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Review

Efficacy and Safety of Stent, Valves, Vapour ablation, Coils and Sealant Therapies in Advanced Emphysema: A Meta-Analysis

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Abstract

Bronchoscopic lung volume reduction (BLVR) methods have emerged as a new treatment option for patients with severe emphysema. Endobronchial valves and coils have been extensively studied. This review assesses efficacy, safety, and cost effectiveness of the BLVR procedures (stent, valves, vapor ablation, endobronchial coils, lung sealant) in patients with severe emphysema. Databases were searched until October 2016, and randomized controlled trials (RCTs) comparing available BLVR procedures to standard medical care or sham bronchoscopy were included. Random effect model and generic inverse variance approach were used for meta-analysis. Out of 381 identified records, 16 RCTs were included. As compared to recommended medical care or sham bronchoscopy, the BLVR procedures are more effective in improving quality of life [SGRQ score (WMD=–6.38; –9.12 to –3.65)] and 6MWT (WMD=24.21; 9.68-38.74) and percentage FEV_1 (WMD=10.48; 7.07-13.89). Increased risk of serious adverse events (RR=2.18; 1.63–2.93), specifically for chronic pulmonary obstructive disease exacerbations and lower respiratory tract infection combined (RR=1.37; 1.07-1.75), were observed with bronchoscopic interventions, while there was no difference in number of deaths (RR=1.25; 0.79–1.99) and respiratory failure (RR=1.13; 0.57–2.21). The BLVR procedures, especially endobronchial coils, were found to be effective in the management of patients with severe emphysema irrespective of collateral ventilation. However, characterization of patients who would be most benefited from these procedures is required, and effectiveness of these procedures in long run needs to be established.

KEYWORDS: Bronchoscopic lung volume reduction, collateral ventilation, COPD, emphysema

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INTRODUCTION

Chronic pulmonary obstructive disease (COPD) is a chronic inflammatory disease of the airways and the lungs. It is expected to be the third leading cause of death by 2020 [1]. It is characterized by a spectrum of small airway abnormalities of which emphysema is a major pathological feature. It is associated with alveolar destruction and loss of surrounding elastic tissue and elastic recoil of the lungs that leads to air trapping and increased lung volumes. These altered pathophysiological changes lead to static and dynamic hyperinflation that causes dyspnea, decreased exercise capacity, and impaired quality of life.

Lung volume reduction surgery (LVRS) improves lung function, quality of life, and survival in a specific subset of patients having advanced heterogeneous upper lobe emphysema, but is associated with considerable post-operative complications and mortality (7.9% after 90 days) [2]. Bronchoscopic lung volume reduction (BLVR) procedures appear promising as compared to standard medical care, and safe alternative to LVRS. Endobronchial valves (EBV), one of the most extensively studied bronchoscopic approach, appear to be promising in patients with complete inter-lobar fissure integrity and no collateral ventilation [3]. Other available BLVR modalities of notable interest are endobronchial coils (EBC) [4,5], thermal vapor ablation (TVA) [6,7], emphysematous lung sealant (ELS) [8], and Exhale Airway Stents for Emphysema (EASE) [9]. As evident need exists to assess role of available minimally invasive BLVR procedures, this review was conducted to evaluate their efficacy and safety in management of patients with advanced emphysema.

Eligibility, Literature Search, and Selection Process

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [10].

Studies published in the English language were identified by searching electronic databases and scanning reference list of articles, as well as through correspondence with authors of included studies. We searched PubMed, Google Scholar,

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Science Citation Index Expanded and Cochrane databases (until July 31, 2018). Randomized controlled trials (RCTs) assessing efficacy and safety of the BLVR procedures compared to recommended medical care were included in this review. Search strategy using the following search terms and their associated medical subject headings was developed: 'emphysema', 'bronchoscopic lung volume reduction', 'endobronchial coil', 'Lung volume reduction coil' and 'airway bypass', 'bronchoscopy glue', 'bronchoscopy sealant', 'bronchoscopy vapor', 'Emphysema airway stent', 'intrabronchial valves' (Table 1).

Two investigators independently screened title and abstract of all search results. Any study found as potentially eligible was read by both authors to determine inclusion. Eligibility criteria were RCTs evaluating BLVR methods compared to recommended medical care or sham bronchoscopy. Both investigators also searched ClinicalTrials.gov and WHO International Clinical Trials Registry Platform search portal without time limits to include any ongoing trials.

Inclusion/exclusion criteria for included trials were: 1) study population: patients with COPD with severe emphysema; 2) any BLVR procedures; 3) study design: an RCT. Studies on animal trial or preclinical studies and non-original articles such as reviews, editorials, letters, and comments were excluded. To resolve disagreements and reaching consensus, multiple rounds of discussion with other co-authors were held.

Data Extraction

Data extraction form was adapted from the Cochrane Airway Review group [11]. It was pilot tested on two included randomly selected studies, and refined accordingly. Two review authors extracted the data that was cross-checked by another review author.

Primary efficacy outcomes for which data were extracted was improvement in patient health status, that is, health-related quality of life measured using the St George's Respiratory Questionnaire (SGRQ) score, which ranges from 0 to 100, with a higher score indicating worse quality of life; exercise capacity measured as 6 Minute Walk Distance (6MWD); and Percentage predicted FEV_1.

Primary safety outcomes assessed were patients experiencing serious adverse events (SAE) reported as deaths, need of hospitalization or any intervention because of occurrence of pneumothorax, COPD exacerbations, lower respiratory infections, hemoptysis, or respiratory failure.

For dichotomous outcome, the number of participants experiencing the event and total in each group was recorded, while for continuous outcomes between-group differences for change in mean and SD at maximum follow-up duration in study trial was included.

Quality Assessment

Methodological quality was independently assessed by two reviewers in accordance with published guidelines [12]. The components assessed were random sequence generation, allocation concealment, blinding of intervention (participants/investigator), blinding of outcome assessment, complete reporting of outcome data, and selective reporting and other bias. Risk of bias for each study was assessed, and in case of any disagreement, the authors resolved it through discussions and building consensus.

Table 1. Search strategy used for this review

Endobronchial coil
OR Lung volume reduction coil
OR Airway bypass
OR Bronchoscopy glue
OR Bronchoscopy sealant
OR Bronchoscopy vapour
OR Airway stent
OR Bronchoscopic lung volume reduction
OR Endobronchial valve
OR Endobronchial valve
OR Intrabronchial valve AND emphysema
OR Emphysema
OR Chronic obstructive pulmonary disease

Data Synthesis

We used the REVMAN software (Version 5.3. Copenhagen, Denmark) (13) for outcome analysis at the longest follow-up time point. Dichotomous outcomes were pooled as summary relative risk (RR) with 95% confidence intervals (CI), and mean difference with standard error was calculated for continuous outcomes through generic inverse variance (GIV) in which the treatment effect is significant at the 5% level. Heterogeneity between trials was quantified by I^2 statistic roughly interpreted as follows: <=25%: absent; 26%-39%: unimportant, 40%-60%: moderate; 60%-100%: substantial heterogeneity (12).

Meta-analysis was performed using the random-effects model, as the studies included are not functionally identical. The subjects and intervention performed in studies are different, and thus common effect size cannot be assumed [14].

RESULTS

Out of 381 records identified, 16 RCTs were included [9,15-29], and 1 RCT by Hartman et al. [30] was excluded as it was subgroup analysis of the patients included in a study done by Klooster et al. (Figure 1) [23]. The study conducted by Gompelmann et al. [19] on patients with positive collateral ventilation was a subpart of the TVA study done by Herth et al. [21]. It was included in the final analysis as the study has shown positive results with vapor ablation therapy in patients with positive collateral ventilation, and the weight of the study is only 4.5%. Excluding from the final analysis did not change the overall effect estimate of all the interventions. A total of 1187 patients were studied for the BLVR interventions and compared to either recommended medical care as per international guidelines or Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria or sham bronchoscopy (828 patients) [31]. Out of 16 trials, 7 trials reported on EBV [16,17,20,22,23,26,28]; 3 on EBCs [18,25,27]; 2 on IBV

Table 2. Study Characteristics of included trials (n=16)

S. No.	Study	Intervention / Sample size	Control/ Sample size	Disease distribution	Participant characteristic and baseline score on outcomes	Maximum follow-up duration considered
1.	Come et al. [15] – ASPIRE	Emphysematous lung sealant (ELS) plus optimal medical therapy/ 61	Optimal medical therapy alone/ 34	Heterogeneous; Upper lobe predominant emphysema; two subsegments appropriate for treatment in two different upper lobe segments in each lung	Age: treatment 65 years versus control 64 years % female: 41% Participants: treatment n=61 versus control n=34 Disease distribution: heterogeneous Baseline score on outcomes: Median FEV_1% predicted (IQR): treatment 29% (23–35) versus control 30% (27 to 38) Median QoL in units total score SGRQ (IQR): treatment 54 units (46–65) versus control 58 units (45–74) Median 6MWD in meters (IQR): treatment 313 m (236–363) versus control 293 m (247–420)	6 months
2.	Criner et al. [16] - LIBERATE	Endobronchial Valve with standard medical management/ 128	Standard medical management/ 62	Heterogeneous emphysema	Age: treatment 64 years versus control 62 years % female: 56% Mean FEV_1% predicted (SD): treatment 28.0 %(7.45) versus control 26.2 (6.28) Mean QoL in units total score on SGRQ (SD): treatment 55.15 (14.08) units versus control 53.10 (14.14) units Mean 6MWD in meters (SD): treatment 311 m (81) versus control 302m (79)	12 months Note: patients with little to no collateral ventilation between target and ipsilateral lobes were selected based on assessment with the Chartis Pulmonary Assessment System
3.	Davey et al. [17] - BeLieVeR-HIFi	Unilateral endobronchial valve placement / 25	Sham valve placement / 25	Heterogeneous emphysema	Age: treatment 62 years versus control 63 years % female: 38% Mean FEV_1% predicted (SD): treatment 31.6% (10.2) versus control 31.8% (10.5) Mean QoL in units total score on SGRQ (SD): treatment 67.79 units (13.17) versus control 70.65 units (12.48) Mean 6MWD in meters (SD): treatment 342 m (94) versus control 334 m (81)	3 months Note: patients with little to no collateral ventilation were selected based on assessment with the Chartis Pulmonary Assessment System
4.	Deslée et al. [18] - REVOLENS	Nitinol coils plus standard medical management / 50	Standard medical management/ 50	Both homogeneous and heterogeneous emphysema	Age: treatment 62 years versus control 63 years % female: 39% Mean FEV_1% predicted (SD): treatment 25.7% (7.5) versus control 27.4% (6.2) Mean QoL in units total score on SGRQ (SD): treatment 60.8 units (12.8) versus control 57.1 units (14.1) Mean 6MWD in meters (SD): treatment 300 m (112) versus control 326 m (121)	12 months
5.	Gompelmann et al. [19]	Vapor ablation treatment in addition to standard medical management / 35	Standard medical management consistent with GOLD guidelines/ 19	Heterogeneous emphysema with upper lobe predominance in both lungs with presence of Collateral	----------	12 months Note: post-hoc analysis of STEP-Up trial

Table 2. Study Characteristics of included trials (n=16) (Continue)

S. No.	Study	Intervention / Sample size	Control/ Sample size	Disease distribution	Participant characteristic and baseline score on outcomes	Maximum follow-up duration considered
				ventilation (fissure integrity <90%) assessed by multidetector computed tomography scan (MDCT)		
6.	Herth et al. [20] - VENT EU	Unilateral endobronchial valve placement plus usual care based on GOLD guidelines / 111	Standard medical care based on GOLD guidelines / 60	Both homogeneous and heterogeneous	Age: treatment 60 years versus control 60 years % female: 25% Mean FEV_1% predicted (SD): treatment 29% (8) versus control 30% (8) Mean QoL in total score on SGRQ (SD): treatment 59 units (13) versus control 56 units (18) Mean 6MWD in meters (SD): treatment 341 m (108) versus control 360 m (117)	12 months
7.	Herth et al. [21] - STEP-UP	Vapor ablation treatment in addition to standard medical management / 46	Standard medical management consistent with GOLD guidelines / 24	Heterogeneous emphysema with upper lobe predominance in both lungs	Age: treatment 64 years versus control 63 years % female: 52% Mean FEV_1% predicted (SD): treatment 33.8% (8.2) versus control 33.7% (8.8) Mean QoL in units total score on SGRQ (SD): treatment 57.7 units (15) versus control 57.3 units (20) Mean 6MWD in meters (SD): treatment 356 m (92) versus control 370 m (111.5)	6 months
8.	Kemp et al. [22] - TRANSFORM	EBV treatment group / 65	SoC group/ 32	Heterogeneous emphysema	Age: treatment 65 years versus control 63 years % female: 43% Mean FEV_1% predicted (SD): treatment 29.75% (9.18) versus control 32.16 (8.35) Mean QoL in units total score on SGRQ (SD): treatment 64.34 (14.39) units versus control 58.07 (13.26) units Mean 6MWD in meters (SD): treatment 282.46 m (94.41) versus control 320.25 m (91.79)	6 months Note: patients with little to no collateral ventilation between target and ipsilateral lobes were selected based on assessment with the Chartis Pulmonary Assessment System
9.	Klooster et al. [23] - STELVIO	Endobronchial valves / 34	Standard medical care / 34	Homogeneous and heterogeneous	Age: treatment 58 years versus control 59 years % female: 68% Mean FEV_1% predicted (SD): treatment 29% (7) versus control 29% (8) Mean QoL in units total score on SGRQ (SD): treatment 59.1 units (13.7) versus control 59.3 units (11.6) Mean 6MWD in meters (SD): treatment 372 m (90) versus control 377 m (84)	6 months
10.	Ninane et al. [24]	Partial bilateral placement of Intra-bronchial valves / 37	Sham control / 36	Heterogeneous	Age: treatment 61 years versus control 62 years % female: 41% Mean FEV_1% predicted (SD):	6 months

Table 2. Study Characteristics of included trials (n=16) (Continue)

S. No.	Study	Intervention / Sample size	Control/ Sample size	Disease distribution	Participant characteristic and baseline score on outcomes	Maximum follow-up duration considered
					treatment 35% (10) versus control 32% (7) Mean QoL in units total score on SGRQ (SD): treatment 61 units (11) versus control 60 units (13) Mean 6MWD in meters (SD): treatment 337 m (106) versus control 346 m (123)	
11.	Sciurba et al. [26] -VENT US	Unilateral endobronchial valve placement plus usual care based on GOLD guidelines / 220	Standard medical care based on GOLD guidelines / 101	Both homogeneous and heterogeneous emphysema	Age: treatment 65 years versus control 65 years % female: 57% Mean FEV_1% predicted (SD): treatment 30% (8) versus control 30% (8) Mean QoL: not reported Mean 6MWD in meters (SD): treatment 334 m (87) versus control 351 m (83)	12 months
12.	Sciurba et al. [25] -RENEW	Nitinol coils plus usual care based on GOLD guidelines / 158	Usual care based on GOLD guidelines / 157	Both heterogeneous and homogeneous emphysema	Age: treatment 63 years versus control 64 years % female: 52.4% Mean FEV_1% predicted (SD): treatment 25.7% (6.3) versus control 26.3% (6.7) Mean QoL in units total score on SGRQ (SD): treatment 60.1 units (12.8) versus control 57.4 units (14.8) Mean 6MWD in meters (SD): treatment 312.0 m (79.1) versus control 302.7 m (79.3)	12 months
13.	Shah et al. [9] - EASE	Exhale drug eluting stent / 208	Sham bronchoscopy/ 107	Homogeneous emphysema	Age: treatment 64 years versus control 64 years % female: 49% Mean FEV_1% predicted (SD): treatment 23.2% (6.1) versus control 23.6% (7.2) Mean QoL in units total score on SGRQ (SD): treatment 56.6 units (12.9) versus control 58.04 units (13.25) Mean 6MWD in meters (SD): treatment 302 m (88) versus control 297 m (85)	12 months
14.	Shah et al. [27] – RESET	LVRC (RePneu coil) / 23	Best medical care / 24	Both homogeneous and heterogeneous emphysema	Age: treatment 62 years versus control 65 % female: 38% Mean FEV_1% predicted (SD): treatment 27.2% (8.0) versus control 28.9% (6.9) Mean QoL in units total score on SGRQ (SD): treatment 65.2 units (8.7) versus control 53.1 units (13.8) Mean 6MWD in meters (SD): treatment 293.7 m (75.5) versus control 346.2 m (110.9)	90 days after final treatment
15.	Valipour et al. [28] – IMPACT	Endobronchial valves / 43	Optimal medical care / 50	Homogeneous	Age: treatment 64 years versus control 63 years % female: 61% Mean FEV_1% predicted (SD): treatment 28.4% (6.3) versus	3 months

Table 2. Study Characteristics of included trials (n=16) (Continue)

S. No.	Study	Intervention / Sample size	Control/ Sample size	Disease distribution	Participant characteristic and baseline score on outcomes	Maximum follow-up duration considered
					control 29.9% (6.6) Mean QoL in units total score on SGRQ (SD): treatment 63.2 units (13.7) versus control 59.3 units (15.6) Mean 6MWD in meters (SD): treatment 308 m (91) versus control 328 m (93)	
16.	Wood et al. [29]	Partial bilateral placement of Intra-bronchial valves / 142	Sham control/ 135	Heterogeneous	Age: treatment 65 years versus control 65 years % female: 43% Mean FEV_1% predicted (SD): treatment 29.8% (7.5) versus control 29.7% (7.9) Mean QoL in units total score on SGRQ (SD): treatment 54.8 units (15.5) versus control 57.1 units (15.2) Mean 6MWD in meters (SD): treatment 314.1 m (88.6) versus control 308.6 m (81.6)	6 months

a: spirometry, unless otherwise specified, ASPIRE included only in safety analysis; b: median (range)

Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flow diagram
*-Gompelmann et al. [19] is a post-hoc analysis of step-up triala

[24,29]; 2 on TVA [4,19]; 1 on ELS [15] and 1 on airway stents (Table 2) [9].

Characteristics of Patients Included

Eight trials included patient predominantly with heterogeneous emphysema [15-17,19,21,22,24,29]; two trials were on patients with homogeneous emphysema [9,28]; and rest trials had patients with both heterogeneous and homogeneous emphysema [18,20,23,25-27]. Mean age of participants was about 60 years. Inclusion of white ethnicity participants (90% or above) was reported in seven trials [9,16,20,21,23,25,26].

A sample size of more than 100 in either or both groups was included in five trials [9,16,25,26,29]. The trials included in the meta-analysis followed patients for duration of 3-12 months.

Risk of Bias

A tool from the Cochrane Collaboration was used to assess the risk of bias of each study. Low risk of performance and detection bias by comparing BLVR to sham bronchoscopy was observed for EBV [17,22], airway stent [9], and IBV trial [24,29]. Risk of bias related to randomization, allocation concealment, attrition, and selective reporting was found to be low for the majority of trials (Figure 2).

Efficacy of Interventions

For studying efficacy outcome, lung sealant trial (15) was excluded from efficacy meta-analysis as it was prematurely terminated and possessed a high risk of bias (Figure 2). Quality of evidence for the efficacy of intervention was assessed for patients with no collateral ventilation undergoing the bronchoscopic procedure for EBV (Table 3) and for EBC (Table 4). Quality of evidence was not assessed for rest of the BLVR modalities as only one or two trials were available with small sample size.

Patient-Centric Outcomes

SGRQ

Pooled analysis revealed that the BLVR procedures significantly reduced the mean SGRQ score compared to control group [WMD=–6.38 (95% CI; –9.12 to –3.65); I^2=76%]. In subgroup analysis, significant reduction in the SGRQ score was observed for EBC trials [WMD=–9.21; 95% CI; –11.41 to –7.02); I^2=0, high quality of evidence] and for EBV in patients with no collateral ventilation [WMD=–7.00; 95% CI; –9.85 to –4.14); I^2=52%, high quality of evidence].

Significant reduction in the SGRQ score was also seen with vapor ablation [WMD=–9.70 (95% CI; –15.7 to –3.70)].

Table 3. GRADE and Summary of findings table for lung volume reduction bronchial valves as compared to standard care in severe emphysema

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lung volume reduction interventions	Standard care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Assessing Efficacy of Bronchoscopic Lung volume Reduction on St. George Respiratory Questionnaire (SGRQ) score – Endobronchial valves with no collateral ventilation												
7	randomized trials	serious[a]	not serious[b]	not serious	not serious	strong association	570	344	-	MD 7.00 lower (9.85 lower to 4.14 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
6 Minute Walk Test - Endobronchial valves with no collateral ventilation												
7	randomized trials	serious[a]	serious[c]	not serious	not serious[d]	strong association	573	346	-	MD 39.86 higher (18.42 higher to 61.29 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT
%FEV1 - Endobronchial valves with no collateral ventilation												
7	randomized trials	not serious	not serious	not serious	not serious	none	557	322	-	MD 18.82 higher (14.18 higher to 23.47 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Total Serious Adverse Events (SAE) - Endobronchial valves												
6	randomized trials	not serious	not seriouse	not serious	not serious	strong association	211/515 (41.0%)	56/304 (18.4%)	RR 3.13 (1.48–6.60)	392 more per 1,000 (from 88 more to 1000 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Death - Endobronchial valves												
7	randomized trials	not serious	not serious	not serious	serious[f]	none	21/626 (3.4%)	9/364 (2.5%)	RR 1.14 (0.55–2.39)	3 more per 1,000 (from 11 fewer to 34 more)	⊕⊕⊕◯ MODERATE	CRITICAL
COPD exacerbation - Endobronchial valves												
7	randomized trials	not serious	not serious	not serious	serious[f]	none	156/626 (24.9%)	92/364 (25.3%)	RR 0.99 (0.82–1.19)	3 fewer per 1,000 (from 45 fewer to 48 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Respiratory Failure Requiring Mechanical Ventilation - Endobronchial valves												
6	randomized trials	not serious	not serious	not serious	serious[f]	none	11/561 (2.0%)	5/332 (1.5%)	RR 1.06 (0.38–2.95)	1 more per 1,000 (from 9 fewer to 29 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Patients with upper lobe emphysema with positive collateral ventilation also scored well with TVA [WMD=–8.40 (95% CI; –17.51-0.71)] (Figure 3a).

6MWT

The BLVR procedures as per pooled analysis improved 6MWT significantly as compared to control group [WMD=24.21; (95% CI; 9.68-38.74); I^2=83%]. Subgroup analysis showed significant improvement in 6MWT for EBCs [WMD=33.52; (95% CI; 5.88-61.16); I^2=65%, very low quality of evidence] and among patients with no collateral ventilation undergoing EBV [WMD=39.86; (95% CI; 18.42-61.29); I^2=77%, moderate quality of evidence]. For subgroup undergoing IBV procedure, the patients in control group

Table 4. GRADE and Summary of findings table for lung volume reduction endobronchial coils as compared to standard care in severe emphysema

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lung volume reduction interventions	Standard care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Assessing Efficacy of Bronchoscopic Lung volume Reduction on St. George Respiratory Questionnaire (SGRQ) score - Bronchial coils												
3	randomized trials	serious[a]	not serious	not serious	not serious	strong association	231	230	230	MD 9.21 lower (11.41 lower to 7.02 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
6 Minute Walk Test - Bronchial Coils												
3	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	211	213	-	MD 33.52 higher (5.88 higher to 61.16 higher)	⊕OOO VERY LOW	IMPORTANT
$\%FEV_1$ - Bronchial Coils												
3	randomized trials	not serious	serious[b]	not serious	serious[c]	none	210	213	-	MD 7.1 higher (0.58 lower to 14.78 higher)	⊕⊕OO LOW	CRITICAL
Total Serious Adverse Events (SAE) - Bronchial Coils												
3	randomized trials	not serious	not serious	not serious	not serious	none	89/231 (38.5%)	53/230 (23.0%)	RR 1.63 (1.23–2.16)	145 more per 1,000 (from 53 more to 267 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Death - Bronchial Coils												
3	randomized trials	not serious	not serious	not serious	serious[d]	none	14/231 (6.1%)	11/230 (4.8%)	RR 1.27 (0.59–2.73)	13 more per 1,000 (from 20 fewer to 83 more)	⊕⊕⊕O MODERATE	CRITICAL
COPD Exacerbation - Bronchial Coils												
3	randomized trials	not serious	not serious	not serious	not serious	strong association	76/231 (32.9%)	36/230 (15.7%)	RR 2.06 (1.46–2.92)	166 more per 1,000 (from 72 more to 301 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Respiratory Failure Requiring Mechanical Ventilation - Bronchial Coils												
3	randomized trials	not serious	not serious	not serious	serious[d]	none	7/231 (3.0%)	9/230 (3.9%)	RR 0.80 (0.30–2.16)	8 fewer per 1,000 (from 27 fewer to 45 more)	⊕⊕⊕O MODERATE	CRITICAL

significantly improved over intervention group [WMD=–19.54; (95% CI; –37.11 to –1.98); I^2=0] (Figure 3b).

Outcomes Related to Lung Function

Percent change in % predicted FEV_1

Pooled analysis for mean change in % predicted FEV_1 significantly improved for patients undergoing bronchoscopic procedure [WMD=10.48; (95% CI; 7.07-13.89); I^2=91%]. Subgroup analysis for patients with no collateral ventilation undergoing EBV procedure (WMD=18.82; 95% CI; 14.18-23.47); I^2=35%, high quality of evidence]; EBC trials [(WMD=7.10; 95% CI; –0.58-14.78); I^2=87%, low quality of evidence] and TVA (WMD=14.70; 95% CI; 7.80-21.60) showed promising results over standard medical care or sham bronchoscopy. The patients with positive collateral ventilation also were significantly benefited by TVA intervention as compared to control group (WMD=14.60; 95% CI; 3.00-26.20) (Figure 3c).

Safety of bronchoscopic intervention

All 15 studies were included for meta-analysis as reporting of adverse events is unlikely to get affected due to high risk of bias.

Serious Adverse Events

Serious adverse events were defined as incidence of deaths or events that required or prolonged hospitalization or were life-threatening. Pooled analysis [(RR=2.18; 95% CI; 1.63-2.93); I^2=62%] and subgroup analysis for EBC [(RR=1.63; 95% CI; 1.23-2.16); I^2=0, high quality of evidence], EBV [(RR=3.13; 95% CI; 1.48-6.60); I^2=83%, high quality of evidence], IBV [(RR=2.71; 95% CI; 1.24-5.93); I^2=13%], and ELS [(RR=3.34; 95% CI; 1.57-7.12) reported significantly higher SAE for intervention group as compared to control group (Figure 4a).

Death and Respiratory Failure

No significant difference was observed in the risk of mortality (Figure 4b) and respiratory failure requiring mechanical ventilation (Figure 4c) in both pooled and subgroup analysis (p>0.05). Heterogeneity was found to be absent (I^2=0), and the quality of evidence was moderate for both EBC (Table 4) and EBV (Table 3).

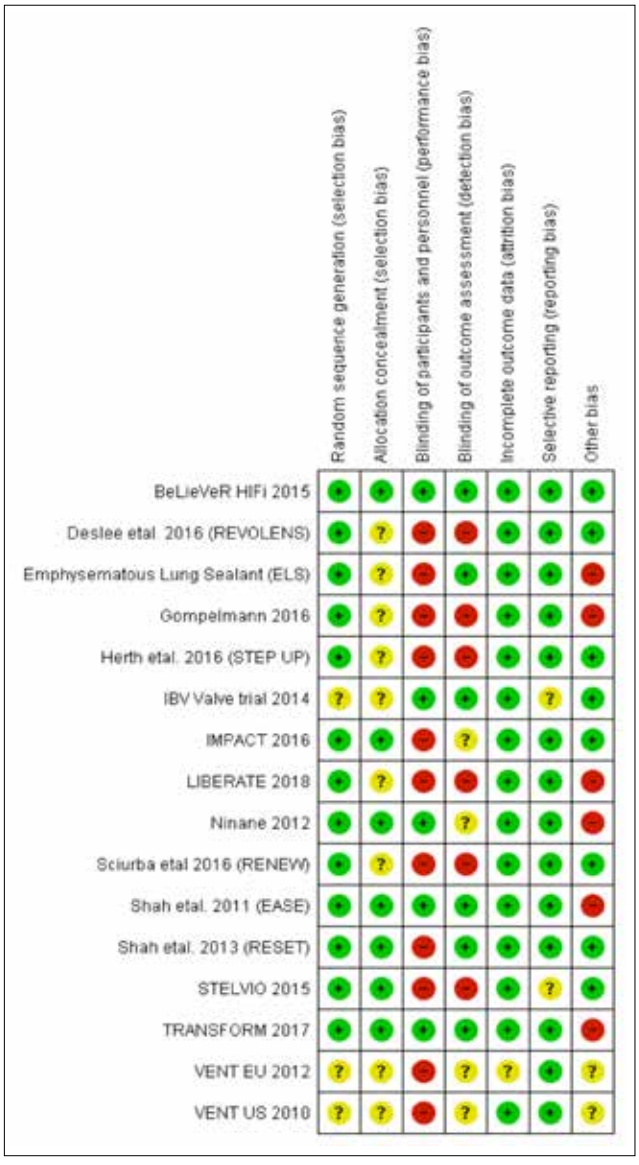

Figure 2. Risk of bias summary for bronchoscopic lung volume reduction interventions studies in patients with severe emphysema

Combined Episodes of COPD Exacerbations and Lower Respiratory Infections (LRTI)

Significantly higher episodes of COPD exacerbations and LRTI combined [RR=1.37; 95% CI; 1.07-1.75); I^2=49%] (Figure 4d) were observed for patients with BLVR in pooled analysis. Subgroup analysis revealed higher risk of COPD exacerbations and LRTI episodes for patients undergoing bronchoscopic procedures in case of EBC [RR=2.06; 95% CI; 1.46-2.92); I^2=0, high quality of evidence] (Table 4) and TVA [RR=3.38; 95% CI; 1.11-10.27) but not for EBV [RR=0.99; 95% CI; 0.82-1.19); I^2=0, moderate quality of evidence] (Table 3) and airway stents [RR=1.89; 95% CI; 0.94-3.80), as compared to control group.

Publication bias

Publication bias was low as the funnel plot for 16 studies appears to be symmetrical around the intervention effect estimate. This review includes only randomized trials, and does not take into account the pilot studies and cohort studies previously published for one or more bronchoscopic interventions. As all types of studies were published for bronchoscopic intervention, publication bias is not detected.

Clinical and Research Consequences

Despite the maximal pharmacological treatment and rehabilitation, the patients with COPD with moderate to severe emphysema remain symptomatic. LVRS has shown long-term benefit only in a specific subset of patients with considerable post-operative morbidity and mortality, and thus the BLVR procedures have evolved in the quest of a safer treatment option for patients with advanced emphysema.

Our systematic review highlights the safety and efficacy of the BLVR procedures over a period of 3-12 months in managing patients with advanced severe emphysema. The inclusion of randomized trials for comparing the BLVR procedures to medical care or sham bronchoscopy provides robust estimates regarding benefits of existing methods as compared to published meta-analyses [32,33]. The strengths of our meta-analysis are that the GIV approach was used. The change from baseline scores was compared for both groups for patient-centric and lung function outcomes using random effect model to account for between studies variance and to ensure generalizability of results.

Earlier trials [20,26] for EBV suggested higher efficacy in patients with no collateral ventilation for both heterogeneous and homogeneous emphysema. In this review, to determine the efficacy of EBV, post-hoc analysis data of patients with no collateral ventilation in Herth et al. [20] and Sciurba FC [26] trials were included along with other trials [16,17,20,22,23,28] that studied only patients with no collateral ventilation.

In the intervention group, significant improvement was observed, and minimal clinically important difference (MCID) was achieved for the quality of life, 6MWD, and percentage change in predicted FEV_1. Higher risk of serious respiratory adverse events especially pneumothorax and

COPD and LRTI exacerbations is also significantly high in the intervention group, and it underscores the need for careful and planned follow-up in patients recruited for EBV.

Pooled mean differences for EBCs showed statistically significant improvement in all studied parameters and more than respective MCIDs for SGRQ score and 6MWT. Suitability of EBCs in patients who are ineligible for either

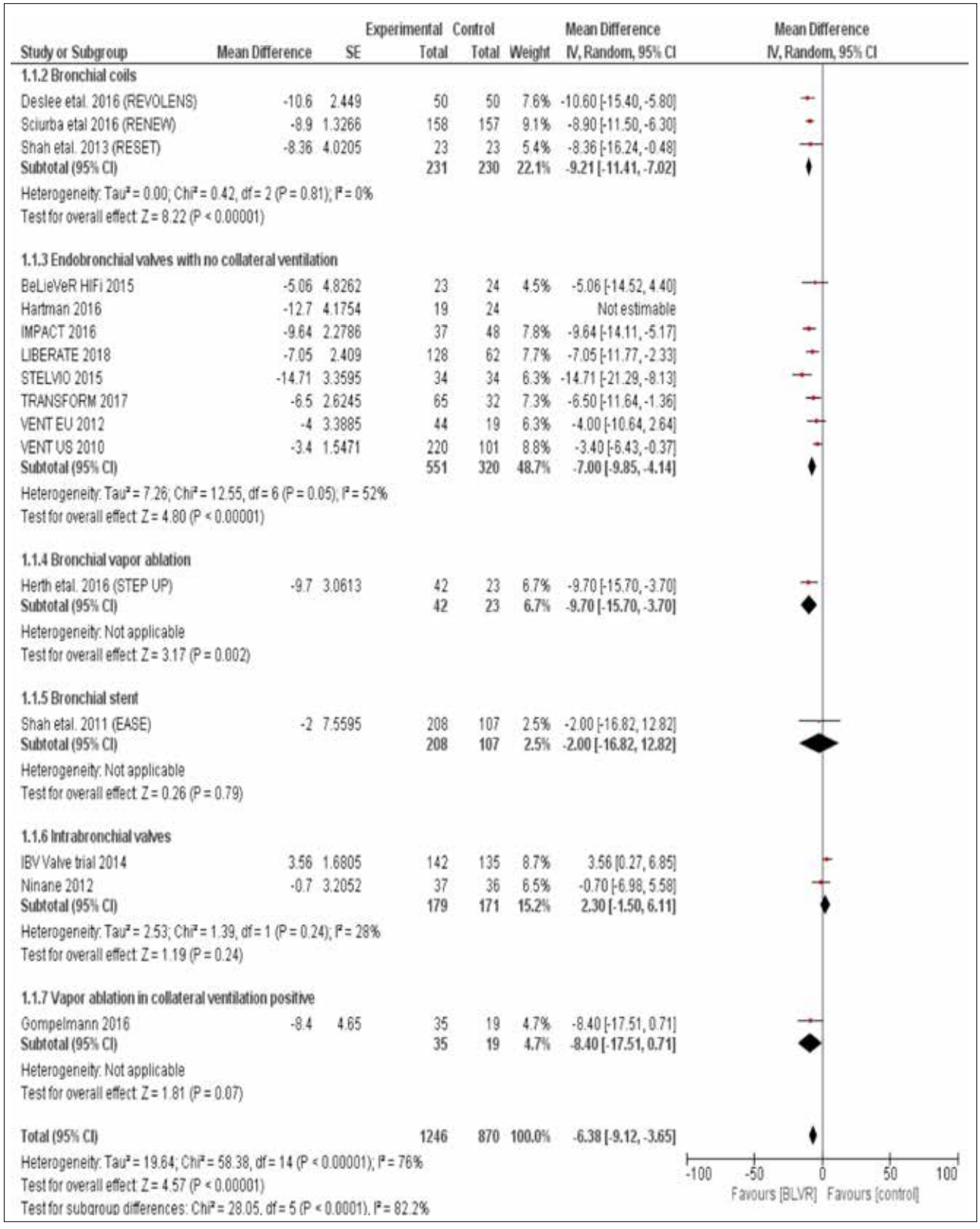

Figure 3a. Efficacy outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: SGRQ Score

LVRS or EBVs and evidence of both efficacy and safety up to 12 months of follow-up is noteworthy. High risk of LRTI (pneumonia) reported in EBC is attributed to local inflammation, ischemia, and scarring of lung parenchyma and not due to infections [25]. Similarly, observed the high risk of pneumothorax is associated with atelectasis, and it rarely requires surgical intervention for management [34]. Currently, the related evidence regarding the efficacy of

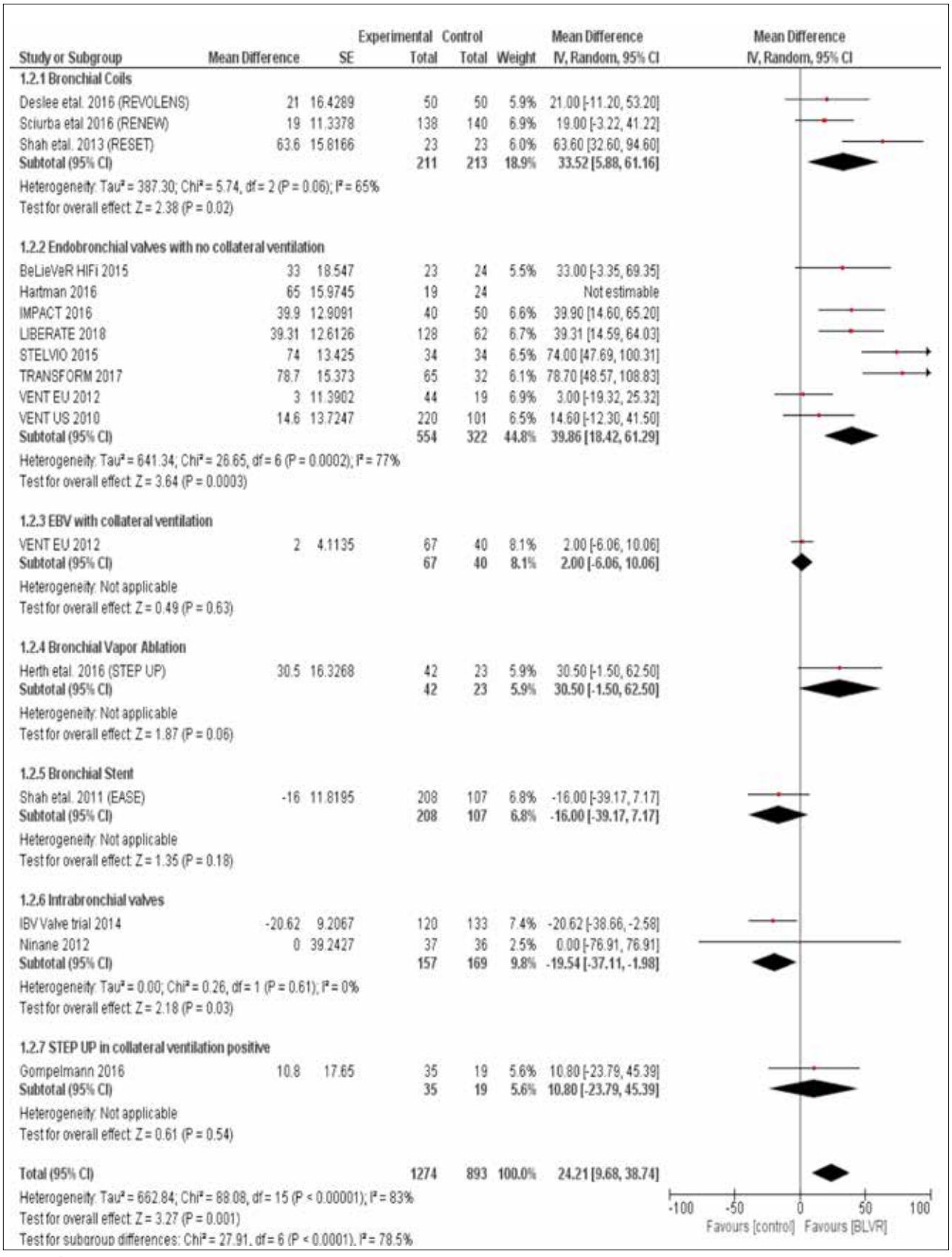

Figure 3b. Efficacy outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: 6MWT

EBCs is not strong as the two out of three included trials with large sample size has a high risk of performance bias (participants not blinded to intervention) and detection bias [18,25]. Higher risk of serious respiratory adverse events in EBC group emphasizes the need for planned follow-up in patients opting for EBC.

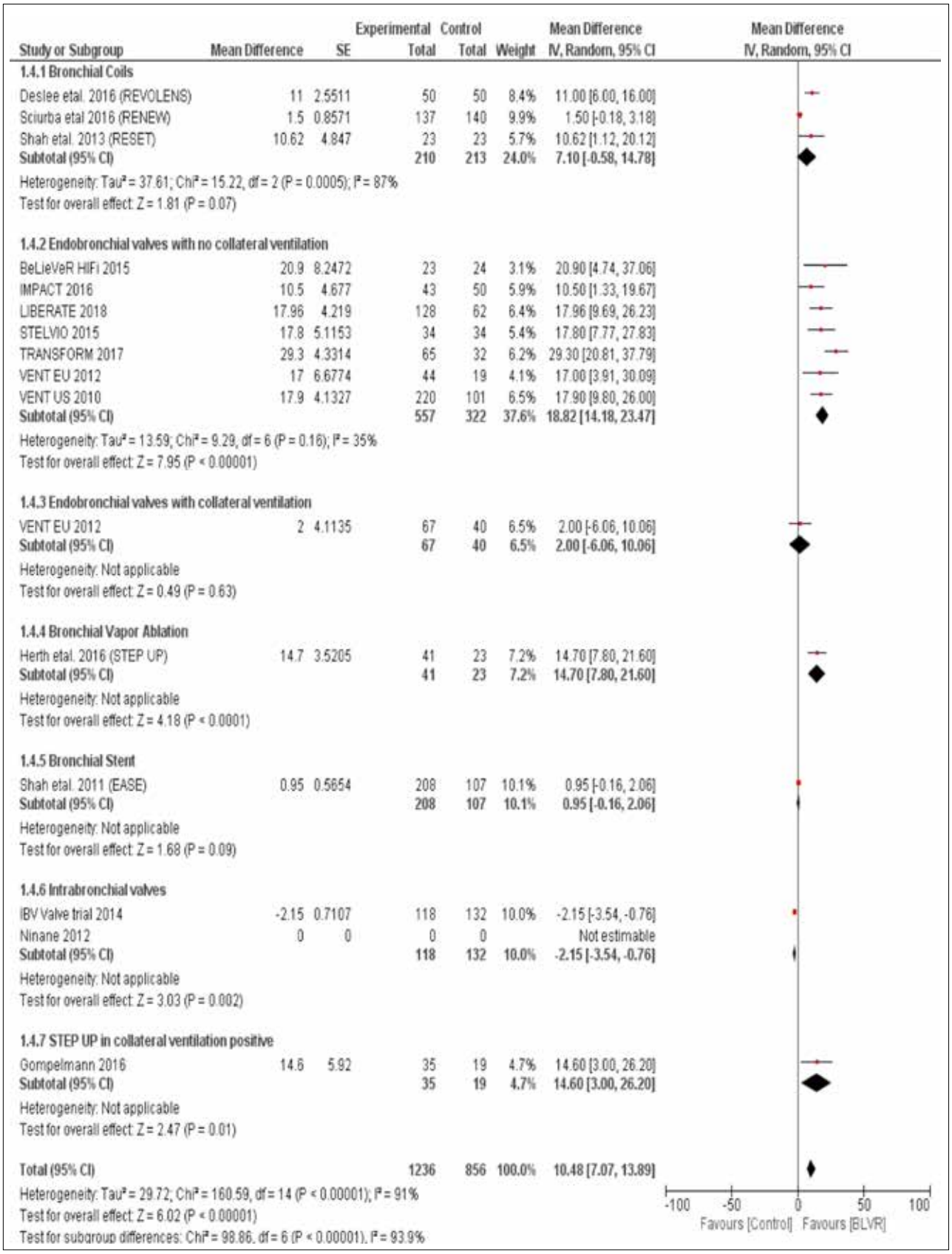

Figure 3c. Efficacy outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: Percentage predicted FEV_1

As reported by Kumar et al. [32] and Iftikhar et al. [33], segmental volume reduction by vapor ablation may appear as a promising approach in patients of upper lobe emphysema with positive collateral ventilation, but it needs to be further substantiated with large sample size randomized trials over a longer duration. Similar to Iftikhar et al. [33], discouraging

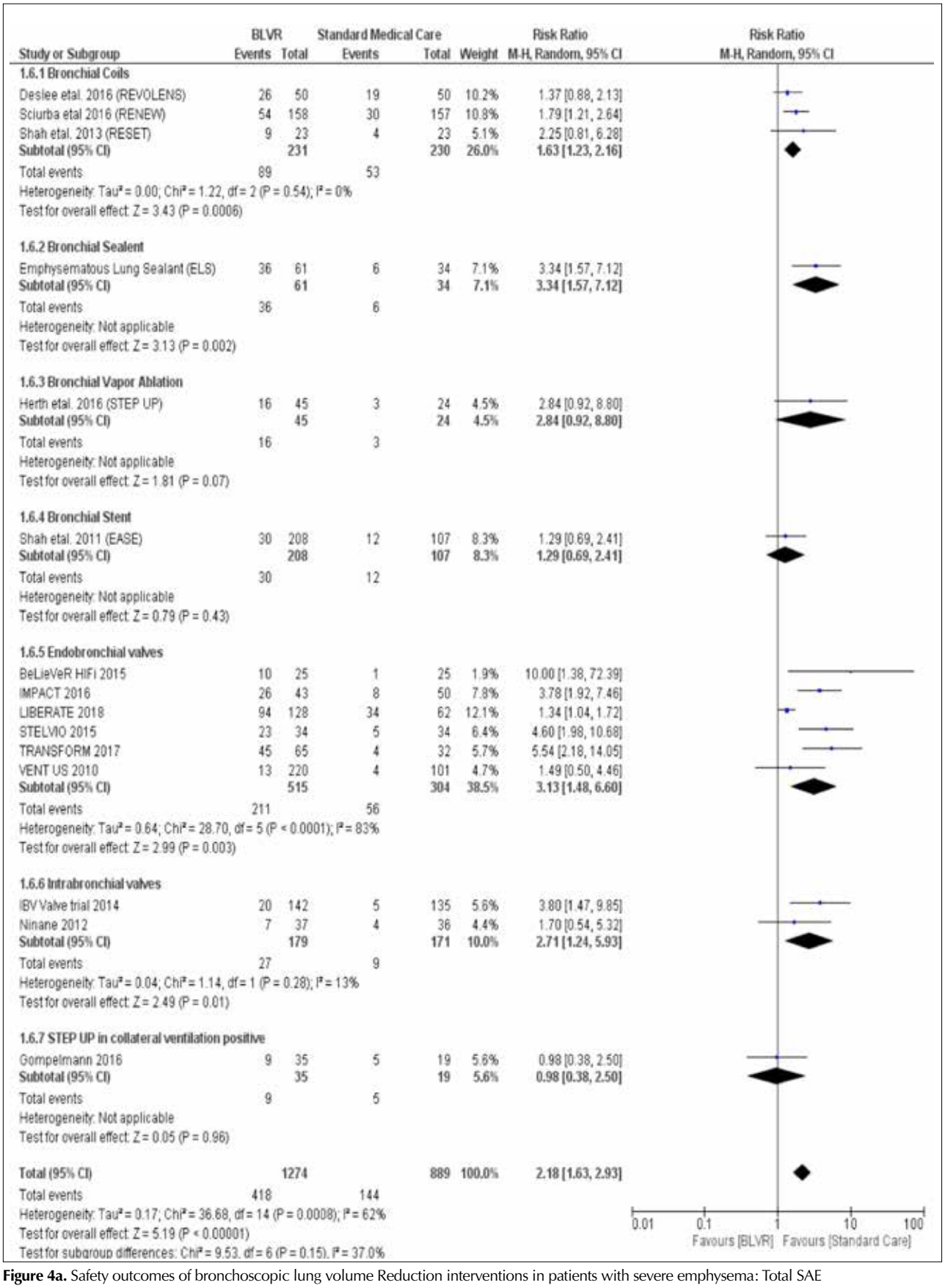

Figure 4a. Safety outcomes of bronchoscopic lung volume Reduction interventions in patients with severe emphysema: Total SAE

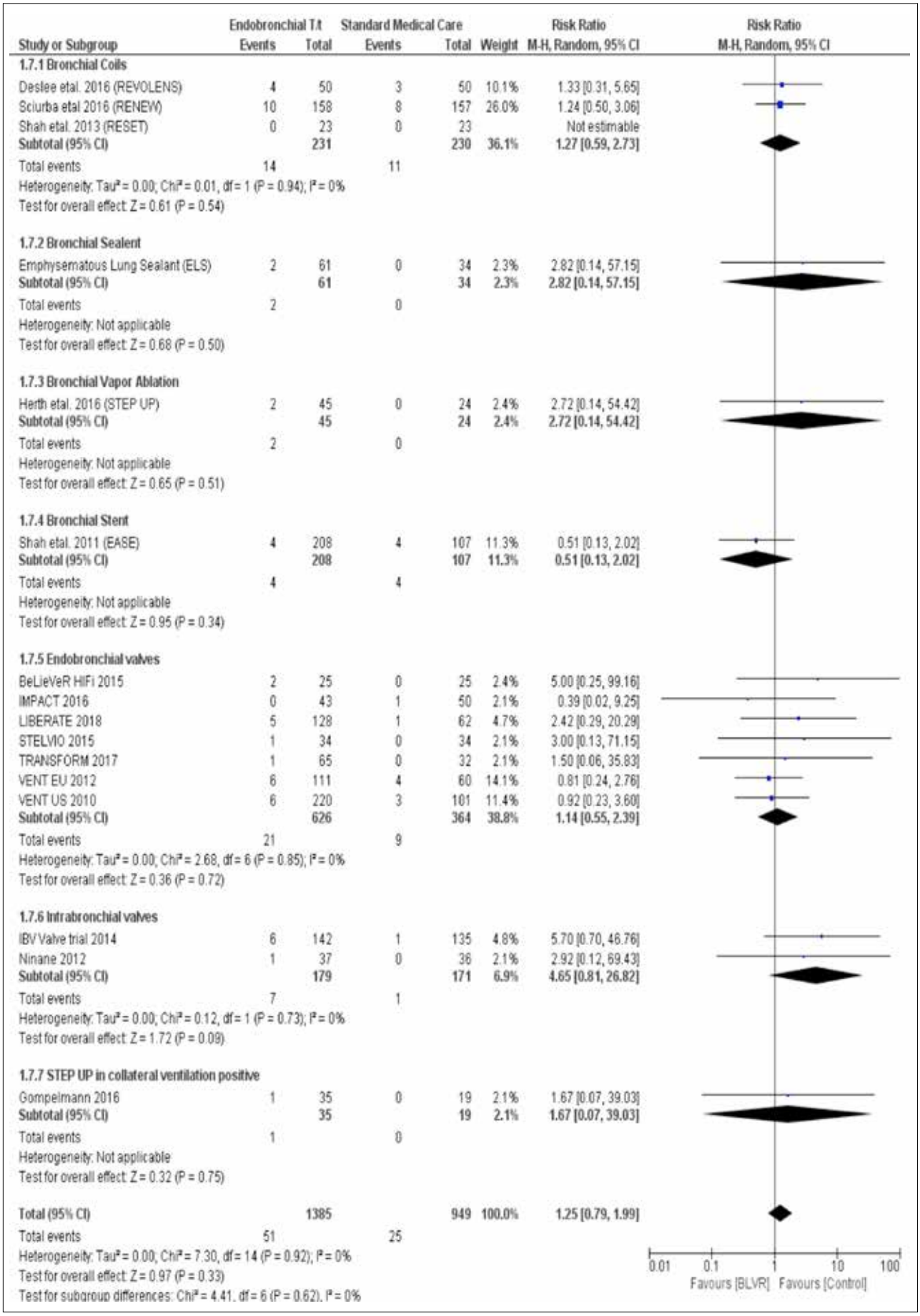

Figure 4b. Safety outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: Death

results regarding the efficacy of stents in patients with severe homogeneous emphysema were observed in our review. Milenkovic et al. [35] reviewed bronchoscopic administration of lung sealants as an effective approach in patients with upper lobe emphysema with both heterogeneous and homogeneous distribution in patients with advanced emphysema. This could not be validated by this review because of the presence of limited evidence in form of prematurely terminated single trial with small sample size and high attrition (15).

Substantial heterogeneity (I^2 >50%) was observed for outcomes possibly due to varied inclusion and exclusion criteria of patients as per pattern of emphysema; the severity of disease (predicted FEV_1, RV and TLC); smoking status and compliance

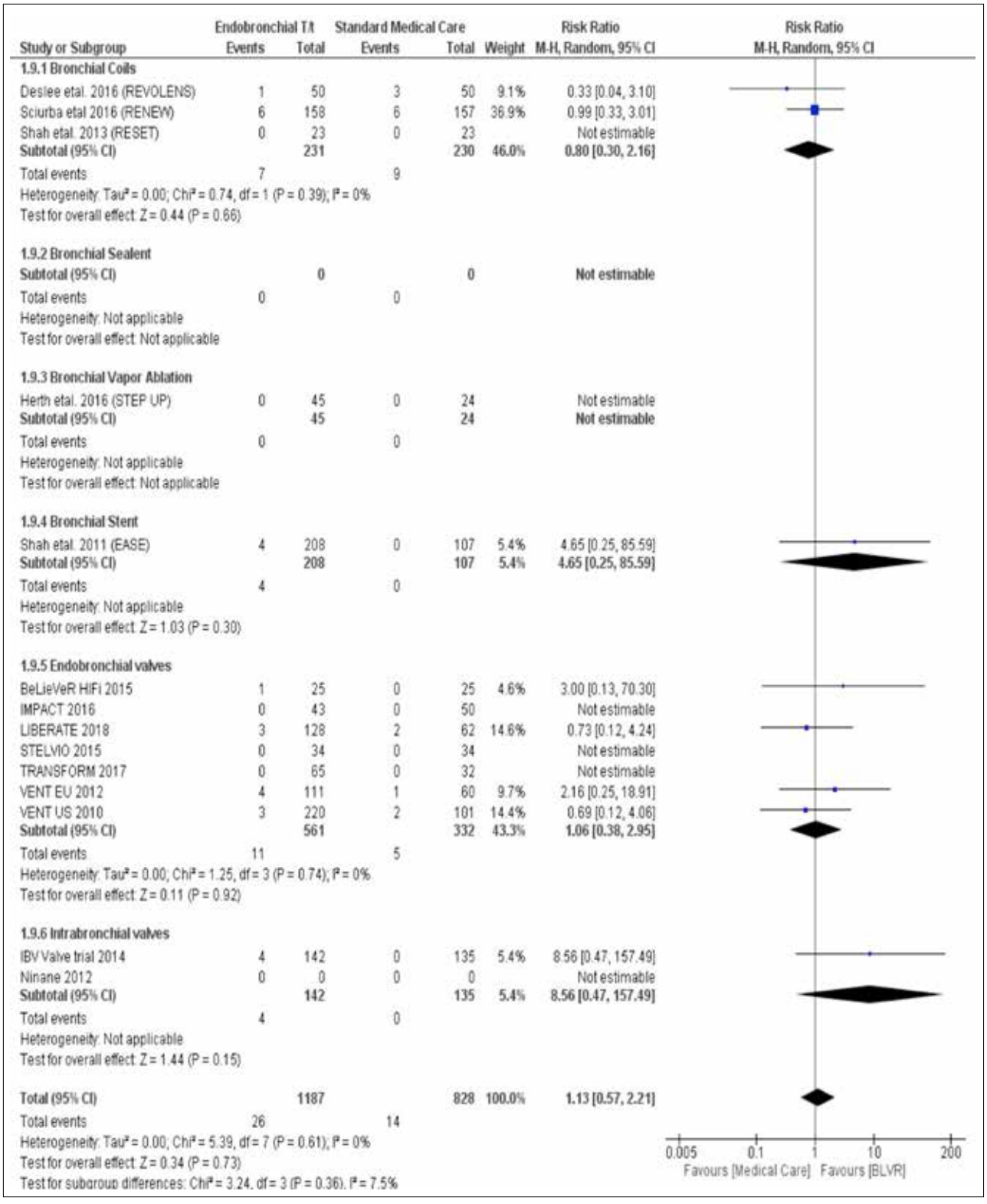

Figure 4c. Safety outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: Respiratory failure requiring mechanical ventilation

to pulmonary rehabilitation guidelines among participants. Also, varied definitions were adopted to estimate both efficacy and safety outcomes. For 6MWT, MCID of 54 m assessed by one trial [18] is more than double of the recommended MCID values for 6MWD (between 25 and 30 m) [36]. Standardized inclusion and exclusion criteria and outcome definition in future trials are thus warranted to assess clinical efficacy and safety of the BLVR interventions. The included trials did not account for the influence of co-morbidities on studied outcomes, and thus the observed effect in our review was unable

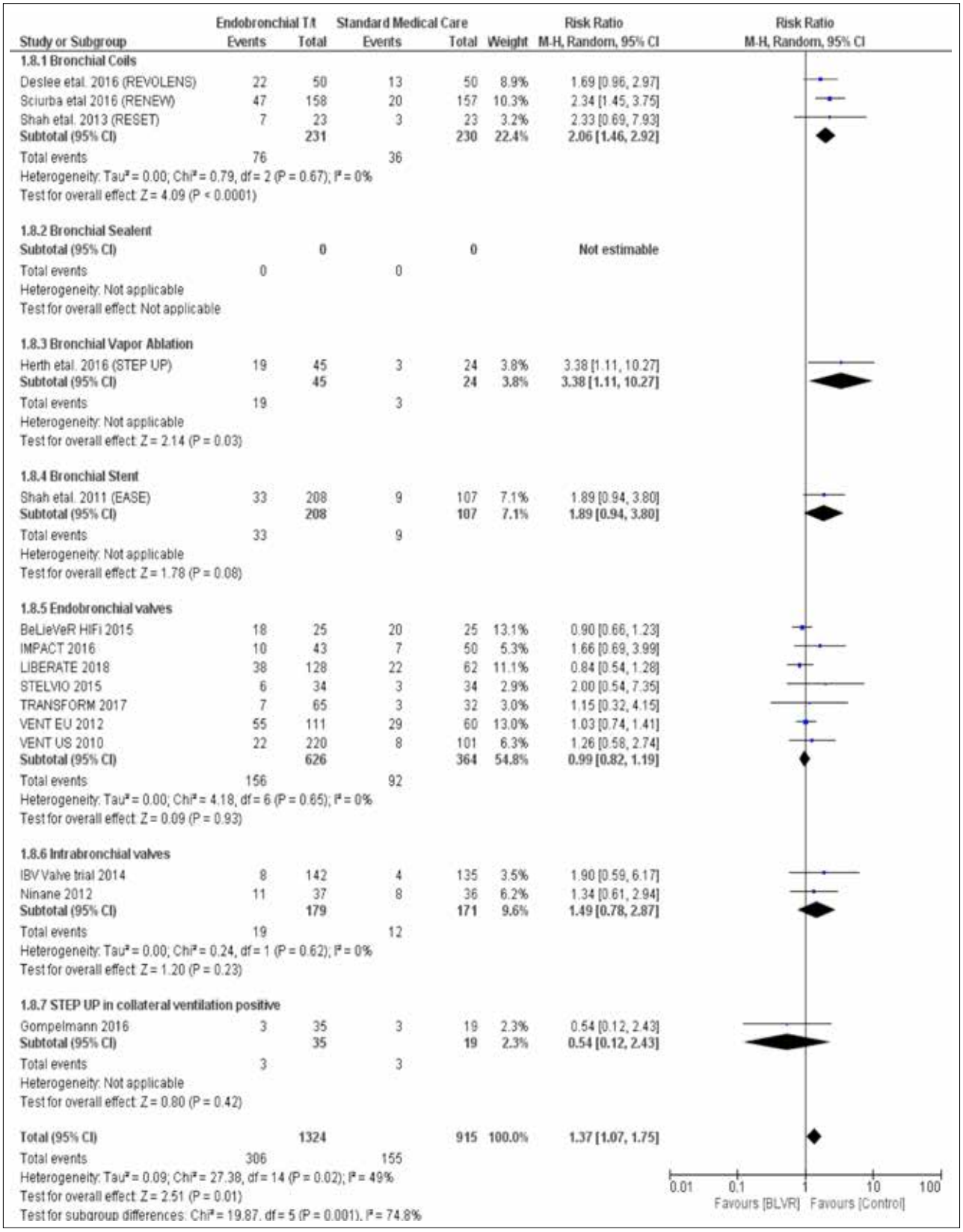

Figure 4d. Safety outcomes of bronchoscopic lung volume reduction interventions in patients with severe emphysema: COPD exacerbations and LRTI

to report outcomes as per the health profile of participants. Also, the results of included trials are not stratified by age, sex, ethnicity, smoking status, and severity of disease that may reportedly influence studied outcomes [37-39]. Thus, this review cannot suggest optimum age, stage of disease, ethnic origin, and sex of a patient for whom the BLVR procedures will be more efficacious with minimum side effects.

Directions for future research

We suggest that the aforementioned limitations should guide future research especially those regarding EBV and EBCs. Future research should focus on optimizing four Ps for better interpretation of evidence, and to reach generalizability regarding available evidence. First P is recognizing patient characteristics by including a large sample size from multiple sites, both from developed and developing economies to stratify patient subgroups and thus getting maximum benefits from the BLVR procedures. Second P and third P are optimizing suitable BLVR Procedure and Provider experience and expertise in carrying out the procedure. This should be complemented with the fourth P in form of planned follow-up for early and successful diagnosis and management of potential complications either due to disease or due to the procedure. At present, evidence of the BLVR interventions is mainly available through studies carried out by an expert group in specialized centers. Research on patient population in less specialized centers and from developing economies is needed to justify the role of the BLVR interventions globally.

Bronchoscopic reduction of lung volume has emerged as a promising intervention for patients with advanced severe emphysema. Patient quality of life, exercise capacity, and lung function tests have been observed to improve with EBV at the cost of increased respiratory adverse events in patients with no collateral ventilation, and existing quality of evidence is high. EBC and TVA appear to be promising modalities, and large sample trials are needed in future to establish robust evidence. Optimizing patient selection for the specific bronchoscopic procedure with planned follow-up care to manage the higher risk of serious respiratory adverse events can prove beneficial for patients with advanced severe emphysema over standard medical care.

Key Message

Among patients with advanced severe emphysema, endobronchial valves and endobronchial coils have shown promising short-term improvement in important disease outcomes with increased risk of serious adverse events. Endobronchial coils are effective in both heterogeneous and homogeneous emphysema irrespective of collateral ventilation status, while endobronchial valves are effective only in patients without collateral ventilation. Among other modalities, bronchoscopic thermal vapor ablation appears promising, but it has not yet been adequately studied to derive any robust conclusion, while intra-bronchial valves, airway stents, and lung sealants are of no proven benefit. Although increased mortality was not observed with any of bronchoscopic procedures, long-term data are required to further substantiate the current findings.

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