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Published in:
Expert review of respiratory medicine

DOI:
10.1080/17476348.2024.2431522

Publication date:
2024

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Expert Review of Respiratory Medicine

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ierx20

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To cite this article: Tadashi Sakaguchi, Jorine E Hartman & Dirk-Jan Slebos (2024) An update on endobronchial valve therapy for severe emphysema: real world data and special indications, Expert Review of Respiratory Medicine, 18:12, 1003-1011, DOI: 10.1080/17476348.2024.2431522

To link to this article: https://doi.org/10.1080/17476348.2024.2431522

Published online: 19 Nov 2024.

EXPERT REVIEW OF RESPIRATORY MEDICINE
2024, VOL. 18, NO. 12, 1003–1011
https://doi.org/10.1080/17476348.2024.2431522

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REVIEW

An update on endobronchial valve therapy for severe emphysema: real world data and special indications

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ABSTRACT

Introduction: Bronchoscopic lung volume reduction (BLVR) using one-way endobronchial valves (EBV) is a guideline therapy for patients with severe emphysema without interlobar collateral ventilation, based on solid results from multiple randomized clinical trials (RCTs). However, whether its efficacy and safety in real-world clinical settings are comparable to those observed in RCTs has not been fully investigated. Additionally, recent reports on EBV therapy have focused on specialized populations (e.g. very low FEV_1, very low D_{LCO}) that were not represented in the RCTs.

Areas covered: We have summarized the efficacy and safety of the publications on BLVR with EBVs in real-world settings and in specialized populations, and have discussed these findings in relation to the RCTs data.

Expert opinion: The benefits of BLVR with EBVs have effectively translated into real-world clinical practice with a tolerable safety profile. These benefits and acceptable safety profile were also observed in specialized populations not fully represented in RCTs. We believe it is crucial to establish a nationwide registry in each country to keep track of outcome for quality and consistency, and to have a multidisciplinary COPD team discussion in each treating institution to keep on ensuring the successful clinical practice of BLVR with EBVs.

ARTICLE HISTORY
Received 28 September 2024
Accepted 15 November 2024

KEYWORDS
Bronchoscopic lung volume reduction; emphysema; endobronchial valves; endoscopic lung volume reduction; real-world data; COPD; bronchoscopy

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous condition characterized by a progressive expiratory airflow limitation and hyperinflation caused by both small airway disease and emphysema, leading to significant respiratory symptoms [1]. Patients with severe COPD suffer from debilitating dyspnea and a reduced quality of life, despite receiving optimal pharmacological and non-pharmacological therapies [2].

To reduce hyperinflation caused by severe emphysema, both surgical and bronchoscopic lung volume reduction approaches are available [3]. These methods reduce the volume of the severely destructed lobe(s) affected by emphysematous changes, allowing the remaining healthier, less compliant lung to function more effectively. This, in turn, reduces the mechanical disadvantage on the respiratory muscles. Lung volume reduction surgery (LVRS) has been shown to improve survival, exercise capacity, and quality of life in appropriately selected patients with heterogeneous emphysema and poor exercise capacity [4–6]. However, concerns regarding the risk of perioperative death and complications have contributed to its underutilization. Bronchoscopic lung volume reduction (BLVR) using one-way endobronchial valves (EBV) has emerged as a less invasive alternative to surgery, offering comparable clinical outcomes [7]. The one-way valve allows air to leave the treated lobe during exhalation but prevents air from entering during inhalation, and can be removed or replaced if necessary after placement. This approach deflates the severely affected lobe(s) and induces lobar atelectasis, providing similar benefits to LVRS but with less morbidity and the potential for reversibility [8].

In the first international multicenter randomized controlled trial (RCT) (the VENT trial), the benefit of BLVR with EBVs was significant but not clinically meaningful compared to the standard of care group [9]. However, post hoc analysis of the initial VENT trial and the VENT European cohort revealed a clinically significant benefit in the subgroup of patients with a complete fissure on CT and complete lobar occlusion following treatment with EBV [9,10]. Subsequent RCTs of BLVR with EBVs have demonstrated significant and clinically important improvements in lung function, exercise tolerance, quality of life, and predictors of survival in carefully selected COPD patients with severe hyperinflation and no interlobar collateral ventilation (CV) between the treated and ipsilateral lobe [11–16]. Although the RCTs have shown a low risk of post-procedural death, pneumothorax was reported as the most common complication in about 20–30% of treated patients, while COPD exacerbation and pneumonia were also common complications of BLVR with EBVs.

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Article highlights

- We summarized the efficacy and safety of BLVR with EBVs treated in the 'real-world clinical setting' and for special indications not fully represented in RCTs.
- Comparable to the extensive RCT data on EBV therapy, BLVR with EBVs also improves lung function, exercise tolerance, and quality of life, with a similar adverse event profile in real-world settings.
- Specialized populations not fully represented in RCTs, including patients with very low forced expiratory volume in 1 second, very low diffusing capacity for carbon monoxide, hypercapnia, pulmonary hypertension, right middle lobe targets, moderate hyperinflation, and alpha-1 antitrypsin deficiency, can also benefit from BLVR with EBVs, maintaining a similar adverse event profile.
- It is crucial to establish a nationwide registry in each country to capture and monitor EBV treatment outcomes with long-term follow-up in clinical practice, ensuring that the efficacy and safety observed in RCTs are effectively translated into real-world settings.
- Careful consideration by a multidisciplinary team is essential for selecting BLVR with EBVs, taking into account the patient's overall condition, the suitability of the treatment target, other treatment options, and patient's preferences.

Following the demonstration of the benefits and acceptable safety profile of BLVR with EBVs, it has become a recommended treatment in national and international guidelines for the management of severe COPD [17,18].

BLVR with EBVs is now widely performed in clinical settings worldwide. However, whether the efficacy and safety of BLVR with EBVs in real-world settings are comparable to those observed in RCTs has not been fully investigated. Additionally, recent reports on BLVR with EBVs have focused on populations not fully represented in RCTs. Therefore, we have summarized the efficacy and safety of BLVR with EBVs in real-world settings and in populations not fully represented by RCTs.

2. Methods

We conducted a search on PubMed on 4 July 2024, to identify clinical data evaluating BLVR with EBVs in patients with emphysema. The search terms used were: 'bronchoscopic lung volume reduction' OR 'endobronchial valves' OR 'EBV' OR 'endoscopic lung volume reduction' OR 'Zephyr' OR 'bronchoscopic interventions and emphysema' AND 'emphysema.'

Among 2,480 records identified, we included only RCTs and studies from real-world settings that were published in English. For RCTs, we selected trials that compared BLVR using EBV valves with standard care or sham control. We excluded RCTs that included patients regardless of CV, because the absence of CV is a critical predictive factor [13].

For real-world data (RWD), we included only studies that evaluated the efficacy and/or safety of BLVR using EBV valves with a minimum follow-up of three months (90 days). Exclusion reasons were: patients treated with EBV valves for indications other than BLVR, studies consisting only of abstracts or case reports, studies only comparing subgroups without data on the overall population, involved matching cohorts for other interventions, focused on populations before the publication of RCTs on BLVR with EBVs, included data on intrabronchial valves (IBVs; Spiration, Olympus, U.S.A.), or included the RCT population. If the target populations of the studies were deemed overlapping, we included the study that was most representative of real-world data, such as those with larger sample sizes, longer follow-up, or more comprehensive outcome information. If studies with potentially overlapping populations provided complementary data, such as one study focusing on efficacy and another on safety, we included data from both. Additionally, we specifically extracted studies focusing on specialized populations treated withEBV valves that were not fully represented by RCTs, separate from the RWD. For specialized populations, we also included studies in which patients were treated with either IBV or EBV, as well as those that partially covered data from RCT populations.

The predefined outcomes included forced expiratory volume in 1 second (FEV_1), residual volume (RV), 6-minute walk distance (6MWD), St George's Respiratory Questionnaire (SGRQ), target lobe volume reduction (TLVR) on CT, and the adverse events pneumothorax, acute exacerbation of COPD, pneumonia, and death. Outcome data were extracted from the published articles and its available supplementary materials.

3. Results

3.1. Summary of RCTs on BLVR with EBVs

Five RCTs were included in this summary: BeLieVeR-HIFi [12], STELVIO [13], IMPACT [14], TRANSFORM [15], and LIBERATE [16]. The VENT trial was excluded because it included patients regardless of CV [9,10]. BeLieVeR-HIFi and STELVIO were single-center RCTs, while the others were multicenter RCTs. BeLieVeR-HIFi was a double-blind, sham-controlled trial, whereas the other RCTs compared BLVR with EBVs to standard care. The BeLieVeR-HIFi, TRANSFORM, and LIBERATE trials focused on patients with heterogeneous emphysema, while the IMPACT trial focused on homogeneous emphysema. The STELVIO trial included patients regardless of emphysema distribution. In the BeLieVeR-HIFi trial, patients were included if their target lobe had intact interlobar fissures on CT, irrespective of Chartis system (Pulmonx Corp. Redwood City, CA) results. In contrast, the other RCTs included patients with absent CV as assessed by the Chartis system.

Summary of efficacy and safety results from RCTs of BLVR with EBVs are shown in Table 1. The overall median (range) change in FEV_1 from baseline to each endpoint period was 0.14 L (0.10 L to 0.18 L), that of RV was −0.50 L (−0.87 L to −0.42 L), that of 6MWD was 29 m (13 m to 60 m), that of SGRQ was −8.6 points (−17.4 points to −7.2 points), and that of TLVR was −1.17 L (−1.37 L to −1.09 L). The overall median (range) for the frequency of pneumothorax during each endpoint was 23.1% (8% to 32.8%), that of COPD exacerbation was 16.3% (9.2% to 64%), that of pneumonia was 6.3% (0% to 9.2%) and that of death was 3% (0% to 8%).

3.2. The summary of RWD on BLVR with EBVs

A total of 2,137 patients were included in 20 trials [19–38]. The summary of efficacy and safety results from real-world studies of BLVR with EBVs is shown in Table 2. The overall median (range) change in FEV_1 from baseline to each endpoint period was 0.14 L (0.06 L to 0.25 L), that of RV was

Table 1. Summary of efficacy outcomes of the change after BLVR with EBVs from baseline and safety outcomes in RCTs.

		Efficacy outcomes: All mean change from baseline to each endpoint period					Safety outcomes			
Study (published year)	N (Endpoint, months)	FEV_1 (L)	RV (L)	6MWD (m)	SGRQ (points)	TLVR (L)	pneumothorax (%)	COPD-E (%)	Pneumonia (%)	Deaths (%)
BeLieVeR-HIFi (2015)	50 (3 m)	0.18	−0.50	29	−8.7	ND	8	64	8	8
STELVIO (2015)	68 (6 m)	0.16	−0.87	60	−17.4	−1.37	18	12	6	3
IMPACT (2016)	93 (3 m)	0.10	−0.42	23	−8.6	−1.20	25.6	16.3	0	0
TRANSFORM (2017)	97 (6 m)	0.14	−0.66	36	−7.2	−1.09	23.1	9.2	9.2	1.5
LIBERATE (2018)	190 (12 m)	0.10	−0.49	13	−7.6	−1.14	32.8	29.7	6.3	3.9
Overall median value (Range)		0.14 (0.1 to 0.18)	−0.50 (−0.87 to −0.42)	29 (13 to 60)	−8.6 (−17.4 to −7.2)	−1.17 (−1.37 to −1.09)	23.1 (8 to 32.8)	16.3 (9.2 to 64)	6.3 (0 to 9.2)	3 (0 to 8)

Abbreviations: BLVR, bronchoscopic lung volume reduction; EBV, endobronchial valve; RCT, randomized controlled trial; FEV_1, forced expiratory volume in 1 s; RV, residual volume; 6MWD, 6-minute walk distance; SGRQ, St George's Respiratory Questionnaire; TLVR, target lobe volume reduction: COPD-E, COPD exacerbation; ND; not determined.

−0.68 L (−1.02 L to −0.26 L), that of 6MWD was 38 m (6 m to 82 m), that of SGRQ was −16.0 points (−20.0 points to −5.8 points), and that of TLVR was −0.73 L (−1.12 L to −0.57 L). The overall median (range) of the frequency of pneumothorax during each endpoint was 12.4% (0% to 36.5%), that of COPD exacerbation was 13.1% (0% to 68.2%), that of pneumonia was 4.1% (1.7% to 30.9%) and that of death was 0% (0% to 12.8%).

3.3. The summary of specialized populations on BLVR with EBVs

A total of 13 trials were included [39–51]. We categorized the specialized populations into patients with very low FEV_1 [39,40], very low diffusing capacity for carbon monoxide (D_{LCO}) [41,42], hypercapnia [43,44], pulmonary hypertension (PH) [45,46], right middle lobe targets [47], moderate hyperinflation [48], and alpha-1 antitrypsin deficiency (AATD) [49–51]. A summary of the efficacy and safety results from studies involving these specific subgroups of BLVR with EBVs is shown in Table 3. In all specialized populations, meaningful improvements were demonstrated in lung function, exercise tolerance, and quality of life, with no procedure-related deaths and no new safety concerns.

4. Discussion

We summarized the efficacy and safety of BLVR with EBVs in real-world settings and in specialized populations not fully represented in RCTs. Comparable to the extensive RCT data on EBV therapy, BLVR with EBVs also improves lung function, exercise tolerance, and quality of life, with a similar safety profile both in a real-world clinical setting and for specialized populations such as very low FEV_1, very low D_{LCO}, hypercapnia, presence of pulmonary hypertension, right middle lobe target, moderate hyperinflation and AATD.

4.1. The performance of BLVR with EBVs in real-world settings

The overall median values in RWD showed equal or numerically greater improvements in pulmonary function, exercise capacity, and quality of life, along with better safety outcomes compared to those observed in RCTs. Most studies in real-world settings selected patients based on appropriate indication criteria, such as severe hyperinflation and the absence of CV, in accordance with treatment predictors examined in RCTs and guideline recommendations [8]. However, potential biases should be considered when interpreting these results. For example, some reports included only the maximal change in lung function [38] or only clinically serious complications [29,31], while some reports excluded patients who had valve removals due to lack of treatment benefit or complications [21,23,27–29,31,38], or excluded patients who died before reaching the endpoint [29,33]. This can result in selection biases and under-reporting of complications.

Although the overall median safety values in RWD were numerically lower than those observed in RCTs, some reports indicated a high frequency of complications. For instance, one study reported a high rate of pneumothoraces (36.5%) [38]. In

Table 2. Summary of efficacy outcomes of the change after BLVR with EBVs from baseline and safety outcomes in RWDs.

		Efficacy outcomes: Mean* or median# change from baseline to endpoint period					Safety outcomes			
First author (published year)	N (Endpoint, months)	FEV_1 (L)	RV (L)	6MWD (m)	SGRQ (points)	TLVR (L)	Pneumothorax (%)	COPD-E (%)	Pneumonia (%)	Deaths (%)
Park TS (2015)	43 (6 m)	**0.24***	ND	**66***	**−11.8***	ND	23.3	0	2.3	9.3
Skowasch D (2016)	343 (6 m)	**0.10***	**-0.43***	ND	ND	ND	12.2	28.6	7.9	0
Fiorelli A (2017)	33 (60 m)	ND	ND	**12***	**−16.0***	ND	6.1	ND	3.0	0
Fiorelli A (2018)	423 (ND)[$]	-	-	-	-	-	17.3	0.9	1.7	1.2
Kristiansen JF (2019)	24 (6 m)	**0.14***	−0.40*	27*	ND	ND	-	-	-	-
Dumanli A (2020)	31 (6 m)	*0.25#*	*-0.26#*	*32#*	ND	ND	9.7	0	3.2	0
Hartman JE (2021)	94 (12 m)	**0.14***	**−0.63***	**43***	**−11.4***	ND	-	-	-	-
Dooms C (2021)	20 (6 m)	*0.17**	*-0.75**	*38**	*-20.0**	ND	10	ND	ND	0
Garner JL (2021)	12 (3 m)	**0.19#**	**−0.90#**	**66#**	−5.8#	**−0.73#**	0	16.7	16.7	0
Posthuma R (2022)	55 (3 m)	**0.19***	**−0.80***	**37***	ND	ND	9.1	27.3	30.9	0
Yu H (2022)	38 (3 m)	**0.12***	**−0.56***	**65***	ND	**−0.57***	0	7.9	2.6	0
Ing AJ (2022)	14 (6 m)	**0.20***	**−0.68***	**82***	**−16.6***	**−0.70***	14.3	ND	ND	ND
Brock JM (2023)	129 (12 m)	**0.06***	**−0.33***	6*	ND	ND	13.2	68.2	ND	ND
Egenod T (2023)	96 (3 m)	ND	*-0.69**	*35**	ND	*-0.84**	12.5	10.4	4.1	0
Sidhu C (2023)	39 (ND)	*0.14**	*-1.02**	ND	ND	ND	36.5	ND	ND	12.8
Wienker J (2024)	300 (6 m)	**0.06#**	**−0.80#**	**30#**	ND	ND	16.4	6.3	ND	ND
Buttery SC (2024)	219 (ND)[$]	-	-	-	-	-	9.1	22.4	9.6	1.8
Huh JY (2024)	137(efficacy:3 m/safety: ND)	*0.13#*	ND	ND	ND	ND	18.9	51.1	ND	0.7
Brown MV (2024)	57 (efficacy:6 m/safety:12 m)	**0.08***	**−0.64***	**45***	ND	−1.12*	17.5	14.0	5.3	0
van der Molen MC (2024)	30 (6 m)	*0.17**	*-0.70**	*54**	*-18.8**	ND	6.1	12.1	ND	3.0
Overall median value (Total $N = 2,137$)		0.14	−0.68	38	−16.0	−0.73	12.4	13.1	4.1	0
(Range)		(0.06 to 0.25)	(−1.02 to −0.26)	(6 to 82)	(−20.0 to −5.8)	(−1.12 to −0.57)	(0 to 36.5)	(0 to 68.2)	(1.7 to 30.9)	(0 to 12.8)

[$]report on adverse events only.

Bold values in efficacy outcomes mean p-value <0.05 in each report. For the values in italic, the p-value was unknown.

Abbreviations: BLVR, bronchoscopic lung volume reduction; EBV, endobronchial valve; RWD, real-world data; FEV_1, forced expiratory volume in 1 s; RV, residual volume; 6MWD, 6-minute walk distance; SGRQ, St George's Respiratory Questionnaire; TLVR, target lobe volume reduction: COPD-E, COPD exacerbation; ND; not determined.

Table 3. Summary of efficacy outcomes of the change after BLVR with EBVs from baseline and safety outcomes in specialized populations.

			Efficacy outcomes: Mean* or median# change from baseline to endpoint period					Safety outcomes			
First author (published year)	N (Endpoint, months)	Group	FEV_1 (L)	RV (L)	6MWD (m)	SGRQ (points)	TLVR (L)	pneumothorax (%)	COPD-E (%)	Pneumonia (%)	Deaths (%)
Very low FEV_1											
Darwiche K (2016)	20 (3 m)	FEV_1 ≤20% pred	**0.10***	**−1.14***	33*	ND	ND	20	10	15	0
Sgarbossa T (2023)	33 (6 m)	FEV_1 ≤20% pred	**0.09***	**−0.71***	**64***	−7.3*	ND	7.7	7.7	7.7	0
Very low D_{LCO}											
van Dijk M (2020)	20 (6 m)	D_{LCO} ≤20% pred	**0.08***	**−0.45***	**37***	**−12.0***	ND	15	15	0	0
Lenga P (2021)	34 (3 m)	D_{LCO} ≤20% pred	0.17*	**−0.50***	38*	**−12.4***	ND	23.1	3.8	0	0
Hypercapnia											
Roetting M (2022)	129 (6 m)	pCO2 ≥ 45 mmHg	**0.08***	**−0.70***	**28***	ND	ND	16	ND	ND	ND
Lenga P (2022)	33 (3 m)	pCO2 > 45 mmHg	0.05*	−0.40*	40*	−2.6*	ND	12.1	6.1	6.1	0
Pulmonary hypertension (PH)											
Eberhardt R (2015)	6 (3 m)	PH	*0.20**	*-0.24**	*59**	*-17.3**	ND	16.6	16.6	ND	0
Fiorelli A (2020)	10 (3 m)	PH (TLVR ≥563 ml)	**0.21***	**−0.33***	**54***	**−4.5***	ND	ND	ND	ND	ND
	3 (3 m)	PH (TLVR <563 ml)	0.00*	−0.15*	9*	−1.2*	ND	ND	ND	ND	ND
Middle lobe											
Klooster K (2023)	15 (6 m)	middle lobe	**0.06#**	**−0.31#**	**40#**	**−6.5#**	**−0.84#**	6.6	0	0	0
Moderate hyperinflation											
Klooster K (2020)	12 (6 m)	RV ≤ 175% pred	**0.43#**	**−0.66#**	**83#**	**−20.0#**	ND	25	0	0	0
Alpha-1 antitrypsin deficiency (AATD)											
Tuohy MM (2013)	6 (ND)	AATD	**0.27#**	**−2.06#**	71#	**−10.9#**	**−0.72#**	33	33	16.6	0
Hillerdal G (2014)	15 (6 m)	AATD	**0.29***	*-0.87**	ND	ND	ND	6.6	0	13.3	0
Everaerts S (2023)	30 (6 m)	AATD	**0.11#**	**−0.47#**	**62#**	**−12.5#**	ND	10	ND	ND	ND
	23 (6 m)	Reduced AAT	**0.28#**	**−0.98#**	**52#**	**−18.7#**	ND	13	ND	ND	ND

Bold values in efficacy outcomes mean p-value <0.05 in each report. For the values in italic, the p-value was unknown.

Abbreviations: BLVR, bronchoscopic lung volume reduction; EBV, endobronchial valve; FEV_1, forced expiratory volume in 1 s; RV, residual volume; 6MWD, 6-minute walk distance; SGRQ, St George's Respiratory Questionnaire; TLVR, target lobe volume reduction; COPD-E, COPD exacerbation; ND; not determined; D_{LCO}, diffusing capacity for carbon monoxide.

this study, all patients underwent quantitative CT analysis and bronchoscopic collateral ventilation assessment with the Chartis System to confirm the absence of CV in the target lobe prior to the EBV procedure. The rate of target-lobe radiographic atelectasis 1-day post-procedure was very high (92.6%), and since post-procedure pneumothorax is correlated with the lung volume reduction effect, this may explain the increased rate of pneumothorax. Furthermore, three patients whose EBVs were removed due to lack of clinical response were excluded from the analysis, which involved a small population; thus, the rate of pneumothorax may appear slightly elevated. Two studies reported a high rate of COPD exacerbations, exceeding 50% [24,29]. One study found that 90% of patients experienced at least one exacerbation in the year before undergoing BLVR with EBVs; additionally, 63.6% had two or more exacerbations in the past year, classifying them as 'frequent exacerbators' who were potentially excluded from RCTs [29]. Furthermore, patients who were lost to follow-up, those who died, or those who had their EBVs removed before 1 year of follow-up were excluded from the analysis, which may have influenced the exacerbation rates. Additionally, this study indicated that BLVR with EBVs shows promise in reducing the exacerbation rate in COPD patients, with similar benefits observed in the LIBERATE trial [16]. Another study with a high exacerbation rate reported a long follow-up period of 10 years in an Asian country, which may contribute to the high COPD exacerbation rate observed [24]. Another study showed a high rate of pneumonia [27], however, it combined data under the category 'pneumonia or airway infection requiring antibiotics,' making it difficult to determine the true rate of pneumonia. Moreover, EBV removal due to recurrent pneumonia was required in only 2 patients, and most cases were manageable and not severe, with no reported mortality within 3 months [27]. As described, no new safety signals were reported in real-world settings.

Although we observed comparable efficacy and safety data in real-world settings compared to RCTs, the quality of real-world data may not be optimal. Clinically important efficacy and safety data are often missed or inaccurately captured due to the lack of fixed follow-up protocols that are present in RCTs. Since the treatment is suitable only for a carefully selected group of severe emphysema patients and requires significant logistics, costs, and expert skills to perform and manage complications [52], we suggested that the introduction and implementation at a national level should be carefully guided to optimize outcomes and protect patients and physicians from potential failures [53]. Therefore, we believe it is crucial to set up a nationwide registry to capture and monitor EBV treatment outcomes in clinical practice in each country, such as the LIVE study in Germany (NCT01580215) [33], the UKLVR registry [22], and the BREATHE-NL registry in the Netherlands (NCT02815683).

4.2. Patient eligibility for BLVR with EBVs among specialized populations not fully represented in RCTs

Very careful patient selection is key to the success of EBV treatment, not only in terms of efficacy but also safety. However, achieving optimal patient selection, where a larger population can benefit from BLVR with EBVs while ensuring safety, remains challenging. We previously reported that only a small proportion of patients referred for BLVR treatment are eligible when applying the inclusion and exclusion criteria based on recent expert panel recommendations [54]. Careful patient selection in most institutions is based on the criteria and outcomes of RCTs, clinical guidelines, and institutional experience. However, there are no absolute spirometry cutoffs when considering patients for EBV treatment. Evidence from the National Emphysema Treatment Trial (NETT) [5], the largest randomized trial of LVRS to date, initially suggested that patients undergoing LVRS with very low FEV_1 (≤20% predicted) and very low D_{LCO} (≤20% predicted) faced a high rate of morbidity and mortality. As a result, only a few patients with very low FEV_1 or D_{LCO} were included in subsequent studies. To minimize the risk of respiratory failure following valve treatment, hypercapnia with a partial pressure of carbon dioxide (pCO2) greater than 50 to 60 mm Hg was an exclusion criterion in some RCTs [13–16]. Additionally, patients with established pulmonary hypertension (sPAP >45 mmHg) were excluded from some RCTs due to the risk of right heart decompensation [14,16]. We summarized reports focusing on these specialized populations not fully represented in RCTs from a safety perspective, and they reported a tolerable adverse event profile along with clinically meaningful efficacy [39–46]. Meanwhile, data on BLVR with EBVs for the middle lobe exclusively or for patients with moderate hyperinflation in emphysema are very limited, as some RCTs excluded these populations due to concerns about efficacy [14–16]. However, we showed improvements in lung function, exercise tolerance, and quality of life in carefully selected patients treated with BLVR with EBVs, with a tolerable safety profile [47,48]. Furthermore, patients with emphysema due to AATD, a rare genetic cause of COPD with a different profile compared to regular COPD, were excluded from some RCTs of BLVR with EBVs [14,16]. However, these patients also demonstrated significant improvements in pulmonary function, exercise capacity, and quality of life, with an acceptable safety profile [49–51]. The development of these new insights in BLVR treatment may lead to changes in the eligibility criteria, potentially broadening the population that can benefit from BLVR with EBVs while ensuring safety. However, in our opinion, patient selection for lung volume reduction should be carefully discussed within a multidisciplinary team (MDT) to determine the best treatment option. Additionally, it is desirable to hold multicenter meetings, such as online conferences, to minimize missed treatment opportunities, ensure accurate patient selection, and provide appropriate follow-up after treatment.

5. Conclusions

Following the promising results of multiple RCTs, BLVR with EBVs has now become a guideline therapy for lung volume reduction in severe emphysema and is widely practiced in clinical settings worldwide. RWD also shows that this treatment effectively improves lung function, exercise tolerance, and quality of life, with a tolerable safety profile. Additionally, in some specialized populations not fully represented in RCTs, meaningful benefits and tolerability have been shown with careful patient selection.

6. Expert opinion

After the VENT trial indicated that the benefit of BLVR with EBVs was significant but not clinically meaningful compared to the standard of care group [9], a post hoc analysis and the VENT European cohort revealed a clinically significant benefit in the subgroup of patients with a complete fissure on CT and complete lobar occlusion following EBV treatment [9,10]. Thereafter, following the development of quantitative CT analysis and the Chartis system for predicting the benefit of EBV treatment by assessing the absence of CV between the target and adjacent lobes, multiple RCTs demonstrated reproducible benefits with clinically meaningful improvement as a trade-off for the increased risk of pneumothorax, which was considered tolerable [12–16]. These promising RCT results have established BLVR with EBVs as a guideline-recommended treatment [17], and it is now widely performed in clinical settings worldwide. RWD following RCTs also demonstrate promising efficacy and safety with careful and appropriate patient selection; however, the influence of various biases should be considered. We believe it is crucial to establish a nationwide registry in each country to capture and monitor EBV treatment outcomes with long-term follow-up in clinical practice. This will help confirm that the efficacy and safety observed in RCTs are effectively translated into real-world clinical practice, particularly in the implementation of interventional treatments like BLVR with EBVs, which require expertise and careful patient selection. Furthermore, it may be desirable to combine all registries into a single international registry to enable monitoring of the treatment on a more global level in the future. In addition, to achieve optimal patient selection and ensure that a broader population can benefit from BLVR with EBVs while maintaining safety, careful evaluations of BLVR with EBVs in specialized populations not fully represented in RCTs are also necessary. Regarding eligibility for BLVR with EBVs, patients should not be simply excluded based on a single criterion that does not meet the recommendations. Instead, careful consideration by a MDT is essential for treatment selection, taking into account the patient's overall condition, the suitability of the treatment target, other treatment options, and the patient's preferences. Furthermore, in the future, we hope that the efficacy and safety of other devices for emphysematous patients with CV will be established and widely applied in clinical practice, allowing many patients around the world whose daily lives are restricted due to symptoms of emphysema to benefit from BLVR. Taken together, we can strongly advocate the next advances in this field:

- Organize high volume expertcenters with COPD expertise and multiple LVR treatment modalities to optimize the outcomes for the individual patients by having maximal exposure to the variation of COPD as a disease, the challenges which can be encountered during the initial procedures, and revision bronchoscopies, as well as follow-up management.
- Discuss every potential COPD patient for LVR options in a multidisciplinary team consisting of at least knowledge of: Lung disease, COPD, Pulmonary rehabilitation, Interventional pulmonology, Surgical LVR options, hono-invasive home ventilation and lung transplantation.
- Maximize the use of widely available quantitative chest-CT scan analysis and for patient selection. Eyeballing alone might disqualify patients.
- 'Think outside the box:' Patients who do not qualify per standard guidelines might be very good candidates for LVR-options (e.g. Low DL_{CO}, Low FEV_1, moderate pulmonary hypertension, lower Residual Volume, above average exercise testing, nickel allergy, low fissure completeness scores, etc.)
- Registration of BLVR & LVR treated patients in a local, national and international databases can be used for quality control, education & training, health technology assessment, and will support the use of these treatments

Next to this, for facilitating the future of valve treatment there is still a need for:

- Improving advanced quantitative imaging possibilities, this by adding CT-derived perfusion, CT derived emphysema phenotype and airway parameters.
- Improving pulmonary function testing world-wide, by developing new techniques for measuring hyperinflation in our patients, mainly because body plethysmography is scarcely available in the world.
- Improving & developing treatments for non-valve patients such as airway bypass, airway supporting devices, endobronchial coils, sclerosing techniques, advances surgical techniques, etc.
- Advocating & promoting the current COPD treatment guidelines/recommendations: Still a huge number of severe COPD patients is underserved with respect to LVR evaluation.

Funding

This paper was not funded.

Declaration of interest

D-J. Slebos is an investigator for PulmAir, U.S.A., and CSA Medical, U.S.A., and an advisor and investigator for PulmonX, U.S.A.; Apreo, U.S.A.; MorAir, U.S.A.; Nuvaira, U.S.A.; FreeFlow medical U.S.A., and PneumRx/BTG, U.S.A. TS and JH have nothing to declare.

Reviewer disclosure

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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