Smooth Muscle & Asthma: Bronchial Thermoplasty *- A Smooth Muscle Modifier*

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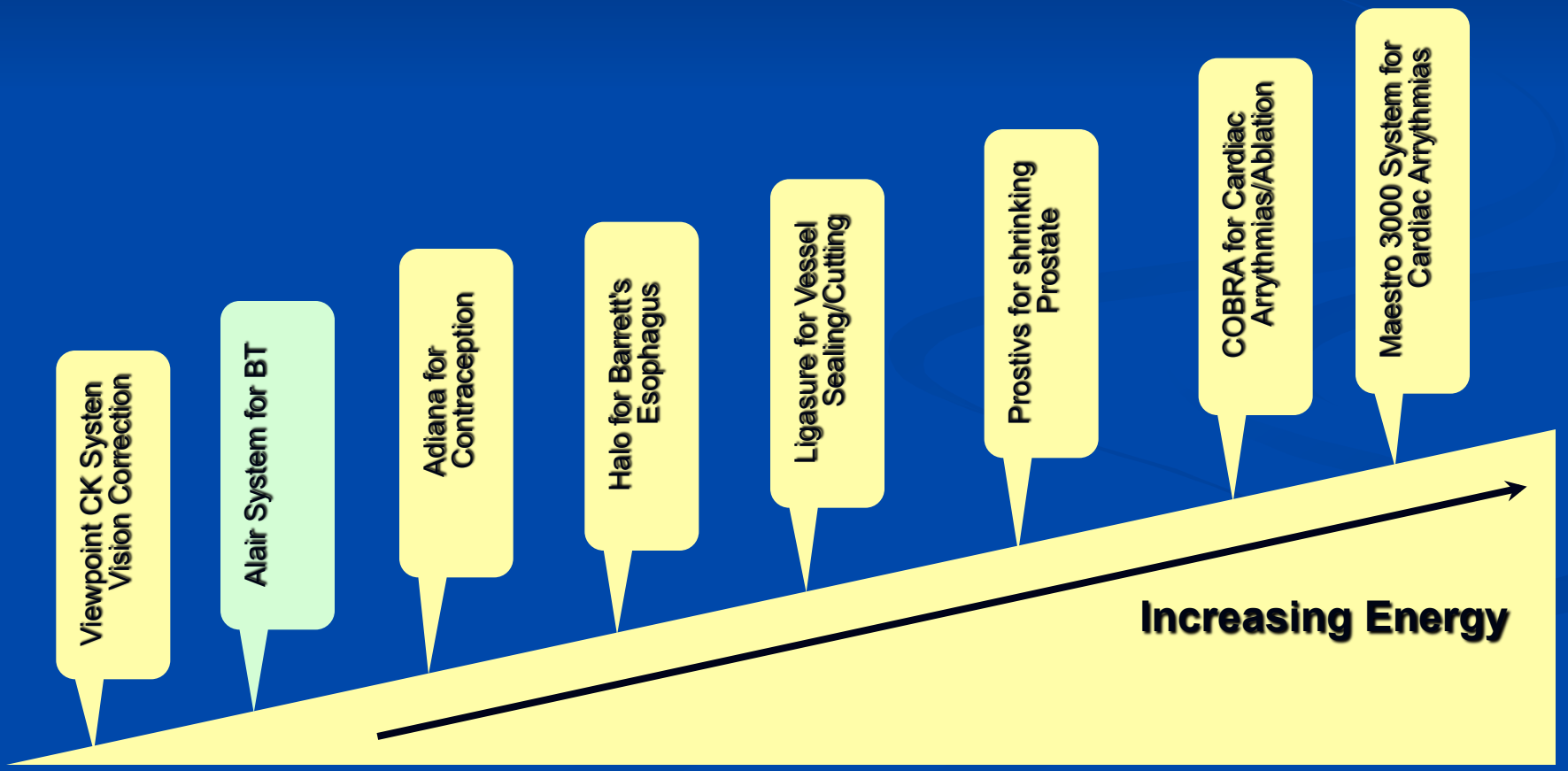
Unmet Need in Severe Persistent Asthma

- Prevalence of severe asthma 5-20% (NAEPP/ NHLBI)
- Many patients remain symptomatic despite standard of care medication
- Treatments are limited, require adherence, and may have serious side effects
- New options are needed

RF Energy to Reduce Excess Airway Smooth Muscle

- History of safe use in medical procedures



Bronchial Thermoplasty Rationale

Reduces Airway Smooth Muscle (ASM)

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Reduced Ability for Bronchoconstriction

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Reduced Asthma Symptoms and Exacerbations

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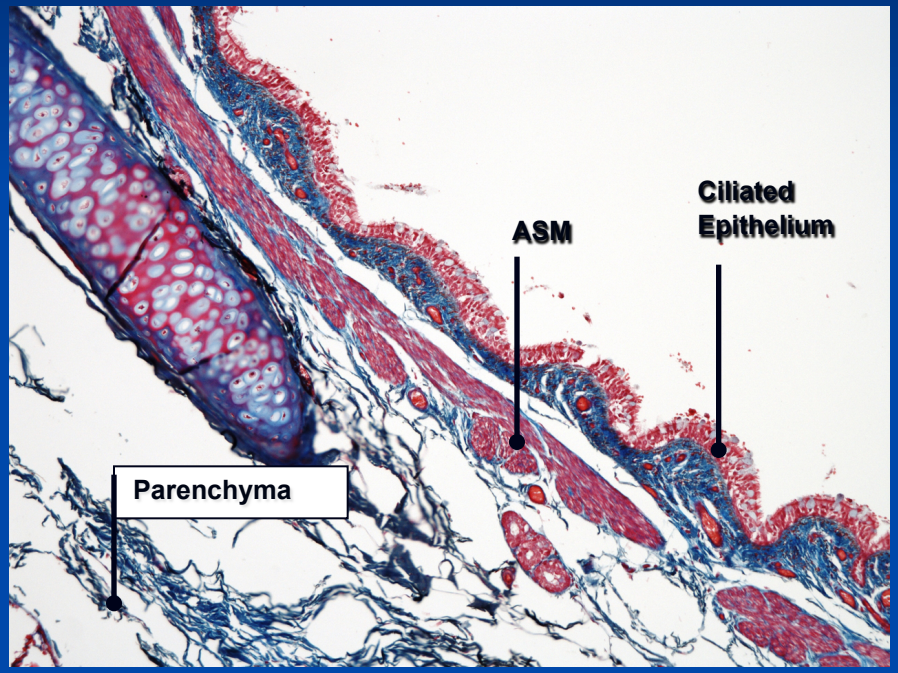
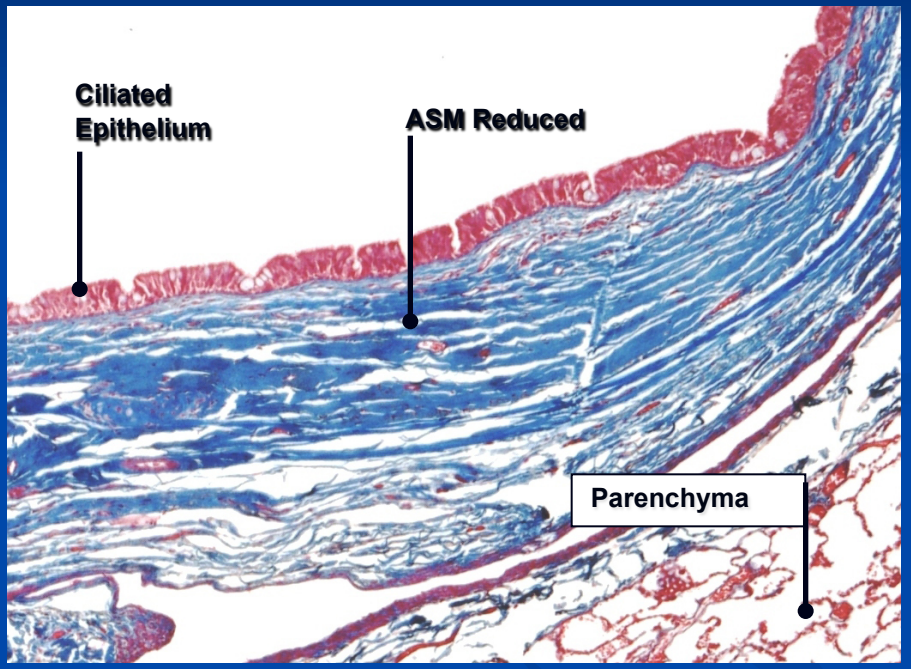
Improved Asthma Control and Quality of Life

Reduced Airway Smooth Muscle
3 years Post-Treatment (Canine Model)

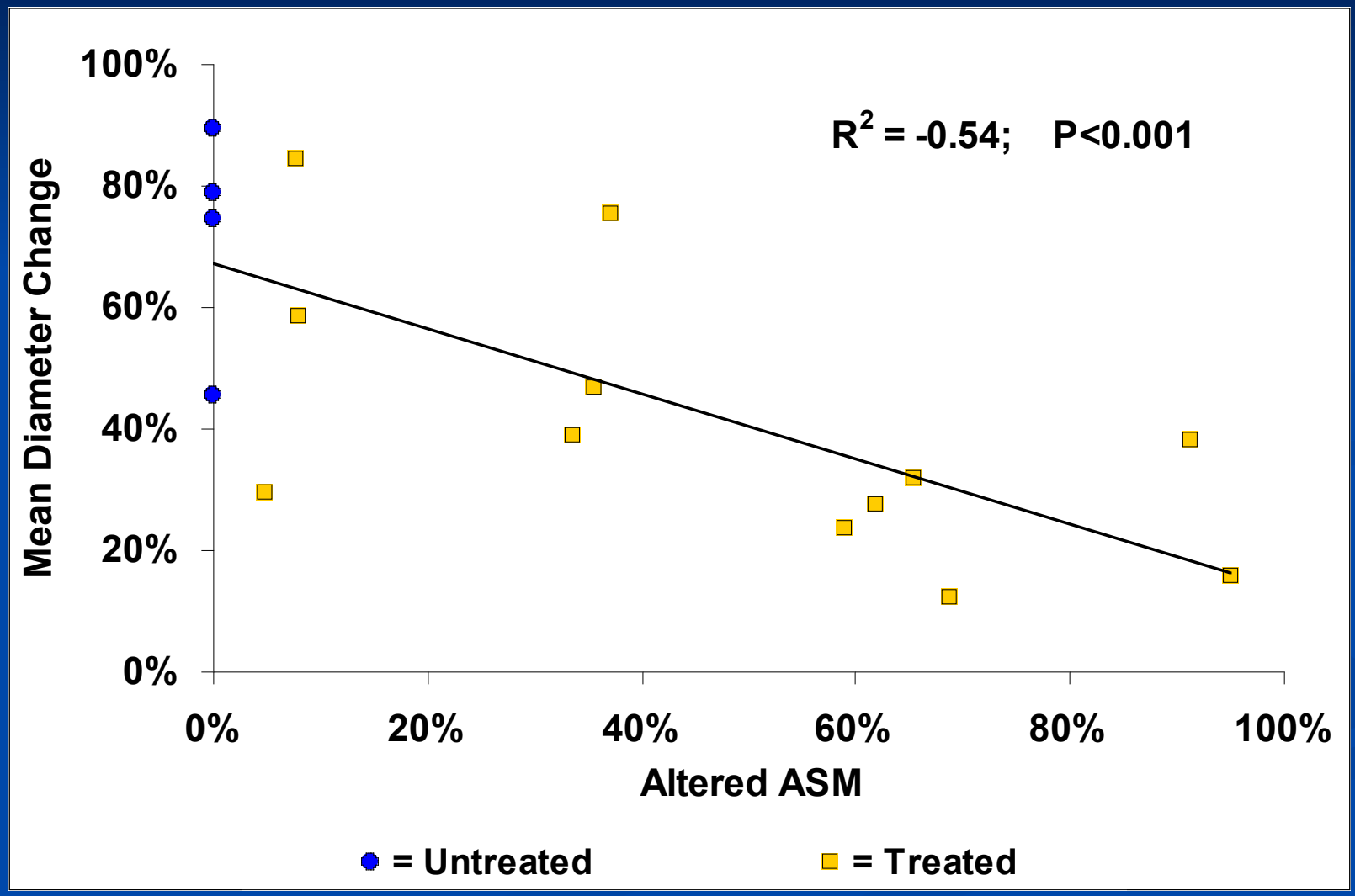


UNTREATED



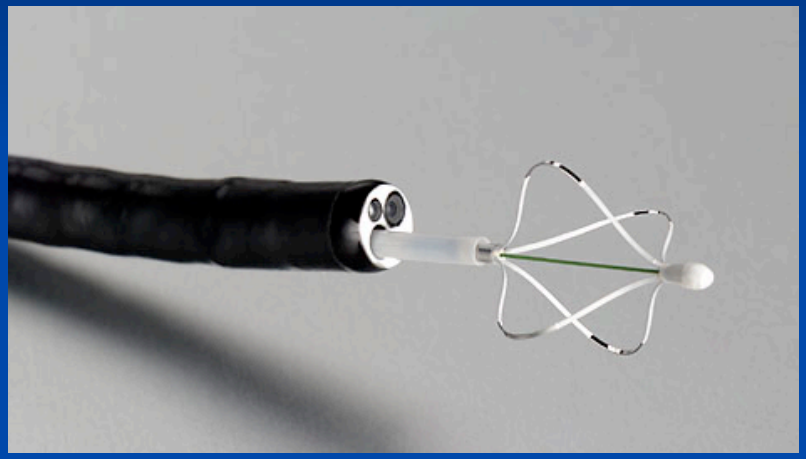
TREATED

Less Airway Constriction with Reduced ASM



Bronchial Thermoplasty

- **The *Alair* Catheter is a flexible tube with an expandable wire array at the tip**



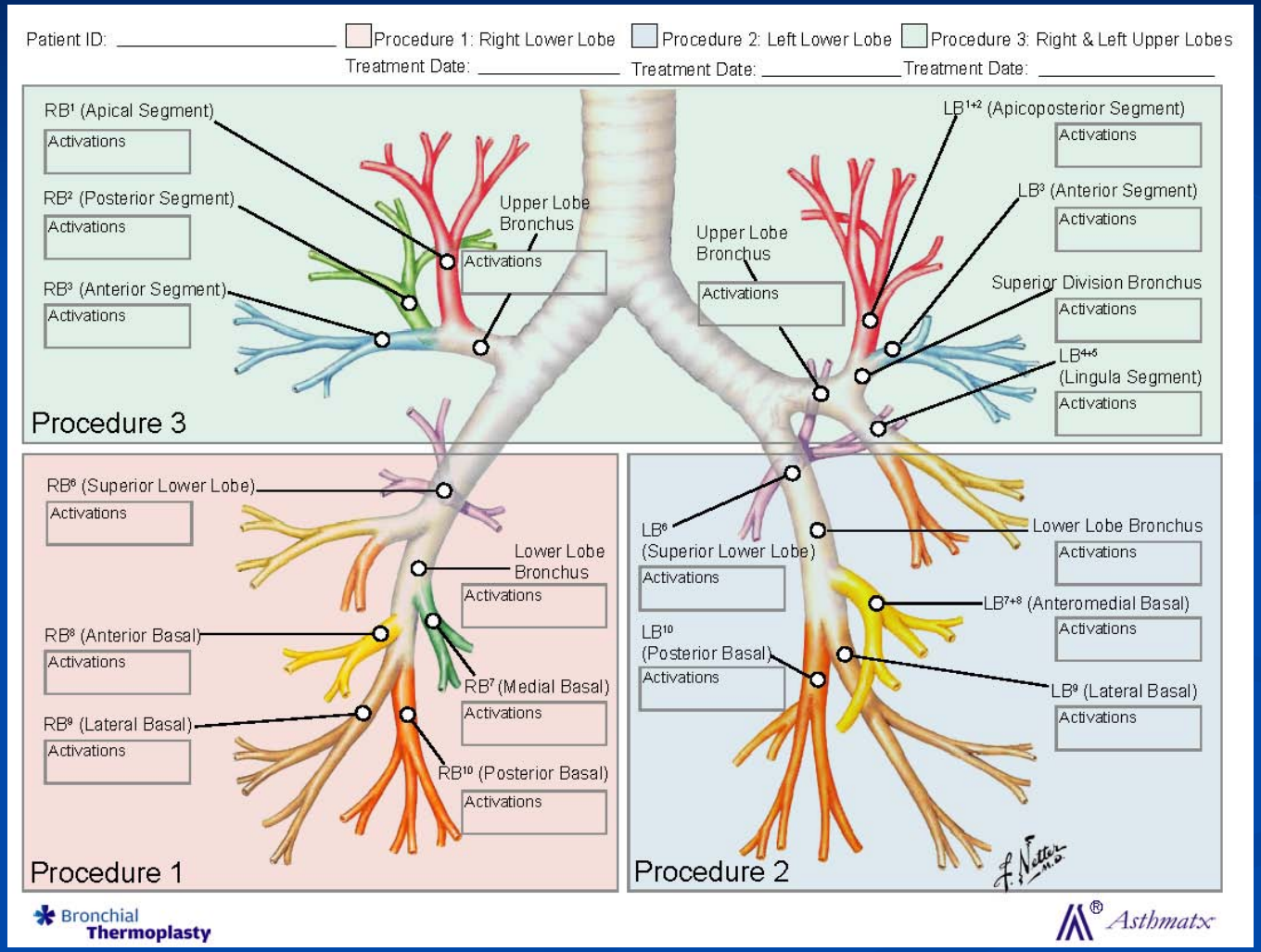
- **The *Alair* Radiofrequency Controller supplies energy that is converted to heat in the airway wall**

- Monopolar radiofrequency (RF) energy
- Temperature controlled: 65 °C
- 10 seconds
- Multiple safety algorithms to ensure controlled energy delivery

Bronchial Thermoplasty Procedure Details

- Patient evaluated 1 week prior to procedure to verify ability to undergo bronchoscopy
- Procedures performed in Bronchoscopy or IP Suite
- Lung function evaluated morning of procedure to assess stability
- Prophylactic medication: Prednisone
  - 50 mg/day for 5 days (3 days prior, Day of, and Day after procedure)
- Standard Sedation and Monitoring techniques for Interventional bronchoscopy
  - Pre-medications: Anti-mucolytic, Albuterol, Midazolam, Fentanyl
  - Topical anesthesia: Lidocaine (vocal cords and airways)
  - Moderate levels of Anxiolysis and Analgesia (Midazolam 0.5 - 2.0 mg IV q 3-5 minutes prn, Fentanyl 25 - 50µg IV q 3-5 minutes prn)

Bronchial Thermoplasty Procedure Map

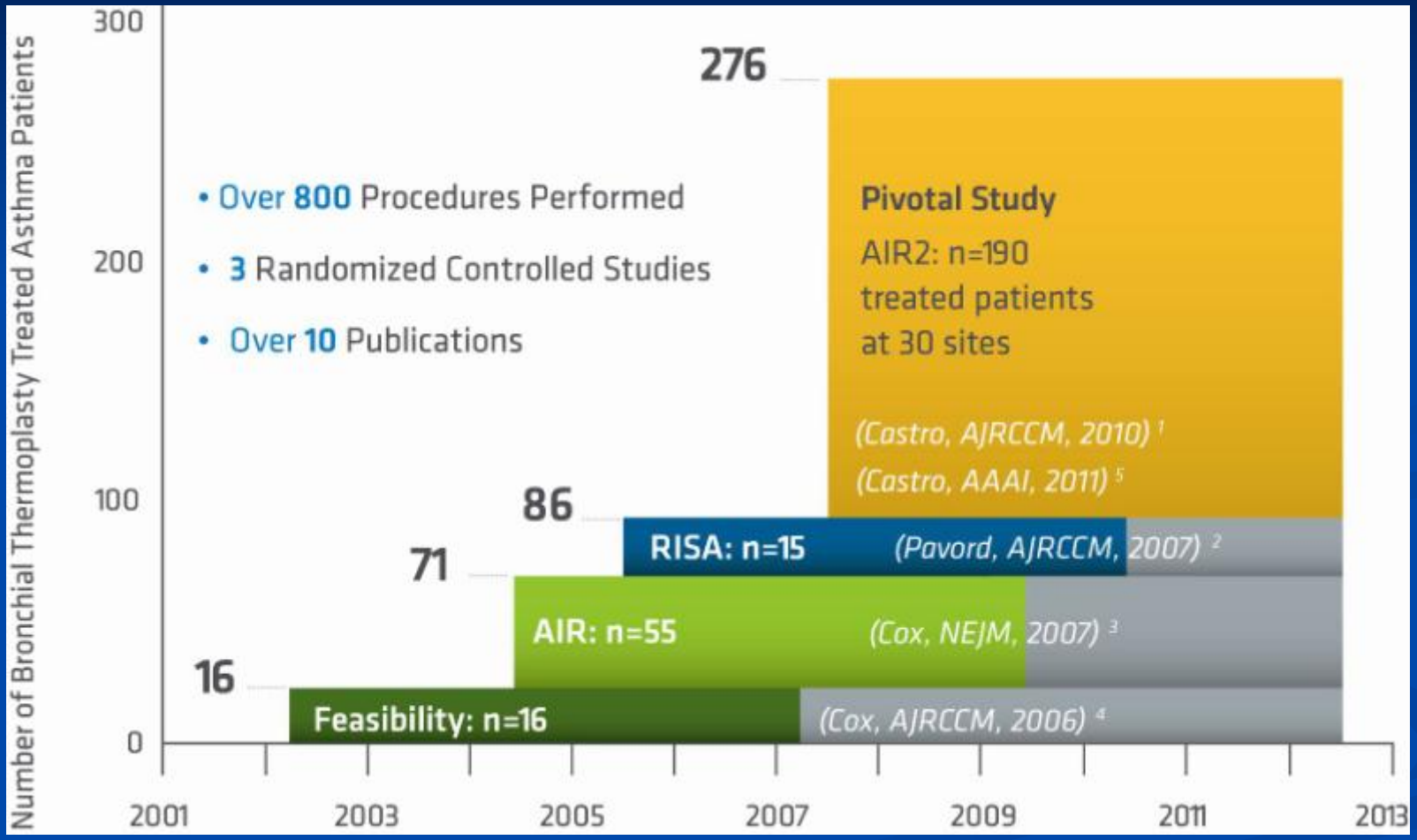


Mayse M, J Bronchol 2007; 14(2): 115-23

Post-BT Procedure/Patient Follow Up

- Patient monitored for 2-4 hours post-op
- Patient discharged from hospital same day:
  - Lung function stable within 80% of pre-procedure post BD FEV1
  - Patient stable, able to take liquids, feeling well
  - Prophylactic OCS continued 1 day after procedure (or longer)
- Patient contacted via phone at 1, 2 and 7 days to assess post procedure status
- Office visit at 2 to 3 weeks to assess clinical stability and schedule subsequent BT procedures as appropriate
- Patient returns to care of primary asthma physician for long term asthma management following BT

Bronchial Thermoplasty Studies To Date

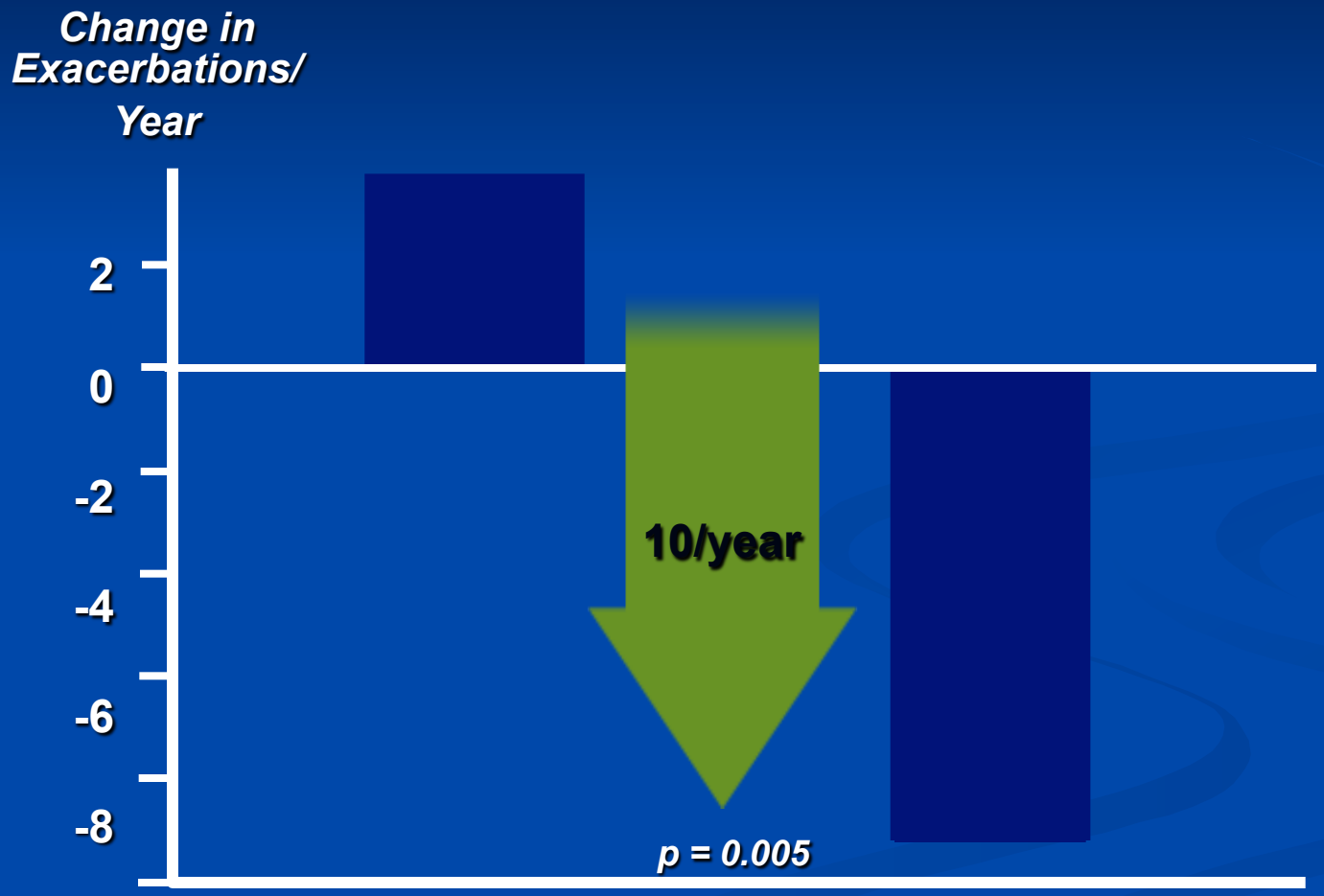


AIR = Asthma Intervention Research Study
RISA = Research in Severe Asthma Study

Baseline Demographics BT Treated Subjects

Parameter	Feasibility	AIR Trial	RISA Trial
Number of Subjects	16	55	15
Age (years)	39.0 ± 8.6	39.4 ± 11.2	39.1 ± 13.0
Gender	F 10 (63%)	F 31 (56%)	F 9 (60%)
Pre-BD FEV_1 (% Pred)	82.2 ± 14.1	72.65 ± 10.41	62.9 ± 12.2
ICS Dose (µg/day) Beclomethasone or Equiv.	900 ± 424	1351 ± 963	2333 ± 817
OCS Dose (mg/day)	0	0	14.4 ± 6.2 (N=8)
% Symptom Free Days	50 ± 33	34 ± 34	5 ± 14

AIR Study
- Reduction in Mild Exacerbations



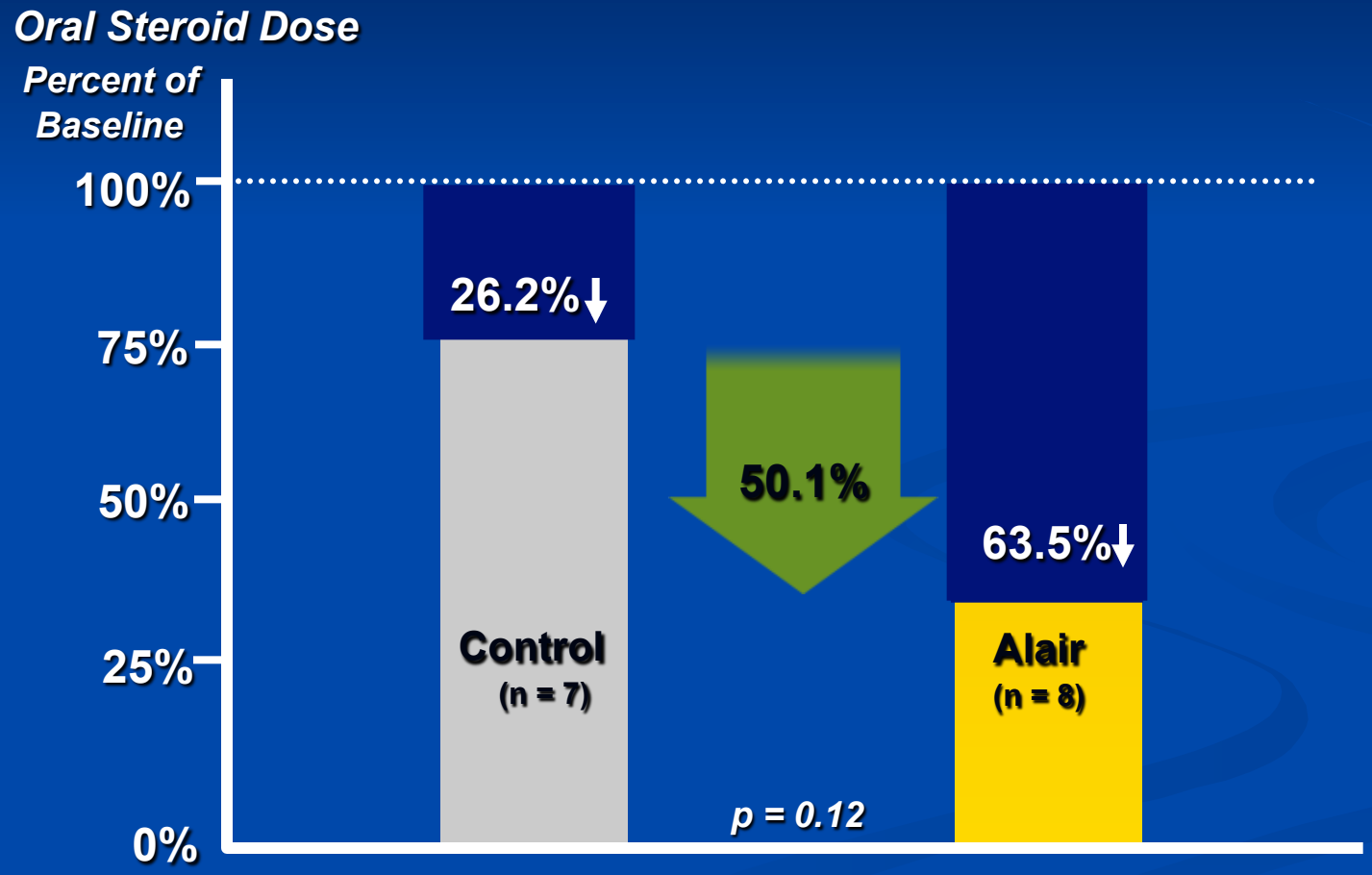
Cox, G, et. al., Asthma control during one year after bronchial thermoplasty, *NEJM*, 2007; 356(13): 1327-1337

BT Clinical Results

Feasibility (n=16)	AIR (RCT, n=109)	RISA* (RCT, n=32)
Well tolerated	AQLQ score	AQLQ score
Lung function	Exacerbations	ACQ score
Symptom Free Days	Rescue medications	Rescue medications
Persistent	Symptom Free Days	Oral steroids

*Pavord, ID, et. al., Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med*, 2007; 176: 1185-1191

RISA Study
-Ability to Wean Patients Off Oral Steroids



Pavord ID, et. al., *Am J Respir Crit Care Med*, 2007; 176: 1185-1191

AIR2 Trial Design

- Primary Endpoint: Asthma Quality of Life Questionnaire (AQLQ)
- Study Design: Sham Controlled, Double Blind
  - 2 : 1 randomization; BT: Sham
  - BT Group (ICS + LABA + BT)
  - Sham Group (ICS + LABA + Sham)
- Study Size: 297 Subjects / 30 centers (International)
- Length of Follow-up: - One year
  - 5-year safety follow-up for BT subjects

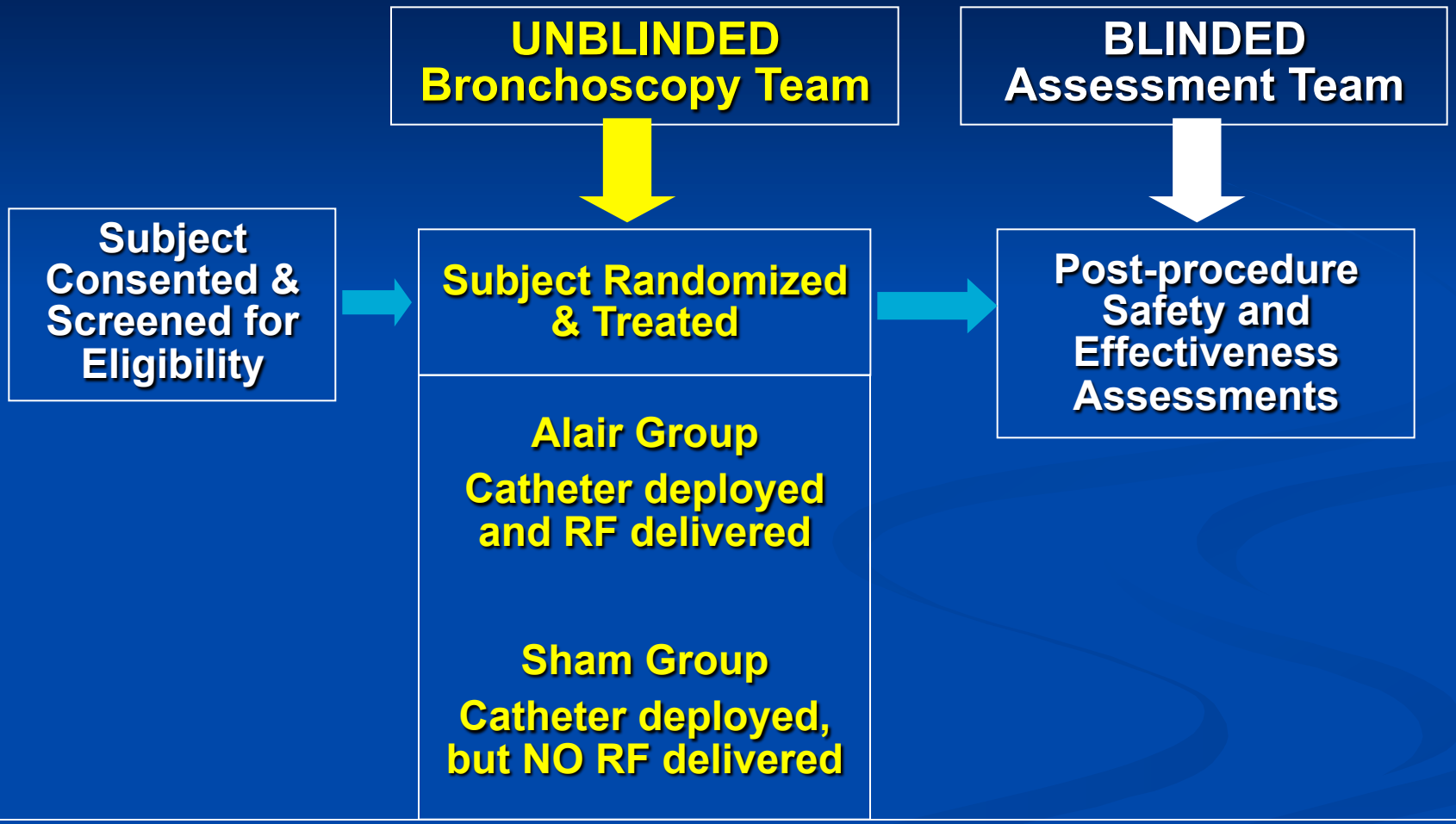
Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

AIR2 Trial
- Key Inclusion Criteria

- ICS >1000ug BDP equiv + LABA; ± OCS ≤10 mg/day
- At least 2 symptom days in 4 week baseline
- Pre-bronchodilator FEV_1 ≥ 60% Predicted
- ≤ 8 puffs/24h rescue medication, excluding for exercise

Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

Double Blind Carefully Maintained



Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

AIR2 Patient Demographics

Parameter	BT	Sham
Number of Subjects	190	98
Age (years)	40.7 ± 11.89	40.6 ± 11.85
Gender, n (%)	Male 81 (43%) Female 109 (57%)	Male 38 (39%) Female 60 (61%)
Race, n (%)	White 151 (80%) Black 19 (10%) Hispanic 6 (3%) Asian 4 (2%) Other 10 (5%)	White 72 (74%) Black 15 (15%) Hispanic 4 (4%) Asian 2 (1%) Other 6 (6%)

Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

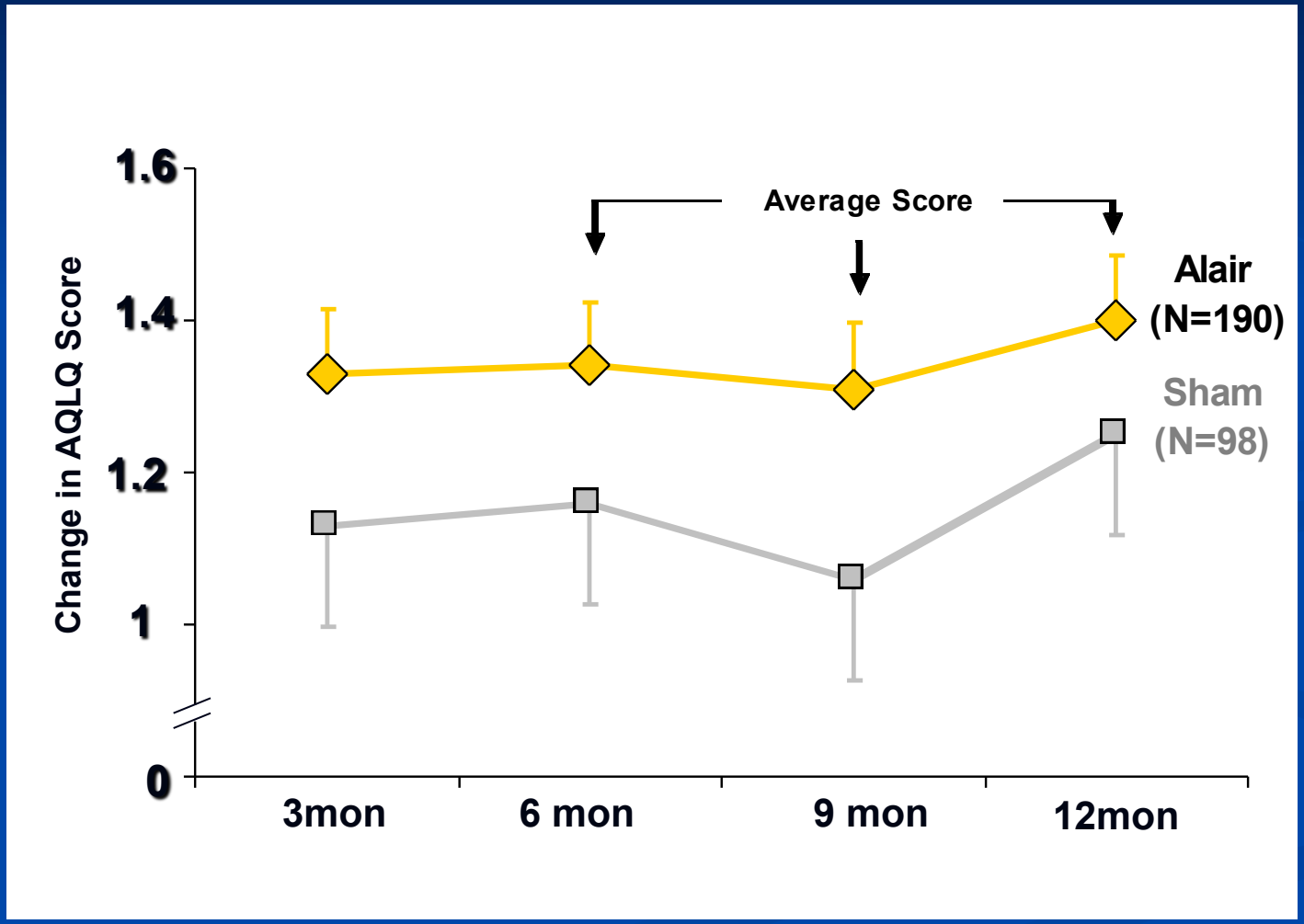
AIR2: Baseline Characteristics

Parameter	BT	Sham
Number of Subjects	190	98
Pre-Bronchodilator FEV_1 (% predicted)	77.8 ± 15.7	79.7 ± 15.1
Inhaled Corticosteroid (beclomethasone equivalent, µg/day)	1961	1835
Long-Acting β_2-Agonist (µg/day)	117	110
AQLQ Score (scale 1-7)	4.30 ± 1.17	4.32 ± 1.21
Symptom-Free Days (%)	16.4 ± 24.0	16.8 ± 23.1
Number and (%) of Subjects on Other Asthma Maintenance Medications:	59 (31.1)	25 (25.5)
OCS	7 (3.7)	1 (1.0)
Leukotriene Modifiers (e.g., Singulair)	47 (24.7)	18 (18.4)
Omalizumab (Xolair)	2 (1.1)	3 (3.1)
Other	21 (11.1)	14 (14.3)

Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

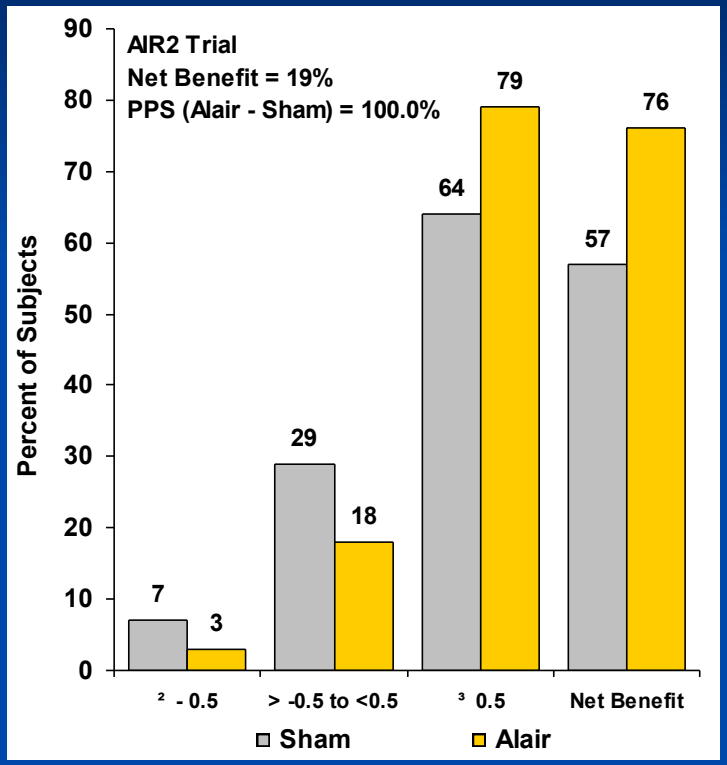
Primary Endpoint: AQLQ

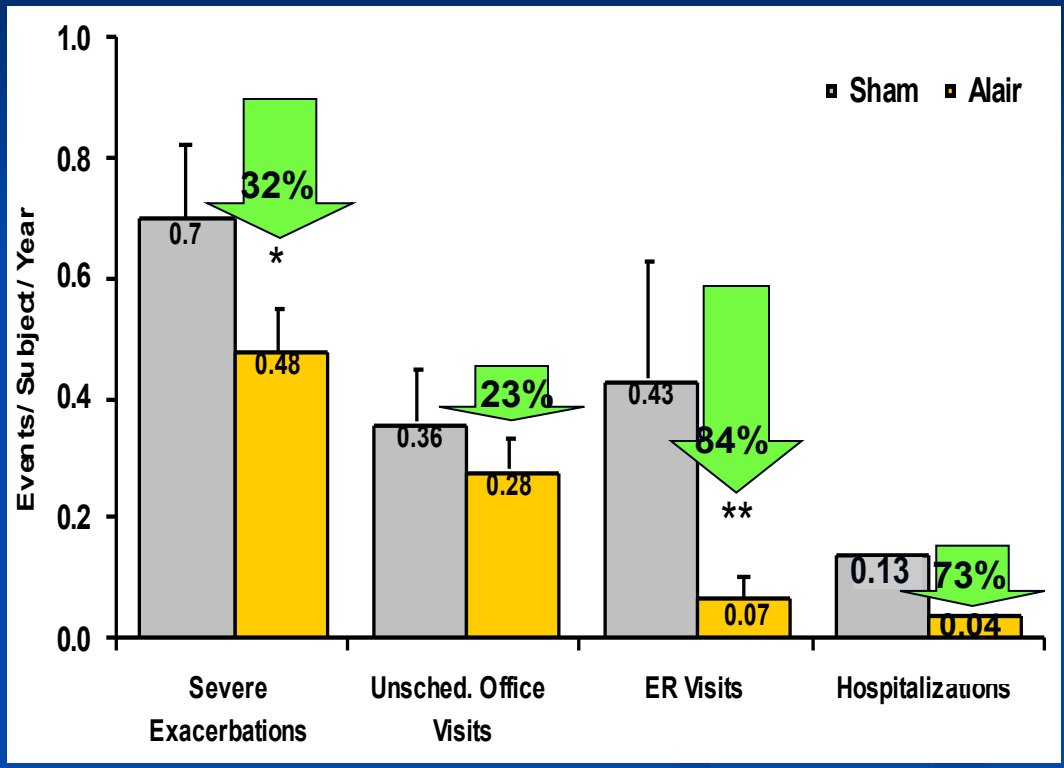
Intent-to-Treat (ITT) Population



Mean Difference = 0.21 (ITT); 0.24 (PP)
Post Prob Sup = 96.0% (ITT); 97.9% (PP)

Bronchial Thermoplasty





*PPS = 95.6%, ** PPS= 95.6%

Castro M et al. Am J Respir Crit Care Med. 2010;181(2):116-24

Secondary Endpoints at 12 Months: Changes from Baseline (ITT)

Endpoint	Alair	Sham	Trend in favor of Alair	Posterior Prob. of Superiority(%)
% Symptom Free Days	24.4	21.0	+	77.6
Total Symptom Score	- 1.7	- 1.6	+	63.7
Rescue Med Use (Puffs/7days)	- 6.0	- 4.3	+	81.3
% Days Rescue Med Used	- 24.0	- 22.0	+	68.0
ACQ Score	- 0.82	- 0.77	+	63.8
am PEF (L/min)	27.8	22.3	+	80.6

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Respiratory Adverse Events

Overall Adverse Events With > 3% Incidence

Adverse Event	Treatment Period (~12 weeks)		Post-Treatment Period (~46 weeks)	
	Alair (N=190) %	Sham (N=98) %	Alair (N=187) %	Sham (N=98) %
Asthma (Multiple Symptom)	52.1	38.8 *	27.3 *	42.9
Wheezing	15.3	6.1 *	4.3	3.1
Atelectasis	4.7	0 *	0	0
Hemoptysis	3.2	0 *	0	0
Lower Respiratory Tract Infection	7.9	2.0 *	3.2	6.1
Upper Respiratory Tract Infection	20.0	11.2 *	29.9	25.5
Nasopharyngitis	4.7	7.1	10.7	5.1 *
Throat irritation	4.7*	12.2	1.1	3.1

* pp superiority >95.0%

Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

Treatment Period Hospitalizations for Respiratory Symptoms

Alair (N=190) 19 Hospitalizations in 16 Subjects No. of Events (Incident Rate %)		Sham (N=98) 2 Hospitalizations in 2 Subjects No. of Events (Incident Rate %)	
Asthma Aggravated	12 (6.3%)	Asthma Aggravated	2 (2.0%)
Atelectasis	3 (1.6%)		
Lower Resp. Tract Infect.	1 (0.5%)		
Hemoptysis	1 (0.5%)		
Low FEV_1	1 (0.5%)		
Aspirated tooth in airway	1 (0.5%)		

Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

AIR2 Summary at 1-Year

- **Improved asthma-related quality of life compared to control (AQLQ score)**
  - 79% of BT treated patients achieved ≥ 0.5 increase
  - Effect persistent across 6, 9, and 12 months
- **Improved clinical outcomes compared to control:**
  - 32% decrease in severe exacerbations
  - 84% reduction in ER visits for respiratory symptoms
  - 73% reduction in hospitalization for respiratory symptoms
  - 66% less days lost from work, school and other daily activities due to asthma
- **Short term risks:**
  - Treatment adverse events related to transient worsening of asthma
  - Typically occur within one day and resolve within one week with standard care

Castro, Am J Respir Crit Care Med. 2010;181(2):116-24

Persistence of BT Effect at Two Years

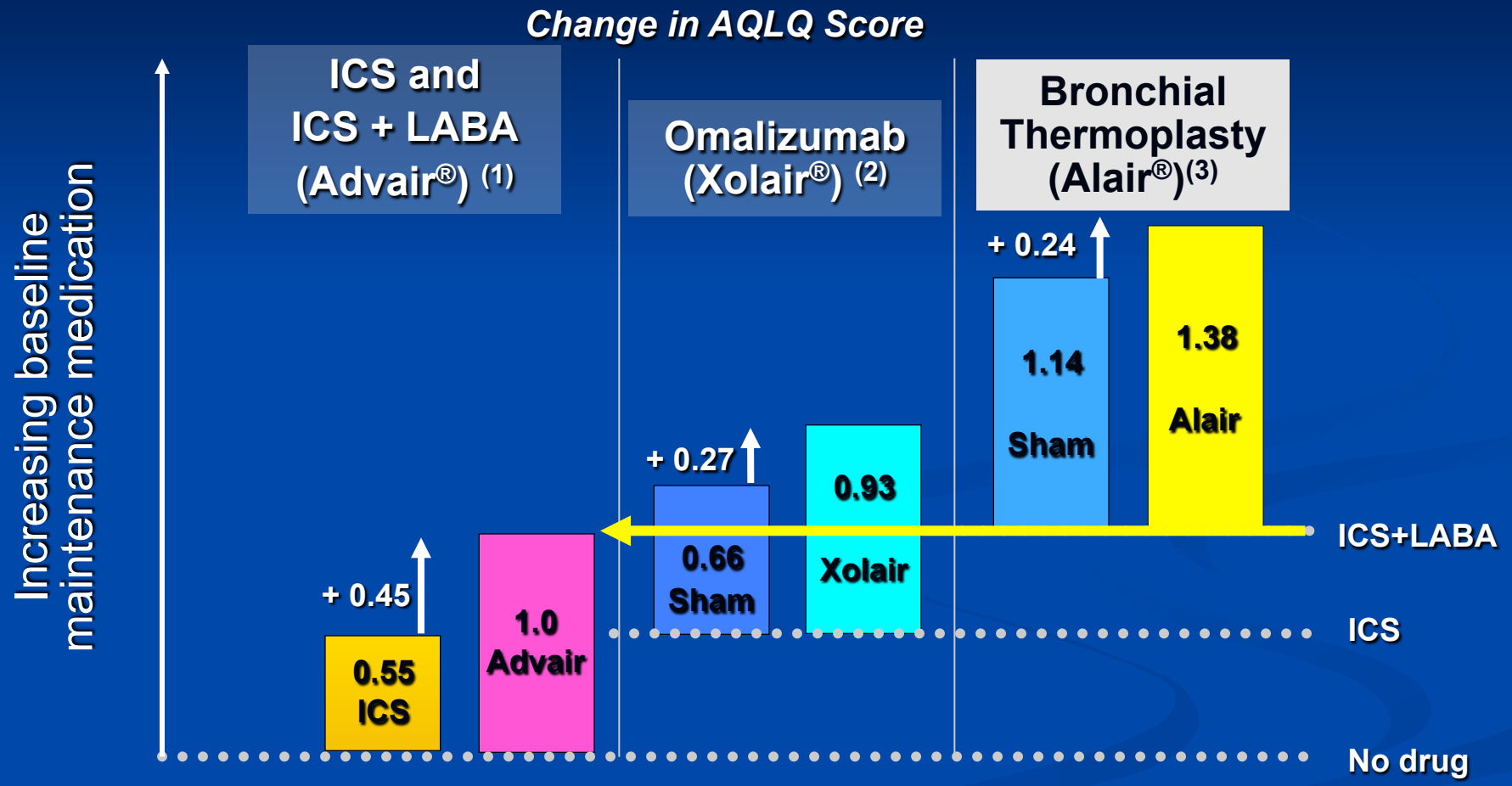
- No difference found in the asthma control for BT-treated subjects in Year 2 versus Year 1 following treatment

	Percent of Subjects		
	Year Prior to Study Entry[a] (n=288)	Year 1 BT (n=181)	Year 2 BT (n=166)
Severe exacerbations	53.4	30.9 (56)	23.0 (38)[b]
ED Visits	29.8	5.0 (9)	6.6 (11)[b]
Hospitalizations	5.5	3.3 (6)	4.2 (7)[b]

a: patient reported for all subjects (BT + Sham) prior to study entry
b: Year 2 BT comparison to Year 1 BT: Not significant by Fisher's Exact Test

Castro M, et al. Ann Allergy Asthma Immunol. 2011 Jul;107(1):65-70

Conceptualizing the Impact of Bronchial Thermoplasty

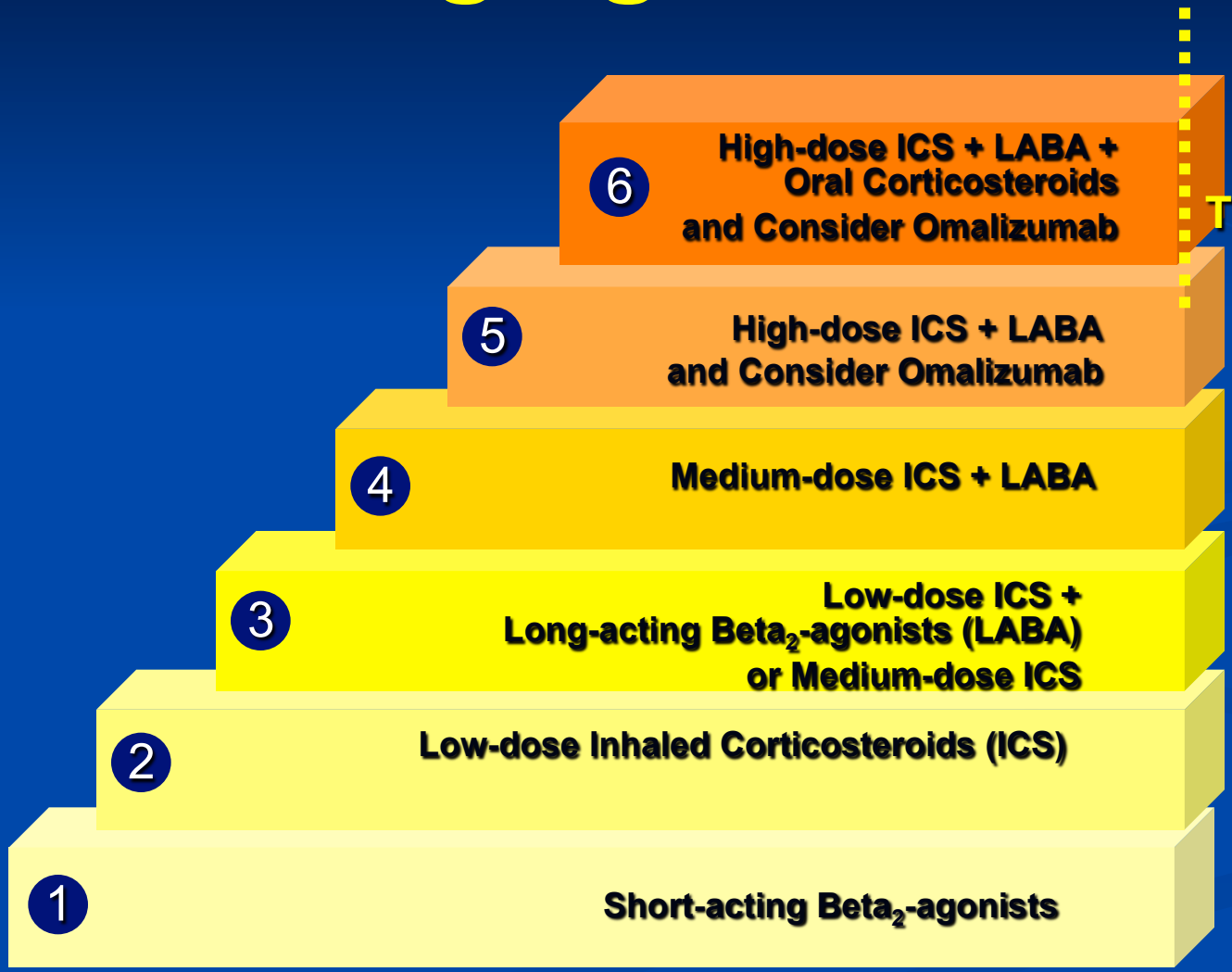


(1) NDA 21-077 Study 3003: Placebo, ICS (Fluticasone 250), and ICS + LABA (Advair 250/50)

(2) BB IND 5369, Study 009: Omalizumab (Xolair), placebo; for allergic asthma only

(3) PMA P080032, AIR2 Trial, Bronchial Thermoplasty (Alair), Sham (PP, n=268)

Stepwise Approach for Managing Asthma



Adapted from National Asthma Education and Prevention Program (NAEPP) Guidelines. Expert Panel Report 3: NIH Publication No. 07-4051, Revised August 2007.

Bronchial Thermoplasty Conclusions

1. Offers a novel treatment for severe asthma where alternative treatments are limited, of unproven efficacy, and have side effects
2. Proven efficacy for reducing severe exacerbations, healthcare utilization, days lost from school/work and improving QOL with acceptable short-term AE profile > NET positive health outcome
3. Long term safety established out to 5 years
4. Since FDA approval over 100 pts have been treated outside of an investigational setting with an acceptable AE profile
   (CTAF testimony Oct 19, 2011)
5. BT is ready for "prime time" in the hands of experienced trained bronchoscopist working in conjunction with clinician with special expertise in evaluation and management of severe asthma