# Valves endobronchiales dans le traitement de l'emphysème pulmonaire avancé: un rapid Health Technology Assessment

*KCE reports 114B*

*Federaal Kenniscentrum voor de Gezondheidszorg*
*Centre fédéral d'expertise des soins de santé*
*2009*

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# Valves endobronchiales dans le traitement de l'emphysème pulmonaire avancé: un rapid Health Technology Assessment.

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HANS VAN BRABANDT, MATTIAS NEYT

*Federaal Kenniscentrum voor de gezondheidszorg*
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| Titre : | Valves endobronchiales dans le traitement de l'emphysème pulmonaire avancé: un rapid Health Technology Assessment. |
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# PRÉFACE

Le terme « broncho-pneumopathie obstructive chronique » ou BPCO est utilisé pour une série d'affections pulmonaires qui entraînent une toux chronique et un essoufflement progressif. Ces affections peuvent entraîner une réduction sévère de la qualité de vie. La cause principale des BPCO est la cigarette ; il s'agit donc d'une maladie évitable.

Chez certains patients, le problème réside surtout dans un rétrécissement des voies aériennes. Ces personnes peuvent souvent être soulagées grâce à des médicaments. Le KCE a récemment publié une étude sur le rapport coût-efficacité d'un de ces médicaments. Chez d'autres patients par contre, notamment ceux qui souffrent d'emphysème pulmonaire, il s'agit d'une dégénérescence du tissu pulmonaire qui, d'une certaine manière, finit par prendre la place des parties saines du poumon. Ces patients répondent moins bien à une thérapie médicamenteuse. D'autres types de traitement ont donc été envisagés, comme une résection chirurgicale des parties malades du poumon de façon à ménager un espace plus grand dans la cage thoracique pour les tissus sains. Cette technique chirurgicale est cependant peu employée, non seulement parce qu'elle n'améliore la situation que d'un très petit nombre de patients mais aussi en raison de son caractère fort invasif. Depuis quelques années, a été développée une technique qui permet de fermer les parties malades du poumon au moyen de valves à une voie introduites via les voie respiratoires (bronchoscopie). On espère ainsi limiter les effets du traitement chirurgical.

Le présent rapport vise à déterminer dans quelle mesure ces valves sont efficaces et coût-efficaces dans le traitement de l'emphysème pulmonaire.

Jean-Pierre CLOSON
Directeur général a.i.

# Résumé


## OBJECTIF

Ce rapid Health Technology Assessment (HTA) fournit une revue systématique de la littérature scientifique sur (le coût)-efficacité des valves endobronchiales (VEB) en tant que modalité thérapeutique adjuvante venant en complément d'une thérapie optimale non invasive chez les patients atteints d'emphysème pulmonaire avancé.

## CONTEXTE CLINIQUE

L'emphysème pulmonaire fait partie de l'entité pathologique des «bronchopneumopathies chroniques obstructives» (BPCO). Ces maladies pulmonaires se caractérisent par une obstruction progressive du passage de l'air, obstruction qui n'est pas entièrement réversible. Cette obstruction est provoquée par la conjonction d'une pathologie des voies respiratoires de fin calibre et d'une destruction du parenchyme pulmonaire, cette dernière étant le processus principal dans l'emphysème pulmonaire. L'impact d'une BPCO sur un patient donné est fonction de l'étendue de la pathologie. Elle peut provoquer des symptômes chroniques tels que la toux, la production d'expectorations, l'essoufflement, une capacité d'effort amoindrie ainsi que toute une série d'effets systémiques, notamment une perte de poids et un dysfonctionnement des muscles squelettiques. Une BPCO est une maladie évolutive dont la cause principale est le tabac, faisant d'elle une affection dans une large mesure évitable.

Le diagnostic de la BPCOse fonde sur les antécédents cliniques, la présence de signes spécifiques et une évaluation de l'obstruction des voies respiratoires au moyen d' « épreuves fonctionnelles respiratoires ». La mesure de la fonction pulmonaire la plus utilisée est le FEV1 (volume expiratoire maximal par seconde). D'autres mesures également employées pour quantifier l'impact d'une BPCO sont : le test de marche de 6 minutes (6MWD), le questionnaire respiratoire de l'Hôpital St Georges (SGRQ) et l'index de dyspnée du Medical Research Council (MRC). On a recours à la tomographie thoracique à haute résolution pour déterminer la présence, l'ampleur et la distribution topographique des lésions emphysémateuses.

Le traitement de la BPCO se fonde sur une approche séquentielle liée à la gravité de la maladie. De nombreux patients ont besoin d'un traitement médical à vie, avec une augmentation des doses et des médicaments supplémentaires durant les exacerbations. Le traitement médical est constitué de bronchodilatateurs, d'agents anti-inflammatoires, d'oxygène et d'une revalidation pulmonaire. Les objectifs thérapeutiques sont : un soulagement des symptômes, la prévention des exacerbations et d'une aggravation de la dégradation de la fonction pulmonaire, ainsi qu'une amélioration des activités de la vie quotidienne, de la qualité de vie et de la survie. Même si le traitement médical se révèle bénéfique pour de nombreux patients BPCO, une minorité significative d'entre eux ne constate qu'une amélioration minime, précisément parce que le traitement médical ne cible que la composante « voies respiratoires » de la maladie. Cet effet limité du traitement médical est surtout observable chez les patients atteints d'emphysème prédominant. Un nombre limité de ces derniers sont candidats pour une greffe du poumon mais pour les autres, la chirurgie de réduction du volume pulmonaire (CRVP) peut constituer une thérapie de dernier recours. Dans cette chirurgie, on procède à l'exérèse de territoires distendus endommagés du parenchyme pulmonaire, ce qui crée un surcroît de capacité dans la cavité pulmonaire pour le poumon résiduel qui a ainsi la possibilité de se dilater davantage et de mieux fonctionner. En raison de la mortalité et de la morbidité élevées consécutives à cette chirurgie, une méthode de substitution moins invasive de réduction du volume pulmonaire a été mise au point. Il s'agit de l'insertion par voie bronchoscopique de valves endobronchiales (VEB). Cette intervention est également appelée « réduction par voie bronchoscopique du volume pulmonaire ». Elle constitue le thème de recherche du présent rapport.

# LA TECHNOLOGIE DES VALVES ENDOBRONCHIALES

Les VEB sont des valves unidirectionnelles introduites dans les voies respiratoires qui mènent au tissu pulmonaire emphysémateux. Ces valves empêchent l'air de pénétrer dans les segments bloqués tout en permettant la sortie de l'air expiré et des sécrétions bronchiques. En fin de compte, la procédure devrait se solder par un affaissement des segments isolés (atélectasies), créant ainsi la réduction voulue du volume pulmonaire. En règle générale, l'insertion des valves se fait sous anesthésie générale et le patient doit normalement séjourner quelques jours à l'hôpital.

La principale expérience avec les VEB a été obtenue avec deux dispositifs différents : le VEB Zephyr (au départ, Emphasys Medical, et actuellement Pulmonx) et la Valve Spiration Intrabronchial (Spiration Inc.). En Belgique, Pulmonx est représenté par RMS Endoscopy et la valve Spiration IBV est distribuée par Olympus.

# EFFICACITE CLINIQUE

## RECHERCHE DANS LA LITTERATURE

Une recherche approfondie de la littérature au moyen de différentes bases de données a permis d'identifier 9 séries de cas. À ce jour, aucun résultat de RCT (« randomised control trials ») n'a été publié sur l'utilisation des VEB. Un RCT non publié, l'essai VENT (« Enbronchial valve for Emphysema Palliation Trial) a finalisé son recrutement en 2007. Certains résultats ont été présentés lors de réunions internationales et des données relativement complètes portant sur le bras américain de l'essai sont disponibles sur le site Internet de la Food and Drug Administration (FDA)[a]. En outre, des informations complémentaires ont été obtenues directement auprès du fabricant.

Outre la sécurité d'utilisation, dans ces études, les indicateurs de résultats les plus fréquemment utilisés étaient le FEV1, le test de marche de 6 minutes (6MWD) et le SGRQ. Dans l'essai VENT, plusieurs autres critères de jugement secondaires de la sécurité d'emploi et de l'efficacité réelle ont été étudiés, notamment le MCC « Major Complications Composite » (qui comprend : le décès, l'empyème, l'hémoptysie massive, la pneumonie en aval d'une valve, le pneumothorax ou une fuite d'air prolongée, et l'insuffisance respiratoire), la capacité d'effort, les besoins en oxygène de même que l'index de dyspnée. D'autres analyses complémentaires préalablement spécifiées étaient : l'indice de bien-être, la réussite technique et le taux de réadmission. L'étude avait pour objectif d'enrôler 270 sujets avec une randomisation de 2:1 pour l'inclusion de VEB. Cet échantillon permettait de déceler une amélioration de 15% du FEV1 et de 17% du test 6MWD dans le bras traité.

[a] La disponibilité des données de l'essai VENT sur le site Internet de la FDA est liée au fait que cet essai de base était imposé au fabricant pour obtenir une autorisation préalable à la mise sur le marché. Le 8 décembre 2008, la FDA a décidé de ne pas approuver le dispositif. Elle a suggéré de nouvelles études visant à identifier des sous-populations potentielles susceptibles de tirer avantage de ce dispositif.

## SECURITE D'EMPLOI

Les complications les plus couramment rapportées dans les séries de cas étaient : les exacerbations de la BPCO (jusqu'à 17%), suivies par le pneumothorax (jusqu'à 5%) et la pneumonie (jusqu'à 5%). Dans le bras US de l'essai VENT, à 6 mois de suivi, les sujets témoins présentaient un taux de MCC de 1.2% (1/87) par rapport à un taux cinq fois supérieur (6.1% - 13/214) chez les patients dotés d'une VEB, une différence qui n'était pas statistiquement significative. Un patient VEB est décédé des suites d'une hémoptysie massive. Dans le bras européen de l'essai VENT, le MCC à 6 mois était nettement plus défavorable et ce de manière statistiquement significative dans le groupe VEB (3.3% vs 13.5%). Dans le bras US, à un an de suivi et par rapport au groupe-témoin, le groupe VEB présentait un taux significativement supérieur d'effets indésirables graves associés à la BPCO (23% vs 10%). On pouvait aussi observer, sur une période de six mois, une tendance à la hausse des taux d'hospitalisation pour les patients VEB (27.1%) par rapport au groupe-témoin (16.1%). Quelque 24% (230/963) des VEB insérées au début de l'étude ont été retirées au cours de la première année en raison d'une migration de la valve, à la demande du patient, à cause d'un placement incorrect ou d'exacerbations récurrentes de la BPCO.

Ces données indiquent qu'il pourrait y avoir des problèmes de sécurité associés à l'utilisation des VEB.

## EFFICACITE REELLE

De par leur nature, les données extraites des séries de cas non contrôlées constituent des preuves de qualité médiocre.

Les données relatives à l'essai VENT, le seul RCT finalisé à ce jour, n'ont pas encore été publiées. Certains résultats peuvent être retrouvés sur le site Internet de la FDA et des informations supplémentaires ont été fournies par le fabricant. En moyenne, 3.8 valves ont été implantées par patient. À 6 mois, le différentiel de FEV1 entre les patients VEB et le groupe-témoin était de 6.8% (58.1 ml). Pour le test 6MWD, cet écart était de 5.8% (19.9 mètres). L'index SGRQ à 6 mois était meilleur dans le groupe actif de 3.4 points en moyenne. Aucune différence mesurable de l'indice de qualité du bien-être n'a été observée entre les deux groupes. À 12 mois, les écarts en pourcentage pour le FEV1 et pour l'indicateur 6MWD par rapport aux valeurs de base dans les analyses « intention de traiter » étaient respectivement de 7.7% et de 3.8%. S'agissant du test 6MWD, la différence n'était désormais plus statistiquement significative. Même si à un certain moment, la FEV1, le test 6MWD et le SGRQ présentaient une différence statistiquement significative dans le groupe actif par rapport au groupe-témoin, leur pertinence clinique reste sujette à caution. Selon les recommandations récemment publiées, la FEV1 devrait s'améliorer de 100-140 ml et le 6MWD de 37-71 mètres pour que ces changements soient perçus comme « importants » (significatifs ?) par les patients. Dans le cas du SGRQ, si la différence moyenne est de 4 unités, le traitement est considéré comme légèrement efficace. En revanche, une différence de 8 unités indique un traitement modérément efficace. Dans toutes les études débattues dans le cadre du présent rapport, ces seuils n'ont été atteints que dans une minorité de cas. De surcroît, le fait que les études n'aient pas été réalisées en aveugle peut avoir contribué à un effet placebo chez les patients dotés d'une VEB.

Tant dans les séries de cas publiées que dans l'essai VENT, certains patients semblent tirer un bénéfice important du traitement. Si ces patients pouvaient être identifiés avant l'intervention, on pourrait escompter de meilleurs résultats de cette thérapie. Cette hypothèse est actuellement testée dans les essais cliniques en cours. Pour l'heure, des preuves solides pour soutenir l'utilisation de la technologie VEB font encore défaut.

# CONSIDERATIONS ECONOMIQUES

Par patient, on estime le coût à plus de 8 000 euros en moyenne pour les valves et les dispositifs d'insertion des valves. Ce montant ne prend pas en considération les frais supplémentaires tels que l'hospitalisation, les médicaments et les honoraires médicaux, de même que les coûts associés à d'éventuels effets indésirables.

# CONCLUSION

Les constats posés sur la base des séries de cas et des résultats de l'essai VENT indiquent que la sécurité de l'insertion de VEB chez les patients souffrant d'emphysème avancé reste préoccupante. En effet, la procédure peut provoquer un pneumothorax tandis que la présence d'un corps étranger dans l'arbre bronchique semble induire des exacerbations de la BPCO et entraîner une augmentation des hospitalisations durant le suivi.

À ce jour, aucune donnée n'a été publiée dans la littérature « peer reviewed ». Certains résultats sont disponibles dans le procès-verbal d'une réunion de la FDA ou ont été fournis par l'un des fabricants du dispositif. Les données actuelles indiquent que l'efficacité théorique des VEB sur les mesures de résultats essentiels pour les patients, est en moyenne limitée. Sur la base des résultats obtenus dans le bras américain de l'essai VENT, la FDA a décidé de ne pas approuver le dispositif pour le marché américain.

Des sous-populations de patients qui n'ont pas encore été identifiées pourraient tirer davantage profit de la procédure, mais des recherches futures doivent d'abord résoudre les problèmes précités.

# RECOMMANDATIONS

À l'heure actuelle, nous ne pouvons pas appuyer le remboursement des VEB chez les patients souffrant d'emphysème pulmonaire en phase terminale. Notre conclusion est motivée par le faible avantage clinique démontré ainsi que par leurs effets indésirables potentiels et leur coût élevé par rapport à une efficacité théorique limitée. Ces dispositifs pourraient apporter un bénéfice plus grand dans certaines sous-populations de patients, mais pour l'instant, nul ne sait avec certitude comment ces sous-groupes pourraient être identifiés ni si l'amélioration clinique dépasserait les effets délétères potentiels. L'avantage possible des VEB dans ces sous-populations devrait être établi dans un RCT prospectif qui contiendrait des critères de jugement orientés vers le patient.

Ce rapport indique que l'attribution d'un label CE à un dispositif médical ne garantit pas son efficacité ou sa sécurité cliniques. Un tel label peut être trompeur tant pour les patients que pour les médecins. Le KCE recommande que cette question soit mise à l'agenda de la Présidence belge de l'Union Européenne en 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?

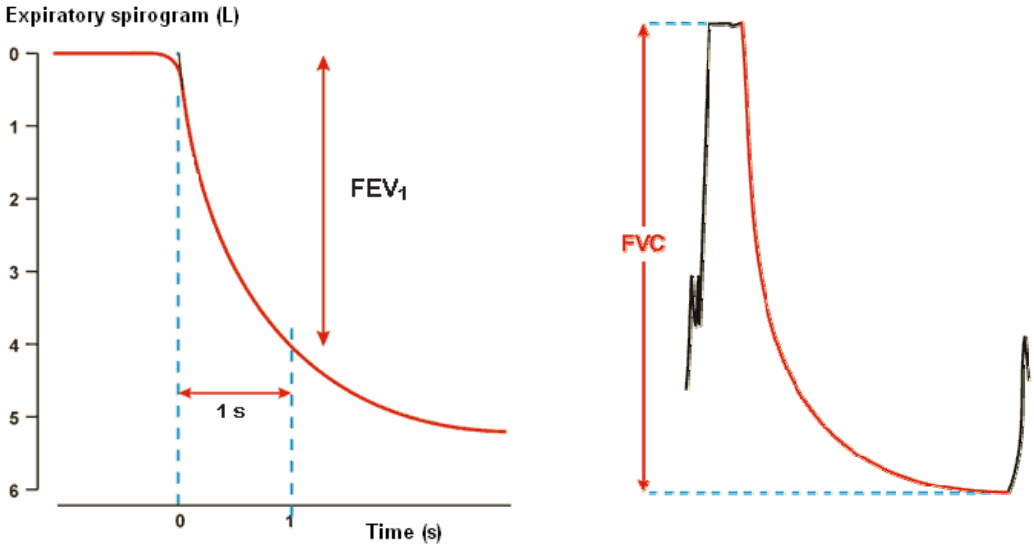
# 2 CLINICAL BACKGROUND

## 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)

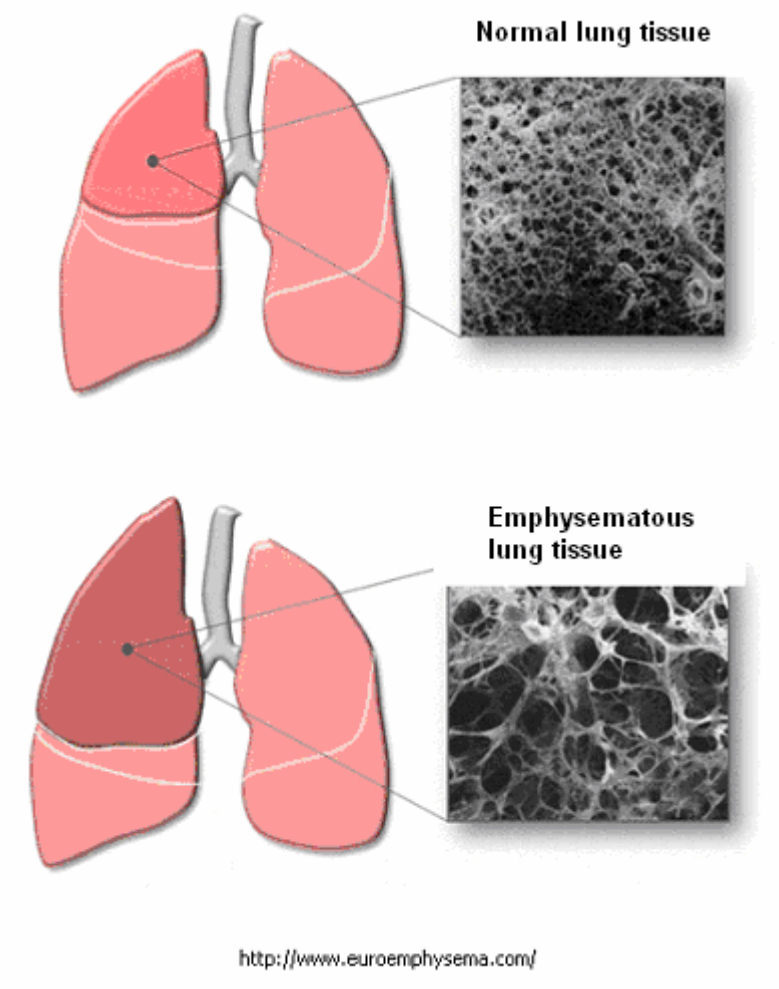
The FEV1 is an important predictor of survival in patients with COPD. The rate of decline in FEV1 is a good marker of disease progression and mortality. However, FEV1 does not adequately reflect all the systemic manifestations of the disease. For example, it correlates weakly with the degree of dyspnoea, 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

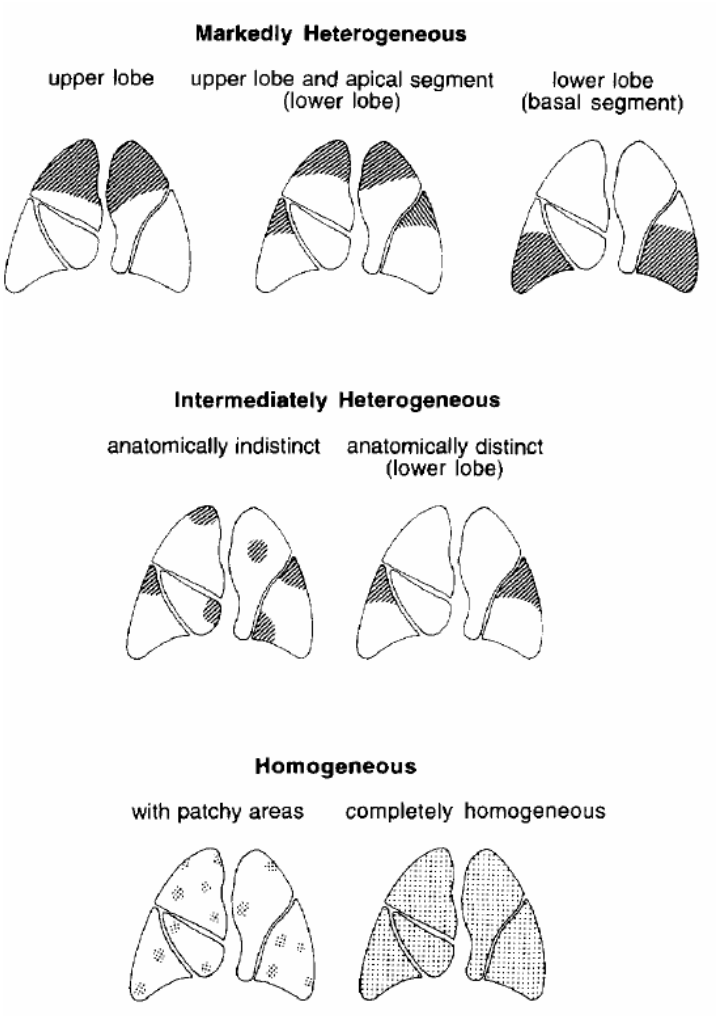
As discussed earlier, the airflow limitation in COPD is caused by a mixture of small airways disease and parenchymal destruction, the relative contributions of which vary from person to person.[1] Small airways disease is caused by chronic inflammation, leading to structural changes and narrowing of 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.**

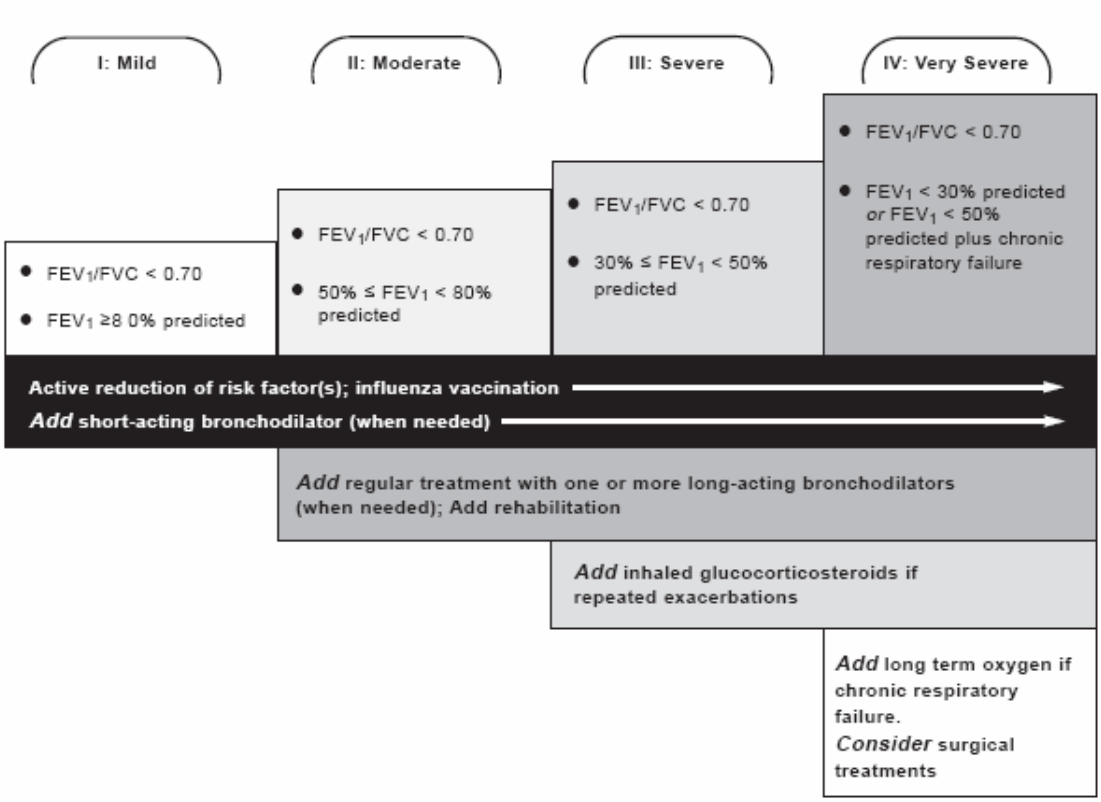



Source: Weder et al.[7]

## 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 40$^{th}$ 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.**

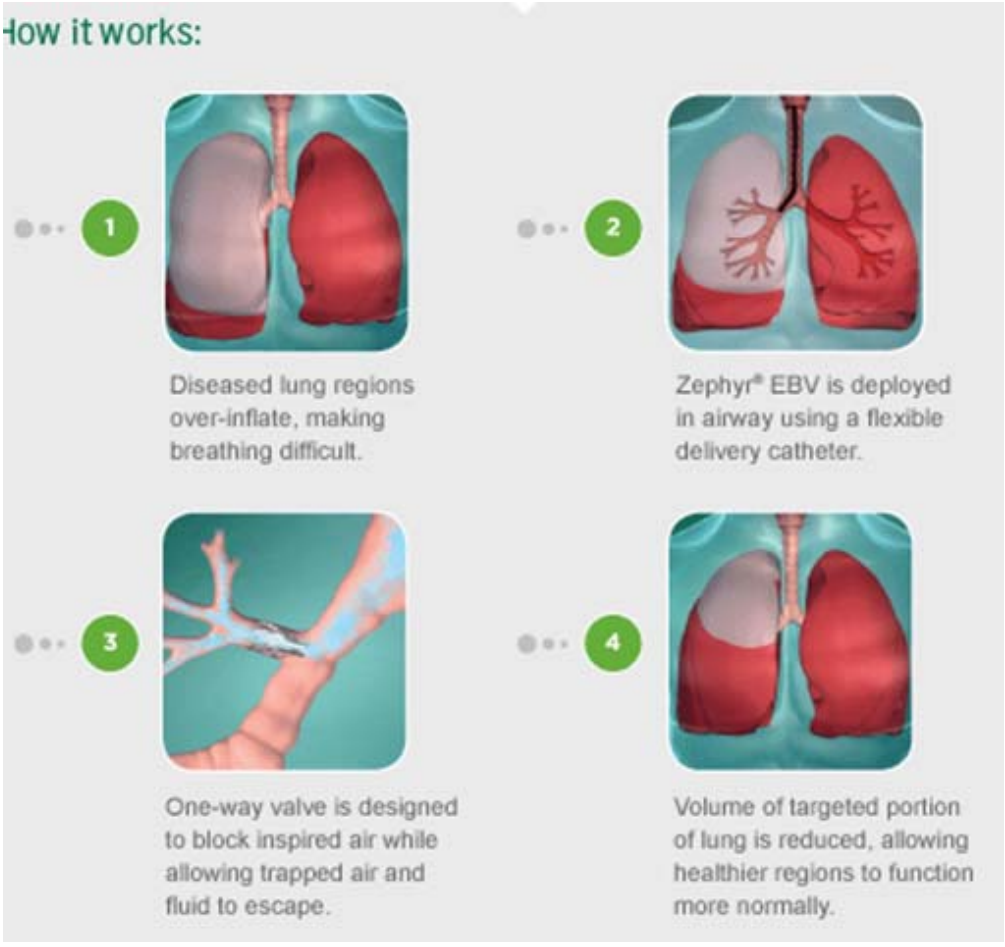
# 3 ENDOBRONCHIAL VALVES TECHNOLOGY

## 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.**

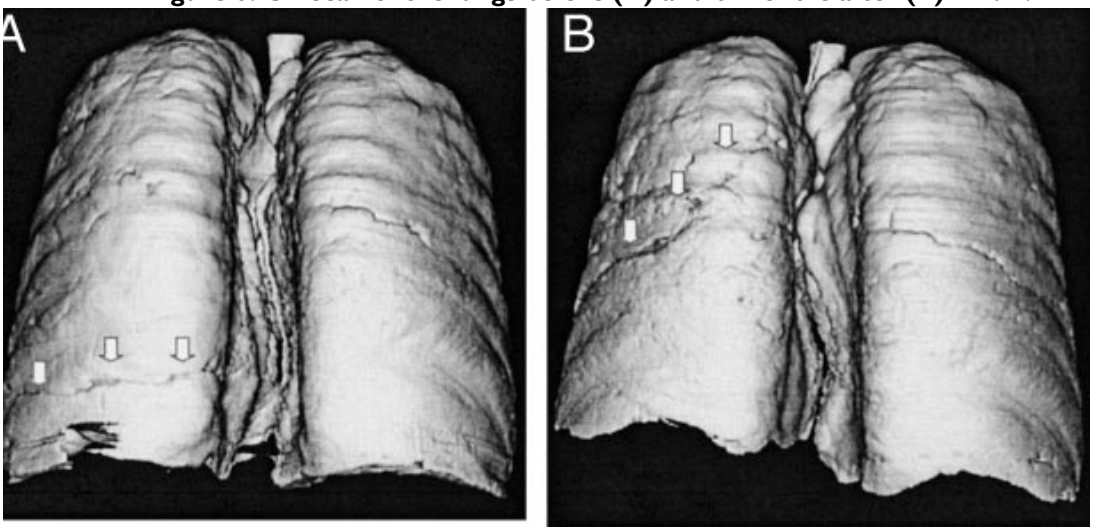



http://www.emphasysmedical.com/valve-therapy/therapy-overview/

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.

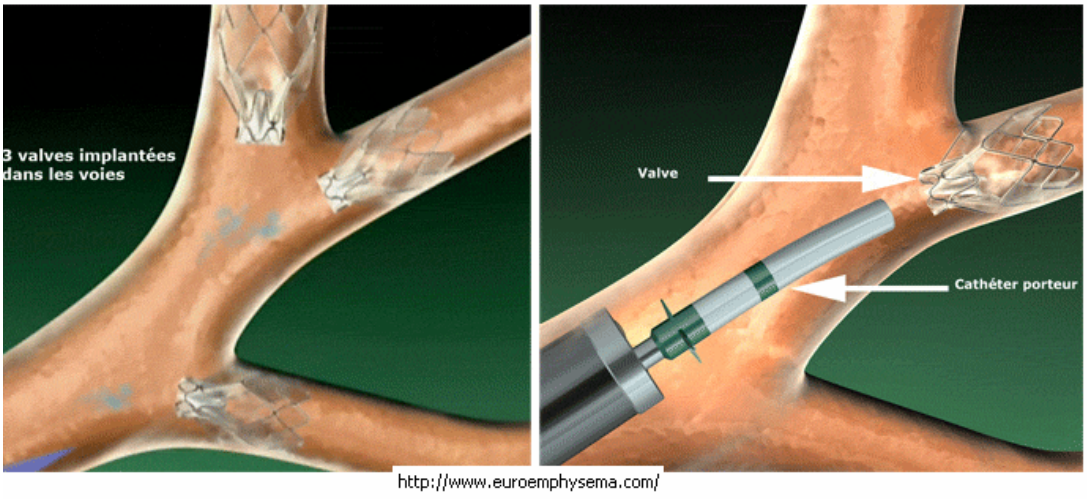
## 3.2 TECHNOLOGY DESCRIPTION

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.

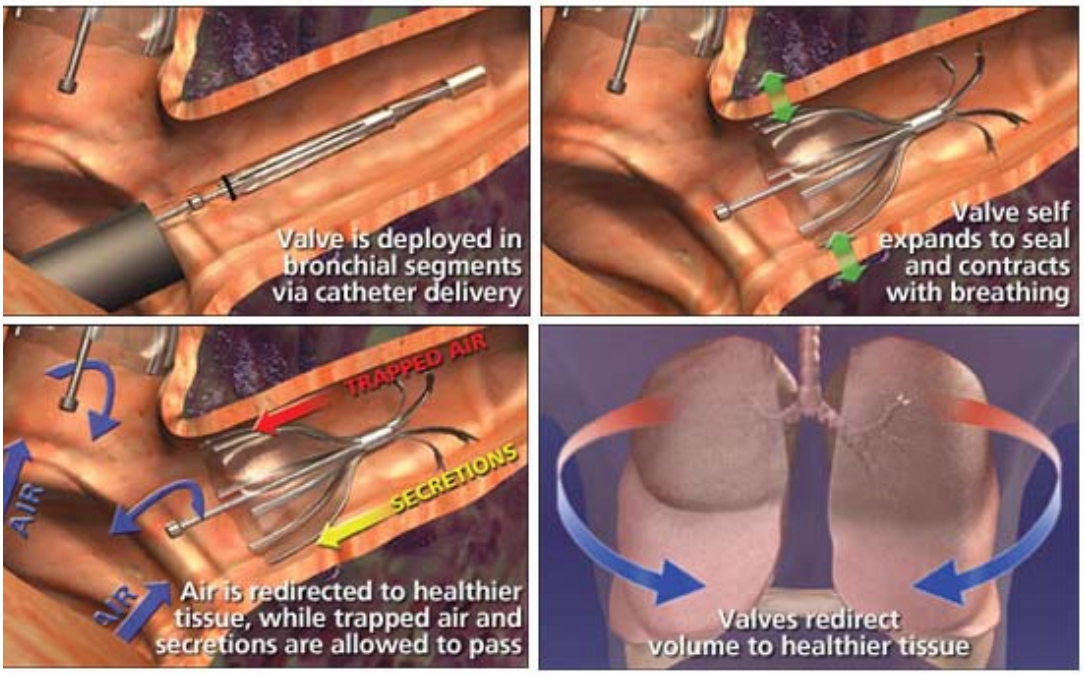
**Figure 7: Placement of the Zephyr EBV and three EBVs in situ.**




### 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]

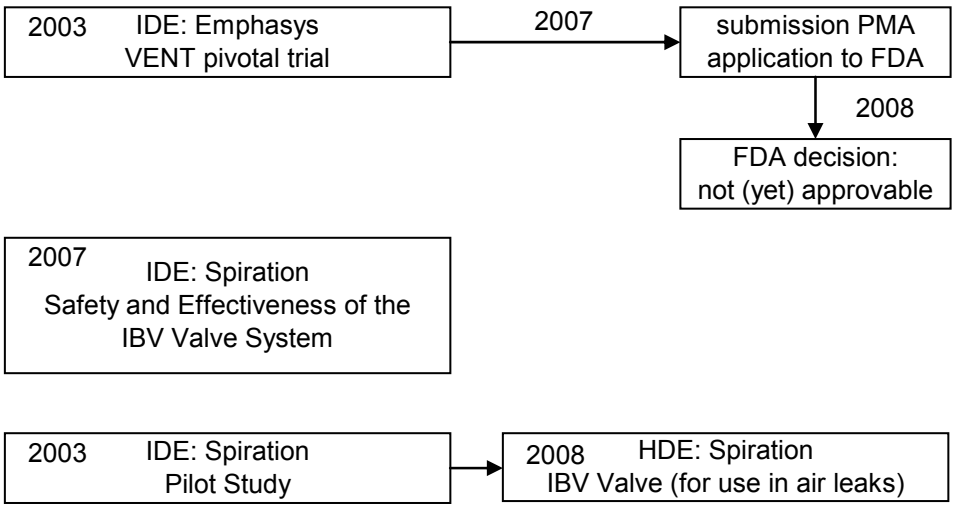
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d Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, Annex IX: classification criteria:
I. Definitions: 1) Duration: long term (normally intended for continuous use for more than 30 days). 2) Invasive Device: implantable device (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<br>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<br>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]

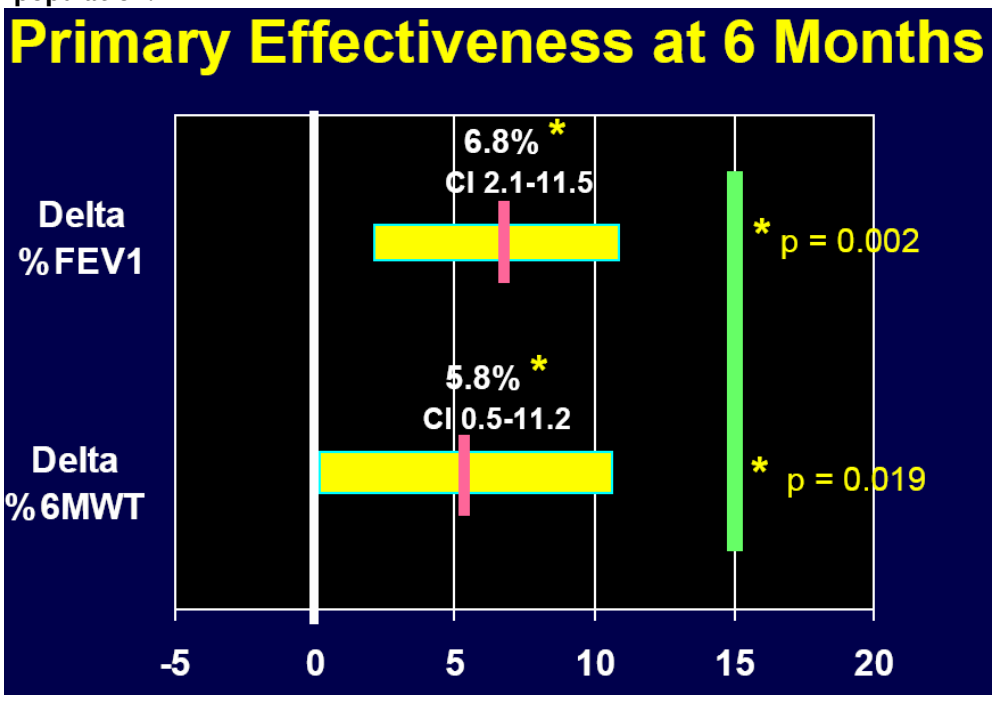
Study endpoints are related to safety of the procedure and to efficacy:

- 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

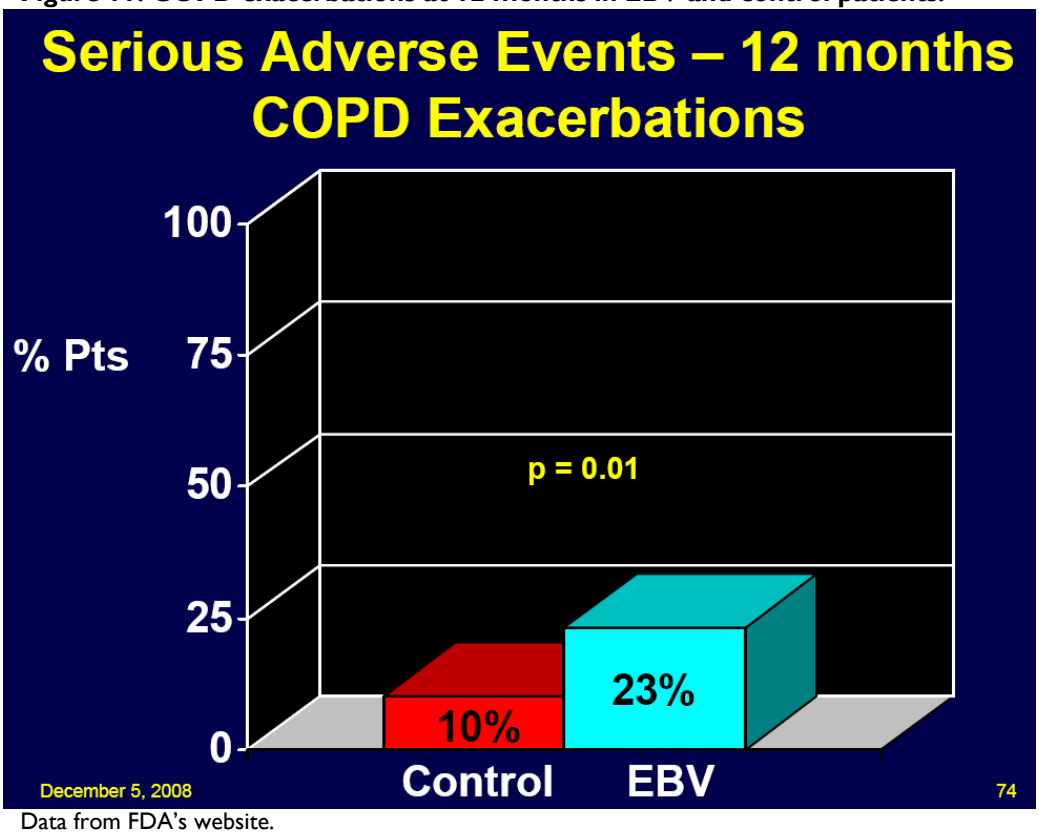
e) The spread was the difference of the absolute values between the treatment and control group at 6 months (except for rehospitalisation)

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.

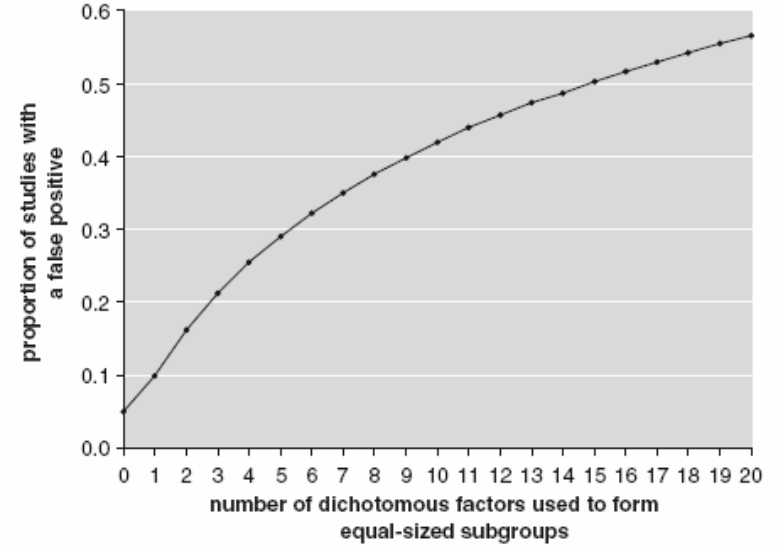
The manufacturer of the Zephyr EBV performed a (so far unpublished) analysis on a subgroup of patients from the VENT trial, with a highly heterogeneous emphysema in combination with an anatomically strictly separated target lobe ("complete fissure"). The effect of EBVs on FEV1 and 6MWD in these patients 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 $\alpha_0$, 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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