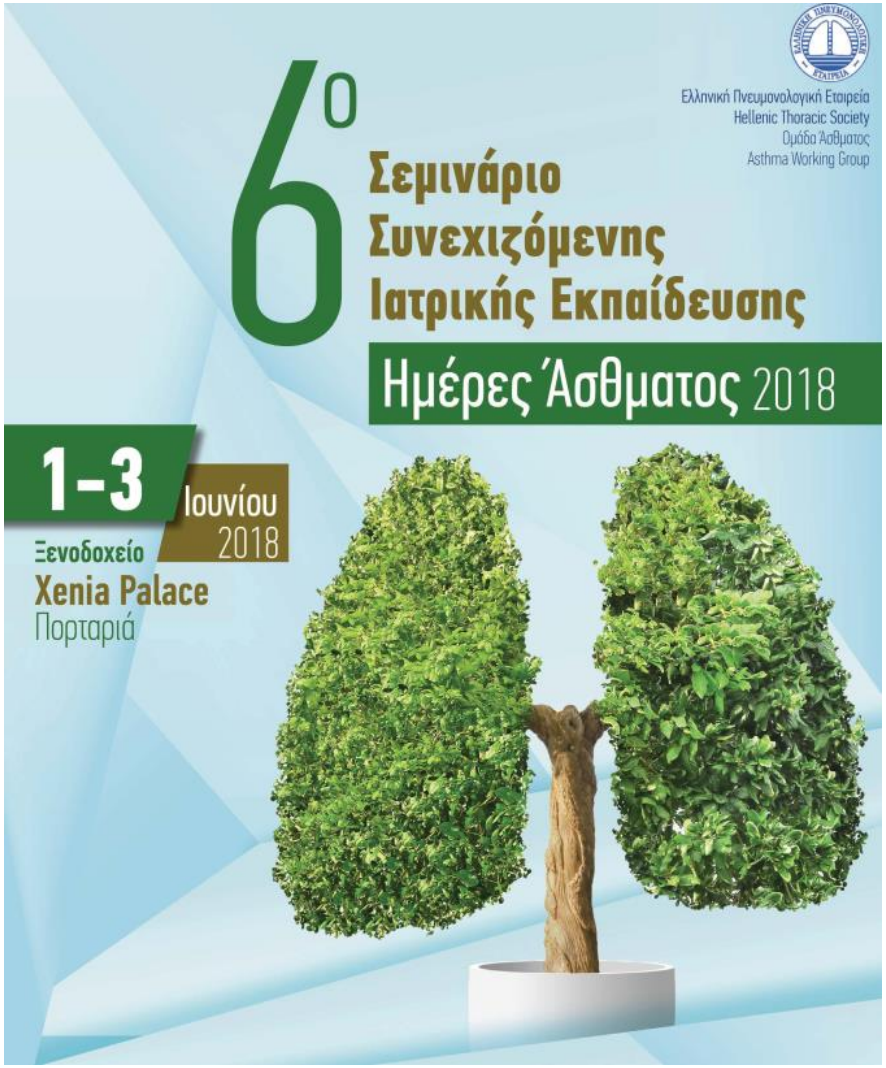
Βρογχοσκοπική θεραπεία στο σοβαρό άσθμα – Bronchial Thermoplasty



Ελευθέριος Ζέρβας,
Πνευμονολόγος Επιμελητής Α΄ ΕΣΥ
Συντονιστής Ομάδας Άσθματος ΕΠΕ
7η Πνευμονολογική Κλινική
Γ.Ν.Ν.Θ.Α «Η ΣΩΤΗΡΙΑ»

Conflict of interest (Δήλωση σύγκρουσης συμφερόντων)

- Συμμετοχή σε advisory board (συμβουλευτική επιτροπή) των φαρμακευτικών εταιρειών Elpen, Astra, Novartis, GSK, Menarini

- Honorarium (τιμητικές αμοιβές) ως προσκεκλημένος ομιλητής από τις φαρμακευτικές εταιρείες Astra, Novartis, Elpen, USB, Menarini, GSK

- Κάλυψη εξόδων συμμετοχής (εγγραφής, ταξιδίου και διαμονής) σε ελληνικά και διεθνή συνέδρια από τις φαρμακευτικές εταιρείες Astra, Novartis, Elpen, Chiezi, USB, GSK, Galenica, Roche, Takeda , MSD

Bronchial Thermoplasty

- **Εισαγωγικά στοιχεία**
- **Ποια η δράση της στους μηχανισμούς του άσθματος – Πως δουλεύει?**
- **Δεδομένα κλινικών μελετών – real life εμπειρίας**
- **Πως γίνεται στην πράξη? Σε ποιους ασθενείς?**
- **Συμπεράσματα**

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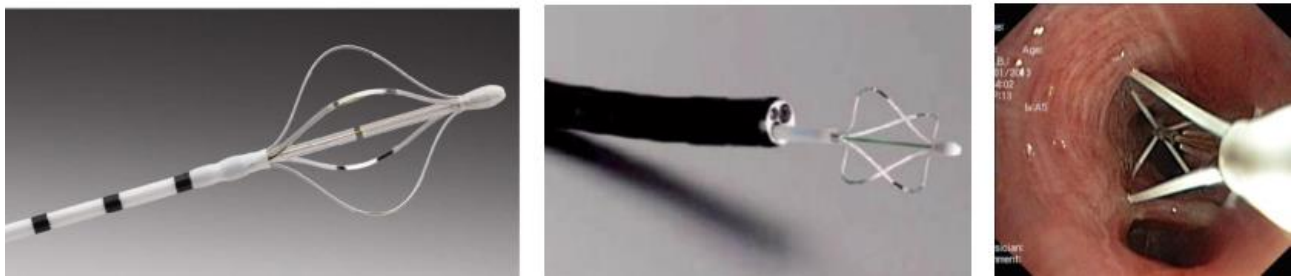
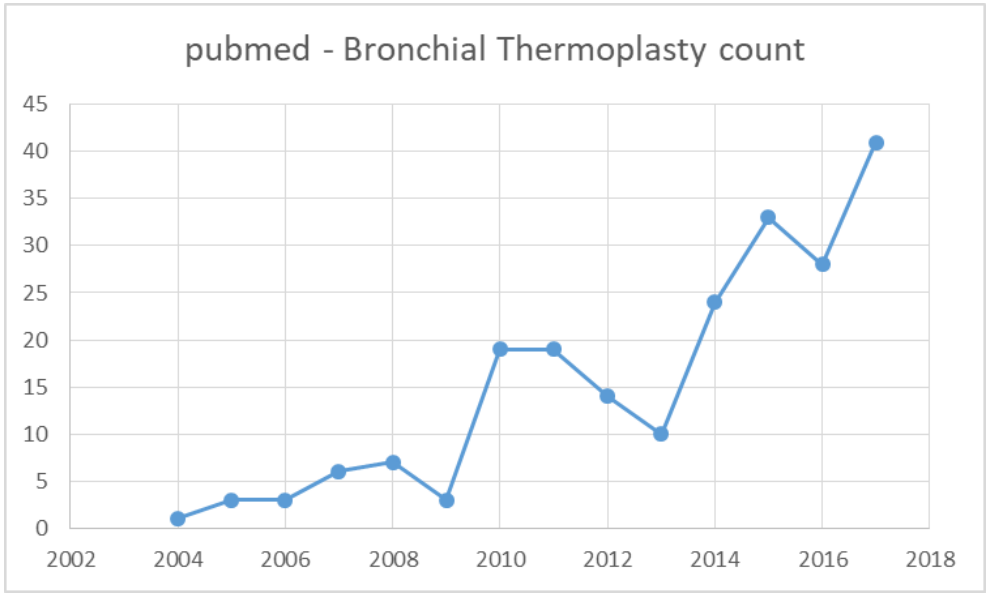
BT – Εισαγωγικά στοιχεία

Bronchial Thermoplasty

- a endoscopic treatment for severe asthma -





BT – Εισαγωγικά στοιχεία

Bronchial thermoplasty is the 1st licensed non-pharmacological treatment for severe asthma

Cox PG, Miller J, Mitzner W, Leff AR. Radiofrequency ablation of airway smooth muscle for sustained treatment of asthma: preliminary investigations. *Eur Respir J*, 24(4), 659-663 (2004).

***The first description of the development of bronchial thermoplasty as procedure to reduce the amount of airway smooth muscle in severe asthma through the local application of thermal energy to the airways with the aim of improving asthma control**

- Bronchial thermoplasty is licensed for the treatment of asthma in the USA, Europe, China and in many other countries.
- The FDA gave premarket approval (PMA) for the Alair® bronchial thermoplasty system as a treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with ICS and LABA in 2010.
- In the European Union, the 'Alair' bronchial thermoplasty system has a CE Mark for the treatment of asthma in patients 18 years and older.

Bronchial Thermoplasty

- **Εισαγωγικά στοιχεία**
- **Ποια η δράση της στους μηχανισμούς του άσθματος – Πως δουλεύει?**
- **Δεδομένα κλινικών μελετών – real life εμπειρίας**
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BT – Πως δουλεύει?

- Several mechanisms of action of BT have been proposed, including alterations to the structure or function of airway smooth muscle and/or other airway cells and structures including epithelial cells, nerves, extracellular matrix and inflammatory cells.

- ***Reduced airway smooth muscle mass***

- ***Altered airway smooth muscle function**, **reduced airway smooth muscle contractility***

- ***Altered airway epithelial cells, glands, nerves, extracellular matrix components***

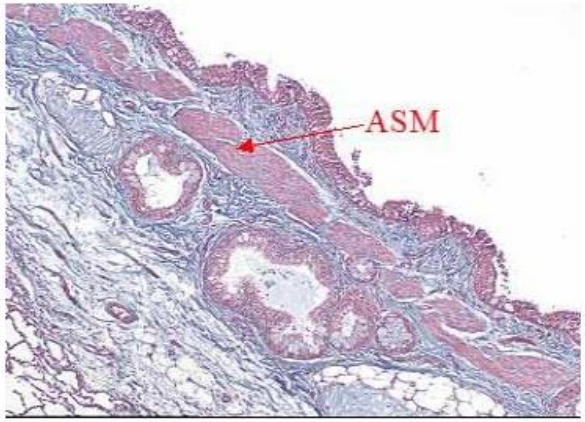
- ***Effects on inflammation? (reduced inflammatory cytokine secretion from airway smooth muscle)***

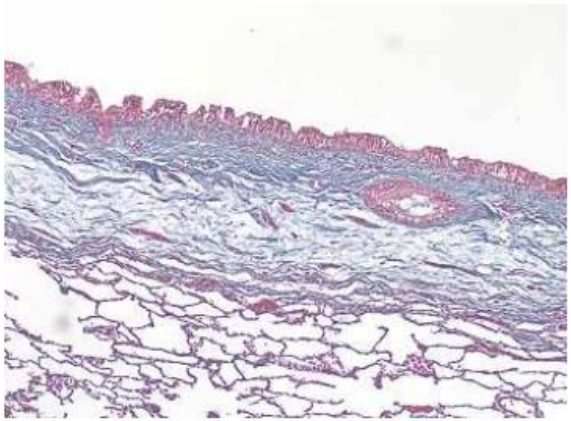
The mechanism of action of this relatively new, endoscopic treatment for asthma is incompletely understood…..

BT – Πως δουλεύει?

- ***Reduced airway smooth muscle mass***
- ***Altered airway smooth muscle function, reduced airway smooth muscle contractility***

Altered Airway Smooth Muscle
12 Weeks Post-Treatment (Canine Model)





UNTREATED

Smooth muscle present

TREATED

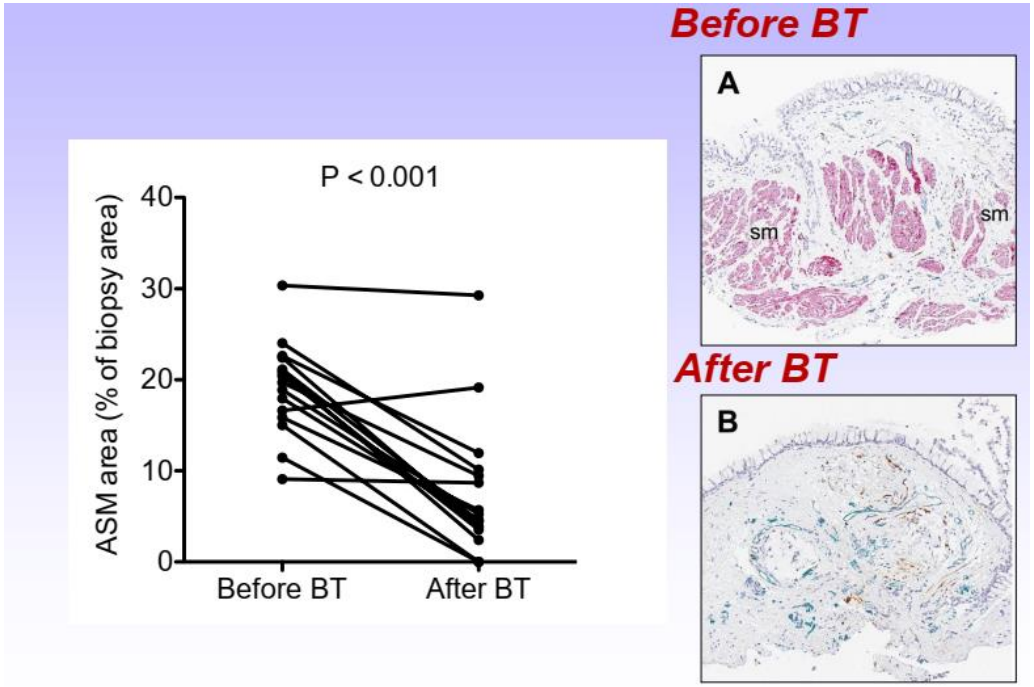
Smooth muscle largely absent

Danek et al. J Appl Physiol. 2004; 97: 1946-1953

BT – Πως δουλεύει?

- ***Reduced airway smooth muscle mass***
- ***Altered airway smooth muscle function, reduced airway smooth muscle contractility***

Effect of bronchial thermoplasty on ASM area
(confirmation in n = 15 severe refractory asthmatics)

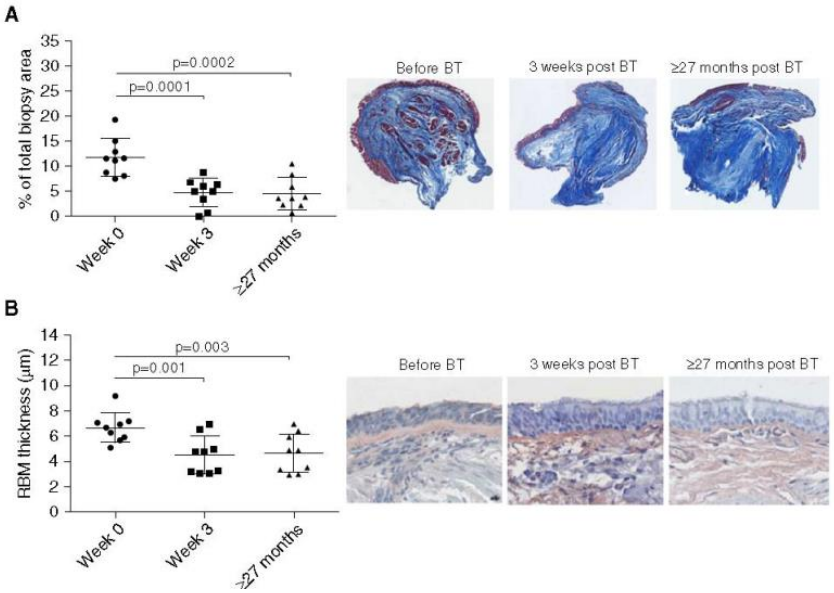


Pretolani Am.J.Respir.Crit.Care Med 2014;190 1452-4

BT – Πως δουλεύει?

- ***Reduced airway smooth muscle mass***
- ***Altered airway smooth muscle function, reduced airway smooth muscle contractility***

Long-Term Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Reticular Basement Membrane Thickness in Severe Asthma



	Before BT	≥27 mo post-BT	*P* Value*
Age, yr†	49 ± 4.7	53 ± 4.6	—
Sex, males/females	6/3	6/3	—
Post-BD FEV_1, L†	2.75 ± 0.33	2.87 ± 0.36	0.41
Percentage of predicted values†	81 ± 5.8%	83.8 ± 6.4%	
ICS doses, μg†	1,093.7 ± 141	1,000 ± 205	0.16
Severe exacerbations‡	2 (0-10)	0 (0-2)	0.016
ACSS score, %†	81.25 ± 4.5	93.75 ± 3.86	0.026

Chakir et al Annals of ATS 2016

BT – Πως δουλεύει?

- ***Reduced airway smooth muscle mass***
- ***Altered airway smooth muscle function, reduced airway smooth muscle contractility***

Eur Respir J. 2018 May 24;51(5). pii: 1701680. doi: 10.1183/13993003.01680-2017. Print 2018 May.

In vitro, in silico and *in vivo* study challenges the impact of bronchial thermoplasty on acute airway smooth muscle mass loss.

Chernyavsky IL[1,2], Russell RJ[3,2], Saunders RM[3,2], Morris GE[4], Berair R[3], Singapuri A[3], Chachi L[3], Mansur AH[5], Howarth PH[6], Dennison P[6], Chaudhuri R[7,8], Bicknell S[7], Rose FRAJ[9], Siddiqui S[3], Brook BS[10,11], Brightling CE[3,11].

Author information

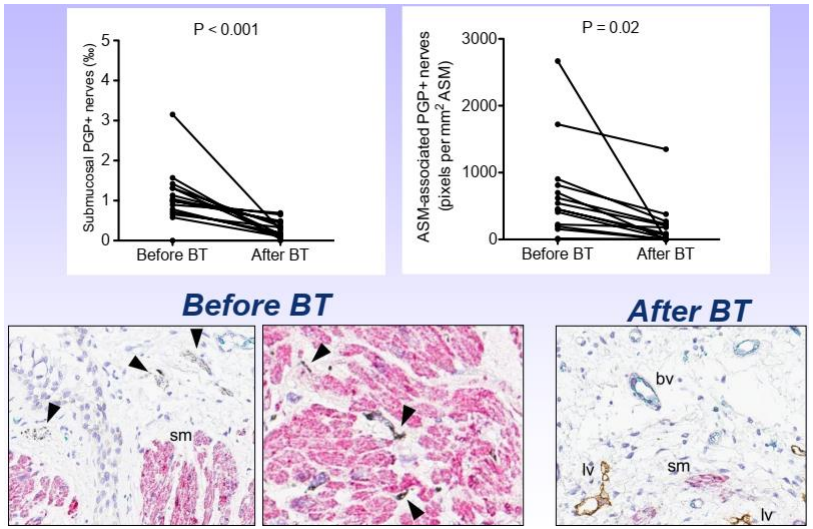
Abstract

Bronchial thermoplasty is a treatment for asthma. It is currently unclear whether its histopathological impact is sufficiently explained by the proportion of airway wall that is exposed to temperatures necessary to affect cell survival.Airway smooth muscle and bronchial epithelial cells were exposed to media (37-70°C) for 10 s to mimic thermoplasty. *In silico* we developed a mathematical model of airway heat distribution post-thermoplasty. *In vivo* we determined airway smooth muscle mass and epithelial integrity pre- and post-thermoplasty in 14 patients with severe asthma.*In vitro* airway smooth muscle and epithelial cell number decreased significantly following the addition of media heated to ≥65°C. *In silico* simulations showed a heterogeneous heat distribution that was amplified in larger airways, with <10% of the airway wall heated to >60°C in airways with an inner radius of ~4 mm. *In vivo* at 6 weeks post-thermoplasty, there was an improvement in asthma control (measured *via* Asthma Control Questionnaire-6; mean difference 0.7, 95% CI 0.1-1.3; p=0.03), airway smooth muscle mass decreased (absolute median reduction 5%, interquartile range (IQR) 0-10; p=0.03) and epithelial integrity increased (14%, IQR 6-29; p=0.007). Neither of the latter two outcomes was related to improved asthma control.Integrated *in vitro* and *in silico* modelling suggest that the reduction in airway smooth muscle post-thermoplasty cannot be fully explained by acute heating, and nor did this reduction confer a greater improvement in asthma control.

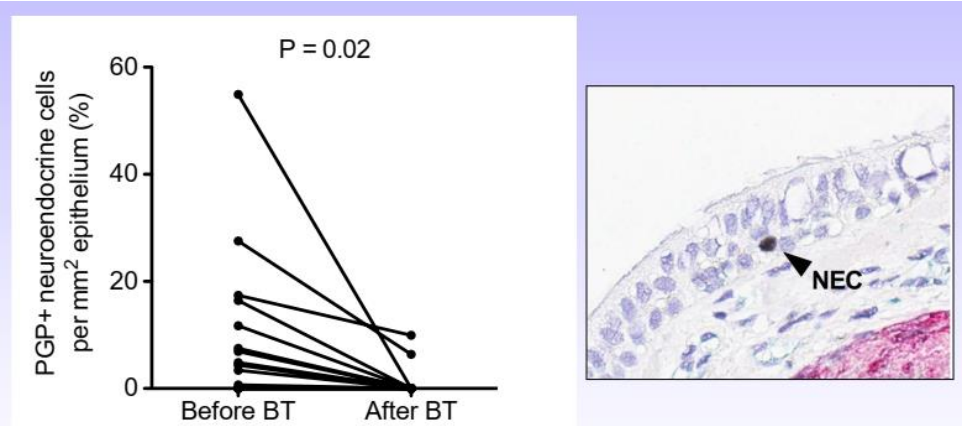
BT – Πως δουλεύει?

- ***Altered airway epithelial cells, glands, nerves, extracellular matrix components***

Effect of bronchial thermoplasty on submucosal and ASM-associated nerve endings (PGP immunostaining)



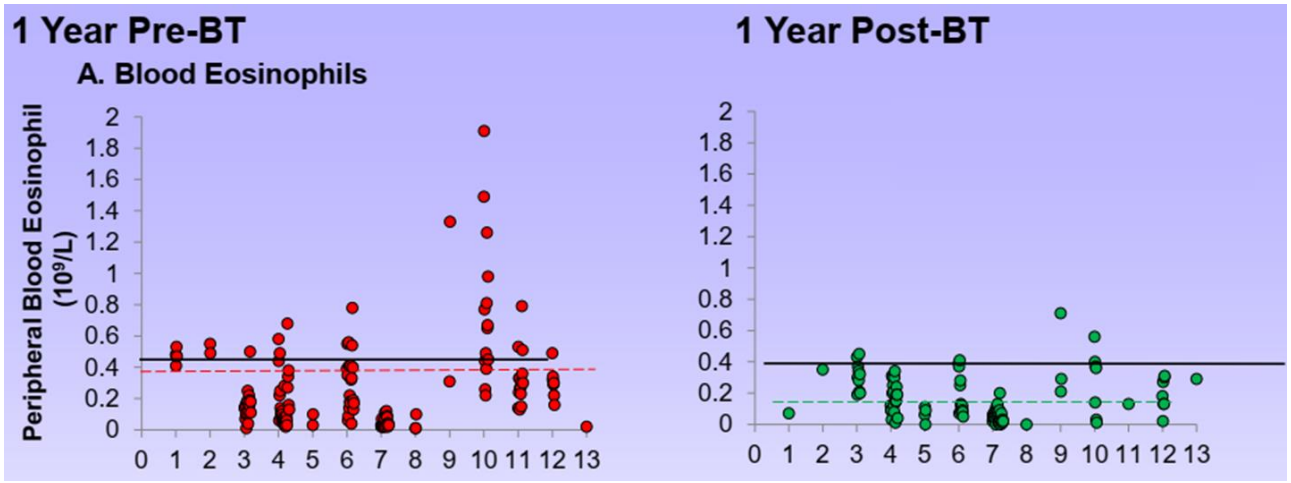
Effect of bronchial thermoplasty on neuroendocrine epithelial cells

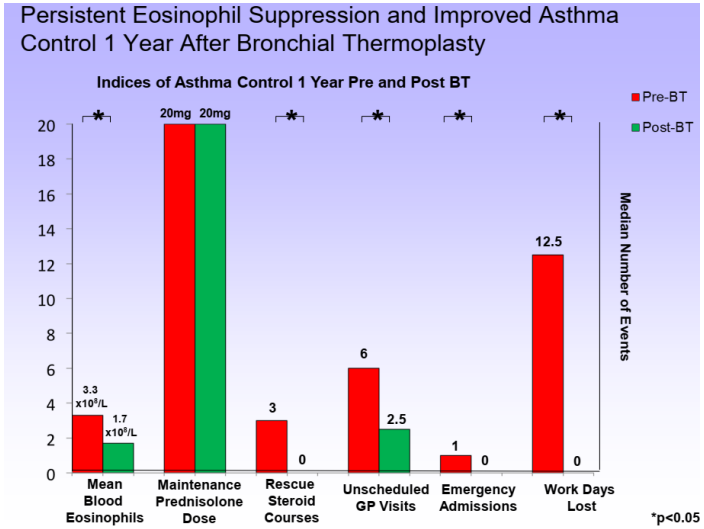


Pretolani Am.J.Respir.Crit.Care Med 2014;190 1452-4

BT – Πως δουλεύει?

- ***Effects on inflammation? (reduced inflammatory cytokine secretion from airway smooth muscle)***





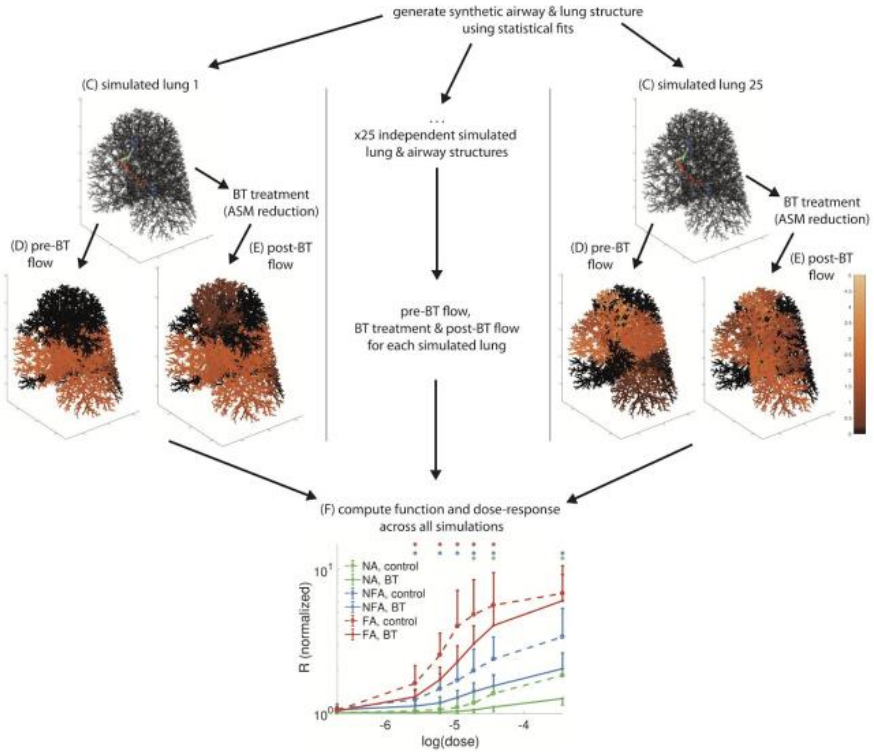
Ryan, Fowler, Niven. J Allergy Clin Immunol. 2016 Jul;138(1):308-310

BT – Πως δουλεύει?

- ***The mechanism of action of this relatively new, endoscopic treatment for asthma is incompletely understood…..***

Bronchial thermoplasty triggers global redistribution of clustered flow patterns, wherein ***structural changes to the treated central airways lead to a re-opening cascade in the small airways and significant improvement in lung function via reduced spatial heterogeneity of flow patterns***

We report a probable mechanism of action for bronchial thermoplasty: ***alteration of lung-wide flow patterns in response to structural alteration of the treated central airways***.



Donovan GM. Am J Respir Cell Mol Biol. 2018 Apr Epub ahead of print

Bronchial Thermoplasty

- Εισαγωγικά στοιχεία
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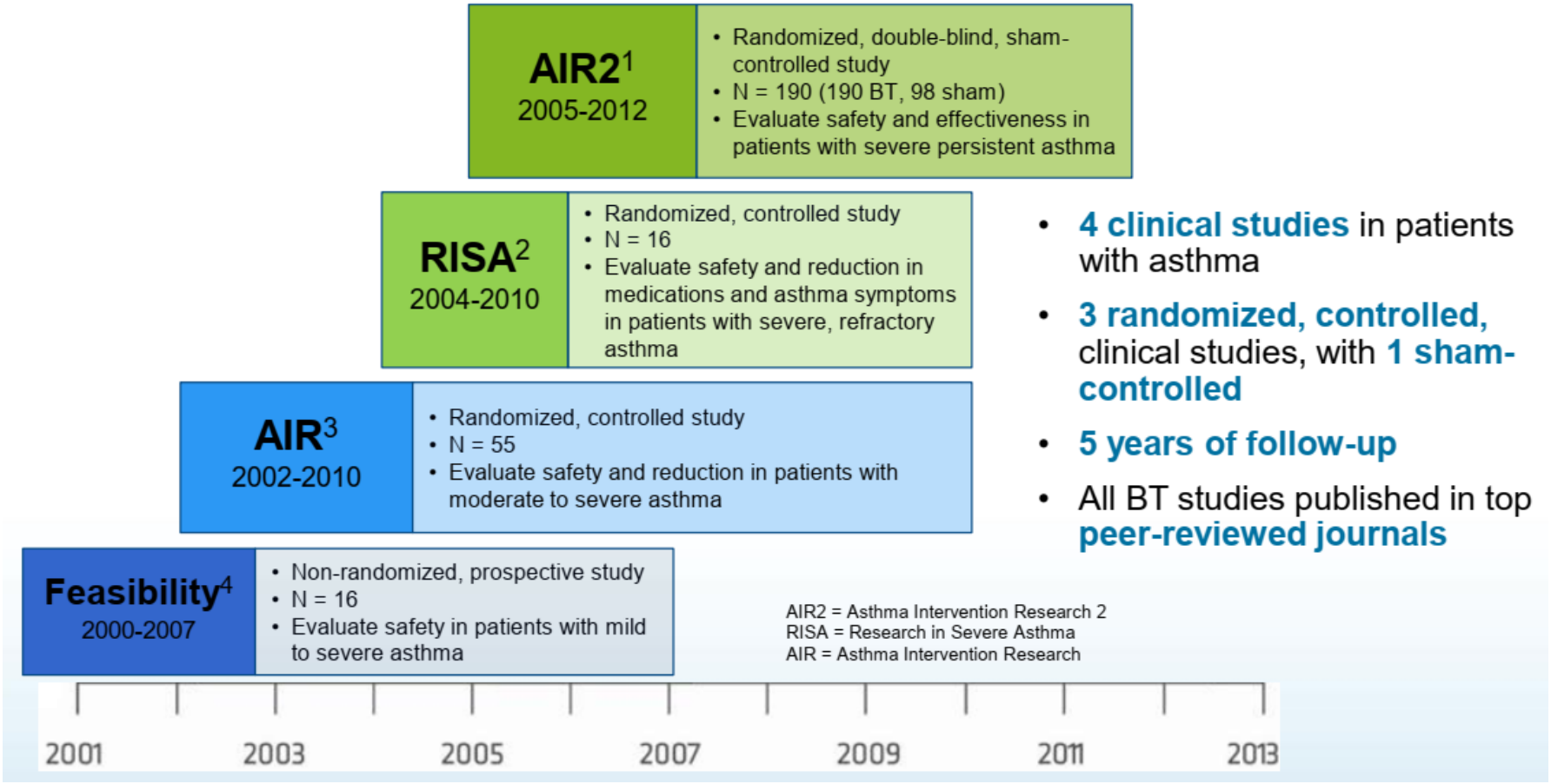
BT – Δεδομένα κλινικών μελετών – real life εμπειρίας



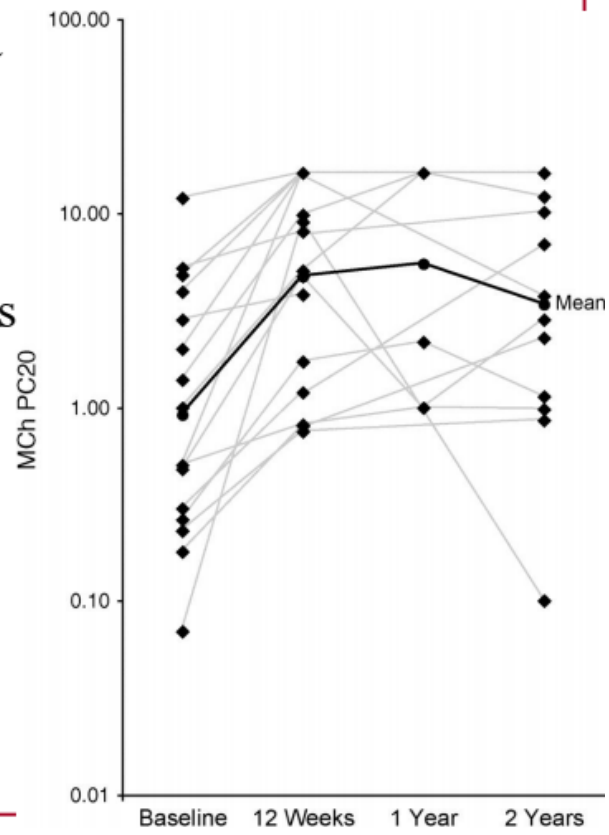
- **4 clinical studies** in patients with asthma
- **3 randomized, controlled,** clinical studies, with **1 sham-controlled**
- **5 years of follow-up**
- All BT studies published in top **peer-reviewed journals**

1. Castro et al., AJRCCM 2010; Castro et al., AnnAAI 2011; Wechsler et al., JACI 2013
2. Pavord et al., AJRCCM 2007; Pavord et al., AnnAA 2013
3. Cox et al., NEJM 2007; Thomson et al., BMC Pulmonary Medicine 2011
4. Cox et al., AJRCCM 2006; Cox et al., AJRCCM 2010

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***BT feasibility study***

- 16 patients mild-moderate asthma
- Well tolerated
- Improvement in BHR / PC20
- Improvement in asthma symptoms
- Stable FEV1



Cox et al., AJRCCM 2006

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

➢ ***AIR study***

- 112 patients (56 BT) with moderate to severe asthma
- RCT design, efficacy / safety
- Endpoints analyzed after discontinuation of LABA

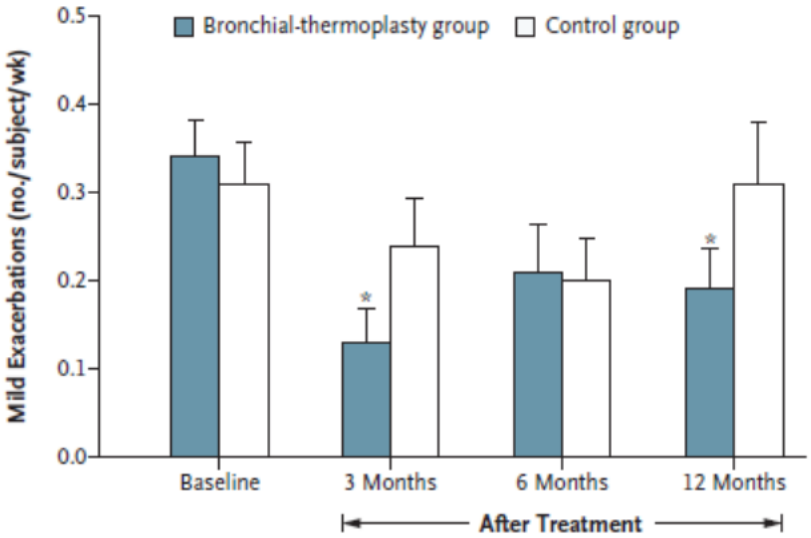
	BT	Control
Numbers (% female)	56 (56%)	56 (57%)
Age, yrs	39	42
FEV1, % pred	72	76
PC_{20} metacholine, mg/ml	0.25	0.35
Oral corticosteroid (OCS) use	none	none
ICS use (equivalent becl), mcg/dg	1351	1264
LABA use (equivalent Salm), mcg/dg	111	105

Cox et al., NEJM 2007

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

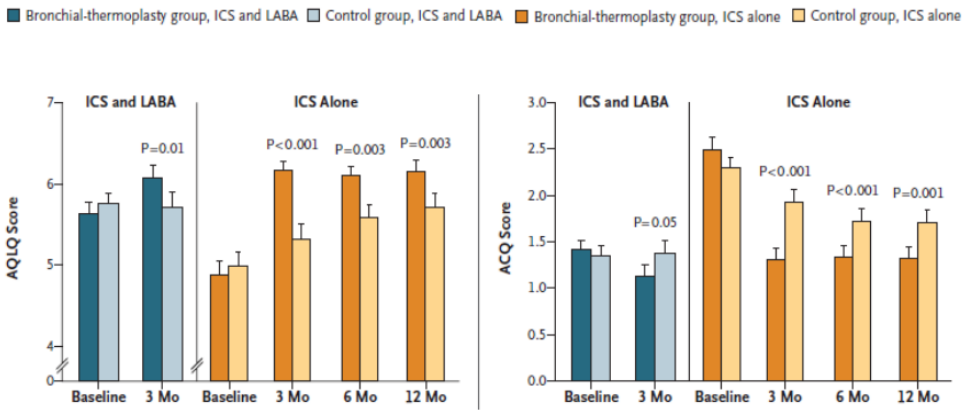
- ***AIR study***

primary endpoint



Mild exacerbation change: -0,16 (BT) vs +0,04 (control)

secondary endpoints



AQLQ change: +1,3 (BT) vs +0,6 (control)

ACQ change -1,2 (BT) vs -0,5 (control)

Cox et al., NEJM 2007

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***AIR study***

other endpoints

Pulmonary function test

- No change in airway hyperresponsiveness
- No change in FEV1

Safety

- Peri-procedural SAE – admissions: 10,9 % vs 3,7%
- Peri-procedural AE (dyspnoe, wheeze etc) were common.
- No difference in (S)AE during follow-up.

Cox et al., NEJM 2007

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

➢ ***RISA trial***

- 34 patients (15 BT) with severe asthma
- RCT, safety / efficacy
- Steroid stable / wean phase

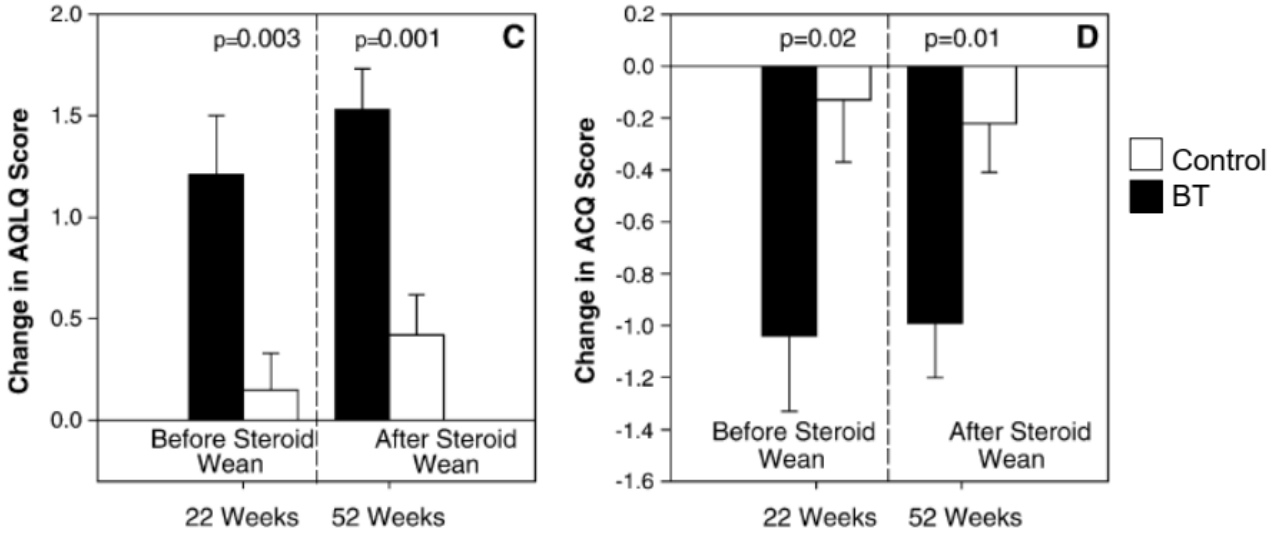
		BT	Control
Numbers (% female)		15 (60)	17 (41)
Age, yrs		39	42
FEV1, % pred		62	66
PC_{20} metacholine, mg/ml		0.19	0.31
Oral corticosteroid (OCS) use:	Number Dosis, mg/dg	8 14	7 19
ICS use (equivalent FLU), mcg/dg		1167	1059
LABA use (equivalent Salm), mcg/dg		111	106
ACQ		2.83	2.23
AQLQ		3.96	4.74

Pavord et al., AJRCCM 2007

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***RISA trial***

RISA trial: efficacy



- Reduction in rescue medication use
- Improvement in FEV1 in steroid stable phase

Steroid wean phase

- OCS dose reduction of 63.5% vs 26,2% for BT vs control

- ICS dose reduction of 28.6% vs 20% for BT vs control

Pavord et al., AJRCCM 2007

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***RISA trial***

RISA trial: safety

Treatment period

- SAE – admissions: 15,6% vs 0%
  - 7 hospitalization in 4 patients
- 2 segmental atelectasis of which 1 required bronchoscopy

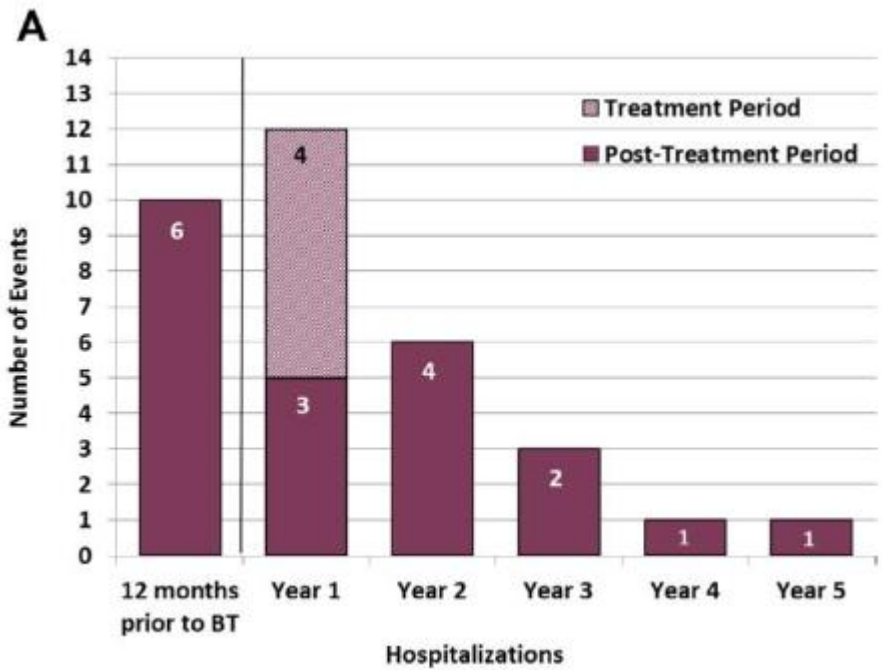
Post-treatment period

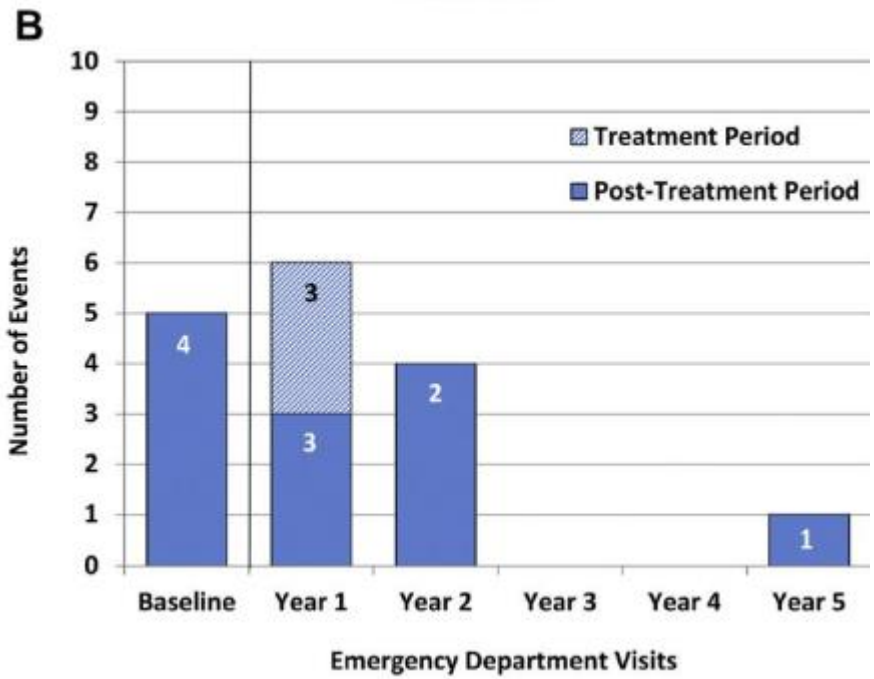
- No difference between treatment groups in SAE

Pavord et al., AJRCCM 2007

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***RISA trial – 5 yr FU***





Stable FEV1 - No long term effect on chest X-ray

Pavord et al, Ann Allergy Asthma Immunol 2013

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

➢ ***AIR2 pivotal trial***

- 288 patients (190 BT) with moderate – severe asthma
- RCT, double-blind, sham-controlled, ITT

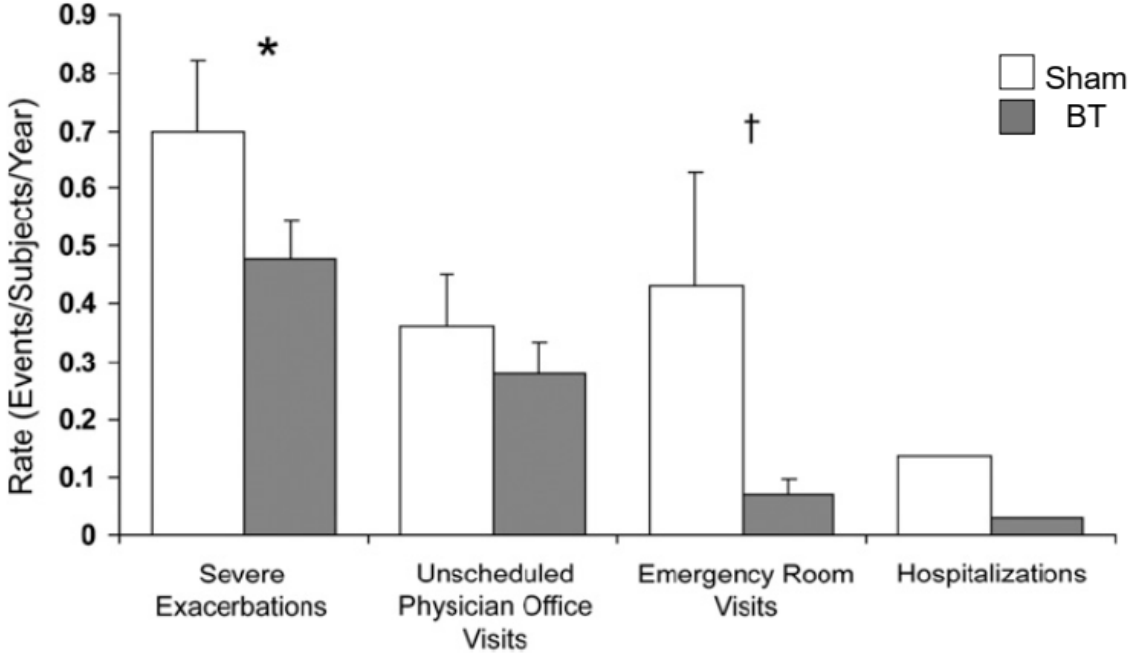
		BT	Control
Numbers (% female)		190 (57,4)	98 (61,2)
Age, yrs		40,7	40,6
FEV1, % pred		77,8	79,7
PC_{20} metacholine, mg/ml		0.27	0.31
Oral corticosteroid (OCS) use:	**Number (%)** **Dosis, mg/dg**	7 (3,7) 6,4	1 (1,0) 5,0
ICS use (equivalent FLU), mcg/dg		1960	1834
LABA use (equivalent Salm), mcg/dg		116,8	110,3
ACQ		2.13	2,09
AQLQ		4,30	4.32

Castro et al., AJRCCM 2010

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***AIR2 pivotal trial***

Health care utilization



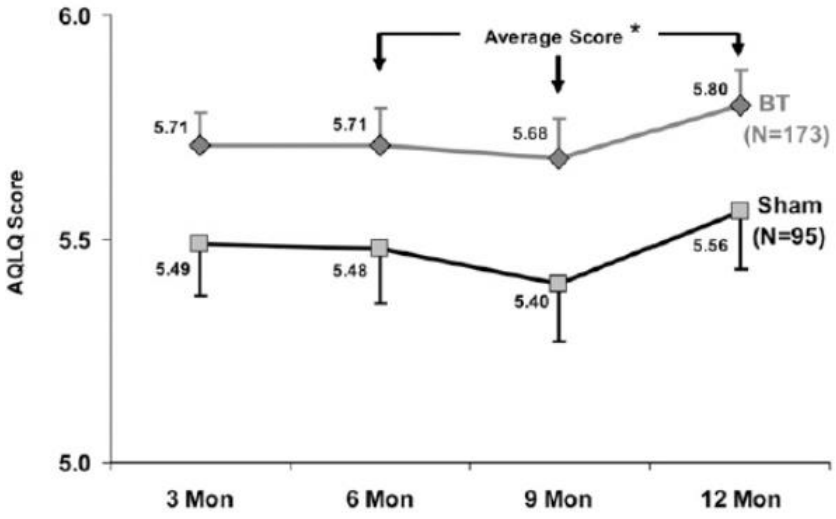
36% risk reduction in severe exacerbations
84% risk reduction in ED visitis;

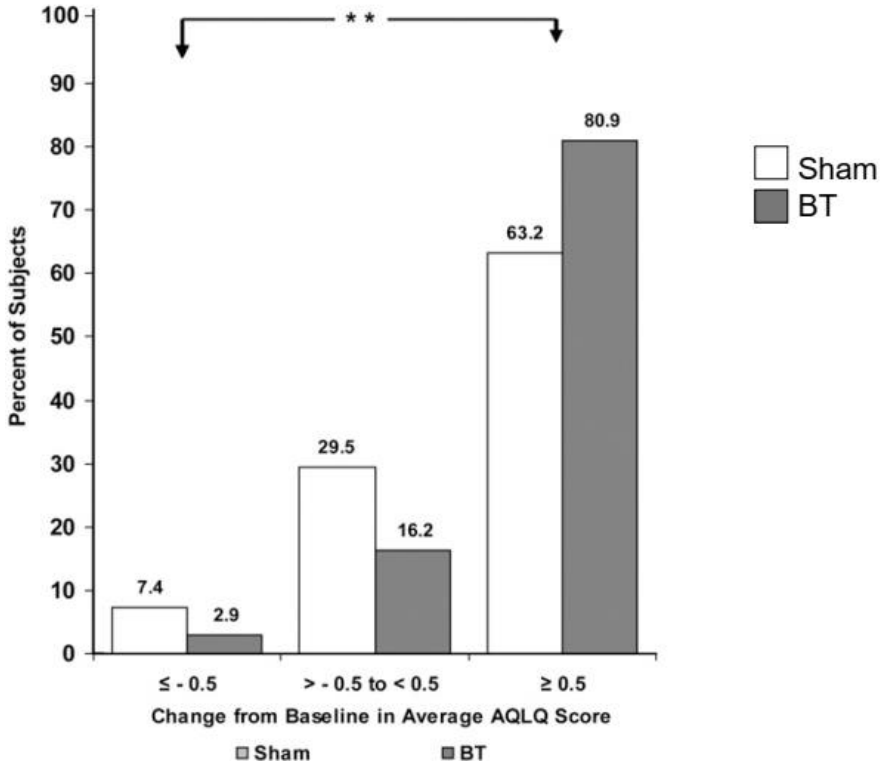
Castro et al., AJRCCM 2010

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***AIR2 pivotal trial***

Quality of Life





Castro et al., AJRCCM 2010

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***AIR2 pivotal trial***

safety

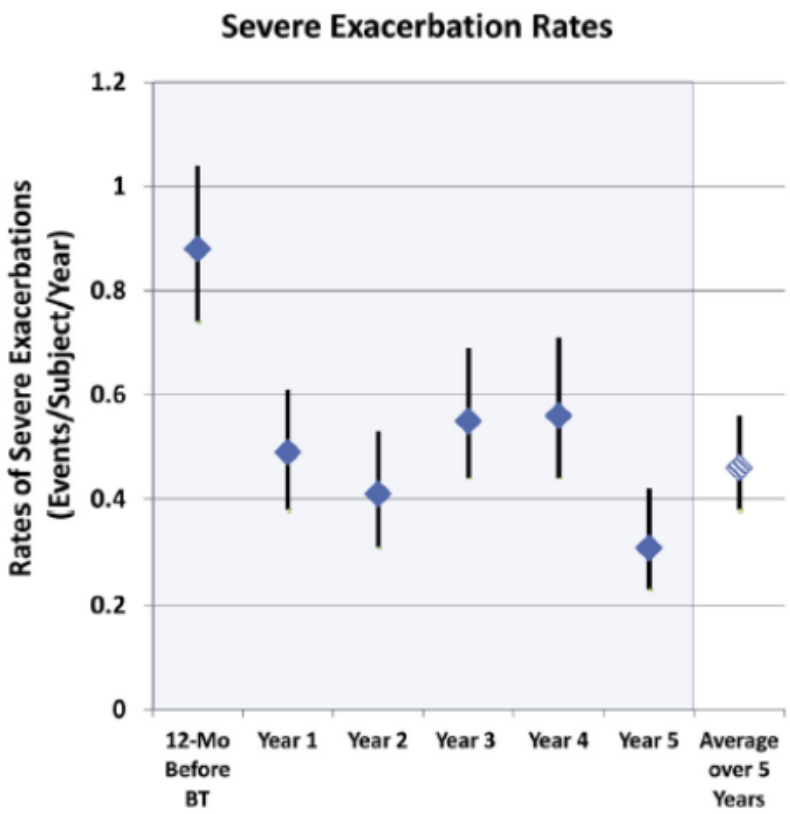
Treatment period

- SAE – admissions: 8,4 % vs 2,0%
  - 19 hospitalization
- 3 segmental atelectasis, 1 hemoptysis

Castro et al., AJRCCM 2010

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***AIR2 pivotal trial – 5 yr FU***



48% reduction

- Stable FEV1

Wechsler et al, 2013 JACI (AIR2)

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***PAS2: FDA Registry: 3 yrs FU***

  - FDA requirements for durability of response and safety
  - Prospective, open-label, observational multicenter study US (23) and Canada (4) centers
  - 284 subjects enrolled from April, 2011 to Oct, 2014
  - Comparison of the first 190 PAS2 subjects to the 190 BT-treated subjects in the AIR2 trial
  - 5 years FU completed in 2020

Chupp G, et al, Eur Respir J 2017

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***PAS2: FDA Registry: 3 yrs FU***

Baseline Patient Characteristics

	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 (μg/day)	2301.04 ± 807.46 (189)	1960.74 ± 745.19 (190)*
LABA (μg/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) 266.83 ± 88.67 (30)	1.1% (2/190)* 350.00 ±35.36 (2)

PAS2 enrolled subjects who may have had poorer asthma control than AIR2 subjects.

- 94.7% of PAS2 subjects are considered severe asthmatics based on ERS/ATS Guidelines

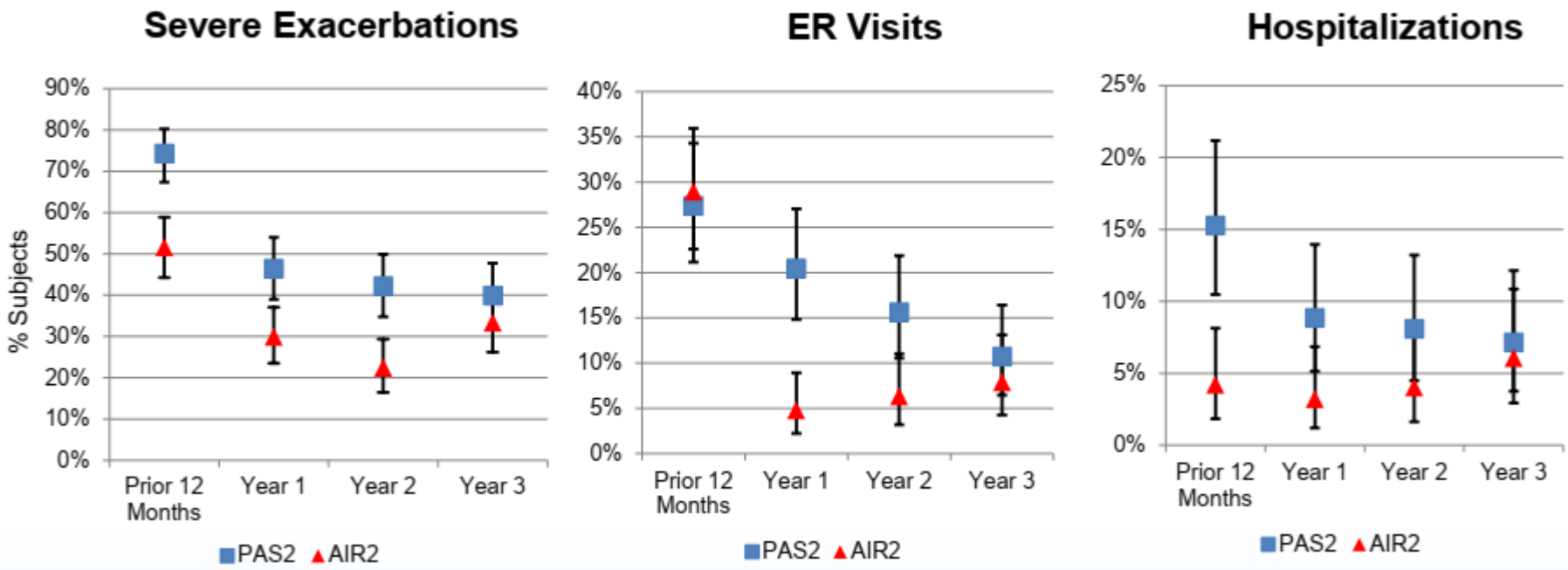
Compared to AIR2, PAS2 patients at baseline

- were older
- had a higher BMI
- had higher rates of severe exacerbations and hospitalizations
- had increased steroid exposure (higher ICS doses, higher % on maintenance OCS)

Chupp G, et al, Eur Respir J 2017

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***PAS2: FDA Registry: 3 yrs FU*** Results to 3 Years



- Data from the real world PAS2 patients (n=190) confirm the results from AIR2 in more severe asthmatics
- At Year 3 after BT, the percentage of PAS2 subjects with severe exacerbations, hospitalizations and ER visits decreased significantly by 45%, 55% and 40% respectively (all $p<0.005$)

Chupp G, et al, Eur Respir J 2017

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***PAS2: FDA Registry: 3 yrs FU*** Results to 3 Years

Medication usage

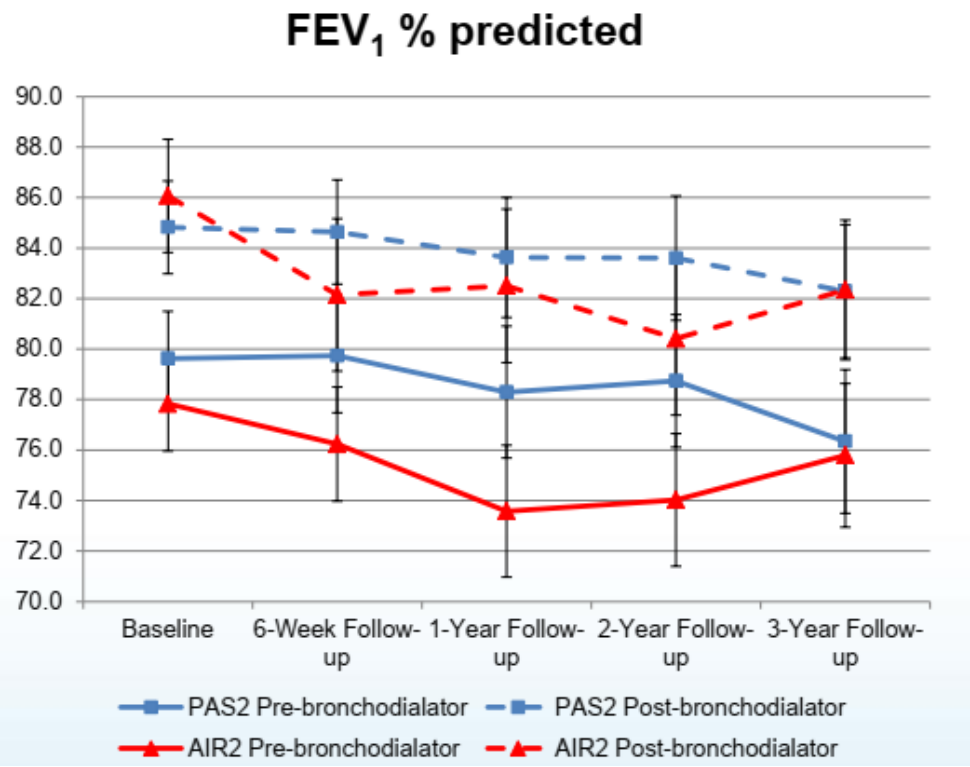
Medication	Baseline	1 Year	2 Years	3 Years
ICS Dose (μg/day)	2301.0 ±807.5 (189)	2108.5±938.3 (175)	1981.±1051.1 (164)	2069.7±1158.2 (157)*
LABA Dose (μg/day)	106.9±39.4 (189)	106.2±50.7 (172)	104.2±49.8 (156)	104.9±53.5 (149)
Short-acting beta agonists (puffs/day)	2.4±1.5 (182)	2.4±1.5 (173)	2.4±1.5 (166)	2.4±1.5 (162)
OCS	18.9% (36/190)	8.9% (16/180)	11.8% (20/270)	10.2% (17/166)*
Leukotriene Modifiers	44.2% (84/190)	45.0% (81/180)	42.4% (72/170)	43.4% (72/166)
Omalizumab – Usage	15.8% (30/190)	14.4% (26/180)	14.1% (24/170)	14.5% (24/166)

* - significantly different from baseline ($p<0.05$)

Chupp G, et al, Eur Respir J 2017

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***PAS2: FDA Registry: 3 yrs FU*** Results to 3 Years



- No effect on pulmonary function

Chupp G, et al, Eur Respir J 2017

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

- ***Συμπεράσματα από κλινικές μελέτες και real life εμπειρία***

Efficacy

BT clinical trials have shown beneficial effects in:

- ✓ Exacerbations rates (AIR, AIR2)
- ✓ Quality of Life (AIR, RISA and AIR2)
- ✓ Asthma control (AIR, RISA)
- ✓ No effect on FEV1 / PC20
- ✓ 'real world' PAS2 data mirror RCT results

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

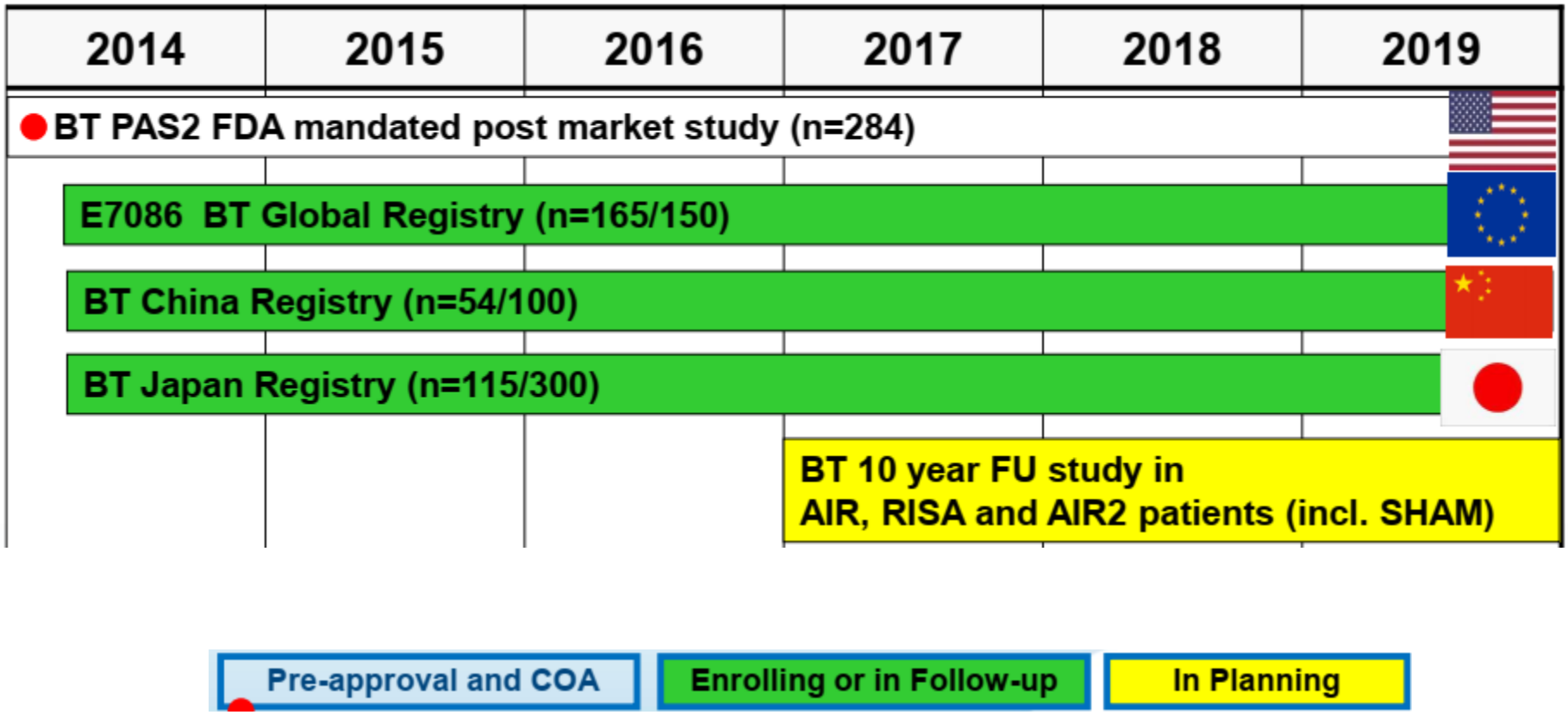
- ***Συμπεράσματα από κλινικές μελέτες και real life εμπειρία***

Safety

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

BT – Δεδομένα κλινικών μελετών – real life εμπειρίας

➢ ***BT Ongoing Clinical Studies***



Bronchial Thermoplasty

- Εισαγωγικά στοιχεία
- Ποια η δράση της στους μηχανισμούς του άσθματος – Πως δουλεύει?
- Δεδομένα κλινικών μελετών – real life εμπειρίας
- **Πως γίνεται στην πράξη? Σε ποιους ασθενείς?**
- Συμπεράσματα

BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***How to plan?***

- MDT / Registry: diagnose / phenotype patient
  - Selection (compliance/co-morbidities)
  - Response
  - Adverse events
- 'Stable' on ICS/LABA +/- immunotherapy
- No exacerbation / infection 3 weeks before
- Exclusion criteria
  - Coagulopathy
  - Bronchiectasis, ILD, EGPA, tracheamalacia
  - Pacemaker / significant cardiac disease

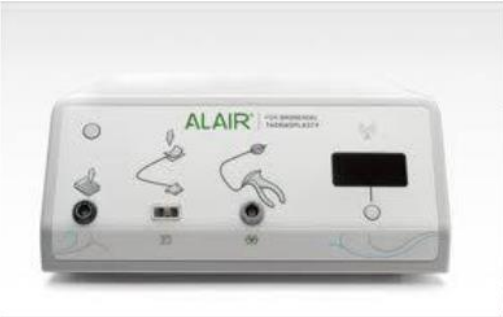
BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***How to prepare on the day of BT?***

- Prednisolone 50mg 1dd 3 days before (total of 5 days)
- History / physical examination
- FEV1
- Nebulize salbutamol/ipratropium
- Endoscopy suite – TOP and pre-assesment

BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***Check- equipment***



RF controller

Incl. grounding patch

2.0mm RF delivery catheter

BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***How to sedate?***

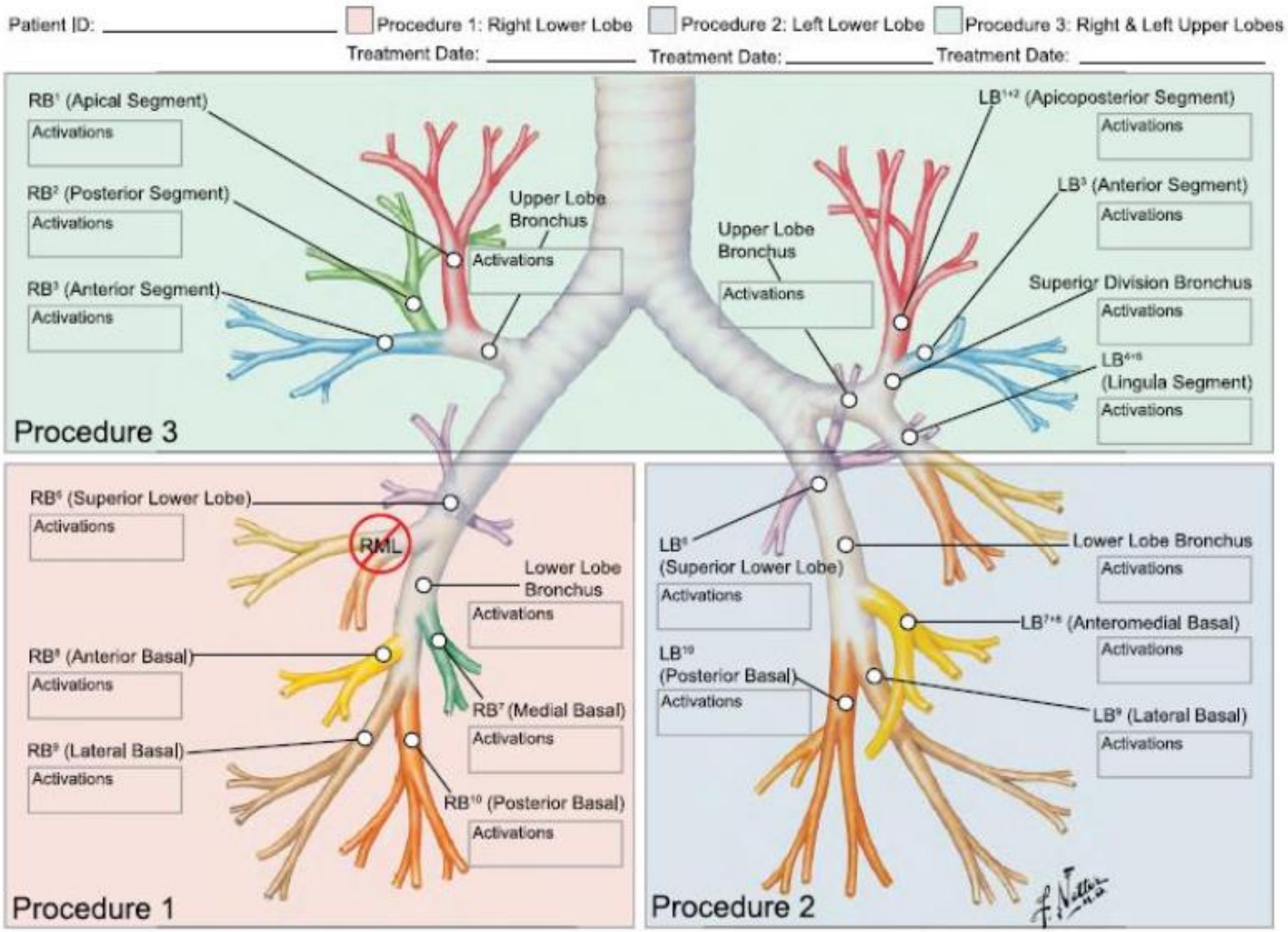
Institute dependent: but cough!

- Local anesthesia (lidocain)

- Midazolam / fentanil
- Propafol / remifentanil TCI -> sedation specialist
- General anesthesa -> anesthesist
  - Laryngeal mask
  - Tube 8
  - Rigid

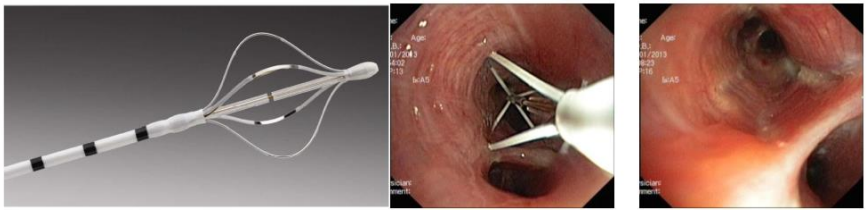
BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***How to perform?***



BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***How to perform?***



- Inspection (tracheamalacia, other abnormalities, BT effect)
- Don't use suction -> swelling
- Bronchial wash (RUL/ML)
- Instructions to nurse
- Advance cathether -> basket just in/out of vision
- Retract per black stripe
- 40 – 100 activations / session -> register
- 45 – 60 minutes / BT

BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***How to monitor?***

Institute dependent

- 2-4 hr recovery
- Intensify nebulisations / steroids / Mg
- Controls (pulse, RR, O2 %) and physical examination
- [Post-BT FEV1 >80%]
- Ensure home medication (ICS/LABA/prednisolone)

- In doubt: admission O/N

BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***Where BT is available?***

BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***Σε ποιους ασθενείς?***

"BT for severe asthma: the perfect candidate ?"

Pascal Chanez

At present non candidate

- Controlled mild asthma
- T2 related inflammatory phenotype
  - Allergic / omalizumab
  - Eosinophilic/anti-IL5
- Non T2 related inflammatory phenotype
  - Responsive to LAMA, macrolides
- Too severe:
  - numerous exacerbations/ high OCS requirement
  - Low FEV1
  - Little smooth muscle mass ?

BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***Σε ποιους ασθενείς?***

"BT for severe asthma: the perfect candidate ?"

Pascal Chanez

At present candidate

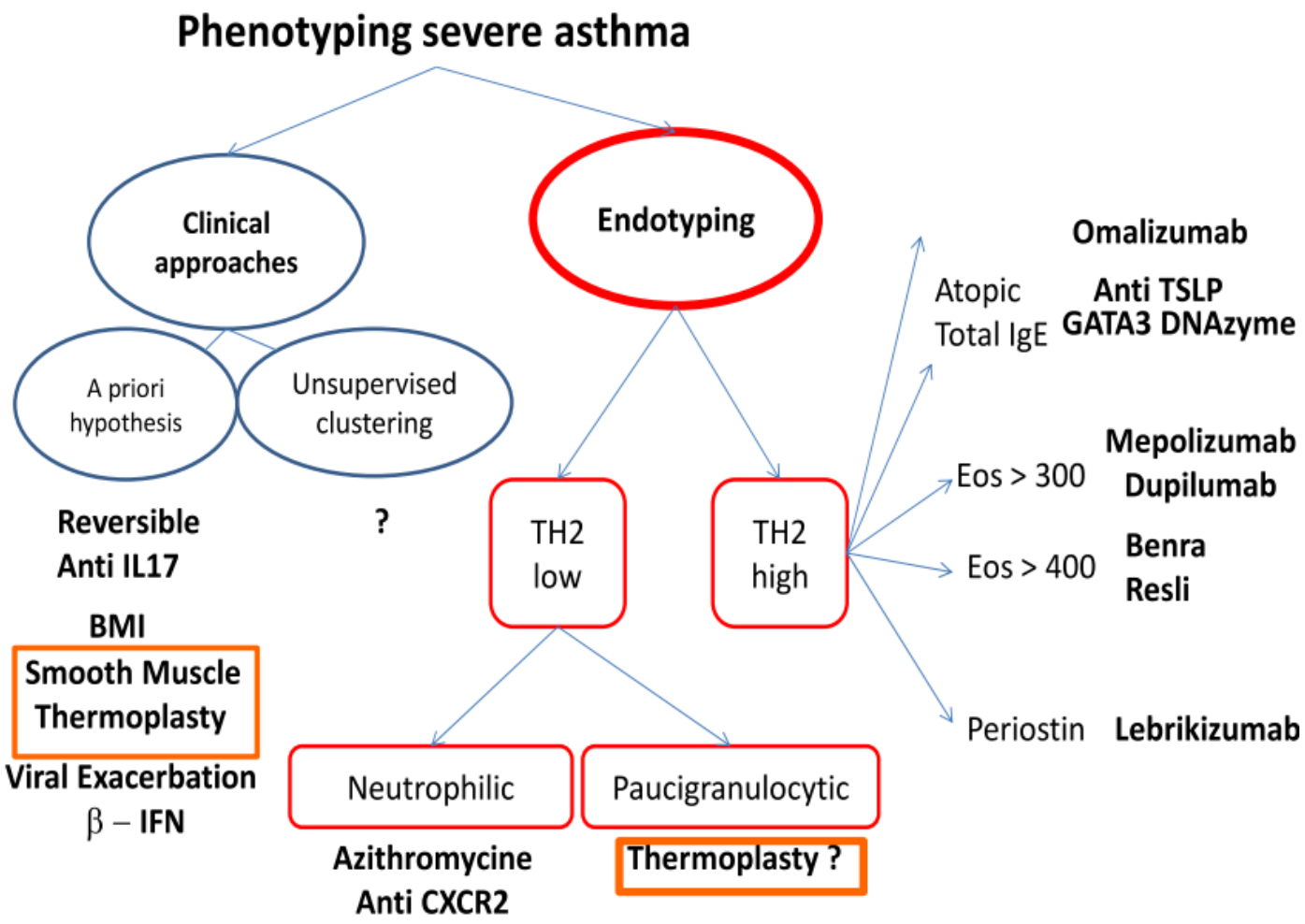
- Severe uncontrolled asthma
- If T2 related inflammatory phenotype
  - Unresponsive to omalizumab
  - Unresponsive to anti-IL5
  - Definition of response ?
- non T2 related inflammatory phenotype
- combined with biologics ?

BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

- ***Σε ποιους ασθενείς?***

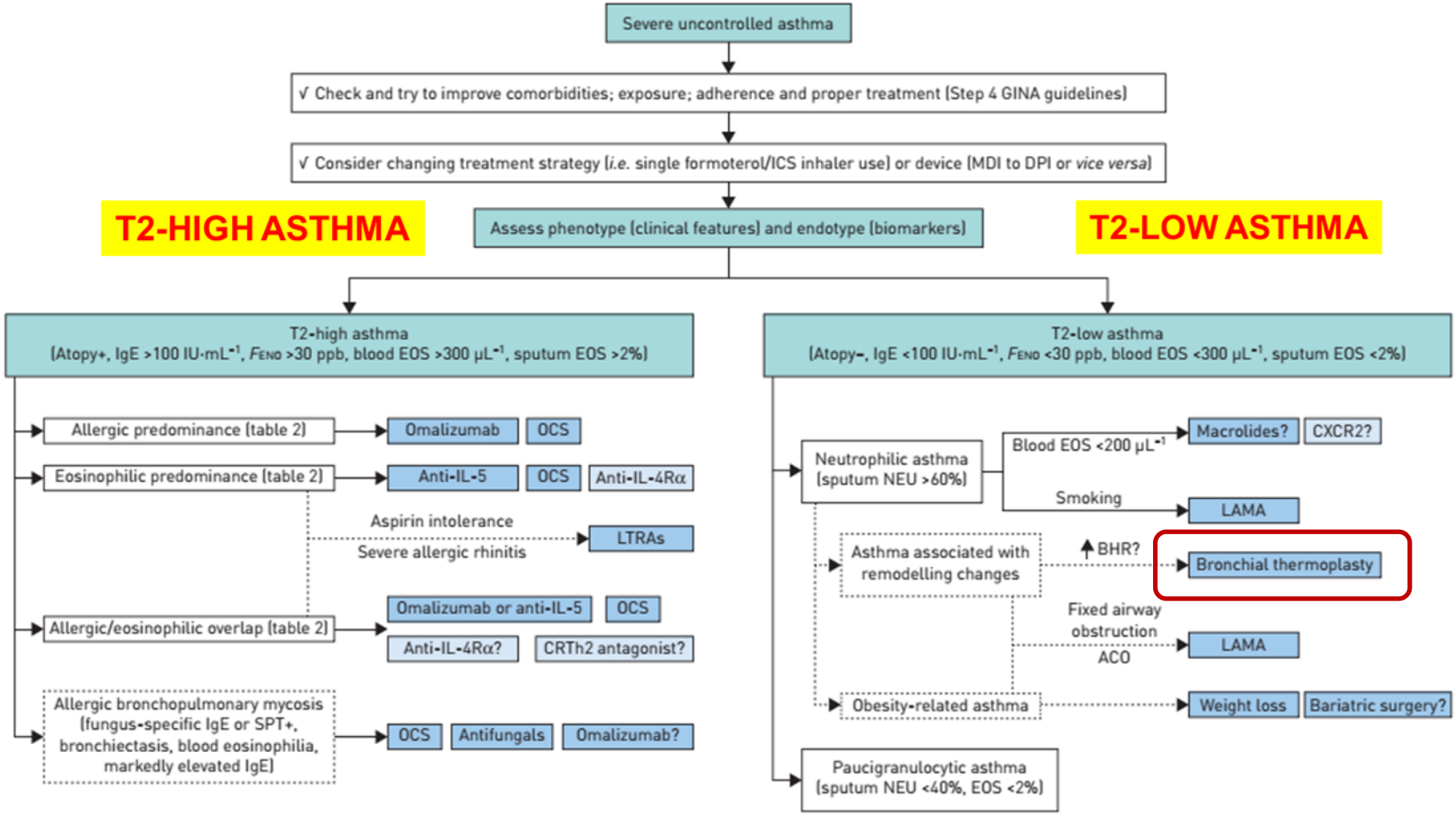
"BT for severe asthma: the perfect candidate ?"

Pascal Chanez



BT – Πως γίνεται στην πράξη? Σε ποιους ασθενείς?

➢ ***Σε ποιους ασθενείς?***



Zervas E. et al ERJ Open Res. 2018 Mar 6;4(1)

Συμπεράσματα

- Mature technique but invasive and not yet widely available
- Safe on short and long term, despite increased morbidity from asthma during treatment
- RCT and real life data show modest improvements in asthma quality of life and reductions in severe exacerbations and emergency department visits
- Mechanisms better described but not yet clearly understand
- Best responder or real non candidate? Currently in T2-low asthma and in non-responders to targeted therapy in T2-high asthma?
- Cost effectiveness? Comparison with other innovative targeted therapies
- The future of BT? Biomarkers of response?

Βρογχοσκοπική θεραπεία στο σοβαρό άσθμα – Bronchial Thermoplasty