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REVIEW ARTICLE

Single inhaler triple therapy (SITT) in asthma: Systematic review and practice implications

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Abstract

A significant number of patients with asthma remain uncontrolled despite treatment with inhaled corticosteroids (ICS) and long-acting β2 adrenergic bronchodilators (LABA). The addition of long-acting antimuscarinic agents (LAMA) can improve the management of asthma in these patients. Recently, three novel triple therapy (ICS/LABA/LAMA) formulations in a single-inhaler device (SITT) have been investigated in patients with uncontrolled asthma despite ICS/LABA treatment. Here, we review systematically the evidence available to date in relation to SITT in patients with uncontrolled asthma despite ICS-LABA treatment and conclude that SITT is a safe and effective therapeutic alternative in these patients. We also discuss how to position this new therapeutic alternative in their practical clinical management as well as the opportunities and challenges that it may generate for patients, physicians, and payers.

KEYWORDS
asthma, asthma treatment, quality-of-life

1 | INTRODUCTION

Asthma is an important global health problem that affects all age groups.[1] Despite effective and safe treatment options, up to 40% of patients with asthma remain uncontrolled.[2] This imposes an unacceptable burden on patients' quality of life, healthcare systems, and society through loss of productivity that has implications for economic burden and quality-adjusted life years.[1] In 2012, Kerstjens et al[3] showed that in patients with poorly controlled asthma despite the use of inhaled glucocorticoids (ICS) and long-acting β2 adrenergic bronchodilators (LABAs), the addition of tiotropium (long-acting antimuscarinic agent—LAMA) significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation. LAMA cause bronchodilation by blocking acetylcholine signalling through airway muscarinic receptors.[4] This is a different mechanism to LABAs, which act through β2 receptors, enabling these different classes of bronchodilators to be combined to produce additive bronchodilator effects. Furthermore, there is also molecular evidence of synergistic interactions between ICS, LABA, and LAMA molecules, supporting the rationale to combine these three different classes of drugs for the treatment of asthma[5,6] Recently, several triple therapy combinations of ICS-LABA-LAMA in a single inhaler (SITT) have been marketed, and the 2021 Global Initiative for Asthma (GINA) recommends adding a LAMA in patients aged ≥18 years who, despite being adherent to inhaled LABA combined with medium- or high-dose ICS, still experience symptoms or exacerbations.[1] Yet, different combinations have been approved so far by the Food and

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Drug Administration (FDA) in the US and the European Medicines Agency (EMA), as detailed in the online supplement. Here, we review systematically the evidence available to date in relation to SITT in patients with uncontrolled asthma despite ICS-LABA treatment, and discuss how to position this new therapeutic alternative in their practical clinical management as well as the opportunities and challenges that it creates both for patients and clinicians.

2 | SYSTEMATIC REVIEW OF AVAILABLE EVIDENCE

To identify published phase III randomized clinical trials (RCTs) assessing the effects of SITT in patients with asthma, we conducted a systematic review according to a predefined protocol compliant with the PRISMA guidelines for systematic reviews (online supplement for a detailed methodological explanation).[7] To this end, a structured search strategy of PubMed and Web of Science was developed to identify all phase III clinical trials investigating SITT in asthma using the combination of the following keywords "asthma" and "single-inhaler" and ("triple therapy" or [beclomethasone or budesonide or fluticasone or mometasone] and [formoterol or indacaterol or olodaterol or salmeterol or vilanterol] and [aclidinium or glycopyrronium or tiotropium or umeclidinium]) up to February 1st, 2021. Studies conducted in COPD or non-RCTs were excluded upon title review. Conference or poster abstracts of studies already included, and reviews and comments were excluded upon full-text review. Search results were reviewed independently by two investigators (LF and LL) to determine the eligibility of potential studies, results were compared, and disagreement was resolved to create the final list of included studies. Risk of bias was assessed using the revised Cochrane risk of bias (RoB) 2 tool for randomized controlled trials.[8] This tool aids in the assessment of the risk of bias in RCTs including the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported results (online supplement for details).

Our search strategy identified 29 studies after removal of duplicates (Figure S1). After full-text screening, five original phase III RCTs published in four manuscripts investigating SITT in asthma (TRIMARAN combined with TRIGGER, IRIDIUM, ARGON and CAPTAIN), and all of them were assessed for risk of bias. Besides, we identified a very recent network meta-analysis by Rogliani et al[9] which, accordingly to the recently revised table of evidence of GINA, is also considered level A of scientific evidence.[1] Table 1 summarizes the main efficacy data of these five RCTs.

TRIMARAN and TRIGGER compared the efficacy and safety of SITT (beclomethasone dipropionate [BDP], formoterol fumarate [FF] and glycopyrronium bromide [GLY]) with medium-dose BDP/FF (TRIMARAN) or high-dose BDP/FF plus tiotropium (TRIGGER) therapy in adult patients with poorly controlled asthma. All drugs (except tiotropium, once-daily) were delivered via a single device (two inhalations/12 h), multi-dose, pressurized metered-dose inhaler (pMDI) containing an extra-fine inhalation solution formulation (Modulite®) during 52 weeks.[10] Of note, TRIMARAN and TRIGGER used two different SITT doses: 200/12/20 (TRIMARAN) and 400/12/20 (TRIGGER). Main results (Figure 1, left column) showed that SITT was associated with: (1) higher FEV_1 at week 26; (2) fewer exacerbations, particularly the severe ones, at 12 months; A pre-specified pooled analysis showed 23% fewer severe exacerbations with BDP/FF/GLY versus BDP/FF ($p = .008$) and a 23.7% reduction in the annual rate of days on systemic steroids ($p = .089$)[11]; (3) no clinically relevant impact on asthma control; and, (4) fewer adverse events (mostly mild-to-moderate exacerbations).[10] Of note, TRIGGER showed non-inferiority of fixed triple combination (high-dose BDP/FF/GLY) versus multiple inhaler devices (Respimat Tiotropium+high-dose BDP/FF).[10] The results of post hoc analysis were only included in the qualitative synthesis of our systematic review. Nevertheless, they can provide additional information of potential interest: (1) SITT was particularly beneficial (in terms of lung function improvement and exacerbation reduction) in patients with persistent airflow limitation at screening[12]; (2) the reduction of moderate-and-severe exacerbations by SITT was particularly seen during winter[13]; and, (3) eosinophil levels did not influence the efficacy of SITT on moderate-to-severe or severe exacerbations, but SITT effects appeared greater in patients with more airflow limitation reversibility to short acting β agonists.[14]

IRIDIUM compared the effects of once-daily SITT (medium- or high-dose mometasone furoate (MF), indacaterol acetate (IND), and glycopyrronium bromide (GLY) *vs*. either once-daily ICS-LABA (medium- or high-dose MF–IND), delivered via a single device, multi-dose dry powder inhaler (DPI, Breezhaler®), or twice-daily high-dose fluticasone–salmeterol (FP-SLM) in patients with uncontrolled asthma delivered via a different single device, multi-dose DPI (Diskus®).[15] Main results (Figure 1, right column) showed that at week 26: (1) both medium- and high-dose SITT were associated with greater improvement in trough FEV1; (2) ACQ-7 score was not different in SITT *vs*. the equivalent MF/IND once-daily dose, but it was better than the combination of FP/SLM twice-daily; (3) SITT did not significantly reduce the annualized rate of moderate or severe exacerbations *vs*. equivalent MF/IND once-daily doses, but it did *vs*. twice-daily FP-SLM; and, (4) adverse events were similar across groups.[15] Notably, due to formulation characteristics, the doses of mometasone in the MF-IND-GLY combinations were halved compared to the corresponding MF-IND comparators.[15,16]

ARGON was a 24-week, open-label RCT that investigated the non-inferiority of SITT (MF/IND/GLY) once-daily delivered via the DPI Breezhaler® *vs*. FP/SLM high dose (twice-daily) delivered via the DPI Diskus® plus tiotropium (TIO; once-daily) delivered via Respimat® in two separate devices on the Asthma Quality of Life Questionnaire (AQLQ) in patients with uncontrolled asthma.[17] Of note, it did not explore other outcomes such as exacerbations. Main results (Figure 2, left column) showed that: (1) AQLQ was not inferior in SITT *vs*. FP/SLM+TIO; (2) MF/IND/GLY high dose improved significantly other scores of respiratory symptoms (ACQ-7 and SGRQ) and lung function (trough FEV1, morning and evening peak expiratory flow) *vs*. FP/SLM high dose via a DPI (Acchuhaler®) plus TIO

TABLE 1 Summary of efficacy data of Phase 3 SITT RCTs *vs.* LABA/ICS in patients with poorly controlled asthma

Study name[ref]	FEV_1 improvement for SITT versus ICS/LABA	Reduction of moderate-severe exacerbation for SITT versus ICS/LABA
TRIMARAN[10] BDP/FF/GLY versus BDP/FF	57 mL (95% CI 15–99; $p = .0080$) for medium dose	15% (RR 0.85, 95% CI 0.73–0.99; $p = .033$) for medium dose
TRIGGER[10] BDP/FF/GLY versus BDP/FF BDP/FF/GLY versus BDP/FF+TIO	73 mL (95% CI 26–120; $p = .0025$) for high dose −45 mL [95% CI−103 to 13; $p = .13$) for high dose	12% (RR 0.88, 95% CI 0.75–1.03; $p = .11$) for high dose 7% (RR1·07, 95% CI 0·88–1·30; $p = .50$) for high dose
IRIDIUM[15] MF/IND/GLY versus MF/IND MF/IND/GLY versus FP/SLM	• 76 mL ($p < .001$) for medium dose • 65 mL ($p < .001$) for high dose • 99 mL ($p < .001$) for medium dose • 119 mL ($p < .001$) for high dose	• 13% (RR 0.87, 95% CI 0.71–1.06; $p = .17$) for medium dose • 15% (RR 0.85, 95% CI 0.68–1.04; $p = .12$) for high dose • 19% r (RR 0.81, 95% CI 0.66–0.99; $p = .041$) for medium dose • 36% (RR 0.64, 95% CI 0.52–0.78; $p < .001$) for high dose
ARGON[17] MF/IND/GLY versus FP/SLM+TIO	High-dose and medium-dose MF/IND/GLY were non-inferior to high-dose FP/SLM+TIO for AQLQ (least square mean treatment difference: 0.073 and−0.038, respectively; both $p < .001$). High-dose MF/IND/GLY improved trough FEV_1 at Weeks 8 (Δ: 67 mL; $p = .007$), 16 (Δ: 66 mL; $p = .007$) and 24 (Δ: 96 mL; $p < .001$) versus high-dose FP/SLM+TIO. Medium-dose MF/IND/GLY medium-dose versus high-dose FP/SLM+TIO at Weeks 8 (Δ: 3 mL; $p = .892$), 16 (Δ: −2 mL; $p = .945$) and 24 (Δ: 9 mL; $p = .713$).	Medium-dose MF/IND/GLY versus FP/SLM high dose+TIO • 4% increase (RR 1.04, 95% CI 0.77, 1.39; $p = .798$) High-dose MF/IND/GLY versus FP/SLM high dose+TIO • 12% reduction (RR 0.88, 95% CI 0.65, 1.19; $p = .414$)
CAPTAIN[18] F/UMEC/VI 100/62.5/25 versus F/VI 100/25 F/UMEC/VI 200/62.5/25 versus F/VI 200/25	110 mL (66, 153; $p < .001$) for medium dose 92 mL (49, 135; $p < .001$) for high dose Adding UMEC 31.25 μg to F/VI produced similar improvements.	No statistically significant difference F/UMEC 62.5 μg/VI versus F/VI (pooled analysis)

Abbreviations: BDP, beclomethasone dipropionate; F, fluticasone furoate; FEV_1, forced expiratory volume in the first second; FF, formoterol fumarate; FP, fluticasone propionate; GLY, glycopyrronium; ICS, inhaled corticosteroids; IND, indacaterol; LABA, long-acting β2-adrenoceptor agonist; MF, mometasone furoate; RCT, randomized controlled trial; SITT, single-inhaler device; SLM, salmeterol; TIO, tiotropium bromide; UMEC, umeclidinium bromide; VI, vilanterol.

delivered through a soft mist inhaler (Respimat®); and, (3) adverse events were comparable across treatments.[17]

CAPTAIN compared the safety and efficacy of SITT (fluticasone furoate/umeclidinium/ vilanterol [F/UMEC/VI]) *vs.* F/VI, all delivered once-daily through a DPI (Ellipta®). At variance with the previous four RCT's, a history of exacerbations in the previous year was not an inclusion criterion in CAPTAIN.[18] Main results (Figure 2, right column) showed that[18]: (1) at week 24, the change from baseline in trough FEV_1 was significantly higher with SITT; (2) overall, SITT did not significantly reduce exacerbation rates but higher ICS doses had a greater effect on exacerbations in patients with biomarkers of type-2 airway inflammation (high blood eosinophil or exhaled nitric oxide values), and a similar trend was observed for FEV1 changes from baseline; (3) there was no clinically relevant impact on asthma control; and, (4) adverse events were similar across treatment groups.[18]

Finally, Rogliani et al[9] published a network meta-analysis of these same five SITT RCTs (TRIMARAN, TRIGGER, IRIDIUM, ARGON and CAPTAIN) that included 9.535 patients. Bayesian network meta-analysis allows the comparison of the results of different therapeutic interventions and enables treatment rankings.[9] Results, not unexpectedly, showed that: (1) SITT with high-dose ICS were more effective than those with medium-dose ICS in terms of lung function improvement and reduction of severe exacerbations; (2) SITT options were similarly effective on asthma control; and, (3) there are no safety concerns. These conclusions are in keeping with those of a recent narrative review on the role of LAMAs in asthma.[6]

3 | IMPLICATIONS FOR CLINICAL PRACTICE

The evidence reviewed above indicates that SITT is a safe and effective therapeutic alternative in patients with poorly controlled asthma despite treatment with ICS-LABA. There are some differences in the results obtained between the three different SITT combinations available today due to either the different

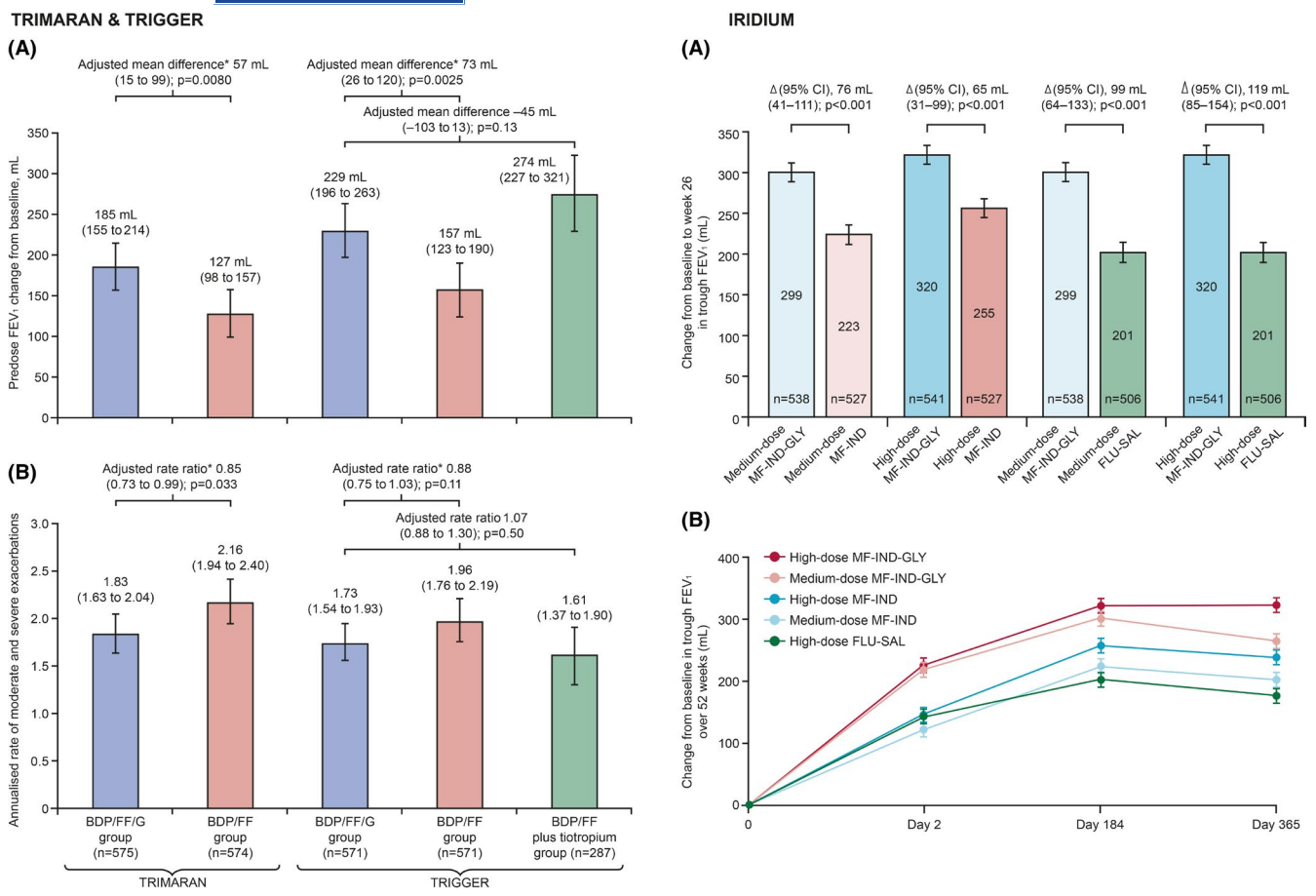

FIGURE 1 Left column. TRIMARAN and TRIGGER studies. Panel A: Mean (95% CI) pre-dose FEV1 change from baseline to week 26. Panel B: Adjusted exacerbation rates per patient per year (95% CI). Right column. IRIDIUM study. Change from baseline in mean (SE) trough FEV1 at week 26 (Panel A) and over 52 weeks (Panel B) in the full analysis set. For further explanations, see text. Reproduced with permission from references[10] and,[15] respectively

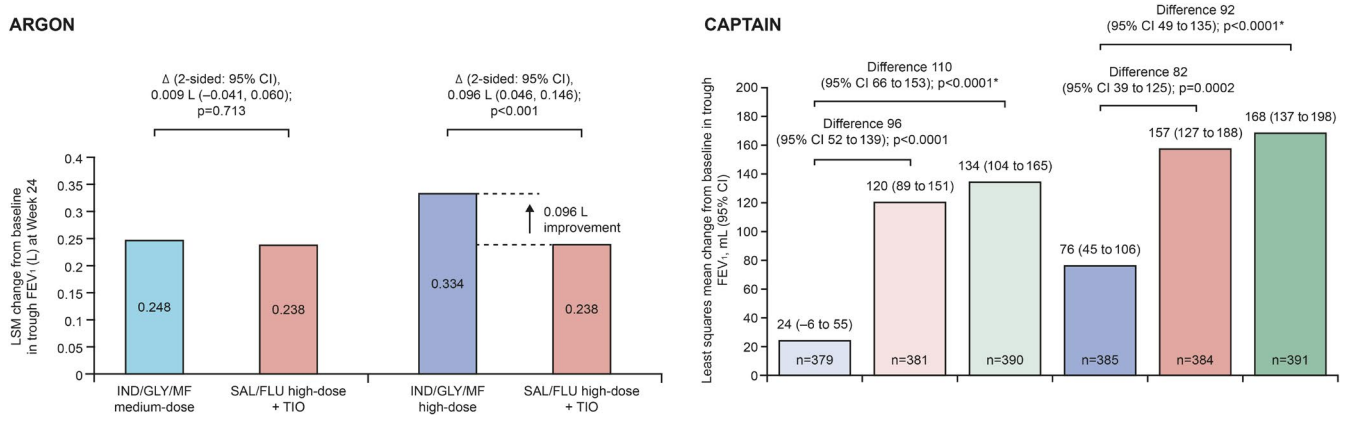

FIGURE 2 Left column. ARGON study. Treatment difference (least squares mean) in trough FEV1 at Week 24. Right column. CAPTAIN study. Least squares mean (LSM) change from baseline in trough FEV1 at Week 24 in the intention to treat population. For further explanations, see text. Reproduced with permission from references[17] and,[18] respectively

pharmacologic agents, their combinations and/or delivery systems, but the overall favorable efficacy/risk ratio has important implications in clinical practice, both for patients and prescribing physicians. These conclusions are also supported by another very recent meta-analysis published during the editorial process of the current paper.[19]

3.1 | The patient perspective

Compliance with any chronic treatment is essential for clinical effectiveness.[20] Unfortunately, in asthma there is significant non-adherence to medication.[21] In a survey of over 2000 adult and adolescent (aged 12–17 years) patients with asthma in Europe (Germany, Italy, Spain and the United Kingdom) and Canada, only half (52%) took their controller medication every day, with one in four reporting not taking it at all.[22] Other sources suggest that suboptimal adherence occurs in 75% of patients with asthma.[23,24] There may be a variety of reasons why patients do not take their medicine: it may simply be because they unintentionally forget; or they have difficulty with the different treatment schedules or inhaler(s; once-daily *vs*. twice-daily dosing, as well as metered-dose inhalers [MDI] *vs*. dry powder [DPI] ones); finally, patients may intentionally adhere less because they experience side effects or perceive little benefit. So patient education about the purpose of their medicine, how to use it correctly (with appropriate follow-up reminders) and what to do about side effects or, equally important, a lack of effect, is vital in helping patients gain the greatest benefit from their treatment. These considerations create an opportunity for the use of SITT, since it has the potential to improve treatment adherence by reducing the number of inhaler devices required for maintenance treatment, with less instructions and no differing dosing regimens, and to reduce dosing and handling errors as well as selective discontinuation of individual anti-asthma therapies.[21-23,25-28] Besides, there may also be synergistic benefits from triple therapy relating to relaxation of medium and small airways.[5] As a result, SITT has the potential to improve asthma control in patients with poorly controlled asthma despite the use of ICS-LABA. On the other hand, patients can be reassured that there are no safety concern for the use of SITT.[9] Finally, in some countries the cost of a triple fixed combination formulation may be higher than that of dual therapy combination inhalers, and this may be relevant for patients depending on the specific conditions for reimbursement in their respective healthcare systems. However, a higher cost of triple therapies should also be balanced with a higher clinical efficiency, at least in some specific outcomes.

3.2 | The physician perspective

Asthma is a complex and heterogeneous disease that requires personalized management. A strategy based on so-called treatable traits (TTs) has been proposed to implement precision medicine of airway diseases, including asthma.[29-32] TT's can be identified based on their observable clinical characteristics (ie, phenotype) and/or through validated biomarkers of underlying biological mechanisms (ie, endotypes) in the pulmonary, extra-pulmonary and behavioral/environmental domains.[29-31] Importantly, different TT's can coexist in the same patient and they may change with time (spontaneously or as a result of treatment).[29-31] When considering how to position SITT in clinical practice, several TTs need to be considered. First, whether or not the patient with uncontrolled asthma complies with the prescribed medications and uses them appropriately in terms of inhalation technique (behavioral/environment domain of TTs). In this setting, the use of a single inhaler can be useful, as discussed above. Indeed, the TRIMARAN-TRIGGER,[10] IRIDIUM[15] and CAPTAIN[18] studies showed that SITT did improve asthma control but changes failed to reach statistical significance perhaps because improved compliance with the comparator intervention (ICS/LABA) due to a Hawthorne effect.[33] Second, if the target TT is persistent airflow limitation, the studies reviewed above[9,10,15,17,18] indicate that SITT consistently improves lung function more than any other ICS/LABA option.[12] Third, if the target TT is the persistence of exacerbations (particularly in patients with biomarkers of type-2 airway inflammation (high blood eosinophil or exhaled nitric oxide values[18]), high-dose ICS SITT is more effective than medium-dose ICS SITT. Fourth, because small airway disease can also be considered a TT, triple therapy targeting small airways (eg, extra-fine BDP/GLY/FF) has the potential to reduce lung hyperinflation and perhaps to influence airway neuronal plasticity, albeit this is a hypothesis that requires further research.[34] Finally, the fact that the different SITTs use devices with completely different characteristics can have an impact on the outcome of the treatment.

Although the use of a single inhaler (SITT) is generally viewed as a better alternative than the use of several devices to deliver triple therapy, it may be argued that using fixed-dose combinations may reduce the flexibility to adjust the dose of each drug independently of the other components of the combination, particularly ICS or LAMA. Indeed, the network meta-analysis by Rogliani et al[9] indicates that the ICS dose used in the SITT has an impact. However, the risk of discontinuing ICS/LABA while continuing treatment with off-label LAMA monotherapy without an anti-inflammatory controller also exists.[35] Besides, several available SITT formulations with different drug dosages have already been marketed to provide added flexibility to patients and healthcare providers, and to enable a more personalized treatment.

3.3 | Recommendations for positioning of SITT in asthma management

Considering all of the above, and acknowledging that research is still needed, we would like to offer our opinion on to the positioning of SITT in the management of asthma. Thus, we would propose that: (1) in patients with uncontrolled asthma despite medium-dose ICS/LABA, adherence should be evaluated, and medium ICS dose in a SITT should be considered particularly for exacerbation prevention in subjects with low T2 markers[18] as an alternative to high-dose ICS-LABA, which increases the risk of local (oral thrush and dysphonia) and systemic (easy bruising, cataracts glaucoma, osteoporosis and adrenal suppression) side effects with little efficacy gain[1,36]; (2) in patients with uncontrolled asthma despite high-dose ICS/LABA, we propose to evaluate adherence and consider high ICS dose SITT

before using oral corticosteroids or a biologic, particularly if there is persistent airflow limitation[12] and/or history of severe exacerbations, or certainly in patients not eligible for biologic treatment; and, (3) in patients who are well-controlled on high-dose ICS/LABA or high ICS dose SITT but at risk for or experiencing ICS-related side effects, we suggest to consider a medium ICS dose in SITT.

3.4 | Single inhaler triple therapy: unresolved questions in clinical management

We also acknowledge that several questions remain unresolved: (1) additional evidence is required to firmly establish the indication of SITT in some specific asthma phenotypes; (2) it is unclear which patients can benefit more from SITT as compared with a biologic treatment because the population examined in the SITT studies (Table 2) was on average older, more obstructed and with a lower frequency of exacerbations as compared to patients' examined in the studies using biologics where most trials included patients with a proven history of exacerbations or high blood eosinophils levels.[37] On the one hand, therefore, it is possible that patients who continue to have impaired lung function despite ICS/LABA will profit preferentially from SITT,[12] while those with normal pulmonary function but who might suffer from frequent moderate-to-severe exacerbations, particularly if they exhibit a high T2 profile, may profit preferentially from biologics. On the other, however, a higher dose of ICS (or a switch to an ICS with higher potency) can be a reasonable choice in patients with normal pulmonary function who suffer from exacerbations (before biologics prescription) and SITT could be effective even in patients with "normal pulmonary function", because they could still be able to significantly improve FEV1 and to reach the "maximum personal value". These questions are clinically relevant and deserve specific investigation; (3) both GINA[1] and NAEP[38] recommend Maintenance and Reliever Treatment (MART) strategy for step 3 and 4, particularly to prevent exacerbations.[39] This recommendation is supported by several adequate randomized clinical trials for mild-moderate patients (GINA step 2–3) treated with low-dose ICS/formoterol given both as maintenance and reliever,[39] with level of evidence A, whereas for more severe asthma patients (steps 4 and 5) it is supported only by three 6-month studies (one positive[40] and two negative for the primary outcome[41-43]), and by one post hoc analysis of five large RCTs[44] (level of evidence D according to GINA).[1] Also, the MART studies were all conducted in asthma patients who were younger and less severe (Table 2) and none recruited patients because they were not controlled by maintenance treatment with regular LABA/ICS, but only patients uncontrolled by ICS only. The bottom line is that for patients with the characteristics examined in the SITT trials (older, more obstructed, possibly more severe, Table 2) there is weak, if any, evidence of the efficacy of MART, suggesting that properly designed and powered RCTs comparing MART with SITT should be performed to address this issue. Thus, while the magnitude of the effects of SITT on moderate-severe exacerbations

TABLE 2 Characteristics of the populations of asthmatics examined in the most relevant SITT or MART studies

	Age (years)	Duration of asthma (years)	FEV_1 (% reference)	No. exacerbations previous years	Duration of study (months)
SITT studies					
Virchow et al. TRIMARAN[10]	53	25	55	≥1	12
Virchow et al. TRIGGER[10]	53	25	52	≥1	12
Kerstjens et al. IRIDIUM[15]	52	18	54	≥1	12
Gessner et al. ARGON[17]	52	20	63	≥1	12
Lee et al. CAPTAIN[18]	53	20	58	≥1[a]	12
MART studies					
Scicchitano et al, 2004[48]	43	12	70	≥1	12
O'Byrne et al, 2005[49]	36	9	73	≥1	12
Rabe et al, 2006[50]	43	10	72	≥1	12
Bousquet et al, 2007[41]	40	14	70	≥1[b]	6
Kuna et al, 2007[40]	38	10	73	≥1[b]	6
Papi et al, 2013[51]	48	9	75	≥1[c]	12
Patel et al, 2013[43]	42	26	80	≥1[b]	6
Papi et al, 2015[52]	42	11	94	≥1[c]	12

Note: The Table shows that SITT studies were conducted only in adult asthmatics as compared to the MART studies that included both adolescent and adults, so patients of SITT studies were older, had longer duration of asthma, and had lower % predicted FEV_1. Both SITT and MART studies included patients with ≥1 moderate or severe exacerbations in the year before the study, except for the CAPTAIN study.[18]

[a]Only documented healthcare contact or documented temporary change in asthma therapy for acute asthma symptoms within 1 year before screening were also required, not moderate-to-severe exacerbations.

[b]Adolescent+adults, 200 μg budesonide/6 μg formoterol.

[c]Adults only, 100 mcg BDP/6 μg formoterol MART.

appears less effective compared to the MART studies,[39] the efficacy of SITT cannot be directly compared with an overall >30% reduction obtained with MART in younger and milder patients (Table 2)[39]; (4) future studies will have to explore also if medium or even lower dose ICS SITT may constitute a valid treatment alternative to low-dose ICS/LABA therapy in milder forms of asthma, such as GINA step 3 patients; (5) high-dose SITT might be a therapeutic option for patients on high-dose ICS/LABA, particularly to avoid maintenance therapy with oral corticosteroids (OCS). A post hoc analyses of TRIMARAN-TRIGGER studies published in abstract form,[45] reported 24% less days of treatment with systemic corticosteroids with high-dose BDP/FF/GLY vs high-dose BDP/FF. However, this observation remains unconfirmed, and the potential OCS-sparing effect of SITT deserves further properly designed prospective research; (6) because of the high economic cost of biologics, many countries require a failed triple inhalation therapy approach before biologics can be added. This may be the correct approach in those with persistent airflow limitation[12] but probably not for those who achieve normal pulmonary function with high-dose ICS/LABA but continue to suffer frequent exacerbations. Again, this alternative requires research; and, finally, (7) it has been recently established that SITT improves survival in patients with chronic obstructive pulmonary disease (COPD) with FEV_1<50% of predicted and a history of >1 moderate or severe (hospitalized) exacerbation, or FEV1 50%–80% of predicted and >2 moderate or 1 severe exacerbation in the previous year.[46] Because mortality is lower in patients with asthma than in those with COPD, this limits the possibility of exploring the effects of SITT on mortality in patients with asthma,[47] but indeed might be considered for future research in severe asthma with persistent airflow limitation and increased risk of exacerbations.

4 | CONCLUSIONS

Single-inhaler triple therapy offers a novel safe and effective therapeutic option for patients with asthma uncontrolled on medium- to high-dose ICS/LABA. In clinical practice, however, several important patient-related factors, including compliance, need to be considered carefully, and the optimum place for these treatments within existing treatment guidelines needs to be properly established.

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CONFLICT OF INTEREST

Dr. Agusti reports personal fees from Chiesi, during the conduct of the study; grants and personal fees from GSK, grants and personal fees from Menarini, grants and personal fees from Chiesi, grants and personal fees from AZ, personal fees from Zambon, outside the submitted work. Dr. Fabbri reports personal fees and non-financial support from AstraZeneca, personal fees and non-financial support from Chiesi, personal fees and non-financial support from GSK, personal fees and non-financial support from Novartis, personal fees and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Zambon, personal fees from Lusofarmaco, outside the submitted work. Dr. Lahousse has nothing to disclose. Dr. Singh reports personal fees from Chiesi, during the conduct of the study; personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from Cipla, personal fees from Genentech, personal fees from GlaxoSmithKline, personal fees from Glenmark, personal fees from Gossamerbio, personal fees from Menarini, personal fees from Mundipharma, personal fees from Novartis, personal fees from Peptinnovate, personal fees from Pfizer, personal fees from Pulmatrix, personal fees from Theravance, personal fees from Verona, outside the submitted work. Dr. Papi reports grants, personal fees, non-financial support and other from GlaxoSmithKline, grants, personal fees and non-financial support from AstraZeneca, grants, personal fees, non-financial support and other from Boehringer Ingelheim, grants, personal fees, non-financial support and other from Chiesi Farmaceutici, grants, personal fees, non-financial support and other from TEVA, personal fees, non-financial support and other from Mundipharma, personal fees, non-financial support and other from Zambon, personal fees, non-financial support and other from Novartis, grants, personal fees and non-financial support from Menarini, personal fees, non-financial support and other from Sanofi/Regeneron, personal fees from Roche, grants from Fondazione Maugeri, grants from Fondazione Chiesi, personal fees from Edmondpharma, outside the submitted work.

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REFERENCES

1. Global strategy for asthma management and prevention (GINA). 2021; https://ginasthma.org/. Accessed April 26, 2021.
2. FitzGerald JM, Sadatsafavi M. Triple therapy in a single inhaler: a new option for uncontrolled asthma. *Lancet*. 2019;394(10210):1690-1692.
3. Kerstjens HAM, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med*. 2012;367(13):1198-1207.
4. Bonini M, Di Paolo M, Bagnasco D, et al. Minimal clinically important difference for asthma endpoints: an expert consensus report. *Eur Respir Rev*. 2020;29(156):190137.
5. Rogliani P, Matera MG, Facciolo F, Page C, Cazzola M, Calzetta L. Beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide: synergy of triple combination therapy on human airway smooth muscle ex vivo. *Br J Pharmacol* 2020;177(5):1150-1163.
6. 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.
7. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine*. 2009;6(7):e1000097.
8. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
9. Rogliani P, Ritondo BL, Calzetta L. Triple therapy in uncontrolled asthma: a network meta-analysis of phase III studies. *Eur Respir J*. 2021;58(3):2004233.

10. 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(10210):1737-1749.
11. Canonica WG, Paggiaro P, Kots M, et al. Reducing the rate of severe asthma exacerbations using single-inhaler extrafine BDP/FF/GB combination compared to BDP/FF in patients with uncontrolled asthma: pooled results from the TRIMARAN and TRIGGER studies. *ATS Annual meeting*. 2019;199: A7363.
12. Singh D, Virchow JC, Canonica GW, et al. Extrafine triple therapy in patients with asthma and persistent airflow limitation. *Eur Respir J*. 2020;56(3):2000476.
13. Papi A, Virchow JC, Singh D, et al. Extrafine triple therapy and asthma exacerbation seasonality: TRIMARAN and TRIGGER post-hoc analyses. *J Allergy Clin Immunol*. 2021;148(1):262-265.e2.
14. 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(1):285.
15. 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(10):1000-1012.
16. Vaidya S, Ziegler D, Tanase AM, et al. Pharmacokinetics of mometasone furoate delivered via two dry powder inhalers. *Pulm Pharmacol Ther*. 2021;70:102019.
17. Gessner C, Kornmann O, Maspero J, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: a randomised, phase IIIb, non-inferiority study (ARGON). *Respir Med*. 2020;170:106021.
18. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma: a double-blind, randomised, Phase IIIA trial (CAPTAIN study). *Lancet Respir Med*. 2020;9:3–5.
19. 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(24):2466-2479.
20. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353(5):487-497.
21. Delea TE, Hagiwara M, Stanford RH, Stempel DA. Effects of fluticasone propionate/salmeterol combination on asthma-related health care resource utilization and costs and adherence in children and adults with asthma. *Clin Ther*. 2008;30(3):560-571.
22. Marceau C, Lemiere C, Berbiche D, Perreault S, Blais L. Persistence, adherence, and effectiveness of combination therapy among adult patients with asthma. *J Allergy Clin Immunol*. 2006;118(3):574-581.
23. Stoloff SW, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol*. 2004;113(2):245-251.
24. Averell CM, Laliberte F, Duh MS, Wu JW, Germain G, Faison S. Characterizing real-world use of tiotropium in asthma in the USA. *J Asthma Allergy*. 2019;12:309-321.
25. Stempel DA, Stoloff SW, Carranza Rosenzweig JR, Stanford RH, Ryskina KL, Legorreta AP. Adherence to asthma controller medication regimens. *Respir Med*. 2005;99(10):1263-1267.
26. Zhang S, King D, Rosen VM, Ismaila AS. Impact of single combination inhaler versus multiple inhalers to deliver the same medications for patients with asthma or COPD: a systematic literature review. *Int J Chron Obstruct Pulmon Dis*. 2020;15:417-438.
27. Parimi M, Svedsater H, Ann Q, et al. Persistence and adherence to ICS/LABA drugs in UK patients with asthma: a retrospective new-user cohort study. *Adv Ther*. 2020;37(6):2916-2931.
28. Stanford RH, Averell C, Parker ED, Blauer-Peterson C, Reinsch TK, Buikema AR. Assessment of adherence and asthma medication ratio for a once-daily and twice-daily inhaled corticosteroid/long-acting beta-agonist for asthma. *J Allergy Clin Immunol Pract*. 2019;7(5):1488-1496 e1487.
29. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of airway diseases. *Eur Respir J*. 2016;47:410-419.
30. Agustí A, Bafadhel M, Beasley R, et al. Precision medicine in airway diseases: moving to clinical practice. *Eur Respir J*. 2017;50(4):1-13.
31. McDonald VM, Fingleton J, Agusti A, et al. Treatable traits: a new paradigm for 21(st) century management of chronic airway diseases. *Eur Respir J*. 2019;53(4);1802058.
32. Hiles SA, Gibson PG, Agusti A, McDonald V. Treatable traits that predict health status and treatment response in airway disease. *J Allergy Clin Immunol Pract*. 2020.9(3):1255–1265.e2.
33. Virchow JC. Assessing the benefits of triple versus dual fixed-dose combinations for the treatment of severe asthma. *Lancet Respir Med*. 2020;8(10):937-939.
34. Finkas LK, Martin R. Role of small airways in asthma. *Immunol Allergy Clin North Am*. 2016;36(3):473-482.
35. Averell CM, Laliberte F, Sheng Dhu M, Wu JW, Germain G, Faison S. Characterizing real-world use of tiotropium in asthma in the USA. *J Asthma Allergy*. 2019;12:309-321.
36. Masoli M, Holt S, Weatherall M, Beasley R. Dose-response relationship of inhaled budesonide in adult asthma: a meta-analysis. *Eur Respir J*. 2004;23(4):552-558.
37. Edris A, De Feyter S, Maes T, Joos G, Lahousse L. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. *Respir Res*. 2019;20(1):179.
38. Cloutier MM, Dixon AE, Krishnan JA, Lemanske RF Jr, Pace W, Schatz M. Managing asthma in adolescents and adults: 2020 asthma guideline update from the national asthma education and prevention program. *JAMA*. 2020;324(22):2301-2317.
39. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA*. 2018;319(14):1485-1496.
40. Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract*. 2007;61(5):725-736.
41. Bousquet J, Boulet L-P, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med*. 2007;101(12):2437-2446.
42. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35-48.
43. Patel M, Pilcher J, Pritchard A, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med*. 2013;1(1):32-42.
44. Bateman ED, Harrison TW, Quirce S, et al. Overall asthma control achieved with budesonide/formoterol maintenance and reliever therapy for patients on different treatment steps. *Respir Res*. 2011;12(1):38.
45. Canonica WG, Paggiaro P, Kots M, et al. Reducing the rate of severe asthma exacerbations using single-inhaler extrafine BDP/FF/GB combination compared to BDP/FF in patients with uncontrolled asthma: pooled results from the TRIMARAN and TRIGGER studies. *Am J Respir Crit Care Med*. 2020;201:A7363.
46. Lipson DA, Crim C, Criner GJ, et al. Reduction in all-cause mortality with fluticasone furoate/umeclidinium/vilanterol in COPD patients. *Am J Respir Crit Care Med*. 2020;201(12):1508-1516.

47. O'Byrne P, Fabbri LM, Pavord ID, Papi A, Petruzzelli S, Lange P. Asthma progression and mortality: the role of inhaled corticosteroids. *Eur Respir J*. 2019;54(1):1900491.
48. Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin*. 2004;20(9):1403-1418.
49. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*. 2005;171(2):129-136.
50. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet*. 2006;368(9537):744-753.
51. Papi A, Corradi M, Pigeon-Francisco C, et al. Beclometasone–formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med*. 2013;1(1):23-31.
52. Papi A, Marku B, Scichilone N, et al. Regular versus as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. *Lancet Respir Med*. 2015;3(2):109-119.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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