Predictors of Response to Endobronchial Coil Therapy in Patients with Advanced Emphysema

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DJS, PLS, FS, GC, AM, ASL, GSB and FJH together designed and executed this analysis. All authors contributed to patient recruitment, follow-up, and revisions of this manuscript. DS, JH, JC, ASL, GSB and PLS drafted the concept and led the writing of the paper, they all had personally reviewed the efficacy data, understand the statistical methods employed for the analysis, and confirmed understanding of this analysis, that the methods are clearly described and that they are a fair way to report the results.

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Abbreviation list

6MWT	-	6-minute walk test
6MWD	-	6-minute walk distance
COPD	-	chronic obstructive pulmonary disease
FEV ₁	-	forced expiratory volume in one second
HRCT	-	high resolution computed tomography
LAA	-	low attenuation area
MCID	-	minimal clinical important difference
mMRC	-	modified medical research council dyspnea score
RV	-	residual volume
SGRQ	-	Saint George's Respiratory Questionnaire
QCT	-	quantitative computed tomography
QVM	-	quantitative visual match

This article has an online data supplement, which is accessible from this issue's table of contents online at www.thorax.bmj.com

ABSTRACT

Background

The RENEW trial demonstrated improvements in quality of life, pulmonary function, and exercise performance after endobronchial coil treatment. The aim of this study was to identify parameters associated with superior clinical outcomes.

Methods

Quantitative computerized analysis by an independent radiology laboratory and a qualitative evaluation by five blinded experts of the baseline thoracic computed tomograms (CT) were performed. Univariate and multivariate logistic regression analyses were performed to elucidate characteristics associated with clinical response.

Results

In total 125 patients received coil treatment and had evaluable 12 month follow up results. Of these, 78 patients received treatment of lobes with the highest emphysematous destruction determined by quantitative CT (QCT) analysis (QVM+), and 47 received treatment in at least one lobe that was not the most destroyed (QVM-). From the 78 patients with QVM+ treatment, a subgroup of 50 patients (64%) was identified with baseline residual volume >200% predicted, emphysema score >20% low attenuation area (LAA), and absence of airways disease. In this subgroup, greater lobar residual volume reduction in the treated lobes was achieved, which was associated with significant improvement in FEV₁ (+15,2%, SE 3.1), SGRQ (-12 points, SE 2), and residual volume (RV) (-0.57L, SE 0.13).

Discussion

This post-hoc analysis showed that both significant hyperinflation ($RV \geq 200\%$ predicted) and CT analysis are critical for patient selection and treatment planning for endobronchial coil therapy. QCT is important to identify optimal lobar treatment and to exclude patients with insufficient emphysema ($<20\%$ LAA), while visual assessment identifies patients with signs of airway disease associated with worse outcomes.

Clinical trial registration nr.:

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Key words:

bronchoscopy, emphysema, endobronchial coils, lung volume reduction, HRCT, COPD

INTRODUCTION

COPD patients with advanced emphysema and severe lung hyperinflation have limited effective treatment options. Generally, lung volume reduction surgery or lung transplantation can be offered to those who meet strict criteria. However, these procedures are infrequently performed due to significant morbidity and mortality.[1] Alternatively, use of endobronchial valves is limited to individuals with intact lobar fissures. Bronchoscopic lung volume reduction using shape-memory nitinol endobronchial coils is a minimally invasive treatment option.[2,3] The safety and effectiveness of endobronchial coils has been evaluated in several studies showing significant benefit of coil treatment on pulmonary function outcomes, exercise performance and quality of life.[4-11]

RENEW (NCT01608490), an international, multicenter randomized controlled trial, assessed endobronchial coil treatment in patients with severe lung hyperinflation and homogeneous or heterogeneous emphysema.[4] The primary outcome measure demonstrated a small but statistically significant improvement in the 6-minute walk distance (6MWD). Larger and statistically significant improvements were observed in outcome measures of Residual Volume (RV), Forced Expiratory Volume in 1 second (FEV₁) and Saint Georges Respiratory Questionnaire (SGRQ) versus control group patients (regular care) at 12 months. The RENEW primary analysis showed pre-specified subgroups with superior outcomes, namely patients with more hyperinflation (RV $\geq$ 225%pred) and patients with heterogeneous emphysema distribution, but a statistical analysis for predictors of response was not performed.[4] Of note, quantitative measures of the inspiratory and expiratory CT scans were not assessed in the primary analysis.

In this post-hoc analysis of the RENEW trial, we performed lobar-based quantitative computed tomography (QCT) measurements and a qualitative expert image review. The purpose of this post-hoc analysis was to identify baseline predictors including quantitative CT measures that identify patients most likely to significantly benefit from endobronchial coil therapy.

METHODS

Patient population

The patients' characteristics and primary results of the RENEW trial have previously been reported.[4] Of 158 patients randomized to the RENEW treatment group, 125 completed bilateral treatment and twelve-month follow-up and had evaluable inspiratory and expiratory CT scans at baseline and 12-month follow-up and were included in the post-hoc analysis (Figure 1). Baseline characteristics are shown in Table 1. The RENEW trial was approved by all the 31 trial sites medical ethical review committees, and all patients provided written informed consent.

Quantitative CT analysis (QCT)

After the RENEW 12-month primary endpoint follow-up visit and study un-blinding, HRCT scans for the coil-treated group were analyzed quantitatively (QCT) (Thirona, Nijmegen, The Netherlands). The QCT analysis included volumetric and densitometry assessment at a lung and lobar basis. Percentage emphysema was calculated as % of low attenuation areas below -950HU on inspiratory scans (%LAA950). Percentage air trapping was calculated as %LAA below -856HU on expiratory scans (%LAA856). Percentage heterogeneity (difference in %LAA950 between ipsilateral lobes) and %fissure integrity (for major fissures on inspiratory scans) were also measured. A "heterogeneous" patient was defined as having $\geq 15\%$ ipsilateral difference in %LAA950 in both lungs, a "homogenous" patient as having $< 15\%$ ipsilateral difference in %LAA950 in both lungs. A "mixed" patient had one heterogeneous lung and one homogeneous lung.

Lobar volume change was calculated as the total change in lobar volume of both treated lobes comparing baseline to 12 months post coil treatment, assessed both with expiratory scans (lobar RV change) and inspiratory scans (lobar TLC change).

Agreement between quantitative and visual analyses of the HRCT (QVM + and QVM-)

The most damaged lobe of each lung determined by QCT analysis was compared to the lobe target determined by the RENEW visual analysis. The RENEW trial used a visual CT analysis to select the most damaged lobes for coil treatment based on a 0 to 5 scoring system of lobar destruction (see Supplement S1). If the quantitative and visual analyses agreed on both treated lobes, the patient was determined to be “quantitative-visual match-positive” or QVM+. If disagreement was observed in one or both treated lobes, the patient was designated as “quantitative-visual match-negative, or QVM-”.

Visual CT Assessment

Five experts (one radiologist, four pulmonologists) conducted a post hoc blinded visual assessment of all baseline inspiratory CTs. Experts noted visual findings including bronchial wall thickening, bronchiectasis, fibrosis/scarring, and suspected pulmonary hypertension. Methods are described in the online data Supplement S1.

Statistical analysis

Univariate analysis and Pearson correlation coefficients were used to investigate associations between QCT measured outcomes, potential baseline predictors and clinical response outcomes. A multivariate logistic regression model was used to identify the association

between baseline measures including QCT and lobar volume reduction at 12 months. Multivariate logistic regressions were performed with stepwise control using minimum Akaike Information Criterion (AICc) stopping rule in forward direction. Clinical response was measured by the RENEW study endpoints at 12 months (6MWD, FEV₁, RV, SGRQ and the minimum clinically important difference (MCID) level response to these four RENEW endpoints (MCID: 6MWD of 25m[12]), FEV₁ of 10%[13], RV of -0.35L[14], SGRQ total score of -4 points[15]).

The QCT measures used in this analysis were %emphysema, %air trapping, %heterogeneity, QVM+, and %fissure integrity. Patient baseline characteristics included demographics (age, BMI), PFTs (plethysmographic lung volumes and forced spirometry), visual CT findings, and treatment factors (total number of coils per lobe volume, and % proportion of each coil size). Differences in baseline characteristics between QVM+ and QVM- patients were evaluated using two-sample t-test or Fisher's exact test. All statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary NC, USA). P-values<0.05 were considered statistically significant.

RESULTS

Association between change in QCT measures and clinical response measures

We examined the association between change in QCT measures and clinical response MCIDs from baseline to 12 months follow up (S2 Table, Supplement). Change in lobar RV in the treated lobes was the only QCT measure that was significantly associated ($p < 0.05$) with all four clinical outcomes. This establishes reduction in expiratory lobar RV as a mechanistically plausible primary effect of the coils that can be analysed in establishing baseline predictors of response.

Impact of matching of QCT and visual CT targeting of lobe with greatest emphysema (QVM)

Using targeting based on the visual scoring algorithm, 38% of patients (47/125) received one or both treatments in the ipsilateral lobe of lesser quantitative CT emphysematous destruction and were designated QVM-. The majority of the QVM- treatments occurred in lungs defined as homogeneous by QCT (Figure 2). The QVM+ subgroup, in which the visual algorithm matched the QCT lobe of greatest destruction, had greater heterogeneity at baseline ($p < 0.0005$), greater % emphysema ($p < 0.005$) and more air trapping ($p < 0.005$) compared to the QVM- group (Table 1).

The multivariate analysis with adjustment for the identified baseline imbalances between the two subgroups showed that QVM+ patients achieved significantly more expiratory lobar volume reduction at 12 months compared to QVM- patients (mean of -0.37 ± 0.05 litres (L) versus -0.13 ± 0.08 L; $p = 0.0064$), even after accounting for baseline differences in %heterogeneity, %air trapping, and %emphysema (S3 Table, Supplement). In addition, between-group differences in change in 6MWD ($+15.4\text{m}$, 95% CI $[-12.1, 42.9]$), FEV₁ ($+6.7\%$, 95%

CI [-0.8,14.2]), RV (-0.12L, 95% CI [-0.41,0.17], and SGRQ (-0.6 point in total score, 95% CI [-5.5,4.3] all favored QVM+ patients. Furthermore, QVM+ emerged as the only significant QCT-based predictor of lobar RV change ($p=0.02$) (S4a+b Tables, Supplement).

Thus, lobar selection with QCT emerged in this analysis as a previously unknown covariate in RENEW that may have obscured the response profile of endobronchial coil therapy in this trial. To account for this, we excluded QVM- patients from the subsequent analyses in which we examine baseline predictors of response.

Baseline predictors of superior response to coil treatment in QVM+ population

Higher baseline %emphysema score and absence of airways disease on visual CT review were associated ($p<0.05$) with lobar RV reduction at 12 months (Figure 3a+b and Table 2). Higher baseline RV% predicted approached significance ($p=0.071$) in the multivariate stepwise model. We next applied a lobar RV change threshold of -320mL to determine the lowest baseline value for RV% predicted and % emphysema score that resulted in a lobar RV response at 12 months. The threshold of -320mL for lobar RV change was determined using an MCID analysis anchored to RV change measured via body plethysmography (Table S5, supplement). Patients with baseline RV<200% predicted or with % emphysema score < 20% in either targeted lobe did not achieve clinically meaningful lobar RV reduction (Figure S6, Supplement).

Sixty-four percent of patients in the QVM+ subgroup (50/78) met all three identified volume reduction criteria: RV $\geq$ 200% predicted, %LAA $\geq$ 20%, and no visually determined presence of airways disease at baseline. This volume reduction criteria subgroup (N=50) demonstrated significant clinical improvement at one-year post-treatment (mean) for RV -570 ml, FEV₁ 97 ml, FEV₁ 15.2 %, and SGRQ -12 points ($p<0.01$) but not for 6MWT (0.1935) (Table 3) compared to

patients who did not meet these criteria. Importantly, this resulted in significant improvements in clinical responder rates when comparing the volume reduction criteria subgroup to those that did not meet these criteria (Figure 4).

Safety in improved patient selection group

We examined the one-year safety profile in all RENEW treatment patients who completed the 12-month follow-up visit (N=125) to assess the safety impact of improved patient selection. No differences approached significance between the Volume Reduction Criteria subgroup and the subgroup without all volume reduction criteria (Table 4).

DISCUSSION

Following early lung volume reduction trials, post-hoc subgroup analysis proposed responder profiles that still define the current use of both surgical therapies and valve therapies.[16,17] The responder subgroup identified in the randomized, controlled VENT trial has been confirmed prospectively, providing necessary selection criteria for real-world therapeutic adoption of endobronchial valves.[18-22] Similarly, this RENEW post-hoc analysis offers rational predictors of response to coil therapy that can now be prospectively confirmed as well.

Endobronchial coils have shown effectiveness in both heterogeneous and homogenous disease, however, no clear single mechanism of action has been defined. Where valves and other therapies based on atelectasis or injury-response fibrosis benefit from the rich evidence base of response mechanisms in lung volume surgery, the mechanisms driving the effects of coil treatment have yet to be defined[23,24]. Despite its early stage, there is accumulating evidence supporting multiple mechanistic effects on the lung induced by coil placement such as reducing static hyperinflation, improving airway resistance, promoting the airway tethering effect, and reducing dynamic hyperinflation[10,25-27]. RENEW has provided substantial opportunity for post-hoc analysis and improved understanding of coil mechanisms and predictors of response.[4] While the design of coils as local, non-blocking devices creates the potential for multiple mechanisms of action, we propose volume reduction as the primary objective of coil therapy and have confirmed the association of lobar RV reduction with clinical responsiveness at one-year post-treatment. We also identified three baseline criteria with proposed inclusion thresholds ($RV \geq 200\%$ predicted, emphysema score $\%LAA \geq 20$, and no presence of airways disease on visual CT) which defined a patient subgroup achieving clinically significant pulmonary function and volume reduction outcomes at 12-months post coil treatment.

Treating the most damaged lobe was shown to be most strongly associated with lobar volume reduction, and we discovered that over 1/3 of patients treated in RENEW did not receive bilateral treatment in the most destroyed lobes according to QCT. When the most damaged lobes were treated (QVM+ subgroup), substantial improvements in physiological and clinical outcomes were demonstrated when compared to the QVM- subgroup. This suggests that using QCT, rather than visual analysis, to target the most damaged lobes for treatment may be associated with improved outcomes in coil treated patients. QCT-visual mismatching was much more common in homogenous patients compared to heterogenous patients; this has important implications given that most volume reduction studies focus almost exclusively on heterogenous patients where the difference between QCT and visual lobar targeting is small and/or negligible. This analysis suggests important limitations of visual lobe targeting for complex and novel interventional therapies, especially in the context of homogeneous patients. There are limitations to this post-hoc analysis, principally the small number of patients because of the exclusion of QVM- treated patients. This is a retrospective subgroup analysis with potential small-n effects. However, the NETT post-hoc responder subgroup represented 11% of the total study population (139/1218 patients with upper-lobe predominant, heterogenous emphysema and low baseline exercise tolerance), and the VENT post-hoc responder subgroup represented approximately 20% of the study population (68/321 patients with intact fissures and heterogeneous emphysema). These post-hoc analyses from 2003[17] and 2010[16] have effectively established appropriate patient selection criteria for these therapies still in use today. We also acknowledge the potential of confounding influences among the factors which emerged as significant in our analysis, particularly for the findings of airway wall thickening which was not under protocol for this analysis.

This analysis is based on a quantitatively measured endpoint (CT expiratory lobar volume) that is somewhat independent of patient effort, although the expiratory scans were not gated using spirometry (see Supplement). Many of the predictors found in our analysis reached statistical and clinical significance despite small subgroups. Our findings are clinically rational and consistent with published literature from earlier emphysema trials.[11,16-18] Our results are promising given that nearly half (44%) of the volume reduction criteria subgroup is comprised of patients with bilateral homogeneity of disease (<15% ipsilateral difference at -950HU), a group of patients not generally considered for lung volume reduction surgery.[1] The REACTION trial exploring physical activity change and physiologic response patterns in coil-treated patients is ongoing and may shed light on this intriguing hypothesis (NCT02179125).

While quantitative assessment of the HRCT is much more reliable in precise emphysema scoring and fissure completeness[28,29], subtle airway wall changes, magnitude of bronchial wall thickening and mild bronchiectasis, and (post-) infectious consolidations are much more difficult to quantify. Although expert CT readers do not have a solid consensus[30], it is possible to make a judgement with clinical implications[28,31] and a thorough qualitative inspection with clinical interpretation of the findings of these features, in addition to routine QCT, is key in selecting out patients with relevant airway disease, who are less likely to benefit from coil treatment.

In conclusion, we identified three baseline criteria with proposed inclusion thresholds ($RV \geq 200\%$ predicted, emphysema score $\%LAA \geq 20$, and absence of airways disease on visual CT) that defined a patient subgroup achieving clinically significant pulmonary function and volume reduction outcomes at 12-months post coil treatment. Patients selected for lobar volume reduction with endobronchial coil treatment should meet all these criteria, and lobe targets

should be confirmed with densitometry analysis to ensure treatment in the lobes of greater destruction. This post-hoc analysis of RENEW data proposes patient selection criteria that improve response to endobronchial coils. These findings warrant prospective confirmation to establish the profile of patients with severe emphysema who should be offered this treatment.

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FIGURE Legends

Figure 1. Flow Diagram of Subjects Included in This Analysis

Figure 2. Baseline QCT characteristics stratified by QCT subgroup.

Figure legend: Baseline QCT characteristics stratified by QCT subgroup. (A) Proportion of treated heterogeneous ($\geq 15\%$ ipsilateral difference in %LAA -950 HU) and homogeneous lobes ($< 15\%$ ipsilateral difference), stratified by whether the treated lobes were QVM+ or QVM-. (B) Proportion of treated patients with heterogeneous (both lungs), homogeneous (both lungs), or mixed (one heterogeneous lung and one homogeneous lung) disease, stratified by whether both lobes were QVM+ or whether one/both lobes were QVM+.

Figure 3a. Scatterplot of emphysema score versus lobar RV reduction in responder analysis cohort (N=78).

Figure legend: The relationship between lobar RV volume change and baseline % emphysema score in treated patients. In this figure, % emphysema is represented as the smaller lobar %LAA -950 HU score of the two treated lobes.

Figure 3b. Expiratory Lobar Volume Reduction in Treated Lobes by Visual Presence of Airway Disease in Responder Analysis Cohort (N=78)

Figure legend: Subjects receiving a score of “2” or “3” (n=19) for presence of airways disease (“Airway Disease”) on visual CT achieved significantly ($p=0.0117$) less expiratory lobar volume at 12-months post coil treatment than patients with scores of “0” or “1” (N=59) (“No Airway Disease”).

Figure 4. Responder rates in patients with and without identified predictive criteria for response

Figure legend: Volume reduction criteria were “No airway disease”, $LAA \geq 20\%$, $RV \geq 200\%$ predicted. Patients who met those criteria, had significantly higher response rates in clinical endpoints, using standard MCID levels: RV -350 ml, FEV1 10%, 6MWD 25m, SGRQ -4 points.

TABLES

Table 1. Baseline Characteristics of All RENEW Coil-Treated Patients and Patients Stratified by QCT Subgroup.

Characteristic*	RENEW (N=125) [†]	QVM+ (N=78)	QVM- (N=47)	P-value [‡]
Age	63.2 ± 8.1	62.9 ± 8.1	63.7 ± 8.3	0.6102
Gender, % Male	46.4 (58)	47.4 (37)	44.7 (21)	0.8536
BMI	24.9 ± 4.6	24.9 ± 4.6	24.9 ± 4.6	0.9649
BODE	6.0 ± 1.3	6.1 ± 1.3	5.8 ± 1.2	0.3184
Mean Comorbidities	2.6 ± 2.1	2.7 ± 2.1	2.3 ± 1.9	0.2910
% 4 or More Comorbidities	29.6 (37)	32.1 (25)	25.5 (12)	0.5449
% Cardiac Comorbidities	24.8 (31)	30.8 (24)	14.9 (7)	0.0555
6MWD, Meters	314.1 ± 79.9	313.8 ± 76.9	314.6 ± 85.6	0.9582
RV % Predicted	244.9 ± 38.5	246.8 ± 40.6	241.8 ± 34.8	0.4883
% RV ≥ 225%	71.2 (89)	74.4 (58)	66.0 (31)	0.4149
RV/TLC	66.8 ± 6.7	67.1 ± 7.3	66.4 ± 5.7	0.5851
FEV ₁ % Predicted, PB	25.6 ± 6.1	25.8 ± 6.4	25.5 ± 5.8	0.7813
SGRQ Total Score	60.0 ± 12.7	60.2 ± 13.6	59.7 ± 11.1	0.8344
% Heterogeneous [§]	19.2 (24)	28.2 (22)	4.3 (2)	0.0001
% Homogeneous	56.8 (71)	43.6 (34)	78.7 (37)	
% Mixed	24.0 (30)	28.2 (22)	17.0 (8)	
% Emphysema (-950 HU)	44.0 ± 13.2	46.9 ± 12.9	39.2 ± 12.2	0.0012
% Air trapping (-856 HU)	75.2 ± 11.6	77.7 ± 10.4	71.1 ± 12.4	0.0017

Definition of abbreviations: BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnea and exercise capacity; 6MWD = 6-minute-walk distance; RV = residual volume; TLC = total lung capacity; FEV₁ = forced expiratory volume in 1 second; PB = post-bronchodilator; SGRQ = St. George's Respiratory Questionnaire; HU = Hounsfield unit.

**Continuous variables presented as mean ± standard deviation; categorical variables as percent (number, n) of patients.*

[†]All RENEW patients bilaterally treated with coils and with evaluable inspiratory and expiratory scans at baseline and 12 months.

[‡]p-values comparing densitometry targeted and non-densitometry targeted groups are based on two-sided t-test for continuous variables and Fisher's exact test for categorical variables.

[§]Requires ≥ 15% difference in % emphysema between upper and lower lobes -950 HU, in both lungs.

^{||}Average value for two QCT targeted lobes.

Table 2. Baseline Characteristics associated with Lobar RV Change at 12-months in Responder Analysis cohort (N=78).

PARAMETER	CORRELATION	P-VALUE	Correlation Coefficient, r
Bivariate			
% Emphysema, Minimum of both treated lobes	-	0.0063	-0.3067
Visual CT presence of airways disease	+	0.0117	0.2841
% Heterogeneity between ipsilateral lobes	-	0.0118	-0.2837
BMI	+	0.0464	0.2262
Multivariate (Stepwise) $R^2 = 0.1773$, $P = 0.0023$			
% Emphysema, Minimum of both treated lobes	-	0.0244	
Visual CT Presence of Airways Disease	+	0.0313	
RV % predicted	-	0.0710	

Only statistically significant predictors are shown for univariate analysis ($P < 0.05$). Multivariate regression model with stepwise control using minimum Akaike Information Criterion (AICc) stopping rule in forward direction. BMI = body mass index; CT = computed tomography; RV = residual volume.

Table 3. Clinical Outcomes by Volume Reduction Criteria* in Responder Analysis cohort (N=78).

	Patients with Volume Reduction Criteria (N=50)				Patients without Volume Reduction Criteria (N=28)				P-Value
	Mean	SE	Median	(IQR)	Mean	SE	Median	(IQR)	
RV, L	-0.57	0.13	-0.44	(-1.19, -0.10)	-0.20	0.16	-0.02	(-0.67, 0.38)	0.0793
VC, L	0.31	0.06	0.27	(0.09, 0.55)	0.11	0.08	0.09	(-0.25, 0.32)	0.0470
FEV1, %	15.2	3.1	13.6	(1.4, 21.9)	0.6	3.5	-0.9	(-13.3, 10.1)	0.0038
FEV1, L	0.097	0.022	0.075	(0.010, 0.145)	-0.005	0.024	-0.005	(-0.103, 0.067)	0.0040
Lobar Volume, mL	-467	64	-402	(-670, -128)	-103	78	-68	(-264, 145)	0.0007
6MWD, m	16	11	24	(-2, 63)	-7	12	-13	(-46, 41)	0.1935
SGRQ, pts	-12	2	-13	(-19, -3)	-4	3	-2	(-9, 6)	0.0100
mMRC, pts	-0.8	0.2	-1.0	(-2.0, 0.0)	-0.8	0.2	-1.0	(-1.8, 0.0)	0.9040

6MWD = 6-minute-walk distance; FEV1 = forced expiratory volume in 1 second; IQR = interquartile range; RV = residual volume; SGRQ = St. George's Respiratory Questionnaire; VC = vital capacity. P-Values = analysis of variance for continuous outcomes, 2-Tail Fisher's exact test for categorical outcomes. *Volume Reduction criteria: QVM+, %Emphysema $\geq$ 20% and RV $\geq$ 200% predicted, no visual CT presence of airways disease.

Table 4. Summary of Major Complications Through 12 Months (N=125)

Major Complication Event	Patients with Volume Reduction Criteria (N=50)		Group without All Volume Reduction Criteria (N=75)		P-value*
	Subject Counts n (%)	Event Counts n	Subject Counts n (%)	Event Counts n	
Total Major Complication Events	14 (28.0%)	17	19 (25.3%)	31	0.8365
Death	0 (0.0%)	0	0 (0.0%)	0	N/A
Pneumothorax	1 (2.0%)	1	0 (0.0%)	0	0.4000
Hemoptysis	0 (0.0%)	0	1 (1.3%)	1	1.0000
COPD Exacerbation	5 (10.0%)	5	8 (10.7%)	11	1.0000
Lower Respiratory Infection	8 (16.0%)	10	12 (16.0%)	16	1.0000
Respiratory Failure	1 (2.0%)	1	3 (4.0%)	3	0.6492
Unanticipated Bronchoscopy	0 (0.0%)	0	0 (0.0%)	0	N/A

*By Fisher's exact test. Subjects are counted at most once for each major complication event.

125 RENEW Patients received bilateral coil treatment with completed 12-month follow-up visit* and analysable CT scans ("RENEW QCT Cohort")

47 Patients that were not treated in the lobes determine by QCT [QVM(-)]

78 Patients treated in the lobes determined by QCT [QVM(+)] ("Responder Analysis Cohort")

28 Patients with low hyperinflation (baseline RV < 200%pred), or low emphysema (lobar %emphysema < 20% in either of the treated lobes), or visual presence of airways disease

50 Patients treated in the lobes determined by QCT and meeting baseline criteria for volume reduction ("Volume Reduction Criteria")

*Any 1 of the PFTs was measured at 12 months.

■ QVM(+)

■ QVM(-)

Expiratory Lobar Volume Reduction in Treated Lobes

Responder rates, % subjects

■ Patients with Volume Reduction Criteria (N=50)

■ Patients without Volume Reduction Criteria (N=28)