informed consent after meeting all the study selection criteria,

After providing informed consent, patients answered the questionnaires and started measurement with an activity meter within 4 weeks. Through 14 consecutive days, measurement was determined per protocol. All the patients with at least 3 days of activity meter measurement were to be included in the FAS population.

Patients for whom the informed consent was explained were entered in the screening list, including those who did not finally provide their consent to participate in the study.

Data source:

Study source data consisted of the following:

- Medical records.
- Questionnaires.
- Records from the activity meter.

Study population:

Eligible patients were continuously enrolled by each investigator through a central registration method so that selection bias could be avoided. Patients were assigned a unique identification number for the study. Study sites retained a confidential correspondence table that linked the unique patient identification numbers to medical records to extract data necessary for the study.

Inclusion criteria:

Patients enrolled in the study had to meet all the following inclusion criteria:

1. Provided written informed consent for participation in this study.
2. Male and female patients aged at least 40 years at the time of enrollment with diagnosis of COPD by a physician, following the Guidelines for Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease of the Japanese Respiratory Society (5th Edition). [12]
3. Patients whose respiratory function test values post-bronchodilator test (forced expiratory volume in 1 second [FEV1], forced vital capacity [FVC], ratio FEV1/FVC, and inspiratory capacity [IC]) were available, either at the time of enrollment or within 3 months prior to enrollment (for patients on a bronchodilator as a long-term controller, respiratory function test values after bronchodilator in the morning of the test were acceptable).
4. Patients whose diffusing capacity of the lung for carbon monoxide (DLCO) values, and data on the presence/absence and degree of emphysema based on a chest computed tomography (CT) scan results, were available within the past 1 year.

Outpatients who were able to answer the questionnaires and start measurement with an activity meter and to measure their activity level for 14 consecutive days within 4 weeks after providing informed consent.

Exclusion criteria:

Patients who met any of the following criteria were excluded from the study:

1. Patients who had participated in any interventional studies such as clinical trials within the past 8 weeks.
2. Patients determined to be inappropriate for enrollment in the study by investigators because they could not comply with the procedures, limitations, and requirements of the study, among other reasons.
3. Patients with an exacerbation of COPD within the 8 weeks prior to study entry (defined as any conditions with increased shortness of breath, increased cough and sputum, occurrence of chest discomfort/uneasiness or its intensification, and which require changes in treatment on disease stable state (excluding cases where there was any other precedent disease such as heart failure, pneumothorax, pulmonary thromboembolism, etc).

4. Patients who required home oxygen therapy (excluding those who used it only during nighttime).

Statistical methods:

Tables and listings were produced in accordance with the principles outlined by the ICH E3 guideline.

All data were descriptively analyzed as follows:

- Quantitative variables were summarized using the following statistics: Number and percentage of non-missing data, number of missing data, mean, standard deviation (SD), median, minimum, and maximum, 1st and 3rd quartiles (Q).
- Qualitative variables were summarized using the following statistics: number and percentage of non-missing data, number of missing data and 95% confidence intervals (CIs) when specified in the analysis.

For all statistical tests, P-values and correlation values were displayed with 3 decimals. Due to the descriptive nature of this study, no adjustment per multiple test was planned.
Missing data or unknown responses were not counted in the percentages. For date of birth, only the month and year were collected so, for the calculation of the age, the day was imputed to 15. In the COPD questionnaire, for all variables collecting time, in case hours were completed but minutes were missing, time was imputed to 30 minutes. In case of hours missing the full measurement was considered missing. No other imputation of missing data had been planned for this study. Incomplete dates were treated as missing.

Analysis set:

Enrollment Population: The enrollment population included those patients fulfilling the inclusion/exclusion criteria and having signed the ICF.

Full Analysis Set (FAS): The FAS was defined as those patients who had measured levels of physical activity using the activity meter for at least 3 days during the study period, based on the data published by Sugino et al, [13] who measured daily activities in patients with COPD using activity meters for 14 days and reported that achieving sufficient reliability for assessment of intraclass correlation coefficients, ie, an index of inter-rater reliability, would require measurement for at least 3 days.

Activity Meter Classification (AMC)-FAS: The AMC-FAS consisted of patients from the FAS who had on ≥3 days at least 8 hours measured time from activity meter on the period recorded on the eCRF, and answered 'Fine or cloudy the day', and 'Same as usual' on the eCRF, having measured the following variables: post-bronchodilator FVC (L); post-bronchodilator FEV_1 (L); post-bronchodilator FEV_1/FVC (FEV_1%); post-bronchodilator percent predicted FEV_1 (%FEV_1); and IC (L).
Major or minor protocol deviations could be defined during the study duration before the database lock. It was decided by the sponsor that patients with major or minor protocol deviations not affecting the ICF process would not be excluded from the FAS.

Results:

The mean daily step count in the AMC-FAS population was 4064.4 (median 3440.8, range 10–17,792). The mean total duration of ≥3 METs activity was just 28.8 minutes/day (median 18.7, range 0–169). Notably, in more than 30% of patients, the time spent in ≥3

METs activity was ≤10 minutes. The mean total duration of ≥2 METs activity was 201.2 minutes (median 186.9, range 13–617).

Pulmonary function, shortness of breath, and age were weakly correlated (magnitude of correlation coefficient between 0.3 and 0.5) with ≥3 METs activity. The correlation between ≥2 METs activity and all items investigated in this study was low (magnitude of correlation coefficient ≤0.3).

The mean total duration of ≥2 METs activity measured using an activity monitor (201.2 minutes) was considerably less than the mean duration of patient-reported light-to-moderate activities, which roughly corresponded to ≥2 METs (366.7 minutes). The relationship between the device-monitored total activity time in patients achieving ≥2 METs and patient-reported durations of walking/standing and physical labor/vigorous sport (activities deemed to be ≥2 METs) indicate that patients tended to overestimate the time spent in activities requiring ≥2 METs in their subjective reports compared with the time measured by an activity monitor (366.7 vs 201.2 minutes).

Correlations between METs and background factors were evaluated using univariate and multivariate analyses. For ≥3.0 METs activity, age (≥74 to <79 years, p=0.0060; ≥79 years, p<0.0001), GOLD stage (stage III, p=0.0008; stage IV, p=0.0019), mMRC dyspnea score (score of 1, p=0.0166; score of ≥2, p=0.0001), and employment status (not employed, p<0.0001) were found to be correlated in the multivariate analysis. In the analysis results for ≥2.0 METs, sex, GOLD stage, employment status, and living with another person were found to be correlated in the multivariate analysis. In the multivariate analysis results for step counts, . mMRC dyspnea score ≥2 and lack of employment were found to be significantly correlated with number of steps (both p<0.0001).

Conclusion:

The objectives of the STEP-COPD study of physical activity of 503 mainly elderly adult Japanese patients showed the following:

- The mean (SD) daily step count in the AMC-FAS was 4064.4 (2984.4) steps/day, and was comparable to that in the FAS of 4059.0 (2832.6) steps/day.
- The results show that COPD patients spent a mean (SD) of 201.2 (99.1) minutes per day in the level of ≥2.0 METs, 408.1 (149.3) minutes in the level of ≤1.5 METs (sedentarism), and 712.7 (133.6) minutes per day in the level of ≤3.0 METs.
- In multivariate analysis, age (≥74 to <79 years, regression coefficient= -10.35, p=0.0060; ≥79 years, coefficient=-20.00, p<0.0001), GOLD stage (stage III, regression coefficient=-12.37 p=0.0008; stage IV, regression coefficient=-24.53, p=0.0019), mMRC dyspnea score (score of 1, regression coefficient=-7.49, p=0.0166; score of ≥2, regression coefficient=-13.97, p=0.0001), and employment status (not

employed, regression coefficient=-13.22, p<0.0001) were correlated with ≥3.0 METs activity.

- In multivariate analysis, sex (male, regression coefficient=-41.22, p=0.0015), GOLD stage (stage III, regression coefficient=-49.67, p<0.0001; stage IV, regression coefficient=-127.59, p<0.0001), employment status (not employed, regression coefficient=-66.37, p<0.0001), and living with another person (no, regression coefficient=-35.03, p=0.0044) were correlated with ≥2.0 METs activity,
- In the multivariate analysis . mMRC dyspnea score (score of ≥2, regression coefficient=-1779.86, p<0.0001) and employment status (not employed, regression coefficient=-1332.31, p<0.0001) were correlated with number of steps with daily step counts.

Publications:

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9. Vaes AW, et al. Changes in physical activity and all-cause mortality in COPD. Eur Respir J 2014. 44(5):1199-1209.
10. Bauman AE, et al. Correlates of physical activity: why are some people physically active and others not? Lancet 2012;380(9838):258-71.
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