EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies

Paola Rogliani, Beatrice Ludovica Ritondo, Luigino Calzetta

Please cite this article as: Rogliani P, Ritondo BL, Calzetta L. Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.04233-2020).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies

Paola Rogliani[1*], Beatrice Ludovica Ritondo[1], Luigino Calzetta[2]

1. Unit of Respiratory Medicine, Department of Experimental Medicine, University of Rome “Tor Vergata”, Rome, Italy.
2. Department of Medicine and Surgery, Respiratory Disease and Lung Function Unit, University of Parma, Parma, Italy.

*Corresponding author: Paola Rogliani, Department of Experimental Medicine, Via Montpellier 1, 00133 - Rome, Italy, Tel: +39 06 2090 4656 E-mail address: paola.rogliani@uniroma2.it.

Take home message

Triple combination therapy by adding either a LAMA to ICS/LABA FDC or escalating ICS on a background of ICS/LABA/LAMA FDC may reduce severe exacerbations and improve lung function; adding a LAMA along with escalating ICS provides incremental effects.

Abstract

Conflicting evidence is currently available concerning the impact on asthma exacerbation of triple inhaled corticosteroid (ICS), long-acting β_2-adrenoceptor agonist (LABA), and long-acting muscarinic receptor antagonist (LAMA) fixed-dose combination (FDC). Since meta-analyses allow settling controversies of apparently inconsistent results, we performed a network meta-analysis of Phase III randomized controlled trials including 9535 patients to assess the effect of ICS/LABA/LAMA combinations in uncontrolled asthma. Triple combination therapies with an ICS administered at high dose (HD) were more effective ($P<0.05$) than medium dose (MD) ICS/LABA/LAMA FDC and both MD and HD ICS/LABA FDCs against moderate to severe exacerbation (relative risk [RR] from 0.61 to 0.80) and increasing trough forced expiratory volume in the 1st second (mL from +33 to +114). Triple combination therapies including HD ICS were superior ($P<0.05$) than MD ICS/LABA/LAMA FDC in preventing severe exacerbation (RR from 0.46 to 0.65), but not with respect to moderate exacerbation ($P>0.05$). Triple combination therapies were equally effective on asthma control, with no safety concerns. This quantitative synthesis suggests that ICS/LABA/LAMA FDCs are effective and safe in uncontrolled asthma, and that the dose of ICS in the combination represents the discriminating factor to treat patients with a history of moderate or severe exacerbation.

Keywords

Asthma; exacerbation; network meta-analysis; triple combination.

Introduction

Adding tiotropium bromide (TIO) to dual inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) fixed-dose combination (FDC) is currently recommended to treat asthmatic patients suffering from the most severe forms of disease [1]. Nevertheless, conflicting data are currently available concerning the real efficacy of triple ICS/LABA/long-acting muscarinic receptor antagonist (LAMA) FDCs in asthma, especially with respect to their effect against the risk of exacerbation in symptomatic patients with uncontrolled asthma [2-4].

Data from well performed meta-analyses of pivotal studies may reach the greater level of evidence [5] and, along with other numerous recognized advantages, meta-analyses may give the opportunity to settle controversies arising from apparently conflicting studies [6]. Moreover, the Bayesian network approach, the so-called network meta-analysis, not only permits to compare the effect estimates of specific outcomes resulting from different medications, but it offers also suitable information for clinicians in the form of treatment rankings, that can be graphically summarized by the surface under the cumulative ranking curve analysis (SUCRA) [7, 8].

Therefore, we have performed an unbiased network meta-analysis of Phase III randomized controlled trials (RCTs) in order to compare and rank the efficacy and safety profile of triple ICS/LABA/LAMA combination therapies in patients with uncontrolled asthma with respect to the risk of exacerbation and lung function. We also investigated the impact of triple therapies on asthma control and serious adverse events (SAEs).

Materials and methods

Detailed methods are reported in the Supplementary Data.

Search strategy and study eligibility

This meta-analysis was performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P,

Protocol ID: CRD42020211870) [9]. The flow diagram and network nodes are shown in Figure 1A and B, and Table S1 reports the PRISMA-P checklist [9].

A comprehensive literature search was performed for Phase III RCTs evaluating the impact of triple combination therapy for the treatment of asthma. As an example, Table S2 reports the literature search terms used for OVID MEDLINE and Appendix 1 shows the summary text of the identified records.

Study selection

Phase III RCTs that enrolled asthmatic patients, lasting ≥24 weeks, and that included at least one arm assessing the effect of any triple combination therapy in asthma were selected.

Data extraction

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [10]. The inter- and intra-rater reliability for data abstraction was assessed via the Cohen's Kappa score, as previously described [11].

Endpoints

The co-primary endpoints were the comparison across the different triple combination therapies and comparators with respect to the risk of moderate to severe asthma exacerbation and the change from baseline in trough forced expiratory volume in the 1st second (FEV_1).

The secondary efficacy endpoint included the comparison across the triple combination therapies and comparators with respect to the change from baseline in asthma control questionnaire (ACQ) score. The safety endpoint was the risk of SAEs, namely pneumonia and serious cardiovascular (CV) adverse events (AEs).

Quality of studies, risk bias, and evidence profile

The summary of the risk of bias for each included RCT was analyzed via the Cochrane Risk of Bias 2 (RoB 2) [12] and Jadad score [13]. The weighted assessment of the overall risk of bias was analyzed via the Cochrane RoB 2 [12], along with the normalized consistency/inconsistency analysis [14]. The

quality of evidence was assessed for the primary endpoint via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [15].

Data synthesis and analysis

A network meta-analysis was performed via full Bayesian random-effect model to compare the impact of the different triple combination therapies and comparators in asthmatic patients. Subset and sensitivity analyses were performed in agreement with average patients' characteristics at baseline. Results are expressed as relative effect (RE) and 95% credible interval (95%CrI) or 95% confidence interval (95%CI). The SUCRA was calculated for both the co-primary and secondary endpoints [16]; the SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [14]. The statistical significance was assessed for $P<0.05$.

Results

Study characteristics

Data obtained from 9535 asthmatic patients were selected from 5 Phase III RCTs (Table S3). All five studies were performed in symptomatic patients suffering from uncontrolled asthma [17-20].

In agreement with the search strategy and study selection criteria, the investigated ICS/LABA/LAMA FDCs included beclomethasone dipropionate (BDP)/formoterol fumarate (FOR)/glycopyrronium bromide (GLY) in 2 studies [20], momethasone furoate (MF)/indacaterol (IND)/glycopyrronium bromide (GLY) in 2 studies, and fluticasone furoate (FF)/vilanterol (VI)/umeclidinium (UMEC) in 1 study [17]. The investigated free combination ICS/LABA FDC + TIO included BDP/FOR + TIO in 1 study [20] and FP/SAL + TIO in 1 study [19].

The active comparators were the ICS/LABA FDCs BDP/FOR, FF/VI, MF/IND, and FP/SAL.

The definition of moderate to severe asthma exacerbation and the level of ICS doses are shown in Table S4 and S5 of the supplement, respectively. The

inter- and intra-rater reliability for data abstraction was generally excellent (Cohen's Kappa >0.90).

Further study characteristics are reported in the Supplementary Data.

Co-primary endpoints

Risk of exacerbation

High dose (HD) ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO were equally effective (P>0.05) in preventing the risk of moderate to severe asthma exacerbation. HD ICS/LABA/LAMA FDC significantly (P<0.05) reduced the risk exacerbation compared to medium dose (MD) ICS/LABA/LAMA FDC and MD ICS/LABA FDC, whereas a trend toward significance (P=0.05) was detected vs. HD ICS/LABA FDC. Detailed RR and 95%CrI values across the investigated combinations are reported in Table 1, with data graphically reported in Figure 2A as forest plot.

The SUCRA analysis indicated that both HD ICS/LABA FDC + TIO and HD ICS/LABA/LAMA FDC were the most effective treatments in reducing the risk of moderate or severe asthma exacerbation (first quartile), followed by HD ICS/LABA FDC (borderline second/third quartile), MD ICS/LABA/LAMA FDC (third quartile), and MD ICS/LABA FDC (fourth quartile) (Figure 3A).

The person-based NNT per year concerning the prevention of moderate to severe asthma exacerbation was 40.29 for HD ICS/LABA/LAMA FDC vs. MD ICS/LABA/LAMA FDC, 32.90 vs. HD ICS/LABA FDC, and 12.08 vs. MD ICS/LABA FDC. Considering MD ICS/LABA/LAMA FDC, the person-based NNT per year was 179.29 vs. HD ICS/LABA FDC and 17.25 vs. MD ICS/LABA FDC. The person-based NNT analysis was performed only for FDCs because the data concerning HD ICS/LABA FDC + TIO were spurious since the ARGON study [19] did not provide data suitable to be included in the NNT analysis. Details on the person-based NNT per year on moderate to severe asthma exacerbation are shown in Table 2.

The subset analysis performed in agreement with the severity of exacerbation reported an overall superiority of both HD ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO over both MD ICS/LABA/LAMA FDC, HD ICS/LABA FDC, and MD ICS/LABA FDC with respect to the protection against the risk of

severe asthma exacerbation. Conversely, MD and HD ICS/LABA/LAMA FDC were superior only to MD ICS/LABA FDC, and not to HD ICS/LABA FDC, in reducing the risk of moderate asthma exacerbation. No significant difference (P>0.05) was recorded across all the triple combination therapies in preventing the risk of moderate asthma exacerbation (Table 3). Another subset analysis performed in agreement with the different doses of UMEC included in the FDCs of the CAPTAIN RCT [17] did not result in significant (P>0.05) differences in the risk of moderate to severe asthma exacerbation, compared to the overall network meta-analysis (data not shown).

A sensitivity analysis was carried out by excluding the CAPTAIN RCT [17] from the Bayesian network, since this was the only study that included a population of asthmatic patients reporting less than 1 exacerbation in the previous year (average rate =0.8). Conversely, all the other investigated RCTs [18-20] enrolled asthmatic patients reporting more than 1 exacerbation in the previous year (average rate ≥1.2). Results of the sensitivity analysis (Table S6) were not significantly (P>0.05) different when compared with those of the overall analysis, although the level of significance between some triple combination therapies and some comparators changed (i.e. HD ICS/LABA/LAMA FDC vs. MD ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO vs. HD ICS/LABA FDC). In any case, the sensitivity analysis carried out specifically on either moderate or severe exacerbation produced results generally consistent (P>0.05) with those of the overall subset analysis (Table S7).

Trough FEV_1

The improvement in trough FEV_1 was not different between HD ICS/LABA/LAMA FDC and HD ICS/LABA FDC + TIO, with both the treatments being significantly (P<0.05) more effective than MD and HD ICS/LABA FDCs. HD ICS/LABA/LAMA FDC was also significantly more effective than MD ICS/LABA/LAMA FDC on trough FEV_1, and in turn MD ICS/LABA/LAMA FDC was significantly (P<0.05) superior than both HD and MD ICS/LABA FDCs. Detailed comparisons across the investigated combinations on trough FEV_1 are reported in Table 1 and Figure 2B.

The SUCRA analysis showed that HD ICS/LABA/LAMA FDC was the most effective treatment improving trough FEV_1, followed by HD ICS/LABA FDC + TIO (borderline first/second quartile), MD ICS/LABA/LAMA FDC (second quartile), HD ICS/LABA FDC (borderline third/fourth quartile), and MD ICS/LABA FDC (fourth quartile) (Figure 3B).

The subset analysis performed in agreement with the different doses of UMEC included in the FDCs of the CAPTAIN RCT [17] did not result in significant (P>0.05) differences in trough FEV_1, compared to the overall network meta-analysis (data not shown).

The sensitivity analysis (Table S6) carried out by excluding the CAPTAIN RCT [17] provided results not significantly (P>0.05) different compared with those of the overall Bayesian network. Only the level of significance between HD ICS/LABA/LAMA FDC and MD ICS/LABA/LAMA FDC changed compared with the overall analysis.

Adding a LAMA and/or escalate ICS in FDC

Adding a LAMA to either MD or HD ICS/LABA FDC reduced the risk of moderate to severe asthma exacerbation (risk difference [RD]: -0.21 95%CrI -0.35 - -0.06 and -0.17 95%CrI -0.31 – 0, respectively; Figure 4A) and increased trough FEV_1 (delta effect, mL: +81 95%CrI 53 – 111 and +91 95%CrI 63 - 121, respectively; Figure 4B), as well as escalating the dose of ICS on a background of MD ICS/LABA/LAMA FDC (RD: -0.20 95%CrI -0.34 - -0.05, Figure 4A; delta effect, mL: +33 95%CrI 5 – 62, Figure 4B). Adding a LAMA along with escalating the dose of ICS further prevented the risk of moderate to severe asthma exacerbation (RD -0.25 95%CrI -0.38 - -0.09, Figure 4A) and improved trough FEV_1 (delta effect, mL: +114 95%CrI 85 – 145, Figure 4B).

Secondary endpoints

Detailed comparisons across the investigated combinations with respect to the secondary endpoints are reported in Table 1.

ACQ

Both MD and HD ICS/LABA/LAMA FDCs and HD ICS/LABA FDC + TIO were equally (P>0.05) effective in improving ACQ, although a trend toward significance (P=0.05) was detected for HD ICS/LABA/LAMA vs. MD ICS/LABA/LAMA FDC (Table 1).

Safety

No significant (P>0.05) difference was detected across the investigated combinations concerning the risk of SAEs, pneumonia, and serious CV AEs (Table 1).

Risk of bias and quality of evidence

The weighted plot for the assessment of the overall risk of bias by domains is shown in Figure S1, and the traffic light plot for the assessment of each included RCT is reported in Figure S2. All Phase III RCTs had a low risk of bias for the randomization process (5 [100.0%]), missing outcome data (5 [100.0%]), and selection of the reported results (5 [100.0%]). Three RCTs (60.0%) had some concerns in the domain of deviations from intended intervention and measurement of the outcomes.

All the studies (100.0%) included in this network meta-analysis were ranked as being of medium- to high-quality in agreement with Jadad score (Table S3).

The normalized consistency/inconsistency analysis showed that all points fit adequately with the line of equality (overall goodness of fit: R^2 0.961; slope 0.993, 95%CI 0.927 – 1.058), indicating that this network meta-analysis was not affected by significant bias with respect to co-primary endpoints (Figure S3A and B). The lack of bias in the overall Bayesian network was further confirmed by the absence of significant (P>0.05) inconsistency factors when the investigated triple combination therapies and active treatments were compared directly or indirectly.

However, a potential source of bias can be related with the fact that the definition of moderate and severe asthma exacerbation was not uniform among the investigated studies [17-20]. The impact of exacerbation frequency in the previous year on the co-primary outcomes was investigated via sensitivity analysis, whose results are shown in Table S6 and S7.

Overall, the assessment of the quality of evidence carried out via the GRADE system reported a general high-quality of evidence (++++) for the results concerning the comparison across the investigated triple combination therapies with respect to the risk of moderate to severe asthma exacerbation and trough FEV_1. Details on the quality of evidence for each specific comparison are shown in Table 1.

Discussion

The overall results of this network meta-analysis provide the high-quality evidence that triple combination therapies including an ICS administered at HD have greater beneficial impact than MD ICS/LABA/LAMA FDC and both MD and HD ICS/LABA FDCs in reducing the risk of moderate to severe exacerbation and improving trough FEV_1 in patients suffering from uncontrolled asthma, regardless of whether the monocomponents were combined in the formulation as FDC or free combination.

Such a superiority on the risk of exacerbation of triple combinations including an ICS at HD was further confirmed by the NNT analysis. In fact, while ≈40 patients had to be treated for one year with HD ICS/LABA/LAMA FDC to prevent one moderate or severe asthma exacerbation compared to MD ICS/LABA/LAMA FDC, the NNT was ≈33 and only ≈12 when compared to HD and MD ICS/LABA FDCs, respectively. Unexpectedly, the treatment with MD ICS/LABA/LAMA FDC resulted in a clinically appreciable NNT value of ≈17 when compared to MD ICS/LABA FDC, but not vs. HD ICS/LABA FDC as the NNT value was ≈179. Since Kaplan-Meyer curves were not available for all the studies that included free combinations of HD ICS/LABA FDC + TIO [19], the available data were spurious and not suitable to adequately assess the NNT of this triple combination. In any case, looking at the specific RR of triple combinations including HD ICS, we can postulate that the NNT values of HD ICS/LABA FDC + TIO could be similar to that of HD ICS/LABA/LAMA FDC.

Overall, the superiority of triple combination therapies with an ICS at HD over MD ICS/LABA/LAMA FDC, and of MD ICS/LABA/LAMA FDC over MD and HD ICS/LABA FDC, was confirmed in the subset analysis on severe asthma

exacerbations. Conversely, all the combinations, excluded MD ICS/LABA FDC, were equally effective in reducing the risk of moderate asthma exacerbation. These findings suggest that triple combinations including an ICS administered at HD may represent the first treatment choice in patients with a history of severe asthma exacerbation, whereas in those patients with a history of moderate asthma exacerbation either MD ICS/LABA/LAMA FDC or HD ICS/LABA FDC, but not MD ICS/LABA FDC, may be used as first line treatment.

Despite the unpredictable nature of asthma exacerbations regardless of disease severity, recent evidence indicates that the past history and severity of exacerbations in the year prior may predict the risk and severity of future asthma exacerbations [21]. In this respect, the results of the subset analysis on exacerbation severity may provide the rationale for a tailored therapy based on the severity of exacerbation that each patient experienced in the previous year, thus leading to the optimization of the dose of ICS and the number of bronchodilators included in the FDC.

Concerning the secondary endpoints investigated in this network meta-analysis, triple combination therapies were equally effective in improving ACQ, and no safety concerns resulted with respect of the risk of SAEs, pneumonia, and serious CV AEs.

Indeed, the studies included in this network meta-analysis enrolled symptomatic patients with uncontrolled asthma [17-20], for which the current Global Initiative for Asthma (GINA) document [1] suggests using MD ICS/LABA FDC at Step 4 and HD ICS/LABA plus either TIO or biologic therapy depending on the phenotypic assessment at Step 5 as preferred controller therapies to control symptoms and prevent exacerbations. Furthermore, GINA [1] recommends HD ICS or add-on TIO at Step 4 as alternative controller option.

Clearly, the evidence raised by this quantitative synthesis provides new horizon for the treatment of severe asthma, in which poorly controlled symptomatic patients could be effectively treated with triple combination therapies including different doses of an ICS according with the severity of

previous exacerbations. The recent approval of the first once-daily single inhaler triple therapy for the treatment of asthma by the Food and Drug Administration (FDA) [22] and the current data resulting from the studies included in this network meta-analysis [17-20] support the clinical benefit of adding a LAMA to ICS/LABA, an effect of class not related with a specific antimuscarinic agent. In the light of this evidence, it is expected that the next iteration of asthma recommendations and guidelines will include also ICS/LABA/LAMA FDCs as effective pharmacological strategies for symptom control and risk reduction. Moreover, and not less important, this meta-analysis allows us to clear the assumption that in the treatment of uncontrolled asthma a LAMA should be combined only with an ICS administered at HD, as well as a LABA, because MD ICS/LABA/LAMA FDC was effective on both symptoms and moderate asthma exacerbations.

The limitations of this study are related with the intrinsic characteristics of the Bayesian network approach [23-25], mainly due to the indirect comparison across treatments and to the fact that only 5 studies [17-20] were included in the quantitative synthesis. However, as shown in Figure 1B, the resulting network included several direct comparisons across the investigated treatments, leading to solid network loops also in the subset analyses carried out in more homogenous asthmatic populations. Therefore, also considering that data from a large number of patients (>9500 subjects) were analysed, the resulting effect estimates were free from any within- and across-studies risk of bias, at least for the co-primary endpoints.

Furthermore, as correctly stated by Mauger and Apter [26], while some degree of variation across study populations could be acceptable in a pairwise meta-analysis, this can lead to biased results in a network meta-analysis. Thus, considering that four [18-20] of the five studies included in the Bayesian network enrolled frequent exacerbators, whereas only the CAPTAIN study [17] enrolled patients reporting less than 1 exacerbation in the previous year, we performed a sensitivity analysis by considering exclusively those studies in which populations of asthmatic patients with frequent exacerbations were investigated. Considering also the severity of exacerbation, the sensitivity analysis basically confirmed the main findings of the overall analysis,

indicating that the results are robust. The small changes in the level of significance detected in the sensitivity analysis could be due by the fact that in the overall analysis some of the 95%CrIs were lying close to the line of equality, thus the reduction in the study population due to the exclusion of the CAPTAIN study [17] changed the 95%CrIs with no relevant modification of the effect estimates. Interestingly, in the sensitivity analysis we found greater consistency in the level of statistical significance between the risk of moderate to severe exacerbation and trough FEV_1 than in the overall analysis. This evidence corroborates the hypothesis that exacerbation-prone asthma may be a specific phenotype with implications for the targeting of exacerbation prevention strategies along with lung function improvement [27].

Certainly, the CAPTAIN study [17] also provided further important information concerning the potential confounder of disparate study populations. Specifically, Lee and colleagues [17] demonstrated that increasing the ICS dose resulted in improved outcomes among the patients with high type 2 inflammatory biomarkers. On the other hand, in patients with low type 2 inflammatory biomarkers the increase in ICS dose provided no further disease improvement, while adding a LAMA was efficacious. This is an important finding supporting an alternative approach by adding a LAMA instead of escalating the dose of ICS in type 2 low asthma.

International recommendations and guidelines [1, 28] provide general definitions of asthma exacerbation, however, despite the attempt to uniform the definition of asthma exacerbation [29, 30], to date there is no consensus on a standardized definition of moderate and severe asthma exacerbation [31-33]. Such a clinical unmet need led to the last intrinsic limitation of this network meta-analysis: apart from the TRIMARAN and TRIGGER RCTs [20], there was not consistence among the investigated studies in the definition of either moderate or severe asthma exacerbation. Unfortunately, this is a limitation that cannot be solved by a sensitivity analysis and that may potentially introduce some unquantifiable bias in the exacerbation outcome.

Concluding, both ICS/LABA/LAMA FDC and free combination of TIO added to ICS/LABA FDC are effective and safe therapeutic strategies in patients suffering from uncontrolled asthma, with the level of the ICS dose

representing the discriminating factor to treat patients with a history of moderate or severe exacerbation. Furthermore, here we provide the clinical evidence that triple FDCs by adding either a LAMA or increase ICS dose on a background of ICS/LABA/LAMA FDC may reduce the risk of severe exacerbation and improve lung function, and that adding a LAMA along with escalating ICS provides incremental effects. Indeed, the evidence raised by this quantitative synthesis may help to solve the inconsistencies across the primary publications [17-20] with respect to the beneficial impact of triple combination therapy against asthma exacerbation. However, there remains the question concerning the correct positioning of triple combination therapy in the GINA stepwise approach for adjusting treatment for individual patient needs [1]. In this respect, MD and HD ICS/LABA/LAMA FDCs should be tested in well-designed Phase III RCTs enrolling separately asthmatic patients at Step 4 and 5 in order to guide clinicians to correctly practice personalized medicine. In any case, the decision of whether or not to first add a LAMA or escalate the dose of ICS, or both, in a poorly controlled patient on MD ICS/LABA FDC remains a clinical matter that may be driven by the overall level of disease control, available biomarkers, or concerns over potential AEs.

Contributors

PR, BLR, and LC had full access to all of the data in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis. PR, BLR, and LC designed the statistical analyses. PR and LC wrote the first draft of the Article, in consultation with BLR for data interpretations. All authors revised the Article critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the Article in ensuring that questions related to the accuracy or integrity of any part of the Article were appropriately investigated and resolved.

Guarantor of the review

PR and LC are the guarantors of this review and meta-analysis.

Funding

Not applicable.

Declaration of interests

PR participated as a lecturer and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Mundipharma, and Novartis, and her department was funded by Almirall, Boehringer Ingelheim, Chiesi Farmaceutici Novartis, and Zambon. BLR has no conflict of interest to declare. LC has participated as advisor in scientific meetings under the sponsorship of Boehringer Ingelheim and Novartis; received nonfinancial support from AstraZeneca; a research grant partially funded by Chiesi Farmaceutici, Boehringer Ingelheim, Novartis, and Almirall; is or has been a consultant to ABC Farmaceutici, Edmond Pharma, Zambon, Verona Pharma, and Ockham Biotech; and his department was funded by Almirall, Boehringer Ingelheim, Chiesi Farmaceutici, Novartis, and Zambon.

Acknowledgments

Not applicable.

References

1. GINA. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Available at: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf. Last accessed September 4, 2020. 2020.
2. Virchow JC. Assessing the benefits of triple versus dual fixed-dose combinations for the treatment of severe asthma. *The Lancet Respiratory Medicine* 2020: 8(10): 937-939.
3. FitzGerald JM, Sadatsafavi M. Triple therapy in a single inhaler: a new option for uncontrolled asthma. *The Lancet* 2019: 394(10210): 1690-1692.
4. Chang AB, Beasley R. More options for managing severe asthma in adults. *The Lancet Respiratory Medicine* 2020.
5. Gershon AS, Jafarzadeh SR, Wilson KC, Walkey AJ. Clinical Knowledge from Observational Studies. Everything You Wanted to Know but Were Afraid to Ask. *Am J Respir Crit Care Med* 2018: 198(7): 859-867.
6. Deeks JJ, Higgins JP, Altman DG, Group CSM. Analysing data and undertaking meta-analyses. *Cochrane handbook for systematic reviews of interventions* 2019: 241-284.
7. Rogliani P, Ritondo BL, Ora J, Cazzola M, Calzetta L. SMART and as-needed therapies in mild to severe asthma: a network meta-analysis. DOI: 10.1183/13993003.00625-2020. *Eur Respir J* 2020.
8. Rogliani P, Matera MG, Ritondo BL, De Guido I, Puxeddu E, Cazzola M, Calzetta L. Efficacy and cardiovascular safety profile of dual bronchodilation therapy in chronic obstructive pulmonary disease: A bidimensional comparative analysis across fixed-dose combinations. *Pulmonary pharmacology & therapeutics* 2019: 59: 101841.
9. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015: 4: 1.
10. Pedder H, Sarri G, Keeney E, Nunes V, Dias S. Data extraction for complex meta-analysis (DECiMAL) guide. *Systematic reviews* 2016: 5(1): 212.
11. Gianinazzi ME, Rueegg CS, Zimmerman K, Kuehni CE, Michel G, Swiss Paediatric Oncology G. Intra-rater and inter-rater reliability of a medical record abstraction study on transition of care after childhood cancer. *PLoS One* 2015: 10(5): e0124290.
12. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from http://www.training.cochrane.org/handbook. 2019: 205-228.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996: 17(1): 1-12.
14. Cazzola M, Rogliani P, Calzetta L, Hanania NA, Matera MG. Impact of Mucolytic Agents on COPD Exacerbations: A Pair-wise and Network Meta-analysis. *COPD* 2017: 14(5): 552-563.

15. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011: 64(4): 383-394.
16. Dobler CC, Wilson ME, Murad MH. A pulmonologist's guide to understanding network meta-analysis. *Eur Respir J* 2018: 52(1).
17. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, Hanania NA, Kerstjens HAM, Kerwin E, Nathan R, Oppenheimer J, Papi A, Pascoe S, Brusselle G, Peachey G, Sule N, Tabberer M, Pavord ID. 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. *The Lancet Respiratory medicine* 2020.
18. Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, Lavecchia C, Pethe A, Shu X, D'Andrea P. 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. *The Lancet Respiratory medicine* 2020.
19. Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Salina A, Gupta P, Bostel S, Fucile S, Conde LG, Pfister P. 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.
20. Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. 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.
21. Bloom CI, Palmer T, Feary J, Quint JK, Cullinan P. Exacerbation patterns in adults with asthma in England. A population-based study. *American Journal of Respiratory and Critical Care Medicine* 2019: 199(4): 446-453.
22. US Food and Drug Administration. NDA 209482/S-010 - NDA 209482/S-011 supplmental approval. Available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/209482Orig1s010,s011ltr.pdf. Last accessed January 5, 2021. 2020 [cited; Available from:
23. Dias S, Caldwell DM. Network meta-analysis explained. *Archives of disease in childhood Fetal and neonatal edition* 2019: 104(1): F8-F12.
24. Jansen JP, Naci H. Is network meta-analysis as valid as standard pairwise meta-analysis? It all depends on the distribution of effect modifiers. *BMC medicine* 2013: 11(1): 159.
25. Jackson D, Barrett JK, Rice S, White IR, Higgins JP. A design-by-treatment interaction model for network meta-analysis with random inconsistency effects. *Statistics in medicine* 2014: 33(21): 3639-3654.
26. Mauger D, Apter AJ. Indirect treatment comparisons and biologics. *J Allergy Clin Immunol* 2019: 143(1): 84-86.

27. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, Castro M, Peters SP, Phipatanakul W, Aujla S. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *American journal of respiratory and critical care medicine* 2017: 195(3): 302-313.
28. Health NIf, Excellence C. Asthma: diagnosis, monitoring and chronic asthma management. Last updated: 12 February 2020. Last access January 5, 2021. *Nice Guideline 80* 2017.
29. Reddel HK, Taylor DR, Bateman ED, Boulet L-P, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *American journal of respiratory and critical care medicine* 2009: 180(1): 59-99.
30. Bousquet J, Mantzouranis E, Cruz AA, Aït-Khaled N, Baena-Cagnani CE, Bleecker ER, Brightling CE, Burney P, Bush A, Busse WW. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *Journal of Allergy and Clinical Immunology* 2010: 126(5): 926-938.
31. Virchow JC, Backer V, de Blay F, Kuna P, Ljørring C, Prieto JL, Villesen HH. Defining moderate asthma exacerbations in clinical trials based on ATS/ERS joint statement. *Respiratory medicine* 2015: 109(5): 547-556.
32. Loymans RJ, ter Riet G, Sterk PJ. Definitions of asthma exacerbations. *Current opinion in allergy and clinical immunology* 2011: 11(3): 181-186.
33. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, Adcock IM, Bateman ED, Bel EH, Bleecker ER, Boulet LP, Brightling C, Chanez P, Dahlen SE, Djukanovic R, Frey U, Gaga M, Gibson P, Hamid Q, Jajour NN, Mauad T, Sorkness RL, Teague WG. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014: 43(2): 343-373.

Table 1. Relative effects with 95%CrI resulting from the overall network meta-analysis. Treatments comparisons have been sorted in agreement with SUCRA[§] findings for the co-primary endpoints reported in Figure 3.

Comparisons		References for direct comparisons	Co-primary endpoints			Secondary endpoints			
			Moderate to severe asthma exacerbation (RR)	Trough FEV_1 (mL)	GRADE	ACQ (points)	SAEs (RR)	Pneumonia (RR)	Serious CV AEs (RR)
HD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC + TIO	[19, 20]	1.02 (0.79 - 1.34)	18.97 (-30.62 - 68.99)	++++	-0.07 (-0.15 - 0.02)	0.92 (0.60 - 1.41)	3.80 (0.68 - 23.45)	0.67 (0.16 - 3.61)
	MD ICS/LABA/LAMA FDC	[17-19]	**0.80 (0.66 - 0.95) ***	**32.72 (5.29 - 61.89) ***	++++	-0.05 (-0.10 - -0.00) [#]	0.98 (0.78 - 1.25)	2.13 (0.91 -5.73)	1.31 (0.53 - 2.69)
	HD ICS/LABA FDC	[17, 18, 20]	0.83 (0.69 - 1.00) [#]	**91.18 (62.85 - 120.94) ***	++++	**-0.08 (-0.12 - -0.03) ***	0.99 (0.78 - 1.28)	1.03 (0.47 - 2.48)	1.36 (0.57 - 2.84)
	MD ICS/LABA FDC	[17, 18]	**0.63 (0.52 - 0.76) ***	**114.18 (85.03 - 146.44) ***	++++	**-0.11 (-0.16 - -0.06) ***	1.08 (0.84 - 1.39)	1.16 (0.47 - 2.89)	1.01 (0.41 - 2.10)
HD ICS/LABA FDC + TIO vs.	MD ICS/LABA/LAMA FDC	[19]	0.78 (0.58 - 1.03)	13.94 (-36.86 - 67.92)	++++	0.02 (-0.07 - 0.11)	1.08 (0.65 - 1.67)	0.56 (0.08 - 4.12)	1.92 (0.32 - 8.31)
	HD ICS/LABA FDC	[20]	0.81 (0.61 - 1.07)	**72.60 (19.86 - 126.45) ***	++++	-0.01 (-0.10 - 0.08)	1.09 (0.68 - 1.69)	0.29 (0.04 - 1.52)	1.93 (0.34 - 9.73)
	MD ICS/LABA FDC	IC	**0.61 (0.45 - 0.82) ***	**95.71 (41.18 - 152.30) ***	++++	-0.05 (-0.14 - 0.05)	1.18 (0.75 - 1.85)	0.32 (0.04 - 1.68)	1.50 (0.24 - 6.83)
MD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC	[17, 18]	1.04 (0.87 - 1.26)	**58.45 (27.45 - 88.78) ***	++++	-0.03 (-0.07 - 0.02)	1.02 (0.79 - 1.29)	0.52 (0.17 - 1.31)	1.04 (0.47 - 2.44)
	MD ICS/LABA FDC	[17, 18, 20]	**0.79 (0.65 - 0.94) ***	**81.49 (52.75 - 110.76) ***	++++	**-0.06 (-0.12 - -0.02) ***	1.10 (0.86 - 1.39)	0.52 (0.19 - 1.43)	0.76 (0.35 - 1.78)
HD ICS/LABA FDC vs.	MD ICS/LABA FDC	IC	**0.75 (0.62 - 0.91) ***	23.00 (-7.30 - 54.06)	+++	-0.04 (-0.09 - 0.01)	1.11 (0.83 - 1.40)	1.06 (0.43 - 2.70)	0.75 (0.32 - 1.75)

[§]The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst.
[#]P=0.05
Bold text with asterisk indicates statistical significance (*P<0.05). ACQ: asthma control questionnaire; AE: adverse event; CrI: credible interval; CV: cardiovascular; FDC: fixed-dose combination; FEV_1: forced expiratory volume in the 1[st] second; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HD: high-dose; IC: indirect comparison; ICS: inhaled corticosteroid; LABA, long-acting β_2-adrenoceptor agonist; MD: medium-dose; RR: relative risk; SAE: serious adverse event; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.

Table 2. Person-based NNT and 95%CI over 52 weeks of treatment concerning the prevention of moderate to severe asthma exacerbation inpatients treated with triple combination therapies vs. active comparators. All data were calculated as weighted average.

Comparisons		NNT[a]
HD ICS/LABA/LAMA FDC (rate: 0.41) vs.	MD ICS/LABA/LAMA FDC (rate: 0.44)	40.29 (19.27 - ∞)
	HD ICS/LABA FDC (rate: 0.44)	32.90 (17.81 - 215.88)
	MD ICS/LABA FDC (rate: 0.49)	12.08 (8.85 - 19.02)
MD ICS/LABA/LAMA FDC (rate: 0.44) vs.	HD ICS/LABA FDC (rate: 0.44)	179.29 (31.15 - ∞)
	MD ICS/LABA FDC (rate: 0.49)	17.25 (11.26 - 36.88)
HD ICS/LABA FDC (rate: 0.44) vs.	MD ICS/LABA FDC (rate: 0.49)	19.09 (12.08 - 45.53)

[a]The NNT was calculated by using the weighted rates of the arms reported in each study.
95%CI: 95% confidence interval; FDC: fixed-dose combination; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; NNT: number needed to treat.

Table 3. Relative effects with 95%CrI resulting from the subset network meta-analysis with respect to the moderate or severe asthma exacerbations. Treatments comparisons have been sorted in agreement with SUCRA[§] findings for the co-primary endpoints reported in Figure 3.

Comparisons		Moderate asthma exacerbation (RR)	Severe asthma exacerbation (RR)
HD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC + TIO	0.87 (0.65 - 1.15)	1.41 (0.92 - 2.21)
	MD ICS/LABA/LAMA FDC	0.91 (0.75 - 1.10)	**0.65 (0.49 - 0.87) ***
	HD ICS/LABA FDC	0.88 (0.73 - 1.06)	0.75 (0.57 - 1.00) [#]
	MD ICS/LABA FDC	**0.67 (0.55 - 0.82) ***	**0.57 (0.42 - 0.78) ***
HD ICS/LABA FDC + TIO vs.	MD ICS/LABA/LAMA FDC	1.04 (0.78 - 1.44)	**0.46 (0.29 - 0.72) ***
	HD ICS/LABA FDC	1.00 (0.76 - 1.39)	**0.53 (0.33 - 0.85) ***
	MD ICS/LABA FDC	0.77 (0.56 - 1.07)	**0.40 (0.24 - 0.66) ***
MD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC	0.96 (0.79 - 1.18)	1.16 (0.87 - 1.58)
	MD ICS/LABA FDC	**0.74 (0.61 - 0.89) ***	0.88 (0.66 - 1.16)
HD ICS/LABA FDC vs.	MD ICS/LABA FDC	**0.76 (0.62 - 0.94) ***	0.76 (0.55 - 1.02)

[§]The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst. Bold text with asterisk indicates statistical significance (*P<0.05).
[#]P=0.05.
CrI: credible interval; CV: cardiovascular; FDC: fixed-dose combination; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; MD: medium-dose; RR: relative risk; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.

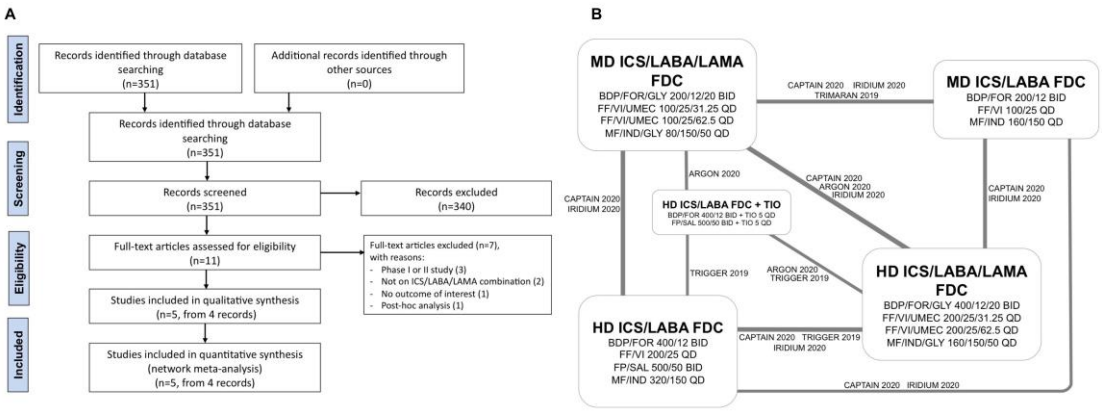
Figures and legends

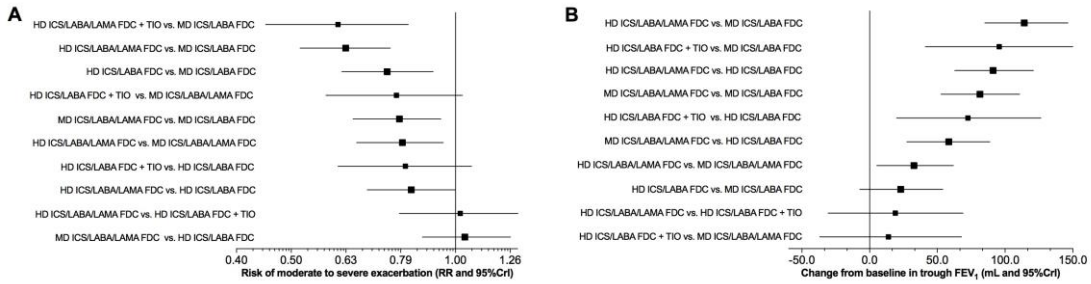
Figure 1. PRISMA-P flow diagram (A) and diagram displaying the network across the treatments (B). The links between the nodes indicate the direct comparisons between pairs of treatments, the thickness of lines is proportional with the number of the patients comparing pairs of treatment head-to-head, and the area of the boxes is proportional with the number of patients receiving the same treatment. BDP: beclomethasone dipropionate; BID: *bis in die*, twice daily; FDC: fixed-dose combination; FF: fluticasone furoate; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium; HD: high-dose; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; MF: momethasone furoate; PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols; QD: *quaque die*, once daily; SAL: salmeterol; TIO: tiotropium bromide; UMEC: umeclidinium; VI: vilanterol.

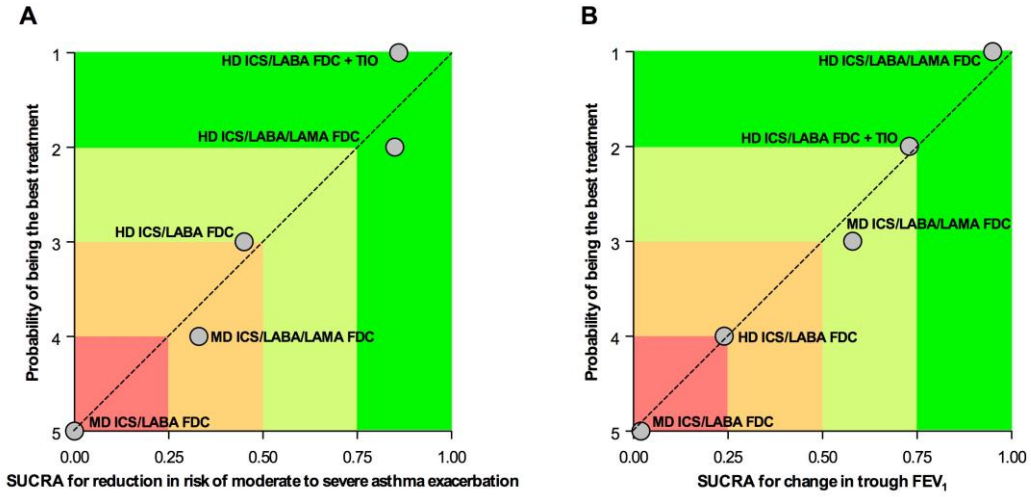
Figure 2. Overall forest plot of the comparisons across different triple combination therapies and active comparators on the risk of moderate to severe asthma exacerbation (A) and on the change from baseline in trough FEV_1 (B). Treatment comparisons have been sorted in agreement with level of efficacy. CrI: credible interval; FDC: fixed-dose combination; FEV_1: forced expiratory volume in the 1^{st} second; HD: high-dose; ICS: inhaled corticosteroid; LABA, long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; RR: relative risk; TIO: tiotropium bromide.

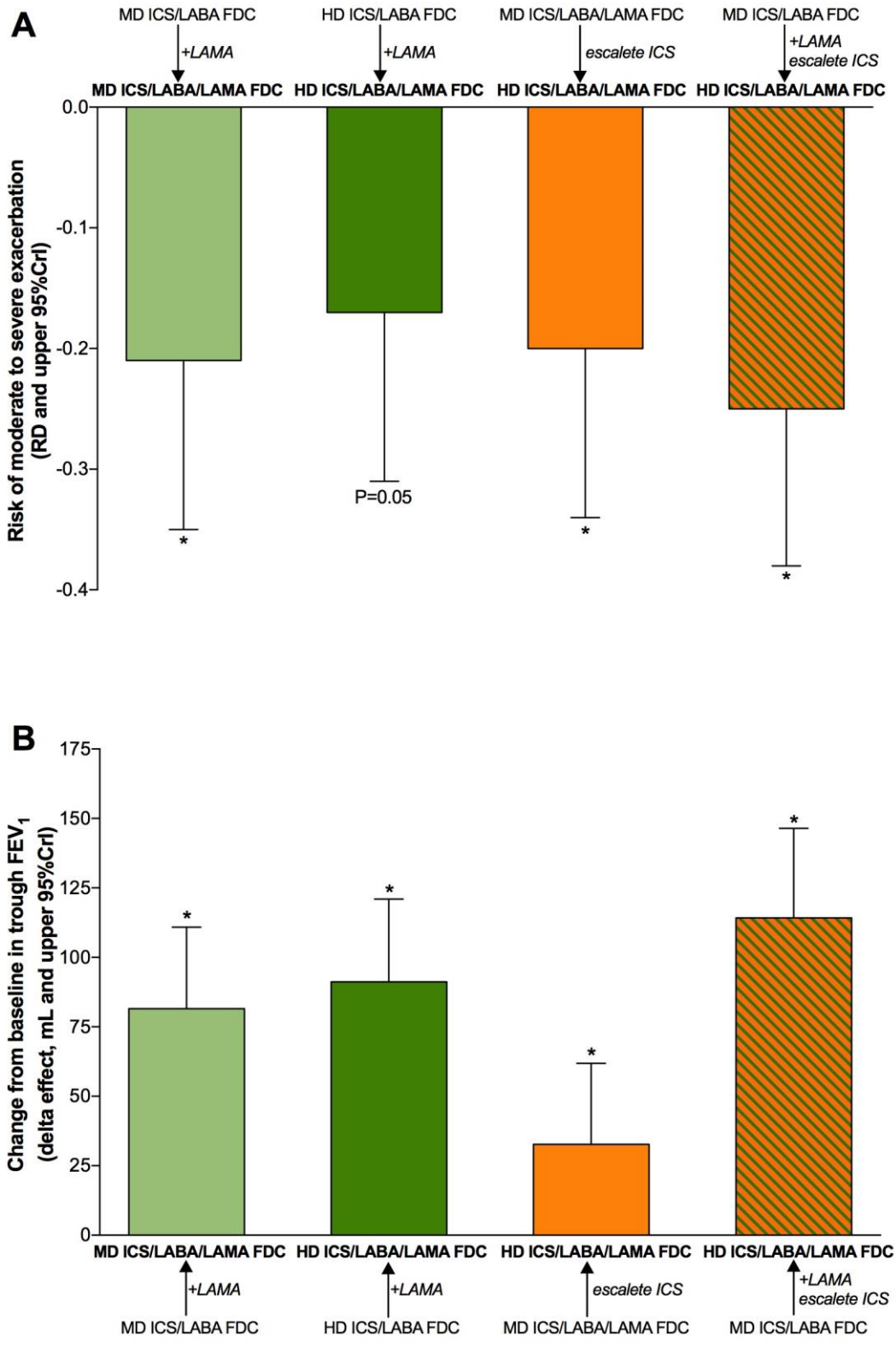
Figure 3. Overall ranking plot of the efficacy of triple combination therapies in preventing the risk of moderate to severe exacerbation (A) and in improving the change from baseline in trough FEV_1 (B) in asthmatic patients. Therapeutic strategies were plotted on X-axis according to the surface under the cumulative ranking curve analysis (SUCRA), where 1 results for a treatment considered to be the best, and 0 for a treatment considered to be the worst. The treatments were plotted on Y-axis according to the rank probability of best therapy, where a score of 1 is assigned to the best therapeutic strategy. FDC: fixed-dose combination; FEV_1: forced expiratory volume in the 1^{st} second; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; MD: medium-dose; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.

Figure 4. RD of moderate to severe exacerbation (A) and delta effect of trough FEV_1 (B) when adding a LAMA to either MD or HD ICS/LABA FDC, escalating the dose of ICS on a background of MD ICS/LABA/LAMA FDC, or both adding a LABA and escalating the dose of ICS in asthmatic patients. *P<0.05. FDC: fixed-dose combination; FEV_1: forced expiratory volume in the 1^{st} second; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; MD: medium-dose; RD: risk difference.


A
Identification
Screening
Eligibility
Included
Records identified through database searching (n=351)
Additional records identified through other sources (n=0)
Records identified through database searching (n=351)
Records screened (n=351)
Records excluded (n=340)
Full-text articles assessed for eligibility (n=11)
Full-text articles excluded (n=7), with reasons:
- Phase I or II study (3)
- Not on ICS/LABA/LAMA combination (2)
- No outcome of interest (1)
- Post-hoc analysis (1)
Studies included in qualitative synthesis (n=5, from 4 records)
Studies included in quantitative synthesis (network meta-analysis) (n=5, from 4 records)
B
MD ICS/LABA/LAMA FDC
BDP/FOR/GLY 200/12/20 BID
FF/VI/UMEC 100/25/31.25 QD
FF/VI/UMEC 100/25/62.5 QD
MF/IND/GLY 80/150/50 QD
MD ICS/LABA FDC
BDP/FOR 200/12 BID
FF/VI 100/25 QD
MF/IND 160/150 QD
HD ICS/LABA FDC + TIO
BDP/FOR 400/12 BID + TIO 5 QD
FP/SAL 500/50 BID + TIO 5 QD
HD ICS/LABA/LAMA FDC
BDP/FOR/GLY 400/12/20 BID
FF/VI/UMEC 200/25/31.25 QD
FF/VI/UMEC 200/25/62.5 QD
MF/IND/GLY 160/150/50 QD
HD ICS/LABA FDC
BDP/FOR 400/12 BID
FF/VI 200/25 QD
FP/SAL 500/50 BID
MF/IND 320/150 QD
CAPTAIN 2020 IRIDIUM 2020 TRIMARAN 2019
ARGON 2020
CAPTAIN 2020 ARGON 2020 IRIDIUM 2020
CAPTAIN 2020 IRIDIUM 2020
CAPTAIN 2020 IRIDIUM 2020
TRIGGER 2019
ARGON 2020 TRIGGER 2019
CAPTAIN 2020 TRIGGER 2019 IRIDIUM 2020
CAPTAIN 2020 IRIDIUM 2020


A
HD ICS/LABA/LAMA FDC + TIO vs. MD ICS/LABA FDC
HD ICS/LABA/LAMA FDC vs. MD ICS/LABA FDC
HD ICS/LABA FDC vs. MD ICS/LABA FDC
HD ICS/LABA FDC + TIO vs. MD ICS/LABA/LAMA FDC
MD ICS/LABA/LAMA FDC vs. MD ICS/LABA FDC
HD ICS/LABA/LAMA FDC vs. MD ICS/LABA/LAMA FDC
HD ICS/LABA FDC + TIO vs. HD ICS/LABA FDC
HD ICS/LABA/LAMA FDC vs. HD ICS/LABA FDC
HD ICS/LABA/LAMA FDC vs. HD ICS/LABA FDC + TIO
MD ICS/LABA/LAMA FDC vs. HD ICS/LABA FDC
0.40
0.50
0.63
0.79
1.00
1.26
Risk of moderate to severe exacerbation (RR and 95%CrI)
B
HD ICS/LABA/LAMA FDC vs. MD ICS/LABA FDC
HD ICS/LABA FDC + TIO vs. MD ICS/LABA FDC
HD ICS/LABA/LAMA FDC vs. HD ICS/LABA FDC
MD ICS/LABA/LAMA FDC vs. MD ICS/LABA FDC
HD ICS/LABA FDC + TIO vs. HD ICS/LABA FDC
MD ICS/LABA/LAMA FDC vs. HD ICS/LABA FDC
HD ICS/LABA/LAMA FDC vs. MD ICS/LABA/LAMA FDC
HD ICS/LABA FDC vs. MD ICS/LABA FDC
HD ICS/LABA/LAMA FDC vs. HD ICS/LABA FDC + TIO
HD ICS/LABA FDC + TIO vs. MD ICS/LABA/LAMA FDC
-50.0
0.0
50.0
100.0
150.0
Change from baseline in trough FEV1 (mL and 95%CrI)


A
HD ICS/LABA FDC + TIO
HD ICS/LABA/LAMA FDC
HD ICS/LABA FDC
MD ICS/LABA/LAMA FDC
MD ICS/LABA FDC
Probability of being the best treatment
1
2
3
4
5
0.00
0.25
0.50
0.75
1.00
SUCRA for reduction in risk of moderate to severe asthma exacerbation
B
HD ICS/LABA/LAMA FDC
HD ICS/LABA FDC + TIO
MD ICS/LABA/LAMA FDC
HD ICS/LABA FDC
MD ICS/LABA FDC
Probability of being the best treatment
SUCRA for change in trough FEV1


A
MD ICS/LABA FDC
+LAMA
HD ICS/LABA FDC
+LAMA
MD ICS/LABA/LAMA FDC
escalete ICS
MD ICS/LABA FDC
+LAMA
escalete ICS
MD ICS/LABA/LAMA FDC
HD ICS/LABA/LAMA FDC
HD ICS/LABA/LAMA FDC
HD ICS/LABA/LAMA FDC
Risk of moderate to severe exacerbation
(RD and upper 95%CrI)
0.0
-0.1
-0.2
-0.3
-0.4
P=0.05
*
B
Change from baseline in trough FEV1
(delta effect, mL and upper 95%CrI)
175
150
125
100
75
50
25
0
MD ICS/LABA/LAMA FDC
HD ICS/LABA/LAMA FDC
HD ICS/LABA/LAMA FDC
HD ICS/LABA/LAMA FDC
+LAMA
MD ICS/LABA FDC
+LAMA
HD ICS/LABA FDC
escalete ICS
MD ICS/LABA/LAMA FDC
+LAMA
escalete ICS
MD ICS/LABA FDC

Supplementary data

Materials and methods

Search strategy and study eligibility

This quantitative synthesis has been registered to the international prospective register of systematic reviews (PROSPERO, Protocol ID: CRD42020211870), and performed in agreement with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [1]. The relative flow diagram and network nodes are shown in Figure 1A and B. This study satisfied all the recommended items reported by the PRISMA-P checklist (Table S1) [1].

A comprehensive literature search was performed for Phase III randomized controlled trials (RCTs) written in English and evaluating the efficacy and safety of triple combination therapies for the treatment of asthma. In this regard, the PICO (Patient problem, Intervention, Comparison, and Outcome) framework was applied to develop the literature search strategy, as previously reported [2]. Namely, the "Patient problem" included patients suffering from asthma; the "Intervention" regarded the administration of different triple combination therapies; the "Comparison" was performed across active combination treatments; the assessed "Outcomes" were the risk of moderate to severe asthma exacerbation, lung function, level of asthma control, and risk of serious adverse events (SAEs), specifically with respect to pneumonia and serious cardiovascular adverse events (AEs).

The search was performed in ClinicalTrials.gov, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, EU Clinical Trials Register, MEDLINE, Scopus, and Web of Science, in order to provide for relevant studies lasting ≥24 weeks, and published up to September 23rd, 2020. The research string was as follows: (((Beclomethasone formoterol glycopyrronium) OR (CHF 5993) OR (CHF5993)) OR (fluticasone furoate vilanterol umeclidinium) OR (mometasone indacaterol glycopyrronium OR (QVM149) OR (QVM 149)) OR ((fluticasone propionate salmeterol tiotropium) OR (ICS LABA tiotropium)) OR triple) AND asthma. Citations of previous published reviews were checked to select further pertinent RCTs, if any.

Literature search results were uploaded to Eppi-Reviewer 4 (EPPI-Centre Software. London, UK), a web-based software program for managing and

analysing data in literature reviews that facilitates collaboration among reviewers during the study selection process.

Study selection

Phase III RCTs that enrolled asthmatic patients, lasting ≥24 weeks, and that included at least one arm assessing the impact of any triple combination therapy in asthma were included in the network meta-analysis. Three reviewers independently examined the studies, and any difference in opinion concerning the selection of relevant Phase III RCTs from literature searches and databases was resolved by consensus.

Data extraction

Data from the RCTs included in this quantitative synthesis were extracted from published papers, and/or supplementary files, and/or the public database ClinicalTrials.gov and/or publically available pharmaceutical companies' clinical databases. Data were checked for study characteristics and duration, number of analysed patients, treatments with doses of medications and regimen of administration, asthma severity and main inclusion criteria, age, gender, asthma duration; forced expiratory volume in the 1st second (FEV_1); level of FEV_1 reversibility; blood eosinophil count at baseline; smoking habit, Asthma Control Questionnaire (ACQ), primary outcomes analysed in every study, Jadad Score [3], and the Cochrane risk of bias [4].

The level of inhaled corticosteroid (ICS) doses (medium-dose [MD] and high-dose [HD]) included in the combinations was ranked in agreement with the current Global Initiative for asthma (GINA) recommendations [5] and the National Institute for Health and Care Excellence (NICE) guidelines [6].

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [7]. The inter- and intra-rater reliability for data abstraction was assessed via the Cohen's Kappa score, as previously described [8]. Briefly, Cohen's Kappa ≥0.80 indicated excellent agreement, coefficients between 0.61 and 0.80 represented substantial agreement, coefficients between 0.41 and 0.61 moderate agreement and <0.41 fair to poor agreement.

Endpoints

Supplementary data

The co-primary endpoints of this network meta-analysis were the comparison across the different triple combination therapies and comparators with respect to the risk of moderate to severe exacerbation in asthmatic patients and the change from baseline in trough FEV_1.

The secondary efficacy endpoint was the comparison across the different triple combination therapies and comparators with respect to the change from baseline in ACQ score. The safety endpoint was the risk of SAEs, namely pneumonia and serious cardiovascular AEs.

Quality of studies, risk bias, and evidence profile

The summary of the risk of bias for each included Phase III RCT was analyzed via the Cochrane Risk of Bias 2 (RoB 2) [4] and Jadad score [3]. The Jadad score ranges from 1 to 5 (score of 5 being the best score), and the quality of studies was ranked as follows: score ≤2, low quality; score =3, medium quality; score ≥4 high quality. The weighted assessment of the risk of bias was analyzed via the Cochrane RoB 2 [4].

The risk of bias was performed for the co-primary endpoints and it was checked via the normalized consistency/inconsistency analysis, a procedure that allows assessing whether the outcomes resulting from the consistency and inconsistency models fit adequately with the line of equality, as previously described [9]. The inconsistency of evidence was also investigated by quantifying the inconsistency factor, that indicates whether one of the treatments had a different effect when it was compared with the others.

The quality of the evidence was assessed for the co-primary endpoints in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system, indicating ++++ for high-quality of evidence, +++ for moderate-quality of evidence, ++ for low-quality of evidence, and + for very low-quality of evidence [10].

Three reviewers independently assessed the quality of studies, risk bias, and evidence profile, and any difference in opinion was resolved by consensus.

Data synthesis and analysis

A network meta-analysis was performed to indirectly compare the impact of the different triple combination therapies and active comparators in asthmatic patients.

Supplementary data

A full Bayesian evidence network was used in the network meta-analysis (chains: 4; initial values scaling: 2.5; tuning iterations: 20.000; simulation iterations: 50.000; tuning interval: 10). The convergence diagnostics for consistency and inconsistency were assessed via the Brooks-Gelman-Rubin method, as previously described [11]. Due to the characteristics of parameters besides the available data, the just proper non-informative distributions specified the prior densities, in agreement with the Bayesian Approaches to Clinical Trials and Health-Care Evaluation [12, 13]. Since the distributions were sufficiently vague, the reference treatment, study baseline effects, and heterogeneity variance were unlikely to have a noticeable impact on model results. In this condition, GeMTC software automatically generates and runs the required Bayesian hierarchical model and selects the prior distributions and starting values as well, via heuristically determining a value for the outcome scale parameter (i.e. outcome scale S) [14, 15]. The posterior mean deviance of data points in the unrelated mean effects model was plotted against their posterior mean deviance in the consistency model in order to provide information for identifying the loops in the treatment network where evidence was inconsistent [16]. Results of the network meta-analysis are expressed as relative effect (RE) and 95% credible interval (95%CrI).

The analysis of the number needed to treat (NNT) was performed on the risk of moderate to severe exacerbations. NNT is the reciprocal of the absolute risk reduction associated with an intervention over a fixed period of time [17-19].

The values of NNT are reported in this study as person-based per year and calculated by analysing the Kaplan-Meyer curves or the Cox proportional hazards model, as previously described [20, 21]. The relative weight of each study resulting from the network meta-analysis was used to calculate the weighted average rate of the investigated treatment arms and to correctly provide NNT values.

Sensitivity analysis was performed in agreement with the patients' characteristics at baseline of each study.

Subset analyses were performed on both moderate or severe exacerbations, and with respect to the different doses of umeclidinium included in the fixed-dose combination (FDC).

Supplementary data

The probability that each intervention arm was the most effective/safe was calculated by counting the proportion of iterations of the chain in which each intervention arm had the best relative effect, and the surface under the cumulative ranking curve analysis (SUCRA), representing the summary of these probabilities [22]. The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [9].

Software and statistical significance

ImageJ was used to extract data from the figures, when necessary [23], GeMTC [24] software was used to perform the network meta-analysis, GraphPad Prism (CA, US) software to graph the data, GRADEpro GDT to assess the quality of evidence [10], and the robvis visualization software to perform the RoB 2 tool [25, 26]. The statistical significance of the effect estimates resulting from the network meta-analysis was assessed for $P<0.05$.

Results

Study characteristics

Data obtained from 9535 asthmatic patients (MD ICS/LABA/LAMA FDC: 26.02%; HD ICS/LABA/LAMA FDC: 25.99%; HD ICS/LABA FDC: 23.23%; MD ICS/LABA FDC: 16.76%; HD ICS/LABA FDC + TIO: 8.00%) were selected from 5 Phase III RCTs published between 2019 and 2020.

The inter-rater reliability for data abstraction was excellent before and after the learning process (Cohen’s Kappa >0.90). The intra-rater reliability produced a Cohen’s Kappa of 1.00 after the learning process.

All the studies included in the network meta-analysis were Phase III RCTs published as full-text papers, with a period of treatment between 24 weeks and 52 weeks.

Supplementary Tables

Table S1. PRISMA-P Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1 main MS
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 main MS
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3 main MS
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3 main MS
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3-4 main MS; 1 suppl. file
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4 main MS; 1 suppl. file
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	1 suppl. file
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	1 suppl. File; Table S2; Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4 main MS; 2 suppl. file
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4 main MS; 2 suppl. file

Supplementary data

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4 main MS; 3 suppl. file
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4 main MS; 3 suppl. file
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5 main MS; 4 suppl. file
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5 main MS; 4-5 suppl. file
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5 main MS; 3 suppl. file
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4 suppl. file
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5 main MS, Figure 1; 5 suppl. file
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5 main MS; Table S3; 5 suppl. file
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8 main MS; Figure S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-8 main MS; Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8 main MS; Table 1; Figure 3; Figure S2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8 main MS; Figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8 main MS; Table 2, Table 3

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-10 main MS
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11 main MS
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11 main MS
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12 main MS

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097.

MS: manuscript; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol.

Supplementary data

Table S2. Literature search terms used for OVID MEDLINE. The final search strategy applied to conduct this network meta-analysis is reported at step #30. The summary text of the identified records is shown in Appendix 1.

#	Search strategy
1	Beclomethasone*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
2	Formoterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
3	Glycopyrronium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
4	CHF 5993.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
5	CHF5993.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
6	Fluticasone furoate*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
7	Vilanterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
8	Umeclidinium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
9	Mometasone*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
10	Indacaterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
11	QVM149.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
12	QVM 149.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
13	Fluticasone propionate*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
14	Salmeterol*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
15	Tiotropium*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
16	ICS*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
17	LABA*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
18	Triple*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
19	Asthma*.mp. [mp=ti, ab, ot, nm, hw, fx, kf, ox, px, rx, ui, sy]
20	1 and 2 and 3
21	4 or 5
22	6 and 7 and 8
23	3 and 9 and 10
24	11 or 12
25	13 and 14 and 15
26	15 and 16 and 17
27	20 or 21
28	23 or 24
29	18 or 22 or 25 or 27 or 28
30	19 and 29

Supplementary data

Table S3. Patient demographics, baseline, study characteristics, and Jadad score.

Study and year and reference	Trial number Identifier	Study characteristics	Study duration (months)	Number of analyzed patients	Triple FDC therapy (doses and regimen of administration)	Comparator (doses and regimen of administration)	Inhaler device (brand)	Patients characteristics	Age (years)	Male (%)	Duration of asthma (years)	Pre-bronchodilator FEV_1 (% predicted)	Reversibility (%)	Rate of exacerbation in the previous year	Blood eosinophil count (cells per µL)	Current smokers (%)	ACQ at baseline (score)	Primary outcome	Jadad score
Lee et al., 2020, CAPTAIN [27]	NCT02924688	Phase IIIA, multicentre, randomized, double-blind, active-controlled, parallel-group	12.0	2436	FF/VI/UMEC (100/25/31.25 µg q.d.), FF/VI/UMEC (100/25/62.5 µg q.d.), FF/VI/UMEC (200/25/31.25 µg q.d.), FF/VI/UMEC (200/25/62.5 µg q.d.)	FF/VI (100/25 µg q.d.), FF/VI (200/25 µg q.d.)	FF/VI/UMEC: DPI (Ellipta®); FF/VI: DPI (Ellipta®)	Inadequately controlled asthma (pre-bronchodilator FEV_1≥30% and <85% predicted; airway reversibility at screening defined as an increase in FEV_1≥12% and ≥200 mL after four inhalations of albuterol or salbutamol; ICS stable use >250 µg per day for ≥6 weeks prior to pre-screening)	53.2	38.0	21.2	58.5	29.9	0.8	228	0.0	2.8	Change in clinic trough FEV_1 at week 24	5
Kerstjens et al., 2020 IRIDIUM [28]	NCT02571777	Phase III, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group	12.0	3092	MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)	MF/IND (80/150 µg q.d.), MF/IND 160/150 µg q.d.), FP/SAL (500/50 µg b.i.d.)	MF/IND/GLY: DPI (Breezhaler®); MF/IND: DPI (Breezhaler®); FP/SAL: DPI (Diskus®)	Symptomatic asthma (pre-bronchodilator FEV_1<80% predicted; ≥1 asthma exacerbation requiring medical care from a physician, ER visit, hospitalization, and systemic corticosteroid treatment in the year prior to screening; airway reversibility defined as an increase in FEV_1≥12% and ≥200 mL after inhalation of albuterol or salbutamol; use of ICS/LABA medium- or high-dose for ≥3 months and at stable dose for ≥1 month prior to screening)	52.2	38.0	18.1	54.8	27.7	1.3	NA	NA	2.5	Change in trough FEV_1 at week 26	5
Gessner et al., 2020 ARGON [29]	NCT03158311	Phase IIIB, multicentre, randomized, non-inferiority, partially-blinded, open-label, active-controlled, parallel-group	5.5	1426	MF/IND/GLY (80/150/50 µg q.d.), MF/IND/GLY (160/150/50 µg q.d.)	FP/SAL (500/50 µg b.i.d.) + TIO (5 µg q.d.)	MF/IND/GLY: DPI (Breezhaler®); FP/SAL: DPI (Accuhaler®); TIO: soft mist inhaler (Respimat®)	Symptomatic asthma (pre-bronchodilator FEV_1<85% predicted; ≥1 severe asthma exacerbation requiring medical care from a physician, ER visit or hospitalization and systemic corticosteroid treatment for at least 3 days in the year prior to study entry; airway reversibility defined as an increase in FEV_1≥12% and ≥200 mL or historical evidence within the past 5 years of reversibility or positive bronchial provocation test; use of ICS/LABA stable medium- or high-dose prior to screening)	52.5	36.7	20.7	62.9	28.1	1.2	NA	2.2	2.6	Change in AQLQ total score	3
Virchow et al., 2019 TRIMARAN [30]	NCT02676076	Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group	12.0	1150	BDP/FOR/GLY (200/12/20 µg b.i.d.)	BDP/FOR (200/12 µg b.i.d.)	BDP/FOR/GLY: pMDI (NA); BDP/FOR: pMDI (NA)	Uncontrolled asthma (pre-bronchodilator FEV_1<80% predicted; ≥1 asthma exacerbation requiring an ER visit or hospitalization or systemic corticosteroid treatment in the year prior to study entry; airway reversibility defined as an increase in FEV_1≥12% and ≥200 mL at 10–15 min after inhalation of salbutamol 400 µg; use of ICS/LABA medium-dose for ≥1 month prior to study entry)	52.6	38.5	25.0	55.5	31.7	1.2	NA	0.0	2.3	Change in trough FEV_1 at week 26, rate of moderate and severe exacerbations	5

Supplementary data

Virchow et al., 2019 TRIGGER [30]	NCT02676089	Phase III, multicentre, randomized, double-blind (BDP/FOR + TIO group was open-label), active-controlled, parallel-group	12.0	1431	BDP/FOR/GLY (400/12/20 µg b.i.d.)	BDP/FOR (400/12 µg b.i.d.) + TIO (5 µg q.d.)	BDP/FOR/GLY: pMDI (NA); BDP/FOR: pMDI (NA); TIO: soft mist inhaler (Respimat®)	Uncontrolled asthma (pre-bronchodilator FEV_1<80% predicted; ≥1 asthma exacerbation requiring an ER visit or hospitalization or systemic corticosteroid treatment in the year prior to study entry; airway reversibility defined as an increase in FEV_1≥12% and ≥200 mL at 10–15 min after inhalation of salbutamol 400 µg; use of ICS/LABA high-dose for ≥1 month prior to study entry)	52.9	38.7	25.2	51.9	34.0	1.2	NA	0.0	2.4	Change in trough FEV_1 at week 26, rate of moderate and severe exacerbations	5

ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; BDP: beclomethasone dipropionate; b.i.d.: *bis in die*, twice-daily; DPI: dry powder inhaler; ER: emergency room; FDC: fixed-dose combination; FEV_1: forced expiratory volume in the 1st second; FF: fluticasone furoate; FOR: formoterol fumarate; FP: fluticasone propionate; GLY: glycopyrronium; ICS: inhaled corticosteroid; IND: indacaterol; LABA: long-acting β_2-adrenoceptor agonist; q.d.: *quaque die*, once daily; MF: momethasone furoate; NA: not available; pMDI: pressurized metered dose inhaler; RCT: randomized controlled trial; SAL: salmeterol; TIO: tiotropium bromide; UMEC: umeclidinium bromide; VI: vilanterol.

Table S4. Definition of moderate and severe asthma exacerbations as reported by the studies included in the network meta-analysis.

Study, year and reference	Study identifier	Definition of asthma exacerbation
Lee et al., 2020, CAPTAIN [27]	NCT02924688	Moderate asthma exacerbation: "deterioration in either asthma symptoms or lung function, or increased rescue bronchodilator use, that required a physician-directed temporary change in maintenance treatment to prevent the exacerbation from becoming a severe exacerbation". Severe asthma exacerbation: "an exacerbation requiring admission to hospital or a visit to an emergency department due to the need for SCSs, or asthma deterioration requiring SCS use (or doubling of the current maintenance SCS dose) for at least 3 days".
Kerstjens et al., 2020 IRIDIUM [28]	NCT02571777	Moderate asthma exacerbation: "the occurrence of two or more of the following: progressive increase of at least one asthma symptom; increased use of rescue medication; or deterioration in lung function lasting for 2 days or more that is usually not severe enough to warrant SCSs for more than 2 days or hospitalization". Severe asthma exacerbation: "an aggravation of asthma symptoms (such as shortness of breath, cough, wheezing, or chest tightness) that requires SCSs for at least 3 consecutive days or a need for an ER visit, hospitalisation owing to asthma, or death due to asthma".
Gessner et al., 2020 ARGON [29]	NCT03158311	Moderate asthma exacerbation: "the occurrence of two or more of the following: 1. progressive increase of at least one of the asthma symptoms like shortness of breath, cough, wheezing, or chest tightness. The symptoms were outside the patient's usual range of day-to-day asthma and lasted at least two consecutive days. 2. increased use of "rescue" inhaled bronchodilators defined by: ≥50% increase in SABA use and >8 puffs on 2 out of any 3 consecutive days compared to baseline captured or night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights. 3. deterioration in lung function, which lasted for two days or more but usually not severe enough to warrant SCSs for more than 2 days or hospitalisation. This deterioration was defined by: ≥20% decrease in FEV_1 from baseline value or ≥20% decrease in morning or evening PEF from baseline on 2 out of any 3 consecutive days compared to baseline or <60% of predicted PEF compared to baseline". Severe asthma exacerbation: "an aggravation of asthma symptoms (like shortness of breath, cough, wheezing, or chest tightness) that required SCS for at least three consecutive days and/or a need for an ER visit (or local equivalent structure), hospitalisation due to asthma or death due to asthma".
Virchow et al., 2019 TRIMARAN [30]	NCT02676076	Moderate asthma exacerbation: "nocturnal awakenings due to asthma requiring a SABA for 2 consecutive nights or an increase of 0.75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of SABA on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings, or 20% or more decrease in FEV_1 from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring SCSs" (definition in accordance with the ATS and ERS joint statement [31]). Severe asthma exacerbation: "worsening of asthma that required treatment with SCSs for at least 3 days (with any associated emergency department visit or admission to hospital documented)".
Virchow et al., 2019 TRIGGER [30]	NCT02676089	Moderate asthma exacerbation: "nocturnal awakenings due to asthma requiring a SABA for 2 consecutive nights or an increase of 0.75 or more from baseline in daily symptom score on 2 consecutive days; increase from baseline in use of SABA on 2 consecutive days (minimum increase 4 puffs per day); 20% or more decrease in PEF from baseline on at least 2 consecutive mornings or evenings, or 20% or more decrease in FEV_1 from baseline; or a visit to an emergency department or a study site for asthma treatment not requiring SCSs" (definition in accordance with the ATS and ERS joint statement [31]). Severe asthma exacerbation: "worsening of asthma that required treatment with SCSs for at least 3 days (with any associated emergency department visit or admission to hospital documented)".

ATS: American Thoracic Society; ER: emergency room; ERS: European Respiratory Society; FEV_1: forced expiratory flow in the 1st second; PEF: peak expiratory flow; SABA: short-acting β_2-adrenoceptor agonist; SCS: systemic corticosteroid.

Supplementary data

Table S5. Level of ICS doses in agreement with the daily doses of medications in adults in the Phase III RCTs included in the network meta-analysis as reported by current GINA recommendations [5] and NICE guidelines [6].

Treatment	Regimen of administration	Daily dose	Level of ICS dose
BDP	200 µg b.i.d.	400 µg	MD
	400 µg b.i.d.	800 µg	HD
FF	100 µg q.d.	100 µg	MD[a]
	200 µg q.d.	200 µg	HD[a]
FP	500 µg b.i.d.	1000 µg	HD
MF	80 µg q.d.	80 µg	MD[b]
	160 µg q.d.	160 µg	HD[b]
	320 µg q.d.	320 µg	HD[b]

[a]The dose levels refer to those reported in the NICE guidelines [32].
[b]The MD 80 µg and the HD 160 µg of MF delivered via Breezhaler® device correspond to the MD 400 µg and the HD 800 µg of MF delivered via the approved Twisthaler® formulation [28, 29].
b.i.d.: *bis in die*, twice-daily; BDP: beclomethasone dipropionate; FF: fluticasone furoate; FP: fluticasone propionate; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; HD: high-dose; MD: medium-dose; MF: mometasone furoate; NICE: National Institute for Health and Care Excellence; PD: pharmacodynamics; PK: pharmacokinetic; q.d.: *quaque die*, once-daily; RCT: randomized controlled trials.

Supplementary data

Table S6. Sensitivity analysis performed by excluding the CAPTAIN study [27] from the Bayesian network concerning the relative effects with 95%CrI of the co-primary endpoints.

Comparisons		Sensitivity analysis		
		References for direct comparisons	**Moderate to severe asthma exacerbation (RR)**	**Trough FEV_1 (mL)**
HD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC + TIO	[29, 30]	1.01 (0.76 - 1.31)	20.11 (-45.84 - 86.08)
	MD ICS/LABA/LAMA FDC	[28, 29]	0.83 (0.66 - 1.03)	30.99 (-18.79 – 82.46)
	HD ICS/LABA FDC	[28, 30]	0.74 (0.59 - 0.92) *	97.13 (43.71 - 150.47) *
	MD ICS/LABA FDC	[28]	0.66 (0.51 - 0.84) *	98.80 (43.55 – 82.46) *
HD ICS/LABA FDC + TIO vs.	MD ICS/LABA/LAMA FDC	[29]	0.83 (0.62 - 1.11)	10.20 (-61.15 - 83.76)
	HD ICS/LABA FDC	[30]	0.73 (0.54 - 0.98) *	76.38 (2.87 – 151.51) *
	MD ICS/LABA FDC	IC	0.65 (0.47 - 0.91) *	80.42 (1.44 - 160.14) *
MD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC	[28]	0.89 (0.69 - 1.12)	65.15 (9.29 – 120.94) *
	MD ICS/LABA FDC	[27, 28, 30]	0.79 (0.63 - 0.99) *	67.55 (16.00 - 118.41) *
HD ICS/LABA FDC vs.	MD ICS/LABA FDC	IC	0.89 (0.69 – 1.15)	1.52 (-56.02 – 62.01)

*P<0.05.

CrI: credible interval; CV: cardiovascular; FDC: fixed-dose combination; FEV_1: forced expiratory volume in the 1st second; HD: high-dose; IC: indirect comparison; ICS: inhaled corticosteroid; LABA, long-acting β_2-adrenoceptor agonist; MD: medium-dose; RR: relative risk; TIO: tiotropium bromide.

Table S7. Sensitivity analysis performed by excluding the CAPTAIN study [27] from the Bayesian network with respect to the moderate or severe asthma exacerbations.

Comparisons		Moderate asthma exacerbation (RR)	Severe asthma exacerbation (RR)
HD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC + TIO	0.86 (0.61 - 1.14)	1.39 (0.85 - 2.36)
	MD ICS/LABA/LAMA FDC	0.95 (0.73 - 1.23)	0.72 (0.48 - 1.09)
	HD ICS/LABA FDC	0.79 (0.60 - 1.01)	0.65 (0.42 - 0.98) *
	MD ICS/LABA FDC	0.74 (0.55 - 0.98) *	0.57 (0.36 - 0.90) *
HD ICS/LABA FDC + TIO vs.	MD ICS/LABA/LAMA FDC	1.10 (0.80 - 1.58)	0.52 (0.29 - 0.89) *
	HD ICS/LABA FDC	0.92 (0.67 - 1.32)	0.46 (0.26 - 0.80) *
	MD ICS/LABA FDC	0.85 (0.60 - 1.28)	0.41 (0.22 - 0.75) *
MD ICS/LABA/LAMA FDC vs.	HD ICS/LABA FDC	0.83 (0.63 - 1.10)	0.89 (0.57 - 1.40)
	MD ICS/LABA FDC	0.77 (0.60 - 1.00) #	0.79 (0.52 - 1.20)
HD ICS/LABA FDC vs.	MD ICS/LABA FDC	0.93 (0.69 - 1.26)	0.88 (0.55 - 1.42)

*P<0.05, #P=0.05.

CrI: credible interval; FDC: fixed-dose combination; HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LAMA: long-acting muscarinic antagonist; MD: medium-dose; RR: relative risk; SUCRA: surface under the cumulative ranking curve; TIO: tiotropium bromide.

Supplementary Figures

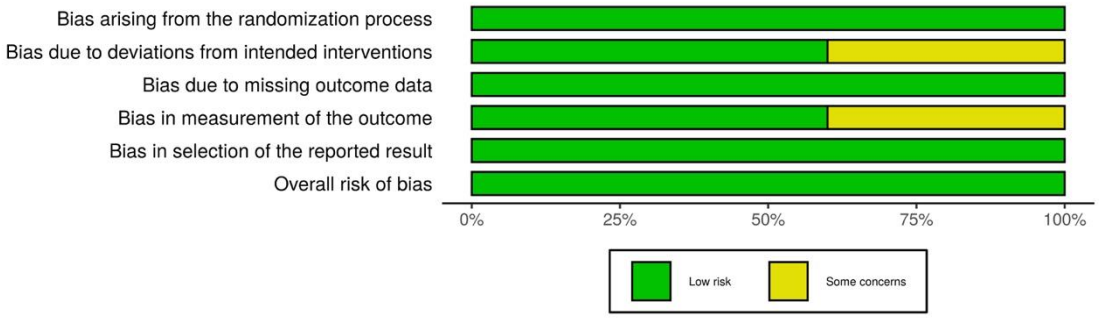


Figure S1. Weighted plot for the assessment of the overall risk of bias via the Cochrane RoB 2 tool (n=5 Phase III RCTs). RCT: randomized controlled trial; RoB 2: Risk of Bias 2.

Supplementary data

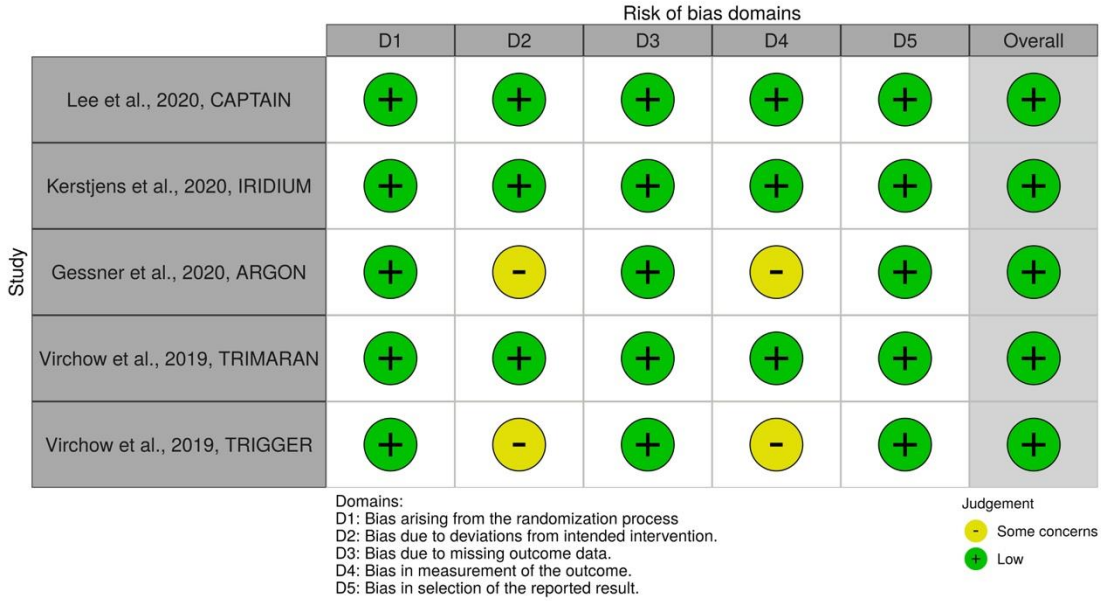


Figure S2. Traffic light plot for assessment of the risk of bias of each included Phase III RCT via the Cochrane RoB 2 tool. D1: bias arising from the randomization process; D2: bias due to deviations from intended intervention; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result; RCT: randomized controlled trial; RoB: risk of bias; robvis: risk of bias visualization tool. Yellow circle indicates some concerns on the risk of bias and green circle represents low risk of bias.

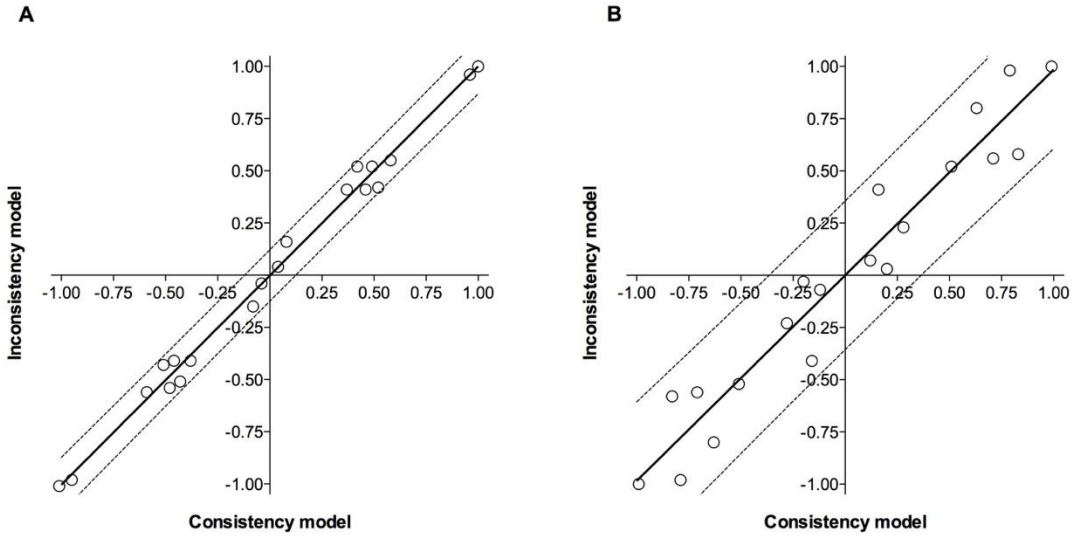


Figure S3. Publication bias assessment via the normalized consistency/inconsistency plot (linear regression and 95% prediction bands) of different triple combination therapies and active comparators with respect to the risk of moderate to severe asthma exacerbation (A) and change from baseline in trough FEV_1 (B). FEV_1: forced expiratory volume in the 1^{st} second.

References

1. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, Group P-P. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015: 4: 1.
2. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007: 7: 16.
3. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996: 17(1): 1-12.
4. Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from http://www.training.cochrane.org/handbook. 2019: 205-228.
5. GINA. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Available at: https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf. Last accessed September 4, 2020. 2020.
6. NICE. National Institute for Health and Care Excellence (NICE). Inhaled corticosteroid doses for NICE's asthma guideline. Available at: http://www.nice.org.uk/guidance/ng80/resources/inhaled-corticosteroid-doses-pdf-4731528781 Last accessed November 26, 2020. 2018.
7. Pedder H, Sarri G, Keeney E, Nunes V, Dias S. Data extraction for complex meta-analysis (DECiMAL) guide. *Systematic reviews* 2016: 5(1): 212.
8. Gianinazzi ME, Rueegg CS, Zimmerman K, Kuehni CE, Michel G, Swiss Paediatric Oncology G. Intra-rater and inter-rater reliability of a medical record abstraction study on transition of care after childhood cancer. *PLoS One* 2015: 10(5): e0124290.
9. Cazzola M, Rogliani P, Calzetta L, Hanania NA, Matera MG. Impact of Mucolytic Agents on COPD Exacerbations: A Pair-wise and Network Meta-analysis. *COPD* 2017: 14(5): 552-563.
10. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011: 64(4): 383-394.
11. Calzetta L, Rogliani P, Ora J, Puxeddu E, Cazzola M, Matera MG. LABA/LAMA combination in COPD: a meta-analysis on the duration of treatment. *European Respiratory Review* 2017: 26(143): 160043.
12. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *Journal of the American Statistical Association* 2006: 101(474): 447-459.
13. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian approaches to clinical trials and health-care evaluation. John Wiley & Sons, 2004.
14. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Research Synthesis Methods* 2012: 3(4): 285-299.
15. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Research synthesis methods* 2016: 7(1): 80-93.
16. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013: 33(5): 641-656.
17. Cazzola M. Application of Number Needed to Treat (NNT) as a Measure of Treatment Effect in Respiratory Medicine. *Treat Respir Med* 2006: 5(2): 79-84.
18. Aaron SD, Fergusson DA. Exaggeration of treatment benefits using the "event-based" number needed to treat. *CMAJ* 2008: 179(7): 669-671.
19. Suissa S. Number needed to treat in COPD: exacerbations versus pneumonias. *Thorax* 2013: 68(6): 540-543.
20. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *Bmj* 1999: 319(7223): 1492-1495.

21. Altman DG. Confidence intervals for the number needed to treat. *BMJ* 1998: 317(7168): 1309-1312.
22. Dobler CC, Wilson ME, Murad MH. A pulmonologist's guide to understanding network meta-analysis. *Eur Respir J* 2018: 52(1).
23. Abràmoff MD, Magalhães PJ, Ram SJ. Image processing with ImageJ. *Biophotonics international* 2004: 11(7): 36-42.
24. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. *Res Synth Methods* 2012: 3(4): 285-299.
25. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj* 2019: 366: l4898.
26. McGuinness LA. robvis: An R package and web application for visualising risk-of-bias assessments. 2019 2019/07/01 [cited; Available from: https://github.com/mcguinlu/robvis
27. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, Hanania NA, Kerstjens HAM, Kerwin E, Nathan R, Oppenheimer J, Papi A, Pascoe S, Brusselle G, Peachey G, Sule N, Tabberer M, Pavord ID. 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. *The Lancet Respiratory medicine* 2020.
28. Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, Lavecchia C, Pethe A, Shu X, D'Andrea P. 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. *The Lancet Respiratory medicine* 2020.
29. Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Salina A, Gupta P, Bostel S, Fucile S, Conde LG, Pfister P. 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.
30. Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. 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.
31. Virchow JC, Backer V, de Blay F, Kuna P, Ljørring C, Prieto JL, Villesen HH. Defining moderate asthma exacerbations in clinical trials based on ATS/ERS joint statement. *Respir Med* 2015: 109(5): 547-556.
32. NICE. National Institute for Health and Care Excellence (NICE). Inhaled corticosteroid doses for NICE's asthma guideline. Available at: http://www.nice.org.uk/guidance/ng80/resources/inhaled-corticosteroid-doses-pdf-4731528781 Last accessed January 16, 2020. 2018.

Appendix

Appendix 1. Summary text of the identified records.

1: Miller D, Vaidya S, Jauernig J, Ethell B, Wagner K, Radhakrishnan R, Tillmann HC. Lung function, pharmacokinetics, and tolerability of inhaled indacaterol maleate and acetate in asthma patients. Respir Res. 2020 Sep 23;21(1):248. doi: 10.1186/s12931-020-01501-1. PMID: 32967685; PMCID: PMC7513528.

2: Table: Correct Use of inhalers for COPD. Med Lett Drugs Ther. 2020 Sep 7;62(1606):e150-e154. PMID: 32960876.

3: Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, Hanania NA, Kerstjens HAM, Kerwin E, Nathan R, Oppenheimer J, Papi A, Pascoe S, Brusselle G, Peachey G, Sule N, Tabberer M, Pavord ID. 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. 2020 Sep 9:S2213-2600(20)30389-1. doi: 10.1016/S2213-2600(20)30389-1. Epub ahead of print. PMID: 32918892.

4: Sarlus H, Codita A, Wang X, Cedazo-Minguez A, Schultzberg M, Oprica M. Chronic Airway Allergy Induces Pro-Inflammatory Responses in the Brain of Wildtype Mice but Not 3xTgAD Mice. Neuroscience. 2020 Sep 8;448:14-27. doi: 10.1016/j.neuroscience.2020.09.005. Epub ahead of print. PMID: 32916195.

5: Di Mauro A, Baldassarre ME, Brindisi G, Zicari AM, Tarantini M, Laera N, Capozza M, Panza R, Salvatore S, Pensabene L, Fanelli M, Laforgia N. Hydrolyzed Protein Formula for Allergy Prevention in Preterm Infants: Follow-Up Analysis of a Randomized, Triple-Blind, Placebo-Controlled Study. Front Pediatr. 2020 Jul 30;8:422. doi: 10.3389/fped.2020.00422. PMID: 32903747; PMCID: PMC7438860.

6: Gessner C, Kornmann O, Maspero J, van Zyl-Smit R, Krüll M, Salina A, Gupta P, Bostel S, Fucile S, Conde LG, Pfister P. 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 Aug-Sep;170:106021. doi: 10.1016/j.rmed.2020.106021. Epub 2020 May 27. PMID: 32843164.

7: Paplinska-Goryca M, Misiukiewicz-Stepien P, Proboszcz M, Nejman-Gryz P, Gorska K, Krenke R. The Expressions of TSLP, IL-33, and IL-17A in Monocyte Derived Dendritic Cells from Asthma and COPD Patients are Related to Epithelial-Macrophage Interactions. Cells. 2020 Aug 22;9(9):E1944. doi: 10.3390/cells9091944. PMID: 32842623.

8: Omori T, Nakamori S, Fujimoto N, Ishida M, Kitagawa K, Ichikawa Y, Kumagai N, Kurita T, Imanaka-Yoshida K, Hiroe M, Sakuma H, Ito M, Dohi K. Myocardial Native T₁ Predicts Load-Independent Left Ventricular Chamber Stiffness In Patients With HFpEF. JACC Cardiovasc Imaging. 2020 Aug 3:S1936-878X(20)30518-0. doi: 10.1016/j.jcmg.2020.05.030. Epub ahead of print. PMID: 32771571.

9: Hong H, Liao S, Chen F, Yang Q, Wang DY. Role of IL-25, IL-33, and TSLP in triggering united airway diseases toward type 2 inflammation. Allergy. 2020 Aug 1. doi: 10.1111/all.14526. Epub ahead of print. PMID: 32737888.

10: Zhang Q, Chen S, Liu A, Wang Y. Quantification of 10 bioactive components of Yazhangsan in rat plasma by LC-MS/MS and its application. Biomed Chromatogr. 2020 Jul 28:e4958. doi: 10.1002/bmc.4958. Epub ahead of print. PMID: 32725639.

11: Ait Bamai Y, Goudarzi H, Araki A, Okada E, Kashino I, Miyashita C, Kishi R. Effect of prenatal exposure to per- and polyfluoroalkyl substances on childhood allergies and common infectious diseases in children up to age 7 years: The Hokkaido study on environment and children's health. Environ Int. 2020 Jul 24;143:105979. doi: 10.1016/j.envint.2020.105979. Epub ahead of print. PMID: 32717646.

12: Luz MI, Aguiar R, Morais-Almeida M. The reality of LAMAs for adult asthmatic patients. Expert Rev Respir Med. 2020 Jul 20:1-8. doi: 10.1080/17476348.2020.1794828. Epub ahead of print. PMID: 32687426.

13: Lipworth B, Chan R, Kuo CR. Systemic Interleukin-6 and Severe Asthma. Am J Respir Crit Care Med. 2020 Jul 20. doi: 10.1164/rccm.202006-2354LE. Epub ahead of print. PMID: 32687393.

14: Virchow JC. Assessing the benefits of triple versus dual fixed-dose

combinations for the treatment of severe asthma. Lancet Respir Med. 2020 Oct;8(10):937-939. doi: 10.1016/S2213-2600(20)30303-9. Epub 2020 Jul 9. PMID: 32653077.

15: van Zyl-Smit RN, Krüll M, Gessner C, Gon Y, Noga O, Richard A, de Los Reyes A, Shu X, Pethe A, Tanase AM, D'Andrea P; PALLADIUM trial investigators. Once-daily mometasone plus indacaterol versus mometasone or twice-daily fluticasone plus salmeterol in patients with inadequately controlled asthma (PALLADIUM): a randomised, double-blind, triple-dummy, controlled phase 3 study. Lancet Respir Med. 2020 Oct;8(10):987-999. doi: 10.1016/S2213-2600(20)30178-8. Epub 2020 Jul 9. PMID: 32653075.

16: Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, Lavecchia C, Pethe A, Shu X, D'Andrea P; IRIDIUM trial investigators. 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 Oct;8(10):1000-1012. doi: 10.1016/S2213-2600(20)30190-9. Epub 2020 Jul 9. PMID: 32653074.

17: Ghasemi Sakha F, Azimi Saeen A, Moazzeni SM, Etesam F, Vaezi G. A Randomized, Triple-blind Placebo-controlled Trial to Determine the Effect of Saffron on the Serum Levels of MMP-9 and TIMP-1 in Patients with Multiple Sclerosis. Iran J Allergy Asthma Immunol. 2020 Jun 23;19(3):297-304. doi: 10.18502/ijaai.v19i3.3457. PMID: 32615663.

18: Avdeev SN, Aisanov ZR, Belevsky AS, Beeh KM, Vizel AA, Zyryanov SK, Ignatova GL, Kostikas K, Leshchenko IV, Ovcharenko SI, Sinopal'nikov AI, Titova ON, Shmelev EI. [The concept of chronic obstructive pulmonary disease clinical control as a decision - making tool in real clinical practice for optimizing of basic pharmacotherapy]. Ter Arkh. 2020 Jan 15;92(1):89-95. Russian. doi: 10.26442/00403660.2020.01.000489. PMID: 32598669.

19: Velázquez-Quesada I, Ruiz-Moreno AJ, Casique-Aguirre D, Aguirre-Alvarado C, Cortés-Mendoza F, de la Fuente-Granada M, García-Pérez C, Pérez-Tapia SM, González-Arenas A, Segura-Cabrera A, Velasco-Velázquez MA. Pranlukast Antagonizes CD49f and Reduces Stemness in Triple-Negative Breast Cancer Cells. Drug Des Devel Ther. 2020 May 12;14:1799-1811. doi: 10.2147/DDDT.S247730. PMID: 32494122; PMCID: PMC7229803.

20: Singh D, Virchow JC, Canonica GW, Vele A, Kots M, Georges G, Papi A. Extrafine triple therapy in patients with asthma and persistent airflow limitation. Eur Respir J. 2020 Sep 24;56(3):2000476. doi: 10.1183/13993003.00476-2020. PMID: 32430414.

21: Chipps B, Mosnaim G, Mathur SK, Shaikh A, Khoury S, Gopalan G, Palli SR, Lamerato L, Casciano J, Dotiwala Z, Settipane R. Add-on tiotropium versus step-up inhaled corticosteroid plus long-acting beta-2-agonist in real-world patients with asthma. Allergy Asthma Proc. 2020 Jul 1;41(4):248-255. doi: 10.2500/aap.2020.41.200036. Epub 2020 May 15. PMID: 32414426.

22: Suzuki T, Fairburn-Beech J, Sato K, Kaise T. Clinical characteristics, treatment patterns, disease burden, and persistence/adherence in patients with asthma initiating inhaled triple therapy: real-world evidence from Japan. Curr Med Res Opin. 2020 Jun;36(6):1049-1057. doi: 10.1080/03007995.2020.1763937. Epub 2020 May 14. PMID: 32363945.

23: Matera MG, Belardo C, Rinaldi M, Rinaldi B, Cazzola M. New perspectives on the role of muscarinic antagonists in asthma therapy. Expert Rev Respir Med. 2020 Aug;14(8):817-824. doi: 10.1080/17476348.2020.1758069. Epub 2020 Apr 26. PMID: 32316778.

24: Matera MG, Belardo C, Rinaldi M, Rinaldi B, Cazzola M. Emerging muscarinic receptor antagonists for the treatment of asthma. Expert Opin Emerg Drugs. 2020 Jun;25(2):123-130. doi: 10.1080/14728214.2020.1758059. Epub 2020 Jun 17. PMID: 32312134.

25: Bloom CI, Douglas I, Usmani OS, Quint JK. Inhaled Corticosteroid Treatment Regimens and Health Outcomes in a UK COPD Population Study. Int J Chron Obstruct Pulmon Dis. 2020 Apr 2;15:701-710. doi: 10.2147/COPD.S241568. Erratum in: Int J Chron Obstruct Pulmon Dis. 2020 Apr 22;15:869. PMID: 32308379; PMCID: PMC7136662.

26: Paplinska-Goryca M, Misiukiewicz-Stepien P, Nejman-Gryz P, Proboszcz M, Mlacki M, Gorska K, Krenke R. Epithelial-macrophage-dendritic cell interactions impact alarmins expression in asthma and COPD. Clin Immunol. 2020 Jun;215:108421. doi: 10.1016/j.clim.2020.108421. Epub 2020 Apr 14. PMID:

32302698.

27: Watz H, Hohlfeld JM, Singh D, Beier J, Diamant Z, Liu J, Hua S, Abd-Elaziz K, Pinot P, Jones I, Tillmann HC. Letter to the editor: indacaterol/glycopyrronium/mometasone furoate compared with salmeterol/fluticasone propionate in patients with asthma: a randomized controlled cross-over study. Respir Res. 2020 Apr 15;21(1):87. doi: 10.1186/s12931-020-01349-5. PMID: 32295593; PMCID: PMC7160900.

28: Nici L, Mammen MJ, Charbek E, Alexander PE, Au DH, Boyd CM, Criner GJ, Donaldson GC, Dreher M, Fan VS, Gershon AS, Han MK, Krishnan JA, Martinez FJ, Meek PM, Morgan M, Polkey MI, Puhan MA, Sadatsafavi M, Sin DD, Washko GR, Wedzicha JA, Aaron SD. Pharmacologic Management of Chronic Obstructive Pulmonary Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020 May 1;201(9):e56-e69. doi: 10.1164/rccm.202003-0625ST. Erratum in: Am J Respir Crit Care Med. 2020 Sep 15;202(6):910. PMID: 32283960; PMCID: PMC7193862.

29: Li Y, Lim J, Stemkowski S, Kaila S, Renda A, Shaikh A. Initiation of triple therapy maintenance treatment among patients with COPD. Am J Manag Care. 2020 Apr 1;26(4):e106-e112. doi: 10.37765/ajmc.2020.42837. PMID: 32270987.

30: Kaplan AG. Inhaled Corticosteroid Treatment in Chronic Obstructive Pulmonary Disease (COPD): Boon or Bane? J Am Board Fam Med. 2020 Mar-Apr;33(2):289-302. doi: 10.3122/jabfm.2020.02.190227. PMID: 32179613.

31: Chung S, Lee YG, Karpurapu M, Englert JA, Ballinger MN, Davis IC, Park GY, Christman JW. Depletion of microRNA-451 in response to allergen exposure accentuates asthmatic inflammation by regulating Sirtuin2. Am J Physiol Lung Cell Mol Physiol. 2020 May 1;318(5):L921-L930. doi: 10.1152/ajplung.00457.2019. Epub 2020 Mar 11. PMID: 32159972; PMCID: PMC7272736.

32: Knibb RC, Alviani C, Garriga-Baraut T, Mortz CG, Vazquez-Ortiz M, Angier E, Blumchen K, Comberiati P, Duca B, DunnGalvin A, Gore C, Hox V, Jensen B, Pite H, Santos AF, Sanchez-Garcia S, Gowland MH, Timmermans F, Roberts G. The effectiveness of interventions to improve self-management for adolescents and young adults with allergic conditions: A systematic review. Allergy. 2020 Aug;75(8):1881-1898. doi: 10.1111/all.14269. PMID: 32159856.

33: Kardos P, Geiss F, Simon J, Franken C, Butt U, Worth H. Duplicate Prescriptions of Inhaled Medications for Obstructive Lung Diseases. Pneumologie. 2020 Mar;74(3):149-158. English. doi: 10.1055/a-1083-7961. Epub 2020 Mar 6. PMID: 32143230.

34: Ishiura Y, Fujimura M, Ohkura N, Hara J, Kasahara K, Ishii N, Sawai Y, Shimizu T, Tamaki T, Nomura S. Triple Therapy with Budesonide/Glycopyrrolate/Formoterol Fumarate Improves Inspiratory Capacity in Patients with Asthma-Chronic Obstructive Pulmonary Disease Overlap. Int J Chron Obstruct Pulmon Dis. 2020 Feb 5;15:269-277. doi: 10.2147/COPD.S231004. PMID: 32103926; PMCID: PMC7014958.

35: Calabria S, Ronconi G, Dondi L, Piccinni C, Pedrini A, Esposito I, Pistelli R, Martini N. Open triple therapy for chronic obstructive pulmonary disease: Patterns of prescription, exacerbations and healthcare costs from a large Italian claims database. Pulm Pharmacol Ther. 2020 Apr;61:101904. doi: 10.1016/j.pupt.2020.101904. Epub 2020 Feb 21. PMID: 32092473.

36: Bousquet J, Farrell J, Illario M; ARIA-MASK study group. Aligning the Good Practice MASK With the Objectives of the European Innovation Partnership on Active and Healthy Ageing. Allergy Asthma Immunol Res. 2020 Mar;12(2):238-258. doi: 10.4168/aair.2020.12.2.238. PMID: 32009320; PMCID: PMC6997284.

37: Ioachimescu OC, Janocko NJ, Ciavatta MM, Howard M, Warnock MV. Obstructive Lung Disease and Obstructive Sleep Apnea (OLDOSA) cohort study: 10-year assessment. J Clin Sleep Med. 2020 Feb 15;16(2):267-277. doi: 10.5664/jcsm.8180. Epub 2020 Jan 13. PMID: 31992433; PMCID: PMC7053033.

38: Matera MG, Rinaldi B, Berardo C, Rinaldi M, Cazzola M. A review of the pharmacokinetics of M₃ muscarinic receptor antagonists used for the treatment of asthma. Expert Opin Drug Metab Toxicol. 2020 Feb;16(2):143-148. doi: 10.1080/17425255.2020.1716730. Epub 2020 Jan 30. PMID: 31958237.

39: Vogelberg C, Goldstein S, Graham L, Kaplan A, de la Hoz A, Hamelmann E. A comparison of tiotropium, long-acting β₂-agonists and leukotriene receptor antagonists on lung function and exacerbations in paediatric patients with asthma. Respir Res. 2020 Jan 13;21(1):19. doi: 10.1186/s12931-020-1282-9.

PMID: 31931792; PMCID: PMC6958672.

40: Jensen ME, Ducharme FM, Alos N, Mailhot G, Mâsse B, White JH, Sadatsafavi M, Khamessan A, Tse SM, Alizadehfar R, Bock DE, Daigneault P, Lemire C, Yang C, Radhakrishnan D. Vitamin D in the prevention of exacerbations of asthma in preschoolers (DIVA): protocol for a multicentre randomised placebo-controlled triple-blind trial. BMJ Open. 2019 Dec 30;9(12):e033075. doi: 10.1136/bmjopen-2019-033075. PMID: 31892662; PMCID: PMC6955525.

41: Messinger AI, Luo G, Deterding RR. The doctor will see you now: How machine learning and artificial intelligence can extend our understanding and treatment of asthma. J Allergy Clin Immunol. 2020 Feb;145(2):476-478. doi: 10.1016/j.jaci.2019.12.898. Epub 2019 Dec 25. PMID: 31883444; PMCID: PMC7035143.

42: LeMessurier KS, Iverson AR, Chang TC, Palipane M, Vogel P, Rosch JW, Samarasinghe AE. Allergic inflammation alters the lung microbiome and hinders synergistic co-infection with H1N1 influenza virus and Streptococcus pneumoniae in C57BL/6 mice. Sci Rep. 2019 Dec 18;9(1):19360. doi: 10.1038/s41598-019-55712-8. PMID: 31852944; PMCID: PMC6920369.

43: Matera MG, Page CP, Calzetta L, Rogliani P, Cazzola M. Pharmacology and Therapeutics of Bronchodilators Revisited. Pharmacol Rev. 2020 Jan;72(1):218-252. doi: 10.1124/pr.119.018150. PMID: 31848208.

44: Sulku J, Janson C, Melhus H, Malinovschi A, Ställberg B, Bröms K, Högman M, Lisspers K, Hammarlund-Udenaes M, Nielsen EI. A Cross-Sectional Study Assessing Appropriateness Of Inhaled Corticosteroid Treatment In Primary And Secondary Care Patients With COPD In Sweden. Int J Chron Obstruct Pulmon Dis. 2019 Nov 5;14:2451-2460. doi: 10.2147/COPD.S218747. PMID: 31806954; PMCID: PMC6842319.

45: Lombardi C, Menzella F, Passalacqua G. Long-term responsiveness to mepolizumab after failure of omalizumab and bronchial thermoplasty: Two triple-switch case reports. Respir Med Case Rep. 2019 Nov 19;29:100967. doi: 10.1016/j.rmcr.2019.100967. PMID: 31799113; PMCID: PMC6881682.

46: Désirée LL, Margarita FV, Mónica RG, María Del Carmen CS, Jorge Agustín LP, José Antonio OM, Blanca DR, Erika Del Carmen LE, Jade RL, Juan Carlos VG, Jorge SP. An online survey detected knowledge gaps and cost-saving opportunities in asthma maintenance treatment among allergists, pulmonologists, ENTs and primary care. World Allergy Organ J. 2019 Nov 19;12(12):100084. doi: 10.1016/j.waojou.2019.100084. PMID: 31768217; PMCID: PMC6872758.

47: Gregoriano C, Tschacher A, Grendelmeier P, Cadus C. Inhalative Therapie bei COPD und Asthma [Development of inhaled therapies for COPD and asthma]. Ther Umsch. 2019 Nov;76(6):301-310. German. doi: 10.1024/0040-5930/a001103. PMID: 31762413.

48: Niimi A, Fukumitsu K, Takeda N, Kanemitsu Y. Interfering with airway nerves in cough associated with asthma. Pulm Pharmacol Ther. 2019 Dec;59:101854. doi: 10.1016/j.pupt.2019.101854. Epub 2019 Nov 1. PMID: 31683030.

49: 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 Mar;177(5):1150-1163. doi: 10.1111/bph.14909. Epub 2020 Jan 29. PMID: 31660611; PMCID: PMC7042115.

50: Cheng WC, Liao WC, Wu BR, Chen CY, Shen MF, Chen WC, Hsia TC, Tu CY, Chen CH, Hsu WH. Clinical predictors of asthmatics in identifying subgroup requiring long-term tiotropium add-on therapy: a real-world study. J Thorac Dis. 2019 Sep;11(9):3785-3793. doi: 10.21037/jtd.2019.09.22. PMID: 31656651; PMCID: PMC6790467.

51: Calzetta L, Matera MG, Cazzola M, Rogliani P. Optimizing the Development Strategy of Combination Therapy in Respiratory Medicine: From Isolated Airways to Patients. Adv Ther. 2019 Dec;36(12):3291-3298. doi: 10.1007/s12325-019-01119-w. Epub 2019 Oct 25. PMID: 31654332; PMCID: PMC6860506.

52: Averell CM, Laliberté F, Duh MS, Wu JW, Germain G, Faison S. Characterizing Real-World Use Of Tiotropium In Asthma In The USA. J Asthma Allergy. 2019 Oct 7;12:309-321. doi: 10.2147/JAA.S216932. PMID: 31632091; PMCID: PMC6789414.

53: Domingo C, Rello J, Sogo A. As-needed ICS-LABA in Mild Asthma: What Does the Evidence Say? Drugs. 2019 Nov;79(16):1729-1737. doi: 10.1007/s40265-019-01202-0. Erratum in: Drugs. 2019 Oct 29;: PMID: 31584145.

54: FitzGerald JM, Sadatsafavi M. Triple therapy in a single inhaler: a new

option for uncontrolled asthma. Lancet. 2019 Nov 9;394(10210):1690-1692. doi: 10.1016/S0140-6736(19)32216-0. Epub 2019 Sep 30. PMID: 31582315.

55: Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, Zuccaro F, Vele A, Kots M, Georges G, Petruzzelli S, Canonica GW. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. Lancet. 2019 Nov 9;394(10210):1737-1749. doi: 10.1016/S0140-6736(19)32215-9. Epub 2019 Sep 30. PMID: 31582314.

56: Fens T, van der Pol S, Kocks JWH, Postma MJ, van Boven JFM. Economic Impact of Reducing Inappropriate Inhaled Corticosteroids Use in Patients With Chronic Obstructive Pulmonary Disease: ISPOR's Guidance on Budget Impact in Practice. Value Health. 2019 Oct;22(10):1092-1101. doi: 10.1016/j.jval.2019.05.006. Epub 2019 Aug 17. PMID: 31563251.

57: Moretz C, Sharpsten L, Bengtson LG, Koep E, Le L, Tong J, Stanford RH, Hahn B, Ray R. Real-world effectiveness of umeclidinium/vilanterol versus fluticasone propionate/salmeterol as initial maintenance therapy for chronic obstructive pulmonary disease (COPD): a retrospective cohort study. Int J Chron Obstruct Pulmon Dis. 2019 Aug 1;14:1721-1737. doi: 10.2147/COPD.S204649. PMID: 31534326; PMCID: PMC6681903.

58: Voorham J, Corradi M, Papi A, Vogelmeier CF, Singh D, Fabbri LM, Kerkhof M, Kocks JH, Carter V, Price D. Comparative effectiveness of triple therapy versus dual bronchodilation in COPD. ERJ Open Res. 2019 Aug 30;5(3):00106-2019. doi: 10.1183/23120541.00106-2019. PMID: 31497610; PMCID: PMC6715826.

59: Moore BJR, Islam B, Ward S, Jackson O, Armitage R, Blackburn J, Haider S, McHugh PC. Repurposing of Tranilast for Potential Neuropathic Pain Treatment by Inhibition of Sepiapterin Reductase in the BH₄ Pathway. ACS Omega. 2019 Jul 10;4(7):11960-11972. doi: 10.1021/acsomega.9b01228. PMID: 31460307; PMCID: PMC6682008.

60: Cazzola M, Rogliani P, Matera MG. Ultra-LABAs for the treatment of asthma. Respir Med. 2019 Sep;156:47-52. doi: 10.1016/j.rmed.2019.08.005. Epub 2019 Aug 12. PMID: 31425937.

61: Cazzola M, Puxeddu E, Matera MG, Rogliani P. A potential role of triple therapy for asthma patients. Expert Rev Respir Med. 2019 Nov;13(11):1079-1085. doi: 10.1080/17476348.2019.1657408. Epub 2019 Sep 1. PMID: 31422716.

62: Pascoe S, Barnes N, Brusselle G, Compton C, Criner GJ, Dransfield MT, Halpin DMG, Han MK, Hartley B, Lange P, Lettis S, Lipson DA, Lomas DA, Martinez FJ, Papi A, Roche N, van der Valk RJP, Wise R, Singh D. Blood eosinophils and treatment response with triple and dual combination therapy in chronic obstructive pulmonary disease: analysis of the IMPACT trial. Lancet Respir Med. 2019 Sep;7(9):745-756. doi: 10.1016/S2213-2600(19)30190-0. Epub 2019 Jul 4. PMID: 31281061.

63: Roberts S, Salmon SL, Steiner DJ, Williams CM, Metzger DW, Furuya Y. Allergic Airway Disease Prevents Lethal Synergy of Influenza A Virus-Streptococcus pneumoniae Coinfection. mBio. 2019 Jul 2;10(4):e01335-19. doi: 10.1128/mBio.01335-19. PMID: 31266877; PMCID: PMC6606812.

64: Wahid B. Successful treatment of HBV, HCV, & HEV, with 12-week long use of tenofovir, sofosbuvir, daclatasvir, and ribavirin: A case report. J Infect Public Health. 2020 Jan;13(1):149-150. doi: 10.1016/j.jiph.2019.06.004. Epub 2019 Jun 21. PMID: 31235341.

65: Ishiura Y, Fujimura M, Ohkura N, Hara J, Kasahara K, Ishii N, Tamaki T, Shimizu T, Nomura S. Effect of triple therapy in patients with asthma-COPD overlap . Int J Clin Pharmacol Ther. 2019 Aug;57(8):384-392. doi: 10.5414/CP203382. PMID: 31232275; PMCID: PMC6637394.

66: Huang WC, Gu PY, Fang LW, Huang YL, Lin CF, Liou CJ. Sophoraflavanone G from Sophora flavescens induces apoptosis in triple-negative breast cancer cells. Phytomedicine. 2019 Aug;61:152852. doi: 10.1016/j.phymed.2019.152852. Epub 2019 Jan 29. PMID: 31035052.

67: Almatrafi A, Alfadhli F, Khan YN, Afzal S, Hashmi JA, Ullah A, Albalawi AM, Basit S. A Heterozygous Mutation in the Triple Helical Region of the Alpha 1 (II) Chain of the COL2A1 Protein Causes Non-Lethal Spondyloepiphyseal Dysplasia Congenita. Genet Test Mol Biomarkers. 2019 May;23(5):310-315. doi: 10.1089/gtmb.2018.0301. Epub 2019 Mar 30. PMID: 30932712.

68: Gaduzo S, McGovern V, Roberts J, Scullion JE, Singh D. When to use single-inhaler triple therapy in COPD: a practical approach for primary care health care professionals. Int J Chron Obstruct Pulmon Dis. 2019 Feb 13;14:391-401. doi: 10.2147/COPD.S173901. PMID: 30863039; PMCID: PMC6388781.

69: Ducharme FM, Jensen M, Mailhot G, Alos N, White J, Rousseau E, Tse SM, Khamessan A, Vinet B. Impact of two oral doses of 100,000 IU of vitamin D₃ in preschoolers with viral-induced asthma: a pilot randomised controlled trial. Trials. 2019 Feb 18;20(1):138. doi: 10.1186/s13063-019-3184-z. PMID: 30777118; PMCID: PMC6379931.

70: Llanos JP, Bell CF, Packnett E, Thiel E, Irwin DE, Hahn B, Ortega H. Real-world characteristics and disease burden of patients with asthma prior to treatment initiation with mepolizumab or omalizumab: a retrospective cohort database study. J Asthma Allergy. 2019 Jan 25;12:43-58. doi: 10.2147/JAA.S189676. PMID: 30774390; PMCID: PMC6354698.

71: Kaplan A, Chapman KR, Anees SM, Mayers I, Rochdi D, Djandji M, Préfontaine D, McIvor A. Real-life effectiveness of indacaterol-glycopyrronium after switching from tiotropium or salmeterol/fluticasone therapy in patients with symptomatic COPD: the POWER study. Int J Chron Obstruct Pulmon Dis. 2019 Jan 18;14:249-260. doi: 10.2147/COPD.S185485. PMID: 30718952; PMCID: PMC6343749.

72: Parmar G, Pundarikakshudu K, Balaraman R. Anti-anaphylactic and antiasthmatic activity of Euphorbia thymifolia L. on experimental animals. J Tradit Complement Med. 2018 Apr 30;9(1):60-65. doi: 10.1016/j.jtcme.2018.03.002. PMID: 30671367; PMCID: PMC6335472.

73: Lee YG, Reader BF, Herman D, Streicher A, Englert JA, Ziegler M, Chung S, Karpurapu M, Park GY, Christman JW, Ballinger MN. Sirtuin 2 enhances allergic asthmatic inflammation. JCI Insight. 2019 Feb 21;4(4):e124710. doi: 10.1172/jci.insight.124710. PMID: 30668546; PMCID: PMC6478424.

74: Lépine M, Sleno L, Lesage J, Gagné S. A validated liquid chromatography/tandem mass spectrometry method for 4,4'-methylenedianiline quantitation in human urine as a measure of 4,4'-methylene diphenyl diisocyanate exposure. Rapid Commun Mass Spectrom. 2019 Mar 30;33(6):600-606. doi: 10.1002/rcm.8380. PMID: 30604511.

75: Yang CH, Su CH, Liu SC, Ng LT. Isolation, Anti-Inflammatory Activity and Physico-chemical Properties of Bioactive Polysaccharides from Fruiting Bodies of Cultivated Cordyceps cicadae (Ascomycetes). Int J Med Mushrooms. 2019;21(10):995-1006. doi: 10.1615/IntJMedMushrooms.2019031922. PMID: 32450036.

76: Vanfleteren L, Fabbri LM, Papi A, Petruzzelli S, Celli B. Triple therapy (ICS/LABA/LAMA) in COPD: time for a reappraisal. Int J Chron Obstruct Pulmon Dis. 2018 Dec 12;13:3971-3981. doi: 10.2147/COPD.S185975. PMID: 30587953; PMCID: PMC6296179.

77: Saito H, Tsuchiya K, Chiba S, Ogata T, Imase R, Yagi T, Mishima Y, Jinta T, Saito K, Taki R, Isogai S, Jin Y, Kawasaki T, Natsume I, Miyashita Y, Takagiwa J, Ishiwata N, Chiaki T, Kishi M, Tsukada Y, Yamasaki M, Inase N, Miyazaki Y. Treatment of asthma in smokers: A questionnaire survey in Japanese clinical practice. Respir Investig. 2019 Mar;57(2):126-132. doi: 10.1016/j.resinv.2018.11.001. Epub 2018 Dec 11. PMID: 30552072.

78: Watz H, Tetzlaff K, Magnussen H, Mueller A, Rodriguez-Roisin R, Wouters EFM, Vogelmeier C, Calverley PMA. Spirometric changes during exacerbations of COPD: a post hoc analysis of the WISDOM trial. Respir Res. 2018 Dec 13;19(1):251. doi: 10.1186/s12931-018-0944-3. PMID: 30545350; PMCID: PMC6293570.

79: Hosseini SA, Zilaee M, Shoushtari MH, Ghasemi Dehcheshmeh M. An evaluation of the effect of saffron supplementation on the antibody titer to heat-shock protein (HSP) 70, hsCRP and spirometry test in patients with mild and moderate persistent allergic asthma: A triple-blind, randomized placebo-controlled trial. Respir Med. 2018 Dec;145:28-34. doi: 10.1016/j.rmed.2018.10.016. Epub 2018 Oct 19. PMID: 30509713.

80: Hamelmann E. Managing Severe Asthma: A Role for the Long-Acting Muscarinic Antagonist Tiotropium. Biomed Res Int. 2018 Oct 24;2018:7473690. doi: 10.1155/2018/7473690. Erratum in: Biomed Res Int. 2019 Jan 29;2019:8515804. PMID: 30474042; PMCID: PMC6220412.

81: Kupczyk M, Kuna P. Beclomethasone dipropionate, formoterol fumarate and glycopyrronium bromide as a combination therapy for chronic obstructive pulmonary disease. Expert Rev Respir Med. 2019 Jan;13(1):5-11. doi:

10.1080/17476348.2019.1548937. Epub 2018 Nov 27. PMID: 30463457.

82: Muller A, Rochoy M. Plongée sous-marine et asthme : revue de littérature [Diving and asthma: Literature review]. Rev Pneumol Clin. 2018 Dec;74(6):416-426. French. doi: 10.1016/j.pneumo.2018.10.002. Epub 2018 Nov 12. PMID: 30442511.

83: Li Y, Li H, Sheng Y, Du X, Yao Y, Luo X, Ma P. Pharmacokinetics of Single and Repeat Doses of Fluticasone Furoate/Umeclidinium/Vilanterol in Healthy Chinese Adults. Clin Pharmacol Drug Dev. 2019 Aug;8(6):721-733. doi: 10.1002/cpdd.626. Epub 2018 Nov 14. PMID: 30427594.

84: Glied SA, Jackson A. How Would Americans' Out-of-Pocket Costs Change If Insurance Plans Were Allowed to Exclude Coverage for Preexisting Conditions? Issue Brief (Commonw Fund). 2018 Nov 1;2018:1-9. PMID: 30387577.

85: Erkman J, Vaynblat A, Thomas K, Segal LN, Levine J, Moy L, Greifer M, Giusti R, Shah R, Kazachkov M. Airway and esophageal eosinophils in children with severe uncontrolled asthma. Pediatr Pulmonol. 2018 Dec;53(12):1598-1603. doi: 10.1002/ppul.24180. Epub 2018 Oct 23. PMID: 30353711.

86: Suissa S, Dell'Aniello S, Ernst P. Comparative effectiveness of LABA-ICS versus LAMA as initial treatment in COPD targeted by blood eosinophils: a population-based cohort study. Lancet Respir Med. 2018 Nov;6(11):855-862. doi: 10.1016/S2213-2600(18)30368-0. Epub 2018 Oct 18. PMID: 30343028.

87: Buhl R, FitzGerald JM, Busse WW. Tiotropium add-on to inhaled corticosteroids versus addition of long-acting β₂-agonists for adults with asthma. Respir Med. 2018 Oct;143:82-90. doi: 10.1016/j.rmed.2018.08.014. Epub 2018 Aug 29. PMID: 30261998.

88: Shi W, Lin Z, Liao C, Zhang J, Liu W, Wang X, Cai J, Zou Z, Wang H, Norback D, Kan H, Huang C, Zhao Z. Urinary phthalate metabolites in relation to childhood asthmatic and allergic symptoms in Shanghai. Environ Int. 2018 Dec;121(Pt 1):276-286. doi: 10.1016/j.envint.2018.08.043. Epub 2018 Sep 15. PMID: 30223204.

89: Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? Int J Chron Obstruct Pulmon Dis. 2018 Aug 27;13:2587-2601. doi: 10.2147/COPD.S172240. PMID: 30214177; PMCID: PMC6118265.

90: Hoshino M, Akitsu K, Ohtawa J. Comparison between montelukast and tiotropium as add-on therapy to inhaled corticosteroids plus a long-acting β₂-agonist in for patients with asthma. J Asthma. 2019 Sep;56(9):995-1003. doi: 10.1080/02770903.2018.1514047. Epub 2018 Sep 13. PMID: 30212239.

91: Buhl R, Criée CP, Kardos P, Vogelmeier CF, Kostikas K, Lossi NS, Worth H. Dual bronchodilation vs triple therapy in the "real-life" COPD DACCORD study. Int J Chron Obstruct Pulmon Dis. 2018 Aug 24;13:2557-2568. doi: 10.2147/COPD.S169958. PMID: 30197512; PMCID: PMC6113909.

92: Hara J, Kasahara K, Ohkura N, Yamamura K, Sakai T, Abo M, Ogawa N, Saeki K, Koba H, Watanabe S, Uchida Y, Tambo Y, Sone T, Kimura H. A Single Institution Retrospective Study of the Clinical Efficacy of Tiotropium Respimat in Never-Smoking Elderly Asthmatics with Irreversible Airflow Limitation. Drug Res (Stuttg). 2019 Apr;69(4):211-217. doi: 10.1055/a-0665-4379. Epub 2018 Sep 7. PMID: 30193393.

93: Lopez-Campos JL, Navarrete BA, Soriano JB, Soler-Cataluña JJ, González-Moro JMR, Ferrer MEF, Rubio MC. Determinants of medical prescriptions for COPD care: an analysis of the EPOCONSUL clinical audit. Int J Chron Obstruct Pulmon Dis. 2018 Jul 27;13:2279-2288. doi: 10.2147/COPD.S160842. PMID: 30100718; PMCID: PMC6067777.

94: Yao XJ, Liu XF, Wang XD. Potential Role of Interleukin-25/Interleukin-33/Thymic Stromal Lymphopoietin-Fibrocyte Axis in the Pathogenesis of Allergic Airway Diseases. Chin Med J (Engl). 2018 Aug 20;131(16):1983-1989. doi: 10.4103/0366-6999.238150. PMID: 30082531; PMCID: PMC6085861.

95: Cheng WC, Wu BR, Liao WC, Chen CY, Chen WC, Hsia TC, Tu CY, Chen CH, Hsu WH. Clinical predictors of the effectiveness of tiotropium in adults with symptomatic asthma: a real-life study. J Thorac Dis. 2018 Jun;10(6):3661-3669. doi: 10.21037/jtd.2018.05.139. PMID: 30069364; PMCID: PMC6051811.

96: Sposato B, Scalese M, Milanese M, Masieri S, Cavaliere C, Ricci A, Paggiaro P. Should omalizumab be used in severe asthma/COPD overlap? J Biol Regul Homeost Agents. 2018 Jul-Aug;32(4):755-761. PMID: 30043557.

97: Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PNR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res. 2018 Jun 18;4(2):00065-2018. doi: 10.1183/23120541.00065-2018. PMID: 29928649; PMCID: PMC6004521.

98: Bonaventure A, Orsi L, Rudant J, Goujon-Bellec S, Leverger G, Baruchel A, Bertrand Y, Nelken B, Pasquet M, Michel G, Sirvent N, Chastagner P, Ducassou S, Thomas C, Besse C, Hémon D, Clavel J. Genetic polymorphisms of Th2 interleukins, history of asthma or eczema and childhood acute lymphoid leukaemia: Findings from the ESCALE study (SFCE). Cancer Epidemiol. 2018 Aug;55:96-103. doi: 10.1016/j.canep.2018.05.004. Epub 2018 Jun 6. PMID: 29883839.

99: Hot topics from the Assemblies. Breathe (Sheff). 2018 Jun;14(2):157-158. doi: 10.1183/20734735.142118. PMID: 29875836; PMCID: PMC5980479.

100: Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Cost Effectiveness of Pharmacological Treatments for Asthma: A Systematic Review. Pharmacoeconomics. 2018 Oct;36(10):1165-1200. doi: 10.1007/s40273-018-0668-8. PMID: 29869050.

101: Spergel JM, Aceves SS, Kliewer K, Gonsalves N, Chehade M, Wechsler JB, Groetch M, Friedlander J, Dellon ES, Book W, Hirano I, Muir AB, Cianferoni A, Spencer L, Liacouras CA, Cheng E, Kottyan L, Wen T, Platts-Mills T, Rothenberg ME. New developments in patients with eosinophilic gastrointestinal diseases presented at the CEGIR/TIGERS Symposium at the 2018 American Academy of Allergy, Asthma & Immunology Meeting. J Allergy Clin Immunol. 2018 Jul;142(1):48-53. doi: 10.1016/j.jaci.2018.05.005. Epub 2018 May 24. PMID: 29803797; PMCID: PMC6129859.

102: Reiger G, Zwick R, Lamprecht B, Kähler C, Burghuber OC, Valipour A. Phenotypes of COPD in an Austrian population : National data from the POPE study. Wien Klin Wochenschr. 2018 Jun;130(11-12):382-389. doi: 10.1007/s00508-018-1347-7. Epub 2018 May 24. PMID: 29797071.

103: Chapman KR, Hurst JR, Frent SM, Larbig M, Fogel R, Guerin T, Banerji D, Patalano F, Goyal P, Pfister P, Kostikas K, Wedzicha JA. Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial. Am J Respir Crit Care Med. 2018 Aug 1;198(3):329-339. doi: 10.1164/rccm.201803-0405OC. PMID: 29779416.

104: Grozdanovic M, Laffey KG, Abdelkarim H, Hitchinson B, Harijith A, Moon HG, Park GY, Rousslang LK, Masterson JC, Furuta GT, Tarasova NI, Gaponenko V, Ackerman SJ. Novel peptide nanoparticle-biased antagonist of CCR3 blocks eosinophil recruitment and airway hyperresponsiveness. J Allergy Clin Immunol. 2019 Feb;143(2):669-680.e12. doi: 10.1016/j.jaci.2018.05.003. Epub 2018 May 17. PMID: 29778505; PMCID: PMC6240402.

105: Dedaj R, Unsel L. Case study: A Combination of Mepolizumab and Omaluzimab injections for severe asthma. J Asthma. 2019 May;56(5):473-474. doi: 10.1080/02770903.2018.1471706. Epub 2018 Oct 25. PMID: 29733738.

106: Suknuntha K, Yubolphan R, Krueaprasertkul K, Srihirun S, Sibmooh N, Vivithanaporn P. Leukotriene Receptor Antagonists Inhibit Mitogenic Activity in Triple Negative Breast Cancer Cells. Asian Pac J Cancer Prev. 2018 Mar 27;19(3):833-837. doi: 10.22034/APJCP.2018.19.3.833. PMID: 29582642; PMCID: PMC5980863.

107: Sobieraj DM, Baker WL, Nguyen E, Weeda ER, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. Association of Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists With Asthma Control in Patients With Uncontrolled, Persistent Asthma: A Systematic Review and Meta-analysis. JAMA. 2018 Apr 10;319(14):1473-1484. doi: 10.1001/jama.2018.2757. Erratum in: JAMA. 2018 May 8;319(18):1939. PMID: 29554174; PMCID: PMC5876909.

108: Hurst JR, Dilleen M, Morris K, Hills S, Emir B, Jones R. Factors influencing treatment escalation from long-acting muscarinic antagonist monotherapy to triple therapy in patients with COPD: a retrospective THIN-database analysis. Int J Chron Obstruct Pulmon Dis. 2018 Mar 5;13:781-792. doi: 10.2147/COPD.S153655. PMID: 29551894; PMCID: PMC5842770.

109: Mesonzhnik NV, Moskaleva NE, Shestakova KM, Kurynina KO, Baranov PA, Gretskaya NM, Serkov IV, Lyubimov II, Bezuglov VV, Appolonova SA. LC-MS/MS

Identification and Structural Characterization of Main Biodegradation Products of Nitroproston - A Novel Prostaglandin-based Pharmaceutical Compound. Drug Metab Lett. 2018;12(1):54-61. doi: 10.2174/1872312812666180309160927. PMID: 29521215.

110: Sobieraj DM, Baker WL, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, Blake KV, Lang JE. Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Mar. Report No.: 17(18)-EHC027-EF. PMID: 29741837.

111: Zhang L, Huang G, Jin L, Han S. Therapeutic Effects of a Long-Acting Cholinergic Receptor Blocker, Tiotropium Bromide, on Asthma. Med Sci Monit. 2018 Feb 15;24:944-950. doi: 10.12659/msm.907950. PMID: 29446377; PMCID: PMC5822933.

112: Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, Singh D. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. Lancet. 2018 Mar 17;391(10125):1076-1084. doi: 10.1016/S0140-6736(18)30206-X. Epub 2018 Feb 9. Erratum in: Lancet. 2018 Feb 26;: PMID: 29429593.

113: Zafari Z, Sadatsafavi M, Mark FitzGerald J; Canadian Respiratory Research Network. Cost-effectiveness of tiotropium versus omalizumab for uncontrolled allergic asthma in US. Cost Eff Resour Alloc. 2018 Jan 30;16:3. doi: 10.1186/s12962-018-0089-8. PMID: 29422778; PMCID: PMC5789632.

114: Song YD, Li XZ, Wu YX, Shen Y, Liu FF, Gao PP, Sun L, Qian F. Emodin alleviates alternatively activated macrophage and asthmatic airway inflammation in a murine asthma model. Acta Pharmacol Sin. 2018 Aug;39(8):1317-1325. doi: 10.1038/aps.2017.147. Epub 2018 Feb 8. PMID: 29417945; PMCID: PMC6289379.

115: Fukumitsu K, Kanemitsu Y, Asano T, Takeda N, Ichikawa H, Yap JMG, Fukuda S, Uemura T, Takakuwa O, Ohkubo H, Maeno K, Ito Y, Oguri T, Nakamura A, Takemura M, Niimi A. Tiotropium Attenuates Refractory Cough and Capsaicin Cough Reflex Sensitivity in Patients with Asthma. J Allergy Clin Immunol Pract. 2018 Sep-Oct;6(5):1613-1620.e2. doi: 10.1016/j.jaip.2018.01.016. Epub 2018 Feb 3. PMID: 29408386.

116: Johansson G, Mushnikov V, Bäckström T, Engström A, Khalid JM, Wall J, Hoti F. Exacerbations and healthcare resource utilization among COPD patients in a Swedish registry-based nation-wide study. BMC Pulm Med. 2018 Jan 25;18(1):17. doi: 10.1186/s12890-018-0573-0. PMID: 29370846; PMCID: PMC5784707.

117: Padrão E, Araújo D, Todo Bom A, Robalo Cordeiro C, Correia de Sousa J, Cardoso J, Morais-Almeida M, Costa R, Pavão F, Leite RB, Marques A. Asthma-COPD overlap: A Portuguese survey. Pulmonology. 2018 Jan 12:S2173-5115(17)30181-1. doi: 10.1016/j.rppnen.2017.11.009. Epub ahead of print. PMID: 29338973.

118: Meltzer EO, Berger WE. A review of the efficacy and safety of once-daily tiotropium Respimat 2.5 micrograms in adults and adolescents with asthma. Allergy Asthma Proc. 2018 Jan 6;39(1):14-26. doi: 10.2500/aap.2018.39.4103. PMID: 29279056.

119: Dreher M, Müller T. Add-on Therapy for Symptomatic Asthma despite Long-Acting Beta-Agonists/Inhaled Corticosteroid. Tuberc Respir Dis (Seoul). 2018 Jan;81(1):1-5. doi: 10.4046/trd.2017.0102. Epub 2017 Dec 13. PMID: 29256220; PMCID: PMC5771741.

120: Corral Gudino L, Borao Cengotita-Bengoa M, Jorge Sánchez RJ, García Aparicio J. El paciente y su travesía entre la atención primaria y la hospitalaria. Revisión sistemática de ensayos clínicos para la implementación de herramientas para la integración en España [The patient and the crossing between Primary and Hospital care. Systematic review of trials for the implementation of tools for integration in Spain]. An Sist Sanit Navar. 2017 Dec 29;40(3):443-459. Spanish. doi: 10.23938/ASSN.0119. PMID: 29215657.

121: Casale TB, Bateman ED, Vandewalker M, Virchow JC, Schmidt H, Engel M, Moroni-Zentgraf P, Kerstjens HAM. Tiotropium Respimat Add-on Is Efficacious in Symptomatic Asthma, Independent of T2 Phenotype. J Allergy Clin Immunol Pract. 2018 May-Jun;6(3):923-935.e9. doi: 10.1016/j.jaip.2017.08.037. Epub 2017 Nov 22. PMID: 29174062.

122: Meltzer EO, Berger WE. A review of the efficacy and safety of once-daily tiotropium Respimat 2.5 micrograms in adults and adolescents with asthma. Allergy Asthma Proc. 2017 Nov 6. doi: 10.2500/aap.2017.38.1403. Epub ahead of

print. PMID: 29108533.

123: Singh D, Corradi M, Spinola M, Papi A, Usmani OS, Scuri M, Petruzzelli S, Vestbo J. Triple therapy in COPD: new evidence with the extrafine fixed combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide. Int J Chron Obstruct Pulmon Dis. 2017 Oct 6;12:2917-2928. doi: 10.2147/COPD.S146822. PMID: 29062229; PMCID: PMC5638574.

124: Lee L, Kerwin E, Collison K, Nelsen L, Wu W, Yang S, Pascoe S. The effect of umeclidinium on lung function and symptoms in patients with fixed airflow obstruction and reversibility to salbutamol: A randomised, 3-phase study. Respir Med. 2017 Oct;131:148-157. doi: 10.1016/j.rmed.2017.08.013. Epub 2017 Aug 14. PMID: 28947022.

125: Nandyal S, Suria S, Chogtu B, Bhattacharjee D. Risk of GERD with Diabetes Mellitus, Hypertension and Bronchial Asthma - A Hospital based Retrospective Cohort Study. J Clin Diagn Res. 2017 Jul;11(7):OC25-OC29. doi: 10.7860/JCDR/2017/25571.10232. Epub 2017 Jul 1. PMID: 28892957; PMCID: PMC5583783.

126: Kalach N, Bontems P, Raymond J. Helicobacter pylori infection in children. Helicobacter. 2017 Sep;22 Suppl 1. doi: 10.1111/hel.12414. PMID: 28891139.

127: Beasley R, Hardy J, Hancox R. Asthma prescribing: Where are we headed? Respirology. 2017 Nov;22(8):1487-1488. doi: 10.1111/resp.13159. Epub 2017 Aug 27. PMID: 28845601.

128: Makadia LD, Roper PJ, Andrews JO, Tingen MS. Tobacco Use and Smoke Exposure in Children: New Trends, Harm, and Strategies to Improve Health Outcomes. Curr Allergy Asthma Rep. 2017 Aug;17(8):55. doi: 10.1007/s11882-017-0723-0. PMID: 28741144.

129: Sánchez J, Zakzuk J, Cardona R. Evaluation of a Guidelines-Based Approach to the Treatment of Chronic Spontaneous Urticaria. J Allergy Clin Immunol Pract. 2018 Jan-Feb;6(1):177-182.e1. doi: 10.1016/j.jaip.2017.06.002. Epub 2017 Jul 12. PMID: 28709817.

130: Mapel D, Laliberté F, Roberts MH, Sama SR, Sundaresan D, Pilon D, Lefebvre P, Duh MS, Patel J. A retrospective study to assess clinical characteristics and time to initiation of open-triple therapy among patients with chronic obstructive pulmonary disease, newly established on long-acting mono- or combination therapy. Int J Chron Obstruct Pulmon Dis. 2017 Jun 21;12:1825-1836. doi: 10.2147/COPD.S129007. PMID: 28684905; PMCID: PMC5485896.

131: Aalbers R, Park HS. Positioning of Long-Acting Muscarinic Antagonists in the Management of Asthma. Allergy Asthma Immunol Res. 2017 Sep;9(5):386-393. doi: 10.4168/aair.2017.9.5.386. PMID: 28677351; PMCID: PMC5500692.

132: Jabbal S, Manoharan A, Lipworth BJ. Bronchoprotective tolerance with indacaterol is not modified by concomitant tiotropium in persistent asthma. Clin Exp Allergy. 2017 Oct;47(10):1239-1245. doi: 10.1111/cea.12972. Epub 2017 Aug 1. PMID: 28665534.

133: Clarke A, Perry E, Kelly C, De Soyza A, Heesom K, Gold LI, Ollier W, Hutchinson D, Eggleton P. Heightened autoantibody immune response to citrullinated calreticulin in bronchiectasis: Implications for rheumatoid arthritis. Int J Biochem Cell Biol. 2017 Aug;89:199-206. doi: 10.1016/j.biocel.2017.06.013. Epub 2017 Jun 24. PMID: 28652209.

134: Miravitlles M, Anzueto A, Jardim JR. Optimizing bronchodilation in the prevention of COPD exacerbations. Respir Res. 2017 Jun 20;18(1):125. doi: 10.1186/s12931-017-0601-2. PMID: 28633665; PMCID: PMC5477752.

135: Wang G, Wang F, Gibson PG, Guo M, Zhang WJ, Gao P, Zhang HP, Harvey ES, Li H, Zhang J. Severe and uncontrolled asthma in China: a cross-sectional survey from the Australasian Severe Asthma Network. J Thorac Dis. 2017 May;9(5):1333-1344. doi: 10.21037/jtd.2017.04.74. PMID: 28616286; PMCID: PMC5465130.

136: Reddel HK, Valenti L, Easton KL, Gordon J, Bayram C, Miller GC. Assessment and management of asthma and chronic obstructive pulmonary disease in Australian general practice. Aust Fam Physician. 2017 Jun;46(6):413-419. PMID: 28609599.

137: Kew KM, Carr R, Crossingham I. Lay-led and peer support interventions for adolescents with asthma. Cochrane Database Syst Rev. 2017 Apr 19;4(4):CD012331. doi: 10.1002/14651858.CD012331.pub2. PMID: 28421600; PMCID: PMC6478329.

138: Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Singh D. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet. 2017 May 13;389(10082):1919-1929. doi: 10.1016/S0140-6736(17)30188-5. Epub 2017 Apr 3. PMID: 28385353.

139: Glassberg J, Minnitti C, Cromwell C, Cytryn L, Kraus T, Skloot GS, Connor JT, Rahman AH, Meurer WJ. Inhaled steroids reduce pain and sVCAM levels in individuals with sickle cell disease: A triple-blind, randomized trial. Am J Hematol. 2017 Jul;92(7):622-631. doi: 10.1002/ajh.24742. Epub 2017 Jun 5. PMID: 28370266; PMCID: PMC5484635.

140: Al-Sheyab NA, Khader YS, Shah S, Roydhouse JK, Gallagher R. The Effect of a "Class Smoke Free Pledge" on Breath Carbon Monoxide in Arabic Male Adolescents. Nicotine Tob Res. 2018 Apr 2;20(5):568-574. doi: 10.1093/ntr/ntx050. PMID: 28340136.

141: Morawska A, Mitchell AE, Burgess S, Fraser J. Fathers' Perceptions of Change Following Parenting Intervention: Randomized Controlled Trial of Triple P for Parents of Children With Asthma or Eczema. J Pediatr Psychol. 2017 Aug 1;42(7):792-803. doi: 10.1093/jpepsy/jsw106. PMID: 28339996.

142: Morawska A, Mitchell A, Burgess S, Fraser J. Randomized controlled trial of Triple P for parents of children with asthma or eczema: Effects on parenting and child behavior. J Consult Clin Psychol. 2017 Apr;85(4):283-296. doi: 10.1037/ccp0000177. PMID: 28333531.

143: Cazzola M, Ora J, Rogliani P, Matera MG. Role of muscarinic antagonists in asthma therapy. Expert Rev Respir Med. 2017 Mar;11(3):239-253. doi: 10.1080/17476348.2017.1289844. Epub 2017 Feb 9. PMID: 28140686.

144: Morawska A, Mitchell AE, Burgess S, Fraser J. Corrigendum to "Effects of Triple P parenting intervention on child health outcomes for childhood asthma and eczema: Randomised controlled trial" [Behav. Res. Ther. 83 (2016) 35-44]. Behav Res Ther. 2017 May;92:107. doi: 10.1016/j.brat.2016.12.017. Epub 2017 Jan 24. Erratum for: Behav Res Ther. 2016 Aug;83:35-44. PMID: 28129879.

145: Hamelmann E, Vogelberg C, Szefler SJ. Tiotropium for the treatment of asthma in adolescents. Expert Opin Pharmacother. 2017 Feb;18(3):305-312. doi: 10.1080/14656566.2017.1285906. Epub 2017 Feb 1. PMID: 28110558.

146: Thomson NC. New and developing non-adrenoreceptor small molecule drugs for the treatment of asthma. Expert Opin Pharmacother. 2017 Feb;18(3):283-293. doi: 10.1080/14656566.2017.1284794. Epub 2017 Feb 1. PMID: 28099820.

147: Araújo D, Padrão E, Morais-Almeida M, Cardoso J, Pavão F, Leite RB, Caldas AC, Marques A. Asthma-chronic obstructive pulmonary disease overlap syndrome - Literature review and contributions towards a Portuguese consensus. Rev Port Pneumol (2006). 2017 Mar-Apr;23(2):90-99. doi: 10.1016/j.rppnen.2016.11.005. Epub 2017 Jan 6. PMID: 28089081.

148: Irshad S, Flores-Borja F, Lawler K, Monypenny J, Evans R, Male V, Gordon P, Cheung A, Gazinska P, Noor F, Wong F, Grigoriadis A, Fruhwirth GO, Barber PR, Woodman N, Patel D, Rodriguez-Justo M, Owen J, Martin SG, Pinder SE, Gillett CE, Poland SP, Ameer-Beg S, McCaughan F, Carlin LM, Hasan U, Withers DR, Lane P, Vojnovic B, Quezada SA, Ellis P, Tutt AN, Ng T. RORγt⁺ Innate Lymphoid Cells Promote Lymph Node Metastasis of Breast Cancers. Cancer Res. 2017 Mar 1;77(5):1083-1096. doi: 10.1158/0008-5472.CAN-16-0598. Epub 2017 Jan 12. PMID: 28082403.

149: Nejatbakhsh F, Karegar-Borzi H, Amin G, Eslaminejad A, Hosseini M, Bozorgi M, Gharabaghi MA. Squill Oxymel, a traditional formulation from Drimia Maritima (L.) Stearn, as an add-on treatment in patients with moderate to severe persistent asthma: A pilot, triple-blind, randomized clinical trial. J Ethnopharmacol. 2017 Jan 20;196:186-192. doi: 10.1016/j.jep.2016.12.032. Epub 2016 Dec 18. PMID: 27998692.

150: Hoshino M, Ohtawa J, Akitsu K. Effects of the addition of tiotropium on airway dimensions in symptomatic asthma. Allergy Asthma Proc. 2016 Nov;37(6):147-153. doi: 10.2500/aap.2016.37.3991. PMID: 27931291.

151: Albertson TE, Chenoweth JA, Adams JY, Sutter ME. Muscarinic antagonists in early stage clinical development for the treatment of asthma. Expert Opin Investig Drugs. 2017 Jan;26(1):35-49. doi: 10.1080/13543784.2017.1264388. Epub 2016 Dec 7. PMID: 27927039.

152: Edwards SC, Fairbrother SE, Scowcroft A, Chiu G, Ternouth A, Lipworth BJ. The burden of chronic obstructive pulmonary disease associated with maintenance monotherapy in the UK. Int J Chron Obstruct Pulmon Dis. 2016 Nov 22;11:2851-2858. doi: 10.2147/COPD.S109707. PMID: 27920512; PMCID: PMC5125989.

153: Tasanarong P, Dechatiwongse Na Ayudhya T, Techanitiswad T, Koontongkaew S. Reduction of viable bacteria in dentinal tubules treated with a novel medicament (Z-Mix). J Dent Sci. 2016 Dec;11(4):419-426. doi: 10.1016/j.jds.2016.06.006. Epub 2016 Aug 10. PMID: 30895007; PMCID: PMC6395269.

154: Montuschi P, Malerba M, Macis G, Mores N, Santini G. Triple inhaled therapy for chronic obstructive pulmonary disease. Drug Discov Today. 2016 Nov;21(11):1820-1827. doi: 10.1016/j.drudis.2016.07.009. Epub 2016 Jul 21. PMID: 27452453.

155: Page C, Cazzola M. Bifunctional Drugs for the Treatment of Respiratory Diseases. Handb Exp Pharmacol. 2017;237:197-212. doi: 10.1007/164_2016_69. PMID: 27787715.

156: Blom RA, Erni ST, Krempaská K, Schaerer O, van Dijk RM, Amacker M, Moser C, Hall SR, von Garnier C, Blank F. A Triple Co-Culture Model of the Human Respiratory Tract to Study Immune-Modulatory Effects of Liposomes and Virosomes. PLoS One. 2016 Sep 29;11(9):e0163539. doi: 10.1371/journal.pone.0163539. PMID: 27685460; PMCID: PMC5042471.

157: Halpin DM. Tiotropium in asthma: what is the evidence and how does it fit in? World Allergy Organ J. 2016 Sep 14;9(1):29. doi: 10.1186/s40413-016-0119-y. PMID: 27679681; PMCID: PMC5022240.

158: Vogelberg C. Tiotropium in the add-on treatment of asthma in adults: clinical trial evidence and experience. Ther Adv Respir Dis. 2016 Dec;10(6):525-533. doi: 10.1177/1753465816662571. Epub 2016 Sep 9. PMID: 27612491; PMCID: PMC5933593.

159: Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet. 2016 Sep 3;388(10048):963-73. doi: 10.1016/S0140-6736(16)31354-X. Epub 2016 Sep 1. PMID: 27598678.

160: Kerstjens HA, Moroni-Zentgraf P, Tashkin DP, Dahl R, Paggiaro P, Vandewalker M, Schmidt H, Engel M, Bateman ED. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. Respir Med. 2016 Aug;117:198-206. doi: 10.1016/j.rmed.2016.06.013. Epub 2016 Jun 14. PMID: 27492532.

161: Morawska A, Mitchell AE, Burgess S, Fraser J. Effects of Triple P parenting intervention on child health outcomes for childhood asthma and eczema: Randomised controlled trial. Behav Res Ther. 2016 Aug;83:35-44. doi: 10.1016/j.brat.2016.06.001. Epub 2016 Jun 3. Erratum in: Behav Res Ther. 2017 May;92 :107. PMID: 27295179.

162: Zhou T, Zeng D, Zhao T, Yang Y, Liu S, Wu J, Xu L, Tan W. In vivo metabolism study of (R)-bambuterol in humans using ultra high performance liquid chromatography with tandem mass spectrometry. J Sep Sci. 2016 Aug;39(15):2896-906. doi: 10.1002/jssc.201600424. Epub 2016 Jun 27. PMID: 27273913.

163: Shibata Y. [Role of ICS/LABA on COPD treatment]. Nihon Rinsho. 2016 May;74(5):827-32. Japanese. PMID: 27254954.

164: Banerji D, Mahler DA, Hanania NA. Efficacy and safety of LABA/LAMA fixed-dose combinations approved in the US for the management of COPD. Expert Rev Respir Med. 2016 Jul;10(7):767-80. doi: 10.1080/17476348.2016.1190276. Epub 2016 May 30. PMID: 27223863.

165: Mariotti F, Ciurlia G, Spaccapelo L, Muraro A, Acerbi D. A Two-Period Open-Label, Single-Dose Crossover Study in Healthy Volunteers to Evaluate the Drug-Drug Interaction Between Cimetidine and Inhaled Extrafine CHF 5993. Eur J Drug Metab Pharmacokinet. 2017 Apr;42(2):269-279. doi: 10.1007/s13318-016-0345-2. PMID: 27209586; PMCID: PMC5340825.

166: Lichtveld M, Kennedy S, Krouse RZ, Grimsley F, El-Dahr J, Bordelon K,

Sterling Y, White L, Barlow N, DeGruy S, Paul D, Denham S, Hayes C, Sanders M, Mvula MM, Thornton E, Chulada P, Mitchell H, Martin WJ 2nd, Stephens KU, Cohn RD. From Design to Dissemination: Implementing Community-Based Participatory Research in Postdisaster Communities. Am J Public Health. 2016 Jul;106(7):1235-42. doi: 10.2105/AJPH.2016.303169. Epub 2016 May 19. PMID: 27196662; PMCID: PMC4984744.

167: Patra J, Maher YI, Mishra S, Bhatia M, Alam D, Malini DS, Gupta PC, Jha P. Effects of body mass index, tobacco smoking, alcohol drinking and solid fuel use on the risk of asthma: Individual Participant Data (IPD) meta-analysis of 175 000 individuals from 51 nationally representative surveys. BMJ Open Respir Res. 2016 Apr 4;3(1):e000121. doi: 10.1136/bmjresp-2015-000121. PMID: 27099758; PMCID: PMC4823466.

168: Abdel-Hameed EA, Rouster SD, Ji H, Ulm A, Hetta HF, Anwar N, Sherman KE, Shata MT. Evaluating the Role of Cellular Immune Responses in the Emergence of HCV NS3 Resistance Mutations During Protease Inhibitor Therapy. Viral Immunol. 2016 May;29(4):252-8. doi: 10.1089/vim.2015.0093. Epub 2016 Feb 17. PMID: 26885675; PMCID: PMC4860622.

169: Busch R, Han MK, Bowler RP, Dransfield MT, Wells JM, Regan EA, Hersh CP; COPDGene Investigators. Risk factors for COPD exacerbations in inhaled medication users: the COPDGene study biannual longitudinal follow-up prospective cohort. BMC Pulm Med. 2016 Feb 10;16:28. doi: 10.1186/s12890-016-0191-7. PMID: 26861867; PMCID: PMC4748594.

170: Mantuani D, Frazee BW, Fahimi J, Nagdev A. Point-of-Care Multi-Organ Ultrasound Improves Diagnostic Accuracy in Adults Presenting to the Emergency Department with Acute Dyspnea. West J Emerg Med. 2016 Jan;17(1):46-53. doi: 10.5811/westjem.2015.11.28525. Epub 2016 Jan 12. PMID: 26823930; PMCID: PMC4729418.

171: Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev. 2016 Jan 21;(1):CD011721. doi: 10.1002/14651858.CD011721.pub2. PMID: 26798035.

172: Wang K, Tian P, Fan Y, Wang Y, Liu C. Assessment of second-line treatments for patients with uncontrolled moderate asthma. Int J Clin Exp Med. 2015 Oct 15;8(10):19476-80. PMID: 26770595; PMCID: PMC4694495.

173: Kim SA, Lee JH, Kim EK, Kim TH, Kim WJ, Lee JH, Yoon HI, Baek S, Lee JS, Oh YM, Lee SD. Outcome of Inhaler Withdrawal in Patients Receiving Triple Therapy for COPD. Tuberc Respir Dis (Seoul). 2016 Jan;79(1):22-30. doi: 10.4046/trd.2016.79.1.22. Epub 2015 Dec 31. Erratum in: Tuberc Respir Dis (Seoul). 2016 Jul;79(3):193. PMID: 26770231; PMCID: PMC4701790.

174: Barrecheguren M, Monteagudo M, Ferrer J, Borrell E, Llor C, Esquinas C, Miravitlles M. Treatment patterns in COPD patients newly diagnosed in primary care. A population-based study. Respir Med. 2016 Feb;111:47-53. doi: 10.1016/j.rmed.2015.12.004. Epub 2015 Dec 23. PMID: 26758585.

175: Covelli H, Pek B, Schenkenberger I, Scott-Wilson C, Emmett A, Crim C. Efficacy and safety of fluticasone furoate/vilanterol or tiotropium in subjects with COPD at cardiovascular risk. Int J Chron Obstruct Pulmon Dis. 2015 Dec 18;11:1-12. doi: 10.2147/COPD.S91407. PMID: 26730183; PMCID: PMC4694692.

176: Woodfolk JA, Glesner J, Wright PW, Kepley CL, Li M, Himly M, Muehling LM, Gustchina A, Wlodawer A, Chapman MD, Pomés A. Antigenic Determinants of the Bilobal Cockroach Allergen Bla g 2. J Biol Chem. 2016 Jan 29;291(5):2288-301. doi: 10.1074/jbc.M115.702324. Epub 2015 Dec 7. PMID: 26644466; PMCID: PMC4732212.

177: Vogelberg C. Emerging role of long-acting anticholinergics in children with asthma. Curr Opin Pulm Med. 2016 Jan;22(1):74-9. doi: 10.1097/MCP.0000000000000229. PMID: 26606079.

178: Pizzichini MM, Kerstjens HA, Pizzichini E. Current role of anticholinergic drugs in the treatment of asthma: key messages for clinical practice. Pol Arch Med Wewn. 2015;125(11):859-66. doi: 10.20452/pamw.3168. Epub 2015 Oct 30. Erratum in: Pol Arch Med Wewn. 2015;125(12):954. PMID: 26529261.

179: Brusselle G, Price D, Gruffydd-Jones K, Miravitlles M, Keininger DL, Stewart R, Baldwin M, Jones RC. The inevitable drift to triple therapy in COPD: an analysis of prescribing pathways in the UK. Int J Chron Obstruct Pulmon Dis. 2015 Oct 15;10:2207-17. doi: 10.2147/COPD.S91694. PMID: 26527869; PMCID: PMC4621207.

180: Wechsler ME, Yawn BP, Fuhlbrigge AL, Pace WD, Pencina MJ, Doros G, Kazani S, Raby BA, Lanzillotti J, Madison S, Israel E; BELT Investigators. Anticholinergic vs Long-Acting β-Agonist in Combination With Inhaled Corticosteroids in Black Adults With Asthma: The BELT Randomized Clinical Trial. JAMA. 2015 Oct 27;314(16):1720-30. doi: 10.1001/jama.2015.13277. PMID: 26505596.

181: Tilp C, Bucher H, Haas H, Duechs MJ, Wex E, Erb KJ. Effects of conventional tobacco smoke and nicotine-free cigarette smoke on airway inflammation, airway remodelling and lung function in a triple allergen model of severe asthma. Clin Exp Allergy. 2016 Jul;46(7):957-72. doi: 10.1111/cea.12665. Epub 2016 May 3. PMID: 26502779.

182: Trudo F, Kern DM, Davis JR, Tunceli O, Zhou S, Graham EL, Strange C, Williams SA. Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments. Int J Chron Obstruct Pulmon Dis. 2015 Sep 28;10:2055-66. doi: 10.2147/COPD.S90658. PMID: 26451101; PMCID: PMC4592033.

183: Hamilton M, Leggett R, Pang C, Charles S, Gillett B, Prime D. In Vitro Dosing Performance of the ELLIPTA® Dry Powder Inhaler Using Asthma and COPD Patient Inhalation Profiles Replicated with the Electronic Lung (eLung™). J Aerosol Med Pulm Drug Deliv. 2015 Dec;28(6):498-506. doi: 10.1089/jamp.2015.1225. Epub 2015 Sep 15. PMID: 26372465; PMCID: PMC4685503.

184: Barnes PJ. Therapeutic approaches to asthma-chronic obstructive pulmonary disease overlap syndromes. J Allergy Clin Immunol. 2015 Sep;136(3):531-45. doi: 10.1016/j.jaci.2015.05.052. PMID: 26343937.

185: Bouwmeester C, Kraft J, Bungay KM. Optimizing inhaler use by pharmacist-provided education to community-dwelling elderly. Respir Med. 2015 Oct;109(10):1363-8. doi: 10.1016/j.rmed.2015.07.013. Epub 2015 Jul 20. PMID: 26341546.

186: Anderson DE, Kew KM, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. Cochrane Database Syst Rev. 2015 Aug 24;(8):CD011397. doi: 10.1002/14651858.CD011397.pub2. PMID: 26301488.

187: Miravitlles M, Alcázar B, Alvarez FJ, Bazús T, Calle M, Casanova C, Cisneros C, de-Torres JP, Entrenas LM, Esteban C, García-Sidro P, Cosio BG, Huerta A, Iriberri M, Izquierdo JL, López-Viña A, López-Campos JL, Martínez-Moragón E, Pérez de Llano L, Perpiñá M, Ros JA, Serrano J, Soler-Cataluña JJ, Torrego A, Urrutia I, Plaza V. What pulmonologists think about the asthma-COPD overlap syndrome. Int J Chron Obstruct Pulmon Dis. 2015 Jul 15;10:1321-30. doi: 10.2147/COPD.S88667. PMID: 26270415; PMCID: PMC4507793.

188: Wang Y, Qin F, Xiong Z, Fu X, Ma C. An LC-MS/MS method for simultaneous determination of trantinterol and its major metabolite in rat plasma and its application to a comparative pharmacokinetic study. J Chromatogr B Analyt Technol Biomed Life Sci. 2015 Sep 1;1000:163-8. doi: 10.1016/j.jchromb.2015.07.022. Epub 2015 Jul 17. PMID: 26245359.

189: Itadani S, Yashiro K, Aratani Y, Sekiguchi T, Kinoshita A, Moriguchi H, Ohta N, Takahashi S, Ishida A, Tajima Y, Hisaichi K, Ima M, Ueda J, Egashira H, Sekioka T, Kadode M, Yonetomi Y, Nakao T, Inoue A, Nomura H, Kitamine T, Fujita M, Nabe T, Yamaura Y, Matsumura N, Imagawa A, Nakayama Y, Takeuchi J, Ohmoto K. Discovery of Gemilukast (ONO-6950), a Dual CysLT1 and CysLT2 Antagonist As a Therapeutic Agent for Asthma. J Med Chem. 2015 Aug 13;58(15):6093-113. doi: 10.1021/acs.jmedchem.5b00741. Epub 2015 Jul 22. PMID: 26200813.

190: Norman P. Developments in inhaled combination therapies: patent activity 2013-2014. Expert Opin Ther Pat. 2015;25(11):1239-45. doi: 10.1517/13543776.2015.1064394. Epub 2015 Jul 2. PMID: 26135360.

191: Bood JR, Sundblad BM, Delin I, Sjödin M, Larsson K, Anderson SD, Wheelock CE, Dahlén SE, Dahlén B. Urinary excretion of lipid mediators in response to repeated eucapnic voluntary hyperpnea in asthmatic subjects. J Appl Physiol (1985). 2015 Aug 1;119(3):272-9. doi: 10.1152/japplphysiol.00301.2015. Epub 2015 Jun 25. PMID: 26112240.

192: Mahler DA, Kerstjens HA, Donohue JF, Buhl R, Lawrence D, Altman P. Indacaterol vs tiotropium in COPD patients classified as GOLD A and B. Respir Med. 2015 Aug;109(8):1031-9. doi: 10.1016/j.rmed.2015.05.012. Epub 2015 May 22. PMID: 26094050.

193: Miyazaki M, Nakamura H, Takahashi S, Chubachi S, Sasaki M, Haraguchi M, Terai H, Ishii M, Fukunaga K, Tasaka S, Soejima K, Asano K, Betsuyaku T; Keio COPD Comorbidity Research (K-CCR) group. The reasons for triple therapy in stable COPD patients in Japanese clinical practice. Int J Chron Obstruct Pulmon Dis. 2015 Jun 4;10:1053-9. doi: 10.2147/COPD.S79864. PMID: 26082629; PMCID: PMC4461139.

194: Kew KM, Evans DJ, Allison DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus addition of long-acting beta2-agonists (LABA) for adults with asthma. Cochrane Database Syst Rev. 2015 Jun 2;2015(6):CD011438. doi: 10.1002/14651858.CD011438.pub2. PMID: 26031392; PMCID: PMC6513433.

195: Matsuse H, Yamagishi T, Kodaka N, Miura A, Kurose Y, Nakano C, Oshio T. Tiotropium bromide as add-on therapy to inhaled corticosteroids for treating asthma. Expert Opin Pharmacother. 2015 Jun;16(9):1403-9. doi: 10.1517/14656566.2015.1045877. PMID: 26001185.

196: Quirce S, Domínguez-Ortega J, Barranco P. Anticholinergics for treatment of asthma. J Investig Allergol Clin Immunol. 2015;25(2):84-93; quiz 94-5. PMID: 25997301.

197: Chen Y, Guo J, Tang Y, Wu L, Tao W, Qian Y, Duan JA. Pharmacokinetic profile and metabolite identification of yuanhuapine, a bioactive component in Daphne genkwa by ultra-high performance liquid chromatography coupled with tandem mass spectrometry. J Pharm Biomed Anal. 2015 Aug 10;112:60-9. doi: 10.1016/j.jpba.2015.04.023. Epub 2015 Apr 25. PMID: 25956226.

198: McKeage K. Tiotropium Respimat®: A Review of Its Use in Asthma Poorly Controlled with Inhaled Corticosteroids and Long-Acting β2-Adrenergic Agonists. Drugs. 2015 May;75(7):809-16. doi: 10.1007/s40265-015-0393-y. PMID: 25895466.

199: Ohta K, Ichinose M, Tohda Y, Engel M, Moroni-Zentgraf P, Kunimitsu S, Sakamoto W, Adachi M. Long-Term Once-Daily Tiotropium Respimat® Is Well Tolerated and Maintains Efficacy over 52 Weeks in Patients with Symptomatic Asthma in Japan: A Randomised, Placebo-Controlled Study. PLoS One. 2015 Apr 20;10(4):e0124109. doi: 10.1371/journal.pone.0124109. PMID: 25894430; PMCID: PMC4404354.

200: Frith PA, Thompson PJ, Ratnavadivel R, Chang CL, Bremner P, Day P, Frenzel C, Kurstjens N; Glisten Study Group. Glycopyrronium once-daily significantly improves lung function and health status when combined with salmeterol/fluticasone in patients with COPD: the GLISTEN study, a randomised controlled trial. Thorax. 2015 Jun;70(6):519-27. doi: 10.1136/thoraxjnl-2014-206670. Epub 2015 Apr 3. PMID: 25841237; PMCID: PMC4453631.

201: Bernstein JA, Moellman JJ, Collins SP, Hart KW, Lindsell CJ. Effectiveness of ecallantide in treating angiotensin-converting enzyme inhibitor-induced angioedema in the emergency department. Ann Allergy Asthma Immunol. 2015 Mar;114(3):245-9. doi: 10.1016/j.anai.2014.12.007. Epub 2015 Jan 16. PMID: 25601538.

202: Kankaanranta H, Harju T, Kilpeläinen M, Mazur W, Lehto JT, Katajisto M, Peisa T, Meinander T, Lehtimäki L. Diagnosis and pharmacotherapy of stable chronic obstructive pulmonary disease: the finnish guidelines. Basic Clin Pharmacol Toxicol. 2015 Apr;116(4):291-307. doi: 10.1111/bcpt.12366. Epub 2015 Jan 22. PMID: 25515181; PMCID: PMC4409821.

203: Salmon M, Tannheimer SL, Gentzler TT, Cui ZH, Sorensen EA, Hartsough KC, Kim M, Purvis LJ, Barrett EG, McDonald JD, Rudolph K, Doyle-Eisele M, Kuehl PJ, Royer CM, Baker WR, Phillips GB, Wright CD. The in vivo efficacy and side effect pharmacology of GS-5759, a novel bifunctional phosphodiesterase 4 inhibitor and long-acting β 2-adrenoceptor agonist in preclinical animal species. Pharmacol Res Perspect. 2014 Aug;2(4):e00046. doi: 10.1002/prp2.46. Epub 2014 Jun 9. PMID: 25505595; PMCID: PMC4186437.

204: Lee LA, Yang S, Kerwin E, Trivedi R, Edwards LD, Pascoe S. The effect of fluticasone furoate/umeclidinium in adult patients with asthma: a randomized, dose-ranging study. Respir Med. 2015 Jan;109(1):54-62. doi: 10.1016/j.rmed.2014.09.012. Epub 2014 Oct 2. PMID: 25452139.

205: Latorre M, Novelli F, Vagaggini B, Braido F, Papi A, Sanduzzi A, Santus P, Scichilone N, Paggiaro P. Differences in the efficacy and safety among inhaled corticosteroids (ICS)/long-acting beta2-agonists (LABA) combinations in the treatment of chronic obstructive pulmonary disease (COPD): Role of ICS. Pulm

Pharmacol Ther. 2015 Feb;30:44-50. doi: 10.1016/j.pupt.2014.10.006. Epub 2014 Nov 6. PMID: 25445928.

206: Abadoglu O, Berk S. Tiotropium may improve asthma symptoms and lung function in asthmatic patients with irreversible airway obstruction: the real-life data. Clin Respir J. 2016 Jul;10(4):421-7. doi: 10.1111/crj.12230. Epub 2014 Nov 9. PMID: 25335652.

207: Otim ME, Jayasinha R, Forbes H, Shah S. Building evidence for peer-led interventions: assessing the cost of the Adolescent Asthma Action program in Australia. Aust J Prim Health. 2015;21(4):438-43. doi: 10.1071/PY14066. PMID: 25230153.

208: Price D, Fromer L, Kaplan A, van der Molen T, Román-Rodríguez M. Is there a rationale and role for long-acting anticholinergic bronchodilators in asthma? NPJ Prim Care Respir Med. 2014 Jul 17;24:14023. doi: 10.1038/npjpcrm.2014.23. PMID: 25030457; PMCID: PMC4373380.

209: Ciprandi G, Schiavetti I, Bellezza Fontana R, Sorbello V, Ricciardolo FL. Overweight and obesity as risk factors for impaired lung function in patients with asthma: A real-life experience. Allergy Asthma Proc. 2014 Jul-Aug;35(4):e62-71. doi: 10.2500/aap.2014.35.3773. PMID: 24992544.

210: Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting β-agonists. Appl Health Econ Health Policy. 2014 Aug;12(4):447-59. doi: 10.1007/s40258-014-0107-8. Erratum in: Appl Health Econ Health Policy. 2016 Feb;14(1):119-25. PMID: 24974107.

211: Tan C, Gao D, Zhang C, Fu Y, Wang BK, Zhu Q, Wang YP. [Research on correlation between lung and large intestine based on meridian and acupoint palpation in patients with bronchial asthma]. Zhongguo Zhen Jiu. 2014 Feb;34(2):145-8. Chinese. PMID: 24796049.

212: Novelli F, Costa F, Latorre M, Malagrinò L, Celi A, Vagaggini B, Paggiaro P. Tiotropium: a new therapeutic option in asthma. Monaldi Arch Chest Dis. 2013 Sep-Dec;79(3-4):109-15. doi: 10.4081/monaldi.2013.5208. PMID: 24761528.

213: Gray TA, Alsamman K, Murray E, Sims AH, Hupp TR. Engineering a synthetic cell panel to identify signalling components reprogrammed by the cell growth regulator anterior gradient-2. Mol Biosyst. 2014 Jun;10(6):1409-25. doi: 10.1039/c4mb00113c. Epub 2014 Apr 7. PMID: 24710632.

214: Page C, Cazzola M. Bifunctional drugs for the treatment of asthma and chronic obstructive pulmonary disease. Eur Respir J. 2014 Aug;44(2):475-82. doi: 10.1183/09031936.00003814. Epub 2014 Apr 2. PMID: 24696121.

215: Duechs MJ, Tilp C, Tomsic C, Gantner F, Erb KJ. Development of a novel severe triple allergen asthma model in mice which is resistant to dexamethasone and partially resistant to TLR7 and TLR9 agonist treatment. PLoS One. 2014 Mar 11;9(3):e91223. doi: 10.1371/journal.pone.0091223. PMID: 24618687; PMCID: PMC3949744.

216: Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. J Asthma Allergy. 2014 Feb 27;7:11-21. doi: 10.2147/JAA.S38841. PMID: 24600237; PMCID: PMC3942115.

217: Rorie A, Goldner WS, Lyden E, Poole JA. Beneficial role for supplemental vitamin D3 treatment in chronic urticaria: a randomized study. Ann Allergy Asthma Immunol. 2014 Apr;112(4):376-82. doi: 10.1016/j.anai.2014.01.010. Epub 2014 Feb 5. PMID: 24507460.

218: Todorova M, Trendafilova A. Sideritis scardica Griseb., an endemic species of Balkan peninsula: traditional uses, cultivation, chemical composition, biological activity. J Ethnopharmacol. 2014 Mar 14;152(2):256-65. doi: 10.1016/j.jep.2014.01.022. Epub 2014 Jan 30. PMID: 24487281.

219: Gruba SM, Meyer AF, Manning BM, Wang Y, Thompson JW, Dalluge JJ, Haynes CL. Time- and concentration-dependent effects of exogenous serotonin and inflammatory cytokines on mast cell function. ACS Chem Biol. 2014 Feb 21;9(2):503-9. doi: 10.1021/cb400787s. Epub 2013 Dec 19. PMID: 24304209; PMCID: PMC4083829.

220: Suijkerbuijk AW, de Wit GA, Wijga AH, Heijmans M, Hoogendoorn M, Rutten-van Mölken M, Maurits EE, Hoogenveen RT, Feenstra TL. Maatschappelijke kosten van astma, COPD en respiratoire allergie [Societal costs of asthma, COPD and

respiratory allergy]. Ned Tijdschr Geneeskd. 2013;157(46):A6562. Dutch. PMID: 24220178.

221: Peters SP, Bleecker ER, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger LC, Engle LL, Dimango EA, Israel E, Kraft M, Lazarus SC, Lemanske RF Jr, Lugogo N, Martin RJ, Meyers DA, Ramsdell J, Sorkness CA, Sutherland ER, Wasserman SI, Walter MJ, Wechsler ME, Chinchilli VM, Szefler SJ; National Heart, Lung, and Blood Institute's Asthma Clinical Research Network. Predictors of response to tiotropium versus salmeterol in asthmatic adults. J Allergy Clin Immunol. 2013 Nov;132(5):1068-1074.e1. doi: 10.1016/j.jaci.2013.08.003. Epub 2013 Sep 29. PMID: 24084072; PMCID: PMC3826080.

222: Park GY, Lee YG, Berdyshev E, Nyenhuis S, Du J, Fu P, Gorshkova IA, Li Y, Chung S, Karpurapu M, Deng J, Ranjan R, Xiao L, Jaffe HA, Corbridge SJ, Kelly EA, Jarjour NN, Chun J, Prestwich GD, Kaffe E, Ninou I, Aidinis V, Morris AJ, Smyth SS, Ackerman SJ, Natarajan V, Christman JW. Autotaxin production of lysophosphatidic acid mediates allergic asthmatic inflammation. Am J Respir Crit Care Med. 2013 Oct 15;188(8):928-40. doi: 10.1164/rccm.201306-1014OC. PMID: 24050723; PMCID: PMC3826286.

223: Morphew T, Scott L, Li M, Galant SP, Wong W, Garcia Lloret MI, Jones F, Bollinger ME, Jones CA. Mobile health care operations and return on investment in predominantly underserved children with asthma: the breathmobile program. Popul Health Manag. 2013 Aug;16(4):261-9. doi: 10.1089/pop.2012.0060. PMID: 23941048.

224: Anderson WJ, Short PM, Williamson PA, Morrison AE, Palmer C, Tavendale R, Lipworth BJ. Proof-of-concept evaluation of trough airway hyper-responsiveness following regular racemic or levosalbutamol in genotype-stratified steroid-treated persistent asthmatic patients. Clin Sci (Lond). 2014 Jan 1;126(1):75-83. doi: 10.1042/CS20130213. PMID: 23829494.

225: Riley JP, Fuchs B, Sjöberg L, Nilsson GP, Karlsson L, Dahlén SE, Rao NL, Adner M. Mast cell mediators cause early allergic bronchoconstriction in guinea-pigs in vivo: a model of relevance to asthma. Clin Sci (Lond). 2013 Dec;125(11):533-42. doi: 10.1042/CS20130092. PMID: 23799245.

226: Guyer AC, Long AA. Long-acting anticholinergics in the treatment of asthma. Curr Opin Allergy Clin Immunol. 2013 Aug;13(4):392-8. doi: 10.1097/ACI.0b013e328362a775. PMID: 23756872.

227: Clarke SA, Calam R, Morawska A, Sanders M. Developing web-based Triple P 'Positive Parenting Programme' for families of children with asthma. Child Care Health Dev. 2014 Jul;40(4):492-7. doi: 10.1111/cch.12073. Epub 2013 May 12. Erratum in: Child Care Health Dev. 2015 May;41(3):503. PMID: 23662595.

228: Caffarelli C, Santamaria F, Vottero A, Bernasconi S. Progress in Pediatrics in 2012: choices in allergy, endocrinology, gastroenterology, hematology, infectious diseases, neurology, nutrition and respiratory tract illnesses. Ital J Pediatr. 2013 May 8;39:26. doi: 10.1186/1824-7288-39-26. PMID: 23651601; PMCID: PMC3660281.

229: Bollmeier SG, Lee SY. The emerging role of tiotropium for patients with asthma. Ann Pharmacother. 2013 May;47(5):704-13. doi: 10.1345/aph.1R641. Epub 2013 Apr 23. PMID: 23613100.

230: Rand TG, Robbins C, Rajaraman D, Sun M, Miller JD. Induction of Dectin-1 and asthma-associated signal transduction pathways in RAW 264.7 cells by a triple-helical (1, 3)-β-D glucan, curdlan. Arch Toxicol. 2013 Oct;87(10):1841-50. doi: 10.1007/s00204-013-1042-4. Epub 2013 Mar 30. PMID: 23543010.

231: Lipworth BJ. Emerging role of long acting muscarinic antagonists for asthma. Br J Clin Pharmacol. 2014 Jan;77(1):55-62. doi: 10.1111/bcp.12123. PMID: 23534447; PMCID: PMC3895347.

232: Amin M, Anwar F, Naz F, Mehmood T, Saari N. Anti-Helicobacter pylori and urease inhibition activities of some traditional medicinal plants. Molecules. 2013 Feb 7;18(2):2135-49. doi: 10.3390/molecules18022135. PMID: 23434867; PMCID: PMC6270356.

233: Sjåheim TB, Bjørtuft Ø, Drabløs PA, Kongerud J, Halstensen TS. Increased bronchial density of CD25+Foxp3+ regulatory T cells in occupational asthma: relationship to current smoking. Scand J Immunol. 2013 May;77(5):398-404. doi: 10.1111/sji.12035. PMID: 23421612.

234: Newcomb DC, Boswell MG, Sherrill TP, Polosukhin VV, Boyd KL, Goleniewska K, Brody SL, Kolls JK, Adler KB, Peebles RS Jr. IL-17A induces signal transducers and activators of transcription-6-independent airway mucous cell metaplasia. Am J Respir Cell Mol Biol. 2013 Jun;48(6):711-6. doi: 10.1165/rcmb.2013-0017OC. PMID: 23392574; PMCID: PMC3727878.

235: Peters SP. Tiotropium bromide triple combination therapy improves lung function and decreases asthma exacerbations. Evid Based Med. 2013 Oct;18(5):179. doi: 10.1136/eb-2012-101100. Epub 2013 Jan 24. PMID: 23349214.

236: Zarowitz BJ, O'Shea T. Chronic obstructive pulmonary disease: prevalence, characteristics, and pharmacologic treatment in nursing home residents with cognitive impairment. J Manag Care Pharm. 2012 Oct;18(8):598-606. doi: 10.18553/jmcp.2012.18.8.598. PMID: 23127147.

237: Adi H, Young PM, Traini D. Co-deposition of a triple therapy drug formulation for the treatment of chronic obstructive pulmonary disease using solution-based pressurised metered dose inhalers. J Pharm Pharmacol. 2012 Sep;64(9):1245-53. doi: 10.1111/j.2042-7158.2011.01370.x. Epub 2011 Oct 27. PMID: 22881437.

238: Al-Sheyab NA, Gallagher R, Roydhouse JK, Crisp J, Shah S. Feasibility of a peer-led, school-based asthma education programme for adolescents in Jordan. East Mediterr Health J. 2012 May;18(5):468-73. doi: 10.26719/2012.18.5.468. PMID: 22764433.

239: Vollmer WM, Feldstein A, Smith DH, Dubanoski JP, Waterbury A, Schneider JL, Clark SA, Rand C. Use of health information technology to improve medication adherence. Am J Manag Care. 2011 Dec;17(12 Spec No.):SP79-87. PMID: 22216772; PMCID: PMC3641901.

240: MacSharry J, O'Mahony C, Shalaby KH, Sheil B, Karmouty-Quintana H, Shanahan F, Martin JG. Immunomodulatory effects of feeding with Bifidobacterium longum on allergen-induced lung inflammation in the mouse. Pulm Pharmacol Ther. 2012 Aug;25(4):325-34. doi: 10.1016/j.pupt.2012.05.011. Epub 2012 Jun 13. PMID: 22705947.

241: Bjerg A, Lundbäck B, Lötvall J. The future of combining inhaled drugs for COPD. Curr Opin Pharmacol. 2012 Jun;12(3):252-5. doi: 10.1016/j.coph.2012.03.004. Epub 2012 Mar 30. PMID: 22465638.

242: Soler-Cataluña JJ, Cosío B, Izquierdo JL, López-Campos JL, Marín JM, Agüero R, Baloira A, Carrizo S, Esteban C, Galdiz JB, González MC, Miravitlles M, Monsó E, Montemayor T, Morera J, Ortega F, Peces-Barba G, Puente L, Rodríguez JM, Sala E, Sauleda J, Soriano JB, Viejo JL. Consensus document on the overlap phenotype COPD-asthma in COPD. Arch Bronconeumol. 2012 Sep;48(9):331-7. English, Spanish. doi: 10.1016/j.arbres.2011.12.009. Epub 2012 Feb 15. PMID: 22341911.

243: Hirsch R, Deng H, Laohachai MN. Azithromycin in periodontal treatment: more than an antibiotic. J Periodontal Res. 2012 Apr;47(2):137-48. doi: 10.1111/j.1600-0765.2011.01418.x. Epub 2011 Nov 4. PMID: 22050485.

244: Lechuga-Ballesteros D, Noga B, Vehring R, Cummings RH, Dwivedi SK. Novel cosuspension metered-dose inhalers for the combination therapy of chronic obstructive pulmonary disease and asthma. Future Med Chem. 2011 Oct;3(13):1703-18. doi: 10.4155/fmc.11.133. PMID: 21942257.

245: Banerjee ER. Triple selectin knockout (ELP-/-) mice fail to develop OVA-induced acute asthma phenotype. J Inflamm (Lond). 2011 Aug 11;8:19. doi: 10.1186/1476-9255-8-19. PMID: 21835035; PMCID: PMC3170177.

246: Feng L, Zhang Y, Chen R, Hao Y. The Chinese version of the Pediatric Quality of Life Inventory™ (PedsQL™) 3.0 Asthma Module: reliability and validity. Health Qual Life Outcomes. 2011 Aug 7;9:64. doi: 10.1186/1477-7525-9-64. PMID: 21819618; PMCID: PMC3161836.

247: Short PM, Williamson PA, Elder DHJ, Lipworth SIW, Schembri S, Lipworth BJ. The impact of tiotropium on mortality and exacerbations when added to inhaled corticosteroids and long-acting β-agonist therapy in COPD. Chest. 2012 Jan;141(1):81-86. doi: 10.1378/chest.11-0038. Epub 2011 Jul 28. PMID: 21799028.

248: Hagan JB, Taylor RL, Kita H, Singh RJ. Analysis of fluticasone propionate in induced sputum by mass spectrometry. Allergy Asthma Proc. 2011 Jul-Aug;32(4):18-21. doi: 10.2500/aap.2011.32.3454. PMID: 21781401.

249: Barnes PJ. Triple inhalers for obstructive airways disease: will they be useful? Expert Rev Respir Med. 2011 Jun;5(3):297-300. doi: 10.1586/ers.11.26. PMID: 21702649.

250: Sung CC, Chi H, Chiu NC, Huang DT, Weng LC, Wang NY, Huang FY. Viral etiology of acute lower respiratory tract infections in hospitalized young children in Northern Taiwan. J Microbiol Immunol Infect. 2011 Jun;44(3):184-90. doi: 10.1016/j.jmii.2011.01.025. Epub 2011 Jan 18. PMID: 21524612; PMCID: PMC7105033.

251: Saini B, Shah S, Kearey P, Bosnic-Anticevich S, Grootjans J, Armour C. An interprofessional learning module on asthma health promotion. Am J Pharm Educ. 2011 Mar 10;75(2):30. doi: 10.5688/ajpe75230. PMID: 21519420; PMCID: PMC3073104.

252: Cazzola M, Segreti A, Bettoncelli G, Calzetta L, Cricelli C, Pasqua F, Rogliani P. Change in asthma and COPD prescribing by Italian general practitioners between 2006 and 2008. Prim Care Respir J. 2011 Sep;20(3):291-8. doi: 10.4104/pcrj.2011.00033. PMID: 21509419; PMCID: PMC6549849.

253: Jonas DE, Wines RCM, DelMonte M, Amick HR, Wilkins TM, Einerson BD, Schuler CL, Wynia BA, Shilliday BB. Drug Class Review: Controller Medications for Asthma: Final Update 1 Report [Internet]. Portland (OR): Oregon Health & Science University; 2011 Apr. PMID: 22132427.

254: Chen R, Hao Y, Feng L, Zhang Y, Huang Z. The Chinese version of the Pediatric Quality of Life Inventory™ (PedsQL™) Family Impact Module: cross-cultural adaptation and psychometric evaluation. Health Qual Life Outcomes. 2011 Mar 23;9:16. doi: 10.1186/1477-7525-9-16. PMID: 21429195; PMCID: PMC3072920.

255: Baloira A. Triple terapia en el tratamiento de la EPOC [Triple therapy in chronic obstructive pulmonary disease]. Arch Bronconeumol. 2010;46 Suppl 8:25-30. Spanish. doi: 10.1016/S0300-2896(10)70064-8. PMID: 21334553.

256: El-Hefnawy AS, Wadie BS. Severe stress urinary incontinence: Objective analysis of risk factors. Maturitas. 2011 Apr;68(4):374-7. doi: 10.1016/j.maturitas.2011.01.005. Epub 2011 Feb 2. PMID: 21292413.

257: Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, Boushey HA, Calhoun WJ, Castro M, Cherniack RM, Craig T, Denlinger L, Engle LL, DiMango EA, Fahy JV, Israel E, Jarjour N, Kazani SD, Kraft M, Lazarus SC, Lemanske RF Jr, Lugogo N, Martin RJ, Meyers DA, Ramsdell J, Sorkness CA, Sutherland ER, Szefler SJ, Wasserman SI, Walter MJ, Wechsler ME, Chinchilli VM, Bleecker ER; National Heart, Lung, and Blood Institute Asthma Clinical Research Network. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med. 2010 Oct 28;363(18):1715-26. doi: 10.1056/NEJMoa1008770. Epub 2010 Sep 19. PMID: 20979471; PMCID: PMC3011177.

258: Malfertheiner P, Selgrad M. Helicobacter pylori infection and current clinical areas of contention. Curr Opin Gastroenterol. 2010 Nov;26(6):618-23. doi: 10.1097/MOG.0b013e32833efede. PMID: 20827182.

259: Rootmensen GN, van Keimpema AR, Jansen HM, de Haan RJ. Predictors of incorrect inhalation technique in patients with asthma or COPD: a study using a validated videotaped scoring method. J Aerosol Med Pulm Drug Deliv. 2010 Oct;23(5):323-8. doi: 10.1089/jamp.2009.0785. PMID: 20804428.

260: Farley MM. 2009 H1N1 influenza: a twenty-first century pandemic with roots in the early twentieth century. Am J Med Sci. 2010 Sep;340(3):202-8. doi: 10.1097/MAJ.0b013e3181e937b0. PMID: 20697263; PMCID: PMC7119454.

261: Barnes PJ. Inhaled corticosteroids in COPD: a controversy. Respiration. 2010;80(2):89-95. doi: 10.1159/000315416. Epub 2010 May 26. PMID: 20501985.

262: Ohar JA, Donohue JF. Mono- and combination therapy of long-acting bronchodilators and inhaled corticosteroids in advanced COPD. Semin Respir Crit Care Med. 2010 Jun;31(3):321-33. doi: 10.1055/s-0030-1254072. Epub 2010 May 21. PMID: 20496301.

263: Williamson PA, Short PM, Clearie KL, Vaidyanathan S, Fardon TC, Howaniec LJ, Lipworth BJ. Paradoxical trough effects of triple therapy with budesonide/formoterol and tiotropium bromide on pulmonary function outcomes in COPD. Chest. 2010 Sep;138(3):595-604. doi: 10.1378/chest.10-0247. Epub 2010 Apr 23. PMID: 20418370.

264: Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, Strunk RC, Szefler SJ, Zeiger RS, Bacharier LB, Covar RA, Guilbert TW, Larsen G, Morgan WJ, Moss MH, Spahn JD, Taussig LM; Childhood Asthma Research

and Education (CARE) Network of the National Heart, Lung, and Blood Institute. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. N Engl J Med. 2010 Mar 18;362(11):975-85. doi: 10.1056/NEJMoa1001278. Epub 2010 Mar 2. PMID: 20197425; PMCID: PMC2989902.

265: Simoni-Wastila L, Blanchette CM, Qian J, Yang HW, Zhao L, Zuckerman IH, Pak GH, Silver H, Dalal AA. Burden of chronic obstructive pulmonary disease in Medicare beneficiaries residing in long-term care facilities. Am J Geriatr Pharmacother. 2009 Oct;7(5):262-70. doi: 10.1016/j.amjopharm.2009.11.003. PMID: 19948302.

266: Molfino NA. Increased vagal airway tone in fatal asthma. Med Hypotheses. 2010 Mar;74(3):521-3. doi: 10.1016/j.mehy.2009.10.002. Epub 2009 Nov 10. PMID: 19906493.

267: Gordon E, Lazarus SC. Management of chronic obstructive pulmonary disease: moving beyond the asthma algorithm. J Allergy Clin Immunol. 2009 Nov;124(5):873-80; quiz 881-2. doi: 10.1016/j.jaci.2009.09.040. PMID: 19895979.

268: Jeppsson MC, Lindh CH, Kristiansson MH, Nielsen J, Jönsson BA. Methylhexahydrophthalic anhydride adducted albumin tryptic peptides in nasal lavage fluid. Inhal Toxicol. 2009 Oct;21(12):1013-20. doi: 10.1080/08958370802715997. PMID: 19772480.

269: Zarei S, Jeddi-Tehrani M, Akhondi MM, Zeraati H, Pourheidari F, Ostadkarampour M, Tavangar B, Shokri F. Primary immunization with a triple diphtheria-tetanus-whole cell pertussis vaccine in Iranian infants: an analysis of antibody response. Iran J Allergy Asthma Immunol. 2009 Jun;8(2):85-93. PMID: 19671937.

270: Vilozni D, Livnat G, Dabbah H, Elias N, Hakim F, Bentur L. The potential use of spirometry during methacholine challenge test in young children with respiratory symptoms. Pediatr Pulmonol. 2009 Jul;44(7):720-7. doi: 10.1002/ppul.20978. PMID: 19499592.

271: Fleischel O, Giménez-Arnau E, Lepoittevin JP. Nuclear magnetic resonance studies on covalent modification of amino acids thiol and amino residues by monofunctional aryl 13C-isocyanates, models of skin and respiratory sensitizers: transformation of thiocarbamates into urea adducts. Chem Res Toxicol. 2009 Jun;22(6):1106-15. doi: 10.1021/tx9000539. PMID: 19405514.

272: Goplen N, Karim MZ, Liang Q, Gorska MM, Rozario S, Guo L, Alam R. Combined sensitization of mice to extracts of dust mite, ragweed, and Aspergillus species breaks through tolerance and establishes chronic features of asthma. J Allergy Clin Immunol. 2009 Apr;123(4):925-32.e11. doi: 10.1016/j.jaci.2009.02.009. PMID: 19348928; PMCID: PMC2683988.

273: Lemmens KM, Nieboer AP, Huijsman R. A systematic review of integrated use of disease-management interventions in asthma and COPD. Respir Med. 2009 May;103(5):670-91. doi: 10.1016/j.rmed.2008.11.017. Epub 2009 Jan 19. PMID: 19155168.

274: Sun RS, Chen XH, Sui JF, Liu RQ, Cheng TM, Ran XZ, Yang T. Detecting anti-FcepsilonRI autoantibodies in patients with asthma by flow cytometry. J Int Med Res. 2008 Nov-Dec;36(6):1214-9. doi: 10.1177/147323000803600607. PMID: 19094429.

275: Shah S, Roydhouse JK, Sawyer SM. Medical students go back to school--the Triple A journey. Aust Fam Physician. 2008 Nov;37(11):952-4. PMID: 19037472.

276: Maffey AF, Venialgo CM, Barrero PR, Fuse VA, Márques Mde L, Saia M, Villalba A, Teper AM, Mistchenko AS. Nuevos virus respiratorios en niños de 2 meses a 3 años con sibilancias recurrentes [New respiratory viruses in children 2 months to 3 years old with recurrent wheeze]. Arch Argent Pediatr. 2008 Aug;106(4):302-9. Spanish. doi: 10.1590/S0325-00752008000400005. PMID: 18766276.

277: Tsuchida H, Takahashi S, Nosaka E, Kuraya T, Yamashita M, Morimoto K. Novel triple neurokinin receptor antagonist CS-003 inhibits respiratory disease models in guinea pigs. Eur J Pharmacol. 2008 Oct 31;596(1-3):153-9. doi: 10.1016/j.ejphar.2008.07.046. Epub 2008 Jul 31. PMID: 18706408.

278: Kumon M, Yabe Y, Kasuya Y, Suzuki M, Kusai A, Yonemochi E, Terada K. Applicability of DPI formulations for novel neurokinin receptor antagonist. Int J Pharm. 2008 May 22;356(1-2):102-9. doi: 10.1016/j.ijpharm.2007.12.044. Epub 2008 Jan 9. PMID: 18294787.

279: Rootmensen GN, van Keimpema AR, Looysen EE, van der Schaaf L, Jansen HM, de Haan RJ. Reliability in the assessment of videotaped inhalation technique. J

Aerosol Med. 2007 Winter;20(4):429-33. doi: 10.1089/jam.2007.0623. PMID: 18158715.

280: Sharif S, Goldberg B. Detection of IgE antibodies to bacitracin using a commercially available streptavidin-linked solid phase in a patient with anaphylaxis to triple antibiotic ointment. Ann Allergy Asthma Immunol. 2007 Jun;98(6):563-6. doi: 10.1016/S1081-1206(10)60736-3. PMID: 17601270.

281: Venkatasamy R, Spina D. Protease inhibitors in respiratory disease: focus on asthma and chronic obstructive pulmonary disease. Expert Rev Clin Immunol. 2007 May;3(3):365-81. doi: 10.1586/1744666X.3.3.365. PMID: 20477680.

282: Matsumoto K, Inoue H, Tsuda M, Nakano T, Komori M, Fukuyama S, Nakanishi Y. Different profiles of IL-10+IFN-gamma-IL-4-CD4+ T cells in the peripheral blood in atopic and non-atopic asthmatics. Respiration. 2008;75(3):281-7. doi: 10.1159/000101475. Epub 2007 Mar 29. PMID: 17396024.

283: Hakim F, Vilozni D, Adler A, Livnat G, Tal A, Bentur L. The effect of montelukast on bronchial hyperreactivity in preschool children. Chest. 2007 Jan;131(1):180-6. doi: 10.1378/chest.06-1402. PMID: 17218573.

284: Bernstein DI, Wang N, Campo P, Chakraborty R, Smith A, Cartier A, Boulet LP, Malo JL, Yucesoy B, Luster M, Tarlo SM, Hershey GK. Diisocyanate asthma and gene-environment interactions with IL4RA, CD-14, and IL-13 genes. Ann Allergy Asthma Immunol. 2006 Dec;97(6):800-6. doi: 10.1016/S1081-1206(10)60972-6. PMID: 17201240.

285: Fardon T, Haggart K, Lee DK, Lipworth BJ. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. Respir Med. 2007 Jun;101(6):1218-28. doi: 10.1016/j.rmed.2006.11.001. Epub 2006 Dec 18. PMID: 17178217.

286: Pahl A, Bauhofer A, Petzold U, Cnota PJ, Maus J, Brune K, Szelenyi S. Synergistic effects of the anti-cholinergic R,R-glycopyrrolate with anti-inflammatory drugs. Biochem Pharmacol. 2006 Dec 15;72(12):1690-6. doi: 10.1016/j.bcp.2006.07.025. Epub 2006 Sep 25. PMID: 16996482.

287: Herszberg B, Ramos-Barbón D, Tamaoka M, Martin JG, Lavoie JP. Heaves, an asthma-like equine disease, involves airway smooth muscle remodeling. J Allergy Clin Immunol. 2006 Aug;118(2):382-8. doi: 10.1016/j.jaci.2006.03.044. Epub 2006 May 30. PMID: 16890762.

288: Currie GP, Lee DK, Menzies D, Lipworth BJ. Evaluating the effects of "triple therapy" with inhaled corticosteroids, long-acting beta2-agonists, and leukotriene modifiers in asthma. Chest. 2006 Jul;130(1):301-2. doi: 10.1378/chest.130.1.301. PMID: 16840420.

289: Larsen K, Macleod D, Nihlberg K, Gürcan E, Bjermer L, Marko-Varga G, Westergren-Thorsson G. Specific haptoglobin expression in bronchoalveolar lavage during differentiation of circulating fibroblast progenitor cells in mild asthma. J Proteome Res. 2006 Jun;5(6):1479-83. doi: 10.1021/pr050462h. PMID: 16739999.

290: Abe M, Hayashi Y, Murai A, Shibata K, Sakata N, Igarashi R, Katsuragi T, Tanaka K. Effects of inducible nitric oxide synthase inhibitors on asthma depending on administration schedule. Free Radic Biol Med. 2006 Mar 15;40(6):1083-95. doi: 10.1016/j.freeradbiomed.2005.10.057. Epub 2005 Nov 21. PMID: 16540403.

291: De Swert KO, Joos GF. Extending the understanding of sensory neuropeptides. Eur J Pharmacol. 2006 Mar 8;533(1-3):171-81. doi: 10.1016/j.ejphar.2005.12.066. Epub 2006 Feb 7. PMID: 16464447.

292: Kritikos V, Saini B, Bosnic-Anticevich SZ, Krass I, Shah S, Taylor S, Armour C. Innovative asthma health promotion by rural community pharmacists: a feasibility study. Health Promot J Austr. 2005 Apr;16(1):69-73. doi: 10.1071/he05069. PMID: 16389935.

293: Schelfhout V, Louis R, Lenz W, Heyrman R, Pauwels R, Joos G. The triple neurokinin-receptor antagonist CS-003 inhibits neurokinin A-induced bronchoconstriction in patients with asthma. Pulm Pharmacol Ther. 2006;19(6):413-8. doi: 10.1016/j.pupt.2005.10.007. Epub 2005 Dec 20. PMID: 16364669.

294: Robbins RA, Thomas AR, Proctor LM, Hoyt JC, Hayden JM. Heat decreases formoterol delivery. Chest. 2005 Dec;128(6):4036-40. doi: 10.1378/chest.128.6.4036. PMID: 16354878.

295: Rice-McDonald G, Bowler S, Staines G, Mitchell C. Doubling daily inhaled corticosteroid dose is ineffective in mild to moderately severe attacks of asthma in adults. Intern Med J. 2005 Dec;35(12):693-8. doi: 10.1111/j.1445-5994.2005.00972.x. PMID: 16313543.

296: Montuschi P, Martello S, Felli M, Mondino C, Barnes PJ, Chiarotti M. Liquid chromatography/mass spectrometry analysis of exhaled leukotriene B4 in asthmatic children. Respir Res. 2005 Oct 19;6(1):119. doi: 10.1186/1465-9921-6-119. PMID: 16236169; PMCID: PMC1283153.

297: Chan HW, Smith NJ, Hannan RD, Thomas WG. Tackling the EGFR in pathological tissue remodelling. Pulm Pharmacol Ther. 2006;19(1):74-8. doi: 10.1016/j.pupt.2005.04.005. Epub 2005 Jun 24. PMID: 15979363.

298: Khanna S, Sobhia ME, Bharatam PV. Additivity of molecular fields: CoMFA study on dual activators of PPARalpha and PPARgamma. J Med Chem. 2005 Apr 21;48(8):3015-25. doi: 10.1021/jm049383s. PMID: 15828840.

299: Wei H, Zhang J, Xiao W, Feng J, Sun R, Tian Z. Involvement of human natural killer cells in asthma pathogenesis: natural killer 2 cells in type 2 cytokine predominance. J Allergy Clin Immunol. 2005 Apr;115(4):841-7. doi: 10.1016/j.jaci.2004.11.026. PMID: 15806008.

300: Benke G, Abramson M, Raven J, Thien FC, Walters EH. Asthma and vaccination history in a young adult cohort. Aust N Z J Public Health. 2004 Aug;28(4):336-8. doi: 10.1111/j.1467-842x.2004.tb00440.x. PMID: 15704697.

301: Meltzer EO, Berman GD, Corren J, Pedinoff AJ, Doyle G, Waksman JA, Butkerait P, Cooper SA, Berlin RG, Wason S. Addition of ibuprofen to pseudoephedrine and chlorpheniramine in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol. 2004 Nov;93(5):452-9. doi: 10.1016/S1081-1206(10)61412-3. PMID: 15562884.

302: Murai A, Abe M, Hayashi Y, Sakata N, Katsuragi T, Tanaka K. Comparison study between the mechanisms of allergic asthma amelioration by a cysteinyl-leukotriene type 1 receptor antagonist montelukast and methylprednisolone. J Pharmacol Exp Ther. 2005 Feb;312(2):432-40. doi: 10.1124/jpet.104.074922. Epub 2004 Oct 6. PMID: 15470084.

303: Lee CG, Cho SJ, Kang MJ, Chapoval SP, Lee PJ, Noble PW, Yehualaeshet T, Lu B, Flavell RA, Milbrandt J, Homer RJ, Elias JA. Early growth response gene 1-mediated apoptosis is essential for transforming growth factor beta1-induced pulmonary fibrosis. J Exp Med. 2004 Aug 2;200(3):377-89. doi: 10.1084/jem.20040104. PMID: 15289506; PMCID: PMC2211975.

304: Hallgren J, Bäckström S, Estrada S, Thuveson M, Pejler G. Histidines are critical for heparin-dependent activation of mast cell tryptase. J Immunol. 2004 Aug 1;173(3):1868-75. doi: 10.4049/jimmunol.173.3.1868. PMID: 15265919.

305: Goleva E, Dunlap A, Leung DY. Differential control of TH1 versus TH2 cell responses by the combination of low-dose steroids with beta2-adrenergic agonists. J Allergy Clin Immunol. 2004 Jul;114(1):183-91. doi: 10.1016/j.jaci.2004.04.001. PMID: 15241363.

306: Aaronson DW, Gandhi TK. Incorrect allergy injections: allergists' experiences and recommendations for prevention. J Allergy Clin Immunol. 2004 Jun;113(6):1117-21. doi: 10.1016/j.jaci.2004.01.756. PMID: 15208593.

307: Soni KK, Khare ML, Saxena RC. Spasmolytic activity of a herbal drug isolated from Tephrosia purpurea in guinea pigs. Anc Sci Life. 2004 Apr;23(4):59-65. PMID: 22557142; PMCID: PMC3330980.

308: Rimaniol AC, Till SJ, Garcia G, Capel F, Godot V, Balabanian K, Durand-Gasselin I, Varga EM, Simonneau G, Emilie D, Durham SR, Humbert M. The CX3C chemokine fractalkine in allergic asthma and rhinitis. J Allergy Clin Immunol. 2003 Dec;112(6):1139-46. doi: 10.1016/j.jaci.2003.09.041. PMID: 14657873.

309: Flores G, Abreu M, Chaisson CE, Sun D. Keeping children out of hospitals: parents' and physicians' perspectives on how pediatric hospitalizations for ambulatory care-sensitive conditions can be avoided. Pediatrics. 2003 Nov;112(5):1021-30. doi: 10.1542/peds.112.5.1021. PMID: 14595041.

310: Köhler D. Novolizer: the new technology for the management of asthma therapy. Curr Opin Pulm Med. 2003 Apr;9 Suppl 1:S11-6. PMID: 12974537.

311: Rizzo CA, Anthes JC, Corboz MR, Chapman RW, Shih NY, Reichard GA, Ng KJ,

Hey JA. Development and potential utility of dual and triple NK receptor antagonists. Curr Top Med Chem. 2003;3(12):1410-22. doi: 10.2174/1568026033451844. PMID: 12871172.

312: Rodrigo GJ, Rodrigo C. Triple inhaled drug protocol for the treatment of acute severe asthma. Chest. 2003 Jun;123(6):1908-15. doi: 10.1378/chest.123.6.1908. PMID: 12796167.

313: Joos GF, De Swert KO, Schelfhout V, Pauwels RA. The role of neural inflammation in asthma and chronic obstructive pulmonary disease. Ann N Y Acad Sci. 2003 May;992:218-30. doi: 10.1111/j.1749-6632.2003.tb03152.x. PMID: 12794061.

314: Cazzola M, Noschese P, Salzillo A, Piccolo A. Asthma treatment must be always tailored to the individual patient. Monaldi Arch Chest Dis. 2002 Jun-Aug;57(3-4):213-7. PMID: 12619388.

315: Bradshaw D, Schneider M, Dorrington R, Bourne DE, Laubscher R. South African cause-of-death profile in transition--1996 and future trends. S Afr Med J. 2002 Aug;92(8):618-23. PMID: 12244621.

316: Zhu Z, Lee CG, Zheng T, Chupp G, Wang J, Homer RJ, Noble PW, Hamid Q, Elias JA. Airway inflammation and remodeling in asthma. Lessons from interleukin 11 and interleukin 13 transgenic mice. Am J Respir Crit Care Med. 2001 Nov 15;164(10 Pt 2):S67-70. doi: 10.1164/ajrccm.164.supplement_2.2106070. PMID: 11734470.

317: Abe M, Shibata K, Akatsu H, Shimizu N, Sakata N, Katsuragi T, Okada H. Contribution of anaphylatoxin C5a to late airway responses after repeated exposure of antigen to allergic rats. J Immunol. 2001 Oct 15;167(8):4651-60. doi: 10.4049/jimmunol.167.8.4651. PMID: 11591795.

318: Fyrnys B, Stang N, Wolf-Heuss E. Stability and performance characteristics of a budesonide powder for inhalation with a novel dry powder inhaler device. Curr Opin Pulm Med. 2001 Apr;7 Suppl 1:S7-11. PMID: 11385814.

319: Dahl M, Nordestgaard BG, Lange P, Tybjaerg-Hansen A. Fifteen-year follow-up of pulmonary function in individuals heterozygous for the cystic fibrosis phenylalanine-508 deletion. J Allergy Clin Immunol. 2001 May;107(5):818-23. doi: 10.1067/mai.2001.114117. PMID: 11344348.

320: Dubé J, Chakir J, Dubé C, Grimard Y, Laviolette M, Boulet LP. Synergistic action of endothelin (ET)-1 on the activation of bronchial fibroblast isolated from normal and asthmatic subjects. Int J Exp Pathol. 2000 Dec;81(6):429-37. doi: 10.1046/j.1365-2613.2000.00173.x. PMID: 11298190; PMCID: PMC2517744.

321: Shah S, Peat JK, Mazurski EJ, Wang H, Sindhusake D, Bruce C, Henry RL, Gibson PG. Effect of peer led programme for asthma education in adolescents: cluster randomised controlled trial. BMJ. 2001 Mar 10;322(7286):583-5. doi: 10.1136/bmj.322.7286.583. PMID: 11238152; PMCID: PMC26550.

322: Danckwerts MP. Optimization and development of a core-in-cup tablet for modulated release of theophylline in simulated gastrointestinal fluids. Drug Dev Ind Pharm. 2000 Jul;26(7):767-72. doi: 10.1081/ddc-100101296. PMID: 10872096.

323: Sacchi S, Kantarjian HM, Freireich EJ, O'Brien S, Cortes J, Rios MB, Kornblau S, Giles FJ, Koller C, Gajewski J, Talpaz M. Unexpected high incidence of severe toxicities associated with alpha interferon, low-dose cytosine arabinoside and all-trans retinoic acid in patients with chronic myelogenous leukemia. Leuk Lymphoma. 1999 Nov;35(5-6):483-9. doi: 10.1080/10428199909169612. PMID: 10609785.

324: Salmon M, Walsh DA, Koto H, Barnes PJ, Chung KF. Repeated allergen exposure of sensitized Brown-Norway rats induces airway cell DNA synthesis and remodelling. Eur Respir J. 1999 Sep;14(3):633-41. doi: 10.1034/j.1399-3003.1999.14c25.x. PMID: 10543287.

325: Baraniuk J, Murray JJ, Nathan RA, Berger WE, Johnson M, Edwards LD, Srebro S, Rickard KA. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. Chest. 1999 Sep;116(3):625-32. doi: 10.1378/chest.116.3.625. PMID: 10492263.

326: Li JT, Goldstein MF, Gross GN, Noonan MJ, Weisberg S, Edwards L, Reed KD, Rogenes PR. Effects of fluticasone propionate, triamcinolone acetonide, prednisone, and placebo on the hypothalamic-pituitary-adrenal axis. J Allergy Clin Immunol. 1999 Apr;103(4):622-9. doi: 10.1016/s0091-6749(99)70234-4. PMID: 10200011.

327: Golish J, Curtis-McCarthy P, McCarthy K, Kavuru M, Wagner W, Beck G, Eng P. Albuterol delivered by metered-dose inhaler (MDI), MDI with spacer, and Rotahaler device--a comparison of efficacy and safety. J Asthma. 1998;35(4):373-9. doi: 10.3109/02770909809075671. PMID: 9669832.

328: Gibson PG, Shah S, Mamoon HA. Peer-led asthma education for adolescents: impact evaluation. J Adolesc Health. 1998 Jan;22(1):66-72. doi: 10.1016/S1054-139X(97)00203-6. PMID: 9436069.

329: Tibes U, Friebe WG. Phospholipase A2 inhibitors in development. Expert Opin Investig Drugs. 1997 Mar;6(3):279-98. doi: 10.1517/13543784.6.3.279. PMID: 15989628.

330: Piletta PA, Wirth S, Hommel L, Saurat JH, Hauser C. Circulating skin-homing T cells in atopic dermatitis. Selective up-regulation of HLA-DR, interleukin-2R, and CD30 and decrease after combined UV-A and UV-B phototherapy. Arch Dermatol. 1996 Oct;132(10):1171-6. doi: 10.1001/archderm.132.10.1171. PMID: 8859027.

331: Spong CY, Sherer DM, Ghidini A, Jenkins CB, Seydel FD, Eglinton GS. Second-trimester amniotic fluid or maternal serum interleukin-10 levels and small for gestational age neonates. Obstet Gynecol. 1996 Jul;88(1):24-8. doi: 10.1016/0029-7844(96)00110-X. PMID: 8684756.

332: Li YQ, Yuan W, Zhang SL. [Clinical and experimental study of xiao er ke cuan ling oral liquid in the treatment of infantile bronchopneumonia]. Zhongguo Zhong Xi Yi Jie He Za Zhi. 1992 Dec;12(12):719-21, 737, 708. Chinese. PMID: 1304839.

333: Vichyanond P, Chokephaibulkit K, Kerdsomnuig S, Visitsuntorn N, Tuchinda M. Clinical evaluation of the "Siriraj Spacer" in asthmatic Thai children. Ann Allergy. 1992 Nov;69(5):433-8. PMID: 1456485.

334: Iamandescu IB. NSAIDs-induced asthma: peculiarities related to background and association with other drug or non-drugs etiological agents. Allergol Immunopathol (Madr). 1989 Nov-Dec;17(6):285-90. PMID: 2635829.

335: Findeisen DG. Unter Stress leiden oder Stress geniessen? Methodik und Ergebnisse einer klinisch bewährten Antistress-Dreiklang-Strategie am Beispiel der Asthmakrankheit [Suffering from stress or enjoying stress? Method and results of a clinically successful anti-stress triple strategy exemplified by asthma]. Fortschr Med. 1989 Mar 30;107(10):72-3. German. PMID: 2714726.

336: Henry DA. Side-effects of non-steroidal anti-inflammatory drugs. Baillieres Clin Rheumatol. 1988 Aug;2(2):425-54. doi: 10.1016/s0950-3579(88)80021-9. PMID: 3066501.

337: van der Vet AP, Kreukniet J, van Drost RH, Maes RA, Fokkens JK, Hamelink MJ. Combination therapy of theophylline and terbutaline as sustained-release preparations in patients with asthmatic bronchitis. Int J Clin Pharmacol Ther Toxicol. 1987 Oct;25(10):558-64. PMID: 2828249.

338: Conradson TB, Eklundh G, Olofsson B, Pahlm O, Persson G. Arrhythmogenicity from combined bronchodilator therapy in patients with obstructive lung disease and concomitant ischemic heart disease. Chest. 1987 Jan;91(1):5-9. doi: 10.1378/chest.91.1.5. PMID: 2431838.

339: Tønnesen P. Intracutaneous and skin prick testing with serotonin and histamine. Allergy. 1986 Apr;41(3):196-202. doi: 10.1111/j.1398-9995.1986.tb00300.x. PMID: 3717531.

340: Kraemer R, Meister B. Fast real-time moment-ratio analysis of multibreath nitrogen washout in children. J Appl Physiol (1985). 1985 Oct;59(4):1137-44. doi: 10.1152/jappl.1985.59.4.1137. PMID: 4055593.

341: Fisher AA. The persulfates: a triple threat. Cutis. 1985 Jun;35(6):520, 523-5. PMID: 4017646.

342: Giles GG, Lickiss N, Gibson HB, Shaw K. Respiratory symptoms in Tasmanian adolescents: a follow up of the 1961 birth cohort. Aust N Z J Med. 1984 Oct;14(5):631-7. doi: 10.1111/j.1445-5994.1984.tb05015.x. PMID: 6597710.

343: Khil'ko TF. Reaktsiia troĭnogo rozetkoobrazovaniia--novyĭ metod otsenki kletochnykh mekhanizmov immuniteta pri vozdeĭstvii faktorov proizvodst-vennoĭ sredy [The triple rosette formation reaction--a new method for assessing the mechanisms of cellular immunity during exposure to factors in the industrial environment]. Gig Tr Prof Zabol. 1984 Sep;(9):20-3. Russian. PMID: 6334007.

344: Rebuck AS, Gent M, Chapman KR. Anticholinergic and sympathomimetic combination therapy of asthma. J Allergy Clin Immunol. 1983 Mar;71(3):317-23. doi: 10.1016/0091-6749(83)90086-6. PMID: 6219156.

345: Lefcoe NM, Toogood JH, Blennerhassett G, Baskerville J, Paterson NA. The addition of an aerosol anticholinergic to an oral beta agonist plus theophylline in asthma and bronchitis. A double-blind single dose study. Chest. 1982 Sep;82(3):300-5. doi: 10.1378/chest.82.3.300. PMID: 6213382.

346: Grimwood K, Johnson-Barrett JJ, Taylor B. Salbutamol: tablets, inhalational powder, or nebuliser? Br Med J (Clin Res Ed). 1981 Jan 10;282(6258):105-6. doi: 10.1136/bmj.282.6258.105. PMID: 6779890; PMCID: PMC1503918.

347: Tripathi RM, Sen PC, Das PK. Studies on the mechanism of action of Albizzia lebbeck, an Indian indigenous drug used in the treatment of atopic allergy. J Ethnopharmacol. 1979 Dec;1(4):385-96. doi: 10.1016/s0378-8741(79)80003-3. PMID: 544953.

348: Muittari A, Mattila MJ. Objective and subjective assessment of ephedrine combinations in asthmatic outpatients. Ann Clin Res. 1979 Jun;11(3):87-9. PMID: 386912.

349: Cohen BM. Physiologic/clinical comparisons of a sustained-release decongestant combination, its components and placebo in patients with allergic rhinitis. J Asthma Res. 1975 Sep;13(1):7-13. doi: 10.3109/02770907509104153. PMID: 57959.

350: Abramson HA. Triple blind disaster. J Asthma Res. 1965 Sep;3(1):1-2. PMID: 5318624.

351: GOLDFARB AA, ROMANOFF A. Clinical evaluation of a new triple drug aerosol for asthma. Ann Allergy. 1962 May;20:307-14. PMID: 13899746.