Endobronchial and Intrabronchial Valves

Effective: September 1, 2019

Next Review: March 2020
Last Review: August 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Endobronchial and intrabronchial valves are synthetic devices that are deployed with bronchoscopy into ventilatory airways of the lung for the purpose of controlling airflow.

MEDICAL POLICY CRITERIA

Endobronchial and intrabronchial valves are considered **investigational** as a treatment for all indications, including but not limited to:

- A. prolonged air leaks; or
- B. chronic obstructive pulmonary disease (COPD); or
- C. emphysema.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

None
Proper lung functioning is dependent upon a separation between the air-containing parts of the lung and the small vacuum-containing space around the lung called the pleural space. When air leaks into the pleural space, the lung is unable to inflate resulting in hypoventilation and hypoxemia; this condition is known as a pneumothorax. A pneumothorax can result from a variety of processes including trauma, high airway pressures induced during mechanical ventilation, lung surgery, and rupture of lung blebs or bullae, which may be congenital or a result of chronic obstructive pulmonary disease (COPD).

Bronchial valves are synthetic devices deployed with bronchoscopy into ventilatory airways of the lung to control airflow. They have been investigated for use in patients who have prolonged bronchopleural air leaks and as an alternative to lung volume reduction surgery in patients with lobar hyperinflation from severe or advanced emphysema.

In emphysematous chronic obstructive pulmonary disease, peripheral lung tissue may form bullae. These diseased portions of the lung ventilate poorly, cause air trapping, and hyperinflate, compressing relatively normal lung tissue. They also may rupture, causing a pneumothorax.

Use of a bronchial valve is thought to prevent hyperinflation of bullae. Their use to treat chronic obstructive pulmonary disease is based on the improvement observed in patients who have undergone lung volume reduction surgery. Lung volume reduction surgery involves excision of peripheral emphysematous lung tissue, generally from the upper lobes. The precise mechanism of clinical improvement for patients undergoing lung volume reduction has not been firmly established. However, it is believed that elastic recoil and diaphragmatic function are improved by reducing the volume of the diseased lung. The procedure is designed to relieve dyspnea and improve functional lung.

Two types of valves are available: endobronchial and intrabronchial. Both are one-way valves, which work to prevent air flow to the diseased area of the lung during inhalation. The valve opens during exhalation to allow air to escape from the diseased area of the lung.

Endobronchial valves are measured to fit the target lumen, and are placed via catheter by flexible or rigid bronchoscopy. Intrabronchial valves, also known as umbrella valves, are placed via flexible bronchoscope, first in a compressed state. A specialized catheter deploys the valve once the target lumen is identified. Struts on the intrabronchial valve covered by a membrane help to keep the valve anchored, and the membrane acts to prevent airflow. Both valves may require repeat procedures to reposition or restore functioning.

**REGULATORY STATUS**

The intrabronchial IBV® Valve System (Spiration, Inc) was approved by the U.S. Food and Drug Administration (FDA) under the Humanitarian Device Exemption (HDE). It is intended for use in controlling prolonged air leaks of the lung or significant air leaks that are likely to become prolonged air leaks following lobectomy, segmentectomy, or lung volume reduction surgery (LVRS), for a duration up to 6 weeks.\[^{[1]}\] FDA product code: OAZ.

Currently, two bronchial valve systems are FDA approved for treatment of patients with severe emphysema. In June 2018, FDA granted the Zephyr® Endobronchial Valve (formerly Emphasys, now Pulmonx) system breakthrough device status with expedited approval for the bronchoscopic treatment of adult patients with hyperinflation associated with severe...
emphysema in regions of the lung that have little to no collateral ventilation.\textsuperscript{[2]} In December 2018, FDA approved the Spiration® Valve System.\textsuperscript{[3]} The Spiration® Valves are one-way endobronchial valves intended for adult patients with shortness of breath and hyperinflation associated with severe emphysema in regions of the lung that have low collateral ventilation. FDA product code: NJK.

**EVIDENCE SUMMARY**

**PROLONGED OR SIGNIFICANT AIR LEAKS**

The principal outcome associated with treatment of prolonged or significant air leaks include resolution of the leak. In order to understand the impact of endobronchial and intrabronchial valves for treatment of prolonged or significant air leaks, well-designed randomized controlled trials (RCTs) that compare this therapy to standard medical treatment, such as chest tube placement, performing a thoracotomy with mechanical or chemical pleurodesis, or additional operations, are needed.\textsuperscript{[1]}

**Systematic Review**

No systematic reviews were identified on the use of endobronchial or intrabronchial valves for prolonged or significant air leaks.

**Randomized Controlled Trials**

No randomized controlled trials (RCTs) were identified on the use of endobronchial or intrabronchial valves for prolonged or significant air leaks.

**Nonrandomized studies**

No comparative observational studies were identified. Nonrandomized studies have reported on the use of either intrabronchial\textsuperscript{[4]}, endobronchial valves\textsuperscript{[5,6]}, or both types\textsuperscript{[7]}. Conclusions cannot be reached from these studies, as the data are limited by a variety of factors, including but not limited to:

- Small study populations, less than 100 patients total, which limit the ability to rule out the role of chance as an explanation of study findings;\textsuperscript{[4,5,7]} and
- Retrospectively abstracted records, leading to potential study bias in sample selection, including selection criteria;\textsuperscript{[5,7]}
- Follow-up of study subjects was over a short period of time, less than 6 months, so medium and long-term effects of endobronchial valves treatment are unknown.\textsuperscript{[4,5,7]}

**ADVANCED EMPHYSEMA**

In patients with advanced emphysema, valves may be compared to other forms of medical treatment, such as bronchodilators, short courses of systemic corticosteroids, noninvasive positive pressure ventilation (NIPPV) and/or oxygen therapy. In patients who have exhausted conservative therapy, valves must be compared to more invasive treatment, such as lung volume reduction surgery. Randomized controlled studies are needed in order to isolate the contribution of these implants from other components of therapy. Further, for treatment of chronic conditions, particularly those with a poor prognosis, an understanding of any adverse treatment effects must be carefully weighed against any benefits to understand the net treatment effect.
Systematic Reviews

Three systematic reviews with meta analyses have recently been published.[8-10] Authors of all of the systematic reviews came to similar conclusions: In patients with severe emphysema and low collateral ventilation, RCTs provide evidence of clinically meaningful benefit for bronchial valves compared to standard medical management on measures of lung function, exercise tolerance, and quality of life, but these benefits should be measured against the greater risk of serious adverse events compared to usual care. Limitations of the evidence included a lack of comparisons to lung volume reduction surgery and significant heterogeneity for some analyses.

The most recent and comprehensive review, conducted by van Geffen (2019), included 7 randomized controlled trials of the Zephyr valve.[10] Five of the studies are included in Table 1 under Endobronchial Valve Studies, and the additional two are LIBERATE[11] and TRANSFORM[12]. Participants in the included studies were those with emphysema, older than 35 years, post-bronchodilator FEV1 < 60% of predicted, and residual volume >150% of predicted (N = 620 total, range per study varied 50-190). Studies lasted from 3-12 months in duration. Meta analyses found adverse events including mortality to be greater in those who received valves: OR 9.58 (5.56 to 16.50), p=<0.00001.

In 2017, a Cochrane Systematic Review evaluating bronchoscopic lung volume procedures for COPD was published by van Agteren.[8] Authors conducted in-depth analyses aimed at assessing the effects of bronchoscopic lung volume reduction procedures on the short- and long-term health outcomes in participants with moderate to severe COPD and determining the effectiveness of each technique. Endobronchial and intrabronchial valves were among the six techniques analyzed; only individually and cluster randomized controlled trials were included. See Table 1 for endobronchial and intrabronchial valve studies included for analyses. Studies including participants with giant or bullous emphysema were excluded. Primary outcomes included: lung capacity as measured by FEV1; survival as measured by perioperative and postoperative mortality; and health-related quality of life, measured by questionnaire (e.g., St Georges Respiratory Questionnaire [SGRQ]). Given the heterogeneity in treatment approaches, outcomes were meta-analyzed only per treatment type. Outcomes for continuous or dichotomous data were analyzed using a fixed-effect model up to the end of follow-up. Continuous outcomes were calculated using mean differences, and dichotomous outcomes with odds ratios, both with 95% confidence intervals. Heterogeneity was calculated using the I^2 statistic, and subgroup analysis was performed as appropriate. Studies were graded for bias as high, low, or unclear, with rationale reported. Quality of evidence was rated using the GRADE scale. Endobronchial and intrabronchial studies included both heterogenous and homogeneous disease status patients, though majority of the endobronchial valve studies included participants with only a heterogenous disease distribution. The average of participants ranged between 58 and 65 years of age; the STELVIO 2015 trial having the youngest average age (58 to 59 years of age); the IBV Valve Trial 2014 and the VENT US 2010 studies having the highest average age ranging between 64.7 and 64.8, and 64.9 and 65.3, respectively. Majority of the trials recruited more males than females.

Table 1. RCTs included in 2017 Cochrane Review

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<thead>
<tr>
<th>Endobronchial Valve Studies (Year)</th>
<th>Intrabronchial Valve Studies (Year)</th>
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### Endobronchial Valve Studies (Year)

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### Intrabronchial Valve Studies (Year)

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<tr>
<td>IBV Valve</td>
<td>(2014)</td>
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<td>Ninane</td>
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## Endobronchial Valves

The Cochrane Review conclusions from the endobronchial valve studies were drawn from five studies totalling 703 participants, which used standard medical care as the comparator. The number of adverse events experienced by patients with endobronchial valves was higher than those who received standard medical treatment (OR [95% confidence interval], 5.85 [2.16, 15.84], high quality of evidence), though no significant difference in mortality was found. From baseline to follow-up, between-group differences in the endobronchial valve group compared to control, change in lung function (FEV1, standardized mean difference [SMD], of 0.48 [95% CI: 0.32 to 0.64], low-quality evidence), quality of life (mean difference [MD], -6.20 units [95% CI: -8.19 to -4.20]; low quality of evidence), and exercise capacity (38.40 meters [95% CI: 24.69 to 52.12]; low quality of evidence) were significantly improved. While positive results may have been found, due to high confidence intervals and standard deviations, the authors urged caution in interpreting the means reported for outcomes of their systematic review. Earlier trials found better outcomes in patients with intact fissures which affected selection criteria in future trials, and thus improvement in functional outcomes.

## Intrabronchial Valves

Two RCTs comparing intrabronchial valves to standard medical treatment were included for review\(^{[17,20]}\) as well as one trial comparing unilateral versus partial bilateral valve placement with intrabronchial valves\(^{[15]}\). Adverse events experienced by patients with intrabronchial valves was higher than those who received standard medical treatment (OR, 3.41 [1.48, 7.84]), and no significant risk in mortality. Between group difference in exercise capacity was found to favor controls (MD -19.54 meters; [95% CI -37.11 to -1.98], moderate-quality evidence), as did lung function. Lack of difference in the IBV Valve (2014) and Ninane (2012) trials may be explained by the Eberhardt (2012) trial, as the latter found those treated with unilateral valve placement as opposed to partial bilateral treatment showed significantly better results in lung function, quality of life, and exercise capacity. The other two trials did not specifically address collateral ventilation, nor did they aim to achieve lobar occlusion; this is supported by the endobronchial valve trials which all aimed to achieve lobar occlusion and found better functional results when achieved.

Overall, findings in the Cochrane meta-analyses are limited by the lack of long-term follow-up data, significant heterogeneity in results, presence of skew and high CIs, and the open-label character of a number of the studies.

Choi (2015) published a systematic review evaluating bronchoscopic lung volume reduction using a one-way endobronchial valve.\(^{[9]}\) The systematic review included 15 studies and meta-analyzed RCTs. Forced expiratory volume in one second (FEV1) improved compared to control groups in favor of the valve group (mean difference of 6.71, 95% CI: 3.31-10.11). The six-minute walking distance and cycle workload were also improved. A subgroup analysis of patients with complete fissure, reported that the FEV1 change was higher in the valve group at six and 12-months compared to the control group. No deaths were reported for the bronchial valve group although the pneumothorax incidence and respiratory failure rates were higher in the endobronchial valve group.
Randomized Controlled Trials

RCTs not included in the above described systematic reviews are summarized here.

In 2017, Zoumot reported additional data from the BeLieVeR-HIFi study not included in the Cochrane review. [30] Control patients in the BeLieVeR-HIFi study who went on to have open label endobronchial valve treatment after completion of the clinical trial (n=12) had three month follow-up data combined with those in the treatment arm. Combined data found FEV1 increased by a mean of 27.3 (SD = 36.4)%, residual volume reduced by mean 0.49 (SD 0.76) L, the 6min walk distance increased by mean 32.6 (SD = 68.7) m, and the St George Respiratory Questionnaire for COPD score improved by mean 8.2 (SD = 20.2) points. Eight of 12 patients treated with valves developed atelectasis or complete lobar collapse on CT, and another two had significant volume loss. In this small trial using a highly selective patient population (patients with heterogeneous emphysema and without interlobar CV) minimal improvements were found, however there was still significant variation in response.

In 2017, Klooster reported one-year follow-up data from the STELVIO study not included in the Cochrane review. [31] An intention-to-treat analysis showed greater improvements in all primary outcomes in the endobronchial valve group compared to the controls. However, of the 64 patients with follow-up data available, 47 serious adverse events were reported from 0-6 mos, and 11 from 6 mos to one year. Two patients in the valve group died.

Nonrandomized Studies

Skowasch (2016) reported six month follow-up results from the VENT trial, a retrospective analysis of registry data for patients who have received endobronchial valves also described below. [32] Although lung function (FEV1 and residual volume), and COPD Assessment Test scores improved, 66 serious adverse events were reported in 55 patients. In the subsequent six months of follow-up, a total of 170 serious adverse events were reported in 125 patients.

Liberator (2016) published a retrospective analysis of the VENT trial. [33] The analysis evaluated outcomes and response based on lobe selection in patients receiving endobronchial valve therapy. The authors concluded that lobe selection does have a major role in endobronchial valve therapy. There was no difference in FEV1 outcomes between upper and lower lobe treatment groups. The authors further conclude that complete fissure status preprocedure has the greatest influence on FEV1 outcome improvement.

Several other small case series (n<100) have been published on the use of the Zephyr or IBV valves for severe emphysema. [19,34-39] Varying numbers of endobronchial valves were placed per patient and follow-up time ranged from three months up to eight years.

Conclusions based upon this data are limited by a variety of factors, including but not limited to:

- Small study populations which limit the ability to rule out the role of chance as an explanation of study findings;
- Follow-up of study subjects was over a short period of time, less than six months;
- Varying numbers of valves were placed per patient. For example, a mean of four (SD: 1.6) and range of 1-8 in one study [40] and a mean of 6.7 and range of 3-11 in the other [34], and unreported mean and range in the third [36,37], limiting comparisons of treatment effectiveness; and
Patient selection criteria differed, along with use of medication, hampering comparisons of target population and exposure of interest.

Although adverse events are not systematically reported in the literature on endobronchial valves, in one report, 38 of 98 patients (39%) treated with endobronchial valves developed a complication following this procedure, ranging from exacerbation of chronic obstructive pulmonary disease to death.[34]

Other indications for endobronchial valves have been reported, including as a treatment for destructive multidrug-resistant tuberculosis[41], bronchopleural fistula[42].

**PRACTICE GUIDELINE SUMMARY**

No evidence-based clinical guidelines or position statements were identified which addressed the use of endobronchial or intrabronchial valves from US-based organizations.

**SUMMARY**

There is not enough research to know if endobronchial valves or intrabronchial valves improve net health outcomes (balance of benefit and harm) compared to current standard of care. The current evidence base reports numerous serious adverse events with the use of endobronchial and intrabronchial valves. Currently, no US-based clinical practice guidelines recommend the use of either valve type. Therefore, endobronchial and intrabronchial valve placement is considered investigational for any indication, including but not limited to patients with air leaks or advanced emphysema.

**REFERENCES**


### CODES

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<th>Number</th>
<th>Description</th>
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<td>Bronchoscopy, rigid or flexible, including fluoroscopic guidance, when performed; with balloon occlusion, when performed, assessment of air leak, airway sizing, and insertion of bronchial valve(s), initial lobe</td>
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| HCPCS | None |

*Date of Origin: February 2012*