



Βρογχοσκοπική θεραπεία σοβαρού εμφυσήματος και άσθματος;;

BLVR/BT: Επιλογή ασθενών και μέθοδοι

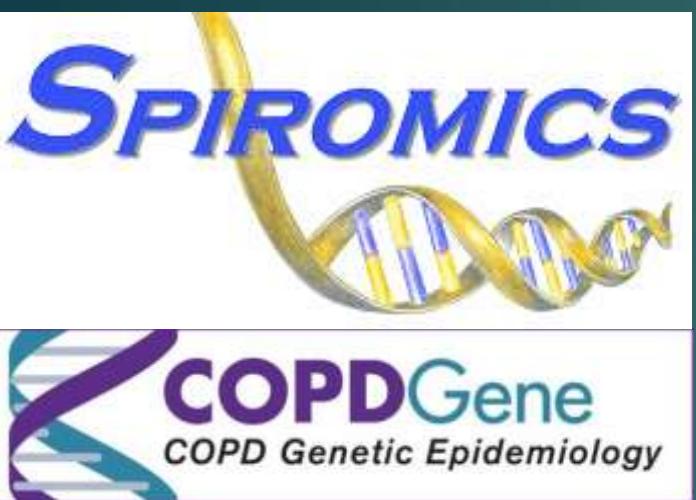
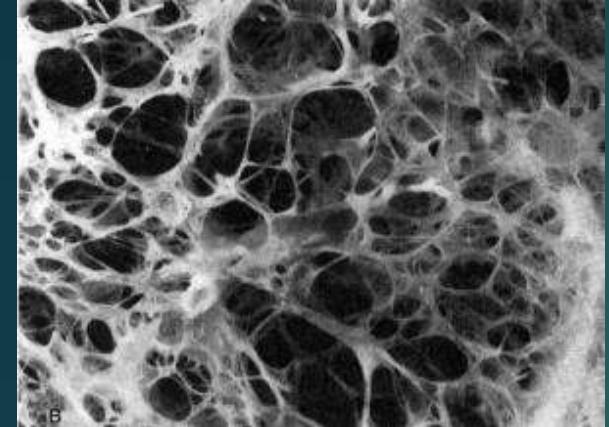
Γρ. Στρατάκος MD, FCCP

Επ. Καθηγητής Πνευμονολογίας

Μονάδα Επεμβατικής Πνευμονολογίας,

1^η Πνευμονολογική Κλινική ΕΚΠΑ, ΝΝΘΑ «Σωτηρία»





Ένας ορισμός για το εμφύσημα...

- ▶ Όλοι οι ασθενείς είχαν YT όπου υπολογίστηκε το ποσοστό των voxels με τιμές λιγότερο από **-950 Hounsfield units**.
- ▶ Η ομάδα αυτή συγκρίθηκε με σημαντικά κλινικά χαρακτηριστικά (outcomes)
- ▶ Οι ασθενείς με **>5% εμφυσηματικό πνεύμονα (<-950 Hounsfield units)**, είχαν περισσότερες παροξύνσεις, χειρότερο St George's RQ και μεγαλύτερη θνητότητα.
- ▶ Η συσχέτιση αυτή ίσχυε μόνο για τους ασθενείς με αποφρακτικό σύνδρομο ($FEV_1/FVC < 70\%$ με GOLD criteria).

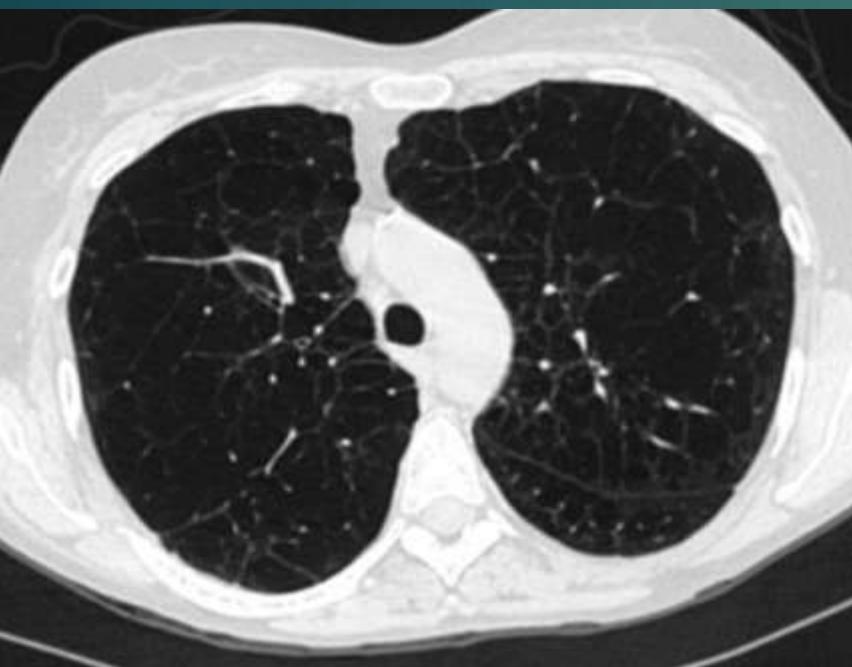
Association between Emphysema and Chronic Obstructive Pulmonary Disease Outcomes in the COPDGene and SPIROMICS Cohorts: A Post Hoc Analysis of Two Clinical Trials.
Am J Resp Crit Care Med, 2018;198: 265–267

FEV₁/FVC<70, >5% (-910HU)

που δεν έχουν «ειδικού» τύπου νόσο:

- ▶ A₁AT deficiency
- ▶ Bullous Disease
- ▶ Paraseptal Emphysema
- ▶ CPFE

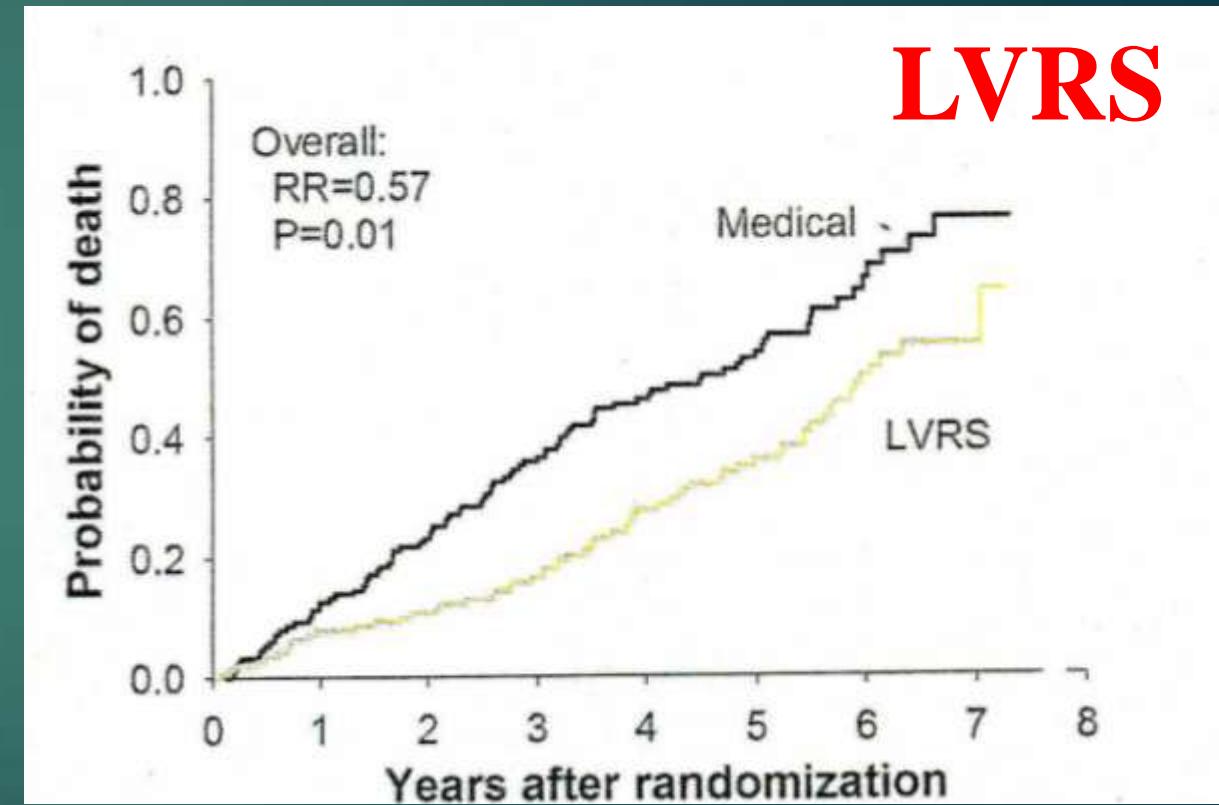




Κεντρολοβιώδες με εντόπιση στους άνω λοβούς
 $DLCO > 20\%$ και μειωμένη αντοχή στην άσκηση :

Low exercise capacity :post rehab baseline max work of ≤ 25 watts for women and ≤ 40 watts for men.

National
Emphysema
Treatment
Trial
1218 pts

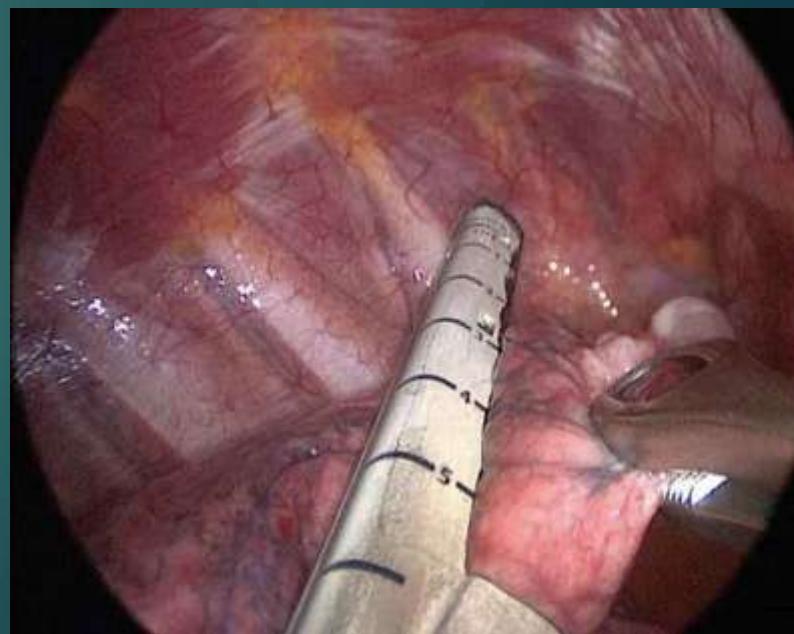


Ann Thorac Surg 2006;82:431-3

Lung Volume Reduction Surgery Since the National Emphysema Treatment Trial: Study of Society of Thoracic Surgeons Database

J Thorac Cardiovasc Surg. 2014 December; 148(6): 2651–2658

- Μεταξύ 2003 και 2011 (8.5 χρόνια) μόνο 538 ασθενείς <65 ετών χειρουργήθηκαν στις ΗΠΑ (20-118/έτος)
Υπολογισμός ασθενών 4.7×10^6
- FEV₁ 31% pred κατά ΜΟ (έναντι 28% της NETT)
- Περισσότεροι ασθενείς έγιναν θωρακοσκοπικά
- Η θνητότητα σε ασθενείς όχι υψηλού κινδύνου ήταν παρ'όλα αυτά 3% μεγαλύτερη της NETT ($p<0.005$)

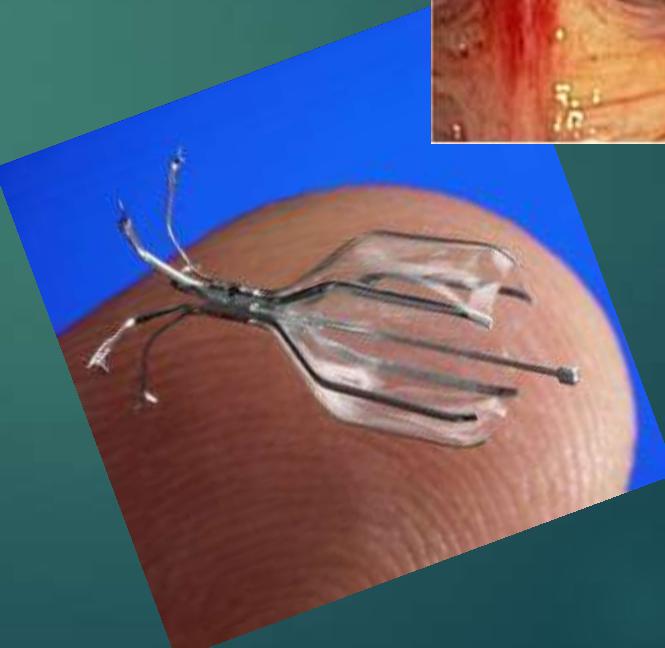


- 33 pts 2009-2014. DLCo <20% The 90-day mortality was 0%.
- FEV1 % at 3 months increased from 23% to 29% ($p < 0.001$).
- DLco increased from 15% to 24% ($p < 0.001$), and median hyperinflation decreased from 76% to 63% ($p < 0.001$).
- A prolonged air leak exceeding 7 days occurred in 48.5%, and 6 required reoperation for fistula closure
- Selected patients with severely impaired DLCo of less than 20% can cautiously be considered as potential candidates if hyperinflation is severe and the lungs show areas with advanced destruction as targets for resection.

Endoscopic LVR

A. Τροποποίηση αεραγωγών και ροής Endobronchial valves

- Emphasis-Zephyr (Pulmonx): One-way Valve
- Spiration: Umbrella



Pulmonx valves



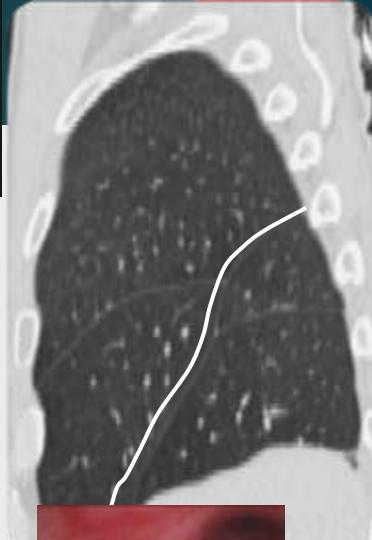
	Primary Safety Endpoint 6 months			Additional Safety Analysis 12 months (cumulative)		
	Control n=101	EBV n=220	p value	Control n=101	EBV n=220	p value
Major Complication Composite (MCC)	1.1%	6.1%	0.0748	4.6%	10.4%	0.1724
Death	0.0%	2.8%	0.1867	3.5%	3.7%	1.0000
Empyema	0.0%	0.0%	----	0.0%	0.0%	----
Massive Hemoptysis	0.0%	0.5%	1.0000	0.0%	0.5%	1.0000
Distal Pneumonia	NA	1.4%	----	NA	4.2%	----
Pneumothorax/air leak > 7 days	1.1%	1.4%	1.0000	1.2%	1.9%	1.0000

nal medical treatment



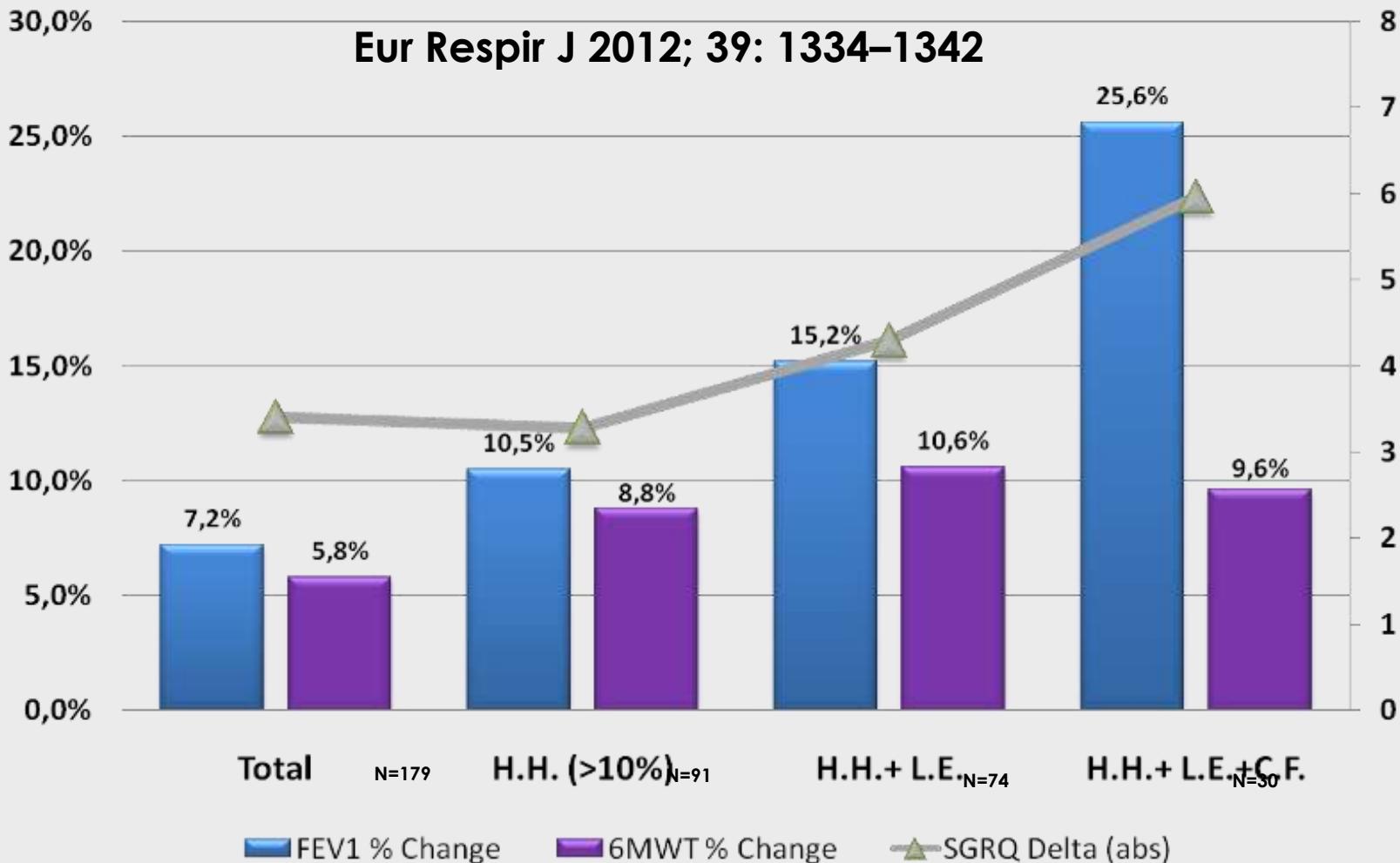
VENT Responder Summary

(Delta Treatment & Control @ 6mons)



N Engl J Med 2010;363:1233-44

Eur Respir J 2012; 39: 1334–1342



H.H. – High Heterogeneity, L.E. – Lobar Exclusion Achieved, C.F. – Low Collateral Flow

	BLVR		Control (n=24)	p value*
	All (n=23)	CV-positive excluded (n=19)		
FEV ₁	9 (39%)	—	1 (4%)	0.0044
>15% Improvement	—	9 (47%)	1 (4%)	0.0022
RV	11 (48%)	—	7 (29%)	0.24
0-35 L reduction ^{**}	—	11 (58%)	7 (29%)	0.07
6MWD	12 (52%)	—	4 (17%)	0.012
26 m improvement ^{**}	—	12 (63%)	4 (17%)	0.004
Endurance cycle time	10 (43%)	—	2 (8%)	0.008
105 s improvement ^{**}	—	9 (47%)	2 (8%)	0.005
SGRQc	11 (48%)	—	11 (46%)	1.0
4 points reduction ^{**}	—	11 (58%)	11 (46%)	0.5
CAT	13 (57%)	—	7 (29%)	0.080
2 points reduction ^{**}	—	13 (68%)	7 (29%)	0.015

Data are n (%). CV-positive=collateral ventilation using Chartis system.

BLVR=bronchoscopic lung volume reduction. FEV₁=forced expiratory volume in 1 s. RV=residual volume. 6MWD=6 min walking distance. SGRQc=St George's respiratory questionnaire for chronic obstructive pulmonary disease (COPD). CAT=COPD assessment test score. * Fisher's exact test (this analysis does not include imputed values).

Table 5: Responder rates according to lung function, health status, and exercise criteria

Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFI study): a randomised controlled trial

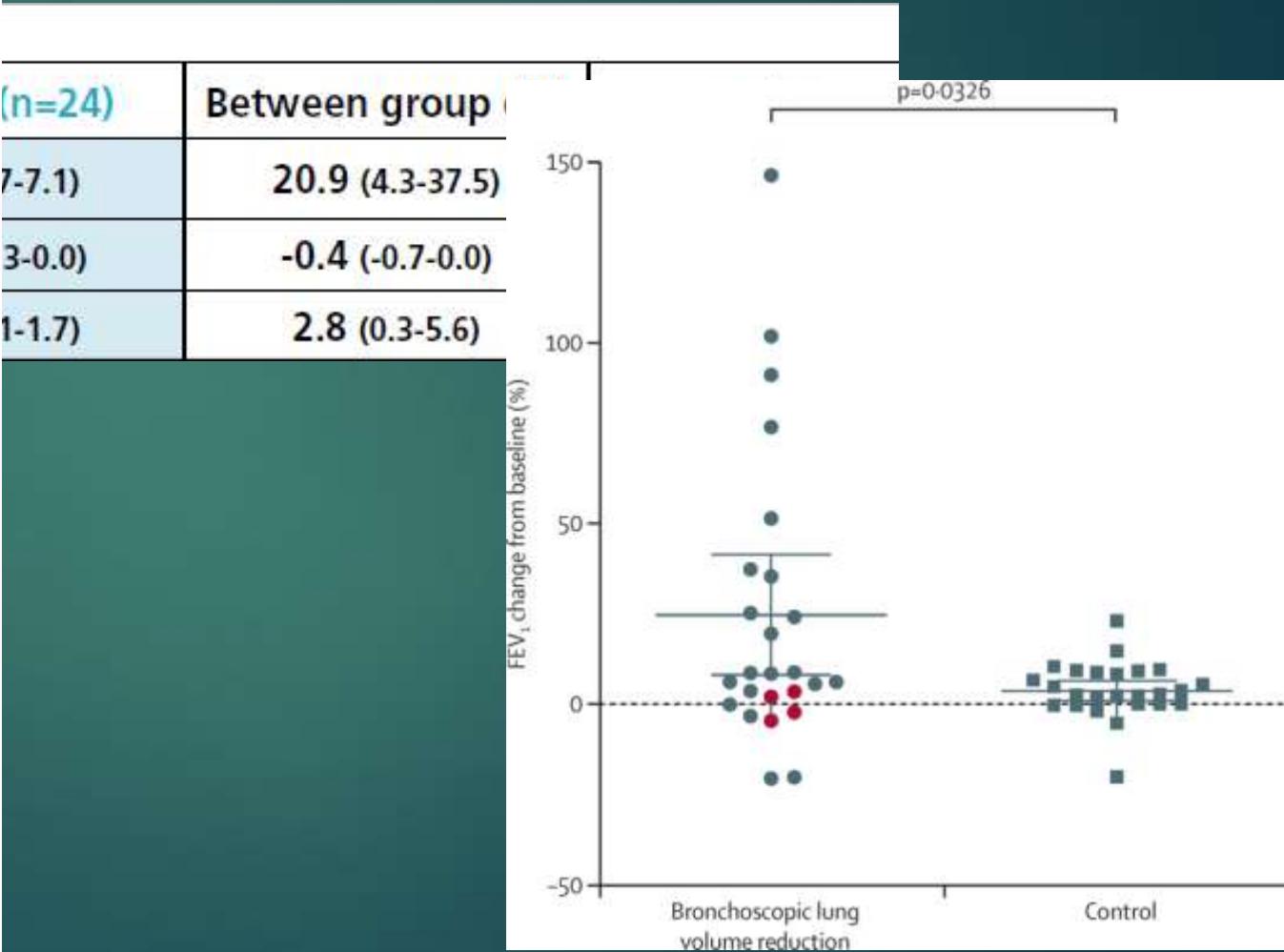
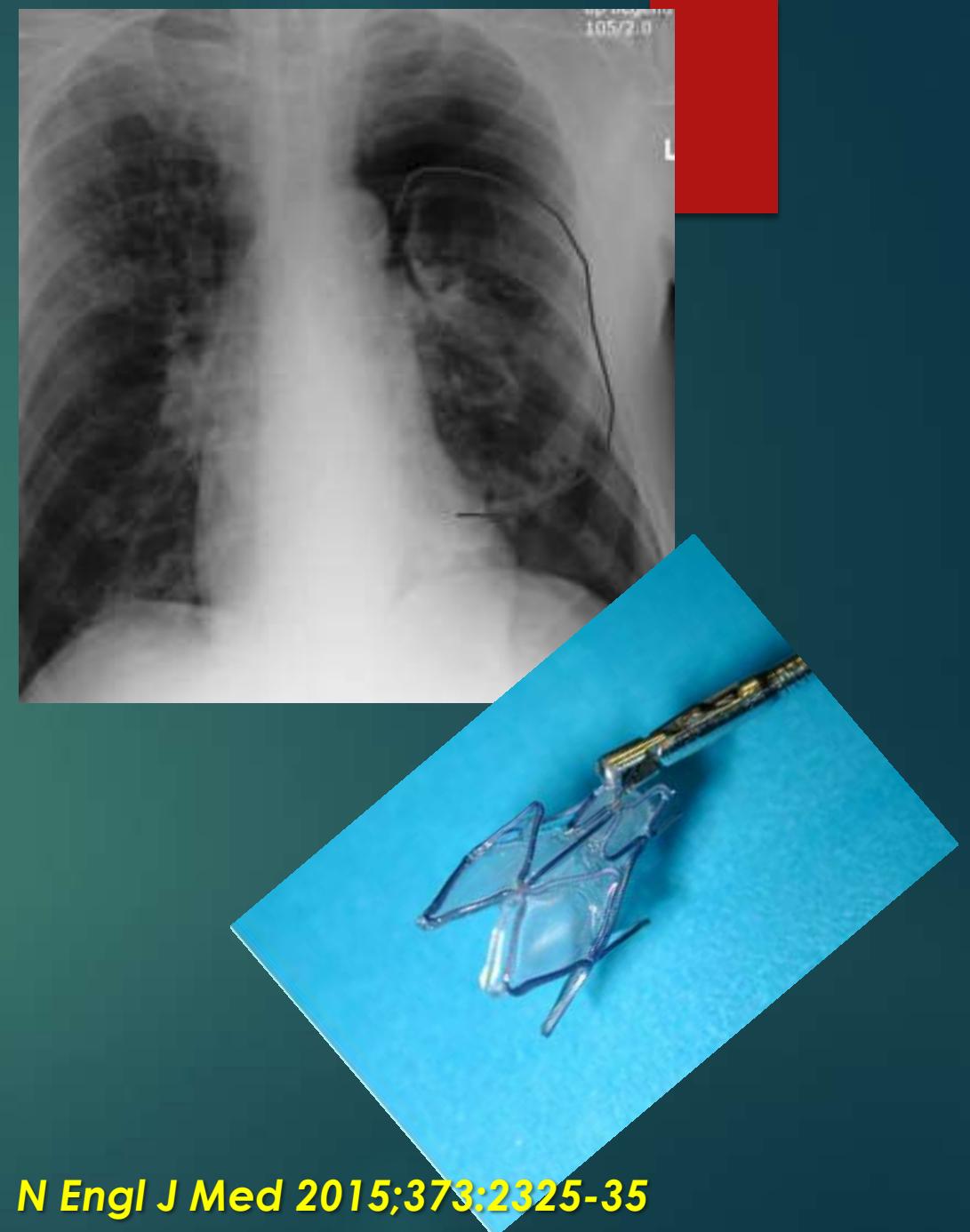


Table 3. Serious Adverse Events during 6 Months of Follow-up.*

Event	EBV Group (N=34)	Control Group (N=34)	P Value†
	no. (%)		
Total no. of serious events	23	5	<0.001
Pulmonary events			
Death	1 (3)‡	0	1.00
COPD exacerbation with hospitalization	4 (12)	2 (6)	0.67
Pneumonia	2 (6)	1 (3)	1.00
Pneumothorax	6 (18)	0	0.02
Resolved ≤14 days after onset, without drainage	1 (3)	0	1.00
Resolved ≤14 days after onset, with drainage	2 (6)	0	0.49
Required temporary valve removal	1 (3)§	NA	NA
Required permanent valve removal because of recurrent pneumothorax	1 (3)	NA	NA
Required permanent valve removal, after temporary removal and reimplantation, because of recurrent pneumothorax	1 (3)	NA	NA
Other EBV-related events requiring permanent removal of all valves			
Torsion of the bronchus	2 (6)¶	NA	NA
Pneumonia distal to valve	1 (3)	NA	NA
Increased sputum, dyspnea, or coughing without patient-perceived treatment benefit	2 (6)	NA	NA
Other EBV-related events requiring valve replacement			
Valve migration	2 (6)	NA	NA
Valve expectoration	0	NA	NA
Valve dislocation due to formation of granulation tissue	1 (3)	NA	NA
Increased sputum, dyspnea, or coughing	1 (3)	NA	NA
Stroke	1 (3)	2 (6)	1.00

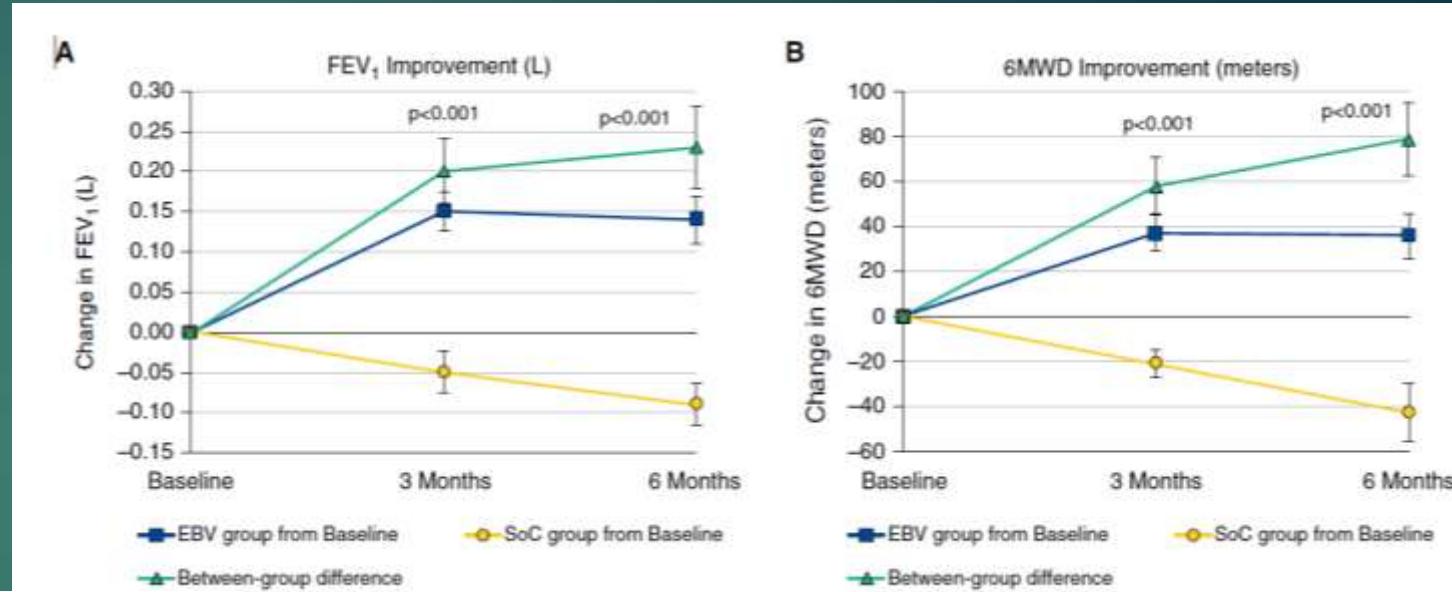
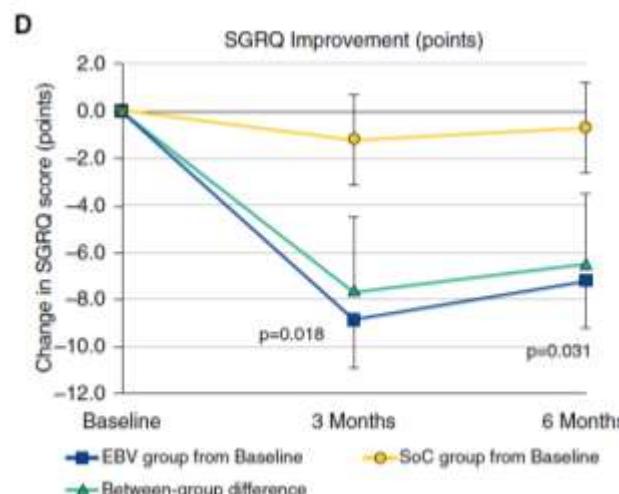
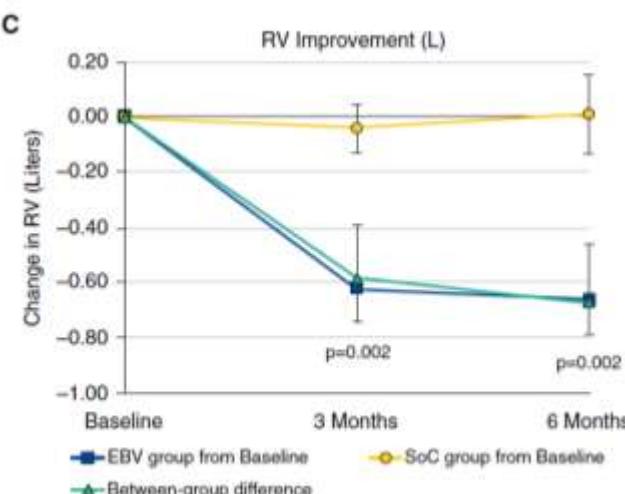


A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM)

Am J Respir Crit Care Med 2017;196:1535–1543

97 pts (65 vs 32)

55.4% of EBV and 6.5% of SoC subjects had an FEV₁ improvement of $\geq 12\%$.

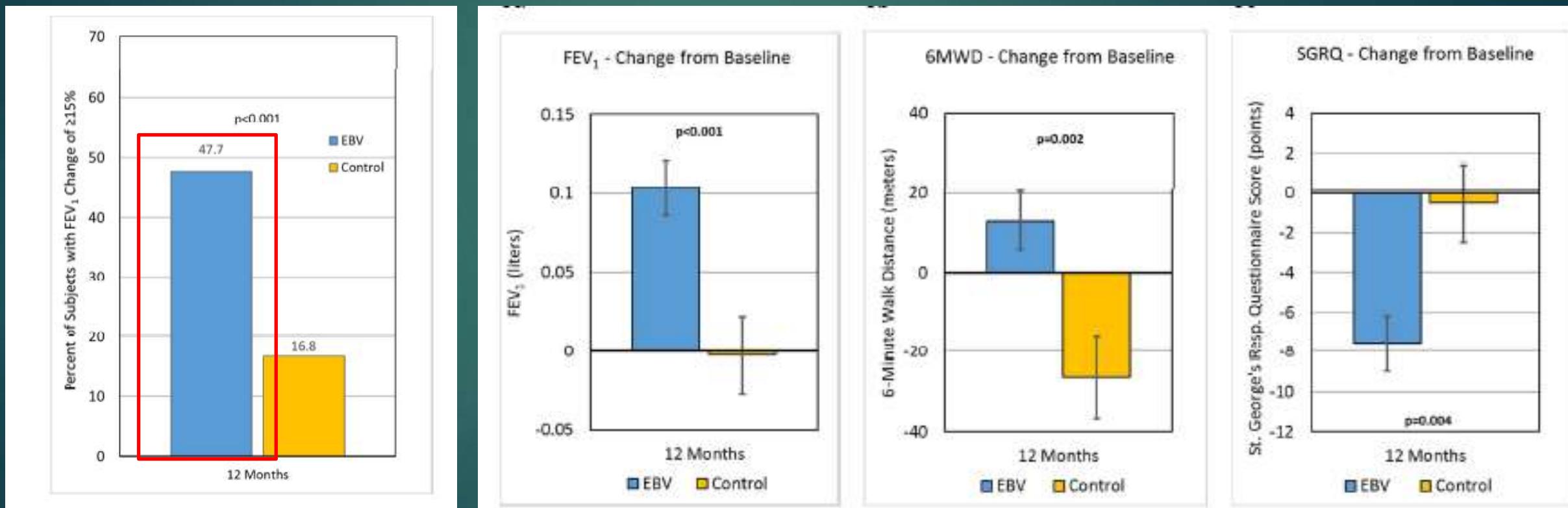


LIBERATE STUDY:

Multicenter RCT to evaluate effectiveness and safety of Zephyr® Endobronchial Valve EBV® out to 12-months.

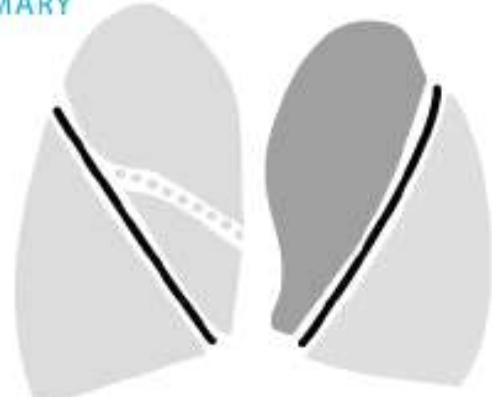
Heterogeneous emphysema with little to no collateral ventilation (CV) in the treated lobe. **190 subjects, 128 EBV and 62 controls.**

Pneumothorax was the most common serious adverse in 34/128 (26.6%) of EBV subjects. Four deaths occurred in the EBV group during this phase, and one each in the EBV and SoC groups between 46 days and 12-months.



Patient ID: NIKA 01.01.1951 Upload Date: April 12, 2018
 Scan ID: 68.188 Report Date: April 13, 2018
 CT Scan Date: Nov 21, 2017 Scan Comments: None

SUMMARY



KEY

- ≥70% Voxel Density Less Than -910 HU
- 60-70% Voxel Density Less Than -910 HU
- 50-60% Voxel Density Less Than -910 HU
- <50% Voxel Density Less Than -910 HU
- ≥95% Fissure Completeness
- 80-95% Fissure Completeness
- <80% Fissure Completeness

RESULTS

	RIGHT LUNG			LEFT LUNG		
	RUL	RUL+RML	RML	RLL	LUL	LLL
% Fissure Completeness	73.9	98.6	78.3	98.6	97.7	97.7
% Voxel Density Less Than -910 HU	52	53	56	51	60	53
% Voxel Density Less Than -950 HU	22	22	22	27	27	26
Inspiratory Volume (ml)	1747	2300	553	1718	2077	1505

STRAT-X assessment system

FEV1<50%, TLC> 100%,
 RV>150%, RV/TLC >0.58,
 DLCO > 20%, 6MWT 150-400m
 &MRC ≥ 3

With complete Fissures and no
 collateral ventilation

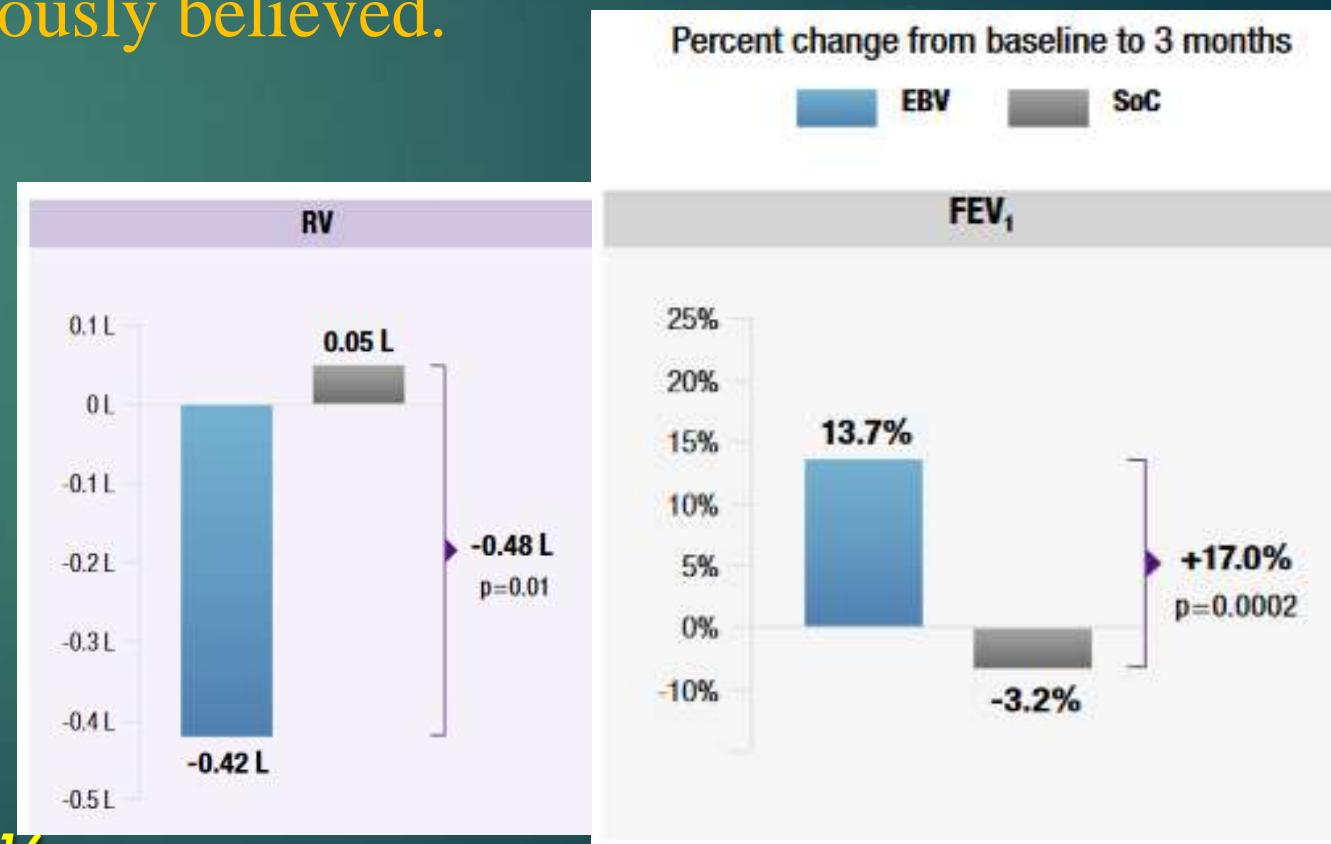
Optimal pharmacological and non pharmacological
 treatment

ΟΜΟΙΟΓΕΝΕΣ ΕΜΦΥΣΗΜΑ: IMPACT - RCT

93 ασθενείς με σοβαρό, ομοιογενές εμφύσημα και απουσία παράπλευρου αερισμού στον λοβό-στόχο.

These data indicate that EBV therapy can benefit substantially more patients than previously believed.

EBV-treated pts experienced improved exercise tolerance, with a 40-meter increase over the control group in the 6MWD, and improved QuoL, with a 10-point improvement in the SGRQ score over the control group.



Endoscopic LVR

Inferior Results

Spiration Intrabronchial Valves (IBV)



Multicentre European study for the treatment of advanced emphysema with bronchial valves

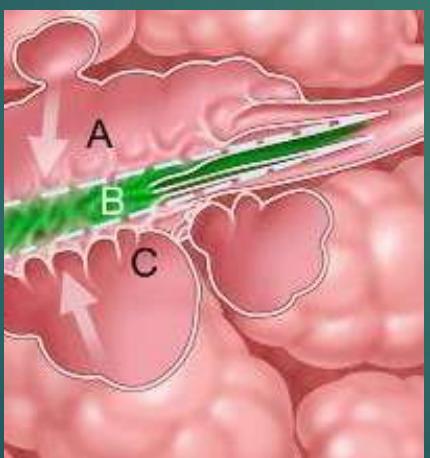
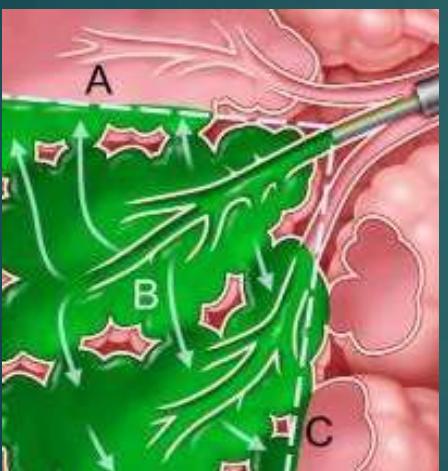
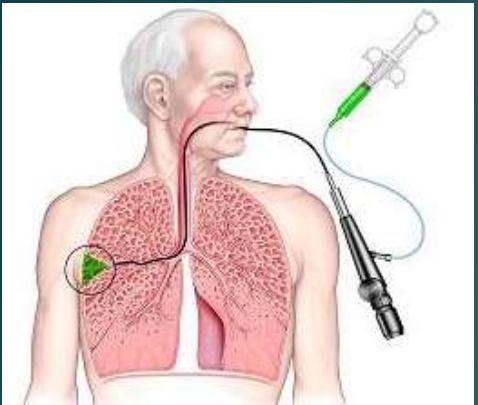
Eur Respir J 2012; 39: 1319–1325



Treatment with bronchial valves without complete lobar occlusion in both upper lobes was safe, but not effective in the majority of patients

B. Τροποποίηση πνευμονικού παρεγχύματος :

1. Polymer sealant LVR



Chest 2007;131:1108–1113.

Criner G et al. BLVR in Advanced Upper lobe Emphysema: Phase 2 Results.

Am J Respir Crit Care Med 2009; 179:791-798

Bilateral upper lobes treatment (8 subsegments).

Increase of FEV₁ by 15% FVC 9% TLC 6% and SGRQ in 12 weeks. NO significant complications.

Rafaely Y et al. BLVR in Advanced Homogeneous emphysema. Eur Respir J 2010;36:20-27

17 pts, (Upper lobes or apical of the lower lobes) 29-47% increase >12% in FEV1 and FVC 65-75%

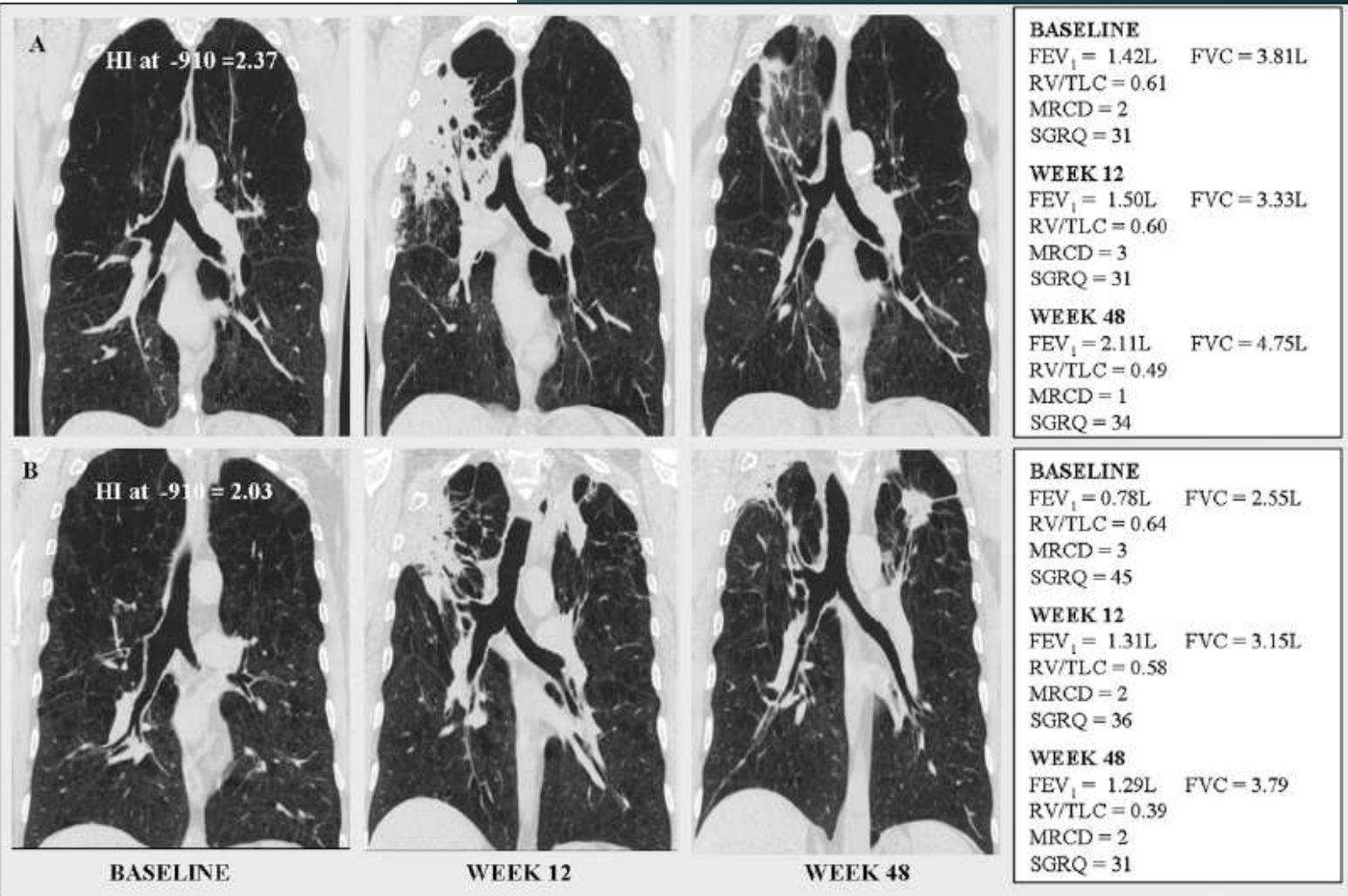
improvement of SGRQ No deaths. 20% AE COPD

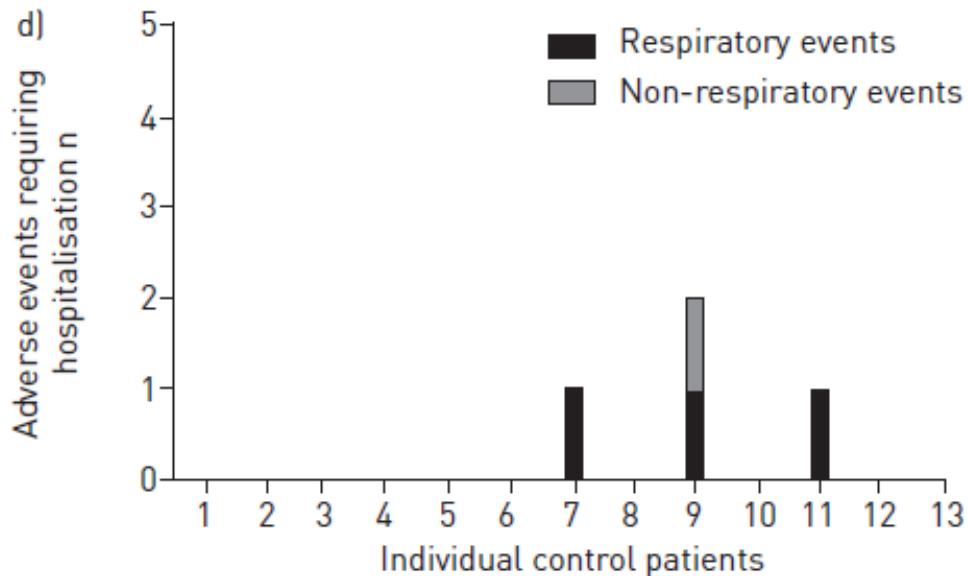
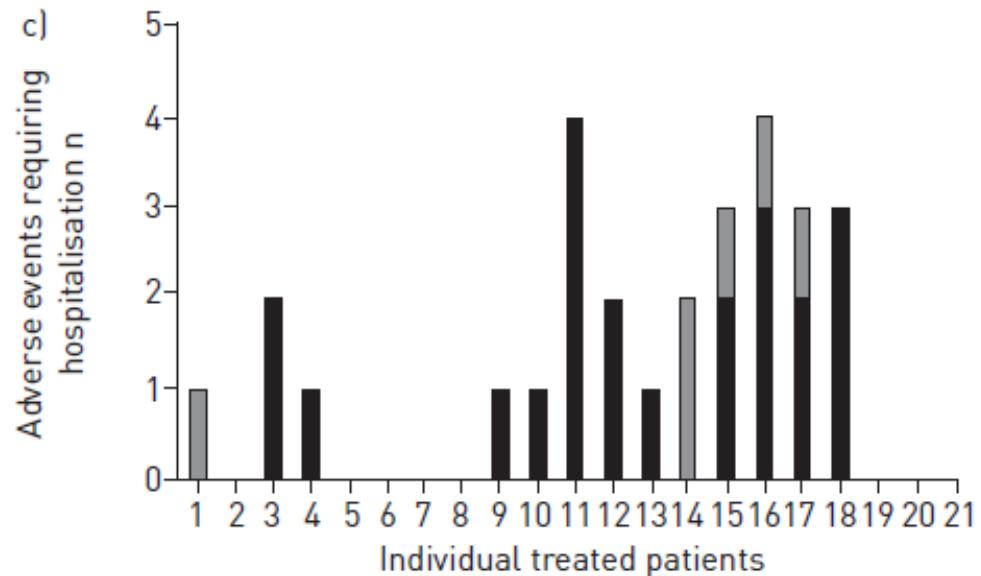


Bilateral Endoscopic Sealant Lung Volume Reduction Therapy for Advanced Emphysema

Mordechai R. Kramer, MD, FCCP; Yael Refael, MD; Nimrod Matmon, MD;
Dror Rosengarten, MD; and Oren Fruchter, MD

CHEST 2012;
142(5):1111–1117



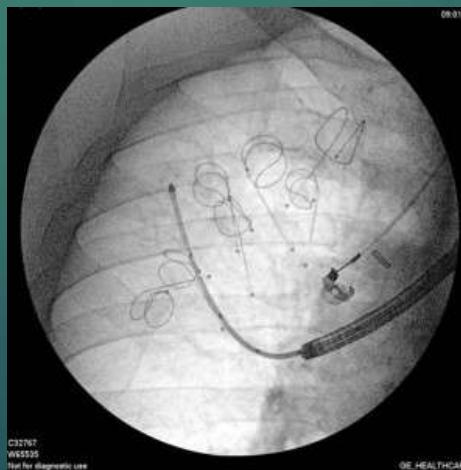
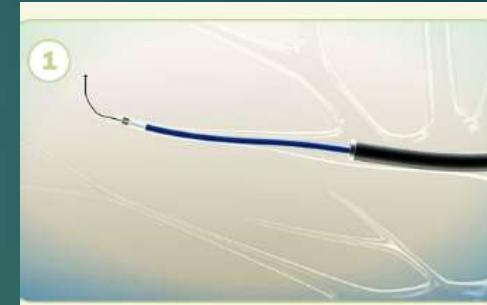
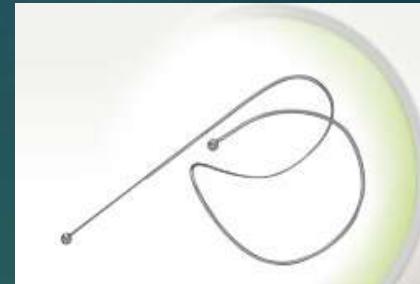
**A randomised trial of lung sealant versus medical therapy for advanced emphysema**

Subjects n	Δ from baseline	6m Treatment G	6m Control G	p
FEV1 [#]	FEV1(% ; mL)	$26 \pm 42\%$; 174 ± 317 mL	3 ± 11 ; 31 ± 145	0.03
SGRQ [¶]	SGRQ(U)	-13 ± 15	-3 ± 6	0.02
mMRC [*]	MRCD(U)	-0.6 ± 1.2	-0.5 ± 0.7	0.61
6MWD [§]	6MWT(m)	16 ± 52	-17 ± 46	0.08

Data are presented as mean \pm SD. [#] George's Respiratory Function Test; [¶] St George's Respiratory Questionnaire; ^{*} modified Medical Research Council classification; [§] six-minute walk distance.

Modifying the pulmonary parenchyma: Endobronchial coils made from nitinol— Pneum RX®

- Introduction under fluoroscopy.
- Not affected by collateral ventilation.
- 10 coils per lobe for volume reduction.
- Not in extreme destruction of the parenchyma-improve elastic properties of the lung.
- Once introduced difficult if not impossible to remove.



RESET trial: randomized, 22 pts vs 23 controls

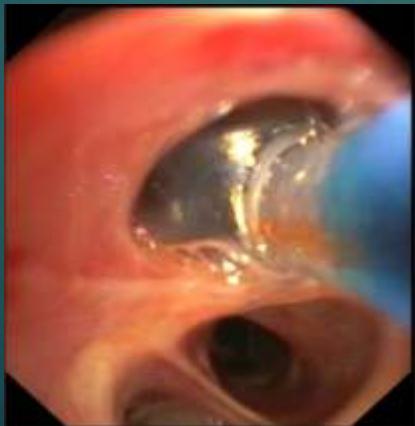
	Treatment	Usual care	Between group difference in change from baseline	P value
Primary outcome				
SGRQ	-8.11 (-13.83 to -2.39)	0.25 (-5.58 to 6.07)	-8.36 (-16.24 to -0.47)	0.04
Secondary outcome				
TLC (L)	-0.24 (-0.38 to -0.10)	-0.13 (-0.27 to 0.01)	-0.11 (-0.29 to 0.07)	0.22
RV (L)	-0.51 (-0.73 to -0.30)	-0.20 (-0.42 to 0.02)	-0.31 (-0.59 to -0.04)	0.03
6 MWT	51.15 (27.65 to 74.66)	-12.39 (-36.61 to 11.83)	63.55 (32.57 to 94.53)	<0.001
%change in FEV1	14.19 (6.84 to 21.55)	3.57 (-4.02 to 11.17)	10.62 (1.12 to 20.12)	0.03
mMRC	-0.24 (-0.57 to 0.09)	-0.09 (-0.44 to 0.26)	-0.15 (-0.60 to 0.30)	0.5

No between-group difference in serious adverse events

Lancet Respir. Med. 2013; 1: 233–40.

Modifying the pulmonary parenchyma: Bronchoscopic Thermal Vapor Ablation InterVapor® System

- Steam administration (5-10 cal/gr) with endobronchial catheter with balloon at segments of targeted lobe.
- Thermal damage that causes scarring and atelectasis.
- Not affected by collateral ventilation.



ULP- E, 45 patients, 24 control, one lobe treated per session.

Bronchoscopic vapour ablation group	Control group	Difference between groups (95% CI)	p value	
FEV ₁ (mL)	70·5 (SD 179·9)	-32·2 (SD 114·3)	102·6 (30·5 to 174·8)	0·0060
FVC (mL)	110·2 (SD 395·4)	-128·3 (SD 409·2)	238·5 (28·6 to 448·3)	0·0269
Residual volume (mL)	-159·1 (SD 572·4)	78·3 (SD 470·0)	-237·4 (-499·2 to 24·5)	0·0747
FRC (mL)	-163·6 (SD 564·5)	82·6 (SD 417·4)	-246·2 (-490·0 to -2·5)	0·0477
6MWT (m)	8·8 (SD 66·5)	5·1 (SD 73·4)	3·6 (-33·3 to 40·6)	0·8442

FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. FRC=functional residual capacity. 6MWT=6 min walk test.

Table: Change In secondary endpoint measures at 12 months after vapour ablation

47 patients: 23 to treatment and 24 to usual care . SGRQ response at 90 days after treatment was greater in the treatment group than it was in the usual care group (between-group difference in change from baseline **-8·36 points** [95% CI -16·24 to -0·47]; p=0·04).

Lung Volume Reduction with Vapor Ablation in the Presence of Incomplete Fissures: 12-Month Results from the STEP-UP Randomized Controlled Study

Respiration 2016;92:397–403

- 78% of treated patients were found to have 1 or more incomplete fissures adjacent to a treated lobe and were considered to be CV+

Table 1. Results for primary efficacy endpoints for patients with incomplete fissures

	Bronchoscopic vapor ablation group	Control group	Difference between groups (95% CI)	p value
Patients with incomplete fissures, n	35	19		
Δ FEV ₁ , %				
3 months	7.9	-1.2	9.1 (0.1 to 18.1)	0.0056
6 months	7.6	-3.4	10.9 (3.6 to 18.4)	0.0024
12 months	9.2	-5.4	14.6 (3.1 to 26.7)	0.0137
Δ SGRQ-C (points)				
3 months	-7.7	-2.2	-5.5 (0.5 to -11.5)	0.0697
6 months	-6.8	-0.6	-6.1 (1.3 to -13.7)	0.1089
12 months	-9.4	-1.0	-8.4 (0.7 to -17.5)	0.0712

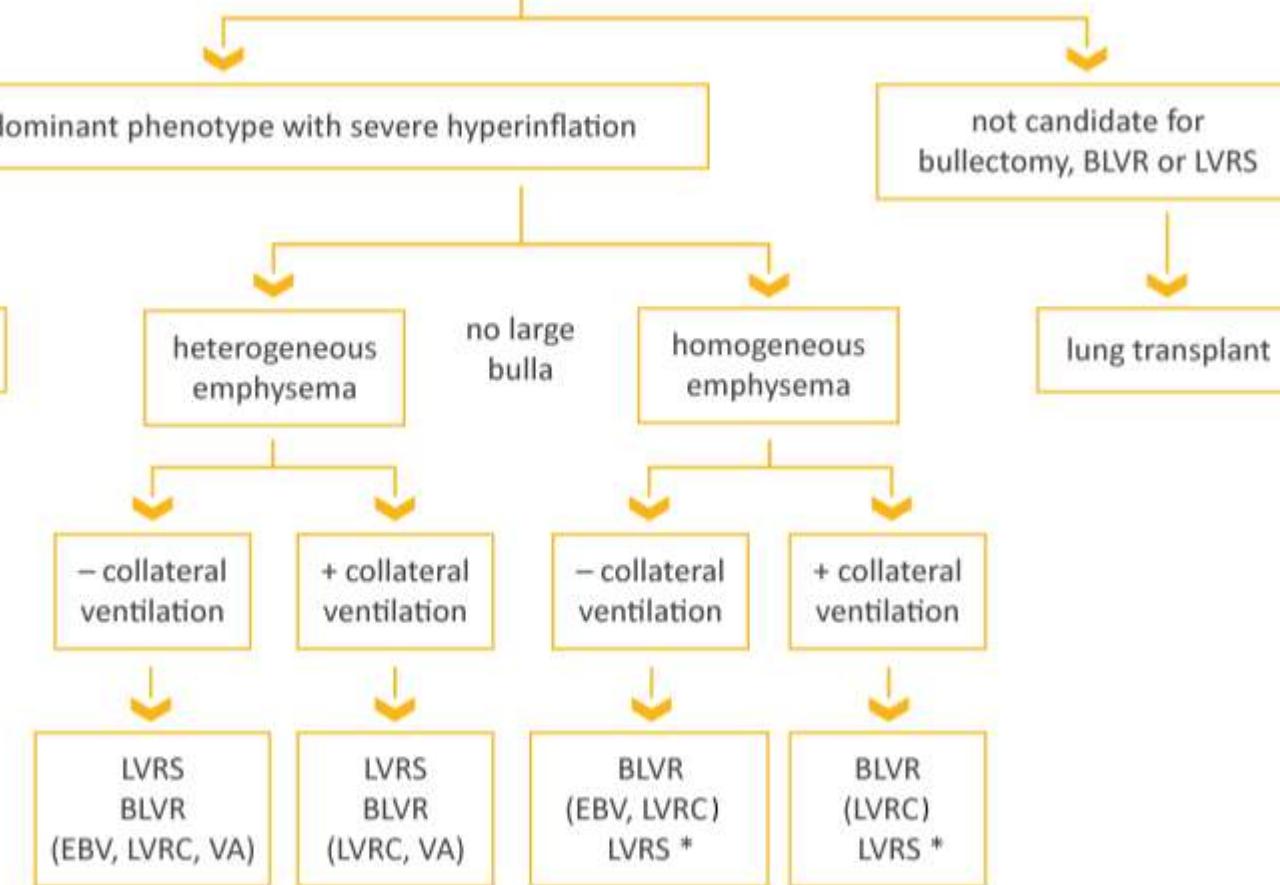
Vapor Ablation in the Presence of Incomplete Fissures: 12-Month Results from the STEP-UP Randomized Controlled Study. Adverse events

Table 3. SAEs and hospital admissions

	Treatment group (<i>n</i> = 35)		Control group (<i>n</i> = 19)	
	0–180 days after treatment ¹	181–365 days after treatment ¹	0–180 days after randomization	181–365 days after randomization
COPD exacerbation	3 (9)	0	1 (5)	2 (11)
Pneumonia or pneumonitis	8 (23)	0	1 (5)	1 (5)
Pneumothorax	1 ² (3)	0	0	0
Hemoptysis	0	0	0	0
Death	1 (3)	0	0	0
Any respiratory SAE	9 (26)	0	2 (11)	3 (16)

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Advanced COPD



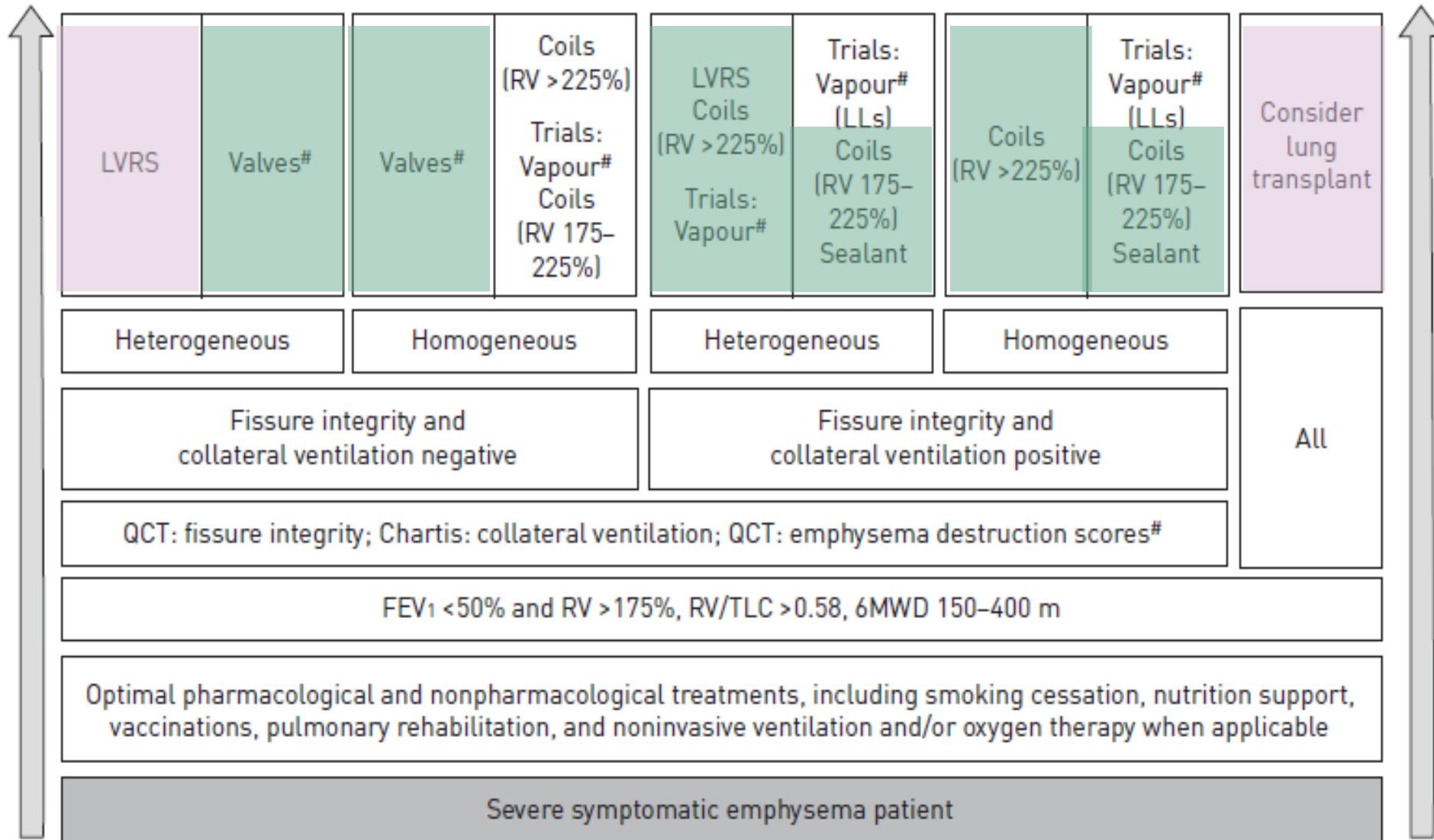
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Definition of Abbreviations: BLVR, Bronchoscopic Lung Volume Reduction, EBV, endobronchial Valve, LVRS, Lung volume reduction surgery, LVRC, Lung volume reduction coil, VA, Vapor ablation

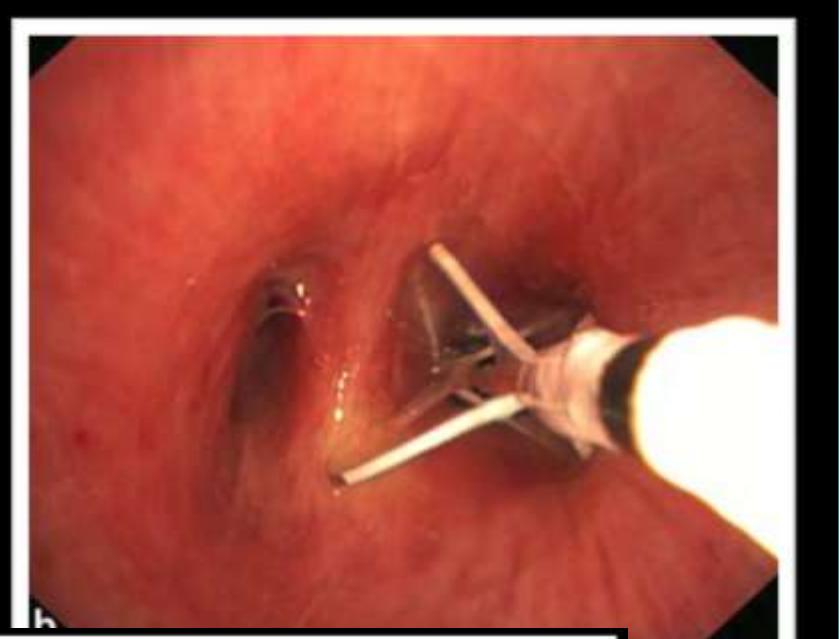
*at some but not all centers

FIGURE 4.5

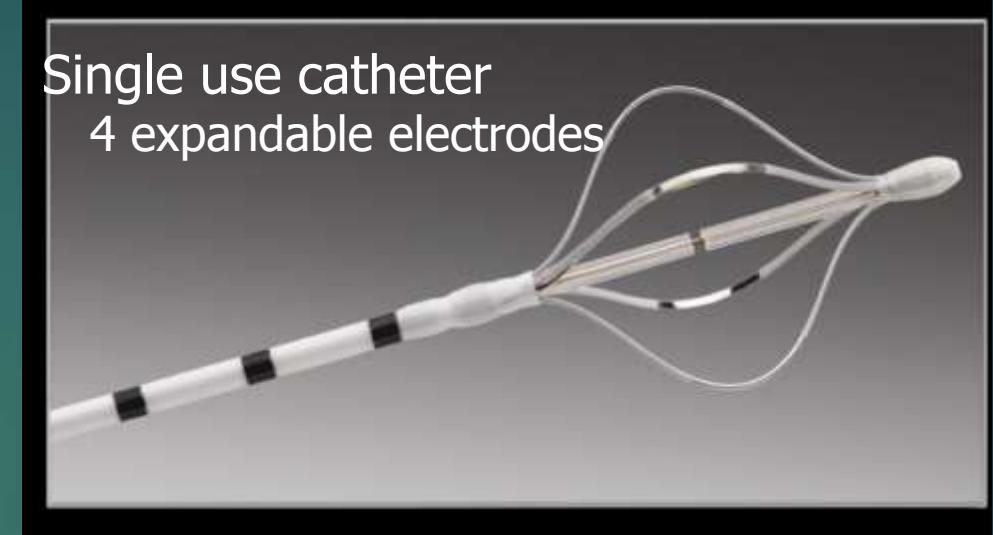




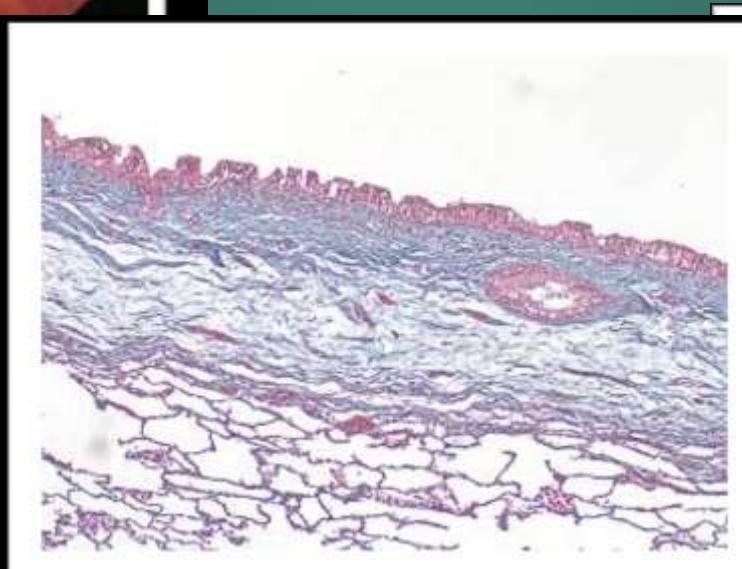
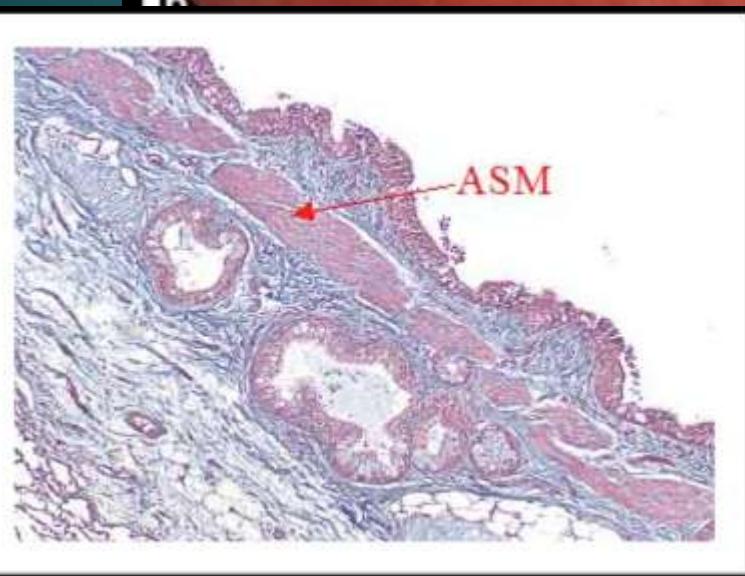
Radiofrequency ... Ablation for ASTHMA

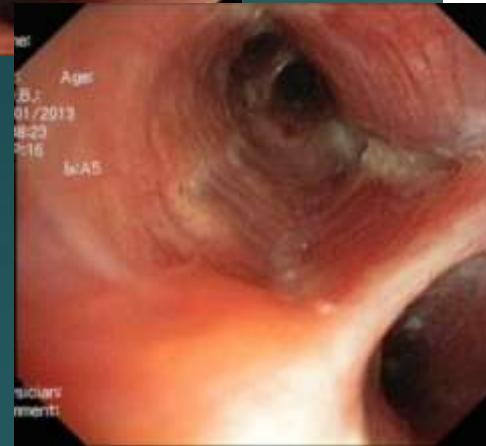
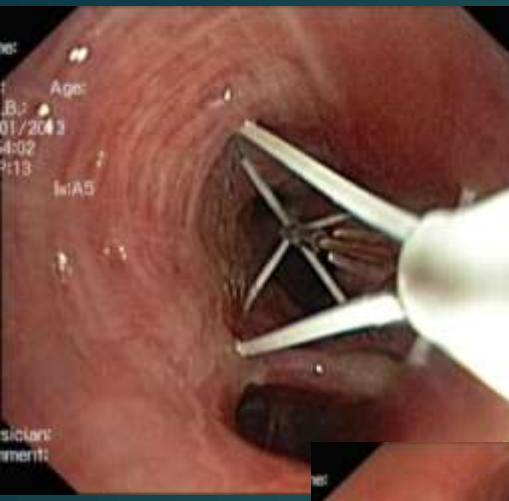


Single use catheter
4 expandable electrodes



Radiofrequency generator
Monopolar 450 – 500 kHz





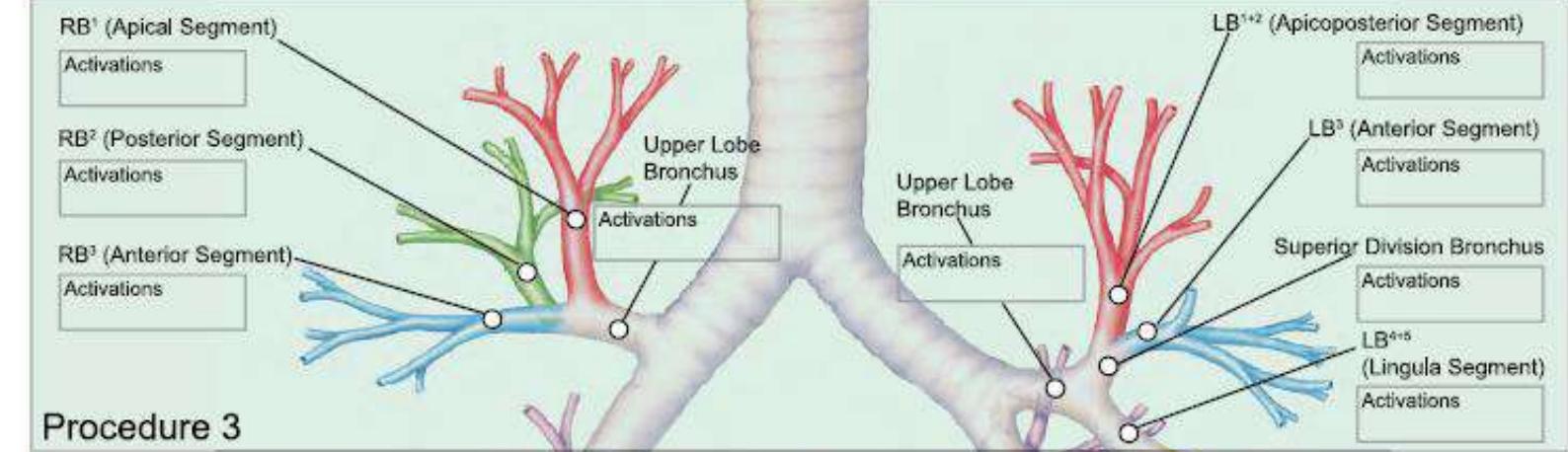
40 – 100
activations/register

45 – 60 minutes / BT

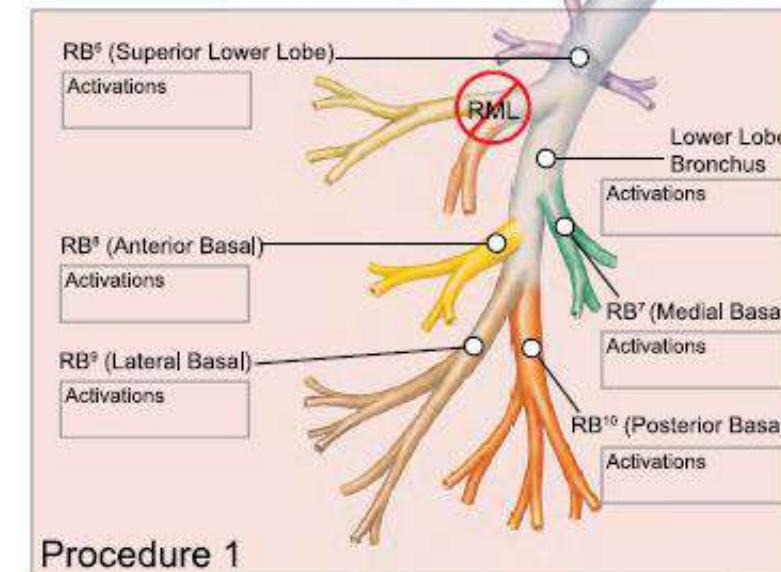


Patient ID: _____ Procedure 1: Right Lower Lobe Procedure 2: Left Lower Lobe Procedure 3: Right & Left Upper Lobes

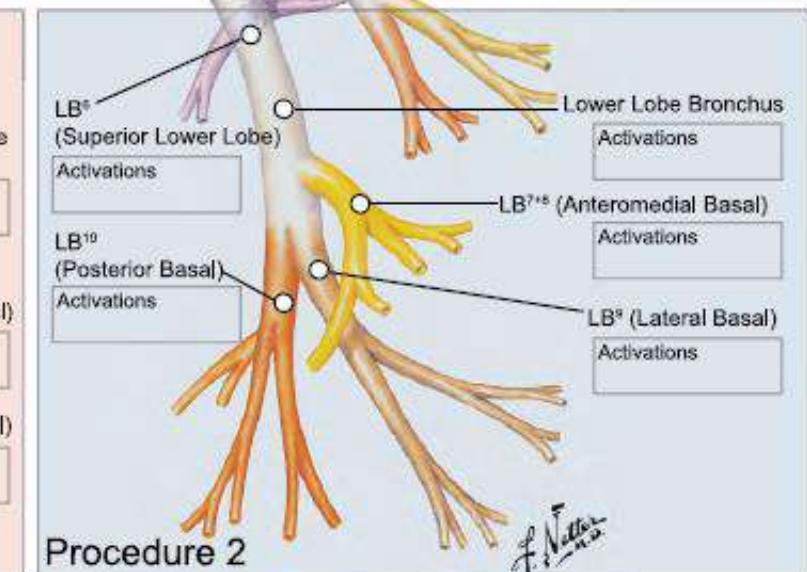
Treatment Date: _____ Treatment Date: _____ Treatment Date: _____ Treatment Date: _____



Procedure 3



Procedure 1

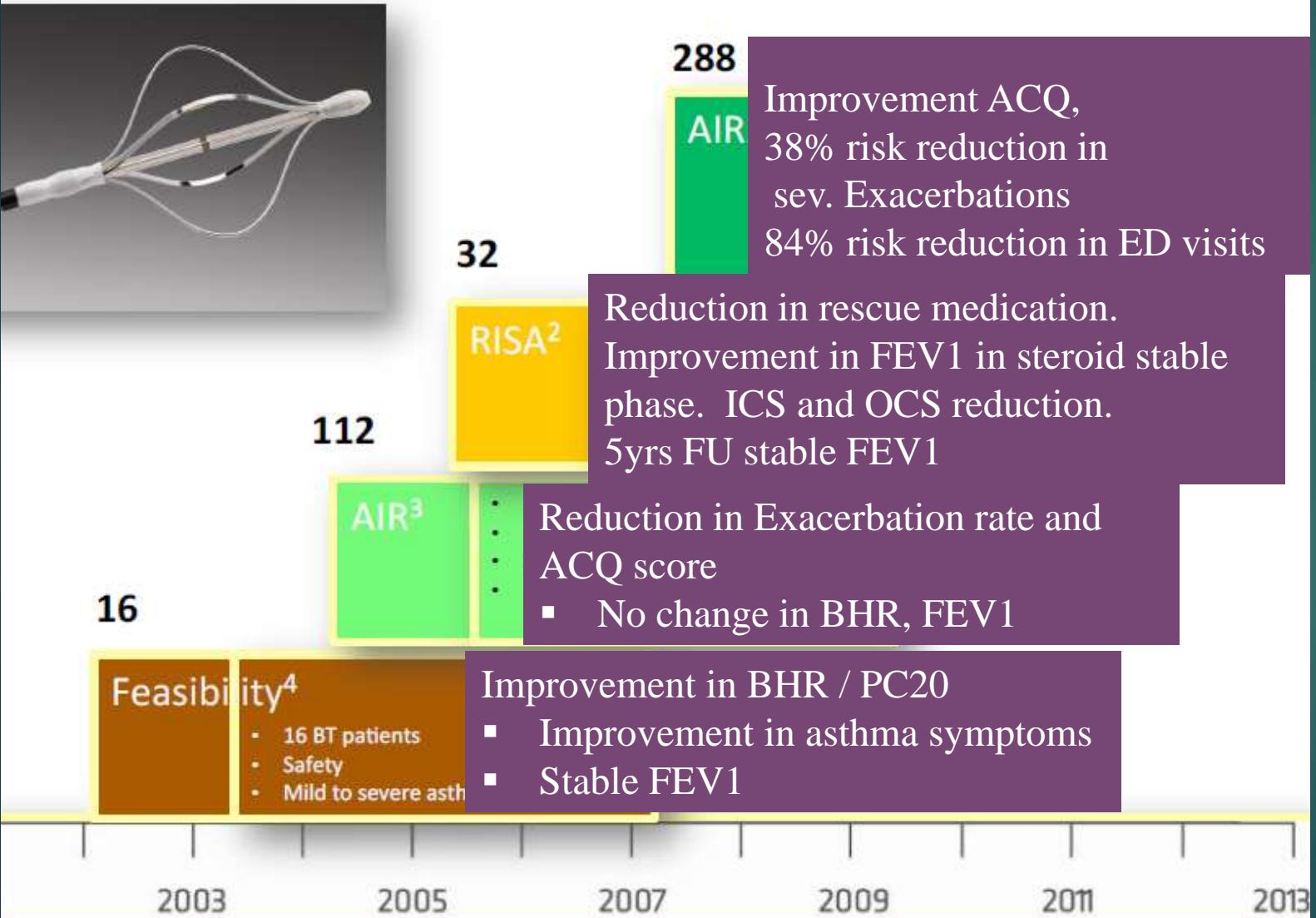


Procedure 2

f. Noller

Boston
Scientific

Clinical trials thermoplasty



- ▶ Πρόκληση θερμότητας ως 65°C
- ▶ Ενέργεια 18 W
- ▶ Εφαρμογή για 10 sec σε κάθε θέση. Στοχεύει τους βρόγχους από το επίπεδο των λοβαίων ως αυτούς με d: 3mm
- ▶ Μείωση της μάζας των λείων μυϊκών ινών κατά 50%
- ▶ Όχι πλήρης καταστροφή τους
- ▶ Δεν επηρεάζει το περιβρογχικό πνευμονικό παρέγχυμα

PAS2: FDA 3 yrs FU

284 subjects enrolled from April, 2011 to Oct, 2014

- Comparison of the first 190 PAS2 subjects with poorer asthma control to the 190 BT-treated subjects in the AIR2 trial
- 5 years FU completed in 2020



Eur Respir J 2017; 50:
1700017



ORIGINAL ARTICLE
ASTHMA

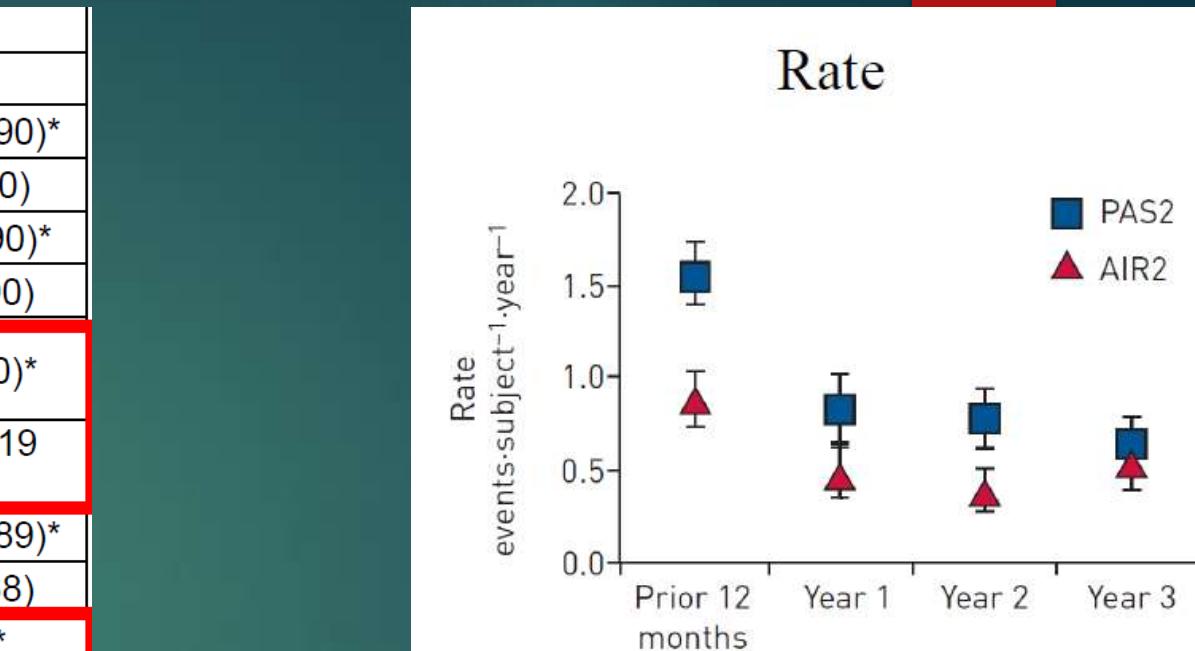


rossMark

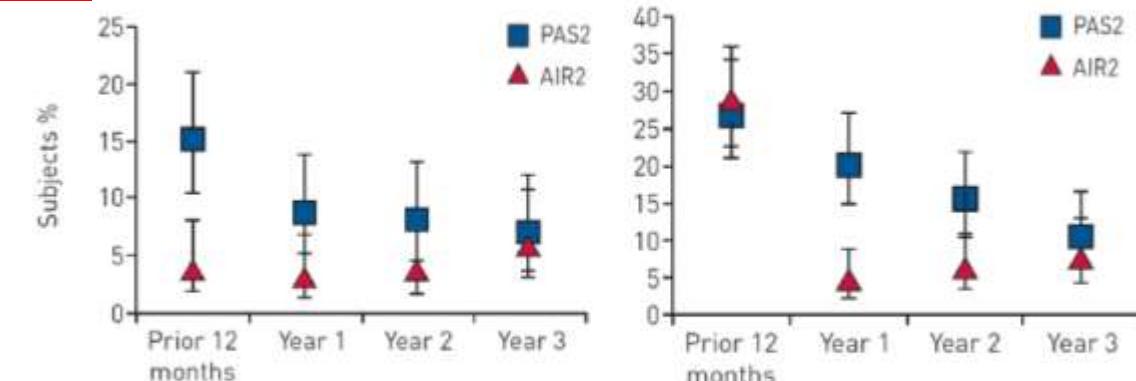
Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies

	PAS2	AIR2
Characteristic	N=190	N=190
Age (years)	45.87 ± 11.39 (190)	40.69 ± 11.89 (190)*
Female	61.6% (117/190)	57.4% (109/190)
Body Mass Index [kg/m ²]	32.50 ± 7.72 (190)	29.29 ± 6.16 (190)*
AQLQ	4.17 ± 1.33 (190)	4.30 ± 1.17 (190)
Severe Asthma (ERS/ATS)	94.7% (180/190)	82.1% (156/190)*
ICS ($\mu\text{g/day}$)	2301.04 ± 807.46 (189)	1960.74 ± 745.19 (190)*
LABA ($\mu\text{g/day}$)	106.87 ± 39.36 (189)	116.8 ± 34.39 (189)*
SABA (puffs/day)	2.38 ± 1.48 (182)	2.24 ± 1.29 (168)
OCS (% and mg/day)	18.9% (36/190)	4.2% (8/190)*
	9.13 ± 2.66 (35)	11.88 ± 15.51 (8)
Omalizumab (% and mg/day)	15.8% (30/190)	1.1% (2/190)*
	266.83 ± 88.67 (30)	350.00 ± 35.36 (2)

- No mortality
- (S)AEs in treatment period, treatable/predictable
- No long term complications
- HRCT: 3% bronchiectasies
- No device related complications
- Pulmonary function tests: stable FEV1

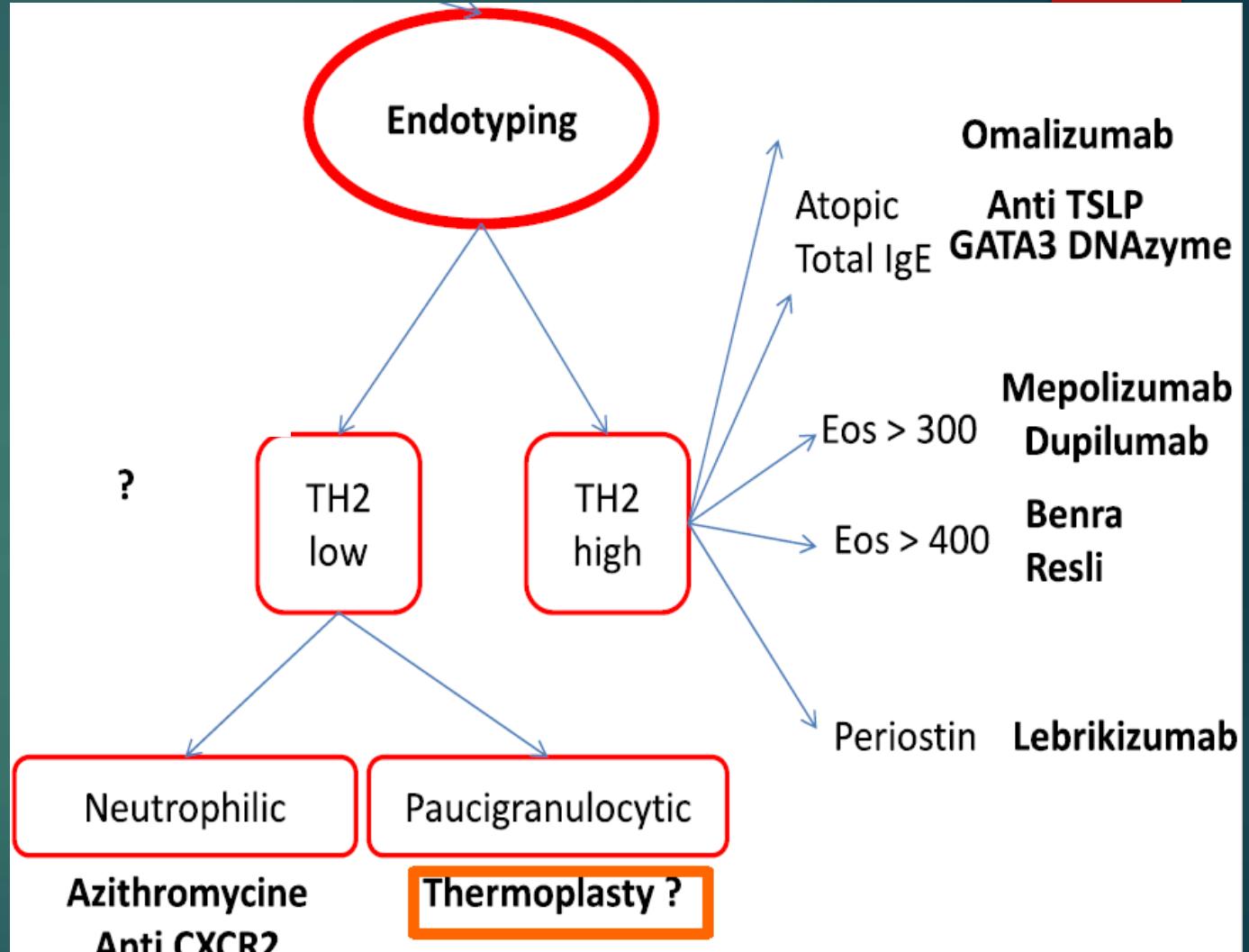


Hospitalizations



Επιλογή ασθενών

- 21 is a minimum age for BT
- Sedation as per local experience and skills
- Treat patients who have responded but only partially to Omalizumab
- BT can be performed safely in any patient with Fev1 > 50% pred
- No evidence supporting re-treatment



Take Home message



BLVR for Pulm. Emphysema

- ▶ Ασθενείς με απόφραξη και υπερδιάταση (TLC>100% RV>175%), με σοβαρό εμφύσημα (-910HU score). Ελέγχεται η ομοιογένεια/ετερογένεια και η ακεραιότητα των μεσολοβίων.
- ▶ CV (-) Valves
- ▶ CV(+) Coils, Sealant, Vapor
- ▶ Ανταπόκριση σε 50-75% των ασθενών
- ▶ Βελτίωση FEV1, RV, TLC
- ▶ Βελτίωση αντοχής στην άσκηση κ QoL

▶ RF Bronchial Thermoplasty for ASTHMA

- ▶ RCTs: AIR/RISA/AIR2:

Κλινική Βελτίωση ACQ/AQLQ

- ▶ Μείωση ρυθμού παροξύνσεων
- ▶ Βρογχική Υπεραντιδραστικότητα και FEV1 παραμένουν σταθερά
- ▶ Την περίοδο της επέμβασης παρατηρούνται παροξύνσεις

▶ Μηχανισμός δράσης της BT?

▶ Ποιοι ασθενείς ωφελούνται περισσότερο?

- ▶ ■ TASMA study: AMC, UMCG, Royal Brompton
- ▶ ■ ASTMATERM study: France

Precision Medicine

PERSPECTIVE
PRECISION MEDICINE FOR AIRWAY DISEASES



Treatable traits: toward precision medicine of airway diseases

Ευχαριστώ

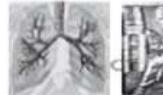
Alvaro Alonso¹, Michael A. Barnes², Mike Thomas³, Claus Vogelmeier⁴,
Guy Brinkmann⁵, Stephen Holgate⁷, Marc Humbert⁸, Paul Jones⁹,
Peter G. Gibson¹⁰, Jørgen Vestbo¹¹, Richard Beasley¹² and Ian D. Pavord¹³

Athens welcomes



6th European Congress
for Bronchology
and Interventional Pulmonology

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