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Systematic review on inhaled corticosteroid monotherapy and its efficacy and safety in long-term treatment of patients with chronic obstructive pulmonary disease (COPD)

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Abstract

Aim: Chronic obstructive pulmonary disease (COPD) is a leading cause of chronic morbidity and mortality throughout the world. Pharmacologic therapy of stable COPD is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and improve exercise tolerance, correlating disease severity. Bronchodilators (beta2-sympathomimetics and anticholinergics) are the mainstay of current drug therapy. Theophylline and derivates are effective in long-term treatment but are judged to be third-line drugs because of their low therapeutic index and several interactions. Continuous therapy with inhaled corticosteroids in COPD is controversially discussed. The aim of this systematic review is to assess the efficacy and safety of inhaled corticosteroids compared to placebo for the long-term treatment of COPD.

Methods: We searched the databases MEDLINE, EMBASE and Cochrane Library. Two reviewers independently scanned titles and abstracts and decided about the eligibility of articles identified by our search regarding preestablished inclusion criteria. Data from eligible articles were extracted followed by a qualitative synthesis of information. We assessed the quality of included trials according the criteria of the German Institute for Quality and Efficiency in Health Care (IQWiG).

Results: Our systematic literature search identified 17 studies. For the total rate of exacerbations only two out of ten studies showed a statistically significant difference in favour of corticosteroid treatment; analyses of oral corticosteroid-treated episodes showed statistically significant differences in favour of the active treatment in all studies. Concerning mortality and fatality no differences between groups could be ascertained. One study demonstrated a higher risk of developing pneumonia after fluticasone treatment than after placebo ($p<0,001$); other differences between the groups regarding adverse events were without clinical relevance. The methodological quality of publications was mostly low generally due to missing information, and therefore the validity of evidence must be questioned.

Conclusions: There are indications of an advantage for the corticosteroid treatment in patients with COPD, but taking into consideration the methodological flaws with high potential of bias the validity of the results has to be considered limited.

Key words: chronic obstructive pulmonary disease, COPD, corticosteroids, systematic review

Zusammenfassung

Ziel: Die chronisch obstruktive Lungenerkrankung (COPD) ist weltweit eine der Hauptursachen chronischer Morbidität und Mortalität. Die medikamentöse Therapie der stabilen COPD dient der Verhinderung und Kontrolle von Symptomen, der Reduktion von Häufigkeit und Schwere von Exazerbationen sowie der Verbesserung des Gesundheitszustands. Bronchodilatatoren (Beta2-Sympathomimetika und Anticholinergika) gehören in der Behandlung der COPD zur Standardtherapie. Theophyllin und Derivate sind in der Langzeittherapie der COPD effektiv, werden aber wegen der geringen therapeutischen Breite und zahlreicher Interaktionen als Bronchodilatatoren der dritten Wahl empfohlen.

Eine Dauerbehandlung mit inhalativ verabreichten Kortikosteroiden ist bei der COPD umstritten. Ziel des vorliegenden systematischen Reviews ist die Überprüfung der Wirksamkeit und Verträglichkeit von inhalativen Kortikosteroiden im Vergleich zu Placebo in der Langzeit-Therapie der COPD.

Methoden: Eine Literaturrecherche wurde in den Datenbanken MEDLINE, EMBASE und Cochrane Library durchgeführt. Die Auswahl der Artikel erfolgte anhand von Titel und Abstract durch zwei unabhängige Wissenschaftler mittels a priori festgelegter Einschlusskriterien. Die Daten entsprechender Publikationen wurden extrahiert und eine qualitative Informationssynthese wurde gebildet. Eine Qualitätsbewertung der eingeschlossenen Publikationen erfolgte anhand der und gemäß den Kriterien des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).

Ergebnisse: Durch die systematische Literaturrecherche wurden 17 relevante Studien identifiziert. In der Reduktion der Gesamtrate von Exazerbationen zeigte sich nur in zwei von zehn Studien ein Vorteil für eine inhalative Kortikosteroid-Behandlung. Hinsichtlich der Häufigkeit von Episoden mit oraler Gabe von Kortikosteroiden waren die Gruppenunterschiede in allen Studien zugunsten der Kortikosteroid-Behandlung statistisch signifikant. Für die Parameter Mortalität und Letalität konnten keine Gruppenunterschiede festgestellt werden. In einer Studie war das Risiko, eine Pneumonie zu entwickeln, in der Kortikosteroid-Gruppe größer ($p<0,001$) als in der Placebo-Gruppe; andere Gruppenunterschiede im Auftreten unerwünschter Ereignisse waren klinisch nicht relevant. Die methodische Qualität der Publikationen war überwiegend gering, sodass die Validität der Aussagen in Frage gestellt werden muss.

Schlussfolgerung: Es gibt Hinweise auf einen Vorteil zugunsten einer Kortikosteroid-Behandlung bei Patienten mit COPD, allerdings schränkt die mangelhafte Qualität der Publikationen mit hohem Verzerrungspotential die Aussagekraft der Ergebnisse ein.

Schlüsselwörter: chronisch obstruktive Lungenerkrankung, COPD, Kortikosteroid, systematischer Review

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of chronic morbidity and mortality throughout the world. COPD is the fourth leading cause of death in the world, and further increases in its prevalence and mortality can be predicted in the coming decades because smoking frequencies rise and the population ages [1,2]. The disease is characterised by a progressive, not fully reversible or partly reversible airflow obstruction based on chronic bronchitis with cough and sputum production or emphysema. The major risk factor for the development of COPD is cigarette smoking, and the most efficacious therapy and sole possibility for decelerating the progression of the disease consists in risk reduction, particularly in stopping tobacco smoking. Pharmacologic therapy of stable COPD is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and improve exercise tolerance, correlating disease severity. Bronchodilators (beta2-sympathomimetics, anticholinergics) are the mainstay of current drug therapy. Theophylline and derivates are effective in long-term treatment but are judged to be third-line drugs because of their low therapeutic index and several interactions [3]. Continuous therapy with inhaled corticosteroids in COPD is controversially discussed: in contrast to the eosinophilic inflammation in asthma bronchiale responding to corticosteroids, patients with COPD show an infiltration of bronchial tissue with neutrophilic granulocytes responding less clear to corticosteroids [4]. Many trials have shown that ICS improve symptoms and decrease the number of exacerbations [5] on the other hand ICS could not demonstrate influence in decline of forced expiratory volume in one second [6]. Therefore, recommendations on pharmacological management are different. The aim of this systematic review was to assess the efficacy and safety of inhaled corticosteroids (ICS) compared to placebo by patient-relevant outcome parameters.

2. Methods

We searched the databases MEDLINE, EMBASE and Cochrane Library (in october 2008) using the keywords „chronic obstructive lung disease“, „bronchodilating agent“, „budesonide“, „fluticasone“, „beclomethasone“, „mometasone“ und „ciclesonide“. We limited the electronic searches to „human” and „English Language”. Websites of health technology assessment (HTA) agencies and medical societies, bibliographies of included papers, and systematic and not systematic reviews were also screened to capture literature relevant to the scope of our topic.

Two reviewers independently scanned titles and abstracts and decided about the eligibility of articles identified by our search. Preestablished inclusion criteria were (1) studies with patients who had received a diagnosis COPD, (2) trials that assigned patients to ICS versus ICS or ICS versus placebo, (3) trials of at least 3 months' duration and (4) number of patients per treatment arm >10. We excluded abstract publications only and publications of the same study without additional information.

We extracted data from eligible articles regarding the outcome parameters exacerbations, mortality, fatality, adverse events, using standardised documentation sheets generating synthesis of information with regards to quality. We assessed the quality of included trials according the criteria of the German Institute for Quality and Efficiency in Health Care (IQWiG). Therefore an adequate concealment and an adequate intention to treat analysis are the most important aspects as well as randomisation, blinding, sample size calculation and withdrawals. Health related quality of life and lung function were not analysed.

3. Results

Overall, 1415 citations were identified, from which 21 fulfilled the inclusion criteria and were enclosed in the analysis (Fig. 1). Our literature search identified 17 double blind randomised controlled trials with data from 21 publications determining the efficacy and safety of an inhaled corticosteroid (ICS) compared with placebo in patients with COPD. Table 1 describes the included studies. Seven studies focused on fixed combination therapies with budesonide/formoterol or salmeterol/fluticasone compared to the single substances and placebo [7], [8], [9], [10], [11], [12]. With exception of the study by Renkema 1996 [13], investigating in addition an ICS combined with prednisolone, all other studies were comparing only two therapies. Thompson et al. 2002 [14] used a crossover design whereas the other studies had a parallel group design (Table 1)

3.1. Quality of publications included

The methodological quality of studies was assessed using informations from publications available. Except for Calverley et al. 2007 [10], Paggiaro et al. 1998 [15], Vestbo et al. 1999 [16], all publications showed gross deficiencies. The procedure of randomisation was not described by Calverley et al. 2003a [7], Hanania et al. 2003 [11], Mahler et al. 2002 [12], Pauwels et al. 1999 [17], Senderovitz et al. 1999 [18], Szafranski et al. 2003 [8], Verhoeven et al. 2002 [19] und Weir et al. 1999, [20] and details concerning adequate concealment of treatment allocation were only presented by Borbeau et al. 1998 [21] and Paggiaro et al. 1998 [15]- for hiding informations sealed envelopes were used. Sample size calculation is not adequately presented by Calverley et al. 2007 [10], Hanania et al. 2003 [11], Mahler et al. 2002 [12], Pauwels et al. 1999 [17], Renkema et al. 1996 [13], Thompson et al. 2002 [14], Verhoeven et al. 2002 [19] and Weir et al. 1999 [20] either completely missing or missing details (e.g. not mentioning level of significance) so that reproducing the sample size calculation is impossible. The number of withdrawals is appropriately given by all publications but Hanania et al. 2003 [11] not stratifying the reasons for discontinuations according to treatment arms. Lack of information about all reasons for withdrawal was given by Hanania et al. 2003 [11], Mahler et al. 2002 [12], Renkema et al. 1996 [13], Senderovitz et al. 1999 [18], Szafranski et al. 2003 [8] and

Weir et al. 1999 [20]. Remarkable in Szafranski et al. 2003 [8] are 102 patients withdrawn (13%) without information about causes.

All studies with patients of mean COPD disease stage III, classified as a result of baseline lung function measurements (FEV_1 % predicted) and according to GOLD [1], [21], [22], [7], [9], [11], [12], [8], [20], showed high withdrawal rates from 25 bis 53% after placebo and rates from 8 to 44% after corticosteroids making systematic bias (attrition bias) possible and resulting in potential distortion of the outcomes. Also among the studies with participants of lower disease severity the withdrawal rates in Pauwels et al. 1999 [17], Renkema et al. 1996 [13], Vestbo et al. 1999 [16] und Paggiaro et al. 1998 [15] from 19-35% after placebo and 9-26% after corticosteroids lead to suppose attrition bias; in Thompson et al. 2002 [14] and Senderovitz et al. 1999 [18] specifications of disease severity are missing, withdrawal rates are only given in total with 31 und 27%. In the publication of Calverley et al. 2003a [17] the authors themselves are discussing that systematic bias due to high withdrawal rates leads to a lower number of exacerbations and that to some extent this bias applies to lung function and HRQL differences as well, probably underestimating the reduction in exacerbations concerning the treatment with budesonide/formoterol compared to placebo. Following the intention to treat principle is adequately described only by Calverley et al. 2007 [10] picturing the method of taking into account data from patients withdrawn prematurely. In conclusion and owing to description above the quality of publications by Vestbo 1999 [16], Calverley 2007 [10] und Paggiaro 1998 [15] is assessed as with low deficiencies and all others as with gross deficiencies (Table 2).

3.2. Exacerbations

Ten studies were comparable with regard to the definition of exacerbation [7], [13], [8], [22], [9], [10], [11], [15], [14], [23]. From these studies only Burge et al. 2000 [22] and Calverley et al. 2003b [9] found statistically significant differences between treatment arms in favour of the inhaled corticosteroids compared to placebo treatment. Time to first exacerbation was analysed in four of these studies [7], [22], [11], [23], but only the results of van der Valk et al. 2002 [23] showed an advantage for ICS with statistically significant differences which must be interpreted cautiously because the authors did not mention the methods of calculation for this parameter in the statistical analysis section and do not give a p-value, so we only have a wide confidence interval with no precise estimation. Five of these studies [7], [8], [22], [9], [10] investigated exacerbations being treated with oral corticosteroids. All differences between the two groups were statistically significant and in favour of corticosteroids (Table 3, 4, 5).

3.3. Mortality/fatality

Only Calverley et al. 2007 [10] analysed mortality and fatality with stochastic methods. Neither for all cause mortality nor for fatality statistically significant differences between the two groups could be found (Table 6).

3.4. Adverse Events

The frequency of adverse events and withdrawals was mostly outlined in publications in a descriptive way. In studies lasting less than one year [21], [18], [11], [12], [15], [14], [13], 19] no statistically significant differences were found with exception of Paggiaro et al. 1998 [15] and Verhoeven et al. 2002 [19]. Paggiaro et al. 1998 [15] noticed a lower plasma cortisol concentration after ICS compared to placebo ($p=0,024$) but the authors stated that it was not associated with any clinical relevance. In the study of Verhoeven et al. 2002 [19] adverse events relating to airways disease and/or study medication were reported more often by patients in the placebo group ($p=0,02$).

In the publications of studies with duration of one year [7], [8], [9] statistically significant differences in the frequency of withdrawals were described. The patients in Calverley et al. 2003a [7] showed significantly more withdrawal due to COPD deterioration after placebo ($p=0,031$), and the total number of withdrawals was higher after placebo ($p=0,007$) in Calverley et al. 2003b [9]. Szafranski et al. 2003 [8] detected a higher number of withdrawals due to COPD deterioration after placebo ($p<0,05$) as well as a higher total number ($p<0,05$).

Among publications about studies lasting three years [22], [10], [17], [16]) Burge et al. 2000 [22],Calverley et al. 2007 [10] and Vestbo et al. 1999 [16] described statistically significant differences between groups in the frequency of withdrawals or adverse events. Burge et al. 2000 [22] stated that more patients in the placebo group than in the corticosteroid group withdrew because of respiratory disease that was not associated with malignancy ($p=0,034$). Mean cortisol concentrations decreased with corticosteroids and increased with placebo ($p\leq0,032$). According to the authors no decreases were associated with any signs or symptoms of hypoadrenalism or other clinical effects. The probability of having pneumonia was found by Calverley et al. 2007 [10] as being higher after corticosteroids than after placebo ($p<0,001$) and the patients of the placebo group in the study of Vestbo et al. 1999 [16] showed a greater frequency of adverse events than the patients of the corticosteroid group ($p=0,01$). None of the publications demonstrated statistically significant differences concerning serious systemic side effects e.g. osteoporosis, glaucoma or cataract (Table 7, 8, 9).

4. Discussion

The aim of this review was to evaluate the safety and efficacy of ICS monotherapy in the long-term treatment of patients with COPD that is a matter of ongoing debate.

We found little evidence that ICS minimize the total exacerbation rates and strong evidence that ICS reduce exacerbation rates requiring treatment with oral corticosteroids. Concerning mortality, fatality and adverse events no group differences could be found with exception of a higher risk of developing pneumonia after fluticasone treatment.

There are certain limitations with the present systematic review. Our literature search identified only randomised controlled trials and studies comparing the ICS budesonide, fluticasone and beclomethasone with placebo; studies testing different ICS against each other and other types of studies couldn't be found. For identifying all relevant publications we used a highly sensitive search strategy in all relevant data bases followed by hand searches, and internet resources were investigated. Nevertheless a systematic error due to incomplete and inadequate reporting (publication bias) cannot be excluded. As in any systematic review, publication bias possibly leads to overestimation of the associations of ICS treatment with favourable outcomes in COPD.

The quality of studies assessed by informations available from publications and according to IQWiG criteria was very low with exception of Vestbo et al. 1999 [16], Calverley et al. 2007 [10] and Paggiaro et al. 1998 [15], therefore conducting meta-analyses and analyses of sensitivity did not seem useful. The assessment of study quality in this review is more rigorous as by Yang et al. 2008 [24] and Drummond et al. 2008 [25]. The distinctions are based on a much more differenciated judgement of study quality according IQWiG standards. While calculating a Jadad-Score Yang et al. 2008 [24] and Drummond et al. 2008 [25] only took into account randomisation, blinding and drop outs, and one of the most important potential biases in randomised trials, namely allocation concealment [26], was not considered. The criteria used in this review can also gather and assess the quality of study planning and data analysis and the representation of the precision of results judged on the information available from publications. In the systematic review of Singh et al. 2009 [27] the authors used the Cochrane Toolkit [26] for the assessment of bias in evaluating each trial for the reporting of sequence generation, allocation concealment, the use of blinding of participants and personnel, and information on loss to follow up. Concerning the reporting of randomisation sequence generation, blinding and the reporting of patients lost to follow-up there are no appraisal differences between the present review and that of Singh et al. 2009 [27]. However the assessments of the adequacy of allocation concealment differ from each other, with less strictly consequences in the review of Singh et al. 2009 [27]. In the Cochrane Toolkit the criteria for the judgement of „No" include the use of an open random allocation schedule likewise described by Calverley et al. 2003b [9] using a list of patient numbers and a list of treatment numbers and by Burge et al. 2000 [22] using a list with treatment numbers, so we assessed the allocation concealment with „not adequate" because of the unconcealed information. Vestbo et al. 1999 [16] described an allocation of study numbers in a

consecutive order but also without information about hiding, and van der Valk et al. 2002 [23] and Calverley 2007 [10] did not report any detail about the allocation concealment only about the generation of allocation sequence, therefore we judged the concealment in each case with „No". The differences between the assessement of Singh et al. 2009 [27] and the present review regarding the concealment of allocation cannot be solved here, therefore the uncertainty about the concealment possibly resulting in biases will remain.

Seven studies included comparisons of several groups [7], [8], [9], [10], [11], [12], 13] but with exception of Calverley 2007 [10] no information is given about the methods of adjustment for multiple testing therefore details on statistically significant differences remain questionable.

Basically placebo comparisons are hiding methodological weakness in the study design: high dropout rates in patients with severe disease especially in placebo-groups lead to attrition bias [28], [29] being considered and acknowledged in some studies [7], [9] by adjusting sample size calculations for a certain dropout rate. This bias creates a causal chain of confounding as the dropout of severely ill patients leads to a lower number of exacerbations simultaneously minimizing the frequency of hospitalizations, lung function is better and the correlation with quality of life is positively affected [30], [31]; in general these drop-outs lead to a healthier study population producing an overestimation of the effects.

One further bias (selection bias) rises already at recruitment of patients for trials with placebo groups because severely ill patients in particular must fear being randomised to a placebo group and don't take the risk of frequent exacerbations associated with higher mortality.

In 10 studies with comparable definition of an exacerbation only Burge et al. 2000 [22] and Calverley et al. 2003b [9] detected a statistically significant difference in favour of the corticosteroid treatment in total rate of exacerbations. In time to first exacerbation only one of four studies [23] found a statistically significant difference with advantage to corticosteroids. Analyses of oral corticosteroid-treated episodes showed statistically significant differences in favour of the corticosteroids in all five studies investigating this outcome. As mentioned above the results are possibly skewed by an attrition bias because the dropout rates in the appropriate trials were very high. In summary there is some evidence for efficacy of steroid treatment in the reduction of exacerbations only the frequency of episodes with oral corticosteroids decreases.Fatality and mortality were solely in one study [10] a priori defined outcomes, no statistically significant differences between the groups were found. With exception of Calverley et al. 2007 [10] adverse events were only analysed descriptively, and apart from known non systemic corticosteroid-related events the authors stated that the frequency of adverse events was similar in the two treatment groups. Calverley et al. 2007 [10] reported a higher risk of having pneumonia for patients with fluticasone treatment (18,3%) versus patients in the placebo group (12,3%), the difference was statistically significant ($p<0,001$). This is actually important because pneumonia in elderly people frequently leads to hospitalizations [28].

Conclusion

There are indications of an advantage for the inhaled corticosteroid monotherapy in long-term treatment of patients with COPD regarding reduced rates of exacerbations with episodes of oral corticosteroids. But taking into consideration the methodological flaws with high potential of bias, in the main by not mentioning or inadequate allocation concealment and high drop-out rates, the validity of the results has to be considered limited.

Abbreviations used

AE adverse events, COPD chronic obstructive pulmonary disease, CCLS Copenhagen City Lung Study, EUROSCOP European Respiratory Society on chronic obstructive pulmonary disease, FEV1 forced expiratory volume in one second, HR hazard ratio, HRQL health- related quality of life, HTA health technology assessment, ICS inhaled corticosteroids, IQWIG institute for quality and efficiency in health care, ISOLDE the Inhaled Steroids in Obstructive Lung Disease in Europe, ITT intention to treat, ns not stated, RR relative risk, SAE serious adverse events, TORCH Towards a Revolution in COPD Health, TRISTAN Trial of Inhaled Steroids and long acting beta agonists

Conflicts of interest

None declared.

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Figure 1. Flowchart on selection of publications included

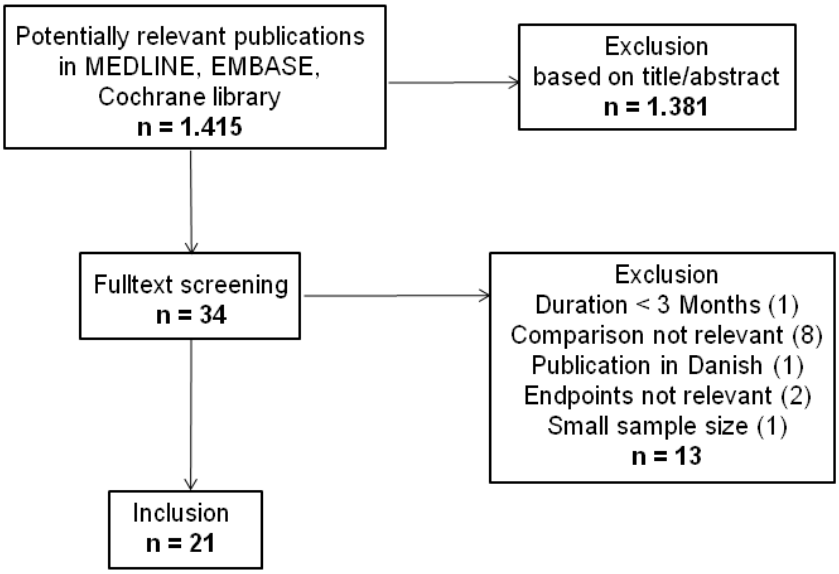

Table 1 Patient demographic characteristics, study duration, dosing

Study	N ICS	N Control	Age ICS[a]	Age Control[a]	Duration	Dosing
Budesonide vs. Placebo						
Bourbeau 1998 [21]	39	40	66 (8)	66 (8)	6 M	2x 400 µg bid
Calverley 2003a [7]	257	256	64 (41-85)[b]	65 (43-85)[b]	1 Y	2x 200 µg bid
Pauwels 1999 EUROSCOP [17]	634	643	52,5 (7,5)	52,4 (7,7)	3 Y	1x 400 µg bid
Renkema 1996 [13]	21	18	56 (8)	54 (10)	2 Y	1x 800 µg bid
Senderovitz 1999 [18]	37[c]	--	58,5 (51-74)[d]	62,5 (57-74)[d]	6 M	1x 400 µg bid
Szafranski 2003 [8]	198	205	64 (40-90)[b]	65 (47-92)[b]	1 Y	2x 200 µg bid
Vestbo 1999 CCLS [16]	145	145	59,0 (8,3)	59,1 (9,7)	3 Y	1x 800 µg/1x 400 µg[e]
Fluticasone vs. Placebo						
Burge 2000 ISOLDE [22]	376	375	63,7 (7,1)	63,8 (7,1)	3 Y	1x 500 µg bid
Calverley 2003b TRISTAN [9]	374	361	63,5 (8,5)	63,4 (8,6)	1 Y	1x 500 µg bid
Calverley 2007 TORCH [10]	1534	1524	65,0 (8,4)	65, 0 (8,2)	3 Y	1x 500 µg bid
Hanania 2003 [11]	183	185	63 (40-84)[b]	65 (40-81) [b]	6 M	1x 250 µg bid
Mahler 2002 [12]	168	181	64,4 (42-82)[b]	64,0 (44-90)[b]	6 M	1x 500 µg bid
Paggiaro 1998 [15]	142	139	62 (49-75)[b]	64 (50-75)[b]	6 M	2x 250 µg bid
Thompson 2002 [14]	52	--[f]	69 (48-80)[d]	--[f]	6 M	2x 220 µg bid
van der Valk 2002 [23]	123	121	64,1 (6,8)	64,0 (7,7)	6 M	1x 500 µg bid
Verhoeven 2002 [19]	10	13	54 (42-65)[b]	56 (42-67)[b]	6 M	1x 500 µg bid
Beclomethasone vs. Placebo						
Weir 1999 [20]	49	49	65,5 (1,0)	67,6 (1,0)	2 Y	4x 250 µg bid[g]

a data are presented as mean with standard deviation in parentheses
b data are presented as mean with range in parentheses
c only data for the whole study population are presented
d data are presented as median with range in parentheses
e morning/evening for 6 M, afterwards 1x 400 µg bid
f crossover design
g 3x 250 µg bid for patients weighing < 50 kg
bid: two times daily, CCLS: Copenhagen City Lung Study, EUROSCOP: European Respiratory Society on chronic obstructive pulmonary disease, ISOLDE: the Inhaled Steroids in Obstructive Lung Disease in Europe, M: Months, TORCH: TOwards a Revolution in COPD Health, TRISTAN: Trial of Inhaled STeroids ANd long acting beta agonists, Y: Year(s)

Table 2 Publication quality

Study	Randomisation[a]/ Concealment[b]	Blinding[c]	Sample size calculation[d]	Drop-Outs/Reasons given	Adequate ITT-Analysis[e]	Publication quality[f]
Budesonide vs. Placebo						
Bourbeau 1998 [21]	yes/unclear	yes	adequate	yes/yes	no	gross deficiencies
Calverley 2003a [7]	unclear/no	yes	adequate	yes/yes	unclear	gross deficiencies
Pauwels 1999 [17]	unclear/no	yes	inadequate	yes/yes	unclear	gross deficiencies
Renkema 1996 [13]	yes/no	yes	no	yes/partial	no	gross deficiencies
Senderovitz 1999 [18]	unclear/no	yes	adequate	yes/partial	no	gross deficiencies
Szafranski 2003 [8]	unclear/no	yes	adequate	yes/partial	unclear	gross deficiencies
Vestbo 1999 [16]	yes/no	yes	adequate	yes/yes	unclear	low deficiencies
Fluticasone vs. Placebo						
Burge 2000 [22]	yes/no	yes	adequate	yes/yes	no	gross deficiencies
Calverley 2003b [9]	yes/no	yes	adequate	yes/yes	unclear	gross deficiencies
Calverley 2007 [10]	yes/no	yes	unclear	yes/yes	yes	low deficiencies
Hanania 2003 [11]	unclear/no	yes	inadequate	yes/partial	no	gross deficiencies
Mahler 2002 [12]	unclear/no	yes	inadequate	yes/partial	no	gross deficiencies
Paggiaro 1998 [15]	yes/unclear	yes	adequate	yes/yes	unclear	low deficiencies
Thompson 2002 [14]	yes/no	yes	no	yes/yes	not relevant[g]	gross deficiencies
van der Valk 2002 [23]	yes/no	yes	adequate	yes/yes	no	gross deficiencies
Verhoeven 2002 [19]	unclear/no	yes	no	not relevant[h]	no	gross deficiencies
Beclomethasone vs. Placebo						
Weir 1999 [20]	unclear/no	yes	inadequate	yes/partial	no	gross deficiencies

a unclear: randomisation only mentioned, method not specified
b no: allocation concealment not mentioned or not adequate, unclear: sealed envelopes used, opaqueness not mentioned (or vice versa), yes: sealed and opaque envelopes used or other adequate method e.g. central telephone randomisation
c double blind def. by Schultz et al. 2002 [32]
d adequate: endpoint, magnitude of expected effect, power, significance level and calculated sample size are stated, inadequate: parts of an adequate sample size calculation are missing, no: sample size calculation is not mentioned
e unclear: method not specified, ITT-population not clearly identifiable, no: missing considerations about drop-outs
f no identifiable deficiencies = unimportant deficiencies, low deficiencies = the overall message of the study must not be called into question, gross deficiencies = the overall message of the study must be called into question
g crossover design
h no drop-outs

Table 3 Exacerbations budesonide vs. placebo

Study	Outcomes	ICS	Placebo	Group difference [95% CI], p-value
Budesonide vs. Placebo				
Calverley 2003a [7]	Definition: need for medical intervention with oral antibiotics and/or corticosteroids or hospitalisation			
	Exacerbations/patient/year	1,60	1,80	ns, p= 0,308
	Time to first exacerbation (days)[a]	178	96	ns, p= 0,512
	Exacerbations/patient/year requiring oral corticosteroids	0,87	1,14	ns, p= 0,044
Renkema 1996 [13]	Definition: conditions with increased complaints of dyspnea and/or cough and/or sputum production with or without fever; treatment with oral corticosteroids, if necessary in combination with antibiotics			
	Exacerbations/year[a]			
	- prestudy year	1 (0-6)	2 (0-3)	ns
	- study year 1	2 (0-7)	2 (0-5)	ns
	- study year 2	1 (0-4)	2,5 (0-5)	ns
	Exacerbation days study year year [a]			
	- prestudy year	14 (0-84)	14 (0-42)	ns
	- study year 1	14 (0-46)	14 (0-54)	ns
	- study year 2	10 (0-45)	16 (0-87)	ns
Senderovitz 1999 [18]	ns			
	Exacerbations	ns	ns	ns, p > 0,04
Szafranski 2003 [8]	Definition: use of oral steroids and/or antibiotics and/or hospitalisation			
	Exacerbations/patient/year	1,59	1,87	0,852 [-10,3; 34,1], p= 0,224
	mild exacerbations	ns	ns	[ns], p< 0,001[b]
	Exacerbations/patient/year requiring oral corticosteroids	0,76	1,07	[ns], p= 0,045
Vestbo 1999 [16]	Definition: affirmative answer to the question „Have you since your last visit experienced more cough and phlegm than usual?“			
	Number of exacerbations[c]	155	161	ns, not significant [d]

no outcome parameter in Bourbeau 1998 [21], Pauwels 1999 [17], Verhoeven 2002 [19]
a data are presented as median with range in parentheses
b in favour of ICS
c absolute values
d the expression „the difference was not significant“ does not explain whether the clinical or the statistical difference is meant
ns: not stated

Table 4 Exacerbations fluticasone vs. placebo

Study	Outcomes	ICS	Placebo	Group difference [95% CI], p-value
Fluticasone vs. Placebo				
Burge 2000 [22]	Definition: worsening of respiratory symptoms that required treatment with oral corticosteroids, or antibiotics, or both			
	Exacerbations/year[a]	1,43 (1,93)	1,90 (2,63)	
	Exacerbations/year[b]	0,99 (0-26)	1,32 (0-30)	-0,3 [-0,4; 0,0], p= 0,026 [c]
	Time to first exacerbation (days)[b, d]	136	164	ns [0,79; 1,09], p= 0,35
	Exacerbations/year			
	Patients with FEV_1 < 50% predicted[b, d]	1,47	1,75	ns [ns], p< 0,022
	Patients mit FEV_1 ≥ 50% predicted[b, d]	0,67	0,92	ns [ns], p= 0,45
	Exacerbations/patient/year			
	requiring oral corticosteroids[d]	ns	ns	ns [ns], p< 0,001[e]
Calverley 2003b [9]	Definition: worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids or both			
	Exacerbations/patient/year[a]	1,05	1,30	ns, p=0,003
	Exacerbations/patient/year			
	requiring oral corticosteroids[a]	0,50	0,76	ns, p= 0,0001
Calverley 2007 [10]	Definition: symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these			
	Exacerbations/year			
	moderate or severe	0,93	1,13	0,82 [0,76; 0,89], p<0,001
	requiring systemic corticosteroids	0,52	0,80	0,65 [0,58; 0,73], p<0,001
	severe (requiring hospitalization)	0,17	0,19	0,88 [0,74; 1,03], p=0,10
Hanania 2003 [11]	Definition: moderate exacerbations requiring treatment with antibiotics and/or corticosteroids, and severe exacerbations requiring hospitalization			
	Exacerbations	ns	ns	ns, not significant[f]
	Time to first exacerbation	ns	ns	ns, not significant[f]
Mahler 2002 [12]	Defined by treatment			
	Exacerbations	ns	ns	ns
	Time to first exacerbation	ns	ns	not statistically significant
Paggiaro 1998 [15]	Definition: worsening of COPD symptoms, requiring changes to normal treatment, including antimicrobial therapy, short courses of oral steroids, and other bronchodilator therapy			
	Exacerbations/patient in total	76/45	111/51	ns [-0,43; -0,1], p=0,067
	- moderate or severe/patient	27/45	44/51	ns. [ns], p< 0,001
	- mild/patient	17/45	7/51	ns. [ns], p< 0,001
Thompson 2002 [14]	Definition: subjective worsening of chronic baseline dyspnea or cough, accompanied by at least a 25% increase in inhaled bronchodilator use and deemed severe enough by the primary care physician to require treatment with systemic corticosteroids			
	Number of patients ≥ 1 exacerbation	4	10	ns [ns], p= 0,11
van der Valk 2002 [23]	Definition: worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids or antibiotics as judged by the study physician			
	Patients ≥ 1 exacerbation	58	69	ns
	First exacerbation			HR 1,5 [1,05; 2,1], ns
	Time to first exacerbation (days)[a]	75,2	42,7	34,6 [15,4; 53,8], ns
	Second exacerbation			HR 2,4 [1,5; 3,9], ns
	Patients (%) with rapid recurrent exacerbations	6 (4,9)	26 (21,5)	RR 4,4 [1,9; 10,3], ns

no outcome parameter in Verhoeven et al. 2002 [19]
a data are presented as mean with standard deviation in parentheses
b data are presented as median with range in parentheses
c p-value of test statistic from the non parametric test, separate calculation of the CI
d publication Jones et al. 2003 [33]
e in favour of ICS
f the expression „the difference was not significant" does not explain whether the clinical or the statistical difference is meant
FEV_1 : forced exspiratory volume in one second, HR: hazard ratio, ns: not stated, RR: relative risk

Table 5 Exacerbations beclomethasone vs. placebo

Study	Outcomes	ICS	Placebo	Group difference [95% CI], p-value
Beclomethasone vs. Placebo				
Weir 1999 [20]	ns			
	Exacerbations/year[a]	0,36 (0,09)	0,57 (0,13)	ns, not statistically significant
a data are presented as mean with standard error of the mean in parentheses ns: not stated				

Table 6 Mortality and fatality

Study	Outcomes	Fluticasone	Placebo	Group difference [95% CI], p-value
Fluticasone vs. Placebo				
Calverley 2007 [10]	death from any cause (%)	246 (16,0)	231 (15,2)	HR 1,060 [0,886; 1,268] p = 0,53
	COPD related deaths (%)	106 (6,9)	91 (6,0)	HR 1,16 [0,88; 1,53] p = 0,30
	cause of death			
	- cardiovaskular (%)	61 (4)	71 (5)	ns
	- pulmonary (%)	91 (6)	74 (5)	
	- cancer (%)	51 (3)	45 (3)	
	- other (%)	30 (2)	23 (2)	
	- unknown (%)	13 (1)	18 (1)	
HR: hazard ratio, ns: not stated				

Table 7 Adverse events budesonide vs. placebo

Study	Drop-Outs*	AE total ≥ 1	Number SAE	Drop-out due to AE/ deaths
Budesonide vs. Placebo				
Bourbeau 1998 [21]				
Budesonide N=39	3 (8)[a]	(59)	ns	1/ns
Placebo N=40	10 (25)[a]	(70)	ns	3/ns
Calverley 2003a [7]				
Budesonide N=257	102[b] (40)	149	88	67/6
Placebo N=256	106 (41)	136	66	71/5
Pauwels 1999 [17]				
Budesonide N=634	176 (28)[a]	ns	177	70/8
Placebo N=643	189 (29)[a]	ns	161	62/10
Renkema 1999 [13]				
Budesonide N=21	2 (10)[a]	ns	ns	0[c]/ns
Placebo N=18	5 (28)[a]	ns	ns	5/ns
Senderovitz 1999[d] [18]				
total N= 37	10 (27)[a]	ns	ns	ns/ns
Szafranski 2003 [8]				
Budesonide N=198	62[e] (31)	ns	35	36/5
Placebo N=205	90 (44)	ns	37	60/9
Vestbo 1999 [16]				
Budesonide N=145	36 (25)[a]	ns.	14[f]	16/4
Placebo N=145	51 (35)[a]	ns	41	17/5

All data are presented as N (%) if possible

* Drop-Outs: including every discontinuation of the study (withdrawal, drop-out and loss to follow-up)
a procentual value by own calculation
b significantly fewer Drop-outs due to COPD worsening in the ICS-group (p=0,031)
c statistically significant difference (p=0,036)
d no differentiated presentation given
e fewer drop-outs due to COPD worsening and all-in rate of drop-outs in ICS-group (p<0,05 each)
f statistically significant difference (p=0,01)
AE: adverse events, ns: not stated, SAE: serious adverse events

Table 8 Adverse events fluticasone vs. placebo

Study	Drop-Outs*	AE total ≥ 1	Number SAE	Drop-out due to AE/ deaths
Fluticasone vs. Placebo				
Burge 2000[a] [22]				
Fluticasone N=376	164 (43,6)[b]	ns	141[c,d]	114/32
Placebo N=375	200 (53,3)[b]	ns	148[c,d]	135/36
Calverley 2003b [9]				
Fluticasone N=374	108 (28,9)[b,e]	70 (19)[f]	ns	55/ns
Placebo N=361	140 (38,8)[b]	49 (14)[f]	ns	68/ns
Calverley 2007[g] [10]				
Fluticasone N=1552	587 (38,3)[h]	(90)	(42)	360[h]/246 (16,0)[h]
Placebo N=1544	673 (44,2)[h]	(90)	(41)	366[h]/231 (15,2)[h]
Hanania 2003 [11]				
Fluticasone N=183	(27)	129 (74)[i]	ns	31i/ 0
Placebo N=185	(32)	118 (64)[i]	ns	
Mahler 2002 [12]				
Fluticasone N=168	(40)	138 (80)[i]	ns	(12,5)/0
Placebo N=181	(38)	127 (69)[i]	ns	(9,4)/3
Paggiaro 1998 [15]				
Fluticasone N=142	19 (13,4)[b]	(64)	ns	9/ns
Placebo N=139	27 (19,4)[b]	(68)	ns	16/ns
Thompson 2002 [14]				
total N=52	16 (31)[b]			
Fluticasone	4	ns	ns	3/ns
Placebo	12	ns	ns	10/ns
van der Valk 2002 [23]				
Fluticasone N=123	1 (0,8)[b]	ns	14	0/1
Placebo N=121	1 (0,8)[b]	ns	24	0/1
Verhoeven 2002 [19]				
Fluticasone N=10	0 (0)	25	ns	0/ns
Placebo N=13	0 (0)	28[k]	ns	0/ns

All data are presented as N (%) if possible

* Drop-Outs: including every discontinuation of the study (withdrawal, drop-out and loss to follow-up)
a data for the whole randomised phase of study
b procentual value by own calculation
c data for the double blind phase of study
d number of patients with SAE
e statistically significant difference (p=0,007)
f only treatment-related AE given
g related to safety population
h related to efficacy population (Fluticasone N=1534, Placebo N=1524)
i incidence AE ≥ 10%
j data not reported separately for the four treatment arms
k less reporting of AE related to airways disease and/or study medication in the ICS-group with statistically significant differences (18 vs. 7, p=0,02)
AE: adverse events, ns: not stated, SAE: serious adverse events

Table 9 Adverse events beclomethasone vs. placebo

Studie	Drop-Outs*	AE total ≥ 1	Number SAE	Drop-out due to AE/ deaths
Beclomethasone vs. Placebo				
Weir 1999	39 in total			
Beclomethasone N=49 Placebo N=49		ns.	ns	ns/ns
All data are presented as N (%) if possible				
* Drop-Outs: including every discontinuation of the study (withdrawal, drop-out and loss to follow-up) AE: adverse events, ns: not stated, SAE: serious adverse events				

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