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FEV$_1$ Minimum Important Difference versus Minimal Detectable Difference? In Search of the Unicorn

To the Editor:

The goals of managing chronic obstructive pulmonary disease (COPD) include optimizing lung function, reducing symptoms, improving health status, and reducing exacerbations. As COPD is multidimensional in nature, composite scores have been proposed to better predict risk of death and assess effects of pharmacological therapies. Regarding the latter, the concept of clinically important deterioration (CID) was proposed using the purported minimum clinically important differences (MCIDs) of health status (St. George's Respiratory Questionnaire ≥4), moderate–severe exacerbation incidence, and lung function (FEV$_1$ ≥ 100 ml) (1). This concept of CID has since been used in subsequent clinical trials. However, the lung function criterion of an MCID of 100 ml was initially posited from a literature review (2), which proffered that although a change of 100 ml can be perceived by a patient, several limitations exist, including placebo effect, reproducibility, and variability, leading to the conclusion that "The MCID in FEV$_1$ remains an important but still undetermined issue for patients with COPD" (2). This is important when considering the American Thoracic Society (ATS)/European Respiratory Society (ERS) Task Force statement on interpretive strategies for lung function testing

Figure 1. Bland-Altman plot depicting the reproducibility between the screening values and measurements at 4 weeks (baseline) for FEV_1 from study HCZ102970 in subjects with COPD (ClinicalTrials.gov NCT01017952). The central horizontal line shows the mean of differences, and the dashed lines represent the 95% limits of agreement. Of the total $N = 421$, data were plotted for $n = 419$ (2 patients had missing data). COPD = chronic obstructive pulmonary disease; CR = coefficient of repeatability.
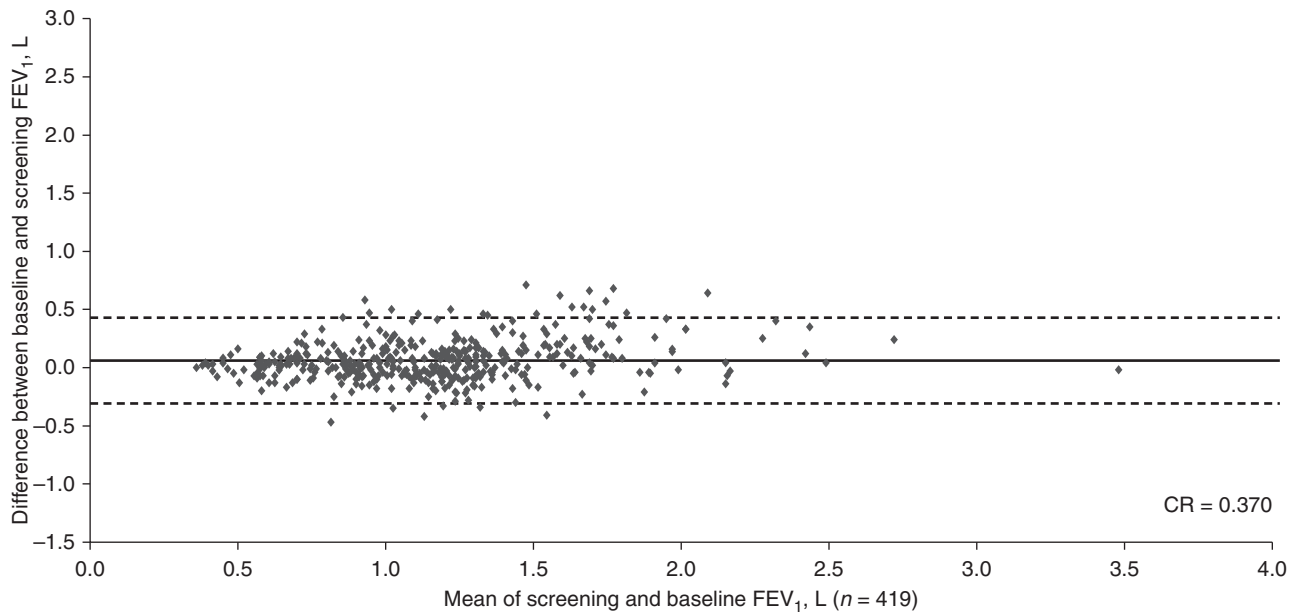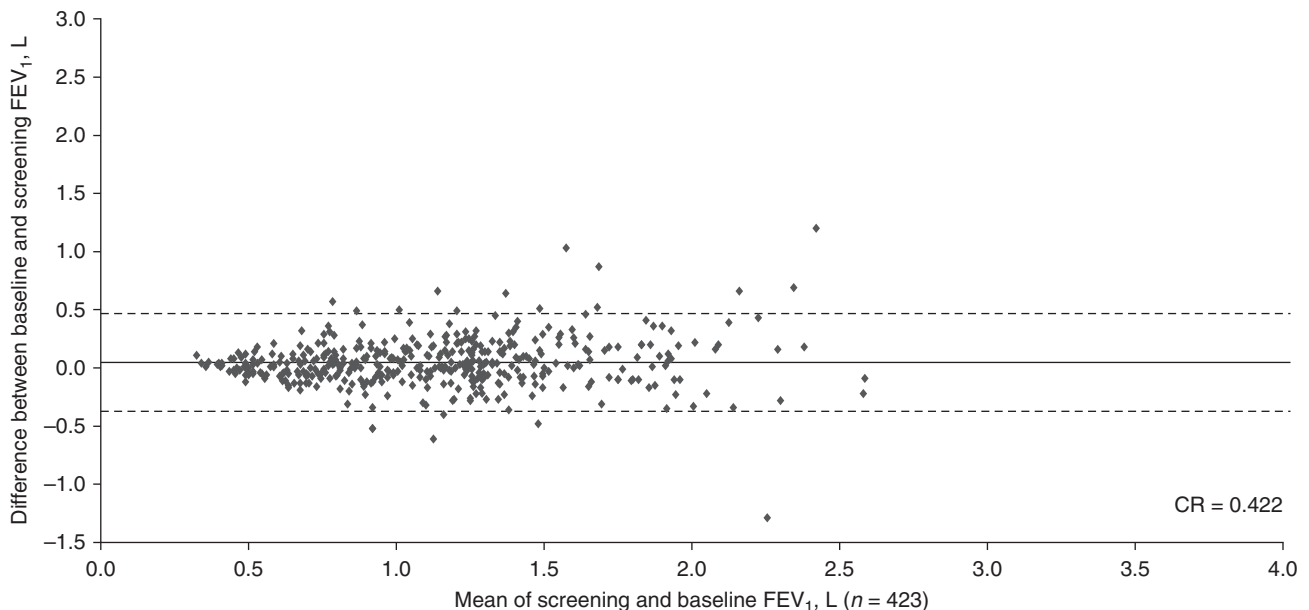

Figure 2. Bland-Altman plot depicting the reproducibility between the screening values and measurements at 4 weeks (baseline) for FEV_1 from study HZC102871 in subjects with COPD (ClinicalTrials.gov NCT01009463). The central horizontal line shows the mean of differences, and the dashed lines represent the 95% limits of agreement. Of the total $N = 427$, data were plotted for $n = 423$ (4 patients had missing data). COPD = chronic obstructive pulmonary disease; CR = coefficient of repeatability.

that suggests, for an individual patient, only changes that fall outside the coefficient of repeatability (CR) should be considered significant (3). CR determination is recommended because it takes into consideration the measurement variability over a specified interval (i.e., measurement noise) and represents the value below

which the absolute difference between two measurements would lie with a 95% probability.

To further explore the robustness and, hence, utility of a 100-ml threshold as gleaned from clinical trials, as the CID was initially proposed using such data, we reviewed data from two clinical studies

in patients with COPD to assess the short-term variability of change-from-baseline FEV_1. We hypothesized that the FEV_1 CR observed in multicenter trials would exceed the 100-ml threshold currently adopted as the MCID.

Methods

We examined data from two COPD trials (HZC102871, NCT01009463; HZC102970, NCT01017952) (4). These were registration studies designed to replicate the efficacy and safety of the inhaled corticosteroid/long-acting β_2-agonist combination fluticasone furoate/vilanterol 100/25 μl. Enrolled patients were ≥40 years old with ATS/ERS-defined COPD history (5), a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤0.70 predicted, and ≥1 documented moderate or severe COPD exacerbation in the year before screening. These trials were selected for *post hoc* analysis as they measured spirometry at baseline and 4 weeks later, during which the patients could not have had an exacerbation, a respiratory tract infection, or a change in their inhaled therapy. The patient subgroup selected for this analysis (HZC102871, $N = 427$; HZC102970, $N = 421$) was already receiving an inhaled fluticasone propionate/salmeterol 250/50 μg combination product. At baseline, patients received open-label inhaled fluticasone propionate/salmeterol for 4 weeks prior to randomization. The spirometry equipment had to meet or exceed the minimum ATS performance recommendations (6), and external spirometric tracing readings were made to assure acceptability and reproducibility. Variability of FEV_1 measurements over the 4-week interval was assessed using Bland-Altman plots (7).

Results

The study design and baseline characteristics of the entire COPD cohort are completely described in the primary publication (4). Patients in this subgroup had a mean age of ∼63 years. In studies HZC102970 and HZC102871, respectively, ∼45% and 55% were male; mean (±SD) FEV_1 values were 1.26 L (±0.42) and 1.22 L (±0.46); and mean (±SD) predicted post-bronchodilator FEV_1 percentages were 45.8% (±12.8) and 43.9% (±13.6). The Bland-Altman plots are shown in Figures 1 and 2; the CR for both COPD trials exceeded the putative MCID of 100 ml (370 ml and 422 ml, respectively).

Discussion

The 4-week CR attained in patients with COPD in multicenter clinical trials exceeds the putative MCID of 100 ml. CR values obtained in both trials are similar to the 3-month CR of 400 ml reported in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study (8). This is notable because in the ECLIPSE report, 37% of the patients with COPD either had an exacerbation or changed their medication during that 3-month window, and the severity of airflow limitation ranged from moderate to very severe. Patients with more severe airflow limitation, and hence lower baseline values, were more likely to demonstrate less variability compared with patients with less impaired airflow and perhaps more demonstrable reversibility. However, the percentage change would likely be of similar magnitude. Conversely, the Figures clearly illustrate the differences in individual variability. According to the ATS/ERS Task Force on interpreting lung function studies,

week-to-week FEV_1 variability should exceed 20% (and year-to-year exceed 15%) before considering it as a significant change in patients with COPD (3).

An MCID should not only represent a change in an endpoint detectable to the patient but also one that the patient or clinician deems as clinically beneficial. A patient with severe/very severe airflow limitation may not only perceive but benefit from a specified improvement in FEV_1 compared with a patient with moderate airflow obstruction. For example, when measured on a seven-category scale ("much worse . . . about the same . . . much better"), a correlation of FEV_1 with dyspnea at $r = 0.29$ (95% confidence interval, 0.22–0.35) and a correlation of FEV_1 with overall health of only 0.10 (95% confidence interval, 0.03–0.17) was reported (9). The rating change from "about the same" to a "little bit better/worse" related to an average FEV_1 change of 112 ml (10). Patients or clinicians could debate whether "little bit better/worse" is clinically meaningful. In the noninterventional ECLIPSE trial, a 100-ml FEV_1 decrease was associated with an increased odds ratio of a subsequent exacerbation (9). However, there are no robust data purporting that an FEV_1 increase of 100 ml decreases exacerbation risk (6), and a recent study demonstrated minimal overlap of FEV_1 "responders" with those of several patient-reported outcome instruments (11).

Clearly, identifying an MCID is important in clinical practice. As with the unicorn, it was often sought but difficult to capture. From this analysis, one cannot conclude that 100 ml is not the MCID but rather that FEV_1 data gleaned from multicenter clinical trials do not support the validity of this adopted value. It is probable that spirometry performed at a single center, with highly trained personnel, allows for determination of "abnormality" by demonstrating a CR for FEV_1 with a value <100 ml. However, although such an abnormality might be detectable to patients, it remains to be proven that it is clinically or biologically important. Therefore, we propose that COPD therapy should be guided to improve FEV_1 above the CR determined in one's pulmonary function laboratory rather than focusing on some "universal" number, while reducing symptoms and exacerbations. ∎

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Endobronchial Valve Lung Volume Reduction and Small Airway Function

To the Editor:

The small airways (those <2 mm internal diameter) offer little resistance to airflow in health; however, the response to repetitive and continual insult by inhaled noxious particles causes them to become the principal site of impediment to airflow in chronic obstructive pulmonary disease (COPD). As disease progresses, several pathophysiological mechanisms collectively lead to emphysema and lung hyperinflation, recognized as significant contributors to the patient's perception of breathlessness and activity limitation that predicts not only the risk and severity of exacerbations but also all-cause mortality. These observations have stimulated interest in lung volume reduction (LVR) techniques, lung volume reduction surgery (LVRS), and more recently, placement of endobronchial valves (EBVs), which limit air entry but permit unimpeded expulsion of air and mucus, to deflate the lung in an attempt to restore respiratory mechanics. Accruing evidence supports the concept of LVR to improve lung function, exercise capacity, quality of life, and survival. Volume reduction is the key driver of the benefit (1).

Although the small airways are the principal site of disease pathogenesis, the effects of LVR on small airway function are largely unknown. Bilateral LVRS undertaken in 29 patients with severe emphysema has demonstrated more efficient small airway lung ventilation with scintigraphic imaging of regional lung ^{133}Xe gas washout (2). Oscillometry in 23 patients whose heterogeneous emphysema or emphysematous bullae had been treated with histoacryl gel, an experimental "biological" LVR not clinically approved for routine practice, showed a decreased R_{5Hz}, with unaltered X_{5Hz} (3).

Here, we study the impact on lung mechanics of EBVs. We hypothesized that EBVs implanted in the proximal bronchi of the most severely diseased lung lobe(s) would lead to functional improvements in the peripheral lung. Small airway function was assessed using oscillometry and ventilation distribution tests.

Methods

In a prospective observational study (ethics reference 14/SC/0193), patients with COPD with severe emphysema and without collateral ventilation underwent EBV placement (Zephyr; PulmonX). During a stable disease state before and 3 months after the procedure, patients underwent clinical phenotyping: symptom scores (modified Medical Research Council dyspnea scale and St. George's Respiratory Questionnaire [SGRQ]), functional exercise capacity (6-min-walk distance), radiological assessment, and lung function testing. After bronchodilation (400 μg albuterol), routine body plethysmography was followed by impulse oscillometry (Cardinal Health) and multiple-breath nitrogen washout (MBN_2W) testing (PK-Morgan), as described previously (4). Wilcoxon signed-rank tests were performed using GraphPad Prism (v8), with significance at $P < 0.05$.

Results

Twelve patients with COPD (five female) participated, with a baseline median modified Medical Research Council dyspnea scale score of 2.5 and SGRQ-total score of 50.9 and features of very severe airflow obstruction (FEV_1 28% predicted), hyperinflation (residual volume [RV] 225% predicted), and radiological signs of emphysema (Table 1). Three months after the procedure, with a radiologically verified median volume reduction of 730 ml, significant gains were observed in spirometry, static lung volumes (RV and RV/TLC), exercise capacity, and SGRQ-activity score (Table 1). Distinct improvements were obtained for impulse oscillometry indices of reactance (X_{5Hz}, $P = 0.013$; and $X_{in5Hz} - X_{ex5Hz}$, $P = 0.010$) (5, 6), and for MBN_2W

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