

Endobronchial lung volume reduction in patients with severe chronic obstructive pulmonary disease

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Endobronchial lung volume reduction in patients with severe chronic obstructive pulmonary disease [Endobronkiell lungvolymsreduktion för patienter med svår kroniskt obstruktiv lungsjukdom]

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Statement from HTA-centrum 2013-03-27

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Method and patient group

Chronic obstructive pulmonary disease (COPD) is common in the adult Swedish population. It is caused by a progressive destruction of the elastic tissue in the small airways that leads to an increase in alveolar size, a narrowing of the small airways and a diminished pulmonary elasticity. As a result, it will become increasingly difficult for the patient to empty the lungs of air.

Endobronchial Lung Volume Reduction (ELVR) uses one-way valves that prevent inhaled air to reach hyperinflated lung segments, but allow trapped air to be exhaled. The valves are placed in the airways of the most destroyed and inflated lung segments. The goal is to cause the lung parenchyma distal to the valve to collapse, and, thereby, to lower 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.

Question 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) or severe pulmonary emphysema?

PICO

P = Patients with severe chronic obstructive pulmonary disease (COPD) or severe pulmonary emphysema (stage 3/4)

I = Lung volume reduction by endobronchial valves

C = Standard medical care such as medication use, oxygen or any type of rehabilitation

O = Mortality, hospitalisation, dyspnea scale, quality of life, six minutes walk test, pulmonary function (FEV1, FVC, RV), complications

Studied risks and benefits for patients of the new health technology

The systematic literature search identified three randomized, controlled trials of the effects of ELVR in patients with severe COPD and advanced emphysema. There was no difference in mortality or in dyspnea between ELVR-treated patients and patients on standard care (Low quality of evidence; GRADE ⊕⊕OO). Furthermore, there were no clinically relevant effects on quality of life, six minutes walk test, or pulmonary function measured as FEV1 (Low quality of evidence; GRADE ⊕⊕OO). The procedure was associated with rather frequent complications such as pneumothorax, pneumonia, COPD exacerbations and valve migration.

Ethical aspects

There are no ethical reasons to favour the introduction of ELVR in the clinical routine at the present time.

Economical aspects

Each endobronchial valve costs about 1 500 € (about 12 000 SEK). Each treatment usually requires the insertion of 4-6 valves, i.e. 6 000 – 9 000 € (about 48 000 – 72 000 SEK) per patient. Additional costs will be added for pre- and postoperative investigations with chest x-rays, CT-scan, and lung function tests.

Concluding remarks

Endobronchial lung volume reduction in patients with advanced chronic obstructive pulmonary disease by placement of one-way valves in affected lung segments have been evaluated in randomized, controlled trials. There were no beneficial effects on critical and important outcome variables such as mortality or dyspnea, and the effects on other outcome variables were of small and of no clinical relevance.

Which health technology or method will be assessed?

1a Who will lead the project?

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1b Who posed the question?

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1e Are there any conflicts of interest for the proposer or any of the participants in the work group?

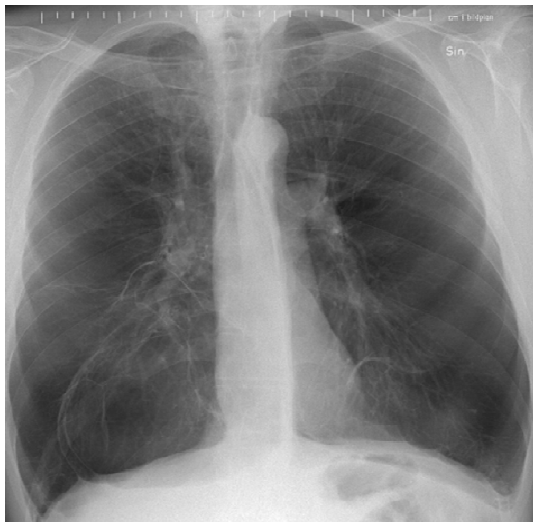
No.

Disease/disorder of Interest and Present Treatment

2a **Chronic obstructive pulmonary disease and emphysema and the degree of severity**

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. COPD 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 heterogenous 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 the lungs of air. The lungs increase in size, become hyperinflated, press the diaphragm downwards and increase the thorax volume. This is illustrated in the chest x-rays below:



Chronic obstructive pulmonary disease is categorized into four different stages (Läkemedelskommittén i Västra Götalandsregionen. Medicinska riktlinjer. KOL – diagnostik och behandling. http://epi.vgregion.se/upload/L%C3%A4kemedel/MR/MR_KOL_tryck.pdf) according to its severity. Presently, the intervention to reduce lung volume with endobronchial valves (Endobronchial Lung Volume Reduction, ELVR) (see below 2c) has been proposed only for patients with the most severe disease who belong to category three and four.

Advanced emphysema is a serious condition with an increased

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

2b Prevalence and incidence of emphysema and chronic obstructive pulmonary disease

The prevalence of COPD and emphysema in the adult population is 5-10 %. It is the cause of considerable morbidity and mortality http://www.slmf.se/kol_nat_progr. 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, (http://www.slmf.se/kol_nat_progr).

According to The Swedish Heart and Lung Association, the number of COPD patients in stage three and four varies between 17 -35 % of all COPD patients. In Sweden this corresponds to 1- 3.5 % of the adult population, i.e. a total of 120 000-420 000 patients.

2c Present treatment of advanced emphysema in the outpatient and the inpatient setting

Standard medical care with pharmacological treatment, oxygen therapy or other type of rehabilitation is used for the vast majority of COPD patients in stage three and four. They are usually treated by general practitioners as outpatients. With increasing severity of COPD they are referred to a pulmonary specialist for further evaluation. The therapy is mainly palliative.

In COPD patients who do not suffer from other severe co-morbid conditions it is sometimes possible to consider open lung volume reduction surgery (LVRS) (A. Fishman NEJM 2003, MA Edwards 2009). The most emphysematous lung tissue areas are then surgically removed to make more space for the remaining healthier lung tissue, and thereby, to improve pulmonary function (GR Washko 2008). However, this surgical procedure is associated with a high mortality, varying between 5 - 10 % (A Fishman 2003, DE Wood 2003). Furthermore, postoperative complications occur in up to 60 % of all patients (MM DeCamp 2008). The largest randomised, controlled multicenter trial of LVRS included 1218 surgically treated patients (MA Edwards 2009). It reported a mortality rate of 7.9 % compared to 1.3 % in the control group (standard medical treatment). It is obvious that less invasive methods of lung volume reduction in patients with severe emphysema are needed, provided that such a method is of long-term benefit.

Lung transplantation for advanced COPD is currently available at two national centers in Sweden. The number of patients that fulfill the current criteria for a lung 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, lung transplantation has only been reported to improve quality of life but not to increase survival (Stavem K et al 2006 JHLT).

2d Number of patients per year who undergo current treatment regimens

The Swedish Heart and Lung Association estimates the current number of COPD patients in stage three or four in Sweden to be 120 000-420 000.

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 that may be candidates for ELVR in Region Västra Götaland will initially be limited to 10-12 per year. It is likely that 1/3 of these patients will be referrals from the region. It is also possible that patients from other regions can be accepted.

2e The normal pathway of a patient through the health care system

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 transplantation or LVRS.

2f Actual wait time in days for medical assessment /treatment

The patient will normally be evaluated at a first clinic visit within three months after referral.

3a Description of endobronchial valves for advanced emphysema

Endobronchial Lung Volume Reduction was introduced in 2002. It uses a conventional flexible bronchoscope to apply one-way valves into segmental airways of the most destroyed and inflated lung areas. Inhaled air is prevented to reach these parts of hyperinflated lung segments, but trapped air can be exhaled during expiration. Secreted 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 to collapse, and, thereby to lower the hyperinflation and the intrathoracic pressure.

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

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

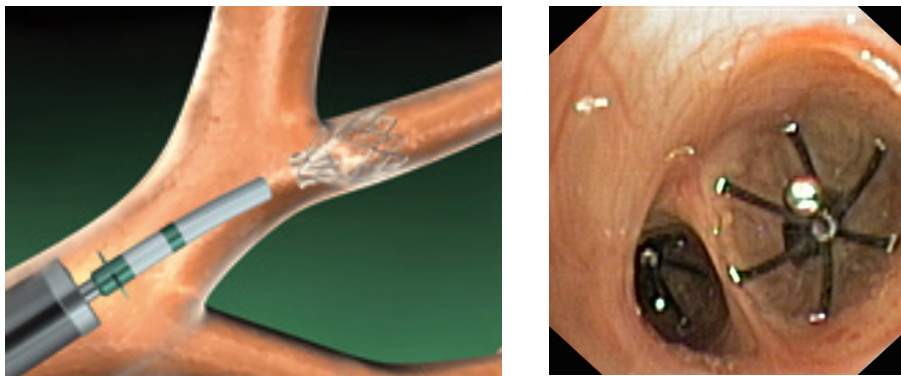


Figure. The Zephyr endobronchial valve, left (published with permission from Pulmonx International Sàrl), and the Spiration endobronchial valve, right (photo by G. Riise).

3b The work group's understanding of the potential value of endobronchial lung volume reduction

The aim of ELVR is to reduce lung volume, and to lower the intrathoracic pressure. Theoretically, this will improve pulmonary function. As a result of such an improvement the dyspnea symptoms are expected to diminish, and the physical performance to increase. Most likely the quality of life will then improve in this group of severely affected emphysema patients who are resistant to other currently available treatment regimens.

3c The central question for the current HTA project in one sentence

Does lung volume reduction by endobronchial valves improve survival, quality of life and pulmonary function in patients with severe chronic obstructive pulmonary disease (COPD) or severe pulmonary emphysema?

3d

PICO

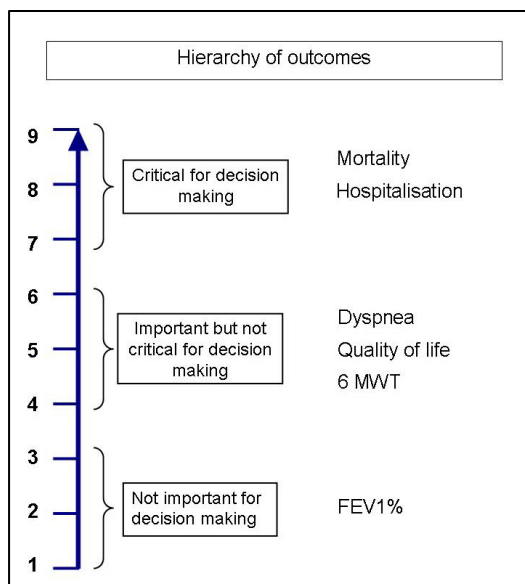
P= Patients, I= Intervention, C= Comparison, O=Outcome

P= Patients with severe chronic obstructive pulmonary disease (COPD) or severe pulmonary emphysema (stage 3/4)

I= Lung volume reduction by endobronchial valves

C= Standard medical care such as medication use, oxygen or any type of rehabilitation

O= Mortality
Hospitalisation
Dyspnea scale
Quality of Life (QoL)
Six minutes walk test
Pulmonary function (FEV1,
FVC, RV)
Complications



Review of the Quality of Evidence

4 Search strategy, study selection and references – appendix 3

(Search strategy, Eligibility criteria, Selection process – flow diagram, References)

During November 2012, two librarians (AL, TS) performed searches in PubMed, EMBASE, the Cochrane Library, and a number of HTA-databases. Reference lists of relevant articles were also scrutinised for additional references. A total of 224 articles were identified (after removal of duplicates), of which the librarians excluded 200 abstracts. The librarians excluded another three articles after having been read in full text. Eighteen articles and three HTA-reports were sent to the work group for assessment. Ten of these articles and two of the HTA-reports were included in the report; three articles were randomised controlled trials (RCTs) and have been critically appraised. The appraisal of articles was based on checklists from SBU regarding randomised controlled trials. Seven articles were published case series.

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in Appendix 3. The librarians independently assessed the obtained abstracts and subsequently a first selection of full-text articles for inclusion or exclusion. Any disagreements were resolved by discussion. Remaining articles were sent to the members of the work group, who also read articles independently and then decided in a consensus meeting which articles to exclude and which to include in the report.

5a Describe briefly the present knowledge of endobronchial lung volume reduction

Two HTA reports have been published on the effects of ELVR. One from Belgium and one from Spain. Both were published in 2009. The Belgian report concluded that the clinical benefit of ELVR in patients with end-stage pulmonary emphysema is poorly demonstrated and has the potential to cause severe adverse effects.

The Spanish report concluded similarly: “available scientific information does not allow for endobronchial valves to be recommended as a treatment for diffuse heterogeneous-type emphysema”.

The systematic literature search identified three multicenter RCTs of the effects of ELVR in patients with severe COPD and advanced emphysema. One used a single-blinded, sham-controlled design with a follow-up of three months, and the other two used an open, controlled, 2:1 treatment:control design, with six months follow-up.

Mortality (Appendix 1:1, Appendix 4)

All three RCTs reported the effect of ELVR on mortality. No study found any significant differences in mortality between the study groups. However, there was a considerable number of drop-outs in two of the trials (16%), in which the vital status of the patients lost to follow-up was unclear.

Conclusion: There was no difference in mortality between ELVR-treated patients and patients on standard care. Low quality of evidence (GRADE ⊕⊕OO).

Hospitalisation

None of the studies has reported any data on hospitalisation rates.

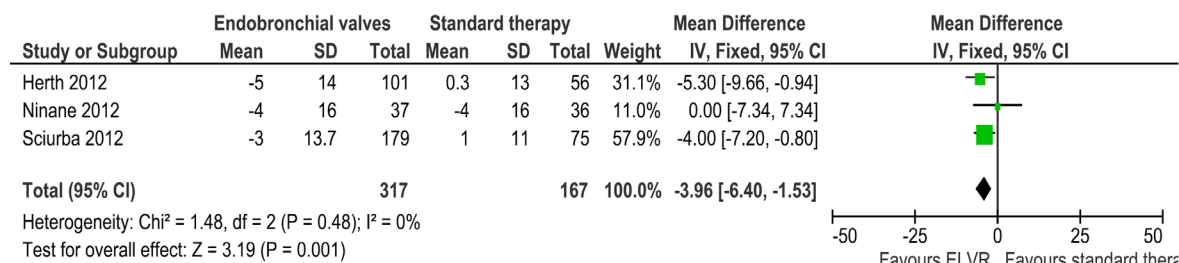
Dyspnea (Appendix 1:2, Appendix 4)

Two RCTs analysed the effect of ELVR on dyspnea using an established and validated questionnaire form (Modified Medical Research Council). The two trials reported no, or no clinically relevant effect on dyspnea (i.e. defined as Δ -score > 1.0).

Conclusion: EVLVR had no clinically relevant effect on dyspnea in comparison with standard therapy. Low quality of evidence (GRADE ⊕⊕OO).

Quality of life (Appendix 1:3, Appendix 4)

All three RCTs analysed the effect of ELVR on quality of life using a validated questionnaire (St. George’s respiratory Questionnaire; 0 – 100 points). A meta-analysis revealed a statistically significant difference of 3.96 points in favor of ELVR.



However, a minimal important clinical effect is defined as a change of four points in this 100 point scale.

Conclusion: There is a small and statistically significant, but not clinically relevant, effect on quality of life by ELVR-treatment compared to standard therapy. Low quality of evidence (GRADE ⊕⊕OO).

Six Minute Walk Test (Appendix 1:4, Appendix 4)

All three RCTs analysed the effect of ELVR on six minute walk test (6MWT). The trials reported slightly different results. The study by Ninane et al., with a follow-up time of three months, found that both the treated and the control groups increased their 6MWT distance by 7 meters. Sciruba et al. found that the EVLR group increased their walking distance by 9 meters, whereas the controls walked 11 meters shorter at 6 months follow-up. In Herth et al. both treated patients (+ 15 meters) and controls (+ 10 meters) increased their 6MWT. Conclusion: ELVR had no clinically relevant effects on 6MWT in comparison with standard therapy. Low quality of evidence (GRADE ⊕⊕OO).

Forced Expiratory Volume in one second – FEV1 (Appendix 1:5, Appendix 4)

All three RCTs analysed the effect of ELVR on FEV1. The results were conflicting. One trial observed a decrease in FEV1 in both study groups without significant difference between them. One trial reported an increased FEV1 in the ELVR group, and a reduced FEV1 in the control group. This difference was statistically significant but very small in absolute terms. The third RCT found a slight improvement in both the ELVR and the control group, without any statistically significant difference.

Conclusion: ELVR had no observed clinical relevant effects on FEV1 in comparison with standard therapy. Low quality of evidence (GRADE ⊕⊕OO).

Complications (Appendix 1:6)

The ELVR procedure was associated with rather high incidences of various complications. Pneumothorax was reported to occur in 0 - 12 % of cases after the procedure. The corresponding incidences for pneumonia were 1 – 14 %, acute exacerbation of COPD 2 – 17 %, and valve migration 2 – 24 %. The time of follow-up in these studies was up to 12 months. Other complications such as hemoptysis, dyspnea, and bronchitis were reported to occur between 2 - 23 %.

5b Outcome tables – appendix 1

5c Excluded articles – appendix 2

5d Ongoing research?

A search in the ClinicalTrials database (www.clinicaltrials.gov) (2013-01-17 using the search terms (*valve OR Zephyr OR spiration*) AND (*endobronchial OR intrabronchial OR bronchial OR bronchoscopy OR bronchoscopic OR transbronchoscopic*)) identified 24 trials. Twelve studies were relevant for our question, ELVR for emphysema. Five are presently recruiting, three are active but not recruiting, and four have been completed but not published. This shows an ongoing interest in the field and it is likely that new information about EVLR will emerge in the coming years.

6 Do any medical societies or health authorities recommend endobronchial lung volume reduction?

Endobronchial lung volume reduction is not recommended by any health authorities or medical society in Sweden.

Ethical aspects

7 Ethical consequences

See Appendix 5.

Organisation

8a **When can endobronchial lung volume reduction be put into practice?**

Endobronchial lung volume reduction is already performed at Sahlgrenska University Hospital for other 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.

8b **Is endobronchial lung volume reduction used in other hospitals in Sweden?**

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.

8c **According to the work group, will there be any consequences of endobronchial lung volume reduction for personnel?**

If the number of patients in need of ELVR should increase additional training of more personnel will be necessary.

8d **Will there be any consequences for other clinics or supporting functions at the hospital or in the whole 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.

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.

Economy

9a **Present costs of currently used technologies**

Conventional treatment of patients with severe COPD includes the costs for pharmacological agents, for follow-up 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 COPD patients of stage 3 or 4.

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

9b **Expected costs of endobronchial lung volume reduction**

Each valve costs about 1500 € (about 12 000 SEK) . Each treatment usually requires the insertion of 4-6 valves, i.e. 6000 – 9000 € (about 48 000 – 72 000 SEK) per patient. Additional costs will be added for pre- and postoperative investigations with chest x-rays, CT-scan, and lung function tests.

9c **Total change of cost**

ELVR will cause increased costs both for the treatment, but also for complications that occur. The cost of the latter is difficult to estimate.

9d **Can endobronchial lung volume reduction be adopted and used within the present budget (clinic budget/hospital budget)?**

No.

9e **Are there any available analyses of health economy? Cost advantages or disadvantages?**

No health economy analyses were identified in the literature search.

Unanswered Questions

10a **Important gaps in scientific knowledge**

It is evident that we currently have not clarified any subcategory of patients with emphysema that may benefit from EVLR. Is it COPD with heterogenous emphysema, or those with a more homogenous disease?

It is also unclear whether one should only treat one lung with ELVR, or to perform it bilaterally. Furthermore, it is not known whether total atelectasis of the treated segment is necessary in order to achieve full effect or not.

Long term follow-up RCTs are still lacking. Thus, it is unclear whether any of the observed effects can improve over time.

10b **Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue**

No, not at the present time.

Statement from HTA-centrum of Region Västra Götaland, Sweden

Endobronchial lung volume reduction in patients with severe chronic obstructive pulmonary disease

Question 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 or severe pulmonary emphysema?

PICO

P = Patients with severe chronic obstructive pulmonary disease (COPD) or severe pulmonary emphysema (stage 3/4)

I = Lung volume reduction by endobronchial valves

C = Standard medical care such as medication use, oxygen or any type of rehabilitation

O = Mortality, hospitalization, dyspnea scale, quality of life, six minutes walk test, pulmonary function (FEV1, FVC, RV), complications

Summary of the health technology assessment

Method and patient category

Chronic obstructive pulmonary disease (COPD), and emphysema, is caused by a progressive destruction of the elastic tissue in the small airways. It results in difficulty for the patient to empty the lungs of air. In the most severe forms the patient suffers from severe shortness of breath.

Endobronchial Lung Volume Reduction (ELVR) uses one-way valves. These valves are placed into the airways of the most destroyed and inflated lung segments. Inhaled air is prevented to reach these parts of hyperinflated lung segments, but trapped air can be exhaled during expiration. The goal is to make the lung parenchyma distal to the valve to collapse, and, thereby to lower the hyperinflation and the intrathoracic pressure. Theoretically, this will improve pulmonary function. As a result of such an improvement the dyspnea symptoms is expected to diminish, and the physical performance to increase.

Scientific documentation

The systematic literature search identified three randomized, controlled trials of the effects of ELVR in patients with severe COPD and advanced emphysema.

There was no difference in mortality or in dyspnea between ELVR-treated patients and patients on standard care (Low quality of evidence; GRADE ⊕⊕OO). Furthermore, there were no clinically relevant effects on quality of life, six minutes walk test, or pulmonary function measured as FEV1 (Low quality of evidence; GRADE ⊕⊕OO).

Side effects and complications

The procedure was associated with high frequencies of various complications such as pneumothorax, pneumonia, COPD exacerbations and valve migration.

Ethical aspects

Should patients with advanced emphysema be treated with endobronchial lung volume reduction by the insertion of valves in affected lung segments when the procedure has not been shown to have any clinically relevant effects, and, furthermore, is associated with serious complications at high rates?

Economical aspects

One endobronchial valve costs about 1 500 € (about 12 000 SEK). Each treatment usually requires the insertion of 4-6 valves, i.e. 6 000 – 9 000 € (about 48 000 – 72 000 SEK) per patient. Additional costs are necessary for pre- and postoperative investigations with chest x-rays, CT-scan, and lung function tests.

Concluding remarks

Endobronchial lung volume reduction in patients with advanced chronic obstructive pulmonary disease by placement of one-way valves in affected lung segments have been evaluated in three randomized, controlled trials. These studies have not shown any beneficial effects on critical and important outcome variables such as mortality or dyspnea, and the effects on other outcome variables have been of small, and of no clinical relevance.

The Regional Health Technology Assessment Centre (HTA-centrum) of Region Västra Götaland, Sweden (VGR) has the task to make statements on HTA reports carried out in VGR. The statement should summarise the question at issue, level of evidence, efficacy, risks, and economical and ethical aspects of the particular health technology that has been assessed in the report. HTA was accomplished during the period of 2012-11-21 – 2013-03-27. Last search updated in November 2012

On behalf of the HTA quality assurance group, in Region Västra Götaland, Sweden
Göteborg, Sweden, 2013-03-27

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Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

Endobronkiell lungvolymsreduktion för patienter med svår kroniskt obstruktiv lungsjukdom

Frågeställning:

Leder reduktion av lungvolym med endobronkiella ventiler till en förbättrad livskvalitet och lungfunktion hos patienter med svår kronisk obstruktiv lungsjukdom och emfysem?

PICO

P = Patienter med svår kronisk obstruktiv lungsjukdom (stadium 3/4) och emfysem

I = Reduktion av lungvolymen med endobronkiella ventiler

C = Konventionell standardbehandling med läkemedel, syrgas och rehabilitering

O = Dödlighet, sjukhusvård, dyspne, livskvalitet, 6 minuters gångtest, lungfunktion (FEV1, FVC, RV), komplikationer

Resultat av HTA-processen

Metod och målgrupp

Kronisk obstruktiv lungsjukdom (KOL), och emfysem, är resultatet av att den elastiska vävnaden i de små luftvägarna successivt förstörs. Denna sjukdomsprocess leder till att patienten får tilltagande svårigheter att tömma sina lungor på luft. I de mest allvarliga stadierna drabbas patienten av en uttalad andfäddhet.

Vid endobronkiell lungvolymsreduktion (ELVR) placeras envägsventiler i de mindre luftvägar som leder in till de lungsegment som är mest skadade och överventilerade med luft. Inandningsluft hindras då från att nå dessa delar av lungorna medan luften däremot kan ventileras ut från dem under utandningsfasen. Målet med detta är att den skadade lungvävnaden distalt om ventilen ska kollapsa. Därigenom minskas såväl överventilationen i detta lungsegment som trycket inne i bröstkorget. Teoretiskt sett skulle detta kunna leda till en förbättrad lungfunktion, och därmed minskade andningsbesvär och en ökad fysisk prestationsförmåga.

Vetenskaplig dokumentation

Den systematiska litteratursökningen identifierade tre randomiserade, kontrollerade studier som analyserat effekten av ELVR hos patienter med svår kronisk obstruktiv lungsjukdom och emfysem.

Ingen av studierna kunde påvisa någon skillnad i mortalitet eller graden av andfäddhet mellan patienter som behandlats med ELVR eller fått konventionell standardbehandling (Begränsat vetenskapligt underlag; GRADE ⊕⊕OO). Man observerade inte heller några kliniskt betydelsefulla skillnader med avseende på livskvalitet, 6 minuters gångtest, eller lungfunktion (Begränsat vetenskapligt underlag; GRADE ⊕⊕OO).

Biverkningar och komplikationer

Endobronkiell lungvolymsreduktion är förenad med en hög frekvens biverkningar och komplikationer. Vanligt förekommande är uppkomst av pneumothorax, lunginflammation, exacerbationer av KOL, samt att ventilerna flyttar på sig.

Etiska aspekter

En viktig etisk fråga är om patienter med avancerad KOL och emfysem ska behandlas med ventiler som placeras in i luftvägarna då behandlingsmetoden inte visat sig ge några kliniskt betydelsefulla effekter och samtidigt är förenad med en hög frekvens komplikationer?

Ekonomiska aspekter

En endobronkiel ventil kostar cirka 12 000 SEK (1 500 €). Vid behandling av en patient placeras i allmänhet 4 - 6 ventiler in i olika luftvägssegment. Detta innebär en genomsnittlig kostnad för enbart ventilerna på 48 000 – 72 000 SEK (6 000 – 9 000 €). Dessutom tillkommer ytterligare kostnader för pre- och postoperativa undersökningar med lungröntgen, datortomografier och lungfunktionstester.

Sammanfattning och slutsats

Effekterna av endobronkiell lungvolymsreduktion hos patienter med svår kroniskt obstruktiv lungsjukdom har utvärderats i tre randomiserade, kontrollerade studier. Studierna har inte kunnat påvisa någon positiv behandlingseffekt med avseende på kritiska och viktiga effektmått såsom dödlighet och andfåddhet. Effekterna av behandlingsmetoden på andra mätbara effektmått är liten och inte kliniskt betydelsefull.

HTA-kvalitetssäkringsgruppen har ett uppdrag att yttra sig över genomförda HTA i Västra Götalandsregionen. Yttrandet skall innefatta sammanfattning av frågeställning, samlat evidensläge, patientnytta, risker samt ekonomiska och etiska aspekter för den studerande teknologin.

Projektet har pågått under perioden 2012-11-21 – 2013-03-27.
Sista uppdatering av artikelsökning november 2012

För HTA-kvalitetssäkringsgruppen 2013-03-27

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Project: Endobronchial valve treatment for advanced emphysema.
 Appendix 1:1
 Outcome variable: Mortality

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n= Follow-up (FU)	With-drawals - dropouts	Result		Comments	* Directness	* Study limitations	* Precision
					Intervention	Control				
Ninane, 2012	Europe	Randomised, single-blinded, sham-controlled trial. Multicentre trial	73 3 months	3	1/37 <i>NS between study groups</i>	0/36	Average age: 62 years	+	+	?
Sciurba, 2010	USA	Randomised, open, controlled trial. Multicentre trial	321 6 months	70	6/220 <i>NS between study groups</i>	0/101	Average age: 65 years Vital status of patients lost to follow-up (n = 67) unknown.	+	?	+
Herth 2012	Europe	Randomised, open, controlled trial. Multicentre trial	171 6 months	17	6/111 <i>NS between study groups</i>	4/60	Average age: 60 years Vital status of patients lost to follow-up (n = 10) unknown.	+	?	?

Project: Endobronchial valve treatment for advanced emphysema.

Appendix 1:2

Outcome variable: Dyspnea. MMRC (Modified Medical Research Council) dyspnea score (0 – 4).

The higher score, the greater dyspnea. Minimal important clinical difference is 1.

* + No problem
? Some problems
- Major problems

Author, year	Country	Study design	Number of patients n=	With-drawals - dropouts	Result		Comments	*	*	*
					Intervention	Control				
Ninane, 2012	Europe	Randomised, single-blinded, sham-controlled trial. Multicentre trial	73 3 months	3	Baseline: 2.8 (sd 0.7) FU: 2.5 (sd 1.0) <i>NS between study groups</i>	Baseline: 2.8 (sd 0.9) FU: 2.7 (sd 0.6)	Average age: 62 years	+	+	?
Scirba, 2010	USA	Randomised, open, controlled trial. Multicentre trial	321 6 months	70	FU: $\Delta = 0.1$ (sd 1.02) (95 % CI: -0.2 ;+ 0.1) <i>p = 0.04 between study groups</i>	FU: $\Delta = 0.2$ (sd 0.88) (95 % CI: 0.0; 0.4)	Average age: 65 years	+	?	+

Project: Endobronchial valve treatment for advanced emphysema.

Appendix 1:3

Outcome variable: Quality of life. SGRQ (St. George's respiratory Questionnaire); score 0 – 100. The higher score, the worse quality of life.

Minimal important clinical effect is a change of 4 points.

* + No problem ? Some problems - Major problems

Author, year	Country	Study design	Number of patients n=	With-drawals - dropouts	Result		Comments	* Directness	* Study limitations	* Precision
					Intervention	Control				
Ninane, 2012	Europe	Randomised, single-blinded, sham-controlled trial. Multicentre trial	73 3 months	3	Baseline: 61 (sd 11) FU: $\Delta = -4$ (sd 16) <i>NS between study groups</i>	Baseline: 60 (sd 13) FU: $\Delta = -4$ (sd 16)	Average age: 62 years	+	+	?
Scirba, 2010	USA	Randomised, open, controlled trial. Multicentre trial	321 6 months	70	FU: $\Delta = -3$ (sd 14) (95% CI: -5; +1) <i>p = 0.04 between study groups</i>	FU: $\Delta = +1$ (sd 11) (95% CI: -2; +3) ¹	Average age: 65 years	+	?	+
Herth 2012	Europe	Randomised, open, controlled trial. Multicentre trial	171 6 months	17	Baseline: 59 (sd 13) FU: $\Delta = -5$ (sd 14) <i>p = 0.047 between study groups</i>	Baseline: 56 (sd 13) FU: $\Delta = +0.3$ (sd 13)	Average age: 60 years	+	?	?

Project: Endobronchial valve treatment for advanced emphysema.
 Appendix 1:4
 Outcome variable: 6 minute walk test (meters)

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	Follow-up (FU)	With-drawals - dropouts	Result		Comments	*	*	*
						Intervention	Control				
Ninane, 2012	Europe	Randomised, single-blinded, sham-controlled trial. Multicentre trial	73	3 months	3	Baseline: 337 (sd 106) FU: 344 (sd 118) <i>NS between study groups</i>	Baseline: 346 (sd 123) FU: 353 (sd 131)	Average age: 62 years	+	+	?
Scirba, 2010	USA	Randomised, open, controlled trial. Multicentre trial	321	6 months	70	Baseline: 334 (sd 87) FU: $\Delta = +9$ (sd 66) (95% CI: -0.5; +19) <i>p = 0.02 between study groups</i>	Baseline: 351 (sd 83) FU: $\Delta = -11$ (sd 81) (95%: -29; +8)	Average age: 65 years	+	?	+
Herth 2012	Europe	Randomised, open, controlled trial. Multicentre trial	171	6 months	17	Baseline: 341 (sd 108) FU: $\Delta = +15$ (sd 91) <i>NS between study groups</i>	Baseline: 360 (sd 117) FU: $\Delta = +10$ (sd 78)	Average age: 60 years	+	?	?

Project: Endobronchial valve treatment for advanced emphysema.
 Appendix 1:5
 Outcome variable: FEV1 % (litres)

* + No problem
 ? Some problems
 - Major problems

Author, year	Country	Study design	Number of patients n=	With-drawals - dropouts	Result		Comments	*	*	*
					Intervention	Control				
Ninane, 2012	Europe	Randomised, single-blinded, sham-controlled trial. Multicentre trial	73 3 months	3	Baseline: 0.99 (sd 0.35) FU: 0.90 (sd 0.34) <i>p = 0.065 between study groups</i>	Baseline: 0.88 (sd 0.29) FU: 0.87 (sd 0.34)	Average age: 62 years	+	+	?
Scirba, 2010	USA	Randomised, open, controlled trial. Multicentre trial	321 6 months	70	Baseline: 0.87 (sd 0.267) FU: 0.90 $\Delta = +0.03$ (95% CI: 0.01; 0.06) <i>p = 0.002 between study groups</i>	Baseline: 0.84 (sd 0.25) FU: 0.81 $\Delta = -0.025$ (95% CI: -0.05; -0.003)	Average age: 65 years	+	?	+
Herth 2012	Europe	Randomised, open, controlled trial. Multicentre trial	171 6 months	17	Baseline: 0.91 (sd 0.29) FU: Δ % = +7 (sd 20) <i>p = 0.067 between study groups</i>	Baseline: 0.94 (sd 0.30) FU: Δ % = +0.5 (sd 19)	Average age: 60 years	+	?	?

Project: Endobronchial valve treatment for severe emphysema
Appendix 1-6. Complications.

Author, year	Country	Number of patients/ Length of follow-up (FU)	With drawals - dropouts	Mortality	Pneumo-thorax	Pneumonia	Valve migration	Acute exacerbations of COPD	Other (hemoptysi, bronchitis dyspnea)	Comments
Gompelmann D, 2010	Germany, and Boston, USA	n = 25 30 days	None	0 %	10 %	5 %	5 %	5 %	10 %	10 % required prolonged hospital stay
Herth FJ, 2012	Germany, Netherlands Sweden	n = 105 30 days	n = 9	5 %	8 %	1 %	Not stated	7 %	2 %	All 19 (table 3 says 18) SAE (20%) caused prolonged hospital stay. 2 unrelated deaths reported (ruptured aneurysm, spinal surgery)
Springmeyer S, 2009	Multicenter USA	n = 98 12 months	Not stated	1 %	8 %	Not stated	Not stated	7 %	Not stated	1 unrelated (?) cardiac arrest reported 2 cases of bronchospasm caused valves removed
Sterman DH 2010	Multicenter USA	n = 91 12 months	n = 26	7 %	12 %	5 %	Not stated	2 %	10 %	Valve removal in 18 % Prolonged hospitalization in 10 % One case of AMI on day three

Project: Endobronchial valve treatment for severe emphysema
Appendix 1-6. Complications.

Author, year	Country	Number of patients/ Length of follow-up (FU)	With drawals - dropouts	Mortality	Pneumo-thorax	Pneumonia	Valve migration	Acute exacerbations of COPD	Other (hemoptysi, bronchitis dyspnea)	Comments
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Van Brabandt 2009	Belgium	n = 275 4 weeks up to 24 months	Not stated	30-day mortality : 1.0 %	Up to 5 %	Up to 5 %	24 %	Up to 17 %	Not stated	Rapid-HTA including 9 studies/ reports
Venuta 2012	Italy	n = 40 2.7 years (median)	Not stated	40 %	2 %	2 %	2 %	Not stated	2 %	3 patients transplanted within one year
Wan I 2006	Multicenter 7 countries	n = 98 1.7 years	Not stated	1 %	5 %	5 %	Not stated	17 %	6 %	Valve removals not specified
Wood 2007	USA	n = 28 6 months	n = 4	0 %	0 %	14 %	Not stated	14 % (during first 30 days)	23 %	Valve removal in 7 pts within the first year because of pneumonia, LVRS or patient request.

Project : Endobronchial valve treatment for severe emphysema

Appendix 2

Study (author, publication year)	Reason for exclusion
-------------------------------------	----------------------

Barua 2012	Does not fulfill AMSTAR- criteria
Brown 2012	Wrong outcome variable
Coxson 2008	Subgroup-analysis of data presented by Springmeyer 2009
Eberhardt 2012	Wrong comparison
Hartman 2012	Mixed methods of intervention
Kotecha 2011	Too few patients
Nachtnebel 2010	No new data presented
Tummino 2012	Only one patient
Yim 2004	Subgroup-analysis of Wan 2006

Appendix 3

Question 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) or severe pulmonary emphysema?

P = Patients with severe chronic obstructive pulmonary disease (COPD) or severe pulmonary emphysema (stage 3/4)

I = Lung volume reduction by endobronchial valves

C = Standard medical care such as medication use, oxygen or any type of rehabilitation

O =

1. Mortality
2. Hospitalization
3. Dyspnea scale
4. Quality of Life (QoL)
5. Six minutes walk test
6. Pulmonary function (FEV1, FVC, RV)
7. Complications

Study design:

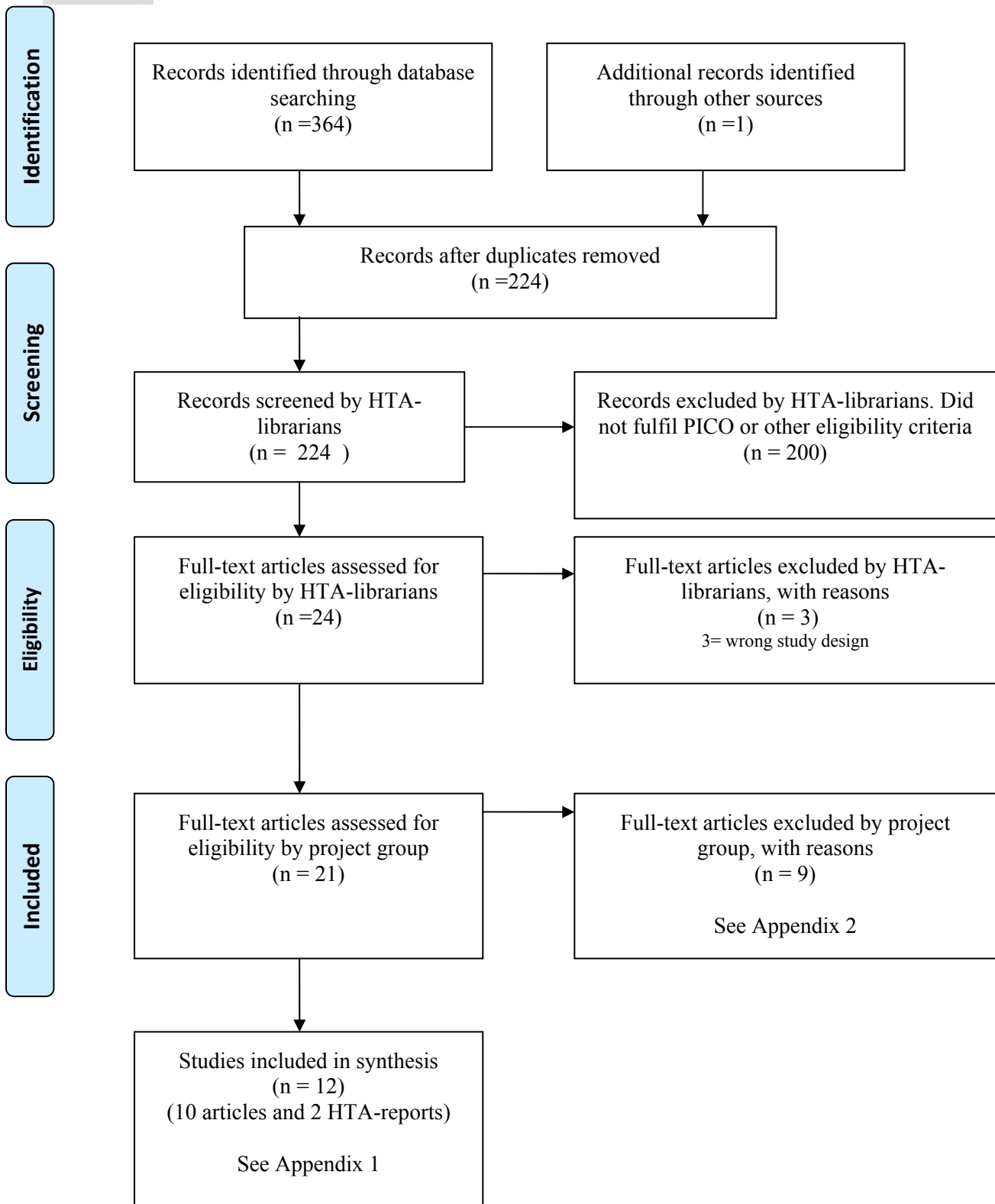
- Randomised controlled trials
- Observational studies/cohort studies
- Case series ≥ 20
- Systematic reviews

Language: English, Swedish, Norwegian, Danish, Spanish, German

Publication year:

2000-

Selection process – flow diagram



Database: PubMed
Date: 2012-11-27
No of results: 150

Search	Query	Result
#17	Select 150 document(s)	150
#16	Search #5 AND #7 Filters: Publication date from 2000/01/01; Danish; English; German; Norwegian; Spanish; Swedish	150
#9	Search #5 AND #7 Filters: Publication date from 2000/01/01	163
#8	Search #5 AND #7	188
#7	Search emphysema[tiab] OR emphysemas[tiab] OR chronic obstructive pulmonary[tiab] OR COPD[tiab] OR Pulmonary Disease, Chronic Obstructive[MeSH] OR Pulmonary Emphysema[MeSH]	55583
#5	Search #3 OR #4	517
#4	Search (endobronchial[tiab] OR endoscopic[tiab] OR bronchoscopic[tiab]) AND (lung volume reduction[tiab])	135
#3	Search #1 AND #2	442
#2	Search valve[tiab] OR valves[tiab] OR Zephyr OR spiration	92435
#1	Search endobronchial[tiab] OR intrabronchial[tiab] OR bronchial[tiab] OR bronchoscopy[tiab] OR bronchoscopic[tiab] OR bronchoscopies[tiab] OR transbronchoscopic[tiab] OR bronchoscopy[MeSH]	89596

Database: EMBASE (OVID)
Date: 2012-11-27
No of results: 183

Search	Query	Results
1	(endobronchial or intrabronchial or bronchial or bronchoscopy or bronchoscopic or bronchoscopies or transbronchoscopic).ti,ab,kw.	99027
2	exp bronchoscopy/	32813
3	1 or 2	113113
4	(valve or valves or Zephyr or spiration).ti,ab,dv,kw.	110879
5	3 and 4	666
6	(endobronchial or endoscopic or bronchoscopic).ti,ab,kw.	133876
7	(lung adj volume adj reduction).ti,ab,kw.	1408
8	6 and 7	224
9	5 or 8	784
10	(emphysema or emphysemas or chronic obstructive pulmonary or COPD).ti,ab,kw.	61785
11	exp chronic obstructive lung disease/	61793
12	exp lung emphysema/	17629
13	10 or 11 or 12	95307
14	9 and 13	312
15	limit 14 to ((danish or english or german or norwegian or spanish or swedish) and yr="2000 -Current")	257
16	limit 15 to (article or conference paper or "review")	183

Database: The Cochrane Library

Date: 2012-11-27

No of results: 26

Cochrane reviews 0

Other reviews 0

Clinical trials 23

Technology assessments 3

Economic evaluations 0

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)	6885
#2	MeSH descriptor: [Bronchoscopy] explode all trees	491
#3	#1 or #2	6885
#4	valve or valves or Zephyr or spiration:ti,ab,kw (Word variations have been searched)	2735
#5	#3 and #4	39
#6	endobronchial or endoscopic or bronchoscopic:ti,ab,kw (Word variations have been searched)	6075
#7	lung next volume next reduction:ti,ab,kw (Word variations have been searched)	126
#8	#6 and #7	10
#9	#5 or #8	45
#10	emphysema or emphysemas or chronic obstructive pulmonary or COPD:ti,ab,kw (Word variations have been searched)	7211
#11	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees	1836
#12	MeSH descriptor: [Pulmonary Emphysema] explode all trees	201
#13	#10 or #11 or #12	7265
#14	#9 and #13 from 2000	26

Database: CRD

Date: 2012-11-27

No of results: 5

ID	Search	Hits
#1	((endobronchial or intrabronchial or bronchial or bronchoscopy or bronchoscopic or bronchoscopies or transbronchoscopic) AND (valve or valves or Zephyr or spiration)) OR ((endobronchial OR endoscopic OR bronchoscopic) AND (lung volume reduction))	5

The web-sites of **SBU, Kunnskapssenteret** and **Sundhedsstyrelsen**, were visited 2012-11-27
Nothing relevant to the question at issue was found

Reference lists

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Appendix 4

Summary of Findings: Endobronchial valve treatment for advanced emphysema.

2013-03-27

Outcome variable Number of studies	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect (95%CI)	Quality of evidence GRADE
---------------------------------------	--------	-------------------	-------------	------------	-----------	------------------	---------------------	-------------------------	-------------------------	---------------------------

Mortality 3	RCT	Serious limitations (-1)	No inconsistency	No uncertainty	Serious imprecision (-1)	Unlikely	Not relevant	1.27 (0.42;3.87)		⊕⊕○○
Dyspnea (MMRC score) 2	RCT	Serious limitations (-1)	Some inconsistency (?)	No uncertainty	Uncertain precision (?)	Unlikely	Not relevant		Δ score = - 0.05 Non-significant	⊕⊕○○
Quality of life (SGRO score) 3	RCT	Serious limitations (-1)	No inconsistency	No uncertainty	No imprecision	Unlikely	Not relevant		Δ score = - 3.96 (-6.4;-1.5)	⊕⊕○○
6 minute walk test 3	RCT	Serious limitations (-1)	Some inconsistency (?)	No uncertainty	Uncertain precision (?)	Unlikely	Not relevant		Δ distance = + 13 meters	⊕⊕○○
FEV1 % 3	RCT	Serious limitations (-1)	Some inconsistency (?)	No uncertainty	Uncertain precision (?)	Unlikely	Not relevant		Δ volume = - 0.06 - + 0.06 litres	⊕⊕○○

High quality of evidence = ⊕⊕⊕⊕
 Moderate quality of evidence = ⊕⊕⊕○

Low quality of evidence = ⊕⊕○○
 Very low quality of evidence = ⊕○○○

Appendix 5.

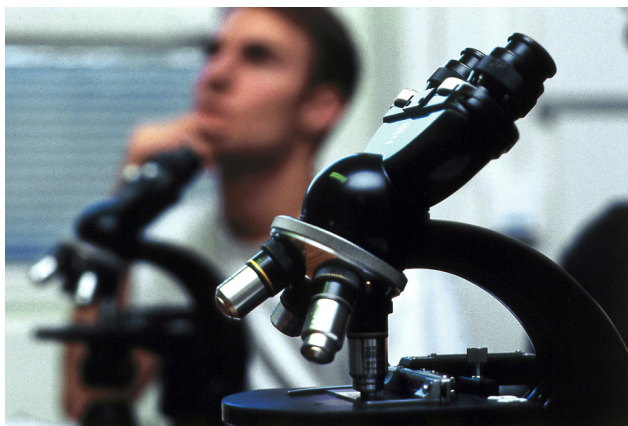
ETHICAL ANALYSIS OF ENDOBRONCHIAL LUNG VOLUME REDUCTION ELVR IN PATIENTS WITH SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Question	Answer/ comment
1. From the patient's perspective, how does ELVR affect the patient's quality of life and life expectancy?	No beneficial effect with regard to quality of life or life expectancy have been 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 in the therapy disease 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, theoretically. If it is documented to be beneficial it would positively improve the patient's total health situation. However, as of today no such beneficial results have been reported.
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?	No health-economy evaluation is available.
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?	If introduced, 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 ELVR influence the trust of the health care system?	If ELVR is introduced based on present data, and then is documented to be a harmful treatment, the trust of the health care system would be negatively affected.
CONCLUSIONS	Based on ethical aspects there are no reasons to favour the introduction of ELVR at the present time. However, it is not ruled out that ELVR could have a beneficial effect in selected cases of severe emphysema and COPD. Ongoing studies will hopefully shed light on this in the future.

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= (GRADE ⊕⊕⊕⊕)
Moderate quality of evidence	= (GRADE ⊕⊕⊕○)
Low quality of evidence	= (GRADE ⊕⊕○○)
Very low quality of evidence	= (GRADE ⊕○○○)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

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