Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe Emphysema

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Original Investigation

Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe Emphysema
The RENEW Randomized Clinical Trial

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IMPORTANCE Preliminary clinical trials have demonstrated that endobronchial coils compress emphysematous lung tissue and may improve lung function, exercise tolerance, and symptoms in patients with emphysema and severe lung hyperinflation.

OBJECTIVE To determine the effectiveness and safety of endobronchial coil treatment.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial conducted among 315 patients with emphysema and severe air trapping recruited from 21 North American and 5 European sites from December 2012 through November 2015.

INTERVENTIONS Participants were randomly assigned to continue usual care alone (guideline based, including pulmonary rehabilitation and bronchodilators; n = 157) vs usual care plus bilateral coil treatment (n = 158) involving 2 sequential procedures 4 months apart in which 10 to 14 coils were bronchoscopically placed in a single lobe of each lung.

MAIN OUTCOMES AND MEASURES The primary effectiveness outcome was difference in absolute change in 6-minute-walk distance between baseline and 12 months (minimal clinically important difference [MCID], 25 m). Secondary end points included the difference between groups in 6-minute walk distance responder rate, absolute change in quality of life using the St George's Respiratory Questionnaire (MCID, 4) and change in forced expiratory volume in the first second (FEV_1; MCID, 10%). The primary safety analysis compared the proportion of participants experiencing at least 1 of 7 prespecified major complications.

RESULTS Among 315 participants (mean age, 64 years; 52% women), 90% completed the 12-month follow-up. Median change in 6-minute walk distance at 12 months was 10.3 m with coil treatment vs −7.6 m with usual care, with a between-group difference of 14.6 m (Hodges-Lehmann 97.5% CI, 0.4 m to ∞; 1-sided $P = .02$). Improvement of at least 25 m occurred in 40.0% of patients in the coil group vs 26.9% with usual care (odds ratio, 1.8 [97.5% CI, 1.1 to ∞]; unadjusted between-group difference, 11.8% [97.5% CI, 1.0% to ∞]; 1-sided $P = .01$). The between-group difference in median change in FEV_1 was 7.0% (97.5% CI, 3.4% to ∞; 1-sided $P < .001$), and the between-group St George's Respiratory Questionnaire score improved −8.9 points (97.5% CI, −∞ to −6.3 points; 1-sided $P < .001$), each favoring the coil group. Major complications (including pneumonia requiring hospitalization and other potentially life-threatening or fatal events) occurred in 34.8% of coil participants vs 19.1% of usual care ($P = .002$). Other serious adverse events including pneumonia (20% coil vs 4.5% usual care) and pneumothorax (9.7% vs 0.6%, respectively) occurred more frequently in the coil group.

CONCLUSIONS AND RELEVANCE Among patients with emphysema and severe hyperinflation treated for 12 months, the use of endobronchial coils compared with usual care resulted in an improvement in median exercise tolerance that was modest and of uncertain clinical importance, with a higher likelihood of major complications. Further follow-up is needed to assess long-term effects on health outcomes.

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Patients with advanced emphysema and severe lung hyperinflation have few treatment options to relieve dyspnea.[1,2] Lung volume reduction surgery has been shown to improve lung function, quality of life, and survival in the subset of patients with advanced, heterogeneous, upper lobe emphysema.[3] However, relatively few patients with emphysema undergo lung volume reduction surgery because a minority have an upper lobe–dominant heterogeneous pattern of destruction and postoperative complications can be severe.[3-5] A less invasive bronchoscopic approach targeting patients with heterogeneous emphysema involves segmental airway placement of unidirectional valves resulting in lobar collapse and clinical improvement; however, this approach is still investigational in North America and restricted to patients without interlobar collateral channels.[6-8] Patients with advanced homogeneous emphysema and/or presence of interlobar collateral ventilation have very limited treatment options, essentially lung transplantation or palliative support.

FEV_1 *forced expiratory volume in the first second*

MCID *minimal clinically important difference*

RV *residual volume*

TLC *total lung capacity*

Endobronchial coils, 10- to 15-cm nitinol wires that regain their preformed shape following deployment, are designed to compress emphysematous tissue, thus restoring elastic properties in adjacent lung tissue and improving ventilatory mechanical function. Endobronchial coils have been tested in patients with both heterogeneous and homogeneous lung destruction with or without incomplete interlobar fissures. Several small clinical trials preliminarily reported that coils may improve quality of life and exercise tolerance.[7,9-14] The recently published REVOLENS randomized clinical trial raised questions with respect to effectiveness, including durability of effect, optimal patient selection criteria, multiperformer technical feasibility, and importance of short- and long-term adverse events including pneumonia.[14] The RENEW trial was conducted to assess 1-year effectiveness and safety of endobronchial coils on exercise tolerance, quality of life, and lung function in patients with severe lung hyperinflation and advanced homogeneous or heterogeneous emphysema.

Methods

Study Oversight and Ethics

The institutional review boards at participating centers approved the study protocol (Supplement 1), which was overseen by an independent data monitoring committee. Patients were screened only after providing written informed consent. This study was conducted in compliance with the principles enunciated in the Declaration of Helsinki, the US clinical investigative laws, and those laws appropriate for participating centers in the European Union and Canada.

Study Participants

The trial enrolled patients aged 35 years or older with medically optimized emphysema (**Figure 1**). Participants were former smokers who recently completed pulmonary rehabilitation and/or were participating in exercise maintenance. Self-reported ethnicity and race were collected as fixed categories per Clinical Data Interchange Standards Consortium standards to appropriately adjust lung function and to account for any potential differences by treatment. Key inclusion criteria included postbronchodilator forced expiratory volume in the first second (FEV_1) of 45% predicted or less, total lung capacity (TLC) of more than 100% predicted, and residual volume (RV) of at least 225% predicted. The RV threshold was lowered to at least 175% predicted following enrollment of 169 patients to address the effectiveness and safety of endobronchial coils in a broader patient population. Severe bronchitis/bronchiectasis, comorbidities potentially affecting trial completion, and significant reversible airflow obstruction (postbronchodilator response >20%) excluded patients from enrollment (eAppendix in Supplement 2).

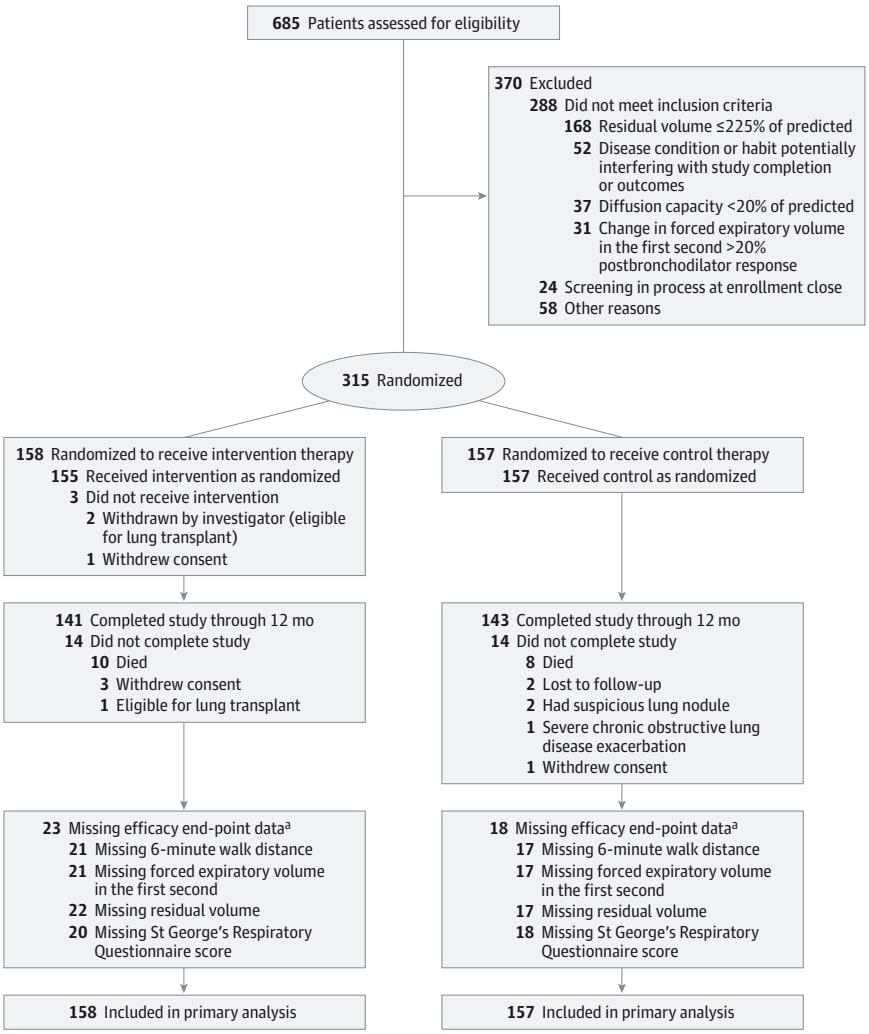
Trial Design

This multicenter, randomized, assessor-blinded study compared outcomes between treatment and control groups at 12 months. A radiology core laboratory reviewed scans for eligibility, identified lobes for treatment, and classified the type of emphysema (heterogeneous or homogeneous) (eFigure 1 in Supplement 2) using a semiquantitative visual assessment (Supplement 1). Upper lobes were preferentially targeted in patients with homogeneously distributed disease based on physiologic modeling, preliminary surgical experience, and a feasibility trial.[12,15] Blinded block randomization (block size of 4) stratified by type of emphysema occurred on a 1:1 basis between usual care (control group) and usual care plus treatment with endobronchial coils (PneumRx Inc) using a computerized, automated system (Datatrak IWRS) directed by an independent contractor (Pharm-Olam International).

Usual care was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[2] guidelines, whereby treatment was optimized in cooperation with the treating physician at the pretreatment visit. Each participant was encouraged to use inhaled long-acting bronchodilators with or without inhaled corticosteroids. Current influenza and pneumococcus vaccinations were encouraged. Participants were required to complete a pulmonary rehabilitation program within 6 months or be performing maintenance rehabilitation prior to baseline testing. During the posttreatment period, medication adjustment for treatment of exacerbations was permitted; however, changes to the medical regimen were otherwise discouraged and participants were encouraged to continue maintenance rehabilitation.

The treatment group, in addition to receiving usual care, underwent implantation of 10 to 14 coils under fluoroscopic guidance via bronchoscopy (eFigures 2 and 3 in Supplement 2). The choice of moderate sedation or general anesthesia was determined by the investigator. The bronchoscopist advanced the bronchoscope to the ostium of the target subsegmental airway and then advanced a catheter with a guide wire into the bronchial segment of the treatment lobe to

Figure 1. Participant Flow in the RENEW Randomized Clinical Trial



[a] Most patients with missing values were included in all categories of missing data.

within a minimum of 3 cm of the pleural surface. The selected coil length (100, 125, or 150 mm) was based on subsegmental airway length. Two sequential single-lobe treatments of contralateral upper or lower lobes were performed 4 months apart (based on a conservative estimate of the recovery time needed after a bronchoscopy for this severely affected patient population) (Supplement 1).

Effectiveness Outcomes

All end points compared baseline data vs results at 12 months after first treatment. Participants were not blinded, although walk and spirometry measurements were obtained using a blinded assessor.

The primary effectiveness variable was the difference in absolute change in 6-minute walk distance between baseline and 12-month visit. Secondary end points included 6-minute walk distance response, defined as a 25-m minimal clinically important difference (MCID)[16] in 6-minute walk distance; mean percent change in FEV_1 (MCID, 10%)[17]; and mean absolute difference in St George's Respiratory Questionnaire score (range, 0-100, with higher scores indicating worse quality of life). Six-minute walk testing, spirometry, and physiologic testing were performed using established standards, with participants carrying their oxygen at the prescribed flow rate when necessary.[18-21]

Other exploratory effectiveness end points included St George's Respiratory Questionnaire response, defined using a 4-point or greater score reduction as the MCID[22]; mean absolute difference in RV (MCID, 0.35 L)[23] measured by body plethysmography; and mean absolute difference in RV/TLC.

Safety Outcome Assessment

The primary safety analysis reports the proportion of participants in the coil and usual care groups who experienced at least 1 major complication within 12 months after baseline (eTable 1 in Supplement 2). All major complications were adjudicated by an independent clinical events committee in an unblinded fashion to facilitate imaging review (eAppendix in Supplement 2).

Some participants experienced a focal lung tissue response to coil treatment, identified on chest imaging and

characterized during the course of this trial as coil-associated opacity (eFigure 4 in Supplement 2). The RENEW data monitoring committee adjudicated the investigator-reported pneumonia adverse events and determined that some of these events were misclassified and represented coil-associated opacity.

Statistical Analysis

Based on previous studies, a sample size of 315 was selected to provide greater than 95% power to detect a treatment difference in effectiveness, assuming 5% lost to follow-up and treatment difference in change in 6-minute walk distance of 59 m (SD, 80 m) (the difference from baseline observed in early feasibility trials) and in FEV_1 of 0.05 L (SD, 0.10 L) using a 1-sided *t* test at α = .025.[6,24] Comparisons of the coil group vs usual care in primary and secondary effectiveness end points were tested using analysis of covariance (or nonparametric rank analysis of covariance in the presence of significant skewness) and logistic regression (for 6-minute walk distance responder end point) controlling for the covariates of corresponding baseline value, analysis center, and emphysema status in an intention-to-treat (ITT) analysis. Missing values were imputed 50 times using the Markov chain Monte Carlo method of multiple imputation. Mean between-treatment differences adjusted for covariates and, for data that were significantly skewed, Hodges-Lehmann median between-treatment differences adjusted for baseline were reported with associated 97.5% confidence intervals. The proportion of responders, odds ratios (ORs), and 97.5% CIs adjusted for covariates are reported for responder end points. This study was designed as a pivotal study to support regulatory product registration by testing the superiority in effectiveness of the coil group over usual care against the null hypothesis of equality or inferiority. Therefore, all effectiveness analyses were 1-sided tests of superiority at the α = .025 significance level comparing endobronchial coil treatment vs usual care. The Hochberg step-up procedure was used to control the study-wise α for multiple comparisons in secondary end points.[25-28]

Other effectiveness end points tested for statistical significance included St George's Respiratory Questionnaire response analysis and mean absolute differences in RV and RV/TLC and were not adjusted for multiple comparisons. Post hoc analyses compared effectiveness between the coil group and usual care separately by prespecified subgroups for type of emphysema and baseline RV measurement using the same methods as the primary and secondary effectiveness analyses.

Between-group comparisons at baseline were based on analysis of variance with a factor for investigational site, stratified Cochran-Mantel-Haenszel test, or Fisher exact test. Between-treatment comparison of proportions of participants experiencing at least 1 major complication were analyzed using a 2-sided Fisher exact test. All analyses were conducted using SAS version 9.3 (SAS Institute Inc). For detailed information about study methods, see the eAppendix in Supplement 2 and the statistical analysis plan in Supplement 3.

Results

Participants

Study enrollment began in December 2012, and the final participant completed 12-month follow-up in November 2015. Six hundred eighty-five patients were screened at 34 sites; 315 patients were randomized to receive either endobronchial coil treatment (n = 158) or usual care (control; n = 157) at 21 North American and 5 European sites. Twelve-month follow-up was completed by 90.2% of participants (Figure 1). Three participants randomized to coil treatment withdrew before the intervention. Baseline characteristics were similar between groups (**Table 1**). This population was notable for the severity of airflow obstruction and hyperinflation, the high prevalence of comorbidities, and the predominance of homogeneous emphysematous destruction on chest computed tomography. Seventy-six percent of coil vs 71% of usual care participants had "very severe" spirometric disease based on the GOLD 4 guidelines. Extreme hyperinflation was present, with a mean RV of 246% (SD, 39%) predicted in the coil group vs 245% (SD, 39%) predicted in usual care participants. The coil group had a median of 2.0 (interquartile range [IQR], 1.0-4.0) nonpulmonary major comorbidities vs 2.0 (IQR, 1.0-3.0) in the usual care group (eTable 3 and eFigure 5 in Supplement 2); 43% vs 41% received long-term oxygen and 31% vs 27% had been hospitalized in the year prior to enrollment in the coil and usual care groups, respectively. Emphysema distribution on computed tomography was similar between groups (77% with homogeneous and 23% with heterogeneous patterns) (eFigure 1 in Supplement 2).

Procedures

Bilateral treatment was completed in 144 of 158 participants assigned to coil treatment; 11 participants completed only unilateral treatment due to death (n = 3) or clinical worsening (n = 8). Among the treatments, 84.2% were in upper lobes and 15.8% were in lower lobes, with a median insertion of 10 and 12 to 13 coils, respectively (eTable 4 in Supplement 2). Procedure duration was 42 minutes (SD, 16 minutes) with a median hospital stay of 1 night (range, 0-15 nights).

Primary and Secondary 6-Minute Walk Distance Effectiveness End Points (ITT Population)

The median prespecified primary effectiveness end point of change in 6-minute walk distance at 12 months was 10.3 m (IQR, −33.0 to 45.0 m) in coil-treated patients vs −7.6 m (IQR, −40.0 to 26.0 m) for usual care, with a median between-group difference of 14.6 m (Hodges-Lehmann 97.5% CI, 0.4 m to ∞; 1-sided *P* = .02) (**Table 2**, **Figure 2**, and eTable 5A in Supplement 2). The secondary effectiveness end point of 6-minute walk distance response rate revealed 40.0% vs 26.9% favoring the coil group (OR, 1.8 [97.5% CI, 1.1 to ∞]; unadjusted between-group difference, 11.8% [97.5% CI, 1.0% to ∞]; 1-sided *P* = .01) A small subset of 12 participants in the coil group and 8 participants in the usual care group reported a 12-month decline of greater than 100 m (4 times the MCID).

Table 1. Baseline Demographics and Disease Characteristics[a]

Characteristics	Coil Treatment (n = 158)	Usual Care (n = 157)
Age, y	63.4 (8.05)	64.3 (7.76)
Female, No. (%)	86 (54.4)	79 (50.3)
Body mass index[b]	24.9 (4.6)	24.5 (4.9)
Hispanic/Latino ethnicity, No. (%)	1 (0.6)	2 (1.3)
Race, No. (%)		
Black or African American	6 (3.8)	4 (2.5)
White	151 (95.6)	152 (96.8)
Asian/other	1 (0.6)	1 (0.6)
GOLD stage 4, No. (%)	120 (75.9)	112 (71.3)
BODE score[33c]	5.96 (1.26)	6.03 (1.32)
Score of 7-10, No. (%)	51 (32.3)	52 (33.1)
Smoking history, pack-years[d]	50.7 (27.9) [n=157]	50.3 (23.5)
No. of nonrespiratory comorbidities[e]	2.6 (2.0)	2.3 (1.8)
Median (IQR)	2.0 (1.0-4.0)	2.0 (1.0-3.0)
≥4 Baseline total nonrespiratory comorbidities, No. (%)	45 (28.5)	39 (24.8)
Receiving continuous oxygen, No. (%)	68 (43.0)	64 (40.8)
Flow rate, L/min	2.5 (0.9)	2.3 (0.9)
Hospital visits, all causes, 0-12 mo prior to baseline, No. (%)	49 (31.0)	43 (27.4)
Baseline inhaler category, No. (%)		
Long-acting β agonist and/or long-acting muscarinic antagonist plus inhaled corticosteroid	136 (86.1)	141 (89.8)
Long-acting β agonist and/or long-acting muscarinic antagonist	15 (9.5)	13 (8.3)
Short-acting β agonist and/or short-acting muscarinic antagonist alone	2 (1.3)	2 (1.3)
None	5 (3.2)	1 (0.6)
6-Minute walk distance, m	312.0 (79.1)	302.7 (79.3)
Median (IQR)	318.3 (251.5-361.0)	300.0 (244.0-356.6)
Type of emphysema, No. (%)		
Heterogeneous	36 (22.8)	36 (22.9)
Homogeneous	122 (77.2)	121 (77.1)
FVC, L	2.47 (0.69)	2.46 (0.75)
FVC, % predicted	67.8 (14.3)	67.4 (15.0)
FEV_1, L	0.71 (0.20)	0.72 (0.21)
FEV_1, % predicted	25.7 (6.3)	26.3 (6.7)
FEV_1/FVC, %	28.8 (6.8)	29.9 (6.8)
RV, L	5.28 (1.06)	5.33 (1.15)
RV, % predicted	245.9 (39.1)	244.5 (38.7)
TLC, L	7.87 (1.35)	7.92 (1.56)
TLC, % predicted	139.2 (15.6)	138.8 (16.1)
RV/TLC, %	67.1 (6.7)	67.3 (6.3)
DLCO, mL/min/mm Hg	8.12 (2.86)	8.15 (2.80)
DLCO, % predicted	34.1 (10.5)	34.5 (10.7)
St George's Respiratory Questionnaire total score[f]	60.1 (12.8)	57.4 (14.8)
mMRC Dyspnea Scale score, No. (%)		
0/1	0	0
2	54 (34.2)	56 (35.7)
3	69 (43.7)	70 (44.6)
4	35 (22.2)	31 (19.7)
$Paco_2$, mm Hg	41.6 (5.6)	41.5 (5.3)
Pao_2, mm Hg	68.0 (10.5)	69.2 (10.9)

Abbreviations: BODE, body mass index, airflow obstruction, dyspnea, and exercise; DLCO, single-breath diffusion capacity for carbon monoxide; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV, forced expiratory volume; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; mMRC, Modified Medical Research Council; RV, residual volume; TLC, total lung capacity.

[a] Data are expressed as mean (SD) unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Scores range from 0 to 10, with higher scores indicating worse prognosis.

[d] One coil group participant had a history of smoking but had missing smoking pack-year data.

[e] See eTable 3 in Supplement 2 for the list of 15 nonrespiratory comorbidities included in this calculation.

[f] Scores range from 0 to 100, with higher scores indicating worse quality of life.

Table 2. Effectiveness End Points for the Intention-to-Treat Population[a]

End Point	Coil Treatment (n = 158) At 12 mo	Coil Treatment (n = 158) Within-Group Change or Rate[b]	Usual Care (n = 157) At 12 mo	Usual Care (n = 157) Within-Group Change or Rate[b]	Between-Group Difference for Coil Treatment vs Usual Care (97.5% CI)[b]	*P* Value[c]
Primary end point						
Change in 6-minute walk distance, median (IQR), m[d]	319.7 (242.9 to 387.7)	10.3 (−33.0 to 45.0)	300.0 (233.2 to 350.0)	−7.6 (−40.0 to 26.0)	14.6 (0.4 to ∞)	.02[e]
Secondary end points						
6-minute walk distance response rate, No. (%) [95% CI][f]	NA	63 (40.0) [31.0 to 49.0]	NA	42 (26.9) [18.9 to 35.0]	11.8 (1.0 to ∞)[g] OR: 1.8 (1.1 to ∞)[h]	.01[i]
Change in FEV_1, median (IQR), %[d]	0.71 (0.58 to 0.88)	3.8 (−6.3 to 16.1)	0.68 (0.54 to 0.82)	−2.5 (−8.9 to 4.4)	7.0 (3.4 to ∞)	<.001[e]
Change in St George's Respiratory Questionnaire score, mean (95% CI)[j]	51.9 (49.5 to 54.4)	−8.1 (−10.2 to −6.0)	58.4 (55.9 to 60.9)	0.8 (−1.2 to 2.9)	−8.9 (−∞ to −6.3)	<.001
Other end points						
St George's Respiratory Questionnaire response rate, No. (%) [95% CI][f]	NA	97 (61.2) [50.9 to 71.4]	NA	43 (27.7) [18.6 to 36.8]	31.6 (20.5 to ∞)[g] OR: 4.1 (2.4 to ∞)[h]	<.001[i]
Change in RV, mean (95% CI), L[j]	4.95 (4.75 to 5.14)	−0.41 (0.57 to −0.25)	5.28 (5.07 to 5.49)	−0.10 (−0.26 to 0.06)	−0.31 (−∞ to −0.11)	.001
Change in RV/TLC, mean (95% CI), %[j]	63.6 (62.4 to 64.8)	−4.0 (−5.1 to −2.9)	67.3 (66.2 to 68.4)	−0.5 (−1.6 to 0.6)	−3.5 (−∞ to −2.1)	<.001

Abbreviations: FEV_1, forced expiratory volume in the first second; IQR, interquartile range; NA, not applicable; OR, odds ratio; RV, residual volume; TLC, total lung capacity.

[a] The full intention-to-treat analysis set comprised all patients who were randomized, with multiple imputation for missing values using the Markov Chain Monte Carlo method.

[b] Response rates are adjusted for emphysema status and analysis center, and corresponding baseline values from logistic regression are presented as No. (%) of patients and odds ratios between treatment groups. The frequency of responders was estimated from multiple imputation results. For 6-minute walk distance, response rates are not adjusted for analysis center because of incomplete model convergence (eAppendix in Supplement 2). Between-treatment differences in response rates are not adjusted for covariates.

[c] By analysis of covariance with factors of treatment, emphysema status, analysis center, and corresponding baseline value, unless otherwise specified.

[d] Median between-treatment differences adjusted for baseline using the Hodges-Lehmann estimator. The nonparametric median between-treatment difference is not the simple between-treatment difference in medians.

[e] By nonparametric rank analysis of covariance with factors of treatment, emphysema status, analysis center, and corresponding baseline value. The Shapiro-Wilk test indicated nonnormality of residuals ($P < .001$).

[f] Response in 6-minute walk distance was defined as an increase of at least 25 meters. Response in St George's Respiratory Questionnaire score was defined as a decrease of at least 4 points. The response rate represents the proportion of patients achieving these minimal clinically important differences.

[g] Unadjusted between-treatment difference in response rate.

[h] Adjusted OR.

[i] By logistic regression with factors of treatment, emphysema status, analysis center, and corresponding baseline value. For 6-minute walk distance response, analysis center was not included as a factor because of incomplete model convergence (eAppendix in Supplement 2).

[j] Mean within-group change and between-treatment difference adjusted for covariates from analysis of covariance.

Other Secondary Effectiveness End Points (ITT Population)

The mean between-group difference in absolute change in the St George's Respiratory Questionnaire total score was −8.9 points (97.5% CI, −∞ to −6.3 points; 1-sided $P < .001$), predominantly achieved through improvement in the coil group. The change in FEV_1 was 3.8% (IQR, −6.3% to 16.1%) in coil-treated patients vs −2.5% (IQR, −8.9% to 4.4%) for usual care, with a between-group difference estimate of 7.0% (Hodges-Lehmann 97.5% CI, 3.4% to ∞; 1-sided $P < .001$) (Table 2, Figure 2, and eTable 5B in Supplement 2).

Exploratory Effectiveness End Points (ITT Population)

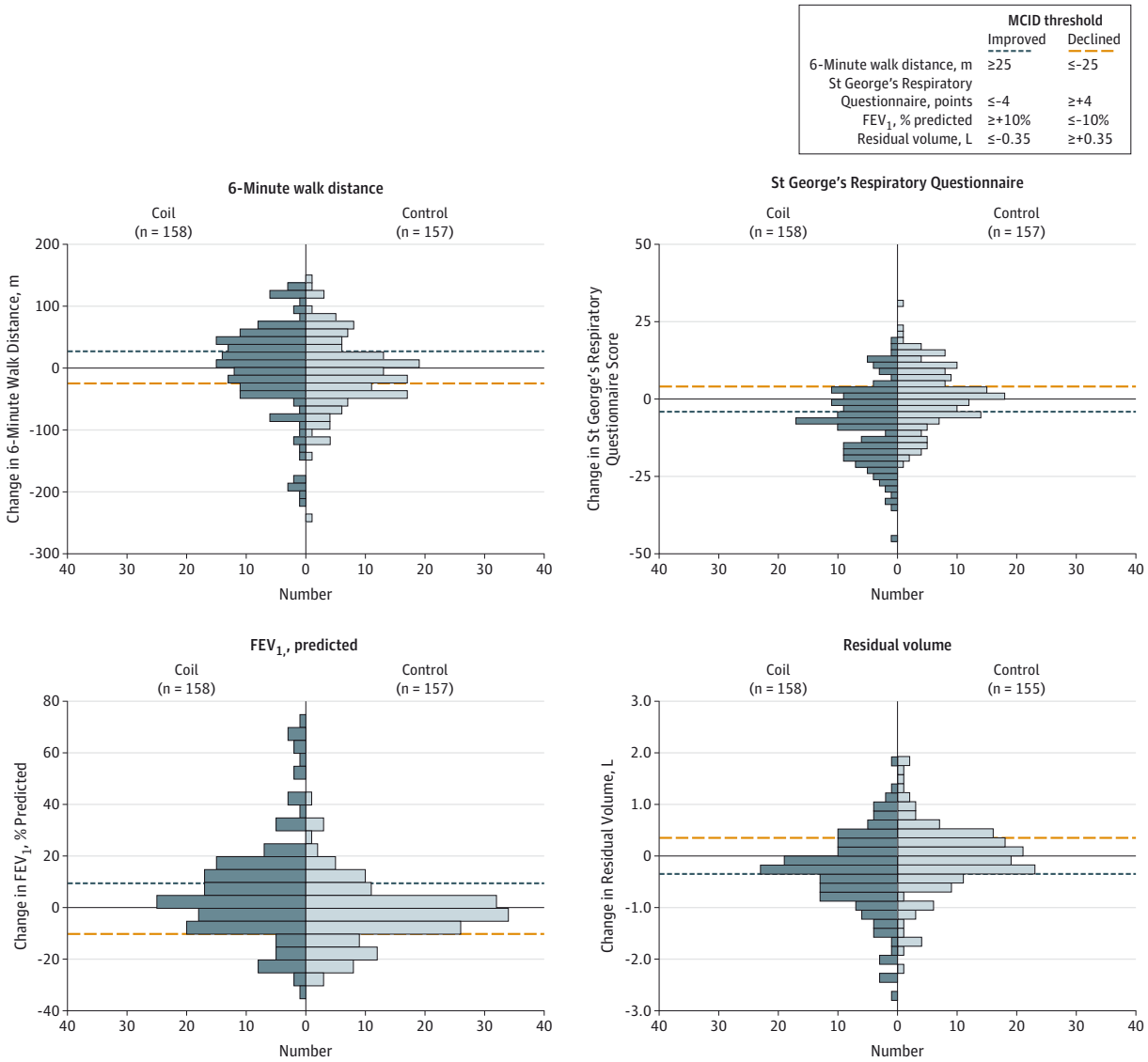
The St George's Respiratory Questionnaire response analysis demonstrated significantly more participants with meaningful improvement in the coil group (61.2%) vs usual care (27.7%); for an unadjusted between-group difference of 31.6% (97.5% CI, 20.5% to ∞; $P < .001$). Resting lung hyperinflation decreased in the coil group relative to usual care, represented by between-group differences for RV of −0.31 L (97.5% CI, −∞ to −0.11 L; 1-sided $P = .001$) and for RV/TLC of −3.5% (97.5% CI, −∞ to −2.1%; 1-sided $P < .001$) (Table 2 and Figure 2). Descriptive results of primary, secondary, and exploratory outcome end points at interim time points are presented in eTable 6 in Supplement 2.

Prespecified subgroup analyses were performed to assess response stratified by degree of air trapping (RV ≥225% vs <225% predicted) and by heterogeneous vs homogeneous emphysema distribution. The RV ≥225% group and the heterogeneous emphysema group each had greater magnitudes of treatment response in all primary and secondary effectiveness end points compared with respective groups with RV of less than 225% and homogeneous destruction, although the study was not powered to test differences between subgroups.

Post Hoc Analyses (ITT Population)

Participants were stratified into 4 subgroups based on the prespecified characteristics associated with lung hyperinfla-

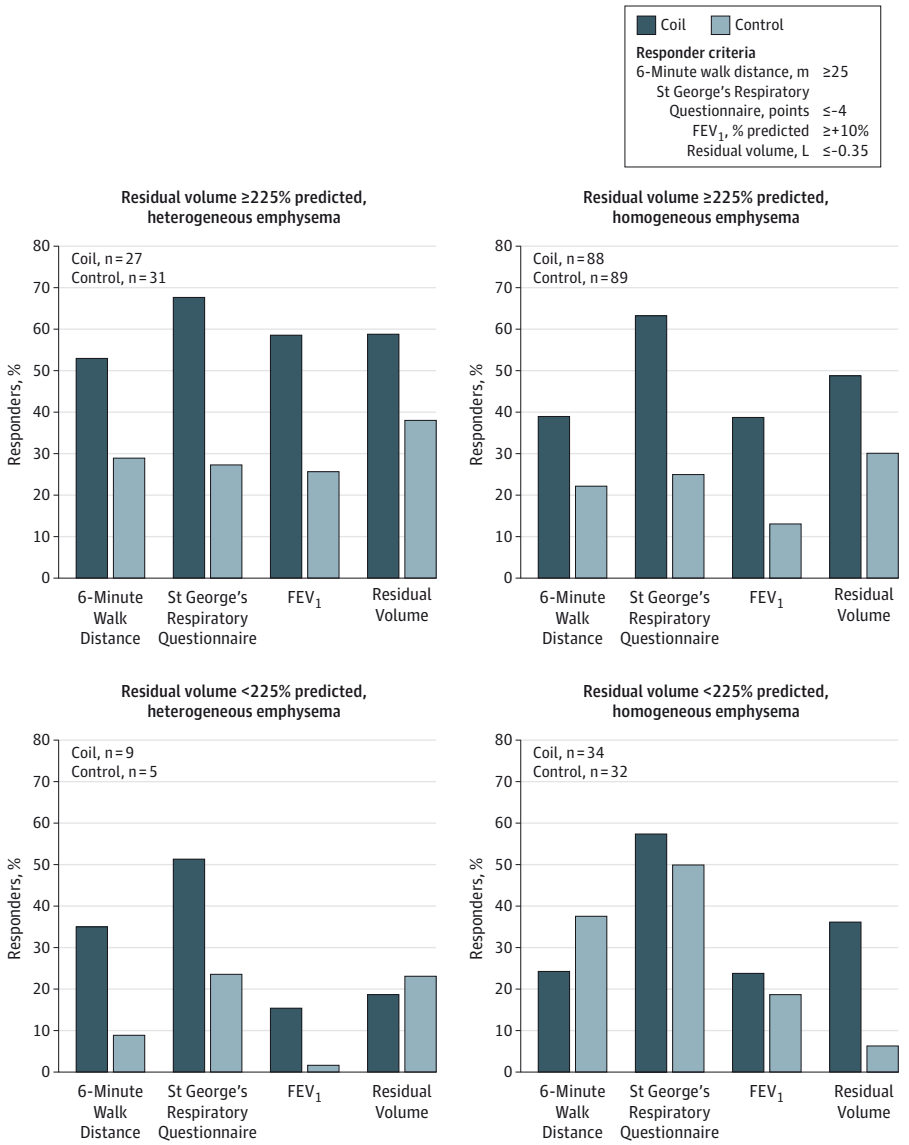
Figure 2. Distribution of Effectiveness End Points for the Intention-to-Treat Analysis for Key Outcome Measures



For all measures, the response rates were higher in the endobronchial coil group based on reported minimal clinically important differences (MCIDs).[16,17,19,23] In contrast, the proportion of participants declining an MCID equivalent was numerically greater for all measures in the usual care group. Note the small number of very significant 6-minute walk distance decliners, particularly in the coil group, that lowered the mean response. All improver and decliner rates were calculated with logistic regression with data from the full intention-to-treat analysis set, with multiple imputation. For each histogram, the bin interval was set at half of the MCID for that measure. In each bin, the data are equal to or greater than the lower limit and less than the upper limit of the bin. The bin widths for each histogram are for residual volume, 175 mL; forced expiratory volume in the first second (FEV_1), 5%; 6-minute walk distance, 12.5 m; and St George's Respiratory Questionnaire, 2 points.

tion and emphysema distribution (**Figure 3** and eTable 7 in Supplement 2). Participants with both favorable attributes (RV ≥225% predicted and heterogeneous distribution) exhibited superior treatment responses (median 6-minute walk distance, +29.1 m, FEV_1 change +12.3%, and mean St George's Respiratory Questionnaire change, −10.1-point difference in the coil group relative to usual care), while those with less air trapping (RV <225% predicted) and homogeneous disease exhibited between-treatment differences of a median −16.7 m for 6-minute walk distance, a median FEV_1 change of 3.5%, and a mean St George's Respiratory Questionnaire change of−3.3 points. The subgroup with homogeneous disease but greater air trapping (RV ≥225% predicted) had a favorable treatment response in all end points (median 6-minute walk distance, +20.7 m; median FEV_1 change, +8.3%; and mean St George's Respiratory Questionnaire change, −10.0-point difference in the coil group relative to usual care). The group expressing heterogeneous disease with RV of less than 225% predicted was too small for data to be interpreted but demonstrated a mixed response. The RV threshold used, albeit prespecified, was arbitrarily chosen, and a post hoc sensitivity analysis

Figure 3. Intention-to-Treat Analysis Response Rates for 4 Effectiveness Measures in Subgroups Stratified by Emphysema Distribution and Degree of Air Trapping



The greatest and most consistent improvements occurred in the residual volume ≥225% subgroups, particularly those with heterogeneous disease. Response rates were calculated with logistic regression with data from the full intention-to-treat analysis set, with multiple imputation. FEV_1 indicates forced expiratory volume in the first second.

(eTable 8 in Supplement 2) indicated that 200% predicted may be a more sensitive response threshold.

The presence of comorbidities reduced the 12-month 6-minute walk distance outcome despite lung function improvements. Compared with usual care, coil-treated participants with 4 or more comorbidities (eTable 9 in Supplement 2) had a 1.1-m relative decline in 6-minute walk distance despite significant reduction in RV, in contrast to participants with 3 or fewer comorbidities, who had a relative 21.0-m improvement in 6-minute walk distance. Participants who exhibited cardiac-related comorbidity also demonstrated a decline in 6-minute walk distance despite improvements in lung function (eTable 10 in Supplement 2). The RV <225% subgroup had the greatest prevalence of cardiac disease and averaged more comorbidities than the subgroup with greater severity of air trapping (RV ≥225%) (eTable 11 in Supplement 2).

Safety End Points

There was no difference in deaths in the coil group (n = 10; 6.5%) vs the usual care group (n = 8; 5.1%) at 1 year (eTable 12 in Supplement 2). Total major complications occurred more frequently in the coil group (n = 54; 34.8%) vs the usual care group (n = 30; 19.1%; $P = .002$) (**Table 3**). This difference was largely due to increased lower respiratory tract infections (18.7% vs 4.5%; $P < .001$). There were 2 cases of hemoptysis requiring intervention in the coil group.

There were 2 direct procedure-associated deaths; one patient died during the initial coil procedure because of pulmonary hemorrhage and respiratory failure leading to

Table 3. Major Complications and Important Serious Adverse Events Through 12 Months in the Safety Population

	No. (%) of Patients[a]			
	Coil Treatment (n = 155)	Usual Care (n = 157)	Difference, % (95% CI)[b]	*P* Value[c]
Major complications				
Any	54 (34.8)	30 (19.1)	15.7 (5.9 to 25.2)	.002
Death	10 (6.5)	8 (5.1)	1.4 (−4.1 to 7.0)	.64
Pneumothorax requiring extended chest tube drainage >7 d	1 (0.6)	1 (0.6)	0.0 (−2.9 to 3.0)	>.99
Hemoptysis requiring intervention	2 (1.3)	0	1.3 (−1.3 to 4.6)	.25
COPD exacerbation requiring extended hospitalization >7 d	18 (11.6)	13 (8.3)	3.3 (−3.4 to 10.2)	.35
Lower respiratory tract infection, including pneumonia, requiring intravenous antibiotics and/or corticosteroids	29 (18.7)	7 (4.5)	14.3 (7.3 to 21.5)	<.001
Respiratory failure requiring mechanical ventilation	6 (3.9)	6 (3.8)	0.0 (−4.7 to 4.8)	>.99
Unanticipated bronchoscopy	0	0	NA	
Other important serious adverse events[d]				
Pneumonia[e]	31 (20.0)	7 (4.5)	15.5 (8.4 to 22.9)	<.001
COPD exacerbation	43 (27.7)	32 (20.4)	7.4 (−2.1 to 16.7)	.15
Hemoptysis	4 (2.6)	0	2.6 (−0.3 to 6.4)	
Pneumothorax[f]	15 (9.7)[f]	1 (0.6)	9.0 (4.3 to 14.7)	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; NA, not applicable.

[a] Patients were counted once at most for an event type.

[b] Confidence intervals calculated using the Newcombe method.

[c] Difference in proportions compared using the Fisher exact test.

[d] The standard definition of serious adverse events includes events that are life-threatening or result in death; require patient hospitalization or prolongation of existing hospitalization; result in persistent or significant disability/incapacity; or require intervention to prevent permanent impairment or damage.

[e] This category combines infectious pneumonia and a localized, noninfectious tissue response identified during the study and adjudicated by the data monitoring committee to be a coil-associated opacity.

[f] Three additional pneumothorax events were reported but did not meet serious adverse event criteria; thus, the total pneumothorax rate in the treatment group was 11.6%.

cardiac arrest, and another patient died of respiratory failure 6 days following the second coil procedure. Overall, serious adverse events were similar between the 2 study groups except with respect to pneumonia (coil group, n = 31 [20%] vs usual care, n = 7 [4.5%]; $P < .001$) and pneumothorax (coil group, n = 15 [9.7%] vs usual care, n = 1 [0.6%]; $P < .001$). Serious adverse events related to chronic obstructive pulmonary disease exacerbations tended to be more frequent with coil treatment (n = 43; 27.7%) vs usual care (n = 32; 20.4%; $P = .15$) but returned to the level of the usual care group in the 9- to 12-month window (eTables 13 and 14 in Supplement 2).

Post Hoc Safety Analysis

Reported pneumonia events adjudicated by the data monitoring committee were determined to be noninfectious coil-associated opacity in 14 of 40 adjudicable cases (35%) (eTable 15 in Supplement 2). Coil participants with adjudicated coil-associated opacity exhibited superior 12-month effectiveness outcomes compared with patients without coil-associated opacities or pneumonia; the median 6-minute walk distance response rate was 47.8% (95% CI, 20.1%-75.6%) vs 38.9% (95% CI, 27.6%-50.2%) and the median FEV_1 change was 10.8% (IQR, 3.5%-22.7%) vs 2.2% (IQR, −7.8% to 14.5%), respectively (eTable 16A in Supplement 2). This contrasts with usual care participants with pneumonia (n=13), who had worsening of all measures, specifically a 7.8% 6-minute walk distance response rate, with a median 6-minute walk distance decline of −25 m (IQR, −66 to −0.6 m) and a median FEV_1 change of −2.9% (IQR, −11.5% to −1.6%) (eTable 16B in Supplement 2).

Discussion

In a multicenter trial, bilateral endobronchial coil treatment in patients with severe lung hyperinflation and homogeneous or heterogeneous emphysema resulted in durable but modest increases in 6-minute walk distance of uncertain clinical importance, along with improved expiratory flow rate averaging less than a clinically important difference, reduced air trapping, and overall clinically important improvements in quality of life. These improvements were associated with a higher rate of pneumothorax, pneumonia, hemoptysis, and chronic obstructive pulmonary disease exacerbations immediately following the coil procedure and for several months after coil implantation.

This study addresses a group of patients with advanced predominantly homogenous emphysema who have few treatment options. More than 75% of participants had a homogeneous emphysema distribution that would exclude them from consideration for surgical lung reduction and from investigational endobronchial valve treatment options.[3,6,8,29] The improvement in lung function associated with quality-of-life improvement greater than 2 times the established MCID at 1-year follow-up was consistent

with reports from several smaller observational and randomized studies.[7,9-14] On the other hand, the difference in 6-minute walk distance of 14.6 m, while statistically significant, was modest and less than the established MCID of 25 m. Furthermore, the lower confidence limit suggests the responder difference between the 2 groups could be as low as 1%. Our results compare with the 21-m 6-minute walk distance improvement reported in the recent REVOLENS randomized trial at the primary 6-month end point and contrast with greater responses observed in previous observational studies.[24] In this trial, the 6-minute walk distance response was skewed such that a significantly greater proportion of clinically important responses in the coil group relative to usual care was balanced by a small proportion of severe declines in both the coil and usual care groups that lowered the mean and median response differences (Figure 2). The variable improvement in walk distance was in part related to this study's less restrictive inclusion criteria; participants with less air trapping (RV <220% predicted) were excluded from REVOLENS. The baseline walk distance, degree of hyperinflation, prevalence of prior hospitalization, and long-term oxygen use in this trial reflect greater impairment than in those enrolled in prior surgical and endobronchial volume reduction trials.[3,6,8] One third of this study's participants would qualify for lung transplantation based on their BODE (body mass index, airflow obstruction, dyspnea, and exercise) scores of 7 or higher.[30] Furthermore, the inclusion of participants with multiple comorbidities in this study's cohort (eTable 3 and eFigure 5 in Supplement 2) and in REVOLENS likely attenuated the 6-minute walk distance response in both studies despite improvements in lung function.

Although adverse events including pneumothorax and hemoptysis were more common in the coil group, the events generally occurred in the periprocedural and postprocedural periods and events returned toward baseline in the months following the second procedure, as has been described in previous series.[31] The 15% excess incidence of pneumonia in the coil group vs usual care was nearly identical to that reported in the REVOLENS trial.[14] This study has expanded the understanding of these pneumonia-classified events by identifying noninfectious coil-associated opacities that represent more than one-third of events. These coil-associated opacities appear to represent coil-induced inflammatory or lung structural changes induced by stress forces from the coils on lung parenchyma.

Treated participants reporting a pneumonia or coil-associated opacity event had better outcomes at 12 months than participants not experiencing these events, in contrast to usual care participants with pneumonia, who did very poorly, suggesting a causal and mechanistic difference between the study groups (eTable 16 in Supplement 2). The planned follow-up of the RENEW cohort for 5 years will better elucidate the long-term response and safety profile of treatment.

We have identified prespecified and mechanistically plausible subgroups defined by degree of air trapping and disease distribution that associate with greater treatment response (Figure 3 and eTable 7 in Supplement 2). The variation in response within these subgroups, given the exploratory nature of this analysis, must be interpreted with caution but offers preliminary evidence to support future validation of these measures to enhance patient selection.

There are limitations in the interpretation of this study's results. The difficulty in implementing a sham control group prevented effective blinding of participants and may have influenced subjective outcomes such as the St George's Respiratory Questionnaire. On the other hand, the St George's Respiratory Questionnaire, which was the most responsive of this study's effectiveness measures, tracked with more objective physiologic measures in the subgroup analysis (Figure 3). Another limitation was the use of 6-minute walk distance as the primary outcome measure. While 6-minute walk distance can integrate the functional effects of complex physiologic changes in lung mechanics such as reductions in hyperinflation and air trapping, which may not always be reflected in more conventional expiratory flow measures, the variance in the measure and ceiling effect can limit the responsiveness of the tool. Inclusion of a practice walk at all evaluation time points or greater vigilance to maintaining rehabilitation following randomization might have increased the responsiveness of 6-minute walk distance and lessened the baseline decline across study groups.[32] Despite these limitations, however, the broadness of this study's inclusion criteria, the large number of enrolled patients, the longer duration of follow-up, and the inclusion of multiple centers and coil implanters provide insights regarding the potential clinical utility of this therapy.

Conclusions

Among patients with emphysema and severe hyperinflation treated for 12 months, the use of an endobronchial coil compared with usual care resulted in an improvement in median exercise tolerance that was modest and of uncertain clinical importance, with a higher likelihood of major complications. Further follow-up is needed to assess long-term effects on health outcomes.

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