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Meta-analysis and Systematic Review of Bronchoscopic Lung Volume Reduction via Endobronchial Valves in Severe Emphysema

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Abstract

Introduction—Pharmacologic therapeutics for advanced emphysema have limited benefit. Bronchoscopic lung volume reduction (BLVR) with endobronchial valves (EBV) have reported improvements in lung function, breathlessness, and quality of life through randomized clinical trials, with less morbidity as comparted to Surgical Lung volume Reduction. We here present a Meta-analysis and systematic review of BLVR in advanced COPD patients

Methods—PubMed (NLM), Embase (Elsevier) and Web of Science (Clarivate Analytics) search was conducted using a combination of keywords and subject headings. The search was confined to the last 15 years and was completed on October 23, 2020. Only placebo controlled RCTs of emphysema patients with EBV were included. Quality assessment was done by two independent reviewers.

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Results—9 studies were included for the Meta-analysis with a total number of 1383 patients of whom 888 received EBV and 495 standard of care (SOC) medications. Our Metanalysis show statistically significant improvement in FEV1, %FEV1, SGRQ and 6MWD in EBV group compared to SOC. Residual volume (RV) had statistically significant reduction after EBV placement compared with SOC. These differences continued to be present during short term(<=6months) and long-term follow-up (>=6months). These improvements were even higher when the EBV patients' Collateral ventilation was negative/fissure was intact (CV −/FI >9 0%). The rate of hemoptysis and pneumothorax was higher in the EBV group compared to SOC, however, did not lead to increased fatal outcomes.

Conclusion—In conclusion, EBV has favorable effects on patients' outcomes in patients who have heterogeneous emphysema particularly with no collateral ventilation

Introduction

Chronic Obstructive Lung Disease (COPD) is the third leading cause of death and fourth leading cause of disability in the United States, responsible for six percent of all deaths globally in 2012.[1] The healthcare burden of COPD is projected to increase exponentially in the coming decades. Pulmonary emphysema, a major pathological subtype of COPD, results from abnormal enlargement of the air spaces distal to the terminal bronchioles.[2] Abnormal parenchyma and airway physiology results in excessive gas trapping during the expiratory phase. Patients with advanced emphysema suffer from static and dynamic hyperinflation that leads to dyspnea, exercise intolerance, muscle wasting, reduced physical activity levels and impairments in quality of life. Moreover, these abnormalities predispose to exacerbations of COPD that are associated with increased morbidity and mortality.[3,4]

Pharmacologic therapeutics for COPD patients that have a predominant emphysema phenotype have limited benefit.[1,5] Inhaled therapies such as short and long-acting bronchodilators have been shown to improve FEV_1 and static and dynamic hyperinflation more than placebo, however, the magnitude of the benefit is limited in patients with advanced emphysema. Other guideline-recommended therapies include smoking cessation, influenza, pneumococcal, pertussis and covid-19 vaccines, pulmonary rehabilitation (PR) and continuous oxygen therapy, however no medical therapy provides relief from the progressive disability of severe emphysema as they do not address the structural and physiological disturbances that results from advanced disease.[6]

Lung volume reduction surgery (LVRS), first performed in 1957, served for decades as the only intervention able to relieve severe hyperinflation in emphysema. The National Emphysema Treatment Trial (NETT) demonstrated survival benefit in the subset of patients with upper lobe predominant emphysema and low exercise capacity compared to medical therapy. However, many patients (80%) are ineligible for LVRS, primarily due to associated morbidity and mortality, especially patients with homogeneous emphysema.[7] Minimally invasive techniques, including one-way endobronchial valves (EBV), were developed over the last two decades to reduce hyperinflation and improve clinical outcomes with less associated morbidity and mortality.

Bronchoscopic lung volume reduction (BLVR) has gained popularity over the course of the last decade after reporting improvements in lung function, breathlessness, and quality of life through randomized clinical trials. Along with improvement in pulmonary function tests (PFTs), imaging studies have shown improved ventilation/perfusion mismatch post BLVR. This was especially seen in heterogeneous emphysema, through decreases in treated lobe perfusion and ventilation with compensatory redistribution to the contralateral lung.[8–10] The procedure has the advantage of being minimally invasive with less morbidity and mortality compared to LVRS.[11,12] Currently there are two FDA approved one-way valve systems that reduce hyperinflation in patients with severe COPD. Herein we present a Meta Analysis and a systematic review of the randomized controlled trials using endobronchial valves to perform BLVR.

Types of Valves

FDA Approved Valves

The Zephyr Valve is an implantable device that consists of a one-way silicone duckbill valve at the end of a Nitinol self-expanding frame that is covered with a silicone membrane. Zephyr valves are available in 4 sizes to accommodate airway diameters of different ranges (see Figure 1). A Chartis pulmonary assessment system can be used to assess for collateral ventilation and the Stratx Lung Analysis platform, a quantitative CT analysis service, assesses emphysema destruction, fissure completeness and lobar volumes to aid in selecting the best lobe for valve placement. The valves are deployed over endobronchial catheters that also aid airway sizing. The 4.0 catheter is also available in a J-configuration for tortuous airways.[13–15]

The Spiration Valve System is an implantable, umbrella shaped, one-way valve delivery system. The valve is composed of a flexible Nitinol frame that anchors it in place. Spiration valves come in 4 different sizes (5-, 6-, 7-, and 9-mm valves) (see Figure 2). A calibrated balloon catheter determines the appropriate valve size and is passed through a 2.0- or 2.6-mm working channel of the bronchoscope.[16,17] The number of valves implanted can range from two to nine valves. On average most lobes require three to five valves.[11]

Non-FDA Approved Valves

MedLung EBV and the endobronchial Miyazawa valve are the other valves that are available outside the United States. However, no randomized clinical trials have been published on these valves. Hence, our review excluded these valve systems.

Patient Selection Criteria

Optimal patient selection is crucial for the successful treatment of hyperinflation utilizing endobronchial valves. Patients should be symptomatic from hyperinflation despite being medically optimized through smoking cessation, bronchodilator therapy, and participation in pulmonary rehabilitation.[18,19] A rigorous work up should be initiated with pulmonary function tests (PFTs), high resolution chest computed tomography (HRCT), and collateral ventilation and fissure analysis.

PFTs

Patients with severe hyperinflation from advanced emphysematous destruction as evidenced by a FEV_1 of ≤45% predicted, RV of ≥150% predicted, and a total lung capacity (TLC) ≥100% are eligible for endobronchial valves. Patients with a FEV_1 ≤15% of predicted, DLCO <20% predicted, PaO_2 <45 mmHg, $PaCO_2$ >50 mmHg, or uncontrolled pulmonary hypertension (including resting systolic pulmonary arterial pressure > 45 mmHg) were excluded in clinical trials. Individuals with a DLCO < 20% had a benefit in a small single center study from 2016 but is a surgical predictor of mortality in patients with homogenous emphysema based on data from NETT.[11,12,20,21] Two other small single center studies reported that EBV can be performed in patients with a FEV_1 < 20% with a success rate of ~50–60%.[22,23] Typically, completion of pulmonary rehabilitation (adapted from the LVRS trials) is recommended prior to undergoing EBV treatment to minimize peri and post-operative complications and maximize post procedural patients exercise tolerance..

HRCT

HRCT allows identification of potential targets for intervention as well as post-intervention to confirm EBV placement and assess for target lobe volume reduction.[24] HRCT is performed with a slice thickness of ≤ 1 mm. Axial, coronal and sagittal images are acquired during both inspiration and expiration. HRCT allows for quantification of the emphysematous destruction of the peripheral lung tissue along with fissure assessment, a surrogate for collateral ventilation. Quantification can be performed by visual scoring, semiquantitative method using densitometry or by quantification using automated software. Both visual scoring and semi-quantitative methods have high inter-operator variability, hence they are not the preferred methods for determining EBV eligibility.[25] Moreover, the accuracy of CT to predict fissure completeness is not consistent and depends on the specific fissure. CT scans were reported to have a 74% accuracy of predicting fissure completeness for the left lung. However, it overestimates completeness of the right minor fissure, and underestimates completeness of the right major fissure.[26] More accurate automated software programs have been developed to calculate the severity and distribution of emphysema and fissure completeness but require validation.[27]

The reporting systems that are currently available include the Stratx lung analysis system and SeleCT Report. These software programs calculate total and lobar lung volumes and emphysema destruction scores (measured in Hounsfield units, HFU) in the different lobes which can also add the calculation of heterogeneity indexes.[28,29]

The radiologic features associated with good clinical outcomes include presence of heterogeneous emphysema and complete interlobar fissures which can be assessed by quantitative HRCT. Typically, greater than 40–50% area of the targeted lobe should be less than −910 to −920 HU as well as a 10–15% difference in emphysema destruction score between the target lobe and ipsilateral adjacent lobe. It is also recommended to have fissure completeness greater than 90% on Qualitative CT evaluation.

In addition, Quantitative CT assessments(~accuracy ~70–75%) has a correlation with Chartis physiologic assessment (described below) for Collateral ventilation assessment

(agreement ~80%) and is an additional tool to select patients for BLVR.[30–33] Combination of quantitative CT and the Chartis System® Collateral ventilation assessment results in a higher diagnostic pre-procedural assessment for predicting response in patients receiving BLVR.[34] Lastly, the Chartis System® can be used as an additional diagnostic tool to confirm the absence of collateral ventilation in selected patients.[11,12,35,36]

Collateral ventilation and fissure analysis

Collateral ventilation (CV) is assessed using the Chartis ™ Pulmonary Assessment System. Both flow and volume are measured distally through a specialized flow catheter while a balloon is inflated proximally, a process that mimics lobar occlusion of the targeted lobe.[37] CV is said to be negative if flow measurements progressively decrease to absence of flow and collateral resistance increases to > 10 cmH_20 × s/ml around the catheter.[38,39] Measurements should be taken meticulously as false negative and positive results may occur. A false CV-negative can occur with failure to obstruct all subsegments and incomplete sealing of the bronchus. By contrast a false positive CV- result can occur due to mucous plugging of the distal catheter tip, rapid collapse of the bronchial wall around the catheter, and distal obstruction of the catheter tip by a secondary carina.

In one prospective study, 36 of the 51 CV negative patients showed a significant total lung volume reduction (≥350 mL). This translated into a positive predictive value of 71%. In comparison, 24 out of 29 CV positive patients failed to show significant lung volume reduction for a negative predictive value of 83%.[40]

Chartis™ has also been validated for intraoperative assessment of fissure integrity with an accuracy of 71%. The sensitivity and specificity of the Chartis measurement were 86% and 61% and 75% and 79% in HRCT fissure analysis.[32]

Nuclear perfusion/ventilation scans

Optimal target lobe selection is dependent on the percentage of perfusion to the target lobe. The 3-dimensional ventilation and perfusion (V/Q) single-photon emission computed tomography (SPECT)/computed tomography (CT) analysis can be used to identify target lobes by quantifying volume, ventilation, and perfusion changes. It can also be used to quantify post-BLVR treatment responses.[41] In BLVR patients, studies have shown robust improvement in exercise capacity (using 6-minute walk test, 6MWT and SGRQ) when target lobe perfusion was <8% of total perfusion in the upper lobes and <13% of total perfusion in the lower lobe targets.[42] In addition, patients with high perfusion in ipsilateral non-target lobes demonstrated greater improvements in 6MWT, while patients with high heterogeneity between target and nontarget lobes are more likely to show greater improvement in FEV_1.[41,43] 133-Xenon ventilation scintigraphy has shown promise in target lobe selection.[44]

Methods

Search Strategy

To identify studies to include or consider for this systematic review, the review team worked with a medical librarian to develop detailed search strategies for each database. The search

was developed for PubMed (NLM) and was translated to Embase (Elsevier) and Web of Science (Clarivate Analytics) using a combination of keywords and subject headings. A grey literature search included bioRxiv and clinicaltrials.gov. The search included no major limits and was confined to the last 15 years. The language was restricted to English without any restrictions to specific populations or geographical areas. The final search was completed on October 23, 2020.

Initial Screen was performed by two independent reviewers using the titles and abstracts to exclude any duplicates, non-COPD trials, COPD trials without lung volume reduction, case reports/series or conference abstracts. After the initial screen, the same two reviewers independently scanned all the articles to identify randomized control trials (RCTs) evaluating the treatment of advanced emphysema patients with EBV. The reviewers independently assessed the full text articles, reviewed them using the inclusion/exclusion criteria below. Any differences were resolved through consensus; with a third reviewer resolving any disagreements.

Inclusion and exclusion criteria

Studies fulfilling the following selection criteria were included in this meta-analysis: Randomized placebo-controlled trials (RCTs) of emphysema patients treated with either EBV or standard medications according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were included. Both experiments and controls should have been available for Odds Ratio (OR), risk differences, weighted mean differences (WMD) and 95% confidence interval (CI). Studies were excluded if one of the following existed: non-EBV treatment of emphysema, not RCTs, reviews, case reports/series and abstracts.

Quality assessment and data extraction

The quality of studies was also independently assessed by the two reviewers who assessed the studies for biases, appropriate outcomes, duration of follow-up and lack of selective reporting.

Data extraction and critical appraisal were carried out by the two reviewers independently. The results were compared, and any discrepancies were resolved by the third reviewer. Using a standardized data extraction spreadsheet, data on first authors' last name, the publication year, study design, the sample size, study population, inclusion criteria, treatment method, length of follow-up, and outcomes were extracted.

Data Analysis

The primary outcomes for the review included change in forced expiratory volume in 1 second (FEV_1), percent predicted FEV_1(%FEV_1), 6-minute walk distance (6-MWD), residual volume (RV) and St. George's respiratory questionnaire (SGRQ) after placement of the EBV. Secondary outcomes included mortality, rate of adverse events including acute respiratory failure, pneumonia, and pneumothorax. Continuous outcomes were measured as the mean difference and 95% confidence intervals (CI), and dichotomous outcomes as odds ratio (OR) and 95% CI. We did not impute missing data for any outcome. We assessed heterogeneity between studies by estimation of the I^2 statistic and by a formal statistical

test to indicate statistically significant heterogeneity. We performed subgroup analyses by follow-up time (<6 months vs & >= 6 months) for the primary outcomes. For adverse events, subgroup analysis was performed by short- and long-term follow-up reported in respective studies. Similarly, subgroup analysis was performed by collateral ventilation (CV) and fissure intact (FI > 90% vs < 90%) status for both primary outcomes and adverse events. We conducted meta-analysis using a fixed effects model and conducted statistical tests for subgroup and overall treatment effects between EBV and control. To ensure the generalizability of the results and robustness of the meta-analysis, we also conducted the meta-analysis using a random effects model (see online supplement for results). P values < 0.05 were considered statistically significant. All data analyses were performed using Stata 17.0 (Stat Corp LLC., College Station, TX).

Results

Initial screening yielded the following results: PubMed (NLM) from inception to 10/23/20 (413 Results), Embase (Elsevier) from inception to 10/23/20 (902 Results), Web of Science (Clarivate Analytics) from inception to 10/23/20 (419 Results). This search resulted in 1,748 studies (14 from grey literature sources). 619 duplicates were identified, and 5 articles were written in languages other than English. There were 582 studies excluded because they involved COPD without lung volume reduction or other diagnoses. All abstracts, case reports/series, and editorials were excluded (274 in total). 33 articles were excluded because they were unrelated to endobronchial valves. A second screening was performed on the remaining 235 studies. 32 studies were found to be non-endobronchial valve BLVR (i.e., coils, vapor ablation, gels). 100 reviews and 94 trials with other EBV related outcomes were removed (see Figure 3). In the end, 9 studies were included for the Meta-analysis with a total number of 1383 randomized patients, of whom 888 received EBV and 495 received standard medications. All eligible studies were of high quality, and with a follow up duration of minimum 3 months. 7 studies were multicenter, while 2 were single centers. Table 1 summarizes some of the outcomes of these trials.

Primary Outcomes

Physiologic parameters (FEV_1, $\%FEV_1$, RV)

Our metanalysis revealed that patients who received EBV had an increase in baseline FEV_1 (WMD=102.61 ml; 95% CI: 82.80 to 122.43; $p < 0.05$; $I^2 = 42.61\%$, $p = 0.08$) compared to the standard of care (SOC) group. The percent FEV_1 change (WMD=11.71; 95% CI: 9 to 14.42; $p < 0.05$; I^2=71.13%, $p < 0.05$) increased in the EBV group compared to the SOC group. RV had a statistically significant reduction in the EBV group compared to the control group (WMD= −533.48 ml; 95% CI, −653.01 to −413.94; $p < 0.05$; $I^2 = 26.90\%$, $p = 0.22$). The improvements in FEV_1 (102.55 ml vs 102.84 ml, p=0.99), $\%FEV_1$ (11.41 vs 12.79, $p = 0.68$) and RV (−537.63 ml vs −520 ml, p=0.90) were similar in both short term (<=6 months) and long-term follow-up (>6 months) (Figure 4).

Quality of life and activity parameters (SGRQ and 6MWD)

There was a significant improvement in patients' SGRQ scores in the EBV arm compared to SOC (WMD=−7.44; 95% CI: −9.01 to −5.86; $p < 0.05$; $I^2 = 50.89\%$; p=0.03). SGRQ

improvements were similar at short- and long-term follow-up (−7.29 versus −8.07, p=0.70). Our meta-analysis showed a statistically significant improvement in 6MWD among patients who received EBV compared with SOC (WMD=37.45; 95% CI: 27.68 to 47.21, p<0.05; I^2 = 72.98%; p <0.05). Improvements in 6MWD were similar at short- and long-term follow-ups (37.10 m versus 39.31 m, p=0.87) (Figure 4). See Supplementary figure 1 for analysis using random effect model

Adverse events

Analyzing all nine studies did not reveal any significant difference between mortality rates between the EBV and control group (OR = 1.08, CI: 0.57 to 2.05, p=0.82; I^2 = 0.0%, p = 0.95). Deaths were not different at short term and long term follow up between the groups (1.36 versus 0.84, p=0.47). There was a significant increase in incidence of pneumothorax in the EBV group compared to SOC (OR = 10.50, 95% CI = 5.31 to 20.79, p < 0.05, I^2 =32.55%, p=0.10). The incidence of pneumothorax was increased more so in short term follow-up (OR = 18.37, 95% CI =7.46 to 45.25) compared to long term follow-up (OR = 2.18, 95% CI = 0.69 to 6.87) (p < 0.05). The incidence of respiratory failure (OR = 0.93, 95% CI = 0.49 to 1.76, p = 0.82; I^2 = 0.00%, p = 0.96) was not statistically significant between the two groups. Increased incidence of pneumonia was noted in short term follow-up (OR = 3.12, 95% CI = 1.47 to 6.64, p<0.05) and overall (OR = 2.18, 95% CI = 1.36 to 3.50, p<0.05; I^2 = 0.0%, p=0.61), however was not statistically significant at long term follow-up (OR = 1.66, 95% CI = 0.90 to 3.06). (Figure 3). Increased incidence of AECOPD was observed in short term follow-up (OR = 1.48, 95% CI = 1.02 to 2.13, p < 0.05), however was not statistically significant overall (OR=1.11, 95% CI = 0.86 to 1.44, p=0.41: I^2 = 31.47%, p = 0.13) and at long term (OR = 0.83, 95% CI 0.57–1.19) follow-up. Hemoptysis was increased in the EBV group compared to the control group (OR = 2.30, 95% CI = 1.31 to 4.03, p<0.05: I^2 = 13.35%, p=0.31). The incidence of hemoptysis was observed more in short term (OR = 3.56, 95% CI =1.41 to 8.96) compared to long term follow-up (OR = 1.65, 95% CI =0.80 to 3.39) (See Figure 5). See Supplementary figure 2 for analysis using random effect model

Physiologic, Quality of life parameters and adverse events by Collateral ventilation/fissure intact (FI) status

Our metanalysis revealed that patients who received EBV with no collateral ventilation (CV −) or Fissure intact > 90% (FI) had significantly more improvement in FEV_1 (123.85 ml vs 61.69 ml, p=0.01), $\%FEV_1$ (19.84 vs 7.91, p < 0.05) and RV (−619.87 ml vs −370 ml, p=0.18) than patients with unknown status of CV/FI. SGRQ improvements were also significantly better in the CV −/FI > 90% group compared to CV/FI unknown group (−9.18 vs −3.58, p<0.05). Improvements in 6MWD were also higher in the CV-/FI>90% group, however they were not statistically significant (52.78 vs 33, p = 0.3) (Figure 6)

Patients in the CV −/FI >90% group had a higher incidence of pneumothorax compared to CV/FI unknown group (OR= 12.54 vs 1.42, p = 0.01). There were no statistically significant differences in rates of pneumonia, AECOPD, respiratory failure and death between the CV −/FI > 90% and CV/FI unknown groups. The rate of hemoptysis however was reduced in the CV – group (OR = 0.77 vs 8.12, p = 0.01) (see Figure 7). See Supplementary figure 3 and 4

for analysis with random effect model. For estimated risk differences for adverse events, see supplementary figure 5 and 6.

Discussion

Currently, the most widely used lung volume reduction method for the treatment of severe emphysema is EBV. Our meta-analysis shows that EBV therapy for advanced emphysema is associated with a statistically significant improvement in physiologic lung function parameters (FEV_1, FEV_1%, RV), functional parameters (6-MWD), and disease specific impact on health parameters (SGRQ) without significant long-term complications. The improvement in lung function parameters and quality of life parameters were even more robust when the patient's CV status was negative.

Although our meta-analysis showed significant improvements in these parameters, it is very important to have a specific selection criterion. VENT, the first RCT, had a statistically significant improvement in FEV_1 by 6.8%, an increase of 20 meters on 6MWT distance, and a reduction of −3.4 in SGRQ scores; however, the magnitude of these mean group changes were not clinically significant balanced against a higher rate of complications in the EBV group.[45] This study emphasized the importance of heterogeneity in emphysema pattern, complete fissure integrity, and complete lobar occlusion during post-hoc analysis. Subsequent studies such as STELVIO, IMPACT, and TRANSFORM utilized these features to improve EBV efficacy to improve lung function and exercise capacity (see table 1).[11,12,36,46–49]. This was followed by landmark trials such as LIBERATE and EMPROVE that led to FDA-approval of the two currently clinically available EBVs in the U.S. The LIBERATE trial used the Zephyr valve system and had 12-month follow-up for safety and efficacy. Besides exercise tolerance and lung function, 12-month follow-up of the LIBERATE also showed meaningful improvements in multidimensional scores (CAT, transitional dyspnea index (TDI)) for breathlessness, activity, and psychosocial parameters, thus improving quality of life.[50] The EMPROVE trial for the Spiration valve system yielded similar clinical improvements. Both trials were performed in patients with heterogeneous emphysema without collateral ventilation. The IMPACT study presented similar results in patients with homogeneous emphysema absent collateral ventilation. STELVIO included homogeneous emphysema, however it was a single center study.[46,48] In addition, different pooled meta-analysis of these RCTs have showed similar statistically significant improvements in FEV_1, 6-MWD and SGRQ.[51–55] These clinical outcomes are independent of target lobe (upper/lower); if interlobar collateral ventilation is low and complete lobar occlusion is achieved.[56,57] Our meta-analysis also demonstrated significantly more improvement in physiologic and quality of life parameters when the collateral ventilation was negative. Small studies have showed maintenance of improved respiratory function parameters for at least 3 years in patients with persistent lobar collapse.[58,59]

Other than physiologic parameters, CT based assessments have shown decrease in treated lobe volumes that correlate well with clinically meaningful improvements in exercise capacity and pulmonary function.[60,61] Lobar collapse following EBV was associated with long term survival benefit in some small studies, however has not been proven in large studies.[62,63] In addition, EBV treatment has also shown to improve three survival indicators

in severe COPD which include inspiratory capacity/total lung capacity ratio, BODE index and 6MWT.[64,65] Lastly, pulmonary rehabilitation post EBV treatment has an additive effect on improvement in exercise tolerance.[19]

BLVR is associated with multiple respiratory complications, predominantly in the perioperative period. In our meta-analysis, there was an increased incidence of pneumothorax, pneumonia, and hemoptysis in the overall groups, however this increase was most notable in the short-term follow-up groups only. The incidence of AECOPD, respiratory failure and death was not statistically different between the two groups.

Overall, respiratory complications occur in 31–35% of patients.[66] The most common adverse event associated with EBV placement is pneumothorax (~25%).[11,12] Pneumothorax, however, has not been associated with poor clinical outcomes if lobar atelectasis is achieved.[67–69] The majority of pneumothorax (86%) occurred within the first 72 hours of EBV implantation and most required chest tube placement for resolution. In situations where the lung does not fully expand or there is a persistent air leak, removal of one or more valves (about 26–31% of cases) may be necessary.[70] Pneumothorax will most often occur in the ipsilateral lung due to rapid expansion of the ipsilateral nontarget lobe after effective TLVR. Higher emphysematous destruction of the ipsilateral nontarget lobe and high residual volume increases the risk of pneumothorax.[71] Pleural adhesions in the treated lung are associated with an increased risk of pneumothorax.[72] In the early trials in the US and European VENT, pneumothorax was reported at a much lower rate compared to subsequent trials. These studies did not select patients based on lack of CV or intact fissures which led to poorer patient selection for successful BLVR. Pneumothorax appeared to be a positive predictor of successful valve therapy, since patients that developed pneumothorax were better responders to implantation (TLVR ≥ 350 ml) compared to non-responders.[66] This was evident from our analysis, which showed majority of the pneumothorax occurred in the CV − group, even though this group had the best clinical outcomes. Although higher rates of microbial colonization and pneumonia have been reported in patients undergoing EBV treatment, there were no differences in acute exacerbations and respiratory failure in patients treated with EBV compared to standard treatments.[66, 73, 74] Although hemoptysis was significant in our analysis, both spiration valve studies did not report any hemoptysis. Of the Zephyr valve system studies, only 3 were reported to be massive, the remaining were mild hemoptysis. Most cases of mild hemoptysis were self-limiting.

Granulation tissue formation is also a long-term complication that occurred in about 40% of EBV patients in our metanalysis. If the granulation is severe, the valve must be removed to allow the airways to heal for 10–12 weeks after which retreatment can be considered.[70] Valve malfunction, incomplete airway occlusion due to use of smaller valves, valve migration are some other complications that can lead to loss of benefit after EBV treatment.

Limitations

There were several limitations in our metanalysis. Firstly, the data regarding long-term clinical outcomes and adverse events with BLVR were limited as the trials were restricted to 12 months. The follow-up intervals for primary outcomes and adverse events were different

across and within the trials which made it challenging to define a specific cutoff period for short- and long-term follow ups. Also, the number of trials reporting clinical outcomes at greater than 6-month follow-up were limited. We were also not able to compare the differences in clinical outcomes with homogenous and heterogenous emphysema, as the homogeneous emphysema trials were limited with a small number of patients enrolled and the short duration of follow-up.

Conclusions

In conclusion, EBV has favorable effects on patients' outcomes similar to surgical lung volume reduction, but with significantly less adverse outcomes especially in patients who have heterogeneous emphysema with no collateral ventilation. Additional studies of larger numbers of patients with homogeneous emphysema followed for longer periods of time needs to be performed to assess the long-term effectiveness of EBV treatment in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial Disclosures:

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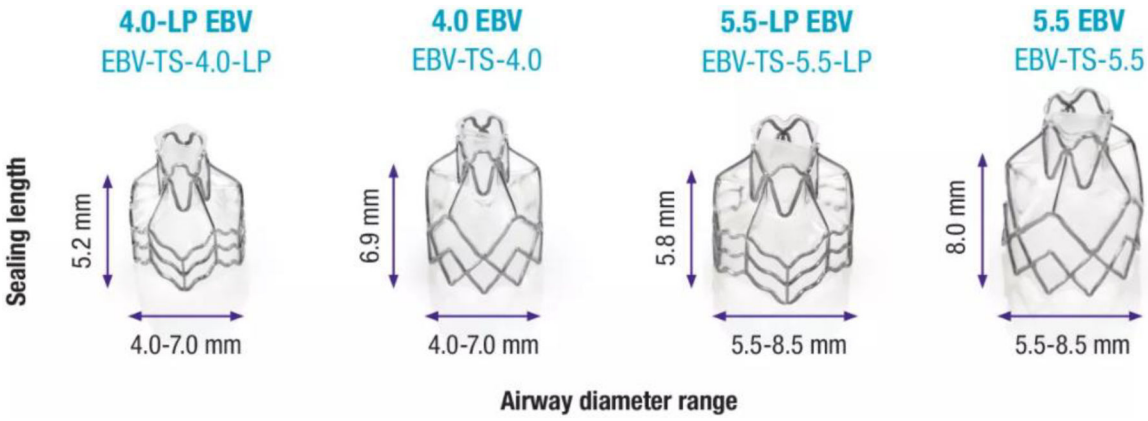

Figure 1:
Different sizes of Zephyr endobronchial valves.

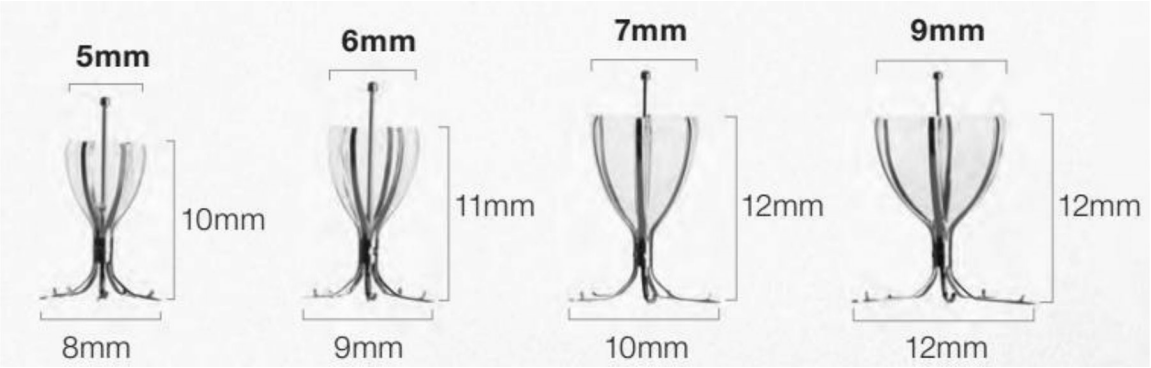

Figure 2:
Different sizes of Spiration Valve system

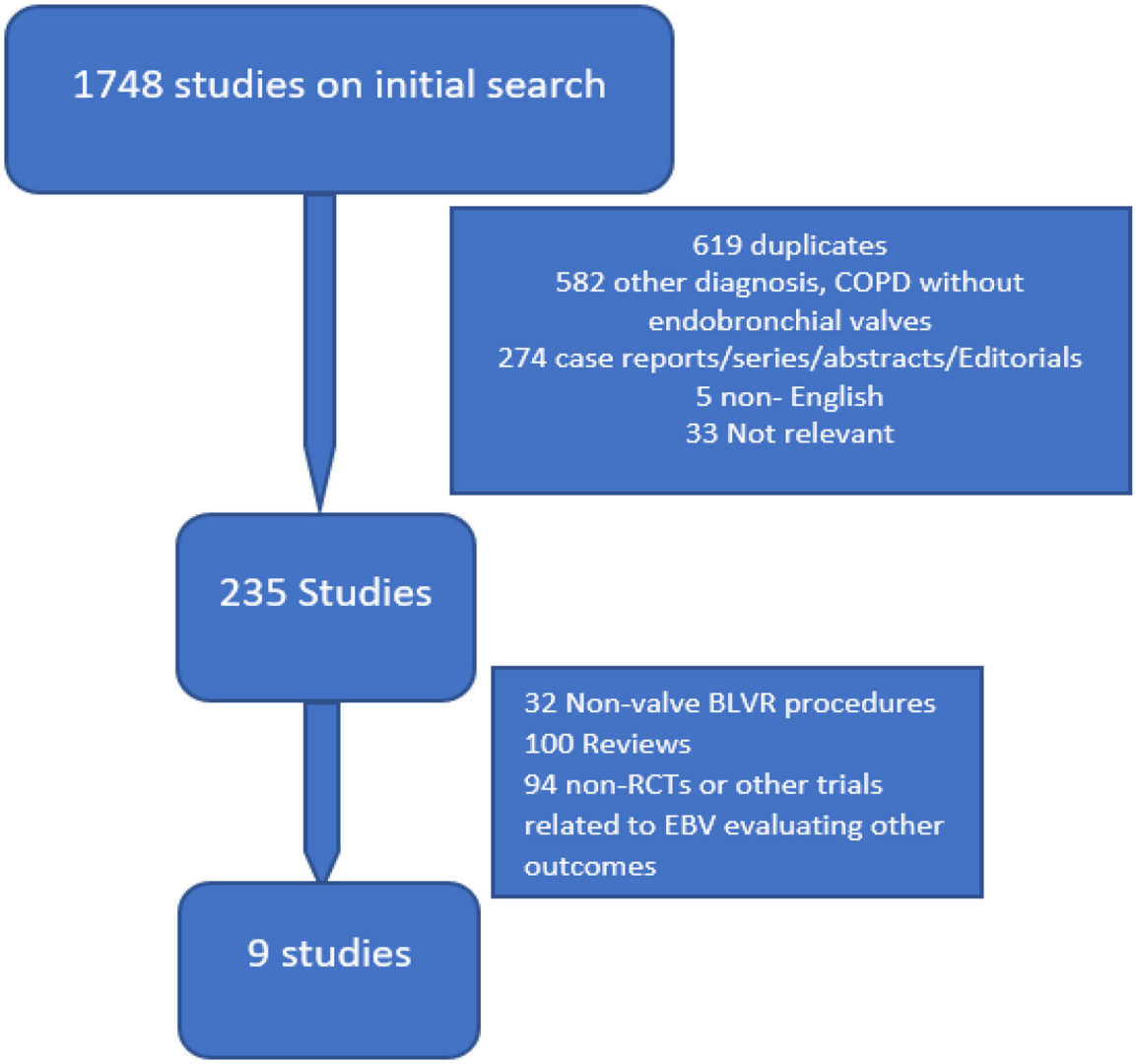

Figure 3:
Consort Flow diagram of our screening process

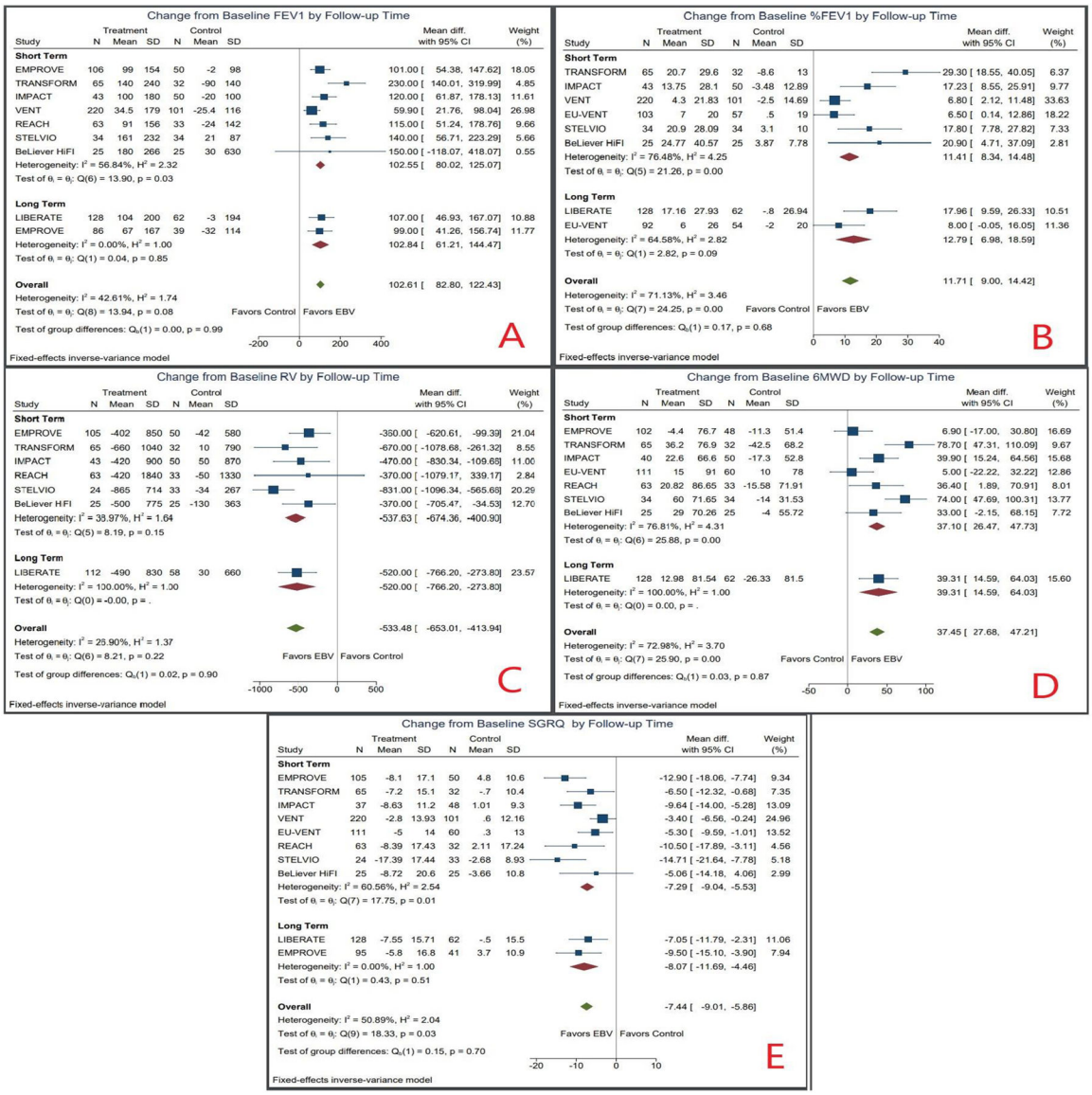

Figure 4:

Forest Plots comparing outcomes between the EBV and the control group. A: change in FEV1, B: Change in %FEV1, C: change in Residual Volume (RV), D: Change in 6-minute walk distance(6MWD), E Changes in SGRQ

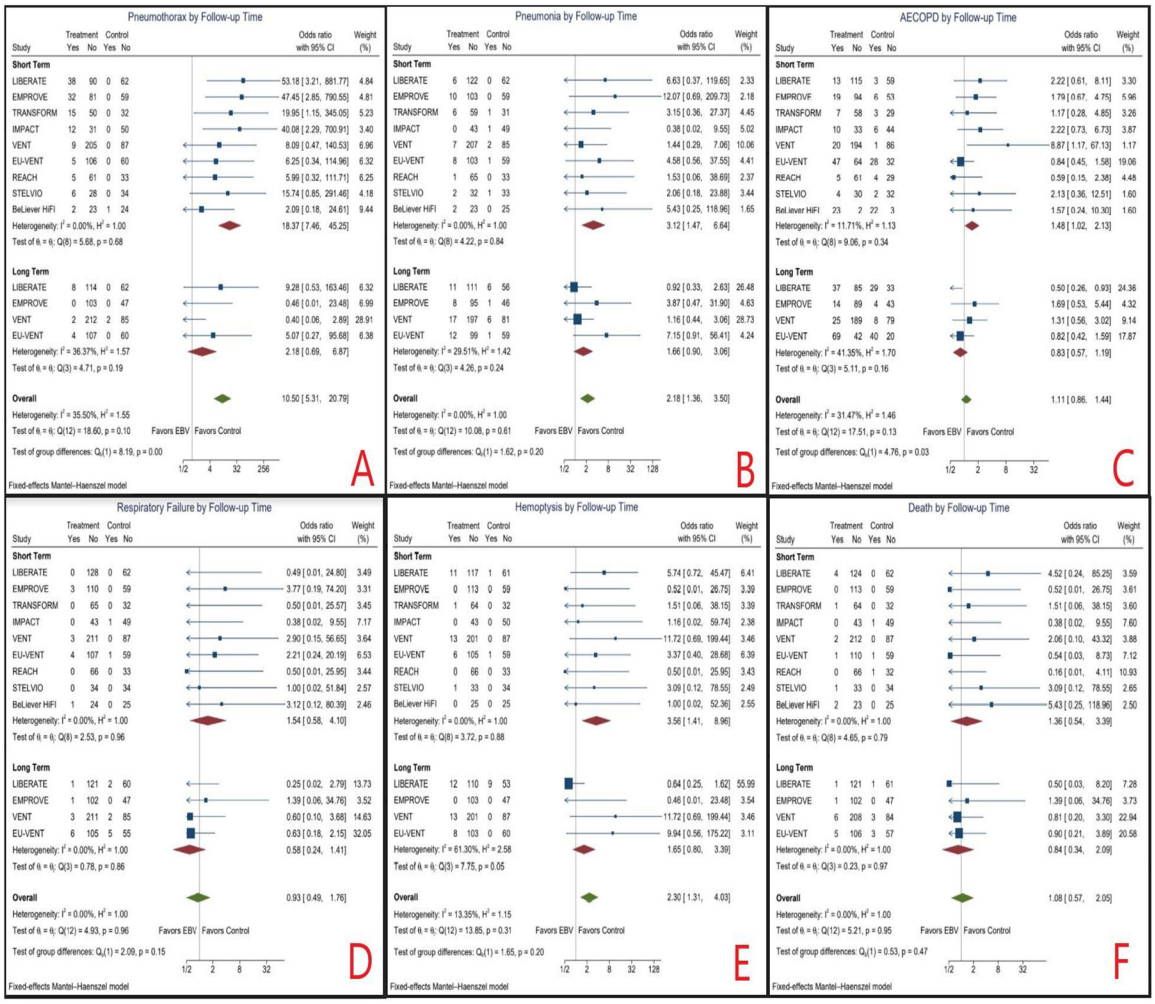

Figure 5:

Forest Plots comparing adverse events between the EBV and the control group. A: pneumothorax, B: Pneumonia, C: Acute exacerbation of COPD (AECOPD) D: Respiratory failure, E: Hemoptysis, F: Death

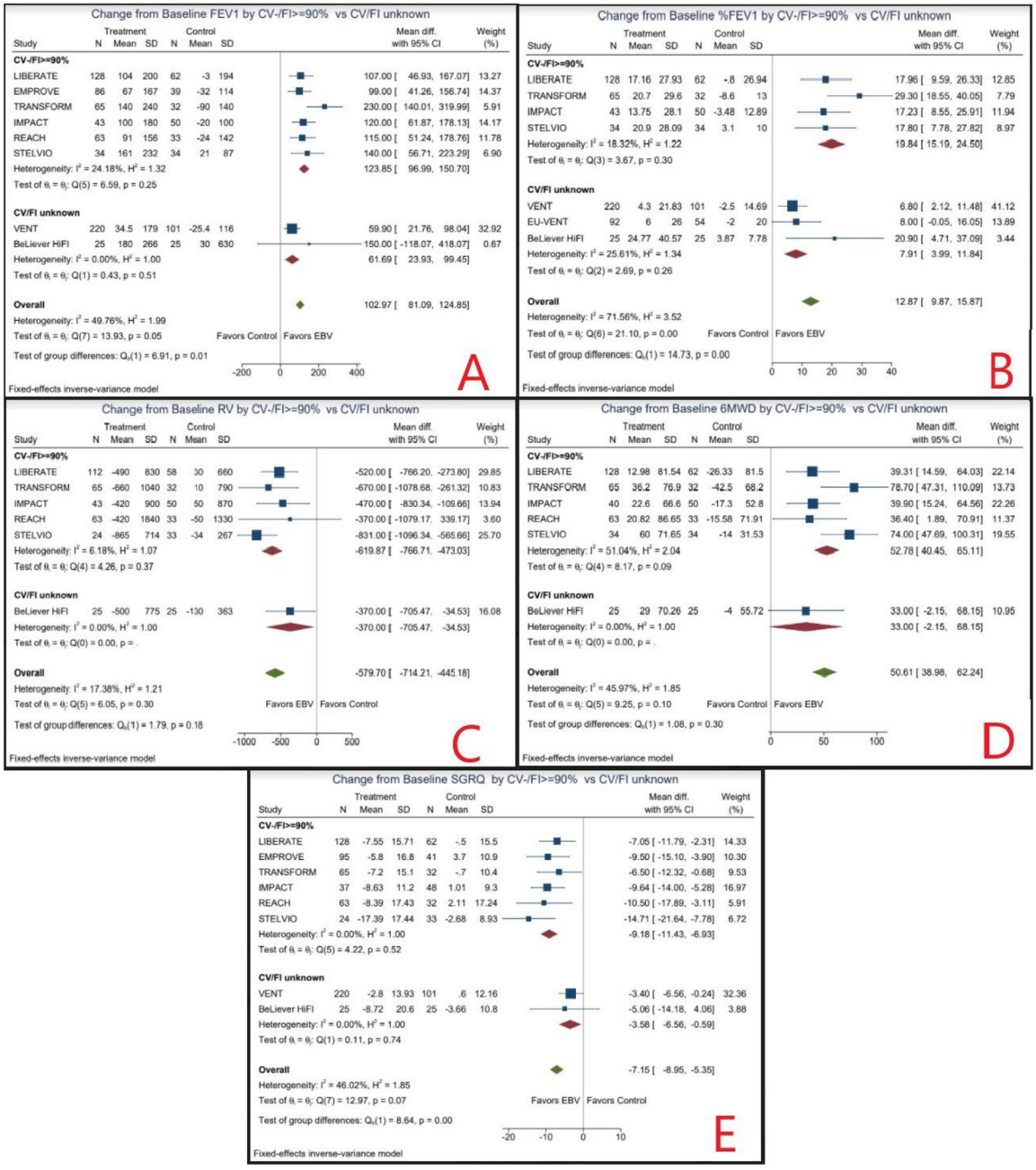

Figure 6:

Forest Plots comparing outcomes between CV + and CV − group. A: change in FEV1, B: Change in %FEV1, C: change in Residual Volume (RV), D: Change in 6-minute walk distance(6MWD), E Changes in SGRQ

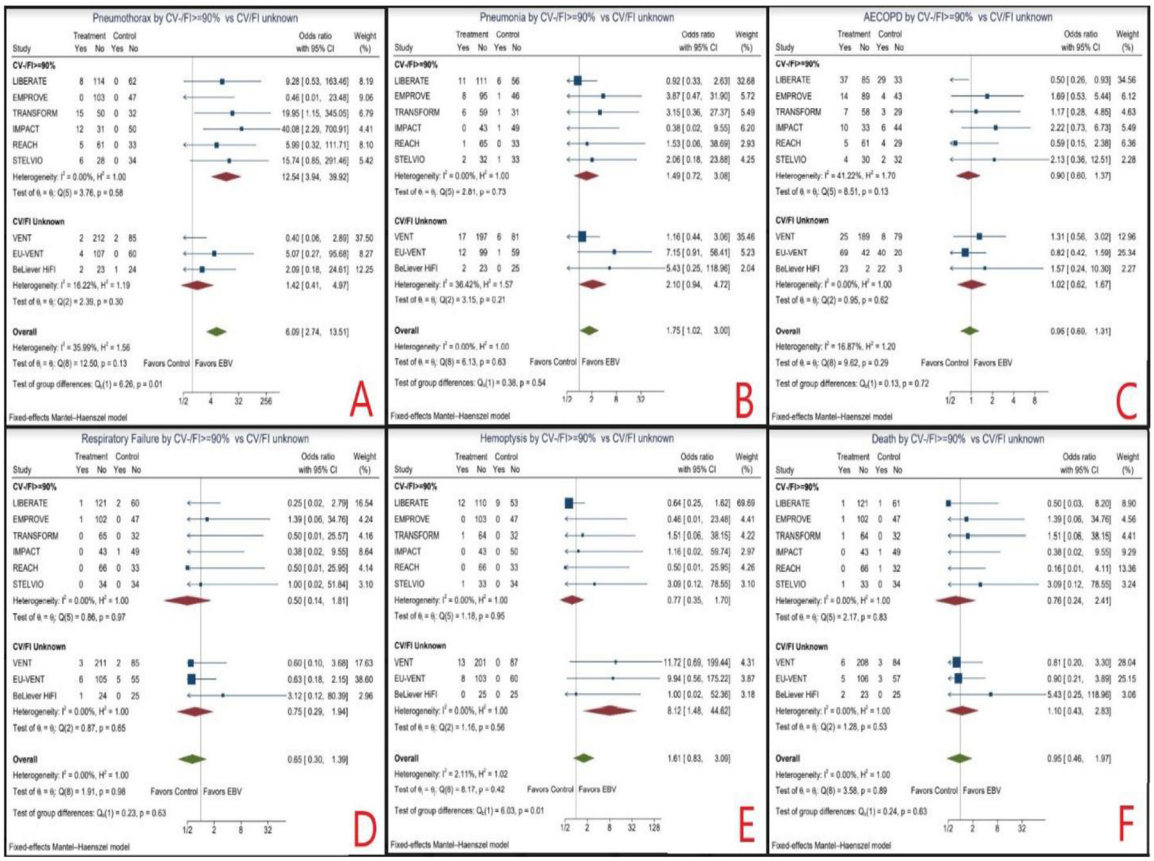

Figure 7:

Forest Plots comparing ADR between CV + and CV − group. A: pneumothorax, B: Pneumonia, C: Acute exacerbation of COPD (AECOPD) D: Respiratory failure, E: Hemoptysis, F: Death

Table 1:

Summary of Clinical outcomes for EBV in Trials (Intention to treat analysis)

						Physiologic parameters (presented as difference between groups, except TLC)			Functional parameters		
Trials	**HE/ HO & CV−/ CV+**	**Year**	**Follow-up in months**	**N**	**Trial Type**	**Post-BD FEV1 percent improvement**	**RV improvement in milliliters (ml)**	**TLC reduction in EBV patients in ml**	**6MWD improvement in meters**	**SGRQ**	**BODE index**
Zephyr valves											
LIBERATE	HE/CV−	2018	12	190	Multicenter Randomized Control trial (RCT)	17.6%	522	1142	39.31	−7.05	−1.2
TRANSFORM	HE/CV−	2017	3	97	Multicenter RCT	29.3%	670	1090	78.7	−6.5	−1.75
IMPACT	HO/ CV−	2016	3	93	Multicenter RCT	16.9	480	NA	40	−7.6	−1.16
STELVIO	HO/ HE/CV−	2015	6	68	Single Center Prospective RCT	17.8%	NA	1366	74	−14.7	NA
BeLiever-HiFi	HE	2015	3	50	Single center, double blind RCT	5.89 %	180	NA	22	−0.83	NA
EU-VENT ^	HE	2012	6	171	Multicenter RCT	20%	NA	50%	24%	−5.3 NS	NA
VENT^	HE	2010	6	321	Multicenter RCT	6.8%	NA	NA	20	−3.4	NA
Spiration Valves											
EMPROVE	HE	2019	6	172	Multicenter RCT	NA 101 ml	361	974	6.9 NS	−13	NA
REACH	HE	2019	6	107	Multicenter unblinded RCT	15.2%	370	757	36.4	−10.5	NA

HE- heterogenous emphysema distribution, HO- homogenous emphysema distribution, CV- Collateral ventilation, FEV_1- Forced expiratory volume in 1 second, RV = residual volume, TLC- total lung capacity, 6MWD- 6-minute walk distance, SGRQ- St. George's respiratory Questionnaire, NS = not significant.