Review

Respiration

Respiration
DOI: 10.1159/000499508

Received: February 5, 2019
Accepted after revision: March 9, 2019
Published online: May 22, 2019

Bronchoscopic Lung Volume Reduction with Endobronchial Zephyr Valves for Severe Emphysema: A Systematic Review and Meta-Analysis

Gonzalo Labarca[a, b] Juan Pablo Uribe[c] Cecilia Pacheco[d] Erik Folch[e] Fayez Kheir[f] Adnan Majid[c] Michael A. Jantz[g] Hiren J. Mehta[g] Neal Patel[h] Felix J.F. Herth[i] Sebastian Fernandez-Bussy[h]

[a]Facultad de Medicina, Universidad San Sebastian, Concepcion, Chile; [b]Complejo Asistencial Dr. Victor Rios Ruiz, Los Angeles, Chile; [c]Division of Thoracic Surgery and Interventional Pulmonology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [d]Cochrane Latin-American Group, Santiago, Chile; [e]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston, MA, USA; [f]Division of Pulmonary, Critical Care Medicine and Environmental Medicine, Tulane University, New Orleans, LA, USA; [g]Division of Pulmonary and Critical Care, University of Florida, Gainesville, FL, USA; [h]Division of Pulmonology and Critical Care Medicine, Mayo Clinic, Jacksonville, FL, USA; [i]Department of Pulmonology and Critical Care, Heidelberg, Germany

Keywords
Emphysema · Endobronchial valve · COPD

Abstract

Background: Endoscopic lung volume reduction using Zephyr® valves has been recently adopted as a treatment option for patients with severe emphysema without collateral ventilation (CV). ***Objectives:*** To assess the efficacy and safety of Zephyr valves in such a population. ***Methods:*** Studies were identified from MEDLINE and EMBASE databases. All searches were current until June 2018. We performed a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the efficacy and safety of Zephyr. We defined as outcome: change in forced expiratory volume in 1 s (FEV_1), in the 6-min walking test (6MWT), in the St George's Respiratory Questionnaire (SGRQ), and in residual volume (RV). Safety analysis included relative risk (RR) of pneumothorax. We assessed the quality of the evidence using GRADE. ***Results:*** 7 RCTs reported on Zephyr valves and 5 RCTs included only patients without CV. Zephyr improved FEV_1 with a mean difference (MD) of 17.36% (CI, 9.28–25.45, I^2 = 78%). Subgroup analysis showed significant FEV_1 improvement following Zephyr placement in patients with heterogeneous distribution: MD = 21.78% (CI, 8.70–34.86, I^2 = 89%) and 16.27% (CI, 8.78–23.76, I^2 = 0%) in patients with homogeneous emphysema. Studies with a follow-up of 3 months reported FEV_1 MD = 17.19% (CI, 3.16–31.22, I^2 = 89%) compared to studies with a follow-up of 6–12 months, which showed a consistent improvement of FEV_1 MD = 17.90% (CI, 11.47–24.33, I^2 = 0%). Zephyr also showed improvement of SGRQ, 6MWT, and RV. RR of pneumothorax was 6.32 (CI, 3.74–10.67, I^2 = 0%). ***Conclusion:*** In this population, Zephyr valves provided significant and clinically meaningful short-term improvements in either homogeneous or heterogeneous emphysema without CV but with an increase in adverse events.

Study register: PROSPERO CRD42016040001.

KARGER

E-Mail karger@karger.com
www.karger.com/res

Dr. Gonzalo Labarca
Facultad de Medicina, Universidad San Sebastian
Lientur 1457
Concepcion 4080871 (Chile)
E-Mail glabarcat@gmail.com

Introduction

Chronic obstructive pulmonary disease (COPD) is a common condition associated with high morbidity and mortality. This condition includes two entities that frequently overlap: chronic bronchitis (chronic inflammation of the central airways) and emphysema (hyperinflation with decreased lung elasticity) [1].

Although several pharmacological treatments exist, their effects are modest. A subgroup of patients with emphysema and hyperinflation are considered candidates for lung volume reduction surgery (LVRS). This procedure carries a significant morbidity and mortality as well as high cost [2]. Less invasive procedures, such as endoscopic lung volume reduction (ELVR), have been developed during the last decade with promising results. ELVR with Zephyr® valves has been recently approved by the FDA [3] and might provide the benefits seen with LVRS, but probably with lower morbidity and mortality. Endobronchial valves (EBVs) are one-way valves placed endoscopically in distal airways, reducing distal air flow into the targeted segmental bronchi, while permitting mucous and air movement into the proximal direction. This will cause target lobe volume reduction effectively by atelectasis in patients without evidence of collateral ventilation (CV) or with intact fissures [4, 5].

Previous meta-analyses of randomized controlled trials (RCTs) have demonstrated possible clinical benefits associated with multiple outcomes in patients with emphysema as compared to medical therapy with encouraging results [6]. However, such results were limited since only 3 RCTs were included [7–9]. We performed this systematic review and meta-analysis based on all available published RCTs to evaluate the overall efficacy and safety of Zephyr® valves in patients with severe emphysema without CV.

Methods

Literature Search

This systematic review was conducted according to the PRISMA statement [10]. We searched MEDLINE, clinicaltrials.gov, Cochrane Library, Lilacs, and EMBASE (until October 2018) using a predefined algorithm strategy (Fig. 1). The previous protocol is available in PROSPERO databases, ID: CRD42016040001.

A comprehensive literature search was performed by an expert librarian (C.P.) and a summary of Mesh terms is shown in the online supplementary material (for the online suppl. material, see www.karger.com/doi/10.1159/000499508). We also identified studies using a manual search of references and included meeting abstracts from 2014 to 2017 from the European Respiratory Society (ERS), the American College of Chest Physicians (ACCP), and the American Thoracic Society (ATS). This search was performed without language restriction.

Potential studies were evaluated by two independent reviewers (G.L. and S.F.-B.) and any disagreements between the reviewers were resolved by a third reviewer (E.F.). We explored the concordance between reviewers using a kappa test (κ). $\kappa \geq 0.6$ was considered as high concordance.

Inclusion Criteria

We included primary studies using the following criteria: (1) adult patients (>18 years old); (2) COPD stages III and IV with severe emphysema and without CV measure by Chartis® system; (3) optimal medical management according to GOLD recommendations; (4) intervention with an EBV (Zephyr®); and (5) comparator: either sham EBV or standard of care (SoC). Finally, we restricted included papers to RCTs.

Exclusion Criteria

Studies were excluded according to the following criteria: non-severe emphysema; COPD stage I to II or without optimal medical therapy, previous emphysema treatment with interventions other than Zephyr® valves; patients with CV, and non-RCT studies.

Quality Assessment

Risk of bias was evaluated in duplicate by two independent reviewers (G.L. and J.P.U.). Quality assessment of the included studies was done using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [11]. Any disagreement between reviewers was resolved by a third reviewer (S.F.-B.).

Data Extraction and Synthesis

Data extraction and synthesis was performed by two reviewers (G.L. and J.P.U.). Information regarding literature search, baseline characteristics, risk of bias assessment, and concordance analysis between reviewers was included as qualitative synthesis.

For the quantitative analysis, pooled data was evaluated using a meta-analysis following the DerSimonian-Laird method with a random-effect model; if heterogeneity was nonsignificant, we used a fixed-effect model. Our outcomes were predefined as change in forced expiratory volume in 1 s (FEV_1) in % of predicted value following EBV intervention in patients with severe emphysema without CV; change in the St George's Respiratory Questionnaire (SGRQ) (total score); change in the 6-min walking test (6MWT) (in meters), and change in residual volume (RV) (in mL). As unit of time, we evaluated outcomes after 3 and 6 months, and 1 year after intervention. For safety analysis, we included data regarding relative risk (RR) of both all-cause mortality and pneumothorax in both groups. In order to be able to calculate the absolute effect in studies without pneumothorax, we checked the baseline risk of pneumothorax in patients with emphysema based on the representative observational study.

For the meta-analysis, we evaluated continuous variables using mean difference (MD), while categorical variables were explored using a RR measure. Heterogeneity between studies was evaluated using a visual inspection of forest plot and using an I^2 test. We considered an I^2 of >50% as significant heterogeneity.

We also explored potential sources of heterogeneity in changes of FEV_1 using a subgroup analysis including reported follow-up (3 or ≥6 months), emphysema distribution (heterogeneous or homo-

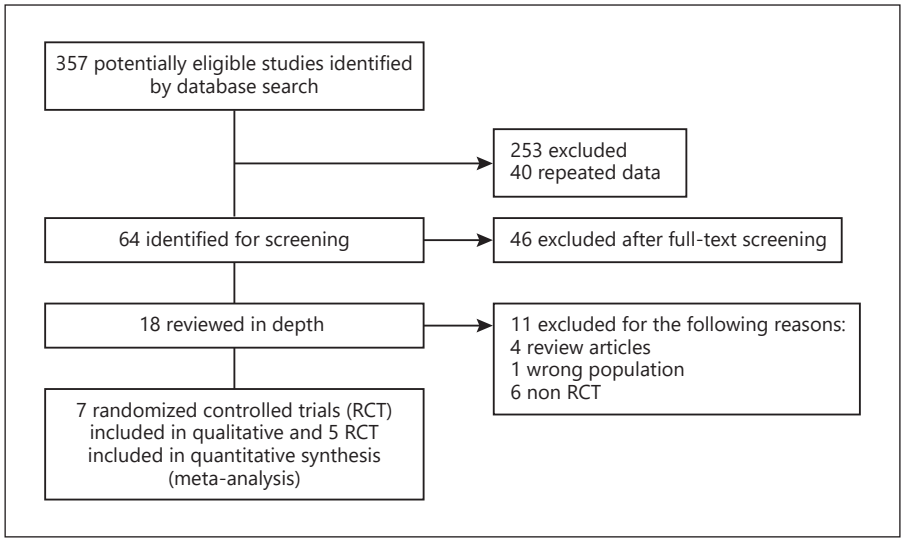

Fig. 1. PRISMA flowchart.

Table 1. Clinical characteristics of the included studies which treated their patients with endobronchial valves (EBV)

	BELIEVER-HIFI [14] (*n* = 50)	IMPACT [13] (*n* = 90)	STELVIO [8] (*n* = 68)	LIBERATE [12] (*n* = 190)	TRANSFORM [15] (*n* = 97)
EBV, *n*	25	43	34	128	65
Age ± SD, years	62.3±7.0	64.3±6.3	58±10	64.9±8.0	64.0±6.85
Male, %	17 (68%)	20 (46.5%)	16 (47%)	37 (56%)	56 (43.7%)
BMI ± SD, kg/m^2	24.5±5.1	23.8±4.4	24.1±3.5	23.7±4.4	24.67±3.9
Smoking history ± SD, pack-years	56±26	41.5±19.6	37±18	42.0±21.5	50.7±26.8
FEV_1 ± SD, % predicted	31.6±10.2	28.4±6.3	29.0±7	29.8±9.2	28.0±7.4
TLC ± SD, % predicted	132±12	144.9±21.2	130±13	139±18.9	133.5±21.1
RV ± SD, mL	219±39	277.3±55.2	216±36	249.4±51.8	224.5±42.4
RV/TLC ± SD, %	60.23±8.06	NR	59±9	NR	0.63±0.09
TLCO ± SD, % predicted	33.8±10.8	NR	38.7±9.1	NR	34.6±11.34
mMRC ± SD	4±1	2.67±0.75	2.7±0.8	3.00±0.77	2.4±0.97
CAT ± SD	25±5	23.4±6.8	NR	NR	19.2±6.32
SGRQ ± SD (total score)	67.79±13.17	63.2±13.7	59±13.7	64.3±14.4	55.15±14.0
6MWD ± SD, m	342±94	308±91	372±90	282±94	311±81
BODE index ± SD	NR	5.69±1.4	NR	6.14±1.68	5.34±1.5
GOLD stage IV, %	NR	27 (32.7%)	NR	39 (60%)	74 (57.8%)
HRCT emphysema score ± SD	NR	68.0±7.22	47.7±8.2	69.3±9.3	70.9±8.52
Heterogeneity ± SD	NR	6.88±6.83	15±11	21.8±14.6	25.5±9.85
Imaging fissure completeness (HRCT)	>90%	<15%	NR	>50%	>90%
Chartis system	Yes	Yes	Yes	Yes	Yes

SD, Standard deviation; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; TLCO, total lung capacity of CO; mMRC, modified medical research council; CAT, COPD assessment test; SGRQ, St George's Respiratory Questionnaire; 6MWD, 6-min walking distance; HRCT, high-resolution computed tomography; NR, not reported.

Fig. 2. Risk of bias assessment of included studies.

geneous), and comparator between trials (SoC or sham valve). Publication bias was explored through a visual inspection of funnel plot analysis. Asymmetry between studies was defined as publication bias.

Finally, we created tables reporting the results of both efficacy and safety analysis. Quality of evidence was ranked by a GRADE panel (G.L. and F.K.) following the GRADE approach. For the meta-analysis and risk of bias assessment, we used RevMan version 5.3. A p value <0.05 was considered statistically significant. Tables and confidence of evidence were created using the GRADE pro software (Hamilton, ON, Canada) (www.gradepro.org).

Results

Literature Search

An electronic database search retrieved 357 citations for which the abstracts were reviewed, and 18 potential studies were identified. After examining those articles in more detail, 11 articles were excluded for reasons shown in Figure 1. Seven studies [7–9, 12–15] with a total of 987 patients met the inclusion criteria and were considered in this review (Fig. 1). Two studies (VENT US and EU) included patients with and without CV and did not report enough data regarding emphysema distribution, so they were excluded for the quantitative analysis (meta-analysis) [7, 9]. Concordance between reviewers was high (κ = 0.85).

Study Characteristics

Patient and study characteristics are shown in Table 1. The average age of the participants ranged from 59.7 to 65.3 years, the average BMI was between 22.9 and 25.1 kg/m^2, tobacco history revealed a range of 37–76.9 pack-years, and the included population reported mostly COPD stage IV. Pulmonary function test showed a predicted (%) FEV_1 between 28 and 31.6%, total lung capacity between 124 and 144.9% predicted, RV between 216 and 277%. Three trials reported a follow-up of 3 months [13–15], 2 others reported a follow-up of 6 months [7, 8], and 1 reported a follow-up of 12 months [12].

Five trials [8, 12–15] included only patients with complete fissures, and emphysema distribution was measured by Chartis® in BELIEVER, STELVIO, IMPACT, TRANSFORM, and LIBERATE. Four studies were included with patients presenting heterogeneous emphysema (BELIEVER, TRANSFORM, and LIBERATE), 1 reported both heterogeneous and homogeneous emphysema (STELVIO), and there was 1 study with homogeneous emphysema only (IMPACT).

Quality Assessment

The included studies reported low bias in most aspects. However, we found high or unclear (performance) bias in 4 studies [8, 9, 12, 15]. Two studies reported unclear risk of selection bias [7, 9]. A full report of risk of bias assessment is shown in Figure 2.

Efficacy Analysis

Changes in FEV_1

Changes in FEV_1 % of predicted following Zephyr® placement in patients without CV were evaluated in 5 studies. Pooled data showed FEV_1 improvement with a MD = 17.36% (CI, 9.28–25.45, I^2 = 78%) (Fig. 3).

Subgroup analysis was performed to explore the effect of FEV_1 improvement following Zephyr® placement and emphysema distribution. A full summary of subgroup analysis on major outcomes is reported in Table 2. The STELVIO trial [8] included patients with heterogeneous and homogeneous emphysema, while the IMPACT trial just included patients with homogeneous

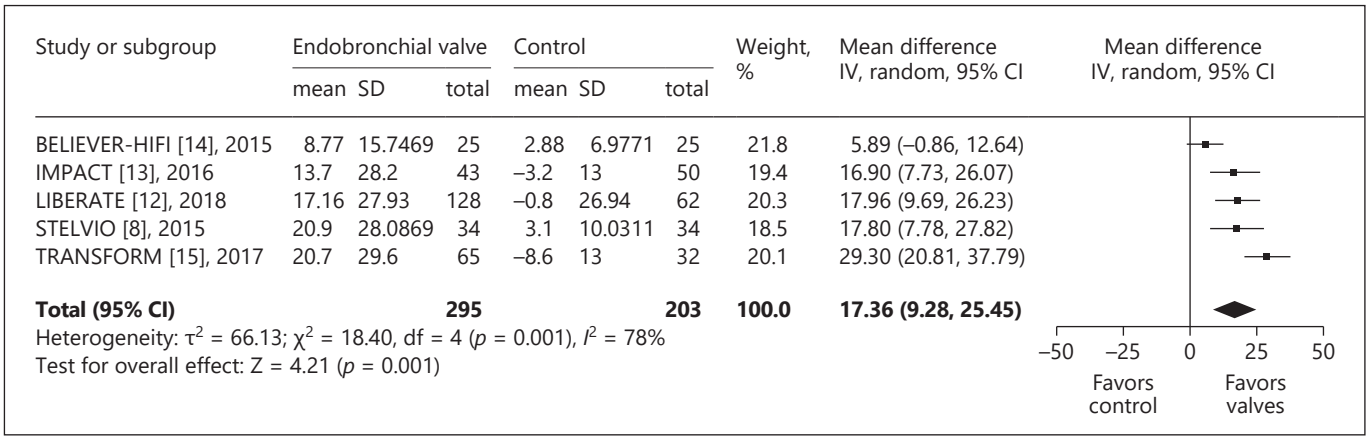

Fig. 3. Change in forced expiratory volume in 1 s in patients with collateral ventilation using Zephyr® valves.

Table 2. Subgroup analysis for major outcomes

Outcome	Emphysema distribution			Follow-up			Comparator		
	homogeneous	heterogeneous	residual I^2	<6 months	6–12 months	residual I^2	sham	SoC	residual I^2
FEV_1	16.27 (8.78, 23.76)	21.78 (8.70, 34.86)	82%*	17.19 (3.16, 31.22)	16.55 (11.35, 21.75)	78%*	5.89 (–0.86, 12.64)	20.67 (14.7, 24.65)	90.3%*
I^2	0%	89%		89%	0%		na	44%	
SGRQ	–10.07 (–13.89, –6.24)	–7.42 (–10.57, –4.28)	8.6%	–8.0 (–11.08, –4.92)	–9.14 (–13.16, –5.11)	0%	–4.97 (–14.23, 4.29)	–8.68 (–11.21, –6.14)	0%
I^2	0%	25%		0%	64%		na	19%	
6MWD	60.9 (40.35, 81.45)	50.36 (36.74, 64.37)	0%	42.18 (27.35, 57)	59.96 (44.23, 75.69)	61.5%	22 (–1.51, 45.51)	55.54 (42.43, 68.65)	83%*
I^2	89%	84%		76%	78%		na	59%	
RV	–0.58 (–0.85, –0.32)	–0.57 (–0.88, –0.27)	0%	–0.41 (–0.61, –0.21)	–0.53 (–0.67, –0.40)	65%	–0.18 (–0.49, 0.13)	–0.61 (–0.76, –0.40)	83.9%*
I^2	0%	73%		51%	59%		na	15%	
Pneumothorax	5.69 (2.56, 12.69)	5.84 (2.96, 11.52)	0%	5.42 (2.75, 10.67)	7.29 (3.29, 16.15)	0%	2.17 (0.42, 11.16)	6.83 (3.92, 11.9)	40%
I^2	0%	5%		0%	0%		na	0%	

Values are given as mean (95% CI). SoC, standard of care; FEV_1, forced expiratory volume in 1 s; RV, residual volume; SGRQ, St George's Respiratory Questionnaire; 6MWD, 6-min walking distance; na, not applicable.

* Statistically significant.

emphysema. In the homogenous emphysema subgroup, Zephyr® valves showed an improvement in FEV_1 of 16.27% (CI, 8.78–23.76, I^2 = 0%). On the other hand, BELIEVER, LIBERATE, TRANSFORM, and STELVIO included data on heterogeneous emphysema. In this subgroup, MD of FEV_1 improvement was 21.78% (CI, 8.70–34.86, I^2 = 89%). For this outcome, intergroup heterogeneity was statistically significant ($p < 0.001$), and I^2 was 82% (Fig. 4).

Regarding follow-up time subgroup analysis following randomization, the results were as follows: for those with 3 months of follow-up, improvement of FEV_1 had a MD = 17.19% (CI, 3.16–31.22, I^2 = 89%); for 6 or more months of follow-up, improvement of FEV_1 had a MD = 17.90% (CI, 11.47–24.33, I^2 = 0%). For this outcome, intergroup heterogeneity was statistically significant (p = 0.002), and I^2 was 78% (see online suppl. Fig. 1).

Finally, subgroup analysis according to type of control group revealed a MD of 5.89% (CI, –0.85 to 12.64, I^2 = not

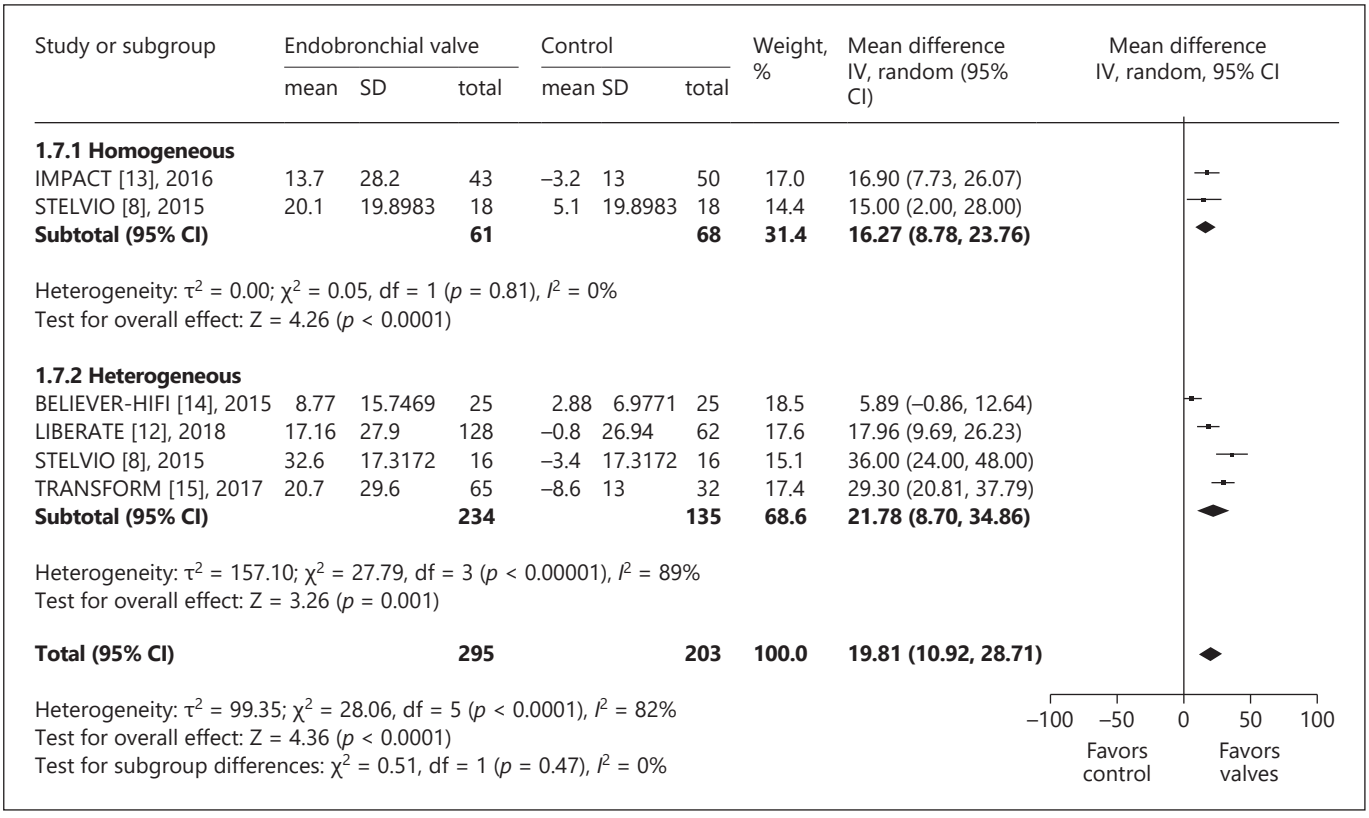

Fig. 4. Subgroup analysis. Change in forced expiratory volume in 1 s after treatment according to emphysema distribution.

Table 3. Summary of the findings

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Participants (studies)	Certainty of the evidence (GRADE)
	risk with medical therapy	risk with EBV			
Change in FEV_1, % of predicted Scale: –100 to 100	**17.36**[#]	17.367[$] (9.28–25.45)	–	498 (5 RCTs)	⊕⊕⊕◯ moderate[a]
Change in SGRQ, points (total score) Scale: –10 to 10	**8.42**[#]	8.47[$] (10.86–5.97)	–	498 (5 RCTs)	⊕⊕⊕⊕ high
Change in 6MWT, m	**49.75**[#]	40.51[$] (28.75–70.75)	–	498 (5 RCTs)	⊕⊕◯◯ low[b, c]
All-cause mortality (mortality)	1 per 100	**1 per 100** (0–2)	**RR 1.26** (0.50–3.15)	498 (5 RCTs)	⊕⊕◯◯ low[c, d]
Risk of pneumothorax (pneumoTx)	4 per 100	**23 per 100** (14–39)	**RR 6.32** (3.74–10.67)	498 (5 RCTs)	⊕⊕⊕⊕ high

Follow-up: range from 3 to 12 months for all outcomes.

EBV, endobronchial valve. FEV_1, forced expiratory volume in 1 s; SGRQ, St George's Respiratory Questionnaire; 6MWT, 6-min walking test; RR, relative risk; RCTs, randomized controlled trials.

*, confidence interval; [#], mean change; [$], mean change in the intervention group.

[a] Risk of bias regarding blinding of participants and personnel in most studies; [b] high residual heterogeneity between studies despite subgroup analysis; [c] non-principal outcome; [d] wide confidence interval with potential adverse effect.

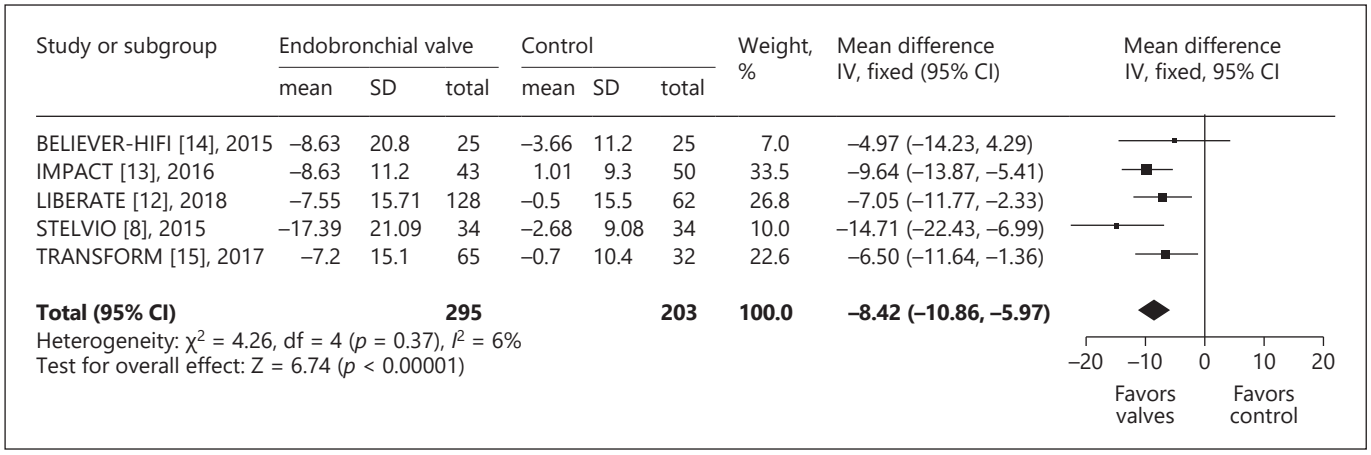

Fig. 5. Changes in the St George's Respiratory Questionnaire (total score) after intervention.

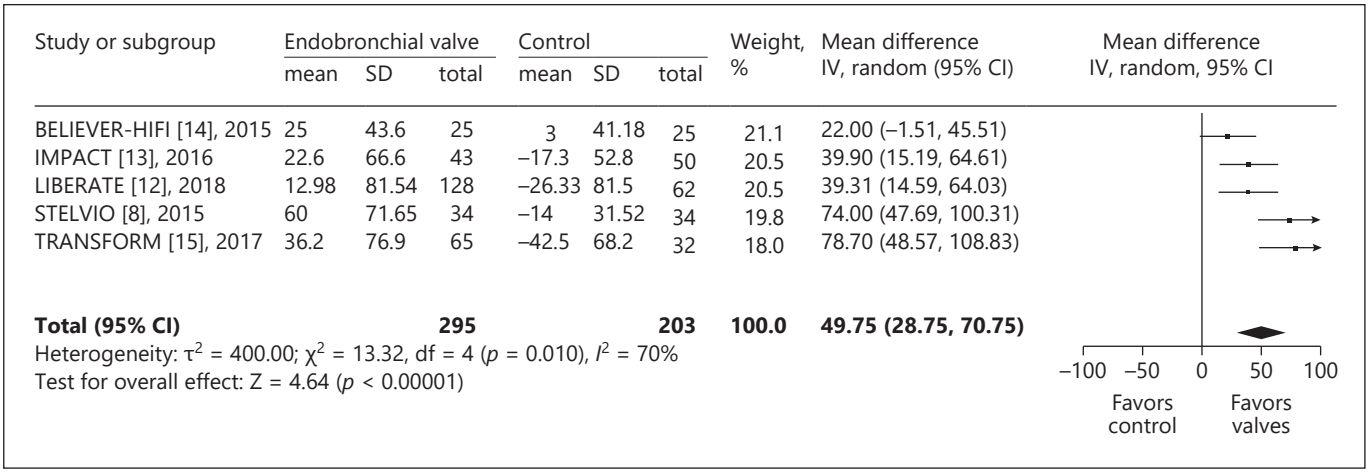

Fig. 6. Comparison 4. Change in 6-min walking test (in meters) after intervention.

applicable), when Zephyr® valves were compared to sham valves, and for the comparison to SoC, MD was 20.67% (CI, 14.70–26.65, I^2 = 44%) for this analysis. Intergroup difference was 90.3% (see online suppl. Fig. 2). We rated this outcome as "moderate" due to serious risk of bias from included studies. A summary of the findings is shown in Table 3.

Changes in Quality of Life

For changes in the SGRQ, a total of 5 trials including 498 participants reported changes in the total score of the questionnaire after Zephyr® intervention with a decrease of MD = –8.42 points (CI, –10.86 to –5.97, I^2 = 6%) (Fig. 5). We graded this outcome as "high". For this outcome, the subgroup analysis reported no statistically significant difference between the subgroups (Table 2).

Changes in 6MWT

A total of 5 trials including 498 participants reported changes in 6MWT following Zephyr® placement with an improvement of MD = 49.75 m (CI, 28.75–70.75, I^2 = 70%). Subgroup analysis by CV and emphysema distribution showed no sources of residual heterogeneity. We rated this outcome as "moderate" due to inconsistency and indirectness (Fig. 6). The subgroup analysis reported a statistical difference between the groups according to comparator (for sham valve), MD was 22 (CI, –1.51, 45.51, I^2 = not applicable) compared to MD = 55.54 (CI,

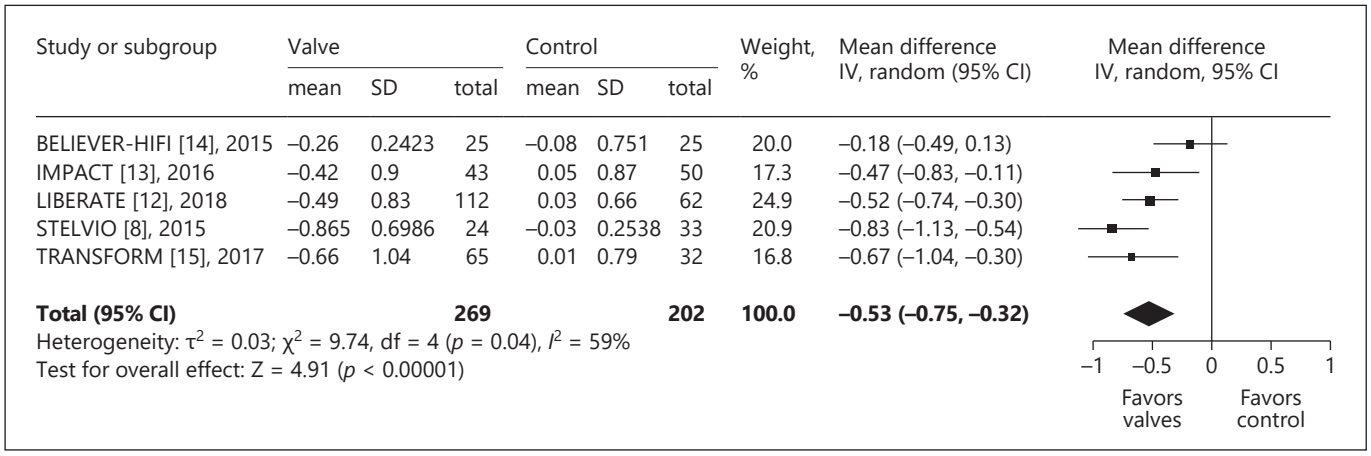

Fig. 7. Change in residual volume (in mL) after intervention.

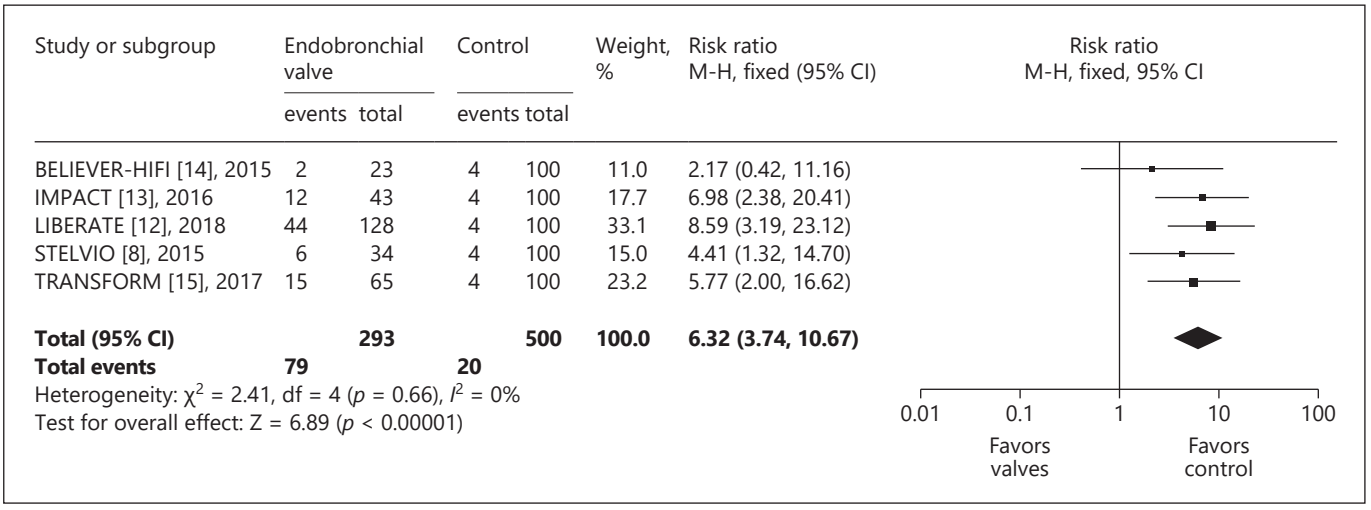

Fig. 8. Relative risk of pneumothorax after intervention.

42.43–68.65, $I^2 = 59\%$) for SoC; intergroup difference was 59% ($p = 0.001$, $I^2 = 83\%$).

Changes in RV

Regarding changes in RV, 5 trials including 471 participants were analyzed. MD of RV improvement was 530 mL (CI, 750–320, $I^2 = 59\%$) (Fig. 7). The subgroup analysis by CV and emphysema distribution showed no sources of residual heterogeneity. The subgroup analysis reported a statistical difference between the groups according to comparator (for sham valve), MD was 180 mL (CI, 490–130, I^2 = not applicable) compared to MD = 610 mL (CI, 760–400, $I^2 = 15\%$) for SoC; intergroup difference was 15% ($p = 0.001$, $I^2 = 83\%$).

Safety Analysis

A total of 5 studies including 793 participants reported all-cause mortality in both intervention and control group. For the Zephyr® group, the RR of mortality was 2.30 (CI, 0.66–8.02, $I^2 = 0\%$) (online suppl. Fig. 3). We rated this outcome as "low" due to imprecision and indirectness.

The risk of pneumothorax was increased in every trial. Zephyr® reports a significantly increased risk of pneumothorax with a RR of 6.32 (CI, 3.74–10.67, $I^2 = 0\%$) (Fig. 8). The subgroup analysis according to emphysema distribution showed a risk of 5.80 (CI, 2.61–12.90, $I^2 = 0\%$) in homogeneous distribution compared to a RR of 6.57 (CI, 3.36–12.85, $I^2 = 5\%$) (online suppl. Fig. 4). Inter-

group difference was not statistically significant, and I^2 was 0%. Regarding follow-up or comparator, we also found no significant intergroup differences. We rated this outcome as "high".

Regarding pneumothorax severity, most participants required medical management with chest tube. The IMPACT and TRANSFORM trials reported that 5 patients required the removal of 1 or more valves. STELVIO reported that 1 patient had temporary valve removal and 2 had permanent valve removal. The LIBERATE trial reported 12 patients requiring removal due to pneumothorax.

Finally, publication bias was rated as "low" in most outcomes through a visual inspection of funnel plot (online suppl. Fig. 5, 10).

Discussion

The results of the current systematic review and meta-analysis confirm that FEV_1 improved significantly following Zephyr® placement in patients with severe emphysema and without CV as measured by Chartis® system. Previous systematic reviews and meta-analyses have already been published on this topic, however, most of them included few studies and pooled data from bronchial valve trials with and without CV [16]. In addition, the meta-analyses included multiple studies which were very variable. Thus, the conclusions could provide a false impression about the efficacy of interventions in patients with severe emphysema, whereas the reality is that Zephyr® valves are helpful in specific carefully selected patients.

Recently, van Geffen et al. [17] evaluated the efficacy of both LVRS and ELVR techniques. They explored multiple interventions, with multiple studies pooling data from different types of emphysema and fissure integrity assessment, among other variables. They concluded that either LVRS or ELVR are useful in patients with severe emphysema and hyperinflation and both EBV and LVRS reported better results than other techniques, without properly addressing the population that might benefit the most [17]. The principal contribution of this systematic review and meta-analysis is to explore Zephyr® valves as intervention and included subgroup analyses to explore the impact of relevant predictors on major outcomes in order to identify potential patient populations.

These results correlate with changes in regional lung volume, suggesting that the mechanisms for improvement and better results are associated with a redirection of the inspired air to less diseased areas of the lung, improving respiratory function and gas exchange [18]. Furthermore, this study suggests that FEV_1 improved significantly in patients with homogenous as well as heterogeneous emphysema, albeit a higher FEV_1 improvement was seen in heterogeneous disease.

Such a finding implicates the importance of CV regardless of emphysema quantification on chest imaging. According to the VENT trial, patients without intact fissures are not good candidates for EBV treatment. In addition, our analysis suggests that in appropriately selected patients, this procedure improves lung function up to a similar magnitude to those seen with LVRS, but with less morbidity and mortality. Pooled results showed an improvement in the predicted FEV_1 (%) of 17.36%, exceeding the minimally clinically important difference of 10%. Quality of evidence was rated as "moderate" due to risk of bias from included studies, especially bias due to a lack of blinding. We do not downgrade by inconsistency (heterogeneity) between the populations included in those studies due to two potential explanations for high heterogeneity: (1) emphysema distribution and (2) follow-up time, both findings from our subgroup analysis.

Regarding the subgroup analysis, we found a believable subgroup effect due to a previous definition of the subgroups, a statistical significance in intergroup analysis, and both large effect and consistency between studies [19].

Based on the results of the current systematic review and meta-analysis, the current evidence suggests that patients with severe emphysema and hyperinflation without CV, regardless of emphysema using Chartis® system, will benefit from Zephyr® placement and should be offered this option if no other contraindications exist. Despite the increased change in FEV_1 of up to 26% reported in the analysis of heterogeneous distribution measure by Chartis®, we could not find any explanation for residual heterogeneity in this group. This greater response in these subgroups supports the importance of adequate patient selection and the use of Chartis® or high-resolution CT as tools in optimizing the evaluation of candidates to this technique, and better results were found in patients who received Zephyr® treatment with high emphysema heterogeneity and with intact fissures [20].

We also found a significant improvement after the procedure in RV, 6MWT, and the SGRQ. This could be explained by the reduction of the most severely diseased lung target along with an expansion of the more viable, less emphysematous lung, resulting in substantial improvements in lung mechanics and gas exchange [21, 22].

According to our findings, the risk of pneumothorax is increased 5 times in comparison with control groups, independently of emphysema distribution; due to a low prevalence in the control groups, we estimate the risk of pneumothorax in the populations with COPD and emphysema, based on data published by Hobbs and colleagues using data from COPDGene, where the odds ratio of pneumothorax was 1.04 (CI, 1.03–1.06) [23]. However, previous analyses showed better outcomes in patients with pneumothorax as compared to no pneumothorax, and the occurrence of this event does not have a negative impact on the clinical outcomes of these patients [24].

Our meta-analysis did not find an improvement in survival in these patients. However, a previous study of 19 patients with heterogeneous emphysema and a follow-up of 10 years demonstrated increased survival in patients where target lung volume reduction was achieved after Zephyr® placement [25]. This suggests that atelectasis might be a predictor of survival probably due to improvement in lung mechanics and better gas exchange [26].

This analysis has several limitations. All included trials reported a relatively short follow-up period ranging between 3 and 12 months, making it difficult to assess the long-term benefits and adverse consequences of Zephyr® placement. According to our findings, we found a subgroup difference between trials with a short follow-up compared to 6 months or more (STELVIO: 6 months, and LIBERATE: 12 months). Moreover, two trials [8, 12] with 6 or more months' follow-up reported 0% heterogeneity, compared with a short follow-up and 89% heterogeneity; this finding suggest a consistency change in FEV_1 between 6 and 12 months. Another subgroup was defined by the type of comparator, we found only 1 trial that used sham valves versus 4 that used SoC; the subgroup analysis according to this variable found significant intergroup differences regarding major outcomes such as FEV_1, 6MWT, and RV. This point should be considered in further trials.

Finally, studies with long-term follow-ups are needed to understand the efficacy and safety of this procedure as well as a potential survival benefit. Furthermore, the results of the studies reported high confidence intervals for multiple outcomes (FEV_1, SGRQ, and 6MWT) that must also be taken into consideration for future trials.

Conclusion

EBV placement using Zephyr® valves provided a short-term (up to 12 months) improvement in quality of life as well as spirometry for selected patients with severe emphysema without CV and either homogeneous or heterogeneous emphysema distribution.

Disclosure Statement

The authors report no conflicts of interest regarding this paper.

Funding Sources

The authors report no funding for this paper.

Author Contributions

G.L.: Manuscript conception, data extraction, data analysis, risk of bias assessment, manuscript redaction, and final approval. Guarantor for the entire manuscript. J.P.U.: Data extraction, data analysis, risk of bias assessment, manuscript redaction, and final approval. C.P.: Manuscript conception, literature search, study inclusion, critical analysis, and final approval. E.F.: Manuscript conception, data extraction, data analysis, risk of bias assessment, manuscript redaction, and final approval. F.K.: Data analysis, risk of bias assessment, manuscript redaction, critical analysis, and final approval. A.M and M.A.J.: Manuscript conception, data extraction, data analysis, risk of bias assessment, manuscript redaction, critical analysis, and final approval. H.J.M and N.P.: Data analysis, risk of bias assessment, manuscript redaction, critical analysis, and final approval. F.J.F.H. and S.F.-B.: Manuscript conception, data analysis, manuscript redaction, critical analysis, and final approval.

References

1 Global Initiative for Chronic Obstructive Lung Disease (GOLD)[Internet]. 2018 Global Strategy for Prevention, Diagnosis and Management of COPD [cited 2019 Jan 5]. Available from: http://www.goldcopd.org/archived-reports.

2 Naunheim KS, Wood DE, Krasna MJ, DeCamp MM Jr, Ginsburg ME, McKenna RJ Jr, et al.; National Emphysema Treatment Trial Research Group. Predictors of operative mortality and cardiopulmonary morbidity in the National Emphysema Treatment Trial. J Thorac Cardiovasc Surg. 2006 Jan;131(1):43–53.

3 FDA U.S. Food & Drug Administration. Zephyr® Endobronchial Valve System - P180002 [cited 2019 Jan 5]. Available from: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/Recently-ApprovedDevices/ucm614563.htm.

4 Mineshita M, Slebos DJ. Bronchoscopic interventions for chronic obstructive pulmonary disease. Respirology. 2014 Nov;19(8):1126–37.
5 Herth FJ, Slebos DJ, Rabe KF, Shah PL. Endoscopic Lung Volume Reduction: An Expert Panel Recommendation. Respiration. 2016; 91(3):241–50.
6 Wang Y, Lai TW, Xu F, Zhou JS, Li ZY, Xu XC, et al. Efficacy and safety of bronchoscopic lung volume reduction therapy in patients with severe emphysema: a meta-analysis of randomized controlled trials. Oncotarget. 2017 Jul;8(44):78031–43.
7 Herth FJ, Noppen M, Valipour A, Leroy S, Vergnon JM, Ficker JH, et al.; International VENT Study Group. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J. 2012 Jun;39(6):1334–42.
8 Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. N Engl J Med. 2015 Dec;373(24):2325–35.
9 Sciurba FC, Ernst A, Herth FJ, Strange C, Criner GJ, Marquette CH, et al.; VENT Study Research Group. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med. 2010 Sep;363(13):1233–44.
10 Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009 Jul;6(7): e1000100.
11 Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. Version 5.1.0 [updated March 2011].
12 Criner GJ, Sue R, Wright S, Dransfield M, Rivas-Perez H, Wiese T, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). Am J Respir Crit Care Med. 2018 Nov;198(9):1151–64.
13 Valipour A, Slebos DJ, Herth F, Darwiche K, Wagner M, Ficker JH, et al.; IMPACT Study Team. Endobronchial Valve Therapy in Patients with Homogeneous Emphysema. Results from the IMPACT Study. Am J Respir Crit Care Med. 2016 Nov;194(9):1073–82.
14 Davey C, Zoumot Z, Jordan S, McNulty WH, Carr DH, Hind MD, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. Lancet. 2015 Sep;386(9998):1066–73.
15 Kemp SV, Slebos DJ, Kirk A, Kornaszewska M, Carron K, Ek L, et al.; TRANSFORM Study Team *. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). Am J Respir Crit Care Med. 2017 Dec;196(12):1535–43.
16 van Agteren JE, Hnin K, Grosser D, Carson KV, Smith BJ. Bronchoscopic lung volume reduction procedures for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2017 Feb;2:CD012158.
17 van Geffen WH, Slebos DJ, Herth FJ, Kemp SV, Weder W, Shah PL. Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis. Lancet Respir Med. 2019 Feb; S2213-2600(18)30431-4.
18 Ramaswamy A, Puchalski J. Bronchoscopic lung volume reduction: recent updates. J Thorac Dis. 2018 Apr;10(4):2519–27.
19 Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010 Mar;340:c117.
20 Gompelmann D, Eberhardt R, Slebos DJ, Brown MS, Abtin F, Kim HJ, et al. Diagnostic performance comparison of the Chartis System and high-resolution computerized tomography fissure analysis for planning endoscopic lung volume reduction. Respirology. 2014 May;19(4):524–30.
21 McKenna RJ Jr, Brenner M, Fischel RJ, Singh N, Yoong B, Gelb AF, et al. Patient selection criteria for lung volume reduction surgery. J Thorac Cardiovasc Surg. 1997 Dec;114(6): 957–64.
22 Fessler HE, Scharf SM, Ingenito EP, McKenna RJ Jr, Sharafkhaneh A. Physiologic basis for improved pulmonary function after lung volume reduction. Proc Am Thorac Soc. 2008 May;5(4):416–20.
23 Hobbs BD, Foreman MG, Bowler R, Jacobson F, Make BJ, Castaldi PJ, et al.; COPDGene Investigators. Pneumothorax risk factors in smokers with and without chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2014 Nov;11(9):1387–94.
24 Gompelmann D, Herth FJ, Slebos DJ, Valipour A, Ernst A, Criner GJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. Respiration. 2014;87(6):485–91.
25 Garner J, Kemp SV, Toma TP, Hansell DM, Polkey MI, Shah PL, et al. Survival after Endobronchial Valve Placement for Emphysema: A 10-Year Follow-up Study. Am J Respir Crit Care Med. 2016 Aug;194(4):519–21.
26 Hopkinson NS, Kemp SV, Toma TP, Hansell DM, Geddes DM, Shah PL, et al. Atelectasis and survival after bronchoscopic lung volume reduction for COPD. Eur Respir J. 2011 Jun; 37(6):1346–51.