Endobronchial valves in the treatment of severe pulmonary emphysema. A rapid Health Technology Assessment.

KCE reports 114C

Federaal Kenniscentrum voor de Gezondheidszorg
Centre fédéral d'expertise des soins de santé
Belgian Health Care Knowledge Centre
2009

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Executive summary

SCOPE

This rapid Health Technology Assessment (HTA) report provides a systematic review of the scientific literature on the (cost-)effectiveness of endobronchial valves (EBVs) as an additional therapeutic modality on top of an optimal non-invasive therapy in patients with severe pulmonary emphysema.

CLINICAL BACKGROUND

Pulmonary emphysema is part of the spectrum of "chronic obstructive pulmonary disease" (COPD) representing lung diseases characterised by a not fully reversible and progressive airflow obstruction. Airflow limitation is caused by a mixture of disease of the smaller airways and destruction of lung parenchyma, the latter being the predominant process in emphysema. The impact of COPD on an individual patient depends on the extent of the pathology. It can cause chronic symptoms of cough, sputum production, breathlessness, decreased exercise capacity and a number of systemic effects such as weight loss and skeletal muscle dysfunction. COPD is a progressive disease. Its main cause is cigarette smoking, making it a largely preventable disease.

Diagnosis of COPD is based on clinical history, the presence of specific signs and an assessment of airway obstruction by means of "lung function tests". The most often used measure of lung function is FEV1, the forced expiratory air volume in 1 second. Other measures that are used to quantify the impact of COPD are the six-minute walking distance (6MWD), St George's Respiratory Questionnaire (SGRQ) and the Medical Research Council (MRC) dyspnoea score. High-resolution chest CT-scanning is used to determine the presence, extent and distribution of emphysema.

The therapy of COPD is based on a stepwise approach, related to the severity of the disease. Many COPD patients need medical treatment for the rest of their lives, with increasing doses and additional medications during exacerbations. Medical therapy consists of bronchodilators, anti-inflammatory agents, oxygen, and pulmonary rehabilitation. The aims of treatment are to alleviate symptoms, to prevent exacerbations and further deterioration of pulmonary function, and to improve activities of daily living, quality of life and survival. Although medical therapy benefits many patients with COPD, a substantial minority derive only limited improvement because medical treatment targets only the airway component of the disease. This is most apparent in COPD patients with predominant emphysema. A limited number of these patients are candidates for lung transplantation. For those that are not, lung volume reduction surgery (LVRS) may represent a therapy of last resort. In LVRS, some of the damaged and hyperinflated portions of the lung are resected, providing more capacity within the chest cavity for the remaining lung to expand and function better. Because of the high mortality and morbidity following this surgical procedure, an alternative and less invasive way for reducing lung volume has been developed by means of the bronchoscopic insertion of endobronchial valves (EBV). It is further referred to as "bronchoscopic lung volume reduction" and it constitutes the research topic of this report.

ENDOBRONCHIAL VALVE TECHNOLOGY

EBVs are one-way valves that are bronchoscopically inserted in airways that lead to emphysematous lung tissue, preventing air from entering the blocked segments while allowing the venting of expired gas and bronchial secretions. This should eventually lead to collapse (atelectasis) of the isolated segments with the subsequent intended reduction in lung volume. The insertion of the valves is generally performed with the patient under general anaesthesia and normally requires a hospital stay of a few days.

The largest experience with EBVs has been obtained with two different devices: the Zephyr EBV (originally Emphasys Medical, currently Pulmonx) and the Spiration Intrabronchial Valve (Spiration Inc.). In Belgium, Pulmonx is represented by RMS Endoscopy and the Spiration IBV valve is distributed by Olympus.

CLINICAL EFFECTIVENESS

LITERATURE SEARCH

An extensive literature search through different databases resulted in the identification of 9 case series. No results from randomised controlled trials (RCT) on the use of EBVs have been published so far. One unpublished RCT, the "Endobronchial Valve for Emphysema Palliation Trial" (VENT trial), has finalised recruitment in 2007. Some of the results have been presented at international meetings, and rather extensive data related to the US-arm of the trial are available from the website of the US' Food and Drug Administration (FDA)[a]. Moreover, additional information has been obtained directly from the manufacturer.

The outcome measures in these studies, next to safety, most often were FEV1, 6MWD and SGRQ. In the VENT trial, several other secondary safety and effectiveness endpoints have been studied, such as a "major complications composite" (MCC - including death, empyema, massive haemoptysis, pneumonia distal to a valve, pneumothorax or a prolonged air leak, and respiratory failure), exercise capacity, oxygen requirement, and a dyspnoea score. Additional pre-specified analyses were the Quality of Well-Being score, technical success, and rehospitalisation rate. The study intended to enrol 270 subjects with a 2:1 randomisation to EBV insertion, and was powered to detect a 15% improvement in the treatment arm in FEV1 and a 17% improvement in 6MWD.

[a] The availability of the data from the VENT trial on the FDA's website is related to the fact that this pivotal trial was needed for the manufacturer to obtain a pre-market approval (PMA) for its device. On December 8, 2008, the FDA voted the device "not approvable" and suggested further studies to identify potential subset populations that may benefit from the device.

SAFETY

The most commonly reported complications in the case series were COPD exacerbations (up to 17%), followed by pneumothorax (lung collapse - up to 5%) and pneumonia (up to 5%). In the US-arm of the VENT trial, at 6 months of follow-up, control subjects had a 1.2% rate (1/87) of MCCs compared with a fivefold higher 6.1% (13/214) for EBV treated patients, a difference that was not statistically significant. One EBV patient died secondary to a massive hemoptysis. In the European arm of this trial, the MCC at 6 months was statistically significantly worse in the EBV group (3.3% vs. 13.5%). In the US-arm, at one year, the EBV group had significantly higher rates of serious COPD-related adverse events than the control group (23% versus 10%). There was a trend towards higher hospitalization rates for EBV subjects (27.1%) compared with control subjects (16.1%) through 6 months, which was borderline non-significant. Twenty-four percent (230/963) of the EBVs inserted at the start of the study were removed within the first year because of valve migration, subject's request, incorrect placement or recurrent COPD exacerbations.

These data indicate that there might be safety issues related to the use of EBVs.

EFFECTIVENESS

Data retrieved from uncontrolled case series, by there very nature offer low quality evidence.

Data related to the VENT trial, the only RCT that has been finalised so far, have not yet been published. Some of the results could be retrieved from the FDA's website and additional data were provided by the manufacturer. A mean of 3.8 valves per patient have been implanted. At 6 months, the FEV1 spread between EBV patients and controls was 6.8% (58.1 mL) and the 6MWD spread was 5.8% (19.9 metres). The SGRQ score at 6 months was better in the intervention group by a mean of 3.4 points. There was no measurable difference in Quality of Well-Being score between both study groups. At 12 months, the difference in percent changes in FEV1 and 6MWD from baseline in the intention-to-treat analyses were 7.7% and 3.8% respectively, the results of the 6MWD being no longer statistically significantly different. Although FEV1, 6MWD and SGRQ at some point were statistically significantly different in the intervention group from those in the control group, their clinical relevance remains questionable. According to recently updated guidelines, FEV1 should improve by 100-140 mL and 6MWD by 37-71 metres to be perceived by patients to be "important". For SGRQ, a mean change score of 4 units is considered as a slightly efficacious treatment, whereas 8 units indicate a moderately efficacious change. These thresholds were attained in only a minority of the patients in any of the studies that were discussed in this report. Moreover, the non-blinded nature of the studies may have contributed to a placebo effect in the EBV treated patients.

Both in the published case series and in the VENT trial, some patients seem to derive a substantial benefit from the treatment. If those could be identified prior to the procedure, better results of EBV therapy might be anticipated. This hypothesis is being tested in ongoing clinical trials. For the time being, solid evidence supporting the use of EBV technology is lacking.

ECONOMIC CONSIDERATIONS

For the valves and the applicators, an average cost of more than €8000 per patient is to be considered. This figure does not take into account additional expenses such as hospitalisation, medication and physician fees, and the costs related to possible adverse events.

Because there is no unequivocal evidence for an improvement in clinically relevant outcomes, a full health economic evaluation of EBVs cannot be performed yet.

CONCLUSION

Findings originating from case series and from the VENT trial indicate that the safety of EBV insertion in patients with severe emphysema remains a concern. The procedure may induce pneumothorax and the presence of a foreign object within the bronchial tree seems to induce COPD exacerbations and to lead to an increased number of hospitalisations during follow-up.

No peer-reviewed data have been published so far. Some results are available from the minutes of an FDA meeting or were provided by one of the manufacturers of the device. Current evidence indicates that the efficacy of EBVs on outcome measures that are important to patients is on average limited. Based on the results obtained in the US-arm of the VENT trial, the FDA decided not to approve the device for the US market.

Subgroups of patients that are yet unidentified, may benefit more substantially from the procedure, but future research needs to resolve those issues.

RECOMMENDATIONS

Reimbursement of EBVs in patients with end-stage pulmonary emphysema can currently not be supported, because of their poorly demonstrated clinical benefit in combination with the potential adverse effects and their high costs in relation to a limited efficacy. These devices may provide a larger benefit in subgroups of patients, but it is as yet unclear how these subgroups can be identified and whether the clinical improvement would outweigh the potential harms. The possible benefit of EBV in such subgroups should be proven in a prospective RCT including patient-oriented endpoints.

This report indicates that the assignment of a CE-label to a medical device does not guarantee its effectiveness or clinical safety. Such labelling may be misleading to both patients and physicians. The KCE recommends this issue to be put on the agenda of the Belgian presidency of the European Union in 2010.

Scientific summary

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GLOSSARY

6MWD	six-minute walk distance
6MWT	six-minute walk test
ATS	American Thoracic Society
BLVR	Bronchoscopic Lung volume reduction
BODE-index	The BODE-index combines body weight, degree of airflow obstruction (FEV1), a dyspnoea score and exercise capacity (six minutes walk test).
CA	Competent Authority
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CHD	Coronary Heart Disease
CRD	Centre for Reviews and Dissemination
CT	computed tomography
DLCO	diffusing capacity of the lung for carbon monoxide
EBV	EndoBronchial Valve
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FMS	Finnish Medical Society
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group
HDE	Humanitarian Device Exemption
HTA	Health Technology Assessment
HUD	Humanitarian Use Device
IBV	IBV Valve System (Spiration)
ICER	Incremental Cost-Effectiveness Ratio
ICSI	Institute for Clinical Systems Improvement
IDE	Investigational Device Exemption
INAHTA	International Network of Agencies for Health Technology Assessment
LUL	Left Upper Lobe
LVRS	Lung Volume Reduction Surgery
MCC	major complication composite
MRC scale	Medical Research Council dyspnoea scale
NB	Notified Body
NETT	National Emphysema Treatment Trial
NHS	National Health Service
NHSEED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Clinical excellence
NIHDI	National Institute for Health and Disability Insurance (=RIZIV/INAMI)
PaCO2	arterial partial pressure of CO2
PaO2	arterial partial pressure of oxygen
PMA	Pre-market Approval
QALY	Quality Adjusted Life Year
QoL	Quality of Life
QWB	quality of well-being
RCT	Randomized Controlled Trial
RIZIV/INAMI	National Institute for Health and Disability Insurance (Rijksinstituut voor Ziekte- en Invaliditeitsverzekering/National d'Assurance Maladie-Invalidité) (=NIHDI)
RUL	Right Upper Lobe
RV	Residual Volume
SF-36	Short-Form Health Survey
SGRQ	St George's Respiratory Questionnaire
SR	Systematic Review

STS	Society of Thoracic Surgeons (Score)
TCI	Technical Council for Implants (=TRI/CTI)
TCT	Technical Cel (Technische Cel / Cellule Technique)
TLC	Total Lung Capacity
TRI/CTI	Technical Council for Implants (Technische Raad voor Implantaten/Conseil Technique des Implants) (=TCI)

1 SCOPE

This rapid Health Technology Assessment (HTA) report provides a systematic review of the scientific literature on the (cost-)effectiveness of endobronchial valves (EBVs) as an additional therapeutic modality on top of current optimal non-invasive therapy, in patients with severe pulmonary emphysema.

The following research questions are considered:

1. Is the bronchoscopic insertion of EBVs in patients with endstage pulmonary emphysema feasible and safe?
2. What is the clinical value of EBV insertion in these patients, when added on top of an optimal non-invasive management?
3. Is EBV insertion a cost-effective additional treatment in patients that are otherwise maximally treated with drugs, pulmonary rehabilitation and oxygen?

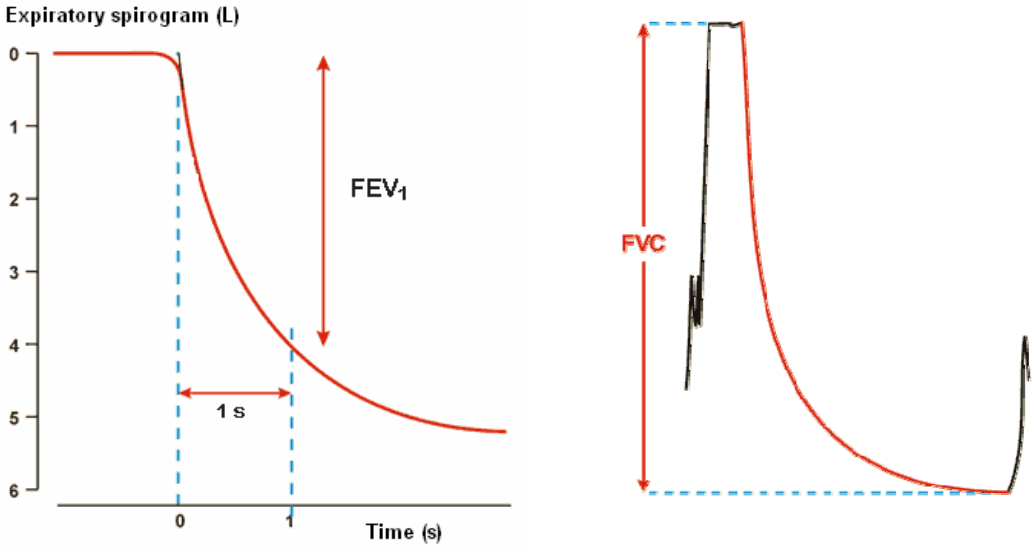
2 CLINICAL BACKGROUND

2.1 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) represents a spectrum of lung diseases characterised by a not fully reversible and progressive limitation of the airflow to the distal parts of the lungs, caused by a mixture of disease of the smaller airways and parenchymal destruction, the relative contribution of which varies from person to person.[1] The impact of COPD on an individual patient depends on the extension of the pathology. COPD can cause chronic symptoms of cough, sputum production, breathlessness, decreased exercise capacity and a number of systemic effects such as weight loss and skeletal muscle dysfunction. COPD is a progressive disease, especially if a patient's exposure to noxious agents continues. The main cause of COPD is cigarette smoking, making it a largely preventable disease. However, about 15% of patients with COPD do not have a history of cigarette smoking.[2]

COPD is a clinical diagnosis based on history taking, the presence of specific signs and an assessment of airway obstruction by means of "lung function testing" or "spirometry". Airflow obstruction is defined as a postbronchodilator Forced Expiratory Volume in 1 second (FEV1) value of less than 80% of predicted, in association with an FEV1 to Forced Vital Capacity ratio (FEV1/FVC) of less than 70% (Figure 1).[3] The presence, extent and distribution of emphysema can be most precisely determined with a high-resolution chest CT scan.[2]

Figure 1: Expiratory spirogram, depicting forced expiratory volume in one second (FEV1) and forced vital capacity (FVC)



Source: http://www.spirxpert.com
FEV1: Forced Expiratory Volume in 1 second (the volume exhaled during the first second of a forced expiratory manoeuvre started from the level of total lung capacity) ; FVC: Forced Vital Capacity (The volume change of the lung between a full inspiration to total lung capacity and a maximal expiration to residual volume)

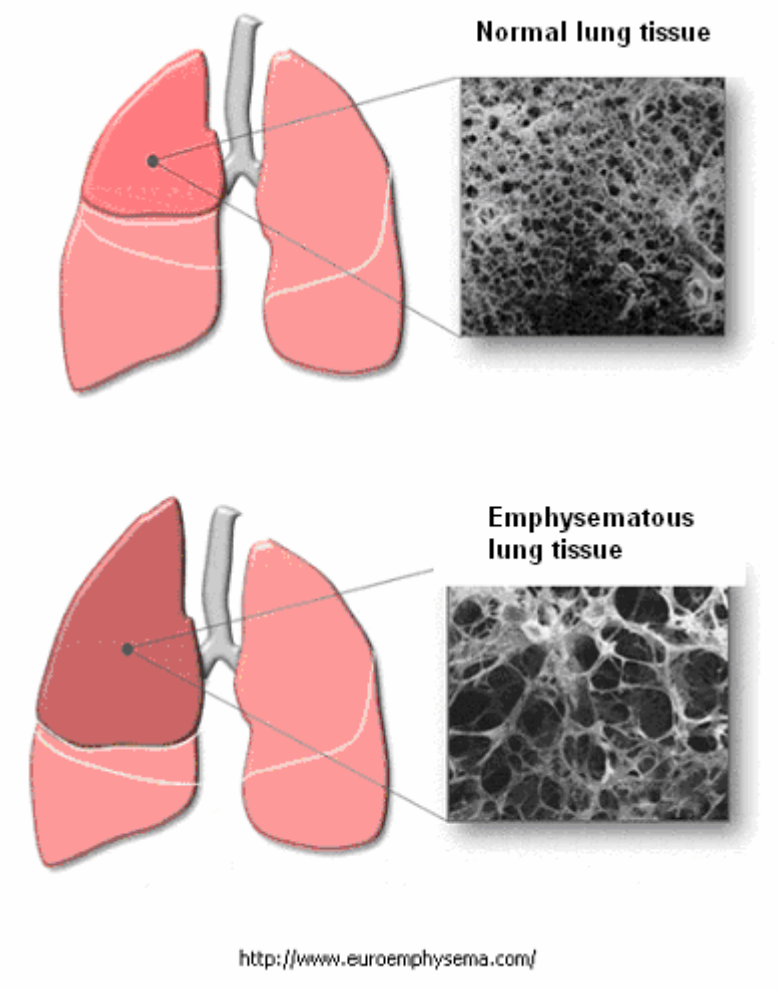
The FEV1 is an important predictor of survival in patients with COPD. The rate of decline in FEV1 is a good marker of disease progression and mortality. However, FEV1 does not adequately reflect all the systemic manifestations of the disease. For example, it correlates weakly with the degree of dyspnoea, and its change does not reflect the rate of decline in patients' health.[4] Prognosis can be better determined if parameters other than those merely reflecting airway obstruction are taken into consideration. The BODE-index has shown to better predict survival than FEV1 alone.

It combines **b**ody weight, degree of airflow **o**bstruction (FEV1), a **d**yspnoea score and **e**xercise capacity (six minutes walk test).[4] In a previous KCE report on pulmonary function testing, international guidelines for assessing the severity of COPD were discussed.[5] Four recently (at the time of release of KCE report 60C) updated international guidelines were identified: (1) Institute for Clinical Systems Improvement (ICSI), available from web site www.icsi.org, (2) Global Initiative for Chronic Obstructive Lung Disease - GOLD,[1] (3) NICE and (4) Finnish Medical Society (FMS), available from web site www.ebm-guidelines.com. All four guidelines classify the severity of COPD based on airflow limitation as measured by spirometry. However, the actual values and categories vary. The most often referred to classification is the one by GOLD (see also Figure 4) and defines mild disease in patients with an FEV1 of more than 80% of the predicted value, moderate disease in patients with an FEV1 between 50% and 80% of predicted, severe disease when FEV1 is between 30% and 50% of predicted and very severe disease when FEV1 is lower than 30% of predicted, or lower than 50% plus chronic respiratory failure, i.e. an arterial partial pressure of oxygen (PaO2) less than 60 mmHg with or without an arterial partial pressure of CO2 (PaCO2) greater than 50 mmHg.[1] Three guidelines (ICSI, GOLD, NICE) emphasize the importance of considering other factors (i.e., signs, symptoms, complications) in addition to FEV1 values in assessing severity of disease. As discussed higher, the BODE-index has been used to predict survival in patients with COPD and takes into account other parameters than just spirometry. The index ranges from 0 to 10 points, with higher scores indicating a higher risk of death. The highest quartile (a BODE score of 7 to 10) is associated with a mortality rate of 80% at 52 months, whereas the lowest quartile, 52 months mortality rate is 20%.[4]

2.2 PULMONARY EMPHYSEMA

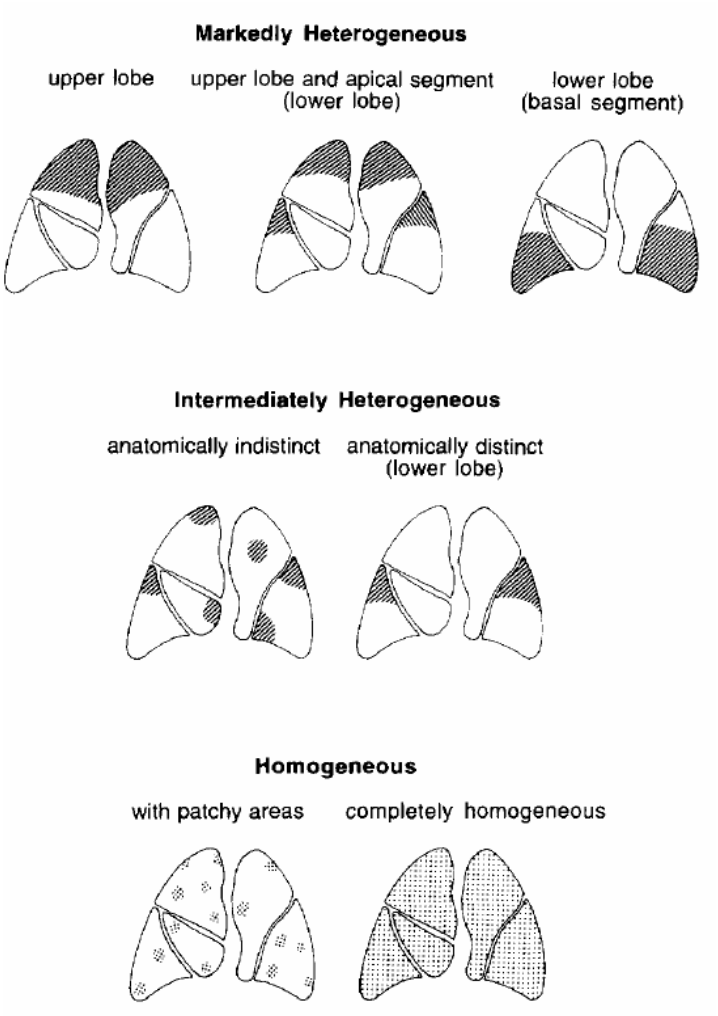
As discussed earlier, the airflow limitation in COPD is caused by a mixture of small airways disease and parenchymal destruction, the relative contributions of which vary from person to person.[1] Small airways disease is caused by chronic inflammation, leading to structural changes and narrowing of the airways.[1] Emphysema on the other hand, represents the condition within the spectrum of COPD in which parenchymal destruction is the predominant feature (Figure 2), leading to an abnormal permanent enlargement of the air spaces distal to the terminal bronchioles and resulting in a loss of elastic recoil ("stretchiness") of the lungs. This prevents the lungs from squeezing the air out of the lungs properly. This leads to the typical hyperexpansion of the chest with a flattened diaphragm, widened intercostal spaces, resulting in increased work of breathing and dyspnoea.[6]

Figure 2: Section of normal and emphysematous lung tissue and corresponding enlargement of the involved right upper lobe (cartoons on the left).



The parenchymal destruction of lung tissue can be unevenly distributed within one lung. As discussed later, the location and the degree of heterogeneity of the emphysemous process may have important consequences as far as therapeutic lung volume reduction is concerned. The severity and distribution of emphysema most often is assessed by high-resolution CT.[7, 8] It can also be estimated by ventilation/perfusion scintigraphy. The emphysema severity of different regions of the lung can be calculated by computer, based on X-rays attenuation (Hounsfield units).[8] In this way, the degree of heterogeneity of the emphysematous disease over both lungs can be established as shown in Figure 3.

Figure 3: Three major types of emphysema distribution.

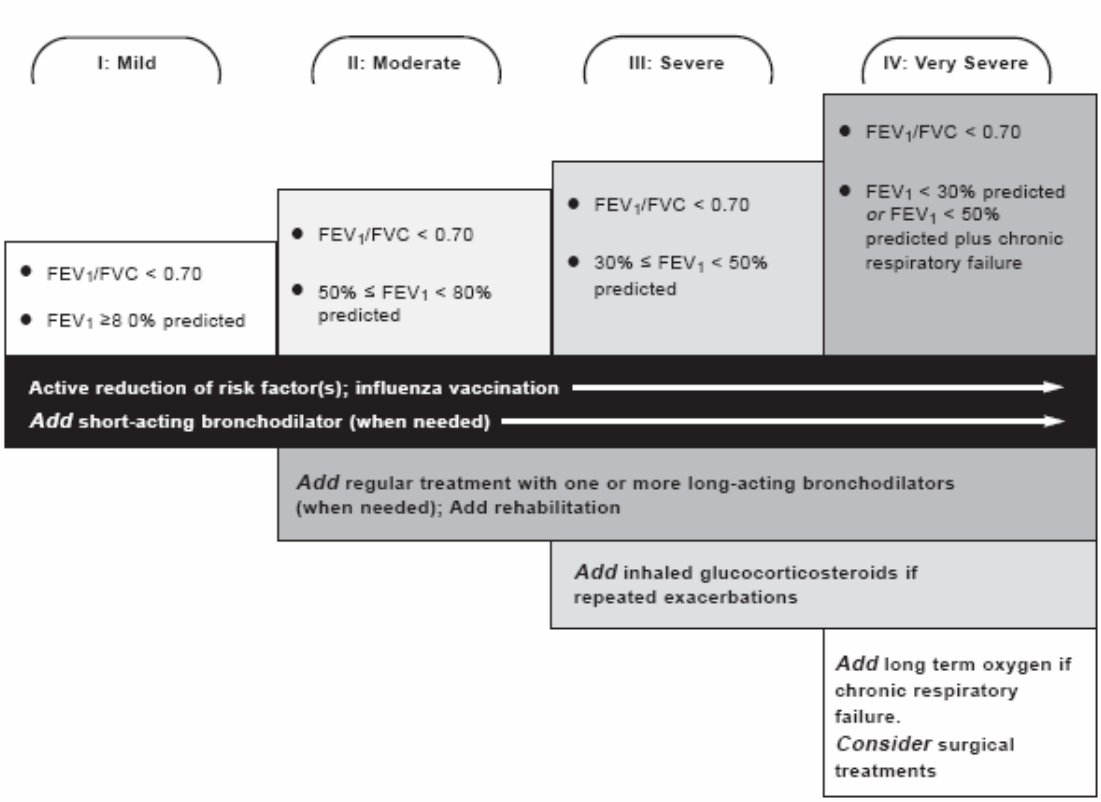


Source: Weder et al.[7]

2.3 COPD MANAGEMENT

The therapy of COPD is based on a stepwise approach, related to the severity of the disease, as depicted in Figure 4. Many COPD patients need medical treatment for the rest of their lives, with increasing doses and additional medications during exacerbations. Medical therapy consists of bronchodilators, anti-inflammatory agents, oxygen therapy, mucolytics, and pulmonary rehabilitation. The aims of treatment are to alleviate symptoms, to prevent exacerbations, to prevent further deterioration of pulmonary function, and to improve activities of daily living, quality of life and survival.

Figure 4: Therapy at different COPD stages



Source: GOLD, 2007[9]

Although medical therapy benefits many patients with COPD, a substantial minority derive only limited improvement because medical treatment targets only the airway component of the disease. Bronchodilator and anti-inflammatory drugs fail to address the physiological deficit associated with the loss of elastic recoil that represents the primary cause of flow limitation in emphysema. In these patients, medical therapy may be minimally effective.[10] A very limited number of patients with end-stage COPD (in Belgium 40-50 per year)[a] are appropriate candidates for lung transplantation. For those that are not, lung volume reduction surgery (LVRS) may represent a therapy of last resort. Although it is directed at only a very small subgroup of patients with "very severe" (i.e. "stage IV) COPD, it will be discussed here in more detail because of its relationship with bronchoscopic lung volume reduction that represents the central issue of this report.

In LVRS, some of the damaged and hyperinflated portions of the lung are resected, providing more capacity within the chest cavity for the remaining lung to expand and function properly. The clinical benefits of LVRS have been investigated in the National Emphysema Treatment Trial (NETT), a large US multicenter randomized trial that compared LVRS plus medical treatment with medical treatment alone in patients with COPD and severe emphysema.[11] An **interim report** on 1033 patients was published in October 2001.[12] The data and safety monitoring board of the study had identified a subgroup of patients in the intervention group at *high risk for early mortality*. For 69 patients who had an FEV1 that was <20% of their predicted value and either a homogeneous distribution of emphysema on CT or a diffusing capacity of the lung (DLCO) <20% of their predicted value, the 30-day mortality rate after surgery was 16%, as compared with a rate of 0% among 70 medically treated patients. Among these high-risk patients, the overall mortality rate during three years of follow-up was higher in surgical patients than medical patients (0.43 deaths per person-year vs. 0.11 deaths per person-year; RR 3.9; 95% CI 1.9 to 9.0).

[a] Data provided by prof. D. Van Raemdonck, KUL.

As compared with medically treated patients, survivors of surgery had small improvements at six months in the maximal workload (4.5±13.0 W) and the 6MWD (14.9±63.7 metre), but a similar health-related quality of life (the score for the Quality of Well-Being questionnaire had decreased by 0.01 unit in both groups at six months (p=0.94)). Because of the dismal mortality data, this type of high-risk patients was no longer eligible for randomisation.

The **major publication** from the NETT research group was published in May 2003.[13] For the *overall population* of 1218 patients, the 90-day mortality rate in the surgery group was 7.9% (95% CI 5.9 to 10.3) and was significantly higher than that in the medical-therapy group where it was 1.3% (95% CI 0.6 to 2.6). Among the 1078 patients who were *not at high risk* (as defined post hoc in the interim report[12]), the 30-day mortality rate was 2.2% in the surgery group, as compared with 0.2% in the medical-therapy group, and the 90-day mortality rate was 5.2% in the surgery group, as compared with 1.5% in the medical-therapy group. After a mean follow-up of 29.2 months, *overall* mortality was unchanged in both study groups, even if the high-risk patients defined earlier were not taken into consideration. Changes in exercise capacity, 6MWT, FEV1, quality of life (QoL) and SGRQ at 6, 12, and 24 months favoured the surgery group, but the improvement was modest (e.g. in the population without the high-risk patients, 20% of the surgical patients had an increase of their maximal workload of more than 15 watt). Further post-hoc subgroup analyses were provided, based on the pattern of emphysema on CT scanning and exercise capacity. Exercise capacity was defined as "low" at the sex-specific 40th percentile of the baseline cycle ergometry (with an increment 5 or 10 W per minute after three minutes of pedaling with the ergometer set at 0 W), corresponding to 25 W for women and 40 W for men. Patients with predominantly *upper-lobe emphysema and a low maximal workload* (n=290, 23.8% of total study group) had lower mortality, a greater probability of improvement in exercise capacity, and a greater probability of improvement in symptoms after LVRS. In contrast, patients with predominantly *non–upper-lobe emphysema and a high maximal workload* had higher mortality if they underwent LVRS, and they had little chance of functional improvement regardless of the treatment they received.

According to **a longer term analysis**, these effects persisted.[14] *The intention-to-treat analysis of the 1218 randomized patients* demonstrated an overall survival advantage for LVRS, with a 5-year risk ratio for death of 0.86 (p= 0.02). Nevertheless, the death rate remained very high: after a median follow-up of 4.3 years, it was 46.5% in the LVRS group vs. 53.1% in the medical group. Overall, clinical improvement was more likely in the LVRS than in the medical group for maximal exercise through 3 years and for health-related quality of life SGRQ through 4 years. Improvement in exercise capacity was defined as an increase in maximum workload >10 watts above the patient's postrehabilitation baseline. This threshold was achieved in 9% of the surgical patients and in 1% of the medically treated group. *The post-hoc defined subgroup of "upper-lobe emphysema patients with low exercise capacity"* demonstrated the best improved survival (5-year RR, 0.67) after LVRS. The absolute mortality after a median follow-up of 4.3 years, was 44.6% in the LVRS group vs. 60.3% in the medical group. In this surgically treated subgroup, there was also an improved exercise tolerance throughout 3 years (21% more than 10 watts increase vs. 0%), and SGRQ through 5 years.

According to a recent (first published 2006, last assessed as up-to-date Sept 2008) Cochrane systematic review on LVRS, patients who survive up to three months after surgery have a significantly better health status and lung function as compared to those with usual medical care.[15] When considering the data from the NETT trial (constituting 75% of the patients pooled in the Cochrane review) this improvement is modest and rather difficult to ascertain because of a high number of "missing data" and the lack of blinding. The latter indicates that there is a possible placebo effect of surgery, and this may contribute to the significant differences in QoL markers.[15]

Even when performed in experienced centres, LVRS is associated with a >5% 90-day mortality, and a 50 to 60% incidence of significant medical complications, including respiratory failure, prolonges air leaks, pneumonia, cardiac arrhythmias, heart failure and gastrointestinal complications.[10]

This has resulted in a limited adoption of LVRS, with only 122 Medicare patients in the US undergoing the procedure in 2006.[b] In Belgium, about 10-15 LVRS are performed annually (Table 1).

Table 1: Lung volume reduction surgery in Belgium (number and NIHDI expenditures)

NIHDI code	description	Number of acts in specific year		NIHDI reimbursement
227570-227581[a]	Heelkunde voor een- of tweezijdige vermindering van het longvolume, exclusief het viscerosynthesemateriaal	2003[b]	3	€2083,98
		2004	15	€10563,6
		2005	11	€7781,85
		2006	10	€6913,56
		2007	12	€9661,27
682533-682544[a]	Geheel van gebruiksmateriaal en implanteerbaar materiaal gebruikt tijdens de verstrekking 227570-227581 via endoscopische weg, bij een éénzijdige vermindering van het longvolume	2007[c]	8	€12585,36
682555-682566[a]	Geheel van gebruiksmateriaal en implanteerbaar materiaal gebruikt tijdens de verstrekking 227570-227581 bij open chirurgie, bij een éénzijdige vermindering van het longvolume	2007[c]	2	€3146,34

NIHDI: National Institute for Health and Disability Insurance
a: only the codes 227581, 682544, and 682566 (i.e. hospitalised) occurred; b: the code was created on April 1, 2003; c: the code was created on February 1, 2007.

The fee and reimbursement for these codes are as follows:

Table 2: Lung volume reduction surgery in Belgium (fee and reimbursement, in €)

NIHDI code	Nomenclature value		reimbursement	
			Non-preferential	preferential
227570-227581[a]	2003[a]	694,66	694,66	694,66
	2004	704,24	704,24	704,24
	2006	720,16	720,16	720,16
	2007	732,04	732,04	732,04
	2008	743,9	743,9	743,9
	2009	776,04	776,04	776,04
682533-682544[a]	2007	2097,55	1573,17 or 1179,88[b]	1573,17
682555-682566[a]	2007	2097,55	1573,17 or 1179,88[b]	1573,17

a: the year in which changes were incorporated in the nomenclature.
b: 1573,17 with a conventioned prescriber and 1179,88 with a non-conventioned prescriber.

[b] http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4405b1-03-Sponsor's%20Executive%20Summary.pdf

2.4 COPD OUTCOME MEASUREMENTS

According to current guidelines, severity grading of COPD depends upon both spirometric and variable QoL measurements. The correlation between airways obstruction in COPD and exercise performance is only modest.[16, 17] Several QoL measurements that are referred to in the studies included in this HTA report, have been used to assess a patient's exercise tolerance before and after EBV insertion, and are discussed hereafter.

2.4.1 Spirometry

Disabiliy is only weakly related to measurements of lung function.[18, 19] This is even more so the case in COPD with predominant emphysema, where parenchymal lung destruction next to airways obstruction contributes largely to the pathogenesis of the disease. Moreover, whether a change in spirometry reflects a true change in clinical status depends on the reproducibility of the spirometric test and on the minimal change in a lung volume parameter that is needed to be clinically relevant to a patient. For a spirometric change to be significant, whether statistical or biological, depends on the particular parameter, the time period between different measurements and the type of patient. For tracking change, FEV1 has the advantage of being the most repeatable lung function parameter.[20] In normal subjects, two-point short-term changes (week to week) of >12% and >200 mL are usually statistically significant and may be clinically important. In COPD patients, the ATS/ERS (American Thoracic Society/European Respiratory Society) in its most recent joint statement on interpretative strategies for lung function tests pointed towards the lack of extensive literature on the subject and suggested (sic) a change in FEV1 to be at least 100-140 mL to be considered clinically important.[21]

2.4.2 Six-minute walk test

The six-minute walk test (6MWT) is a popular clinical exercise test in COPD. The test is widely used because it involves a familiar daily activity and involves the use of minimal technical resources.[22] It measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes and is a measure of functional capacity, targeted at people with at least moderately severe functional impairment. This test evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. [23] It is not known whether it is best for clinical purposes to express change in 6MWD (six-minute walking distance) as (1) an absolute value, (2) a percentage change, or (3) a change in the percentage of predicted value. The ATS recommends in its guideline that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A point of particular interest is the reproducibility of a walking test for which there seems to be a learning effect. In one study, 36 patients with COPD were studied to examine the reproducibility and order effect of repeated walking tests when performed over consecutive days or consecutive weeks. In a first trial, where 12 patients performed 12 walks over three consecutive days, five minute walking distance increased by 33% between walks 1 and 12 (half of the increase occurring after the first three walks). In a second trial, where 24 patients performed 12 walks over four consecutive weeks, five minute walking distance increased by 8.5% between walks 1 and 12.[24] The study concluded that the learning effects seen on repeated performance of walking tests over short intervals should be considered when an individual's response to treatment is being interpreted. As a result, a placebo group or randomised crossover design is essential when walking tests are used in clinical trials.[24] A more recent study looked at the effect of repeated 6-minute walks on a separate day in 470 patients with severe emphysema who were participants in the National Emphysema Treatment Trial.[25] There was a statistically significant improvement, averaging 7% (SD 15.2%, with 70% of people improving) when the test was repeated on a second day. Expressed in metres, the second 6MWD was greater by 20.14±44.5 metres. The authors attributed this improvement to familiarity with the walking course, better pacing, or motivational factors.

It was also deemed possible that the patients were less fatigued on the second test day because the test had not been preceded by an oxygen titration test requiring treadmill walking at 1 to 2 miles per hour. Also other factors may have an effect on the results, such as the course layout: participants tested on continuous courses had a 28.1 metres longer walking distance than those tested on straight courses. The implication of these results is that clinical trials that rely on 6MWD before and after an intervention should include appropriate control groups, or repeated tests, to account for this learning effect. If a single 6MWT is used, there should be a contemporaneous control group and the tests should be spaced several weeks apart to minimize the learning effect.[25] Despite this learning effect, according to the ATS guidelines, the reproducibility of the 6MWT appears to be better than the reproducibility of FEV1 in patients with COPD.[23] Furthermore, these guidelines also do not require a practice walk.[23]

A statistically significant mean increase in 6MWD in a study group not necessarily indicates a clinically significant increase for an individual patient. In a study of 112 patients with stable, severe COPD, the smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was a mean of 54 m (95% CI, 37–71 m).[26] This study suggests that for individual patients with COPD, an improvement of more than 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant.[23] This is similar to the results in a study of Sciurba et al. where a second 6MWD was observed to be 66.1±146 feet greater. The authors argue that "an individual patient would need to improve by more than 352 feet (or 107.29 m) (66 feet + 1.96 x 146 feet) to be 95% confident that there had been improvement. If the short term learning effect is discounted, for example in tests done 4 weeks apart, then an improvement of 286 feet (or 87.17 m) (1.96 x 146) is necessary to be 95% confident that the change was not random variation."[25]

2.4.3 St George's Respiratory Questionnaire

The St George's Respiratory Questionnaire (SGRQ) has been introduced because the symptomatic gain in individual patients in routine practice cannot always be inferred reliably from spirometric changes since many factors influence the development and perception of respiratory symptoms and the ensuing disability.[18] It is a disease-specific instrument for measuring impaired health and perceived well-being in patients with COPD. It contains 76 items in three subscales: symptoms (frequency and severity), activity (activities that cause or are limited by breathlessness) and impacts (social functioning, psychological disturbances resulting from airways disease). Each response has an empirically derived weight. The total score is calculated from responses to all items, and range from 0 to 100, with 0 reflecting no impairment and 100 the worst impairment.[27, 28] Jones mentions that there is no universally agreed definition of worthwhile benefit in chronic disease, but a common view is that a benefit is considered clinically significant if a patient can detect a definite reduction in his symptoms or of the impact of the disease on his daily life. A threshold of 4 units in the SGRQ has been previously suggested by Jones to be associated with a patients' overall assessment that a treatment was "effective".[18] The ATS website[c] mentions that based on empirical data and interviews with patients, a mean change score of 4 units is associated with slightly efficacious treatment, 8 units for moderately efficacious change and 12 units for very efficacious treatment, referring to two publications of the same author.[27, 29] No explanation for the 8- and 12-unit threshold was found in the original publications referred to. Concerning the 4-unit threshold for a (slightly) efficacious treatment, a model was created in which the effect on SGRQ score of hypothesized differences in health between population could be tested.[27] Coefficients obtained from a multivariate model were used to estimate the effect of differences in mean 6MWD, MRC dyspnoea scale, and anxiety scores, added with frequency of wheeze and cough. Two output examples of this model were given. The first one included a 6% difference (or 22 m) for the 6MWD and 10% differences for the four other variables. This resulted in a 4.5 difference (or 9.8%) in the total SGRQ score.

[c] http://www.atsqol.org/sections/instruments/pt/pages/george.html

It is not clear whether the results of this model (with e.g. a difference of 22 m in 6MWD) can be interpreted as a clinically relevant improvement.

In a population of patients with stable COPD the short term repeatability of this questionnaire seemed to be good. The correlation between SGRQ measurements made 2 weeks apart was 0.92,[28] but the correlation coefficient did not give the full picture since the standard deviation for the difference between the two measurements was ±9 units. Jones mentions that approximately half of the patients will show a change in SGRQ score that is greater or less than the 4 unit threshold for a clinically significant change, whether or not there has been a real change in their state. Equally, in other patients who have a "true" worthwhile benefit, the health status score may change by less than the clinically significant threshold.[18]

2.4.4 Medical Research Council dyspnoea scale

The Medical Research Council (MRC) dyspnoea scale grades the effect of breathlessness on daily activities. This scale measures perceived respiratory disability, the WHO definition of disability being "any restriction or lack of ability to perform an activity in the manner or within the range considered normal for a human being".[19] The 5 grades of the MRC dyspnoea scale are shown in Table 3.

Table 3: Medical Research Council dyspnoea scale

Grade	Degree of breathlessness related to activities
1	"I only get breathless with strenuous exercise"
2	"I get short of breath when hurrying on the level or up a slight hill"
3	"I walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level"
4	"I stop for breath after walking 100 yards or after a few minutes on the level"
5	"I am too breathless to leave the house"

Source: .Bestall et al.[19]

Grades 3, 4, or 5 from the MRC dyspnoea scale correspond to moderate to severe disability due to dyspnoea, while grades 1 or 2 correspond to mild disability due to dyspnoea.[19] In the study of Bestall et al, 32, 34 and 34 patients were classified as having MRC grade 3, 4 and 5 dyspnoea, respectively. In their analysis, FEV1 was not associated with MRC grade.[19] There is no report of the change in MRC score that is associated with a clinically significant improvement or deterioration.[30]

2.4.5 BODE index.

As discussed earlier, FEV1 weakly correlates with the degree of dyspnoea, and its change does not reflect the rate of decline in patients' health. Prognosis can be better determined if parameters other than those merely reflecting airway obstruction are taken into consideration. The BODE-index has been developed to better predict survival than FEV1 (alone). It combines body mass index (BMI), FEV1, a dyspnoea score and exercise capacity (6MWD).[4] Except for BMI that is scored above (0 points) or below 21 (1 point), the other parameters are scored from 0 to 3, a higher number indicating a weaker performance. When these points are added, the resulting BODE index ranges from 0 to 10 points, with higher scores indicating a greater risk of death.

2.4.6 Generic instruments

In clinical studies, the most often used instruments to measure QoL are disease-specific questionnaires. However, generic instruments such as the EQ-5D are considered to be more useful where measurements of patient utilities are required for economic evaluation. The index-based utility scores can be used to compare burden of disease across different conditions and facilitate the calculation of quality adjusted life years (QALYs) that are incorporated into economic evaluations of health care interventions.[31] In contrast, disease specific instruments may fail to capture all aspects of HRQoL, e.g. comorbidities and side effects of an intervention.

Specifically for COPD patients, van Manen et al.[32] showed that impairments in physical functioning, vitality, and general health are related to COPD and to some extent to comorbidity, while impairments in social and emotional functioning do not seem to be related to COPD, but only to comorbidity.

Generic questionnaires would be relatively insensitive to worthwhile treatment effects in COPD,[33, 34] although e.g. the generic SF-36 has shown responsiveness in pulmonary rehabilitation.[35]

EQ-5D has gained widespread use for several reasons. It is a brief, simple measure for patients to understand and to complete, imposing minimal respondent burden and the measure is easy to score and interpret.[36] As mentioned before, the outcomes can be used in economic evaluation. In contrast to the EQ-5D questionnaire, there is no clear economic methodology to value the gain in QoL from disease-specific instruments. In general, generic instruments should be implemented more often in studies to allow inclusion of outcomes in economic evaluations.[37]

Key points

COPD and COPD treatment

- **Chronic Obstructive Pulmonary Disease (COPD) represents a spectrum of lung disease, characterised by a not fully reversible and progressive limitation of airflow to the lungs, due to a combination of disease of the smaller airways and parenchymal destruction.**
- **Pulmonary emphysema is part of the spectrum of COPD in which parenchymal destruction is the predominant pathophysiological feature.**
- **The main cause of COPD is cigarette smoking.**
- **Treatment of stable COPD consists of smoking cessation, bronchodilator medications, steroids in severe case cases and exercise training.**
- **In very severe cases, oxygen therapy is recommended. A limited number of patients are candidates for lung transplantation. For those that are not, lung volume reduction surgery (LVRS) may represent a therapy of last resort (in Belgium currently limited to 10 to 15 cases per year).**

COPD outcome measures

- **In COPD patients, a change in FEV1 of at least 100-140 mL is required between week-to-week tests to be considered clinically important.**
- **When an individual's response to treatment is being assessed, in order to be 95% confident that an increase in 6 minute walk distance (6MWD) is not due to random variation, it should be at least 70 metres. A placebo group or randomised crossover design is essential when using a walking test in clinical trials.**
- **The St George's Respiratory Questionnaire (SGRQ) provides a score between 0 and 100, reflecting QoL in patients with COPD. An improvement of 4 units is considered a slightly, 8 units a moderately, and 12 units a very efficacious treatment. These thresholds however have been poorly validated.**
- **The BODE index has been advocated to provide a quantitative estimation of survival in COPD patients.**
- **Disease specific intruments for QoL estimation are often used in clinical studies, but their usefulness in economic evaluations, where generic instruments are required, is limited.**

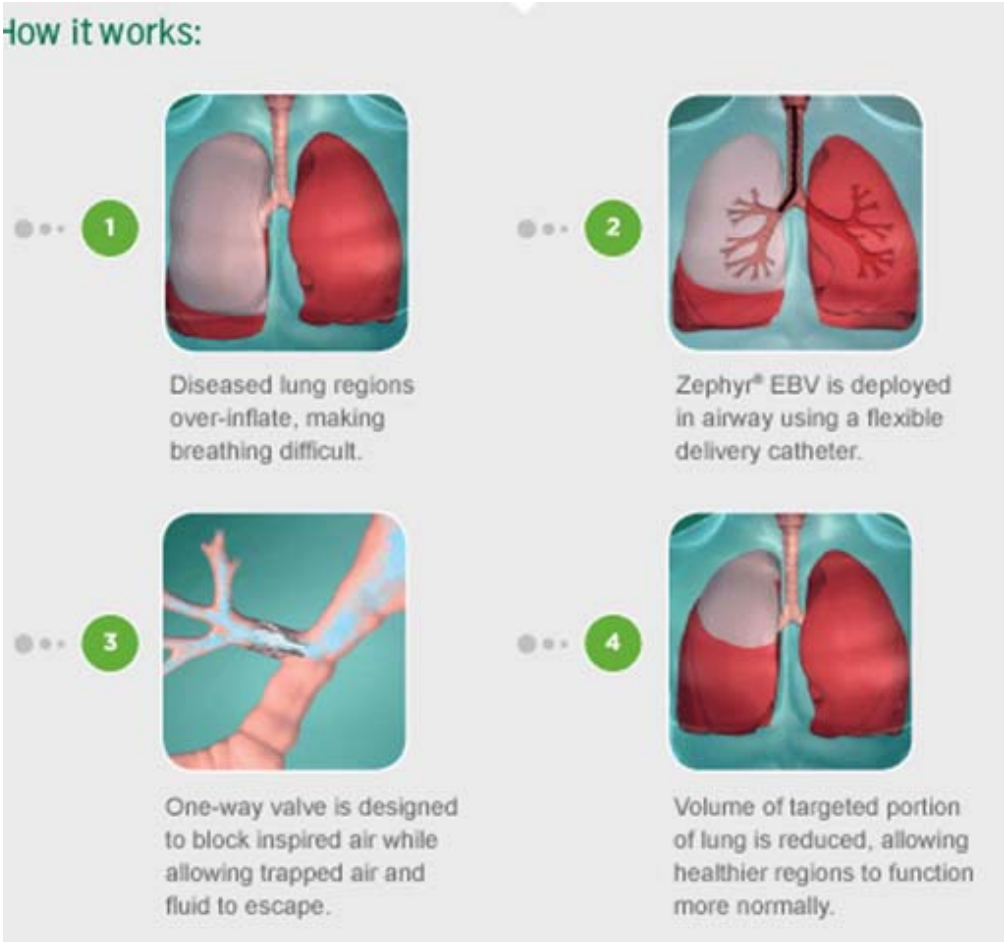
3 ENDOBRONCHIAL VALVES TECHNOLOGY

3.1 RATIONALE

The bronchoscopic insertion of endobronchial valves (EBV) aims at duplicating the results obtained by LVRS and is referred to as bronchoscopic lung volume reduction (BLVR). Its development has been encouraged by the poor response of emphysema patients to medical therapy, by the positive findings of LVRS, but the high mortality and morbidity that accompanied this surgical procedure.

These one-way valves prevent air from entering the blocked emphysematous segment, while allowing the venting of expired gas and bronchial secretions, leading to atelectasis of the isolated segments with subsequent reduction in lung volume.[38] This is illustrated in Figure 5, which is adapted from a figure displayed in www.euroemphysema.com.

Figure 5: Mode of operation of EBVs.

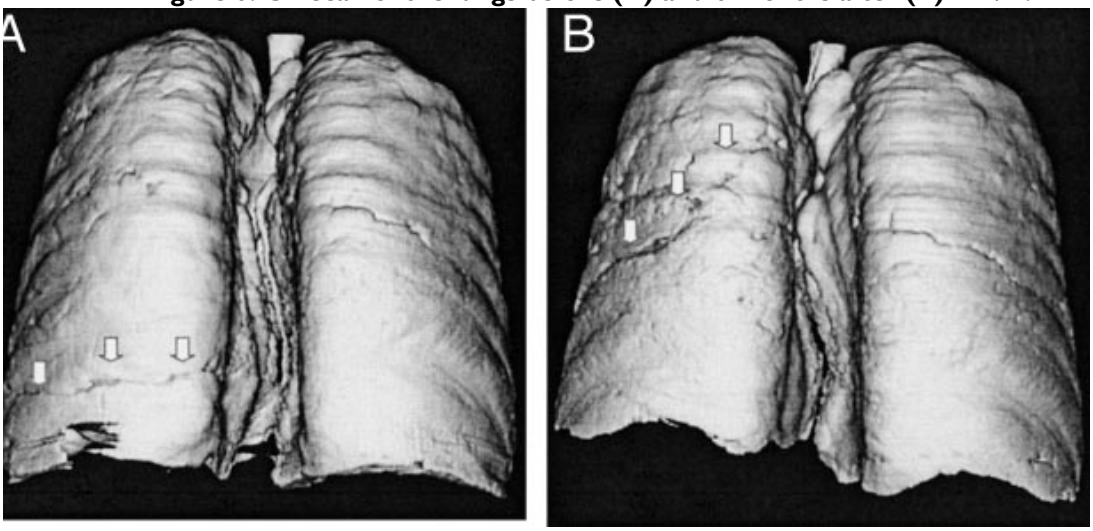


http://www.emphasysmedical.com/valve-therapy/therapy-overview/

This effect has been illustrated in some patients by a CT scan taken before and after such a procedure. Figure 6 shows a three-dimensional CT reconstruction of the lungs before and 6 months after BLVR. The oblique fissure of the left lung is highlighted (white arrows), and the image illustrates how the reduction of the upper lobe volume resulted in a re-expansion of the lower lobe.[39] Further studies have indicated however that this substantial reduction in the size of the EBV-treated lungs could be demonstrated in only a minority of patients. This is explained by the phenomenon of collateral ventilation, i.e. the ventilation of alveoli through anatomic channels that bypass normal airways, preventing the development of areas of atelectasis in the setting of airways obstructed by EBVs.6

Notwithstanding the absence of radiological atelectasis, some patients did show some improvement in exercise tolerance following BLVR, which then was ascribed to the prevention of hyperinflation of the affected lung segments during exercise by the one-way valves.[40] Hyperinflation of certain lung segments during exercise seems to be a key element in the ventilatory limitation of exercise in COPD, where expiratory flow limitation leads to a progressive increase in endexpiratory lung volume and consequently restricts the tidal volume that can be achieved.[41]

Figure 6: CT scan of the lungs before (A) and 6 months after (B) BLVR.[39]



The oblique fissure of the left lung is indicated by white arrows. After insertion of EBVs into the left upper lobe bronchi, the volume of the left upper lobe is reduced and gave rise to a re-expansion of the lower lobe.

Next tot EBV, other bronchoscopic techniques aimed at obtaining LVR are in development, such as the instillation of a biocompatible substance into emphysematous lung segments, or the creation of bronchoparenchymal passages to facilitate expiration and prevent dynamic hyperinflation of diseased segments. These procedures however are less well studied than the EBVs, and are beyond the scope of this HTA.

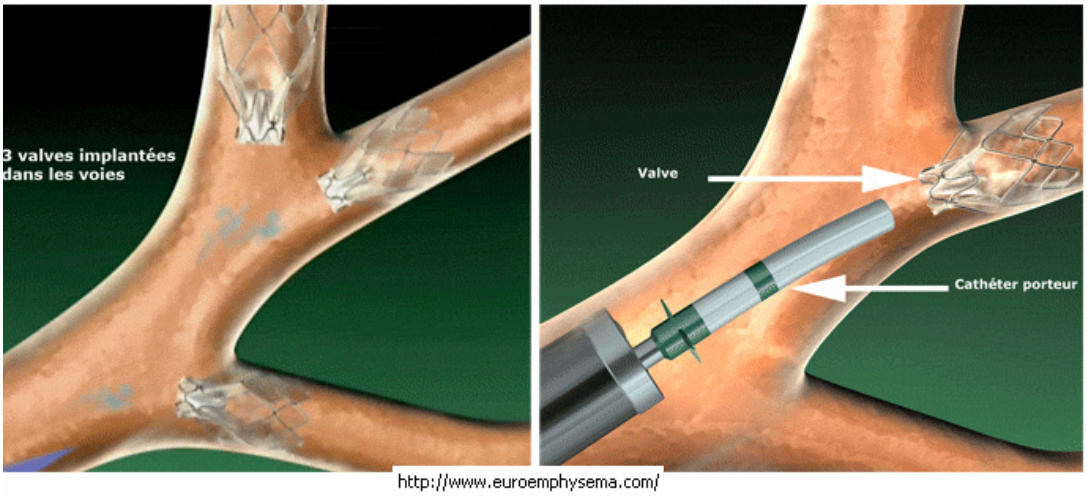
3.2 TECHNOLOGY DESCRIPTION

The largest experience with EBVs has been obtained with two different devices: the Zephyr endobronchial valve (originally Emphasys Medical, currently Pulmonx) and the Spiration Intrabronchial Valve (Spiration Inc.). In Belgium, Pulmonx is represented by RMS Endoscopy and the Spiration IBV valve is distributed by Olympus.

3.2.1 Emphasys Medical: Zephyr EBV

The Emphasys Medical EBV is a silicone-based, one-way valve mounted on a nitinol stent. The first published pilot study in which it was used, was by Toma in 2003.[42] In its initial presentation, the device was introduced into the bronchi over a guidewire, but modifications ultimately lead to a third generation device, termed the "Zephyr" EBV. The latter can be deployed through the working channel of a bronchoscope (Figure 7) and offers less resistance to expiratory flow than previous models.[38] The Zephyr EBV is currently manufactured in two sizes with overlapping diameter ranges (4.0-7.0 mm and 5.5-8.5 mm), in order to provide a proper fit within the bronchus.

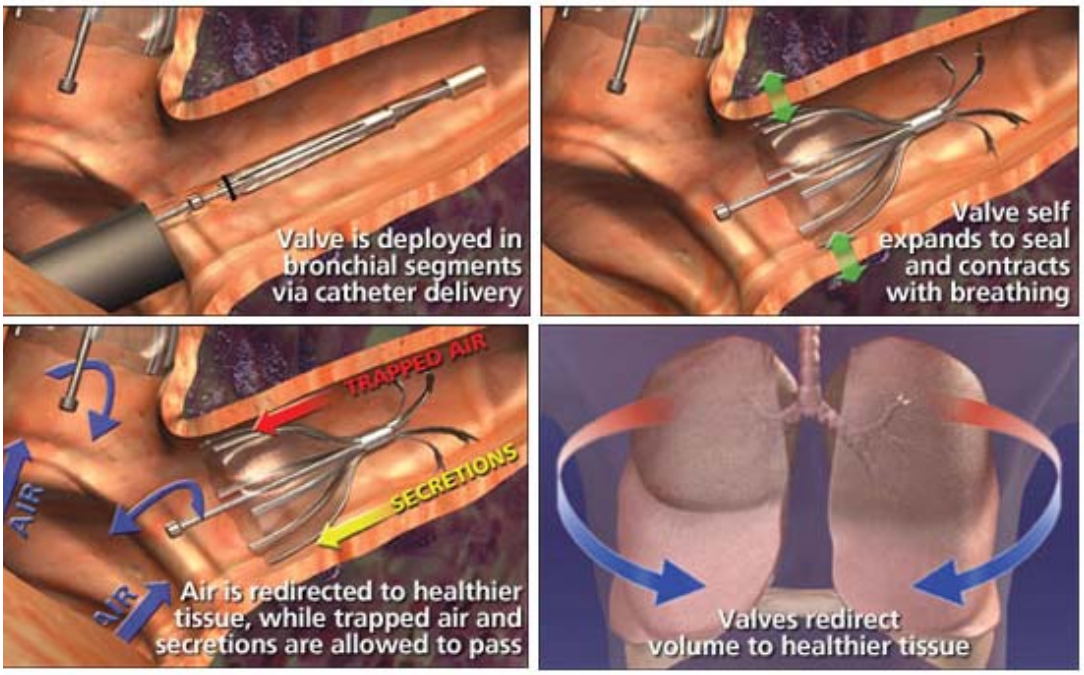
Figure 7: Placement of the Zephyr EBV and three EBVs in situ.



3.2.2 Spiration, Inc.: IBV Valve System

The Spiration IBV valve is a one-way valve built on six nitinol struts covered by polyurethane in the shape of an umbrella to allow conformation and sealing to the airways with minimal pressure on the mucosa. Figure 8 shows a schematic representation of the application of a Spiration IBV valve, together with an illustration of the mode of action of the device.

Figure 8: The Spiration IBV valve system.



Source: http://www.spirationinc.com/ibv_valve_system.asp

A pilot study in which the Spiration IBV was used, was published by Wood et al.[43] This multicentre observational study from 5 clinical centres enrolled 30 patients. It will be discussed in a later chapter.

3.3 REGULATORY STATUS

3.3.1 European Union

Unlike the pharmaceutical sector, where new drugs have to undergo series of regulatory clinical trials during development, the evaluation and timing of health technologies such as medical devices is less demarcated. For instance, no pre-market clinical trials are required for obtaining "CE marking" of medical devices. According to the European directive on medical devices (annex IX directive 92/42/ECC) implantable devices are defined as "any device which is intended to be totally introduced into the human body or to replace an epithelial surface or the surface of the eye by surgical intervention and which is intended to remain in place after the procedure". The regulation of medical devices in Europe was introduced in 1991 with the Medical Devices Directive. Medical devices are classified in four classes: class I (low risk), II a (medium risk), II b (elevated risk) and III (high risk) according to the risk linked to the device. The higher the classification, the more elaborate the level of the required assessment will be. Endobronchial valves are placed in class III.[d] In this class, a CE mark for marketing can only be affixed by the manufacturer after approval of the "Design Dossier" by a Notified Body (NB), designated by a Competent Authority (CA). The CE mark denotes a formal statement by the manufacturer of compliance with the directives' requirements.

According to the manufacturer's website (http://www.emphasysmedical.com, accessed March 30, 2009) "the Zephyr EBV system has received CE mark approval and is commercially available throughout many parts of Europe. The Zephyr EBV system is also commercially available in Australia, Hong Kong and Singapore. Spiration's IBV Valve System has also received market clearance through CE Mark in Europe.

3.3.2 United States

EBVs are not yet commercially available in the United States. The regulation of medical devices is different in the US as compared to the European Union. The most remarkable difference with EU countries is the requirement for the demonstration of a medical device's clinical effectiveness as a precondition for marketing. As in the EU, in the US medical devices are classified into classes depending on the intended use of the device, indications for use, and risk. In the US there are three classes for which regulatory control increases from Class I to Class III. Most Class III devices require Pre-market Approval (PMA). An investigational device exemption (IDE) can be provided to allow the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a PMA application submission to FDA. For the Zephyr Endobronchial Valve system, an IDE for the pivotal VENT Pivotal Trial (ClinicalTrials.gov Identifier: NCT00129584) was approved by the FDA in August 2003. In September 2007 the Company submitted a PMA application to the FDA seeking approval to market the device in the U.S.[e]

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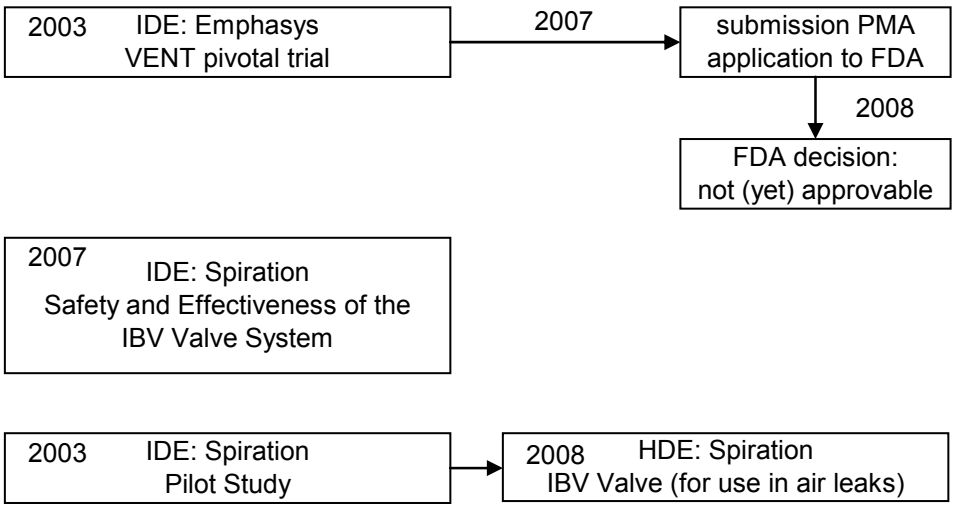
d Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, Annex IX: classification criteria:
I. Definitions: 1) Duration: long term (normally intended for continuous use for more than 30 days). 2) Invasive Device: implantable device (any device which is intended to be totally introduced into the human body … by surgical intervention which is intended to remain in place after the procedure).
III. Classification: 2) Invasive Devices, 2.4. Rule 8: All implantable devices and long-term surgically invasive devices are in Class IIb unless they are intended:
- to be placed in the teeth, in which cast they are in Class IIa,
- to be used in direct contact with the heart, the central circulatory system or the central nervous system, in which case they are in Class III,
- *to have a biological effect* or to be wholly or mainly absorbed, in which case they are in *Class III*,
- or to undergo chemical change in the body, except if the devices are placed in the teeth, or to administer medicines, in which case they are in Class III.
No changes to this rule were made in the new Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007.

e The FDA on December 5, 2008 voted the application to be found "not approvable." (http://www.fda.gov/cdrh/panel/summary/anesth-120508.html).

Subsequently, a meeting of the Anesthesiology and Respiratory Therapy Devices Panel was held on December 5, 2008, to discuss the Premarket Approval Application for this device. Following presentations by the sponsor and the FDA, and after questioning the sponsor and deliberating, the Panel voted (11-2) that the application be found "not approvable." [f] For the Spiration device, a randomized, prospective, double-blind, controlled U.S. pivotal trial to evaluate safety and effectiveness of the IBV Valve System for the treatment of severe emphysema, is currently enrolling patients (ClinicalTrials.gov Identifier: NCT00475007).

Figure 9: Status by the end of 2008 of EBVs regulation within the US' FDA.



IDE: investigational device exemption. HDE: humanitarian device exemption. Study references mentioned in Table 7.

An exemption on the effectiveness requirements is possible for a so-called Humanitarian Use Device (HUD). A HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4 000 individuals in the United States per year. FDA may authorize a company to market their HUD by approving a Humanitarian Device Exemption (HDE), which is similar to a PMA application, but exempt from the effectiveness requirements. [g] Reasonable evidence of safety and only probability of benefit are required for this exemption. Based on the analysis of a subgroup of patients from the Spiration Pilot Study (NCT00145548 - Table 7) the Spiration IBV Valve System, has received HDE approval on Oct 24, 2008 for its use to control air leaks of the lungs.[h]

[f] http://www.fda.gov/cdrh/panel/summary/anesth-120508.html

[g] http://www.fda.gov/cdrh/ode/guidance/1381.html#f1 (accessed September 15, 2008)

[h] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm?t_id=367937&c_id=249

Key points

- **EBVs are intended to mimic the effect of LVRS by preventing air from entering the blocked emphysematous lung segment, leading to atelectasis of the isolated segments.**
- **Two EBV types underwent a relatively extensive clinical evaluation: Emphasys Medical (currently Pulmonx)'s Zephyr and Spiration Inc.'s Spiration IBV device.**
- **Both the Zephyr EBV and the Spiration IBV have received market clearance through CE marking in the EU.**
- **In the United States, their use in the treatment of severe emphysema is limited within the boundaries of specific trials through an Investigational Device Exemption (IDE).**
- **The FDA in December 2008 declined a Pre Market Approval for the Zephyr EBV following examination of the VENT-IDE trial.**

4 CLINICAL EFFECTIVENESS

4.1 LITERATURE SEARCH

4.1.1 Search strategy and eligibility

4.1.1.1 Health technology assessments

In order to find previously published HTA reports we performed a search on Jan 19, 2009 by consulting the database of CRD (Centre for Reviews and Dissemination), making use of the following search strings: "lung volume reduction", "emphysema", and the MeSH term: "Pulmonary Disease, Chronic Obstructive". This resulted in no hits other than those related to surgical lung volume reduction. Searching the INAHTA (International Network of Agencies for Health Technology Assessment) database revealed two hits related to EBV: one originating from the Canadian HTA agency and one from the Dutch "College voor Zorgverzekeringen". The Canadian report was a one-page "Health Technology Update", issued in May 2007 and summarising the current state of affairs with no recommendations being put forward.[i] The Dutch HTA report was issued on June 30, 2008 and will be discussed later.

4.1.1.2 Primary studies and systematic reviews

Searching the database of CRD and the Cochrane database revealed no systematic reviews on EBV.

The Cochrane Central Register of Controlled Trials 2009 Issue 1 referred to the VENT trial through two references.[44, 45] Searching the Cochrane Database of Systematic Reviews resulted in one review on "Lung volume reduction surgery for diffuse emphysema". This review was last assessed as up-to-date on September 25, 2008. No reference was made to noninvasive endobronchial therapy.

On Jan 26, 2009, we performed a Medline search via PubMed, starting the search from Jan 1, 2000 on. We used the following search string:

(("Pulmonary Disease, Chronic Obstructive"[Mesh] OR "Pulmonary Emphysema"[Mesh] OR "Emphysema"[Mesh]) AND ("Bronchoscopy"[Mesh] OR endobronchial valve)) AND Humans[Mesh]

This resulted in 220 hits. Based on title, 184 references were discarded. Of the remaining 36 hits, 9 were discarded based on reading the abstract. 27 references were studied in depth.

On January 29, 2009 we searched EMBASE by using the following search string: ('lung emphysema'/exp OR 'emphysema'/exp) AND 'bronchoscopy'/exp AND [humans]/lim AND [2000-2008]/py. This resulted in 410 hits. Based on title, 45 papers were retrieved, of which 29 were also identified by our PubMed search. The remaining 16 articles were evaluated based on the abstract, which resulted in 12 papers that were retrieved for full text evaluation.

4.1.1.3 Grey literature

A search through ClinicalTrials.gov, a website developed by the U.S. National Institutes of Health in collaboration with the FDA, revealed 5 registered trials. Through contacts with the manufacturers and the principal investigators of these studies, data on some of the trials could be identified. The FDA's website revealed comprehensive data of one of them, the VENT trial.

[i] http://cadth.ca/index.php/en/hta/reports-publications/health-technology-update/health-tech-update-issue6/valves-emphysema

4.1.2 Data extraction

The following data were extracted: year of publication, principal investigator, methodology of the study, number of patients included, device tested, sponsor of the study, number of valves inplanted and whether they were implanted in one (unilateral) or both (bilateral) lungs. The following outcome parametes were sought for: complications, lung function, quality of life, exercise tolerance and quantitative CT-scan data.

The quality of evidence generated by the study, as assessed by using the GRADE-tool.[46] The quality of evidence is graded as high, moderate, low or very low.

4.2 LITERATURE REVIEW

4.2.1 Health Technology Assessment

Our literature search for HTA reports resulted in one report originating from the Dutch "College voor Zorgverzekeringen" (CVZ), issued on June 30, 2008.[47] The authors searched literature until February, 2008. Eight small and short-term (mostly less than 3 months) observational studies were identified.[40, 42, 43, 48-52] In 5 of these, pulmonary function and exercise capacity improved after EBV insertion as compared to pre-procedural values. The clinical relevance of these improvements was not clear. There were no long-term morbidity or mortality data, neither could a target patient population be clearly identified.

CVZ concluded that the technique of endobronchial valves seems to be safe but is otherwise to be considered as experimental and hence, should not be reimbursed.

4.2.2 Published data

No randomised controlled trial (RCT) on the efficacy of EBV could be identified. The literature search resulted in the identification of 9 case series reported in peer reviewed journals (Table 4). As compared to the Dutch HTA report, we identified one extra case series,[53] representing an extension of Wood's series.[43]

Table 4: Published series of patients, treated with EBVs.

Year	Reference	Study design	Device, Sponor	Unilateral / Bilateral	n	Age	number of valves per patient	follow-up time
2002	Toma[42]	case series, pilot study	Zephyr, Royal Brompton, Emphasys	uni	8	59 (43-69)	3,13	4 wks
2003	Snell[49]	case series, pilot study	Zephyr, Emphasys	bi	10	60,1 (51-69)	mean 6,7±2,2	30 days
2004	Yim[52]	case series	Zephyr, Emphasys	bi	21	68,55±7,40	4,14	90 days
2005	Hopkinson[48]	case series, pilot study	Zephyr, Wellcome trust, EU, Emphasys	uni	19	58,7±8,7	NA	4 wks
2005	Venuta[50]	case series	Zephyr, Emphasys	bi	13	56 (32-71)	4,5 (range 2-6)	3 months
2006	De Oliveira[40]	case series	Zephyr, Emphasys	bi	19	67,6±8,71	3,4	1-24 months
2006	Wan[51]	case series	Zephyr, Emphasys	65,3% uni, 34,7% bi	98	63±10	4,0±1,6	90 days
2007	Wood[43]	case series, pilot study	Spiration IBV, Spiration	bi	30	64±10	6,1	1-12 mo
2008	Coxson[53]	case series	Spiration IBV, Spiration	bi	57	NA	6,06±1,96	1-6 mo

By there very nature, these uncontrolled case series constitute low quality evidence. Moreover, most of them enrolled few patients, further decreasing the quality of evidence they provide, thus constituting "very low quality of evidence" according the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[46]

4.2.2.1 *Toma et al.*[42]

In this pilot study, 25 Emphasys valves were unilaterally implanted in 8 patients with predominantly upper lobe heterogeneous emphysema. After valve insertions, the median FEV1 increased from 0.79 L (range 0.61–1.07) to 1.06 L (0.75–1.22) (difference 34%). This was mainly due to a substantial improvement of FEV1 in 2 patients. The median diffusing capacity increased from 3.05 mL/min/mm Hg (2.35–4.71) to 3.92 mL/min/mmHg (2.89–5.40) (difference 29%). The increase was especially clear in 2 patients. Two patients developed a transient pneumothorax (collapse of the lung). No other important adverse effects were recorded during follow-up. After 4 weeks of follow-up, there were no changes in walking distance or QoL score (SGRQ). CT scans showed radiographic signs of reduction in regional volume with collapse of the target lobe in four of the eight patients.

4.2.2.2 *Snell et al.*[49]

This is a pilot study on 10 patients with apical emphysema, that were otherwise suitable candidates for LVRS. Four to 11 Emphasys prostheses were implanted per patient. Follow-up time was 30 days during which no severe complications were seen. Three patients had a COPD exacerbation, there was one asymptomatic pneumothorax and one pneumonia. No major change in radiologic findings, lung function tests or 6MWD was evident at 1 month. Symptomatic improvement was reportedly noted in four patients, but the mean MRC dyspnoea score among the ten patients was not significantly improved (3.8 vs. 3.5).

The authors elaborate on their finding of an overall lack of change in lung volumes, which contrasted dramatically with their previous findings in sheep experiments. They argue that collateral ventilation from neighbouring portions of lung might be the major responsible mechanism.

4.2.2.3 *Yim et al.*[52]

A total of 21 patients with incapacitating emphysema underwent Emphasys valves insertion. Data were available from 20 patients because 1 patient declined follow-up investigations. Each patient received between 2 and 8 valves (mean 4.14). There was no procedure-related death. Follow-up time was 90 days. Pneumothorax occurred in 4 patients, one case being a bilateral pneumothorax. The latter patient required thoracoscopic exploration and excision of a ruptured bulla.

There was a statistically significant improvement in the mean values of pulmonary function (FEV1 from 0.73±0.26 to 0.92±0.34 at 3 months), exercise tolerance (6MWD from 251.6 to 322.3), MRC grade (from 3 to 1), SF-36 and SGRQ (62.7 to 39.3). Induced lobar collapse was evident on CT in only 10 of 20 patients (10 of 23 lobes).

4.2.2.4 *Hopkinson et al.*[48]

This article updates the experience of London based investigators with the Emphasys endobronchial valves. Their initial experience with 8 patients was published by Toma et al. in 2003 and has been discussed earlier in this chapter (4.2.2.1).[42] These cases are included in this series of 19 patients. It is not stated how many valves were inserted in each patient. Some of the procedures were performed with sedation only, and some of these were staged, with valves being inserted on two separate occasions, 1 to 2 weeks apart.

Follow-up time was 4 weeks. Two pneumothoraces and 5 transient exacerbation of symptoms due to infection were reported. Radiologic evidence of atelectasis was present in five subjects (26%). Mean FEV1 increased from 0.90±0.4 L to 0.99±0.4 L at 4 weeks, which was labelled as statistically not significant. Some pulmonary function parameters were significantly improved: FEV1 as expressed as % of predicted (from 28.4 to 31.5%), total lung capacity (TLC) (from 9.06 L to 8.75 L) and DLCO. In absolute values, FEV1 increased from 0.90±0.40 L at baseline to 0.99±0.40 L at 4 weeks. This increase was not statistically different. Exercise capacity was measured as endurance at 80% of maximum workload on a cycle ergometer. In the overall group there was a 39% improvement in mean cycle exercise time from 227 to 315 seconds, giving a mean increase of 88 seconds. Nine patients (47%) met the 60-second and 30% increase criteria considered to represent a clinically significant benefit. QoL was assessed on the basis of St George's Respiratory Questionnaire and the Short Form-36. In the group as a whole, there was no significant change in any dimension of QoL measured.

4.2.2.5 Venuta et al.[50]

This Italian pilot study included 11 patients that underwent unilateral BLVR and 2 undergoing staged bilateral procedures, all under general anaesthesia. Follow-up extended to 3 months. Fifty-nine Emphasys valves were placed, a median of 4 per patient (range 2 to 6). There was no procedure related mortality. Six complications occurred in 3 patients: two bilateral and one contralateral pneumothorax, one pneumonia, and two episodes of bronchospasm. Functional results at 3 months showed a significant improvement in terms of FEV1 (from 0.75 to 1.0 L) and a decrease of residual volume (from 5.3 to 4.5 L). 6MWT increased from 223 metres (120-460) preprocedural to 410 metres (245-520) at 3 months.

4.2.2.6 De Oliveira et al.[40]

These authors report their experience with the Emphasys EBV in 19 patients, with 11 patients completing a 12 month follow-up and 5 completing a 24 month follow-up. Initially they used the first generation "over the wire" valves, but from the eighth patient on, the transbronchocopic valve that can be introduced directly through the bronchoscope without a guide wire, was inserted. Pneumothorax occurred in two patients and bronchospasm in another two. One patient died 4 months after valve insertion because of a massive gastro-intestinal bleeding. Atelectasis developed in only 2 out of 19 patients. In two patients, one or all valves were removed. In one patient, a right upper lobe (RUL) valve was removed because of a pneumothorax, resistant to drainage. In another patient, the valves in both the RUL and left upper lobe (LUL) were removed because of bronchial hypersecretion and respiratory dysfunction. Eighteen patients completed the 1-month and 3-month follow-up, 14 patients completed the 6-month follow-up, 11 patients completed the 12-month follow-up, and 5 patients completed the 24-month follow-up. Concerning pulmonary function, no significant improvement was observed in any test. Their was an improvement in the 6MWD after 1 month (mean: 264±111 to 307±86 m) which persisted no longer after 6 months (in 14 individuals: from mean: 257±119 to 282±111 m). A significant improvement in SGRQ was observed at 3 (-4.29 points) and 6 (-6.32 points) months in three of four domains. This improvement did not persist at 12 and 24 months.

4.2.2.7 Wan et al.[51]

This article represents a multicentre experience in 98 patients from 9 centres in 7 countries with the Emphasys endobronchial valve system in patients with endstage emphysema. All the centres discussed earlier in this chapter are represented in this survey. It is the most extensive series on the Emphasys EBV published so far.

Ninety-eight patients with mean FEV1 of 0.9±0.3 L (30.1±10.7% of predicted) and residual volume (RV) of 5.1±1.3 L (244.3±0.3% of predicted) were treated. An average of 4.0±1.6 (range 1-8) valves was inserted per patient. There were eight serious complications (8.2%), including one death (1.0%), 3 pneumothoraces requiring surgery and a prolonged air leak in 4 patients. The fatal complication was caused by pneumonia, leading to respiratory failure and death on day 25.

Thirty patients had other complications, including 17 COPD exacerbations and 5 pneumonias, and 5 pneumothoraces that required an intervention.

Spirometry, plethysmography, DLCO and exercise testing were performed at 30 days and 90 days after the procedure. There was a significant improvement of lung function tests. RV decreased by 4.9±17.4% ($p<0.025$), FEV1 increased by 10.7±26.2% ($p<0.007$), FVC increased by 9.0±23.9% ($p<0.024$). The absolute change of FEV1 was a mean of 0.06±0.21 L and a median of 0.04L (range: -0.04 to 0.16 L). The 6MWD increased by 23.0±55.3% ($p<0.001$). In absolute values, this was a mean improvement of 36.9±90.0 m and a median improvement of 18.0 m (range: -10.7 to 79.2 m). QoL indices pre- or post-procedure were not provided. Because no uniform method of assessing atelectasis was done across centres, no data on CT-findings were reported in this multicentre series.

4.2.2.8 *Wood et al.*[43]

This article represents a multicentre experience with the Spiration IBV valve. Five centres treated 30 patients. Patient follow-up ranged from 1 to 12 months. A mean of 6.1 (range: 5-10 valves) valves were placed per patient. The following adverse events were noticed during the first 30 days: 4 bronchospasm, 6 arrhythmia, 11 infections. There were no pneumothoraces. One patient was readmitted at day 33 with an acute respiratory distress, resulting in a cardiopulmonary arrest, attributed to an acute myocardial infarction. The patient recovered successfully.

The only consistent evidence of efficacy was documented by an improvement in SGRQ. There were significant changes in the SGRQ scores at all postprocedure time points compared with the preprocedure baseline. The mean change at 6 months was -6.8±14.3 points. Fifty-two percent of the patients had a clinically meaningful response (SGRQ score improved by at least 4 points) at 6 months after valve implantation. The physiologic and exercise outcomes did not show statistically significant improvements at any postprocedure endpoint (1 mo, 3 mo, 6 mo). At 6 months, FEV improved with more than 15% from baseline (i.e. >130 mL) in 2/26 patients. 6MWT improved by more than 15% from baseline (i.e. >50 m) in 6/25 patients. Atelectasis in treated segments was achieved in "only a few times" in this study (exact data not reported). Patients underwent a per-protocol defined control bronchoscopy at 1 month after EBV placement. More than half of them (17/30) either had valve removal (8), valve replacement (16) or additional valves placed (15). Reasons for valve revisions at 1 month were visual judgment that valves were angulated or too distal in an airway, resulting in incomplete contact between the membrane and an airway wall.

4.2.2.9 *Coxson et al.*[53]

This series extends the one reported by Wood et al. (4.2.2.8).[43] Its specific aim was to correlate clinical outcome measures with regional lung volumes assessed by CT-scan. It reports data on 57 subjects from a subset of 98 patients from the North American pilot study (ClinicalTrials.gov identifier NCT00145548) for whom successive CT scan were available. A total number of 346 valves, with a mean of 6.06±1.96 per subject, were placed at the initial procedure. Adverse events occurring within a day of the procedure were pneumothorax in four and bronchospasm in two subjects. Within a 30-day period there were 10 patients with a COPD exacerbation with an additional 10 in a 90-day period. There were six cases with an episode of bronchitis within 30 days and two more within 90 days.

There was no significant improvement in FEV1, FVC or DLCO, no significant decrease in TLC or RV, and a trend for improvement in the 6MWT distance (12 m = 3.6%). The only significant and clinically meaningful change was an improvement in SGRQ. At baseline, SGRQ was 58.2±12.6, and it was 50.0±19.1 at 6 months, a difference of -8.95±16.22 ($p<0.0001$). On follow-up, moderate or complete lobar atelectasis was observed in 12 (21%) out of 57 subjects at some point in the 6 months following valve implantation. There was no atelectasis observed at any time point in 24 (42%) subjects and a linear or mild degree of atelectasis was present in 21 (37%) subjects.

While total lung volume, as measured by CT and many other parameters such as TLC and FEV1, did not change, there was a significant decrease in the volume of the upper lobes, with a compensatory change in the volume of the non-upper lobes. An improved SGRQ was correlated with a non-upper lobe volume increase. The authors suggest that the mechanism of action of EBVs is a redirection of inspired air to the untreated and less diseased non-upper lobes.

4.2.2.10 Summary of published literature

So far, no randomised controlled trials have been published on the use of EBV for the treatment of pulmonary emphysema. Data is limited to case series and is related to two types of EBV: the Emphasys EBV and the Spiration IBV valves. Nine series could be identified through different databases. A summary of findings from these studies is depicted in Table 5.

Table 5: Summary of findings from 9 case series on endobronchial valves.

SUMMARY OF FINDINGS EMPHASYS EBV							
Reference	n	follow-up	OUTCOME				
			Walking distance (mean improvement in metres)	**QoL**	**Spirometry (mean improvement in mL)**	**CT-scan**	**Complications**
Toma	8	4 weeks	unchanged (NA)	unchanged (SGRQ)	median FEV1 and DLCO improved (especially so in 2 patients) (median: 270 mL)	volume reduction in 4/8 patients	2 pneumothorax, 3 infections
Snell	10	30 days	unchanged (6 m)	unchanged (MRC)	unchanged (except for DLCO) (20 mL)	no major change	1 pneumothorax, 3 infections
Yim	21	90 days	improved (71 m)	improved (SGRQ, MRC grade, SF-36)	improved (190 mL)	induced lobar collapse in 10/23 lobes	4 pneumothorax
Hopkinson	19	4 weeks	improved (NA, Cycling)	unchanged (SGRQ, SF-36)	improved (90 mL)	atelectasis in 5/19 (26%) subjects	2 pneumothorax, 5 infections
Venuta	13	3 months	improved (187 m)	improved (MRC)	improved (250 mL)	NA	3 pneumothorax, 1 pneumonia, 2 bronchospasm
De Oliveira	19	1-24 months	improved at 1 month, not persisting at 6 months (25 m)	improvement in SGRQ at 3 and 6 months, not persisting at 12 months	unchanged (0 mL)	non-sustained atelectasis in 2/19 patients	2 pneumothorax, 1 respiratory dysfunction, 2 bronchospasm
Wan	98	90 days	improved (37 m)	NA	improved (60 mL)	NA	1 death, 5 pneumothoraces needing intervention, 17 COPD exacerbations, 5 pneumonias

SUMMARY OF FINDINGS SPIRATION IBV							
Reference	n	follow-up	OUTCOME				
			Walking distance (mean improvement in metres)	**QoL**	**Spirometry (mean improvement in mL)**	**CT-scan**	**Complications**
Wood	30	1-12 months	unaffected (NA, ns)	improved (SGRQ)	unaffected (NA, ns)	atelectasis noted "only a few times"	<30 days: 1 cardiac arrest due to MI, 4 bronchospasm, 6 arrhythmia, 11 infections
Coxson	57	1-6 months	unaffected (12 m)	improved (SGRQ)	unaffected (40 mL)	atelectasis in 12/57 patients	4 pneumothorax, 2 bronchospasm, 10 copd exacerbations

References as indicated in Table 4. n= number of patient included in the series. "improved" indicates that after EBV insertion, a statistically significant improvement was observed but this does not mean that the improvement was clinically relevant, as defined in 2.4)

The case series suggest that the insertion of up to 10 EBVs in selected patients with severe pulmonary emphysema is **feasible** and can be performed with an acceptable **safety** profile, both under local or general aneasthesia. 30-day mortality was 1/98 (1.0%) with the Emphasys and nil with the Spiration IBV valves (n = 57). Pneumothorax was reported in 14 of 89 cases (15.7%) from single centre Emphasys series and required surgery or chest suction in 5 (5%).[51] Pneumothoraces were less often reported with the Spiration IBV device: none occurred in the intitial series reported by Wood[43] but 4 (7.0%) were reported by Coxson in the extended series.[53] Other adverse events were bronchospasm, pneumonia and COPD exacerbations. Different outcome measures related to the device's **effectiveness** are reported: lung function tests, exercise tolerance tests (mostly 6MWT), quantitative CT-scan, and QoL parameters. The effect of EBV valve insertion on spirometry is inconsistent across the series. Some tests showed a post-procedural improvement, whilst others were not significantly affected. *FEV1* increase ranged from 20[49] to 250[50] mL. In de Oliveira's series,[40] 4 out of 18 patients had an FEV1 improvement of >12% or >150 mL whereas in Wood's series[43] 5/28 and 2/26 patients had an improvement of at least 15% at 3 and 6 months respectively. An improvement of exercise tolerance, as measured by the *6MWD* ranged from -10 to +187 metres. Although the primary goal of EBV insertion is mimicking the effect of LVR surgery, post-procedural *radiology* most often did not demonstrate atelectasis of the treated segments. In the study of Coxson that specifically assessed radiological changes following EBV insertion, quantitative CT measurements showed that there was no change in total lung volume. However, there was a significant decrease at all time points in the treated upper lobe volume and an increase in the untreated non-upper lobes volumes.[53] Data on *quality of life* in most series are limited to disease-specific questionnaires such as SGRQ or the MRC dyspnoea score. These show inconsistent results among studies. Short-Form Health Survey (SF-36) scores are reported in three of the series.[43, 48, 52] Post-procedural measures improved in one and remained unchanged in two of them.

Two of the published series are to be considered as an update and summary of previously published data: Wan's paper related to 98 patients treated with the Emphasys EBV[51] and Coxson's paper on 57 patients treated with the Spiration IBV Valve System.[53] The clinical outcomes reported in these papers are shown in Table 6. The absolute spirometric volume changes at 90 days follow-up in Wan's series demonstrate a statistically significant, yet unimpressive, improvement of FEV1, FVC, and RV. In Coxson's series on the other hand, there was no statistically significant improvement in any spirometric value. Wan's series showed an improvement of exercise tolerance with an increase in 6MWT of 36.9±90.0 m (23.0±55.3%), whereas in Coxson's series, there was a 9±57 m (2.6%) increase in 6MWT. None of the two summary series reached the clinical benefit threshold required for FEV1 (>20%) or 6MWT (70 to 90 m) to be clinically relevant as dicussed in chapter 2.4. QoL data are not provided by Wan, whereas Coxson's data are limited to the SGRQ. This parameter improved with 5.49, 4.28 and 8.95 points at 1, 3 and 6 months respectively and represents a "slightly-to-moderately efficacious change" according to the ATS (cfr. Chapter 2.4.3).

Table 6: Outcome measures as reported in representative published case series.

Outcome variable	Baseline findings		Absolute difference at follow-up		
	Wan (n=98)	Coxson (n=57)	Wan	Coxson	
	Emphasys EBV	Spiration IBV	3 months	3 months	6 months
Complications	1 procedure related death (day 25, due to respiratory failure)	day 1: 4 PT and 2 bronchospasm	8 (8,2%) serious complications (1 early death on day 25, 3 surgery for PT 4 prolonged air leak) and 30 patients (30,6%) with other complications (17 COPD exacerbations, 5 pneumonias, 2 PT)	20 patients with COPD exacerbation	NA
CT scan	NA		NA	atelectasis in 12/57 (21%) patients at some point in the 6 month followuw-up	
FEV1 (mL)	900 ± 300	840 ± 230	60 ± 210	-30 ± 170	-40 ± 160
FVC (mL)	2500 ± 800	2760 ± 840	120 ± 470	-120 ± 460	-110 ± 600
RV (mL)	5100 ± 1300	4900 ± 1040	-350 ± 970	190 ± 930	20 ± 940
6MWT (m)	303 ± 118	336 ± 85	36,9 ± 90,0	9 ± 57	12± 65
SGRQ	NA	58,2 ± 12,6	NA	-4,28 ± 15,81	-8,95 ± 16,22

Values are in mean±SD. CT scan: high definition CT. Wan refers to [51]. Coxson refers to [53]. FEV1: forced expiratory volume in 1 second. FVC: forced vital capacity. RV: residual volume. 6MWT: six minutes walk test. SGRQ: St George's Respiratory Questionnaire. PT: pneumothorax. NA: not available.

4.2.3 Unpublished data

In some of the articles mentioned before, the authors refer to an RCT being in progress or in the stage of preparation, "in order to objectively assess the efficacy of EBV in the treatment of endstage pulmonary emphysema".[48, 51-53] A search through ClinicalTrials.gov, revealed 5 registered trials (Table 7). The study protocol of one of these has been published in a peer reviewed journal,[45] whereas two of the aforementioned case series[43, 53] are part of one of them (ClinicalTrials.gov identifier NCT00145548).

Table 7: Endobronchial valve trials registered on ClinicalTrials.gov's website.

	STUDY NAME	STUDY DESIGN	US STUDY STATUS	DEVICE	START DATE	ENROLLMENT STATUS (March 2009)
PILOT	Pilot Study of the Spiration IBV System - NCT00145548	Non-Randomized, Open Label, Uncontrolled, Single Group Assignment, Safety Study	IDE	Spiration IBV	December 2003	ongoing, not recruiting
PIVOTAL ZEPHYR	Endobronchial Valve for Emphysema Palliation Trial (VENT). Phase III trial. - NCT00129584	Randomized, Open Label, Active Control, Parallel Assignment	IDE	Zephyr	January 2004	ongoing not recruiting
	Endobronchial Valve for Emphysema PalliatioN Trial (VENT) Cost-Effectiveness Sub-Study - NCT00137956*		IDE	Zephyr	December 2004	ongoing, not recruiting
EU	EUROPT Clinical Trial to Study the Efficacy of One-Way Valve Implantation (New Treatment Algorithm) in Patients With Heterogeneous Emphysema. Phase IV trial. - NCT00730301	Non-Randomized, Open Label, Historical Control, Single Group Assignment	NA	Zephyr	July 2007	recruiting
PIVOTAL SPIRATION	Clinical Trial to Evaluate the Safety and Effectiveness of the IBV Valve System for the Treatment of Severe Emphysema. Phase III trial. - NCT00475007	Randomized, Double Blind (Subject, Outcomes Assessor), Placebo Control, Parallel Assignment	IDE	Spiration IBV	September 2007	recruiting

Description of "US study status": cfr. Chapter 3.3.2 and Figure 9.
* This study has been stopped.

Through contacts with the manufacturers and principal investigators of these studies, and by searching the grey literature, data on some of the registered trials could be identified. These are summarized herafter.

4.2.3.1 The VENT trials

Two different studies related to the "Endobronchial Valve for Emphysema PalliatioN Trial" (VENT) were registered on ClinicalTrials.gov's website: (1) a phase III clinical trial that started in January 2004 and was posted on ClinicalTrials.gov on August 10, 2005 and (2) an economic substudy of the VENT trial, the "Endobronchial Valve for Emphysema PalliatioN Trial (VENT) Cost-Effectiveness Sub-Study", that was posted on ClinicalTrials.gov on August 26, 2005. The latter's purpose was to gather healthcare utilization and QoL information on patients enrolled in the clinical VENT study in order to analyze the relative cost-effectiveness of the EBV procedure. In response to an e-mail request, the company declared "Emphasys Medical decided to discontinue the study due to resources and cost required to execute the study as compared to the amount of additional data being received. The data had been analyzed neither by the sponsor nor by the investigators prior to the study being discontinued." (e-mail, April 26, 2009) A third study that is related to the VENT trial and that sometimes is referred to as the European arm of the VENT trial, is the Zephyr EBV Europe trial. Its protocol is nearly identical to the VENT pivotal trial with the same endpoints. In this study, 171 subjects have been included (111 EBV and 60 controls) between June 2004 and January 2006. A few data from this trial are also available from the FDA's website. Because the VENT trial is the only RCT on EBVs that has been finalised so far, its results are further discussed in detail in this report, although it should be kept in mind that the data provided have not yet been published and have not been peer-reviewed.

The **trial protocol of the clinical VENT trial** was published by the end of 2004 in a French journal[44] and in July 2007 in BMC Pulmonary Medicine.[45] The study hypothesised that occlusion of a single pulmonary lobe through bronchoscopically placed Zephyr EBVs would significantly improve lung function and exercise tolerance with an acceptable risk profile in advanced emphysema. The VENT design largely followed that of the surgical NETT trial and the inclusion/exclusion criteria were similar.[13] Patients with severe heterogeneous emphysema were enrolled and both studies required pulmonary rehabilitation prior to randomisation. Both studies allowed treatment of the upper or lower lobes based on CT analysis; however, the NETT required bilateral treatment whereas VENT treatments were unilateral only. A double-blinded sham controlled design was deemed unsuitable because of the radio-opacity of the EBVs. Moreover, performing a sham bronchoscopic implant in control subjects was considered to carry unacceptable risk, given their fragile health status.[45]

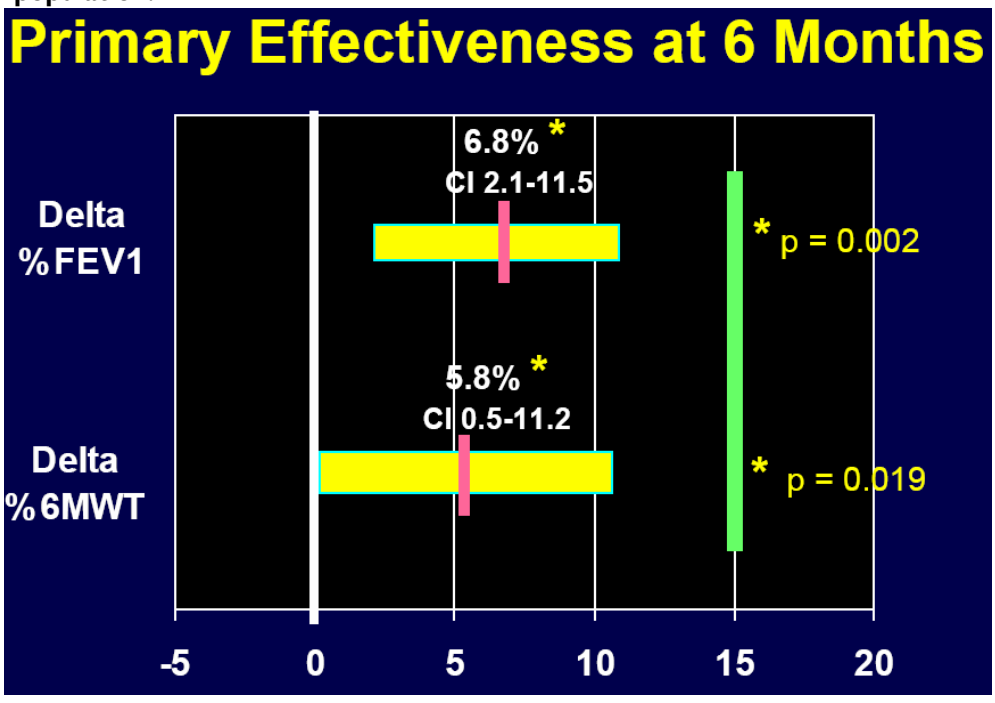
Study endpoints are related to safety of the procedure and to efficacy:

- The co-primary effectiveness endpoints were the mean percent change in both FEV1 and 6MWD in the treatment group as compared to the control group (optimal medical management) at 180 days (6 mo) after randomisation.
- The primary safety endpoint was a comparison of a composite of major complications (MCC) between the two groups over the initial follow-up period of 180 days. The MCC included death, empyema, massive haemoptysis, pneumonia distal to a valve, pneumothorax or a prolonged air leak, and respiratory failure requiring >24h mechanical ventilation. Additionally, patients would be followed for up to 3 years post randomisation for long term safety assessment.
- Secondary effectiveness outcome measures were disease specific QoL (as measured by SGRQ), exercise capacity as measured by incremental cycle ergometry, daily supplemental oxygen requirement, and dyspnoea (as measured by the MRC dyspnoea scale).
- "Additional pre-specified analyses": effect on residual volume, DLCO, an ill-defined "Quality of Well-Being score", BODE index, technical success, rehospitalisation.

- Secondary safety endpoints were complications and device-related adverse events.

The study intended to enrol 270 subjects with a 2:1 randomisation to EBV insertion, and was powered to detect a 15% improvement in the treatment arm in FEV1 and a 17% improvement in 6 MWD. Six-month follow-up data were presented in September 2007 at the Annual Congress of the European Respiratory Society, and in October 2007 at the annual meeting of the American College of Chest Physicians. These results have not yet been published in a peer reviewed journal and the data presented here are retrieved from webposted press releases[54, 55] and from the minutes of the FDA Anesthesiology and Respiratory Devices Panel meeting, held on December 5, 2008 and available from the FDA's website.[i] The data reported are those from US patients, i.e. from the VENT Pivotal trial. 963 valves were initially deployed during the procedure and 143 (14.8%) were removed in 96 patients during the initial implantation procedure. 87 valves (9%) were removed later on in the course of the one-year follow-up because of migration, subject's request, incorrect placement, "continuing COPD exacerbation", etc. Hence, 23.9% (230/963) of the EBVs inserted at the start of the study were removed later on within the first year. The trial is reported having met its **co-primary efficacy endpoints**. Among the 220 treated patients who received (3 to 5) valves, at 6 months, FEV1 had improved by 5.8%, whereas for the 101 controls, FEV1 declined by 0.6%, a spread of 6.4% (6.8% according to the data on FDA's website) which was statistically significant. For the other primary study endpoint, the 6MWD, treated patients improved their distance by 1.7% (about 15 metres) after 6 months, whereas the controls' distance declined by 4.0%. This 5.7% spread was also statistically significant (5.8% according to the data on FDA's website). 7.3% of the EBV group and 1.4% of the control group had a 15% improvement in both FEV1 and the 6MWD. Results from the European arm of the VENT trial were as follows: for FEV1 the spread between the two study groups was 5.8%, and it was 1.98% for 6MWD. Although the analysis of the co-primary effectiveness endpoints showed statistically significant differences at 6 months, none reached the pre-specified clinical significant improvement of 15% on which the design of the study was based (Figure 10).

Figure 10: Co-primary effectiveness endpoint results in the intention to treat population.



Pink bars represents point estimate of effect. Yellow bars: 95% confidence intervals. Green bar (+15%): minimum difference required to be clinically important. Slide from FDA's website.

[i] http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4405b1-00-Index.html

Secondary effectiveness outcomes were also reported to significantly improve. The difference between the EBV group and the control group was -3.4 points for SGRQ (p=0.017), -0.26 points for MRC (p=0.018), +3.8 watts for cycle ergometry (p=0.020) and -12.0 litres per day for supplemental oxygen use (p=0.020)[k] Lung volumina assessed by CT-scanning revealed that EBV treatment resulted in a net reduction of 19% of the target lobe as compared to the control group. There was a significant association between this volume reduction and FEV1 (r^2=0.279, p<0.001, n=179). Some of the further analyses were performed on a pre-specified population, the so-called "completed cases – CC", i.e. patients who received study-directed treatment and who had 6-months follow-up. This group represents approximately 80% of the study population. In this subgroup, the treatment effect on primary and secondary effectiveness outcomes was similar or slightly better than in the overall population. Additional pre-specified analyses in the CC population included percent change in residual volume, DLCO and a quality of well-being scale. For none of these measures was there a significant difference between groups.

Two independent predictor variables were retained as interactors in the multivariate model: the emphysema heterogeneity and the presence of a complete fissure. Additional analyses were performed for these **subgroups**. The heterogeneity score measures the difference in disease severity between lung lobes on quantitative CT-scan. It is considered as a reference that quantifies the difference in percentage destruction of the treated and untreated portion of the lung. The median baseline value of 15% was chosen as the threshold for the high heterogeneity subgroup. CCs with a *high heterogeneity score* (n=91 cases and 40 controls) experienced greater FEV1 (+12.3%) and 6MWD (+14.4%) at 6 months. CCs with *complete fissures* separating the target lobe from adjacent lung tissue (n=68 cases and 33 controls) were found to experience a greater percent FEV1 increase at 6 months (+16.2%). Fissure integrity however was not a predictor for change in 6MWD (exact data not provided). Additional data related to patients from the CC population with a *high heterogeneity score AND a complete fissure* were provided by the manufacturer. The percentage changes difference between intervention group and controls were 20.8% for FEV1, 14.8% for 6MWD, 2.7 points for SGRQ, 0.42 points for the MRC score, 1.9 watt difference in cycle performance and 1.05 points in the BODE index (Table 8). It has to be stressed that these data are not peer-reviewed and that differences with the data on the FDA website have been noticed (e.g. pneumothorax incidence for the first year was 1.1% (1/87) and 1.9% (4/214) in the control and treatment group, respectively, in the FDA document. In contrast, this was 2.3% and 5.1%, respectively, in the data received from the manufacturer.

[k] http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4405b1-03-Sponsor's%20Executive%20Summary.pdf

Table 8: Additional unpublished data from the VENT trial, provided by the manufacturer and related to all "Completed Cases"* and to a subgroup of patients with "high heterogeneity and complete fissure".

All "Completed Cases"*

	treatment		control		spread[e]
	6 months	12 months	6 months	12 months	
Co-primary effectiveness endpoints					
FEV1	5.3% (179)	6.7% (175)	-1.9 (75)	-1.42 (74)	7.2%
6MWD	4.3% (178)	-0.35 (174)	-1.5% (73)	-3.93% (75)	5.8%
Primary safety endpoint					
MCC[a]	6.1% (13/214)	10.3% (22/214)	1.1% (1/87)	4.6% (4/87)	5%
Secondary effectiveness endpoints[b]					
SGRQ (points)	-2.7 (158)	-1.67 (149)	0.7 (62)	1.34 (61)	-3.4 points
exercise capacity (watts)	0.1 (169)	-1.95 (154)	-4.4 (69)	-5.14 (69)	4.5 watts
MRC (points)	-0.09 (162)	0.14 (66)	0.21 (159)	0.03 (66)	-0.30 points
Additional pre-specified analyses[c]					
BODE	-0.21 (160)	/	0.32 (59)	/	-0.53 points
rehospitalisation[d]	/	39.7% (85/214)	/	25.3% (22/87)	14.4%

Subgroup with "high heterogeneity and complete fissure"

	treatment		control		spread[e]
	6 months	12 months	6 months	12 months	
Co-primary effectiveness endpoints					
FEV1	16.2% (43)	/	-4.6% (19)	/	20.8%
6MWD	3.6% (43)	/	-11.2% (18)	/	14.8%
Primary safety endpoint					
MCC[a]	2% (1/51)	9.8% (5/51)	0% (0/23)	0% (0/23)	2%
Secondary effectiveness endpoints[b]					
SGRQ (points)	-2,2 points (35)	/	0.5 points (17)	/	-2.7 points
exercise capacity (watts)	0 watts (42)	/	-1,9 watts (18)	/	1.9 watts
MRC (points)	-0.29 points (38)	/	0.13 points (16)	/	-0.42 points
Additional pre-specified analyses[c]					
BODE	-0.41 points (37)	/	0.64 points (14)	/	-1.05 points
rehospitalisation[d]	/	33.3% (17/51)	/	21.7% (5/23)	11.6%

Numbers are in percent (number at risk between brackets).

* Completed cases defined by manufacturer as "subjects with evaluable data" . It is not clear whether this refers to the same patient group as the CC-subgroup referred to in the FDA documents ("patients who received study-directed treatment and who had 6-months follow-up"). These are non peer-reviewed data received from the manufacturer.

FEV1: forced expiratory volume in 1 second; 6MWD: six-minute walk distance; MCC: major complication composite; SGRQ: St George's Respiratory Questionnaire; MRC: Medical Research Council dyspnoea scale; BODE: The BODE-index combines body weight, degree of airflow obstruction (FEV1), a dyspnoea score and exercise capacity (six minutes walk test); /: data currently not received

a) The researchers of the VENT study remark: 1) a higher rate was expected for an active intervention (i.e. bronchoscopy) treatment arm. The control arm had no intervention. 2) 25% of the treatment arm rehospitalisations were ≤1 day length of stay (LOS). 3) mean LOS: 5.8 days for the treatment arm vs. 8.6 for the control arm.

b) Information on daily supplemental oxygen requirement was currently lacking.

c) Information on residual volume (RV), diffusing capacity of the lung for carbon monoxide (DLCO), quality of well-being (QWB), and technical succes was currently lacking.

d) Rehospitalisation for any reason 0-386 days. Some patients had multiple rehospitalisations

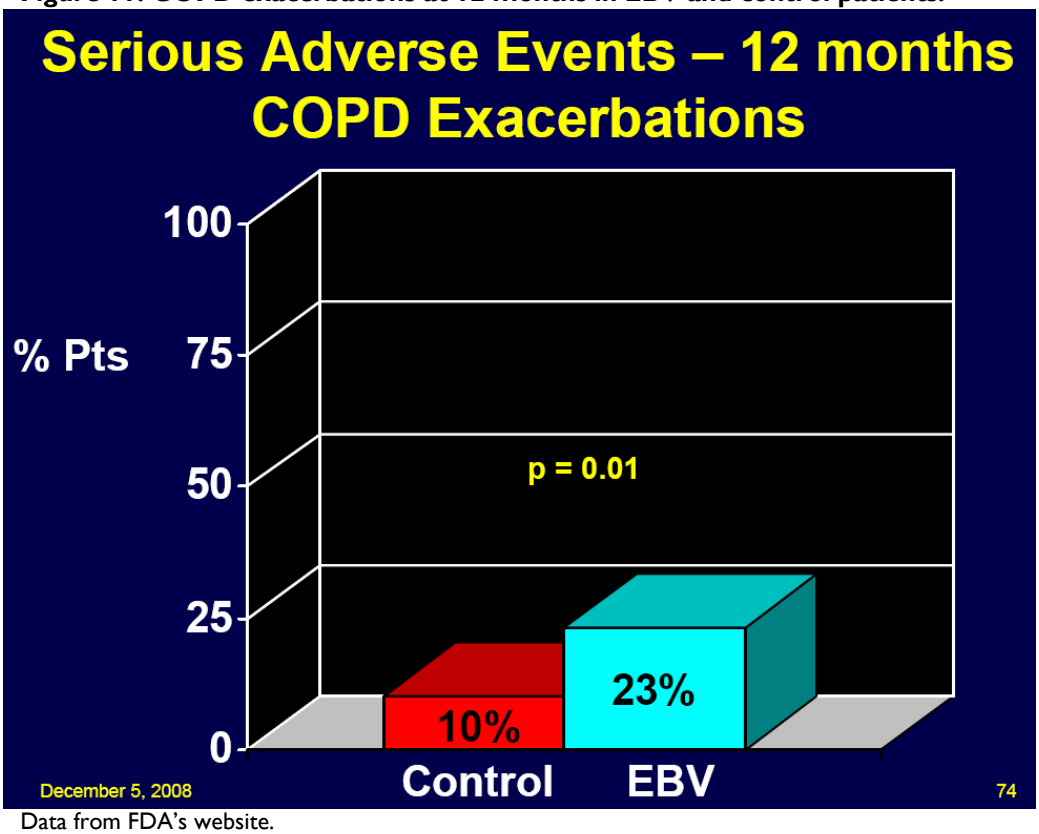
e) The spread was the difference of the absolute values between the treatment and control group at 6 months (except for rehospitalisation)

A responder analysis was performed for the CCs population. The proportion of CC EBV subjects with >15% improvement in FEV1 from baseline to 6 months was 23.5% compared with 10.7% of control subjects. The proportion of EBV subjects with >15% improvement in 6MWD from baseline to 6 months was 25.3% compared with 17.8% of control subjects.

The FDA's website[l] provides the following primary **safety outcome data**: at 6 months of follow-up, control subjects had a 1.2% rate (1/87) of major complication composite events (MCCs) compared with a fivefold higher 6.1% (13/214) for EBV treated patients, a trend that however was not statistically significant (p=0.075). In the Zephyr EBV Europe trial, the MCC at 6 months was significantly worse in the EBV group compared to the control group (3.33% vs. 13.51%; p=0.0348). While no deaths were reported in the control group at 6 months, 6 patients (2.8%) died in the (twice as large) EBV group, all but one COPD related.[56] The difference in MCCs between the two study groups was primarily driven by this trend to a greater 6-month mortality in the EBV patients that included one death from massive hemoptysis that was related to the device. At 12 months, although the number of MCCs in the intervention group was still twice that in the control group (10.3% vs. 4.6%), this difference remained statistically not significant (p=0.172, Fisher's exact test).

The VENT trial revealed the high degree of pulmonary morbidity present in subjects with severe emphysema, with 77.6% of EBV subjects and 62.1% of controls having one or more COPD/emphysema category adverse events (i.e. COPD exacerbation, respiratory failure, pneumonia, altered blood gases); this difference was significant (p=0.0095). At one year, the EBV group had higher rates of serious adverse events related to COPD than the control group (23% versus 10%, p=0.01) (Figure 11).[56]

Figure 11: COPD exacerbations at 12 months in EBV and control patients.



Data from FDA's website.

[l] http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4405b1-07-Clinical%20Study%20Report%20Pages%201-100.pdf

There was a trend towards higher hospitalization rates for EBV subjects (27.1%) compared with control subjects (16.1%) through 6 months, which was borderline non-significant (p = 0.052). For the period from 6 to 12 months, these figures were 19.6% for EBV subjects and 12.6% for controls (p=0.182). Most of the difference in hospitalisations was noticed during the first 97 days (16.82% of the EBV patients and 5.75% of the controls). COPD exacerbations occurred more often in the EBV patients, especially during the first 97 days: exacerbation rates in this time window were 9.35% for EBV patients vs. 1.15% for controls.

12-month follow-up data were not required by the VENT trial protocol that envisaged a follow-up duration of 6 months, but the FDA requested the sponsor to collect also effectiveness endpoints through 12 months. The difference in percent changes in FEV1 and 6MWD from baseline to 12 months in the intention-to-treat analyses were 7.7% (95% CI: 2.6 to 12.7) and 3.8% (95% CI: -1.4 to 9.0), hence the results of the 6MWD dropping below statistical significance.

4.2.3.2 Pilot Study of the Spiration IBV System

Interim analyses on the Pilot Study of the Spiration IBV System (ClinicalTrials.gov identifier NCT00145548) have been partly presented in two of the aforementioned case series which have been discussed in a previous chapter.[43, 53] Information regarding this study on ClinicalTrials.gov (accessed April 21, 2009) has been last updated on May 16, 2007 and no results have been posted so far.

4.2.3.3 Other registered trials

In the EUROPT clinical trial, it is hypothesised that treatment with EBVs will only lead to a significant clinical improvement in those patients in whom lung volume reduction is successfully achieved. Therefore, only patients diagnosed with heterogeneous emphysema and at least one complete oblique fissure are eligible for enrolment. No control group is envisaged in this trial, with a "non-randomized, open label, historical control, single group assignment" design. On January 29, 2009, we contacted investigators of the non-randomized European "EUROPT" clinical trial (ClinicalTrials.gov identifier NCT00730301). No data could be provided so far. Recruitment was expected to be stopped in April 2009. A request for information (Jan 29, 2009) from Spiration's medical director remained unanswered.

Key points

- **Peer-reviewed evidence on the use of EBVs, is limited to small and short-term uncontrolled case series, constituting very low quality of evidence. Comprehensive data from the as yet unpublished VENT RCT are available from the FDA's website.**
- **Additional unpublished and non peer-reviewed information has been provided by the manufacturer.**
- **The insertion of up to 10 EBVs in selected patients with severe pulmonary emphysema is feasible and can be safely performed. One procedure related death (1/155) has been reported in the case series and one (1/214) in the VENT trial.**
- **In the VENT trial, 24% of the EBVs inserted at the start of the study were removed within the first year because of valve misplacement or migration, patient's request, incorrect placement or COPD exacerbation.**
- **Device safety remains a concern in the VENT study, especially in the first 100 days following EBV insertion. Patients treated with EBVs have a higher number of "major complications", more COPD exacerbations and more hospitalisations.**
- **Although an improvement in spirometry and exercise capacity after EBV was observed in some case series, and statistically significant differences at 6 months were apparent between study groups in the VENT trial, at no time point did either of the endpoints reach clinical significance.**
- **The FDA panel, on December 8, 2008, voted the Emphasys EBV for the treatment of severe emphysema to be "not approvable". The panel suggested further studies to identify potential subset populations that may benefit from the device.**
- **The results of the VENT trial are disappointing for the selected population. However, researchers are now focussing on a subgroup of patients (high heterogeneity and complete fissure). Nevertheless, the preliminary data are unconvincing. The possible benefit of EBV in this subgroup has to be shown in a prospective randomized trial including patient-oriented endpoints.**

5 ECONOMIC EVALUATION

5.1 ECONOMIC EVALUATIONS

A review of the literature was undertaken (April 3, 2009) to identify all literature that may provide evidence with regard to the cost effectiveness of EBV. Initially, websites of HTA institutes were consulted. The search of INAHTA's (International Network of Agencies for Health Technology Assessment) databases helped to identify assessment reports issued by national or regional HTA agencies on EBV. This consultation was completed by a manual search of the websites of HTA institutes mentioned on the INAHTA website (Table 9). The text word 'endobronchial valve' was used to search these websites.

Table 9: List of INAHTA member websites searched

Organisation		Country
INAHTA	International Network of Agencies for Health Technology Assessment	International
AETMIS	Agence d´Évaluation des Technologies et des Modes d´Intervention en Santé	Canada
AETS	Agencia de Evaluación de Tecnologias Sanitarias	Spain
AETSA	Andalusian Agency for Health Technology Assessment	Spain
AHRQ	Agency for Healthcare Research and Quality	USA
AHTA	Adelaide Health Technology Assessment	Australia
AHTAPol	Agency for Health Technology Assessment in Poland	Poland
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures -Surgical	Australia
AVALIA-T	Galician Agency for Health Technology Assessment	Spain
CADTH	Canadian Agency for Drugs and Technologies in Health	Canada
CAHTA	Catalan Agency for Health Technology Assessment and Research	Spain
CDE	Center for Drug Evaluation	Taiwan, Republic of China
CEDIT	Comité dÉvaluation et de Diffusion des Innovations Technologiques	France
CENETEC	Centro Nacional de Excelencia Tecnológica en Salud Reforma	Mexico
CMT	Center for Medical Technology Assessment	Sweden
CRD	Centre for Reviews and Dissemination	United Kingdom
CVZ	College voor Zorgverzekeringen	The Netherlands
DACEHTA	Danish Centre for Evaluation and Health Technology Assessment	Denmark
DAHTA @DIMDI	German Agency for HTA at the German Institute for Medical Documentation and Information	Germany
DECIT-CGATS	Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia	Brazil
DSI	Danish Institute for Health Services Research	Denmark
FinOHTA	Finnish Office for Health Care Technology Assessment	Finland
GR	Gezondheidsraad	The Netherlands
HAS	Haute Autorité de Santé	France
HunHTA	Unit of Health Economics and Health Technology Assessment	Hungary
IAHS	Institute of Applied Health Sciences	United Kingdom
ICTAHC	Israel Center for Technology Assessment in Health Care	Israel
IECS	Institute for Clinical Effectiveness and Health Policy	Argentina
IHE	Institute of Health Economics	Canada
IMSS	Mexican Institute of Social Security	Mexico
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen	Germany
KCE	Belgian Federal Health Care Knowledge Centre	Belgium
LBI of HTA	Ludwig Boltzmann Institut für Health Technonoly Assessment	Austria
MAS	Medical Advisory Secretariat	Canada
MSAC	Medicare Services Advisory Committee	Australia
MTU-SFOPH	Medical Technology Unit - Swiss Federal Office of Public Health	Switzerland
NCCHTA	National Coordinating Centre for Health Technology Assessment	United Kingdom
NHS QIS	Quality Improvement Scotland	United Kingdom
NHSC	National Horizon Scanning Center	United Kingdom
NOKC	Norwegian Knowledge Centre for Health Services	Norway
NZHTA	New Zealand Health Technology Assessment	New Zealand
OSTEBA	Basque Office for Health Technology Assessment	Spain
SBU	Swedish Council on Technology Assessment in Health Care	Sweden
UETS	Unidad de evaluacíon Technologias Santarias	Spain
VATAP	VA Technology Assessment Program	USA
VSMTVA	Health Statistics and Medical Technologies State Agency	Latvia
ZonMw	The Medical and Health Research Council of The Netherlands	The Netherlands

Only two references were identified, one of the 'Canadian Agency for Drugs and Technologies in Health' (CADTH) and one of the 'College voor Zorgverzekeringen' (CVZ). Both references did however not include an economic part. In April 2009, the following databases were searched: Centre for Reviews and Dissemination (CRD) (both the NHS EED (Economic Evaluation Database) and HTA databases), Medline (through PubMed and OVID, both '1996 -March week 4, 2009' and 'In-Process & Other Non-Indexed Citations April 2, 2009' databases), Embase, and CDSR (Cochrane Database of Systematic Reviews, both the 'Technology Assessments' and 'Economic Evaluations' databases). Since there is no MeSH or EMTREE term for endobronchial valve, the text word was used in our search for relevant documents. Only 91 references were identified as such. Instead of selecting some of these references by adding restrictions in our search strategy, relevant articles were retrieved by looking at the title, keywords and abstracts. Only one article[57] mentioned 'cost-effectiveness analysis' as a keyword and was retrieved for full text analysis. However, it was not a full economic evaluation.

It is not surprising that no full economic evaluations are found for this technology. To date, not enough evidence has been put forward that shows the clinical benefit of EBV versus standard treatment on patient relevant outcomes. Until these data are not provided, it remains difficult to make a reliable and transparent calculation of the intervention's cost effectiveness.

5.2 THE VENT COST-EFFECTIVENESS SUB-STUDY

As mentioned before, the "Endobronchial Valve for Emphysema PalliatioN Trial (VENT) Cost-Effectiveness Sub-Study" was set up to gather healthcare utilization and QoL information on patients enrolled in the clinical VENT study in order to analyze the relative cost-effectiveness of the EBV procedure. As mentioned before, this sub-study has been stopped and in response to an e-mail request, the company declared "Emphasys Medical decided to discontinue the study due to resources and cost required to execute the study as compared to the amount of additional data being received. The data had not been analyzed by Sponsor nor investigators prior to the study being discontinued." (e-mail, April 26, 2009)

Nevertheless, looking at the retrieved results from the VENT trial, some observations can be made with respect to:

a) Primary effectiveness endpoints (FEV1 and 6MWD):

- After 6 months follow-up, FEV1 had improved by 5.8% in the treatment group, whereas it declined by 0.6% in the control group, a spread of 6.4% which was statistically significant. The 6MWD improved the distance by 1.7% (about 15 metres) in the treatment group, whereas the controls' distance declined by 4.0%. This 5.7% spread was also statistically significant.
- After 12 months follow-up, the difference in percent changes in FEV1 was 7.7% (95% CI: 2.6 to 12.7) and 3.8% (95% CI: -1.4 to 9.0) for the 6MWD, the latter not being statistically significant.
- The FDA stressed that, although the analysis of the co-primary effectiveness endpoints showed statistically significant differences at 6 months, at no time point did either of the endpoints reach clinical significance (i.e. resulting in an improvement of at least 15%).

b) QoL measurements:

- The difference between the treatment group and the control group was -3.4 points for SGRQ (p=0.017), -0.26 points for MRC (p=0.018), +3.8 watts for cycle ergometry (p=0.020) and -12.0 liters per day for supplemental oxygen use (p=0.020). The difference in the SGRQ, although statistically significant, is not clinically relevant. For the MRC, there is no threshold value that helps to identify clinically relevant differences.
- No results of generic QoL measurements have been published.

c) Adverse events:

- Data requested by the FDA showed that, at 12 months, there was no significant difference in the MCC between the treatment and control groups. However, the treatment group had higher rates of serious adverse events related to COPD than the control group (23% versus 10%, p=0.01) and EBV-treated patients were also more likely to be hospitalized (39.7% versus 25.3%, p=0.024).

These observations have to be taken into account in an economic evaluation. If we look at the parameters of the incremental cost-effectiveness ratio (ICER), the following remarks can be made:

Incremental costs:

- The extra costs of the initial intervention have to be taken into account (see 5.3).
- The costs related to adverse events, which were significantly higher, have to be included.

Incremental benefit:

- Currently, there is no evidence that there is a gain in life years.
- Currently, there is no evidence that QoL measured with a generic instrument improves. Measuring the impact on QoL, researchers also have to consider the impact of adverse events and hospitalisations.

5.3 COST DATA

The Spiration products are distributed in Belgium by Olympus Belgium NV. The prices for the different parts are as follows:

- IBV-V5, 6 or 7 (valve of 5, 6 or 7mm in cartridge): €1500 excl TAV
- IBV-C26 (catheter and loader (once-only per patient) for placing the valves: €600 excl TAV
- IBV-SK (sizing kit (micro syringe, gauge and worksheet) for calibration of the balloon catheter): €200 excl TAV
- B5-2C (balloon catheter): €165 excl TAV.

With an average of 6 valves in the Coxson study[53], this would amount to a cost of €9965 excl TAV or €10 563 incl TAV.

The Emphasys products are distributed by RMS in Belgium. The prices for the different parts are as follows:

- Zephyr valve: €1900 excl TAV
- Applicator to place the device: €200 excl TAV

The applicator can be used to place up to four valves. For four valves, i.e. the average in the Wan study[51], the cost would amount to €7800 excl TAV, or €8268 incl TAV.

5.4 CONCLUSION

The costs for (the placement of) endobronchial valves is substantial (on average >€8000). These costs do even not take other costs (such as hospitalisation, medication and physician fees) of the procedure or possible adverse events into account. In contrast, the evidence for improvement of clinically relevant outcomes is not persuasive or currently lacking.

6 DISCUSSION

The rationale for EBV therapy in patients with severe pulmonary emphysema is to try to mimic the clinical benefit of lung volume reduction as reported with LVRS, yet avoiding the mortality and morbidity associated with the surgical procedure. The evidence in favour of LVRS is predominantly derived from the NETT trial. The best results from surgery were obtained in a post hoc defined subgroup of patients with upper lobe emphysema and low exercise capacity. 24 months after randomisation, 30% of these patients (25/84) had an improvement in exercise capacity, defined as an increase in maximal workload of more than 10 W from the postrehabilitation baseline value, whereas such an improvement was noticed in none (0/92) of the medically treated patients.[38] A long-term analysis of all 1218 randomized patients in the NETT trial demonstrated an overall survival advantage for LVRS, with a 5-year risk of death of 46.5% in the LVRS group vs. 53.1% in the medical group, i.e. a 5-year risk ratio of 0.86 (p= 0.02).[14]

Data on EBV insertion published in peer-reviewed journals are limited to case series. These are enlisted in Table 5. As discussed earlier, two of these series are an updated summary of the other series: Wan's data on the Zephyr EBV[51] and Coxson's paper on the Spiration IBV Valve System.[53] No results from RCTs on the use of EBVs have been published so far. One RCT, the VENT trial, has finalised recruitment in 2007 but results have not yet been published. Data are however available from presentations at international meetings and from webposted reports on the FDA's website.[m]

6.1 SAFETY

Complications reported in the case series are depicted in Table 5. In Wan's series,[51] there were eight serious complications (8.2%), including one death (1%). The most common complications were COPD exacerbations (17%), followed by pneumothoraces (5%) and pneumonia (5%).[38] In Wood's series, complications developed in 17% of the patients, with periprocedural arrhythmia, bronchospasm, pneumonia, and COPD exacerbations occurring most frequently. No pneumothoraces were reported by Wood et al[43] but an update of this series mentions 4 pneumothoraces.[53]

In the VENT trial, at 6 months of follow-up, control subjects had a 1.2% rate (1/87) of "major complication composite events" (MCCs) compared with a fivefold higher 6.1% (13/214) for EBV treated patients, a trend that was not statistically significant (p=0.075). One EBV patient died from massive hemoptysis related to the device. All-cause mortality over 12 months was equivalent for the two groups: 3.5% for the controls and 3.7% for the EBV subjects. In the European arm of the trial, the MCC at 6 months was statistically significantly worse in the EBV group (3.33% vs. 13.51%; p=0.0348). In the US pivotal trial, at one year, the EBV group had higher rates of serious adverse events related to COPD than the control group (23% versus 10%, p=0.01). There was a trend towards higher hospitalization rates for EBV subjects (27.1%) compared with control subjects (16.1%) through 6 months, which was borderline non-significant (p = 0.052). Almost a quarter (230/963) of the EBVs inserted at the start of the VENT study were removed within the first year. Longer term implications of an atelectatic pulmonary lobe remain unclear.

These findings indicate that device safety remains a concern.

6.2 CLINICAL EFFECTIVENESS

The clinical effectiveness of EBV mostly is presented in terms of spirometric improvements (especially FEV1) or in terms of QoL parameters, most often the 6MWT and the SGRQ. Data retrieved from the largest published case series and from the VENT trial, as discussed earlier, are presented in Table 10.

[m] http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4405b1-00-Index.html

Table 10: Summary of clinical effectiveness of EBV from representative case series and from the not yet published VENT randomised controlled trial.

	Wan (n=98)		Coxson (n=56)			VENT trial				
	Baseline	Absolute Δ at 3 mo*	Baseline	Absolute Δ at 3 mo	Absolute Δ at 6 mo	Baseline Control group (n=101)	Baseline EBV group (n=220)	Δ at 6 mo**	Absolute Δ at 6 months***	Absolute Δ at 1 year§
6MWD (m)	303±118	36,9±90	336±85	9±57	12±65	351	334	5,8%	19,9	14
SGRQ (points)	NA	NA	58,2±12,6	-4,28±15,81	-8,95±16,22	50,1	51,5	-3,4	-3,4	-3,0
FEV1 (mL)	900±300	60±210	840±230	-30±170	-40±160	840	870	6,8%	58,1	64,3

Data retrieved from Wan[51], Coxson[53] and the FDA's website (http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4405b1-07-Clinical%20Study%20Report%20Pages%201-100.pdf). 6MWD: six minutes walking distance. SGRQ: St George's Respiratory Questionnaire (decreasing value indicates improvement). FEV1: forced expiratory volume in 1 second. N=number of patients. Values are mean ± SD. *: Δ = absolute difference pre and post intervention. **: Δ = [% increase in intervention group (I) + % decrease in control group (C)]. *** Calculated absolute difference at 6 months between value in intervention group and mean baseline value [(I+C)/2]. § data related to "completed cases - CC" (cfr text):175 EBV, 74 controls.

In the published case series, a mean of 4[51] and 6[53] EBVs were implanted per patient. At 3 months follow-up there was a small improvement of FEV1 in Wan's series, whereas in Coxson's series, FEV1 remained unchanged after EBV insertion. Wan's series showed an increase in 6MWD of 36.9±90.0 m, as compared to an increase of 9±57 m in Coxson's series. QoL data are not provided by Wan, whereas Coxson found an improvement in SGRQ with 5.49, 4.28 and 8.95 points at 1, 3 and 6 months respectively. In the VENT trial, a mean of 3.8 valves were implanted. The co-primary effectiveness endpoints improved statistically significantly. At 6 months, the FEV1 spread between EBV patients and controls was 6.8% (58.1 mL) and the 6MWD spread was 5.8% (19.9 metres). 7.3% of the EBV group and 1.4% of the control group had a 15% improvement in both FEV1 and the 6MWD. The secondary effectiveness outcomes at 6 months were also better for the intervention group, and among them, the SGRQ score improved by 3.4 points (-6.6 to -0.3). There was no significant difference in the percent change in residual volume or in DLCO between both study groups, and there was no measurable difference in "quality of well-being". At 12 months, the difference in percent changes in FEV1 and 6MWD from baseline in the intention-to-treat analyses were 7.7% and 3.8% respectively, the results of the 6MWD dropping below statistical significance.

Although some of the outcomes in the intervention group were at some point significantly different from those in the control group, their clinical relevance remains questionable. Moreover, the non-blinded nature of the study may contribute to a placebo effect in the EBV treated patients. The mean post-procedural increase in FEV1 was negative in Coxson's series[53] and 60 mL or about 7% in Wan's series[51] and in the VENT trial (Table 10). This is clearly below the 100-140 mL threshold suggested (sic) by the ATS/ERS Task Force to be clinically meaningful[21] and below the 15% improvement that by the VENT trial design was considered to be clinically different. An improvement of 6MWD of 36.9 metres[51] or 9 metres[53] was observed in the largest case series. As discussed earlier, an increase in 6MWD should be at least 70 m in order to be 95% confident that the change is not due to random variation. In the VENT trial, the mean 6MWD was 20 m higher in the intervention group than in the control group, which is less than the 54 m difference that is needed for patients to experience a difference in exercise performance.[26] Thus the observed improvement in 6MWD in different studies is too low an increase to be clinically meaningful. It can be inferred from Table 10 that the SGRQ score improved with a mean of 3.4 and 3.0 points in the VENT trial, and with 4.28 and 8.95 points in Coxson's series at 6 months and 1 year respectively, indicating a "slightly efficacious" and a "moderately efficacious" change respectively.

Some authors have suggested that a small group of patients treated with EBVs may derive a substantial benefit from EBV insertion, but that this beneficial effect remains unnoticed when mixed among the results in all patients thus treated.

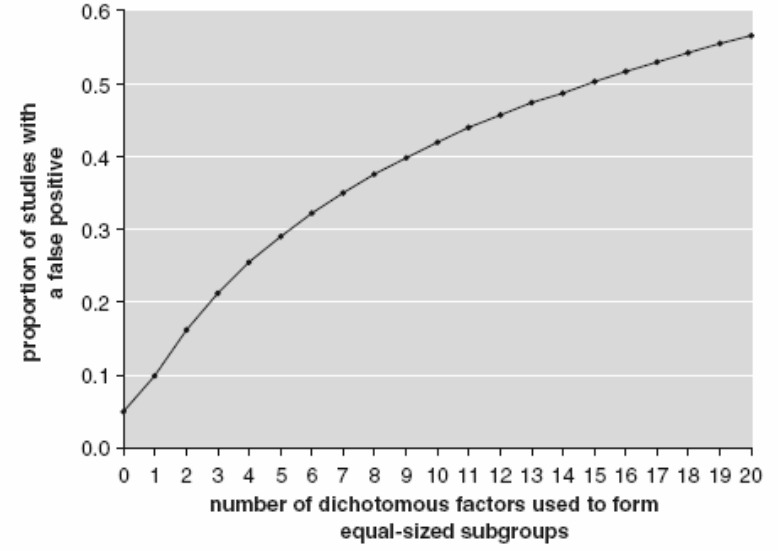
The manufacturer of the Zephyr EBV performed a (so far unpublished) analysis on a subgroup of patients from the VENT trial, with a highly heterogeneous emphysema in combination with an anatomically strictly separated target lobe ("complete fissure"). The effect of EBVs on FEV1 and 6MWD in these patients was clearly better than those observed in the overall population. Given the methodological shortcomings and the statistical uncertainties associated with such subgroup analyses, the small number of patients involved, and the fact that the data have not been peer-reviewed, these data should be regarded cautiously. The results from ongoing trials should be awaited before further conclusions can be drawn on the clinical effectiveness of EBVs in certain subgroups of patients.

The efficacy of EBVs on outcome measures that are important to patients, even in a reportedly "ideal subgroup", remains disappointing. No other conclusion can be drawn that EBVs have not been shown to provide a meaningful clinical improvement for end-stage emphysema patients. Moreover, they are accompanied with an increased number of COPD related events and hospitalisations, at least during the first 100 days following the procedure.

6.3 POST-HOC SUBGROUP ANALYSIS

Post-hoc analysis refers to re-examining an existing data set after an experiment has been conducted for patterns that were not specified a priori. In practice, this is usually related to detecting treatment effects or other patterns in subgroups. Subgroup analyses are problematic both in terms of false-positive and false-negative results. Every statistical test carries the risk of a false-positive result (a statistically significant finding that is actually due to chance rather than to any inherent difference in the comparison groups) and as more tests are performed the probability of a false-positive finding increases.[58, 59] As mentioned by Fayers et al.: "*If k independent hypothesis tests are carried out, each with a significance level (P value) of α_0, the overall probability of a type I error (false positive) is $\alpha = 1 - (1 - \alpha_0)^k$.*"[59] With e.g. 4 independent subgroups, the probability that at least one of these subgroups is falsely significant, with P<0.05, is $1 - (1 - 0.05)^4$, which equals 0.1855. For multiple (dependent) subgroup analyses, Fayers et al. have estimated the type-I error with computer simulations with the assumptions that there was, in truth, no treatment effect in any of the subgroups, and that the outcome of interest followed a normal distribution, and that a t-test would be applied. They used 40000 randomly generated data from normal distributions with equal means and variances. The following figure shows the increase in type I error as the number of dichotomous factors used to form equal-sized subgroups increases.

Figure 12: The relation between the number of dichotomous factors used to form equal-sized subgroups and the proportion of studies with a false positive result.



Source: Fayers et al.[59]

The results show that, for example, if a sample is dichotomised into equal-sized subgroups, successively using four factors that are irrelevant (independent) of the outcome, the false positive rate is over 25% when using a nominal P<0.05 with each subgroup.[59]

The most known published example of inappropriate subgroup analysis was published in the Lancet in 1988.[60] The odds of vascular death after streptokinase, aspirin, both, or neither for acute myocardial infarction were reported in a table for several subgroups. For people labouring under the star signs Gemini and Libra, aspirin was no better than placebo. For others, aspirin had a strongly beneficial effect. The authors wanted to add these pointless results, simply to stress the reliance readers might put (or not) on the validity of these subgroup analyses.[61] Fayers and King give another abstract example of observed data were there is an 'almost significant' result. "*The basic problem is that if we now divide the data into two halves, it is very unlikely that one will find precisely the same effect in both of those halves. This is true even if the subgroup factor is irrelevant to the outcome. Therefore, we will almost inevitably observe a larger treatment effect in one of the subgroups, and a correspondingly smaller treatment effect in the other subgroup. And, if the overall difference from the trial was approaching significance, one of these subgroups may therefore show what appears to be a large effect.*"[59]

Similar to false-positive results, more false-negative results (i.e. failing to detect a true difference in effect) can occur. Power calculations for RCTs are generally based on detecting the overall treatment effect. Subgroup-specific testing requires the data to be split and these smaller datasets will have reduced power to detect a similar treatment effect. As a result, more false-negative results may occur.[58] Few RCTs pre-specify subgroup analyses, probably in part because this would necessitate considerably larger sample sizes.[59]

Although the problems of false results can be reduced by the use of specific tests (e.g. a test for interaction between treatment and subgroup to examine whether treatment effects differ between subgroups[n]) they are by no means eliminated.[58] Post-hoc subgroup analysis increases the risk of obtaining a 'significant' result, just by chance.

Although the problem that subgroup analyses may produce spurious results is recognised, Brookes et al. mention that the extend of the problem may be underestimated.[62] Even with prespecified subgroup analyses, post-hoc emphasis on the most fascinating subgroup finding inevitably leads to exaggerated claims.[63] Subgroup-specific analyses are particularly unreliable and are affected by many factors and the results from any subgroup analyses should not be over-interpreted. Unless there is strong supporting evidence, they are best viewed as a exploratory or hypothesis-generation exercise.[58, 63] Only exceptionally they could affect a trial's conclusions.[63]

To avoid misleading readers, results of such analyses should be explicitly labeled as post-hoc analyses. "*The overall 'average' result of a randomised clinical trial is usually a more reliable estimate of treatment effect in the various subgroups examined than are the observed effects in individual subgroups.*"[64] Therefore, emphasis should be placed on overall results, which may be considered better estimates of treatment effects than the subgroup effects.[59]

n A test for interaction involves one statistical test irrespective of the number of subgroups and partially overcomes the concerns of a false positive conclusion of a treatment–subgroup interaction. However, such tests are likely to be underpowered to detect a true differential treatment effect across subgroups since power calculations for RCTs usually relate to the overall treatment effect rather than the interaction. "Reports of formal tests of interaction in RCTs should not be over-emphasized unless a power calculation has specifically been *performed with such analyses in mind, even if the variables for which subgroup analyses have been performed were specified in advance*."[62]

6.4 ECONOMIC CONSIDERATIONS

For the valves and the applicators, an average cost of more than €8000 per patient is to be considered. This figure does not take into account additional expenses such as hospitalisation, medication and physician fees, and the costs related to possible adverse events.

Because there is no unequivocal evidence for an improvement in clinically relevant outcomes, a full health economic evaluation of EBVs cannot be performed yet.

6.5 CONCLUSION

Findings originating from published case series and the VENT trial indicate that safety issues remain a concern when inserting EBVs in patients with severe emphysema. The procedure may induce pneumothorax and the presence of a foreign object within the bronchial tree seems to induce COPD exacerbations and to lead to an increased number of hospitalisations during follow-up.

No peer-reviewed data from RCTs have been published so far. Some results are available from the minutes of an FDA meeting and some were obtained from one of the manufacturers of the device. These data indicate that the efficacy of EBVs on outcome measures that are important to patients are on average very modest. Subgroups of patients that are yet unidentified, may benefit more substantially from the procedure. This hypothesis is currently being tested in clinical trials.

Key points

- **Endobronchial valve (EBV) insertion in patients with severe pulmonary emphysema is feasible with an acceptable risk profile.**
- **Short term (<1 year) safety remains a concern, since EBV treated patients develop more COPD exacerbations. Longer term safety data are lacking but will be available once the planned 3-year safety assessment of the VENT trial data are published.**
- **Bronchoscopic lung volume reduction involves the placement of on average 4 to 6 EBVs per patient. In Belgium, this entails a cost of more than €8 000 (incl TAV) for the EBVs and delivery devices, exclusive costs for hospitalisation, medication, physician fees, and costs related to possible adverse events.**
- **Clinical effectiveness, derived from small published case series suggest that EBVs may provide a small clinical benefit.**
- **Clinical effectiveness, derived from one unpublished randomised open-label clinical trial, indicate that EBVs provide a statistically significant but a clinically questionable benefit.**
- **Subgroups of patients may benefit more substantially from EBVs in terms of FEV1 and 6MWD. This post-hoc subgroup analysis should be viewed as a hypothesis-generating exercise that needs to be explored in a prospective study.**
- **Moreover, it remains to be shown whether these improvements in intermediate endpoints reflect a change in a patient's perception of well-being.**
- **It is not clear if the perceived modest clinical improvements observed with EBVs outweigh the modestly increased risks.**

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