ONLINE SUPPLEMENT

Dransfield et al. Impact of Zephyr Endobronchial Valves on Dyspnea, Activity Levels and Quality of Life at One Year

1. Methodology

Study participants were former smokers aged between 40 and 75 years of age, with evidence of severe airflow limitation (post-bronchodilator forced expiratory volume in 1 second, FEV_1, of 15 to 45% of predicted), hyperinflation (total lung capacity, TLC, > 100% of predicted and residual volume, RV ≥175% predicted), gas transfer (DLCO) ≥ 20% of predicted, and a Six-Minute Walk Distance (6MWD) between 100 and 500 meters after a supervised pulmonary rehabilitation program. Selection of the target lobe was based on greater than 50% emphysematous destruction at -910 Hounsfield units (HU) with little or no interlobar collateral ventilation using the Chartis® System (Chartis; Pulmonx Corp., Redwood City, CA, USA) and 15% heterogeneity with the ipsilateral lobe using Myrian quantitative computed tomography (QCT) analysis. At day 45 follow-up, subjects were eligible for Zephyr Valve adjustment/replacement if QCT analysis showed target lobe volume reduction (TLVR) of less than 50% and demonstrated signs indicative of incomplete occlusion, including no valve in a segmental airway, anatomic variation resulting in the valve not occluding accessory branches, leakage around the valve, or incorrect placement.

Further assessments were performed at 3-, 6-, 9-, and 12-months. The primary endpoint was the difference in the percentages of subjects in the two groups achieving an improvement in post-bronchodilator FEV_1 ≥15% at 12-months. Secondary endpoints included group differences at 12-months for changes in FEV_1 (ml), six-minute walk distance (meters), and St. George's Respiratory Questionnaire Total score (SGRQ, Total score) (previously reported, (1)).

2. Patient-Reported Outcome (PRO) Assessment Tools

The modified Medical Research Council (mMRC) Dyspnea scale(2) provides a simple means of categorising patients in terms of the disability associated with breathlessness due to COPD(3). A minimum clinically important difference (MCID) of -1 is considered meaningful(4).

The St George's Respiratory Questionnaire (SGRQ) is a 50-item multidimensional instrument to measure quality of life in patients with airways obstruction and to quantify changes after therapy(5, 6). Scores are calculated for three domains: Symptoms (frequency and severity), Activities (that cause or are limited by breathlessness), and Impacts (psycho-social disturbance resulting from airways disease), that are combined to generate a total score. Scores range from 0 to 100, with higher scores indicating more severe limitation. An MCID of -4 is considered meaningful(7).

The COPD Assessment Test (CAT) is an 8-item multidimensional tool that evaluates the impact of the disease (cough, sputum, dyspnea, chest tightness) on health status (8). CAT scores range from 0 to 40, with higher scores denoting more severe impact on an individual's life.

The Transitional Dyspnea Index (TDI) provide multidimensional measurements of dyspnoea based on activities of daily living in symptomatic individuals(9). Scores are calculated for three domains: Functional impairment, Magnitude of Task, and Magnitude of Effort relating to daily activities in the 2 weeks prior to administration. The TDI score ranges from −3 (major deterioration) to +3 (major improvement) for each domain: The sum of all three domains yields the TDI focal score (−9 to +9), with lower scores representing more severe dyspnoea. An MCID of +1 for TDI is considered meaningful(10).

The EXAcerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome (EXACT-PRO) is a 14-item daily diary for evaluating frequency, severity and duration of COPD exacerbations(11) using a personal digital assistant (PDA) device. Higher scores indicate more severe health or exacerbation. An MCID is not yet established.

The modified Borg scale is an instrument for measuring the intensity of breathlessness before and after activity for example, the six-minute walk test, and response to therapy(12). A MCID of -1 is considered meaningful(13).

3. Timing of Questionnaires

Table E1: Timing of Questionnaire Administration

	Baseline	45-days	3-months	6-months	9-months	12-months
HEALTH SURVEYS						
SGRQ	X		X	X		X
mMRC	X	X		X		X
BDI/TDI	X		X	X	X	X
CAT	X		X	X	X	X
Health Care Utilization	X		X	X	X	X
DAILY DIARY						
PR Program Compliance	X	X	X	X	X	X
EXACT-PRO	X	X	X	X	X	X
Health Status Change	X	X	X	X	X	X

4. Baseline Demographics

Table E2: Baseline Demographics and Clinical Characteristics

Criner G et al. Am J Respir Crit Care Med, 2018. 198(9): p. 1151-1164.
The Am J Respir Crit Care Med is an official journal of the American Thoracic Society.

Variable	Zephyr Valve (n=128)	SoC (n=62)	t-test p-value
Gender	56 Males (43.8%) 72 Females (56.3%)	33 Males (53.2%) 29 Females (46.8%)	NS
Age (years)	64.0 ± 6.85	62.5 ± 7.12	NS
Smoking history (pack years)	50.78 ± 26.88	48.59 ± 28.48	NS
Clinical Characteristics			
GOLD Stage	Stage III: 54 (42.2%) Stage IV: 74 (57.8%)	Stage III: 16 (25.8%) Stage IV: 46 (74.2%)	0.037
Emphysema score of the target lobe at -910 HU*	70.9 ± 8.52	70.9 ± 8.77	NS
Post-BD Forced Expiratory Volume in 1 sec. (FEV_1) (L)	0.76 ± 0.25	0.75 ± 0.22	NS
Post-BD Forced Expiratory Volume in 1 sec. (FEV_1) (% predicted)	28.0 ± 7.45	26.2 ± 6.28	NS
Post-BD FEV_1 /FVC Ratio	0.30 ± 0.06	0.29 ± 0.06	NS
DLCO (mL CO/min/mmHg)	8.53 ± 3.48	8.34 ± 2.70	NS
DLCO (% predicted)	34.6 ± 11.34	33.1 ± 9.84	NS
Residual Volume (L)	4.71 ± 1.05	4.76 ± 0.90	NS
Residual Volume (% predicted)	224.5 ± 42.45	224.6 ± 38.86	NS
Total Lung Capacity (L)	7.54 ± 1.59	7.63 ± 1.37	NS
Total Lung Capacity (% predicted)	133.5 ± 21.17	130.2 ± 12.44	NS
RV/TLC Ratio	0.63 ± 0.09	0.63 ± 0.07	NS
6 Minute Walk Distance (m)	311 ± 81	302 ± 79	NS
SGRQ Total Score ‡	55.15 ± 14.08	53.10 ± 14.14	NS
mMRC Score §	2.4 ± 0.97	2.2 ± 0.83	NS
BODE Index **	5.34 ± 1.52	5.32 ± 1.56	NS††
COPD Assessment Test (CAT)	19.2 ± 6.32	19.3 ± 6.35	NS
Patients on Continuous Oxygen Usage	46 (35.9%)	17 (27.4%)	NS

Values are means ± standard deviation

* Emphysema destruction score was assessed as the percentage of voxels of less than −910 Hounsfield units on CT.

† Heterogeneity Index was assessed as the difference in the Emphysema score between the target and the ipsilateral lobe.

‡ SGRQ (St. George's Respiratory Questionnaire) scores range from 0 to 100, with higher scores indicating worse quality of life.

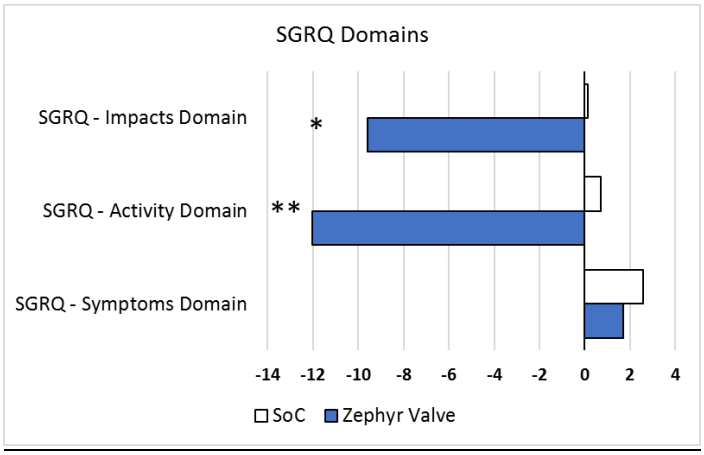
§ mMRC (Modified Medical Research Council Dyspnea Scale) scores scale ranges from 0 to 4, with higher scores indicating more severe dyspnea.

** BODE Index score ranges from 0 to 10 based on a multidimensional scoring system to include FEV_1, body-mass index, 6 Minute Walk Distance, and the modified MRC dyspnea score. Higher scores denote a greater risk of mortality.

††: Wilcoxon signed-rank test.

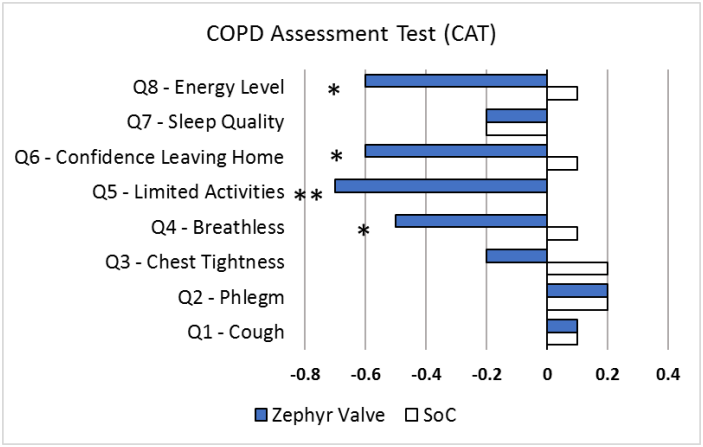
5. Absolute changes from baseline to 12-months for the SGRQ domains (Figure E1), the TDI domains (Figure E2) and the individual questions in CAT (Figure E3).

Figure E1: SGRQ Individual Domains – Change from Baseline to 12-months



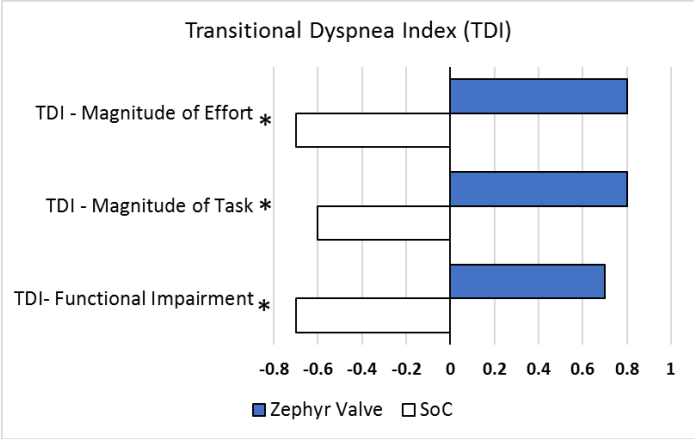
* p<0.05; ** p<0.001
(Analysis of covariance with factor of treatment and baseline value as covariate).

Figure E2: CAT Individual Question Responses – Change from Baseline to 12-Months



* p<0.05; ** p=0.004 (Wilcoxon Rank Sum Test).

Figure E3: Transitional Dyspnea Index – Change from Baseline to 12-Months



* p<0.001 (Wilcoxon Rank Sum Test).

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