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RESEARCH

Comparative effectiveness of long term drug treatment strategies to prevent asthma exacerbations: network meta-analysis

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Abstract

Objective To determine the comparative effectiveness and safety of current maintenance strategies in preventing exacerbations of asthma.

Design Systematic review and network meta-analysis using Bayesian statistics.

Data sources Cochrane systematic reviews on chronic asthma, complemented by an updated search when appropriate.

Eligibility criteria Trials of adults with asthma randomised to maintenance treatments of at least 24 weeks duration and that reported on asthma exacerbations in full text. Low dose inhaled corticosteroid treatment was the comparator strategy. The primary effectiveness outcome was the rate of severe exacerbations. The secondary outcome was the composite of moderate or severe exacerbations. The rate of withdrawal was analysed as a safety outcome.

Results 64 trials with 59 622 patient years of follow-up comparing 15 strategies and placebo were included. For prevention of severe exacerbations, combined inhaled corticosteroids and long acting β agonists as maintenance and reliever treatment and combined inhaled corticosteroids and long acting β agonists in a fixed daily dose performed equally well and were ranked first for effectiveness. The rate ratios compared with low dose inhaled corticosteroids were 0.44 (95% credible interval 0.29 to 0.66) and 0.51 (0.35 to 0.77), respectively. Other combined strategies were not superior to inhaled corticosteroids and all single drug treatments were inferior to single low dose inhaled corticosteroids. Safety was best for conventional best (guideline based) practice and combined maintenance and reliever therapy.

Conclusions Strategies with combined inhaled corticosteroids and long acting β agonists are most effective and safe in preventing severe exacerbations of asthma, although some heterogeneity was observed in this network meta-analysis of full text reports.

Introduction

Asthma is a widespread chronic airway disease characterised by an unpredictable course.[1] Preventing exacerbations is considered a major long term treatment goal in international guidelines.[1] These episodes of sudden deterioration of symptoms and airways obstruction result in a burden to the patient and use of expensive medical resources. Asthma related healthcare expenses in patients with exacerbations are double ($1740 (£1035; €1257) *v* $847) those of patients without exacerbations.[2 3]

Although inhaled corticosteroids—anti-inflammatory controller drugs—are currently the cornerstone of preventing asthma exacerbations,[4-6] several other agents or combination strategies

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Table S1: data from included studies
Table S2: risk of bias assessment of included studies
Table S3: reported harms in included studies
Figure S1: analysis with non-imputed data
Figure S2: sensitivity analyses for severe exacerbations
Figure S3: funnel plots of direct comparisons with five or more studies, for severe exacerbations

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have been investigated.[7] Such strategies include combinations of existing agents, such as inhaled corticosteroids and long acting β agonists,[8-10] and other agents, such as leukotriene receptor antagonists[11] and anti-IgE antibodies,[12] which have been tested in multiple clinical trials.

Previous research syntheses on the effectiveness of different strategies in asthma have been informative but have drawbacks, such as only comparing pairs of strategies, non-standardised definitions of drug dosages and outcomes, and inclusion of mainly trials with a follow-up of less than 20 weeks.[13 14] Hence a more standardised comparison of all relevant drug maintenance strategies to prevent asthma exacerbations is needed. Network meta-analysis (also called multiple treatment comparison) is a relatively new approach that uses all available evidence and formally compares all existing strategies.[15 16]

We determined the comparative effectiveness and safety of all available maintenance treatment strategies for chronic asthma for their ability to reduce consistently defined exacerbations during long term treatment, and to rank them for these outcomes. We carried out a network meta-analysis of drug interventions to prevent exacerbations in patients with persistent asthma, in trials of at least 24 weeks' duration, and with exacerbations defined according to the American Thoracic Society/European Respiratory Society.[17]

Methods

Systematic review and data extraction

To identify randomised controlled trials we assessed all Cochrane systematic reviews on chronic asthma (http://airways.cochrane.org/our-reviews) published before 1 August 2011 and selected the 16 on drug interventions in adults.[18-33] We assessed all studies included in these reviews, as well as those that were listed as having been rejected by the Cochrane authors. We carried out an update search for all reviews using the identical search terms reported in these reviews. This search was performed on 1 August 2013 in the Cochrane Airways Group register of trials, which consists, among others, of trials on asthma in Medline, Embase, and the Cochrane Central Register of Controlled Trials (http://airways.cochrane.org/trials-register). We screened all references of included reports for eligible trials.

Eligible reports were full text randomised controlled trials lasting at least 24 weeks that compared different drug strategies for the maintenance treatment of asthma in adults and reported on exacerbations. We applied no restrictions on language or publication date. For an intervention to be included in the analysis, it had to be evaluated in at least two separate trials.

One investigator removed all reports that were not full text publications and reports on interventions lasting less than 24 weeks. Two investigators independently assessed all remaining reports on title and abstract. The full text of those remaining was assessed against the inclusion criteria. Two investigators (RL and JC) used standardised forms to independently extract data on the characteristics of publication, patients, intervention, outcomes, and risk of bias. We assessed risk of bias from selection, performance, attrition, detection, and selective reporting according to recommendations in the Cochrane handbook.[34] Differences were resolved by agreement, after which we entered data in a database using a dedicated entry screen. To screen for publication bias we created funnel plots for all direct comparisons yielding five or more studies. We emailed the corresponding authors for missing data on outcomes. After data extraction, we evaluated studies against the similarity assumptions required for network meta-analysis—that is, the extent to which covariates, such as patient characteristics, that would act as modifiers of relative treatment effect were similar across studies.[35] For this reason we included only full text reports: abstracts presented at conferences and from manufacturer's websites do not contain sufficient information on patient characteristics, methods, and quality to assess whether similarity assumptions are met. Also, we omitted trials on tailored strategies with monoclonal antibodies or maintenance treatment with systemic corticosteroids, since these strategies are only used for specific patient phenotypes with severe asthma.

Measuring treatment effect

Given the known wide variation in definitions of asthma exacerbations in the literature,[17] we created standardised criteria for moderate and severe exacerbations before data extraction that were consistent with American Thoracic Society/European Respiratory Society recommendations.[17] If a report defined exacerbations as hospital admission, visit to an emergency department, or prescription of systemic corticosteroids for at least three days, we classified the events as severe exacerbations. We classified events as moderate exacerbations if they were defined by a decrease in pulmonary function (peak flow or forced expiratory volume), increased use of rescue drugs, or night time waking because of asthma symptoms (all for at least two consecutive days), or by unscheduled visits to or by a doctor. Unless the report stated that most events fulfilled the criteria for severe exacerbations, we classified events defined by elements of both severe and moderate exacerbations as moderate exacerbations.

We converted all doses of inhaled corticosteroids into dose equivalents of beclometasone by multiplying with conversion factors[1]: 1.0 for beclometasone with chlorofluorocarbon propellant, 2.0 for beclometasone with hydrofluoroalkane propellant, 1.25 for budesonide chlorofluorocarbon, 1.25 for budesonide hydrofluoroalkane, 3.15 for ciclesonide chlorofluorocarbon, 6.3 for ciclesonide hydrofluoroalkane, 0.5 for flunisolide, 2.0 for fluticasone propionate, 1.25 for mometasone, and 0.5 for triamcinolone, with a threshold of 500 μg beclometasone chlorofluorocarbon a day to discriminate low doses from medium or high doses. We regarded fluticasone propionate 2.5 as equipotent to fluticasone fuorate 1.0 according to the manufacturer's summary of product characteristics. Trial arms with similar strategies in a single trial were included and analysed as one—for example, if two arms had different doses of inhaled corticosteroids in the same (low or high) dose range, we classified both as either high or low dose.

In asthma literature, exacerbations are commonly reported as the number of events per trial arm, the proportion of patients with at least one exacerbation, or exacerbation rates (numbers per person time of follow-up). We calculated rates per trial arm from the numbers of exacerbations and patient years; the numbers of patient years were estimated by multiplying the number of patients by the intended follow-up time, assuming that patients who withdrew during the intervention had done so halfway through the trial. If numbers of exacerbations were not available, we used the reported exacerbation rates, and we distinguished between rates weighted by follow-up duration and those not weighted, since non-weighted rates tend to yield exaggerated effect estimates.[36 37] If numbers of patients with exacerbations were only reported, we imputed the number of exacerbations with estimations using median regression with linear and quadratic terms of numbers of patients with exacerbations and patient years as covariates.

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Measuring safety

Owing to the wide variation in reporting of adverse events, we analysed reported withdrawals as a result of adverse events as the primary safety variable. These rates were reported in most studies, varied little in definition, and were considered most likely to reflect the reasons for decisions to withdraw. As a secondary safety outcome we analysed the total number of withdrawals.

Statistical analysis

We used Bayesian hierarchical random effects models,[38] fully preserving randomised treatment effects within trials and accounting for correlation between comparisons within multiarm trials.[39] Adjusting for patient years under all situations, we used a log-linear Poisson model (exacerbation rate ratios) to analyse the number of exacerbations and a logistic model (odds ratios) with complementary log-log link function to analyse the numbers of patients with at least one exacerbation and the number of study withdrawals. We fitted models with Markov chain Monte Carlo simulations with non-informative priors.[15] Pooled rate ratios were estimated from the median of the posterior distribution of the difference in risk estimate between two treatments and corresponding 95% credible intervals derived. For each strategy we estimated the probability of its rank order and 95% credible interval by determining the median rank based on draws from the estimated effect size distributions in Markov chain Monte Carlo simulations; displayed in rankograms.[40] The primary analysis was of the rate of severe exacerbations, using data from all studies. We also carried out analyses for the composite of moderate or severe exacerbations combined, when both were reported. Preplanned subgroup analyses were based on risk of bias assessment, asthma severity[41] (based on prestudy treatment step[1]), study size, and duration of intervention. Additional sensitivity analyses were done only with non-imputed data (that is, excluding studies in which numbers of exacerbations or patient years were not reported) and with exclusion of open label studies.

We estimated heterogeneity between trials from the median of the posterior distribution of the between trial variance τ^2.[42] Such heterogeneity was considered to be low if τ^2 estimates were around 0.04, moderate if estimates approached 0.14, and large if estimates were around 0.40. We assessed the consistency of the model by comparing effect estimates derived through a meta-analysis including only direct comparisons between pairs of treatments, with the indirect effect estimates derived through a network-meta analysis excluding the respective direct comparison. We applied this procedure to all existing pairwise comparisons in the analysis dataset. The network was regarded as consistent when fewer than 5% of the differences between direct and indirect estimates differed from zero.

WinBUGS 1.4.3 was used for the Markov chain Monte Carlo simulations, Stata 12 for data preparation and post-processing of simulation results, and SAS 9.3 for evaluation of rankograms.

Results

From the Cochrane reviews[18-32] we identified 4851 records and assessed 170 full text reports, of which 70 met our inclusion criteria (fig 1⇓). We excluded four strategies from analysis—cromoglycate,[43] theophylline,[44] azithromycin add-on treatment,[45] and combined inhaled corticosteroids, long acting β agonists, and theophylline[46]—as they were identified as a strategy in only one eligible trial. Six reports yielded data that could not be synthesised, mainly because of lack of data on exacerbations[47-49] and patient years.[50-52] Overall, 64 reports describing 66 trials containing 59 622 patient years were included in the analysis (also see web extra table S1).[4-6 8 9 11 44 53-108] Of the 13 corresponding authors contacted, three provided additional data.

The intervention lasted approximately six months in more than half of the reports (37/64, 58%), one year in 25 (39%), and more than one year in only two.

Classification of treatment strategies

A total of 16 interventions were analysed (table⇓ and fig 2⇓): regular short or long acting β agonists; leukotriene receptor antagonists; and low dose inhaled corticosteroids (the reference strategy) or high dose inhaled corticosteroids separately or combined with regular short or long acting β agonists or with leukotriene receptor antagonists. For combination therapy (combined inhaled corticosteroids and long acting β agonists in a single inhaler), we identified four strategies: combined fixed dose treatment with low or high steroid doses and short acting β agonists as reliever; combined adjustable maintenance dose and short acting β agonists as reliever, in which maintenance therapy was adjusted by either the doctor or the patient; and combined maintenance and reliever therapy, in which the combined inhaler was prescribed for both fixed maintenance dosing and "as needed" reliever. Some studies compared the index intervention with placebo, others to current guidelines (best practice). Some minor treatment variations were included: combined fixed dose treatment with as needed long acting β agonists[89] was included in combined fixed dose treatment, and combined fixed dose treatment plus additional maintenance inhaled corticosteroids with as needed short acting β agonists[83] was included in combined fixed dose treatment with high dose steroids.

Risk of bias

Poor reporting hampered complete assessment of risk of bias, with 179/448 (40%) of the items classified as unclear (see web extra table S2). In about 30% of the trials the risk of selection bias (sequence generation and allocation concealment) was deemed to be low. Twenty two per cent (14/64) of the trials were deemed to be at high risk of bias because of problems with blinding. To deal with this we performed an additional sensitivity analysis. Incomplete outcomes were tackled relatively well, with approximately 80% assessed as being at low risk of bias. Although after 2005 most trials were registered, they were not all assessed as being at low risk of selective outcome reporting, as some trials were registered retrospectively or outcome variables were not registered before the start of the trial. All reports except two[106 107] were linked with the pharmaceutical industry through authorship (52/64), sponsorship or funding (56/64), or both (45/64). Funnel plots of all direct comparisons with five or more studies did not show clear evidence of small study bias (see web extra figure S3), although assessment was hampered by sparse data: no direct comparisons concerned 10 or more studies.

Severe exacerbations

We analysed 57 trials, including 53 309 patient years, for severe exacerbations. Low dose inhaled corticosteroids (the reference strategy) were superior to all other single agent strategies in preventing severe exacerbations (fig 3⇓). The rate ratio for placebo compared with low dose inhaled corticosteroids was 4.19 (95% credible interval 2.87 to 6.16). For preventing severe exacerbations, only combined maintenance and reliever treatment and combined fixed dose treatment performed

significantly better than low dose inhaled corticosteroids, with rate ratios of 0.44 (0.29 to 0.66) for combined maintenance and reliever treatment and 0.51 (0.35 to 0.77) for combined fixed dose treatment (fig 3). All other treatment strategies that used combined inhaled corticosteroids and another agent, whether by single or separate inhalers, tended to perform better than low dose inhaled corticosteroids, although the difference was not statistically significant. Data for exacerbation rates without imputation were available for 45 trials (see web extra figure S1); results were largely similar to the primary analysis, although in severe exacerbations the difference between the common comparator and combined fixed dose treatment was no longer significant (0.63, 0.40 to 1.02).

Figure 3 also shows the estimated ranks of effectiveness for all strategies, with associated 95% credible intervals. The rankograms (fig 4⇓) show the probability of the effectiveness of each strategy, ordered from the highest rank (combined maintenance and reliever treatment and combined fixed dose treatment) to the lowest rank (placebo).

We carried out preplanned stratified analyses based on risk of bias assessment, study duration, study size, and prestudy treatment step[1] (see web extra figures S2 A-D), and additional sensitivity analyses excluding studies that reported non-weighted exacerbation rates (web extra figure S2 E) and unblinded studies (web extra figure S2 F). These analyses did not show clear differences from the primary analysis; eight out of 17 trials that studied combined maintenance and reliever treatment (containing 2656/8174 patient years) were excluded in this sensitivity analysis, but similar rate ratios and rank orders were observed. Some of the sensitivity analyses (for example, in studies of more than 30 weeks' duration) were hampered by small numbers of events, resulting in wide credible intervals.

The estimate of between study variance (heterogeneity) was moderate; τ^2=0.102. For five out of 31 comparisons (inhaled corticosteroids versus inhaled corticosteroids and long acting β agonists, inhaled corticosteroids versus combined maintenance and reliever treatment, inhaled corticosteroids and regular short acting β agonists versus regular short acting β agonists, combined fixed dose treatment versus combined maintenance and reliever treatment, and regular long acting β agonists versus regular short acting beta agonists) we found statistical evidence for inconsistency between direct and indirect comparisons (fig 5⇓), predominantly in direct comparisons including only one or two studies.

Composite of moderate or severe exacerbations

For the composite of moderate or severe exacerbations, we analysed 61 trials including 39 237 patient years (fig 3). Although point estimates for rate ratios differed from those for severe exacerbations, and credible limits were narrower—for example, combined maintenance and reliever treatment 0.54 (95% credible interval 0.42 to 0.69) and combined fixed dose treatment 0.68 (0.54 to 0.85)—overall trends were similar. Figure 4 shows rankograms for the composite of moderate or severe exacerbations, with combined maintenance and reliever treatment ranking highest. Heterogeneity was low; τ^2=0.070. For two out of 33 comparisons (inhaled corticosteroids versus high dose inhaled corticosteroids with regular long acting β agonists and high dose inhaled corticosteroids with regular long acting β agonists versus combined maintenance and reliever treatment, we found statistical evidence for inconsistency between direct and indirect comparisons (fig 6⇓).

Safety outcomes

Figure 7⇓ shows the risk ratios and the probability based rank order with corresponding 95% credible intervals for withdrawal as a result of adverse events for each strategy. Best practice had the lowest rate of withdrawals due to adverse events. Combined maintenance and reliever treatment was also associated with significantly fewer withdrawals because of adverse events compared with low dose inhaled corticosteroids. There was little variation in withdrawal rates between the other treatment strategies and no statistically significant differences from the reference strategy. These results were largely confirmed by total number of withdrawals (fig 7). (See web extra table S3 for reported harms.)

Discussion

The purpose of this systematic review and network meta-analysis was to identify all commonly used strategies for the prevention of exacerbations of chronic asthma, estimate their efficacy and safety compared with low dose inhaled corticosteroids, and order them by rank. Our primary analysis shows that both combined inhaled corticosteroids and long acting β agonists as maintenance and reliever treatment and combined inhaled corticosteroids and long acting β agonists as fixed dose treatment significantly reduced the risk of severe exacerbations compared with low dose inhaled corticosteroids alone, with the combination strategies having similar rate ratios and a similar ranking in the probability analysis. Other strategies that included more than one agent performed similarly to each other compared with low dose inhaled corticosteroids, and were not statistically worse than combined maintenance and reliever treatment or combined fixed dose treatment. All combined strategies outperformed single agent strategies of regular leukotriene receptor antagonists or long acting β agonists. When the total exacerbation burden was considered, using studies that reported both moderate and severe exacerbations, combined maintenance and reliever treatment ranked highest, approximately halving the risk of exacerbations compared with low dose inhaled corticosteroids. These results provide an overview of efficacy of all common treatment regimens in the prophylaxis of asthma exacerbations, which can be used as a starting point in clinical practice.

Comparison with other studies

Our approach is novel in that it includes all published treatment options in a single analysis, allowing quantitative ranking of all the available evidence. Our findings confirm and extend previous focused studies based on direct pairwise comparisons of treatments. Two meta-analyses, a Cochrane review[25] and an industry sponsored analysis,[109] favoured combined maintenance and reliever treatment over specific comparators in reducing severe exacerbations, including combined fixed dose treatment. In the more extensive analysis of the present study, apart from combined maintenance and reliever treatment and combined fixed dose treatment, treatment strategies involving an inhaled corticosteroid and another agent, whether in one device or two devices, did not perform statistically significantly better than our reference strategy, low dose inhaled corticosteroids. The combined strategies performed equally well in preventing severe exacerbations, an observation challenging a previous meta-analysis of six studies, four of which were of 4-12 weeks' duration.[22] The meta-analysis concluded that the addition of long acting β agonists to inhaled corticosteroids was favoured over the addition of leukotriene receptor antagonists. In our network meta-analysis, in which inhaled corticosteroid doses

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were classified as either low or moderate or high, we were unable to confirm the previously reported positive effects of increasing doses of inhaled corticosteroids in preventing exacerbations.[13] This is probably because in the included studies the intervention of inhaled corticosteroid dose was typically double that of the control inhaled corticosteroid dose, but both doses may still have fallen within either our low dose or moderate or high dose inhaled corticosteroid categories. Another explanation may be underlying differences in the original patient populations. For example, there were differences in baseline forced expiratory volume in one second (%) predicted between patients in trials using high dose inhaled corticosteroids (median 72.2%, range 64.0-95.5%, interquartile range 69.0-75.4%) and those using low dose inhaled corticosteroids (median 82.3%, range 65.6-102.0%, interquartile range 75.4-88.8%). For severe exacerbations as well as the composite of moderate or severe exacerbations, low dose inhaled corticosteroids seemed to be superior to regular short or long acting β agonists or to leukotriene receptor antagonists alone, a finding that has been observed previously.[20 27]

Strengths and limitations of this study

Our study has several strengths. Firstly, network meta-analysis allowed comparison of all available strategies in a single analysis, giving a combined total of 59 622 patient years of treatment, rather than separate and disconnected meta-analyses for individual pairs of treatments. By conducting a network meta-analysis we were able to provide a formal rank order for treatment strategies by their capacity to reduce exacerbations, while capturing the imprecision of such rankings.

Secondly, we carefully developed the inclusion criteria for trials. As exacerbations are relatively infrequent outcomes, we restricted our study to reports with treatment durations of at least 24 weeks (close to six months) to reflect the effects of long term treatment in a variable disease. In several other meta-analyses with exacerbations as an outcome variable, the bulk of the evidence has originated from studies with durations of intervention between three and six months, a relatively short period as asthma treatment usually lasts for years, and in clinical trials the effects of treatment seem to decrease with increasing duration of intervention.[13 17 22 24]

Thirdly, where the interpretation of previous reviews was hampered by pooling of data based on variously defined exacerbations, we applied predetermined standardised definitions based on those of the American Thoracic Society/European Respiratory Society.[17] This allowed a comprehensive cross comparison of all studies. As recommended by the report of the American Thoracic Society/European Respiratory Society, we did not attempt to classify mild exacerbations. The composite of moderate or severe exacerbations combined can thus be regarded for clinical interpretation as representing the total number of exacerbations. Thirty nine studies measured severe exacerbations, but only 17 were consistent with this current definition. In addition, we found that exacerbation outcomes, particularly for severe exacerbations, were reported in several ways (number of exacerbations, number of patients with at least one exacerbation, and weighted or non-weighted exacerbation rates (annually or in other time frames)), underscoring the value of our recalculations to reliably compare strategies.

We acknowledge the following limitations to our work. Firstly, the criteria for selection of strategies was based on existing Cochrane reviews and our own searches to update those reviews, so the comprehensiveness of our study depends on the adequacy of the original Cochrane research questions and search terms. Secondly, we did not include unpublished or premarketing studies from drug regulatory agencies such as the Food and Drug Administration and European Medicines Agency; this might have led to a reporting bias.[110] However, since all included studies were related to the pharmaceutical industry, differential reporting bias may have been reduced.[111] Thirdly, there was heterogeneity between trial populations—for example, in baseline lung function. This might explain some of the observed inconsistency and heterogeneity for the primary outcome of severe exacerbations. If this were the case, we would expect the same pattern in the analysis of the secondary composite outcome of moderate or severe exacerbations. However, this analysis yielded low heterogeneity and little evidence for inconsistency. Moreover, inconsistencies were nearly exclusively observed in direct comparisons with only one or two trials. Therefore we believe that the patients included in our component trials were sufficiently similar to meet the similarity assumptions for network meta-analysis. Finally, the generalisability of the findings is limited by the original trial inclusion criteria—for example, many studies required non-smokers with significant bronchodilator reversibility, so participants were not necessarily representative of the general population with asthma.[112] However, a requirement for an exacerbation in the previous 12 months, seen in more recent studies, is not regarded as a limitation if the aim of the study was to reduce exacerbations.

Policy implications

Low dose inhaled corticosteroids are highly effective in reducing severe asthma exacerbations, with patients receiving placebo having a rate ratio of over 4 for experiencing a severe exacerbation within six months. In comparison with low dose inhaled corticosteroids, we identified combined maintenance and reliever treatment as the highest ranked strategy for preventing total exacerbations (composite of moderate or severe), and equally ranked with combined fixed dose treatment for preventing severe exacerbations. It has been proposed that the mechanism for greater reduction of exacerbations with the combined maintenance and reliever treatment strategy is from either an early (patient initiated) up-titration of inhaled corticosteroids and β agonist dose as soon as asthma symptoms worsen, thus avoiding delays by doctors or patients, or greater adherence with drugs containing inhaled corticosteroids. Both of these ideas was supported by one of the included studies, independent of pharmaceutical companies, using real time electronic monitoring of all inhalers supports.[107] Although some of the studies of combined maintenance and reliever treatment included in the present analysis were unblinded, a sensitivity analysis omitting unblinded trials (eight trials with 2656 patient years of the combined maintenance and reliever treatment strategy), showed similar results to the primary analysis.

All strategies consisting of inhaled corticosteroids together with another agent had rate ratios below 1, suggesting better performance than inhaled corticosteroids used alone, although none of these differences, other than combined maintenance and reliever treatment and combined fixed dose treatment, were statistically significant for severe exacerbations. This does not, however, allow the conclusion that these two strategies are statistically better than other combination strategies. Not unexpectedly, the rank numbers of these inhaled corticosteroids combined with other agent strategies have broad credible intervals and therefore may be regarded as equally effective in preventing exacerbations. Therefore, a choice of any treatment containing inhaled corticosteroids should be based on other factors, such as impact on control of asthma symptoms,[113] patient or doctor preference, cost, availability, or potential for side

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effects. Monotherapy with agents other than inhaled corticosteroids was not as effective in preventing exacerbations. Subsequent network meta-analysis may show whether this also holds for outcomes such as symptoms, lung function, and cost, although the heterogeneity between studies in reporting of such outcomes is even more noticeable than for exacerbations, and there is increasing recognition of discordance between current asthma control and adverse outcomes such as exacerbations.[17]

In terms of safety, it was not surprising that the best practice strategy had the lowest withdrawal rate. This intervention, in which the patient and practitioner are free to choose the drug or regimen that they believe is superior or safer than others, is only possible in open label trials. In an open label study, both patients and practitioners are less likely to withdraw from a familiar treatment (best practice) than from an unfamiliar (new) treatment. In contrast with best practice, all other interventions (including combined maintenance and reliever treatment and combined fixed dose treatment) were found in both open label and double blind trials. Withdrawal rates are typically higher in double blind trials. Combined maintenance and reliever treatment ranked second only to current best practice in the safety measures. For other strategies, withdrawals as a result of adverse events were not significantly different from those of low dose inhaled corticosteroids; total numbers of withdrawals were significantly higher with placebo and with long acting β agonists compared with low dose inhaled corticosteroids.

Conclusions

This comprehensive network meta-analysis shows that combined inhaled corticosteroids and long acting β agonists as maintenance and reliever treatment has a good safety profile and is better in preventing total asthma exacerbations than low dose inhaled corticosteroids alone. Treatment with a combined fixed dose was equally effective at reducing severe exacerbations. All combinations of inhaled corticosteroids and other agents seem to be similarly effective and not significantly better than low dose inhaled corticosteroids. These results suggest that, when low dose inhaled corticosteroids are not sufficiently effective, combined maintenance and reliever treatment or combined fixed dose treatment may be preferred for the reduction of exacerbations.

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This study was registered in the PROSPERO database as CRD4201200199 (www.crd.york.ac.uk/Prospero/).

Contributors: GtR and RJBL conceived the study. RJBL, GtR, SMR, HKR, JC, PJS, PJ, and AG contributed to the study protocol. RJBL and JC selected reports and extracted the data. RJBL, AG, GtR, and PJ analysed and interpreted the data. RJBL and GtR wrote the first draft of the manuscript. All authors critically revised the manuscript for intellectual content and approved the final version. They had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. RJBL and GtR act as guarantors.

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Data sharing: Dataset and statistical code are available from the corresponding author at r.j.loijmans@amc.nl.

Transparency: The lead author (the manuscript's guarantor), affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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What is already known on this topic

Adding long acting β agonists to asthma treatment is preferred to raising the dose of inhaled corticosteroids to prevent exacerbations

Several meta-analyses have assessed other treatment strategies, such as leukotriene antagonists and single inhaler combination devices

What this study adds

Combined inhaled corticosteroids and long acting β agonists as maintenance and reliever treatment or in a fixed daily dose are the only strategies better than low dose inhaled corticosteroids in preventing total asthma exacerbations

These two strategies seem preferred when low dose inhaled corticosteroids are not sufficient, and step-up of treatment is warranted

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Table

Table 1| Identified strategies for maintenance treatment of asthma

Strategy and generic name	Daily dose (µg)	Medium/high dose ICS strategy	Daily dose (µg)
SABA:			
Salbutamol	NS	—	—
Terbutaline	NS	—	—
LABA*:			
Formoterol	NS	—	—
Salmeterol	NS	—	—
LTRA*:			
Montelukast	12	—	—
ICS*:			
Beclometasone	200-500	ICS H*	>500
Budesonide	200-400	ICS H*	>400
Fluticasone	100-250	ICS H*	>250
Ciclesonide	80-160	ICS H*	>160
Mometasone	200-400	ICS H*	>400
ICS+SABA*	Combined as above, in separate inhalers		
ICS H+SABA*	Combined as above, in separate inhalers		
ICS+LABA*	Combined as above, in separate inhalers		
ICS H+LABA*	Combined as above, in separate inhalers		
ICS+LTRA*	Combined as above, in separate inhalers		
COMBI FIX*			
Beclometasone/formoterol	100/6-200/12	COMBI FIX H*	>200/12
Budesonide/formoterol	200/6-400/12	COMBI FIX H*	>400/12
Fluticasone/salmeterol	250/50	COMBI FIX H*	>250/50
Mometasone/formoterol	100/5-400/20	COMBI FIX H*	>400/20
COMBI AMD*	As COMBI FIX, but dose regularly adapted by doctor or patient, guided by symptoms		
COMBI MAR	As COMBI FIX, but combination agent also used as relief or rescue agent when warranted		
Best Practice	Doctors requested to treat patients according to current or local asthma treatment guidelines		
Placebo	Non-active comparator		

ICS=inhaled corticosteroids; SABA=short acting β agonists, regular use; NS=not specified; LABA=long acting β agonists, regular use; LTRA=leukotriene receptor antagonist; H=high daily dose inhaled corticosteroids (>500 µg beclometasone equivalents); COMBI=combined ICS and LABA in single inhaler; COMBI FIX=COMBI in fixed daily dose; COMBI AMD=COMBI in adjustable maintenance dose; COMBI MAR=COMBI as maintenance and reliever treatment.
ICS doses by approximation, for analysis dose equivalents of beclometasone was used as stated in methods section.
*Relief or rescue drug with short acting β agonists allowed.

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Figures

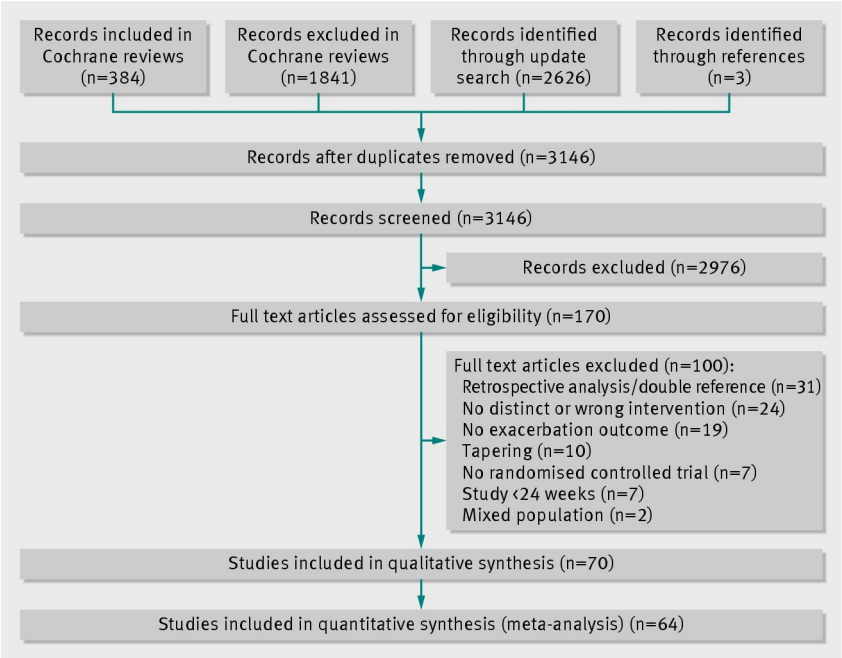

Fig 1 Flow chart of study selection

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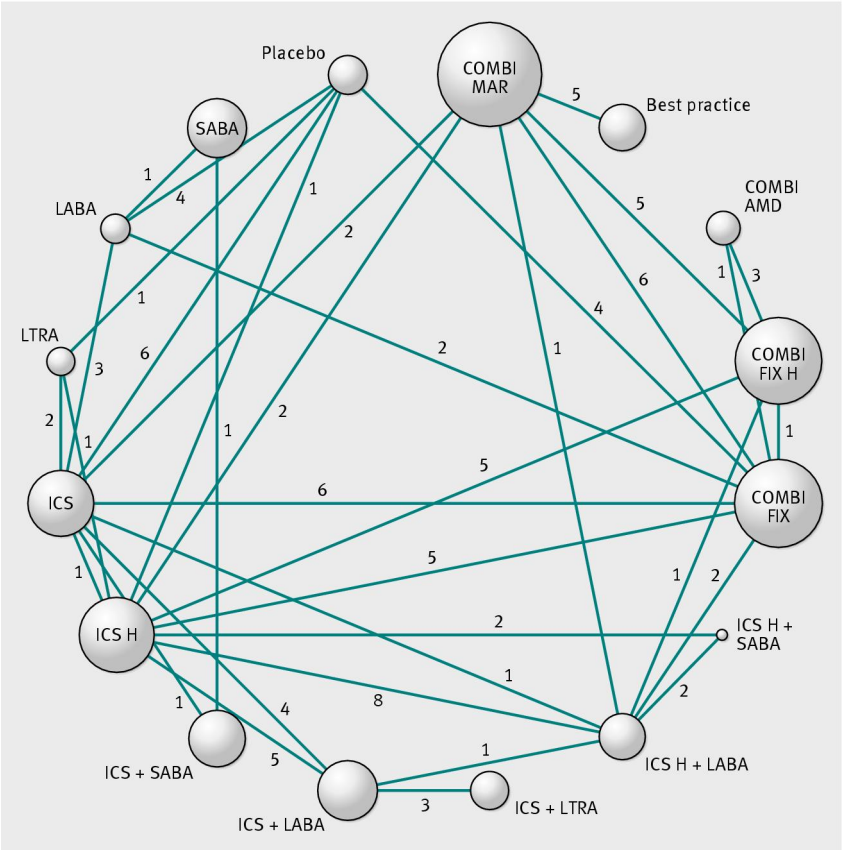

Fig 2 Overview of treatment strategies, with lines representing direct (head to head) comparisons; surface areas of circles proportional to number of patients identified in strategy. Numbers in lines are number of direct comparisons. COMBI=combined inhaled corticosteroid (ICS) and long acting β agonist (LABA) in single inhaler; COMBI MAR=COMBI as maintenance and reliever treatment; COMBI FIX=COMBI in fixed daily dose; COMBI AMD=COMBI in adjustable maintenance dose; H=high dose; LABA=long acting β agonists, regular use; LTRA=leukotriene receptor antagonist; SABA=short acting β agonists, regular use

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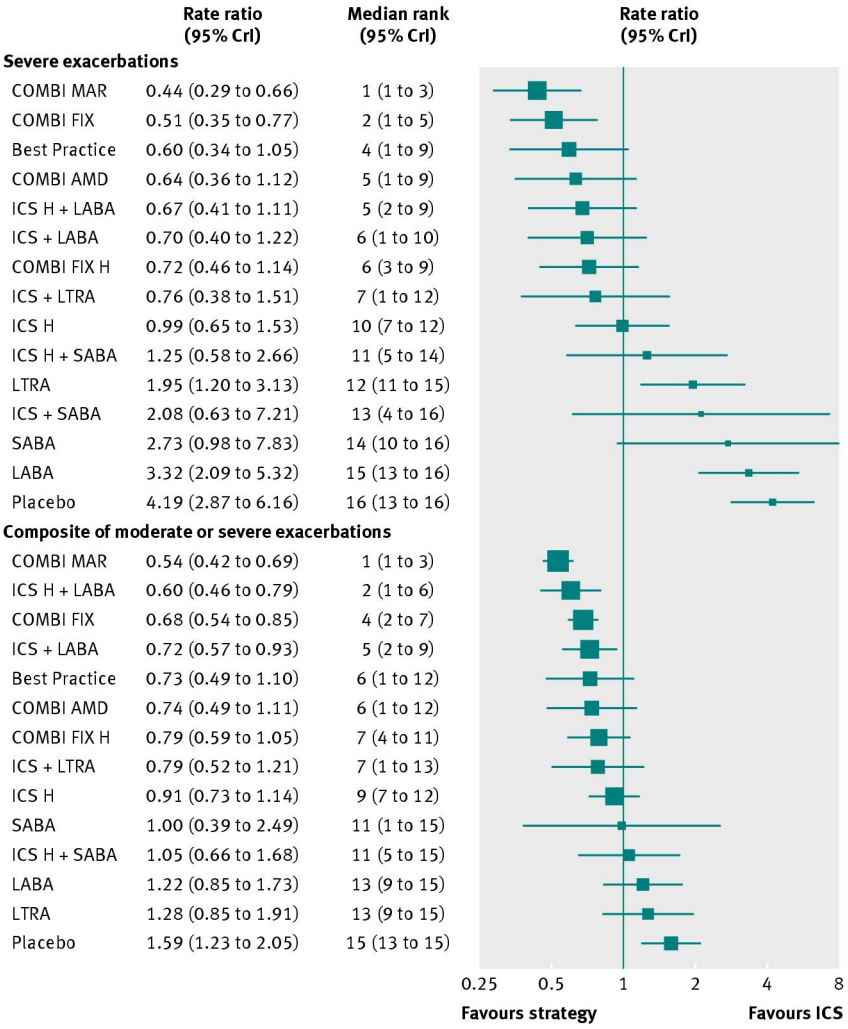

Fig 3 Forest plot showing asthma exacerbation rate ratios and median ranks with corresponding 95% credible intervals for each strategy compared with low dose inhaled corticosteroids (ICS). COMBI=combined ICS and long acting β agonist (LABA) in single inhaler; COMBI MAR=COMBI as maintenance and reliever treatment; COMBI FIX=COMBI in fixed daily dose; COMBI AMD=COMBI in adjustable maintenance dose; H=high dose; LABA=long acting β agonists, regular use; LTRA=leukotriene receptor antagonist; SABA=short acting β agonists, regular use

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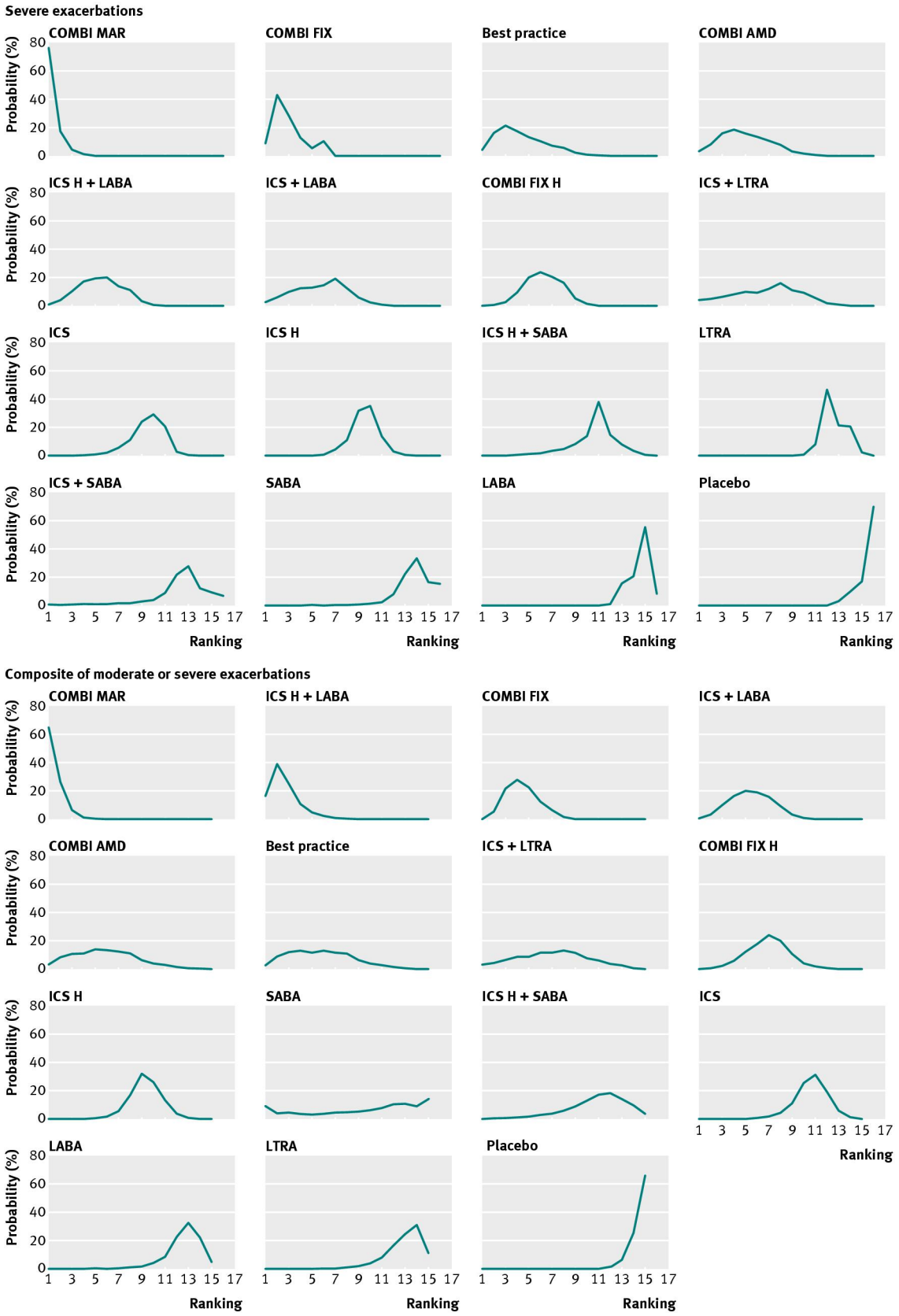

Fig 4 Rankograms showing probability (percentage) of each strategy having each specific rank (1-16) for effectiveness in the prevention of severe and composite of moderate or severe asthma exacerbations. Strategies ordered by rank from top left to bottom right. In severe exacerbations, combined inhaled corticosteroids (ICS) and long acting β agonists (LABA) in single inhaler as maintenance and reliever treatment (COMBI MAR), and in fixed daily dose (COMBI FIX) have highest probabilities to be ranked first and placebo the highest probability to be ranked last. COMBI AMD=combined ICS and LABA in adjustable maintenance dose; H=high dose; LTRA=leukotriene receptor antagonist; SABA=short acting β agonists, regular use

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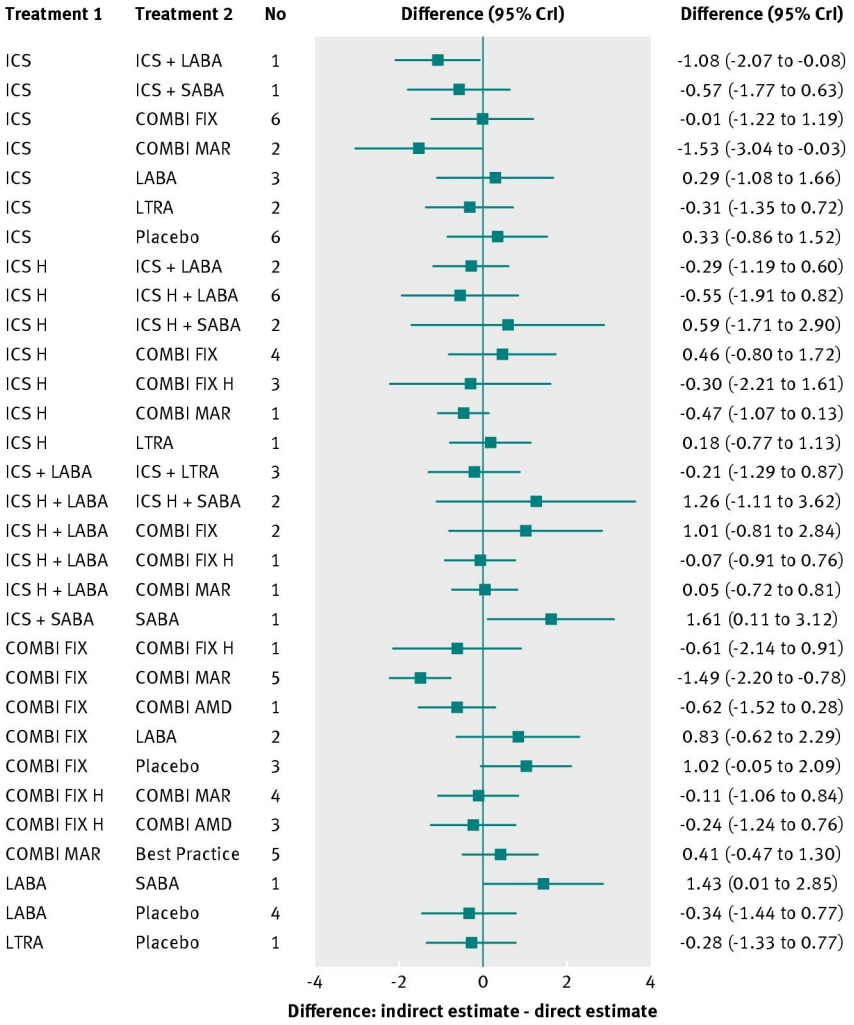

Fig 5 Difference in estimated treatment effects for severe asthma exacerbations between direct comparison (based on classic meta-analysis) and indirect estimate from multi-treatment comparison (without respective direct comparison). Difference on log-relative risk scale for rates; variance constructed by adding up variances of both estimates. Best practice is an open label comparator in which practitioners are encouraged to treat patients according to current treatment guidelines. COMBI=combined ICS and long acting β agonist (LABA) in single inhaler; COMBI MAR=COMBI as maintenance and reliever treatment; COMBI FIX=COMBI in fixed daily dose; COMBI AMD=COMBI in adjustable maintenance dose; H=high dose; LABA=long acting β agonists, regular use; LTRA=leukotriene receptor antagonist; SABA=short acting β agonists, regular use

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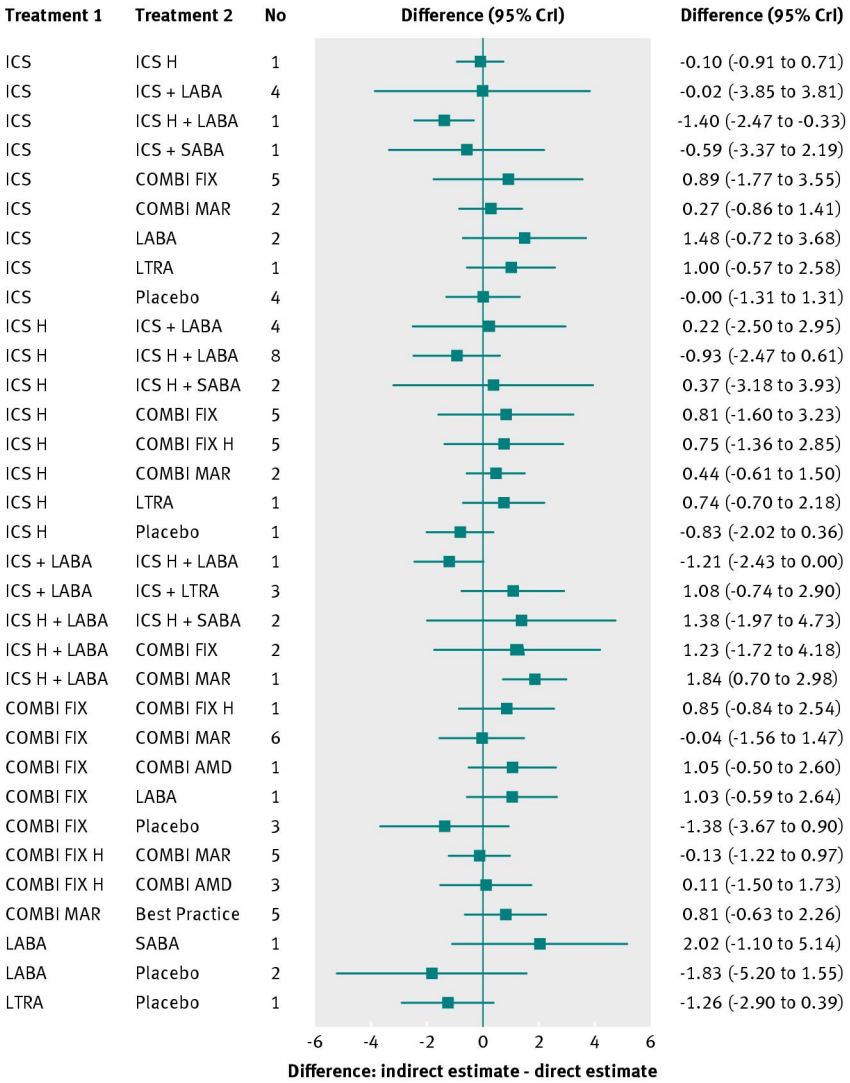

Fig 6 Difference in estimated treatment effect for composite of moderate or severe asthma exacerbations between direct comparison (based on classic meta-analysis) and indirect estimate from multi-treatment comparison (without respective direct comparison). Difference on log-relative risk scale for rates; variance constructed by adding up variances of both estimates. Best practice is an open label comparator in which practitioners are encouraged to treat patients according to current treatment guidelines. COMBI=combined ICS and long acting β agonist (LABA) in single inhaler; COMBI MAR=COMBI as maintenance and reliever treatment; COMBI FIX=COMBI in fixed daily dose; COMBI AMD=COMBI in adjustable maintenance dose; H=high dose; LABA=long acting β agonists, regular use; LTRA=leukotriene receptor antagonist; SABA=short acting β agonists, regular use

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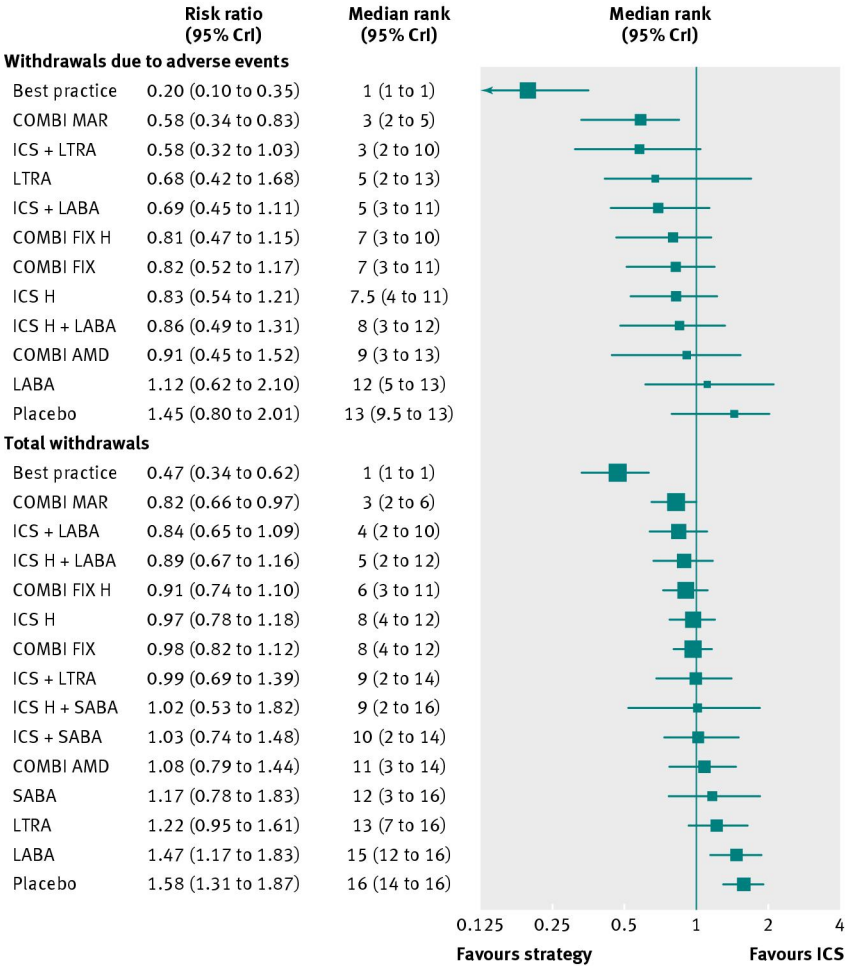

Fig 7 Forest plot showing withdrawals as a result of adverse events and total number of withdrawals compared with low dose inhaled corticosteroids (ICS). Best practice is an open label comparator in which practitioners are encouraged to treat patients according to current treatment guidelines. COMBI=combined ICS and long acting β agonist (LABA) in single inhaler; COMBI MAR=COMBI as maintenance and reliever treatment; COMBI FIX=COMBI in fixed daily dose; COMBI AMD=COMBI in adjustable maintenance dose; H=high dose; LABA=long acting β agonists, regular use; LTRA=leukotriene receptor antagonist; SABA=short acting β agonists, regular use

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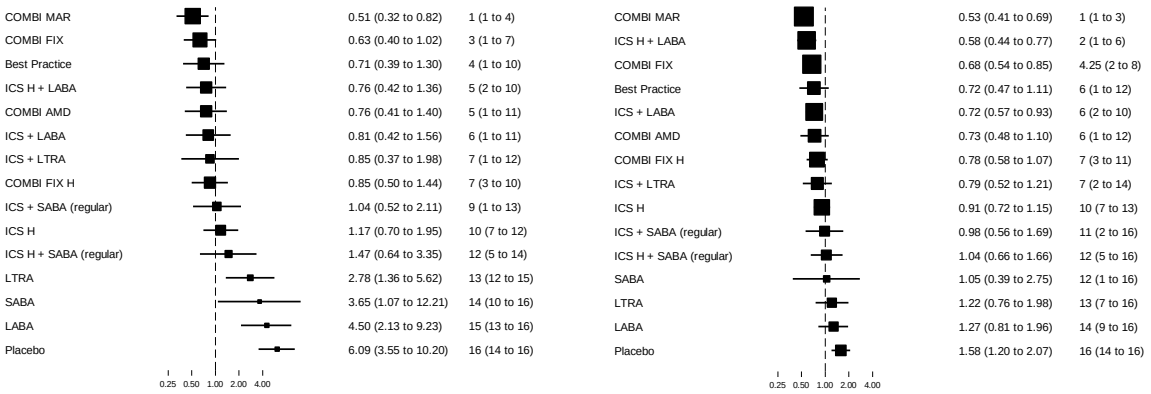
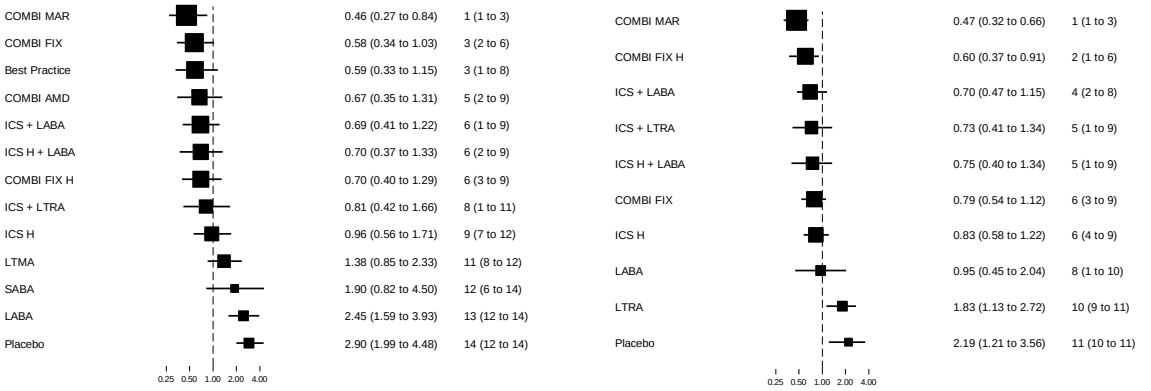
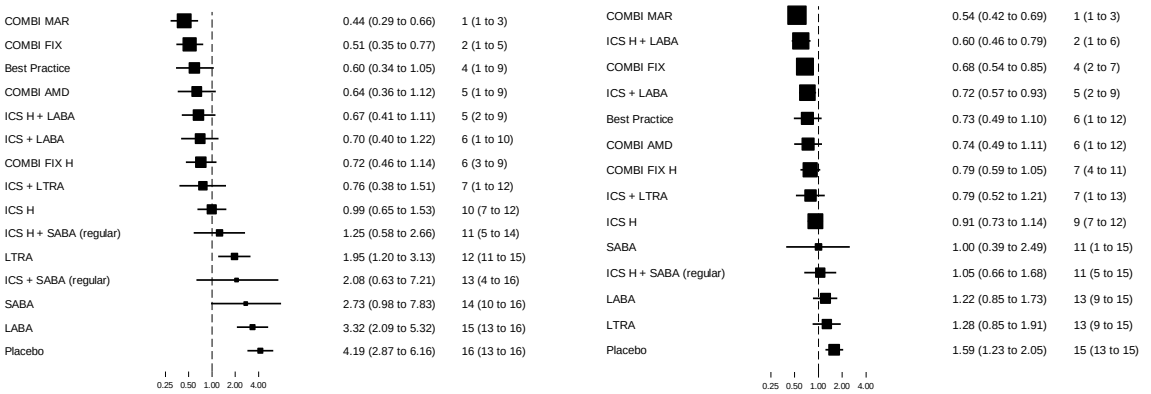
Figure S1: Analysis of effect of strategies on exacerbations, with non-imputed data.
All forest plot show rate ratios and their 95% credible intervals (95%CI), median ranks (95%CI), compared to low dose inhaled corticosteroids.



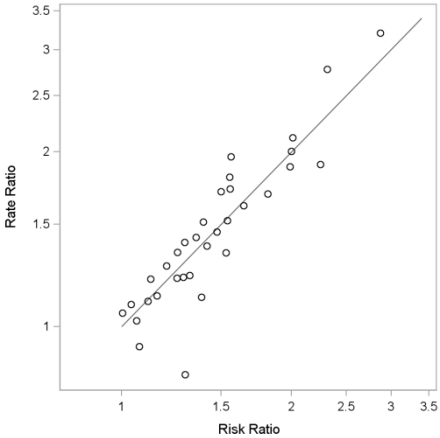
S1A Numbers of exacerbations per year, not imputed, for severe (left, 45 trials; τ^2= 0.110) and composite moderate or severe exacerbations (right, 56 trials; τ^2= 0.070).

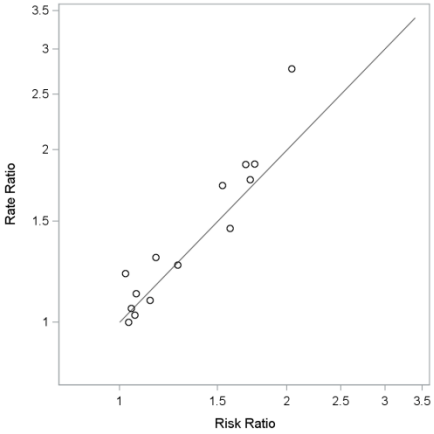


S1B Patients with ≥ 1 exacerbations, not imputed, for severe (left, 43 trials; τ^2= 0.029) and composite moderate or severe exacerbations (right, 18 trials; τ^2= 0.010).



S1C Numbers of exacerbations per year, imputed with data from patients with ≥ 1 exacerbations when numbers of exacerbations were not available, for severe (left, 57 trials; τ^2=0.102) and composite moderate or severe exacerbations (right, 61 trials; τ^2=0.070).

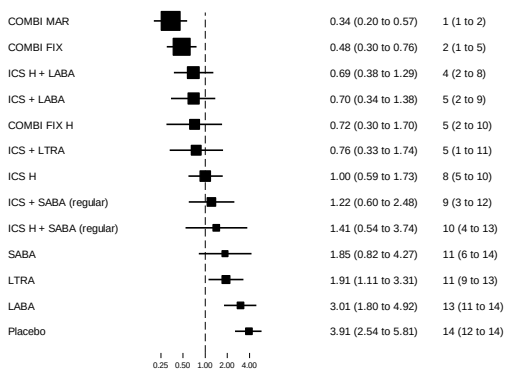




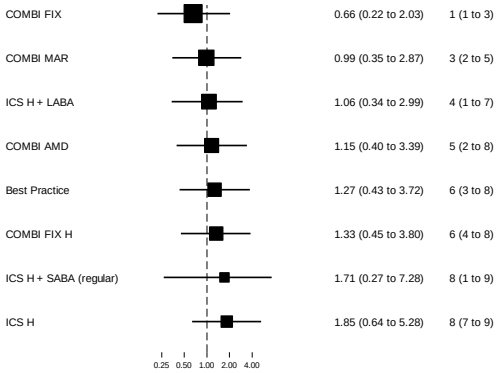
S1D Risk ratio (log scale) versus rate ratio (log scale) for treatment effects on exacerbations (accounting for study duration (patient years)) for severe (left) and composite moderate or severe exacerbations (right).

COMBI = combined ICS and LABA in a single inhaler; COMBI AMD = COMBI in an adjustable maintenance dose; COMBI FIX = COMBI in a fixed daily dose; COMBI MAR = COMBI as maintenance and reliever therapy; ICS (H) = inhaled corticosteroids (H=high dose ICS); LABA = long-acting beta-agonists; LTRA = leukotriene receptor antagonist; SABA = short -acting beta-agonists.
Best Practice is an open label comparator in which practitioners are free to choose therapy at their own discretion but are encouraged to treat patients according to current treatment guidelines.

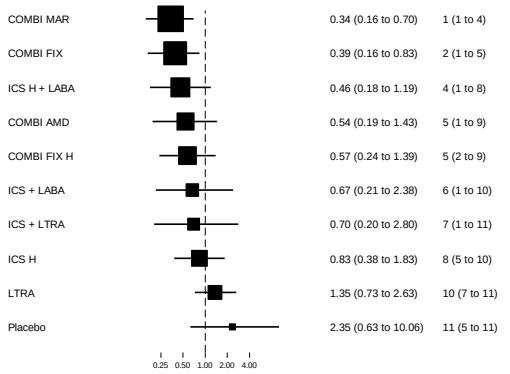
Figure S2: Sensitivity analyses for severe exacerbations (n = trials).
All forest plot show rate ratios and their 95% credible intervals (95%CI), median ranks (95%CI), compared to low dose inhaled corticosteroids.



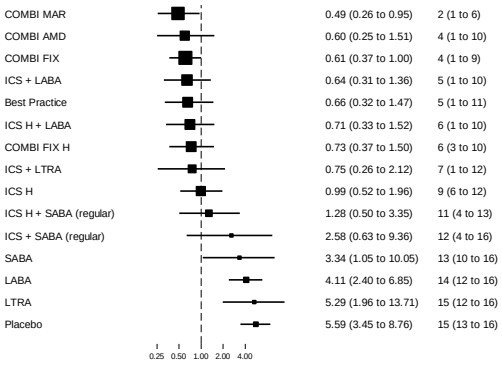
S2A GINA treatment step 1&2
n=36; τ^2=0.150



GINA treatment step 3, 4&5
n=21; τ^2=0.006

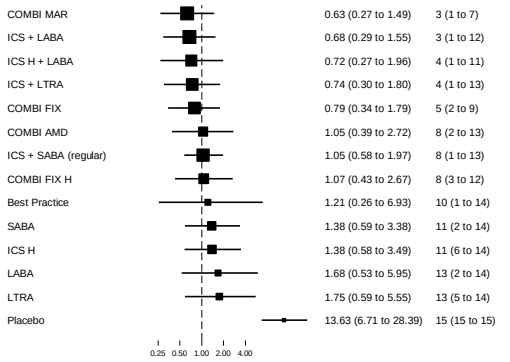


S2B* low risk of bias
n=20; τ^2=0.112

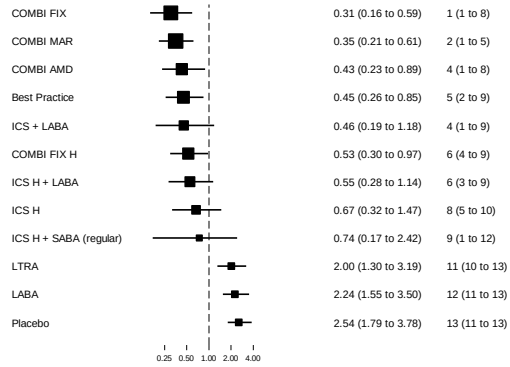


high risk of bias
n=37; τ^2=0.113

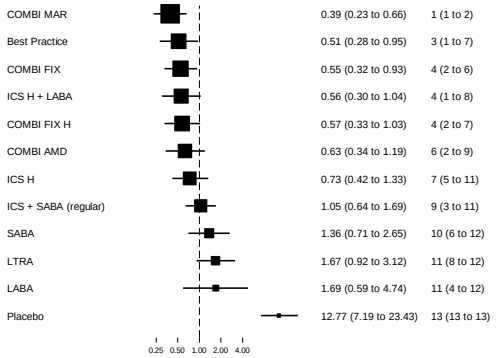
*For analysis purposes, studies were classified as having overall low risk of bias if more than 50% of the individual items were scored as low risk of bias, while according the Cochrane Handbook a low risk of bias should be assigned when all domains are scored as low.



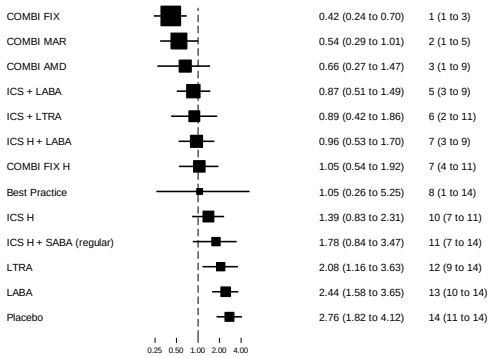
S2C intervention longer than 30 weeks
n=26; τ^2=0.066



intervention shorter than 30 weeks
n=31; τ^2=0.015

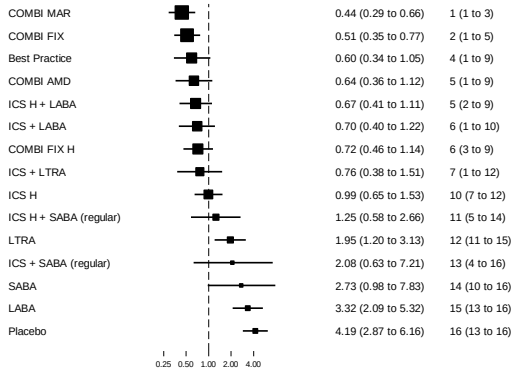


S2D* more than 250 patients/study arm
n=27; τ^2=0.041

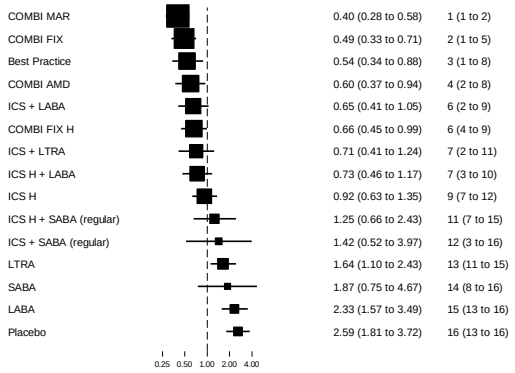


less than 250 patients/study arm
n=28; τ^2=0.026

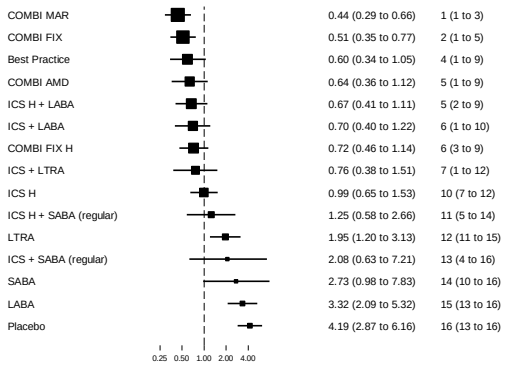
*2 trials (ref 14&15) were omitted because they spanned their own network.



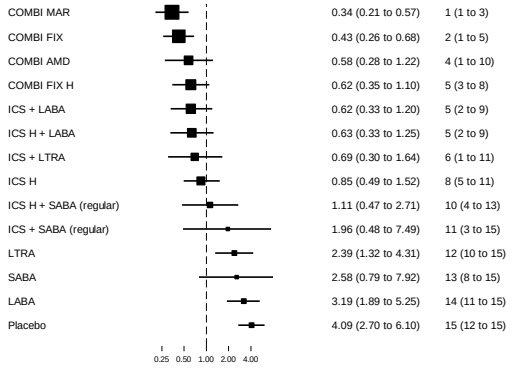
S2E complete analysis severe exacerbations
n=57 ; τ_2=0.102



excluding trials reporting average numbers of exacerbations per patient
n=54 ; τ_2=0.045



S2F complete analysis severe exacerbations
n=57 ; τ_2=0.102



excluding trials without double-blinding
n=44 ; τ_2=0.129

COMBI = combined ICS and LABA in a single inhaler; COMBI AMD = COMBI in an adjustable maintenance dose; COMBI FIX = COMBI in a fixed daily dose; COMBI MAR = COMBI as maintenance and reliever therapy; ICS (H) = inhaled corticosteroids (H=high dose ICS); LABA = long-acting beta-agonists; LTRA = leukotriene receptor antagonist; SABA = short -acting beta-agonists.
Best Practice is an open label comparator in which practitioners are free to choose therapy at their own discretion but are encouraged to treat patients according to current treatment guidelines.

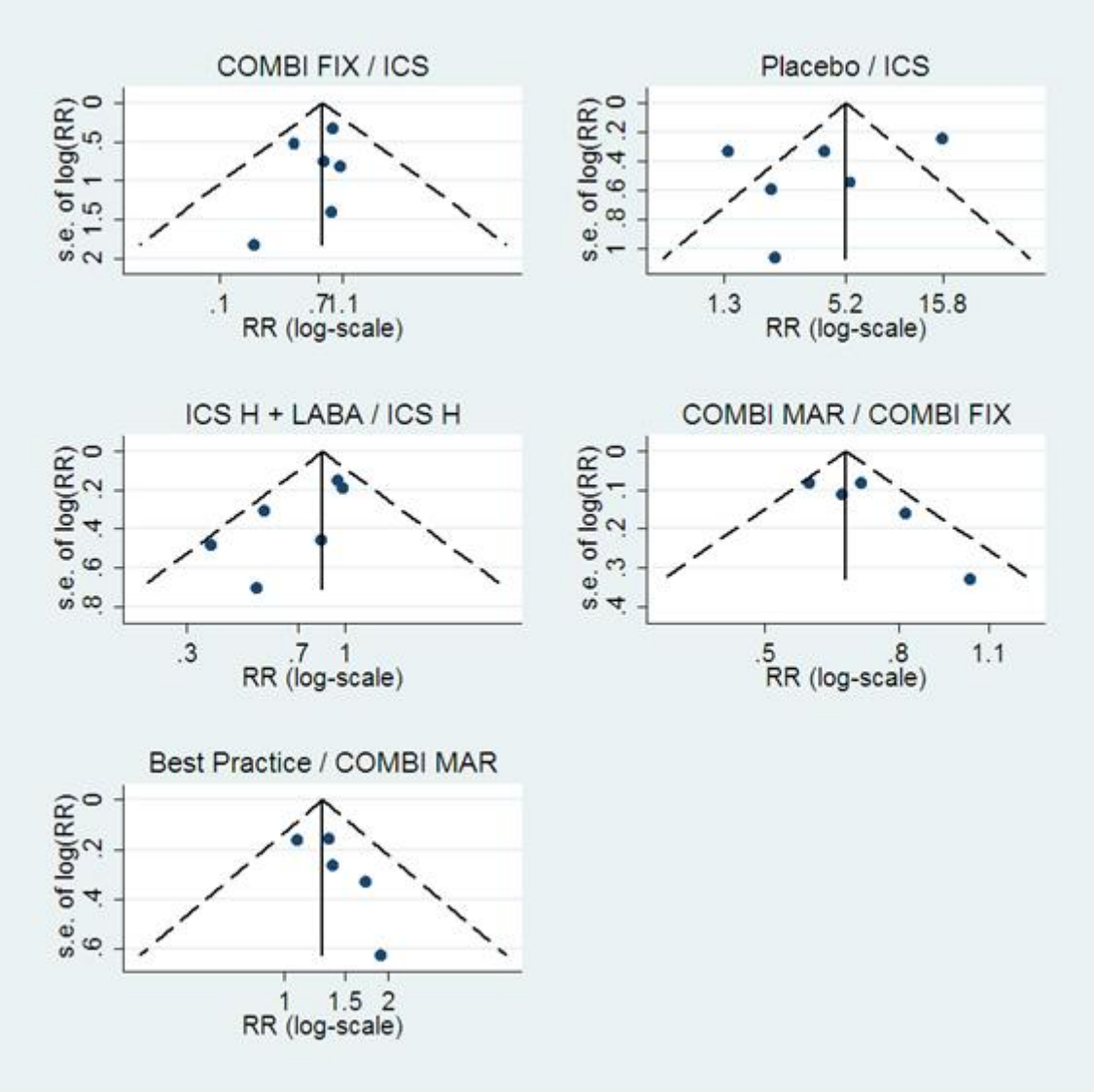


Figure S3: Funnel plots of all direct comparisons with five or more studies, for the severe exacerbations

ICS (H) = inhaled corticosteroids (H=high dose ICS); LABA = long-acting beta-agonists.
COMBI = combined ICS and LABA in a single inhaler; COMBI FIX = COMBI in a fixed daily dose; COMBI MAR = COMBI as maintenance and reliever therapy
Best Practice is an open label comparator in which practitioners are free to choose therapy at their own discretion but are encouraged to treat patients according to current treatment guidelines.

Table S1: Data from included studies				Strategy 1					Strategy 2					Strategy 3					Strategy 4				
Author	ref	Duration (wks)	GINA step*	Treatment	FEV1	PatYrs	S	M+S	Treatment	FEV1	PatYrs	S	M+S	Treatment	FEV1	PatYrs	S	M+S	Treatment	FEV1	PatYrs	S	M+S
Papi (2007)	99	24	1-2	ICS	88.8	45.0	4	66	Placebo	88.9	50.3	10	166										
Reddel (2008)	105	48	1-2	ICS	102	18.9	1	22	Placebo	96.6	16.2	3	58										
Pauwels (1997)	5	52	2-3	ICS	75.8	192.8	.	6106	ICS H	75.4	193.7	.	4379	ICS + LABA	75.7	190.1	.	4105	ICS H + LABA	76.3	194.6	.	2298
Nathan (2010)	77	26	2-3	ICS	72.6	87.8	11	.	LABA	73.2	79.8	39	.	COMBI FIX	72.4	86.8	5	.	Placebo	72.4	78.8	42	.
Meltzer (2012)	100	26	2-3	ICS	75.4	83.8	4	190	LABA	74.5	78.8	17	242	COMBI FIX	74.9	82.0	3	128	Placebo	75.6	76.0	20	286
Nathan (1999)	76	26	1	ICS	77.9	58.8	16	107	LABA	78.7	56.5	21	109	Placebo	80.5	57.5	21	.					
Busse (2001)	11	24	1	ICS	65.6	107.3	11	56	LTRA	65.4	103.6	19	76										
Meltzer (2002)	74	24	1	ICS	65.9	105.2	13	71	LTRA	65.6	106.4	21	74										
Dennis (2000)	106	52	2	ICS	85,0	403.0	220	658	ICS + SABA	86,0	418.5	239	664										
Obyrne (2001)	4	52	2	ICS	.	592.8	.	556	ICS + LABA	.	596.5	.	275										
Price (2002)	82	24	1-2	ICS	84.5	104.8	.	2233	ICS + LABA	85.3	104.1	.	1520										
Chuchalin (2005)	58	52	2	ICS	97.0	217.0	27	27	ICS + LABA	98.0	222.5	19	19										
Renzi (2010)	87	24	1	ICS	92.7	110.8	3	3	COMBI FIX	92.8	104.5	3	3										
Bailey (2008)	54	52	2	ICS	77.9	193.5	2	85	COMBI FIX	77.8	204.0	0	69										
Chuchalin (2008)	59	52	1	ICS	96.1	915.0	19	1309	COMBI FIX	96.7	898.0	17	1696	Placebo	98.0	287.5	94	922					
Strand (2004)	96	24	1	ICS	83.0	30.2	1	1	COMBI FIX	77.0	33.5	1	1										
Sovani (2008)	93	24	3	ICS	82.3	13.2	6	18	COMBI MAR	88.1	15.9	6	12										
Rabe (2006)	85	24	2	ICS	75.0	150.7	57	151	COMBI MAR	75.0	157.6	14	57										
Price (2011)	83	104	1	ICS H	.	307.0	53	53	LTRA	.	279.0	61	61										
Condemi (1999)	60	24	1-2	ICS H	.	92.8	41	.	ICS + LABA	.	97.6	26	.										
Greening (1994)	64	26	2	ICS H	.	86.8	25	473	ICS + LABA	.	92.3	22	417										
Kelsen (1999)	69	24	3	ICS H	64.1	101.3	.	58	ICS + LABA	64.9	99.2	.	52										
Murray (1999)	75	24	3	ICS H	64.0	104.1	.	56	ICS + LABA	65.2	108.5	.	52										
Fitzgerald (1999)	62	24	3	ICS H	79.9	37.8	6	21	ICS H + SABA	80.4	37.6	5	22	ICS H + LABA	79.1	37.2	3	19					
Taylor (1998)	104	24	2	ICS H	79.8	73.4	29	200	ICS H + SABA	79.8	72.5	36	199	ICS H + LABA	79.8	74.5	16	75					
Ind (2003) †	67	24	3	ICS H ‡	.	141.5	27	160	ICS H + LABA	.	72.7	5	58										
Woolcock (1996)	10	24	3	ICS H	75.0	107.8	.	131	ICS H + LABA ‡	71.5	212.3	.	153										
D'Urzo (2001)	61	24	2-3	ICS H	.	184.8	89	89	ICS H + LABA	.	189.7	86	86										
vd Molen (1997)	97	24	2-3	ICS H	66.0	49.6	55	55	ICS H + LABA	68.0	53.5	58	58										
Huchon (2009)	65	24	2-3	ICS H	65.3	93.7	10	419	ICS H + LABA	66.2	97.8	9	343	COMBI FIX	64.5	94.8	2	277					
Postma (2011)	81	52	1	ICS H	95.5	188.0	21	83	COMBI FIX	95.7	201.0	7	49	Placebo	97.6	189.5	.	91					
Obyrne (2005) †	78	52	3	ICS H	73.0	855.0	.	581	COMBI FIX	73.0	835.0	.	567	COMBI MAR	73.0	864.0	.	311					
Busse (2013)	101	52	2-3	ICS H	74.2	85.5	3	3	COMBI FIX	74.1	181.0	3	3	COMBI FIX H	75.2	180.5	6	6					
Brown (2012)	102	52	2-3	ICS H	78.2	302.5	61	61	COMBI FIX	77,0	302.5	36	36										
Kerwin (2011)	70	52	3	ICS H	69.7	276.7	87	87	COMBI FIX H	69.1	269.7	75	75										
Kaital (2011)	68	52	3	ICS H	69.0	278.5	83	670	COMBI FIX H	68.9	265.5	49	541										
Peters (2008)	80	52	3	ICS H	72.2	120.0	.	37	COMBI FIX H ‡	72.4	523.5	.	91										
Jenkins (2000)	8	24	3	ICS H	72.0	72.9	1	112	COMBI FIX H	68.0	76.4	.	108										
Scicchitano (2004) †	9	52	3	ICS H	70.0	856.5	349	895	COMBI MAR	70.0	875.0	197	528										
Pauwels (2003)	6	156	1-2	ICS + SABA	86.3	9306.0	1009	.	SABA	86.6	9174.0	1099	.										
Bjermer (2003)	55	48	2-3	ICS + LABA	72.7	635.1	135	215	ICS + LTRA	71.3	631.8	144	226										
Ilowite (2004)	66	48	2-3	ICS + LABA	74.3	621.7	163	120	ICS + LTRA	74.3	626.8	191	147										
Price (2011)	83	104	2	ICS + LABA	.	360.0	109	109	ICS + LTRA	.	333.0	103	103										
Rosenhall (2002)	89	26	3	ICS H + LABA	95.4	92.8	34	.	COMBI FIX H	94.1	188.3	76	.										
Stallberg (2008)	95	52	2-3	ICS H + LABA	96.0	410.5	57	178	COMBI FIX	97.0	426.0	64	211	COMBI MAR	95.0	834.0	103	476					
Rabe (2006) †	86	52	2-3	COMBI FIX ‡	72.0	2142.5	673	673	COMBI MAR	72.0	1055.0	194	194										
Pavord (2009)	79	52	3	COMBI FIX	80.6	60.5	18	18	COMBI MAR	81.4	62.0	19	19										
Papi (2013)	108	48	2-3	COMBI FIX	74,0	733.4	196	2985	COMBI MAR	75,0	740.8	130	2977										

				Strategy 1					Strategy 2					Strategy 3					Strategy 4				
Author	ref	Duration (wks)	GINA step*	Treatment	FEV1	PatYrs	S	M+S	Treatment	FEV1	PatYrs	S	M+S	Treatment	FEV1	PatYrs	S	M+S	Treatment	FEV1	PatYrs	S	M+S
Atienza (2013)	103	52	2-3	COMBI FIX	70.2	987.0	363	363	COMBI MAR	69.64	1002.5	259	259										
Fitzgerald (2005)	63	52	3	COMBI FIX	82.0	304.0	50	50	COMBI AMD	81.0	297.5	96	96										
Stallberg (2003)	94	26	3	COMBI FIX H	95.4	252.0	66	66	COMBI AMD	95.8	250.8	49	49										
Aalbers (2004)	53	32	4	COMBI FIX H ‡	84.5	252.9	109	109	COMBI AMD	84.0	126.5	35	35										
Busse (2008)	57	28	3	COMBI FIX H ‡	78.6	428.6	91	91	COMBI AMD	78.9	197.9	38	38										
Bousquet (2007) †	56	26	3	COMBI FIX H	71.0	549.3	173	173	COMBI MAR	70.2	553.3	137	137										
Vogelmeier (2005) †	98	52	3	COMBI FIX H	73.0	1001.0	230	540	COMBI MAR	73.0	1007.5	191	432										
Lundborg (2006)	73	24	4	COMBI FIX H	96.5	70.8	.	17	COMBI MAR ‡	96.0	141.7	.	30										
Kuna (2007)	71	24	3	COMBI FIX H ‡	73.0	1003.4	381	381	COMBI MAR	72.0	498.2	125	125										
Patel (2013)	107	24	2-3	COMBI FIX H	81.6	67.6	66	66	COMBI MAR	80.4	65.8	35	35										
Riemersma (2012)	88	52	3	COMBI MAR	96.0	50.0	4	4	Best Practice	101.5	46.0	7	7										
Sears (2008)	91	26	3	COMBI MAR	94.8	363.3	69	69	Best Practice	94.1	371.3	77	77										
SoesPetersen (2011)	92	26	3	COMBI MAR	105.9	432.3	69	69	Best Practice	105.0	443.0	95	95										
Quirce (2011)	84	26	3	COMBI MAR	.	149.5	24	24	Best Practice	.	153.8	34	34										
Louis (2009)	72	26	3	COMBI MAR	.	218.3	14	14	Best Practice	.	225.5	25	25										
Chuchalin (2005)	58	52	1	LABA	101.0	321.5	18	18	SABA	100.0	328.0	15	15										
Rosenthal (1999)	90	24	1	LABA	84.2	85.4	31	31	Placebo	84.3	82.8	42	42										
Irvin (2007)	44	24	1	LTRA	77.5	67.6	32	268	Placebo	80.2	67.8	34	327										

*GINA treatment step of baseline population according to reference 1

FEV1 = mean Forced Expiratory Volume/1 second, % predicted post bronchodilation, or, if not available % predicted pre-bronchodilation, or, if not available % predicted PEF

S = number of analysed severe exacerbations, M+S = number of analysed composite moderate or severe exacerbations

† previous exacerbation, at least 1 in the previous year was an inclusion criterion

‡ two arms with similar strategies were merged

COMBI = combined ICS and LABA in a single inhaler; COMBI AMD = COMBI in an adjustable maintenance dose; COMBI FIX = COMBI in a fixed daily dose; COMBI MAR = COMBI as maintenance and reliever therapy; ICS (H) = inhaled corticosteroids (H=high dose ICS); LABA = long-acting beta-agonists; LTRA = leukotriene receptor antagonist; SABA = short -acting beta-agonists.
Best Practice is an open label comparator in which practitioners are free to choose therapy at their own discretion but are encouraged to treat patients according to current treatment guidelines.

author	year	sequence generation [1]	allocation concealment [2]	patient blinding [3]	physician blinding [4]	Incomplete outcome data: ITT [5]	Incomplete outcome data: drop outs [6]	selective outcome reporting [7]
Greening	1994	U	U	L	L	U	L	U
Woolcock	1996	U	U	U	U	L	U	U
vd Molen	1997	U	U	U	U	U	L	U
Pauwels	1997	U	U	U	U	L	H	U
Taylor	1998	U	U	L	L	U	L	U
Condemi	1999	U	U	L	L	L	L	U
Kelsen	1999	L	L	U	U	L	L	U
Murray	1999	U	U	L	L	L	L	U
FitzGerald	1999	U	U	U	U	U	U	U
Nathan	1999	U	U	L	L	L	U	U
Rosenthal	1999	U	U	U	U	L	L	U
Jenkins	2000	U	U	L	L	U	L	U
Dennis	2000	U	U	L	U	H	U	U
Duzro	2001	U	U	U	U	L	L	U
Busse	2001	L	L	L	L	L	L	U
Obyrne	2001	U	U	U	U	L	H	U
Meltzer	2002	L	L	L	L	L	L	U
Price	2002	U	U	U	U	L	L	U
Rosenhall	2002	U	U	H	H	L	L	U
Ind	2003	U	U	U	U	L	U	U
Bjermer	2003	L	L	L	L	L	L	U
Pauwels	2003	L	L	U	U	L	L	U
Stallberg	2003	U	U	H	H	L	U	U
Ilowite	2004	L	U	L	L	U	L	U
Strand	2004	U	U	U	U	L	L	U
Scicchitanc	2004	L	L	L	L	L	L	U
Aalbers	2004	L	L	L	L	L	L	U
Obyrne	2005	L	L	L	L	L	L	U
Vogelmeier	2005	L	L	H	H	L	L	U
Fitzgerald	2005	U	U	L	L	L	L	U
Chuchalin	2005	U	U	U	U	L	L	U
Rabe	2006	U	U	L	L	L	L	U
Rabe	2006	L	L	L	L	L	L	U
Lundborg	2006	U	H	H	H	U	L	U
Bousquet	2007	L	L	L	L	L	L	U
Kuna	2007	L	L	L	L	L	L	U
Irvin	2007	U	U	L	L	U	L	U
Papi	2007	L	L	L	L	L	L	U
Bailey	2008	U	U	U	U	L	U	U
Chuchalin	2008	U	U	L	L	L	L	U
Sears	2008	U	U	H	H	U	L	U
Sovani	2008	L	L	H	H	L	H	U
Stallberg	2008	L	L	H	H	L	L	U
Busse	2008	U	U	H	H	L	L	U
Peters	2008	L	L	L	L	L	L	U
Reddel	2008	L	L	L	L	U	L	U
Huchon	2009	L	U	L	L	L	L	U
Pavord	2009	L	U	L	L	L	L	U
Louis	2009	U	U	H	H	L	L	U
Nathan	2010	U	U	L	L	U	L	U
Renzi	2010	U	U	U	U	L	L	U
Soes Peters	2011	U	U	H	H	L	L	U
Quirce	2011	U	U	H	H	L	L	U
Postma	2011	U	U	L	L	L	U	U
Kaital	2011	U	U	U	U	L	L	L
Price	2011	L	L	H	H	L	L	L
Kerwin	2011	U	U	U	U	L	H	L
Riemersma	2012	U	U	H	H	L	L	U
Meltzer	2012	U	U	L	L	U	L	L
Brown	2012	L	L	L	L	U	L	H
Patel	2013	L	L	H	H	L	L	L
Papi	2013	L	L	U	U	L	L	U
Busse	2013	L	L	L	L	L	L	L
Atienza	2013	L	L	L	L	L	L	L

L=low, U=unclear, H=high risk of bias; Unclear was assigned when report did not provide sufficient data to assign Low or High

1 sequence generation	L= description of correct method of sequence generation (e.g. computer generated) H=incorrect method
2 allocation concealment	L=description of correct method of allocation concealment (e.g. central allocation) H=incorrect method
3 patient blinding	L=stated as blinded and explained how (blinded medication devices, dummy inhaler devices) H=open label study
4 physician blinding	L=stated (double) blinded and explained how (blinded medication devices, double dummy) H=open label study
5 Incomplete outcome data: ITT	L=stated intention to treat analysis with correct description of analysed population H = per protocol analysis
6 Incomplete outcome data: drop outs	L=withdrawal rate per arm <30%, with complete explanation of reasons H= withdrawal rate ≥30%, without explanation of reasons
7 selective outcome reporting	L=exacerbation as outcome parameter mentioned in trial registry H=exacerbation not mentioned in trial registry U= no prospective trialregistration available

Table S3: Reported harms		Strategy 1						Strategy 2						Strategy 3						Strategy 4					
Author	ref	Treatment	AE	AE_SR	SAE	SAE_SR	Mortality	Treatment	AE	AE_SR	SAE	SAE_SR	Mortality	Treatment	AE	AE_SR	SAE	SAE_SR	Mortality	Treatment	AE	AE_SR	SAE	SAE_SR	Mortality
Papi (2007)	99	ICS	x					Placebo							x										
Reddel (2008)	105	ICS	x					Placebo	x																
Pauwels (1997)	5	ICS	x					ICS H	x					ICS + LABA	x					ICS H + LABA	x				
Nathan (2010)	77	ICS	46%	5.7%				LABA	45%	5.4%				COMBI FIX	51%	8.9%				Placebo	42%	7.7%			
Meltzer (2012)	100	ICS	46%	5.3%	4.3%		0	LABA	40%	8.0%	3.7%		0	COMBI FIX	41%	8.8%	4.9%		0	Placebo	35%	4.3%	2.7%		0
Nathan (1999)	76	ICS		13%	< 1%	0		LABA		11%	< 1%	0		Placebo		5%	< 1%	0							
Busse (2001)	11	ICS	71%					LTRA	68%																
Meltzer (2002)	74	ICS	x					LTRA	x																
Dennis (2000)	106	ICS	5%		0			ICS + SABA	8%		0														
Obyrne (2001)	4	ICS	x		x			ICS + LABA	x		x														
Price (2002)	82	ICS	x					ICS + LABA	x																
Chuchalin (2005)	58	ICS	68%		6%	0		ICS + LABA	58%		5%	0													
Renzi (2010)	87	ICS	x		1%	0	1	COMBI FIX	x		1%	0	0												
Bailey (2008)	54	ICS	68%		6.7%		0	COMBI FIX	61%		3.8%		0												
Chuchalin (2008)	59	ICS	63%		3%			COMBI FIX	60%		3%			Placebo	65%		6%		1*						
Strand (2004)	96	ICS	58%		2.8%			COMBI FIX	62%		1.3%														
Sovani (2008)	93	ICS						COMBI MAR																	
Rabe (2006)	85	ICS	41%		2.3%			COMBI MAR	38%		1.7%														
Price (2011)	83	ICS H						LTRA																	
Condemi (1999)	60	ICS H	86%	14%	< 1%	0		ICS + LABA	86%	10%	< 1%	0													
Greening (1994)	64	ICS H			1.5%	0		ICS + LABA			3.2%	0													
Kelsen (1999)	69	ICS H		14%				ICS + LABA		11%															
Murray (1999)	75	ICS H	x					ICS + LABA	x																
Fitzgerald (1999)	62	ICS H		10%				ICS H + SABA		12%				ICS H + LABA		15%									
Taylor (1998)	104	ICS H						ICS H + SABA						ICS H + LABA											
Ind (2003)	67	ICS H ‡						ICS H + LABA																	
Woolcock (1996)	10	ICS H	x					ICS H + LABA ‡	x																
D'Urzo (2001)	61	ICS H					1	ICS H + LABA					2												
vd Molen (1997)	97	ICS H						ICS H + LABA																	
Huchon (2009)	65	ICS H	62%	15%				ICS H + LABA	65%	17%				COMBI FIX	60%	12%									
Postma (2011)	81	ICS H	73%					COMBI FIX	64%					Placebo	74%										
Obyrne (2005)	78	ICS H	57%		5%			COMBI FIX	52%		7%			COMBI MAR	54%		5%								
Busse (2013)	101	ICS H	73%		7%		0	COMBI FIX	69%		1%		0	COMBI FIX H	66%		< 1%		0						
Brown (2012)	102	ICS H	48%					COMBI FIX	51%																
Kerwin (2011)	70	ICS H	82%	8%	2.5%	< 1%	1	COMBI FIX H	78%	8%	1.9%	< 1%	1												
Kaital (2011)	68	ICS H		x	3.2%		0	COMBI FIX H		x	4.5%		0												
Peters (2008)	80	ICS H	89%		5.7%		0	COMBI FIX H ‡	88%		3.8%		0												
Jenkins (2000)	8	ICS H		18%				COMBI FIX H		13%															
Scicchitano (2004)	9	ICS H	57%		5.8%	0	2	COMBI MAR	56%		6.1%	< 1%	1												
Pauwels (2003)	6	ICS + SABA	x				3	SABA	x				8*												
Bjermer (2003)	55	ICS + LABA	72%	10.0%	7.4%		1*	ICS + LTRA	71%	6.3%	4.6%		0												
Ilowite (2004)	66	ICS + LABA		10.0%	3.7%			ICS + LTRA		8.6%	3.0%														
Price (2011)	83	ICS + LABA						ICS + LTRA																	
Rosenhall (2002)	89	ICS H + LABA	69%		2.6%			COMBI FIX H	77%		3.3%														
Stallberg (2008)	95	ICS H + LABA			x			COMBI FIX			x			COMBI MAR			x								
Rabe (2006)	86	COMBI FIX ‡			4.8%	2%	3	COMBI MAR			6.3%	1%	1												
Pavord (2009)	79	COMBI FIX	x		7.9%	0	0	COMBI MAR	x		4.7%	0	0												
Papi (2013)	108	COMBI FIX			4%			COMBI MAR			5%														

		Strategy 1						Strategy 2						Strategy 3						Strategy 4					
Author	ref	Treatment	AE	AE_SR	SAE	SAE_SR	Mortality	Treatment	AE	AE_SR	SAE	SAE_SR	Mortality	Treatment	AE	AE_SR	SAE	SAE_SR	Mortality	Treatment	AE	AE_SR	SAE	SAE_SR	Mortality
Atienza (2013)	103	COMBI FIX	58%	3.5%	7.1%	3.0%	1	COMBI MAR	57%	3.9%	4.0%	< 1%	1												
Fitzgerald (2005)	63	COMBI FIX	49%	6.3%	2.6%			COMBI AMD	52%	5.9%	2.5%														
Stallberg (2003)	94	COMBI FIX H			2%	0	0	COMBI AMD			3%	0	0												
Aalbers (2004)	53	COMBI FIX H ‡	62%		3.6%	< 1%		COMBI AMD	57%		3.7%	< 1%													
Busse (2008)	57	COMBI FIX H ‡	60%					COMBI AMD	58%																
Bousquet (2007)	56	COMBI FIX H	40%		3%			COMBI MAR	39%		3%														
Vogelmeier (2005)	98	COMBI FIX H	x		8.2%	< 1%	2	COMBI MAR	x		7.5%	< 1%	0												
Lundborg (2006)	73	COMBI FIX H			x			COMBI MAR ‡			x														
Kuna (2007)	71	COMBI FIX H ‡			3%		1	COMBI MAR			3%		1												
Patel (2013)	107	COMBI FIX H					0	COMBI MAR					0												
Riemersma (2012)	88	COMBI MAR						Best Practice																	
Sears (2008)	91	COMBI MAR	61%		2.1%		2	Best Practice	64%		1.7%		1												
SoesPetersen (2011)	92	COMBI MAR			2.7%		1	Best Practice			2.7%		0												
Quirce (2011)	84	COMBI MAR	51%		2.8%		0	Best Practice	48%		1.5%		0												
Louis (2009)	72	COMBI MAR			2.4%		2	Best Practice			2.6%		0												
Chuchalin (2005)	58	LABA	61%		2%	0		SABA	59%		2%	0													
Rosenthal (1999)	90	LABA	74%		3.4%	0		Placebo	73%		< 1%	0													
Irvin (2007)	44	LTRA	x					Placebo	x																

(S)AE = (Serious) Adverse Event
SR = Study (either intervention or asthma) related
* = 1 death (possibly) related to intervention or asthma
x = no (significant) difference between groups marked with 'x'
‡ two arms with similar strategies were merged

COMBI = combined ICS and LABA in a single inhaler; COMBI AMD = COMBI in an adjustable maintenance dose; COMBI FIX = COMBI in a fixed daily dose; COMBI MAR = COMBI as maintenance and reliever therapy; ICS (H) = inhaled corticosteroids (H=high dose ICS); LABA = long-acting beta-agonists; LTRA = leukotriene receptor antagonist; SABA = short -acting beta-agonists.
Best Practice is an open label comparator in which practitioners are free to choose therapy at their own discretion but are encouraged to treat patients according to current treatment guidelines.