Comparative Effectiveness Review
Number 202

Effectiveness and Safety of Bronchial Thermoplasty in Management of Asthma

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Key Messages

Purpose of Review

To evaluate the effectiveness and safety of bronchial thermoplasty (BT), a procedure that uses heat to remove muscle tissue from the airways of adults with moderate to severe asthma. BT is usually given as three treatments 3 weeks apart.

Key Messages

- BT along with standard medical management, compared to medical management alone, may improve asthma control and quality of life, but evidence is insufficient to determine impact on asthma exacerbations.
- BT along with standard medical management, compared to a similar procedure without the heat (sham procedure), does not improve asthma control or hospitalizations but may reduce severe exacerbations and emergency room visits.
- BT causes more adverse events (such as worsening of asthma symptoms, respiratory infections, and coughing up blood) during the treatment period than standard treatment. Based on the available literature, there is still uncertainty about the balance of benefits and harms, and about which patients are most likely to benefit from the procedure.

This report is based on research conducted by the ECRI Institute–Penn Medicine Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00005-I). The National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) sponsored the report. The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ or NIH/NHLBI. Therefore, no statement in this report should be construed as an official position of AHRQ, NIH/NHLBI, or the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information (i.e., in the context of available resources and circumstances presented by individual patients).

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program Web site at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The National Heart, Lung, and Blood Institute, one of the National Institutes of Health, requested that AHRQ conduct a systematic review of the benefits and harms of bronchial thermoplasty for the management of asthma in adults and provided funding for this.

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodologic and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality-improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officers named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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We also thank AHRQ Task Order Officers, Aysegul Gozu, M.D., M.P.H., and David W. Niebuhr, M.D., M.P.H. M.Sc., and the following individuals at National Heart, Lung, and Blood Institute (NHLBI): Janet M. DeJesus, M.S., Michelle Freemer, M.D., M.P.H., and Rachael L. Tracy, M.P.H. We appreciate the collaboration of our colleagues at other EPCs preparing reports for NHLBI, and particularly thank Diana Sobieraj and others at the University of Connecticut EPC, who provided the table and references for minimally important differences in Appendix D.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Before publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Effectiveness and Safety of Bronchial Thermoplasty in Management of Asthma

Structured Abstract

Objective. This review assesses the effectiveness and safety of bronchial thermoplasty (BT) in adults with asthma.

Data sources. We systematically searched the gray literature and five bibliographic databases, MEDLINE®, Embase®, PubMed®, CINAHL®, and the Cochrane Library, through April 20, 2017.

Review methods. Eligible studies included systematic reviews, meta-analyses, randomized controlled trials (RCTs), and nonrandomized interventional studies with concurrent controls. Case reports and series were also considered for describing adverse events. Studies were evaluated for risk of bias using the Cochrane Risk of Bias instrument, and the evidence base was assessed using the methods guidance established by the Evidence-based Practice Center program.

Results. Fifteen studies, including three RCTs with 5-year single-arm followup in BT-treated patients (n=432 for the RCTs), examined the impact of BT in addition to standard care (continued medical management) on patients with asthma. BT and standard care improved asthma control (defined by the Asthma Control Questionnaire [ACQ] change from baseline to 12 months) and Asthma Quality of Life Questionnaire (AQLQ) scores more than standard care alone to a degree that was statistically significant but not clinically important (low strength of evidence [SOE]). However, BT and standard care, compared with a sham bronchoscopic procedure and standard care, did not improve asthma control (defined as ACQ change from baseline to 12 months), hospitalizations for respiratory symptoms, use of rescue medications, pulmonary physiology measures, or AQLQ scores (in the intention-to-treat analysis) (low SOE). In the same sham-controlled trial, BT reduced severe exacerbations after the 12-week treatment period to a statistically but not clinically important degree (low SOE), and patients undergoing BT had fewer emergency department visits than patients who had the sham bronchoscopic procedure (moderate SOE). In the RCTs comparing BT and standard care to standard care alone, evidence was insufficient to assess if BT reduced rates of severe exacerbations.
Common adverse events following BT during the 12-week treatment period in the RCTs included bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing. Hospitalizations were more common in patients undergoing BT than with either standard care alone or sham bronchoscopy during the 12-week treatment period, as were upper respiratory tract infections, wheezing, dyspnea, lower respiratory tract infections, anxiety, and segmental atelectasis, but the events were too infrequent to achieve statistical significance. Severe adverse events (including post-procedure segmental atelectasis due to mucus plugging, hemoptysis, chest infections requiring hospitalization, and bronchial artery pseudoaneurysm) were also reported in six case reports and two small case series. Following the 12-week treatment period, rates of respiratory-related hospitalizations were not significantly different between groups for up to 5 years of followup. No deaths were attributed to BT.

Conclusions. While asthma control and quality of life measures modestly improved in patients undergoing BT compared to medical management alone in two controlled but nonblinded studies, these measures did not improve in the sham-controlled study. The sham-controlled, blinded study found modest improvements in severe exacerbations and significantly fewer

emergency department visits following BT compared to the sham bronchoscopic procedure, but serious adverse events and post-procedure hospitalizations were more common during the 12-week treatment period in patients undergoing BT than in patients undergoing sham treatment. The available body of literature on BT is small and uncertainty remains about appropriate patient selection criteria and the effects of the treatment beyond 5 years.

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Evidence Summary

Objectives and Rationale for Review

This report summarizes a systematic review, "Effectiveness and Safety of Bronchial Thermoplasty in Management of Asthma," and identifies needs for future research. This was one of the six high-priority topics within asthma identified by an National Heart, Lung, and Blood Institute Advisory Council Asthma Expert Working Group.[1]

The objective of the systematic review is to assess the effectiveness and safety of bronchial thermoplasty (BT) in adults with asthma.

Background

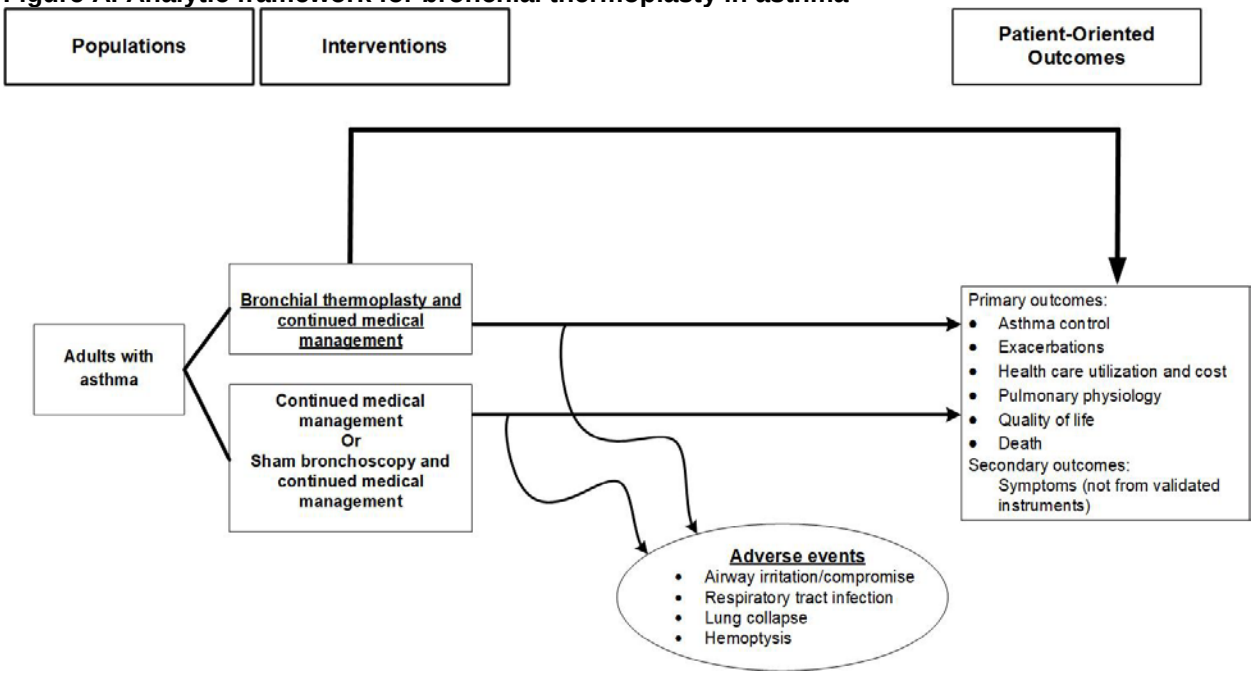
Patients with severe, persistent asthma are managed with multiple medications that may include inhaled, orally administered, and biologic therapeutics. Some of these patients might be eligible for BT, an interventional treatment option that involves the delivery of controlled radiofrequency thermal energy to the walls of accessible proximal airways with the intent of reducing excess airway smooth muscle tissue in the airways and reducing the frequency of severe asthma exacerbations on a long-term basis. In April 2010, the U.S. Food and Drug Administration approved the Alair BT system for use in patients 18 years of age or older with severe, persistent asthma.

This report's main objective is to conduct a systematic review of the benefits and harms of BT for the management of asthma in adults. In this review, we address the following Key Question (KQ):

What are the benefits and harms of using BT in addition to standard treatment for the treatment of adult (≥18 years) patients with asthma?

Figure A shows the analytic framework for the review.

Figure A. Analytic framework for bronchial thermoplasty in asthma



Data Sources

MEDLINE®, Embase®, PubMed®, CINAHL®, the Cochrane Library, and the gray literature were searched through April 20, 2017. The systematic review protocol is available in the full report.

Results

Fifteen studies, including three randomized controlled trials (RCTs) with 5-year single-arm followup in BT-treated patients (n=432 for the RCTs), examined the impact of BT on patients with severe asthma. The key findings of the review are listed below along with the strength of evidence (SOE).

- Patients treated with BT and standard care (medical management) showed statistically greater improvements in asthma control (as measured by the Asthma Control Questionnaire [ACQ]) and quality of life (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) compared with patients undergoing standard care (medical management) only (SOE: low). However, the clinical importance of the changes is unclear.
- Evidence as to whether patients treated with BT and standard care versus standard care alone experienced different rates of severe exacerbations following treatment was inconclusive (SOE: insufficient). While rates of mild exacerbations improved to a greater extent in the BT and standard care group than in the standard care only group, the clinical importance of the difference is unclear. (SOE: low).
- Patients treated with BT and standard care used statistically significantly less rescue medication than patients receiving standard care alone, but the clinical importance of the difference is unclear. (SOE: low).

- Patients given BT and standard care compared with patients given the sham bronchoscopic procedure and standard care had no difference in asthma control scores, as measured by ACQ; in hospitalizations for respiratory symptoms; in use of rescue medication; in number of days rescue medications were required; or in pulmonary physiology measures (forced expiratory volume in 1 second [FEV1] and morning peak expiratory flow [PEF]) (SOE for all outcomes: low).
- Patients treated with BT and standard care experienced statistically significantly fewer exacerbations (those requiring systemic corticosteroids or doubling of inhaled corticosteroid dose) compared with those receiving the sham bronchoscopic procedure and standard care after the treatment period was complete (3 procedures over 6 weeks, followed by an additional 6 weeks) through the 12-month followup (post-treatment period), but the clinical importance of this difference was unclear (SOE: low).
- Patients treated with BT and standard care had fewer emergency department (ED) visits compared with those receiving the sham bronchoscopic procedure and standard care during the post-treatment period (SOE: moderate).
- Evidence as to whether patients receiving BT and standard care versus the sham bronchoscopic procedure and standard care had different quality of life (AQLQ) scores was inconclusive (SOE: insufficient). Analysis of results for the intention-to-treat population did not find improvement, but analysis of results for the per-protocol population found a difference that may not be clinically important, as it did not achieve the minimum important difference for this measure. A responder analysis (proportion of patients who achieved the minimum important difference) favored the BT and standard care group, but this outcome was not prespecified.
- Patients treated with BT developed the following common adverse events: bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing. Serious adverse events occurred more frequently in BT-treated patients than in patients receiving sham treatment and/or standard care during the 12-week treatment period. No deaths were attributed to BT.

Discussion

We identified three primary RCTs (n=432) of BT, as well as their associated followup studies (n=245). Nine observational studies (n=55) also reported outcomes associated with BT. Relatively few randomized studies have examined BT in patients with severe asthma and addressed the question in this review, with only two multicenter RCTs comparing BT with standard care (medical management), and one multicenter RCT comparing BT to a sham bronchoscopy intervention with standard care continued in both groups. Compared with standard care, the evidence from two RCTs suggests that BT improved asthma control (defined by the ACQ change from baseline to 12 months), health care utilization (defined by rescue medication use), and quality of life (low strength of evidence [SOE]). However, the minimally important difference (MID) was not met for these measures, and the clinical relevance of these findings is uncertain. Similarly, rates of mild exacerbations were reduced following BT (low SOE), but concerns about the magnitude of the effect and directness of the findings led us to conclude that the clinical relevance of this finding was uncertain. The evidence base was insufficient to draw conclusions about BT's effects on severe exacerbations, FEV1, and airway hyper-responsiveness compared with standard care.

Compared with sham treatment, the intention-to-treat analysis in a single RCT suggests that BT had no effect on asthma control (defined as improvement in ACQ from baseline), hospitalizations for respiratory symptoms, health care utilization (rescue medication usage), pulmonary physiology measures (FEV1 % predicted and morning PEF [L/min]), or other asthma symptoms outcomes (low SOE). However, reduced risk of severe exacerbations was suggested (low SOE), although the clinical importance of this difference was unclear. BT was associated with fewer ED visits than sham treatment during the post-treatment period (moderate SOE). The evidence was inconclusive regarding quality of life scores following BT or sham (insufficient SOE). Serious adverse events attributed to BT were infrequent, and no deaths were reported.

Clinicians whose patients are potential candidates for BT may want to consider the evidence presented in this review, including the highly selected and heterogeneous study populations, limited improvement in outcomes, and rates of adverse events (including asthma worsening and respiratory tract infections during the treatment period) when determining BT's appropriateness for their patients.

Conclusions

Three RCTs and several descriptive studies meeting our inclusion criteria have evaluated BT. Based on the available literature, BT may be modestly beneficial in some patients with asthma, but is not without risks in any population. The risk of adverse events is higher early in treatment, while benefit is typically observed weeks to months after therapy and can last for at least 5 years, after which the effect is unknown

Reference

1. National Heart, Lung, and Blood Advisory Council Asthma Expert Working Group. Needs Assessment Report for Potential Update of the Expert Panel Report-3 (2007): Guidelines for the Diagnosis and Management of Asthma. 2015.

Introduction

Background

Asthma is a chronic inflammatory disorder of the airways, characterized by varying degrees of airflow obstruction. Bronchoconstriction, inflammatory cell infiltration, and airway edema reduce airflow intermittently, often in response to specific exposures, resulting in respiratory symptoms.[1] In the United States, asthma's prevalence has increased over the past decade, from an estimated 22.2 million Americans in 2005 to 24 million Americans in 2014.[2,3] Asthma can significantly affect patients' and families' quality of life and ability to pursue activities such as school, work, and exercise. Globally, asthma ranks 14th in prevalence based on the burden of disease, as measured by disability-adjusted life years.[4] In the United States, asthma contributes significantly to health care resource utilization and associated costs. For example, in 2012, asthma was one of the top 20 leading diagnosis groups for primary care visits and was the main reason for 1.8 million emergency department visits and 439,000 hospitalizations. While the severity of disease varies between patients and over time in the same patient, asthma can be fatal, accounting for approximately 1 death per 100,000 Americans.[5]

Role of Bronchial Thermoplasty in Management of Asthma

Patients with severe, persistent asthma are managed with multiple medications that may include inhaled, orally administered, and biologic therapeutics. Some of these patients might be eligible for bronchial thermoplasty (BT), an interventional treatment option that involves the delivery of controlled radiofrequency (RF) thermal energy to the walls of accessible proximal airways with the intent of reducing excess smooth muscle tissue in the airways. The Alair™ Bronchial Thermoplasty System (Boston Scientific Corp.) consists of a radiofrequency controller, footswitch, and a patient return electrode, which provides temperature-controlled delivery of RF energy to a disposable, single-use catheter for a predetermined duration. The Alair Catheter was designed for use with high-frequency compatible flexible bronchoscopes, delivering energy to the desired airway site while relaying temperature feedback to the controller. Physicians perform three bronchoscopic procedures to different areas of the lung approximately 3 weeks apart: the lower lobe of the right lung, the lower lobe of the left lung, then both upper lobes in the final procedure. In each procedure, the physician performs about 45 to 60 smooth muscle ablations heating the airway wall to about 150ºF for 10 seconds. Each procedure usually takes under an hour. Sedation for BT typically involves a combination of moderate or deep sedation and local anesthesia.[6] In April 2010, the U.S. Food and Drug Administration approved the Alair BT system for use in patients 18 years of age or older with severe, persistent asthma.

Purpose of Systematic Review

In 1989, the National Heart, Lung, and Blood Institute (NHLBI) initiated the National Asthma Education and Prevention Program (NAEPP) to address the growing concern about asthma in the United States. One of NAEPP's first accomplishments was to convene a panel of experts, who produced a report in 1991, *The National Asthma Education and Prevention Program Expert Panel Report (EPR): Guidelines for the Diagnosis and Management of Asthma*. The guidelines address the diagnosis, evaluation, and treatment of asthma. Given that the most recent report, EPR-3, was published in 2007,[1] NHLBI assessed the need for an update by

requesting information from the public, NAEPP Coordinating Committee Members, its affiliates, and members of the 2007 Expert Panel. Collected information was provided to the NHLBI Advisory Council Asthma Expert Working Group, which produced a report to summarize the process and recommendations from their needs assessment.[7] The Working Group identified six high-priority topics that should be updated. For each topic, Key Questions meriting a systematic literature review were formulated. NHLBI engaged the Agency for Healthcare Research and Quality to perform the systematic reviews through its Evidence-Based Practice Centers. This document represents the systematic review "Role of Bronchial Thermoplasty in Management of Asthma."

Scope and Key Question

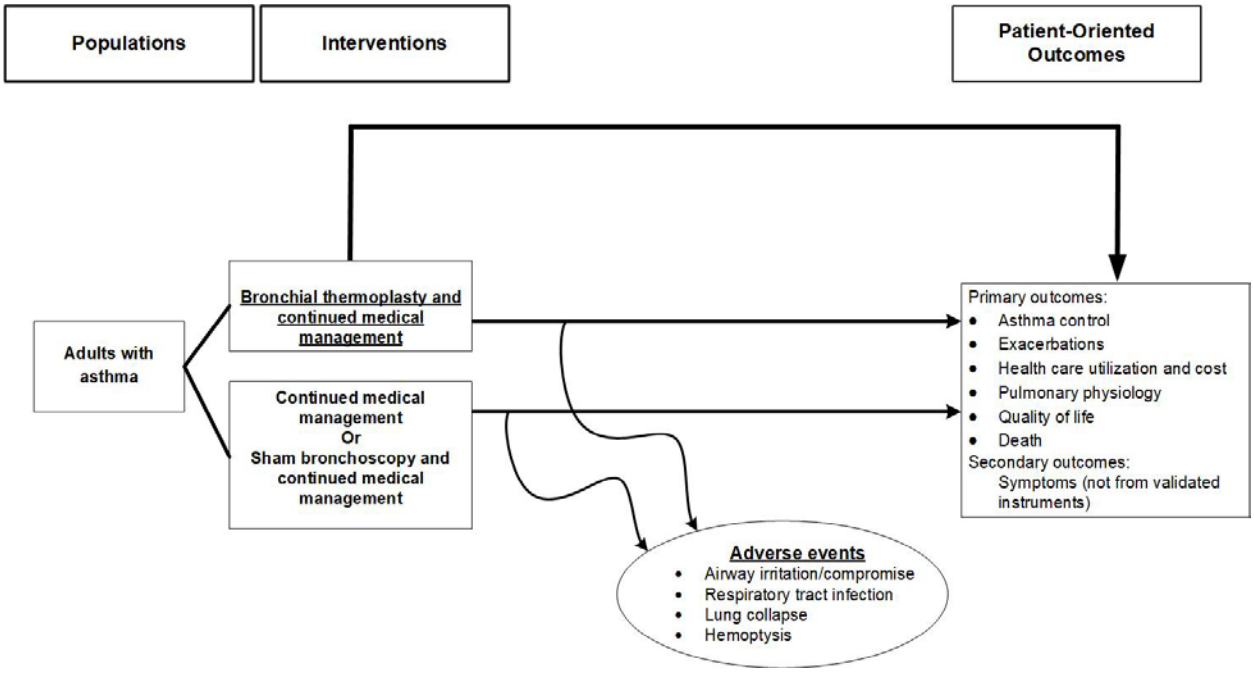
This report's main objective is to conduct a systematic review of the benefits and harms of BT for the management of asthma in adults. In this review, we address the following Key Question (KQ):

Key Question 1: What are the benefits and harms of using BT in addition to standard treatment for the treatment of adult (≥18 years) patients with asthma?

Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure 1).

Figure 1. Analytic framework for bronchial thermoplasty in asthma



Organization of This Report

In the remaining three chapters of this report, we describe the methods for this systematic review, present the results for the KQ, and discuss the overall findings. In the Results chapter, we provide the results of the literature searches and screening procedures, as well as descriptions of included studies, key points, detailed syntheses of the studies, and strength-of-evidence tables for the KQ. The Discussion chapter reviews the key findings and strength of evidence for the KQ, places the findings in the context of previous systematic reviews and clinical practice guidelines, examines the general applicability of the studies, discusses implications for decisionmaking, describes limitations of the systematic review process and the evidence base for the KQ, and identifies knowledge gaps that require further research.

A list of acronyms and abbreviations appears after the references, followed by six appendixes: Appendix A. Search Strategies; Appendix B. Excluded Studies; Appendix C. Evidence Tables; Appendix D. Minimally Important Differences for Asthma Study Outcomes; Appendix E. Ongoing Clinical Trials; and Appendix F. Reference List for Appendixes B, C, and C.

Methods

Topic Refinement and Review Protocol

The National Heart, Lung, and Blood Institute (NHLBI) initially nominated this topic, as described in the Introduction. We generated an analytic framework, preliminary Key Questions (KQs), and preliminary inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, and settings). A Technical Expert Panel (TEP) was convened for this report. The TEP consisted of nine scientists and clinicians, including individuals with expertise in the clinical management of pediatric and adult asthma, the use of bronchial thermoplasty (BT), and implementation of environmental-control interventions to reduce exposure to allergens in the home. TEP members participated in conference calls and discussions through email to review the scope, analytic framework, KQs, and PICOTS, and provided input on the information and categories included in evidence tables and the analysis. A list of the TEP members is included in the front matter of this report. The final protocol of the review was posted on the Effective Health Care Web site on October 11, 2016. A full version of our protocol for this systematic review is available online (https://effectivehealthcare.ahrq.gov/ehc/products/643/2318/asthma-nonpharmacologic-treatment-protocol-161004.pdf),[8] and is registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO) registration number CRD42017055547).[9]

Based on peer review and public feedback on the draft report, we separated the two KQs described in the protocol into two separate reports. The guidance provided by the TEP and the content included in the posted protocol reflect the larger scope of work as initially planned.

Literature Search Strategy

Search Strategy

Literature searches were performed by Medical Librarians at the ECRI Institute Evidence-based Practice Center (EPC) Information Center and followed established systematic review protocols. Searches covered the literature published from database inception (dates vary, see Appendix A) through April 20, 2017.

We searched the following databases using controlled vocabulary and text words: Embase® and MEDLINE® (searched together on the EMBASE.com platform), PubMed ® (In Process citations), CINAHL® (Cumulative Index to Nursing and Allied Health Literature), and the Cochrane Library.

We used text words to search gray literature sources and the Web sites of relevant organizations, such as the U.S. Food and Drug Administration Web site, identified by the clinical experts on the project team. A complete list of the resources we searched, as well as search concepts and strategies, are available in Appendix A.

Reference lists from systematic reviews and meta-analyses were reviewed and compared against our retrieved articles. If a systematic review contained references that appeared to meet our inclusion criteria, but had not been captured by our initial search results, the search strategy was refined to include these articles. Supplemental Evidence and Data for Systematic Reviews submitted by interested parties were also reviewed.

Literature screening was performed in duplicate using the database Distiller SR (Evidence Partners, Ottawa, Ontario, Canada). Literature search results were initially screened for

relevancy. Relevant abstracts were screened against the inclusion and exclusion criteria in duplicate. Studies that appeared to meet the inclusion criteria were retrieved and screened again in duplicate against the inclusion and exclusion criteria. All disagreements were resolved by consensus discussion between the two original screeners.

Inclusion and Exclusion Criteria

Publication Criteria

Included articles must have been published as full-length, peer-reviewed studies. Abstracts and meeting presentations were not included because they do not include sufficient details about experimental methods to permit an evaluation of study design and conduct; they may also contain only a subset of measured outcomes.[10,11] Additionally, it is not uncommon for abstracts that are published as part of conference proceedings to have inconsistencies compared with the final study publication or to describe studies that are never published as full articles.[12-16]

When a study with an English-language abstract but published in a foreign language was identified, the abstract was assessed against the full set of inclusion/exclusion criteria. If the study appeared to fit the inclusion criteria, we evaluated whether excluding the study might result in language bias (e.g., if the findings differ from other included studies.) If language bias seemed unlikely, the study was excluded.

Study Selection

We followed the PICOTS (Table 1) framework to develop the inclusion criteria for studies. We included studies of adults with a diagnosis of asthma who underwent BT. Studies had to report on the outcomes prespecified in our PICOTS. Study inclusion was not restricted by language of publication or treatment duration. Randomized controlled trials (RCTs) and nonrandomized interventional studies with concurrent controls (e.g., nonrandomized trials) were considered for inclusion for assessment of benefits. Single-arm extensions of RCTs were included to describe long-term changes in efficacy or safety in patients treated with BT. Case reports or case series that describe adverse events were also considered for inclusion for reporting adverse events. *In vivo*, *in vitro*, and animal studies were excluded.

Table 1. PICOTS (populations, interventions, comparisons, outcomes, timing, and setting) criteria for including studies in the review

PICOTS	Criteria
Populations	• Asthma • ≥18 years old
Interventions	• Bronchial thermoplasty
Comparators	Treatments used in patients with asthma excluding thermoplasty • Standard care: medical management as determined by treating physician • Sham: bronchoscopy without thermoplasty
Outcomes	**Primary Outcomes** • Asthma control o Asthma Control Test™ (ACT™) / Childhood ACT o Asthma Control Questionnaire (ACQ) • Exacerbations o Systemic corticosteroids for asthma for at least 3 days o Asthma-specific hospitalizations o Asthma-specific emergency department visits o Asthma-specific urgent care visits (other than emergency department) o Asthma-specific admissions to intensive care unit, or intubations • Health care utilization and costs o Asthma-specific ambulatory care visits o Asthma-specific medication use (including medication name, dose, duration) o Asthma-specific hospitalizations, emergency department visits, urgent care visits o Resource use related to the intervention • Pulmonary physiology o Peak expiratory flow o Spirometry o Airway hyper-responsiveness • Quality of life o Asthma Quality of Life Questionnaire • Death, asthma-specific and all cause **Adverse events** • Patient-reported airway irritation (cough, wheezing, dyspnea, chest discomfort) • Airway compromise • Upper or lower respiratory tract infections • Lung collapse • Hemoptysis
Timing	• Studies with all lengths of followup duration will be considered
Setting	• Clinical settings

Data Extraction

Data were extracted using Microsoft Word. All extracted data were double-checked by a second investigator. All discrepancies were resolved by consensus discussion among the two investigators and an additional person as needed. Elements abstracted included general study characteristics, patient characteristics, details of interventions, outcomes data, and risk of bias items.

Risk of Bias Assessment of Individual Studies

We used the Cochrane Collaboration's tool for assessing risk of bias in RCTs.[17] Study characteristics were rated as introducing "low," "high," or "unclear" risk of bias. Two independent reviewers assessed risk of bias, and discrepancies were addressed through consensus discussion.

We considered the funding source of individual studies as presenting a potentially important risk of bias. Therefore, we noted in the risk of bias table any study that reported receiving all or

part of its funding from a commercial manufacturer of an intervention or was coauthored by one or more of its employees. We rated the "Other Sources of Bias" component in the Cochrane scale as "high" in cases in which study funding presented a potential conflict of interest.

We created a summary assessment of "Overall Risk of Bias" by grouping the criteria included in the Cochrane tool into four categories based on the nature of their respective threats to validity. The four categories address: (1) participant enrollment (comprising "sequence generation" and "allocation concealment"), (2) blinding ("blinding of participants, personnel and outcome assessors"), (3) outcome data ("incomplete outcome data" and "selective outcome reporting"), and (4) other sources of bias. We then concluded that an individual study was at "high" overall risk of bias if it was assigned a "high" risk rating for one or more discrete criteria in at least two different *categories.* A study was determined to be at "medium" overall risk of bias if it was assigned a "high" risk rating in only one discrete criterion, or in two criteria within the same *category*. For example, if a study was at "high" risk of bias for both "sequence generation" and "incomplete outcome data," the overall risk would be "high" because there is concern about two different categories. Conversely, if a study was at "high" risk of bias for "sequence generation" and "allocation concealment," then the overall risk would be "medium" because the two criteria are in the same category. If no criteria were assessed to be at "high" risk, then the overall risk of bias was "low." However, if we rated the risk as "Unclear" in two or more categories, then the overall risk was "unclear."

Data Synthesis

We synthesized the data qualitatively. Due to the clinical heterogeneity and the small number of included studies, we did not attempt to combine data from the studies quantitatively using meta-analyses.

We have described outcomes as statistically significant when identified as such by the authors of the primary studies or by the EPC's calculations from reported data. Statistical significance, however, does not always equate with clinically significant changes in outcomes. In the strength of evidence (SOE) tables, we note any cases in which a statistically significant result was not associated with a minimum important difference (see Appendix D). We calculated effect sizes and 95% confidence intervals for within study comparisons when the publications provided sufficient data.

Critical outcomes for the KQ included the following validated outcomes: asthma-control measures (Asthma Control Questionnaire), asthma-exacerbation measures, asthma-related health care utilization and costs (use of rescue medication), asthma-related pulmonary physiology (forced expiratory volume in 1 second [or as % predicted] and morning peak expiratory flow), and the Asthma Quality of Life Questionnaire. We also considered symptoms reported in other ways and adverse events as critical outcomes.

Strength of Body of Evidence

We graded the SOE based on the methods guidance established by the EPC program. This approach incorporates five key domains: study limitations, consistency, directness, precision, and reporting bias.

We determined study limitations by appraising the degree to which the included studies had adequate protection against bias (i.e., good internal validity). We downgraded for study limitations when 50 percent or more of the studies evaluated for a given outcome were at "high" overall risk of bias as described above. If the evidence permits a conclusion, then, all else being

equal, a set of studies at low risk of bias yields a higher SOE rating than a set of studies at high risk of bias.

We assessed consistency of results for the same outcome among the available studies in terms of the direction and magnitude of effect. We downgraded for inconsistency when there was heterogeneity in the effects of an intervention across studies for a given outcome that could not be explained through identifiable differences in study characteristics. We downgraded for unknown consistency when only a single study was included for an outcome.

The evidence was considered indirect if the populations, interventions, comparisons, or outcomes used within studies did not directly correspond to the comparisons we were evaluating, and we suspected there may be differences in effect based on that indirectness.

Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome and is affected by sample size and number of events and most commonly represented by the width of confidence intervals. We also considered the evidence to be imprecise when key components of the outcome data that studies provided were not fully reported (e.g., measures of variance were not included) or when it was not possible to derive an estimate of effect based on the available data.

Reporting bias includes publication bias, outcome-reporting bias, and analysis-reporting bias. Given the small number of studies we evaluated, we did not examine funnel plots. We downgraded for reporting bias when we detected a likelihood of outcome-reporting bias (important clinical outcomes appear to have been collected but not reported by the studies within a comparison) or analysis reporting bias (important comparisons were not analyzed).

Applicability

Several *a priori* factors of this evidence base may limit the applicability of findings. We evaluated the available literature in context with our specific PICOTS criteria and have described differences between them in the Discussion chapter. The major issues related to applicability of this evidence base include patient selection criteria and characteristics as well as the choice of comparators and outcomes reported in the studies.

Peer Review and Public Commentary

Experts in clinical management of asthma, and strategies to minimize the presence and effect of indoor inhalant allergens, were invited to provide external peer review of the draft report. Agency for Healthcare Research and Quality (AHRQ) staff, an Associate Editor, and representatives from NHLBI reviewed the draft report before it was distributed for peer review. The draft report was also posted on the AHRQ Web site from April 26, 2017, to May 25, 2017, to enable public comment. We revised the report based on peer and public feedback, and noted these revisions in the Disposition of Comments Report. The disposition report is made available 3 months after the final review is posted on the AHRQ Web site.

Several important revisions were made to the report in response to peer review and public comment. As noted above, this review was initially designed to include the current Key Question as well as an additional Key Question addressing the effectiveness of indoor allergen reduction. We separated the larger review into two independent reports in response to substantial feedback. We clarified some of the study characteristics, outcomes, and terminology used throughout the review, and reorganized the results to increase clarity. Finally, we expanded the Discussion to address the important need for further sham-controlled studies.

Results

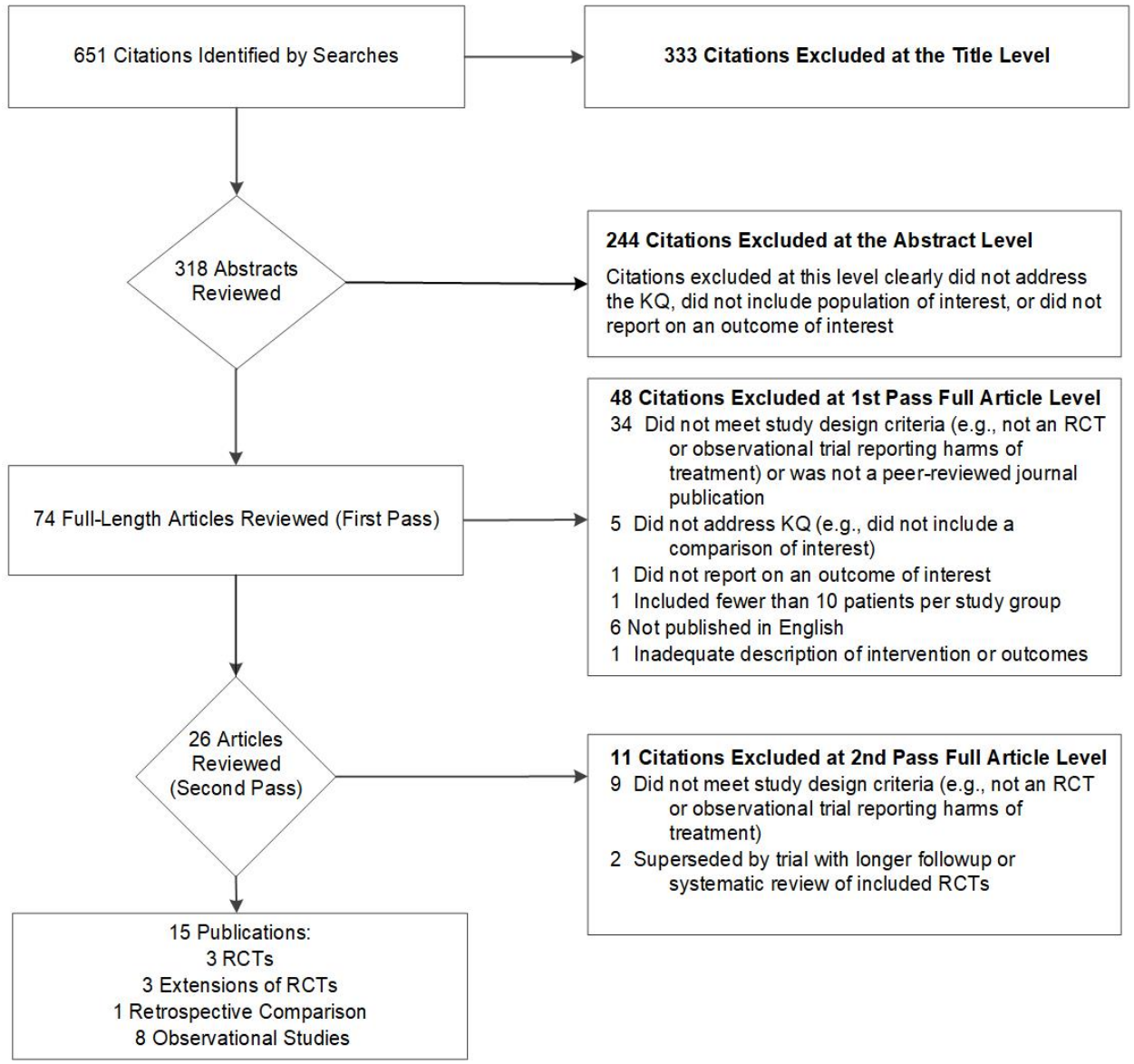
Introduction

We begin by describing the results of our literature searches. We then provide a brief description of the included studies. We provide a detailed description of the studies, key summary points, a detailed analysis of the results, and a table that presents the strength of evidence (SOE).

Results of Literature Searches

The literature searches identified three randomized controlled trials (RCTs) and 12 additional studies (see Figure 2). Articles that were excluded at the full-text level with reasons for their exclusion are listed in Appendix B.

Figure 2. Literature flow diagram



KQ=Key Question; RCT=randomized controlled trial

Key Question 1. What are the benefits and harms of using bronchial thermoplasty in addition to standard treatment for the treatment of adult (≥18 years) patients with asthma?

Description of Included Studies

Fifteen studies were included to address the benefits and harms of bronchial thermoplasty (BT). Six trials, including three RCTs (n=432)[18-20] and their 5-year, single-arm extension studies,[21-23] provided outcomes related to safety and efficacy. One of the extension studies also reported data for the control arm through 3 years. Two of the RCTs (Research In Severe Asthma [RISA][20] [n=32] and Asthma Intervention Research [AIR][19] [n=112]) compared BT plus standard care (i.e., medical management as determined by treating physician) to standard care alone for up to 12 months. The third RCT[18] (AIR 2, n=288) compared BT (with standard care) with bronchoscopic sham procedures (i.e., bronchoscopy without thermoplasty, along with standard care) as a control for up to 12 months. The manufacturer of the Alair BT system, Boston Scientific, funded all three RCTs. To better assess the generalizability of these studies, we included an additional study comparing outcomes of patients receiving BT as part of an RCT with those of "real-world" patients not enrolled in an RCT who were receiving BT at the same clinic.[24] For additional consideration of the potential harms of BT, eight descriptive studies were included, consisting of six case studies[25-30] and two case series.[31,32]

The U.S. Food and Drug Administration (FDA)-approved indication for the Alair system is for severe, persistent asthma in adults whose asthma is not controlled by inhaled corticosteroids (ICS) and long-acting beta agonists (LABA). However, the RCTs included patients with a range of asthma severity. We provide the detailed study inclusion criteria in Table 2.

Table 2. Patient inclusion criteria for the randomized controlled trials of bronchial thermoplasty

Study	Study Inclusion Criteria
RISA Study (Pavord 2007[20]) BT and standard care vs. standard care N=34	***Asthma severity:*** severe, requiring daily ICS at >750 mcg fluticasone equivalent and LABA 100 mcg salmeterol equivalent; ≤30 mg/d prednisone equivalent*;* ***Spirometry****:* prebronchodilator FEV_1 ≥50% predicted; airway hyperresponsiveness (methacholine challenge or response to bronchodilator) ***Additional****:* Uncontrolled symptoms while on maintenance therapy – rescue medication used on 8 of 14 days prior to enrollment or daytime symptoms on 10 of 14 days; nonsmoker ≥1 year
AIR Study (Cox 2007[19]) BT and standard care vs. standard care N=112	***Asthma severity:*** moderate or severe, requiring daily ICS at >200 mcg BPD equivalent and LABA 100 mcg salmeterol equivalent; stable disease in 6 weeks prior to entry ***Spirometry****:* prebronchodilator FEV_1 60 to 85% predicted; Methacholine PC_{20} <8mg/mL ***Additional****:* Worsening of ACQ ≥0.5 when off LABA for 2 weeks; <3 lower respiratory tract infections requiring antibiotics in previous 12 months, none in prior 6 weeks; nonsmoker ≥1 year; <4 puffs/day short-acting beta-2 agonist
AIR 2 (Castro 2010[18]) BT and standard care vs. sham (bronchoscopy without thermoplasty) and standard care N=297	***Asthma severity:*** severe asthma requiring daily ICS at >1,000 mcg BPD equivalent and LABA 100 mcg salmeterol equivalent; <10 mg OCS/day; ≥2 symptomatic days in prior 4 weeks ***Spirometry****:* prebronchodilator FEV_1 ≥60% predicted; Methacholine PC_{20} <8mg/mL ***Additional****:* AQLQ ≤6.25;<3 hospitalizations for asthma; <3 lower respiratory tract infections and <4 pulses of OCS in prior year; ***Additional exclusions:*** "life threatening" asthma; use of immunosuppressants, beta-adrenergic blocking agents or anticoagulants; chronic sinus disease or emphysema; smoking in past year or ≥ 10 pack-year smoking history

ACQ: Asthma Control Questionnaire (Range 0–6); AIR: Asthma Intervention Research; AQLQ: Asthma Quality of Life Questionnaire (Range 1–7); BT: bronchial thermoplasty; ED: emergency department; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; mcg: microgram; mg/mL: milligrams per milliliter; OCS: oral corticosteroids; PC_{20}=provocative concentration of methacholine causing a 20% drop in FEV_1; RISA: Research In Severe Asthma

The standard care provided during the course of the studies was a continuation of maintenance treatments (e.g., ICS with or without oral corticosteroids, LABA) at entry. Patients in the AIR study received prednisone 50 mg the day of and day after each BT procedure, then maintenance therapy until month 3, at which point the LABA was withdrawn for at least 2 weeks. If symptoms emerged, the LABA was resumed, and additional attempts were made to withdraw it at 6 months and 12 months.[19] In the RISA study, patients in both groups were given 50 mg of prednisone per day for 5 days starting 3 days before each BT procedure (or comparable clinic visit for controls). Steroid dose was kept stable until 22 weeks ("steroid stable phase"), then attempts were made to reduce the dose of oral corticosteroids and ICS gradually over the remaining 30 weeks ("steroid wean phase," weeks 22–36; "reduced steroid phase," weeks 36–52).[20] The AIR 2 study publications do not describe a specific protocol for changes to maintenance medications during follow up.[18]

The schedule for BT procedures was uniform across studies, i.e., three procedures were performed 3 weeks apart. The 6 weeks after the third BT procedure was also considered a part of the "treatment period" in all of the studies.

Detailed evidence tables presenting information on the design of the studies, study inclusion criteria, study population descriptions, findings, risk-of-bias assessments and detailed strength of evidence assessments are located in Appendix C. A table of minimum important differences in asthma-related outcomes is provided in Appendix D. A table of ongoing clinical trials is presented as Appendix E.

Key Points

- Patients treated with BT and standard care (medical management) showed statistically greater improvements in asthma control (as measured by the Asthma Control Questionnaire [ACQ]), and quality of life (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) compared with patients undergoing standard care (medical management) only (SOE: low). However, the clinical importance of the changes is unclear.
- Evidence as to whether patients treated with BT and standard care versus standard care alone experienced different rates of severe exacerbations following the treatment period (3 procedures over 6 weeks, followed by an additional 6 weeks) was inconclusive (SOE: insufficient). While rates of mild exacerbations improved to a greater extent in the BT and standard care group than in the standard care only group, the clinical importance of the difference is unclear. (SOE: low).
- Patients treated with BT and standard care used statistically significantly less rescue medication than patients receiving standard care alone, but the clinical importance of the difference is unclear. (SOE: low).
- Patients given BT and standard care had no difference in asthma control scores, as measured by ACQ; in hospitalizations for respiratory symptoms; in use of rescue medication; in number of days rescue medications were required; or in pulmonary physiology measures (forced expiratory volume in 1 second [FEV_{1}] and morning peak expiratory flow [PEF]) compared with patients given the sham bronchoscopic procedure and standard care (SOE for all outcomes: low).
- Patients treated with BT and standard care experienced statistically significantly fewer exacerbations (those requiring systemic corticosteroids or doubling of inhaled corticosteroid dose) compared with those receiving the sham bronchoscopic procedure and standard care after the treatment period (3 procedures over 6 weeks, followed by an additional 6 weeks) was complete through the 12-month followup (post-treatment period), but the clinical importance of this difference was unclear (SOE: low).
- Patients treated with BT and standard care had fewer emergency department (ED) visits compared with those receiving the sham bronchoscopic procedure and standard care during the post-treatment period. (SOE: moderate).
- Evidence as to whether patients receiving BT and standard care versus the sham bronchoscopic procedure and standard care had different quality of life (AQLQ) scores was inconclusive (SOE: insufficient). Analysis of results for the intention-to-treat population found no improvement, but analysis of results for the per-protocol population found a difference that may not be clinically important, as it did not achieve the minimum important difference for this measure. A responder analysis (proportion of patients who achieved the minimum important difference) favored the BT and standard care intervention, but this outcome was not prespecified.
- Patients treated with BT developed the following common adverse events: bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing. Serious adverse events occurred more frequently in BT treated patients than in patients receiving the sham bronchoscopic procedure and/or standard care during the 12-week treatment period. No deaths were attributed to BT.

Detailed Synthesis

Asthma Control

Low-strength evidence from two RCTs (AIR [n=112] and RISA [n=32]) suggests that patients with moderate to severe asthma (AIR) and severe asthma (RISA) treated with BT and standard care have greater improvement in ACQ scores than patients treated with standard care alone. (We calculated the following from data in the publications: AIR: Standardized mean difference [SMD] in ACQ change score:-0.78, 95% Confidence Interval [CI]: -1.17 to -0.39; RISA: SMD in ACQ score change=-0.96, 95% CI: -1.69 to -0.23.)[19,20] The clinical significance of this finding is uncertain as the upper bounds of the CI is less than the minimum important difference of 0.5 (See Table D-1 in Appendix D). In contrast, low-strength evidence in the AIR 2 trial comparing BT and standard care with a sham bronchoscopic procedure and standard care found no difference in ACQ scores. (We calculated SMD in ACQ change score:-0.05, 95% CI: -0.29 to 0.19).[18]

A small retrospective study (n=25) compared 10 patients presenting at a clinic for BT treatment with 15 patients treated at the same institution who enrolled in RCTs of BT. The study suggests that patients treated with BT while enrolled in an RCT at this site saw statistically greater but not clinically important, improvement in ACQ than those treated with BT outside an RCT (clinic: mean change=-0.5; 95% CI: -1.5 to 0.4; RCT: mean change=-0.8; 95% CI:-1.4 to -0.1, [upper bound below the minimum important difference]).[24] However, due to limitations related to the study design, lack of precision in the results (small sample size), and unknown consistency, insufficient evidence exists to determine whether differences in patient characteristics explain lower rates of success in the clinic patients. For example, patients not in RCTs who received BT were allowed to be on omalizumab, high-dose oral prednisolone, and were not excluded based on frequency of exacerbations, characteristics that could have made some patients ineligible for the RCTs. They were also on higher doses of ICS and were more likely to be at Step 5 than patients enrolled in RCTs.

Exacerbations

In the AIR RCT, investigators derived exacerbation data from daily diaries that recorded any of the following on two consecutive days during a 2-week period of abstinence from LABA at 3, 6, and 12 months:

- Reduction in the morning PEF of at least 20% below the average (based on the value measured in the week prior to withdrawal of LABA at baseline)
- Requiring three or more puffs of rescue medication above their average use (based on the average number of puffs per day prior to withdrawal of LABA at baseline)
- Night awakening due to asthma symptoms.

The evidence from the AIR RCT comparing BT and standard care to standard care alone (n=112) was inconclusive regarding differences in rates of severe exacerbations (those requiring systemic corticosteroids or a reduction in PEF of at least 30% below average) at 12 months.[19] The study found a statistically significant reduction in mild exacerbations in the BT and standard care group compared to the change in mild exacerbations in the standard care only group (calculated mean difference=-0.20, 95% CI=-0.95 to -0.15 mild exacerbations per patient per week, or approximately 10 fewer mild exacerbations per year, 95% CI=3 to 18 fewer per year) at 12 months. We assessed the SOE as low given the study limitations, unknown consistency, and indirectness of measuring exacerbations only while patients were abstaining from LABA for 2 weeks.

The AIR RCT comparing BT and standard care to standard care alone (n=112) reported no difference in rates of hospitalization for respiratory events (3 hospitalizations in 3 patients in BT

and standard care group vs. 3 hospitalizations in 2 patients in the standard care group) during the post-treatment period (up to 12 months after the last treatment).[19] The single-arm extension study reported that the rate of hospitalizations "did not get worse compared to year 1 after BT (p=0.15; repeated measures analysis for proportion of subjects)."[22]

The RISA RCT comparing BT and standard care to standard care alone (n=32) also found no between-group difference in hospitalizations for respiratory events (BT: 5 hospitalizations vs. standard care: 4 hospitalizations, reported p-value =0.32) during the post-treatment period (6 weeks after the third BT procedure through 52 weeks).[20] In the single-arm extension of this study, overall respiratory-related hospitalizations decreased in patients treated with BT and standard care over 5 years compared with baseline, but the change was not statistically significant.[23] Similarly, while the rate of ED visits over 5 years declined compared to the baseline rate, the change was not statistically significant in this small study.[23]

Low-strength evidence from the AIR 2 trial (n=288) found that patients treated with BT and standard care had fewer severe exacerbations (those requiring systemic corticosteroids or doubling of ICS dose) in the post-treatment period (i.e., 6 weeks after the last BT procedure through 12 months) than patients treated with the sham bronchoscopic procedure and standard care. The posterior probability of superiority (PPS) for this result was 95.5 percent, meeting the study's criterion for statistical significance for this outcome.[18] However, the FDA statistician noted in his presentation to the Anesthesiology and Respiratory Therapy Devices Panel that the credible interval for the difference crossed 0 (i.e., difference in severe exacerbations per subject per year =0.48 in the BT group versus 0.70 in the sham group, credible interval for the difference of -0.31 to 0.52).[33] Use of the PPS to determine statistical significance is a less stringent criterion than considering the width of the credible interval. After considering the data presented by FDA, we determined that the findings were imprecise.

In the AIR 2 extension study, the reductions in the proportion of BT-treated patients experiencing severe exacerbations in each of the 5 years compared to the proportion in year 1 were not significantly different, since the upper 95% confidence limits for the differences in proportions were each less than the pre-defined noninferiority margin of 20 percent. However, exacerbations during years 2 to 5 were only ascertained at annual visits and confirmed by medical record review. This method of data collection differed from the use of diaries for recording exacerbations during the original study, and there was no information provided on the completeness or reliability of exacerbation reporting at the annual visits.[21]

The AIR 2 study found no difference in respiratory-related hospitalizations (10.5% vs. 5.1%; PPS for the rate in the sham bronchoscopic procedure group being higher than for the BT group, 57.2%) through 12 months.[18] Compared with the sham bronchoscopic procedure and standard care, the AIR 2 RCT found that BT and standard care reduced the rate of ED visits for respiratory symptoms by 84 percent, (0.45 visits per subject over 12 months in the sham and standard care group versus 0.13 visits per subject over 12 months in the BT and standard care group; PPS 99.9%, meeting the study's criterion for statistical significance for this outcome) (moderate SOE).[18] In the long-term extension of this RCT, ED visits (per subject per year) for respiratory symptoms were reduced in patients treated with BT and standard care by 88 percent over 5 years compared with 12 months before the procedure.[21] ED visits and hospitalizations were reported by patients only at annual visits during years 2 to 5.

Other Measures of Health Care Utilization

Two RCTs suggested that BT and standard care reduced rescue medication use compared with standard care alone at 12 months but the difference did not meet the minimally important difference (MID).[19,20] Inconclusive evidence from the AIR 2 RCT found no difference between BT with standard care and the sham bronchoscopic procedure with standard care in reducing

rescue medication or percentage of days with use of rescue medication at the 12-month followup (PPS: 81.3% and 68.0%).[18]

Pulmonary Physiology

The three RCTs with 5-year followup and a retrospective comparative trial reported spirometry data (either FEV_1 or PEF). When measured prior to administration of a bronchodilator, FEV_1 improved transiently in the patients treated with BT and standard care in the RISA trial (n=30) compared with standard care alone at 22 weeks from baseline (i.e., during the steroid stable phase; between-group mean difference calculated based on reported data: 15.8%, 95% CI:1.8: 1.8% to 29.8%). However, there was no significant difference between groups in FEV_1 when measured postbronchodilator or at a later followup once steroids had been weaned and stabilized (i.e., by 52 weeks).[20] In the RISA extension, postbronchodilator FEV_1 (% predicted) did not significantly decline in the group receiving BT and standard care over 5 years of followup or in the control group over 3 years of followup.[23]

In the AIR study (n=112), patients treated with BT and standard care had greater increases in morning and evening PEF compared with standard care alone) from baseline to 12 months; differences in FEV_1 (% predicted, prebronchodilator) were not significant.[19] This evidence from the AIR and RISA trials was considered inconclusive (SOE: insufficient). Mean FEV_1 (% predicted, postbronchodilator) remained stable in the control group (i.e. in the 24 of 49 who agreed to long-term followup) over 3 years of followup and in BT-treated patients through the 5-year followup.[22]

In the AIR 2 RCT (n=288) comparing BT and standard care to the sham bronchoscopic procedure and standard care treatment, there was no change in FEV_1 (% predicted, prebronchodilator) or morning PEF (L/min) between baseline and 12 months (PPS 24.1% and 80.6%, respectively) (SOE: low). No statistically significant change in FEV_1 occurred in BT-treated patients from the 12-month through the 5-year followup.[18,21]

In the comparison of clinic patients treated with BT to randomized patients treated with BT, FEV_1 (% predicted, prebronchodilator) change at 12 months was not significantly different.[24]

The AIR RCT found that BT and standard care did not improve airway hyper-responsiveness (defined by a provocative concentration of methacholine required to lower the FEV1 by 20% (PC20) of less than 8 mg per milliliter), compared with standard care alone between baseline and 12 months.[19] But in the AIR extension study, airway hyper-responsiveness remained relatively stable in patients treated with BT and standard care while it worsened in the control group treated with standard care alone who agreed to followup in years 2 and 3.[22]

Asthma-Related Quality of Life

Two studies (AIR and RISA) with low-strength evidence suggested that BT and standard care significantly improved AQLQ scores compared with standard care alone at 12 months from baseline.[19,20] The mean difference in improvement exceeded the MID in both studies, but the lower bounds of the 95% CI for the estimate from the AIR study did not exceed the MID. Consequently, we consider the result imprecise and the clinical importance uncertain (SOE: low).

The AIR 2 RCT found a statistically greater increase in AQLQ score with BT and standard care compared with the sham bronchoscopic procedure and standard care in the per-protocol population (PPS, 97.9%), but not in the intent-to-treat population (PPS, 96.0% [target PPS for this outcome was 96.4%]). The difference between groups in the change in AQLQ from baseline to the 12-month followup was less than the MID of 0.5 in both intent-to-treat and per-protocol populations (see Table D-1 in Appendix D). The proportion of patients with improvement in AQLQ score greater than the MID was higher after BT and standard care than after the sham bronchoscopic procedure and standard care (PPS, 99.6%). However, this was not a prespecified

outcome, raising concern about the possibility of outcome reporting bias.[18] Given the differences in results from these three different analytic approaches, we assessed the findings as inconclusive and the SOE as insufficient.

In the observational study comparing two populations undergoing BT, no difference was observed in AQLQ between patients treated with BT in the context of a RCT compared with patients treated with BT outside the RCTs.[24] However, due to limitations related to the observational nature of the study design, lack of precision in the results, and unknown consistency, insufficient evidence exists to determine whether differences in patient populations factor significantly into patient outcomes in RCTs of BT.

Asthma Symptoms (Secondary Outcome)

Low-quality evidence from the AIR RCT (n=112) suggests that BT and standard care statistically significantly improved total symptom score from baseline to 12 months compared with standard care alone (between-group mean difference in total symptom score [range 0 to 18] calculated from reported data: -1.20, 95% CI: -2.10 to -0.30.).[19] We did not identify a minimum important difference for this outcome, but calculating the effect size using Hedges g suggests that this is not an important difference (-0.52, 95% CI -0.91 to -0.12) as the confidence interval is not fully within a margin of 0.2 from 0.

In the AIR 2 study comparing BT and standard care to the sham bronchoscopic procedure and standard care, self-reported symptom scores improved in both groups from baseline. There were no differences between the treatment conditions at 12-month followup (between-group mean difference in total symptom score [range 0 to 18] calculated from reported data: -0.10, 95% CI: -0.66 to 0.46) (SOE: low).[18]

Table 3 presents the findings and SOE ratings for all the comparisons and outcomes assessed.

Table 3. Strength of evidence for bronchial thermoplasty interventions

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
BT and standard care (medical management) vs. standard care alone	Asthma control	**Favors BT, but clinical importance unclear:** ACQ scores improved in patients who underwent BT compared to those who received standard medical management, but the upper bounds of the confidence interval was less than the MID.	2 RCTs[19,20] n=144	**Low** (Medium[c] study limitations Imprecise; MID not met)
	Exacerbations Severe	**Inconclusive:** Rates of severe exacerbations per patient per week did not vary between treatment conditions. Exacerbations were counted during 2-week periods at 3, 6 and 12 months when LABA were discontinued.	1 RCT[19] n=112	**Insufficient** (Medium[c] study limitations, indirect [measured while off LABA], unknown consistency, Imprecise)
	Exacerbations Mild	**Favors BT, but clinical importance unclear:** Rates of mild exacerbations per patient per week were lower at 3 and 12 months but not at 6 months in patients who received BT and standard care. Exacerbations were counted only during 2-week periods at 3, 6 and 12 months when LABA were discontinued.	1 RCT[19] n=112	**Low** (Medium[c] study limitations, indirect [measured while off LABA], unknown consistency)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Hospitalizations (after treatment period)	**No difference:** Rates of hospitalizations were not different in patients who received BT and standard care versus those treated with standard care alone.	1 RCT n=32	**Low** (Medium[c] study limitations Imprecise)
	Health care utilization (other than exacerbations)	**Favors BT, but clinical importance unclear:** Use of rescue medication (puffs per week) was reduced to a greater extent in the BT group than standard care group but does not meet the MID criterion The overall reduction in oral or inhaled corticosteroid dose was not different between treatment groups in 1 small trial.[20]	2 RCTs[19,20] n=144	**Low** (Medium[c] study limitations, Imprecise)
	Pulmonary physiology: Spirometry	**Inconclusive:** In 1 small trial, BT and standard care improved FEV_1 at 22 weeks from baseline; the between-group difference was not significant at 52 weeks.[20] In the other study, patients treated with BT and standard care had greater increases in morning and evening peak flow compared with standard care alone from baseline to 12 months. Between-group change in FEV_1 was not significant.[19]	2 RCTs[19,20] n=144	**Insufficient** (Medium[c] study limitations, Inconsistent, Imprecise)
	Pulmonary physiology: Airway hyper-responsiveness	**Inconclusive:** Airway hyper-responsiveness did not vary between treatment groups	1 RCT[19] n=112	**Insufficient** (Medium[c] study limitations, unknown consistency, imprecise)
	Quality of life	**Favors BT, but clinical importance unclear:** AQLQ scores improved in patients who underwent BT and received standard care compared to those who received standard medical management alone. The result from the larger study did not exceed the minimum important difference criterion (lower bounds of the 95% CI was less than 0.5).	2 RCTs[19,20] n=144	**Low** (Medium[c] study limitations, Imprecise)
	Symptoms (Secondary outcome)	**Favors BT, but clinical importance unclear:** BT and standard care improved total symptom score from baseline to 12 months compared with medical management alone but the difference may not be clinically important.	1 RCT[19] n=112	**Low** (Medium[c] study limitations, unknown consistency)
BT and standard care vs. the sham	Asthma control	**No difference:** ACQ scores did not differ at 12 months after either BT and standard care or the sham bronchoscopic procedure and standard care	1 RCT[18] n=288	**Low** (unknown consistency, imprecise)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
bronchoscopic procedure and standard care	Exacerbations: Severe events (after treatment period)	**Favors BT, but clinical importance unclear:** Patients who underwent BT and standard care had fewer severe exacerbations per patient per year than the sham bronchoscopic procedure and standard care during weeks 12 to 52. Fewer patients experienced severe exacerbations in the BT and standard care group than in the sham group.	1 RCT[18] n=288	**Low** (Unknown consistency, imprecise [credible interval crosses 0])
	Exacerbations: Severe events (during treatment period)	**Favors the sham bronchoscopic procedure and standard care**: During the treatment period (up to 6 weeks following the 3rd BT or sham treatment), the number of patients experiencing severe exacerbations was higher in the BT group than in the sham group.	1 RCT[18] n=288	**Moderate** (Unknown consistency)
	Exacerbations: ED visits (after treatment period)	**Favors BT:** Rates of ED visits for respiratory symptoms were lower over 12 months following BT and standard care relative to the sham bronchoscopic procedure and standard care	1 RCT[18] n=288	**Moderate** (Unknown consistency)
	Exacerbations: Hospitalizations (after treatment period)	**No difference:** Hospitalizations for respiratory symptoms at 12 month followup	1 RCT[18] n=288	**Low** (Unknown consistency, imprecise)
	Exacerbations: Hospitalizations (during treatment period)	**No difference:** Hospitalizations for respiratory symptoms during the treatment period (up to 6 weeks following the 3rd BT or sham bronchoscopic procedure) were higher in the BT group than the sham group (but the RR crossed 1)	1 RCT[18] n=288	**Low** (Unknown consistency, imprecise)
	Health care utilization: Rescue medication actuations	**No difference:** Use of rescue medication at 12 month followup	1 RCT[18] n=288	**Low** (Unknown consistency, imprecise)
	Health care utilization: Days rescue medication required	**No difference:** % days rescue medication used at 12 month followup	1 RCT[18] n=288	**Low** (Unknown consistency, imprecise)
	Pulmonary physiology	**No difference:** FEV_1 and morning peak flow in patients treated with BT and standard care compared with the sham bronchoscopic procedure and standard care from baseline to 12 months	1 RCT[18] n=288	**Low** (Unknown consistency, imprecise)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Quality of life	**Inconclusive:** Change in AQLQ scores did not differ in intent-to-treat patients 12 months after either BT and standard care or the sham bronchoscopic procedure and standard care AQLQ improved in per-protocol patients treated with BT and standard care compared with the sham bronchoscopic procedure and standard care at 12 months. However the difference did not achieve the minimum important difference. The proportion of patients with improvement in AQLQ score greater than the minimum important difference was higher after BT and standard care than after the sham bronchoscopic procedure and standard care. However, this was not a prespecified outcome.	1 RCT[18] intent-to-treat=288 per protocol=268	**Insufficient** (Medium study limitations for per protocol analysis, unknown consistency, Imprecise [95% credible interval for continuous measure crosses 0; upper bound is less than MID], selective reporting possible).
	Symptoms (Secondary outcome)	**No difference:** Symptom scores improved over time in both treatment groups but did not differ as a function of treatment condition	1 RCT[18] n=288	**Low** (Unknown consistency, imprecise)
BT in RCT patients vs. BT in "real world" clinic patients	Asthma control	**Inconclusive:** Although ACQ scores were significantly better following BT in patients who were enrolled in the RCTs compared to the patients from clinic who underwent BT, this 1 small nonrandomized study is insufficient for drawing a conclusion. The change from baseline in each group was clinically significant.	1 non-RCT[24] n=25	**Insufficient** (High study limitations,[d] unknown consistency, Imprecise)
	Exacerbations	**Inconclusive:** Rates of exacerbations were low in both treatment groups and did not vary statistically	1 non-RCT[24] n=25	**Insufficient** (High study limitations,[d] unknown consistency, Imprecise)
	Health care utilization	**Not evaluable:** Data on hospitalizations and medication use not reported in a comparable manner for treatment groups	NA	NA
	Pulmonary physiology	**Inconclusive:** FEV_1 did not differ significantly between groups	1 non-RCT[24] n=25	**Insufficient** (High study limitations,[d] unknown consistency, Imprecise)
	Quality of life	**Inconclusive:** AQLQ scores improved to a clinically significant degree in both treatment groups; difference between groups not significantly different, but sample size was small	1 non-RCT[24] n=25	**Insufficient** (High study limitations,[d] unknown consistency, Imprecise)

Comparison	Outcome[a]	Conclusion	Study Design and Sample Size	Overall Evidence Strength (Limitations[b])
	Symptoms (Secondary outcome)	**Not evaluable:** Not reported	NA	NA

[a]Outcomes of Asthma control, Exacerbations, Health care utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;33 outcomes of Quality of life and Symptoms as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
[c]Study limitations: Lack of participant and outcome assessor blinding were the main concerns. Lack of clarity regarding the role of the funding entity was also considered in this domain, but deemed a lesser concern.
[d] Observational study, retrospective, groups not comparable on baseline characteristics
ACQ: Asthma Control Questionnaire (Range 0–6); AQLQ: Asthma Quality of Life Questionnaire (Range 1–7); BT: bronchial thermoplasty; CI: confidence interval; ED: emergency department; FEV_1: forced expiratory volume in 1 second; ; LABA: long-acting beta-2 agonist; MID: minimallym important difference; NA: not available; PEF: peak expiratory flow; PPS: posterior probability of superiority; RCT: randomized controlled trial; RR: relative risk

Adverse Events and Mortality

Two RCTs (RISA and AIR) that compared BT to standard care reported that the most common adverse events in patients treated with BT up to six weeks following the third BT procedure (treatment period) were bronchial irritation, chest discomfort, cough, discolored sputum, dyspnea, night awakenings, and wheezing.[19,20] In both studies, respiratory adverse events were higher in the BT group during the treatment period, but rates did not differ between BT and standard care groups in either study during the post-treatment period through 12-month followup. The RISA RCT (n=32) found that during the 12-week treatment period (i.e., 6 weeks during which 3 BT procedures were performed 3 weeks apart, followed by an additional 6 weeks), 4 of 15 patients treated with BT experienced 7 hospitalizations due to respiratory adverse events compared with no hospitalizations in 17 patients treated with standard care alone.[20] In the AIR RCT, 4 of 52 patients undergoing BT required 6 hospitalizations during the 12-week treatment period compared to 2 of 48 patients requiring 1 hospitalization each in the standard care control group.[19]

During the AIR extension study, patients from the BT group (n=45) and control group (n=24) were followed for 3 years. During years 2 and 3, there were no significant differences between BT (1.1 to 1.3 events/subject/year) and control group rates (1.2 and 1.3 events/subject/year) of respiratory related events, ascertained at annual visits.[22]

At year 5 of the RISA extension, adverse event rates in patients treated with BT were chest discomfort (8.3%), cough (0%), discolored sputum (0%), and wheezing (8.3%).[23] The control group was not included in the 5-year followup. At year 5 of the AIR extension, rates of these common adverse events were bronchial irritation (2.4%), chest discomfort (4.8%), cough (4.8%), discolored sputum (0%), dyspnea (9.5%), productive cough (2.4%), night awakenings (0%), and wheezing (4.8%). The control group was not included in the 5-year followup.[19,20]

We supplemented the information on the comparison of adverse events in the AIR 2 trial comparing BT and standard care to a sham bronchoscopic procedure and standard care reported in the journal publication[18] with data from the FDA presentation to the Anesthesiology and Respiratory Therapy Devices Panel on October 28, 2009.[33] During the 12-week treatment period, there were 0.20 respiratory adverse events per patient per week in the BT group versus 0.14 in the sham group (169/190 [84%] of patients in the BT group vs. 74/98 [76%] in the sham group experienced a respiratory adverse event). Of these, serious respiratory adverse events constituted 0.007 events per patient per week in the BT group versus 0.002 in the sham group (15/190 [8%]

of patients in the BT group vs. 2/98 [2%] in the sham group). The adverse events occurring more frequently during the treatment period in those treated with BT versus those undergoing the. sham bronchoscopic procedure were asthma (defined as multiple symptoms; 52% vs. 39%), upper-respiratory-tract infections (20% vs. 11%), wheezing (15% vs. 6%), dyspnea (11% vs. 6%), lower respiratory tract infection (8% vs. 2%), anxiety (4% vs. 0%), atelectasis (4% vs. 0%), and hemoptysis (3% vs. 0%).[18,33] Among the six patients who experienced hemoptysis, five had mild to moderate hemoptysis that was self-limiting; however, one patient had severe hemoptysis (defined as >100cc) at 31 days following the procedure, and required intervention.[33]

During the treatment period (up to six weeks after last BT or sham bronchoscopic procedure) in the AIR 2 study, 16 of 190 patients in the BT group required 19 hospitalizations for respiratory adverse events versus only 2 of 98 patients in the sham group. The BT-treated patients requiring hospitalization included ten patients hospitalized for worsening of asthma symptoms, two patients for segmental atelectasis, one for lower respiratory tract infection, one for low FEV_1, one for aspirated prosthetic tooth, and one for hemoptysis. In the sham-treated subjects, the two hospitalizations during the treatment period were for worsening of asthma.[18] The investigators state that all adverse events were treated with "standard therapy" (including bronchial artery embolization for hemoptysis). In the 5-year extension that followed the BT arm of the study, respiratory adverse events and asthma symptoms were reduced compared to the first year. Respiratory adverse events occurring at an incidence rate of ≥3% of patients in any of the years 1 through 5 were similar to those listed in the RISA and AIR RCTs above, and included influenza, nasopharyngitis, pneumonia, rhinitis, and sinusitis. There were no cases of pneumothorax, mechanical ventilation, cardiac arrhythmias, or death attributed to BT in the AIR 2 trial.[21]

The nonserious adverse events (e.g., cough, throat irritation, headache, hoarseness) reported in descriptive studies were consistent with those reported in RCTs, although no event rates can be determined from these reports. The serious adverse events reported in the 30 patients described in five case reports and two small case series (including one published in 2006) included five cases of hemoptysis, four cases of atelectasis (often described as due to mucus plugging and requiring hospitalization), two cases of lower respiratory tract infection requiring hospitalization, and one case of lung abscess in the treated lung segment requiring prolonged antibiotic therapy. Additionally, one patient with atelectasis also experienced acute respiratory failure on two occasions, with severe bronchospasm and tachypnea. One patient developed a pulmonary embolism with pleural effusion and bilateral lower-extremity deep venous thrombi following BT. During anticoagulation, she developed a mediastinal hematoma and bloody pleural effusion and was found to have hemorrhaged from a pseudoaneurysm of the bronchial artery thought possibly due to thermal injury from BT. Further details are provided in Appendix Table C-5.

Finally, no deaths were attributed to BT in any of the 15 studies.

Discussion

Key Findings and Strength of Evidence

We identified three primary randomized controlled trials (RCTs, n=432)[18-20] of bronchial thermoplasty (BT), as well as their associated extension studies (n=245).[21-23] One retrospective comparison[24] and eight descriptive studies (n=55)[25-32] also reported outcomes associated with BT. Two multicenter RCTs compared BT with standard care (medical management),[19,20] and one multicenter RCT compared BT to a sham bronchoscopic procedure with standard care continued in both groups.[18]

Compared with standard care alone, the evidence from two RCTs suggests that BT with standard care improved asthma control (defined by the Asthma Control Questionnaire [ACQ], rates of mild exacerbations change from baseline to 12 months), utilization of rescue medication and quality of life (low strength of evidence [SOE]), but the clinical importance of the findings for each of these outcomes is unclear. Rates of hospitalizations for respiratory symptoms were not different for these comparators during the post-treatment period (6 weeks after the third BT treatment through 12-month followup) (SOE: low). The evidence base was insufficient to draw conclusions about BT's effects on severe exacerbations or pulmonary physiologic measures compared with standard care.[19,20]

Compared with the sham bronchoscopic procedure and standard care, the intention-to-treat analysis in a single RCT suggests that BT with standard care had no effect on asthma control (defined as improvement in ACQ from baseline), hospitalizations for respiratory symptoms, rescue medication usage, pulmonary physiologic measures, or other asthma symptom scores (low SOE). Reduced risk of severe exacerbations was suggested (low SOE), but the clinical importance of the degree of the reduction was unclear. Rates of emergency department visits for exacerbations during the post-treatment period were significantly lower in patients receiving the BT and standard care than in those who received the sham bronchoscopic procedure and standard care (moderate SOE).[18]Serious adverse events attributed to BT occurred during the 12-week treatment period, and no deaths were reported.

Findings Compared to What Is Already Known

A 2014 Cochrane review[34] of BT examined the same three RCTs as we did and described the benefits of BT as modest but not clinically significant. Unlike the Cochrane review authors, we did not pool the trial results because of differences in study designs and populations. We also had greater concern about risk of bias in the trials, and therefore graded outcomes more conservatively. These findings are consistent with other systematic reviews and technology assessments.[35-37]

Current clinical practice guidelines suggest a cautious approach to use of BT. For example, the American Thoracic Society (ATS)-European Respiratory Society (ERS) guidelines on definition, evaluation and treatment of severe asthma recommends BT be "performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study."[38] The authors state that they placed greater weight on avoiding adverse effects and increased use of resources, while noting the uncertainty of benefit in terms of symptoms and quality of life, the lack of data on patients with more severe asthma (forced expiratory volume in 1 second [FEV_1] <60% of predicted value), and the need for ways to determine which patients might benefit.[39] Although BT has been approved for use in Japan since 2015, the Japanese Society for Allergology guidelines recommend further study of BT.

Describing the AIR 2 study, they note that despite the 5-year results, longer term efficacy and safety should still be examined.[38]

The United Kingdom National Institute for Health and Care Excellence (NICE) guidance also calls for longer term safety data, and requires clinicians performing BT to submit patient details to a centralized registry. They state that clinicians should "Ensure that patients understand the uncertainty about the procedure's efficacy and long-term safety, and the possibility of initial worsening of their symptoms, and provide them with clear written information."[40] Similarly, the 2011 British Thoracic Society guideline describes the procedure as "a possible treatment option in selected patients with severe persistent asthma already on maximal therapy, although its place in the treatment of asthma remains to be established."[41] The 2014 Scottish Intercollegiate Guidelines Network also describes BT as a procedure that "may be considered for patients with poorly controlled asthma despite optimal therapy."[42]

Finally, the Guideline from the Global Initiative for Asthma states:

> [F]or highly-selected adult patients with uncontrolled asthma despite use of recommended therapeutic regimens and referral to an asthma specialty center (Step 5), bronchial thermoplasty is a potential treatment option in some countries. (Evidence level B [RCTs. Limited body of data]) Caution should be used in selecting patients for this procedure as the number of studies is small, and people with chronic sinus disease, frequent chest infections or FEV_1<60% predicted were excluded. (Evidence D [panel consensus judgment])"[43]

Applicability

Although BT is approved for treating patients with severe persistent asthma, there was heterogeneity in the severity of asthma in the populations included in the three RCTs. The evidence from one of the RCTs is applicable to adult patients with asthma who require ≤30 mg per day of prednisone for maintenance while on high-dose inhaled corticosteroids (ICS) and long-acting beta-2 agonists (Research in Severe Asthma Trial [RISA]).[20] One small trial was designed to compare "real-world" patients, including those with high rates of exacerbations and with no limitation on medication use, and reported that the clinical response was lower and more variable than in the RCTs.[24] The number of patients in the comparison was too small to draw firm conclusions about the relative benefits of BT in patients who are sicker than those in the RCTs or about the possibility of selection bias in RCTs.

One study enrolled patients on lower doses of ICS (200 mcg/day), but the mean dose at baseline was similar to that in the other trials (Asthma Intervention Research Trial [AIR]).[19] Some studies restricted enrollment to patients on <10mg per day of oral corticosteroid, fewer than three hospitalizations (AIR-2),[18] fewer than four episodes requiring systemic steroids in the prior year (AIR) and use of no more than four puffs of short-acting beta-2 agonist per day (AIR and AIR-2).

The BT procedure itself appears to be similar across these studies, and was performed in several countries, in settings comparable to those in most bronchoscopy centers. Additional information about the concomitant medical therapy in the BT groups as well as in the control groups would be helpful for translating the findings to practice.

Implications for Clinical and Policy Decisionmaking

Clinicians whose patients are potential candidates for BT may want to consider the evidence presented in this review, including the highly selected and yet heterogeneous study populations,

limited improvement in outcomes, and rates of adverse events (including asthma worsening and respiratory tract infections during the treatment period) when determining BT's appropriateness for their patients. Only one small RCT included patients taking more than 10 mg per day of oral corticosteroids and patients with FEV_1 as low as 50 percent predicted.

Current guidelines stress the importance of assessing patients' adherence to prescribed therapies and their technique in using inhalers prior to considering BT. One of the U.S. Food and Drug Administration (FDA) presenters to the Anesthesiology and Respiratory Therapy Devices Panel noted that patients in the AIR 2 trial at sites in Brazil, who made up 30 percent of the study population, were all given maintenance medications at no cost. The intention-to-treat analysis of Asthma Quality of Life Questionnaire (AQLQ) results for the patients in Brazil found greater improvement in the group receiving the sham bronchoscopic procedure than in the group undergoing BT.[33]

The primary efficacy endpoint used for BT's regulatory filings with FDA was the AQLQ score change from baseline to the average of 6-, 9-, and 12-month followup from the pivotal AIR 2 sham-controlled trial.[33] The improvement did not meet the prespecified level of statistical significance in the intention-to-treat population, but did in the per protocol analysis. Nonetheless, the degree of improvement was less than the MID, so it may not be clinically important. While the sham bronchoscopic procedure in this study was associated with some post-procedure respiratory events, there were more adverse events and more events requiring hospitalization in the BT group during the treatment period, although the latter was not a statistically significant difference. Clinicians and patients must balance this risk of adverse events in the treatment period against the evidence for later modest improvements in rates of severe exacerbations and more robust evidence for reduction in emergency department visits for exacerbation.

Limitations of the Systematic Review Process

The scope of this review may have introduced some important limitations. First, we included only trials with concurrent controls when assessing BT's effectiveness. Similarly, conference abstracts without subsequent full publications were excluded because it is difficult to assess study risk of bias and selective outcome reporting from abstracts, and because results presented in abstracts are frequently different in final publications.

Limitations of the Evidence Base

This evidence base contains several limitations. Only one of three trials was a blinded, sham-controlled trial. As seen in our evidence analysis, this study did not show similar findings to the nonblinded, RCTs comparing BT to standard care. Outcome measures were not ascertained using the same assessment procedures. In one study, for example, exacerbations were counted only during 2-week periods when patients were asked to abstain from use of maintenance long-acting beta agonist therapy.

Evidence Gaps

Several types of evidence gaps could be addressed in future research. Our conclusions for several outcomes were limited by the small number of studies and low numbers of patients. In some instances, the effect sizes had fairly wide confidence intervals (exceeding minimally important differences) which led us to assess the evidence as imprecise. While the RCTs were multicenter, there was only one RCT using a sham control. Given the difference in findings when the sham control was used, and the subjective nature of the majority of outcomes, it would

be informative to have data from additional studies enrolling similar patients and using the same design.

Two of the three RCTs were assessed as having medium risk of bias, and one low risk of bias. The risk of bias in future studies could be improved by describing both appropriate allocation of treatment and concealment, blinding patients and outcome assessors, and clarifying the role of funders.

Studies using a standard care or medical management control could be improved by reporting concomitant therapies more clearly. Greater uniformity in outcome measures, particularly for exacerbations, would be helpful. In addition, studies could address clinically important differences in outcomes, using data that have been validated by other investigators not involved in the trial (as in Appendix D).

As noted above, only one sham-controlled trial of BT has been published. Given that BT is an invasive procedure and that patients receiving the sham treatment appeared to improve on certain outcomes, further studies using a sham comparison are needed to strengthen the evidence base and help guide appropriate use of BT. Studies could also be undertaken to test BT in other populations, especially patients with poor asthma control who experience higher rates of exacerbations. The studies included in this analysis also did not examine the efficacy of BT stratified by asthma phenotype (e.g., eosinophilic, neutrophilic, paucigranulocytic). Future studies might better elucidate whether BT is more effective in certain asthma phenotypes. As of July 19, 2017, ClinicalTrials.gov listed 18 trials investigating BT that are ongoing, planned, or of unknown status. (See Appendix E.) Most are single-arm observational studies. The randomized trials examine BT administered with traditional bronchoscopy or with other image-guided interventions. No sham-controlled trials are currently registered.

Conclusions

Three RCTs and several descriptive studies meeting our inclusion criteria have evaluated BT. Based on the available literature, BT may be modestly beneficial in some patients with asthma, but is not without risks in any population. The risk of adverse events is higher during the treatment period and for several weeks afterward. Benefit is typically observed weeks to months after therapy and can last for at least 5 years, after which the duration of effect is unknown.

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42. Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society. British guideline on the management of asthma. A national clinical guideline. Edinburgh (Scotland): Scottish Intercollegiate Guidelines Network (SIGN); 2014 Oct. 199 p.

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Abbreviations and Acronyms

ACQ: Asthma Control Questionnaire
ACT: Asthma Control Test
AHRQ: Agency for Healthcare Research and Quality
AIR: Asthma Intervention Research Trial
AIR 2: Asthma Intervention Research Trial 2
AQLQ: Asthma Quality of Life Questionnaire
BT: bronchial thermoplasty
CI: confidence interval
ED: emergency department
EPC: Evidence-based Practice Center
EPR: Expert Panel Report
FDA: U.S. Food and Drug Administration
FEV_1: forced expiratory volume in one second
KQ: Key Question
GRADE: Grading of Recommendations Assessment, Development and Evaluation
MID: minimally important difference
NAEPP: National Asthma Education and Prevention Program
NHLBI: National Heart, Lung, and Blood Institutes
PEF: peak expiratory flow
PICOTS: patient populations, interventions, comparators, outcomes, timing, and settings
PPS: posterior probability of superiority
RCT: randomized clinical trial
RISA: Research in Severe Asthma Trial
SOE: strength of evidence
TEP: Technical Expert Panel

Appendix A. Search Strategies

Resources Searched

ECRI Institute information specialists searched the following databases for relevant information. Search terms and strategies for each resource appear below.

Table A-1. Databases searched

Name	Date Limits	Platform/Provider
The Cochrane Central Register of Controlled Trials (CENTRAL)	Inception [1999] through April 20, 2017	Wiley
The Cochrane Database of Systematic Reviews (Cochrane Reviews)	Inception [1999] through April 20, 2017	Wiley
Cumulative Index of Nursing and Allied Health Literature (CINAHL)	Inception [1981] through April 20, 2017	EBSCOhost
Database of Abstracts of Reviews of Effects (DARE) (part of the Cochrane Library)	Inception [1999] through April 20, 2017	Wiley
EMBASE (Excerpta Medica)	Inception [1966] through April 20, 2017	Embase.com
Health Technology Assessment Database (HTA) (part of the Cochrane Library)	Inception [1999] through April 20, 2017	Wiley
MEDLINE	Inception [1966] through April 20, 2017	Embase.com
PUBMED (In Process citations)	Inception [1966] through April 20, 2017	NLM
U.K. National Health Service Economic Evaluation Database (NHS EED) (part of the Cochrane Library)	Inception [1999] through April 20, 2017	Wiley
Associations and Societies		
American Academy of Allergy, Asthma, and Immunology	June 29, 2016	https://www.aaaai.org/
Asthma and Allergy Foundation of America	June 30, 2016	http://www.aafa.org/
American College of Allergy, Asthma, and Immunology	June 29, 2016	http://acaai.org/
Agency for Healthcare Research and Quality Technology Assessment Program	June 29, 2016	http://www.ahrq.gov/research/findings/ta/index.html
American Lung Association	June 29, 2016	http://www.lung.org/
American Thoracic Society	June 29, 2016	https://www.thoracic.org/
Centers for Disease Control and Prevention	June 28, 2016	https://www.cdc.gov/
National Academy of Medicine	June 28, 2016	https://nam.edu/
National Heart, Lung, and Blood Institute	June 30, 2016	https://www.nhlbi.nih.gov/
Other Gray Literature Resources		
ClinicalTrials.gov	Searched April 20, 2017	NIH
Centers for Medicare and Medicaid (CMS) - Medicare Coverage Database	Searched July 14, 2016	CMS
ECRI Institute Library Catalog	Searched June 24, 2016	ECRI Institute
ECRI Institute Members Website	Searched June 24, 2016	ECRI Institute
Health Devices	Searched June 24, 2016	ECRI Institute
Healthcare Standards	Searched June 24, 2016	ECRI Institute
Internet	Searched June 27, 2016	Google; Bing
Manufacturers	Searched June 24, 2016	Boston Scientific
Medscape	Searched June 22, 2016	WebMD
National Guideline Clearinghouse™	Searched June 24, 2016	AHRQ
National Institute for Health and Care Excellence, U.K.	Searched June 24, 2016	NHS
TRIP (Turning Research Into Practice) Database	Searched June 27, 2016	Trip Database, Ltd.
U.S. Food and Drug Administration (FDA), including Medical Device databases	Searched April 20, 2017	FDA

Reimbursement

The following Web sites were searched for reimbursement policies: Aetna, Anthem BCBS, BCBS Florida, BCBS of Illinois, BCBS of Texas, BCBS of California, CIGNA, Humana, United Healthcare, Regence.

Hand Searches of Journal and Gray Literature

Journals and supplements maintained in ECRI Institute's collections were routinely reviewed. Nonjournal publications from professional organizations, private agencies, and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and gray literature. (Gray literature consists of reports, studies, articles, and monographs produced by federal and local government agencies, private organizations, educational facilities, consulting firms, and corporations. These documents do not appear in the peer-reviewed journal literature.)

Topic-Specific Search Terms

The search strategies employed combinations of free-text keywords as well as controlled vocabulary terms including (but not limited to) the following concepts. Strategies for each bibliographic database follow this table.

Table A-2. Topic-specific search terms

Concept	Controlled Vocabulary	Keywords
Asthma	**EMBASE (EMTREE)** asthma/exp 'allergic asthma'/exp 'asthmatic state'/exp 'extrinsic asthma'/exp 'intrinsic asthma'/exp 'mild intermittent asthma'/exp 'mild persistent asthma'/exp 'nocturnal asthma'/exp 'occupational asthma'/exp 'severe persistent asthma'/exp **MEDLINE/PubMed(MeSH)** Asthma[mh] **CINAHL** (MH "Asthma+") (MH "Asthma, Occupational")	Asthma*

Concept	Controlled Vocabulary	Keywords
General Allergy terms	**EMBASE (EMTREE)** allergen/exp 'disease exacerbation'/exp 'environmental exposure'/exp 'health hazard'/exp **MEDLINE/PubMed (MeSH)** Allergens[mh] "environmental exposure"[mh] **CINAHL** (MH "Allergens+") (MH "Disease Exacerbation") (MH "Environmental Exposure+")	Allergen exacerbation exacerbate irritant sensitive sensitivity trigger
Bronchial Thermoplasty	**EMBASE (EMTREE)** 'bronchial thermoplasty device'/exp **MEDLINE/PubMed (MeSH)** No equivalent MeSH terms **CINAHL** No equivalent controlled term	Alair* asthmatx Bronchial thermoplasty bronchiothermoplasty
Bronchial Disease	**EMBASE (EMTREE)** bronchoscopy/exp bronchoscope/exp bronchoconstriction/exp bronchospasm/exp 'bronchus disease'/exp bronchus/exp bronchoplasty/exp 'airway smooth muscle cell'/exp **MEDLINE/PubMed (MeSH)** bronchoscopy[mh] bronchoscopes[mh] bronchoconstriction[mh] or "bronchial spasm"[mh] "bronchial diseases"[mh] bronchi[mh] **CINAHL** (MH "Bronchoscopy") (MH "Bronchoconstriction") (MH "Bronchial Diseases+") (MH "Bronchial Spasm") (MH "Bronchi+")	airway smooth muscle bronchial constriction bronchial spasm bronchoscope bronchoconstriction bronchospasm bronchus constriction bronchus spasm

Concept	Controlled Vocabulary	Keywords
Radiofrequency ablation terms	**EMBASE (EMTREE)** 'radiofrequency ablation'/exp 'radiofrequency ablation device'/exp 'catheter ablation'/exp 'pulsed radiofrequency treatment'/exp **MEDLINE/PubMed (MeSH)** "Catheter Ablation"[mh] "Pulsed Radiofrequency Treatment"[mh] **CINAHL** (MH "Catheter Ablation")	catheter ablation heat ablation radiofrequency ablation rf ablation thermal ablation thermoplasty

Search Strategies

Table A-3. Embase/MEDLINE

Set Number	Concept	Search Statement
1	Bronchial Thermoplasty	'bronchial thermoplasty device'/exp OR Alair* OR bronchothermoplast* OR asthmatx* OR bronchiothermoplast* OR (bronchial AND thermoplast*)
2	Asthma	asthma/exp OR asthma*
3	Bronchial disease	'bronchoscopy'/exp OR 'bronchoscope'/exp OR 'bronchoconstriction'/exp OR 'bronchospasm'/exp OR 'bronchus disease'/exp OR 'bronchus'/exp OR 'bronchoplasty'/exp OR 'airway smooth muscle cell'/exp OR bronchoscop* OR bronchoconstrict* OR bronchospasm* OR ((bronchial OR bronchus OR bronchi) NEAR/4 (constrict OR spasm*)) OR “airway smooth muscle”
4	Combine Sets – asthma and/or bronchial disease	2 OR 3
5	Radiofrequency ablation terms	'radiofrequency ablation'/exp OR 'radiofrequency ablation device'/exp OR 'catheter ablation'/exp OR 'pulsed radiofrequency treatment'/exp OR thermoplast* OR ((radiofrequency OR thermal OR heat OR catheter* OR “RF”) NEAR/4 ablat*)
6	Combine sets	4 AND 5
7	Combine sets	1 OR 6
8	Remove unwanted publication types	7 NOT (abstract:nc OR annual:nc OR book/de OR conference:nc OR 'conference abstract':it OR 'conference paper'/de OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR editorial/de OR editorial:it OR erratum/de OR letter:it OR note/de OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/de OR symposium:nc)
9	Limit 8 to Humans;	8 AND [humans]/lim

EMBASE.com Syntax:

* = truncation character (wildcard)

NEAR/*n* = search terms within a specified number (*n*) of words from each other in any order

NEXT/*n* = search terms within a specified number (*n*) of words from each other in the order specified

/ = search as a subject heading

exp = “explodes” controlled vocabulary term (e.g., expands search to all more specific related terms in the vocabulary’s hierarchy)

mj = denotes a term that has been searched as a major subject heading

:de = search in the descriptors field (controlled terms and keywords)

:lnk = floating subheading

/lim = limiter

:it,pt. = source item or publication type

:ti. = limit to title

:ti,ab. = limit to title and abstract fields

PubMed (PreMEDLINE)

Table A-4. PubMed in process citations

Set Number	Concept	Search Statement
1	Bronchial Thermoplasty	Alair* OR bronchothermoplast* OR asthmatx* OR bronchiothermoplast* OR (bronchial AND thermoplast*)
2	Asthma	Asthma[mh] OR asthma*
3	Bronchial disease	"Bronchoscopy"[Mesh] OR "Bronchoscopes"[Mesh] OR "Bronchoconstriction"[Mesh] OR "Bronchial Spasm"[Mesh] OR "Bronchial Diseases"[Mesh] OR "Bronchi"[Mesh] OR bronchoscop* OR bronchoconstrict* OR bronchospasm* OR ((bronchial[tiab] OR bronchus[tiab] OR bronchi[tiab]) AND (constrict[tiab] OR spasm*[tiab])) OR “airway smooth muscle”
4	Combine Sets – asthma and/or bronchial disease	2 OR 3
5	RF ablation terms	"Catheter Ablation"[Mesh] OR "Pulsed Radiofrequency Treatment"[Mesh] OR thermoplast* OR ((radiofrequency OR thermal OR heat OR catheter*) AND ablat*) OR “rf ablation”
6	Combine sets	4 AND 5
7	Combine sets	1 OR 6
8	Remove unwanted publication types	7 NOT (comment[pt] OR editorial[pt] OR letter[pt] OR news[pt] OR "Textbooks" [pt] OR "Book Reviews"[pt]OR "Book Illustrations"[pt] OR book OR books OR textbook*)
9	In process citations	8 AND ("inprocess"[sb] OR publisher[sb] OR pubmednotmedline[sb])

PubMed Syntax:

*	=	truncation character (wildcard)
[mh]/[MesH]	=	controlled vocabulary term
[sb]	=	subset
[ti]	=	limit to title field
[tiab]	=	limit to title and abstract fields
[tw]	=	text word

CINAHL

Table A-5. CINAHL

Set Number	Concept	Search Statement
1	Bronchial Thermoplasty	Alair* OR bronchothermoplast* OR asthmatx* OR bronchiothermoplast* OR (bronchial AND thermoplast*)
2	Asthma	(MH "Asthma+") OR asthma*
3	Bronchial disease	(MH "Bronchoscopy") OR (MH "Bronchoconstriction") OR (MH "Bronchial Diseases+") OR (MH "Bronchial Spasm") OR (MH "Bronchi+") OR bronchoscop* OR bronchoconstrict* OR bronchospasm* OR ((bronchial OR bronchus OR bronchi) AND (constrict* OR spasm*)) OR “airway smooth muscle”
4	Combine Sets – asthma and/or bronchial disease	2 OR 3
5	RF ablation terms	(MH "Catheter Ablation") OR thermoplast* OR ((radiofrequency OR thermal OR heat OR catheter*) AND ablat*) OR “rf ablation” OR “rf-ablation”
6	Combine sets	4 AND 5
7	Combine sets	1 OR 6
8	Remove Medline records	

CINAHL Syntax:

…+ = explode

* = truncation character (wildcard)

N*n* = search terms within a specified number (*n*) of words from each other in any order

TI = limit to title field

AB = limit to title and abstract fields

MH = MeSH heading

MJ = MeSH heading designated as major topic

PT = publication type

Appendix B. Excluded Studies

Ryan DM, Fowler SJ, Niven RM. Reduction in peripheral blood eosinophil counts after bronchial thermoplasty. J Allergy Clin Immunol. 2016 Mar 4. Also available: http://dx.doi.org/10.1016/j.jaci.2015.11.044. PMID: 26953157. **Single-arm study; no adverse events**

Zhou JP, Feng Y, Wang Q, et al. Long-term efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma: A systemic review and meta-analysis. J Asthma. 2016 Jan 2;53(1):94-100. Also available: http://dx.doi.org/10.3109/02770903.2015.1065424. **Systematic review of included individual studies**[1-3]

Ansarin K, Attaran D, Jamaati H, et al. Approach to patients with severe asthma: a consensus statement from the Respiratory Care Experts' Input Forum (RC-EIF), Iran. Tanaffos. 2015;14(2):73-94. PMID: 26528362. **Consensus statement**

Chakir J, Haj-Salem I, Gras D, et al. Effects of bronchial thermoplasty on airway smooth muscle and collagen deposition in asthma. Ann Am Thorac Soc. 2015 Sep 1;12(11):1612-8. Also available: http://dx.doi.org/10.1513/AnnalsATS.201504-208OC. PMID: 26325484. **Single-arm study; no adverse events**

Denner DR, Doeing DC, Hogarth DK, et al. Airway inflammation after bronchial thermoplasty for severe asthma. Ann Am Thorac Soc. 2015 Sep 1;12(9):1302-9. Also available: http://dx.doi.org/10.1513/AnnalsATS.201502-082OC. **Single-arm study; no adverse events**

Dheda K, Koegelenberg CF, Esmail A, et al. Recommendations for the use of bronchial thermoplasty in the management of severe asthma. S Afr Med J. 2015 Sep;105(9):726-32. PMID: 26428967. **Systematic review of included individual studies**[1-3]

Grant MD, Blue Cross Blue Shield Association. Bronchial thermoplasty for treatment of inadequately controlled severe asthma. Technol Eval Cent Asses Program Exec Summ. 2015 Mar;29(12):1-5. PMID: 25962190. **Systematic review of included individual studies**[1-3]

Torrego A, Sola I, Munoz AM, et al. Bronchial thermoplasty for moderate or severe persistent asthma in adults. Cochrane Database Syst Rev. 2014;3(3):CD009910. PMID: 24585221. **Systematic review of included individual studies**[1-3]

Castro M, Rubin A, Laviolette M, et al. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. Ann Allergy Asthma Immunol. 2011 Jul;107(1):65-70. Also available: http://dx.doi.org/10.1016/j.anai.2011.03.005. PMID: 21704887. **Superseded by related study with longer followup**[4]

Wu Q, Xing Y, Zhou X, et al. Meta-analysis of the efficacy and safety of bronchial thermoplasty in patients with moderate-to-severe persistent asthma. J Int Med Res. 2011;39(1):10-22. PMID: 21672303. **Systematic review of included individual studies**[1-3]

Appendix C. Evidence Tables

Key Question: What are the benefits and harms of using bronchial thermoplasty in addition to standard treatment for the treatment of adult (≥18 years) patients with severe asthma?

Table C-1. Study characteristics of comparative trials

Study	Intervention	Study Design	Study Inclusion Criteria	Demographic Factors	Clinical Characteristics at Baseline
Bicknell et al. 2016[5]	BT in clinic population vs. BT in patients participating in RCTs	***Type of study:*** Retrospective, comparative ***Total population:*** N=10 clinic patients N=15 patients from this site participating in RCTs of BT (Cox et al. 2007[3], Pavord et al. 2007[2], and Castro et al. 2010[1]) ***Country:*** U.K. ***Followup:*** 1 year	Clinic patient inclusion criteria described as similar but not identical to Cox et al. 2007[3], Pavord et al. 2007[2], and Castro et al. 2010[1] (RCT participants from this site met individual study criteria) ***Asthma severity in non-RCT patients (clinic):***, requiring daily ICS at >1,000 mcg BPD equivalent and LABA 100 mcg salmeterol equivalent; No restriction on OCS dose, use of omalizumab, or frequency of exacerbations	***Age (mean [SD]):*** Clinic: 48 (10) years RCT: 43 (12) years ***% Male:*** Clinic: 70% RCT: 67% ***Race:*** Clinic: % NR RCT: % NR	***Inhaled corticosteroid dose:*** Clinic: BDP equivalent 2,580 (SD 1,425) mcg/d RCT: BDP equivalent 1,757 (SD 1,578) mcg/d ***Oral corticosteroids:*** 4 of 10 clinic patients on oral prednisolone (dose not reported) ***Omalizumab treatment:*** used in 2/10 clinic patients for >3years ***FEV_1 (mean [range]):*** % predicted: Clinic: 72% (±16) RCT: 74% (±12) ***PC_{20} (mg/ml [SD]):*** Clinic: NR RCT: 0.54 (0.84) ***Asthma severity:*** British Thoracic Society Steps 4 and 5 ***Comorbidity:*** NR
Pavord et al. 2013[6] RISA Extension Study 5-year followup of Pavord et al. 2007[2]	BT alone	***Type of study:*** RCT Extension—1 arm ***Total population:*** N=14 BT ***Country:*** U.K. ***Followup:*** 4 years (years 2–5)	***Age:*** 18-65 y/o ***Asthma severity:*** severe, requiring daily ICS at >750 mcg fluticasone equivalent and LABA 100 mcg salmeterol equivalent; ≤30 mg/d prednisone equivalent; ***Spirometry:*** prebronchodilator FEV1 ≥50% predicted; airway hyperresponsiveness (methacholine challenge	***Age (mean years [SD]):*** 38.6 (13.3) ***% Male:*** 43% ***Race:*** 100% Caucasian	***Inhaled corticosteroid dose (SD):*** BT: fluticasone equivalent 1,166.7 (421) mcg/d ***FEV_1 (mean [SD]): % predicted:*** BT: 63.5% (12.5) ***PC_{20} (mg/ml geometric mean [range]):*** BT: 0.24 (0.1–1.1) ***Asthma severity:*** All met the Global Initiative for Asthma (GINA) criteria for severe persistent asthma All but one met the American Thoracic Society criteria for refractory asthma ***Comorbidity:*** Seasonal allergies 71%

Study	Intervention	Study Design	Study Inclusion Criteria	Demographic Factors	Clinical Characteristics at Baseline
			or response to bronchodilator) ***Additional**:* Uncontrolled symptoms while on maintenance therapy – rescue medication used on 8 of 14 days prior to enrollment or daytime symptoms on 10 of 14 days; nonsmoker ≥1 year		
Wechsler et al. 2013[7] AIR 2 Extension 5-year followup of Castro et al. 2010[1]	BT alone	***Type of study:*** RCT Extension—1 arm ***Total population:*** N=162 BT ***Country:*** U.S. ***Followup:*** 5 years	***Age:*** 18-65 y/o ***Asthma severity:,*** requiring daily ICS at >1,000 mcg BPD equivalent and LABA 100 mcg salmeterol equivalent; <10 mg OCS/day; ≥2 symptomatic days in prior 4 weeks ***Spirometry**:* prebronchodilator FEV1 ≥60% predicted; Methacholine PC_{20} <8mg/mL ***Additional**:* AQLQ ≤6.25;<3 hospitalizations for asthma; <3 lower respiratory infection and <4 pulses of OCS in prior year	***Age (mean years [SD]):*** 41.5 (11.8) ***% Male:*** 42% ***Race:*** 82.7% Caucasian	***Inhaled corticosteroid dose mean (median):*** BT: BDP equivalent 1,960.7 (2000) mcg/d Control: BDP equivalent 1,834.8 (2,000) mcg/d ***FEV_1 (mean [SD]):*** % predicted: BT: 77.8% (15.84) ***PC_{20} (mg/ml geometric mean [range]):*** BT: 0.27 (0.21–0.35) ***Asthma severity:*** STEPS 5 or 6 ***Comorbidity:*** NR
Thompson et al. 2011[4] AIR Study extension 5-year followup of Cox et al. 2007[3]	BT vs. medical management	***Type of study:*** RCT Extension—Both arms ***Total population:*** N=45 BT N=24 control ***Country:*** U.K. ***Followup:*** 5 years	***Age:*** 18-65 y/o ***Asthma severity:*** moderate or severe, requiring daily ICS at >200 mcg BPD equivalent and LABA 100 mcg salmeterol equivalent; stable disease ***Spirometry**:* prebronchodilator FEV1 60 to 85% predicted;	***Age (mean years [SD]):*** BT: 40.0 (11.2) Control: 40.8 (12.1) ***% Male:*** BT: 42% Control: 38% ***Race:*** BT: 91% Caucasian Control: 92% Caucasian	***Inhaled corticosteroid dose (SD):*** BT: BDP equivalent 1,305 (880) mcg/d Control: BDP equivalent 1,141 (1,053) mcg/d ***FEV_1 (mean [SD]):*** % predicted: BT: 72.5% (10.9) Control: 74.9% (8.9) ***PC_{20} (mg/ml geometric mean [range]):*** BT: 0.25 (0.2–0.4) Control: 0.28 (0.1-0.6) ***Asthma severity:*** NR ***Comorbidity:*** NR

Study	Intervention	Study Design	Study Inclusion Criteria	Demographic Factors	Clinical Characteristics at Baseline
			Methacholine PC_{20} <8mg/mL ***Additional****:* Worsening of ACQ ≥0.5 when off LABA for 2 weeks; <3 lower respiratory tract infections in previous 12 months, none in prior 6 weeks; nonsmoker ≥1 year; <4 puffs/day short-acting beta-2 agonist		
Castro et al. 2010[1] AIR 2 Study	BT vs. sham	***Type of study:*** RCT ***Total population:*** N=190 BT N=98 control ***Country:*** U.S. ***Followup:*** 1 year	***Age:*** 18-65 y/o ***Asthma severity:,*** requiring daily ICS at >1,000 mcg BPD equivalent and LABA 100 mcg salmeterol equivalent; <10 mg OCS/day; ≥2 symptomatic days in prior 4 weeks ***Spirometry****:* prebronchodilator FEV1 ≥60% predicted; Methacholine PC_{20} <8mg/mL ***Additional****:* AQLQ ≤6.25;<3 hospitalizations for asthma; <3 lower respiratory infection and <4 pulses of OCS in prior year	***Age (mean years [SD]):*** BT: 40.7 (11.89) Control: 40.6 (11.85) ***% Male:*** BT: 43% Control: 39% ***Race:*** BT: 80% Caucasian Control: 74% Caucasian	***Inhaled corticosteroid dose mean (median):*** BT: BDP equivalent 1,960.7 (2,000) mcg/d Control: BDP equivalent 1,834.8 (2,000) mcg/d ***Oral corticosteroids (dose as mean, SD):*** BT: 6.4 mg (1.97), n=7 Control: 5mg, n=1 ***Omalizumab treatment:*** BT: n=2 Control: n=3 ***Leukotriene modifiers*** BT: n=47 (24.7%) Control: n=18 (18.4%) ***FEV_1 (mean [SD]):*** % predicted: BT: 77.8% (15.65) Control: 79.7% (15.14) ***PC_{20} (mg/ml geometric mean [range]):*** BT: 0.27 (0.22–0.34) Control: 0.31 (0.22–0.43) ***Asthma severity:*** NR ***Comorbidity:*** NR
Cox et al. 2007[3] AIR Study	BT vs. medical management	***Type of study:*** RCT ***Total population:*** N=56 BT N=56 control ***Country:*** Canada ***Followup:*** 1 year	***Age:*** 18-65 y/o ***Asthma severity:*** moderate or severe, requiring daily ICS at >200 mcg BPD equivalent and LABA 100 mcg salmeterol equivalent; stable disease ***Spirometry****:* prebronchodilator FEV1	***Age (mean years [SD]):*** BT: 39.36 (11.18) Control: 41.65 (11.35) ***% Male:*** BT: 44% Control: 43% ***Race:*** BT: 93% Caucasian Control: 93% Caucasian	***Inhaled corticosteroid dose (SD):*** BT: BDP equivalent 1,351 (963) mcg/d Control: BDP equivalent 1,264 (916) mcg/d ***FEV_1 (mean [SD]):*** % predicted: BT: 72.65% (10.41) Control: 76.12% (9.28) ***PC_{20} (mg/ml [95% CI]):*** BT: 0.25 (0.16–0.40) Control: 0.35 (0.23–0.52) ***Asthma severity:*** Moderate persistent- severe persistent ***Comorbidity:*** Seasonal allergies

Study	Intervention	Study Design	Study Inclusion Criteria	Demographic Factors	Clinical Characteristics at Baseline
			60 to 85% predicted; PC_{20} <8 mg/mL ***Additional****:* Worsening of ACQ ≥0.5 when off LABA for 2 weeks; <3 lower respiratory tract infections in previous 12 months, none in prior 6 weeks and <4 puffs/day short-acting beta-2 agonist		BT: 62% Control 65%
Pavord et al. 2007[2] RISA Study	BT vs. medical management	***Type of study:*** RCT ***Total population:*** N=15 BT N=17 control ***Country:*** U.K. ***Followup:*** 1 year	***Age:*** *18-65 y/o* ***Asthma severity:*** moderate or severe, requiring daily ICS at >750 mcg fluticasone equivalent and LABA 100 mcg salmeterol equivalent; ≤30 mg/d prednisone equivalent; ***Spirometry****:* prebronchodilator FEV1 ≥50% predicted; airway hyperresponsiveness (methacholine challenge or response to bronchodilator) ***Additional****:* Uncontrolled symptoms while on maintenance therapy – rescue medication used on 8 of 14 days prior to enrollment or daytime symptoms on 10 of 14 days; nonsmoker ≥1 year	***Age (mean years [SD]):*** BT: 39.1 (13.0) Control: 42.1 (12.6) ***% Male:*** BT: 40% Control: 59% ***Race:*** BT: 100% Caucasian Control: 100% Caucasian	***Inhaled corticosteroid dose (median):*** BT: fluticasone equivalent 1,166.7 (1000) mcg/d Control: fluticasone equivalent 1,058.9 (1000) mcg/d ***FEV_1 (mean [SD]): % predicted:*** BT: 62.9% (12.2) Control: 66.4% (17.8) ***PC_{20} (mg/ml geometric mean [range]):*** BT: 0.19 (0.05–0.76) Control: 0.31 (0.08–1.26) ***Asthma severity:*** All met the Global Initiative for Asthma (GINA) criteria for severe persistent asthma All but one met the American Thoracic Society criteria for refractory asthma ***Comorbidity:*** Seasonal allergies BT: 67% Control: 53%

AIR 2 Study=Asthma Intervention Research Trial 2; ATS=American Thoracic Study; BDP: beclomethasone dipropionate equivalent doses; BT=bronchial thermoplasty; FEV_1=forced expiratory volume; ICS=inhaled corticosteroid; OCS=oral corticosteroid; NR=not reported; PC_{20}=provocative concentration of methacholine causing a 20% drop in FEV_1; RCT=randomized clinical trial; RISA Study=Research in Severe Asthma Trial Study; SD=standard deviation; U.K.=United Kingdom.; U.S.=United States

Table C-2 Outcomes of comparative bronchial thermoplasty studies and associated followup studies

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
Bicknell et al. 2016[5]	Not applicable	***ACQ7 from baseline to 12 months (mean difference; MID -0.5) scores:*** Clinic: -0.5 (-1.5 to 0.4) RCT: -0.8 (-1.4 to -0.1) Clinic vs. RCT: p=0.003	***Exacerbations from baseline to 12 months (mean difference; MID 1):*** Clinic: -1 (-2 to 1) RCT: 0 (-1 to 0) Clinic vs. RCT: p=0.098 ***Hospital admissions in past 12 months (MID 1):*** Clinic: 0 (-2 to 1) RCT: 0 (0 to 0) Clinic vs. RCT: p=0.192	***Hospitalizations:*** Clinic: 3 (2 for asthma; 1 partial lung collapse) RCT: NR ***ICS use BDP equivalent (mcg [SD]):*** Clinic baseline: 2,980 (1,000) Clinic 12 months: 1,757 (1,578) Clinic change from baseline: p=0.406 RCT baseline: 1,757 (1,578) RCT 12 months: NR	***AQLQ scores, change from baseline*** AQLQ (MID -0.5) Clinic: 0.7 (-0.1 to 1.6) RCT: 1.1 (0.4 to 1.7) Clinic vs. RCT: p=0.085	***FEV_1 % predicted, difference from baseline (range):*** Clinic: -5 (-11 to 2) RCT: 6 (-4 to 15) Clinic vs. RCT: p=0.632	NR	Clinic: AEs reported as similar to events reported in clinical trials Clinic: One hospitalization for a partial lung collapse during the periprocedure period (0–6 weeks)

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
Pavord et al. 2013[6] RISA Extension Study 5-year followup of Pavord et al. 2007[2]	BT arm Baseline n=15 Year 1: n=14; 6% Year 2: n=14; 6% Year 3: n=14; 6% Year 4: n=12; 20% Year 5: n=12; 20%	NR	***Patients requiring maintenance OCS* at 5 years** (baseline n=7): Decreased dose: n=4 (2 weaned off OCS) Maintained dose: n=2 Increased dose: n=1 One patient of those not taking maintenance OCS at baseline (n=7) required maintenance OCS at year 5 ***ED visits per patient per year:*** before BT: 0.36 5 years after BT: 0.12 P-value for a repeated-measures logistic regression modeling the percentage of patients reporting an ED visit was 0.22 for the trend in the proportion of patients with ED visits for respiratory symptoms across years 1 to 5. ***Respiratory-related hospitalizations during followup period:*** 11 events in 5 patients from years 2–5 Hospitalizations for asthma exacerbations: 7 events (1 lower respiratory tract infection, 1 wheeze,	***ICS dose (compared with baseline):*** Unchanged: n=4 Increased: n=3 Decreased: n=5 ***Maintenance asthma medication use:*** No significant changes were found in inhaled maintenance asthma medication use overall. LABA dose 5 years after BT compared with baseline: Unchanged: n=2 Increased: n=2 Decreased: n=2	***Satisfaction*** 11/12 respondents at 5-years***:*** Definitely would undergo BT again: n=10 Would recommend BT to a friend or family member: n=9 "definitely yes", n=2 "probably yes"	Mean pre-bronchodilator and post-bronchodilator FEV_1 were unchanged in the 5-year period after BT	NR	***Respiratory AEs:*** ***% of patients experiencing AE:*** The rate of respiratory AEs in people treated with BT were unchanged in years 2 to 5 Asthma% Years 1–5: 7.1%, 35.7%, 50.0%, 16.7%, 41.7% Bronchitis Years 1–5: 7.1%, 14.3%, 21.4%, 8.3%, 8.3% Bronchospasm Years 1–5: 0%, 7.1%, 0%, 0%, 0% Chest discomfort Years 1–5: 21.4%, 0%, 0%, 8.3% Chest pain Years 1–5: 7.1%, 0%, 5.9%, 14.3%, 8.3% Cough Years 1–5: 42.9%, 0%, 7.1%, 0%, 0% Dyspnea Years 1–5: 64.3%, 0%, 0%, 8.3%, 0% Dyspnea exacerbated Years 1–5: 14.3%, 0%, 0%, 0% 0% Epistaxis Years 1–5: 14.3%, 0%, 0%, 0%, 0% Hemoptysis Years 1–5: 7.1%, 0%, 0%, 0%, 0%, Hoarseness Years 1–5: 7.1%, 0%, 7.1%, 0%, 0% LRTI Years 1–5: 42.9%, 35.7%, 28.6%, 41.7%, 58.3%

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
			2 semi-elective for prophylactic intravenous infusion of aminophylline) 1 patient accounted for 6 hospitalizations ***Respiratory-related hospitalizations per patient per year:*** 12 months before study: 0.71 Year 1: 0.36 Year 2: 0.43 Year 3: 0.21 Year 4: 0.08 Year 5: 0.08 Overall 5 years after BT: 0.23 per patient per year (68% reduction from 12 months prior to BT)					LRT inflammation Years 1–5: 0%, 0%, 0%, 0%, 8.3% Nasal congestion Years 1–5: 35.7%, 0%, 0%, 0%, 0% Nasopharyngitis Years 1–5: 28.6%, 0%, 7.1%, 8.3%, 8.3% Nocturnal dyspnea Years 1–5: 21.4%, 0%, 0%, 0%, 0% Pharyngolaryngeal pain Years 1–5: 14.3%, 0%, 0%, 8.3% 0% Productive cough Years 1–5: 64.3%, 0%, 7.1%, 0%, 0% Rhinitis Years 1–5: 7.1%, 0%, 14.3%, 0%, 0% Sinusitis Years 1–5: 0%, 0%, 7.1%, 8.3%, 0% Sputum discolored Years 1–5: 21.4%, 0%, 0%, 0%, 0% Throat irritation Years 1–5: 0%, 0%, 0%, 0%, 8.3% URTI Years 1-5: 35.7%, 0% 14.3%, 16.7%, 16.7% Wheezing Years 1–5: 71.4%, 7.1%, 14.3%, 0%, 8.3%

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
Wechsler et al. 2013[7] AIR 2 Extension 5-year followup of Castro et al. 2010[1]	BT treated patients n=162; of 190 BT-treated patients from AIR 2 study, 85.3% completed 5-year followup Year 1: n=181; 4% Year 2: n=165; 13% Year 3: n=162; 14% Year 4: n=159; 16% Year 5: n=162; 14%	NR	***ED visit for serious respiratory symptoms:*** Average reduction 12 months before BT vs. over the 5 years after BT: 78% ***ED visits:*** Average reduction 12 months before BT vs. over 5 years after BT: 88% ***Hospitalizations for respiratory symptoms (Events/patient/ year [95% CI]):*** 12 months before BT 0.053 [0.04–0.08] Year 1: 0.04 [0.025–0.060] Year: 0.061 [0.042–0.087] Year 3: 0.068 [0.048–0.096] Year 4: 0.076 [0.054–0.105] Year 5: 0.025 [0.014–0.044] Average over 5 years: 0.053 [0.038–0.073] The proportion of respiratory hospitalizations for respiratory symptoms did not increase over 5 years ***Severe exacerbations:*** Frequency in years 2–5 compared with	***Maintenance medication changes*** Baseline: 72% of patients were prescribed 2 maintenance medications (i.e., high dose ICS >1,000 µg BDP equivalent and LABA), and 28% of people were prescribed 3 or more maintenance medications. At 5 years following BT: 27% of patients decreased ICS by 50% or more; half of patients reduced daily ICS to ≥500 mcg/day BDP equivalent; 5% of patients increased ICS by 50% or greater; Patients who changed ICS dose by 50% or greater were more likely to decrease ICS compared to increase ICS (p<0.001); Overall reduction of 17% in the average ICS dose at 5 years; 12% were completely weaned off LABA, 9% were weaned off ICS and LABA maintenance medications, and 7% were no longer taking any maintenance asthma medications	NR	% predicted pre-bronchodilator FEV_1 values remained unchanged over the 5 years Baseline BT (n=190): FEV1 % prebronchodilator: 77.8±15.65% At 5 years following BT: BT (n=162): FEV1 % prebronchodilator: 77.8±15.84 % predicted post-bronchodilator FEV_1 values remained unchanged over the 5 years Baseline BT (n=190): FEV1 % post-bronchodilator: 86.1±15.76% At 5 years following BT: BT (n=162): FEV1 % post-bronchodilator: 85.9±15.83	NR	***Respiratory adverse events occurring in ≥3.0% of patients in years 1 through 5:*** Asthma (multiple symptoms) Bronchitis Cough Influenza Lower respiratory tract infections Nasopharyngitis Pneumonia Rhinitis Sinusitis Upper respiratory tract infections Wheezing ***Respiratory AEs (Events/patient/year [95% CI]):*** 12 months before BT: NA Year 1: 2.02 [1.764–2.318] Year 2: 1.22 [1.013–1.465] Year 3: 1.25 [1.037–1.499] Year 4: 1.18 [0.971–1.424] Year 5: 0.78 [0.616–0.982] Average over 5 years: 1.30 [1.149–1.481] The proportion of respiratory AEs did not increase over 5 years ***Asthma AEs (Events/patient/year [95% CI]):*** 12 months before BT: NA

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
			year 1 were not significant Patients reporting severe exacerbations in the year after BT: 30.9% 12 months before BT: 51.6% Reductions maintained for 5 years with an average decrease of 44% ***Severe exacerbations (matched pairs analysis n=162 at years 1, 2, 3, 4, and 5):*** 30.9%, 23.5%, 34.0%, 36.4%, and 21.6%; 53.1% experienced 1 or more exacerbations 12 months before BT; Average reduction over 5 years compared to the 12 months prior to BT: 48% (upper 95% confidence limit for Years 2, 3, 4, and 5 compared to Year 1 was 0.5, 11.3, 14.0, and -1.6, respectively; all less than the predefined non-inferiority margin of 20%)					Year 1: 0.481 [0.379–0.609] Year 2: 0.461 [0.357–0.594] Year 3: 0.506 [0.396–0.646] Year 4: 0.503 [0.393–0.644] Year 5: 0.321 [0.236–0.436] Average over 5 years: 0.45 [0.374–0.554] The proportion of asthma (multiple symptoms) did not increase over 5 years

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
Thompson 2011[4] AIR Study extension 5-year followup of Cox 2007[3]	Baseline BT: n=52 Control: n=49 <u>Year 2</u>: BT: n=45; 13% Control: n=24; 51% <u>Year 3</u>: BT: n=43; 17% Control: n=21; 57% <u>Year 4</u>: BT n=43; 17% <u>Year 5</u>: BT: n=42; 20%	NR	***Oral corticosteroid use (high-dose pulses/patient/year (% of patients)):*** <u>Year :</u> BT: 0.60 (24.5%) Control: 0.42 (20.8%) <u>Year :</u> BT: 0.49 (24.5%) Control: 0.54 (33.3%) <u>Year 3:</u> BT: 0.33 (25.6%) Control: 0.52 (23.8%) <u>Year 4:</u> BT: 0.63 (27.9%) <u>Year 5:</u> BT: 0.62 (30.9%) ***Hospitalizations*** <u>Year 1:</u> BT: 6.7% Control: 0% BT vs. control: p=0.55 <u>Year 2:</u> BT: 6.7% Control: 0% BT vs. control: p=0.55 <u>Year 3:</u> BT: 2.3% Control: 4.8% BT vs. control: p=1.00 Hospitalizations for respiratory symptoms in the BT arm did not increase over 5-year followup compared with year 1 after BT (p=0.16; repeated measures analysis for proportion of subjects)	***LABA use (BT over 5 years, Control over 3 years compared with baseline):*** BT decrease: 57% Control decrease: 54% BT no change: 40% Control no change: 43% BT increase: 3% Control increase: 3% BT discontinued use: 49% Control discontinued use: 47% ***ICS (mean) reduction from baseline:*** <u>BT Year 1:</u> 182 µg/day (p=0.09) <u>BT Year 2:</u> 135 µg/day (p=0.32) <u>BT Year 3:</u> 150 µg/day (p=0.25) <u>BT Year 4:</u> 151 µg/day (p=0.23) <u>BT Year 5:</u> 194 µg/day (p=0.16) (p-values from a Signed Rank test). <u>Control Year 3:</u> 112 µg/day (p=not significant) Comparison at 3 years: BT decrease: 27% Control decrease: 29% BT no change: 56% Control no change: 52% BT increase: 17% Control increase: 19%	NR	***Pulmonary function tests:*** ***FEV_1 and FVC*** did not deteriorate over 5 years post-BT ***PC20 doublings (SD):*** <u>Year 1:</u> BT: 1.53 (2.29) Control: 1.00 (2.46) BT vs. control: p=0.378 <u>Year 2:</u> BT: 1.21 (2.99) Control: -0.47 (2.31) BT vs. control: p=0.024 <u>Year 3:</u> BT: 1.31 (2.96) Control: -0.44 (2.27) BT vs. control: p=0.025	None	**Treatment period plus 6 weeks *Respiratory adverse events (events per patient):*** <u>Year 1</u>: BT: 4.5, Control: 3.1 <u>Year 2</u>: BT: 1.2, Control: 1.2 <u>Year 3</u>: BT: 1.3, Control: 1.3 <u>Year 4</u>: BT: 1.2 <u>Year 5</u>: BT: 1.1 ***Adverse events (% of patients experiencing AE):*** <u>Dyspnea</u> BT Years 1–5: 42.2%, 8.9%, 9.3%, 9.3%, 9.5% Control Years 1–3: 50.0%, 12.5%, 14.3% <u>Cough</u> BT Years 1–5: 37.8%, 8.9%, 4.7%, 7.0%, 4.8% Control years 1–3: 29.2%, 4.2%, 14.3% <u>Wheeze</u> BT years 1–5: 31.1%, 4.4%, 7.0%, 7.0%, 4.8% Control years 1–3: 16.7%, 4.2%, 4.8% <u>Nasal congestion</u> BT years 1–5: 28.9%, 4.4%, 0%, 0%, 2.4% Control years 1–3: 20.8%, 0%, 0% <u>Upper respiratory tract infection</u> BT years 1–5:

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
			Emergency department visits: Year 1: BT: 4.4% Control: 0% BT vs. control: p=0.54 Year 2: BT: 6.7% Control:12.5% BT vs. control: p=0.41 Year 3: BT: 4.7% Control: 4.8% BT vs. control: p=1.00					22.2%, 24.4%, 18.6%, 18.6%, 9.5% Control years 1–3: 8.3%, 16.7%, 19.1% Productive cough BT year 1–5: 20.0%, 4.4%, 4.7%, 0%, 2.4% Control years 1–3: 20.8%, 4.2%, 0% Chest discomfort BT years 1–5: 17.8%, 4.4%, 7.0%, 2.3 %, 4.8% Control years 1–3: 12.5%, 8.3%, 4.8% Nasopharyngitis BT years 1–5: 13.3%, 2.2%, 0%, 2.3%, 2.4% Control years 1–3: 0%, 0%, 0% Nocturnal dyspnea BT years 1–5: 13.3%, 0%, 0%, 0%, 0% Control years 1–3: 8.3%, 0%, 0% Respiratory tract infection BT years 1–5: 11.1%, 6.7%, 11.6%, 11.6%, 9.5% Control years 1–3: 20.8%, 8.3%, 4.8% Pharyngolaryngeal pain BT years 1–5: 11.1%, 0%, 0%, 0%, 0% Control years 1–3: 12.5%, 0%, 0% Respiratory Tract congestion

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
								BT years 1–5: 8.9%, 0%, 0%, 0%, 0% Control years 1–3: 8.3%, 0%, 0% <u>Discolored sputum</u> BT years 1–5: 8.9%, 6.7%, 0%, 0%, 0% Control years 1–3: 0%, 0%, 0% <u>Rhinitis</u> BT years 1–5: 4.4%, 0%, 2.3%, 0% 4.8% Control years 1–3: 0%, 0%, 0% <u>Bronchitis</u> BT years 1–5: 2.2%, 2.2%, 2.3%, 2.3%, 2.4% Control years 1–3: 0%, 4.2%, 9.5% <u>Pharyngitis</u> BT: years 1–5: 2.2%, 0%, 0%, 0%, 0% Control years 1–3: 4.2%, 0%, 0% <u>Pleuritic Pain</u> BT years 1–5: 2.2%, 0%, 0%, 0%, 0% Control years 1–3: 4.2%, 0%, 0% <u>Rhinorrhea</u> BT years 1–5: 2.2%, 0%, 2.3%, 0%, 0% Control years 1–3: 4.2%, 0%, 0% <u>Asthma (multiple symptoms)</u> BT: years 1–5: 0%, 8.9%, 16.3%, 16.3%, 14.3%

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
								Control years 1–3: 0%, 8.3%, 4.8% Sinusitis BT years 1–5: 0%, 2.2%, 4.7%, 4.7%, 4.8% Control years 1–3: 0%, 4.2%, 0% Nasal polyps BT years 1–5: 0%, 2.2%, 0%, 4.7%, 0% Control years 1–3: 0%, 0%, 0% Pneumonia BT years 1–5: 0%, 0%, 2.3%, 0%, 0% Control years 1–3: 0% 0%, 4.8%
Castro 2010[1] AIR 2 Study ITT results	BT: N=190 Sham: N=98 Completed 12 month followup: BT: N=181; 5% Sham: N=97; 1% 96.5% completed study	***ACQ scores at 12-month followup:*** BT: 1.31 (0.94) Sham: 1.32 (0.91)	***Severe exacerbation rate over 12 months, severe exacerbations per patient/year):*** BT: 0.48 (0.067) Sham: 0.70 (0.122) BT vs. sham: PPS: 95.5% ***Hospitalizations for respiratory symptoms:*** BT: 5 people (2.6%) had a total of 6 hospitalizations Sham: 4 people (4.1%) had 12 hospitalizations (one person had 9 hospitalizations) ***Number of severe exacerbations over the entire study period per patient:***	***Rescue medication use (puffs/7 days):*** BT baseline: 13.4 (19.17) BT 12 months: 7.4 (15.01) Sham baseline: 11.8 (11.24) Sham 12 months: 7.5 (12.60) BT vs. sham: PPS: 81.3 ***% days rescue medication used:*** BT baseline: 52.1 (36.48) BT 12 months: 28.0 (36.09) Sham baseline: 51.8 (35.41) Sham 12 months: 29.8 (34.96) BT vs. sham: PPS: 68.0%	***AQLQ change from baseline at 12 month followup (SD):*** BT: 1.35 (1.10) Sham: 1.16 (1.23) BT vs. sham: PPS: 96.0% ***Clinically meaningful improvement in AQLQ score 0.5 or greater:*** BT: 79% Sham: 64% BT vs. sham: PPS: 99.6%	**FEV_1 pre-bronchodilator, % predicted baseline to 12 months:** BT baseline: 77.8 (15.65) BT 12 months: 76.6 (17.74) Sham baseline: 79.7 (15.14) Sham 12 months: 79.1 (15.98) BT vs. sham: PPS: 24.1% ***Morning PEF (L/min):*** BT baseline: 383.8 (104.32) BT 12 months: 411.6 (110.45) Sham baseline: 386.3 (112.59) Sham 12 months: 408.7 (117.56) BT vs. sham:	***Percent symptom-free days:*** BT baseline: 16.4 (24.04) BT 12 months: 40.8 (38.22) Sham baseline: 16.8 (23.10) Sham 12 months: 37.9 (36.95) BT vs. sham: p=0.776 ***Total symptom score:*** BT baseline: 3.8 (2.34) BT 12 months: 2.1 (2.22)	***Adverse events:*** BT: 85% (1.0 events/ bronchoscopy) Sham: 76% of patients (0.7 events/ bronchoscopy) ***Severity of respiratory adverse events:*** Mild BT: 43.6%; Sham: 58.7% Moderate BT: 53.2%; Sham: 39.8% Severe BT: 3.1%; Sham: 1.5% ***Most common airway irritation events after procedure:*** Worsening asthma symptoms (wheezing, chest discomfort, cough, and chest pain) and upper respiratory tract infections

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
			BT: 1.02 (53.6% of patients) Sham: 0.91 (45.9% of patients) PPS sham >BT: 25.8% ***ED visits for respiratory symptoms per patient over 12 months:*** BT: 0.13 (8.4% of subjects) Sham: 0.45 (15.3% of subjects) PPS >BT: 99.7% ***Number of respiratory-related hospitalizations per subject:*** BT: 0.13 (10.5% of subjects) Sham: 0.14 (5.1% of subjects) PPS sham >BT: 57.2% ***Risk reduction in ED visits for respiratory symptoms BT vs. sham:*** 0.07 vs. 0.43 visits/subject/year 84% reduction PPS: 99.9%	***Days lost from work/school/other activities due to asthma at 12 months:*** BT: 1.315 (0.361) Sham: 3.915 (1.553) BT vs. sham: PPS: 99.3%		PPS: 80.6% ***Airway responsiveness, PC20*** defined by a provocative concentration of methacholine required to lower the FEV1 by 20% (PC20) of less than 8 mg per milliliter, BT baseline: geometric mean (95%C.I.) PC20 0.24(0.15, 0.4) BT 12 months: 0.61(0.36, 1.03) mg/ml, or 1.31±2.39 doubling concentrations over baseline Control baseline: 0.32(0.20, 0.51) Control 12 months: 0.5(0.31, 0.80) mg/ml, or 0.66±2.69 doublings "The differences over baseline between groups did not reach statistical significance at any time point (P=0.06, 0.18 and 0.17 for 3, 6 and 12 months respectively)" (data supplement)	Sham baseline: 3.9 (2.53) Sham 12 months: 2.3 (2.17) BT vs. sham: PPS: 63.7%	<u>During the treatment period</u> BT: 16 people (8.4%) required 19 hospitalizations (10 occurred on the day of the procedure) for respiratory symptoms (worsening of asthma, 12 in 10 subjects; segmental atelectasis, 3 in 2 subjects; lower respiratory tract infection, 1 subject; low FEV_1, 1 subject; hemoptysis, 1 subject; and aspirated prosthetic tooth; one subject) Sham: Two patients (2.0%) required two hospitalizations (both worsening of asthma) <u>During the post treatment period</u> BT: 70% reported respiratory AEs Sham: 80% reported respiratory AEs ***Proportion of people reporting worsening of asthma:*** BT: 27.3; Sham: 42.9% BT vs. sham: PPS: 99.7% ***Rate of upper and lower respiratory tract infections requiring antibiotics (SD):*** BT: 0.007 (0.014) events/ subject/week (24.1% of patients)

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
								Sham: 0.006 (0.012) events/subject/week (24.5% of patients)
Cox 2007[3] AIR Study	BT: N=56 at baseline 7% attrition at 12 months Control: N=56 at baseline 12.5% attrition at 12 months	***ACQ score:*** BT baseline: 2.50 (0.92) BT 12 months: 1.32 (0.85) Control baseline: 2.16 (0.86) Control 12 months: 1.69 (0.99) BT vs control: p=0.001 SMD=-0.402 SE=0.201 ***Patients taking high dose ICS (post-hoc analysis n=32; 16 BT, 16 Control) who required >1,000 µg BDP or equivalent at baseline:*** <u>ACQ</u> BT: 2.88 (0.63) to 1.34 (0.95) Control: 2.20 (0.67) to 1.99 (1.02)	***Severe exacerbations per patient per week in past 12 months (Mean ± SD) BT vs. Control:*** BT baseline: 0.07±0.18 BT 12 months: 0.01±0.08 Control baseline: 0.09±0.31 Control 12 months: 0.06±0.24 Difference between the two groups in the change from baseline at 12 months=n.s. ***Exacerbations during the 2-week periods at 3, 6, and 12 months when patients were treated with ICS alone compared with baseline:*** BT: -0.16±0.37 Control: 0.04±0.29 BT vs. control: p=0.005 Analysis with Wilcoxon rank-sum method (p=0.01 between the groups) ***Mild exacerbations per patients per week in past 12 months (Mean ±SD) BT vs. control:***	***Rescue medication use (puffs per week)*** BT baseline: 19.8 (17.2) BT 12 months: 10.9 (15.0) Control baseline: 16.0 (18.8) Control 12 months: 14.8 (21.2) p=0.04	***AQLQ score (SD)*** BT baseline: 4.91 (1.23) BT 12 months: 6.18 (0.88) Control baseline: 5.15 (1.19) Control 12 months: 5.72 (1.11) BT vs. control: p=0.003 ***High Dose ICS (post-hoc analysis n=32; 16 BT, 16 Control) who required >1000 µg BDP or equivalent at baseline*** <u>*AQLQ*</u> BT: 4.45 (1.48) to 6.17 (0.89) Control: 5.41 (0.81) to 5.67 (1.13) BT vs. control: p=0.002	***Morning PEF, L/min (SD):*** BT baseline: 349.3 (90.6) BT 12 months: 388.6 (105.0) Control baseline: 372.4 (99.9) Control 12 months: 380.9 (92.9) BT vs. control: p=0.003 ***Evening PEF:*** BT baseline: 359.7 (88.4) BT 12 months: 397.4 (102.8) Control baseline: 379.1 (98.7) Control 12 months: 389.0 (93.9) BT vs. control: p=0.006 ***Pre-bronchodilator FEV1 % predicted (SD), baseline and 12 months:*** BT baseline: 70.4 (12.1) BT 12 months: 75.2 (13.9) Control baseline: 70.7 (10.5) Control 12 months: 72.4 (12.6) BT vs. control: not significant ***Airway hyper-responsivenessPC_{20} geometric mean, mg/ml (95% CI):***	***Symptom-free days:*** BT baseline: 24.7 (30.5) BT 12 months: 65.4 (40.4) Control baseline: 32.3 (34.3) Control 12 months: 49.4 (41.3) BT vs. control: p=0.005 Study extrapolated that BT group might gain 148 symptom-free days per year compared with 62 for control group ***Total symptom score:*** BT baseline: 3.16 (2.21) BT 12 months: 1.25 (1.97) Control baseline: 2.65 (2.55) Control 12 months: 2.00 (2.23)	***Treatment period plus 6 week AE frequency (% patients with AE)*** <u>Dyspnea</u> BT: 70.9%, Control: 33.3% BT vs. control: p<0.001 <u>Wheezing</u> BT: 61.8%, Control: 13.0% BT vs. control: p<0.001 <u>Cough</u> BT: 52.7%. Control: 18.5% BT vs. control: p<0.001 <u>Chest discomfort</u> BT: 47.3%, Control: 20.4% BT vs. control: p=0.004 <u>Night awakenings</u> BT: 40.0%, Control: 9.3% BT vs. control: p<0.001 <u>Productive cough</u> BT: 40.0%, Control: 11.1% BT vs. control: p<0.001 <u>Upper respiratory tract infection</u> BT: 12.7%, Control: 3.7% BT vs. control: p=0.16 <u>Bronchial irritation</u> BT: 9.1%, Control: 0% BT vs. control: p=0.06 <u>Nasal congestion</u> BT: 12.7%, Control: 11.1% BT vs. control: p=1.00 <u>Sputum discolored</u>

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
		BT vs. control: p=0.004	BT baseline: 0.35±0.32 BT 12 months: 0.18±0.31 Control baseline: 0.28±0.31 Control 12 months: 0.31±0.46 Difference between the two groups in the change from baseline at 12 months: p=0.03			BT baseline: 0.24 (0.15–0.4) BT 12 months: 0.61 (0.36–1.03) 1.31 (2.39) doubling concentrations over baseline Control baseline: 0.32 (0.20–0.51) Control 12 months: 0.5 (0.31–0.80) 0.66 (2.69) doublings p=0.17 ***Patients taking high dose ICS (post-hoc analysis n=32; 16 BT, 16 Control) who required >1000 µg BDP or equivalent at baseline:*** Morning PEF BT baseline: 378.2 (69.8) BT 12 months: 441.8 (103.9) Control baseline: 321.9 (65.9) Control 12 months: 346.2 (66.4) BT vs. control: p=0.05 Airway hyper-responsiveness BT baseline: 0.33 (0.11–0.97) BT 12 months: 1.71 (0.65–4.49) 2.39 (SD 2.78) doublings from baseline Control baseline: 0.45 (0.19–1.03)	BT vs. control: p=0.01 SMD=-0.617 SE=0.204	BT: 10.9%, Control: 0% BT vs. control: p=0.03 Dry mouth BT: 3.6%, Control: 0% BT vs. control: p=0.50 Abnormal chest sound BT: 5.5%, Control: 0% BT vs. control: p=0.24 Bronchospasm BT: 7.3%, Control: 0% BT vs. control: p=0.12 ***Post-treatment period (6 weeks–12 months)*** Dyspnea BT: 49.1%, Control: 53.8% BT vs. control: p=0.70 Cough BT: 38.2%, Control: 36.5% BT vs. control: p=1.00 Nasal congestion BT: 27.3%, Control: 26.9% BT vs. control: p=1.00 Wheezing BT: 29.1%, Control: 23.1% BT vs. control: p=0.52 Productive cough BT: 23.6%, Control: 23.1% BT vs. control: p=1.00 Chest discomfort BT: 21.8%, Control: 13.5% BT vs. control: p=0.32 Upper respiratory tract infection BT: 18.2%, Control: 5.8% BT vs. control: p=0.07

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
						Control 12 months: 0.30 (0.09–1.01) -0.57 (SD 3.04) doublings from baseline BT vs. control: p=0.03		Night awakenings BT: 12.7%, Control: 9.6% BT vs. control: p=0.76 Pharyngolaryngeal pain BT: 10.9%, Control: 13.5% BT vs. control: p=0.77 Nasopharyngitis BT: 10.9% vs, Control: 5.8% BT vs. control: p=0.49 Respiratory tract congestion BT: 9.1%, Control: 3.8% BT vs. control: p=0.44 Respiratory tract infection BT: 9.1%, Control: 17.3% BT vs. control: p=0.26 Bronchitis BT: 1.8%, Control: 0% BT vs. control: p=1.00 Throat irritation BT: 3.6%, Control: 3.8% BT vs. control: p=1.00
Pavord 2007[2] RISA Study	BT: 17 patients assigned, 2 withdrew prior to BT; 11% attrition by 52 weeks Control: 17 assigned; 0% attrition	***ACQ score change:*** BT: -0.99 (0.83) Control: -0.22 (0.78) BT vs. control: p=0.01 SMD=-0.958 SE=0.374	***Number of patients able to wean off OCS*** (through week 52): BT: 4 of 8 patients Control: 1 of 7 patients BT vs. control: p=0.28 ***Mean reduction in OCS dose:*** BT: 63.5 (45.4) % Control: 26.2 (40.7) % BT vs. control: p=0.12 ***Treatment period hospitalizations for respiratory adverse events:***	***Overall reduction in ICS dose*** BT: 28.6 (30.4) % Control: 20.0 (32.9) % (p=0.59) ***Reduction in short-acting b2-agonist use at 52 weeks, puffs/week:*** BT: -25.6 (31.2) Control: -6.1 (12.4) BT vs. control: p<0.05 ***Rescue medication use at 22 weeks (puffs/week)*** BT: -26.6 (40.1) Control: -1.5 (11.7)	***AQLQ score (change from baseline to 12 months)*** BT: 1.53 (0.79) Control: 0.42 (0.82) BT vs. control: p=0.001	**Mean % change in pre-bronchodilator FEV1 (% predicted)** BT: 7.97%, SD 19.13% Control group: 1.89%, SD 15.00% (p=0.322)	NR	***Respiratory AEs during treatment period*** Wheezing BT: 17.6%, Control: 7.0% BT vs. control: p=0.072 Cough BT: 16.9%, Control: 17.5% BT vs. control: p=1.000 Chest discomfort BT: 15.4%, Control: 5.3% BT vs. control: p=0.057 Dyspnea BT: 15.4%, Control: 15.8% BT vs. control: p=1.000

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
			BT: 7 in 4 patients Events were due to asthma exacerbations and two events included partial collapse of a lower lobe of the lung 1 and 2 days after BT, respectively Control: No hospitalizations Median length of stay per hospitalization: 2 days ***Post-treatment period hospitalizations:*** BT: 5 occurred in 3 patients Control: 4 in 1 patient BT vs. control: p=0.32 ***Exacerbations:*** Control: 1 patient on Day 42 ICU (respiratory failure)	BT vs. control: p=0.05				Productive cough BT: 11.8%, Control: 17.5% BT vs. control: p=0.355 Sputum discolored BT: 5.1%, Control: 0.0% BT vs. control: p=0.107 Nasal congestion BT: 2.9%, Control: 5.3% BT vs. control: p=0.423 Nasopharyngitis BT: 2.2%, Control: 7.0% BT vs. control: p=0.198 Pharyngolaryngeal pain BT: 2.2%, Control: 1.8% BT vs. control: p=1.000 Atelectasis BT: 1.5%, Control: 0.0% BT vs. control: p=1.000 Bronchial irritation BT: 1.5%, Control: 0.0% BT vs. control: p=1.000 Lower respiratory tract infection BT: 1.5%, Control: 8.8% BT vs. control: p=0.025 Upper respiratory tract infection BT: 1.5%, Control: 5.3% BT vs. control: p=0.154 ***Post-treatment period*** Wheezing BT: 15.6%, Control: 15.4% BT vs. control: p=1.000 Cough BT: 10.7%, Control: 8.9% BT vs control: p=0.674 Chest discomfort BT: 3.3%, Control: 12.2% BT vs. control: p=0.015

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
								Dyspnea BT: 20.5%, Control: 25.2% BT vs. control: p=0.447 Productive cough BT: 13.9%, Control: 11.4% BT vs. control: p=0.570 Sputum discolored BT: 0%, Control: 0% BT vs. control: p=1.000 Nasal congestion BT: 4.1%, Control: 4.9% BT vs. control: p=1.000 Nasopharyngitis BT: 5.7%, Control: 4.9% BT vs. control: p=0.784 Pharyngolaryngeal pain BT: 1.6%, Control: 0.8% BT vs. control: p=0.622 Atelectasis BT: 0%, Control: 0% BT vs. control: p=1.000 Bronchial irritation BT: 0%, Control: 0% BT vs. control: p=1.000 Lower respiratory tract infection BT: 7.4%, Control: 4.9% BT vs. control: p=0.439 Upper respiratory tract infection BT: 8.2%, Control: 6.5% BT vs. control: p=0.634 ***Respiratory AEs during treatment period:*** BT: 136 AEs; Mild: 49%; Moderate: 41%; Severe: 10% Control: 57 AEs; Mild: 49%;

Reference	Attrition N, %	Asthma Control	Exacerbations	Healthcare Utilization and Costs	Quality of Life	Pulmonary Physiology	Symptoms	Adverse Events
								Moderate: 47%; Severe: 4% ***Treatment period severe respiratory AEs*** BT: 2 people had 5 events (chest infection, increased wheeze, cough, and shortness of breath on exertion) Control: 2 patients (dyspnea, chest infection) that did not require hospitalization ***Post-treatment period severe respiratory AEs*** BT: 2 patients had 5 severe respiratory AEs (increased wheeze, chest tightness, increased breathlessness, nocturnal wheeze, and chest infection) Control: 1 patient had one severe respiratory AE (flu-like syndrome)

ACQ=Asthma Control Questionnaire; ACQ7=Asthma Control Questionnaire 7; AE=adverse event; AQLQ=Asthma Quality of Life Questionnaire; scores range from 1 to 7; BDP= beclomethasone dipropionate equivalent doses; BT=bronchial thermoplasty; CT=computed tomography; ED=emergency department; FEV_1=forced expiratory volume; ICS=inhaled corticosteroid; ICU=intensive care unit; ITT-intention-to-treat analysis; LABA=long acting beta-agonist; MID=minimal clinical important difference; NR=not reported; OCS=oral corticosteroid; PC_{20}=provocative concentration of methacholine causing a 20% drop in FEV_1; PEF=peak expiratory flow; PPS=posterior probability of superiority; RCT=randomized clinical trial; SD=standard deviation; SE=standard error; SMD=standardized mean difference: Calculated by ECRI Institute

Table C-3. Risk of bias assessment for included RCTs

Study	Sequence Generation	Allocation Concealment	Blinding of Participants, Personnel and Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall Risk of Bias	Comments
Castro et al. 2010[1] AIR 2 Study	Low	Unclear	Low	Low	Low	High	Medium	Study was randomized, double-blind, sham-controlled trial; patients and outcome assessors blinded; intent-to-treat analysis used; allocation method described but concealment not explicit; study funded by BT device manufacturer
Cox et al. 2007[3] AIR Study	Low	Low	High	Low	Low	High	High	Unblinded study; intent-to-treat analysis used; study funded by BT device manufacturer
Pavord et al. 2007[2] RISA Study	Low	Low	High	Low	Low	High	High	Unblinded study; full followup of all patients who began trial; lack of clarity regarding role of funding entity; study funded by BT device manufacturer

AIR=Asthma Intervention Research Trial 2; BT=bronchial thermoplasty; RISA=Research in Severe Asthma Trial

Table C-4. Strength of evidence assessments

Comparison	Outcome[a]	Study Results	Study Design and Sample Size	Study Limitations[b]	Directness	Consistency	Precision	Reporting Bias	Overall Evidence Strength
BT and standard care (medical management) vs. standard care alone	Asthma control	**Favors BT, but clinical importance unclear:** ACQ scores (scale 0 to 6; lower scores indicate better control; MID=0.5) improved in patients who underwent BT compared to those who received standard medical management Calculated based on data reported in the publications: AIR: Mean difference in ACQ change score:-0.71, 95% CI: -1.05 to -0.37 (at 12 months after last BT treatment); upper bound is less than MID RISA: Mean difference in ACQ score change=-0.77, 95% CI: -1.33 to -0.21 (at week 52, which was 46 weeks after last BT treatment); upper bound is less than MID	2 RCTs[2,3] n=144	Medium[c]	Direct	Consistent	Imprecise; lack of precision in reporting test statistics; MID not met	Not detected	Low
	Exacerbations Severe (after treatment period)	**Inconclusive:** Rates of severe exacerbations per patient per week did not vary between treatment conditions. Exacerbations were counted during 2-week periods at 3, 6 and 12 months while LABA were withheld from patients who needed them Calculated mean difference: -0.03 severe exacerbations per subject per week, 95% CI: -0.12 to 0.06 (at 12 months after last BT treatment)	1 RCT[3] n=112	Medium[c]	Indirect (measured while patients off LABA)	Unknown	Imprecise	Not detected	Insufficient

Comparison	Outcome[a]	Study Results	Study Design and Sample Size	Study Limitations[b]	Directness	Consistency	Precision	Reporting Bias	Overall Evidence Strength
	Exacerbations Mild (after treatment period)	**Favors BT, but clinical importance unclear**: Rates of mild exacerbations per patient per week were lower at 12 months in patients who received BT and standard care. Exacerbations were counted while LABA were withheld from patients who needed them Calculated mean difference: -0.20 mild exacerbations per subject per week, 95% CI=-0.34 to -0.06 (at 12 months after last BT treatment). Translates to 10 fewer mild exacerbations per year, 95% CI=3 to 18 fewer exacerbations.	1 RCT[3] n=112	Medium[c]	Indirect: measured while patients off LABA for 2 weeks	Unknown	Precise	Not detected	Low
	Hospitalizations (after treatment period)	**No difference:** Rates of hospitalizations were not different in patients who received BT and standard care versus those treated with standard care alone: RISA: 5 hospitalizations in BT and standard care vs. 4 hospitalizations in standard care group, reported p =0.32 AIR: 3 hospitalizations in 3 patients in BT and standard care vs. 3 hospitalizations n 2 patients in standard care group, no statistics reported	2 RCTs[2,3] n=144	Medium[c]	Direct	Consistent	Imprecise	Not detected	Low

Comparison	Outcome[a]	Study Results	Study Design and Sample Size	Study Limitations[b]	Directness	Consistency	Precision	Reporting Bias	Overall Evidence Strength
	Health care utilization (other than exacerbations)	**Favors BT, but clinical importance unclear:** Use of rescue medication (puffs per week) was reduced to a greater extent in the BT group than standard care group but does not meet the MID criterion Calculated mean difference in number of puffs per week for BT and standard care compared to standard care alone: AIR[3]: -7.8 puffs/wk, 95% CI=-14.78 to -0.82 (MID is -5.67 puffs/wk) RISA[2]: -19.49 puffs/wk, 95% CI=-35.5 to -3.41 (MID is -5.67 puffs/wk) The overall reduction in oral corticosteroid dose was not different (p=0.12, Wilcoxon sum rank test) between treatment groups in 1 small trial.[2] The reduction in inhaled corticosteroid dose was not different (p=0.59, Wilcoxon sum rank test)	2 RCTs[2,3] n=144	Medium[c]	Direct	Consistent	Imprecise: Upper bounds of 95% CIs is less than MID	Not detected	Low
	Pulmonary physiology: Spirometry	**Inconclusive:** In 1 small trial, BT and standard care improved FEV_1 at 22 weeks from baseline; the between-group difference was not significant at 52 weeks.[2] In the other study, patients treated with BT and standard care had greater increases in morning and evening peak flow compared with standard care alone from baseline to 12 months. Between-group change in FEV_1 was not significant.[3]	2 RCTs[2,3] n=144	Medium[c]	Direct	Inconsistent	Imprecise	Not detected	Insufficient
	Pulmonary physiology: Airway hyper-responsiveness	**Inconclusive:** Airway hyper-responsiveness did not vary between treatment groups	1 RCT[3] n=112	Medium[c]	Direct	Unknown	Imprecise	Not detected	Insufficient

Comparison	Outcome[a]	Study Results	Study Design and Sample Size	Study Limitations[b]	Directness	Consistency	Precision	Reporting Bias	Overall Evidence Strength
	Quality of life	**Favors BT, but clinical importance unclear:** AQLQ scores (scale 1-7, higher indicating better quality of life, MID 0.5) improved in patients who underwent BT and received standard care compared to those who received standard medical management alone. The result from the larger study did not exceed the MID criterion (calculated mean difference 0.7, 95% CI=0.28 to 1.12) Other calculated values: AIR (n=112): SMD 0.62, 95% CI=0.24 to 1.01 (12 months after last BT treatment) RISA (n=32): SMD 1.38, 95% CI 0.60 to 2.15 (46 weeks after last BT treatment)	2 RCTs[2,3] n=144	Medium[c]	Direct	Consistent	Imprecise: lower bounds of the 95% CI was less than 0.5, the MID for AQLQ for the larger study	Not detected	Low
	Symptoms (Secondary outcome)	**Favors BT, but clinical importance unclear:** BT and standard care significantly improved total symptom score [range 0 to 18, higher scores indicating more symptoms] from baseline to 12 months compared with medical management alone Calculated between-group mean difference in total symptom score: -1.20, 95% CI: -2.10 to -0.30 (no MID available; Hedges g values suggest this is less than an important difference)	1 RCT[3] n=112	Medium[c]	Direct	Unknown	Precise	Not detected	Low
BT and standard care vs. sham (bronchoscopy	Asthma control	**No difference:** ACQ scores did not differ at 12 months after either BT and standard care or sham and standard care. Calculated SMD:-0.05, 95% CI: -0.29 to 0.19	1 RCT[1] n=288	Low	Direct	Unknown	Imprecise	Not detected	Low

Comparison	Outcome[a]	Study Results	Study Design and Sample Size	Study Limitations[b]	Directness	Consistency	Precision	Reporting Bias	Overall Evidence Strength
only) and standard care	Exacerbations: Severe events (after treatment period)	**Favors BT, but clinical importance unclear:** Patients who underwent BT and standard care had fewer severe exacerbations per patient per year than sham and standard care during weeks 12 to 52. Reported as 0.48 for BT vs. 0.70 for Sham exacerbations/subject/year, PPS, 95.5%; FDA reports credible interval for the difference: -0.031 to 0.520. The number of patients experiencing severe exacerbations was significantly less in the BT group than sham group. (Calculated RR: 0.66, 95% CI=0.47 to 0.93)	1 RCT[1] n=288	Low	Direct	Unknown	Imprecise: reported credible interval crosses 0	Not detected	Low
	Exacerbations: Severe events (during treatment period)	**Favors sham and standard care**: During the treatment period (up to 6 weeks following the 3rd BT or sham treatment), the number of patients experiencing severe exacerbations was significantly higher in the BT group (52 of 190) than in the sham group (6 of 98); Calculated RR:4.47, 95% CI=1.99 to 10.04	1 RCT[1] n=288	Low	Direct	Unknown	Precise	Not detected	Moderate
	Exacerbations: ED visits (after treatment period)	**Favors BT:** Rates of ED visits for respiratory symptoms were lower over 12 months following BT and standard care relative to sham and standard care. Reported as 0.07 vs. 0.43 visits/subject/yr; PPS 99.9%; FDA reported credible interval for sham minus BT (0.111 to 0.832)	1 RCT[1] n=288	Low	Direct	Unknown	Precise	Not detected	Moderate
	Exacerbations: Hospitalizations (after treatment period)	**No difference:** Hospitalizations for respiratory symptoms after last BT treatment to 12 month followup Reported as 5 patients with 6 hospitalizations in BT group; 12 hospitalizations in 4 patients in sham group; Calculated RR: 0.64, 95% CI=0.18 to 2.35	1 RCT[1] n=288	Low	Direct	Unknown	Imprecise: lack of precision in reporting statistical findings	Not detected	Low

Comparison	Outcome[a]	Study Results	Study Design and Sample Size	Study Limitations[b]	Directness	Consistency	Precision	Reporting Bias	Overall Evidence Strength
	Exacerbations: Hospitalizations (during treatment period)	**No difference:** Hospitalizations for respiratory symptoms during the treatment period (up to 6 weeks following the 3rd BT or sham treatment) were higher in the BT group than the sham group Reported as 16 patients with19 hospitalizations in BT group, 2 patients with 2 hospitalizations in sham; Calculated RR: 4.13, 95% CI=0.97 to 17.58)	1 RCT[1] n=288	Low	Direct	Unknown	Imprecise	Not detected	Low
	Health care utilization: Rescue medication actuations	**No difference:** Use of rescue medication at 12 month followup (MID is -5.67 puffs/wk) Calculated difference in means: -1.7 puffs/wk, 95% CI -5.56 to 2.16 puffs	1 RCT[1] n=288	Low	Direct	Unknown	Imprecise	Not detected	Low
	Health care utilization: Days rescue medication required	**No difference:** % days rescue medication used at 12 month followup Calculated difference in means: -2.1%, 95% CI=-10.86% to 6.66%	1 RCT[1] n=288	Low	Direct	Unknown	Imprecise	Not detected	Low
	Pulmonary physiology	**No difference:** FEV_1 and morning peak flow in patients treated with BT and standard care compared with sham and standard care from baseline to 12 months	1 RCT[1] n=288	Low	Direct	Unknown	Imprecise	Not detected	Low

Comparison	Outcome[a]	Study Results	Study Design and Sample Size	Study Limitations[b]	Directness	Consistency	Precision	Reporting Bias	Overall Evidence Strength
	Quality of life	**Inconclusive:** Change in AQLQ scores did not differ in intent-to-treat patients 12 months after either BT and standard care or sham intervention and standard care Reported in FDA presentation as a difference of 0.21 on the AQLQ 7-point scale (PPS 96%) (below MID of 0.5); credible interval -0.025 to 0.445. AQLQ improved in per-protocol patients treated with BT and standard care compared with sham and standard care at 12 months. Reported in FDA presentation as a difference of 0.24, PPS 97.9% (below MID of 0.5); credible interval 0.009 to, 0.478. The proportion of patients with improvement in AQLQ score greater than the minimum important difference was higher after BT and standard care than after the sham intervention and standard care. Reported in FDA presentation as "150 of 190 patients in BT group, 63 of 98 in sham group, a difference of 14.6% favoring BT, but with no control for type I error, and this was not a prespecified outcome."	1 RCT[1] intent-to-treat: n=288 per protocol: n=268	Low for ITT analysis and responder analysis; Medium for per protocol analysis	Direct	Unknown	Imprecise: 95% credible interval for continuous measure crosses 0 in the intent-to-treat patients; the result and upper bound of the credible interval is less than MID in the per-protocol population	Possible selective outcome reporting. This outcome was not prespecified	Insufficient
	Symptoms (Secondary outcome)	**No difference:** Symptom scores (scale 0 to 18, higher score indicating more symptoms) improved over time in both treatment groups but did not differ as a function of treatment condition Calculated mean difference -0.10, 95% CI=-0.66 to 0.46	1 RCT[1] n=288	Low	Direct	Unknown	Imprecise	Not detected	Low

Comparison	Outcome[a]	Study Results	Study Design and Sample Size	Study Limitations[b]	Directness	Consistency	Precision	Reporting Bias	Overall Evidence Strength
BT in RCT patients vs. BT in "real world" clinic patients	Asthma control	**Inconclusive:** Although ACQ scores were significantly better following BT in patients who were enrolled in the RCTs compared to the patients from clinic who underwent BT, this 1 small nonrandomized study is insufficient for drawing a conclusion. The change from baseline in each group was clinically significant.	1 non-RCT[5] n=25	High[d]	Direct	Unknown	Imprecise	Not detected	Insufficient
	Exacerbations	**Inconclusive:** Rates of exacerbations were low in both treatment groups and did not vary statistically	1 non-RCT[5] n=25	High[d]	Direct	Unknown	Imprecise	Not detected	Insufficient
	Health care utilization	**Not evaluable:** Data on hospitalizations and medication use not reported in a comparable manner for treatment groups	NA	NA	NA	NA	NA	NA	NA
	Pulmonary physiology	**Inconclusive:** FEV_1 did not differ significantly between groups	1 non-RCT[5] n=25	High[d]	Direct	Unknown	Imprecise	Not detected	Insufficient
	Quality of life	**Inconclusive:** AQLQ scores improved to a clinically significant degree in both treatment groups; difference between groups not significantly different, but sample size was small	1 non-RCT[5] n=25	High[d]	Direct	Unknown	Imprecise	Not detected	Insufficient
	Symptoms (Secondary outcome)	**Not evaluable:** Not reported	NA	NA	NA	NA	NA	NA	NA

[a]Outcomes of Asthma control, Exacerbations, Health care utilization, and Pulmonary physiology as defined by Asthma Outcomes workshop;33 outcomes of Quality of life and Symptoms as defined by study authors.
[b]Study limitations derived from Risk of Bias assessments in Appendix C.
[c]Study limitations: Lack of participant and outcome assessor blinding were the main concerns. Lack of clarity regarding the role of the funding agency was also considered in this domain, but deemed a lesser concern.
[d]Observational study, retrospective, groups not comparable on baseline characteristics
ACQ=Asthma Control Questionnaire (Range 0–6); AQLQ=Asthma Quality of Life Questionnaire (Range 1–7); BT=bronchial thermoplasty; CI=confidence interval; ED=emergency department; FEV_1=forced expiratory volume in 1 second; ITT=intention-to-treat; LABA=long acting beta-agonist; MID=minimum important difference; NA=not available; PEF=peak expiratory flow; PPS=posterior probability of superiority; RCT=randomized controlled trial; RISA=Research in Severe Asthma Trial; RR=relative risk; SMD=standardized mean difference; wk=week; yr=year

Table C-5. Study and patient characteristics of descriptive studies (case reports and case series)

Study	Intervention	Study Design	Demographic Factors	Clinical Factors
McCambridge et al. 2016[8]	BT	***Type of study:*** *Case Study* ***Total population:*** N=1 ***Country:*** U.S. ***Followup:*** 6 months	***Age:*** 77 years ***Sex***: Female ***Race:*** NR	***Inhaled corticosteroid dose:*** NR ***FEV_1:*** NR ***PC_{20}:*** NR ***Asthma severity:*** Severe, Step NR ***Comorbidity:*** NR
Nguyen et al. 2016[9]	BT	***Type of study:*** *Case Study* ***Total population:*** N=1 ***Country:*** U.S. ***Followup****:* 3 days for complications	***Age:*** 66 years ***Sex:*** Female ***Race:*** NR	***Inhaled corticosteroid dose:*** NR ***FEV_1:*** NR ***PC_{20}:*** NR ***Asthma severity:*** Severe, Step NR ***Comorbidity:*** Hypertension
Balu et al. 2015[10]	BT	***Type of study:*** *Case Study* ***Total population:*** N=1 ***Country:*** U.K. ***Followup:*** 9 weeks	***Age:*** 43 years ***Sex:*** Female ***Race:*** Caucasian	***Inhaled corticosteroid dose:*** NR ***FEV_1:*** Pre-bronchodilator ***PC_{20}:*** NR ***Asthma severity:*** Severe; Step 5 ***Comorbidity:*** Bipolar disorder
Facciolongo et al. 2015[11]	BT	***Type of study:*** *Case Study* ***Total population:*** N=1 ***Country:*** Italy ***Followup:*** 12 months	***Age:*** 49 years ***Sex:*** Male ***Race:*** Caucasian	***Inhaled corticosteroid dose:*** Budesonide/formoterol ***Dosage:*** *8*00/24 mcg/d ***FEV_1:*** Pre-bronchodilator, 66% predicted ***PC_{20}:*** NR ***Asthma severity:*** Severe, Step NR ***Comorbidity:*** Common variable immunodeficiency
Doeing et al. 2013[12]	BT	***Type of study:*** *Case Study* ***Total population:*** N=1 ***Country:*** U.S. ***Followup:*** 6 months	***Mean age:*** 62 years ***Sex:*** Female ***Race:*** Caucasian	***Inhaled corticosteroid dose:*** Fluticasone/salmeterol ***Dosage:*** 500/50 mcg/d ***FEV_1:*** Pre-bronchodilator, 26% predicted ***Asthma severity:*** STEP 6 ***Comorbidity:*** Gastroesophageal reflux disease and obstructive sleep apnea
Doeing et al. 2013[13]	BT	***Type of study:*** *Retrospective*, observational ***Total population:*** N=8 ***Country:*** U.S. ***Followup:*** Up to 72 weeks	***Mean age (SEM):*** 47 (4.3) years ***Sex:*** 50% male ***Race:*** 63% Caucasian	***Inhaled corticosteroid dose:*** Fluticasone or equivalent ***Dosage:*** 1,000 mcg/d ***FEV_1:*** Pre-bronchodilator, 51.8% (8.6) predicted ***Asthma severity:*** STEP 5 or 6 ***Comorbidity:*** NR
Mahajan et al. 2012[14]	BT	***Type of study:*** *C*ase study ***Total population:*** N=1 ***Country:*** U.S. ***Followup:*** 1 year	***Age:*** 42 years ***Sex:*** Female ***Race:*** South Asian	***Inhaled corticosteroid dose:*** Fluticasone ***Dosage:*** 1,000 mcg/d ***FEV_1:*** 0.95 L ***Asthma severity:*** Severe; Step NR ***Comorbidity:*** History of eczema and recurrent sinus infections; unable to tolerate oral corticosteroids due to the dysphoria and suicidal ideations

Study	Intervention	Study Design	Demographic Factors	Clinical Factors
Cox et al. 2006[15]	BT	***Type of study:*** *Prospective*, observational ***Total population:*** N=16 ***Country:*** Canada ***Followup:*** 2 year	***Mean age (range):*** 39 years (24–58) ***Sex:*** 38% male ***Race:*** 94% Caucasian	***Inhaled corticosteroid dose:*** Fluticasone or equivalent ***Dosage (% of patients)*** None: 1 (6.3%) Low dose <250 mcg/d: 1 (6.3%) Medium dose 250–500 mcg/d: 13 (81.3%) High dose >500 mcg/d: 1 (6.3%) ***FEV_1***: Pre-bronchodilator, 82.28% (13.97) predicted ***PC_{20} (95% CI):*** 0.92 (0.42–1.99) ***Asthma severity:*** Severe; Step NR ***Comorbidity:*** NR

BT=bronchial thermoplasty; CI=confidence interval; FEV_1=forced expiratory volume; NR=not reported; PC_{20}=provocative concentration of methacholine causing a 20% drop in FEV_1; RCT=randomized clinical trial; SD=standard deviation; SEM=standard error of the mean; U.K.=United Kingdom; U.S.=United States

Table C-6. Outcomes of descriptive bronchial thermoplasty studies (case reports and case series)

Reference	Adverse Events
McCambridge et al. 2016[8]	7 days after BT, bilateral bronchial wall thickening, which resolved by 40 days after BT
Nguyen et al. 2016[9]	***Adverse events*** Distress, wheezing, tachycardia, inspiratory lung crackles, diminished breath sounds, reddened airways, dynamic airway collapse and mucous plugging ***Serious adverse events*** Pulmonary embolism with pleural effusion requiring mechanical ventilation Bilateral lower extremity deep venous thrombi Hemothorax with bleeding from bronchial artery pseudoaneurysm while anticoagulated for venous thromboemboli
Balu et al. 2015[10]	Lung abscess in area of BT treatment with associated asthma exacerbation; treated with intravenous antibiotics followed by prolonged course of oral antibiotics
Facciolongo et al. 2015[11]	First BT session: Acute respiratory failure, reduced breath sounds, severe bronchospasm with tachypnea, atelectasis, lung occlusion by bronchus-shaped plugs Second BT session: Severe bronchospasm with respiratory failure, atelectasis, mucus plug occluding bronchus
Doeing 2013[12]	First BT procedure: Hospitalized overnight due to requiring frequent nebulized albuterol treatments Second BT procedure: Asthma exacerbation Final BT procedure: Hospitalized overnight due to requiring frequent nebulized albuterol treatments
Doeing 2013[13]	After initial BT procedure: Patients (n=4) required overnight observation due to wheezing and/or increased frequency of rescue bronchodilator use After second BT procedure: Patients (n=2) required overnight observation: one had atelectasis; one required increased bronchodilator use After third BT procedure: Patients (n=3) required overnight observation: two required admissions for frequent bronchodilator use and one had a lower respiratory tract infection One additional patient developed mild hemoptysis and lower respiratory tract infection

Reference	Adverse Events
Mahajan 2012[14]	First BT: Dyspnea refractory to nebulized albuterol requiring hospitalization Second BT: Atelectasis secondary to mucus plugging requiring hospitalization Third BT: Dyspnea with wheezing requiring hospitalization
Cox 2006[15]	***Device- related Adverse events (%):*** Cough: 21% Dyspnea: 12% Wheezing: 11% Bronchospasm: 10% Fever: 9% Chest discomfort: 8% Mucus production: 7% Throat irritation: 5% Headache: 3% Congestion: 3% Hemoptysis: 3% Localized heat: 2% Retained mucus: 2% Bronchitis: 1% Hypoxemia: 1% Hoarseness: 1% Lower back pain: 1%

BT=bronchial thermoplasty

Appendix D. Minimally Important Differences for Asthma Study Outcomes

It is important to evaluate whether a measured change in an asthma outcome is clinically meaningful as well as statistically significant. Thresholds for determining clinically significant improvement have been established for some measures of asthma control, asthma-related quality of life, pulmonary physiology, and healthcare utilization, and are presented in Table E-1. The data in this table are reproduced with permission from the AHRQ EPC report, "Systematic Review of Intermittent Inhaled Corticosteroids and of Long-acting Muscarinic Antagonists for Asthma," by the University of Connecticut Evidence-based Practice Center.

Table D-1. Thresholds for clinical significance

Instrument/ Outcome	Range (points)	Final score	Threshold
ACT	5 to 25	Well controlled: ≥20 Not well controlled: ≤19	≥12 y: Δ 3 points[16]
ACQ5, ACQ6	0 to 6	Uncontrolled: ≥1.5 Well-controlled: <0.75	≥18 y: Δ 0.5 points[17]
ACQ7	0 to 6	Uncontrolled: ≥1.5 Well-controlled: <0.75	≥6 y: Δ 0.5 points[17,18]
AQLQ,AQLQ(S), AQLQ-mini	1 to 7	Severe impairment = 1 No impairment= 7	≥18 y: Δ 0.5 points[19-21]
AQLQ12+	1 to 7	Severe impairment = 1 No impairment= 7	≥12 y: Δ 0.5 points[22,23]
PAQLQ, PACQLQ	1 to 7	Severe impairment = 1 No impairment= 7	7-17 y: Δ 0.5 points[24,25]
FEV1	Continuous measure, L	NA	≥18 y: -0.2 L[26]
Rescue medication use	Continuous measure, puffs per unit of time	NA	≥18 y: -0.81 puffs/day[26]

ACT=asthma control test; ACQ=asthma control questionnaire; AQLQ=asthma quality of life questionnaire; AQLQ-mini=asthma quality of life questionnaire-15 items; AQLQ(S)=Sydney asthma quality of life questionnaire or Asthma quality of life questionnaire-standardized version AQLQ12+=asthma quality of life questionnaire with standardized activities (12 and older); FEV_1=forced expiratory volume; NA=not available; PACQLQ=pediatric asthma caregiver's quality of life questionnaire; PAQLQ=pediatric asthma quality of life questionnaire

Appendix E. Ongoing Clinical Trials

Table E-1. Ongoing clinical trials

Study Name NCT Identifier Sponsor	Planned Enrollment	Study Design and Objective Primary Endpoints	Estimated Final Completion Date
RISA Extension Study - Long Term Safety NCT00401986 Asthmatx, Inc.	n=15 patients with severe uncontrolled asthma; enrollment limited to patients who participated in the RISA Trial (NCT00214539).	Prospective observational cohort study evaluating long-term safety of BT Primary endpoint: Not provided	No completion date provided; status of trial is listed as unknown, but is linked to Pavord et al. 2013[6]
Efficacy of Bronchial Thermoplasty in Korean NCT02031263 Asan Medical Center	n=9 patients with severe uncontrolled asthma	Open-label, single-arm trial investigating the safety and efficacy of BT in a Korean population Primary endpoint: Changes in the Quality of Life Questionnaire for Adult Korean Asthmatics from baseline to 3 month post-treatment	February 2015 The status of this trial is unknown
Bronchial Thermoplasty: Effect on Neuronal and Chemosensitive Component of the Bronchial Mucosa NCT01839591 Arcispedale Santa Maria Nuova-IRCCS	n=12 patients with severe uncontrolled asthma	Open-label, single-arm trial investigating the safety and efficacy of BT, and the impact of BT on potential sources of bronchospasm in the bronchial mucosa Primary endpoint: Changes in ACT and AQLQ scores from baseline to one year post-treatment	December 2015 The status of this trial is unknown
Spirometric Response to Bronchial Thermoplasty in Patients With Severe Asthma NCT02241265 University of Oklahoma	n=20 patients with severe asthma	Open-label, single-arm trial assessing the impact of BT on FEV_1 Primary endpoint: Changes in prebronchodilator FEV_1 and FVC from baseline to 12 months post-treatment	July 2016 The status of this trial is unknown
Study of Physiopathological Mechanisms and Results of Treatment With Bronchial Thermoplasty in Severe Asthma NCT01974921 Fundació Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	n=15 patients with severe asthma and at least 2 exacerbations in the past year	Open-label, single-arm trial investigating the safety, efficacy, and histology of BT Primary endpoint: Changes in bronchial smooth muscle from baseline to 6 months post-treatment	September 2016 This trial is listed as still recruiting

Study Name NCT Identifier Sponsor	Planned Enrollment	Study Design and Objective Primary Endpoints	Estimated Final Completion Date
Bronchial Thermoplasty for Severe Asthmatics Guided by HXe MRI NCT01832363 Xemed LLC Collaborators: National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) Washington University School of Medicine University of Virginia	n=30 patients with severe asthma	Double-blind (patient, outcome assessor) RCT to determine the utility of using hyperpolarized xenon (HXe) lung MRI to guide BT (HXe-guided BT vs. Standard BT) Primary endpoint: Change in AQLQ scores from baseline to 2.5 years post-treatment	August 2017
Bicentric Prospective Study, Evaluating Bronchial Thermoplasty in a Patient Presenting Severe Uncontrolled Asthma (ASMATHERM) NCT01777360 Assistance Publique - Hôpitaux de Paris **Collaborator:** Boston Scientific Corporation	n=46 patients with severe uncontrolled asthma receiving optimal treatment and experiencing at least one exacerbation requiring oral steroids in the past year	Open-label, single-arm trial designed to determine which patients might be “best candidates” for BT Primary endpoint: Reduction in smooth muscle surface area from baseline to 3 months post-treatment	September 2017
Effect of Bronchial Thermoplasty on Moderate Bronchial Asthma in China NCT02965807 Guangzhou Institute of Respiratory Disease	n=50 patients with moderate asthma	Open-label, single-arm trial investigating the safety and efficacy of BT Primary endpoint: Change in AQLQ from baseline over a 12-month period	December 2017
Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma (TASMA) NCT02225392 Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA) **Collaborators:** ZonMw: The Netherlands Organisation for Health Research and Development The Netherlands Asthma Foundation Boston Scientific Corporation	n=40 patients with severe asthma	Non-blinded RCT comparing patients who undergo immediate BT to a control group (BT delayed until after primary endpoint for immediate BT group—25 weeks) Primary endpoint: Change in ASM mass between BT treated and control (25 weeks)	April 2018

Study Name NCT Identifier Sponsor	Planned Enrollment	Study Design and Objective Primary Endpoints	Estimated Final Completion Date
Bronchial Thermoplasty: Mechanism of Action and Defining Asthma Phenotype NCT02075151 National University Hospital, Singapore	n=50 patients with poorly controlled severe asthma (ACT score <20 even with use of >500 mcg fluticasone/d or >800 mcg budesonide/d)	Open-label, single-arm trial investigating the safety and efficacy of BT Primary endpoint: Change in ACT scores from baseline over a 2-year period	May 2018
Bronchial Thermoplasty in Severe Asthma With Frequent Exacerbations (THERMASCORT) NCT02464995 University Hospital, Strasbourg, France	n=34 with severe asthma and frequent severe exacerbations (4 or more episodes requiring systemic steroids for more than 3 days) in the past year	Non-blinded RCT comparing patients who undergo BT + medical management to those receiving medical management alone Primary endpoint: Change in severe exacerbations from baseline over a 12-month period	November 2018
Bronchial Thermoplasty Global Registry NCT02104856 Boston Scientific Corporation	n=160 patients undergoing BT according to labeled indications	Observational patient registry following patient outcomes in "real world" BT patients Primary endpoint: Proportion of patients experiencing severe exacerbations up to 2 years post-treatment	June 2019
China Alair System Registry Study-CARE Study NCT02206269 BSC International Medical Trading (Shanghai) Co., Ltd.	n=225 patients with severe persistent asthma undergoing BT according to labeled indications	Observational patient registry following patient outcomes in "real world" BT patients Primary endpoint: Rates of severe asthma exacerbations following BT with the Alair System up to 1 year post-treatment	June 2019
Bronchial Thermoplasty for Severe Asthma With Dynamic Hyperinflation (HEAT-SA) NCT02618551 University Hospital, Toulouse	n=15 patients with uncontrolled severe asthma receiving optimal treatment and who experienced at least 2 exacerbations requiring systemic steroids in the past year	Open-label, single-arm trial investigating the impact of BT on dynamic hyperinflation phenomenon, which is a worsening of bronchial obstruction following exercise Primary endpoint: Change in dynamic hyperinflation from baseline to 3 months post-BT	December 2018
Hyperpolarized Magnetic Resonance Imaging in Asthma Pre- and Post-Bronchial Thermoplasty NCT02263794 Dr. Grace Parraga, University of Western Ontario, Canada	n=14 patients with severe asthma	RCT comparing conventional BT to image-guided BT (Outcome assessor-blinded study) Primary endpoint: Whole lung and lobe specific VDP	December 2019

Study Name NCT Identifier Sponsor	Planned Enrollment	Study Design and Objective Primary Endpoints	Estimated Final Completion Date
Bronchial Thermoplasty in Severe Persistent Asthma NCT01350336 Boston Scientific Corporation	n=284 patients with severe persistent asthma	Open-label, single arm post-marketing study intended to assess long-term safety and durability of BT efficacy in patients 18 years and older with severe persistent asthma Primary endpoint: Proportion of patients experiencing severe exacerbations up to 5 years post-treatment	January 2020
A Prospective Observational Study of Biopredictors of Bronchial Thermoplasty Response in Patients With Severe Refractory Asthma (BTR Study) NCT01185275 Washington University School of Medicine Collaborators: The Cleveland Clinic National Jewish Health University of Arizona University of Chicago Louisiana State University Health Sciences Center in New Orleans University of Alabama at Birmingham Creighton University	n=190 patients with severe asthma	Prospective observational cohort study evaluating the role of baseline clinical, physiologic, biologic and imaging markers in clinical response to BT Primary endpoint: Improvement in asthma quality of life 12 months post-treatment	August 2020
Unraveling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma (TASMA) Extension Study NCT02975284 Extension study of NCT02225392 Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA) Collaborator: University Medical Center Groningen	n=40 patients with severe asthma	Prospective observational cohort study evaluating long-term (5 years) clinical outcomes in patients enrolled in the TASMA RCT Primary endpoint: Rates of severe exacerbations, emergency room visits and/or hospitalizations for respiratory symptoms up to 5 years post-treatment	September 2024

ACT=Asthma Control Test; AQLQ=Asthma Quality of Life Questionnaire; ASM=airway smooth muscle; BT=bronchial thermoplasty; FEV_1=forced expiratory volume; FVC=forced vital capacity; HXe MRI=hyperpolarized xenon-129 magnetic resonance imaging; RCT=randomized controlled trial; RISA=Research in Severe Asthma Trial; VDP=ventilation defect percent

Appendix F. Reference List for Appendixes B, C, and D

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