

Triple Therapy in Asthma: Real-World Evidence Supports Earlier Use

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Current asthma management guidelines often advocate for a step-up approach, escalating therapy only after control is not achieved with lower-tier treatments. However, emerging real-world data suggests that a more proactive strategy, involving earlier initiation of triple therapy, may offer clinical benefits for patients with inadequately controlled asthma.

KEY TAKEAWAYS

- **The Pivot:** Real-world evidence challenges the traditional step-up approach, supporting earlier triple therapy.
- **The Data:** Patients initiating triple therapy earlier demonstrated reduced exacerbation rates and improved lung function.
- **The Action:** Clinicians should consider earlier triple therapy for patients not achieving control on dual therapy, rather than waiting for further deterioration.

Asthma, a chronic inflammatory airway disease, affects millions globally, with a significant proportion experiencing persistent symptoms despite conventional treatment. The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach, progressing from inhaled corticosteroids (ICS) alone, to ICS/long-acting beta-agonists (LABA) combination, and then to triple therapy (ICS/LABA/long-acting muscarinic antagonist, LAMA) for patients whose asthma remains uncontrolled. This sequential escalation is predicated on balancing efficacy with potential side effects and cost. However, the practical application of this strategy often results in prolonged periods of suboptimal control for patients, leading to increased exacerbations, hospitalisations, and a diminished quality of life. The question of whether earlier intervention with more comprehensive therapy could mitigate these outcomes has been a subject of ongoing debate and research. Approximately 5-10% of adult asthma patients worldwide experience severe asthma, which often requires higher-tier treatments to achieve control. For these patients, the timely introduction of effective therapies is crucial to prevent irreversible airway remodeling and preserve lung function.

Real-World Evidence on Triple Therapy Escalation

A recent analysis presented at ATS 2026 examined real-world data from a large cohort of patients with moderate to severe asthma, focusing on the timing of triple therapy initiation. The study included N=15,420 adult patients diagnosed with asthma who were receiving dual therapy (ICS/LABA) but continued to experience uncontrolled symptoms, defined by frequent exacerbations or persistent airflow limitation. Patients were stratified into two groups: those who escalated to triple therapy within 6 months of uncontrolled symptoms on dual therapy (early escalation group, n=7,810) and those

who escalated after 6 months (late escalation group, $n=7,610$). The primary outcomes assessed were the rate of severe asthma exacerbations (requiring systemic corticosteroids, emergency department visits, or hospitalisation) and changes in forced expiratory volume in 1 second (FEV1) over a 12-month follow-up period. The study population comprised a diverse demographic, reflecting typical real-world asthma patient profiles, with a mean age of 52 years and a slight female predominance. All patients had a documented history of moderate to severe asthma, confirmed by spirometry and clinical assessment, and had been on stable ICS/LABA therapy for at least 3 months prior to the index date.¹ The analysis revealed that patients in the early escalation group experienced a significantly lower rate of severe asthma exacerbations compared to the late escalation group. The adjusted incidence rate ratio (IRR) for exacerbations was 0.72 (95% CI: 0.68-0.76, $p<0.001$) in favour of early escalation. This translates to a 28% reduction in exacerbation risk. Furthermore, the early escalation group demonstrated a greater improvement in lung function, with an average increase in FEV1 of +120 mL (95% CI: +105 mL to +135 mL, $p<0.001$) from baseline, compared to an increase of +65 mL (95% CI: +50 mL to +80 mL, $p<0.001$) in the late escalation group. The difference in FEV1 improvement between the two groups was +55 mL (95% CI: +35 mL to +75 mL, $p<0.001$). Triple therapy, by combining the anti-inflammatory effects of ICS, the bronchodilatory effects of LABA, and the additional bronchodilation and mucus reduction from LAMA, addresses multiple pathophysiological pathways of asthma, potentially leading to more comprehensive disease control. Secondary outcomes, including asthma-related hospitalisations and oral corticosteroid burden, also favoured early escalation. The hazard ratio (HR) for asthma-related hospitalisation was 0.65 (95% CI: 0.58-0.73, $p<0.001$) for the early escalation group. The mean annual oral corticosteroid dose was also lower in the early escalation group, indicating a reduction in systemic steroid exposure.¹

Limitations and Context

While these real-world data provide compelling evidence, it is important to acknowledge the inherent limitations of observational studies. Confounding by indication, where patients with more severe disease might be escalated earlier, could influence outcomes despite statistical adjustments. However, the large sample size and comprehensive adjustment for baseline characteristics, including disease severity markers, comorbidity burden, and prior medication use, strengthen the validity of the findings. The study utilized propensity score matching and inverse probability of treatment weighting to minimize bias from observed confounders. Despite these robust statistical methods, unmeasured confounders, such as patient adherence to medication or specific environmental triggers, could still influence the results. The study did not include a direct comparison with biologics, which represent another escalation option for severe asthma. Future research should aim to compare the efficacy and cost-effectiveness of early triple therapy versus early biologic initiation in specific patient phenotypes. The generalisability of these findings may also be limited to populations similar to those included in the study, primarily from developed healthcare systems.¹

For a comprehensive understanding of current asthma management strategies and other respiratory conditions, consult the latest edition of the Oxford Handbook of Respiratory Medicine.

CLINICAL IMPLICATIONS

The data presented at ATS 2026 on earlier triple therapy for uncontrolled asthma challenges the inertia often seen in clinical practice. For too long, clinicians have adhered rigidly to a step-up approach, often waiting for

multiple exacerbations or significant lung function decline before considering a more potent regimen. This new real-world evidence suggests that such delays may be detrimental, prolonging patient suffering and increasing healthcare resource utilisation. It is time to question whether the perceived risks of earlier triple therapy outweigh the documented benefits of improved control and reduced exacerbations.

The pharmaceutical industry, particularly manufacturers of ICS/LABA/LAMA fixed-dose combinations, will undoubtedly leverage these findings. Companies like GSK, AstraZeneca, and Boehringer Ingelheim, with established triple therapy products, now have stronger evidence to advocate for earlier adoption. This could lead to a shift in prescribing patterns, potentially increasing market penetration for these therapies. However, prescribers must remain vigilant, ensuring that the decision to escalate is based on individual patient assessment and not solely on promotional efforts, especially given the higher cost associated with triple therapy compared to dual combinations.

Ultimately, this evidence should prompt a re-evaluation of current GINA guidelines regarding the timing of triple therapy initiation. While a personalised approach remains paramount, the data support a more proactive stance for patients failing to achieve control on dual therapy. This could mean fewer emergency department visits, fewer hospitalisations, and a better quality of life for patients, moving beyond the reactive management of asthma exacerbations towards a more preventative strategy.

EDITORIAL & AI STANDARDS

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REFERENCES

1. Data on file. Presented at ATS 2026.

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