Table 1 Summary of the available RCTs on the use of endobronchial valves in emphysematous patients

First author, journal, year	Trial	Aim	Design	Inclusion/Exclusion criteria	Study groups	Outcome measure	Main results	Conclusion	Strenghts/limitations/notes
Sciurba, NEJM, 2010, USA (13)	VENT (Endobronchial Valve for Emphysema Palliation Trial)	Compare the safety and efficacy of EBV therapy in patients with heterogeneous emphysema *vs.* standard medical care	Multicenter (31 centers), RCT	Inclusion: age 40–75 years, heterogeneous emphysema, FEV_1 15–45% pred, TLC >100% pred, RV >150% pred, BMI ≤31.1 (men) or 32.2 (women), $PaCO_2$ <50 mmHg, PaO_2 >45 mmHg, post-rehabilitation distance at 6MWT ≥140 m; exclusion: DLCO <20% pred, giant bullae, α_1-antitrypsin deficiency, previous thoracotomy, excessive sputum, severe pulmonary hypertension, active infection, unstable cardiac conditions	Randomly assignment in a 2:1 ratio to receive therapy with a Zephyr® endobronchial valve (EBV group: 220 pts) *vs.* SoC (control group: 101 patients)	Coprimary effectiveness endpoints: change in FEV_1 and distance walked at the 6MWT at 6 months. Primary safety endpoint: difference in the rate of a composite of six major complications (death, empyema, massive hemoptysis, pneumonia distal to valves, pneumothorax or air leak of more than 7-day duration, or ventilator-dependent respiratory failure for more than 24 hours' duration) at 6 months. Secondary efficacy endpoints: mean changes in patients' quality of life (SGRQ, incremental cycle exercise capacity, MMRC)	At 6 months, endobronchial LVR procedure was significantly better (between groups difference in FEV1 +60 mL, P=0.002; FEV1 +6.8%, P=0.005; 6MWD +19.1 m, P=0.02; SGRQ −3.4 points, P=0.04; MMRC −0.3 points, P=0.04) although the magnitude of results was modest. By 6 months, the between-group difference in rate of the composite of six major complications was 4.9% (95% CI, 1.0–8.8%)	EBV treatment induced modest improvements in lung function, exercise tolerance, and symptoms at the cost of more frequent COPD exacerbations and hemoptysis after implantation. Greater heterogeneity of emphysema between lobes and intact interlobar fissures appear to identify patients with a greater likelihood of clinically important functional and physiological responses to EBV therapy	The VENT study had a smaller European subgroup of patients, whose results were reported separately in 2012 (14). The 111 participants assigned to the EBV group had a significant improvement in cycle ergometry (P=0.04), SGRQ (P=0.047) and a border line result in FEV_1 (P=0.067) compared to the 70 controls. Completeness of fissure and lobar exclusion were confirmed as predictors of higher changes while heterogeneity of emphysema was not a critical factor. Serious complications did not differ between groups
Davey, Lancet, 2015, UK (15)	BeLieVeR-HIFi (Bronchoscopic lung volume reduction –BLVR- with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures on CT could improve outcomes, through the placement of EBV	Establish whether targeting patients with heterogeneous emphysema and intact interlobar fissures on CT could improve outcomes, through the placement of EBV	Single-center, randomized, double-blind sham-controlled trial	Inclusion: FEV_1 <50% pred; TLC >100% pred, RV >150% pred; distance at 6MWT <450 m, MRC ≥3, heterogeneous emphysema at CT scan with a defined target lobe with lung destruction and intact adjacent interlobar fissures. Exclusion: substantial comorbidity restricting exercise capacity or prognosis; substantial daily sputum production; hypoxia; patients considered to be too restricted or frail to undergo bronchoscopy or to tolerate a pneumothorax	Randomly assignment in a 2:1 ratio to placement of Zephyr® EBV valves plus medical therapy (n=25) *vs.* sham bronchoscopy plus medical therapy (n=25)	Primary endpoint: the between group difference in the % change in FEV_1 at 3 months. Secondary endpoints: change in endurance time (T_{LIM}) on cycle ergometry at 70% of maximum achieved workload and changes in end-expiratory lung volume at isotime; change in distance at 6MWT, changes in health status (CAT and SGRQ)	In the EBV group, FEV_1 increased by a median 8.77% (60 mL) *vs.* 2.88% (30 mL) in the control group (P=0.03). The BLVR group had a significant improvement in 6MWT (25 *vs.* 3 m, P=0.01) and T_{LIM} on cycle ergometry (+25 *vs.* −10.8 s. P=0.03). This result was accompanied by significant improvements in lung volumes and gas transfer. CAT and SGRQ scores improved more in the BLVR group but compared with the control group were not statistically significant	Placement of EBV in patients with severe COPD who have heterogeneous emphysema and intact interlobar fissures on CT scan was associated with improvements in lung function and exercise capacity	There were two deaths in the EBV group, one after tension pneumothorax following removal of valves because of cough and the other for COPD with cor pulmonale. Benefit from treatment appeared to be restricted to subjects without collateral ventilation
Klooster, NEJM, 2015, the Netherlands (16)	STELVIO	Comparing endobronchial-valve treatment with standard medical care	Single center, RCT	Inclusion: age >35 years, stopped smoking >6 months earlier, post-bronchodilator FEV_1 <60% pred, TLC >100% pred, RV >150% pred, mMRC >1. Complete or nearly complete fissure between the target lobe and the adjacent lobe as visually judged on HRCT. Exclusion: evidence of collateral ventilation in the target lobe and failure to achieve lobar occlusion with endobronchial valves, by Chartis system	Randomly assignment in a 1:1 ratio to receive Zephyr® EBV valves (34 cases) *vs.* SoC (34 cases, control group)	Primary outcome: improvements in FEV_1, FVC, and 6MWT at 6 months. Secondary outcome: improvements in FEV_1, FVC, 6MWT, SGRQ; CCQ and the total volume of the treated lobe on inspiratory HRCT, at 6 months. MCID from baseline: 10% increase for FEV_1; 26-m increase for 6MWT; 4-point reduction for SGRQ; 0.4-point reduction for CCQ; 350-mL reduction as volume for the treated lobe; and 430-mL reduction for residual volume	Changes from baseline to 6 months in FEV_1, FVC, and 6MWT were significantly greater in the EBV group than in the control group. Between-group difference: 140 mL in FEV_1, 347 mL in FVC, 74 m in distance at 6MWT (P<0.01 for all comparisons). Significantly more patients in the EBV group than in the control group had changes from baseline measures that exceeded the established MCID (P<0.001 for all comparisons)	In patients with severe emphysema with absence of interlobar collateral ventilation, EBV treatment improved pulmonary function, exercise capacity, and quality of life, even when considering patients in whom valve removal was required. Adverse events, including potentially life-threatening events, occurred and required careful follow-up	By 6 months, 23 serious adverse events had been reported in the EBV group, as compared with 5 in the control group (P<0.001). One patient in the EBV group died because of end-stage COPD with respiratory failure 58 days after treatment. Serious treatment-related adverse events in EBV group included pneumothoraces (18%) and events requiring valve replacement (12%) or removal (15%)
Valipour, AJRCCM, 2016, Europe (17)	IMPACT (Improving Patient Outcomes by Selective Implantation of the Zephyr® EBV)	Evaluating the safety and efficacy of EBV therapy in patients with homogeneous emphysema and absence of collateral ventilation	Multicenter (16 sites), RCT	Inclusion: age >40 years, ex-smokers, severe emphysematous type of COPD, FEV, 15–45% pred, TLC >100% pred, RV >200% pred, distance at 6MWT ≥150 m. Exclusion: >3 exacerbations with hospitalizations over the past 12 months, pulmonary hypertension, alpha1antitrypsin deficiency, prior LVR procedures, pulmonary nodule requiring follow-up within the target lobe, >20% difference in perfusion between left and right lung, $PaCO_2$ >55 mmHg, asthma, severe bullous emphysema (>1/3 of the hemithorax)	Randomly assignment in a 1:1 ratio to receive EBV treatment (43 pts) or SoC (50 pts, control group)	Primary outcome: % change in FEV_1 at 3 months. Secondary outcomes: absolute change in FEV_1 at 3 months, % of subjects in the EBV group achieving the MCID for FEV_1 (improvement of at least 15% or an improvement of at least 100 mL and at least 12%), RV (reduction equal to or less than −430 mL), 6MWT (improvement of ≥26 m), SGRQ (reduction of ≥4 points), and mMRC (reduction of ≥1 point) at 3 months, compared with the SoC group	EBV group had a significant improvement in % (+17%, P=0.0002) and absolute (120ml, P<0.0001) change of FEV_1 at 3 months. Significant changes were also obtained in SGRQ, 6MWT (40 m) and target lobe volume reduction	EBV in patients with homogeneous emphysema without collateral ventilation results in clinically meaningful benefits of improved lung function, exercise tolerance, and quality of life	The positive outcomes associated with EBV therapy in homogeneous emphysema were accompanied by a higher incidence of serious adverse events (SAEs), predominantly pneumothoraces (11 patients, 25.6%)
Kemp, AJRCCM, 2017, Europe (18)	TRANSFORM	To evaluate the efficacy and safety of Zephyr® EBV in heterogeneous emphysema and absence of collateral ventilation	Multicenter (17 sites) RCT	Inclusion: ex-smokers, ≥40 years of age, severe emphysema, FEV, 15–45% pred, TLC >100% pred, RV ≥180% pred, 6MWT 150–450 m. Exclusion: presence of collateral ventilation at Chartis system	Randomly assignment in a 2:1 ratio to receive EBVs plus standard of care (65 patients) *vs.* SoC alone (32 patients)	Primary outcome: % of pts with FEV_1 ≥ 12%, at 3 months. Secondary outcomes: absolute and % changes and responder rates at 3 and 6 months for FEV_1 (≥12%), RV (≤−430 mL), SGRQ (≤−4 points), 6MWT (≥26 m), mMRC (≤−1 point), and, for the EBV group only, the absolute and % change in target lobe volume reduction (TLVR) at 45 days post-procedure and % of subjects meeting the TLVR MCID of ≥350 mL relative to baseline	At 3 months, 55.4% of EBV and 6.5% of SoC subjects had an FEV, improvement ≥12% (P<0.001). Improvements were maintained at 6 months. 89.8% of EBV subjects had TLVR ≥350 mL, mean 1.09±0.62 L (P<0.001). Between-group differences at 6 months were statistically and clinically significant for RV (−700 mL), 6MWT (+78.7 m), SGRQ (−6.5 points), mMRC (−0.6 points) and BODE index (−1.8 points) (all P<0.05)	EBV treatment in hyperinflated patients with heterogeneous emphysema without collateral ventilation resulted in clinically significant benefits in lung function, dyspnea, exercise tolerance, and quality of life, with an acceptable safety profile	Pneumothorax occurred in 19 of 65 (29.2%) of EBV subjects

BLVR, bronchoscopic lung volume reduction; BMI, body-mass index; CAT, COPD Assessment Test, CCQ, Clinical COPD Questionnaire; CI, confidence interval; DLCO, diffusing capacity for carbon monoxide; EBV, endobronchial valve; FEV1, forced expiratory volume in the 1st second; FVC, forced vital capacity; LVR, lung volume reduction; MCID, Minimal clinically important difference; MMRC, Modified Medical Research Council; PaO2, partial pressure of oxygen; PaCO2, partial pressure of carbon dioxide; pred, predicted; pts, patients; RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire; SoC, standard of care; 6MWT, 6-minute walking test.