Surgical and endoscopic interventions that reduce lung volume for emphysema

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Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis

Wouter H van Geffen, Dirk-Jan Slebos, Felix J Herth, Samuel V Kemp, Walter Weder, Pallav L Shah

Summary

Background Severe emphysema is a debilitating condition with few treatment options. Lung volume reduction procedures in the treatment of severe emphysema have shown excellent results in selected patients but their exact role remains unclear with studies reporting a wide variation in outcomes. We therefore aimed to evaluate the effects of volume reduction.

Methods We did a systematic review and meta-analysis. We searched MEDLINE on Sept 29, 2016, for trials of lung volume reduction in patients with emphysema, and we did an updated search on Embase and PubMed on June 18, 2018. We only included randomised controlled studies published in English evaluating the intervention with either sham or standard of care. Inclusion was limited to trials of techniques in which there was sustainable volume reduction. Primary outcomes were residual volume, FEV_1, St George's Respiratory Questionnaire (SGRQ), and 6-min walk distance (6MWT). Secondary outcomes were severe adverse events (including mortality), short-term mortality, and overall mortality. We extracted summary level data from the trial publications and where necessary we obtained unpublished data. A random-effects model with the I^2 statistic was used to determine heterogeneity and trial weight in each analysis. The study is registered with the PROSPERO database, number CRD42016045705.

Findings We identified 4747 references in the search, and included 20 randomised controlled trials of lung volume reduction involving 2794 participants with emphysema. Following lung volume reduction from any of the interventions in pooled analyses (ie, surgery, endobronchial valve, endobronchial coil, or sclerosing agents), the mean differences compared with the control were reduction in residual volume of 0·58 L (95% CI –0·80 to –0·37), increase in FEV_1 of 15·87% (95% CI 12·27 to 19·47), improvement in 6MWT of 43·28 m (31·36 to 55·21), and reduction in the SGRQ of 9·39 points (–10·92 to –7·86). The odds ratio for a severe adverse event, which included mortality, was 6·21 (95% CI 4·02 to 9·58) following intervention. Regression analysis showed improvements relative to the degree of volume reduction: FEV_1 (r^2=0·86; p<0·0001), 6MWT (r^2=0·77; p<0·0001), and SGRQ (r^2=0·70; p<0·0001). Most studies were at high risk of bias for lack of blinding, and heterogeneity was high for some outcomes when pooled across all interventions, but was generally lower in the subgroups by intervention type.

Interpretation Despite limitations of high risk of bias and heterogeneity for some analyses, our results provide support that lung volume reduction in patients with severe emphysema on maximal medical treatment has clinically meaningful benefits. These benefits should be considered alongside potential adverse events.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide.[1] The emphysema phenotype of COPD is characterised by the destruction of lung and alveolar tissues resulting in air trapping and hyperinflation of the lung.[2] Standard therapy includes smoking cessation, inhaled long-acting bronchodilators, inhaled steroids, oral bronchodilators, pulmonary rehabilitation, optimal nutrition, and vaccination. However, because of the destructive nature of emphysema, these treatments only have a modest effect on symptoms. Lung volume reduction has been shown to reduce exertional breathlessness at a given workload, improve lung function, and even prolongs survival. These effects are attributed to a combination of reduced thoracic hyperinflation, reduced work of breathing, and reduced mechanical constraints on lung volume expansion.[3] More recently, lung volume reduction has been shown to improve oxygen kinetics and reduces chest wall asynchrony.[4,5]

The first available option for lung volume reduction was surgery.[6] A Cochrane meta-analysis,[7] which evaluated lung volume reduction surgery, surmised that patients undergoing surgery had a significantly greater risk of death at 3 months but did acknowledge clinical benefit in the surviving patients. The perceived morbidity and mortality has stimulated the development of other less invasive methods for inducing volume reduction—eg, endobronchial valves, endobronchial coils, and sclerosing agents.[8] Additionally, airway bypass was tested in a randomised sham-controlled trial but as the benefit was not sustained this procedure has not been developed further.[9]

Research in context

Evidence before this study

Severe emphysema is a debilitating condition with few treatment options. Lung volume reduction procedures in the treatment of severe emphysema have shown excellent results in selected patients. We searched MEDLINE on Sept 29, 2016, for trials of lung volume reduction in patients with emphysema, and updated the search on June 18, 2018. Two Cochrane meta-analyses were identified that looked at surgical lung volume reduction and bronchoscopic lung volume reduction separately. However, they included trials in which lung volume reduction was not sustained, and therefore the role of lung volume reduction on outcomes was unclear. The Cochrane reviews suggest modest clinical improvements but cautioned regarding early surgical mortality. Furthermore, they were not able to make any clear recommendations around treatment strategy.

Added value of this study

This study, to our knowledge, is the first to show a consistent relationship between actual lung volume reduction and clinical benefit across all treatment interventions.

Implications of all the available evidence

The available evidence shows that lung volume reduction in patients with emphysema and severe hyperinflation on maximal medical treatment improves pulmonary function, exercise capacity, and quality of life. The greater the reduction in residual volume the greater the improvements in these outcome measures. Treatment with endobronchial valves and surgery have the greatest potential to reduce lung volume and should be considered first depending on the collateral ventilation status of the individual. The increased potential of adverse events following treatment should also be taken into consideration. The remaining therapies should be considered second line until further evidence is available.

Controversy exists about whether therapeutic benefit requires volume reduction and the preferred method for lung volume reduction.[7,10,11] From the development of endobronchial valves, it is apparent that only patients with no evidence of collateral ventilation and complete lobar exclusion benefit.[12] The Cochrane analysis on bronchoscopic lung volume reduction[11] included trials for which no perceptible volume reduction was reported at the study endpoint—eg, the trials with endobronchial valves in patients with collateral ventilation, intrabronchial valve in which the treatment lobe was not completely occluded,[13–15] and the EASE trial in which there was occlusion of the airway bypass stents within 8 weeks of treatment.[9] Hence, the perceived overall changes were modest.

For the **Rayyan software** see http://rayyan.qcri.org

We therefore aimed to assess the effects of the available interventions for emphysema, which effectively reduce lung volume. The review questions tested were the following: does actual lung volume reduction improve outcomes in patients with emphysema compared with standard of care? Are these interventions associated with major adverse events compared with standard of care?

For the **protocol** see www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016045705

Methods

Search strategy and selection criteria

We did a systematic review and meta-analysis. We searched MEDLINE on Sept 29, 2016, for clinical trials evaluating lung volume reduction in patients with emphysema, and we did an updated search on June 18, 2018, using PubMed and Embase. We had no date restrictions and the search terms used and findings are available in the appendix, no date restrictions. We only included randomised controlled studies published in English that evaluated the intervention (endobronchial valves, endobronchial coils, sclerosing agents, and surgical lung volume reduction) with a control (either sham or standard of care). Trials were included with the following participants: patients with emphysema who were older than 35 years, post-bronchodilator FEV_1 of less than 60% of the predicted value, and a residual volume that was more than 150% of the predicted value. Exclusion criteria were techniques in which there was no perceptible lung volume reduction at the study endpoint and patients treated for a different indication other than emphysema or COPD. If studies included participants who both did and did not meet our inclusion criteria, we contacted investigators to obtain raw data. When available, we calculated summary estimates for the people who did meet our inclusion criteria for that trial. Rayyan software was used to process and assess the search results. Two independent reviewers (WHvG, D-JS) screened all the abstracts for inclusion and the full-text articles of all the randomised controlled studies identified. Conflicts were resolved by consensus within the review team.

See Online for appendix

Our study protocol has been prospectively registered and published in the PROSPERO database, number CRD42016045705.

Data analysis

Two independent review authors (WHvG, D-JS) extracted the trial characteristics from the included studies. Disagreements were solved through discussion or, if required, a third review author (PLS). Data not reported in the original paper or reported in such a way that was unsuitable for meta-analysis were requested from the authors of the included trials.

The predefined primary outcomes were residual volume, FEV_1, St George's Respiratory Questionnaire (SGRQ), and 6-min walk distance (6MWT). The secondary outcomes were occurrence of severe adverse events (all adverse events including mortality that are reported in the trials are included), early mortality (at 45 days), and overall mortality (all mortality measured at any timepoint). Summary measures for continuous outcomes were mean differences with 95% CIs, and odds ratios (ORs) with 95% CIs for adverse events and mortality. Owing to differences in how adverse events were reported in the trials, we reported the OR for an individual developing any adverse event rather than the total number of adverse events.

A random-effects model was used and the standard deviations were used to standardise the mean differences to a single scale and compute trial weights. The most important unit of analysis issue that was encountered was the different timing of the primary endpoints of each trial. Although not ideal, the decision was prospectively taken to pool the primary endpoints if timepoints were between 3 months and 12 months. The I^2 statistic was used to assess heterogeneity among the studies in each analysis.[16] Review Manager (version 5.3), provided by Cochrane, was used to meta-analyse data and generate forest plots.

To evaluate the effect of residual volume on the other primary outcomes of FEV_1, SGRQ, and 6MWT, we did regression analysis using Microsoft Excel 365 with the Analysis ToolPak add-on to assess the validity of the assumption that improvements in clinical outcomes would be proportional to the degree of lung volume reduction.

We assessed publication bias and risk of bias using Review Manager (version 5.3). Publication bias was assessed in a funnel plot, and risk of bias was assessed

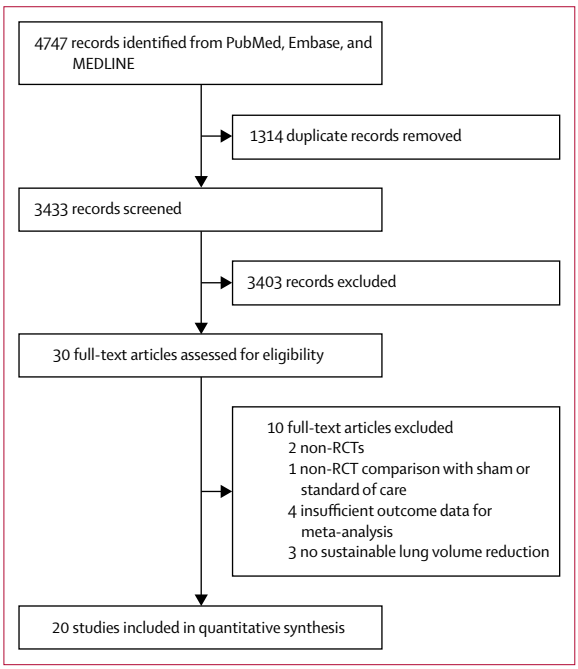


Figure 1: **PRISMA flow diagram for meta-analysis of randomised controlled trials of lung volume reduction in emphysema**
RCT=randomised controlled trial. PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

	Study design	Primary endpoint time	Comparator	Number of participants (safety population)	Data source*
Surgery					
Clarenbach et al (2015)[21]	RCT, single centre	3 months	Standard medical care, waiting list placement	27 patients with COPD (FEV_1 ≤50% predicted, substantial hyperinflation)	Paper
Geddes et al (2000)[18]	RCT, single centre	6 months	Standard medical care	48 patients with COPD (FEV_1 greater than 500 mL, substantial hyperinflation)	Paper, no unpublished data available
Goldstein et al (2003)[22]	RCT, single-blinded, single centre	12 months	Standard medical care	55 patients with COPD (FEV_1 <40% predicted, FEV_1/FVC <0·7, substantial hyperinflation)	Paper, no unpublished data available
Hillerdal et al (2005)[20]	RCT, multicentre	12 months	Standard medical care and 1 year of supervised medical training	92 patients with COPD (FEV1 ≤35% predicted RV≥200% predicted)	Paper, no unpublished data available
Miller et al (2005)[17]	RCT, two combined trials, single-blinded, multicentre	6 months	Standard medical care	90 patients with COPD (CLVR=FEV_1 15–40% predicted, RV to total lung capacity ratio of ≥60% predicted; OBEST=FEV_1 ≤40% predicted RV >175% predicted)	Paper, no unpublished data available
Fishman et al (2003; NETT trial)[6]	RCT, multicentre	24 months	Standard medical care	1218 patients with COPD (FEV_1 ≤45% predicted, RV ≥150% predicted)	Paper and unpublished data
Pompeo et al (2000)[19]	RCT, single centre	6 months	Standard medical care and at least 6 weeks of rehabilitation	60 patients with COPD (FEV_1 ≤40% predicted, RV >180% predicted, DLCO >20% predicted)	Paper and unpublished data

(Table continues on next page)

	Study design	Primary endpoint time	Comparator	Number of participants (safety population)	Data source*
(Continued from previous page)					
Endobronchial valves					
Criner et al (2018; LIBERATE trial)[23]	RCT, multicentre	12 months	Standard medical care	190 patients with COPD (FEV_1 15–45% predicted, RV >175% predicted, DLCO ≥20% predicted)	Paper
Davey et al (2015; BeLieVeR-HIFi study)[24]	RCT, single centre, double-blinded, sham	3 months	Standard medical care and bronchoscopy with sham valve placement	50 patients with COPD (FEV_1 <50% predicted, RV >150% predicted)	Paper and unpublished data
Kemp et al (2017; TRANSFORM trial)[25]	RCT, multicentre	3 months	Standard medical care	97 patients with COPD (FEV_1 15–45% predicted, RV ≥180% predicted)	Paper
Klooster et al (2015; STELVIO trial)[26]	RCT, single centre	6 months	Standard medical care	68 patients with COPD (FEV_1 <60% predicted, RV >150% predicted)	Paper and unpublished data
Valipour et al (2016; IMPACT study)[27]	RCT, multicentre	3 months	Standard medical care	93 patients with COPD (FEV_1 15–45% predicted, RV >200% predicted)	Paper
VENT trial: Sciurba et al (2010)[13] and Herth et al (2012)[14]	RCT, multicentre, two combined trials	6 months	Standard medical care	122 patients with COPD (FEV_1 15–45% predicted, RV >150% predicted, DLCO ≥20% predicted)	Paper and unpublished data; subgroup data only
Endobronchial coils					
Deslee et al (2016; REVOLENS trial)[31]	RCT, multicentre	6 months	Standard medical care	100 patients with COPD (FEV_1 <50% predicted RV >220% predicted)	Paper
Sciurba et al (2016; RENEW trial)[32]	RCT, multicentre	12 months	Standard medical care	312 patients with COPD (FEV_1 <45% predicted RV >225% predicted)	Paper
Shah et al (2013; RESET trial)[30]	RCT, multicentre	3 months after last procedure	Standard medical care	46 patients with COPD (FEV_1 ≤45% predicted, DLCO ≥20% predicted, substantial hyperinflation)	Paper
Sclerosing agents					
Come et al (2015; ASPIRE trial)[34]	RCT, multicentre	3 months†	Standard medical care	57 patients with COPD (FEV_1 <50%, RV >150%, DLCO 20–60% predicted)	Paper and unpublished data
Herth et al (2016; STEP-UP)[33]	RCT, multicentre	6 months	Standard medical care	69 patients with COPD (FEV_1 20–45% predicted, substantial hyperinflation)	Paper and unpublished data

Miller et al[17] reported on two separate clinical trials in one publication. RCT=randomised controlled trial. FVC=forced vital capacity. RV=residual volume. CLVR=Canadian Lung Volume Reduction. OBEST= Overholt-Blue Cross Emphysema Surgery Trial. DLCO=Diffusing capacity of the lungs for carbon monoxide. *Data were requested for all incomplete sets. †Trial was terminated prematurely.

Table: **Characteristics of studies for lung volume reduction**

with the Cochrane risk of bias tool for randomised controlled trials, both individually for each study as well as across studies.

This study is registered with the PROSPERO database, number CRD42016045705.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

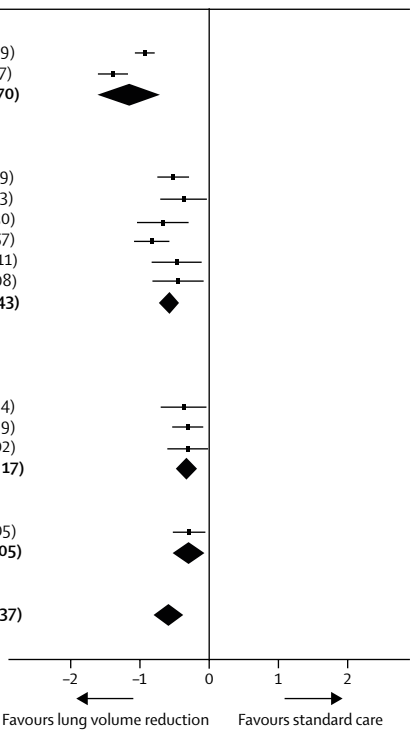
Results

We found and assessed a total of 4747 records. The data of 2794 participants involved in 20 trials were included in the quantitative analysis (figure 1). One paper included two trials[17] and the VENT trial of one data set had two papers.[13,14] The funnel plot for the included studies does not suggest any significant publication bias (appendix p 2). The risk of bias assessments for the individual studies are reported in the appendix (p 4). All but one study was at high risk for performance bias (participants were not masked to treatment) and most studies were at high risk for detection bias (investigator blinding). All other domains were generally at low risk of bias for all studies.

Seven surgical lung volume reduction trials were included (table).[6,17–22] Owing to differences between the endpoints and presentation of the data, not all trials could be included in each analysis. Raw data was requested but could not always be obtained, most often because of the age

A

	Lung volume reduction		Standard care		Weight	Mean difference (95% CI)
	Mean (SD)	Total	Mean (SD)	Total		
Surgery						
Fishman et al (2003; NETT trial)[6]	−0·89 (0·91)	323	0·04 (0·85)	261	9·3%	−0·93 (−1·07 to −0·79)
Pompeo et al (2000)[19]	−1·40 (0·6)	30	−0·01 (0·09)	30	8·9%	−1·39 (−1·61 to −1·17)
Subtotal		**353**		**291**	**18·2%**	**−1·15 (−1·60 to −0·70)**
Heterogeneity I^2=92% (p=0·0005)						
Overall effect p<0·0001						
Endobronchial valves						
Criner et al (2018; LIBERATE trial)[23]	−0·49 (0·83)	112	0·03 (0·66)	58	8·8%	−0·52 (−0·75 to −0·29)
Davey et al (2015; BeLieVeR-HIFi study)[24]	−0·50 (0·78)	25	−0·13 (0·36)	25	7·9%	−0·37 (−0·71 to −0·03)
Kemp et al (2017; TRANSFORM trial)[25]	−0·66 (1·04)	65	0·01 (0·79)	32	7·6%	−0·67 (−1·04 to −0·30)
Klooster et al (2015; STELVIO trial)[26]	−0·86 (0·71)	34	−0·03 (0·27)	34	8·6%	−0·83 (−1·09 to −0·57)
Valipour et al (2016; IMPACT study)[27]	−0·42 (0·9)	43	0·05 (0·87)	50	7·7%	−0·47 (−0·83 to −0· 11)
VENT trial: Sciurba et al (2010)[13] and Herth et al (2012)[14]	−0·53 (1·1)	61	−0·08 (0·98)	61	7·6%	−0·45 (−0·82 to −0·08)
Subtotal		**340**		**260**	**48·0%**	**−0·57 (−0·71 to −0·43)**
Heterogeneity I^2=23% (p=0·26)						
Overall effect p<0·0001						
Endobronchial coils						
Deslee et al (2016; REVOLENS trial)[31]						
Sciurba et al (2016; RENEW trial)[32]	−0·52 (0·77)	50	−0·15 (0·91)	50	7·9%	−0·37 (−0·70 to −0·04)
Shah et al (2013; RESET trial)[30]	−0·41 (1·02)	158	−0·10 (1·01)	157	8·8%	−0·31 (−0·53 to −0·09)
Subtotal	−0·51 (0·51)	23	−0·20 (0·51)	23	8·2%	−0·31 (−0·60 to −0·02)
Heterogeneity I^2=0% (p=0·95)		**231**		**230**	**25·0%**	**−0·32 (−0·48 to −0· 17)**
Overall effect p<0·0001						
Sclerosing agents						
Herth et al (2016; STEP-UP)[33]	−0·26 (0·51)	41	0·03 (0·43)	23	8·7%	−0·29 (−0·53 to −0·05)
Subtotal		**41**		**23**	**8·7%**	**−0·29 (−0·53 to −0·05)**
Heterogeneity I^2=NA						
Overall effect p=0·02						
Total		**965**		**804**	**100·0%**	**−0·58 (−0·80 to −0·37)**
Heterogeneity I^2=88% (p<0·0001)						
Overall effect p<0·0001						
Subgroup differences I^2=82% (p=0·0001)						



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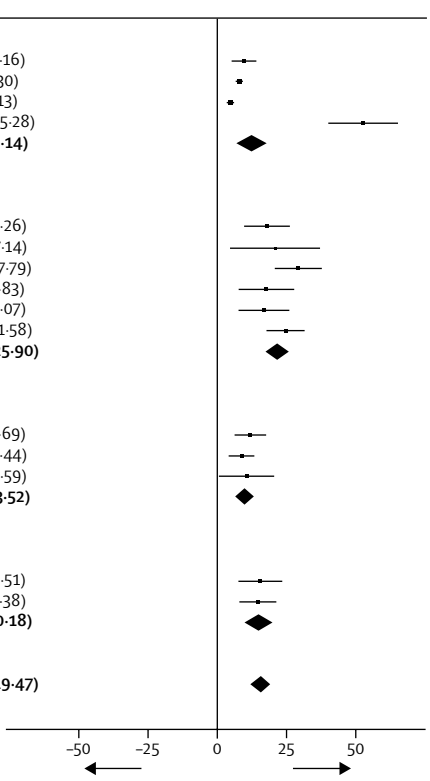
Surgery						
Clarenbach et al (2015)[21]	8·1 (7·5)	14	−1·6 (3·9)	13	8·2%	9·70 (5·24 to 14·16)
Hillerdal et al (2005)[20]	7·0 (3·5)	38	−1·0 (2·0)	34	9·3%	8·00 (6·70 to 9·30)
Fishman et al (2003; NETT trial)[6]	4·5 (8·9)	324	−0·3 (7·5)	263	9·3%	4·80 (3·47 to 6·13)
Pompeo et al (2000)[19]	53·0 (35·0)	30	0·3 (3·2)	30	4·4%	52·70 (40·12 to 65·28)
Subtotal		**406**		**340**	**31·2%**	**12·71 (7·27 to 18·14)**
Heterogeneity I^2=95% (p<0·0001)						
Overall effect p<0·0001						
Endobronchial valves						
Criner et al (2018; LIBERATE trial)[23]	17·2 (27·9)	128	−0·8 (26·9)	62	6·3%	18·00 (9·74 to 26·26)
Davey et al (2015; BeLieVeR-HIFi study)[24]	24·8 (40·7)	25	3·9 (7·8)	25	3·2%	20·90 (4·66 to 37·14)
Kemp et al (2017; TRANSFORM trial)[25]	20·7 (29·6)	65	−8·6 (13·0)	32	6·2%	29·30 (20·81 to 37·79)
Klooster et al (2015; STELVIO trial)[26]	20·9 (28·1)	34	3·1 (10·0)	34	5·4%	17·80 (7·77 to 27·83)
Valipour et al (2016; IMPACT study)[27]	13·7 (28·2)	43	−3·2 (13·0)	50	5·8%	16·90 (7·73 to 26·07)
VENT trial: Sciurba et al (2010)[13] and Herth et al (2012)[14]	23·5 (24·2)	61	−1·2 (12·9)	61	7·0%	24·70 (17·82 to 31·58)
Subtotal		**356**		**264**	**34·0%**	**21·77 (17·63 to 25·90)**
Heterogeneity I^2=20% (p=0·29)						
Overall effect p<0·0001						
Endobronchial coils						
Deslee et al (2016; REVOLENS trial)[31]	9·0 (17·6)	50	−3·0 (10·6)	50	7·6%	12·00 (6·31 to 17·69)
Sciurba et al (2016; RENEW trial)[32]	8·0 (21·0)	158	−0·8 (21·0)	157	8·1%	8·80 (4·16 to 13·44)
Shah et al (2013; RESET trial)[30]	14·19 (17·0)	23	3·57 (17·51)	23	5·5%	10·62 (0·65 to 20·59)
Subtotal		**231**		**230**	**21·2%**	**10·14 (6·76 to 13·52)**
Heterogeneity I^2=0% (p=0·69)						
Overall effect p<0·0001						
Sclerosing agents						
Come et al (2015; ASPIRE trial)[34]	16·1 (19·7)	34	0·5 (10·6)	23	6·5%	15·60 (7·69 to 23·51)
Herth et al (2016; STEP-UP)[33]	11·0 (16·0)	41	−3·7 (11·1)	23	7·1%	14·70 (8·02 to 21·38)
Subtotal		**75**		**46**	**13·6%**	**15·07 (9·97 to 20·18)**
Heterogeneity I^2=0% (p=0·86)						
Overall effect p<0·0001						
Total		**1068**		**880**	**100·0%**	**15·87 (12·27 to 19·47)**
Heterogeneity I^2=90% (p<0·0001)						
Overall effect p<0·0001						
Subgroup differences I^2=84% (p=0·0003)						



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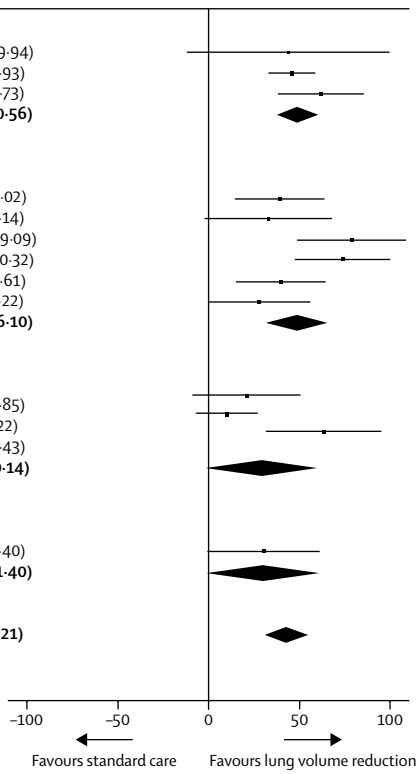
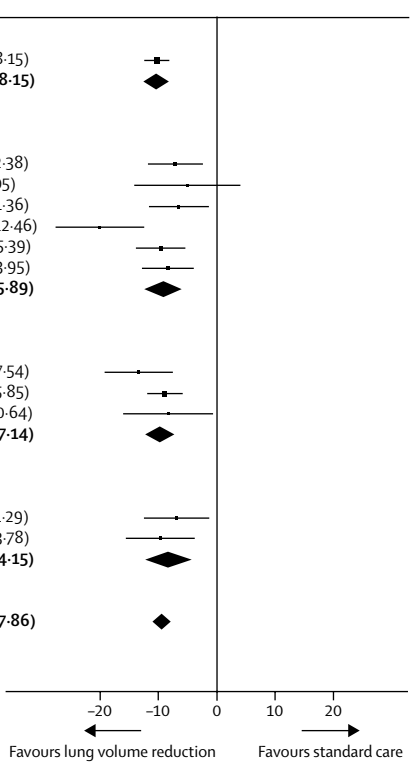
C

	Lung volume reduction		Standard care		Weight	Mean difference (95% CI)
	Mean (SD)	Total	Mean (SD)	Total		
Surgery						
Clarenbach et al (2015)[21]	67·0 (86)	14	23·0 (61·0)	13	3·4%	44·00 (−11·94 to 99·94)
Fishman et al (2003; NETT trial)[6]	50·0 (68)	235	4·0 (84·0)	296	11·3%	46·00 (33·07 to 58·93)
Pompeo et al (2000)[19]	93·0 (61)	30	31·0 (26·0)	30	8·6%	62·00 (38·27 to 85·73)
Subtotal		**279**		**339**	**23·3%**	**49·44 (38·31 to 60·56)**
Heterogeneity I^2=0% (p=0·50)						
Overall effect p<0·0001						
Endobronchial valves						
Criner et al (2018; LIBERATE trial)[23]	13·0 (81·5)	128	−26·3 (81·5)	62	8·4%	39·30 (14·58 to 64·02)
Davey et al (2015; BeLieVeR-HIFi study)[24]	29·0 (70·0)	25	−4·0 (56·0)	25	6·1%	33·00 (−2·14 to 68·14)
Kemp et al (2017; TRANSFORM trial)[25]	36·0 (77·0)	65	−43·0 (68·0)	32	7·1%	79·00 (48·91 to 109·09)
Klooster et al (2015; STELVIO trial)[26]	60·0 (71·7)	34	−14·0 (31·5)	34	8·0%	74·00 (47·68 to 100·32)
Valipour et al (2016; IMPACT study)[27]	22·6 (66·6)	43	−17·3 (52·8)	50	8·4%	39·90 (15·19 to 64·61)
VENT trial: Sciurba et al (2010)[13] and Herth et al (2012)[14]	29·0 (70·0)	61	1·0 (8·0)	61	7·5%	28·00 (−0·22 to 56·22)
Subtotal		**356**		**264**	**45·5%**	**49·00 (31·89 to 66·10)**
Heterogeneity I^2=56% (p=0·05)						
Overall effect p<0·0001						
Endobronchial coils						
Deslee et al (2016; REVOLENS trial)[31]	18·0 (84·4)	50	−3·0 (66·86)	50	7·2%	21·00 (−8·85 to 50·85)
Sciurba et al (2016; RENEW trial)[32]	−0·6 (79·0)	158	−10·7 (76·0)	157	10·3%	10·10 (−7·02 to 27·22)
Shah et al (2013; RESET trial)[30]	51·15 (54·34)	23	−12·39 (56·01)	23	6·8%	63·54 (31·65 to 95·43)
Subtotal		**231**		**230**	**24·2%**	**29·49 (−1·16 to 60·14)**
Heterogeneity I^2=76% (p=0·02)						
Overall effect p=0·06						
Sclerosing agents						
Herth et al (2016; STEP-UP)[33]	20·0 (56·7)	42	−10·4 (61·8)	23	6·9%	30·40 (−0·60 to 61·40)
Subtotal		**42**		**23**	**6·9%**	**30·40 (−0·60 to 61·40)**
Heterogeneity I^2=NA						
Overall effect p=0·05						
Total		**908**		**856**	**100·0%**	**43·28 (31·36 to 55·21)**
Heterogeneity I^2=64% (p=0·0008)						
Overall effect p<0·0001						
Subgroup differences I^2=0% (p=0·46)						



D

Surgery						
Fishman et al (2003; NETT trial)[6]	−6·7 (15·8)	367	3·6 (13)	320	22·3%	−10·30 (−12·45 to −8·15)
Subtotal		**367**		**320**	**22·3%**	**−10·30 (−12·45 to −8·15)**
Heterogeneity I^2=NA						
Overall effect p<0·0001						
Endobronchial valves						
Criner et al (2018; LIBERATE trial)[23]	−7·6 (15·7)	128	−0·5 (15·5)	62	8·3%	−7·10 (−11·82 to −2·38)
Davey et al (2015; BeLieVeR-HIFi study)[24]	−8·72 (20·59)	25	−3·66 (10·8)	25	2·6%	−5·06 (14·17 to 4·05)
Kemp et al (2017; TRANSFORM trial)[25]	−7·2 (15·1)	65	−0·7 (10·4)	32	7·2%	−6·50 (−11·64 to −1·36)
Klooster et al (2015; STELVIO trial)[26]	−17·39 (17·43)	24	2·68 (8·94)	33	3·7%	−20·07 (−27·68 to −12·46)
Valipour et al (2016; IMPACT study)[27]	−8·63 (11·25)	43	1·01 (9·36)	50	9·8%	−9·64 (−13·89 to −5·39)
VENT trial: Sciurba et al (2010)[13] and Herth et al (2012)[14]	−6·73 (12·72)	61	1·67 (12·35)	61	9·1%	−8·40 (−12·85 to −3·95)
Subtotal		**346**		**263**	**40·8%**	**−9·13 (−12·37 to −5·89)**
Heterogeneity I^2=52% (p=0·06)						
Overall effect p<0·0001						
Endobronchial coils						
Deslee et al (2016; REVOLENS trial)[31]	−11·1 (16·9)	50	2·3 (12·7)	50	5·8%	−13·40 (−19·26 to −7·54)
Sciurba et al (2016; RENEW trial)[32]	−8·1 (13·8)	158	0·8 (13·8)	157	15·5%	−8·90 (−11·95 to −5·85)
Shah et al (2013; RESET trial)[30]	−8·11 (13·23)	23	0·25 (13·48)	23	3·6%	−8·36 (−16·08 to −0·64)
Subtotal		**231**		**230**	**24·9%**	**9·69 (−12·25 to −7·14)**
Heterogeneity I^2=0 (p=0·38)						
Overall effect p<0·0001						
Sclerosing agents						
Come et al (2015; ASPIRE trial)[34]	−9·2 (13·0)	34	−2·3 (8·6)	23	6·3%	−6·90 (−12·51 to −1·29)
Herth et al (2016; STEP-UP)[33]	−9·7 (14·4)	42	0·0 (9·8)	23	5·7%	−9·70 (−15·62 to −3·78)
Subtotal		**76**		**46**	**12·0%**	**−8·23 (−12·30 to −4·15)**
Heterogeneity I^2=0% (p=0·50)						
Overall effect p<0·0001						
Total		**1020**		**859**	**100·0%**	**−9·39 (−10·92 to −7·86)**
Heterogeneity I^2=22% (p=0·22)						
Overall effect p<0·0001						
Subgroup differences I^2=0% (p=0·82)						



of the trials and retirement of the investigators. The largest trial included was the NETT trial.[6] The original publication did not report on data such as changes in residual volume or 6MWT; therefore, raw data from this multicentre trial was obtained from the authors.[6] All surgical trials combined allowed the assessment of 1590 patients.

Six trials were included for the endobronchial valves, all using Pulmonx Zephyr valves.[13,14,23–27] No randomised trials with intrabronchial valves were available that assessed patients without collateral flow or complete fissures.[15,28,29] The VENT trial was reported in two separate articles, and we obtained unpublished data for cases with a complete fissure and lobar occlusion from the whole trial combined, as prospectively planned. This trial together with the IMPACT, TRANSFORM, and LIBERATE trials are multicentre studies, whereas the STELVIO trial and Believer-HIFi study were single centre studies.[23–27] A total of 620 participants were randomly assigned. Follow-up data were available up to 12 months. Patients included were characterised by severe emphysema, although trial entry criteria differed with respect to emphysema distribution.

Three studies for endobronchial coils were included.[30–32] These were all multicentre studies. A total of 461 participants were randomly assigned. Follow-up data were available up to 12 months. Patients included were characterised by severe emphysema, with both homogeneous and heterogeneous distributions.

Two trials assessing sclerosing agents were included.[33,34] One trial used bronchoscopic thermal vapour ablation.[33] A total of 65 participants were randomly assigned, with follow-up data available up to 6 months. The second trial was terminated by the sponsor owing to inadequate financial resources after 95 of 300 planned patients had been enrolled. This trial assessed the AeriSeal Emphysema Lung Sealant.[34] Follow-up data from a total of 57 randomly assigned participants were available up to 3 months.

Details of studies excluded at full-text assessment are available in the appendix. The EASE trial was excluded from the meta-analysis as there was no significant volume reduction at 12 months.[9] This trial evaluated the airway bypass procedure in which transbronchial passages supported with paclitaxel-coated stents were created to release trapped air, to ease the mechanics of breathing. However, there was occlusion of these transbronchial passages within 8 weeks and consequent loss of clinical benefit.[9] Similarly, two trials with the intrabronchial valve that used a strategy of incomplete lobar occlusion were excluded.[15,28]

The combined results for all the interventions are as follows. The forest plots summarise the outcomes with the available data for all the methods of lung volume reduction (figure 2). All the interventions successfully reduced lung volume in comparison with the control groups, and had corresponding improvements in clinical outcomes. In the intervention groups, the mean reduction for residual volume compared with the control groups was 0·58 L (95% CI –0·80 to –0·37). There were corresponding improvements in clinical outcome: FEV_1 increased by 15·87% (95% CI 12·27 to 19·47), 6MWT improved by 43·28 m (31·36 to 55·21), and SGRQ decreased by –9·39 points (–10·92 to –7·86). However, the OR for an adverse event, which included mortality, increased following an intervention in comparison with the control (6·21, 95% CI 4·02 to 9·58; figure 3A).

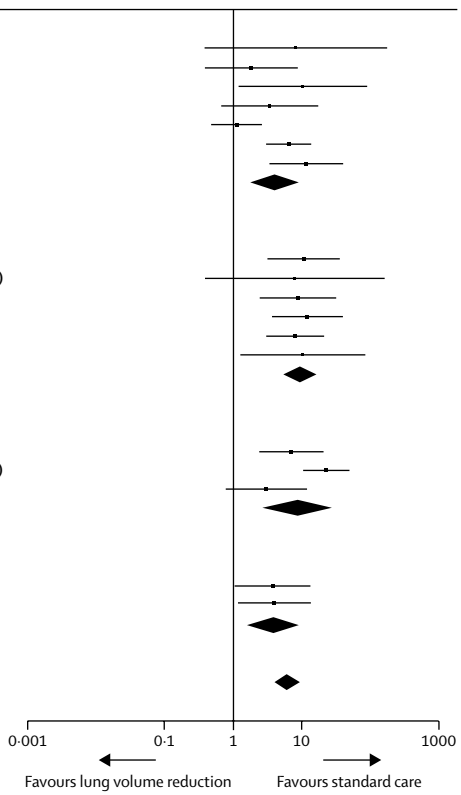
Surgically treated patients showed a reduction in residual volume of 1·15 L (95% CI –1·60 to –0·70), although this value was based on only two trials (figure 2A). The mean increase in FEV_1 of 12·71% (95% CI 7·27 to 18·14) and decrease in SGRQ of 10·30 points (–12·45 to –8·15) from surgery compared with the control was observed (figures 2B and 2D). Exercise data also show an advantage in favour of surgery (mean improvement over control of 49·44 m (95% CI 38·31 to 60·56; figure 2C). The OR for an adverse event was 4·08 (95% CI 1·82 to 9·14; figure 3A). An increase in early mortality was observed in the patients who underwent lung volume reduction surgery compared with standard medical care (OR 12·25, 95% CI 3·72 to 40·28; figure 3B). However, no significant difference between groups in overall mortality was observed (OR 1·06, 95% CI 0·84 to 1·36; figure 3C). Prolonged air leaks were the main complication noted.

Endobronchial valves reduced residual volume by 0·57 L (95% CI –0·71 to –0·43; figure 2A) and increased FEV_1 by 21·77% (17·63 to 25·90; figure 2B) when patients without collateral ventilation in the target lobe are treated. Additionally, exercise capacity measured with the 6MWT improved by 49·00 m (95% CI 31·89 to 66·10) for the use of endobronchial valves compared with the control (figure 2C). Quality of life improved by 9·13 points on the SGRQ (95% CI –12·37 to –5·89) compared with standard of care (figure 2D). The standard of care group encountered fewer adverse events than the patients treated with valves (OR 9·58, 95% CI 5·56 to 16·50; figure 3A). The most frequent adverse events with endobronchial valve treatment were pneumothorax (incidence across studies were 1·4–25%) and COPD exacerbations (4–20%). The difference in early mortality between endobronchial valves and the control groups was not significant, but confidence intervals were wide (OR 3·04, 95% CI 0·51 to 18·16; figure 3B). The OR for early mortality compared with the control groups was lower with endobronchial valves (OR 3·04) than with surgery (12·25), but we did not do a formal statistical comparison of valves versus surgery. Overall mortality was not significantly different between the use of valves

Figure 2: **Forest plots showing mean differences in residual volume (A), FEV_1 (B), 6-min walk tests (C), and St George Respiratory Questionnaire (D) between interventions of lung volume reduction and standard of care**
NA=not applicable.

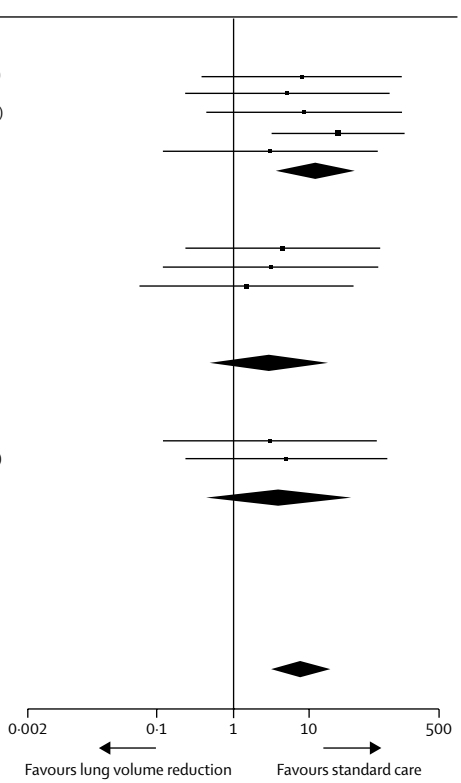
A

	Lung volume reduction		Standard care		Weight	Odds ratio (95% CI)
	Events	Total	Events	Total		
Surgery						
Clarenbach et al (2015)[21]	3	14	0	13	1·7%	8·22 (0·38–176·27)
Geddes et al (2000)[18]	5	24	3	24	4·7%	1·84 (0·39–8·77)
Goldstein et al (2003)[22]	8	28	1	27	3·0%	10·40 (1·20–90·09)
Hillerdal et al (2005)[20]	7	49	2	43	4·4%	3·42 (0·67–17·43)
Miller et al (2005)[17]	21	51	15	39	8·1%	1·12 (0·48–2·63)
Fishman et al (2003; NETT trial)[6]	48	608	8	610	8·7%	6·45 (3·02–13·75)
Pompeo et al (2000)[19]	21	30	5	30	6·0%	11·67 (3·38–40·22)
Subtotal	**113**	**804**	**34**	**786**	**36·7%**	**4·08 (1·82–9·14)**
Heterogeneity I^2=60% (p=0·02)						
Overall effect p=0·0006						
Endobronchial valves						
Criner et al (2018; LIBERATE trial)[23]	45	128	3	62	6·1%	10·66 (3·16–35·95)
Davey et al (2015; BeLieVeR-HIFi study)[24]	25	25	22	25	1·8%	7·93 (0·39–162·07)
Kemp et al (2017; TRANSFORM trial)[25]	31	65	3	32	5·8%	8·81 (2·44–31·84)
Klooster et al (2015; STELVIO trial)[26]	23	34	5	34	6·3%	12·13 (3·69–39·88)
Valipour et al (2016; IMPACT study)[27]	26	43	8	50	7·4%	8·03 (3·04–21·23)
VENT trial: Sciurba et al (2010)[13] and Herth et al (2012)[14]	9	61	1	61	3·1%	10·38 (1·27–84·73)
Subtotal	**159**	**356**	**42**	**264**	**30·5%**	**9·58 (5·56–16·50)**
Heterogeneity I^2=0% (p=1·00)						
Overall effect p<0·00001						
Endobronchial coils						
Deslee et al (2016; REVOLENS trial)[31]	45	50	28	50	6·8%	7·07 (2·40–20·81)
Sciurba et al (2016; RENEW trial)[32]	147	155	70	157	8·6%	22·84 (10·49–49·72)
Shah et al (2013; RESET trial)[30]	9	23	4	23	5·4%	3·05 (0·78–11·96)
Subtotal	**201**	**228**	**102**	**230**	**20·8%**	**8·73 (2·69–28·32)**
Heterogeneity I^2=73% (p=0·02)						
Overall effect p=0·0003						
Sclerosing agents						
Come et al (2015; ASPIRE trial)[34]	15	34	4	23	5·9%	3·75 (1·05–13·39)
Herth et al (2016; STEP-UP)[33]	20	45	4	24	6·1%	4·00 (1·18–13·60)
Subtotal	**35**	**79**	**8**	**47**	**12·0%**	**3·88 (1·60–9·37)**
Heterogeneity I^2=0% (p=0·94)						
Overall effect p=0·003						
Total	**508**	**1467**	**186**	**1327**	**100·0%**	**6·21 (4·02–9·58)**
Heterogeneity I^2=52% (p=0·005)						
Overall effect p<0·00001						
Subgroup differences I^2=37% (p=0·19)						



B

Surgery						
Clarenbach et al (2015)[21]	0	14	0	13	..	NE
Geddes et al (2000)[18]	3	24	0	24	7·7%	7·98 (0·39–163·33)
Goldstein et al (2003)[22]	2	28	0	27	8·4%	5·19 (0·24–113·22)
Hillerdal et al (2005)[20]	4	49	0	43	8·7%	8·60 (0·45–164·59)
Fishman et al (2003; NETT trial)[6]	23	608	1	610	17·3%	23·94 (3·22–177·87)
Pompeo et al (2000)[19]	1	30	0	30	8·5%	3·10 (0·12–79·23)
Subtotal	**33**	**753**	**1**	**747**	**50·6%**	**12·25 (3·72–40·28)**
Heterogeneity I^2=0% (p=0·82)						
Overall effect p<0·0001						
Endobronchial valves						
Criner et al (2018; LIBERATE trial)[23]	4	128	0	62	11·7%	4·52 (0·24–85·25)
Davey et al (2015; BeLieVeR-HIFi study)[24]	1	25	0	25	8·5%	3·12 (0·12–80·39)
Kemp et al (2017; TRANSFORM trial)[25]	1	65	0	32	11·7%	1·51 (0·06–38·15)
Klooster et al (2015; STELVIO trial)[26]	0	34	0	34	..	NE
Valipour et al (2016; IMPACT study)[27]	0	43	0	50	..	NE
VENT trial: Sciurba et al (2010)[13] and Herth et al (2012)[14]	0	61	0	61	..	NE
Subtotal	**6**	**356**	**0**	**264**	**31·8%**	**3·04 (0·51–18·16)**
Heterogeneity I^2=0% (p=0·88)						
Overall effect p=0·22						
Endobronchial coils						
Deslee et al (2016; REVOLENS trial)[31]	1	50	0	50	8·7%	3·06 (0·12–76·95)
Sciurba et al (2016; RENEW trial)[32]	2	158	0	157	8·9%	5·03 (0·24–105·66)
Shah et al (2013; RESET trial)[30]	0	23	0	23	..	NE
Subtotal	**3**	**231**	**0**	**230**	**17·6%**	**4·05 (0·45–36·68)**
Heterogeneity I^2=0% (p=0·83)						
Overall effect p=0·21						
Sclerosing agents						
Come et al (2015; ASPIRE trial)[34]	0	34	0	23	..	NE
Herth et al (2016; STEP-UP)[33]	0	45	0	24	..	NE
Subtotal	0	79	0	47	..	NE
Heterogeneity I^2=NA						
Overall effect p=NA						
Total	**42**	**1419**	**1**	**1288**	**100·0%**	**7·88 (3·24–19·13)**
Heterogeneity I^2=0% (p=0·94)						
Overall effect p<0·00001						
Subgroup differences I^2=0% (p=0·38)						



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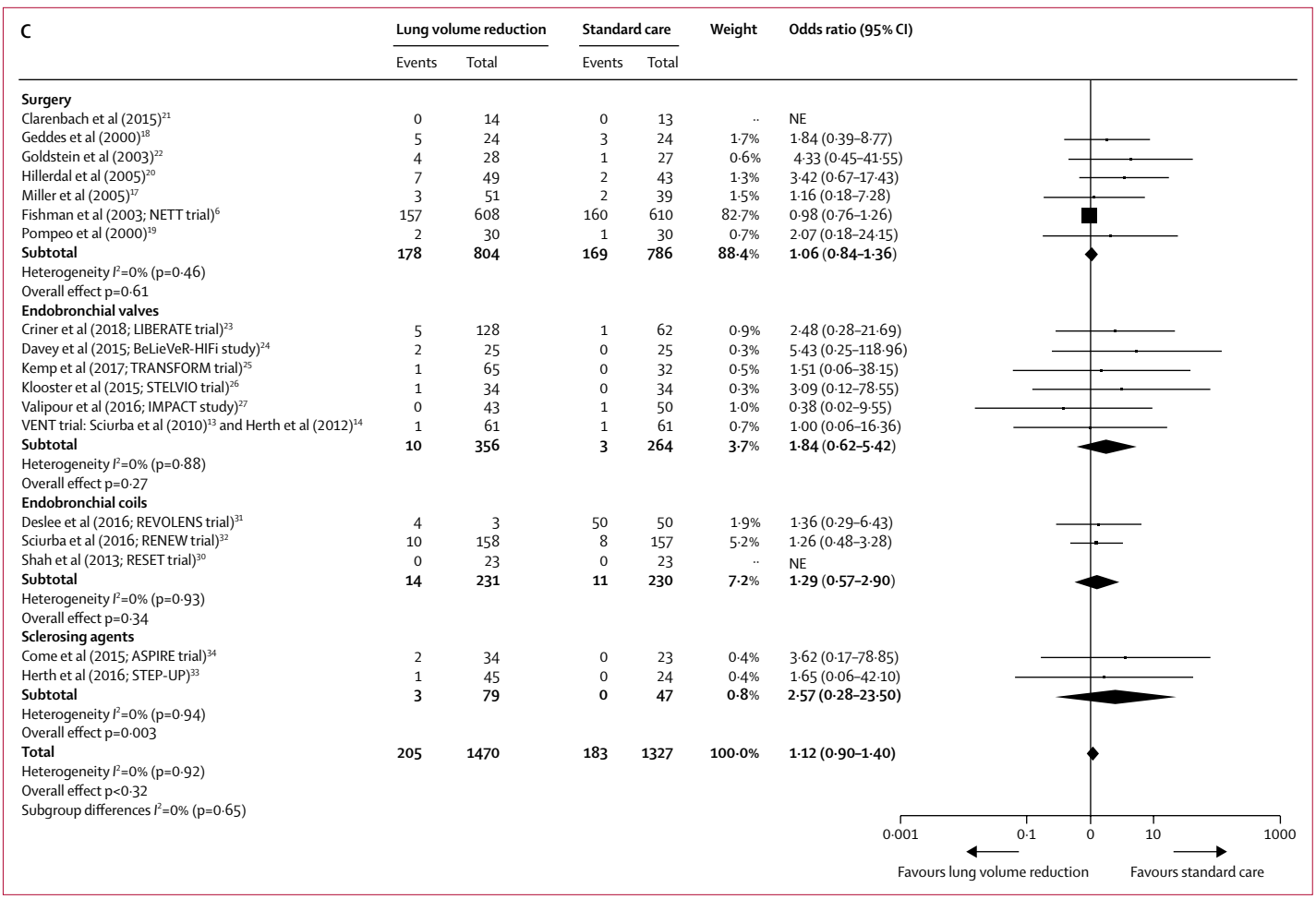

Figure 3: **Odds ratio for adverse events, including mortality, achieved in the different studies (A); odds ratio for 45-day mortality (B); and odds ratio for overall mortality (C) between interventions of lung volume reduction and standard of care**
NA=not applicable. NE=not estimable.

and the control, although again confidence intervals were wide (OR 1·84, 95% CI 0·62 to 5·42; figure 3C).

Endobronchial coils showed a reduction in residual volume (0·32 L, 95% CI –0·48 to –0·17; figure 2A) and an increase in FEV_1 (10·14%, 6·76 to 13·52; figure 2B) compared with the control. The 6MWT improved by 29·49 m compared with the control, but the confidence intervals were wide and crossed the line of no effect (95% CI –1·16 to 60·14; figure 2C). Quality of life also improved by 9·69 points on the SGRQ (95% CI –12·25 to –7·14; figure 2D). Adverse events were more common in the patients treated with coils than with the control (OR 8·73, 95% CI 2·69 to 28·32; figure 3A). The most common adverse events were pneumonia (incidence across studies were 5–20%), a substantial portion of which have been subsequently recognised as a coil-associated opacity that might occur because of strain of the coils on lung tissue; COPD exacerbations (7–28%); and pneumothorax (5–10%). Of note, patients who developed a coil-associated opacity had a greater reduction in residual volume and a greater improvement in clinical outcome measures than those who did not develop a coil-associated opacity. The difference in early mortality between coil and the control groups was not significant, but the CIs were very wide (OR 4·05, 95% CI 0·45 to 36·68; figure 3B), whereas, there was no significant difference in the longer term mortality in comparson to control (1·29, 0·57 to 2·90; figure 3C).

The data from the sclerosing agents showed that they decreased residual volume by 0·29 L (95% CI –0·53 to –0·05; figure 2A) and improved FEV_1 by 15·07% (9·97 to 20·18; figure 2B) and quality of life on the SGRQ by 8·23 points (–12·30 to –4·15; figure 2D). The STEP-UP trial showed an increase in exercise capacity that was not significant and a decrease in residual volume in favour of thermal treatment,[33] but these data could not be pooled because they were not collected in the ASPIRE trial.[34] Adverse events are also increased in the treated groups compared with the control groups (OR 3·88, 95% CI 1·60–9·37; figure 3A). Thermal vapour ablation

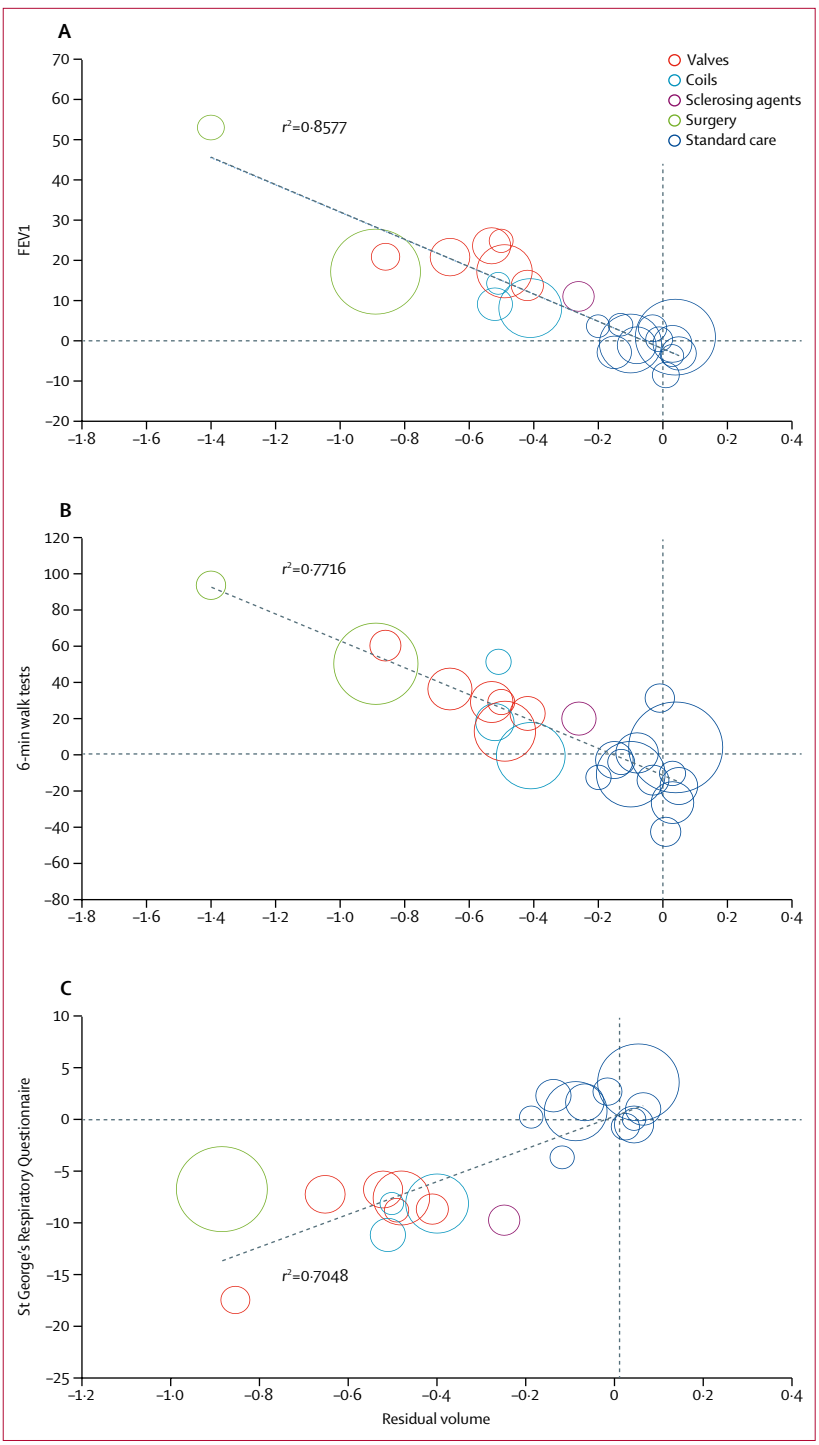

Figure 4: **Regression plots for FEV_1 (A), 6-min walk tests (B), and St George's Respiratory Questionnaire (C) against the reduction in residual volume achieved in the different studies**

most commonly resulted in exacerbations of COPD, pneumonitis, and pneumonia. For the AeriSeal trial, the most common adverse events were respiratory failure, exacerbations of COPD, pneumonitis, and pneumonia. No deaths occurred in either group within 45 days. Overall mortality was not significantly different but confidence intervals were wide (OR 2·57, 95% CI 0·28–23·50; figure 3C).

The regression plots showed that the degree of volume reduction is correlated with improvements in FEV_1 (r^2=0·86; p<0·0001), 6MWT (r^2=0·77; p<0·0001), and SGRQ (r^2=0·70; p<0·0001; figure 4).

Discussion

This systematic review and meta-analysis confirms that interventions designed to reduce lung volume, especially residual volume, in patients with severe emphysema who are hyperinflated and on optimal medical treatment, leads to improvements in lung function, exercise capacity, and quality of life. In this meta-analysis, the greatest improvements in FEV_1 (21·77%) and 6MWT (increase of 49 m) were observed following treatment with endobronchial valves. Although the changes in FEV_1 in the randomised trials of surgery are lower (12·71%) than trials of endobronchial valves, some uncontrolled series report higher improvements of FEV_1 of up to 60% at 6 months depending on the emphysema morphology.[35–37] A possible interpretation of the meta-analysis is that wherever possible the technique that induces the greatest degree of volume reduction should be considered as first-line treatment, but the choice needs to tempered by the potential for adverse events. Although no direct comparative studies between the endobronchial techniques and surgery were identified, we need to consider the absolute event rates in the intervention groups for overall mortality (2·8% with valves and 22% with surgery). However, surgical mortality has decreased in newer reports and was at 90 days as low as 0%,[38] or less than 1·5% in 420 consecutive cases.[36,37] Furthermore, surgical techniques have progressed from median sternotomy to video-assisted thoracoscopic approaches. With endobronchial valves, there is a risk of a pneumothorax within the first 72 h of treatment, and the ability to identify factors that predict those with the greatest pneumothorax risk will be useful. The ongoing randomised controlled study between surgery and endobronchial valves (CELEB trial; ISRCTN19684749) might inform decision making but a limiting factor is that endobronchial valves are only a suitable option for patients without interlobar collateral ventilation. The alternative endoscopic approaches in those with collateral ventilation are endobronchial coils and sclerosants. The main risk in patients managed with endobronchial coils is the incidence of pneumonia and respiratory exacerbations. Whether these coils confer greater risk of infections remains unclear. The sclerosing therapies appear to have a similar risk profile as the other therapies but are associated with the occurrence of an inflammatory response around 7–10 days after treatment. The severity of this response is difficult to estimate, and in the early trials some patients developed a severe inflammatory response necessitating ventilation and critical care.[39]

One of the main limitations of this meta-analysis is that despite the number of clinical studies there is a paucity of long-term data, and subsequently some imprecise results. The NETT trial[6] is exemplary with up to 6 years of controlled follow-up data, whereas the non-surgical approaches often only have 6 months of controlled data, with only a few studies having controlled data up to 1 year. This limitation is particularly important in assessing the safety of the various treatment options, as the studies have reported the adverse events over different timepoints (peri-procedure and after the procedure) and with differing endpoints. For example, the valve trials have reported all serious adverse events including the incidence of a pneumothorax whereas the surgical trials have only reported prolonged pneumothoraces. Some of the non-surgical approaches do have some limited long-term data on safety, but not with a control group. A 10-year follow-up of a cohort of patients successfully treated with endobronchial valves between 2002 and 2004 has shown a significant survival benefit.[40] A further limitation is that not all the studies have collected all the parameters that we have evaluated, and four trials were excluded from the meta-analysis for lack of necessary data. The excluded studies of lung volume reduction surgery did broadly indicate patient benefit but did not report or collect data on change in residual volume and hence their data are available in some of the forest plots but not in the regression plots. The differing inclusion criteria from severity of emphysema to varying endpoints and duration of the studies also limits the strength of this analysis.

The outcomes evaluated in this meta-analysis are well standardised and were measured in a consistent manner across the studies. There was good consistency and low heterogeneity within the endoscopic trials and the individual approaches. The high overall heterogeneity for the outcome parameters (residual volume, FEV_1, and 6MWT) was primarily due to the inclusion of the surgical studies. Mortality rates even in the control group of the surgical series are higher than the other lung volume reduction interventions, indicating differences in the patient population. Furthermore, the surgical studies were all done at least a decade or two before the endoscopic studies, and differences in the standard of care and the severity of the disease in the participants might further contribute to the heterogeneity. The varying designs and outcome measures used in the surgical studies could also have contributed to the heterogeneity whereas the subsequent bronchoscopic studies appear to have more uniformity in their approach. Pooling the data across different timepoints with some studies reporting at 3 months after the interventions and others at 6 months or 12 months is a potential concern. In addition, some studies report 3 months after baseline and others 3 months after the last intervention. We are however reassured about the validity of our findings for several reasons: the consistency in the data across trials (ie, reductions in residual volume are associated with improved outcomes), the magnitude of benefit correlates with the degree of change in residual volume, the changes in all the individual trials are consistent across all the parameters measuring outcome (ie, in all the trials if there is a reduction of residual volume then there is an improvement in all measures of benefit and in none of the trials was there only one signal of benefit but a deterioration in the other parameters), and the long-term results albeit in the absence of a control arm also demonstrate consistency in the findings.[41-43] The bias assessment of the studies is discussed further in the appendix and the main limitation is that only one study was a double-blind sham controlled study.[24]

In conclusion, despite the limitations noted, the data confirm that lung volume reduction in patients with emphysema and hyperinflation is associated with benefits in lung function, quality of life, and exercise capacity, but increases adverse effects compared with controls. The relationship between degree of volume reduction and clinical benefit suggests that endobronchial valves and surgery should be considered first depending on the collateral ventilation status and patient choice. Endobronchial coils, AeriSeal, and vapour treatment should only be considered as second-line options.

Contributors

All authors contributed to the manuscript and approved the final version. WHvG and PLS designed the framework, did the data analysis, literature search, extracted data, and wrote the first draft. D-JS extracted data and revised the report. SVK created the bias charts.

Declaration of interests

WHvG reports a grant from Novartis (an institutional grant) and the European Respiratory Society (fellowship), outside the submitted work. D-JS reports grants, personal fees, non-financial support, and other (devices and treatments for clinical trials) from Pulmonx and PneumRx/BTG; and being an advisor for PneumRx/BTG. D-JS has been an investigator in trials of endobronchial valves, coils, AeriSeal, and the airway bypass procedure. FJH reports personal fees (advisory board and lecture fees) from Plumonx, PneumRx/BTG, Olympus, and Uptake. FJH has been an investigator in trials of endobronchial valves, coils, thermal ablation, AeriSeal, and the airway bypass procedure. SVK reports personal fees from Pulmonx (lecture fees) and Boston Scientific (consultancy fees), and other (institution reimbursement for trial expenses) from Pulmonx and PneumRx/BTG. SVK has been an investigator in trials of endobronchial valves, coils, and the airway bypass procedure. PLS reports personal fees (consultancy on scientific advisory boards) from Boston Scientific, CSA Medical, Olympus, PneumRX/BTG, Broncus, Medtronic, Creo Medical, and Nuvaira; and other (sponsorship for a bronchoscopy course at Imperial College) from ERBE, Cook Medical, Medtronic, Boston Scientific, Broncus, Pulmonx, Olympus, and PneumRx/BTG. PLS has been an investigator in trials of endobronchial valves, coils, thermal ablation, and the airway bypass procedure. WW declares no competing interests.

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