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Effects of lung volume reduction with endobronchial valves in patients with severe chronic obstructive pulmonary disease

Updated report.

Riise GC, Svanberg T, Samuelsson O.

VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Effects of lung volume reduction with endobronchial valves in patients with severe chronic obstructive pulmonary disease

[Effekterna av lungvolymsreduktion med endobronkiella ventiler hos patienter med svår kronisk obstruktiv lungsjukdom]

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1. Abstract

Background
Chronic obstructive pulmonary disease (COPD) is caused by a progressive destruction of the elastic tissue in the small airways that leads to difficulties for the patient to empty the lungs of air. Lung volume reduction with one-way valves can prevent inhaled air to reach hyperinflated lung segments, but allow trapped air to be exhaled. The purpose is to cause the lung parenchyma distal to the valve to collapse, and, thereby, to lower the hyperinflation and intrathoracic pressure. This will, theoretically, lead to an improvement in pulmonary function.

In 2013 we published an HTA-report on the effects of the placement of endobronchial one-way valves (EBVs) in affected lung segments. It was based on three randomised controlled trials (RCT) and the results were inconclusive. Between January 2013 and June 2018 six additional RCTs on the effects of lung volume reduction with EBVs have been published.

Objectives
To assess whether lung volume reduction by EBVs improve survival, quality of life and pulmonary function in patients with severe COPD and severe pulmonary emphysema.
To assess whether there are differences in outcome in patients treated with EBVs bilaterally or unilaterally.
To assess whether there are differences in outcome in patients with homogeneous or heterogeneous emphysema.

Methods
A systematic literature search was conducted in April and July 2018 in Medline, Embase, and the Cochrane Library. The certainty of evidence was graded according to the GRADE system.

Main results
Nine RCTs that studied the effects of insertion of EBVs in patients with severe or advanced emphysema were identified. In two of the RCTs both lungs were treated, i.e. bilateral placements of EBVs, whereas the other seven trials only used a unilateral approach.

In comparison with optimal medical therapy the unilateral placement of EBVs probably results in clinically and statistically significant improvements in lung function, quality of life, and physical capacity in patients with heterogeneous or homogeneous emphysema (Moderate certainty of evidence; GRADE ⊕⊕⊕O). During three to 12 months follow-up there may be no significant differences in mortality (Low certainty of evidence; GRADE ⊕⊕OO), but the frequency of serious complications and adverse events was higher (High certainty of evidence; GRADE ⊕⊕⊕⊕).

In patients who had EBVs inserted in both lungs, i.e. bilaterally, there is probably no improvements in the outcome variables (Moderate certainty of evidence; GRADE ⊕⊕⊕O).

Concluding remark
Based on moderate certainty of evidence, lung volume reduction in patients with advanced chronic obstructive pulmonary disease and emphysema by the insertion of one-way valves in affected lung segments probably leads to clinically relevant improvement in lung function, quality of life, and physical capacity up to 12 months after treatment. Short-term complications to the procedure are frequent and reliable data on mortality are still lacking. Further long-term studies are needed to address whether the effects are sustainable and to clarify the effects on long-term survival.

2. Svensk sammanfattning – Swedish summary

Bakgrund

Kronisk obstruktiv lungsjukdom (KOL) är en lungsjukdom där luftrören blir trånga och det blir svårare att ventilera lungorna. Det blir svårare att andas ut all luft och volymen ökar i delar av lungorna. Den orsakas av en progressiv destruktion av den elastiska vävnaden i de mindre luftvägarna. En minskning av volymen i expanderade lungsegment genom att sätta in envägs ventiler som tillåter luft att lämna dessa områden men förhindrar att luft kommer in är en metod att reducera hyperinhalerade ineffektiva lungområden, Därigenom kan trycket i bröstkorgen minskas och underlätta för välfungerande lungvävnad att utföra utbytet av syre och koldioxid mellan blod och luft, dvs. förbättra patientens lungfunktion.

2013 publicerade vi en HTA-rapport som utvärderade effekterna av behandling med endobronkiella ventiler (EBV) hos patienter med svår KOL och emfysem. Den baserades på tre publicerade randomiserade studier (RCT). Dokumentationen räckte då inte till någon säker slutsats Sedan januari 2013 till juni 2018 har ytterligare sex RCT publicerats.

Syfte

Att utvärdera om reduktion av lungvolym med EBV ökar överlevnaden och förbättrar livskvalitet och lungfunktion hos patienter med svår KOL och lungemfysem.
Att utvärdera om det föreligger skillnader i effekt hos patienter som får EBV i båda lungorna eller endast i en lunga.
Att utvärdera om det föreligger skillnader i effekt hos patienter som har heterogent eller homogent emfysem.

Metoder

Under april 2018 med en uppdatering i juli 2018 gjordes systematiska litteratursökningar i PubMed, Embase, och i the Cochrane Library. Minst två författare granskade titlar, abstrakts och fulltextartiklar, värderade studiekvalitet och extraherade data oberoende av varandra. Det vetenskapliga underlagets styrka bedömdes enligt GRADE-systemet.

Resultat

Nio RCT har studerat effekterna av inläggning av EBV hos patienter med avancerat emfysem. I två av studierna har bägge lungorna erhållit ventiler, dvs. bilateral EBV behandling, och i de övriga sju studierna har ventilerna endast placerats unilateralt, dvs. bara i en lunga.

Inläggning av EBV ensidigt i en lunga resulterade i kliniskt betydelsefulla och statistiskt signifikanta förbättringar i livskvalitet, fysisk prestationsförmåga och lungfunktion hos patienter med heterogent eller homogent emfysem (Måttligt vetenskapligt underlag; GRADE ⊕⊕⊕O) jämfört med optimal medicinsk behandling. Det är osäkert om överlevnaden påverkas under en uppföljningstid av 3 till 12 månader (Lågt vetenskapligt underlag; GRADE ⊕⊕OO). Allvarliga komplikationer i direkt anslutning till inläggning av EBV är vanligt (Starkt vetenskapligt underlag; GRADE ⊕⊕⊕⊕). Hos patienter som behandlas med EBV i bägge lungorna observeras ingen förbättring i lungfunktion eller i övriga utfallsvariabler (Måttligt vetenskapligt underlag; GRADE ⊕⊕⊕O).

Avslutande kommentar

Behandling av patienter med avancerat emfysem med inläggning av envägsventiler i affekterade lungsegment i en av lungorna förbättrar troligen livskvalitet, fysisk prestationsförmåga och lungfunktion. Om effekterna kvarstår under längre tid än ett år och om överlevnaden påverkas behöver studeras i långtidsstudier.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review intended for decision makers, and is ended with a concluding summary.

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Head of HTA-centrum of Region Västra Götaland, Sweden, 2018-09-26

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3. Summary of Findings

Bilateral placement of endobronchial valves (EBVs).

Outcomes	Study design No of studies No of patients	Relative effect (95% CI)	Absolute effect Mean difference (95% CI)	Certainty of evidence GRADE
Mortality	2 RCTs 350	OR 4.8 (0.81,28.5)		⊕⊕OO[1]
Dyspnoea (mMRC score)	1 RCT 277		-0.10 (-0.34,0.14)	⊕⊕⊕O[1]
HRQoL (SGRQ score)	2 RCTs 350		+11.5 (-12.1,35.1)	⊕⊕⊕O[1]
6 MWD (meters)	2 RCTs 350		-19.6 (-36.5,-2.8)	⊕⊕⊕O[1]
FEV_{1s} ml	1 RCT 277		-70.0 (-108.9,-31.1)	⊕⊕⊕O[1]
FEV_{1s} %	1 RCT 277		-2.2 (-3.5,-0.8)	⊕⊕⊕O[1]
RV (litre)	1 RCT 249		+0.38 (0.09,0.67)	⊕⊕⊕O[1]
Serious adverse events	2 RCTs 350	RR 2.7 (1.2,5.9)		⊕⊕⊕⊕

Unilateral placement of EBVs.

Outcomes	Study design No of studies No of patients	Relative effect (95% CI)	Absolute effect Mean difference (95% CI)	Certainty of evidence GRADE
Mortality	7 RCTs 970	OR 1.3 (0.6,2.9)		⊕⊕OO[1]
Dyspnoea (mMRC score)	5 RCTs 631		-0.59 (-0.81,-0.38)	⊕⊕⊕O[2]
HRQoL (SGRQ score)[3]	7 RCTs 982		-7.0 (-9.6,-4,4)	⊕⊕⊕O[2]
6 MWD (meters)	7 RCTs 987		+41.5 (21.0,62.1)	⊕⊕⊕O[2]
FEV1s ml	3 RCTs 380		+148.7 (78.6,218.8)	⊕⊕⊕O[2]
FEV_{1s} %	7 RCTs 990		+16.2 (9.4,23.0)	⊕⊕⊕O[2]
RV (litre)	4 RCTs 410		-0.50 (-0.66,-0.34)	⊕⊕⊕O[2]
Serious adverse events	5 RCTs 732	RR 4.9 (3.0,8.0)		⊕⊕⊕⊕

Footnotes:

1. Downgraded due to severe imprecision.
2. Downgraded due to study limitations (patients and investigators not blinded to treatment).
3. A reduction in the SGRQ score means an improvement in HRQoL.

Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

COPD	Chronic Obstructive Pulmonary Disease
EBV	Endobronchial valve
ELVR	Endobronchial Lung Volume Reduction
FEV_{1s}	Forced Expiratory Volume in 1 second
HRQoL	Health Related Quality of Life
mMRC	modified Medical Research Council
RCT	Randomised Controlled Trial
RV	Residual Volume
SAE	Serious Adverse Event
SGRQ	St:George's Respiratory Questionnaire
6MWD	6 Minute Walk Distance

5. Background

Chronic obstructive pulmonary disease (COPD) and emphysema, is caused by a progressive destruction of the elastic tissue in the small airways due to a chronic inflammatory process. It is mainly a smoking-related disease that results in a diffuse, *homogenous* emphysema as well as peripheral small airway narrowing in the lungs. To a lesser extent more *heterogeneous* emphysema, predominantly in the lower lobes, is caused by an inherited lack of the pulmonary protective enzyme alpha-1-antitrypsine.

The increase in alveolar size, the narrowing of the small airways, and the diminished pulmonary elasticity result in difficulty for the patient to empty air from his/her lungs. The lungs increase in size, become hyperinflated, press the diaphragm downwards and increase the thorax volume.

Chronic obstructive pulmonary disease is categorized into four different stages according to its severity. Presently, the vast majority of all patients are treated pharmacologically and the most severe cases also need treatment with oxygen therapy. The intervention to reduce lung volume with surgery, endobronchial coils or valves (Endobronchial Lung Volume Reduction, ELVR) has been used and proposed only for patients with the most severe disease who belong to stage three and four.

Advanced emphysema is a serious condition with an increased risk of

- premature death
- permanent illness or damage
- disability and health related quality of life

In 2013 we published an HTA-report on the effects of the placement of endobronchial one-way valves in affected lung segments (Riise et al., 2013). It was based on three randomised controlled trials (RCT) and concluded that there were no beneficial effects on critical and important outcome variables such as mortality or dyspnoea, and that the effects on other outcome variables were small and of no clinical relevance (Low certainty of evidence GRADE ⊕⊕OO). However, we also identified two major scientific questions to be addressed in future trials. It needs to be clarified whether there are any subcategories of patients with emphysema that specifically may benefit from ELVR with endobronchial valves (EBVs), such as patients with heterogeneous or homogenous emphysema? Secondly, should one only treat one lung, or should EBVs be placed bilaterally?

Between January 2013 and June 2018 six additional RCTs on the effects of ELVR with valves have been published. This makes it meaningful to update the initial report and to address the above acknowledged gaps of knowledge.

Prevalence and incidence

The prevalence of COPD in the adult Swedish population is currently not known. It is estimated that between 400 000 to 700 000 individuals have COPD. This includes all patients with various severity of the disease (SLMF, 2013). It is the cause of considerable morbidity and mortality. Chronic obstructive pulmonary disease was the direct cause of 34 deaths per 100 000 male inhabitants, and 26 deaths per 100 000 females in Sweden 2010 (SLMF, 2013).

The great majority of COPD patients are in stage one and two, i.e. do not have severe COPD. The prevalence of the more severe COPD, i.e. three and four, in Sweden is estimated to be about 70 000 and 10 000 patients, respectively.

Present treatment

Medical therapy with pharmacological treatment, oxygen therapy or other type of rehabilitation is used for the majority of COPD patients in stage three and four.
They are usually treated by general practitioners as outpatients. However, with increasing severity of COPD they are referred to pulmonary specialists for further evaluation.

In COPD patients who do not suffer from other severe co-morbid conditions it is sometimes possible to consider lung volume reduction either by surgery, or by the insertion of endobronchial coils or valves. In surgery, the most emphysematous lung tissue areas are removed to make more space for the remaining healthier lung tissue, which thereby improves pulmonary function (Washko et al., 2008). The surgical procedure is associated with a high mortality, varying between 5 - 10 % (Fishman et al., 2003, Wood et al., 2003). Furthermore, postoperative complications occur in up to 60 % of all patients (DeCamp et al., 2008). The largest randomised, controlled trial reported a mortality rate of 7.9 % compared to 1.3 % in the control group, which received optimal medical treatment (Edwards et al., 2009).

Lung transplantation for advanced COPD is currently available at two national centres in Sweden. The number of patients who fulfil the current criteria for a transplant is less than 30 patients per year. Nevertheless, lung transplantation has been shown to significantly increase survival in alpha-1-AT deficiency emphysema (Tanash et al., 2011). For other types of COPD patients with homogenous emphysema, transplantation has only been reported to improve quality of life but not to increase survival (Stavem et al., 2006).

Lung Volume Reduction EBVs uses one-way valves that prevent inhaled air from reaching hyperinflated lung segments, but allow trapped air to be exhaled. The valves are placed in the airways of the most destroyed and hyperinflated lung segments. The goal is to cause the lung parenchyma distal to the valve to collapse, thereby lowering the hyperinflation and the intrathoracic pressure. The reduction in lung volume and the decrease in the intrathoracic pressure will, theoretically, lead to an improvement in pulmonary function

The normal pathway through the health care system and current wait time for medical assessment /treatment

Patients with advanced COPD are normally referred to a specialist in pulmonary medicine by a general practitioner for evaluation of oxygen therapy, non-invasive ventilation, lung volume reduction or lung transplantation. In Sweden a patient will normally be evaluated at a first clinic visit within three months after referral.

Number of patients per year who undergo current treatment regimen

The number of patients treated surgically with lung volume reduction is presently very low. Lung transplantation for advanced COPD is done in about 30 patients per year.

The number of patients with very severe COPD and emphysema that may be candidates for insertion of endobronchial valves (EBVs) is estimated to be 10-12 per year in Region Västra Götaland.

Present recommendations from medical societies or health authorities

In December 2017 the National Institute for Health and Care Excellence (NICE) in the UK published a recommendation to use EBV insertion in patients with emphysema. It was based on eight RCTs. The patient selection should be done by multidisciplinary team with experience in managing emphysema. The procedure should only be done to occlude volumes of the lung where there is no collateral ventilation (NICE 2017 IPG600).

6. Endobronchial valves in severe emphysema

Endobronchial lung volume reduction was introduced in 2002. It uses a conventional flexible bronchoscope to apply one-way valves into airways of the most destroyed and hyperinflated lung areas. Inhaled air is prevented from reaching the hyperinflated lung segments, but trapped air can be exhaled during expiration. Mucus is also allowed to be excreted through the valve. This will result in a reduction of the volume of the affected lung segments. The goal is to make the lung parenchyma distal to the valve collapse, thereby lowering the hyperinflation and the intrathoracic pressure.

Endobronchial lung volume reduction is also used for treatment of persistent airway leaks or bronchopleural fistulas in patients who are not eligible for surgical intervention (Riise et al., 2013).

Currently, there are two commercially available EBVs. One from Pulmonx named Zephyr®, and the other from Olympus named Spiration®.

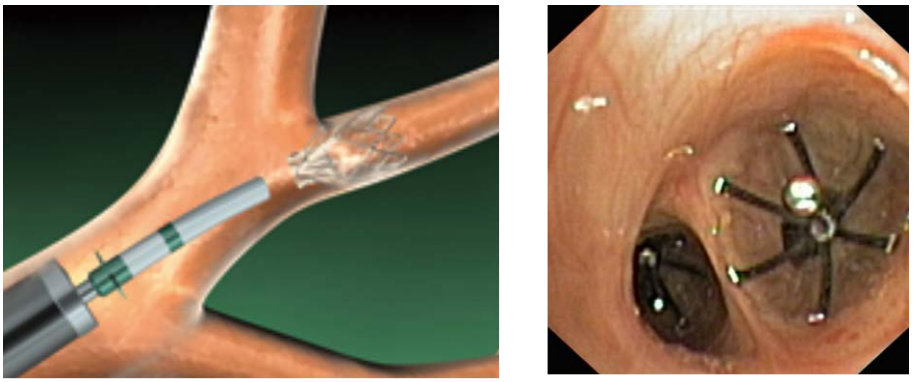

Figure. The Zephyr endobronchial valve, left (published with permission from Pulmonx International Sàrl), and the Spiration endobronchial valve, right (photo by G. Riise).

In order to choose the most suitable patients and the lobe or segments that should be targeted with EBVs the presence or absence of collateral ventilation is measured with the Chartis system (Herth 2013). In the trials published after 2012 only patients who did not have any collateral ventilation from the targeted lobe or segments were included..

7. Objective

Does lung volume reduction by endobronchial valves improve survival, quality of life and pulmonary function in patients with severe chronic obstructive pulmonary disease **(**COPD) and severe pulmonary emphysema?
Are there differences in outcome in patients treated with endobronchial valves bilaterally or unilaterally?
Are there differences in outcome in patients with homogeneous or heterogeneous emphysema?

PICO **P= Patients, I= Intervention, C= Comparison, O=Outcome**

P	Patients with severe COPD (stage 3-4) and severe pulmonary emphysema
I	Lung volume reduction by endobronchial valves
C	Standard medical care such as medication use, oxygen or any type of rehabilitation
O	Critical for decision making Mortality Hospitalisation Important for decision making Dyspnoea Quality of Life Six minutes' walk distance (6MWD) Not important for decision making Pulmonary function (FEV1, FVC, RV) Complications

In the literature the minimal clinically important difference (MCID) for five of the outcome variables have been defined:

Outcome variable	MCID	Reference
mMRC	Reduction ≥ 1.0 points (Scale 0 -5)	Valipour et al., 2016
SGRQ	Reduction ≥ 4 points Reduction ≥ 7 points (Scale 0 – 100)	Jones, 2005 Welling, et al., 2015
6MWD	Improvement ≥ 26 m	Puhan et al., 2011
FEV1	Improvement ≥ 10 %	Donohue, 2005
Residual volume	Reduction ≥ 430 ml	Hartman et al., 2012

8. Methods

Systematic literature search (Appendix 1)

In April and July 2018 one of the authors (TS) performed systematic searches in PubMed, Embase, and the Cochrane Library, updating the previous searches done for the 2013:59 report. Search strategies, eligibility criteria, and a graphic presentation of the selection process are presented in Appendix 1. Two authors (TS, OS) selected studies, and independently of one another, assessed the obtained abstracts and made a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved in consensus. Two authors (GR, OS) read the full-text articles independently of one another and finally decided in a consensus meeting which articles should be included in the updated HTA report.

Critical appraisal and certainty of evidence

The included studies, their design, and patient characteristics are presented in Appendix 2. The excluded studies and the reasons for exclusion are presented in Appendix 3. The included studies, except for the case series, have been critically appraised using a checklist from the SBU for assessment of randomised controlled trials, modified by HTA-centrum, and a checklist for assessment of cohort studies, also from SBU and modified by HTA-centrum.

The results of each article have been summarised per outcome in Appendix 4. Data have been pooled in meta-analyses in RevMan 5.2 using a random effects model and presented as forest plots in Appendix 5. A summary result per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 8). The certainty of evidence was defined according to the GRADE system (Atkins et al. 2004; GRADE Work group).

Ongoing research

A search in the ClinicalTrials database (www.clinicaltrials.gov) using the search terms (valve OR valves OR Zephyr OR Spiration) AND (endobronchial OR intrabronchial OR bronchial OR bronchoscopy OR bronchoscopic OR transbronchoscopic) was performed 2018-07-02. It identified 85 ongoing trials.

9. Results

Systematic literature search (Appendix 1)

The systematic literature search identified a total of 996 articles. After removing duplicates 376 abstracts were read and thereafter 47 articles were obtained in full text. Nine RCTs that studied the effects of lung volume reduction with EBVs in patients with severe or advanced emphysema were identified. The quality of the trials are summarised below, Table 1, and the main features of the trials are presented in Appendix 2.

Table 1. Quality of included RCTs.

Study	Risk of Bias							Directness	Precision
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias		
VENT-US, 2010	?	?	-	?	+	+	+	+	+
VENT-EU, 2012	?	?	-	?	+	+	+	+	+
Ninane, 2012	+	?	+	?	+	?	-	+	?
IBV Valve trial, 2014	?	?	+	+	+	+	+	+	+
BeLieVeR-HiFi, 2015	+	+	-	+	+	+	+	+	+
STELVIO, 2015	+	+	-	-	+	+	+	+	+
IMPACT, 2016	+	+	-	-	+	+	+	+	+
TRANSFORM, 2017	+	+	-	-	+	+	+	+	+
LIBERATE 2018	+	+	-	-	+	+	+	+	+

+ Low risk
? Moderate risk
- High risk

Two of the RCTs treated both lungs, i.e. bilateral placements of EBVs, whereas the other seven trials used a unilateral approach. One RCT included only patients with homogeneous emphysema, and four RCTs included only patients with heterogeneous emphysema. The remaining four RCTs did not specify the type of emphysema other than to be "severe" or "advanced". In all six RCTs published after 2012 only patients without collateral ventilation were included.

Only one RCT had a follow-up of one year. The other trials followed their patients for 3 or 6 months.

The literature search also identified seven systematic reviews with meta-analyses that were published from 2014 through 2017, and three case series. The two latest systematic reviews, of which one is a Cochrane review, included six and seven RCTs, respectively, in their analyses (Wang et al., 2017, van Agteren et al., 2017). None of the systematic reviews identified any RCT that was not included in the present HTA-report. The Cochrane review concluded that EBVs "can provide significant and meaningful short-term (up to one year) improvements in health outcomes, but this was at the expense of increased adverse events".

Outcome variables critical for decision making

Mortality (Appendix 5)
Mortality was reported in all nine RCTs. Altogether, there were 26 deaths in 799 patients who received valves and 8 deaths in 521 medically treated patients. Overall there was no significant difference between the study groups with an Odds Ratio (OR) of 1.6 (95% CI: 0.76, 3.40). In the subcategory of patients treated with unilateral placement of valves the OR was lower 1.26 (0.55, 2.90).
Conclusion: The unilateral insertion of EBVs in patients with severe emphysema may be associated with a mortality risk ranging from slightly decreased to strongly increased (GRADE ⊕⊕OO).
The bilateral insertion of EBVs in patients with severe emphysema may result in little or no difference in mortality compared with treatment with optimal medical therapy.
Low certainty of evidence (GRADE ⊕⊕OO).

Hospitalisation
None of the studies reported data on hospitalisation

Outcome variables important for decision-making

Dyspnoea (Appendix 4.2, Appendix 5)
Dyspnoea in daily living was evaluated by the mMRC scale in one RCT of bilateral placement of valves and in five RCTs of unilaterally placed valves. The scale consists of five statements that describe the entire range of dyspnoea from none (Grade 0) to almost complete incapacity (Grade 4). There was no difference between study groups in the RCT that inserted EBVs bilaterally, but a statistically significant improvement with a reduction of 0.59 points (summary estimate) in patients treated unilaterally. However, according to the predefined definition this is not regarded as clinically relevant (see page 12). The patients with homogenous emphysema experienced the same improvement as those with heterogeneous emphysema.
Conclusion: The unilateral insertion of EBVs in patients with severe emphysema probably improves dyspnoea compared with treatment with optimal medical therapy.
Moderate certainty of evidence (GRADE ⊕⊕⊕O).
The bilateral insertion of EBVs in patients with severe emphysema probably results in little or no difference in dyspnoea compared with treatment with optimal medical therapy.
Moderate certainty of evidence (GRADE ⊕⊕⊕O).

Health Related Quality of Life (Appendix 4.2, Appendix 5)

Health related quality of life (HRQoL) was measured by the St. George's Respiratory Questionnaire (SGRQ). It ranges from a score of 0 to 100 with a higher score indicating a worse quality of life. All the nine RCTs reported this outcome variable.

There were no significant changes in the trials that used bilateral placement of valves, whereas a statistically significant improvement with a reduction of 7 points (summary estimate) was observed in the trials of unilaterally placed valves. The patients with homogenous emphysema experienced the same improvement as those with heterogeneous emphysema.

Conclusion: The unilateral insertion of EBVs in patients with severe emphysema probably improves HRQoL compared with treatment with optimal medical therapy.

Moderate certainty of evidence (GRADE ⊕⊕⊕O).

The bilateral insertion of EBVs in patients with severe emphysema probably results in little or no difference in HRQoL compared with treatment with optimal medical therapy.

Moderate certainty of evidence (GRADE ⊕⊕⊕O).

6 Minute Walk Distance (Appendix 4.2, Appendix 5)

All nine RCTs evaluated physical capacity by measuring the walking distance during six minutes (6MWD). In one of the two RCTs of bilaterally placed valves there was no effect on 6MWD, whereas the other observed a reduction of an average of 21 meters. In contrast, all the RCTs of unilaterally placed valves observed a statistically significant improvement in the 6MWD with a summary estimate of 41.5 metres. The patients with homogenous emphysema experienced the same improvement as those with heterogeneous emphysema.

Conclusion: The unilateral insertion of EBVs in patients with severe emphysema probably improves physical capacity compared to treatment with optimal medical therapy.

Moderate certainty of evidence (GRADE ⊕⊕⊕O).

The bilateral insertion of EBVs in patients with severe emphysema probably results in a reduction in physical capacity compared to treatment with optimal medical therapy. Moderate certainty of evidence (GRADE ⊕⊕⊕O).

Outcome variables not important for decision-making

Forced Expiratory Volume (Appendix 4.1, Appendix 5)

The change in forced expiratory volume was the primary outcome variable in all seven RCTs that studied unilaterally placed valves. A statistically significant improvement was observed in all trials with a summary estimate of 16 % in FEV_{1s}. Three of the trials also reported the absolute change, with a summary estimate of 149 ml. One of the RCTs of bilaterally placed valves reported a decrease in FEV_{1s} of 70 ml (-2 %).

Conclusion: The unilateral insertion of EBVs in patients with severe emphysema probably improves forced expiratory volume compared with treatment with optimal medical therapy.

Moderate certainty of evidence (GRADE ⊕⊕⊕O).

The bilateral insertion of EBVs in patients with severe emphysema probably results in a reduction in forced expiratory volume compared with treatment with optimal medical therapy. Moderate certainty of evidence (GRADE ⊕⊕⊕O).

Complications *(Appendix 4.2, Appendix 5)*

Patients treated with EBVs had a statistically significant higher frequency of major complications (Serious Adverse Events, SAE) than patients who only received optimal medical therapy. This was observed both in patients treated bilaterally as well as unilaterally. The relative risks were 2.7 and 4.1, respectively. Pneumothorax was the most common SAE with a frequency up to 25 % of all patients treated with EBVs. Pneumonia and COPD exacerbations were also more common in patients with valves compared to patients on medical treatment alone.

Conclusion: The insertion of EBVs in patients with severe emphysema results in a higher frequency of SAE compared to treatment with optimal medical therapy.
High certainty of evidence (GRADE ⊕⊕⊕⊕).

Other findings
After the original presentations of the main results of the included RCTs, subgroup and post-hoc analyses have been published from some of the trials. The purpose of these latter analyses has been to look for predictors of successful outcome.

In the VENT-EU and US trials it was found that EBV patients with complete fissure and complete lobar occlusion had better clinical outcome than patients with incomplete fissure and/or incomplete lobar occlusion (Herth et al., 2012). The VENT trials also reported that patients with lower or upper lobe emphysema in whom complete lobar occlusion had been achieved benefitted equally well provided that there was a complete fissure (i.e. 90 % or more fissure integrity) with no or very low collateral ventilation (Eberhardt et al., 2015, Liberator et al.,2016). These findings are supported by a meta-analysis of five studies, one of which was the VENT trial (Iftikhar et al., 2014).

In the VENT trials it was also observed that patients with low regional perfusion in the target lobe prior to the insertion of EBVs had a better outcome than those with higher regional perfusion, and that this observation was independent of the degree of target lobe destruction (Argula et al., 2013). However, this could not be confirmed in a study from Germany (Thomsen et al., 2016).

10. Ethical issues

Based on ethical aspects there are good reasons to favour the introduction of lung volume reduction with EBVs. See Appendix 6.

11. Organisational aspects

Time frame for the putative introduction of endobronchial lung volume reduction
Endobronchial lung volume reduction is already performed at Sahlgrenska University Hospital for pulmonary disorders such as closure of bronchopleural fistulas, and treatment of native lung hyperinflation after single-lung transplantation. Thus, the technical skills needed to perform the procedure are already at hand.

Present use of the technology in other hospitals in the Region Västra Götaland
Apart from the Sahlgrenska University Hospital ELVR is available at the University hospitals in Lund, Umeå and Stockholm, but not in any other hospital in the Region Västra Götaland.

Consequences of the new health technology for personnel
If the number of patients in need of ELVR should increase, additional training of more personnel will be necessary.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland
The treatment procedure will take place in the Diagnostic Department of Pulmonary Medicine with the use of the presently available personnel. No extra resources for anesthesia or special surveillance will be needed. However, extra equipment to assess lobar integrity preoperatively will be needed, either by the Chartis method or enhanced CT-scan measurements.

Also, at least three days in hospital will be required for immediate post-op patient observation due to the high risk of SAE, mainly pneumothorax and pneumonia after the EBV treatment.
Presently, mainly pulmonologists and internists in hospital settings treat patients with severe COPD and lung emphysema. Patients will be followed as out-patients after the procedure. This may involve their primary care physicians.

12. Economic aspects

Present costs of currently used technologies

Conventional treatment of patients with severe COPD includes the costs for pharmacological agents, for follow-up check-ups at 4-6 months intervals at the out-patient clinic, and in selected cases also for oxygen treatment. Since the intensity of these treatments can vary considerably between patients, it is difficult to estimate the average cost for emphysema and COPD patients of stage 3 or 4.

All the costs for the ELVR intervention will be in addition to the cost of the conventional treatment of the patients.

Expected costs of lung volume reduction with endobronchial valves

One valve costs about 1 500 € (about 15 450 SEK, 1 € ≈ 10.30 SEK). Each treatment usually requires the insertion of 4-6 valves, i.e. 6 000 – 9 000 € (about 61 800 – 92 700 SEK) per patient. The current cost for hospital stay is on average 4 500 SEK per patient and day, and each patient will be hospitalized for at least 3 days. The additional cost for the bronchoscopic procedure with the insertion of the valves is 3 000 SEK. Thus, provided that the patient will be treated with an average of five EBVs, and there is no serious complication following the procedure the cost per patient will be 117 750 SEK (5 x 15 450 + 3 x 4 500 + 4 500).

Total change of cost

The additional total cost for 12 patients treated each year with insertion of EBVs will be a minimum of 918 000 SEK. However, it is important to realize that ELVR with valves will cause increased costs not only for the treatment per se, but also for complications that are likely to occur. The costs of the latter are difficult to estimate. However, considering the high risk for pneumothorax (25%) after EBV insertion, it can be estimated at least an additional cost for another three days in hospital for tube drainage treatment for these patients.

Possibility to adopt and use endobronchial valves within the present budget

There is no money in the present budget that will cover the additional costs of ELVR.

Available economic evaluations or cost advantages/disadvantages

One cost-effectiveness analysis, based on the outcome of the STELVIO randomised trial, was published recently (Hartman et al., 2018). The costs per gained QALY in the long-term (during 5 years using a Markov simulation) was estimated to be € 39 000 (corresponding to about 390 000 SEK).

13. Discussion

Summary of main results

In comparison to optimal medical therapy the unilateral placement of EBVs results in clinically significant improvements in lung function, quality of life, and physical capacity in patients with heterogeneous or homogeneous emphysema.

During 3 to 12 months follow-up no significant differences in mortality have been observed, but the frequency of serious complications and adverse events has been higher.

Overall completeness and applicability of evidence

In the previous HTA-report two major questions were raised. Based on the results of the trials that have been published after 2013 both these question have been answered. The use of EBVs seems to be equally effective in patients with heterogeneous and homogeneous emphysema. Furthermore, it is obvious that by a proper selection of patients, i.e. without collateral ventilation, valves should only be placed in one lung, whereas the insertion of valves bilaterally does not seem to have any beneficial effects.

The magnitudes of the summary estimates of the mean differences with regard to the outcome variables of lung function, quality of life and physical capacity were all beyond or precisely at the limits that previously have been defined as clinically important. These findings were robust for patients with unilaterally placed EBVs.

The most frequent and a relatively common complication following the insertion of valves is pneumothorax. However, this is not an unexpected complication and can be anticipated and successfully treated when it occurs. Since most patients with pneumothorax suffer this within 72 hours of the procedure it is recommended that patients should stay in hospital at least three days after the procedure (Gompelman et al., 2016). It has been reported that strict bed rest and pharmacological cough suppression during the first 48 hours may reduce the incidence of pneumothorax (Herzog et al., 2015). It is important to inform the patients of the symptoms of this particular complication at discharge from the hospital so that they will return immediately if they experience such problems.

Agreements and disagreements with other studies and reviews

The findings in the present HTA are in full agreement with previously published reviews. In addition to the seven RCTs included in the Cochrane systematic review, published in 2017 (van Agteren et al., 2017), two new RCTs with 287 additional patients, of which 190 were studied for 12 months, were included in our analyses. The addition of these two trials firmly confirms the conclusions of earlier reviews.

Implications for research

Ongoing studies will hopefully clarify whether there are differences in effectiveness and complication rates between the two available commercial valve types (see below). There is also an interest to develop non-invasive imaging methods that can replace the Chartis method for evaluation of lobar integrity. Also, a future field of study would be to develop methods that can predict which patients that have a high risk of developing SAE such as pneumothorax or pneumonia.

14. Future perspective

Scientific knowledge gaps

Studies with longer duration than one year are still lacking. Thus, long-term complications of EBVs are currently unknown.

Ongoing research

The search in ClinicalTrials identified 85 studies. Seven of them are of interest. They are presented below. The REACH study (NCT01989182) has been presented as an abstract, but detailed results have not yet been published.

NCT Number	Title	Design	Completed Yes/No	Estimated completion date
NCT01457833	Implantation of Endobronchial Valves versus Intrabronchial Valves in Patients with Severe Heterogeneous Emphysema	RCT	Unknown	May 2012
NCT03264768	Endoscopic Long Volume Reduction by Endobronchial Valves in Belgium (BEVA)	Non-randomised controlled study	No	December 2020
NCT02823223	Endobronchial Valve in Patients with Heterogeneous Emphysema	RCT	No	July 2018
NCT01580215	Long Term Follow up Investigation of Endobronchial Valves in Emphysema (LIVE)	Observational 5 years	Yes September 2016	
NCT03474471	A Trial on the Effects of Bronchoscopic Lung Volume Reduction in Severe Emphysema. (SOLVE)	RCT	No	March 2022
NCT01812447	Evaluation of the Spiration® Valve System for Emphysema to Improve Lung Function (EMPROVE)	RCT	No	May 2022
NCT01989182	The Spiration Valve System for the Treatment of Severe Emphysema (REACH)	RCT	Yes March 2017	

15. Participants in the project

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Declaration of interest
None of the authors has any conflict of interest

Project time

The updated HTA report was accomplished during the period of 2018-04-09 – 2108-09-26. Literature searches were made in 2012-11-27 (1st report), 2018-04-09 and 2018-07-02 (updated report).

Appendix 1: Search strategy, study selection and references

Question(s) at issue: Does lung volume reduction by endobronchial valves improve survival, quality of life and pulmonary function in patients with severe chronic obstructive pulmonary disease **(**COPD) and severe pulmonary emphysema?
Are there differences in outcome in patients treated with endobronchial valves bilaterally or unilaterally?
Are there differences in outcome in patients with homogeneous or heterogeneous emphysema?

PICO P= Patients, I= Intervention, C= Comparison, O=Outcome

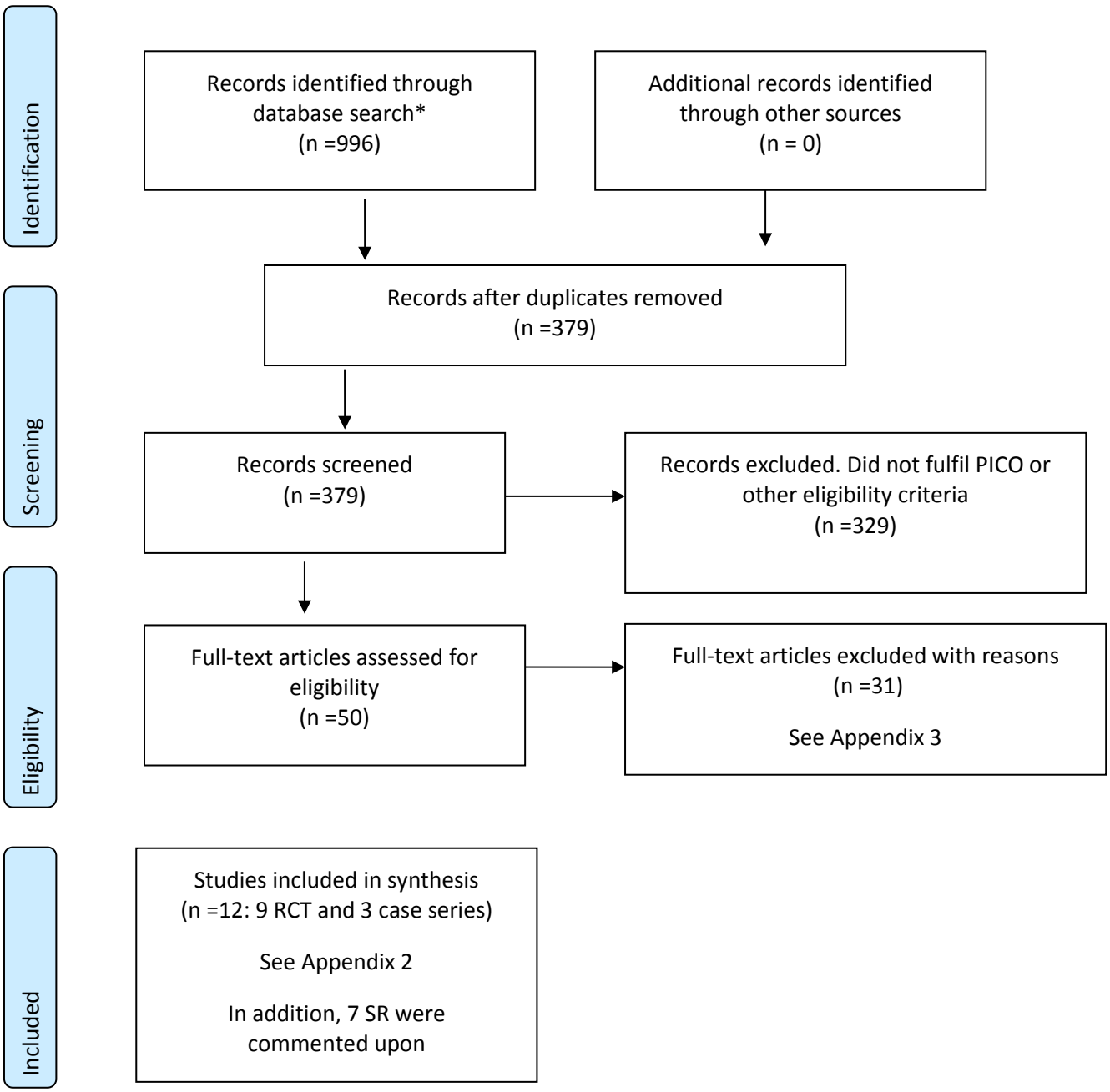
P	Patients with severe COPD (stage 3-4) and severe pulmonary emphysema
I	Lung volume reduction by endobronchial valves
C	Standard medical care such as medication use, oxygen or any type of rehabilitation
O	<u>Critical for decision making</u> Mortality Hospitalisation <u>Important for decision making</u> Dyspnoea Quality of Life Six minutes' walk distance (6MWD) <u>Not important for decision making</u> Pulmonary function (FEV1, FVC, RV) Complications

Study design:
- Randomised controlled trials
- Observational studies/cohort studies
- Case series ≥ 20
- Systematic reviews

Language: English, Swedish, Norwegian, Danish

Publication year:
2000-

Selection process – flow diagram



* This number includes the records identified in the previous search 2012-11-27. Throughout the rest of this flow chart, only numbers concerning the present report are accounted for, except for 3 RCT included in both old and new versions.

Search strategies

Database: PubMed
Date: 2018-04-09
No of results: 391
Search updated: 2018-07-02, 11 new results

Search	Query	Items found
#32	Search #12 AND #13 Filters: Publication date from 2000/01/01; Danish; English; German; Norwegian; Spanish; Swedish	391
#28	Search #12 AND #13 Filters: Publication date from 2000/01/01	415
#14	Search #12 AND #13 Sort by: Author	444
#13	Search emphysema[tiab] OR emphysemas[tiab] OR chronic obstructive pulmonary[tiab] OR COPD[tiab] OR Pulmonary Disease, Chronic Obstructive[MeSH] OR Pulmonary Emphysema[MeSH]	82856
#12	Search #10 OR #11	934
#11	Search (endobronchial[tiab] OR endoscopic[tiab] OR bronchoscopic[tiab]) AND (lung volume reduction[tiab])	341
#10	Search #8 AND #9	766
#9	Search valve[tiab] OR valves[tiab] OR Zephyr OR spiration	129797
#8	Search endobronchial[tiab] OR intrabronchial[tiab] OR bronchial[tiab] OR bronchoscopy[tiab] OR bronchoscopic[tiab] OR bronchoscopies[tiab] OR transbronchoscopic[tiab] OR bronchoscopy[MeSH]	107861

Database: Embase 1974 to 2018 June 29 (OvidSP)
Date: 2018-07-02
No of results: 455

#	Searches	Results
1	(endobronchial or intrabronchial or bronchial or bronchoscopy or bronchoscopic or bronchoscopies or transbronchoscopic).ab,kw,ti.	137176
2	exp bronchoscopy/	52005
3	1 or 2	157303
4	(valve or valves or Zephyr or spiration).ab,dv,kw,ti.	179115
5	3 and 4	1509
6	(endobronchial or endoscopic or bronchoscopic).ab,kw,ti.	226073
7	(lung adj volume adj reduction).ab,kw,ti.	2172
8	6 and 7	712
9	5 or 8	1833
10	(emphysema or emphysemas or chronic obstructive pulmonary or COPD).ab,kw,ti.	116388
11	exp chronic obstructive lung disease/	110370
12	exp lung emphysema/	21697
13	10 or 11 or 12	164961
14	9 and 13	940
15	limit 14 to ((danish or english or german or norwegian or spanish or swedish) and yr="2000 -Current")	861
16	**limit 15 to (article or conference paper or "review")**	**455**

Database: The Cochrane Library
Date: 2018-07-02
No of results: 139
Cochrane reviews 1
Other reviews -
Trials 132
Technology assessments 5
Economic evaluations 1

ID	Search	Hits
#1	endobronchial or intrabronchial or bronchial or bronchoscopy or bronchoscopic or bronchoscopies or transbronchoscopic:ti,ab,kw (Word variations have been searched)	9352
#2	MeSH descriptor: [Bronchoscopy] explode all trees	691
#3	#1 or #2	9352
#4	valve or valves or Zephyr or spiration:ti,ab,kw (Word variations have been searched)	6617
#5	#3 and #4	153
#6	endobronchial or endoscopic or bronchoscopic:ti,ab,kw (Word variations have been searched)	14257
#7	lung next volume next reduction:ti,ab,kw (Word variations have been searched)	238
#8	#6 and #7	79
#9	#5 or #8	191
#10	emphysema or emphysemas or chronic obstructive pulmonary or COPD:ti,ab,kw (Word variations have been searched)	16258
#11	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees	5067
#12	MeSH descriptor: [Pulmonary Emphysema] explode all trees	0
#13	#10 or #11 or #12	16338
#14	**#9 and #13**	**139**

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Appendix 2. Characteristics of included studies.

Abbreviations: RCT=Randomised Controlled Trial, SB=Single-blind, DB=Double-blind, FEV=Forced Expiratory Volume, 6MWD=6 Minute Walk Distance, SGRO=St George's Respiratory Questionnaire,, mMRC score=modified MRC dyspnea score.

Author, Study acronym, Year, Country	Study Design	Length of Follow-Up	Study Groups (n); Endobronchial valves (I) vs Optimal medical therapy (C)	With-drawals - Dropouts (n)	Intervention Unilateral/ Bilateral	Control Sham Yes/No	Mean Age (years)	Men (%)	Outcome variables	Comments
Scurbia, ***VENT-US***, 2010, USA	RCT, open	6 months	I = 220 C = 101	67	Unilateral	No	65	57	FEV 1s, Cycle ergometer, 6MWD, QoL (SGRO), mMRC score	Zephyr valve. Heterogenous emphysema.
Herth, ***VENT-EU***, 2012, Europe	RCT, open	6 months	I = 111 C = 60	22	Unilateral	No	60	72	FEV 1s, Cycle ergometer, 6MWD, QoL (SGRQ)	Zephyr valve. Homo-and heterogenous emphysema.
Ninane, 2012, Austria, Belgium, Italy, Spain,United Kingdom, USA	RCT, SB	3 months	I = 37 C = 36	3	Bilateral	Yes	62	59	FEV 1s, Lung volumes, 6MWD, QoL (SGRQ), mMRC score	Spiration valve. "Advanced" emphysema.
Wood, ***IBV Valve trial***, 2014, USA, Canada, United Kingdom	RCT, DB	6 months	I = 142 C = 135	17	Bilateral	Yes	65	No data	FEV 1s, Lung volumes, 6MWD, QoL (SGRQ), mMRC score	Spiration valve. "Severe" emphysema.
Davey, ***BeLieVeR-HiFi***, 2015, United Kingdom	RCT, DB	3 months	I = 25 C = 25	3	Unilateral	Yes	63	62	FEV 1s, Cycle ergometer, Lung volumes, 6MWD, QoL (SGRQ), mMRC score	Zephyr valve. Heterogenous emphysema.

Appendix 2. Characteristics of included studies.

Abbreviations: RCT=Randomised Controlled Trial, SB=Single-blind, DB=Double-blind, FEV=Forced Expiratory Volume, 6MWD=6 Minute Walk Distance, SGRO=St George's Respiratory Questionnaire,, mMRC score=modified MRC dyspnea score.

Author, Study acronym, Year, Country	**Study Design**	**Length of Follow-Up**	**Study Groups (n); Endobronchial valves (I) vs Optimal medical therapy (C)**	**With-drawals - Dropouts (n)**	**Intervention Unilateral/ Bilateral**	**Control Sham Yes/No**	**Mean Age (years)**	**Men (%)**	**Outcome variables**	**Comments**
Kloster, ***STELVIO***, 2015, Netherlands	RCT, open	6 months	I = 34 C = 34	2	Unilateral	No	59	32	FEV 1s, Lung volumes, 6MWD, QoL (SGRQ), mMRC score	Zephyr valve. "Severe" emphysema.
Valipour, ***IMPACT***, 2016, Austria, Germany, Netherlands	RCT, open	3 months	I = 43 C = 50	14	Unilateral	No	63	39	FEV 1s, Lung volumes, 6MWD, QoL (SGRQ) mMRC score	Zephyr valve. Homogenous emphysema.
Kemp, ***TRANSFORM***, 2017, 6 European countries	RCT, open	3 months	I = 65 C = 32	No data	Unilateral	No	64	60	FEV 1s, Lung volumes, 6MWD, QoL (SGRQ) mMRC score	Zephyr valve. Heterogenous emphysema.
Criner, ***LIBERATE***, 2018, USA, United Kingdom, Brazil, Netherlands	RCT, open	12 months	I = 128 C = 62	15	Unilateral	No	64	47	FEV 1s, Lung volumes, 6MWD, QoL (SGRQ) mMRC score	Zephyr valve. Heterogenous emphysema.

Appendix 2. Characteristics of included studies.

Abbreviations: RCT=Randomised Controlled Trial, SB=Single-blind, DB=Double-blind, FEV=Forced Expiratory Volume, 6MWD=6 Minute Walk Distance, SGRO=St George's Respiratory Questionnaire,, mMRC score=modified MRC dyspnea score.

Author, Study acronym, Year, Country	Study Design	Length of Follow-Up	Study Groups (n); Endobronchial valves (I) vs Optimal medical therapy (C)	With-drawals - Dropouts (n)	Intervention Unilateral/ Bilateral	Control Sham Yes/No	Mean Age (years)	Men (%)	Outcome variables	Comments
Darwiche, 2016, Germany	Retro-spec-tive case series	90 days	20	-	Unilateral	-	59	55	Complications	Zephyr valve. Heterogenous emphysema.
Park, 2015, South Korea	Retro-spec-tive case series	6 months	43	-	Unilateral	-	68	93	Complications	Zephyr valve. Heterogenous emphysema.
Skowasch, 2016, Gerrmany	Pro-spec-tive case series	6 months	343	-	Not reported	-	65	56	Complications	Zephyr valve. Unspecified emphysema

Project: Endobronchial lung volume reduction in patients with severe chronic obstructive pulmonary disease
Appendix 3. Excluded articles

Author, year	Reason for exclusion
Argula, 2013	Outcome variable not included in PICO.
Bolitschek, 2016	Publication in the German language
Coxson, 2012	Conference abstract (IBV Trial)
Eberhardt, 2015	Outcome variable not included in PICO.
Eberhardt, 2017	Publication in the German language
Elstad, 2012	Conference abstract (IBV Trial)
Fiorelli, 2014	No intervention.
Fiorelli, 2016	Intervention differed from PICO (sequential bilateral approach)
Fiorelli, 2017	Intervention differed from PICO in a subset of patients (sequential bilateral approach)
Gompelman, 2016:1	Only patients with pneumothorax due to valve insertion
Gompelman, 2016:2	No control group. No data on complications
Gompelman, 2016:3	No control group. Subset of all patients who had ELVR treatment
Hartman, 2015	Conference abstract
Hartman, 2016	Outcome variable not included in PICO.
Hartman, 2018	Outcome variable not included in PICO
Herth, 2016	Publication in German of the same data as presented in the included publication by Kloster et al. 2015
Herzog, 2015	Interventions following valve insertions were not specified in PICO
Klooster, 2017	Follow-up after patients in the control group have been crossed-over to EBV treatment.
Klooster 2015	Conference abstract (STELVIO study)
Klooster 2017	Pooled data of two RCTs which are already included in the present assessement
Li, 2016	Conference abstract (REACH study)
Liberator, 2016	Outcome variable not included in PICO
Pizarro, 2015:1	Outcome variable not included in PICO
Pizarro, 2015:2	Outcome variable not included in PICO
Slebos, 2017	Conference abstract (IMPACT study)
Thomsen, 2016	Analysis of predictors of outcome.
Trudzinski, 2016	Incomplete reporting of serious adverse events/major complications
Valipour, 2014	Outcome variable not included in PICO
Welling, 2015	Outcome variable not included in PICO
Welling, 2018	Outcome variable not included in PICO
Zoumot, 2015	All results already published by Davey et al. 2015.

Appendix 4:1 – Outcome variables: Mortality, modified MRC dyspnea score (mMRC score), St George's Respiratory Questionnaire (SGRQ), and Six Minute Walk Distance (6MWD).

Author, Study acronym, Year		**Mortality**		**mMRC (score 0-4)**		**SGRQ (score 0-100)**		**6MWD (meters)**	
		Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy
Scurbia, ***VENT-US***, 2010	Baseline	2/214	0/87	No data	No data	No data	No data	334 (sd 87.4)	351 (sd 83.2)
	Δ 6 months			-0.1 (sd 1.1)	+0.2 (sd 0.9) p=0.04	-2.8 (sd 14)	+0.6 (sd 12) p=0.04	+9 (sd 74.2)	-11 (sd 96.7) p=0.04
Herth, ***VENT-EU***, 2012	Baseline	6/111	4/60	No data	No data	59 (sd 13)	56 (sd 18)	341 (sd 108)	360 (sd 117)
	Δ 6 months			No data	No data	-5 (sd 14)	+0.3 (sd 13) p<0.05	+15 (sd 91)	+10 (sd 78) NS
Ninane, 2012	Baseline	1/37	0/36	2.8 (sd 0.7)	2.8 (sd 0.9)	61 (sd 11)	62 (sd 6)	337 (sd 106)	346 (sd 123)
	Δ 3 months			-0.3	-0.1 NS	-4 (sd 16)	-4 (sd 11) NS	+7	+7 NS
Wood, ***IBV Valve trial***, 2014	Baseline	6/142	1/135	2.7 (sd 0.7)	2.7 (sd 0.7)	55 (sd 15)	57 (sd 15)	314 (sd 89)	309 (sd 82)
	Δ 6 months			-0.2 (sd 1.0)	-0.1 (sd 1) NS	+2 (sd 16)	-1 (sd 11) p<0.05	-24 (sd 70)	-3 (sd 77) p<0.05
Davey, ***BeLieVeR-HiFi***, 2015	Baseline	4/25	0/25	4 (sd 1)	4 (sd 1)	69 (sd 13)	68 (sd 13)	342 (sd 94)	334 (sd 81)
	Δ 3 months			±0 (sd 1.0)	±0 (sd 1) NS	-4 (sd 30)	--4 (sd 13) NS	+25 (sd 73)	+3 (sd 43) p=0.01

Appendix 4:1 – Outcome variables: Mortality, modified MRC dyspnea score (mMRC score), St George's Respiratory Questionnaire (SGRQ), and Six Minute Walk Distance (6MWD).

Author, Study acronym, Year		**Mortality**		**mMRC (score 0-4)**		**SGRQ (score 0-100)**		**6MWD (meters)**	
		Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy
Kloster, ***STELVIO*** 2015, Netherl.	Baseline	1/34	0/34	No data	No data	59 (sd 14)	59 (sd 12)	372 (sd 90)	377 (sd 84)
	Δ 6 months			No data	No data NS	-17 (sd 22)	-3 (sd 9) p<0.001	+60 (sd 74)	-14 (sd 33) p<0.001
Valipour ***IMPACT***, 2016, Austria, Germany, Netherl.	Baseline	0/43	1/50	2.7 (sd 0.8)	2.4 (sd 1.0)	63 (sd 14)	59 (sd 16)	308 (sd 91)	328 (sd 93)
	Δ 3 months			-0.4 (sd 1.0)	+0.2 (sd 1) p<0.01	-9 (sd 11)	+1 (sd 9) p<0.001	+23 (sd 67)	-17 (sd 53) p=0.002
Kemp, ***TRANS-FORM***, 2017, 6 Eur. countries	Baseline	1/65	0/32	3.0 (sd 0.8)	2.9 (sd 0.8)	64 (sd 14)	58 (sd 13)	282 (sd 94)	320 (sd 92)
	Δ 3 months			-0.6 (sd 1.0)	±0.0 (sd 0.9) p=0.01	-7 (sd 15)	-1 (sd 10) p=0.03	+23 (sd 67)	-17 (sd 53) p=0.002
Criner, ***LIBE-RATE***, 2018, USA, UK Brazil, Netherl.	Baseline	5/128	2/62	2.4 (sd 1.0)	2.2 (sd 0.8)	55 (sd 14)	53 (sd 14)	311 (sd 81)	302 (sd 79)
	Δ 12 months			-0.5 (sd 1.2)	+0.3 (sd 1.0) p<0.001	-8 (sd 16)	-0.5 (sd 16) p=0.004	+13 (sd 81)	-26 (sd 82) p=0.002

Footnote:

* total number of events, no data on whether the same patient could have more than one serious adverse event

Appendix 4:2 – Outcome variables: Forced Expiratory Volume during 1 second (FEV_{1s}), Residual Volume (RV) and serious adverse events (SAE).

Author, Study acronym, Year		**FEV_{1s} (%)**		**FEV_{1s} (ml)**		**RV (L)**		**SAE (Number of patients)**	
		Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy
Scurbia, ***VENT-US***, 2010	Baseline	30 (sd 8)	30 (sd 8)	870 (sd 260)	840 (sd 250)	4.79 (sd 1.15)	4.63 (sd 1.20)		
	Δ 6 months	+4.3 (sd 21.9)	-2.5 (sd 14.9) p=0.005	+34.5 (sd 179.7)	-25.4 (sd 117.2) p=0.002	No data	No data	9/214	0/87
Herth, ***VENT-EU***, 2012	Baseline	29 (sd 8)	30 (sd 8)	910 (sd 290)	940 (sd 300)	5.02 (sd 1.16)	4.98 (sd 1.07)		
	Δ 6 months	+7 (sd 20)	0.5 (sd 19) p=0.07	No data	No data	No data	No data	No data	No data
Ninane, 2012	Baseline	35 (sd 10)	32 (sd 7)	990 (sd 350)	880 (sd 290)	4.65 (sd 1.30)	5.26 (sd 1.18)		
	Δ 3 months	No data	No data	-90	-10 NS	+0.21	-0.21 p=0.01	7/37	4/36
Wood, ***IBV Valve trial***, 2014	Baseline	29.8 (sd 7.5)	29.7 (sd 7.9)	870 (sd 270)	850 (sd 290)	4.64 (sd 1.07)	4.64 (sd 1.32)		
	Δ 6 months	-2.1 (sd 5.4)	+0.04 (sd 5.7) p<0.05	-70 (sd 170)	±0 (sd 160) p<0.05	+0.31 (sd 1.00)	-0.07 (sd 1.29) p<0.05	20/142	5/135
Davey, ***BeLieVeR-HiFi***, 2015	Baseline	31.6 (sd 10.2)	31.8 (sd 10.5)	930 (sd 350)	850 (sd 300)	No data	No data		
	Δ 3 months	+8.8 (sd 42.8)	+2.9 (sd 10.9) p=0.03	+60 (sd 459)	+30 (sd 77) p=0.03	-0.26 (sd 1.16)	-0.08 (sd 0.40) NS	10/25	1/25

Appendix 4:2 – Outcome variables: Forced Expiratory Volume during 1 second (FEV_{1s}), Residual Volume (RV) and serious adverse events (SAE).

Author, Study acronym, Year		**FEV_{1s} (%)**		**FEV_{1s} (ml)**		**RV (L)**		**SAE (Number of patients)**	
		Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy
Kloster, ***STELVIO*** 2015, Netherl.	Baseline	29 (sd 7)	29 (sd 8)	860 (sd 300)	790 (sd 270)	4.64 (sd 1.31)	4.43 (sd 0.72)		
	Δ 6 months	+21 (sd 29)	+3 (sd 10) p=0.001	+161 (sd 241)	+21 (sd 91) p=0.002	-0.87 (sd 0.87)	-0.03 (sd 0.03) p<0.001	23/34*	5/34*
Valipour ***IMPACT***, 2016, Austria, Germany, Netherl.	Baseline	No data	No data	No data	No data	No data	No data		
	Δ 3 months	+14 (sd 28)	-3 (sd 13) p<0.001	+100 (sd 180)	-20 (sd 100) p<0.001	-0.42 (sd 0.90)	+0.05 (sd 0.87) p=0.01	26/44	8/50
Kemp, ***TRANS-FORM***, 2017, 6 Eur. countries	Baseline	30 (sd 9)	32 (sd 8)	780 (sd 240)	940 (sd 310)	No data	No data		
	Δ 3 months	+21 (sd 30)	-9 (sd 13) p<0.001	+140 (sd 240)	-90 (sd 140) p<0.001	-0.66 (sd 1.04)	+0.01 (sd 0.79) p=0.002	31/65	3/32
Criner, ***LIBE-RATE***, 2018, USA, UK Brazil, Netherl.	Baseline	28 (sd 7)	26 (sd 6)	760 (sd 250)	750 (sd 220)	4.71 (sd 1.05)	4.76 (sd 0.90)		
	Δ 12 months	+17 (sd 28)	-1 (sd 27) p<0.001	+104 (sd 200)	-3 (sd 194) p<0.001	-0.49 (sd 0.83)	+0.03 (sd 0.66) p<0.001	45/128	3/62
Darwiche, 2016, Germany	90 days							10/20*	

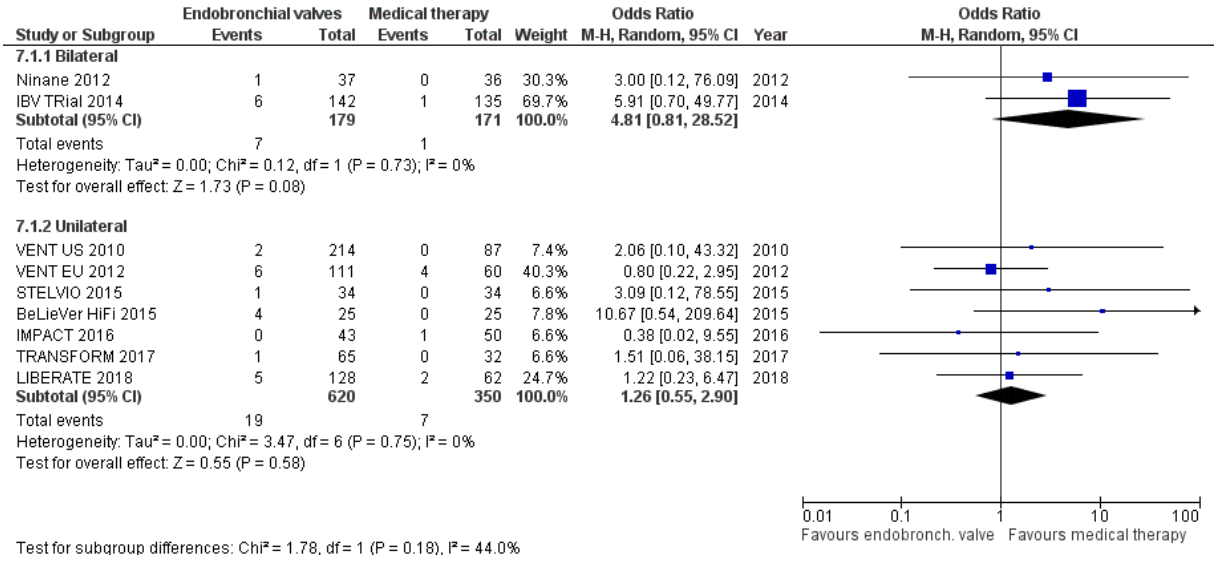
Appendix 4:2 – Outcome variables: Forced Expiratory Volume during 1 second (FEV_{1s}), Residual Volume (RV) and serious adverse events (SAE).

Author, Study acronym, Year		**FEV_{1s} (%)**		**FEV_{1s} (ml)**		**RV (L)**		**SAE (Number of patients)**	
		Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy	Endobronch. valves	Medical therapy
Park, 2015, South Korea	6 months							13/43	
Skowasch, 2016, Gerrmany	6 months							43/343	

Footnote:

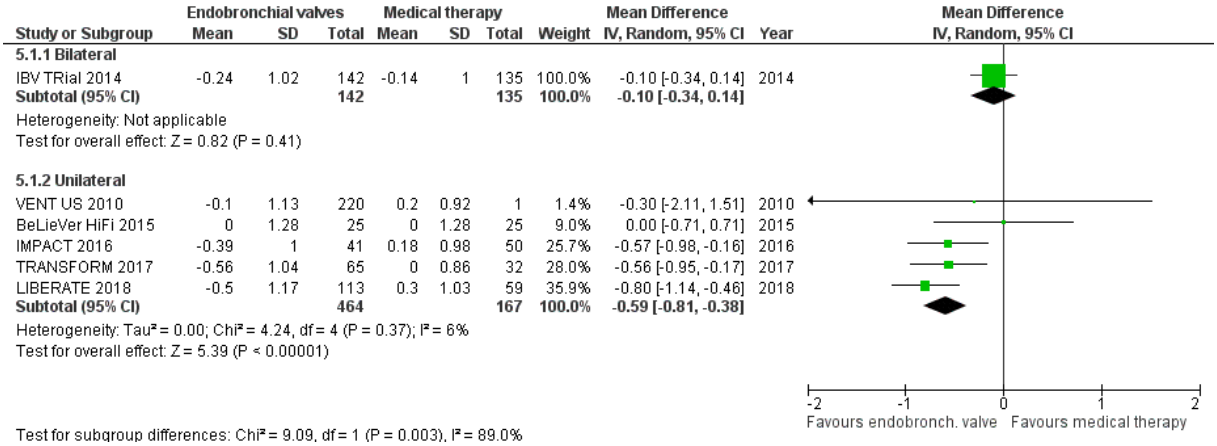
* total number of events, no data on whether the same patient could have more than one serious adverse event

Endobronchial valves versus optimal medical therapy. Mortality.



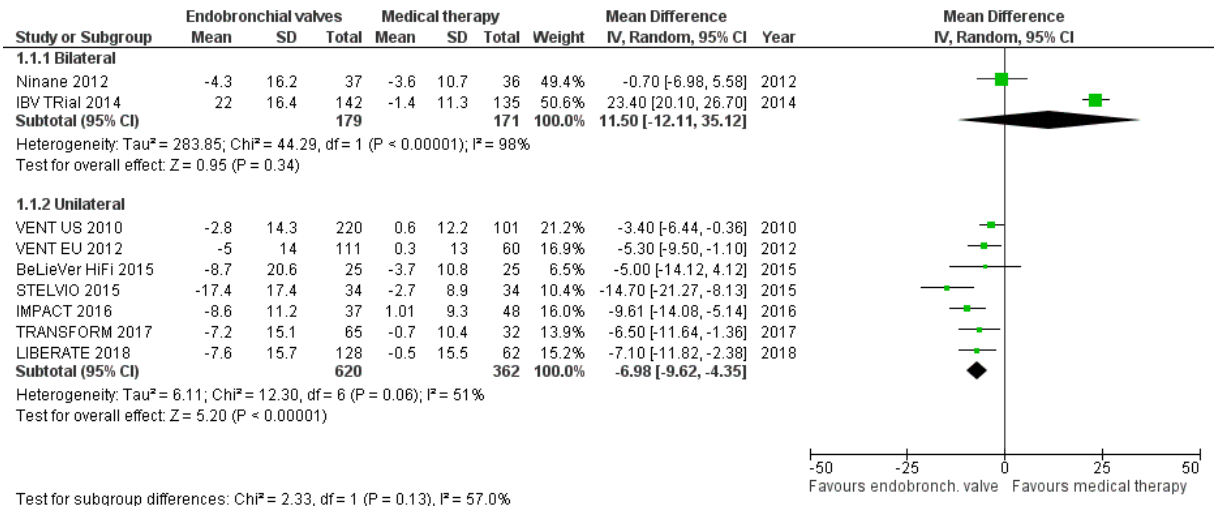
Test for subgroup differences: Chi² = 1.78, df = 1 (P = 0.18), I² = 44.0%

Endobronchial valves versus optimal medical therapy. Outcome change in mMRC score.



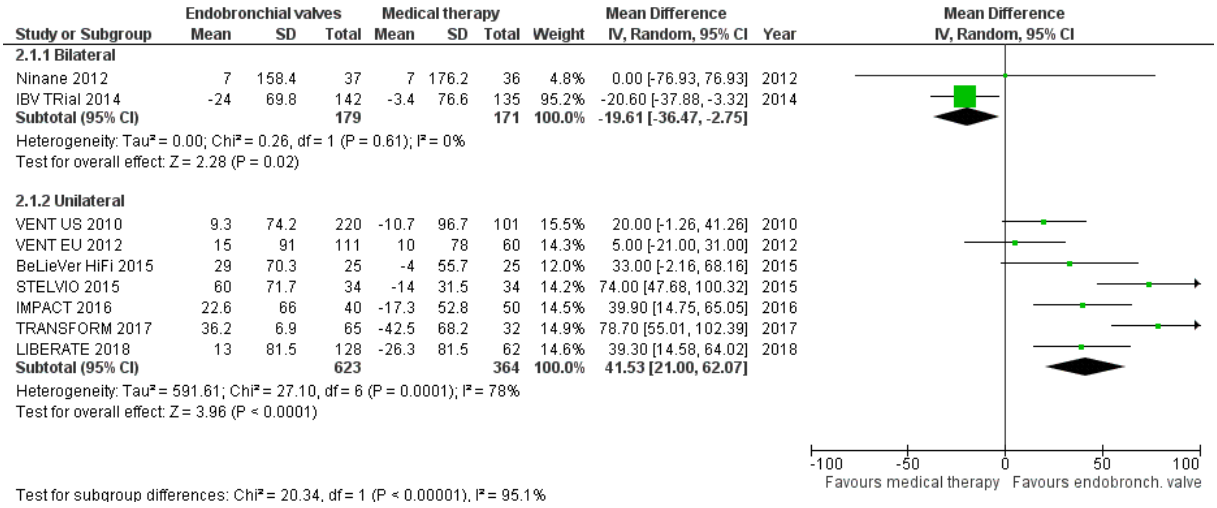
Test for subgroup differences: Chi² = 9.09, df = 1 (P = 0.003), I² = 89.0%

Endobronchial valves versus optimal medical therapy. Outcome change in SGRQ.

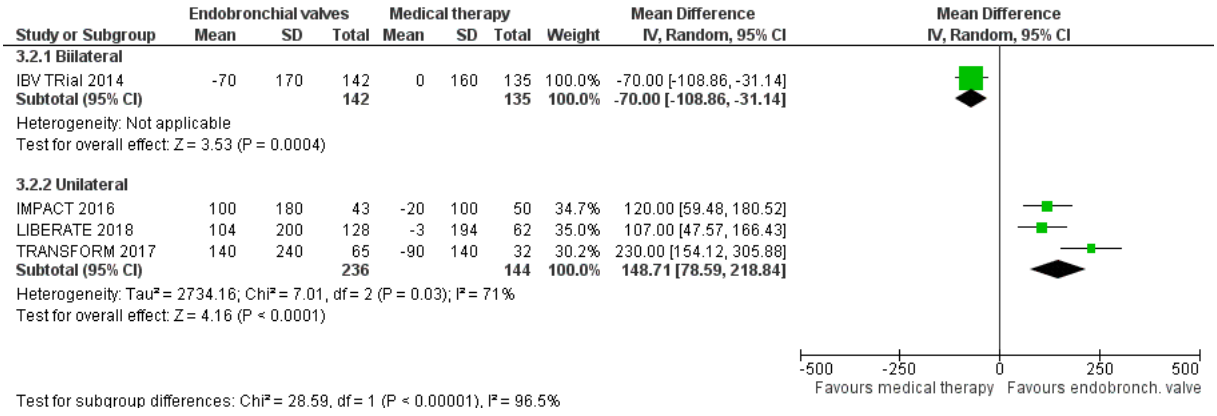


Test for subgroup differences: Chi² = 2.33, df = 1 (P = 0.13), I² = 57.0%

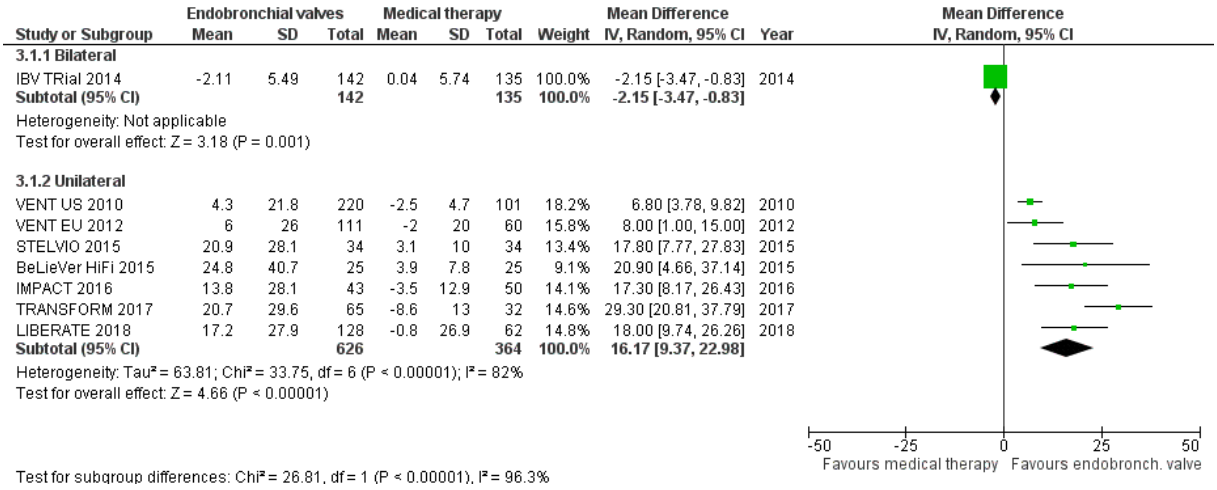
Endobronchial valves versus optimal medical therapy. Outcome change in 6MWD m.



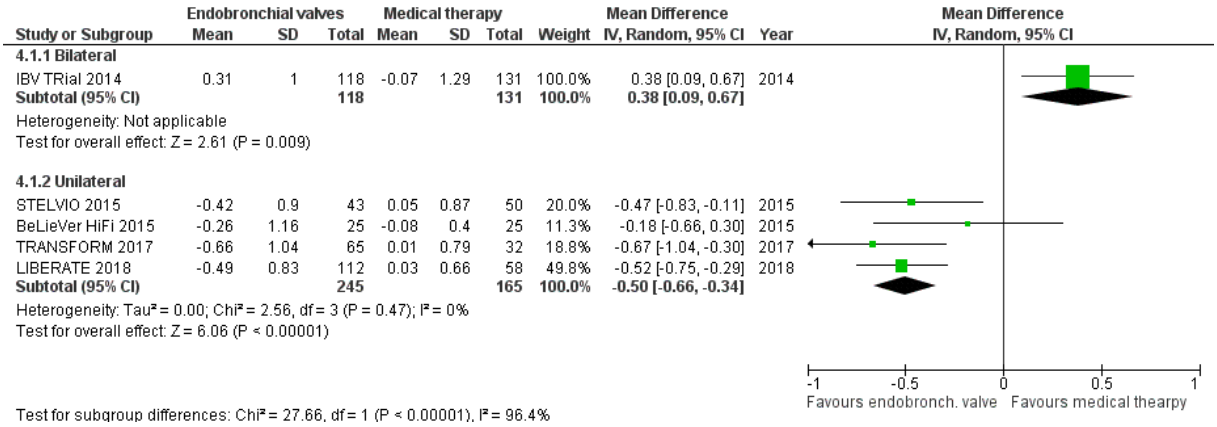
Endobronchial valves versus optimal medical therapy. Outcome change in FEV_{1s} ml.



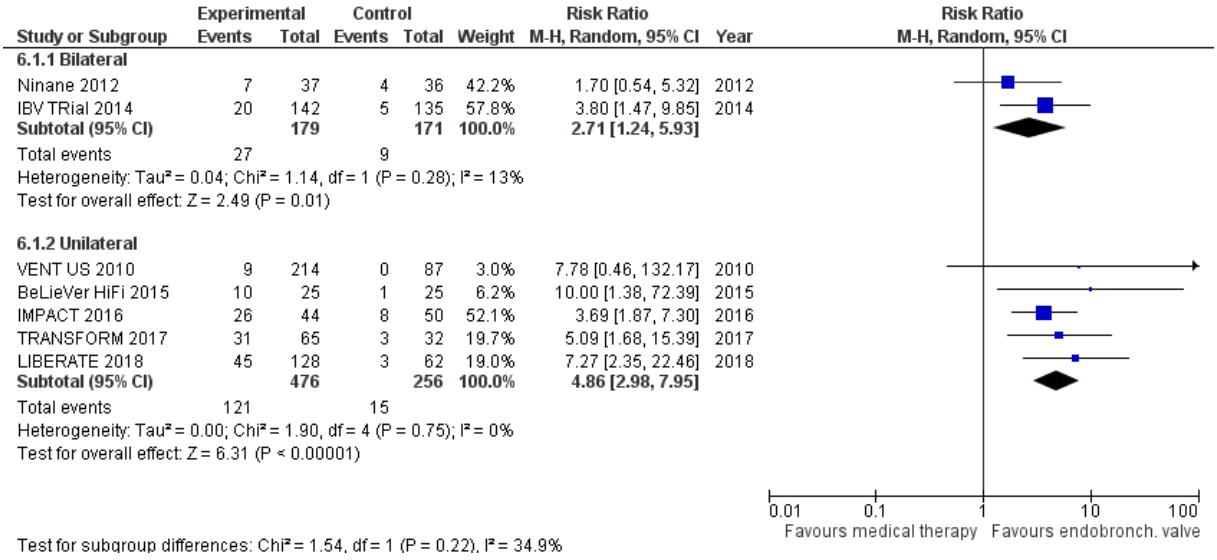
Endobronchial valves versus optimal medical therapy. Outcome change in FEV_{1s} %.



Endobronchial valves versus optimal medical therapy. Outcome change in RV L.



Endobronchial valves versus optimal medical therapy. Outcome Serious adverse events.



Appendix 6. Ethical analysis of endobronchial lung volume reduction withvalves in patients with severe chronic obstructive pulmonary disease.

Question	Answer/ comment
1. From the patient's perspective, how does ELVR affect the patient's quality of life and life expectancy?	The quality of life will improve. The potential effects on life expectancy remain to be documented.
2. How severe is the patient's need that the ELVR must meet?	Chronic obstructive lung disease of stage three and four, and emphysema are severe medical conditions. The patient's need for improvement is great.
3. Does ELVR have any influence on how others view the patient (concerning humanity and human dignity), or on how the patient views himself or herself (concerning humanity and human dignity)?	No.
4. Can ELVR affect the patient's ability and possibility to be independent?	Yes. It will improve the patient's total health situation and physical capacities. This will have a positive impact of the patient's independence.
5. If implemented, does ELVR require any special steps to not compromise the patient's autonomy?	No.
6. How does ELVR affect the patient's physical, moral and personal integrity?	Bronchial valves affect the patients physical integrity, and may negatively do so due to a rather high risk of complications. The valves do not affect the moral or personal integrity of the patient.
7. Is ELVR cost-effective?	?????
8. Does ELVR affect resources?	Yes, to a great extent.
9. Is ELVR in conflict with professional values?	No.
10. Does ELVR change the role of the professional in relation to the patient?	No.
11. Does ELVR affect, or does it put any new demands on, a third party?	No.
12. Is there any legislation of relevance with regard to ELVR?	Not at the present time.
13. Is there any risk of conflict between the procedure of ELVR and values of the society, or values of different groups?	It could lead to a conflict with both professionals that advocate surgical interventions for COPD, and with professionals that propose a conservative treatment.

14. Is there a risk that an introduction of ELVR will cause a conflict with particular interests?	No.
15. Can an introduction of ELVR influence the trust of the health care system?	If ELVR is introduced based on present data, and it is later documented in long-term follow-up studies to be a harmful treatment, the trust of the health care system would be negatively affected.
CONCLUSIONS	Based on ethical aspects there are good reasons to favour the introduction of ELVR.