Pulm Ther
https://doi.org/10.1007/s41030-025-00323-0

REVIEW

# Misconceptions of Traits to Predict Response to Inhaled Corticosteroid and Bronchodilator Therapies in Asthma: A Narrative Review

Guy Brusselle · Jodie Crawford · Peter G. Gibson · David Leather · Alison Moore · John J. Oppenheimer · Ian D. Pavord · Marcus Stanaland · Emilio Pizzichini

Received: June 12, 2025 / Accepted: September 19, 2025


## ABSTRACT

The "treatable traits" approach to asthma management has helped revolutionize severe asthma treatment with biologic therapy and includes using biomarkers to identify patients most likely to benefit from a specific treatment. The ability to understand which characteristics predict response to inhaled corticosteroid (ICS) or bronchodilator therapy in mild and moderate-to-severe asthma is also vital for physicians to provide treatment tailored to an individual's phenotype/endotype. Here, we identified studies of inhaled treatments in asthma exploring treatment outcomes based upon subgroups of baseline characteristics, including type 2 biomarkers, asthma attack history, baseline lung function, bronchodilator reversibility, patient age and age at asthma onset, body mass index, smoking status, sex, and ethnicity. We assessed the available evidence regarding the influence of each characteristic on lung function, asthma attacks or asthma control in patients with asthma following treatment with either ICS, ICS/long-acting $\beta_2$-agonist (LABA) therapy, or ICS/LABA/long-acting muscarinic antagonist therapy. Of all the characteristics examined, only type 2

The affiliation of the author Emilio Pizzichini was the affiliation at the time of review article conception.

Prof. G. Brusselle MD, PhD
Ghent University Hospital, Ghent, Belgium

Mrs J. Crawford MSc
Development Statistics, GSK, London, UK

Prof. P. G. Gibson DMed
Department of Respiratory and Sleep Medicine, John Hunter Hospital, Hunter Medical Research Institute, Newcastle, NSW 2305, Australia

Prof. P. G. Gibson DMed
Centres of Excellence in Severe Asthma and Treatable Traits, University of Newcastle, Newcastle, NSW 2308, Australia

Dr D. Leather MBChB · Dr A. Moore PhD (✉) · Prof. E. Pizzichini MD, PhD
Global Medical Affairs, General Medicines, GSK, 79 New Oxford Street, London WC1A 1DG, UK
e-mail: alison.c.moore@gsk.com

Prof. J. J. Oppenheimer MD
Rutgers New Jersey Medical School, Newark, NJ, USA

Prof. I. D. Pavord FMedSci
NIHR Respiratory BRC, Nuffield Department of Medicine, University of Oxford, Oxford, UK

Dr M. Stanaland PharmD, MBA
GSK, Research Triangle Park, Durham, NC, USA

Prof. E. Pizzichini MD, PhD
Federal University of Santa Catarina, Santa Catarina, Brazil

Published online: 01 December 2025

biomarkers (blood eosinophil levels and fractional exhaled nitric oxide) appear to consistently predict treatment response, particularly regarding ICS. For all other characteristics, we found either evidence that baseline values are not predictive of response to inhaled treatment or mixed and inconclusive evidence requiring further investigation.

**Keywords:** Asthma; Biomarker; Eosinophil; Exacerbation; FeNO; Treatment response

**Key Summary Points**

In the authors' experiences, perceptions of the prognostic and predictive value of clinical characteristics and pathophysiological characteristics, in terms of patient response to inhaled maintenance therapies in asthma, varies among clinicians.

This narrative review addresses misconceptions about predictors of response to inhaled maintenance treatment in asthma, including type 2 biomarkers, asthma attack history, baseline lung function, bronchodilator reversibility, patient age and age at asthma onset, body mass index, smoking status, sex, and ethnicity.

Of the characteristics examined, only type 2 inflammation was found to predict treatment response to inhaled maintenance therapies, particularly ICS, in moderate-to-severe asthma.

Future research is needed to determine if other baseline characteristics influence treatment response to inhaled maintenance therapies in patients with asthma.

## INTRODUCTION

Treatment response to inhaled corticosteroid (ICS) and bronchodilator therapy in asthma may be influenced by factors including medication adherence, inhaler technique, comorbidities, and socioeconomic status [1]. Despite a paucity of supportive evidence, widespread perceptions exist among clinicians that some clinical characteristics (i.e., phenotypes) and pathophysiological mechanistic characteristics (i.e., endotypes), in addition to being prognostic of asthma outcomes, may predict treatment responses [2–9]. The "treatable traits" or "personalized medicine" approach represents an evolution in treatment where discriminative factors related to a defined pathogenic mechanism are used to identify which patients will benefit most from targeted treatments, as shown with biologic therapy in severe asthma [7, 10–17]. Previous studies have demonstrated differential responses to inhaled corticosteroids/long-acting $\beta_2$-agonists (ICS/LABA) in patients with asthma based on varying ICS dose [18], or pharmacogenetic mechanisms [19, 20], highlighting the value of identifying reliable biomarkers to optimize outcomes. Understanding which characteristics may predict treatment response is also important when selecting inhaled treatments for mild and moderate-to-severe asthma so that physicians can provide a personalized medicine approach tailored to individual patients.

Maintenance ICS therapy is used to treat airway inflammation and improve symptom control and lung function in patients with asthma. ICS medication is often used in combination with a LABA, as recommended in a stepwise fashion in the Global Initiative for Asthma (GINA) 2025 [1]. Increasing ICS dose is recommended through Steps 3 and 4 (Track 2) for patients uncontrolled on ICS/LABA therapy; however, only 50–70% of adults achieve good disease control even with maximum ICS/LABA dose [18, 21, 22]. An option recommended by GINA at Step 5 is the addition of a long-acting muscarinic antagonist (LAMA) to ICS/LABA for patients with persistent uncontrolled asthma [1]. Until recently, LAMAs were primarily considered beneficial in patients with chronic obstructive pulmonary disease [23, 24]. However, several studies demonstrated that LAMA added to ICS/LABA improves lung function and symptom control and modestly reduces moderate/severe attacks in patients whose asthma was poorly controlled despite medium-dose ICS/LABA therapy [25–28]. As patient responses to

the individual components vary, add-on LAMA (i.e., triple therapy) may provide improvements in lung function and symptom control over ICS/LABA therapy without the need to increase the ICS dose, particularly in the absence of eosinophilic airway inflammation [1, 3, 25, 27].

This review addresses some misconceptions (in the authors' experience) surrounding treatment response predictors in asthma by presenting data from key studies that have investigated the influence of patient characteristics on response. Although numerous studies have been included, particular emphasis is given to the CAPTAIN study [27], which was uniquely designed to address questions around which treatment is most appropriate for specific patient types based on assessment of inflammatory biomarkers and the desired treatment outcome. CAPTAIN was a phase 3A trial comparing the impact of adding a LAMA (umeclidinium; UMEC) to, and/or increasing the ICS dose in an ICS/LABA (fluticasone furoate/vilanterol [FF/VI]) single-inhaler triple therapy (SITT) combination in patients with uncontrolled moderate/severe asthma. Moreover, the eligibility criteria did not include a requirement for an exacerbation in the year prior to the study, making the study population more representative of patients on mid-/high-dose ICS/LABA with uncontrolled asthma [27].

### Search Strategy

The misconceptions about predictors of treatment response in asthma covered in this article were developed through consensus of the authors. A literature search was performed in EMBASE (Elsevier Ltd, Amsterdam, Netherlands) in June 2023 to identify randomized controlled trials (RCTs) or observational studies examining inhaled therapies (ICS/LABA or ICS/LAMA/LABA SITT combinations) for asthma that presented treatment outcomes according to specific patient subgroups or the presence of increased type 2 (T2) inflammatory biomarkers. Of studies of triple therapy, those evaluating multiple inhaler therapy were excluded. As this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, ethical approval was not required.

### Categorical and Continuous Variables

This review includes data from subgroup analyses in which continuous variables were categorized into predefined groups, and data from fractional polynomial models [29, 30] where the continuous variable is analyzed without being categorized. While categorical analyses are statistically simpler and the results more easily interpreted, valuable information may be lost as a result of introducing an arbitrary, single threshold cut-off by dichotomizing the baseline variable of interest [31, 32]. Additionally, categorical analyses assume that patients with a variable just below a threshold cut-off will have different responses than patients whose variable falls just above the threshold, when in fact these responses are likely to be similar [31]. Fractional polynomial analysis avoids this potential information loss, using flexible regression models to provide an accurate approximation of the relationship between the continuous variable of interest and the response.

## MISCONCEPTIONS ABOUT PREDICTORS OF TREATMENT RESPONSE

### Misconception: T2 Inflammatory Biomarkers Are Only Predictive of Treatment Response with Biologics in Severe Asthma

#### *Evidence: T2 Inflammatory Biomarkers Are Also Useful in Informing Choice of Inhaled Therapy in Mild and Moderate-to-Severe Asthma*

Total blood eosinophil (EOS) counts and fractional exhaled nitric oxide (FeNO) have been identified as complementary biomarkers of T2 airway inflammation in patients with asthma. The T2 "high" endotype is typically associated with blood eosinophilia and elevated FeNO levels compared with the T2 "low" endotype [33].

Additionally, among patients with asthma, higher blood EOS counts have been associated with risk of future severe attacks [34], with measurement of these biomarkers forming the basis of early iterations of a risk calculator for future asthma attacks [35].

There is a wealth of data examining the predictive value of T2 biomarkers on response to inhaled asthma therapy (summarized in Table 1). Given the wide range of study types, differing methodologies, and some cases of post hoc analyses (i.e., likely not statistically powered), it is unsurprising that there is variation in the findings. Notably, several publications [3, 36–42] support findings from the CAPTAIN study that show that T2 biomarkers (particularly blood EOS and FeNO) hold the most predictive value for ICS treatment response versus other baseline characteristics. However, it should be noted that this observation is based on separate subgroup analyses rather than a single model assessing all characteristics simultaneously.

In CAPTAIN post hoc analyses, response to inhaled therapy varied according to baseline blood EOS and FeNO levels [27] (Fig. 1). The addition of UMEC to FF/VI numerically reduced moderate/severe attack rates primarily in patients with lower levels of these biomarkers, although this was to a much smaller magnitude than when the FF dose was doubled in patients with high T2 endotype, and 95% confidence intervals (CI) were wide. This aligned with results from the prespecified analyses regardless of T2 biomarker status for both triple versus dual therapy and high- versus low-dose ICS. Compared with FF/VI 100/25 µg, the adjusted rate ratio (aRR; 95% CI) was 0.78 (0.61–1.01) in the FF/UMEC/VI 100/62.5/25 µg group and 0.88 (0.68–1.13) in the FF/UMEC/VI 100/31.25/25 µg group; compared with FF/VI 200/25 µg, the aRR was 0.97 (0.73–1.28) in the FF/UMEC/VI 200/62.5/25 µg group, and 1.08 (0.82–1.42) in the FF/UMEC/VI 200/31.25/25 µg group. Mean (95% CI) annualized attack rates were numerically lower with FF 200 µg-containing therapies compared with FF 100 µg-containing therapies (FF/VI 200/25 µg: 0.57 [0.47–0.69] vs. 100/25 µg: 0.87 [0.73–1.04]; FF/UMEC/VI 200/62.5/25 µg: 0.55 [0.45–0.67]) vs. 100/62.5/25 µg: 0.68 [0.56–0.82]; FF/UMEC/VI 200/31.25/25 µg: 0.61 [0.50–0.74] vs. 100/31.25/25 µg: 0.76 [0.64–0.92]) [27]. Of note, the rates of exacerbations observed in the CAPTAIN trial were low overall, regardless of T2 status, likely due to inclusion criteria not requiring a history of exacerbations, and the inclusion of a stabilization period with FF/VI (100/25 µg) prior to randomization.

Among patients with high baseline levels of both biomarkers, a smaller proportion (13%) in the FF 200 µg dose group had a severe attack versus the FF 100 µg dose group (33%; Fig. 2) [27]; however, numbers were small ($n = 71$ and 67, respectively), hence these results should be interpreted with caution. CAPTAIN was not sufficiently powered to detect a difference in annualized attack rates between treatment arms, primarily due to a lower attack rate than assumed in the power calculations. Additionally, evidence of a prior attack was not required for study entry (thus, unlike other triple therapy studies [e.g., TRIGGER, TRIMARAN [43]], CAPTAIN was not enriched for patients likely to experience asthma attacks). In a post hoc analysis of CAPTAIN (intent-to-treat population: $n = 2436$), baseline levels of serum immunoglobulin E (IgE) measured as a trichotomous variable ($\leq 85, > 85 – \leq 306, > 306$ KU/L) did not appear to have any predictive value on treatment response from adding UMEC and/or doubling FF dose, despite IgE also being considered as a marker of T2 inflammation [44].

Like CAPTAIN, several other studies found that T2 biomarker status is predictive of ICS therapy response. In a study of adults with respiratory symptoms without a confirmed asthma diagnosis, FeNO measured as a trichotomous variable ($\leq 25$, 26–49, $\geq 50$ parts per billion) was shown to predict the efficacy of beclometasone dipropionate (BDP) versus placebo; higher baseline FeNO values were associated with an increased likelihood of a positive treatment response as assessed by lung function (forced expiratory volume in 1 s [$FEV_1$]) and asthma control (Asthma Control Questionnaire [ACQ-7]) [37]. Similarly, in the SIENA study, sputum

**Table 1** Relationship between T2 biomarkers and response to inhaled treatment, indicating if a T2 biomarker is predictive (P) of treatment response, not predictive (NP) of treatment response, or if predictive value for treatment response is mixed/unclear (M/U); dash indicates T2 biomarker not measured

| Reference(s) | Study name/Trial registry number | Study type | Patient Population | Treatment Strategy | Outcomes | T2 biomarker | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Blood EOS | Sputum EOS | FeNO | IgE |
| **Adding a LAMA** | | | | | | | | | |
| Lee et al. 2021 [27], Boulet et al. 2024 [44] | CAPTAIN NCT02924688 | Phase 3A | Uncontrolled | FF/UMEC/VI vs. FF/VI | Lung function | *NP* | – | *NP* | *NP* |
| | | | | | Attacks | *NP* | – | *NP* | *NP* |
| | | | | | Asthma control | – | – | – | *NP* |
| Singh et al. 2020 [43] | TRIMARAN NCT02676076 | Phase 3 | Uncontrolled | BDP/GLY/FOR vs. BDP/FOR | Lung function | *P* | – | – | – |
| | | | | | Attacks | *NP* | – | – | – |
| Singh et al. 2020 [43] | TRIGGER NCT02676089 | Phase 3 | Uncontrolled | BDP/GLY/FOR vs. BDP/FOR | Lung function | *NP* | – | – | – |
| | | | | | Attacks | *NP* | – | – | – |
| Peters et al. 2013 [2] | TALC NCT00565266 | Phase 3 | Uncontrolled | BDP/TIO vs. BDP/SAL | Lung function | – | *NP* | *NP* | *NP* |
| | | | | | Asthma control | – | *NP* | *NP* | *NP* |
| Kostikas et al. 2023 [46] | NCT02571777 | Phase 3 | Uncontrolled | MF/IND/GLY vs. MF/IND and FLU/SAL | Lung function | *NP* | – | – | – |
| | | | | | Attacks | *NP* | – | – | – |

**Table 1** continued

| Reference(s) | Study name/Trial registry number | Study type | Patient Population | Treatment Strategy | Outcomes | T2 biomarker | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Blood EOS | Sputum EOS | FeNO | IgE |
| **Increasing ICS dose** | | | | | | | | | |
| Lee et al. 2021 [27], Boulet et al. 2024 [44] | CAPTAIN NCT02924688 | Phase 3A | Uncontrolled | FF/VI 200/25 µg vs. 100/25 µg or FF/UMEC/VI 200/62.5/25 µg vs. 100/62.5/25 µg | Lung function | *P* | – | *P* | *NP* |
| | | | | | Attacks | *P* | – | *P* | *NP* |
| | | | | | Asthma control | – | – | – | *NP* |
| Pavord et al. 2020 [74], Beasley et al. 2019 [53] | Novel START ACTRN12615000999538 | Phase 3 | Mild | As-needed BUD/FOR vs. as-needed SABA | Attacks | *NP* | – | *NP* | – |
| | | | | | Asthma control | *NP* | – | *NP* | – |
| | | | | Maintenance BUD + as-needed SABA vs. as-needed SABA | Attacks | *M/U* | – | *M/U* | – |
| | | | | | Asthma control | *NP* | – | *NP* | – |
| Rhyou et al. 2020 [36] | N/A | Retrospective real-world | Newly diagnosed (ICS naïve) | Moderate ICS | Attacks | *P* | *NP* | *NP* | *NP* |
| Krishnan et al. 2022 [42] | SIENA NCT02066298 | Phase 3 | Mild persistent | MF vs. PBO | Asthma control[a] | *P* | *P* | *P* | *NP* |
| Price et al. 2018 [37] | NCT02294279 | Phase 4 | Undiagnosed | BDP vs. PBO | Lung function | – | – | P | – |
| | | | | | Asthma control | – | – | P | – |

**Table 1** continued

| Reference(s) | Study name/Trial registry number | Study type | Patient Population | Treatment Strategy | Outcomes | T2 biomarker | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Blood EOS | Sputum EOS | FeNO | IgE |
| Dunn et al. 2015 [38] | Combined analysis of 10 trials | N/A | Mild to moderate | Treatment unspecified: comparison between treatment failures and responders | Treatment failure[b] | *P* | *NP* | *NP* | *P* |
| Syk et al. 2013 [39] | NOAK/NCT00421018 | N/A | Atopic asthma | ICS treatment vs. regular care-guided treatment | Lung function | – | – | *NP* | – |
| | | | | | Attacks | – | – | *P* | – |
| | | | | | Asthma control | – | – | *P* | – |
| Martin et al. 2007 [5] | PRICE | Multicenter | Not defined | BDP | Lung function | – | *M/U* | *NP* | *NP* |
| Smith et al. 2005 [40] | – | N/A | Undiagnosed | FP vs. placebo | Lung function | – | – | *P* | – |
| Szefler et al. 2002 [3] | – | – | Persistent (ICS naïve) | BDP vs. FP | Lung function | – | – | *P* | – |
| Hao et al. 2021 [41][c] | ChiCTR2000029065 | Prospective cohort | Symptomatic | ICS/LABA | Lung function | – | – | *P* | – |
| Israel et al. 2022 [75] | – | Pragmatic, randomized | Uncontrolled | As-needed BDP + usual care vs. usual care | Asthma attacks | *NP* | – | *NP* | – |

[a]Findings in adults only. There was some indication of predictive response of IgE in adolescents but not adults; [b]Treatment failures defined as any of the following: an asthma exacerbation requiring oral corticosteroid or emergency room visit, worsening of lung function, increased use of asthma medication, or physician clinical judgement; [c]Joint model with bronchodilator reversibility (improved $FEV_1 > 3.5\%$ with salbutamol) and elevated FeNO (> 33 ppb)

*BDP* beclomethasone dipropionate; *BUD* budesonide; *EOS* eosinophil; *FeNO* fractional exhaled nitric oxide; *$FEV_1$* forced expiratory volume in 1 s; *FF* fluticasone furoate; *FLU* fluticasone; *FOR* formoterol fumarate; *FP* fluticasone propionate; *GLY* glycopyrronium; *ICS* inhaled corticosteroid; *IgE* immunoglobulin E; *IND* indacaterol; *LABA*, long-acting $\beta_2$-agonist; *LAMA* long-acting muscarinic antagonist; *MF* mometasone furoate; *N/A* not applicable; *PBO* placebo; *ppb* parts per billion; *SABA* short-acting $\beta_2$-agonist; *SAL* salmeterol; *T2* type 2; *TIO* tiotropium; *UMEC* umeclidinium; *VI* vilanterol

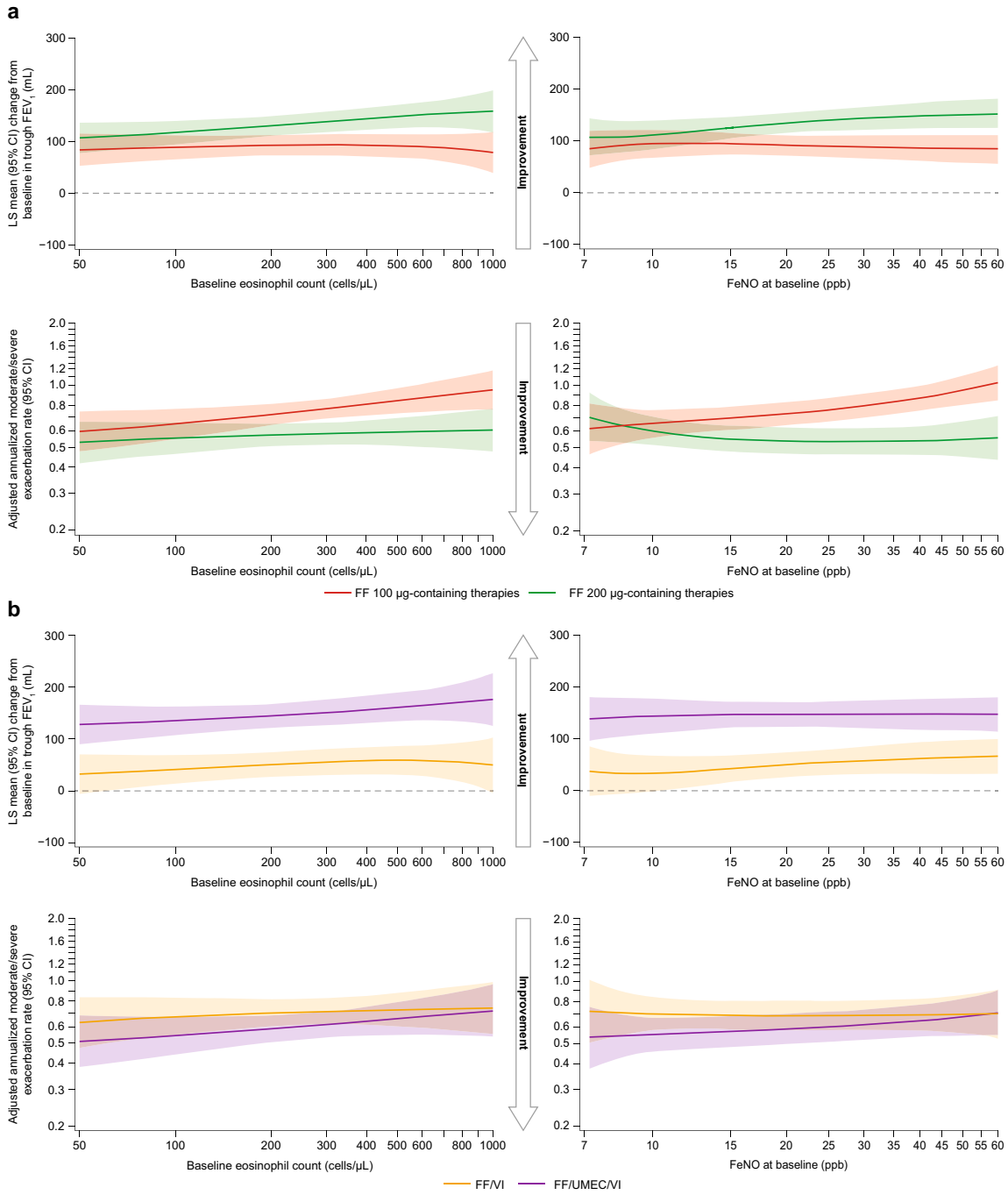


**Fig. 1** Association between baseline blood eosinophils and fractional exhaled nitric oxide and the effects of doubling FF dose (**a**) and adding UMEC (**b**) on trough $FEV_1$ (at week 24) and moderate and/or severe exacerbation rates (weeks 1–52) in the CAPTAIN study. Post hoc pooled analysis of the CAPTAIN study; *CI* confidence interval; *FeNO* fractional exhaled nitric oxide; *$FEV_1$* forced expiratory volume in 1 s; *FF* fluticasone furoate; *LS* least squares; *ppb* parts per billion; *UMEC* umeclidinium; *VI* vilanterol. Reprinted from Lancet Respir Med; Lee, L.A., et al., Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomized, phase 3A trial, 9(1): p 69–84, Copyright (2021), with permission from Elsevier

and blood EOS and FeNO, measured as continuous variables, were predictive of the efficacy of mometasone furoate (MF) versus placebo in patients with uncontrolled, mild, persistent asthma, assessed by a composite asthma control outcome (treatment failure, asthma control days, and $FEV_1$) [42].

However, adding LAMA to ICS/LABA therapy was found to be beneficial regardless of T2 inflammation status in most studies. For example, in the phase 3 TRIGGER study, blood EOS levels (≤300 and>300 cells/μl) had no predictive value on the relative efficacy of BDP/glycopyrronium (GLY)/formoterol fumarate (FOR) versus BDP/FOR (both high-dose BDP) on lung function (trough $FEV_1$) at week 26 [43]. In a similar study (TRIMARAN), greater improvement in trough $FEV_1$ at week 26 was seen with BDP/GLY/FOR versus BDP/FOR (both mid-dose BDP) in the lower versus higher blood EOS subgroup (though this was a post hoc, dichotomous analysis, rather than a continuous variable analysis) [43]. An exploratory follow-up analysis of a large phase 3 study examining LAMA or short-acting $\beta_2$-agonist (SABA) therapy as add-on to ICS (TALC [45]) demonstrated no association between positive clinical response to add-on tiotropium and sputum EOS and FeNO [2]. This was also demonstrated in a study evaluating LAMA as part of SITT versus ICS/LABA therapies (IRIDIUM [46]), reporting that T2 biomarkers provided no predictive value for added LAMA treatment responses in lung function and symptoms (Table 1).

Despite the evidence supporting the predictive value of T2 biomarkers on ICS response, they have not been routinely measured in many phase 3 trials or integrated in clinical care. For example, a recent post hoc analysis from the IRIDIUM study examined the effect of baseline EOS levels (≤300 and>300 cells/μl) on the efficacy of LAMA (GLY) in addition to ICS/LABA (MF/indacaterol acetate [IND]), but did not examine the effect on ICS response [46]. In conclusion, T2 inflammatory biomarkers are useful in informing choice of inhaled therapy in mild and moderate-to-severe asthma and should be considered a routine measure in clinical trials.

## Misconception: Attack History Predicts Response to Inhaled Treatment in Asthma

### *Evidence: Attack History Does Not Appear to Predict Response to Inhaled Treatment in Asthma*

A history of severe asthma attacks has been shown to predict future attacks in prospective studies conducted in the USA and Japan [8, 47]. Risk score calculators taking into account previous severe attacks and T2 inflammation may therefore be helpful when assessing future attack risk [48]. However, data regarding attack history as a predictor of inhaled treatment response are inconsistent.

CAPTAIN reported treatment outcomes for subgroups of patients with a history of≥1 severe attack at baseline versus those without a prior severe attack [49]. Addition of UMEC to FF/VI resulted in improvements in trough $FEV_1$ and $FEV_1$ 3 h post dose (post hoc analysis) in both subgroup populations (consistent across FF 100 μg- and FF 200 μg-containing therapies) and attack rates (FF 100 μg-containing therapies), with a possible trend for greater numerical improvements in these outcomes in patients without a history of severe attacks (prespecified analysis). Doubling the FF dose was associated with improved lung function and a reduction in attack rates regardless of severe attack history (post hoc analysis). These findings are supported by other studies, with attack history having no clear predictive value in terms of treatment response (Table 2). This is consistent with the heterogenous nature of attacks, with the majority of events unrelated to T2 inflammation [50], but rather primarily associated with viral infections [51]. However, although attack history may not influence response to inhaled asthma treatments in terms of relative risk reduction, it will impact the absolute risk and thus the number of patients needed to treat to prevent a severe attack.

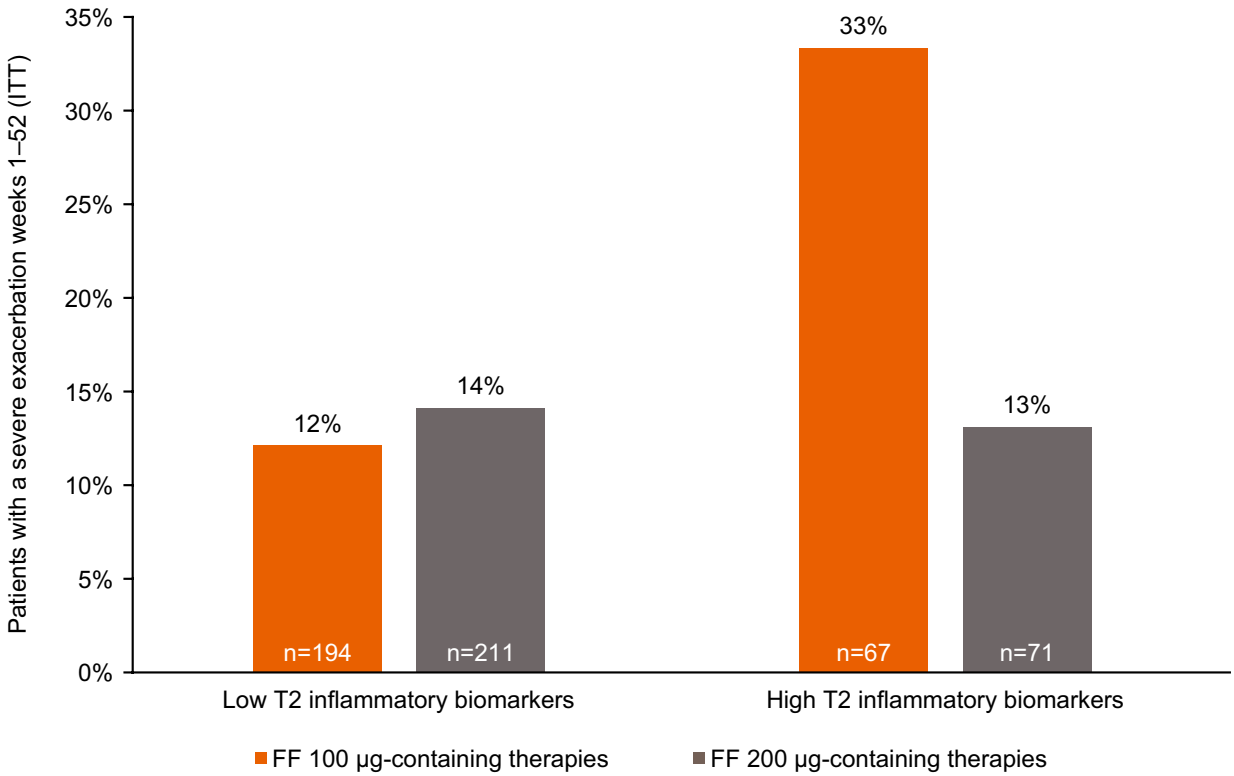


**Fig. 2** Impact of FF dose on proportion of patients with T2 low or T2 high asthma experiencing severe exacerbations (weeks 1–52) in the CAPTAIN study; post hoc pooled analysis of the CAPTAIN study; *n* = patients with analyzable data. Low T2 inflammatory biomarkers defined as eosinophils < 150 cells/µl and FeNO < 20 ppb at baseline. High T2 inflammatory biomarkers defined as eosinophils ≥ 300 cells/µl and FeNO > 50 ppb. FF 100 µg-containing therapies: pooled FF/VI 100/25 µg + FF 100 µg/UMEC 31.25 + 62.5 µg/VI. FF 200 µg-containing therapies: pooled FF/VI 200/25 µg + FF 200 µg/UMEC 31.25 + 62.5 µg/VI. *FeNO* fractional exhaled nitric oxide, *FF* fluticasone furoate, *ppb* parts per billion, *ITT* intent-to-treat, *UMEC* umeclidinium, *T2* type 2, *VI* vilanterol

## Misconception: Treatment Response to Inhaled Therapies Can Be Affected by Lung Function or Bronchodilator Reversibility

### *Evidence: Baseline Lung Function Does Not Appear To Predict Treatment Response, and Evidence Is Inconclusive as to Whether Bronchodilator Reversibility Influences Responses to Inhaled Treatments*

Although there is some evidence from several small studies that compared with patients with greater lung function, those with reduced baseline lung function may have a greater response to ICS [3, 5] and ICS/LABA ± LAMA [2, 52], larger studies have not found an association (Table 2), and interpretation of the findings is not straightforward because of potential confounding by the ceiling effect. Several studies showed that treatment efficacy was independent of baseline lung function [4, 53]. Post hoc analyses from CAPTAIN supported these findings, whereby baseline lung function and bronchodilator reversibility did not impact treatment response to inhaled therapy [44]. However, since inclusion in the CAPTAIN trial required a reversibility of ≥ 12% of prebronchodilator $FEV_1$ and ≥ 200 mL [27], the full effect of reversibility on response to inhaled therapy could not be examined.

**Table 2** Summary of key studies reporting the influence of baseline characteristics on response to inhaled treatment in asthma

| Baseline characteristic | Predictive value | Treatment outcome | | | | | |
|---|---|---|---|---|---|---|---|
| | | Lung function | | Attacks | | Asthma control | |
| | | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA |
| Lung function | Predictive | Szefler et al. (2002) [3],[a] Martin et al. (2007) [5], Ohwada et al. (2011) [54][a] | Peters et al. (2013) [2] | – | – | – | – |
| | Non-predictive | Papi et al. (2021) [76] | Casale et al. (2019) [4], Boulet et al. (2024) [44], Papi et al. (2021) [76], Van Zyl-Smit et al. (2023) [77] | Boulet et al. (2024) [44], Beasley et al. (2019) [53],[b] Papi et al. (2022) [78] | Casale et al. (2019) [4], Boulet et al. (2024) [44], Van Zyl-Smit et al. (2023) [77] | Beasley et al. (2019) [53][b] | Peters et al. (2013) [2], Casale et al. (2019) [4] |
| | Mixed/unclear | – | Singh et al. (2020) [52] | – | Singh et al. (2020) [52] | – | – |
| Reversibility | Predictive | Szefler et al. (2002) [3],[a] Martin et al. (2007) [5], Hao et al. (2021) [41], Ohwada et al. (2011) [54][a] | Peters et al. (2013) [2] | – | Singh et al. (2020) [43] | – | – |
| | Non-predictive | Lee et al. (2021) [27] | Casale et al. (2019) [4], Lee et al. (2021) [27], Singh et al. (2020) [43] | Lee et al. (2021) [27] | Lee et al. (2021) [27] | – | Peters et al. (2013) [2] |

Table 2 continued

| Baseline characteristic | Predictive value | Treatment outcome | | | | | |
|---|---|---|---|---|---|---|---|
| | | Lung function | | Attacks | | Asthma control | |
| | | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA |
| | Mixed/unclear | – | – | – | Casale et al. (2019) [4] | – | Casale et al. (2019) [4] |
| Age | Predictive | Dunn et al. (2015) [38][b] | – | Dunn et al. (2015) [38][b] | – | – | Peters et al. (2013) [2] |
| | Non-predictive | Martin et al. (2007) [5], Boulet et al. (2020) [79], | Peters et al. (2013) [2], Casale et al. (2019) [4], Kerstjens et al. (2020) [26], Singh et al. (2020) [43], Boulet et al. (2024) [44], Doherty et al. (2020) [70], Boulet et al. (2020) [79] | Boulet et al. (2024) [44], Beasley et al. (2019) [53],[b] Papi et al. (2022) [78] | Casale et al. (2019) [4], Kerstjens et al. (2020) [26], Singh et al. (2020) [43] | Boulet et al. (2024) [44], Beasley et al. (2019) [53],[b] Haughney et al. (2011) [69] | Casale et al. (2019) [4], Boulet et al. (2024) [44], Doherty et al. (2020) [70] |
| | Mixed/unclear | – | Kerstjens et al. (2022) [80] | Boulet et al. (2020) [79] | Boulet et al. (2020) [79], Boulet et al. (2024) [44], Kerstjens et al. (2022) [80] | – | – |
| Age at onset | Predictive | Szefler et al. (2002) [3][a] | – | – | – | – | – |

Table 2 continued

| Baseline characteristic | Predictive value | Treatment outcome | | | | | |
|---|---|---|---|---|---|---|---|
| | | Lung function | | Attacks | | Asthma control | |
| | | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA |
| | Non-predictive | Boulet et al. (2024) [44] | Casale et al. (2019) [4], Boulet et al. (2024) [44] | Boulet et al. (2024) [44] | Casale et al. (2019) [4] | – | Casale et al. (2019) [4], Boulet et al. (2024) [44] |
| | Mixed/unclear | Boulet et al. (2024) [44] | Boulet et al. (2024) [44], Kerstjens et al. (2022) [80] | Boulet et al. (2024) [44] | Boulet et al. (2024) [44] | Boulet et al. (2024) [44] | – |
| BMI | Predictive | Sutherland et al. (2009) [59] | – | – | – | Peters-Golden et al. (2006) [60] | – |
| | Non-predictive | Peters-Golden et al. (2006) [60] | Peters et al. (2013) [2], Casale et al. (2019) [4], Singh et al. (2020) [43], Maselli et al. (2021) [58] | Israel et al. (2022) [75] | Casale et al. (2019) [4], Maselli et al. (2021) [58] | – | Peters et al. (2013) [2] |
| | Mixed/unclear | – | Kerstjens et al. (2022) [80] | – | Singh et al. (2020) [43] | – | Casale et al. (2019) [4] |

Table 2 continued

| Baseline characteristic | Predictive value | Treatment outcome | | | | | |
|---|---|---|---|---|---|---|---|
| | | Lung function | | Attacks | | Asthma control | |
| | | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA |
| Smoking status | Predictive | Chalmers et al. (2002) [63], Chaudhuri et al. (2003) [64], Tomlinson et al. (2005) [65], Lazarus et al. (2007) [66], Pedersen et al. (2007) [68] | – | Tomlinson et al. (2005) [65] | – | Chaudhuri et al. (2003) [64] | |
| | Non-predictive | Brusselle et al. (2012) [81] | Casale et al. (2019) [4], Singh et al. (2020) [43] | Beasley et al. (2019) [53],[b] Papi et al. (2022) [78], Israel et al. (2022) [75], Papi et al. (2020) [82] | Casale et al. (2019) [4], Singh et al. (2020) [43] | Beasley et al. (2019) [53],[b] Woodcock et al. (2017) [67], Brusselle et al. (2012) [81] | Casale et al. (2019) [4] |
| | Mixed/unclear | – | – | – | – | – | – |
| Sex | Predictive | – | – | – | – | – | – |
| | Non-predictive | Martin et al. (2007) [5], Dunn et al. (2015) [38][b] | Peters et al. (2013) [2], Casale et al. (2019) [4], Singh et al. (2020) [43] | Dunn et al. (2015) [38],[b] Beasley et al. (2019) [53][b] | Casale et al. (2019) [4], Singh et al. (2020) [43] | Dunn et al. (2015) [38],[b] Beasley et al. (2019) [53][b] | Peters et al. (2013) [2], Casale et al. (2019) [4] |
| | Mixed/unclear | – | Papi et al. (2022) [83] | Papi et al. (2022) [78] | – | – | – |
| Ethnicity | Predictive | – | – | – | – | – | – |

Table 2 continued

| Baseline characteristic | Predictive value | Treatment outcome | | | | | |
|---|---|---|---|---|---|---|---|
| | | Lung function | | Attacks | | Asthma control | |
| | | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA | ICS or ICS/LABA | ICS/LABA/LAMA |
| | Non-predictive | Martin et al. (2007) [5], Hardy et al. (2020) [84] | Peters et al. (2013) [2], Casale et al. (2019) [4] | Hardy et al. (2020) [84] | Casale et al. (2019) [4] | Hardy et al. (2020) [84] | Peters et al. (2013) [2] |
| | Mixed/unclear | – | – | – | – | – | Casale et al. (2019) [4] |
| Attack history | Predictive | – | – | – | – | – | – |
| | Non-predictive | Oppenheimer et al. (2020) [49] | Kerstjens et al. (2020) [26] | Oppenheimer et al. (2020) [49], Beasley et al. (2019) [53],[b] Papi et al. (2022) [78], Israel et al. (2022) [75] | Kerstjens et al. (2020) [26] | Beasley et al. (2019) [53],[b] Woodcock et al. (2017) [67] | – |
| | Mixed/unclear | – | Singh et al. (2020) [43], Oppenheimer et al. (2020) [49] | – | Singh et al. (2020) [43], Oppenheimer et al. (2020) [49] | – | – |

Non-significant data indicating predictive value have been classed as mixed/unclear; An en dash (–) indicates where data are not available

[a]Reference [3, 54] study with ICS-naïve patients; [b]References [38, 53] reported as treatment failure, defined as any of the following: an asthma exacerbation requiring oral corticosteroid or emergency room visit, worsening of lung function, increased use of asthma medication, or physician clinical judgment

*BMI* body mass index; *ICS* inhaled corticosteroid; *LABA* long-acting, $\beta_2$-agonist; *LAMA* long-acting muscarinic antagonist

Along with CAPTAIN [44], findings from the MezzoTinA, TRIMARAN, and TRIGGER studies showed that the effect of dual or triple therapy on lung function was independent of baseline bronchodilator reversibility [4, 43]. However, in the TRIMARAN and TRIGGER studies, patients with higher reversibility at baseline achieved the greatest reductions in moderate and severe attacks with BDP/GLY/FOR versus BDP/FOR [43]. It should be noted that, similar to CAPTAIN, a degree of bronchodilator reversibility was needed for inclusion in these studies, so data on the relationship between the full range of baseline bronchodilator reversibility and treatment responses are lacking. Regardless, in the authors' experience, bronchodilator reversibility to a SABA is typically not predictive of treatment benefit nor the type of inflammatory response in the airways. While some evidence suggests it may be predictive of improvements in lung function with ICS/LABA therapy in ICS-naïve patients [54], collectively, published data for inhaled triple and dual therapies do not appear to support the perception that bronchodilator reversibility is predictive of treatment response (Table 2). It should be noted that the lung function of small airways was not assessed, as testing for lung function in these studies was done via spirometry testing rather than small airways oscillometry.

## Misconception: Treatment Response to Inhaled Therapies Is Diminished in Patients with Obesity or Smokers

### *Evidence: Obesity Is Not a Reliable Predictor of Treatment Response, and Further Evidence Is Required to Determine Whether Smoking Influences Response to Inhaled Treatments*

Several studies have suggested that obesity is associated with reduced lung function, poor asthma control, worsening of asthma symptoms [55, 56] and a more severe asthma phenotype [56, 57]. Perceptions exist that obesity may result in a reduced response to inhaled therapies compared with response in non-obese patients, though the evidence is inconclusive (Table 2). Prespecified analyses from CAPTAIN showed that adding UMEC to FF 100 µg/VI resulted in numerical reductions in moderate/severe attacks in the obese subgroup, similar to the non-obese group [58], although the study population was not enriched for exacerbations. In addition, the smaller sample size in the obese versus non-obese group should be noted along with the higher attack rate typically observed in patients with obesity at baseline. Other studies reported smaller improvements in lung function [59] and asthma control [60] in patients who were overweight/with obesity versus patients of normal body weight, but this finding was not consistent across literature. Data from CAPTAIN indicate that obesity does not influence treatment response in terms of lung function regardless of the treatment strategy assessed [58]. Additionally, the efficacy of inhaled therapy assessed by lung function, asthma control and time to severe attack in the MezzoTinA studies [4], and by lung function and asthma attacks in the TRIMARAN and TRIGGER studies [43], was generally independent of baseline body mass index (BMI). Overall, these findings show that the impact of obesity on treatment outcomes is not well established and may be complicated by the different inflammatory phenotypes seen in patients with obesity with asthma [61]. While further research may be warranted, obesity is unlikely to be a reliable predictor for treatment outcomes.

Increased airway inflammation associated with smoking can also be problematic among patients with asthma, leading to reduced ICS effects [62]. Numerous studies suggest that smoking reduces a patient's response to ICS [63–66], for example, as shown in a study demonstrating reduced $FEV_1$ (L) after 8 weeks of treatment with beclomethasone in smokers (0.06 [95% CI, 0.04–0.16]) compared with non-smokers (0.17 [95% CI, 0.08–0.26]), $p=0.09$ [67]. However, findings from the Salford Lung Study showed that the efficacy of FF/VI was independent of smoking status [67]. Additionally, current smokers are often excluded from RCTs, so data are largely constrained to ex-smokers with potentially limited smoking history. However, several publications suggest that smoking history can influence response to inhaled asthma treatment (Table 2). In the 1-year, randomized

Gaining Optimal Asthma controL (GOAL) study, non-smokers demonstrated numerically greater improvements in lung function in response to FP and FP/salmeterol (SAL) versus former and current smokers [68]. In CAPTAIN prespecified analyses [27], there was a numerical trend for a greater reduction in moderate/severe attacks among ex-smokers versus patients without smoking history after adding UMEC to FF/VI, although, as with other studies, the number of ex-smokers was low versus the other subgroups, and smoking history was limited (i.e., < 10 pack years). In contrast, other studies with inhaled therapy, including the MezzoTinA-asthma and the TRIMARAN and TRIGGER studies showed that treatment outcomes with ICS + LAMA and ICS/LAMA/LABA, respectively, were independent of smoking status [4, 43]. Collectively, these findings warrant further research to determine whether smoking history should be considered when tailoring treatment.

**Misconception: The Effect of Inhaled Therapies Is Impacted by Baseline Characteristics (Or Non-Modifiable Traits)**

***Evidence: Patient Age, Age of Asthma Onset, Sex and Ethnicity Do Not Appear to Reliably Predict Treatment Response to Inhaled Drugs in Asthma***

Although there is a perception that treatment response worsens with age, most published data indicate that inhaled therapies are beneficial regardless of age or age at disease onset (Table 2). Findings from several studies including TRIMARAN, TRIGGER [43], the IRIDIUM [26], the EUROSMART study [69], and the MezzoTinA-asthma studies [4, 70] indicate that treatment effect is largely independent of age. Notably, post hoc analyses from the CAPTAIN study showed that age and age of asthma onset do not predict response to inhaled therapy [44]. There are a small number of studies [2, 38, 44] that suggest treatment effect is pronounced in younger patients; however, further investigations are required to draw definitive conclusions. Taken with the wealth of clinical trial data, it is unlikely that age is a reliable predictor for inhaled treatment outcomes. Findings were similar with age of asthma onset (Table 2), though data for this variable were more limited and generally assessed post hoc.

Differences in asthma phenotypes are observed between male and female patients, in both children and adults [71]. Similarly, prevalence and severity of asthma varies among different ethnic groups, potentially due to genetic variation and differences in socioeconomic status, among other factors [72]. While it is feasible to consider that these differences could potentially manifest in differential responses to asthma treatment, the evidence shown in Table 2 indicates that sex and ethnicity are unlikely to impact response to inhaled therapies.

## CONCLUSIONS

Measurement of T2 inflammatory biomarkers such as blood EOS and FeNO has revolutionized the treatment of severe asthma using biologics, allowing for the prediction of a patient's likely response to treatment. Although such measurements are not currently widely used in routine clinical practice (beyond phenotyping for biologics), data indicate that a similar approach should be used to inform choice of inhaled treatment for patients with less severe asthma [35], whereby patient phenotype would guide treatment decisions, ushering in the era of personalized medicine in asthma. Numerous studies have provided evidence that T2 inflammatory biomarkers may be associated with future risk of attack, especially in patients with not well-controlled asthma [34, 35]. In addition, higher levels of T2 inflammatory biomarkers are indicative of patients who are likely to benefit from increasing ICS dose. However, for a subset of patients with severe asthma but low T2 inflammation, alternative biomarkers and treatment strategies will be needed to provide optimal personalized care [73]. While some published studies suggest that baseline demographic characteristics such as sex, ethnicity, age, and smoking status, and physiological characteristics such as BMI, age at asthma onset, and bronchodilator reversibility do not appear to reliably predict inhaled therapy response, the TALC study suggests that these characteristics may have

predictive value [2]. It should be noted that the majority of clinical studies assessed here reported use of daily ICS maintenance therapy rather than maintenance and reliever therapy, which is the preferred treatment strategy recommended by GINA [1]. The misconceptions discussed in this review were based on a consensus view from all authors and the literature search conducted here highlights areas of conflicting evidence. Future research is needed to confirm some of these findings and to help further define a reliable approach for predicting response to inhaled therapies in asthma.

## ACKNOWLEDGEMENTS

The authors thank the participants of the studies included in this narrative review.

***Medical Writing, Editorial, and Other Assistance.*** Editorial support (in the form of writing assistance, including preparation of the draft manuscript under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing, and referencing) was provided by Hayley Butler, PhD, and Aisling Towell, PhD, of Fishawack Indicia Ltd, UK, part of Avalere Health, and was funded by GSK.

***Author Contributions.*** All authors contributed to the writing and reviewing of the manuscript and have given final approval for the version to be published. Guy Brusselle, Jodie Crawford, Peter G. Gibson, David Leather, Alison Moore, John J. Oppenheimer, Ian D. Pavord, and Marcus Stanaland contributed to data analysis and interpretation. Emilio Pizzichini contributed to study conception and design, and data analysis and interpretation.

***Funding.*** This review was supported by GSK and GSK funded the journal's Rapid Service and Open Access Fee.

***Data Availability.*** Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

***Declarations***

***Conflict of interest.*** Guy Brusselle has received speaker fees from and served on advisory boards for AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, MSD, Novartis, and Sanofi. Peter G. Gibson has received speaker's fees, and research grants from AstraZeneca, Chiesi, GSK, and Novartis. John J. Oppenheimer has served on adjudication committees or data and safety monitoring boards for AstraZeneca, GSK, Novartis, and Sanofi/Regeneron, and has received grants and personal fees from GSK. Ian D. Pavord has received speaker's honoraria for speaking at sponsored meetings from AstraZeneca, Aerocrine, Almirall, Sanofi/Regeneron, Menarini, and GSK, and payments for organizing educational events from AstraZeneca, GSK, and Sanofi/Regeneron. He has received honoraria for attending advisory panels with Sanofi/Regeneron, AstraZeneca, GSK, Merck, Circassia, Chiesi, and Areteia. He has received sponsorship to attend international scientific meetings from GSK, AstraZeneca, and Sanofi/Regeneron. David Leather and Emilio Pizzichini are former employees of GSK and David Leather holds financial equities in GSK. Jodie Crawford, Alison Moore, and Marcus Stanaland are employees of GSK and hold financial equities in GSK.

***Ethical Approval.*** Ethical approval was not required as this article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## REFERENCES


1. Global Initiative for Asthma. Global Initative for Asthma: Global Strategy for Asthma Management and Prevention. 2025. Available from: https://ginasthma.org/2025-gina-strategy-report/. Accessed May 2025.
2. Peters SP, Bleecker ER, Kunselman SJ, et al. Predictors of response to tiotropium versus salmeterol in asthmatic adults. J Allergy Clin Immunol. 2013;132(1068–74):e1.
3. Szefler SJ, Martin RJ, King TS, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol. 2002;109:410–8.
4. Casale TB, Aalbers R, Bleecker ER, et al. Tiotropium Respimat(R) add-on therapy to inhaled corticosteroids in patients with symptomatic asthma improves clinical outcomes regardless of baseline characteristics. Respir Med. 2019;158:97–109.
5. Martin RJ, Szefler SJ, King TS, et al. The predicting response to inhaled corticosteroid efficacy (PRICE) trial. J Allergy Clin Immunol. 2007;119:73–80.
6. Janson C, Malinovschi A, Amaral AFS, et al. Bronchodilator reversibility in asthma and COPD: findings from three large population studies. Eur Respir J. 2019. https://doi.org/10.1183/13993003.00561-2019.
7. Lemiere C, Taille C, Lee JK, et al. Impact of baseline clinical asthma characteristics on the response to mepolizumab: a post hoc meta-analysis of two phase III trials. Respir Res. 2021;22:184.
8. Tanaka A, Uno T, Sato H, et al. Predicting future risk of exacerbations in Japanese patients with adult asthma: a prospective 1-year follow up study. Allergol Int. 2017;66:568–73.
9. Tupper OD, Ulrik CS. Long-term predictors of severe exacerbations and mortality in a cohort of well-characterised adults with asthma. Respir Res. 2021;22:269.
10. Pavord ID, Beasley R, Agusti A, et al. After asthma: redefining airways diseases. Lancet. 2018;391:350–400.
11. Bleecker ER, Wechsler ME, FitzGerald JM, et al. Baseline patient factors impact on the clinical efficacy of benralizumab for severe asthma. Eur Respir J. 2018. https://doi.org/10.1183/13993003.00936-2018.
12. Brusselle G, Germinaro M, Weiss S, Zangrilli J. Reslizumab in patients with inadequately controlled late-onset asthma and elevated blood eosinophils. Pulm Pharmacol Ther. 2017;43:39–45.
13. Busse WW, Paggiaro P, Muñoz X, et al. Impact of baseline patient characteristics on dupilumab efficacy in type 2 asthma. Eur Respir J. 2021. https://doi.org/10.1183/13993003.04605-2020.
14. Geng B, Dixon AE, Ko J, et al. Impact of body mass index on omalizumab response in adults with moderate-to-severe allergic asthma. Ann Allergy Asthma Immunol. 2022. https://doi.org/10.1016/j.anai.2022.01.025.
15. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. N Engl J Med. 2022;386:157–71.
16. Kroes JA, Zielhuis SW, van Roon EN, Ten Brinke A. Prediction of response to biological treatment with monoclonal antibodies in severe asthma. Biochem Pharmacol. 2020;179:113978.
17. Mukherjee M, Paramo FA, Kjarsgaard M, et al. Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. Am J Respir Crit Care Med. 2018;197:38–46.
18. Beasley R, Braithwaite I, Semprini A, Kearns C, Weatherall M, Pavord ID. Optimal asthma control: time for a new target. Am J Respir Crit Care Med. 2020;201:1480–7.
19. Edris A, de Roos EW, McGeachie MJ, et al. Pharmacogenetics of inhaled corticosteroids and exacerbation risk in adults with asthma. Clin Exp Allergy. 2022;52:33–45.
20. Wechsler ME, Kunselman SJ, Chinchilli VM, et al. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet. 2009;374:1754–64.
21. Oppenheimer J, Slade DJ, Hahn BA, et al. Real-world evidence: Patient views on asthma in respiratory specialist clinics in America. Ann Allergy Asthma Immunol. 2021;126:385–932.

22. Nwaru BI, Ekstrom M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting beta2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020; 55.

23. Barnes PJ. Distribution of receptor targets in the lung. Proc Am Thorac Soc. 2004;1:345–51.

24. Papi A, Fabbri LM, Kerstjens HAM, Rogliani P, Watz H, Singh D. Inhaled long-acting muscarinic antagonists in asthma - a narrative review. Eur J Intern Med. 2021;85:14–22.

25. Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. Lancet. 2019;394:1737–49.

26. Kerstjens HAM, Maspero J, Chapman KR, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. Lancet Respir Med. 2020;8:1000–12.

27. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. Lancet Respir Med. 2021;9:69–84.

28. Kim LHY, Saleh C, Whalen-Browne A, O'Byrne PM, Chu DK. Triple vs dual inhaler therapy and asthma outcomes in moderate to severe asthma: a systematic review and meta-analysis. JAMA. 2021;325:2466–79.

29. Royston P, Sauerbrei W. A new approach to modelling interactions between treatment and continuous covariates in clinical trials by using fractional polynomials. Stat Med. 2004;23:2509–25.

30. Royston P, Altman DG. Regression using fractional polynomials of continuous covariates: parsimonious parametric modelling. Appl Stat. 1994;43:429–53.

31. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006;332:1080.

32. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med. 2006;25:127–41.

33. Busse WW, Kraft M, Rabe KF, et al. Understanding the key issues in the treatment of uncontrolled persistent asthma with type 2 inflammation. Eur Respir J. 2021. https://doi.org/10.1183/13993003.03393-2020.

34. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med. 2015;3:849–58.

35. Couillard S, Do WIH, Beasley R, Hinks TSC, Pavord ID. Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype Oxford Asthma Attack Risk Scale (ORACLE). ERJ Open Res. 2022. https://doi.org/10.1183/23120541.00570-2021.

36. Rhyou HI, Nam YH. Predictive factors of response to inhaled corticosteroids in newly diagnosed asthma: a real-world observational study. Ann Allergy Asthma Immunol. 2020;125:177–81.

37. Price DB, Buhl R, Chan A, et al. Fractional exhaled nitric oxide as a predictor of response to inhaled corticosteroids in patients with non-specific respiratory symptoms and insignificant bronchodilator reversibility: a randomised controlled trial. Lancet Respir Med. 2018;6:29–39.

38. Dunn RM, Lehman E, Chinchilli VM, et al. Impact of age and sex on response to asthma therapy. Am J Respir Crit Care Med. 2015;192:551–8.

39. Syk J, Malinovschi A, Johansson G, et al. Anti-inflammatory treatment of atopic asthma guided by exhaled nitric oxide: a randomized, controlled trial. J Allergy Clin Immunol Pract. 2013;1:639–481.

40. Smith AD, Cowan JO, Brassett KP, et al. Exhaled nitric oxide: a predictor of steroid response. Am J Respir Crit Care Med. 2005;172:453–9.

41. Hao H, Bao W, Xue Y, et al. Spirometric changes in bronchodilation tests as predictors of asthma diagnosis and treatment response in patients with FEV1 >/=80% predicted. J Allergy Clin Immunol Prac. 2021;9:3098–1084.

42. Krishnan JA, Lazarus SC, Blake KV, et al. Biomarkers to predict response to inhaled corticosteroids and long-acting muscarinic antagonists in adolescents and adults with mild persistent asthma. Ann Am Thorac Soc. 2022;19:372–80.

43. Singh D, Virchow JC, Canonica GW, et al. Determinants of response to inhaled extrafine triple therapy in asthma: analyses of TRIMARAN and TRIGGER. Respir Res. 2020;21:285.

44. Boulet L-P, Abbott C, Brusselle G, et al. Baseline characteristics and ICS/LAMA/LABA response in Asthma: analyses from the CAPTAIN study. the

journal of allergy and clinical immunology. In Practice. 2024;12:1244–538.

45. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010;363:1715–26.

46. Kostikas K, Maspero JF, Chapman KR, et al. Efficacy of mometasone/indacaterol/glycopyrronium in patients with inadequately controlled asthma with respect to baseline eosinophil count: post hoc analysis of IRIDIUM study. Respir Med. 2023;217:107334.

47. Miller MK, Lee JH, Miller DP, Wenzel SE. Recent asthma exacerbations: a key predictor of future exacerbations. Respir Med. 2007;101:481–9.

48. Couillard S, Laugerud A, Jabeen M, et al. Derivation of a prototype asthma attack risk scale centred on blood eosinophils and exhaled nitric oxide. Thorax. 2022;77:199–202.

49. Oppenheimer J, Brusselle G, Busse W, et al. P202 CAPTAIN STUDY: Treatment outcomes from fluticasone furoate/umeclidinium/vilanterol according to history of severe asthma exacerbations. Ann Allergy Asthma Immunol. 2020;125:S26–7.

50. Jayaram L, Pizzichini MM, Cook RJ, et al. Determining asthma treatment by monitoring sputum cell counts: effect on exacerbations. Eur Respir J. 2006;27:483.

51. Jackson DJ, Sykes A, Mallia P, Johnston SL. Asthma exacerbations: origin, effect, and prevention. J Allergy Clin Immunol. 2011;128:1165–74.

52. Singh D, Virchow JC, Canonica GW, et al. Extrafine triple therapy in patients with asthma and persistent airflow limitation. Eur Respir J. 2020. https://doi.org/10.1183/13993003.00476-2020.

53. Beasley R, Holliday M, Reddel HK, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med. 2019;380:2020–30.

54. Ohwada A, Inami K, Onuma E, Matsumoto-Yamazaki M, Atsuta R, Takahashi K. Bronchial reversibility with a short-acting β2-agonist predicts the FEV1 response to administration of a long-acting β2-agonist with inhaled corticosteroids in patients with bronchial asthma. Exp Ther Med. 2011;2:619–23.

55. Arismendi E, Bantulà M, Perpiñá M, Picado C. Effects of obesity and asthma on lung function and airway dysanapsis in adults and children. J Clin Med. 2020. https://doi.org/10.3390/jcm9113762.

56. Peters U, Dixon AE, Forno E. Obesity and asthma. J Allergy Clin Immunol. 2018;141:1169–79.

57. Sin DD, Sutherland ER. Obesity and the lung: 4. Obesity and asthma. Thorax. 2008;63:1018–23.

58. Maselli D, Chang S, Fowler A, et al. CAPTAIN: effects of Body Mass Index (BMI) on response to triple therapy in patients with inadequately controlled asthma on inhaled corticosteroids/Long-acting β2-agonists (ICS/LABA). J Allergy Clin Immunol. 2021;147:AB57.

59. Sutherland ER, Lehman EB, Teodorescu M, Wechsler ME. Body mass index and phenotype in subjects with mild-to-moderate persistent asthma. J Allergy Clin Immunol. 2009;123:1328–41.

60. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. Eur Respir J. 2006;27:495–503.

61. Scott HA, Gibson PG, Garg ML, et al. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. Clin Exp Allergy. 2013;43:36–49.

62. Shimoda T, Obase Y, Kishikawa R, Iwanaga T. Influence of cigarette smoking on airway inflammation and inhaled corticosteroid treatment in patients with asthma. Allergy Asthma Proc. 2016;37:50–8.

63. Chalmers GW, Macleod KJ, Little SA, Thomson LJ, McSharry CP, Thomson NC. Influence of cigarette smoking on inhaled corticosteroid treatment in mild asthma. Thorax. 2002;57:226–30.

64. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. Am J Respir Crit Care Med. 2003;168:1308–11.

65. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. Thorax. 2005;60:282–7.

66. Lazarus SC, Chinchilli VM, Rollings NJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. Am J Respir Crit Care Med. 2007;175:783–90.

67. Woodcock A, Vestbo J, Bakerly ND, et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet. 2017;390:2247–55.

68. Pedersen SE, Bateman ED, Bousquet J, et al. Determinants of response to fluticasone propionate and salmeterol/fluticasone propionate combination in the gaining optimal asthma control study. J Allergy Clin Immunol. 2007;120:1036–42.

69. Haughney J, Aubier M, Jørgensen L, et al. Comparing asthma treatment in elderly versus younger patients. Respir Med. 2011;105:838–45.

70. Doherty DE, Bleecker ER, Moroni-Zentgraf P, Zaremba-Pechmann L, Kerstjens HAM. Tiotropium respimat efficacy and safety in asthma: relationship to age. J Allergy Clin Immunol Pract. 2020;8:2653–604.

71. Chowdhury NU, Guntur VP, Newcomb DC, Wechsler ME. Sex and gender in asthma. Eur Respir Rev. 2021. https://doi.org/10.1183/16000617.0067-2021.

72. Forno E, Celedon JC. Asthma and ethnic minorities: socioeconomic status and beyond. Curr Opin Allergy Clin Immunol. 2009;9:154–60.

73. Peters MC, McGrath KW, Hawkins GA, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. Lancet Respir Med. 2016;4:574–84.

74. Pavord ID, Holliday M, Reddel HK, et al. Predictive value of blood eosinophils and exhaled nitric oxide in adults with mild asthma: a prespecified subgroup analysis of an open-label, parallel-group, randomised controlled trial. Lancet Respir Med. 2020;8:671–80.

75. Israel E, Cardet JC, Carroll JK, et al. Reliever-triggered inhaled glucocorticoid in Black and Latinx adults with asthma. N Engl J Med. 2022;386:1505–18.

76. Papi A, Barnes N, Fowler A, et al. CAPTAIN: Effects of lung function at screening (FEV1 % predicted) as a continuous variable on treatment outcomes. Eur Respir J. 2021;58:1487.

77. Van Zyl-Smit RN, Kerstjens HA, Maspero JF, et al. Efficacy of once-daily, single-inhaler, fixed-dose combination of mometasone/indacaterol/glycopyrronium in patients with asthma with or without persistent airflow limitation: post hoc analysis from the IRIDIUM study. Respir Med. 2023;211:107172.

78. Papi A, Chipps BE, Beasley R, et al. Albuterol-budesonide fixed-dose combination rescue inhaler for asthma. N Engl J Med. 2022;386:2071–83.

79. Boulet L, Lee L, Kerstjens H, *et al.*, editors. CAPTAIN: Effects of age on response to triple therapy in patients with inadequately controlled asthma on ICS/LABA. Poster presented at European Respiratory Society 2021; 2020; https://www.ersnet.org/congress-and-events/congress/.

80. Kerstjens HA, Lawrence D, Mezzi K, Brittain D, Jaumont X, Chapman KR, editors. Effect of once daily (o.d.) mometasone/indacaterol/glycopyrronium (MF/IND/GLY) vs o.d. MF/IND and twice daily (b.i.d.) fluticasone/salmeterol (FLU/SAL) with respect to age, age at asthma-onset and BMI at baseline: Subgroup analysis from IRIDIUM study. Poster presented at European Respiratory Society 2022; 2022; Barcelona.

81. Brusselle G, Peché R, Van den Brande P, Verhulst A, Hollanders W, Bruhwyler J. Real-life effectiveness of extrafine beclometasone dipropionate/formoterol in adults with persistent asthma according to smoking status. Respir Med. 2012;106:811–9.

82. Papi A, Lee L, Kerstjens H, *et al.*, editors. CAPTAIN: Effects of smoking status on response to triple therapy in patients with inadequately controlled asthma on ICS/LABA. Poster presented at European Respiratory Society 2020; 2020.

83. Papi A, Singh D, Virchow JC, Canonica GW, Vele A, Georges G. Normalisation of airflow limitation in asthma: post-hoc analyses of TRIMARAN and TRIGGER. Clin Transl Allergy. 2022;12:e12145.

84. Hardy J, Tewhaiti-Smith J, Baggott C, et al. Combination budesonide/formoterol inhaler as sole reliever therapy in Māori and Pacific people with mild and moderate asthma. N Z Med J. 2020;133:61–72.