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SMART and as-needed therapies in mild to severe asthma: a network meta-analysis

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Abstract

To date there are no network meta-analyses comparing the impact of as-needed treatments in asthma, including the single maintenance and reliever therapy (known as SMART or MART – for simplicity SMART will be used hereafter) and the use of inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) combination exclusively on an as-needed basis. Therefore, we performed a systematic review and network meta-analysis concerning the efficacy and safety of SMART and as-needed therapies in asthma. Data of 32096 asthmatic patients were extracted from 21 studies, lasting from 6 to 12 months. In adult mild to moderate asthmatic patients low-dose (LD) SMART and as-needed LD ICS/LABA combination were significantly (relative effect <0.78, P<0.05) more effective than the other as-needed therapies in reducing the risk of exacerbation, and both were ranked as the first treatment option reaching the first quartile of the surface under the cumulative ranking curve analysis (SUCRA). In adult moderate to severe asthmatic patients LD to medium-dose (MD) SMART and high-dose (HD) ICS/LABA + as-needed short-acting β_2-agonist were equally effective in reducing the risk of severe asthma exacerbation (P>0.05), although only LD to MD SMART was ranked as the first treatment option (first SUCRA quartile). Overall, these treatments were well tolerated and effective also on lung function and disease control. This study supports SMART and as-needed therapies as a suitable therapeutic option for asthma, by providing the most effective positioning of each specific treatment according to the disease severity.

Keywords

Asthma; as-needed; exacerbation; MART; network meta-analysis; SMART.

Introduction

Since 2006, the Global Initiative for asthma (GINA 2006) recommends a stepwise approach for the pharmacological management of asthma [1]. Accordingly with the GINA recommendations updated in 2020 [2], patients suffering from mild asthma should be controlled with Step 1 or 2 treatments, either with as-needed low-dose (LD) inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) combinations or maintenance treatment with LD ICS as preferred controller therapy. Moderate asthma should be controlled with Step 3 treatment, namely maintenance treatment with LD ICS/LABA combinations. Finally, controlling severe asthma requires Step 4 and 5 treatments, that include maintenance treatment with medium-dose (MD) to high-dose (HD) ICS/LABA combinations and add-on tiotropium and/or monoclonal antibody therapy in those patients that remain uncontrolled despite maintenance therapy.

A recent pairwise meta-analysis performed by Sobieraj et al. [3] has investigated the impact of ICS/LABA as the controller and the quick relief therapy, named single maintenance and reliever therapy (known as SMART or MART – for simplicity SMART will be used hereafter) in patients with persistent asthma [3]. Interestingly, SMART was associated with a lower risk of asthma exacerbation when compared with maintenance therapy with ICSs (with or without a LABA) plus a short-acting β_2-agonist (SABA) as the relief treatment [3]. Some of the studies [4-9] included in that pairwise meta-analysis [3] may have introduced a risk of bias due to the small number of patients enrolled in the randomized controlled trials (RCTs), leading to the so-called “small-study effect” [10]. Furthermore, the safety profile of SMART was not investigated [3].

Besides SMART, an alternative approach in the treatment of mild asthma is the use of ICS/LABA fixed-dose combination on an as-needed basis, a strategy that might overcome the poor adherence to maintenance treatment with an ICS, and the overreliance on SABAs for symptom relief. This approach has been investigated in the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 and 2 [11, 12].

Indeed, the current scenario indicates that there is the need of improving the tailored approach of asthma treatment, by ranking the efficacy profile of SMART and as-needed therapies in asthmatic patients matched with the severity of disease. In this respect, the study of Sobieraj et al. [3] was a pairwise meta-analysis that did not compare all the currently available SMART and as-needed therapies for the treatment of asthma. Moreover, to date no comparison has been performed between SMART and the use of ICS/LABA administered exclusively on an as-needed basis.

A well conducted meta-analysis of RCTs provides the highest level of evidence, even greater than that obtained by single large RCTs. Moreover, along with the effect estimates, network meta-analyses may produce supporting information of considerable interest for clinicians in the form of treatment rankings, generally summarized by an outcome named the surface under the cumulative ranking curve analysis (SUCRA) [13].

Therefore, considering that to date there are no network meta-analyses comparing the impact of the as-needed treatments in asthma, including SMART and ICS/LABA on an as-needed basis, we have carried out a quantitative synthesis via Bayesian network approach by considering Phase III RCTs in order to rank and compare the efficacy and safety profile of the currently available SMART and as-needed therapeutic strategies in asthma. The primary efficacy outcome of this study was the risk reduction in severe asthma exacerbation.

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: CRD42019136443) [14]. The flow diagram and network nodes are shown in Figure 1A and B, and Table S1 reports the PRISMA-P checklist [14].

A comprehensive literature search was performed for Phase III RCTs evaluating the impact of SMART and as-needed therapies for the treatment of asthma. As an example, Table S2 reports the literature search terms used for OVID MEDLINE and Annex 1 shows the summary text of the identified records.

Study selection

Phase III RCTs that enrolled asthmatic patients, lasting ≥6 months, and that included at least one arm assessing the effect of any SMART and/or as-needed therapies were selected.

Data extraction

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [15]. The inter- and intra-rater reliability for data abstraction was assessed via the Cohen's Kappa score, as previously described [16].

Endpoints

The primary endpoint was the comparison across the different SMART and as-needed therapies with respect to the risk of severe asthma exacerbation. The secondary endpoints included the comparisons across the different SMART and as-needed therapies with respect to the changes from baseline in forced expiratory volume in 1 second (FEV_1), morning and evening peak expiratory flow (PEF), changes from baseline in asthma control questionnaire (ACQ) score, and risk of severe adverse events (SAEs).

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) [17] and Jadad score [18]. The weighted assessment of the overall risk of bias was analyzed via the Cochrane RoB 2 [17], along with the normalized consistency/inconsistency analysis [19]. The quality of evidence was assessed for the primary endpoint via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system [20].

Data synthesis and analysis

A network meta-analysis was performed via full Bayesian random-effect model to compare the impact of the different SMART and as-needed therapies in asthmatic patients. Subset analyses were performed in agreement with average patients' characteristics at baseline. Results are expressed as relative effect (RE) and 95% credible interval (95%CrI). The SUCRA was calculated for both the primary and secondary endpoints [21]; the SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [19]. The statistical significance was assessed for $P<0.05$.

Results

Study characteristics

Data obtained from 32096 asthmatic patients were selected from 21 Phase III RCTs (Table S3). Four studies were performed in mild asthma [11, 12, 22, 23], three in moderate asthma [8, 24, 25], four in mild to moderate asthma [26-29], and ten in moderate to severe asthma [6, 7, 30-37].

In agreement with the search strategy and study selection criteria, the investigated ICS/LABA combinations included budesonide/formoterol in 20 studies [6-8, 11, 12, 22-24, 26-37], fluticasone/salmeterol in 4 studies [30, 32, 33, 35], and beclometasone/formoterol in 1 study [25]. The only ICS administered as monocomponent was budesonide in 10 studies [6, 11, 12, 22, 24, 26, 28, 29, 36, 37]. Formoterol was the only LABA used alone as-needed in 3 studies [8, 23, 34], whereas a SABA, either salbutamol or terbutaline, was used alone as-needed in 19 studies [6, 7, 11, 12, 22, 24-37].

The definition of 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 between 0.96 and 1.00). Further study characteristics are reported in the Supplementary Data.

Primary endpoint

Overall analysis

The overall network meta-analysis indicated that LD to MD SMART was as effective as HD ICS/LABA + as-needed SABA in reducing the risk of severe asthma exacerbation, and that generally SMART was significantly ($P<0.05$) more effective than treating asthmatic patients with either lower doses of ICS/LABA + as-needed LABA or SABA, or ICS/LABA used exclusively on an as-needed basis, or ICS + as-needed SABA. No significant difference ($P>0.05$) was found when comparing HD ICS/LABA + as-needed SABA with either lower doses of ICS/LABA + as-needed LABA or SABA, or ICS/LABA used exclusively on an as-needed basis, or ICS + as-needed SABA. Moreover, administering ICS/LABA exclusively on an as-needed basis or lower doses of ICS/LABA + as-needed LABA or SABA had the same effect on the risk of severe asthma exacerbation ($P>0.05$), although only the former therapy was significantly ($P<0.05$) more effective than ICS + as-needed SABA. All the investigated treatments were significantly ($P<0.05$) more effective than as-needed SABA in reducing the risk of severe asthma exacerbation, and detailed RE with 95%CrI are shown in Table 1. The forest plot of the overall comparisons across the investigated treatments is shown in Figure 2A. The SUCRA confirmed the comparison resulting from the overall network meta-analysis, by positioning LD to MD SMART in the first quartile along with HD ICS/LABA + as-needed SABA therapy (Figure 3A).

Subset analyses

The subset network meta-analysis performed on adult mild to moderate asthmatic patients reported that LD SMART and ICS/LABA used exclusively on an as-needed basis were equally effective ($P>0.05$) in preventing the risk of severe asthma exacerbation. LD SMART was significantly ($P<0.05$) more effective than both ICS/LABA + as-needed SABA and ICS + as-needed SABA, whereas the efficacy of as-needed ICS/LABA on the risk of severe asthma exacerbation was significantly ($P<0.05$) superior to ICS + as-needed SABA but not to ICS/LABA + as-needed SABA ($P>0.05$). All the above reported treatments were significantly ($P<0.05$) more effective than as-needed SABA in reducing the risk of severe asthma exacerbation, and detailed RE with 95%CrI are shown in Table 2. The forest plot of the comparisons across the investigated treatments in adult mild to moderate asthmatics is shown in

Figure 2B. The SUCRA confirmed the subset analysis on adult mild to moderate asthmatic patients, with LD SMART and ICS/LABA used exclusively on an as-needed basis positioned in the first quartile (Figure 3B).

The subset network meta-analysis performed on adult moderate to severe asthmatic patients showed that LD to MD SMART and HD ICS/LABA + as-needed SABA were equally effective in reducing the risk of severe asthma exacerbation (P>0.05). LD to MD SMART, but not HD ICS/LABA + as-needed SABA, was generally significantly (P<0.05) more effective against the risk of severe asthma exacerbation than lower doses of ICS/LABA + as-needed LABA or SABA and ICS + as-needed SABA. Detailed RE with 95%CrI of the subset analysis performed in adult moderate to severe asthmatic patients are reported in Table 4. The forest plot of the comparisons across the investigated treatments in adult moderate to severe asthmatics is shown in Figure 2C. Figure 3C reports the SUCRA in which the LD to MD SMART was ranked in the first quartile. The diagram displaying the network and the relative nodes of this subset analysis are shown in Figure S3A and S3B of the Supplement.

Secondary endpoints

PEF

The results of the overall network meta-analysis showed that LD to MD SMART and HD ICS/LABA + as-needed SABA were equally effective (P>0.05) in improving morning and evening PEF, and that both these therapeutic strategies were generally significantly (P<0.05) more effective than lower doses of ICS/LABA + as-needed SABA or LABA, ICS/LABA used exclusively on an as-needed basis, ICS + as-needed SABA, and as-needed SABA. The efficacy of lower doses of ICS/LABA + as-needed SABA or LABA on the improvement in morning and evening PEF was generally significantly (P<0.05) greater than as-needed ICS/LABA, ICS + as-needed SABA, and as-needed SABA. Administering ICS/LABA exclusively on an as-needed basis significantly (P<0.05) improved PEF when compared to ICS + as-needed SABA, LD ICS/LABA + as-needed SABA, and as-needed SABA.

Detailed RE with 95%CrI of the overall network meta-analysis on morning and evening PEF are reported in Table 1 and SUCRA values in Table S6.

FEV_1

The overall network meta-analysis indicated that LD to MD SMART and both ICS/LABA + as-needed SABA or LABA were generally equally effective in improving FEV_1 ($P>0.05$). LD to MD SMART, but not HD ICS/LABA + as-needed SABA, was generally significantly ($P<0.05$) more effective than ICS + as-needed SABA. Lower doses of ICS/LABA + as-needed SABA or LABA significantly ($P<0.05$) improved FEV_1 when compared with LD ICS + as-needed SABA, but not when compared with MD ICS + as-needed SABA ($P>0.05$). Administering ICS/LABA exclusively on an as-needed basis was generally significantly ($P<0.05$) less effective in improving FEV_1 compared to LD to MD SMART and ICS/LABA + as-needed LABA or SABA. The above reported treatments were significantly ($P<0.05$) more effective than as-needed SABA in improving FEV_1.

Detailed RE with 95%CrI of the overall network meta-analysis on FEV_1 are reported in Table 1 and SUCRA values in Table S6.

ACQ

Data concerning the change in ACQ were spurious when compared with the previously reported outcomes. In any case, when possible the overall network meta-analysis indicated that LD SMART therapy was significantly ($P<0.05$) more effective than LD ICS/LABA + as-needed SABA or LABA, as-needed LD ICS/LABA, ICS + as-needed SABA, and as-needed SABA in reducing ACQ. LD ICS/LABA + as-needed SABA or LABA significantly ($P<0.05$) reduced ACQ compared to both as-needed ICS/LABA and as-needed SABA. Administering either ICS/LABA exclusively on as-needed basis or ICS + as-needed SABA significantly ($P<0.05$) improved ACQ only with respect of as-needed SABA. MD ICS/LABA + as-needed LABA was significantly ($P<0.05$) more effective than all the above reported therapeutic options in reducing ACQ.

Detailed RE with 95%CrI of the overall network meta-analysis on ACQ are shown in Table 1 and SUCRA values in Table S6.

SAEs

No statistically significant (P>0.05) differences were found across the investigated treatments with respect to their impact on the risk of SAEs, excluded a significant (P<0.05) reduction in the risk of SAEs detected for LD SMART compared to LD ICS/LABA + as-needed SABA. Detailed information on the RE with 95%CrI of the risk of SAEs is reported in Table 1 and SUCRA values in Table S6.

Subset analyses

Table 2 and 3 show results of the subset analyses on adult mild to moderate and moderate to severe asthmatic patients, respectively.

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 4, and the traffic light plot for the assessment of each included RCT is reported in Figure S1. Most the RCTs had a low risk of bias for the randomization process (17 [81.0%]), missing outcome data (19 [90.5%]), measurement of the outcomes (11 [52.4%]), and selection of the reported results (13 [61.9%]). Of the 21 RCTs, 4 (19.0%) had a high risk of bias due to the measurement of the outcomes, 3 (14.3%) due to deviations from intended intervention, and 1 (4.8%) due to missing outcome. Ten studies (47.6%) had some concerns on the risk of bias in the domain of deviations from intended intervention.

Most the studies (90.47%) included in this network meta-analysis were ranked as being of medium to high quality in agreement with Jadad score, whereas only 9.53% of them were characterized by low quality level. The sensitivity analysis performed by excluding the two studies [6, 7] reporting a Jadad score ≤2, and for which the RoB 2 tool mainly provided some concerns to high risk of bias (Figure S1), did not result in significant (P>0.05) differences in both the RE and SUCRA, compared with the overall network meta-analysis.

The normalized consistency/inconsistency analysis showed that all points fit adequately with the line of equality (overall goodness of fit: R2 0.997; slope 1.027, 95%CI 1.022 – 1.032), indicating that this network meta-analysis was not affected by significant bias (Figure S2A-F). 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 as-needed therapies were compared directly or indirectly. No significant (P>0.05) inconsistency resulted for the subset analyses of both primary and secondary endpoints performed in agreement with disease severity.

The overall quality of evidence ranked in agreement with the GRADE system concerning the impact of each SMART and as-needed treatment in preventing the risk of severe asthma exacerbation is reported in Table 1. The specific GRADE analysis performed in adult mild to moderate asthmatic patients indicated that the LD SMART and the use of ICS/LABA used exclusively on an as-needed basis, both therapeutic strategies positioned in the first quartile by SUCRA, were ranked as having a high quality of evidence (median value: ++++). In adult moderate to severe patients LD to MD SMART, the only therapeutic strategy positioned in the first quartile by SUCRA, was also ranked as having a high quality of evidence (median value: ++++) in preventing severe asthma exacerbation.

Discussion

The main finding resulting from the meta-analysis of the primary endpoint is that SMART and as-needed therapies are effective strategies in preventing the risk of severe asthma exacerbation, and that as-needed SABA administered as monotherapy should be avoided in all asthmatic patients. Specifically, the treatment ranking analysis of the efficacy of specific as-needed therapies against the risk of severe asthma exacerbation provides the high quality of evidence that both LD SMART and administering ICS/LABA exclusively on an as-needed basis are the best therapeutic options in adult patients suffering from mild to moderate asthma, and that LD to MD SMART should be considered the first therapeutic strategy in adult moderate to severe asthmatic patients. By a clinical point of view, the effect estimate resulting from the network meta-analysis in adult mild to moderate asthmatic patients indicates that both LD SMART and the use of ICS/LABA exclusively on an as-needed basis overlapped the minimal clinically important difference (MCID: at least a reduction from 4 to 3 exacerbations/year, meaning ≈0.75 RR) [38, 39]

in reducing the risk of severe asthma exacerbation compared to either ICS/LABA + as-needed SABA, or ICS + as-needed SABA, or as-needed SABA. Generally SMART reached such a level of MCID also in patients suffering from moderate to severe asthma vs. LD to MD ICS/LABA + as-needed LABA or SABA, and ICS + as-needed SABA, but not when compared to higher dose of ICS/LABA + as-needed SABA. Thus, since HD ICS/LABA + as-needed SABA was ranked in the upper position of the second quartile of SUCRA, this therapeutic approach could be considered as second line treatment in preventing the risk of severe asthma exacerbation.

SMART was effective also on secondary endpoints, as it generally improved lung function and disease control compared to the other as-needed therapies in adult mild to moderate asthmatic patients. Conversely, in adult patients with moderate to severe asthma LD to MD SMART was only partially more effective than the other as-needed therapies on lung function and asthma control. Unexpectedly, no differences were found on the safety profile measured as the risk of experiencing SAEs across all the investigated therapeutic strategies and clustered in agreement with disease severity.

The findings of this network meta-analysis concerning the efficacy of as-needed ICS/LABA treatments strongly support the evidences raised from the SYGMA 1 and 2 studies [11, 12], in which it resulted that although the treatment with as-needed budesonide/formoterol prevented severe exacerbations, this therapeutic option was less effective than budesonide maintenance therapy at mitigating symptoms and improving lung function [40]. In any case, the differences in these treatment outcomes were smaller than the accepted MCIDs for these endpoints [12].

The fraction of exhaled nitric oxide (F_{ENO}) is useful to predict the response to ICS treatment, to monitor the adherence to therapy, and as a diagnostic tool in ICS-naïve patients [41]. F_{ENO} seems to be also a predictive factor for the risk of asthma exacerbation [41, 42]. In this respect, the Novel START Study [22] documented a greater reduction in the F_{ENO} levels among patients treated with either as-needed budesonide/formoterol or budesonide maintenance therapy compared to those treated with as-needed SABA. Nevertheless, although budesonide maintenance therapy resulted significantly more

effective than as-needed budesonide/formoterol in reducing F_{ENO} [22], the findings of our study demonstrate that as-needed ICS/LABA is significantly more effective than maintenance ICS therapy + as-needed SABA in preventing the risk of severe exacerbation in mild to moderate asthmatic patients.

The discrepancy between the results of this meta-analysis and the assumption that the levels of F_{ENO} are related with the risk of asthma exacerbation [41, 42] could be explained by considering that F_{ENO} levels are poorly reproducible and do not correlate with the severity of exacerbations [43]. As a matter of fact, recent evidences from an open-label RCT performed in mild asthmatic patients reported no significant interaction between baseline biomarkers, namely blood eosinophil count and F_{ENO} levels, and the effect of as-needed budesonide/formoterol for exacerbations and severe exacerbations [44].

The evidences raised from this study further endorse the last version of the current GINA 2020 document that suggests to administer LD as-needed ICS/LABA in mild asthma, LD ICS/LABA + as-needed LD ICS/LABA (LD SMART) in moderate asthma, and MD ICS/LABA + as-needed LD ICS/LABA (MD SMART) as preferred therapy in severe asthma [2]. Certainly, across the available ICS/LABA combinations, the current evidence supports prevalently the use of as-needed budesonide/formoterol to treat mild asthmatic patients [11, 12, 22], and budesonide/formoterol to be administered as SMART in mild to moderate [27-29] and moderate to severe asthma [7, 35, 37, 45-47]. Only one study was performed to test the efficacy of beclometasone/formoterol used as SMART in patients with moderate asthma [25]. However, we cannot omit that a recent study [26] provided the indication that budesonide/formoterol used as-needed for symptom relief was effective in reducing the risk of severe asthma exacerbation in a population that included also moderate asthmatic patients. A further important point is that the current literature does not provide evidence for using as-needed budesonide/formoterol on top of non-formoterol containing combination therapies.

Although this quantitative synthesis clearly provides the rank of efficacy for the as-needed therapies in asthma, an issue could remain concerning the comparison between MD ICS/LABA + as-needed LD ICS/LABA (MD SMART) and HD ICS/LABA + as-needed SABA in severe, not moderate, asthmatic patients. In fact the studies that directly compared these two therapeutic options were carried out in patients suffering from moderate to severe asthma [9, 48, 49]. However, we have to highlight that despite in the study of Pavord et al. [9] budesonide/formoterol maintenance and reliever therapy was compared with 4-fold higher maintenance dose of budesonide, the MD SMART regimen resulted as effective as HD ICS/LABA + as-needed SABA in preventing the risk of severe asthma exacerbation. Thus we could argue that budesonide/formoterol maintenance and reliever therapy is a suitable choice also for the most severe patients.

Network meta-analytic procedures are relatively new and they have been criticized especially for their recent use in the indirect comparison across biologic treatments in severe asthma [50]. We agree that when a network meta-analysis includes treatments that have been never compared head-to-head in RCTs, the resulting effect estimates from indirect comparisons could be uncertain [50]. Furthermore, although some degree of variation across study populations could be acceptable in pairwise meta-analyses, this can be disastrous in network meta-analyses [50]. Fortunately, several treatments we have assessed in the overall network meta-analysis were directly compared in head-to-head RCTs, leading to network loops that were further consolidated in the subset analyses performed in more homogenous populations, namely adult patients suffering from either mild to moderate or moderate to severe asthma. Definitely, the methods used in our study permitted to maintain a low and not significant level of inconsistency across the nodes of the Bayesian evidence network [51-53].

However, this study has also limitations. First, some RCTs led to concerns on the overall risk of bias related with the deviation from intended intervention and selection of the reported results. Second, considering the number of outcomes that were assessed, some statistically significant associations may represent type I error. Third, the SUCRA should be interpreted in agreement

with the quality of evidence, where the lower the quality of evidence the worse the accuracy of SUCRA. Since several outcomes have been investigated in this network meta-analysis, the SUCRA should be considered specifically for each outcome. Moreover, the extent of differences in the effects between treatments is not considered during the computation of SUCRA and, not less important, SUCRA does not allow assessing any statistically significant difference [54].

Indeed, the burden of severe asthma is associated with detrimental clinical impact in patients and increasing health care costs [55-57]. Furthermore, therapeutic strategy should be optimized in difficult-to-treat asthma before escalating to add on treatments such as oral corticosteroids or biologic therapy [58, 59]. In this regard, there is the medical and scientific need of balanced and well-designed head-to-head RCTs to assess the extent of superiority of SMART in reducing the risk of severe exacerbation in Step 5 asthmatic patients compared to HD ICS/LABA + as-needed SABA.

Concluding, the evidence raised by this network meta-analysis clearly indicates that both SMART and as-needed therapies represent suitable therapeutic options to reduce the risk of severe asthma exacerbation, by providing the most effective positioning of each specific treatment in the management of asthma according to the disease severity. In particular, while LD SMART was the first therapeutic choice at every level of disease severity, as-needed LD ICS/LABA resulted as effective as LD SMART in mild to moderate asthma being ranked borderline between the first and second treatment option. Conversely, as-needed LD ICS/LABA was ranked only as the sixth option in moderate to severe asthma. Although there may be discussion around the regular use of ICS vs. as-needed ICS/LABA to treat specifically mild asthmatic patients, to date there is definitely no rationale for using as-needed SABA as monotherapy in asthma. The findings of this study suggest the correct therapeutic indications to clinicians, that however should be interpreted in agreement with the medical needs of each single asthmatic patient.

Contributors

PR, BLR, JO, MC, 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 in consultation with JO, MC. PR and LC wrote the first draft of the Article, in consultation with, JO, BLR, MC 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.

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Declaration of interests

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

Comparisons		References for direct comparisons	Primary endpoint		Secondary endpoints				
			Severe asthma exacerbation (RR)	GRADE	Morning PEF (L/min)	Evening PEF (L/min)	FEV_1 (mL)	ACQ (points)	SAEs (RR)
LD SMART vs.	MD SMART	IC	0.98 (0.68 - 1.45)	+++	-11.50 (-26.63 - 11.28)	-15.76 (-29.95 - 0.37)	-26.62 (-169.04 - 113.68)	NA	0.95 (0.45 - 1.89)
	HD ICS/LABA + as-needed SABA	[31]	0.78 (0.51 - 1.21)	++++	-12.75 (-29.34 - 6.46)	-14.17 (-30.28 - 1.56)	-64.28 (-327.49 - 188.04)	NA	0.92 (0.39 - 2.14)
	LD ICS/LABA + as-needed LABA	[34]	**0.73 (0.57 - 0.92) ***	++++	**4.61 (0.09 - 8.79) ***	**5.19 (1.14 - 8.69) ***	33.89 (-20.88 - 83.05)	**-0.09 (-0.16 - -0.01) ***	1.05 (0.59 - 1.72)
	MD ICS/LABA + as-needed SABA	[33]	**0.71 (0.56 - 0.91) ***	++++	-2.01 (-6.27 - 2.37)	-0.45 (-4.62 - 3.52)	9.62 (-44.76 - 63.67)	NA	0.92 (0.62 - 1.37)
	as-needed LD ICS/LABA	IC	**0.61 (0.42 - 0.86) ***	+++	**29.86 (23.59 - 35.67) ***	**23.59 (18.31 - 29.10) ***	**188.03 (101.19 - 265.90) ***	**-0.30 (-0.44 - -0.17) ***	0.59 (0.16 - 2.17)
	MD ICS + as-needed SABA	[28, 36, 37]	**0.59 (0.47 - 0.73) ***	++++	**20.21 (13.83 - 26.67) ***	**13.77 (8.16 - 19.73) ***	**91.29 (17.21 - 165.01) ***	NA	0.99 (0.56 - 1.62)
	LD ICS/LABA + as-needed SABA	[25, 27, 28, 34, 36]	**0.55 (0.47 - 0.64) ***	++++	**6.90 (3.36 - 10.12) ***	**5.81 (2.95 - 8.69) ***	**47.36 (5.41 - 83.12) ***	**-0.11 (-0.17 - -0.06) ***	**0.68 (0.47 - 0.89) ***
	LD ICS + as-needed SABA	[6, 29]	**0.50 (0.34 - 0.69) ***	++++	**20.52 (14.57 - 26.84) ***	**17.22 (12.57 - 22.60) ***	**158.97 (67.05 - 242.68) ***	**-0.17 (-0.33 - -0.04) ***	0.73 (0.21 - 2.55)
	as-needed SABA	IC	**0.26 (0.17 - 0.39) ***	++++	**42.02 (35.27 - 49.08) ***	**34.47 (29.02 - 40.75) ***	**236.49 (137.22 - 318.76) ***	**-0.46 (-0.62 - -0.32) ***	0.57 (0.15 - 2.18)
	as-needed LABA	IC	NA	NA	NA	NA	**283.57 (141.37 - 422.87) ***	NA	3.07 (0.17 - 153.23)
	MD ICS/LABA + as-needed LABA	[8]	NA	NA	NA	NA	NA	**0.22 (0.07 - 0.35) ***	NA
MD SMART vs.	HD ICS/LABA + as-needed SABA	[30, 32]	0.80 (0.59 - 1.08)	++++	-1.24 (-7.19 - 4.93)	1.46 (-3.88 - 6.82)	-36.66 (-330.11 - 248.47)	NA	0.97 (0.52 - 1.84)
	LD ICS/LABA + as-needed LABA	IC	**0.57 (0.36 - 0.84) ***	+++	16.02 (-5.84 - 31.81)	**20.83 (5.07 - 35.25) ***	59.68 (-89.53 - 210.03)	NA	1.09 (0.46 - 2.61)
	MD ICS/LABA + as-needed SABA	[7, 35]	**0.73 (0.52 - 0.98) ***	++++	9.60 (-12.78 - 23.97)	**14.94 (0.06 - 29.58) ***	36.47 (-94.03 - 167.32)	NA	0.97 (0.53 - 1.87)
	as-needed LD ICS/LABA	IC	0.62 (0.36 - 1.00)	++	**41.32 (18.75 - 57.12) ***	**39.11 (23.58 - 54.77) ***	**214.22 (48.05 - 376.70) ***	NA	0.62 (0.14 - 2.75)
	MD ICS + as-needed SABA	IC	**0.60 (0.38 - 0.91) ***	+++	**31.55 (12.59 - 48.40) ***	**28.80 (12.99 - 45.36) ***	117.55 (-43.19 - 272.57)	NA	1.04 (0.44 - 2.52)
	LD ICS/LABA + as-needed SABA	IC	0.74 (0.46 - 1.14)	++	18.54 (-3.32 - 33.62)	**21.49 (5.48 - 35.82) ***	73.75 (-74.65 - 219.95)	NA	0.72 (0.33 - 1.50)
	LD ICS + as-needed SABA	IC	**0.50 (0.28 - 0.80) ***	+++	**32.32 (8.71 - 48.73) ***	**32.76 (17.55 - 47.96) ***	**185.87 (16.08 - 349.25) ***	NA	0.77 (0.18 - 3.29)
	as-needed SABA	IC	**0.27 (0.15 -**	++++	**53.77 (28.54 -**	**50.10 (34.59 -**	**262.83 (90.03 -**	NA	0.60 (0.13 -

			0.45) *		**70.47) ***	**65.84)***	**427.03) ***		2.79)
	as-needed LABA	IC	NA	NA	NA	NA	**309.55 (107.36 - 513.75) ***	NA	3.19 (0.15 - 176.00)
HD ICS/LABA + as-needed SABA vs.	LD ICS/LABA + as-needed LABA	IC	0.94 (0.56 - 1.49)	+++	17.37 (-1.18 - 34.23)	**19.53 (3.55 - 35.45) ***	99.43 (-160.11 - 365.93)	NA	1.13 (0.43 - 3.07)
	MD ICS/LABA + as-needed SABA	IC	0.91 (0.60 - 1.32)	+++	10.65 (-8.09 - 26.89)	13.60 (-1.51 - 29.69)	75.43 (-183.27 - 340.31)	NA	0.99 (0.45 - 2.30)
	as-needed LD ICS/LABA	IC	0.78 (0.43 - 1.29)	++	**42.36 (23.37 - 59.41) ***	**37.76 (21.57 - 54.62) ***	253.77 (-15.66 - 528.58)	NA	0.65 (0.13 - 2.96)
	MD ICS + as-needed SABA	IC	0.75 (0.46 - 1.19)	+++	**32.66 (14.57 - 51.37) ***	**27.33 (11.39 - 45.50) ***	155.92 (-103.46 - 430.86)	NA	1.06 (0.38 - 2.94)
	LD ICS/LABA + as-needed SABA	IC	0.71 (0.44 - 1.11)	+++	**19.66 (1.37 - 36.24) ***	**19.90 (3.98 - 36.39) ***	112.29 (-144.13 - 379.64)	NA	0.74 (0.29 - 1.80)
	LD ICS + as-needed SABA	IC	0.63 (0.35 - 1.05)	+++	**33.40 (13.40 - 51.08) ***	**31.23 (15.57 - 47.65) ***	226.88 (-42.13 - 503.22)	NA	0.81 (0.18 - 3.67)
	as-needed SABA	IC	**0.33 (0.18 - 0.59) ***	++++	**54.95 (33.19 - 72.75) ***	**48.59 (32.75 - 65.53) ***	**303.23 (27.21 - 579.57) ***	NA	0.63 (0.13 - 3.11)
	as-needed LABA	IC	NA	NA	NA	NA	**349.51 (59.02 - 645.32) ***	NA	3.30 (0.16 - 182.35)
LD ICS/LABA + as-needed LABA vs.	MD ICS/LABA + as-needed SABA	IC	0.97 (0.71 - 1.42)	+++	**-6.77 (-12.56 - -0.16) ***	**-5.60 (-11.06 - -0.09) ***	-23.63 (-95.93 - 51.11)	NA	0.88 (0.47 - 1.73)
	as-needed LD ICS/LABA	IC	0.83 (0.56 - 1.26)	+++	**25.15 (18.28 - 32.10) ***	**18.57 (12.18 - 24.83) ***	**154.57 (59.64 - 236.98) ***	**-0.21 (-0.36 - -0.07) ***	0.57 (0.14 - 2.29)
	MD ICS + as-needed SABA	IC	0.81 (0.59 - 1.12)	+++	**15.77 (7.92 - 23.82) ***	**8.66 (1.82 - 15.67) ***	57.57 (-31.75 - 149.59)	NA	0.94 (0.46 - 1.91)
	LD ICS/LABA + as-needed SABA	[34]	**0.76 (0.60 - 0.97) ***	++++	2.39 (-1.86 - 6.84)	0.69 (-3.29 - 4.71)	14.08 (-39.06 - 64.47)	-0.02 (-0.10 - 0.05)	0.65 (0.38, 1.07)
	LD ICS + as-needed SABA	IC	0.68 (0.44 - 1.01)	+++	**15.78 (9.25 - 23.58) ***	**12.26 (6.46 - 18.51) ***	**126.34 (26.46 - 215.54) ***	-0.08 (-0.25 - 0.06)	0.69 (0.19 - 2.75)
	as-needed SABA	IC	**0.36 (0.23 - 0.57) ***	+++	**37.54 (30.00 - 45.48) ***	**29.37 (22.46 - 36.53) ***	**203.36 (96.72 - 293.53) ***	**-0.38 (-0.54 - -0.23) ***	0.54 (0.14 - 2.37)
	as-needed LABA	IC	NA	NA	NA	NA	**249.15 (102.38 - 395.39) ***	NA	2.91 (0.16, 154.46)
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	NA	**0.31 (0.14 - 0.46) ***	NA
MD ICS/LABA + as-needed SABA vs.	as-needed LD ICS/LABA	IC	0.85 (0.55 - 1.30)	++	**31.64 (24.20 - 39.14) ***	**24.25 (17.66 - 30.99) ***	**178.09 (74.96 - 270.28) ***	NA	0.65 (0.16 - 2.45)
	MD ICS + as-needed SABA	IC	0.83 (0.59 - 1.14)	+++	**22.41 (14.36 - 30.15) ***	**14.23 (7.60 - 21.37) ***	80.98 (-9.79 - 172.69)	NA	1.07 (0.55 - 2.01)
	LD ICS/LABA + as-needed SABA	IC	0.78 (0.57 - 1.02)	+++	**8.93 (3.28 - 14.20) ***	**6.26 (1.52 - 11.25) ***	37.43 (-31.14 - 100.70)	NA	0.74 (0.44 - 1.16)

	LD ICS + as-needed SABA	IC	0.70 (0.44 - 1.05)	+++	**22.38 (15.06 - 30.22) ***	**17.79 (11.60 - 24.38) ***	**149.35 (45.23 - 244.11) ***	NA	0.80 (0.22 - 2.94)
	as-needed SABA	IC	**0.37 (0.23 - 0.59) ***	+++	**44.08 (35.91 - 52.42) ***	**34.91 (28.23 - 42.62) ***	**226.26 (115.92 - 323.73) ***	NA	0.62 (0.15 - 2.48)
	as-needed LABA	IC	NA	NA	NA	NA	**274.27 (121.52 - 421.81) ***	NA	3.26 (0.17 - 174.97)
As-needed LD ICS/LABA vs.	MD ICS + as-needed SABA	IC	0.98 (0.65 - 1.48)	+++	**-9.36 (-18.53 - -0.67) ***	**-9.84 (-17.61 - -1.92) ***	-98.06 (-201.53 - 18.24)	NA	1.67 (0.40 - 6.94)
	LD ICS/LABA + as-needed SABA	[24]	0.92 (0.65 - 1.28)	++++	**-22.76 (-28.56 - -16.97) ***	**-17.84 (-23.30 - -12.65) ***	**-141.76 (-212.10 - -61.81) ***	**0.18 (0.06 - 0.31) ***	1.16 (0.30 - 4.35)
	LD ICS + as-needed SABA	[11, 12, 22, 26]	**0.82 (0.66 - 0.96) ***	++++	**-9.26 (-13.03 - -4.85) ***	**-6.10 (-9.69 - -2.52) ***	-29.07 (-59.24 - 4.54)	**0.12 (0.07 - 0.18) ***	1.23 (0.87 - 1.85)
	as-needed SABA	[11, 22]	**0.43 (0.34 - 0.56) ***	++++	**12.29 (8.16 - 16.93) ***	**10.95 (7.30 - 14.89) ***	**48.78 (5.78 - 86.72) ***	**-0.17 (-0.23 - -0.10) ***	0.95 (0.60 - 1.65)
	as-needed LABA	[23]	NA	NA	NA	NA	96.17 (-17.79 - 213.74)	NA	4.69 (0.42 - 248.00)
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	NA	**0.53 (0.32 - 0.69) ***	NA
MD ICS + as-needed SABA vs.	LD ICS/LABA + as-needed SABA	[28, 36]	0.94 (0.73 - 1.17)	++++	**-13.48 (-20.91 - -6.10) ***	**-7.99 (-14.65 - -1.81) ***	-43.56 (-129.19 - 37.03)	NA	0.69 (0.39 - 1.14)
	LD ICS + as-needed SABA	IC	0.84 (0.54 - 1.23)	+++	0.15 (-8.39 - 9.68)	3.68 (-3.98 - 11.21)	68.84 (-49.12 - 176.28)	NA	0.74 (0.20 - 2.97)
	as-needed SABA	IC	**0.45 (0.28 - 0.69) ***	+++	**21.78 (12.49 - 31.89) ***	**20.94 (12.51 - 28.72) ***	**146.87 (19.58 - 253.07) ***	NA	0.57 (0.14 - 2.57)
	as-needed LABA	IC	NA	NA	NA	NA	**193.08 (30.74 - 350.57) ***	NA	3.13 (0.16 - 158.98)
LD ICS/LABA + as-needed SABA vs.	LD ICS + as-needed SABA	IC	0.89 (0.62 - 1.25)	+++	**13.63 (7.82 - 20.28) ***	**11.47 (6.51 - 16.79) ***	**112.34 (32.26 - 188.35) ***	-0.06 (-0.21 - 0.07)	1.07 (0.31 - 3.95)
	as-needed SABA	IC	**0.48 (0.31 - 0.72) ***	+++	**35.22 (28.45 - 42.20) ***	**28.70 (23.11 - 35.06) ***	**189.78 (98.49 - 267.49) ***	**-0.35 (-0.50 - -0.22) ***	0.82 (0.22 - 3.48)
	as-needed LABA	IC	NA	NA	NA	NA	**236.57 (98.01 - 371.48) ***	NA	4.47 (0.25 - 229.04)
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	NA	**0.34 (0.17 - 0.50) ***	NA
LD ICS + as-needed SABA vs.	as-needed SABA	[11, 22]	**0.53 (0.42 - 0.70) ***	++++	**21.45 (17.05 - 25.99) ***	**17.27 (13.49 - 20.95) ***	**77.10 (33.14 - 114.57) ***	**-0.29 (-0.36 - -0.23) ***	0.78 (0.49 - 1.29)
	as-needed LABA	IC	NA	NA	NA	NA	**124.52 (4.84 - 245.54) ***	NA	3.90 (0.32 - 194.53)
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	NA	**0.40 (0.19 - 0.57) ***	NA

As-needed LABA vs.	as-needed SABA	IC	NA	NA	NA	NA	-48.00 (-172.18 - 72.04)	NA	0.20 (0.00 - 2.61)
MD ICS/LABA + as-needed LABA vs.	as-needed SABA	IC	NA	NA	NA	NA	NA	**-0.69 (-0.88 - -0.48) ***	NA

[§]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). ACQ: asthma control questionnaire; CrI: credible interval; FEV_1: forced expiratory volume in 1 second; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; HD: high-dose; IC: indirect comparison; ICS: inhaled corticosteroid; LABA, long-acting β_2-agonist; LD: low-dose; MD: medium-dose; NA: not available; PEF: peak expiratory flow; RR: relative risk; SABA: short-acting β_2-agonist; SAEs: serious adverse events; SMART: single maintenance and reliever therapy (known as SMART or MART - for simplicity SMART is used in the Table); SUCRA: surface under the cumulative ranking curve.

Table 2. Relative effects with 95%CrI resulting from the subset network meta-analysis in adult mild to moderate asthmatic patients. Treatments comparisons have been sorted in agreement with SUCRA[§] findings for the primary endpoint reported in Figure 3B.

Comparisons		References for direct comparisons	Primary endpoint	Secondary endpoints				
			Severe asthma exacerbation (RR)	Morning PEF (L/min)	Evening PEF (L/min)	FEV_1 (mL)	ACQ (points)	SAEs (RR)
LD SMART vs.	as-needed LD ICS/LABA	IC	0.65 (0.41 - 1.06)	**29.42 (19.37 - 40.04) ***	**23.52 (15.15 - 31.07) ***	**171.28 (68.49 - 267.32) ***	**-0.29 (-0.44 - -0.12) ***	0.55 (0.14 - 2.20)
	LD ICS/LABA + as-needed SABA	[25, 27]	**0.63 (0.46 - 0.87) ***	6.34 (-0.71 - 13.87)	5.46 (-0.75 - 10.91)	21.27 (-33.53 - 75.55)	**-0.09 (-0.17- -0.01) ***	0.63 (0.35 - 1.15)
	LD ICS + as-needed SABA	[29]	**0.51 (0.31 - 0.79) ***	**20.49 (10.97 - 30.37) ***	**17.46 (9.68 - 24.85) ***	**143.54 (38.94 - 248.66) ***	-0.16 (-0.32 - 0.00)	0.68 (0.19 - 2.60)
	as-needed SABA	IC	**0.28 (0.16 - 0.49) ***	**41.79 (30.55 - 54.08) ***	**34.53 (24.74 - 43.79) ***	**220.24 (109.46 - 322.91) ***	**-0.46 (-0.62 - -0.28) ***	0.53 (0.14 - 2.29)
	as-needed LABA	IC	NA	NA	NA	**268.31 (115.56 - 422.41) ***	NA	3.00 (0.15 - 124.99)
	MD ICS/LABA + as-needed LABA	[8]	NA	NA	NA	NA	**0.23 (0.06 - 0.38) ***	NA
As-needed LD ICS/LABA vs.	LD ICS/LABA + as-needed SABA	[24]	0.98 (0.61 - 1.51)	**-22.91 (-32.15 - -14.18) ***	**-18.09 (-26.01 - -10.05) ***	**-149.52 (-232.01 - -65.89) ***	**0.19 (0.06 - 0.32) ***	1.15 (0.27 - 5.27)
	LD ICS + as-needed SABA	[11, 12, 22, 26]	**0.78 (0.57 - 0.95) ***	**-8.97 (-17.23 - -1.15) ***	-6.05 (-11.86 - 0.34)	-27.99 (-58.80 - 12.02)	**0.12 (0.07 - 0.17) ***	1.24 (0.85 - 1.95)
	as-needed SABA	[11, 22]	**0.43 (0.31 - 0.59) ***	**12.44 (3.85 - 21.09) ***	**10.94 (4.30 - 18.02) ***	**49.71 (5.13 - 89.26) ***	**-0.17 (-0.24 - -0.10) ***	0.97 (0.61 - 1.78)
	as-needed LABA	[23]	NA	NA	NA	97.54 (-20.90 - 217.70)	NA	5.29 (0.44 - 180.30)
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	**0.51 (0.29 - 0.73) ***	NA
LD ICS/LABA + as-needed SABA vs.	LD ICS + as-needed SABA	IC	0.79 (0.49 - 1.23)	**14.11 (4.36 - 24.04) ***	**12.06 (3.92 - 20.46) ***	**121.59 (36.59 - 214.08) ***	-0.07 (-0.21 - 0.07)	1.07 (0.26 - 4.46)
	as-needed SABA	IC	**0.44 (0.26 - 0.77) ***	**35.64 (23.77 - 47.04) ***	**29.07 (19.39 - 38.64) ***	**198.50 (102.66 - 290.01) ***	**-0.37 (-0.51 - -0.21) ***	0.83 (0.20 - 4.03)
	as-needed LABA	IC	NA	NA	NA	**247.84 (101.82 - 390.62) ***	NA	4.77 (0.22 - 189.79)
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	**0.32 (0.14 - 0.50) ***	NA
LD ICS + as-needed SABA vs.	as-needed SABA	[11, 22]	**0.55 (0.41 - 0.79) ***	**21.57 (13.29 - 30.08) ***	**17.03 (9.98 - 23.73) ***	**77.35 (28.53 - 114.13) ***	**-0.30 (-0.36 - -0.22) ***	0.78 (0.47 - 1.38)

	as-needed LABA	IC	NA	NA	NA	125.47 (-0.82 - 248.49)	NA	4.22 (0.33 - 145.40)
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	**0.39 (0.16 - 0.62) ***	NA
As-needed LABA vs.	as-needed SABA	IC	NA	NA	NA	-48.78 (-178.92 - 76.60)	NA	0.19 (0.01 - 2.43)
MD ICS/LABA + as-needed LABA vs.	as-needed SABA	IC	NA	NA	NA	NA	**-0.68 (-0.92 - -0.44) ***	NA

§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). ACQ: asthma control questionnaire; CrI: credible interval; FEV_1: forced expiratory volume in 1 second; IC: indirect comparison; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LD: low-dose; MD: medium-dose; NA: not available; PEF: peak expiratory flow; RR: relative risk; SABA: short-acting β_2-agonist; SAEs: severe adverse events; SMART: single maintenance and reliever therapy (known as SMART or MART - for simplicity SMART is used in the Table); SUCRA: surface under the cumulative ranking curve.

Table 3. Relative effects with 95%CrI resulting from the subset network meta-analysis in adult moderate to severe asthmatic patients. Treatments comparisons have been sorted in agreement with SUCRA[§] findings for the primary endpoint reported in Figure 3C.

Comparisons		References for direct comparisons	Primary endpoint	Secondary endpoints				
			Severe asthma exacerbation (RR)	Morning PEF (L/min)	Evening PEF (L/min)	FEV_1 (mL)	ACQ (points)	SAEs (RR)
LD SMART vs.	MD SMART	IC	0.96 (0.68 - 1.40)	-11.35 (-28.58 - 7.13)	-13.97 (-31.17 - 0.76)	-32.15 (-223.45 - 158.34)	NA	0.93 (0.55 - 1.55)
	HD ICS/LABA + as-needed SABA	[31]	0.76 (0.50 - 1.20)	-12.30 (-30.97 - 8.16)	-12.57 (-31.62 - 3.57)	-60.28 (-335.04 - 216.93)	NA	0.91 (0.48 - 1.71)
	LD ICS/LABA + as-needed LABA	[34]	**0.73 (0.60 - 0.92)***	4.32 (-2.57 - 10.97)	5.13 (-1.25 - 10.90)	36.25 (-62.47 - 135.70)	-0.09 (-0.24 - 0.08)	1.19 (0.84 - 1.68)
	MD ICS/LABA + as-needed SABA	[33]	**0.71 (0.58 - 0.90) ***	-1.77 (-8.27 - 4.13)	-0.33 (-6.11 - 5.22)	10.78 (-81.05 - 105.56)	NA	0.89 (0.64 - 1.21)
	as-needed LD ICS/LABA	IC	0.62 (0.39 - 1.01)	**26.55 (15.10 - 37.47) ***	**22.56 (12.21 - 32.87) ***	**200.82 (41.18 - 353.62) ***	**-0.30 (-0.56 - -0.03) ***	NA
	MD ICS + as-needed SABA	[36, 37]	**0.57 (0.45 - 0.70) ***	**20.03 (11.38 - 29.31) ***	**14.04 (6.00 - 21.64) ***	88.89 (-48.26 - 217.52)	NA	1.12 (0.79 - 1.62)
	LD ICS/LABA + as-needed SABA	[25, 34, 36]	**0.56 (0.48 - 0.67) ***	**6.59 (0.80 - 12.04) ***	**5.83 (0.31 - 10.80) ***	52.44 (-33.04 - 130.77)	-0.11 (-0.24 - 0.03)	0.89 (0.69 - 1.14)
	LD ICS + as-needed SABA	[6]	NA	NA	NA	4.02 (-280.75 - 297.51)	0.12 (-0.81 - 1.08)	NA
	MD ICS/LABA + as-needed LABA	[8]	NA	NA	NA	NA	**0.22 (0.02 - 0.41) ***	NA
MD SMART vs.	HD ICS/LABA + as-needed SABA	[30, 32]	0.79 (0.60 - 1.04)	-0.95 (-9.74 - 8.01)	0.91 (-6.59 - 9.36)	-25.71 (-372.87 - 294.78)	NA	0.99 (0.59 - 1.60)
	LD ICS/LABA + as-needed LABA	IC	0.76 (0.49 - 1.12)	15.58 (-3.55 - 33.59)	**19.97 (2.95 - 37.26) ***	67.69 (-148.81 - 279.18)	NA	1.28 (0.68 - 2.41)
	MD ICS/LABA + as-needed SABA	[7, 35]	**0.74 (0.54 - 0.99) ***	9.39 (-7.82 - 25.42)	**13.71 (0.38 - 29.99) ***	42.23 (-125.97 - 209.38)	NA	0.95 (0.62 - 1.53)
	as-needed LD ICS/LABA	IC	0.66 (0.38 - 1.12)	**37.83 (16.75 - 58.09)***	**36.86 (19.34 - 57.15) ***	232.57 (-12.72 - 475.30)	NA	NA
	MD ICS + as-needed SABA	IC	**0.59 (0.38 - 0.88) ***	**31.65 (10.55 - 50.69) ***	**27.89 (10.96 - 47.42) ***	120.01 (-119.69 - 351.05)	NA	1.20 (0.65 - 2.26)
	LD ICS/LABA + as-needed SABA	IC	**0.58 (0.39 - 0.83) ***	17.88 (-1.25 - 35.69)	**19.88 (4.12 - 37.27) ***	84.63 (-123.81 - 284.85)	NA	0.95 (0.54 - 1.67)
	LD ICS + as-needed SABA	IC	NA	NA	NA	39.16 (-304.93 - 390.50)	NA	NA
HD ICS/LABA + as-needed SABA vs.	LD ICS/LABA + as-needed LABA	IC	0.96 (0.59 - 1.51)	16.65 (-4.76 - 36.60)	**19.85 (0.27 - 37.59) ***	95.49 (-189.25 - 386.68)	NA	1.30 (0.64 - 2.81)
	MD ICS/LABA + as-	IC	0.93 (0.62 - 1.34)	10.42 (-8.76 -	12.34 (-2.89 -	70.84 (-217.80 -	NA	0.96 (0.53 -

	needed SABA			28.48)	30.86)	365.94)		1.79)
	as-needed LD ICS/LABA	IC	0.84 (0.46 - 1.45)	**38.87 (15.32 - 60.51) ***	**36.93 (16.18 - 57.40) ***	259.88 (-51.06 - 578.35)	NA	NA
	MD ICS + as-needed SABA	IC	0.74 (0.45 - 1.18)	**32.61 (10.53 - 54.04) ***	**26.53 (7.99 - 47.80) ***	147.03 (-152.48 - 445.61)	NA	1.23 (0.60 - 2.63)
	LD ICS/LABA + as-needed SABA	IC	0.73 (0.46 - 1.13)	18.99 (-2.39 - 38.52)	**18.78 (1.24 - 37.68) ***	111.06 (-169.97 - 396.84)	NA	0.97 (0.49 - 1.94)
	LD ICS + as-needed SABA	IC	NA	NA	NA	64.88 (-326.36 - 476.42)	NA	NA
LD ICS/LABA + as-needed LABA vs.	MD ICS/LABA + as-needed SABA	IC	0.96 (0.72 - 1.32)	-6.22 (-15.59 - 2.82)	-5.89 (-13.38 - 3.08)	-24.91 (-160.76 - 108.45)	NA	0.75 (0.46 - 1.18)
	as-needed LD ICS/LABA	IC	0.85 (0.51 - 1.38)	**22.33 (10.42 - 33.38) ***	**16.89 (6.76 - 28.49) ***	164.85 (-3.95 - 329.39)	-0.21 (-0.49 - 0.06)	NA
	MD ICS + as-needed SABA	IC	0.78 (0.57 - 1.02)	**15.61 (4.97 - 27.52) ***	9.04 (-1.21 - 18.87)	53.62 (-115.48 - 216.76)	NA	0.94 (0.58 - 1.51)
	LD ICS/LABA + as-needed SABA	[34]	**0.77 (0.62 - 0.95)***	2.26 (-4.74 - 8.59)	0.38 (-5.40 - 6.60)	16.74 (-85.31 - 112.72)	-0.02 (-0.18 - 0.13)	0.75 (0.52 - 1.06)
	LD ICS + as-needed SABA	IC	NA	NA	NA	-30.84 (-331.96 - 274.13)	NA	NA
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	**0.31 (0.05 - 0.54) ***	NA
MD ICS/LABA + as-needed SABA vs.	as-needed LD ICS/LABA	IC	0.88 (0.56 - 1.43)	**28.45 (15.33 - 41.04) ***	**23.30 (10.81 - 34.39) ***	**190.55 (2.88 - 369.40) ***	NA	
	MD ICS + as-needed SABA	IC	0.81 (0.57 - 1.06)	**21.94 (12.13 - 33.35) ***	**14.64 (4.39 - 23.72) ***	77.79 (-83.32 - 234.96)	NA	1.25 (0.78 - 2.05)
	LD ICS/LABA + as-needed SABA	IC	0.79 (0.60 - 1.03)	**8.30 (0.05 - 17.00) ***	6.35 (-1.60 - 13.60)	41.26 (-87.69 - 164.51)	NA	0.99 (0.67 - 1.50)
	LD ICS + as-needed SABA	IC	NA	NA	NA	-5.51 (-303.26 - 294.65)	0.21 (-0.74 - 1.18)	NA
As-needed LD ICS/LABA vs.	MD ICS + as-needed SABA	IC	0.90 (0.46 - 1.55)	-6.44 (-19.92 - 8.54)	-8.50 (-21.74 - 4.33)	-112.59 (-317.64 - 93.56)	NA	NA
	LD ICS/LABA + as-needed SABA	[24]	0.90 (0.58 - 1.38)	**-20.01 (-29.64 - -10.21) ***	**-17.04 (-25.79 - -7.92) ***	**-149.21 (-280.78 - -13.66) ***	0.19 (-0.03 - 0.41)	NA
	LD ICS + as-needed SABA	IC	NA	NA	NA	-193.68 (-515.35 - 124.58)	0.43 (-0.55 - 1.43)	NA
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	**0.52 (0.18 - 0.83) ***	NA
MD ICS + as-needed SABA vs.	LD ICS/LABA + as-needed SABA	[36]	0.98 (0.78 - 1.30)	**-13.37 (-24.68 - -3.96) ***	-8.36 (-17.52 - 1.52)	-36.58 (-191.89 - 120.07)	NA	0.79 (0.55 - 1.14)
	LD ICS + as-needed SABA	IC	NA	NA	NA	-81.81 (-396.22 - 228.68)	NA	NA

LD ICS/LABA + as-needed SABA vs.	LD ICS + as-needed SABA	IC	NA	NA	NA	-46.32 (-339.41 - 249.50)	0.22 (-0.72 - 1.21)	NA
	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	**0.33 (0.09 - 0.55) ***	NA
LD ICS + as-needed SABA vs.	MD ICS/LABA + as-needed LABA	IC	NA	NA	NA	NA	0.09 (-0.90 - 1.04)	NA

[§]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). ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in 1 second; HD: high-dose; IC: indirect comparison; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LD: low-dose; MD: medium-dose; NA: not available; PEF: peak expiratory flow; RR: relative risk; SABA: short-acting β_2-agonist; SAEs: severe adverse events; SMART: single maintenance and reliever therapy (known as SMART or MART - for simplicity SMART is used in the Table); SUCRA: surface under the cumulative ranking curve.

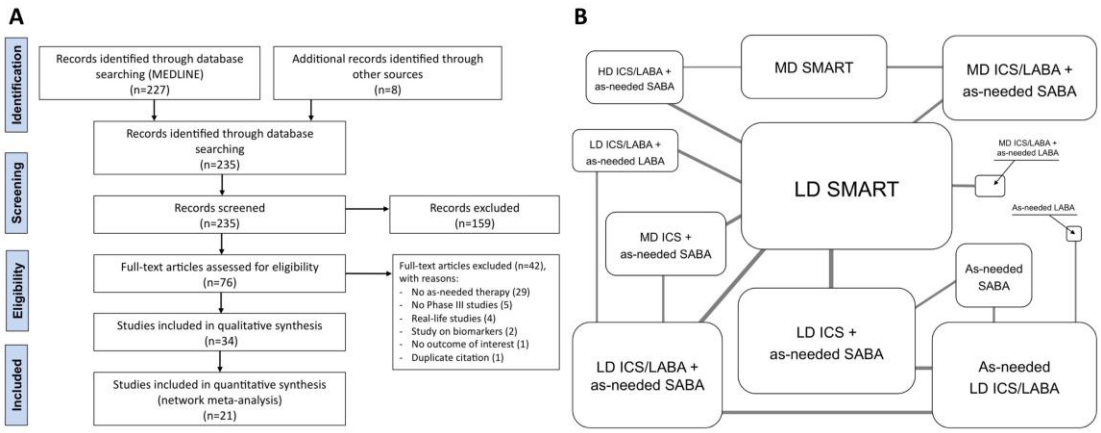
Figures and legends

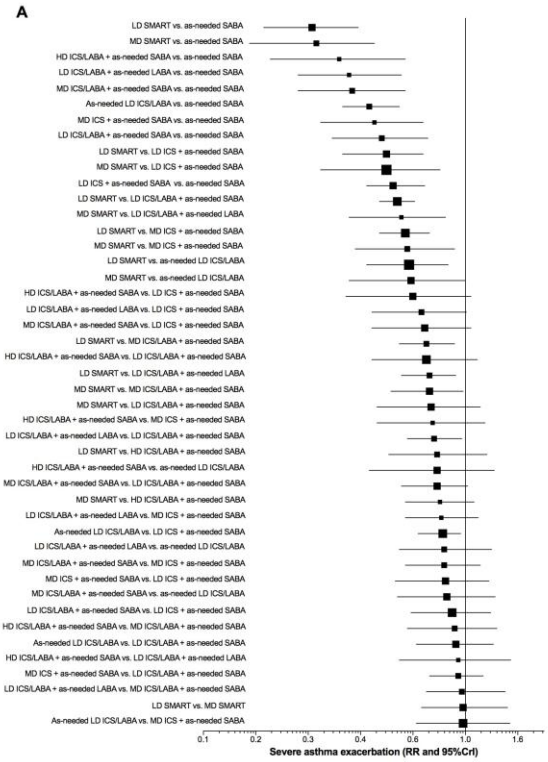
Figure 1. PRISMA-P flow diagram (A) and diagram displaying the network across the treatments (B). The links between the nodes indicate the direct comparisons between pairs of treatments, the thickness of lines is proportional with the number of the patients comparing pairs of treatment head-to-head, and the area of the boxes is proportional with the number of patients receiving the same treatment. HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-adrenoceptor agonist; LD: low-dose; MD: medium-dose; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols; SABA: short-acting β_2-agonist; SMART: single maintenance and reliever therapy (known as SMART or MART - for simplicity SMART is used in the Figure).

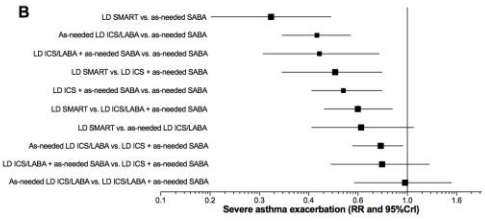
Figure 2. Overall forest plot of the comparisons across different SMART and as-needed therapies on the risk of severe asthma exacerbation (A) and subset network meta-analyses in adult mild to moderate (B) and moderate to severe (C) asthmatic patients. Treatments comparisons have been sorted in agreement with level of efficacy. CrI: credible interval; HD: high-dose; ICS: inhaled corticosteroid; LABA, long-acting β_2-agonist; LD: low-dose; MD: medium-dose; RR: relative risk; SABA: short-acting β_2-agonist; SMART: single maintenance and reliever therapy (known as SMART or MART - for simplicity SMART is used in the Figure).

Figure 3. Ranking plot of the efficacy of as-needed therapies in preventing the risk of severe exacerbation. Overall ranking plot displaying the efficacy of as-needed therapies in preventing the risk of severe exacerbation in asthmatic patients (A) and subset analyses on adult mild to moderate (B) and moderate to severe (C) 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. HD: high-dose; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LD: low-dose; MD: medium-dose; SABA: short-acting β_2-agonist; SMART: single maintenance and reliever therapy (known as SMART or MART - for simplicity SMART is used in the Figure); SUCRA: surface under the cumulative ranking curve.

Figure 4. Weighted plot for the assessment of the overall risk of bias via the Cochrane RoB 2 tool (n=21 studies).


A
Identification
Screening
Eligibility
Included
Records identified through database searching (MEDLINE) (n=227)
Additional records identified through other sources (n=8)
Records identified through database searching (n=235)
Records screened (n=235)
Records excluded (n=159)
Full-text articles assessed for eligibility (n=76)
Full-text articles excluded (n=42), with reasons:
- No as-needed therapy (29)
- No Phase III studies (5)
- Real-life studies (4)
- Study on biomarkers (2)
- No outcome of interest (1)
- Duplicate citation (1)
Studies included in qualitative synthesis (n=34)
Studies included in quantitative synthesis (network meta-analysis) (n=21)
B
HD ICS/LABA + as-needed SABA
MD SMART
MD ICS/LABA + as-needed SABA
LD ICS/LABA + as-needed LABA
LD SMART
MD ICS/LABA + as-needed LABA
As-needed LABA
MD ICS + as-needed SABA
As-needed SABA
LD ICS + as-needed SABA
LD ICS/LABA + as-needed SABA
As-needed LD ICS/LABA


A
LD SMART vs. as-needed SABA
MD SMART vs. as-needed SABA
HD ICS/LABA + as-needed SABA vs. as-needed SABA
LD ICS/LABA + as-needed LABA vs. as-needed SABA
MD ICS/LABA + as-needed SABA vs. as-needed SABA
As-needed LD ICS/LABA vs. as-needed SABA
MD ICS + as-needed SABA vs. as-needed SABA
LD ICS/LABA + as-needed SABA vs. as-needed SABA
LD SMART vs. LD ICS + as-needed SABA
MD SMART vs. LD ICS + as-needed SABA
LD ICS + as-needed SABA vs. as-needed SABA
LD SMART vs. LD ICS/LABA + as-needed SABA
MD SMART vs. LD ICS/LABA + as-needed LABA
LD SMART vs. MD ICS + as-needed SABA
MD SMART vs. MD ICS + as-needed SABA
LD SMART vs. as-needed LD ICS/LABA
MD SMART vs. as-needed LD ICS/LABA
HD ICS/LABA + as-needed SABA vs. LD ICS + as-needed SABA
LD ICS/LABA + as-needed LABA vs. LD ICS + as-needed SABA
MD ICS/LABA + as-needed SABA vs. LD ICS + as-needed SABA
LD SMART vs. MD ICS/LABA + as-needed SABA
HD ICS/LABA + as-needed SABA vs. LD ICS/LABA + as-needed SABA
LD SMART vs. LD ICS/LABA + as-needed LABA
MD SMART vs. MD ICS/LABA + as-needed SABA
MD SMART vs. LD ICS/LABA + as-needed SABA
HD ICS/LABA + as-needed SABA vs. MD ICS + as-needed SABA
LD ICS/LABA + as-needed LABA vs. LD ICS/LABA + as-needed SABA
LD SMART vs. HD ICS/LABA + as-needed SABA
HD ICS/LABA + as-needed SABA vs. as-needed LD ICS/LABA
MD ICS/LABA + as-needed SABA vs. LD ICS/LABA + as-needed SABA
MD SMART vs. HD ICS/LABA + as-needed SABA
LD ICS/LABA + as-needed LABA vs. MD ICS + as-needed SABA
As-needed LD ICS/LABA vs. LD ICS + as-needed SABA
LD ICS/LABA + as-needed LABA vs. as-needed LD ICS/LABA
MD ICS/LABA + as-needed SABA vs. MD ICS + as-needed SABA
MD ICS + as-needed SABA vs. LD ICS + as-needed SABA
MD ICS/LABA + as-needed SABA vs. as-needed LD ICS/LABA
LD ICS/LABA + as-needed SABA vs. LD ICS + as-needed SABA
HD ICS/LABA + as-needed SABA vs. MD ICS/LABA + as-needed SABA
As-needed LD ICS/LABA vs. LD ICS/LABA + as-needed SABA
HD ICS/LABA + as-needed SABA vs. LD ICS/LABA + as-needed LABA
MD ICS + as-needed SABA vs. LD ICS/LABA + as-needed SABA
LD ICS/LABA + as-needed LABA vs. MD ICS/LABA + as-needed SABA
LD SMART vs. MD SMART
As-needed LD ICS/LABA vs. MD ICS + as-needed SABA
0.1
0.2
0.3
0.4
0.6
1.0
1.6
Severe asthma exacerbation (RR and 95%CrI)


B
LD SMART vs. as-needed SABA
As-needed LD ICS/LABA vs. as-needed SABA
LD ICS/LABA + as-needed SABA vs. as-needed SABA
LD SMART vs. LD ICS + as-needed SABA
LD ICS + as-needed SABA vs. as-needed SABA
LD SMART vs. LD ICS/LABA + as-needed SABA
LD SMART vs. as-needed LD ICS/LABA
As-needed LD ICS/LABA vs. LD ICS + as-needed SABA
LD ICS/LABA + as-needed SABA vs. LD ICS + as-needed SABA
As-needed LD ICS/LABA vs. LD ICS/LABA + as-needed SABA
0.1
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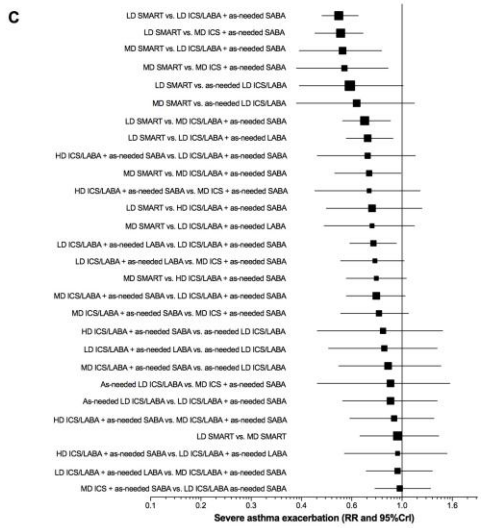
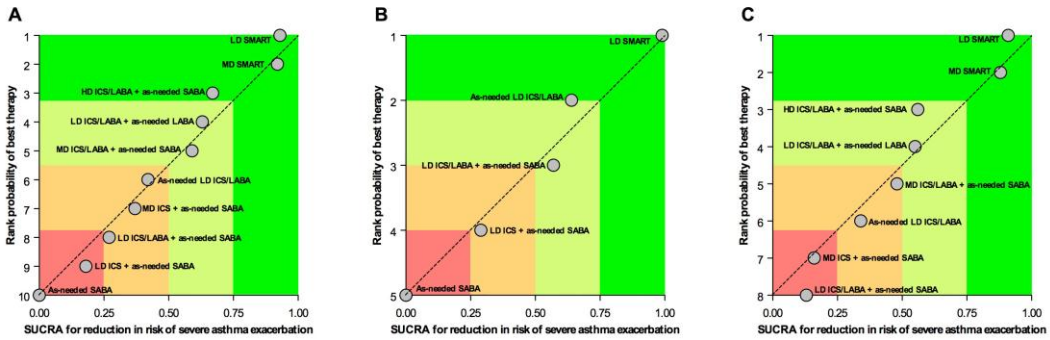
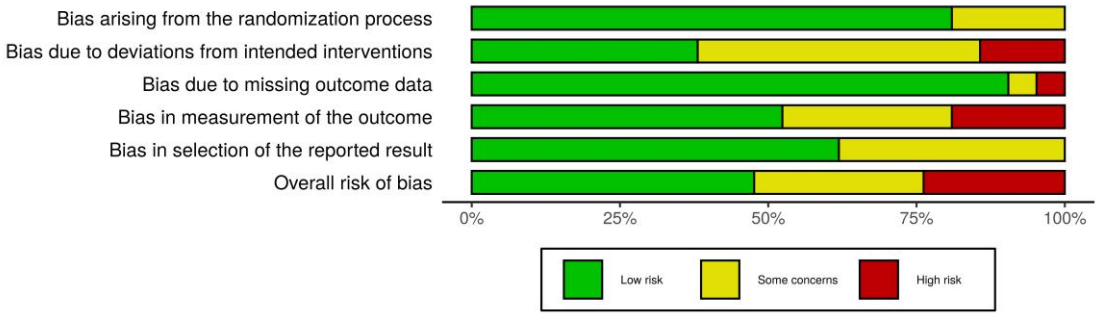
0.6
1.0
1.6
Severe asthma exacerbation (RR and 95%CrI)


C
LD SMART vs. LD ICS/LABA + as-needed SABA
LD SMART vs. MD ICS + as-needed SABA
MD SMART vs. LD ICS/LABA + as-needed SABA
MD SMART vs. MD ICS + as-needed SABA
LD SMART vs. as-needed LD ICS/LABA
MD SMART vs. as-needed LD ICS/LABA
LD SMART vs. MD ICS/LABA + as-needed SABA
LD SMART vs. LD ICS/LABA + as-needed LABA
HD ICS/LABA + as-needed SABA vs. LD ICS/LABA + as-needed SABA
MD SMART vs. MD ICS/LABA + as-needed SABA
HD ICS/LABA + as-needed SABA vs. MD ICS + as-needed SABA
LD SMART vs. HD ICS/LABA + as-needed SABA
MD SMART vs. LD ICS/LABA + as-needed LABA
LD ICS/LABA + as-needed LABA vs. LD ICS/LABA + as-needed SABA
LD ICS/LABA + as-needed LABA vs. MD ICS + as-needed SABA
MD SMART vs. HD ICS/LABA + as-needed SABA
MD ICS/LABA + as-needed SABA vs. LD ICS/LABA + as-needed SABA
MD ICS/LABA + as-needed SABA vs. MD ICS + as-needed SABA
HD ICS/LABA + as-needed SABA vs. as-needed LD ICS/LABA
LD ICS/LABA + as-needed LABA vs. as-needed LD ICS/LABA
MD ICS/LABA + as-needed SABA vs. as-needed LD ICS/LABA
As-needed LD ICS/LABA vs. MD ICS + as-needed SABA
As-needed LD ICS/LABA vs. LD ICS/LABA + as-needed SABA
HD ICS/LABA + as-needed SABA vs. MD ICS/LABA + as-needed SABA
LD SMART vs. MD SMART
HD ICS/LABA + as-needed SABA vs. LD ICS/LABA + as-needed LABA
LD ICS/LABA + as-needed LABA vs. MD ICS/LABA + as-needed SABA
MD ICS + as-needed SABA vs. LD ICS/LABA as-needed SABA
0.1
0.2
0.3
0.4
0.6
1.0
1.6
Severe asthma exacerbation (RR and 95%CrI)


A
LD SMART
MD SMART
HD ICS/LABA + as-needed SABA
LD ICS/LABA + as-needed LABA
MD ICS/LABA + as-needed SABA
As-needed LD ICS/LABA
MD ICS + as-needed SABA
LD ICS/LABA + as-needed SABA
LD ICS + as-needed SABA
As-needed SABA
Rank probability of best therapy
SUCRA for reduction in risk of severe asthma exacerbation
B
LD SMART
As-needed LD ICS/LABA
LD ICS/LABA + as-needed SABA
LD ICS + as-needed SABA
As-needed SABA
Rank probability of best therapy
SUCRA for reduction in risk of severe asthma exacerbation
C
LD SMART
MD SMART
HD ICS/LABA + as-needed SABA
LD ICS/LABA + as-needed LABA
MD ICS/LABA + as-needed SABA
As-needed LD ICS/LABA
MD ICS + as-needed SABA
LD ICS/LABA + as-needed SABA
Rank probability of best therapy
SUCRA for reduction in risk of severe asthma exacerbation


Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
Overall risk of bias
0%
25%
50%
75%
100%
Low risk
Some concerns
High risk

Materials and methods

Search strategy and study eligibility

This quantitative synthesis has been registered to the international prospective register of systematic reviews (PROSPERO, registration number: CRD42019136443, available at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=136443), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 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 [1].

A comprehensive literature search was performed for Phase III RCTs written in English and evaluating the efficacy and safety of single maintenance and reliever therapy (known as SMART or MART – for simplicity SMART will be used hereafter) and as-needed 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 SMART and as-needed therapies for the treatment of asthma; the "Comparison" was performed across different SMART and as-needed therapeutic strategies; the assessed "Outcomes" were the risk of severe asthma exacerbation, lung function, level of asthma control, and risk of serious adverse events (SAEs).

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 ≥6 months, and published up to January 8th, 2020. The research string was as follows: ("asthma"[MeSH Terms] OR "asthma"[All Fields]) AND (("beclomethasone"[MeSH Terms] OR "beclomethasone"[All Fields]) OR ("budesonide"[MeSH Terms] OR "budesonide"[All Fields]) OR ("fluticasone"[MeSH Terms] OR "fluticasone"[All Fields])) AND (("formoterol fumarate"[MeSH Terms] OR ("formoterol"[All Fields] AND "fumarate"[All Fields]) OR "formoterol fumarate"[All Fields] OR "formoterol"[All Fields]) OR

("salmeterol xinafoate"[MeSH Terms] OR ("salmeterol"[All Fields] AND "xinafoate"[All Fields]) OR "salmeterol xinafoate"[All Fields] OR "salmeterol"[All Fields]) OR ("vilanterol"[Supplementary Concept] OR "vilanterol"[All Fields])) AND (("health services needs and demand"[MeSH Terms] OR ("health"[All Fields] AND "services"[All Fields] AND "needs"[All Fields] AND "demand"[All Fields]) OR "health services needs and demand"[All Fields] OR "needed"[All Fields]) OR relief[All Fields]). Citations of previous published reviews were checked to select further pertinent RCTs, if any [3].
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 ≥6 months, and that included at least one arm assessing the impact of any SMART and/or as-needed therapy were included in the network meta-analysis. When the Phase of the trial was not reported in the study, it was assessed by using previously published criteria [4, 5]. 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. 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, smoking habit, use of rescue medication, number of patients that experienced at least one severe asthma exacerbation, forced expiratory volume in 1 s (FEV_1), Asthma Control Questionnaire (ACQ), number of patients that experienced at least one SAE, and Jadad Score [6].

The level of ICSs doses (LD, MD, HD) was ranked in agreement with the current Global Initiative for asthma (GINA) recommendations [7] and the National Institute for Health and Care Excellence (NICE) guidelines [8].

Data were extracted in agreement with Data Extraction for Complex Meta-anALysis (DECiMAL) recommendations [9]. The inter- and intra-rater reliability for data abstraction was assessed via the Cohen's Kappa score, as previously described [10]. 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

The primary endpoint of this network meta-analysis was the comparison across the different SMART and as-needed therapies with respect to the risk of severe exacerbations in asthmatic patients.

The secondary endpoints included the comparisons across the different SMART and as-needed therapies with respect to the changes from baseline in FEV_1, morning and evening peak expiratory flow (PEF), changes from baseline in ACQ score, and risk of SAEs.

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) [11] and Jadad score [6]. The Jadad score ranges form 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 [11].

The risk of bias was performed for the primary and secondary 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 [12]. 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 primary endpoint 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 [13].

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 SMART and as-needed therapies in asthmatic patients.

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 [14]. 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 [15, 16]. 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) [17, 18]. 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 [19]. Results of the network meta-analysis are expressed as relative effect (RE) and 95% credible interval (95%CrI).

Sensitivity analysis was performed by excluding the studies characterized by a Jadad score ≤2, and that may have introduced inconsistency and potential bias in the effect estimate of primary endpoint. Since inconsistency and bias may propagate through a network of RCTs, and thus affect the estimates differentially across regions of the network, this approach permitted to assess whether low-quality studies might alter the correct results of the network meta-analysis.

Subset analyses were performed in adult patients (age ≥18 years) in agreement with the severity of disease, namely mild and/or moderate and/or severe asthma. The severity of asthma was assessed in agreement with the current GINA recommendations [7] and NICE guidelines [8].

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 [20]. The SUCRA is 1 when a treatment is considered to be the best, and 0 when a treatment is considered to be the worst [12].

Software and statistical significance

ImageJ was used to extract data from the figures, when necessary [21], GeMTC [22] 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 [13], and the robvis visualization software to perform the RoB 2 tool [23, 24]. 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 32096 asthmatic patients (LD SMART: 21.45%; LD ICS + as-needed short-acting β_2-agonist (SABA): 15.09%; as-needed LD ICS/long-acting β_2-agonist (LABA): 13.90%; LD ICS/LABA + as-needed SABA: 12.63%; MD ICS/LABA + as-needed SABA: 10.39%; MD SMART: 7.37%; MD ICS + as-needed SABA: 6.15%; as-needed SABA: 4.67%; HD ICS/LABA + as-needed SABA: 4.14; LD ICS/LABA + as-needed LABA: 3.54%; MD ICS/LABA + as-needed LABA: 0.51%; as-needed LABA: 0.15%) were selected from 21 studies published between 2004 and 2019.

The inter-rater reliability for data abstraction was excellent before and after the learning process (Cohen's Kappa 0.96 and 1.00, respectively). 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 6 and 12 months.

Subset analyses

Since most the studies were performed in populations of asthmatic patients that not necessarily suffered from a specific level of disease severity, it was not possible to perform subset analyses focused specifically on mild, moderate, and severe asthma. Furthermore, even if some studies were performed in either mild or moderate asthmatics, the subset analyses could not have been performed due to the sparsity of the evidence in the network. Therefore, we have carried out subset analyses in populations of patients characterized by either mild to moderate or moderate to severe asthma. This approach permitted to maintain a low and not significant ($P>0.05$) level of inconsistency across the nodes of the Bayesian evidence network [25-27].

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, 4 main MS
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4 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.	4 main MS; 1 suppl. data 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.	5 main MS; 1 suppl. data 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.	5 main MS; 1 suppl. data file
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	1, 2, 10, 28-39 suppl. data file
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).	5 main MS; 2 suppl. data 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.	5 main MS; 2, 3 suppl. data file
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5 main MS; 3 suppl. data 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.	5, 6 main MS; 3, 4 suppl. data file
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6 main MS; 4, 5 suppl. data 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.	6 main MS; 4, 5 suppl. data 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, 6 main MS; 3, 4 suppl. data file
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6 main MS; 5 suppl. data 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.	33 main MS; 5, 6 suppl. data file. Figure 1
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.	6 main MS; 5, 6 suppl. data 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).	10, 11 main MS; 22, 23 suppl. data file.

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.	24-32 main MS; 11-14, 17-21 suppl. data file. Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	24-32 main MS; 11-14, 17-21 suppl. data file. Figure 2, 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, 11 main MS; 22, 23 suppl. data file. Figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11 main MS; 17-21 suppl. data file.
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).	12-15 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).	15 main MS
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15, 16 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.	17 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.

Table S2. Literature search terms used for OVID MEDLINE. The final search strategy applied to conduct this network meta-analysis is reported at step #19. The summary text of the identified records is shown in Appendix 1.

#	Search strategy
1	asthma*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
2	beclomethasone*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
3	budesonide*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
4	fluticasone*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
5	formoterol*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
6	salmeterol*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
7	vilanterol*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
8	(health services needs and demand*).mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
9	health*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
10	services*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
11	needs*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
12	demand*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
13	as needed*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
14	relief*.mp. [mp=ti, ab, tx, ct, sh, ot, nm, hw, fx, kf, ox, px, rx, an, ui, sy]
15	2 or 3 or 4
16	5 or 6 or 7
17	9 and 10 and 11 and 12
18	8 or 13 or 14 or 17
19	1 and 15 and 16 and 18

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

Study, year and reference	Trial number Identifier and/or Company ID	Study characteristics	Study duration (months)	Number of analyzed patients	Maintenance therapy (dose and regimen of administration)	As-needed treatment (dose of administration)	Inhaler device (brand)	Asthma severity and main inclusion criteria	Age (years)	Male (%)	Inclusion criteria for the number of exacerbations before study entry	Duration of asthma (years)	Pre-bronchodilator FEV_1 (% predicted)	Rescue inhaler use (puffs/day)	Current smokers (%)	ACQ at baseline (score)	Extracted outcomes	Jadad score
Hardy et al., 2019, PRACTICAL [28]	ACTRN12616000377437	Phase III, multicenter, randomized, open-label, active-controlled, parallel-group	12	885	NA or BUD (200 µg b.i.d.)	BUD/FOR (200/6 µg) or terbutaline (500 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); BUD: DPI (Pulmicort® Turbuhaler®); terbutaline: DPI (Turbuhaler®)	Mild to moderate asthma (patients not treated with ICS in the past 12 wks prior to study entry: presence of asthma symptoms or in need for SABA use ≥2 occasions in the past 4 wks, or waking because of asthma at least once in the past 4 wks, or a history of a severe asthma exacerbation requiring OCS in the past 52 wks; patients treated with low or moderate doses of BUD or equivalent ICS ≤800 µg/day in the previous 12 wks prior to study entry: partly or well controlled asthma or uncontrolled asthma with poor adherence or unsatisfactory inhaler technique)	43.1	45.0	NA	NA	87.6	1.4	7.5	1.2	Severe asthma exacerbation, FEV_1, ACQ, SAEs	3
Beasley et al., 2019, Novel START [29]	ACTRN12615000999538	Phase III, multicentre, randomized, open-label, active-controlled, parallel-group	12	668	NA or BUD (200 µg b.i.d.)	Salbutamol (200 µg) or BUD/FOR (200/6 µg)	BUD: DPI (Pulmicort® Turbuhaler®); salbutamol: pMDI (Ventolin®); BUD/FOR: DPI (Turbuhaler®)	Mild asthma (pre-bronchodilator FEV_1 >50% predicted; patients treated with SABA as sole asthma therapy for the past 3 months prior to study entry, and in need for SABA use ≥2 occasions, but on average ≤2 occasions/day, in the past 4 wks prior to study entry)	35.6	45.5	NA	NA	89.8	0.9	9.6	1.1	Severe asthma exacerbation, FEV_1, ACQ, SAEs	3
O'Byrne et al., 2018, SYGMA 1 [30]	NCT02149199	Phase III, multicentre, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group	12	3836	PCB (b.i.d.) or BUD (200 µg b.i.d.)	BUD/FOR (200/6 µg) or terbutaline (500 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); BUD: DPI (Pulmicort® Turbuhaler®); terbutaline: DPI (Turbuhaler®)	Mild asthma (patients with uncontrolled symptoms of asthma by as-needed SABA and/or short-acting anticholinergic agent for the past month prior to study entry, with pre-bronchodilator FEV_1 ≥60% predicted; patients with controlled symptoms of asthma with a stable dose of BUD or equivalent ≤400 µg/day or by treatment with LTRA with as-needed SABA and/or short-acting anticholinergic agent for the past month prior to study entry, with pre-bronchodilator FEV_1 ≥80% predicted)	39.6	38.9	NA	6.4	84.2	NA	NA	1.57	Severe asthma exacerbation, PEF, FEV_1, ACQ, SAEs	4
Bateman et al., 2018, SYGMA 2 [31]	NCT02224157	Phase III, multicentre, randomized, double-blind, placebo- and active-controlled, parallel-group	12	4176	PCB (b.i.d.) or BUD (200 µg b.i.d.)	BUD/FOR (200/6 µg) or terbutaline (500 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); budenoside: DPI (Pulmicort® Turbuhaler®); terbutaline: DPI (Turbuhaler®)	Mild asthma (patients with uncontrolled symptoms of asthma by as-needed SABA and/or short-acting anticholinergic agent for the past month prior to study entry, with pre-bronchodilator FEV_1 ≥60% predicted; patients with controlled symptoms of asthma with a stable dose of BUD or equivalent ≤400 µg/day or by treatment with LTRA with as-needed SABA and/or short-acting anticholinergic agent for the past month prior to study entry, with pre-bronchodilator FEV_1 ≥80% predicted)	41.0	37.8	NA	7.6	84.3	NA	2.6	1.51	Severe asthma exacerbation, FEV_1, ACQ, SAEs	5

Papi et al., 2015 [32]	NCT00849095	Phase III, multicentre, randomized, double-blind, placebo-controlled, non-inferiority, parallel-group	12	817	PCB (b.i.d.) or BUD/FOR (160/4.5 µg b.i.d.)	BUD/FOR (160/4.5 µg) or terbutaline (500 µg)	DPI (Turbuhaler®)	Moderate persistent asthma (patients with uncontrolled symptoms of asthma by low-dose of BUD or equivalent ICS ≤500 µg/day; patients with controlled symptoms of asthma by fixed combination of low-dose ICS and LABA b.i.d. for the past 2 months prior to study entry)	42.7	41.5	NA	10.97	94.1	0.01	0.0	0.55	Severe asthma exacerbation, PEF, FEV_1, ACQ	5
Takeyama et al., 2014 [33]	NA	Single-centre, randomized, NA, active-controlled, parallel-group	12	63	BUD/FOR (320/9 µg b.i.d.)	BUD/FOR (160/4.5 µg) or salbutamol (100 µg)	NA	Moderate to severe persistent asthma (pre-bronchodilator FEV_1 ≥60% predicted; patients treated with BUD 320-640 µg/day or FLU 200-500 µg/day and LABA for ≥3 months prior to study entry)	40.0	36.7	≥1 exacerbation in the previous 12 months	NA	69.3	NA	0.0	NA	PEF, FEV_1	1
Atienza et al., 2013 [34]	NCT00839800	Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group	12	2091	BUD/FOR (160/4.5 µg b.i.d.)	BUD/FOR (160/4.5 µg) or terbutaline (400 µg)	DPI (Turbuhaler®)	Mild to moderate persistent asthma (pre-bronchodilator FEV_1 ≥50% predicted; patients treated with ICS for ≥3 months prior to study entry and at constant dose for ≥4 wks prior to study entry)	45.7	32.4	≥1 exacerbation in the previous 12 months	12.0	69.9	2.4	3.8	NA	Severe asthma exacerbation, PEF, FEV_1, ACQ, SAEs	5
Papi et al., 2013 [35]	NCT00861926	Phase III, multicentre, randomized, double-blind, active-controlled, parallel-group	11	1701	BDP/FOR (100/6 µg b.i.d.)	BDP/FOR (100/6 µg) or salbutamol (100 µg)	BDP/FOR: pMDI (Foster®); salbutamol: pMDI (Ventolin®)	Moderate persistent asthma (pre-bronchodilator FEV_1 ≥60% predicted; patients treated with BDP or equivalent ICS ≥1000 µg/day or with BDP or equivalent ICS ≥500 µg/day and LABA for the past 2 months prior to study entry)	48.0	39.9	≥1 severe exacerbation in the previous 12 months but none in the month prior to study entry	9.0	74.5	1.0	NA	1.89	Severe asthma exacerbation, PEF, FEV_1, ACQ, SAEs	5
Lin et al., 2012 [36]	NCT00242775	Phase III, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group	6	222	BUD/FOR (320/9 µg b.i.d.) or FLU/SAL (500/50 µg b.i.d.)	BUD/FOR (160/4.5 µg) or terbutaline (400 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); FLU/SAL: DPI (Seretide® Diskus®); terbutaline: MDI (Bricanyl® Turbuhaler®)	Moderate to severe persistent asthma (pre-bronchodilator FEV_1 ≥50% predicted; patients treated with ICS alone at stable dose of 800–1600 µg/day or with ICS 400–1000 µg/day and LABA for ≥3 months prior to study entry)	49.7	45.0	≥1 clinically important exacerbation in the previous 12 months	9.5	63.7	NA	0	NA	Severe asthma exacerbation, SAEs	5
Pavord et al., 2009 [37]	NCT00244608	Phase III, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group	12	127	BUD/FOR (200/6 µg b.i.d.) or BUD/FOR (400/12 µg b.i.d.) + BUD (400 µg b.i.d.)	BUD/FOR (200/6 µg) or terbutaline (500 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); BUD: DPI (Pulmicort® Turbuhaler®); terbutaline: MDI (Bricanyl® Turbuhaler®)	Moderate to severe asthma (pre-bronchodilator FEV_1 ≥60% predicted; patients treated with ICS alone 800-1600 µg/day or with ICS 400-1000 µg/day and LABA prior to study entry)	40.0	54.5	NA	20.5	81.0	1.4	NA	NA	FEV_1, SAEs	5
Sovani et al., 2008 [38]	NA	Single-centre, randomized, open-label, active-controlled, parallel-group	6	71	BUD/FOR (200/6 µg q.d.) or BUD (200 µg b.i.d.)	BUD/FOR (200/6 µg) or usual SABA (NA µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); BUD: DPI (Pulmicort® Turbuhaler®), SABA: NA	Moderate to severe poorly controlled persistent asthma (patients treated with BDP or equivalent ICS 400-1000 µg/day prior to study entry)	40.3	45.1	NA	13.0	85.2	NA	42.5	2.0	FEV_1, ACQ	2
Bousquet et al., 2007, AHEAD [39]	NCT00242775; D5890C00002	Phase III, multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group	6	2309	BUD/FOR (320/9 µg b.i.d.) or FLU/SAL (500/50 µg b.i.d.)	BUD/FOR (160/4.5 µg) or terbutaline (400 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); terbutaline: MDI (Bricanyl® Turbuhaler®); FLU/SAL: DPI (Seretide® Diskus®)	Moderate to severe persistent asthma (pre-bronchodilator FEV_1 ≥50% predicted; patients treated with ICS alone at 800–1600 µg/day or with ICS at 400–1000 µg/day and LABA for ≥3 months prior to study entry)	39.5	38.0	≥1 clinically important exacerbation in the previous 12 month but none in the months prior to study entry	13.5	70.6	NA	4.5	NA	Severe asthma exacerbation, PEF, ACQ, SAEs	5

Kuna et al., 2007, COMPASS [40]	SD-039-0735	Phase III[a], multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group	6	3335	BUD/FOR (160/4.5 µg b.i.d.) or BUD/FOR (320/9 µg b.i.d.) or FLU/SAL (500/50 µg b.i.d.)	BUD/FOR (160/4.5 µg) or terbutaline (400 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler® SMART®); FLU/SAL: pMDI (Seretide® Advair® Evohaler®); terbutaline: DPI (Bricanyl® Turbuhaler®)	Moderate to severe asthma (pre-bronchodilator FEV_1 ≥50% predicted; patients treated with BUD or FLU ≥500 µg/day for ≥3 months prior to study entry or with another ICS ≥1000 µg/day for ≥1 month prior to study entry)	38.0	42.3	≥1 exacerbation in the previous 12 months but none in the month prior to study entry	NA	72.7	NA	5.7	NA	Severe asthma exacerbation, PEF, FEV_1, SAEs	5
Bisgaard et al., 2006 [41]	SD-039–0673	Phase III[a], multicentre, randomized, double-blind, active-controlled, parallel-group	12	341	BUD/FOR (80/4.5 µg q.d.) or BUD (320 µg q.d.)	BUD/FOR (80/4.5 µg) or terbutaline (400 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); BUD: DPI (Turbuhaler®); terbutaline: DPI (Turbuhaler®)	Mild to moderate persistent asthma (pre-bronchodilator FEV_1 ≥60% predicted; patients treated with ICS at constant dose of 200-500 µg/day for ≥3 months prior to study entry)	8.0	69.3	≥1 clinically important exacerbation in the previous 12 months	3.0	76.0	1.6	0.0	NA	Severe asthma exacerbation, SAEs	5
Lundborg et al., 2006 [42]	NA	Phase III[a], multicentre, randomized, open-label, active-controlled, parallel-group	6	491	Adult patients: BUD/FOR (160/4.5 µg q.d. or b.i.d.) or BUD/FOR (320/9 µg b.i.d.); 6-11 years old patients: BUD/FOR (80/4.5 µg q.d or b.i.d.) or BUD/FOR (160/9 µg b.i.d.)	Adult patients: BUD/FOR (160/4.5 µg) or FOR (4.5 µg); 6-11 years old patients: BUD/FOR (80/4.5 µg) or FOR (4.5 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); FOR: NA	Moderate persistent asthma (FEV_1 ≥60% predicted; adult patients treated with ICS at constant dose of 500-1200 µg/day for the past month prior to study entry; 6-11 years old patients treated with ICS at constant dose of 250-600 µg/day for the past month prior to study entry)	39.6	47.0	NA	NA	96.0	NA	NA	NA	ACQ	3
Rabe et al., 2006 [43]	NA	Phase III[a], multicentre, randomized, double-blind, active-controlled, parallel-group	6	3382	BUD/FOR (160/4.5 µg b.i.d.)	BUD/FOR (160/4.5 µg) or terbutaline (400 µg) or FOR (4.5 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); terbutaline: MDI (Bricanyl® Turbuhaler®); FOR: DPI (Oxis® Turbuhaler®)	Moderate to severe persistent asthma (pre-bronchodilator FEV_1≥50% predicted; patients treated with ICS for ≥3 months prior to study entry and at constant dose for ≥ 4 wks prior to study entry)	38.0	39.3	≥1 severe exacerbation in the previous 12 months	10.0	72.0	NA	NA	1.9	Severe asthma exacerbation, PEF, FEV_1, ACQ, SAEs	4
Haahtela et al., 2006, SOMA [44]	NA	Multicentre, randomized, active-controlled, double-blind, parallel-group	6	92	NA	BUD/FOR (160/4.5 µg) or FOR (4.5 µg)	FOR: DPI (Oxis® Turbuhaler®); BUD/FOR: DPI (Symbicort® Turbuhaler®)	Mild intermittent asthma (pre-bronchodilator FEV_1 ≥80% predicted)	35.7	65.2	NA	NA	101.0	NA	NA	NA	FEV_1, SAEs	4
Rabe et al., 2006 [45]	Study No. 0667	Phase III[a], multicentre, randomized, double-blind, active-controlled, parallel-group	6	696	BUD/FOR (160/9 µg q.d.) or BUD (320 q.d.)	BUD/FOR (80/4.5 µg) or terbutaline (400 µg)	DPI (NA)	Mild to moderate asthma (pre-bronchodilator FEV_1 ≥60% predicted; patients treated with ICS at 200-500 µg/day for ≥3 months prior to study entry and at constant dose for ≥ 4 wks prior to study entry)	38.0	38.5	NA	10.0	75.0	NA	27.5	NA	Severe asthma exacerbation, PEF, SAEs	5
Vogelmeier et al., 2005, COSMOS [46]	NA	Phase III[a], multicentre, randomized, open-label, active-controlled, parallel-group	12	2143	BUD/FOR (320/9 µg b.i.d.) or FLU/SAL (250/50 µg b.i.d.)	BUD/FOR (160/4.5 µg) or salbutamol (100 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); FLU/SAL: DPI (Seretide® Diskus®); salbutamol: DPI or pMDI (Ventolin®)	Moderate to severe persistent asthma (pre-bronchodilator FEV_1 ≥40% and ≤90% predicted; patients treated with BUD or FLU ≥500 µg/day for or with another ICS ≥1000 µg/day for ≥1 month prior to study entry)	45.0	69.8	≥1 severe exacerbation in the previous 12 months but none over the 2 wks prior to study entry	12.5	73.0	2.7	NA	1.9	Severe asthma exacerbation, SAEs	3

O'Byrne et al., 2005, STAY [47]	NA	Phase III[a], multicentre, randomized, double-blind, active-controlled, parallel-group	12	2760	Adult patients: BUD/FOR (80/4.5 µg b.i.d.) or BUD (320 µg b.i.d.); 4-11 years old patients: BUD/FOR (80/4.5 µg q.d.) or BUD (320 µg q.d.)	BUD/FOR (80/4.5 µg) or terbutaline (400 µg)	DPI (Turbuhaler®)	Moderate to severe persistent asthma (FEV_1 ≥60% predicted; adult patients treated with ICS at constant dose of 400-1000 µg/day for ≥3 months prior to study entry; 4-11 years old patients treated with ICS at constant dose of 200-500 µg/day for ≥3 months prior to study entry)	35.6	44.6	≥1 exacerbation in the previous 12 months	9.0	73.0	1.7	NA	NA	Severe asthma exacerbation, SAEs	3
Scicchitano et al., 2004 [48]	NA	Phase III[a], multicentre, randomized, double-blind, double-dummy, active-controlled, parallel-group	12	1890	BUD/FOR (320/9 µg q.d.) or BUD (320 µg b.i.d.)	BUD/FOR (160/4.5 µg) or terbutaline (400 µg)	BUD/FOR: DPI (Symbicort® Turbuhaler®); BUD: DPI (Pulmicort® Turbuhaler®), terbutaline: MDI (Bricanyl® Turbuhaler®)	Moderate to severe persistent asthma (pre-bronchodilator FEV_1 ≥50% and ≤90% predicted; patients treated with ICS at 400-1600 µg/day for ≥3 months prior to study entry and at constant dose for ≥ 4 wks prior to study entry)	43.0	42.0	≥1 clinically important exacerbation in the previous 12 months but none in the month prior to study entry	12.0	70.0	2.0	NA	NA	Severe asthma exacerbation, PEF, FEV_1, SAEs	5

[a] Phase III study assessment in agreement with "Key Concepts of Clinical Trials: A Narrative Review".[4]

BDP: beclometasone dipropionate; b.i.d.: *bis in die*, twice-daily; BUD: budesonide; d: day; DPI: Dry Powder Inhaler; FEV_1: forced expiratory flow in 1 second; FF: fluticasone furoate; FLU: fluticasone propionate; FOR: formoterol; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; MDI: Metered Dose Inhaler; MF: mometasone furoate; NA: not available; OCS: oral corticosteroid; PCB: placebo; PEF: peak expiratory flow; pMDI: Pressurised Metered Dose Inhaler; q.d.: *quaque die*, once-daily; SABA: short-acting β_2-agonist; SAEs: severe adverse events; SAL: salmeterol; wks: weeks.

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

Study, year and reference	Study identifier	Definition of severe asthma exacerbation
Hardy et al., 2019, PRACTICAL [28]	ACTRN12616000377437	"Use of systemic corticosteroids for ≥3 days because of asthma, or hospital admission or ED visit because of asthma, requiring systemic corticosteroids"
Beasley et al., 2019, Novel START [29]	ACTRN12615000999538	"Worsening asthma that resulted in one or more of the following: an urgent medical care consultation (e.g., a primary care visit, an ED visit, or hospital admission); a prescription of systemic glucocorticoids for any duration; or an episode of high β_2-agonist use, which was defined as more than 16 actuations of albuterol or more than 8 actuations of budesonide–formoterol over the course of 24 hours"
Bateman et al., 2018, SYGMA 2 [31]	NCT02224157	"Worsening asthma leading to systemic glucocorticoid treatment for ≥3 days, hospitalization, or an emergency department visit leading to systemic glucocorticoid treatment"
O'Byrne et al., 2018, SYGMA 1 [30]	NCT02149199	"Worsening asthma leading to the use of systemic glucocorticoids for ≥3 days, inpatient hospitalization, or an ED visit leading to the use of systemic glucocorticoids"
Papi et al., 2015 [32]	NCT00849095	"Treatment with steroids and/or admission to the ER or hospitalization"
Takeyama et al., 2014 [33]	NA	"Deterioration in asthma leading to ED visits, systemic steroid use, or hospitalization"
Atienza et al., 2013 [34]	NCT00839800	"Deterioration in asthma leading to oral corticosteroid treatment for ≥3 days, or hospitalization or ER treatment due to asthma"
Papi et al., 2013 [49]	NCT00861926	"Deterioration in asthma resulting in hospitalization or visit to the ED, or requiring systemic steroids for ≥3 days"
Lin et al., 2012 [36]	NCT00242775	"Deterioration in asthma leading to hospitalization/emergency (or equivalent) treatment and/or the need for oral corticosteroid treatment for ≥3 days"
Pavord et al., 2009 [37]	NCT00244608	"Deterioration in asthma symptoms resulting in hospitalization/ER treatment and/or oral steroid use for ≥3 days"
Sovani et al., 2008 [38]	NA	NA
Bousquet et al., 2007, AHEAD [39]	NCT00242775	"Deterioration in asthma leading to hospitalization/ER treatment and/or oral corticosteroid treatment for ≥3 days"
Kuna et al., 2007 COMPASS [40]	SD-039-0735	"Deterioration in asthma leading to hospitalization or ER treatment or need for oral steroids for ≥3 days"
Rabe et al., 2006 [43]	NA	"Deterioration in asthma leading to hospitalization or ER treatment or need for oral steroids for ≥3 days"
Haahtela et al., 2006, SOMA [44]	NA	NA
Rabe et al., 2006 [45]	NA	"Hospitalization/ED treatment due to asthma worsening, oral steroids use for asthma, or ≥30% decrease from baseline in morning PEF on 2 consecutive days"
Bisgaard et al., 2006 [41]	SD-039–0673	"Deterioration in asthma leading to hospitalization/ED treatment; treatment with oral steroids; an increase in ICS (via a separate inhaler, that is not study medication) and/or any other additional treatment, or PEF to ≤70% of baseline on 2 consecutive days"
Lundborg et al., 2006 [42]	NA	One or several of the following: "an asthma-related serious adverse event, treatment at a medical care center with parenteral or nebulized bronchodilators, use of inhaled or oral corticosteroids due to worsening of asthma and/or withdrawal from the study because of need of added asthma maintenance"
Vogelmeier et al., 2005, COSMOS [46]	NA	"Deterioration in asthma leading to hospitalization/ER treatment, oral corticosteroid treatment for ≥3 days or an unscheduled visit (i.e. patient initiated) leading to treatment change"
O'Byrne et al., 2005, STAY [47]	NA	"Deterioration in asthma leading to hospitalization/ER treatment, oral steroid treatment (or an increase in ICS use via a separate inhaler and/or other additional treatment for children aged 4–11 years), or morning PEF to ≤70% of baseline on 2 consecutive days"
Scicchitano et al., 2004 [48]	NA	"Asthma worsening leading to hospitalization/ER treatment or systemic steroid treatment or a fall in morning PEF to ≤70% of baseline on 2 consecutive days"

ED: emergency department; ER: emergency room; ICS: inhaled corticosteroid; NA: not available; PEF: peak expiratory flow.

Table S5. Level of ICS doses in agreement with the daily doses of medications in adults and children in the studies included in network meta-analysis as reported by current GINA recommendations [7] and NICE guidelines [8].

Treatment	Regimen of administration	Daily dose	Level of ICS dose
BUD	80 µg QD	80 µg	LD[a]
	80 µg BID	160 µg	LD[a]
	80 µg BID	160 µg	LD
	100 µg BID	200 µg	LD
	160 µg QD	160 µg	LD
	160 µg BID	320 µg	LD
	200 µg QD	200 µg	LD
	200 µg BID	400 µg	LD
	320 µg QD	320 µg	LD
	160 µg BID	320 µg	MD[a]
	320 µg QD	320 µg	MD[a]
	320 µg BID	640 µg	MD
	400 µg BID	800 µg	MD
	800 µg BID	1600 µg	HD
BDP	100 µg BID	200 µg	LD
FF	100 µg QD	100 µg	MD[b]
FLU	250 µg BID	500 µg	MD
	500 µg BID	1000 µg	HD

[a] in children; [b] level of dose refers to that reported in the NICE guidelines [8].
b.i.d.: bis in die, twice-daily; BUD: budesonide; BDP: beclomethasone dipropionate; FF: fluticasone furoate; FLU: fluticasone propionate; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; HD: high-dose; LD: low-dose; MD: medium-dose; NICE: National Institute for Health and Care Excellence; q.d.: quaque die, once-daily.

Table S6. Rank probability of best therapy and SUCRA values for different SMART and as-needed therapies in the overall asthmatic population and in adults with mild to moderate and moderate to severe asthma with respect to the secondary endpoints. SUCRA is 1 for a treatment considered to be the best, and 0 for a treatment considered to be the worst.

Rank probability of best therapy	Morning PEF			Evening PEF			FEV_1			ACQ			SAEs		
	Overall	Mild to moderate	Moderate to severe	Overall	Mild to moderate	Moderate to severe	Overall	Mild to moderate	Moderate to severe	Overall	Mild to moderate	Moderate to severe	Overall	Mild to moderate	Moderate to severe
1	HD ICS/LABA + as-needed SABA (0.93)	LD SMART (0.98)	HD ICS/LABA + as-needed SABA (0.90)	MD SMART (0.95)	LD SMART (0.99)	MD SMART (0.94)	HD ICS/LABA + as-needed SABA (0.84)	LD SMART (0.95)	HD ICS/LABA + as-needed SABA (0.74)	MD ICS/LABA + as-needed LABA (1.00)	MD ICS/LABA + as-needed LABA (1.00)	MD ICS/LABA + as-needed LABA (0.90)	As-needed LABA (0.79)	As-needed LABA (0.86)	LD ICS/LABA + as-needed LABA (0.80)
2	MD SMART (0.89)	LD ICS/LABA + as-needed SABA (0.75)	MD SMART (0.87)	HD ICS/LABA + as-needed SABA (0.91)	LD ICS/LABA + as-needed SABA (0.76)	HD ICS/LABA + as-needed SABA (0.88)	MD SMART (0.83)	LD ICS/LABA + as-needed SABA (0.83)	MD SMART (0.72)	LD SMART (0.83)	LD SMART (0.79)	LD SMART (0.66)	LD ICS/LABA + as-needed LABA (0.66)	LD SMART (0.71)	MD ICS + as-needed SABA (0.74)
3	MD ICS/LABA + as-needed SABA (0.78)	LD ICS + as-needed SABA (0.50)	MD ICS/LABA + as-needed SABA (0.70)	MD ICS/LABA + as-needed SABA (0.73)	LD ICS + as-needed SABA (0.50)	MD ICS/LABA + as-needed SABA (0.64)	LD SMART (0.81)	LD ICS + as-needed SABA (0.59)	LD SMART (0.68)	LD ICS/LABA + as-needed LABA (0.60)	LD ICS/LABA + as-needed SABA (0.74)	LD ICS/LABA + as-needed LABA (0.42)	LD SMART (0.63)	LD ICS/LABA + as-needed SABA (0.38)	LD SMART (0.55)
4	LD SMART (0.71)	As-needed LD ICS/LABA (0.25)	LD SMART (0.62)	LD SMART (0.73)	As-needed LD ICS/LABA (0.26)	LD SMART (0.64)	MD ICS/LABA + as-needed SABA (0.75)	As-needed LD ICS/LABA (0.40)	MD ICS/LABA + as-needed SABA (0.61)	LD ICS/LABA + as-needed SABA (0.51)	LD ICS + as-needed SABA (0.43)	LD ICS/LABA + as-needed SABA (0.33)	MD ICS/LABA + as-needed SABA (0.52)	LD ICS + as-needed SABA (0.54)	LD ICS/LABA + as-needed SABA (0.28)
5	LD ICS/LABA + as-needed LABA (0.55)	As-needed SABA (0.00)	LD ICS/LABA + as-needed LABA (0.43)	LD ICS/LABA + as-needed LABA (0.52)	As-needed SABA (0.00)	LD ICS/LABA + as-needed LABA (0.39)	LD ICS/LABA + as-needed LABA (0.63)	As-needed SABA (0.16)	LD ICS/LABA + as-needed LABA (0.49)	LD ICS + as-needed SABA (0.39)	As-needed LD ICS/LABA (0.20)	As-needed LD ICS/LABA (0.07)	MD ICS + as-needed SABA (0.61)	As-needed LD ICS/LABA (0.27)	MD ICS/LABA + as-needed SABA (0.31)
6	LD ICS/LABA + as-needed SABA (0.46)	NA	LD ICS/LABA + as-needed SABA (0.33)	LD ICS/LABA + as-needed SABA (0.48)	NA	LD ICS/LABA + as-needed SABA (0.36)	LD ICS/LABA + as-needed SABA (0.57)	As-needed LABA (0.06)	LD ICS/LABA + as-needed SABA (0.38)	As-needed LD ICS/LABA (0.17)	As-needed SABA (0.00)	LD ICS + as-needed SABA (0.62)	MD SMART (0.56)	A-needed SABA (0.26)	MD SMART (0.43)
7	MD ICS + as-needed SABA (0.28)	NA	MD ICS + as-needed SABA (0.12)	MD ICS + as-needed SABA (0.31)	NA	MD ICS + as-needed SABA (0.14)	MD ICS + as-needed SABA (0.44)	NA	MD ICS + as-needed SABA (0.27)	As-needed SABA (0.00)	NA	NA	LD ICS/LABA + as-needed SABA (0.25)	NA	HD ICS/LABA + as-needed SABA (0.41)
8	LD ICS + as-needed SABA (0.28)	NA	As-needed LD ICS/LABA (0.02)	LD ICS + as-needed SABA (0.24)	NA	As-needed LD ICS/LABA (0.01)	LD ICS + as-needed SABA (0.31)	NA	LD ICS + as-needed SABA (0.57)	NA	NA	NA	LD ICS + as-needed SABA (0.43)	NA	NA
9	As-needed LD ICS/LABA (0.11)	NA	NA	As-needed LD ICS/LABA (0.11)	NA	NA	As-needed LD ICS/LABA (0.20)	NA	As-needed LD ICS/LABA (0.04)	NA	NA	NA	As-needed LD ICS/LABA (0.26)	NA	NA
10	As-needed SABA (0.00)	NA	NA	As-needed SABA (0.00)	NA	NA	As-needed SABA (0.08)	NA	NA	NA	NA	NA	As-needed SABA (0.23)	NA	NA
11	NA	NA	NA	NA	NA	NA	As-needed LABA (0.03)	NA	NA	NA	NA	NA	HD ICS/LABA + as-needed SABA (0.55)	NA	NA

SUCRA values are reported in brackets. ACQ: asthma control questionnaire; FEV_1: forced expiratory volume in 1 second; HD: high-dose; ICS: inhaled corticosteroid; LABA, long-acting β_2-agonist; LD: low-dose; MD: medium-dose; NA: not available; PEF: peak expiratory flow; SABA: short-acting β_2-agonist; SAEs: serious adverse events; SMART: single maintenance and reliever therapy (known as SMART or MART - for simplicity SMART is used in the Table); SUCRA: surface under the cumulative ranking curve analysis.

Supplementary Figures

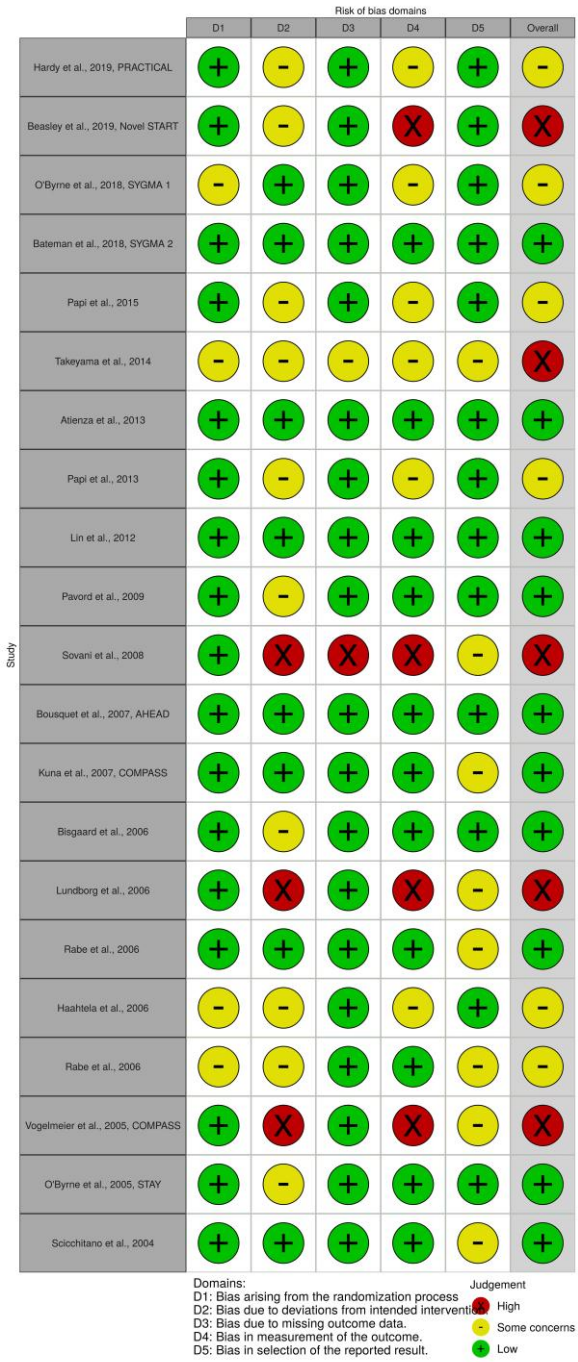


Figure S1. Traffic light plot for assessment of the risk of bias of each included RCT via the Cochrane RoB 2 tool. D1: bias arising from the randomization process; D2: bias due to deviations from intended intervention; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result; RCT: randomized controlled trial; RoB: risk of bias; robvis: risk of bias visualization tool. Red circle indicates high risk of bias, yellow circle indicates some concerns on the risk of bias, and green circle represents low risk of bias.

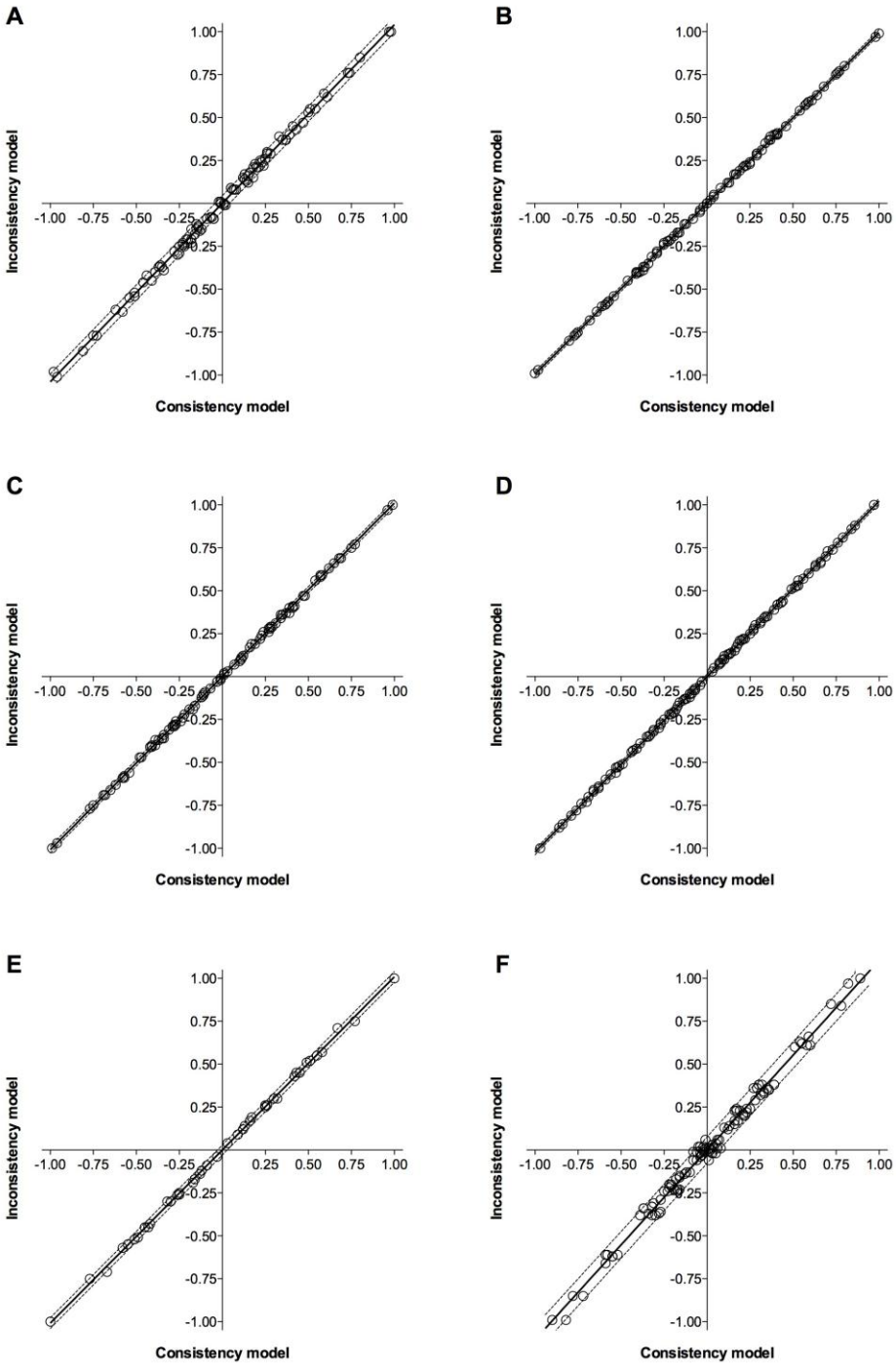


Figure S2. Publication bias assessment via the normalized consistency/inconsistency plot (linear regression and 95% prediction bands) of different as-needed therapies in patients with asthma with respect to the risk of severe asthma exacerbation (A), change from baseline in morning PEF (B), evening PEF (C), FEV_1 (D), ACQ (E), and SAEs (F). ACQ: asthma control questionnaire; FEV_1: forced expiratory volume in 1 s; PEF: peak expiratory flow; SAEs: serious adverse events.

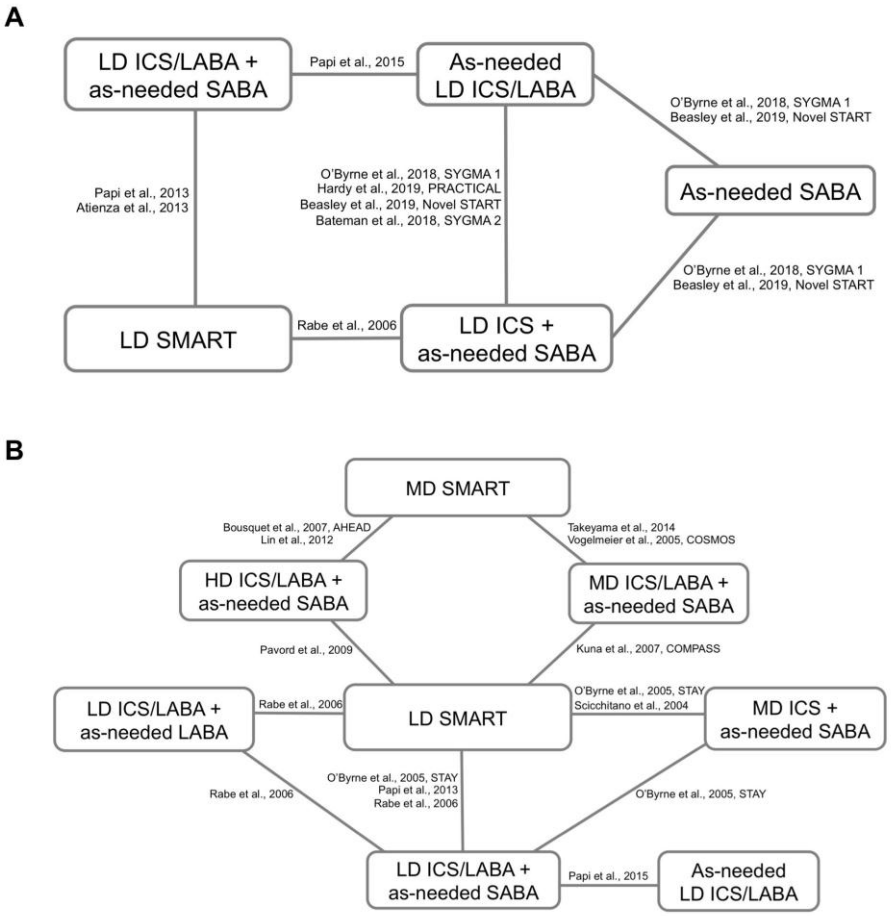


Figure S3. Network diagram displaying treatments in adult patients with mild to moderate (A) and moderate to severe (B) asthma. HD, high-dose; ICS, inhaled corticosteroid; LABA: long-acting β_2-agonist; LD: low-dose; MD: medium-dose; SABA: short-acting β_2-agonist; SMART: single maintenance and reliever therapy (known as SMART or MART - for simplicity SMART is used in the Table).

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Appendix

Appendix 1. Summary text of the identified records.

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