CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Endobronchial Valves for the Management of Emphysema: A Review of Clinical Effectiveness

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	November 06, 2019
Report Length:	21 Pages

CADTH

Authors: Khai Tran, Caitlyn Ford

Cite As: Endobronchial Valves for the Management of Emphysema: Clinical Effectiveness. Ottawa: CADTH; 2019 Nov. (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to Requests@CADTH.ca

Abbreviations

AMSTAR	Assessing the Methodological Quality of Systematic Reviews
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
EBV	Endobronchial valve
FEV_1	The forced expiratory volume in one second
GRADE	The Grading of Recommendations Assessment, Development and Evaluation
HTA	Health technology assessment
LRTI	Lower respiratory tract infection
MA	Meta-analysis
mMRC	Modified Medical Research Council (points)
6MWT	6-minute walk test
NA	Not applicable
NR	Not reported
PICO	Population, Intervention, Comparator, and Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of life
RCT	Randomized controlled trial
RV	Residual volume
SAEs	Serious adverse events
SD	Standard deviation
SGRQ	The St George's Respiratory Questionnaire
SR	Systematic review
SVS	Spiration Valve System
TLC	Total lung capacity

Context and Policy Issues

Chronic obstructive pulmonary disease (COPD) is a term for a group of lung diseases, which include chronic bronchitis and emphysema.[1] COPD is progressive and characterized by shortness of breath, cough, phlegm production, and limited exercise capacity.[2] Emphysema is caused by alveolar destruction due to prolonged exposure to harmful inhaled agents, such as cigarette smoking and environmental or occupational hazardous agents, and leads to impairment in gas exchange, an increase in residual volume, and lung hyperinflation.[2] Standard medical care comprises short- and long-term acting bronchodilators, inhaled or oral corticosteroids, pulmonary rehabilitation, prophylactic antibiotics, oxygen support, and smoking cessation.[3]

There are few lung volume reduction treatment options for emphysema. Lung volume reduction surgery (LVRS) seems to be an option for patients with severe emphysema that is poorly controlled with standard medical care.[2] However, because of its invasiveness, high cost and increased risk of morbidity and mortality associated with surgery, LVRS is not commonly offered or usually declined by patients.[4] Endoscopic lung volume reduction treatment with endobronchial valves is a minimally invasive and reversible procedure that has been demonstrated to have a more acceptable risk/benefit ratio compared to LVRS.[5,6] The overall objective of endobronchial valves is to decrease thoracic volume in order to improve the mechanics of the lung, chest wall and respiratory muscles.[7]

There are four types of endobronchial valves in the literature: the Zephyr® one-way endobronchial valve (EBV) (PulmonX Corp., USA); the Spiration Valve System (Spiration, Inc., USA); MedLung EBV (MedLung, Russia); and the endobronchial Miyazawa valve (Novatech, France).[6] The one-way valves inserted at the affected lobes allow air to exit during expiration, but block air from entering during inspiration. The endobronchial valve treatment with Zephyr EBV has been approved by the United States Food and Drug Administration (FDA),[8] and recommended by National Institute for Heath and Care Excellence (NICE)[9] and Global Initiative Care for Chronic Obstructive Lung Disease (GOLD).[10] The Spiration Valve System has also been recently approved by FDA.[11] Recent reviews of the literature found no information about the MedLung EBV and Miyazawa valve.[6,7,12]

The aim of this report is to review the clinical effectiveness and safety of endobronchial valves for the management of severe emphysema.

Research Question

1. What is the clinical effectiveness of endobronchial valves for people with severe emphysema?

Key Findings

This review identified one systematic review and two randomized controlled trials assessing the efficacy and safety of two types of endobronchial valves (i.e., Zephyr one-way EBV and Spiration Valve System) for bronchoscopic lung volume reduction in patients with severe emphysema. Endobronchial valve therapy with Zephyr EBV

was associated with significantly greater lung function, exercise capacity, quality of life, and significantly reduced dyspnea for up to 12 months, with increased risk of serious adverse events, compared to standard medical care. Although Spiration Valve System-treated patients showed significantly greater lung function and quality of life in comparison to patients treated with standard medical care, further work is required to demonstrate with confidence the efficacy and safety of Spiration Valve System. Pneumothorax was the most reported complication during treatment with endobronchial valves.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were endobronchial valves and emphysema. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2014 and October 3, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 2.

Table 1: Selection Criteria

Population	People with severe emphysema (that has not adequately responded to medication)
Intervention	Bronchoscopic lung volume reduction treatment with endobronchial valves (e.g., Zephyr one-way EBV [PulmonX Corp., Redwood City, CA, USA], Spiration Valve System [Spiration, Inc., Redmond, WA, USA], MedLung EBV [MedLung, Barnaul, Russia], endobronchial Miyazawa valve [Novatech, La Ciotat, France])
Comparator	Standard of care (e.g., lung volume reduction surgery, lung transplant, drug therapy, pulmonary rehabilitation, nutrition therapy, oxygen)
Outcomes	Clinical effectiveness (e.g., change in lung function [FEV_1], exercise capacity [e.g., six-minute walk test], physical activity, dyspnea, quality of life) and safety
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 2 or if they were published prior to 2014. Systematic reviews (SRs) were excluded if they included studies that were fully captured in other more recent SRs (i.e., complete

overlap of primary studies). Primary studies were excluded if they were already captured in an included SR.

Critical Appraisal of Individual Studies

A MeaSurement Tool to Assess systematic Reviews (AMSTAR)-2 checklist was used to assess the quality of the identified SR.[13] The version 2 of the Cochrane risk-of-bias assessment tool was used to assess the quality of the identified randomized controlled trials (RCTs).[14] Summary scores were not calculated for the included studies; rather, the strengths and weaknesses were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 167 citations were identified in the literature search. Following screening of titles and abstracts, 152 citations were excluded and 15 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the 15 potentially relevant articles, 12 publications were excluded for various reasons, while three studies (one SR and two RCTs) met the inclusion criteria and was included in this report. Appendix 1 presents the PRISMA flowchart[15] of the study selection.

Summary of Study Characteristics

The characteristics of the identified SR (Table 2) and RCTs (Table 3) are presented in Appendix 2.

Study Design

One SR[16] was identified that assessed the efficacy and safety of various bronchoscopic lung volume reduction interventions including endobronchial valves in patients with severe emphysema. Within the SR, seven RCTs that reported on Zephyr one-way EBV were included for meta-analysis. The RCTs were multi-centered, conducted in the US, UK and Europe. Of the seven RCTs cited in the SR, only one was a double-blind sham-controlled trial, while the remaining trials were open-label. The methodological quality of the RCTs was assessed using the Cochrane risk of bias tool, and the level of evidence of each outcome was rated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The authors of the SR declared that no financial support had been received for the study.

Two additional RCTs[17,18] that investigated the Spiration Valve System (SVS) were identified. Both were prospective, multicentre, open-label, parallel (2:1) RCTs, and were funded by Spiration Inc./Olympus Respiratory America.[17,18]

Country of Origin

The SR[16] was conducted by authors in India.

One included RCT (EMPROVE trial)[17] was undertaken at 41 clinical sites in the US and Canada while the other (REACH trial)[18] was undertaken at 12 clinical sites in China.

Population

The cited RCTs in the SR[16] included adult patients with severe heterogeneous (defined as > 10 to 20% difference in emphysema destruction score between target

lobe and ipsilateral lobe) or homogeneous (defined as < 15% difference) emphysema with no collateral ventilation. The mean age of patients ranged from 58 to 65 years across studies. The mean of the forced expiratory volume in one second (FEV_1) percent predicted (defined as FEV1% of the patient divided by the average FEV1% in the population for any person of similar age, sex, height and race) ranged from 26% to 32%, and the mean distance covered in the six-minute walk test (6MWT) ranged from 282 m to 372 m. The mean quality of life (QoL), as measured by the St George's Respiratory Questionnaire (SGRQ), ranged from total scores of 53 to 70. SGRQ has scores ranging from 0 to 100, with higher scores indicating more limitations.

The two included RCTs[17,18] also included adult patients with severe heterogeneous emphysema with no collateral ventilation. The mean age was 67 years in EMPROVE trial[17] and 63 years in REACH trial.[18] In both RCTs,[17,18] the mean FEV_1 % predicted was around 29%, the mean 6MWT was 318 m, and the mean QoL score on SGRQ was 57.

Interventions and Comparators

All RCTs on EBV cited in the identified SR[16] compared Zephyr one-way endobronchial EBV with standard medical care (not defined in the SR). Follow-up ranged from 3 to 12 months.

Both included RCTs[17,18] compared SVS with standard medical care (not defined). The EMPROVE trial[17] had follow-up of 6 and 12 months, while the REACH trial[18] had follow-up of 3 and 6 months.

Outcomes

The outcomes reported in the SR[16] included QoL (as measured by the SGRQ), 6MWT (a measure for global response of cardiopulmonary and musculoskeletal systems involved in exercise), responder rates (with a responder being ≥ 15% improvement in FEV_1), and total serious adverse events (SAEs). SAEs were reported as death, need of hospitalization, or any intervention due to occurrence of pneumothorax, or COPD exacerbations, lower respiratory infections, hemoptysis, or respiratory failure.

The primary outcome in the EMPROVE trial was the mean change in FEV_1 from baseline to 6 months,[17] while that in the REACH trial was the mean change in FEV_1 from baseline to 3 months.[18] Secondary outcomes in both trials[17,18] were responder rate (defined as a ≥ 15% improvement in FEV_1), QoL (as measured by the SGRQ), dyspnea (measured by modified Medical Research Council [mMRC]), 6MWT, and SAEs. One RCT[17] also assessed hyperinflation, measured by the ratio of residual volume to total lung capacity (RV/TLC).

Summary of Critical Appraisal

The assessments of the methodological quality of the identified SR[16] (Table 4) and RCTs[17,18] (Table 5) are presented in Appendix 3.

The authors of the SR[16] provided appropriate research questions, explanations for selection of the study designs for the inclusion in the review, and used comprehensive literature search strategies. The authors performed study selection and data extraction in duplicate, and described the included studies in adequate detail. The authors used the Cochrane risk of bias tool to assess the quality of the included RCTs, and used GRADE to rate the level of evidence of each outcome. The authors

performed meta-analysis using appropriate methods for statistical combination of the results. Risk of bias in individual studies was accounted for when interpreting and discussing the results. The authors provided satisfactory explanations for any heterogeneity observed in the results. Conflicts of interest and financial disclosure were declared in the review.

In terms of limitations, the authors of the SR[16] did not provide an explicit statement that a protocol had been established prior to the conduct of the review. The authors did not provide a list of excluded studies or the sources of funding for the included studies. The authors did not perform subgroup analysis based on the level of risk of bias in individual studies.

With respect to the included RCTs, there were some concerns regarding bias arising from the randomization process in both RCTs.[17,18] Although the allocation sequence was random, and there were no differences between intervention groups in patient demographics at baseline, there was no information regarding whether the allocation sequence was concealed until participants were enrolled and assigned to interventions.

In both identified RCTs,[17,18] there were also some concerns regarding bias due to deviations from intended interventions. As both RCTs were open-label, participants were probably aware of their assigned intervention during trial, and physicians and care givers who delivered the interventions were also aware of participants' assigned intervention. However, there was no information if additional interventions or exposures were balanced between groups. Both RCTs used appropriate analysis to estimate the effects of assignment to the intervention or comparator groups.

Both RCTs[17,18] had low risk of bias due to missing outcome data, as the data for each outcome were available for nearly all participants randomized. In the EMPROVE trial,[17] individuals with missing data were included in the analysis via Bayesian multiple imputation. In the REACH trial,[18] missing values were imputed using last observation carried forward for individuals with at least one follow-up assessment.

Both RCTs[17,18] had high risk of bias in the measurement of outcomes. The methods of measuring the outcomes were likely appropriate, and there was no evidence that the measurements of outcomes differed between intervention groups, however the assessment of the outcomes could have been influenced by the assessors' knowledge of the intervention received by the study participants.

Both RCTs[17,18] had low risk of bias in selection of reported results. The results were analyzed in accordance with a prespecified analysis plan. There was no evidence that the numerical results being assessed were likely to have been selected from multiple eligible outcome measurements or from multiple analyses of the data.

Summary of Findings

The main findings and conclusion of the included SR[16] (Table 6) and RCTs[17,18] (Table 7) are presented in Appendix 4.

Clinical Effectiveness of Endobronchial Valves

The included SR[16] conducted meta-analysis of seven RCTs comparing the effectiveness of Zephyr one-way EBV versus standard medical care. Pooled analysis revealed that QoL was significantly greater in the EBV group compared to the standard medical care group (mean between-group difference of 7-points on the

SGRQ; high quality evidence). The EBV group also had significantly greater 6MWT (+ 39.86 m) (moderate quality evidence), and % FEV_1 responders (+ 18.82%) (high quality evidence) as compared with the standard medical care group. EBV treatment was associated with significantly higher risk of SAEs (defined as incidence of deaths or events that required prolonged hospitalization or were life-threatening; RR 3.13; 95% CI 1.48 to 6.60) as compared with standard medical care (high quality evidence). However, there were no significant differences between EBV and standard medical care groups regarding death, COPD exacerbation, or respiratory failure requiring ventilation. The SR did not report on the incidence of pneumothorax, a main complication associated with EBV.

The two included RCTs[17,18] investigated the effectiveness of the Spiration Valve System (SVS) compared with standard medical care.

In the EMPROVE trial,[17] patients treated with SVS compared to standard medical care had significantly better FEV_1 (+ 97 mL), % FEV_1 responders (+ 23.4%), QoL (SGRQ score; -12.9 points), and dyspnea (-0.6 points) at 6-month follow-up, and after 12 months significant differences were + 88 ml, + 24.9%, -8.7 points and -0.8 points respectively. However, there was no significant difference between groups in mean change in 6MWT from baseline to 6 months. SVS treatment was associated with significantly greater total SAEs compared to standard medical care (+ 19.1%) at 6 months of follow-up, which was mainly due to pneumothorax (+ 12.4%). From 6 to 12 months of follow-up, there was no significant difference between groups in total SAEs.

In the REACH trial,[18] patients treated with SVS compared to standard medical care had significantly better FEV_1 (+ 101 mL), but not in QoL (measured by SGRQ), dyspnea or 6MWT, after 3 months. After 6 months, FEV_1 (+ 115 mL), SGRQ (- 10.5 points), and 6MWT (+ 36.4 m) were significantly better in the SVS group versus the standard medical care group, but dyspnea was not significantly different between groups. The % FEV_1 responders was 48% and 13% at 3 months, and 41% and 21% at 6 months in the SVS group and the control group, respectively (statistical analysis for the between-group difference was not reported). At 6 months of follow-up, total incidence of SAEs was 33.3% in the SVS group compared to 24.2% in the control group (statistical analysis for the between-group difference was not reported). In the SVS group, the device-related pneumothorax rate was 7.6%. The rate of acute exacerbations of COPD was 19.7% in the SVS group and 12.1% in the control group (statistical analysis for the between-group difference was not reported). There was one death in the control group (3%) and none in the SVS group.

Limitations

Due to open-label nature of most trials in this report, the non-blinding of patients and outcome assessors may have introduced bias to the 6MWT and QoL assessments, however detection bias was less likely in the objective measurements of lung function. Pooling data across different time points (i.e., 3, 6 and 12 months) in the SR was a concern because of the potential differences in short- and long-term efficacy among trials. This review did not identify any studies comparing EBV with interventions other than standard medical care; therefore, the comparative effectiveness of EBV versus other interventions (such as lung volume reduction surgery, lung transplant, or pulmonary rehabilitation) is uncertain. The protocol for one ongoing RCT (CELEB trial) was identified, in which the effectiveness of EBV will be compared with lung volume reduction surgery in patients with severe heterogeneous emphysema.[19]

Conclusions and Implications for Decision or Policy Making

This review identified one SR[16] and two RCTs[17,18] that assessed the efficacy and safety of two types of endobronchial valves (i.e., Zephyr one-way EBV and Spiration Valve System) compared to standard medical care for bronchoscopic lung volume reduction in patients with severe emphysema.

Evidence from a single SR identified that endobronchial valve therapy with the Zephyr EBV was associated with significantly greater lung function, exercise capacity, and quality of life, and significantly lower dyspnea for up to 12 months, with increased risk SAEs compared to standard medical care.[16] Consistent with these findings, the use of Zephyr one-way EBV has been recommended by NICE in UK[20] as a standard of care therapy, provided that patient selection should be carefully done by a multidisciplinary team.[12]

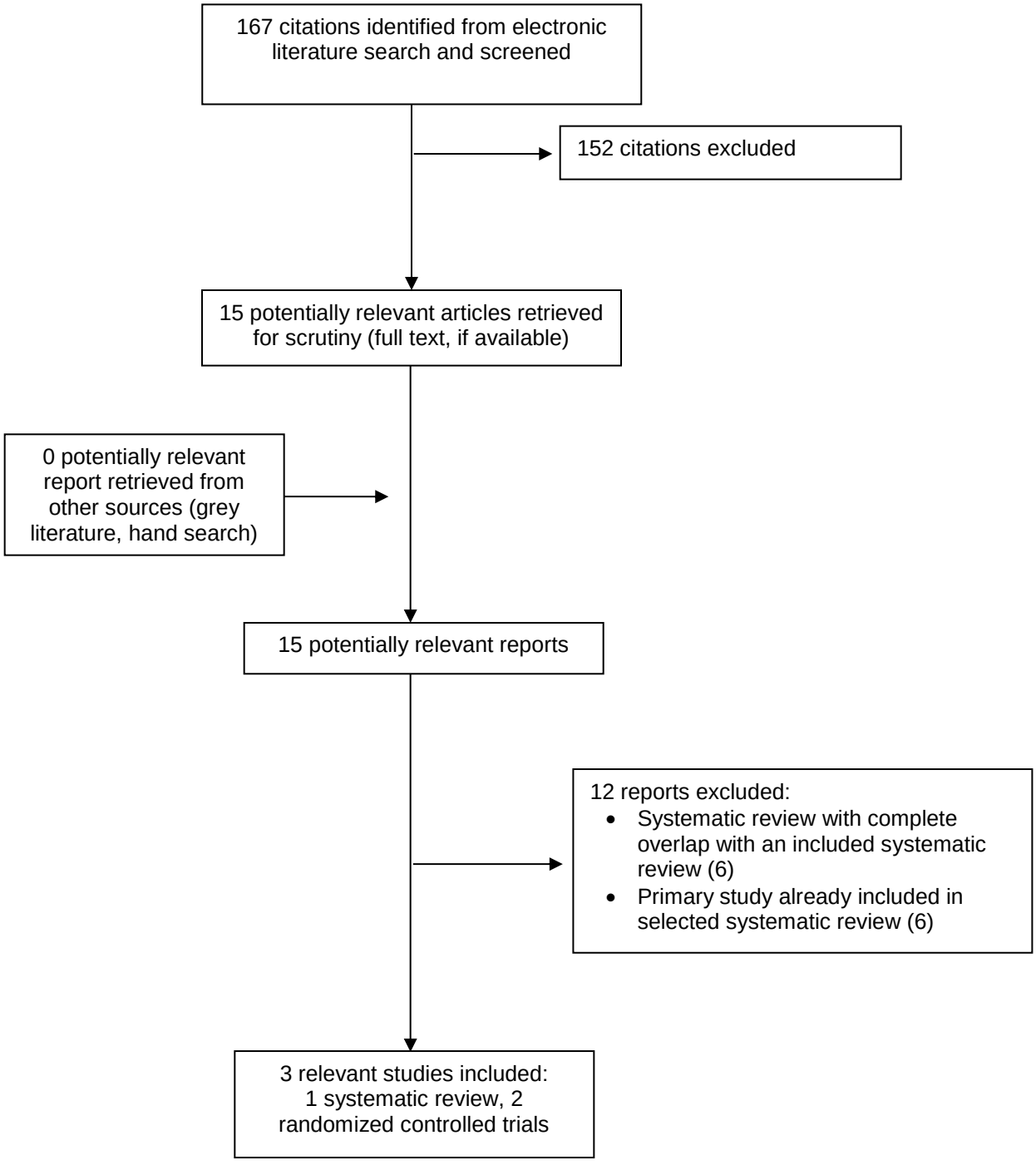
One RCT[18] on SVS conducted in China showed significantly greater lung function (as assessed by FEV_1), while the other RCT[17] conducted in the US and Canada showed statistically significant greater lung function and QoL, and significantly lower dyspnea for up to 12 months, but no significant difference in exercise capacity reported at 6 months, compared to standard medical care. Further work is required to demonstrate with confidence the efficacy and safety of Spiration Valve System. Pneumothorax was the most reported complication associated with both EBV interventions. As the complication was found to occur most commonly within the first three days after valve insertion, it was recommended by the Endoscopic Lung Volume Reduction Expert Panel that patients after having valve insertion should be admitted to a hospital and monitored for at least three days.[5,12]

Given that patients were followed for a maximum 12 months post-intervention across all included studies, the long-term efficacy and safety of EBV remain to be determined.

References

1. Public Health Agency of Canada. Chronic Obstructive Pulmonary Disease (COPD). Ottawa (ON): Government of Canada; 2018: https://www.canada.ca/en/public-health/services/chronic-diseases/chronic-respiratory-diseases/chronic-obstructive-pulmonary-disease-copd.html. Accessed Oct 21 2019.
2. Han MK, Dransfield M, Martinez FJ. Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis, and staging. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2019: https://www.uptodate.com/. Accessed 2019 Oct 21.
3. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Eur Respir J.* 2017;49(3).
4. Marruchella A, Faverio P, Bonaiti G, Pesci A. History of lung volume reduction procedures. *J Thorac Dis.* 2018;10(Suppl 27):S3326-s3334.
5. Slebos DJ, Shah PL, Herth FJ, Valipour A. Endobronchial valves for endoscopic lung volume reduction: Best practice recommendations from Expert Panel on Endoscopic Lung Volume Reduction. *Respiration.* 2017;93(2):138-150.
6. Hartman JE, Vanfleteren L, van Rikxoort EM, Klooster K, Slebos DJ. Endobronchial valves for severe emphysema. *Eur Respir Rev.* 2019;28(152).
7. Bezzi M, Luzzi V, Novali M, Comel A, Polese G, Corbetta L. Competence in bronchoscopic treatments in emphysema. *Panminerva Med.* 2019;61(3):401-421.
8. Zephyr® endobronchial valve system. Silver Spring (MD): U.S. Food & Drug Administration 2018: https://www.fda.gov/medical-devices/recently-approved-devices/zephyrr-endobronchial-valve-system-p180002. Accessed 2019 Oct 21.
9. Shah PL. The National Institute for Health and Care Excellence (NICE) updated guidance on endobronchial valves: What was behind the decision and what does it mean for pulmonologists? *EMJ Respir.* 2018;6(1):86-89. https://www.emjreviews.com/respiratory/article/the-national-institute-for-health-and-care-excellence-nice-updated-guidance-on-endobronchial-valves-what-was-behind-the-decision-and-what-does-it-mean-for-pulmonologists/. Accessed 2019 Oct 21.
10. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease : 2019 report. Fontana (WI): Global Initiative for Chronic Obstructive Lung Disease, Inc.; 2019: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf. Accessed 2019 Oct 21.
11. Spiration Valve® System - P180007. Silver Spring (MD): U.S. Food & Drug Administration; 2018: https://www.fda.gov/medical-devices/recently-approved-devices/spiration-valver-system-p180007. Accessed 2019 Oct 21.
12. Herth FJF, Slebos DJ, Criner GJ, Valipour A, Sciurba F, Shah PL. Endoscopic lung volume reduction: An Expert Panel recommendation - Update 2019. *Respiration.* 2019;97(6):548-557.
13. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Oct 21.
14. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;366:l4898.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche 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. *J Clin Epidemiol.* 2009;62(10):e1-e34.
16. Rustagi N, Singh S, Dutt N, Kuwal A, Chaudhry K, Shekhar S, et al. Efficacy and safety of stent, valves, vapour ablation, coils and sealant therapies in advanced emphysema: A meta-analysis. *Turk Thorac J.* 2019;20(1):43-60.
17. Criner GJ, Delage A, Voelker K, Hogarth DK, Majid A, Zgoda M, et al. Improving Lung Function in Severe Heterogenous Emphysema with the Spiration(R) Valve System (EMPROVE): A multicenter, open-label, randomized, controlled trial. *Am J Respir Crit Care Med.* 2019.
18. Li S, Wang G, Wang C, Gao X, Jin F, Yang H, et al. The REACH Trial: A Randomized Controlled Trial Assessing the Safety and Effectiveness of the Spiration(R) Valve System in the Treatment of Severe Emphysema. *Respiration.* 2019;97(5):416-427.
19. Buttery S, Kemp SV, Shah PL, Waller D, Jordan S, Lee JT, et al. CELEB trial: Comparative Effectiveness of Lung volume reduction surgery for Emphysema and Bronchoscopic lung volume reduction with valve placement: a protocol for a randomised controlled trial. *BMJ open.* 2018;8(10):e021368.
20. Endobronchial valve insertion to reduce lung volume in emphysema. *(Interventional procedures guidance [IPG600])*. London (GB): National Institute for Health and Care Excellence; 2017: https://www.nice.org.uk/guidance/ipg600. Accessed 2019 Oct 16.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Systematic Review

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Types of Comparisons, Treatment Setting, Follow-up	Outcomes
Rustagi et al., 2019[16] India Funding: No financial support	Objective: To assess the efficacy and safety of bronchoscopic lung volume reduction procedures in patients with severe emphysema Total 16 RCTs; 7 RCTs reported on Zephyr one-way endobronchial valves (EBV) and were relevant to the current report Quality assessment tool: Cochrane risk of bias Assessment of level of evidence: GRADE Databases: PubMed, Google Scholar, Science Citation Index Expanded and Cochrane databases Search date: Until July 31, 2018	Adult patients with severe emphysema with no collateral ventilation Mean age: 58 to 65 years % Female: 25 to 68 Mean FEV_1 % predicted: 26 to 32 Mean 6MWT: 282 to 372 m Mean QoL in units total score on SGRQ: 53 to 70	EBV (n = 551) Standard medical care (n = 320) Setting: Hospital Follow-up: 3 to 12 months	– QoL (measured with SGRQ) – 6MWT (a measure of exercise capacity) – Responder rates (≥ 15% improvement in FEV_1) – Total SAEs (death, need of hospitalization, or any intervention due to occurrence of pneumothorax, COPD exacerbations, lower respiratory infections, hemoptysis, or respiratory failure) – Death – Respiratory failure requiring mechanical ventilation – COPD exacerbations and LRTI

COPD = chronic obstructive pulmonary disease; EBV = endobronchial valve; FEV_1 = The forced expiratory volume in one second; GRADE = The Grading of Recommendations Assessment, Development and Evaluation; LRTI = lower respiratory tract infection; m = meter; 6MWT = 6-minute walk test; QoL = quality of life; RCT = randomized controlled trial; SAEs = serious adverse events; SGRQ = The St George's Respiratory Questionnaire (range from 0 to 100; with higher scores indicating more limitations).

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Criner et al. (EMPROVE), 2019[17] USA and Canada Funding: Spiration Inc./Olympus Respiratory America	Prospective, multicentre (41 sites), open-label, parallel (2:1), RCT Sample size calculation: Yes Bayesian adaptive design was used for two interim analyses Follow-up: 6 months and 12 months	Adult patients having ≥ 40% emphysema destruction in the target lobe and ≥ 10% disease emphysema severity difference with the ipsilateral lobe, severe dyspnea (mMRC ≥ 2), severe obstructive disease FEV1 ≤ 45% of predicted after bronchodilators, hyperinflation (TLC ≥ 100% and RV ≥ 150%) Mean age: 67 years % male: 56 Mean FEV_1 % predicted: 29 Mean 6MWT: 305 m Mean QoL in units total score on SGRQ: 56	Spiration Valve System (SVS) (n = 113)	Standard medical care (n = 59)	Primary endpoint: – Mean change in FEV_1 (baseline to 6 months) Secondary endpoints: – Responder rates (≥ 15% improvement in FEV_1) – Hyperinflation (RV/TLC) – Health status and QoL (SGRQ) – Dyspnea (mMRC) – Exercise capacity (6MWT) – SAEs
Li et al. (REACH), 2019[18] China Funding: Spiration Inc./Olympus Respiratory America	Prospective, multicentre (12 sites), open-label, parallel (2:1), RCT Sample size calculation: Yes Follow-up: 3 months and 6 months	Adult patients with severe dyspnea (mMRC ≥ 2), severe airflow obstruction (post-bronchodilator FEV1 ≤ 45%, hyperinflation (TLC ≥ 100% and RV ≥ 150%) Mean age: 63 years % male: 98 Mean FEV_1 % predicted: 28 Mean 6MWT: 330 m Mean QoL in units total score on SGRQ: 57	Spiration Valve System (SVS) (n = 66)	Standard medical care (n = 33)	Primary endpoint: – Mean change in FEV_1 (baseline to 3 months) Secondary endpoints: – Responder rates (≥ 15% improvement in FEV_1) – Health status and QoL (SGRQ) – Dyspnea (mMRC) – Exercise capacity (6MWT) – SAEs

FEV_1 = The forced expiratory volume in one second; mMRC = modified Medical Research Council (points); 6MWT = 6-minute walk test; QoL = quality of life; RCT = randomized controlled trial; RV = residual volume; SAEs = serious adverse events; SGRQ = The St George's Respiratory Questionnaire (range from 0 to 100; with higher scores indicating more limitations); SVS = Spiration Valve System; TLC = total lung capacity.

Appendix 3: Quality Assessment of Included Studies

Table 4: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[13]	Rustagi et al., 2019[16]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; NA = not applicable; PICO = Population, Intervention, Comparator, and Outcome.

Table 5: Quality Assessment of Randomized Controlled Trials

Cochrane risk-of-bias assessment tool version 2[14]	Criner et al. (EMPROVE), 2019[17]	Li et al. (REACH), 2019[18]
Bias arising from the randomization process		
1.1 Was the allocation sequence random?	Y (lower)	Y (lower)
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI (other)	NI (other)
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N (lower)	N (lower)
Risk-of-bias judgement (low/high/some concerns)	Some concerns	Some concerns
Bias due to deviations from intended interventions		
2.1 Were participants aware of their assigned intervention during trial?	PY (higher)	PY (higher)
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y (higher)	Y (higher)
2.3 If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups??	NI (other)	NI (other)
2.4 If Y/PY/NI to 2.3: Were these deviations likely to have affected the outcome?	--	--
2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	--	--
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	--	--
Risk-of-bias judgement (low/high/some concerns)	Some concerns	Some concerns
Bias due to missing outcome data		
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y (lower)	Y (lower)
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	--	--
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	--	--
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depend on its true value?	--	--
Risk-of-bias judgement (low/high/some concerns)	Low	Low
Bias in measurement of the outcome		
4.1 Was the method of measuring the outcome inappropriate?	PN (lower)	PN (lower)
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN (lower)	PN (lower)
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y (higher)	Y (higher)

Cochrane risk-of-bias assessment tool version 2[14]	Criner et al. (EMPROVE), 2019[17]	Li et al. (REACH), 2019[18]
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PY (higher)	PY (higher)
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	PY (higher)	PY (higher)
Risk-of-bias judgement (low/high/some concerns)	High	High
Bias in selection of the reported results		
5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y (lower)	Y (lower)
Is the numerical result being assessed likely to have been selected, on the basis of the results, from:		
5.2 … multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	PN (lower)	PN (lower)
5.3 … multiple analysis of the data?	PN (lower)	PN (lower)
Risk-of-bias judgement (low/high/some concerns)	Low	Low
Overall bias		
Risk-of-bias judgement (low/high/some concerns)	High	High

N = no; NI = no information; PN = probably no; Y = yes; PY = probably yes; RoB = risk of bias.

"Lower", "higher" or "other" in the parentheses denoted lower RoB, higher RoB or other RoB.

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Systematic Review

Main Study Findings	Author's Conclusions
Rustagi et al., 2019[16]	
Endobronchial valves (Zephyr one-way EBV) versus standard medical care • SGRQ score (7 trials; n = 871) MD (95% CI) = -7.00 (-9.85 to -4.14) Quality of evidence: high • 6MWT (7 trials; n = 876) MD (95% CI) = 39.86 m (18.42 to 61.29) Quality of evidence: moderate • % FEV_1 (7 trials; n = 879) MD (95% CI) = 18.82 % (14.18 to 23.47) Quality of evidence: high • SAEs (6 trials; n = 819) RR (95% CI) = 3.13 (1.48 to 6.60) Absolute (95% CI) = 392 more per 1,000 (from 88 more to 1000 more) Quality of evidence: high • Death (7 trials; n = 990) RR (95% CI) = 1.14 (0.55 to 2.39) Absolute (95% CI) = 3 more per 1,000 (from 11 fewer to 34 more) Quality of evidence: moderate • COPD exacerbation (7 trials; n = 990) RR (95% CI) = 0.99 (0.82 to 1.19) Absolute (95% CI) = 3 fewer per 1,000 (from 45 fewer to 48 more) Quality of evidence: moderate • Respiratory failure required ventilation (6 trials; n = 893) RR (95% CI) = 1.06 (0.38 to 2.95) Absolute (95% CI) = 1 more per 1,000 (from 9 fewer to 29 more) Quality of evidence: moderate	*"Among patients with advanced severe emphysema, endobronchial valves … have shown promising short-term improvement in important disease outcomes with increased risk of serious adverse events."*[16] p. 59

CI = confidence interval; COPD = chronic obstructive pulmonary disease; EBV = endobronchial valve; FEV_1 = The forced expiratory volume in one second; LRTI = lower respiratory tract infection; m = meter; MD = mean difference; 6MWT = 6-minute walk test; QoL = quality of life; RCT = randomized controlled trial; RR = risk ratio; SAEs = serious adverse events; SGRQ = The St George's Respiratory Questionnaire (range from 0 to 100; with higher scores indicating more limitations).

Table 7: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Criner et al., (EMPROVE) 2019[17]	
Spiration Valve System (n = 113) versus standard medical care (n = 59) **Efficacy outcomes (all differences are between-group differences)** • FEV_1 Difference (95% BCI) at 6 months = 97 mL (57 to 138) Difference (95% BCI) at 12 months = 88 mL (37 to 137) • % FEV_1 responders (≥ 15% improvement) Difference (95% BCI) at 6 months = 23.4% (10.7 to 35.8) Difference (95% BCI) at 12 months = 24.9% (12.0 to 37.3) • Hyperinflation (RV/TLC) Difference (95% BCI) at 6 months = -0.039 (-0.058 to -0.020) • QoL (SGRQ score) Difference (95% BCI) at 6 months = -12.9 (-17.3 to -8.5) Difference (95% BCI) at 12 months = -8.7 (-13.4 to -4.0) • Dyspnea (mMRC score) Difference (95% BCI) at 6 months = -0.6 (-0.9 to -0.3) Difference (95% BCI) at 12 months = -0.8 (-1.1 to -0.5) • 6MWT Difference (95% BCI) at 6 months = 5.0 m (-16.2 to 26.2) **Safety outcomes** Short-term (0 to 6 months) • Total SAEs Difference (95% BCI) = 19.1% (5.9 to 29.7) • Acute exacerbation of COPD Difference (95% BCI) = 6.6% (-5.1 to 16.0) • Death from procedure or device Difference (95% BCI) = 0.0% (-5.3 to 2.3) • Pneumonia in the valve-treated lobe Difference (95% BCI) = 1.8% (-3.9 to 5.2) • Pneumonia not in the valve-treated lobe Difference (95% BCI) = 5.4% (-2.4 to 11.1) • Pneumothorax requiring surgical intervention or prolonged air leak > 7 days Difference (95% BCI) = 12.4% (4.6 to 18.6) • Tension pneumothorax Difference (95% BCI) = 1.8% (-3.9 to 5.2) • Respiratory failure Difference (95% BCI) = 2.7% (-3.2 to 6.4) Long-term (6 to 12 months) • Total SAEs	*"In patients with severe heterogeneous emphysema, the Spiration Valve System shows significant improvement in multiple efficacy outcomes, with an acceptable safety profile."*[17] p. 2

Main Study Findings	Author's Conclusions
Difference (95% BCI) = 10.7% (-3.0 to 21.2) • Acute exacerbation of COPD Difference (95% BCI) = 5.1% (-7.4 to 14.2) • Death from procedure or device Difference (95% BCI) = 1.0% (-5.9 to 4.1) • Pneumonia in the valve-treated lobe Difference (95% BCI) = 1.0% (-5.9 to 4.1) • Pneumonia not in the valve-treated lobe Difference (95% BCI) = 5.6% (-3.8 to 11.9) • Pneumothorax requiring surgical intervention or prolonged air leak > 7 days Difference (95% BCI) = 0.0% (-6.6 to 2.4) • Tension pneumothorax Difference (95% BCI) = 0.0% (-6.6 to 2.4) • Respiratory failure Difference (95% BCI) = 1.0% (-5.9 to 4.1)	
Li et al., (REACH) 2019[18]	
Spiration Valve System (n = 66) versus standard medical care (n = 33) **Efficacy outcomes (all *P* values are for between-group differences)** • FEV1 Mean change (95% CI) from baseline to 3 months SVS: 104 mL (60 to 148) Control: 3 mL (-47 to 54); *P* = 0.001 Mean change (95% CI) from baseline to 6 months SVS: 91 mL (52 to 129) Control: -24 mL (-72 to 24); *P* < 0.001 • SGRQ Mean change (95% CI) from baseline to 3 months SVS: -7.92 points (-12.17 to -3.68) Control: -0.73 points (-6.68 to 5.22); *P* = 0.058 Mean change (95% CI) from baseline to 6 months SVS: -8.39 points (-12.69 to -4.08) Control: 2.11 points (-3.87 to 8.08); *P* = 0.007 • % FEV_1 responders (≥ 15% improvement) At 3 months SVS: 48% Control: 13%; *P* value not reported At 6 months SVS: 41% Control: 21%; *P* value not reported • Dyspnea (mMRC score) Mean change (95% CI) from baseline to 3 months SVS: -0.73 (-0.94 to -0.52) Control: -0.41 (-0.70 to -0.12); *P* = 0.076	*"The SVS represents a novel approach for the treatment of severe emphysema with a clinically acceptable risk-benefit profile."*[18] p. 2

Main Study Findings	Author's Conclusions
Mean change (95% CI) from baseline to 6 months SVS: -0.73 (-0.96 to -0.50) Control: -0.36 (-0.71 to -0.01); *P* = 0.091 • 6MWT Mean change (95% CI) from baseline to 3 months SVS: 20.17 m (9.40 to 44.94) Control: 7.50 m (-9.97 to 24.97); *P* = 0.126 Mean change (95% CI) from baseline to 6 months SVS: 20.82 m (-0.58 to 42.22) Control: -15.58 m (-40.12 to 8.96); *P* = 0.042 **Safety outcomes (0 to 6 months)** • Total SAEs – SVS: 33.3%; Control: 24.2%; *P* value not provided Device-related Acute exacerbations of COPD – SVS: 7.6% Pneumothorax – SVS: 1.5% Procedure-related Anesthesia – SVS: 3.0% Acute heart failure – SVS: 1.5% Device- and procedure-related Pneumothorax – SVS: 6.1% Anesthesia – SVS: 1.5% Unrelated Acute exacerbations of COPD – SVS: 12.1%; Control: 12.1% Pneumonia – SVS: 1.5%; Control: 0% Other – SVS: 3.0%; Control: 9.1% Death – SVS: 0%; Control: 3.0%	

COPD = chronic obstructive pulmonary disease; BCI = Bayesian credible interval; FEV_1 = The forced expiratory volume in one second; m = meter; mL = millilitres; mMRC = modified Medical Research Council (points); 6MWT = 6-minute walk test; QoL = quality of life; RV = residual volume; SAEs = serious adverse events; SGRQ = The St George's Respiratory Questionnaire (range from 0 to 100; with higher scores indicating more limitations); SVS = Spiration Valve System; TLC = total lung capacity.